

Electronic Cover Sheet		
PI: Zhu, Zoe	Title: Development of an Oral Microbiome Foundation Model for Systemic Diseases Assessment	
Received: 10/14/2025	Opportunity: PA-24-182	Council: 05/2026
Competition ID: FORMS-I	FOA Title: Mentored Clinical Scientist Research Career Development Award (Parent K08 Independent Clinical Trial Not Allowed)	
1K08DE036336-01	Dual:	Accession Number: 5206700
IPF: 8422704	Organization: TUFTS UNIVERSITY BOSTON	
Former Number:	Department:	
IRG/SRG: ZRG1 MSOS-F (22)S	AIDS: N	Expedited: N
<u>Subtotal Direct Costs</u> <u>(excludes consortium F&A)</u> Year 1: 116,347 Year 2: 119,101 Year 3: 119,365 Year 4: 119,331 Year 5: 119,365	Animals: N Humans: Y Clinical Trial: N Current HS Code: 20 HESC: N HFT: N Special Topics: Data Management Sharing	New Investigator: Early Stage Investigator:
<i>Senior/Key Personnel:</i>	<i>Organization:</i>	<i>Role Category:</i>
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Reference Letters

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Thomas Van Dyke	ADA Forsyth Institute	10/14/2025
Athena Papas	Tufts University School of Dental Medicine	10/14/2025

Additions for Review

Accepted Publication

Post Submission Materials
(accepted publications)

Other

Post Submission Materials
(one-page update with
preliminary data)

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE		State Application Identifier
1. TYPE OF SUBMISSION*		4.a. Federal Identifier
<input type="radio"/> Pre-application <input checked="" type="radio"/> Application <input type="radio"/> Changed/Corrected Application		b. Agency Routing Number
2. DATE SUBMITTED	Application Identifier	c. Previous Grants.gov Tracking Number
5. APPLICANT INFORMATION		UEI*: C1F5LNUF7W86
Legal Name*: TUFTS UNIVERSITY BOSTON		
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6. EMPLOYER IDENTIFICATION NUMBER (EIN) or (TIN)*		0142103634A5
7. TYPE OF APPLICANT*		O: Private Institution of Higher Education
Other (Specify):		
Small Business Organization Type <input type="radio"/> Women Owned <input type="radio"/> Socially and Economically Disadvantaged		
8. TYPE OF APPLICATION*		If Revision, mark appropriate box(es).
<input checked="" type="radio"/> New <input type="radio"/> Resubmission		<input type="radio"/> A. Increase Award <input type="radio"/> B. Decrease Award <input type="radio"/> C. Increase Duration
<input type="radio"/> Renewal <input type="radio"/> Continuation <input type="radio"/> Revision		<input type="radio"/> D. Decrease Duration <input type="radio"/> E. Other (specify):
Is this application being submitted to other agencies?* <input type="radio"/> Yes <input checked="" type="radio"/> No What other Agencies?		
9. NAME OF FEDERAL AGENCY* National Institutes of Health		10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER TITLE:
11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT* Development of an Oral Microbiome Foundation Model for Systemic Diseases Assessment		
12. PROPOSED PROJECT Start Date* Ending Date* 07/01/2026 06/30/2031		13. CONGRESSIONAL DISTRICTS OF APPLICANT MA-007

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE**Page 2****14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION**

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15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested* \$640,988.78
b. Total Non-Federal Funds* \$0.00
c. Total Federal & Non-Federal Funds* \$640,988.78
d. Estimated Program Income* \$0.00

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:
b. NO ☒ PROGRAM IS NOT COVERED BY E.O. 12372; OR
☐ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

☒ I agree*

* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION

File Name:

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Signature of Authorized Representative*

Colleen Donaghey

Date Signed*

10/14/2025

20. PRE-APPLICATION File Name:**21. COVER LETTER ATTACHMENT** File Name: CoverLetter_K08.pdf

424 R&R and PHS-398 Specific

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Project/Performance Site Location(s)**Project/Performance Site Primary Location**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

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UEI: C1F5LNUF7W86
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State*: MA: Massachusetts
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Country*: USA: UNITED STATES
Zip / Postal Code*: 02111-1527
Project/Performance Site Congressional District*: MA-007

Project/Performance Site Location 1

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

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Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 02111-1527
Project/Performance Site Congressional District*: MA-007

Additional Location(s)

File Name:

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* <input checked="" type="radio"/> Yes <input type="radio"/> No	
1.a. If YES to Human Subjects	
Is the Project Exempt from Federal regulations? <input type="radio"/> Yes <input checked="" type="radio"/> No	
If YES, check appropriate exemption number: <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> 8	
If NO, is the IRB review Pending? <input checked="" type="radio"/> Yes <input type="radio"/> No	
IRB Approval Date:	
Human Subject Assurance Number	00004517
2. Are Vertebrate Animals Used?* <input type="radio"/> Yes <input checked="" type="radio"/> No	
2.a. If YES to Vertebrate Animals	
Is the IACUC review Pending? <input type="radio"/> Yes <input type="radio"/> No	
IACUC Approval Date:	
Animal Welfare Assurance Number	
3. Is proprietary/privileged information included in the application?* <input type="radio"/> Yes <input checked="" type="radio"/> No	
4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* <input type="radio"/> Yes <input checked="" type="radio"/> No	
4.b. If yes, please explain:	
4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? <input type="radio"/> Yes <input type="radio"/> No	
4.d. If yes, please explain:	
5. Is the research performance site designated, or eligible to be designated, as a historic place?* <input type="radio"/> Yes <input checked="" type="radio"/> No	
5.a. If yes, please explain:	
6. Does this project involve activities outside the United States or partnership with international collaborators?* <input type="radio"/> Yes <input checked="" type="radio"/> No	
6.a. If yes, identify countries:	
6.b. Optional Explanation:	
7. Project Summary/Abstract*	Filename ProjectSummary.pdf
8. Project Narrative*	Project_Narrative.pdf
9. Bibliography & References Cited	Bibliography.pdf
10. Facilities & Other Resources	Facilities_And_Resources.pdf
11. Equipment	Equipment_K08.pdf

PROJECT SUMMARY

Oral microbiome dysbiosis is increasingly recognized as a driver of not only oral diseases such as periodontitis but also systemic disorders including Alzheimer's disease (AD). Although large-scale datasets from 16S rRNA and shotgun metagenomic datasets enable high-throughput microbial analysis, these data are typically disease-specific, limited in scale, and analyzed using conventional methods that may overlook fine-grain microbial interactions. These limitations hinder our understanding of the oral-systemic health axis and the development of predictive models for systemic diseases. To address these gaps, we propose to develop a **Transformer-based Oral Microbiome Foundation Model (OMFM)**, the first large-scale foundation model trained on oral microbiome data. This scalable platform will learn contextualized microbial embeddings that capture nuanced taxa interactions and establish a population-level baseline for oral microbiome research. More importantly, our OMFM will enable multiple downstream applications, with a focus in this K08 project on **predicting Alzheimer's disease** from oral microbial profiles.

We propose three specific aims: **Aim 1** will build and validate the OMFM using the ELECTRA Transformer architecture, optimizing hyperparameters and benchmarking against state-of-the-art models (BERT, TabTransformer, and MGM 2.0). **Aim 2** will fine-tune the pretrained OMFM on a curated AD-labeled dataset to develop a predictive model for AD diagnosis and benchmark performance against traditional machine learning baselines. Model interpretability will be assessed using SHAP and Integrated Gradients to reveal biologically meaningful microbial associations. External validation will employ the WHICAP cohort to test generalizability across populations. **Aim 3** will explore clinical translation through an IRB-approved pilot study at Tufts to evaluate diagnostic accuracy across oral sampling sites. By integrating WHICAP and Tufts longitudinal data, we will test whether baseline oral microbiome patterns can forecast one-year cognitive changes, pioneering a non-invasive biomarker for early AD detection.

The **candidate**, a DDS/PhD junior faculty member, has a strong interdisciplinary background in oral-systemic health, large-scale sequencing data analysis, and machine learning model development for oral disease prediction. Mentored by a multidisciplinary team of experts in oral biology, microbiology, AI in healthcare, and clinical neurology, this K08 award will provide structured training in deep learning, translational microbiome research, and clinical implementation. Through formal coursework, mentored research, and monthly progress meetings, this program will prepare the candidate for independent R01 funding and establish a long-term research trajectory focused on AI-driven diagnostics for oral-systemic health.

PROJECT NARRATIVE

This project will develop a novel Oral Microbiome Foundation Model (OMFM) leveraging extensive oral microbiome samples and advanced deep learning (Transformer-based architecture). By addressing limitations of disease-specific datasets and conventional analysis methods, OMFM will establish a scalable, population-level baseline for oral microbiome research and will demonstrate clinical utility through fine-tuning for Alzheimer's disease prediction with external and clinical validation. This research will advance understanding of oral-systemic relationships and will establish a non-invasive, cost-effective screening tool (~\$45/test) deployable in dental clinics for Alzheimer's disease and other systemic conditions.

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FACILITIES & OTHER RESOURCES

Laboratory, Office & Computer

The PI, Dr. Zoe Zhu, has a dedicated office space (M&V811OS) located next to the research lab. Dr. Zhu has a MacBook Air M2 with a printer in the office. Dr. Zhu's laptop has access to Tufts axiUm electronic dental database. The adjacent laboratory space is equipped with instruments and equipment for sample processing required for the proposed work. In addition, the lab has four Windows desktop computers: two Windows computers control various instruments, and two Windows computers for general use. Laser printers are available for this project. The computers are all connected to the Internet, Tufts University Network, Medline, and other medical databases and are all email accessible. All the desktops at clinics of Tufts Dental School are installed with axiUm.

Support from Tufts Dental School

- Clinical Research Center (CRC) at Tufts University School of Dental Medicine (TUSDM)

TUSDM clinical research center has an excellent clinical setting to conduct the proposed clinical research in this K08 application. TUSDM CRC has four clinical research coordinators who assist investigators in conducting patient recruitment, screening, and providing informed consent, to assist in capturing the data at all visits and creating case reports. The coordinator can also assist in taking X-rays and keeping study data/files organized and available throughout the study. Dr. Zhu has worked with the CRC on multiple clinical studies as a clinical investigator and is familiar with their operational procedures and resources.

- TUSDM Technology Services – Clinical Research Data Management and Information Security

The Tufts Technology Services team at the Dental School offers a comprehensive and strategic program for health information (axiUm data) management and systems security specifically tailored for the Tufts Dental School. They focus on maintaining up-to-date dental record data and privacy policies, understanding legislative changes, and ensuring compliance with regulations. Additionally, they support the dental school and its departments in dental research and handling privacy and security concerns, ensuring confidentiality and risk minimization of protected information.

Institutional Support at Tufts University

- Tufts Institute of Artificial Intelligence (TIAI)

Dr. Zhu was recently awarded the highly competitive TIAI Seed Fund (Nov 2025 - Nov 2027), which provides strong support for her AI research training. This award includes an annual budget for project costs and, more importantly, a senior data scientist assigned at 0.5 Full-Time Equivalent (20 hours per week) to work directly with Dr. Zhu on her research projects. This dedicated data scientist will serve as a hands-on collaborator, providing real-time advice on machine learning methodologies throughout each phase of the proposed AI work. The intensive training structure ensures Dr. Zhu will master essential AI and computational skills during the K08 period, including advanced machine learning techniques, algorithm development, model validation, and best practices in AI-driven research. This support facilitates Dr. Zhu's progressive independence in applying AI methods to oral-systemic health research and ensures successful completion of the proposed research aims.

- Computing Resources

Dr. Zoe Zhu has strong collaboration and connections with the Tufts computer science and AI community. She is familiar with the computing resources and has access to most of them.

The Tufts University High-Performance Compute (HPC) cluster is comprised of 207 Cisco, IBM and Penguin nodes running the Redhat Linux 6.9 operating system. Nodes are interconnected via 10Gig network with future expansion in the works to 100GB and 200GB ethernet and InfiniBand. Memory configurations range from 32GB, 128GB, 256GB, 384GB and 1TB along with CPU core counts from 16, 20, 40 and 72. Total 64-bit, x86 CPU/core count is ~6504, with more nodes being added on a regular basis so the system will soon reach 10,000 cores. The system can also accommodate FPGA-style cards in addition to GPU cards. There are currently 12 Nvidia GPU systems available with new P100 and V100 GPU nodes currently being added. Dedicated login, management, file transfer, compute, storage and virtualization nodes are available on the cluster, all connected via a dedicated network infrastructure. Users access the system locally and remotely through SSH clients as

well as a number of web-based scientific gateways and portals, enabling not only access for experienced users but also emerging interests across all domains. The system was also one of the first to support singularity, the emerging container standard for high-performance computing which has proven popular among users of the machine and deep learning software stacks as well as providing facilities to port the NSF-funded OnDemand (OOD) HPC portal software to the Slurm scheduler.

Currently, Tufts University offers a total of 1.6PB+ of storage capacity for desktops and instrumentation to help researchers safely store their data. This is based on a clustered storage system from NetApp which provides redundancy at all levels from disk, to network, to server. Storage is backed up on a daily basis with up to 1 year of back-up kept off-site at any moment in addition to hourly and daily snapshots. Research storage space is also available for users of the Tufts High Performance Compute (HPC) cluster, via a Data Direct Network (DDN) parallel file system (gpfs) and Web Object Storage (WOS). This helps leverage the cluster resources (CPU, memory, storage, networking) for large-scale analysis. Requests for storage on both systems are free and provisioned up to 4TB. Above that storage is provisioned, at no charge, after proper consultation and assessment of needs and availability. For last-minute or unusual requests IT staff can work with users to develop custom solutions. Additionally, the research cluster allows for faculty and grant-funded compute nodes which buys priority access to resources while benefiting the entire cluster community.

Tufts' Department of Information Technology provides: an IBM 50-node cluster with 472 64-bit cores (Red Hat Enterprise Linux 5, 16 to 32GB RAM per node, Infiniband interconnect). Many commercial software packages are available on the university's research cluster (Abaqus, Ansys, Comsol, Deform, Fluent, Maple, Materials Studio, MATLAB, Mathematica, and Stata), as well as network concurrent licensing for desktop machines. The Tufts Center for Scientific Visualization uses a dedicated graphics workstation that allows researchers to display stereo high-resolution images (4096x2160) on a 15ft x 8ft visualization wall using either Red Hat Linux Enterprise (64-bit) or Windows (32-bit or 64-bit). An access grid videoconference node is installed in the Tufts Center for Scientific Visualization. The Access Grid is an ensemble of resources including multimedia large-format displays, presentation and interactive environments, and interfaces to grid middleware and visualization environments. Tufts provides bioinformatics services that incorporate techniques from multiple disciplines to solve biological problems in areas that include applied mathematics, informatics, statistics, and computer science. Services include a gene sequencing package Emboss/wEmboss and a micro-array analysis server. The bioinformatics server can also support open-source research codes. Statistical consulting assistance is readily available to faculty and students for both research technology and instructional projects.

Tufts Analytics Platform (TAP) and The Data Intensive Studies Center (DISC) provide high-performance hardware for large-scale bioinformatic analysis and machine-learning-based exploratory data analysis. TAP ingests multiscale clinical (including imaging) and multi-omics datasets for predictive model development. In addition, TAP is now adding bio/cheminformatics capabilities that seamlessly combine machine learning with clinical phenotyping, biological target profiling and ligand optimization for those interested specifically in biomarker discovery and early-stage drug discovery.

- Tufts University Core Facility - Genomics Core (TUGC)

Dr. Zhu has previously collaborated with the TUGC for single-cell RNA sequencing in her other research project. She has hands-on experience in the whole process of single-cell sequencing and is familiar with the related equipment at TUGC. Dr. Albert Tai, the Associate Director of the TUGC, is a long-term collaborator of Dr. Zhu.

The TUGC provides the key instruments that will be used to support this proposal. They include an Illumina NovaSeq 6000 (NIH S10OD032203), a HiSeq 2500, a NextSeq 550 and two MiSeq sequencers, a 10X Chromium Controller for single-cell RNA-Seq, as well as other supporting equipment. The TUGC also offers an array of supportive services via its dedicated 5-member team, including DNA / RNA extraction, NGS library preparation, sample QC, data storage, and post-sequence data processing.

- Libraries

The Tufts University Libraries share an Integrated Library System that provides access to resources physically and virtually available within the seven individual libraries' facilities. These libraries house almost 3 million bibliographic items, including books, microfilms, slides, and government documents.

- Scientific Environment at Tufts

The scientific environment at Tufts fosters synergy and collaboration among investigators, students, and faculty. State-of-the-art laboratories are maintained in both individual faculty programs, and more importantly as core facilities available to all students and faculty. The Science and Engineering Complex houses the Metabolomics core facility. Sequencing is available on a fee-for-service basis. Examples of other resources include the more unique Biophysical Characterization Lab, Protein Processing Lab, and Advanced Technology Lab, as well as more traditional facilities (e.g., Protein Chemistry Core for Sequencing and Peptide Synthesis, Proteomics, Cell Sorting Lab, Clinical Translation Center, and many others). Tufts also runs the unique NIH-sponsored P41 Resource Center on Tissue Engineering, with a collaborative partnership with Columbia University. The Science & Engineering Center (SEC) is a prime example of the above synergy, as it is a newly constructed building housing faculty and students with shared interests, with an eye to the future to be adapted and configured as themes and priorities of Tufts research evolve.

External support

- Oral Microbiome Expertise and Analysis Support

The ADA Forsyth Institute's Oral Microbiome Core (FOMC) specializes in microbial analysis of samples from the human oral cavity, though analyses of samples from all human, animal, and environmental sites are also available. Dr. Xuesong He, a Professor at the Forsyth Institute and Dr. Zhu's co-mentor, is affiliated with this core and will provide direct expertise in oral microbiome research and facilitate access to FOMC's advanced sequencing and analytical capabilities.

- Back-up Next-Generation Sequencing Resources

Recognizing the high demand for next-generation sequencing and the potential delays it may cause, in addition to TUGC, additional resources have been secured for the project's sequencing needs.

The Forsyth Bioinformatics Core (FBC) was established alongside the Human Oral Microbiome Database (HOMD) in 2006. Together with FOMC, FBC offers Next Generation Sequencing (NGS) and comprehensive data analyses, including interpretation for 16S rRNA gene amplicon sequences and other big data sequence applications. Led by Dr. Tsute (George) Chen, a human oral microbiome data analysis expert, the core has been developing bioinformatics tools to analyze NGS data for the research community in the oral/dental and nasal study fields. The core houses an array of high-performance multi-CPU computers with high memory that can analyze NGS data. Dr. George Chen, the director of FOMC and FBC, is a consultant for this K08 application.

The Single Cell Genomics Core (SCGC) at Dartmouth Cancer Center: Dr. Zoe Zhu has a history of successful collaboration with SCGC and its director, **Dr. Fred Kolling**, having previously acquired valuable spatial transcriptomics data from OSCC tissue sections through this partnership.

- Alzheimer's Disease and Oral-Systemic Research Support

The Columbia Mentoring Team: **Dr. Panos Papapanou** and **Dr. James Noble** at Columbia University bring complementary expertise that will be invaluable to this project. Dr. Papapanou is a renowned periodontist and epidemiologist at Columbia University College of Dental Medicine whose groundbreaking work on the epidemiology of periodontal disease has significantly advanced our understanding of the oral-systemic link. Dr. James Noble, a leading neurologist at Columbia University Irving Medical Center, specializes in neurodegenerative disorders, including Alzheimer's disease, and integrates clinical insights with innovative diagnostic approaches. They are the PIs on the ongoing WHICAP Periodontal Infection and Alzheimer's study, and have committed access to their data for this training grant. In addition, with the support of this K08 grant, Dr. Zhu plans to visit their team at Columbia and receive hands-on training in dental and neurological clinical research.

EQUIPMENT

The following major equipment is available for this K08 application, as the **wet lab setting for the sample storage, DNA extraction**, etc., a CFX Opus 96 Real-Time PCR System from Bio-Rad; a Nikon epifluorescent microscope with a photomicrographic system and image analysis software; an Olympus inverted microscope with phase contrast illustration; Sorvall analytic preparative ultracentrifuges (high speed); centrifuges (benchtop, free-standing, refrigerated, microfuges); micro plate readers; a spectrophotometer; a scintillation counter and a new Faxitron X-ray inspection unit; histology room equipped with a tissue embedder and Leica microtome for tissue section preparation; cell culture facilities; electrophoresis apparatus; PCRs; a sequencer and power supply; analytic balances; water baths; a luminometer; a DNA fluorometer; a shaking incubator; a hybridization oven; a water purification system; a large autoclave chamber, BSL-2 level biosafety cabinets, sinks, incubators (dry, humidified, CO₂), freezers (-70°C, -20°C), refrigerators, pH meters.

Dr. Zhu, the PI, has access to research facilities that include Tufts/TMC Small Animal Imaging/Preclinical Testing Facility (with micro-CT, IVIS Spectrum CT); FACS facilities (with Flow Cytometry equipment), CNS imaging core (with confocal microscope), Tufts University Genomics Core (TUGC, with 10X Genomics Chromium Controller, Agilent Fragment Analyzer and Illumina NovaSeq 6000 sequencer) and Comparative Pathology and Genomics Resource (CPGSR, GeoMX platform). The genomics core is equipped with the instrument needed for the **next generation sequencing (NGS)**.

Computing resources. The Tufts University High-Performance Compute (HPC) cluster is comprised of 207 Cisco, IBM and Penguin nodes running the Redhat Linux 6.9 operating system. Nodes are interconnected via 10Gig network with future expansion in the works to 100GB and 200GB ethernet and InfiniBand. Memory configurations range from 32GB, 128GB, 256GB, 384GB and 1TB along with CPU core counts from 16, 20, 40 and 72. Total 64-bit, x86 CPU/core count is ~6504, with more nodes being added on a regular basis so we will soon reach 10,000 cores. The system can also accommodate FPGA-style cards in addition to GPU cards. There are currently 12 Nvidia GPU systems available with new P100 and V100 GPU nodes currently being added. Dedicated login, management, file transfer, compute, storage and virtualization nodes are available on the cluster, all connected via a dedicated network infrastructure. Users access the system locally and remotely through SSH client as well as a number of web-based scientific gateways and portals, enabling not only access for experienced users but emerging interests across all domains. The system was also one of the first to support singularity, the emerging container standard for high-performance computing which has proven popular among users of the machine and deep learning software stacks as well as providing facilities to port the NSF-funded OnDemand (OOD) HPC portal software to the Slurm scheduler.

In addition, Dr. Zhu has established a productive collaboration with the Tufts Analytics Platform (TAP), which provides high-performance computing hardware essential for large-scale data analysis and machine learning model development. Through her involvement in TAP pilot projects and the Tufts Institute of Artificial Intelligence (TIAI) seed fund initiative, Dr. Zhu has secured access to the necessary computational infrastructure to handle the substantial data processing and model training requirements of this proposed work at a subsidized cost.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

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City*:	New York			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	100320000			
Phone Number*: 212-342-4126	Fax Number:			
E-Mail*: jn2054@columbia.edu				
Credential, e.g., agency login: JN2054				
Project Role*: Other (Specify)		Other Project Role Category: Co-Mentor		
Degree Type: MD,MS,BS		Degree Year: 2002,2008,1998		
Attach Biographical Sketch*:	File Name:	Biosketch_7_Noble.pdf		
Attach Current & Pending Support:	File Name:	OS_7_Noble.pdf		

PROFILE - Senior/Key Person				
Prefix:	First Name*: ATHANASIOS	Middle Name I	Last Name*: ZAVRAS	Suffix:
Position/Title*:	Asst. Dean for Faculty, Dept Chair, Prof			
Organization Name*:	Tufts University			
Department:				
Division:				
Street1*:	1 Kneeland Street			
Street2:	Suite 1534			
City*:	Boston			
County:				
State*:	MA: Massachusetts			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	021110000			
Phone Number*: 6178180573	Fax Number:			
E-Mail*: athanasios.zavras@tufts.edu				
Credential, e.g., agency login: TZAVRAS				
Project Role*: Other (Specify)		Other Project Role Category: Co-Mentor		
Degree Type: DDS,DMD,DSC,MS,DMSC		Degree Year: 2012,1991,1999,1994,1999		
Attach Biographical Sketch*:	File Name:	Biosketch_8_Zavras.pdf		
Attach Current & Pending Support:	File Name:	OS_8_Zavras.pdf		

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Zhu, Zoe

eRA COMMONS USER NAME (credential, e.g., agency login): zoezhu

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Shandong University, Jinan	BA	09/2008	Linguistics-French
Shandong University, Jinan	DDS	09/2011	Dentistry
Shanghai Jiaotong University, Shanghai	PHD	05/2020	Oral and Maxillofacial Surgery, Oral Biology
Tufts University, Boston, MA	Postdoctoral Fellow	06/2022	Oral Biology

A. Personal Statement

As a dentist-scientist, my research has focused on the intersection of oral health and computational biology to uncover the biological and predictive links between oral and systemic health. My scientific journey began during dental school in China, where I received funding from the National Student Innovative Research Program to investigate the adherence of oral pathogens to various dental implant surfaces. Subsequent postgraduate research enabled me to master molecular and cellular biology techniques, next-generation sequencing, and bioinformatics. These experiences laid the foundation for my current research exploring how oral pathogens contribute to the pathogenesis of oral and systemic diseases, including Alzheimer’s disease (AD). More recently, I have expanded my work to include machine learning models for oral disease prediction, reinforcing my long-term commitment to advancing translational and data-driven oral health research.

Building on this foundation, my K08 proposal outlines a plan to develop a Transformer-based Oral Microbiome Foundation Model (OMFM) that leverages extensive unlabeled 16S rRNA data to capture nuanced microbial interactions and harness the predictive potential of oral microbiomes in AD. The OMFM will establish a scalable, population-level baseline for oral microbiome research and be fine-tuned for AD prediction, addressing key limitations in data reuse and conventional analytical approaches. External validation will be performed using the WHICAP Periodontal Infections and AD study dataset. A pilot study at Tufts Dental School will assess feasibility for future large-scale translational studies and to explore novel longitudinal AD risk assessment.

My work at the intersection of artificial intelligence (AI) and oral health has been supported by multiple awards. In March 2025, I received Colgate CARE Program funding (2-3 awards granted nationwide each year) to develop a machine learning model for periodontitis assessment. In September 2025, I was awarded the highly competitive Tufts Institute for Artificial Intelligence (TIAI) Seed Fund to advance AI applications in oral health, which provides both funding support and the dedicated effort of a senior data scientist at 0.5 FTE (20 hours per week) for two years to collaborate on my AI research. In addition, I was selected as a mentee in the AADOCR MIND the Future Program (Cohort 5), which has provided invaluable mentorship and structured training in scientific leadership, research design, and career development. Collectively, these experiences have strengthened my technical expertise, collaborative network, and readiness to undertake the proposed K08 research and training plan.

Supported by this K08 award and a multidisciplinary mentoring team that includes experts in oral biology, microbiology, AI in healthcare, and clinical research in dentistry and neurology, I will receive comprehensive training through monthly mentoring meetings, formal coursework in deep learning and microbiome analysis, and hands on experience in sample processing and clinical research. This K08 project builds directly on my existing strengths and provides the essential training and mentorship to establish my independent research program at

the intersection of oral and systemic health. Successful completion will lay the foundation for future R01 funding and the development of noninvasive, clinically deployable screening tools for systemic diseases linked to oral health.

Ongoing and recently completed projects that I would like to highlight include:

2025-2027 Tufts Institute for Artificial Intelligence (TIAI) Seed Grant; AI-Driven Home-Based Screening for Periodontitis

Role: PI

2025-2026 Colgate Award for Research Excellence (CARE) Program; Development of a Machine Learning Tool for Periodontitis Assessment.

Role: PI

2020-25 NIDCR/NIH Grant # 1UE5DE029439; AADOCR MIND the Future Program. PI/Project Leader: Christopher Fox (AADOCR), David Drake (University of Iowa), Effie Ioannidou (UCSF).

Role: Cohort 5 Mentee

2024 Tufts Do-IT Grant; Application of Single-Cell Genomics and Bioinformatic in Dental Research.

Role: PI

The following recently published papers showcase my expertise in periodontal research, the oral-AD connection, and the application of AI in oral health—areas that are all central to the current proposal.

1. Zhu Z, Wu X, Zhu L, Uzel N, Zavras A, Tu Q, Chen J. Development of a Machine Learning Tool for Home-Based Assessment of Periodontitis. medRxiv. 2025 Mar 11; PubMed Central PMCID: PMC11952591.
2. El-Araby RE, Wasif K, Johnson R, Tu Q, Aboushousha T, Zhu Z, Chen J. Establishment of a novel cellular model for Alzheimer's disease in vitro studies. Exp Neurol. 2024 Aug;378:114820. PubMed Central PMCID: PMC11318039.
3. Zhu Z, Liu Y, Wang J, Xie Y, Li RY, Ma Q, Tu Q, Melhem NA, Couldwell S, El-Araby RE, Tai A, Van Dyke TE, Karimbux N, Jeong YN, Chen JJ. A novel lncRNA-mediated epigenetic regulatory mechanism in periodontitis. Int J Biol Sci. 2023;19(16):5187-5203. PubMed Central PMCID: PMC10620817.
4. Wu H, Qiu W, Zhu Z, Li X, Xie Z, Carreras I, Dedeoglu A, Van Dyke T, Han YW, Karimbux N, Tu Q, Cheng L, Chen J. The Periodontal Pathogen *Fusobacterium nucleatum* Exacerbates Alzheimer's Pathogenesis via Specific Pathways. Front Aging Neurosci. 2022;14:912709. PubMed Central ID: PMC9260256.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2022 -	Assistant Professor, Tufts University School of Dental Medicine, Boston, MA
2025 -	Vice President, AADOCR Boston Chapter, Boston, MA
2024 -	Committee Member, AADOCR Fellowship Committee, Boston, MA
2024 -	Guest Editor, Frontiers in Oral Health - 1) AI applications in Dentistry, 2) Diabetes and Oral Health
2024 -	IVACS Program Chair, Society of In Vitro Biology (SIVB), Millersville, MD
2018 - 2022	Postdoctoral Research Fellow, Division of Oral Biology, Tufts University, Boston, MA
2016 - 2018	Research Assistant, Tufts University, Boston, MA
2011 - 2015	Research Assistant, School of Dental Medicine, Shanghai Jiao Tong University, Shanghai

Honors

2024 - 2025	Cohort 5 Mentee, NIDCR-funded AADOCR MIND the Future Program
2025	Colgate Award for Research Excellence, Colgate-Palmolive Company

2024	First Prize, IADR Clinical Translational Science Network Outstanding Award
2024	Early Career Reviewer, NIH Center for Scientific Review (CSR)
2023	TUSDM DO-IT grant, Tufts University
2023	SIVB 2023 Annual Meeting Service Award, Society of In Vitro Biology
2023	AAODCR Joseph Lister Award for New Investigators Competition Finalist, AAODCR
2021	ASBMR Annual Meeting Late Breaking Travel Grant, American Society for Bone and Mineral Research
2018	FASEB Mentored Platform Presenter Award, Federation of American Societies for Experimental Biology
2018	ASBMR Young Investigator Award, American Society for Bone and Mineral Research
2018	Young Investigator Recognition Award, Mechanistic and Therapeutic Advances in Rare Skeletal Diseases Meeting
2017	AADR Hatton Award Finalist, IADR/AADR

C. Contribution to Science

1. Bone Remodeling and Orthodontic Tooth Movement Mechanisms

My early research focused on understanding the molecular mechanisms underlying accelerated bone remodeling in orthodontics. In surgery-first accelerated orthognathic surgery (SFA), I investigated the clinical phenomenon of accelerated alveolar bone remodeling and tooth movement after maxillary osteotomy, revealing significantly accelerated bone remodeling via the RANK-RANKL-OPG signaling pathway. Building on this foundation, I identified 6-shogaol, a natural compound from ginger, as a potential alternative to corticotomy in orthodontics. Our studies demonstrated that 6-shogaol promotes osteoclast differentiation and bone resorption via the JNK-NFATc1 signaling axis, representing a novel non-invasive approach to accelerate orthodontic tooth movement.

- a. Zhu X, Yuan H, Ningjuan O, Trotman CA, Van Dyke TE, Chen JJ, Shen G. 6-Shogaol promotes bone resorption and accelerates orthodontic tooth movement through the JNK-NFATc1 signaling axis. *J Bone Miner Metab.* 2021 Nov;39(6):962-973. PubMed Central PMCID: PMC8595588.
- b. Yuan H, Zhu X, Lu J, Dai J, Fang B, Shen SG. Accelerated orthodontic tooth movement following le fort I osteotomy in a rodent model. *J Oral Maxillofac Surg.* 2014 Apr;72(4):764-72. PubMed PMID: 24635855.

2. Identification of the Roles of Irisin in Bone Metabolism and Osteoarthritis

Metabolic bone diseases caused by abnormalities of mineralization, such as rickets, osteoporosis, osteopetrosis are among the most common public health issues. Irisin is a polypeptide hormone derived from the proteolytic cleavage of fibronectin-type III domain-containing 5 (FNDC5) protein. Recent studies reported the involvement of the irisin in many physiological and pathological conditions with bone mineral density changes, such as osteoporotic fractures. In this project, we demonstrated the roles of irisin in bone metabolism in both cell culture and genetic mouse models. The results provided important preliminary data and a solid basis for further study of the functions of FNDC5 and irisin.

- a. Li X, Zhu X, Wu H, Van Dyke TE, Xu X, Morgan EF, Fu W, Liu C, Tu Q, Huang D, Chen J. Roles and Mechanisms of Irisin in Attenuating Pathological Features of Osteoarthritis. *Front Cell Dev Biol.* 2021;9:703670. PubMed Central PMCID: PMC8509718.
- b. Zhu X, Li X, Wang X, Chen T, Tao F, Liu C, Tu Q, Shen G, Chen JJ. Irisin deficiency disturbs bone metabolism. *J Cell Physiol.* 2021 Jan;236(1):664-676. PubMed Central PMCID: PMC7722136.
- c. Zhang J, Valverde P, Zhu X, Murray D, Wu Y, Yu L, Jiang H, Dard MM, Huang J, Xu Z, Tu Q, Chen J. Exercise-induced irisin in bone and systemic irisin administration reveal new regulatory mechanisms of bone metabolism. *Bone Res.* 2017;5:16056. PubMed Central PMCID: PMC5605767.

3. Non-coding RNA Therapeutic Mechanisms in Periodontitis

Periodontitis is a highly prevalent chronic inflammatory disease characterized by periodontal tissue breakdown and subsequent tooth loss due to excessive host immune response. Our work on miR-335-5p revealed its potential roles in experimental periodontitis pathogenesis, contributing to our understanding of

microRNA-mediated regulation in periodontal disease. Building on this foundation, I demonstrated for the first time the regulatory mechanisms and therapeutic effects of a novel long non-coding RNA, lncR-APDC, on periodontitis using advanced approaches including gene knockout mouse models, experimental periodontitis surgery models, and single-cell RNA sequencing (scRNA-seq). This work revealed altered immune cell proportions and functions in gingival tissue and identified Tff2 as a key downstream factor of lncR-APDC, with therapeutic potential demonstrated through customized adeno-associated virus delivery systems.

- a. Zhu ZX, Liu Y, Wang J, Xie Y, Li RY, Ma Q, Tu Q, Melhem NA, Couldwell S, El-Araby RE, Tai A, Van Dyke TE, Karimbux N, Jeong YN, Chen JJ. A novel lncRNA-mediated epigenetic regulatory mechanism in periodontitis. *Int J Biol Sci.* 2023;19(16):5187-5203. PubMed Central PMCID: PMC10620817.
- b. Liu Y, Zhu ZX, Zboinski EK, Qiu W, Lian J, Liu S, Van Dyke TE, Johansson HE, Tu Q, Luo E, Chen JJ. Long non-coding RNA APDC plays important regulatory roles in metabolism of bone and adipose tissues. *RNA Biol.* 2023 Jan;20(1):836-846. PubMed Central PMCID: PMC10653663.
- c. Lian J, Wu X, Liu Y, Qiu W, Zhu X, Wang X, Meng S, Valverde P, Steffensen B, Tu Q, Pan J, Chen J. Potential roles of miR-335-5p on pathogenesis of experimental periodontitis. *J Periodontal Res.* 2020 Apr;55(2):191-198. PubMed Central PMCID: PMC7680696.

4. Periodontal Disease-Alzheimer's Disease Connection

Our recent research revealed the critical link between periodontal disease and Alzheimer's disease (AD), investigating how oral pathogens contribute to AD pathogenesis. We demonstrated that the periodontal pathogen *Fusobacterium nucleatum* exacerbates Alzheimer's pathogenesis via specific pathways, providing mechanistic insights into the oral-brain axis. Furthermore, we established a novel cellular model for Alzheimer's disease in vitro studies, enabling better investigation of periodontal pathogen-induced neurodegeneration mechanisms.

- a. El-Araby RE, Wasif K, Johnson R, Tu Q, Aboushousha T, Zhu ZX, Chen J. Establishment of a novel cellular model for Alzheimer's disease in vitro studies. *Exp Neurol.* 2024 Aug;378:114820. PubMed Central PMCID: PMC11318039.
- b. Wu H, Qiu W, Zhu X, Li X, Xie Z, Carreras I, Dedeoglu A, Van Dyke T, Han YW, Karimbux N, Tu Q, Cheng L, Chen J. The Periodontal Pathogen *Fusobacterium nucleatum* Exacerbates Alzheimer's Pathogenesis via Specific Pathways. *Front Aging Neurosci.* 2022;14:912709. PubMed Central PMCID: PMC9260256.

5. Development of machine learning tools for oral disease diagnosis

Periodontitis is a prevalent oral health condition characterized by chronic inflammation, bone resorption, and subsequent teeth loss, which significantly impact patients' life quality. Access to dental care, particularly periodontal exams, remains challenging for many individuals, and consequently leads to negative outcomes, including uncontrolled periodontitis progression, systemic health complications, impaired oral function. Our study aims to develop a machine learning (ML) tool that allows individuals to perform periodontal self-assessment at home through simple survey. This innovative tool has immense potential to benefit a substantial population, including those may already be afflicted with undiagnosed periodontal issues that require prompt or routine treatment, yet remain unaware of their condition. We utilized the NHANES database and ML algorithms proficient in handling complex tabular datasets. In model development, we established a baseline model with Logistic Regression using multinomial-output, then performed Ensemble Methods and Support Vector Machine. The model demonstrated well-behaved classification performance without overfitting. Our study establishes a proof-of-concept showcasing the predictive capabilities of patient demography, lifestyle, systemic conditions, and oral care habits in determining periodontitis stages.

- a. Zhu ZX, Wu X, Zhu L, Uzel N, Zavras A, Tu Q, Chen J. Development of a Machine Learning Tool for Home-Based Assessment of Periodontitis. *medRxiv.* 2025 Mar 11; PubMed Central PMCID: PMC11952591.

Complete List of Published Work in My Bibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/1bKW4h9ke7-Af/bibliography/public/>

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: CHEN, JAKE JINKUN

eRA COMMONS USER NAME (credential, e.g., agency login): JCHEN14

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
UNIVERSITY OF CONNECTICUT, Farmington, CT	MS	12/1988	DENTAL SCIENCE,
UNIVERSITY OF TORONTO	PHD	03/1993	BIOMEDICAL SCIENCE,
Tufts University School of Dental Medicine, Boston	DMD	05/2009	Dentistry
Harvard School of Dental Medicine, Boston, MA	Fellow	11/1985	Research Fellow - Oral Pathology
University of Connecticut, Farmington, CT	Resident	12/1988	Specialty Certificate - Oral Pathology
University of Connecticut Health Center, John Dempsey Hospital, Farmington, CT	Resident	12/1988	Resident Pathologist

A. Personal Statement

Oral and systemic diseases have numerous associations, highlighting the interconnected nature of human health. I have a background in both clinical and basic science research. I earned my Ph.D. degree in 1993 from the University of Toronto, where I gained firsthand bench experience in bone biology and basic science research working with a talented group of bone research scientists and specialists. Additionally, I was trained as an oral pathologist at the University of Connecticut, which could significantly benefit the work proposed in this project. My laboratory focuses on researching the intricate relationships between the oral health and various systemic conditions, such as diabetes, bone metabolism, and Alzheimer's disease.

I am very pleased to serve as one of the co-primary mentors for Dr. Zhu's K08 career development application. This K08 aims to support her interesting research project and career development, focusing on the development of an oral microbiome foundation model for systemic diseases assessment. Together with Dr. Zhu, we have developed a comprehensive career development plan. I will guide Dr. Zhu in areas related to the connections between oral and systemic diseases, from basic science to translational study and the pilot clinical study she proposed. Dr. Hassoun will provide her expertise on deep learning techniques and their application in microbiome research. Additionally, our co-mentors (Dr. He, Dr. Bonham, Dr. Papapanou, Dr. Noble, Dr. Teles, and Dr. Zavras) will offer guidance in their respective fields: microbiology, computational biology, periodontal pathogens and Alzheimer's disease (AD), clinical assessment and diagnosis of AD, and career development as a junior faculty.

I am the PI of multiple active R01s, which demonstrates my capability to lead and mentor in significant research projects. I am also an experienced mentor. I mentored and co-mentored approximately 97 predoctoral and postdoctoral individuals, including dental students, postdoctoral fellows, and junior faculty.

Ongoing and recently completed projects that I would like to highlight include:

R01 DE032006 Chen (PI) 06/15/23 – 04/30/28
NIH/NIDCR
Potentials of Epigenetic Molecules in Attenuating the Phenotypes of Periodontitis

R01 DK131444 Chen (PI) 08/16/22 – 07/31/27
NIH/NIDDK
Therapeutic Potentials of a New Long Noncoding RNA in Diabetic Bone Wound Repair

R01 DE30074 Chen (PI) 12/01/21 – 11/30/25
 NIH/NIDCR
 A Long Noncoding RNA Ameliorates Periodontitis via Distinct Epigenetic Pathways

R01 DE25681 Chen (PI) 09/01/20 – 08/31/25
 NIH/NIDCR
 Roles of Noncoding RNA in Bone Regeneration

B. Positions, Scientific Appointments, and Honors

Positions and Employment

1985 - 1985 Instructor/Research Fellow, Harvard University, School of Dental Medicine, Boston, MA
 1990 - 1991 Instructor, University of Toronto, Faculty of Dentistry, Toronto, Canada
 1993 - 1998 Assistant Professor, University of Texas Health Science Center at San Antonio, San Antonio, TX
 1998 - 2001 Associate Professor (tenured), University of Texas Health Science Center at San Antonio, San Antonio, TX
 1998 - 2001 Associate Professor, University of Texas Health Science Center at San Antonio, Department of Pathology, San Antonio, TX
 1998 - 2001 Faculty Member for Graduate Students, Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, San Antonio, TX
 2002 - Professor (tenured), Tufts University School of Dental Medicine, Boston, MA
 2002 - Director, Division of Oral Biology, Tufts University School of Dental Medicine, Boston, MA
 2003 - Professor, Department of Genetics, Cellular and Molecular Biology, Tufts University School of Medicine and School of Graduate Biomedical Sciences, Boston, MA.

Other Experience and Professional Memberships (Items before 2000 not included)

2001 to 02 Chair, Science Advisory Board, The Fund for International AIDS Research and Education
 2001 to 05 Member, Literature Selection Technical Review Committee, National Library of Medicine, NIH
 2001 to 05 Standing member, ODSC Study Section, NIH
 2003 Ad Hoc Reviewer for RFA: Mechanisms of Mineralization in Bone, NIAMS, NIH
 2003 External Reviewer, Health Research Foundation, British Columbia
 2004 Ad Hoc Reviewer, Special Emphasis Panel/Initial Review Group, ODCS, NIH
 2004 Ad Hoc Reviewer for RFA: Specialized Centers for Oral, Dental and Craniofacial Research, ODCS Study Section, NIH
 2004 to 05 President, International Association for Biological and Medical Research, Boston, MA
 2008 - Grant Review Panel Member, Department of Veteran Affairs
 2014- 2014, Ad Hoc Reviewer, ODCS Study Section, NIH; 2016, Ad Hoc Reviewer, ODCS Study Section, NIH; 2017, Reviewer, ZRG1 MOSS-S (02) S, NIH.
 2018 Ad Hoc Reviewer, ODCS Study Section, NIH (Feb. 2018 and June 2018)
 2018 Ad Hoc Reviewer, SBDD Study Section, NIH (Oct. 2018)
 2018 Reviewer for NIH Director's Early Independence Awards (DP5), NIH (Dec. 2018)
 2020 Ad Hoc Reviewer, SBDD Study Section, NIH (Feb. 2020); MTE Study Section, NIH (June 2020)
 2021 MTE Study Section, NIH (February 2021)
 2022 Reviewer for grants submitted to Department of Veterans Affairs (April 2022)

Honors (Items before 2012 not included due to the limitation of space)

2012 Keynote Speaker, 10th International Conference on Bone and Mineral Research and 11th International Osteoporosis Symposium, ASBMR
 2012 Innovation in Implant Sciences Award, IADR/AO
 2014 Innovation in Oral Care Award, IADR/GSK

- 2012 – Ten (10) National and International Awards and Prizes won by the trainees in the Chen Lab, 2012 to 2017.
- 2018 ASBMR 2018 Annual Meeting, 9/28 to 10/1 in Montreal, Canada, Dr. Chen's research team received 8 Awards and Recognitions.
- 2019 ASBMR Fellow Class of 2019
- 2021 Two "Late Breaking" epigenetic research work from our lab were presented in the ASBMR Annual Meeting, Oct. 1 to 4, 2021 in San Diego, CA.

C. Contributions to Science

1. Treating diabetes-associated bone disorders with adiponectin

Adiponectin, a primary adipokine, has insulin-sensitizing and anti-diabetic properties. Our recent studies show that adiponectin increases osteoclast apoptosis, inhibits osteoclastogenesis, and decreases survival/proliferation of osteoclast precursor cells through down-regulation of Akt1 activity. We have also shown that adiponectin promotes the osteoblast niche and ameliorates 'mobilopathy' of mesenchymal cells in diabetic mice through a novel signal pathway. We have also shown that the sustained release of adiponectin improves the restoration of bone defects under osteoporotic conditions in ovariectomized animals in which osteoclasts are highly activated.

- a. Jiang H, Wu Y, Valverde P, Murray D, Tang J, Yao Q, Han Q, Zhang J, Zhang L, Sui L, Tang Y, Tu Q, **Chen J**. Central adiponectin induces trabecular bone mass partly through epigenetic downregulation of cannabinoid receptor CB1. *Journal of cellular physiology*. 2018; PubMed [journal] PMID: 30479003
- b. Yu L, Tu Q, Han Q, Zhang L, Sui L, Zheng L, Meng S, Tang Y, Xuan DY, Zhang J, Murray D, Shen Q, Cheng J, Kim SH, Dong LQ, Valverde P, Xao X, **Chen J**. Adiponectin Regulates Bone Marrow Mesenchymal Stem Cell Niche Through a Unique Signal Transduction Pathway – An Approach for Treating Bone Disease In Diabetes. *Stem Cells*. 33(1): 240-52, 2015.
- c. Wu Y, Tu Q, Valverde P, Zhang J, Murray D, Dong L, Cheng J, Jiang H, Rios M, Morgan E, Tang Z, **Chen J**. Central Adiponectin Administration Reveals New Regulatory Mechanisms of Bone Metabolism in Mice. *Am J Physiol Endocrinol Metab*. 306(12): E1418-30, 2014. PMCID: PMC4059988
- d. Zhang L, Meng S, Tu Q, Yu L, Tang Y, Dard MM, Kim SH, Valverde P, Zhou X, **Chen J**. Adiponectin Ameliorates Experimental Periodontitis in Diet-Induced Obesity Mice. *PLoS One*. 9(5): e97824, 2014. PMCID: PMC4023953

2. Translational studies for bone related disorders.

In 2011 my lab presented the first report of induced pluripotent stem (iPS) cells that could be used to regenerate periodontal tissues including PDL, cementum and alveolar bone. SATB2 is one of the critical osteogenic transcriptional factors. In our periodontal defect model, we found that SATB2 significantly increased expression levels of bone matrix proteins, transcription factors, and VEGF, and played an important role in periodontal regeneration.

- a. Wu X, Qiu W, Hu Z, Lian J, Liu Y, Zhu X, Tu M, Fang F, Yu Y, Valverde P, Tu Q, Yu Y, **Chen J**. An Adiponectin Receptor Agonist Reduces Type 2 Diabetic Periodontitis. *J Dent Res* [Internet]. 2019 Mar 1 [cited 2019 Feb 25];98(3):313–21.
- b. Duan X, Tu QS, Zhang J, Ye JH, Sommer C, Mostoslavsky G, Kaplan D, Yang PS and **Chen J**. Application of Induced Pluripotent Stem (iPS) Cells in Periodontal Tissue Regeneration. Featured as a Contents Image in that issue. *J Cell Physiol*. 226: 150-157, 2011. PMCID: PMC4137963
- c. Zhang J, Tu Q, Grosschedl R, Kim MS, Griffin T, Drissi H, Yang, P and **Chen J**. Roles of SATB2 in Osteogenic Differentiation and Bone Regeneration. *Tissue Eng Part A*. 17(13-14): 1767-76. 2011. PMCID: PMC3118613
- d. Yan SG, Zhang J, Tu Q, Ye JH, Luo E, Schuler M, Dard MM, Yu Y, Murray D, Cochran DL, Kim SH, Yang P, **Chen J**. Transcription factor and bone marrow stromal cells in osseointegration of dental implants. *European Cells and Materials (eCM)*, 26:263-271, 2013.

3. Epigenetic approaches to treat periodontitis and bone disorders

I have applied cutting-edge research techniques in an attempt to treat periodontal disease. We have recently explored the roles of epigenetic factors and found that JQ1, a BET inhibitor, dramatically inhibited inflammatory cytokine expression in diseased gingival tissues, reduced the number of osteoclasts, and alleviated alveolar bone loss in our murine periodontitis model. These unprecedented results suggest that an

epigenetic modulator could serve as a prospective new approach for treating periodontitis. In addition to miR-335-5p we recently identified miR-99a and its target KDM6B gene as novel modulators of osteogenic differentiation of bone mesenchymal stem cells (BMSCs). In another epigenetic study we found that PHF8, a major H4K20/H3K9 demethylase, plays a critical role in craniofacial and bone development. We first demonstrated that PHF8 epigenetically modulates SATB2 activity, triggering BMSCs osteogenic differentiation and facilitating bone formation and regeneration.

- a. Meng S, Zhang L, Tang Y, Tu Q, Zheng L, Yu L, Murray D, Cheng J, Kim SH, Zhou X, **Chen J**. BET Inhibitor JQ1 Blocks Inflammation and Bone Destruction. *J Dent Res*. 93(7):657-662, 2014. PMID: PMC4107547
- b. Xuan D, Han Q, Tu Q, Valverde P, Zhang L, Yu L, Murry D, Zhang J and **Chen J**. Epigenetic modulation in periodontitis: interaction of adiponectin and jmjd3-IRF4 axis in macrophage transformation. *J Cell Physiol* 231:1090-1096, 2016.
- c. Tang Y, Zhang L, Tu T, Li Y, Murray D, Tu Q and **Chen J**. MicroRNA-99a is a novel regulator of KDM6B-mediated osteogenic differentiation of BMSCs. *J Cell Mol Med* 22 (4) 2162-76, 2018.
- d. Han Q, Yang P, Wu Y, Meng S, Sui L, Zhang L, Yu L, Tang Y, Jiang H, Xuan D, Kaplan DL, Kim SH, Tu Q, **Chen J**. Epigenetically Modified Bone Marrow Stromal Cells (BMSCs) in Silk Scaffolds Promote Craniofacial Bone Repair and Wound Healing. *Tissue Eng Part A*. 21 (15-16):2156-65, 2015.

4. *Non-coding RNAs play important epigenetic roles in bone repair and regeneration*

We were the first to identify miR-335-5p that regulated DKK1 protein levels through an extensive investigation. MiR-335-5p has a pivotal role in osteogenic differentiation and regulating bone development. We recently generated a transgenic mouse line specifically overexpressing miR-335-5p. Analysis revealed higher bone mass and increased parameters of bone formation in transgenic mice than in wild-type littermates. BMSCs from transgenic mice were able to repair bone defects effectively. We applied lipidoid nanoparticles to deliver miR-335-5p molecules and achieved extremely interesting and important results. We have recently shown that miR-335-5p has critical protective roles on pathogenesis of experimental periodontitis. We will further study the roles of this miRNA in PD associated AD in the current application.

- a. Lian J, Wu X, Liu Y, Qiu W, Zhu X, Wang X, Meng S, Valverde P, Steffensen B, Tu Q, Pan J, **Chen J**. Potential roles of miR-335-5p on pathogenesis of experimental periodontitis. *J Periodontal Res*. 2020 55 (2):191-198.
- b. Zhang L, Tang Y, Zhu X, Tu T, Sui L, Han Q, Yu L, Meng S, Zheng L, Valverde P, Tang J, Murray D, Zhou X, Drissi H, Dard MM, Tu Q, **Chen J**. Overexpression of MiR-335-5p Promotes Bone Formation and Regeneration in Mice. *J Bone Miner Res*. 32 (12): 2466-75, 2017.
- c. Zhang J, Tu Q, Bonewald LF, He X, Stein G, Lian J, **Chen J**. Effects of miR-335-5p in Modulating Osteogenic Differentiation by Specifically Down-Regulating Wnt Antagonist DKK1. *J Bone Miner Res*. 26(8): 1953-63, 2011. PMID: PMC3810406
- d. Sui L, Wang M, Han Q, Yu L, Zhang L, Zheng L, Lian J, Zhang J, Valverde P, Xu Q, Tu Q, **Chen J**. A novel Lipidoid-MicroRNA formulation promotes calvarial bone regeneration, *Biomaterials*, in press, May 23, 2018.

5. *Cell based gene therapy for bone regeneration*

Irisin is a polypeptide hormone derived from the FNDC5 protein. Once released to circulation upon exercise or cold exposure, irisin stimulates browning of white adipose tissue (WAT) and uncoupling protein 1 (UCP1) expression, leading to an increase in total body energy expenditure. Lentiviral FNDC5 IP administration increased cortical bone thickness. In vitro studies in bone cells revealed irisin increases osteoblastogenesis and mineralization and inhibits RANKL-induced osteoclastogenesis. Taken together, our findings show that voluntary exercise increases irisin production in bone, and that an increase in circulating irisin levels enhances osteogenesis in mice.

- a. Zhang J, Valverde P, Zhu X, Murray D, Wu Y, Yu L, Jiang H, Dard M, Huang J, Xu Z, Tu Q, **Chen J**. Exercise-induced irisin in bone and systemic irisin administration reveal new regulatory mechanisms of bone metabolism. *Bone Research*. 2017 21; 5:16056.
- b. Yan S, Zhang J, Tu Q, Ye J, Luo E, Schuler M, Kim M, Griffin T, Zhao J, Duan X, Cochran DL, Murray D, Yang PS and **Chen J**. Enhanced osseointegration of titanium implant through the local delivery of transcription factor SATB2. *Biomaterials*. 32(33): 8676-83, 2011.
- c. Ye JH, Xu YJ, Gao J, Yan SG, Zhao J, Tu QS, Zhang J, Duan XJ, Sommer CA, Mostoslavsky G, Kaplan D, Wu YN, Zhang CP, Wang L and **Chen J**. Critical-Size Calvarial Bone Defects Healing in a Mouse Model with Silk Scaffolds and SATB2-Modified iPSCs. *Biomaterials* 32:5065-5076, 2011.

- d. Zhang J and **Chen J**. Bone Tissue Regeneration - Application of Mesenchymal Stem Cells and Cellular and Molecular Mechanisms. Curr Stem Cell Res Ther. 5(12) 357-364, 2017.

Complete List of Published Work in My Bibliography (102):

<https://www.ncbi.nlm.nih.gov/sites/myncbi/10yQfzeZqJ3Ac/bibliography/53399115/public/?sort=date&direction=descending>

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Soha Hassoun

eRA COMMONS USER NAME (credential, e.g., agency login): SHASSOUN

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
South Dakota State University	BS	06/1986	Electrical Engineering
Massachusetts Institute of Technology	MS	06/1988	Electrical Engineering & Computer Science
University of Washington, Seattle	PHD	06/1997	Computer Science & Engineering

A. Personal Statement

My lab's mission is to develop novel machine-learning models to advance biological and biomedical discovery. My lab has extensive experience with deep learning models, where we have developed multiple software tools to investigate problems related to metabolomics and the promiscuity of enzymes. My research is funded from NIH and DoD.

My interest in Large Language Models (LLMs) stems from realizing that the world will swiftly change due to this disruptive technology. I am currently working on a metabolomics project with collaborator, Dr. Louis-Félix Nothias, Centre National de la Recherche Scientifique & Université Cote d'Azur, France, on creating *per-sample* metabolomics knowledge graph and using LLMs to reason over the graph. We are learning and adapting to new techniques and software tools at an unprecedented speed, with rapidly evolving infrastructure for the development and deployment of LLMs for real world applications.

LLMs offer transformative capabilities. LLMs understand text and human language, thus positioning them as an ideal interface between human and machine. When I read through Zoe's research proposal, I was very excited by her idea that train a foundation model to learn the microbiome "language", which applying the similar idea as LLMs in the microbiome research.

My collaboration with Dr. Zhu began last year on a project involving the search and retrieval of dental records using Large Language Models (LLMs), which has been submitted to NIDCR as an R21 application. Throughout our numerous discussions on AI applications in dental healthcare, I have been thoroughly impressed by Dr. Zhu's rapid learning and her ability to effectively apply AI methods to solve dental research questions. In addition to our collaborative project, Dr. Zhu has independently led a project utilizing high-quality dental axiUm data to develop a machine learning model for periodontitis prediction. Her unique combination of skills makes her exceptionally well-suited for work in the emerging field of dental-AI.

I am delighted to serve as Zoe's co-primary mentor, alongside Dr. Chen, on this K08 award application. With the training opportunities provided by this award, including participation in an online master's program in computer science and direct supervision from me (we propose Dr. Zhu work in my lab for three months to enhance her AI skills), I strongly believe she will make significant scientific contributions to this field.

Ongoing and recently completed projects that I would like to highlight include:

R01 GM132391 Hassoun (PI) 09/20/19-09/19/23
 Computational Techniques for Advancing Untargeted Metabolomics Analysis
 The goal of this study is to develop and validate new computational methods for the interpretation of untargeted metabolomics.
 Role: PI

DoD Multidisciplinary Research Program of the University Research Initiative (MURI)
 Ajo-Franklin (PI) 10/01/22-09/30/27
 Faster, More Efficient, and Hybrid Computation in Microbial Bioelectronic Systems
 The goal of this study is to develop, implement, and evaluate new concepts for bidirectional electrical communication between microbes and microelectronics.
 Role: Co-PI

R03 OD036490 Hassoun (PI) 09/20/23-09/19/24
 Using Common Fund Datasets to Illuminate Drug-Microbial Interactions
 This study utilizes a computational pipeline to predict how gut microbes degrade drugs.
 Role: PI

Citations:

- **Soha Hassoun**, Felicia Jefferson, Xinghua Shi, Brian Stucky, Jin Wang, and Epaminondas Rosa Jr. "Artificial intelligence for biology." Integrative and Comparative Biology 61, no. 6 (2021): 2267-2275.
- Xiaohui Chen, Yinkai Wang, Yuanqi Du, **Soha Hassoun**, and Li-Ping Liu. "On Separate Normalization in Self-supervised Transformers." Conference and Workshop on Neural Information Processing Systems (NeurIPS) (2023)
- Gian Marco Visani, Michael Hughes, **Soha Hassoun**, "Enzyme promiscuity prediction using hierarchy-informed multi-label classification", Bioinformatics (2021), DOI: 10.1093/bioinformatics/btab054. PMID: 33515234, PMCID: PMC8337005.
- Julie Jiang, Liping Liu, and **Soha Hassoun**, "Learning graph representations of biochemical networks and its application to enzymatic link prediction", Bioinformatics, 2020, doi:10.1093/bioinformatics/btaa881. PMID: 33051674, PMCID: PMC8097755.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

1988 – 1991	Senior Hardware Engineer, Digital Equipment Corporation, Hudson, MA
1998 – 2004	Assistant Professor, Department of Computer Science, Tufts University, Medford, MA
2002	Visiting Researcher, IBM Austin Research Labs. Austin, TX
2002 – 2004	Assistant Professor (Adjunct Appointment), Department of Electrical and Computer Engineering, Tufts University, Medford, MA
2007	Consultant, Carbon Design Systems, Waltham, MA
2004 – 2014	Associate Professor, Department of Computer Science, Tufts University, Medford, MA
2004 – 2015	Associate Professor (Adjunct Appointment), Department of Electrical and Computer Engineering, Tufts University, Medford, MA
2012 – 2013	Associate Chair, Department of Computer Science, Tufts University, Medford, MA
2014 – 2015	Associate Professor Adjunct Appointment), Department of Chemical and Biological Engineering, Tufts University, Medford, MA
2013 – 2016	Chair, Department of Computer Science, Tufts University, Medford, MA
2015 – Present	Professor, Department of Computer Science, Tufts University, Medford, MA
2015 – Present	Professor, (Adjunct Appointment) Department of Chemical and Biological Engineering and Department of Electrical and Computer Engineering, Tufts University, Medford, MA

Other Experience and Professional Memberships

1998 – 2007 Institute of Electronics and Electrical Engineers (IEEE), member

1998 – 2014	Association of Computing Machinery (ACM)
2007 –	Institute of Electronics and Electrical Engineers (IEEE), senior member
2014 –	Association of Computing Machinery (ACM), senior member
2011 –	American Institute of Chemical Engineers (AIChE), member
2011 –	Society of Biological Engineers, member
2009	Co-Founder, the International Workshop on Biology Design Automation (IWBDa)
2009 – 2012	Steering committee member, the International Workshop on Biology Design Automation
2016, 2018	Co-organizer of Workshop on Microbiomics, Metagenomics, and Metabolomics at ACM Conference on Bioinformatics, Comp. Biology and Biomedical Informatics
2017 –	Metabolomics Society, member
2016 –	Board member, the Computing Research Association's Committee on the Status of Women in Computing Research (CRA-W)

Honors (since 2000)

2000	ACM/SIGDA Service Award
2001	National Science Foundation (NSF) CAREER award
2002	ACM/SIGDA Technical Leadership Award
2003	Tufts University Mellon Fellowship
2007	ACM/SIGDA Distinguished Service Award
2011 – 2009	Member, Defense Science Study Group, Institute for Defense Analysis, Nominated by Tufts Dean of Engineering and appointed by DARPA
2013	Design Automation Conference Service Award, for creating "the Design Automation Summer School"
2013	Recognized as 1 of 33 luminaries in the field of Electronic Design Automation by the Electronic Design Automation Consortium
2013	Design Automation Conference Innovation Award, for creating "the Designer Track"
2013	Design Automation Conference Innovation Award, for creating "the Work-in-Progress Sessions" sessions
2015	Winner, Tufts Ideas Competition, the Gordon Institute, Tufts University for "TRAG: At-home diagnostics system and app for tracking the gut microbiota"
2020	Keynote Speaker, Women in Data Science (WiDS) regional conference, Saudi Arabia

C. Contribution to Science

1. Predicting enzyme promiscuity and enzymatic products

I have developed a prediction tool, PROXIMAL (Prediction of Xenobiotic Metabolism), for identifying putative products of xenobiotic chemicals in the liver. Using reaction data from DrugBank and KEGG, PROXIMAL builds look-up tables that catalog the sites and types of structural modifications performed by Phase I and Phase II enzymes. Given a compound of interest, PROXIMAL searches for substructures that match the sites cataloged in the look-up tables, applies the corresponding modifications to generate a panel of possible transformation products, and ranks the products based on the activity and abundance of the enzymes involved. While developed to predict xenobiotic derivatives, the methodology is general. We have successfully used this method to advance metabolomics and biological engineering applications.

- a. Mona Yousofshahi, Sara Manteiga, Charmian Wu, Kyongbum Lee and Soha Hassoun, "PROXIMAL: A method for prediction of xenobiotic metabolism", BMC Systems Biology, (2015):9:94. DOI:10.1186/s12918-015-0241-4. PMID: 26695483, PMCID: PMC4687097.
- b. Porokhin, Vladimir, Sara A. Amin, Trevor B. Nicks, Venkatesh Endalur Gopinarayanan, Nikhil Unni Nair, and Soha Hassoun. "Analysis of Metabolic Network Disruption in Engineered Microbial Hosts due to Enzyme Promiscuity." Metabolic Engineering Communication. 2021 Mar 7;12:e00170. DOI: 10.1016/j.mec.2021.e00170. PMID: 33850714; PMCID: PMC8039717.
- c. Neda Hassanpour, Nicholas Alden, Rani Menon, Arul Jayaraman, Kyongbum Lee, and Soha Hassoun, "Biological Filtering and Substrate Promiscuity Prediction for Annotating Untargeted Metabolomics." Metabolites 10, no. 4 (2020): 160. PMID: 32326153. PMC7241244

- d. Sara A. Amin, Elizabeth Chavez, Vladimir Porokhin, Nikhil U. Nair, and Soha Hassoun. "Towards creating an extended metabolic model (EMM) for E. coli using enzyme promiscuity prediction and metabolomics data." *Microbial cell factories* 18, no. 1 (2019): 109, PMID: 31196115. PMC6567437

2. Synthesis of metabolic pathways and strain optimization in metabolic networks

Motivated by the need to develop effective design automation tools for metabolic networks, I have contributed and led efforts to develop several novel computational techniques. To engineer non-native synthesis pathways in microbial hosts, we developed a pathway construction algorithm, *ProPath*, for identifying viable synthesis pathways compatible with balanced cell growth. The algorithm is based on probabilistic selection, instead of exhaustive exploration, of reactions from the KEGG database to construct synthesis pathways. *ProPath* was used to construct high-throughput selection pathways for directed evolution to isolate the variant(s) with desired enzymatic properties. The quality of results resembles those obtained through limited-depth exhaustive enumeration and, for several test cases, identified synthesis pathway had been experimentally confirmed in the literature. We also developed a technique, *CCOpt*, to identify reactions whose activities should be modified to achieve the desired cellular objective. The technique addresses uncertainties in implementing the reaction activity modifications. The novelty of the approach is in modeling uncertainties as probability distributions of the flux carrying capacities of reactions. When applied to some test cases, the approach was shown to consistently outperform the intervention set selected by deterministic methods in terms of tolerance to flux capacity variations. We also developed a technique, gEFM, to identify elementary modes in a metabolic network. The technique relies on graph traversal to identify pathways within the network that are thermodynamic feasibility and can operate independently under steady-state operation. The main advantage of gEFM is utilizing the underlying structural network information to derive a constraint ordering that leads to improved performance over other tools.

- a. Mona Yousofshahi, Kyongbum Lee, and Soha Hassoun, "Probabilistic Pathway Construction", *Metabolic Engineering*, July 2011, 13 (4), pp. 435-444, doi:10.1016/j.ymben.2011.01.006. PMCID: Not applicable.
- b. Mona Yousofshahi, Michael Orshansky, Kyongbum Lee, and Soha Hassoun, "Probabilistic Strain Optimization Under Constraint Uncertainty", *BMC Systems Biology* 2013, 7:29 doi:10.1186/1752-0509-7-29. PMC3626866
- c. Neda Hassanpour, Ehsan Ullah, Mona Yousofshahi, Nikhil U. Nair, Soha Hassoun, "Selection Finder (SelFi): A Computational Metabolic Engineering Tool to Enable Directed Evolution of Enzymes.", *Metabolic Engineering Communications* (2017). PMC5779715.
- d. Ehsan Ullah, Shuchin Aeron, and Soha Hassoun, "gEFM: An Algorithm for Computing Elementary Flux Modes Using Graph Traversal", *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 2015. PMCID: Not applicable.

3. Understanding organizing principles in metabolic networks

Sponsored by NSF, and in collaboration with Dr. Lee, I have focused on utilizing cyclical motifs to identify hierarchical modularity. We developed a new round trip distance metric, termed Shortest Retroactive Distance (ShReD), to characterize the retroactive connectivity between any two reactions in a biochemical network and to group together network components that mutually influence each other. Evaluating the metric using a signaling network and a metabolic network suggests that retroactive interactions arising from feedback loops and metabolic cycles significantly contribute to the modularity of biochemical networks. This work was further extended to study state dependent changes in network modularity. A weighting scheme, based on metabolic flux data, was developed to adjust the network interaction distances. The weighting scheme was utilized in hierarchical partitioning to examine the effects of cellular differentiation and enzyme inhibitions on the functional organization of adipocyte metabolism. The analysis found that the differences between various metabolic states primarily involved the assignment of two specific reactions in fatty acid synthesis and glycerogenesis. The analysis also identified cyclical interactions between reactions that are robust with respect to metabolic state, suggesting possible co-regulation. Taken together, the results support the notion that network modularity is influenced by both the connectivity of the network's components as well as the relative engagements of the connections. Further, we investigated how to identify substrate cycles within metabolic networks. Using a previously published large-scale liver model, uncovered potentially novel substrate cycles that have not been

previously reported in literature were uncovered.

- a. Gautham Sridharan, Soha Hassoun, and Kyongbum Lee, "Identification of Biochemical Network Modules based on Shortest Retroactive Distances", PLoS Computational Biology, 2011. PMC3213171.
- b. Gautham Vivek Sridharan, Michael Yi, Soha Hassoun and Kyongbum Lee, "Metabolic Flux-Based Modularity using Shortest Retroactive Distances", BMC Systems Biology, 2012. PMC3556310.
- c. Gautham Sridharan, Ehsan Ullah, Soha Hassoun, and Kyongbum Lee, "Discovery of Substrate Cycles in Large Scale Metabolic Networks Using Hierarchical Modularity", BMC Systems Biology, 2015. PMC4349670.

4. Contributions to Electronic Design Automation

Before devoting 100% of my research efforts to machine learning for biological applications, I worked in the area of electronics design and electronic design automation. My earlier industrial contributions led to two successful microprocessors and an emulation platform. My research focus was on logic design, and understanding the impact of new technologies, namely FinFET and 3- Dimensional integration, on design. My work in this area is published in refereed papers in top journal and conference venues, and has resulted in 6 granted patents, an edited book, and two book chapters.

- a. Brad D. Gaynor, and Soha Hassoun. "Fin shape impact on FinFET leakage with application to multithreshold and ultralow-leakage FinFET design." IEEE Transactions on Electron Devices 61, no. 8 (2014): 2738-2744. PMCID: Not applicable.
- b. Hassoun, Soha, and Tsutomu Sasao, eds. "Logic synthesis and verification". Vol. 654. Springer Science & Business Media, 2012. PMCID: Not applicable.
- c. Nauman H. Khan, Syed M. Alam, and Soha Hassoun. "Power delivery design for 3-D ICs using different through-silicon via (TSV) technologies." IEEE Transactions on Very Large-Scale Integration (VLSI) Systems 19, no. 4 (2011): 647-658. PMCID: Not applicable.
- d. Brian Swahn, and Soha Hassoun. "Gate sizing: FinFETs vs 32nm bulk MOSFETs." In Proceedings of the Design Automation Conference, pp. 528-531. 2006.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: HE, XUESONG

eRA COMMONS USER NAME (credential, e.g., agency login): xuesonghe2

POSITION TITLE: Professor

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Peking University School of Stomatology, China	DDS	09/1997	Dentistry
Indiana University, Bloomington, Indiana, USA	PhD	06/2006	Microbiology
University of California, Los Angeles, CA	Postdoctoral	07/2010	Microbiology

A. Personal Statement

I am very excited to work with Dr. Zhu in her proposed study titled "Development of a Foundational Oral Microbiome Deep Learning Model for Systemic Diseases Assessment". Trained as a dentist and microbiologist, I am fascinated with the host-associated microbial world and amazed by their significant roles in the hosts' health and disease. I have been in the oral microbiology field for over 17 years. I have extensive expertise in bacterial inter-species interactions, microbial ecology, microbiome, microbial host interaction, and oral microbiome-systemic links which are integral to the proposed study. Particularly, I am interested in understanding the systemic impacts of the oral microbiome. The proposed project fits my research interests and expertise. Currently, I am the contact PI of two active R01s and Co-PI of a multiple-PI R01 grant, which focus on different aspects of human oral microbiome research, including microbial-host interaction:

In the past 10 years, I have been actively involved in mentoring or co-mentoring predoctoral (total 8) and postdoctoral (total 12) trainees, with many of them receiving F award or K99 award. Some of the trainees have become faculty members in research institutes and others have joined the biotech company. I am very much looking forward to serving on the advisory board for Dr. Zhu. In summary, my expertise in the field of microbial-host interaction in combination with my experience in multidisciplinary collaboration will ensure my contribution to Dr. Zhu's training.

Ongoing projects that I would like to highlight include:

NIH/NIDCR R01DE023810 PI: He 09/01/2014 – 08/31/2029
Domestication and characterization of TM7-the most elusive oral phylum

NIH/NIDCR R01 DE029479A PI: Sun/He 09/01/2021 – 08/31/2026
Preventing dental caries through targeted treatment of acid-producing bacteria

NIH/NIDCR R01 DE030943 PI: He 04/01/2022 – 03/31/2027
Host tRNA-derived small RNAs (tsRNAs) mediate interactions between host and oral microbes

Citations:

- Guo, L., JS. McLean, Y. Yang, R. Eckert, C.W. Kaplan, P. Kyme, O. Sheikh, B. Varnum, R. Lux, W. Shi and X. He. 2015 A precision-guided antimicrobial peptide as a targeted modulator of human microbial ecology. *Proc Natl Acad Sci USA* 112(24): 7569-7574 PMID:PMC4575959
- Wang, X., Sun, Z., Jia, H., Michel-Mata, S., Angulo, M.T., Dai, L., He, X., Weiss, S., Liu, Y. 2023. Identifying keystone species in microbial communities using deep learning. *Nature Ecology Evolution*. PMID:37974003

3. Yang, M., Dong, P.T., Cen, L., Shi, W., He, X*, and Li, J*. 2023. Targeting *Fusobacterium nucleatum* through chemical modification of host-derived transfer RNA fragments. *ISME J.* * co-corresponding author
4. Baker, J., Mark Welch, J., Kauffman, K., McLean, J., and He, X. 2023. The oral microbiome: diversity, biogeography, and systemic influences. *Nature Reviews Microbiology*. PMID:37700024

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

07/2022-current	Senior Member of Staff (Professor), The ADA Forsyth Institute, Cambridge, MA
07/2022-12/2023	Assistant Professor, Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, MA.
01/2018-07/2022	Associate Member of Staff, The ADA Forsyth Institute, Cambridge, MA
07/2020-07/2022	Member of Faculty, Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, MA.
07/2017-12/2017	Associate Professor, UCLA School of Dentistry, Los Angeles, CA
07/2010-07/2017	Assistant Professor, UCLA School of Dentistry, Los Angeles, CA
07/2006-07/2010	Postdoctoral Researcher, Lab of Dr. Wenyuan Shi, UCLA School of Dentistry, Los Angeles, CA
09/2000-07/2006	Ph.D. candidate, Laboratory of Dr. Clay Fuqua, Indiana University, Bloomington, IN
09/1997-07/1999	Resident, School of Stomatology, Beijing University Dental School, Beijing, China

Other Experience and Professional Memberships

Professional Society

2012 -- Present	American Association for Dental Research
2005 – Present	American Association for the Advancement of Science (AAAS)

Reviewer for NIH NIDCR study section

2022	NIDCR Oral, Dental and Craniofacial Sciences Study Section	NIH Standing Member
2020	NIDCR Special Grant Review: DSR Study Section June 17 th 2020	NIH Ad hoc Member
2019	NIDCR Special Grant Review: DSR Study Section Oct. 17 th 2019	NIH Ad hoc Member
2017	Oral, Dental and Craniofacial Sciences Study Section Oct. 13 th 2017	NIH Ad hoc Member

Editorial Activities

2021-present	Editorial Board Member	Journal of Oral Microbiology
2021-present	Editor	Frontiers in Oral Infections and Microbes
2019-present	Editor	Frontiers in Molecular Bacterial Pathogenesis
2019-present	Editor	Frontiers in Systems Microbiology
2016-present	Editorial Board	Frontiers in Cellular and Infection Microbiology
2016-present	Editorial Board Member	Scientific Reports

Honors

2022	Forsyth/Harvard School of Dental Medicine Collaborative Grant
2019	Forsyth Collaborative grant, Forsyth Institute
2013	Dean's Faculty Seed Grant, UCLA

C. Contributions to Science

1. Domestication of yet-to-be cultured host-associated microbes

One of the biggest challenges in oral microbial research is to culture those yet-to-be cultured species for detailed physiological/pathogenic analysis. By using a novel culturing method, my team successfully isolated and cultivated from the oral cavity the first TM7 strain (named TM7x), which belongs to TM7, a bacterial phylum that is omnipresent, particularly in the human oral cavity, and associated with periodontal disease. We also revealed its unique epibiotic/parasitic lifestyle with its bacterial hosts. Furthermore, TM7 belongs to Candidate Phyla Radiation (CPR), a unique class of bacteria recently revealed by metagenomics-based approach and estimated

to account for over a quarter of microbial diversity. Thus far, TM7 remains the only phylum with cultivated representatives in the CPR group. Our study has received media attention through joint press releases with NIDCR. Our study in this area was recently highlighted in a NIH review, titled **"A review of 10 years of human microbiome research activities at the US National Institutes of Health, Fiscal Year 2007-2016"**, published in a Feb. 2019 issue of *Microbiome*. Currently, we are using TM7x and their bacterial host as a model system to further study their unique lifestyle, their ecological impact, as well their role in host health and diseases. The knowledge gained will be fundamental in better understanding other CPR bacteria, which make up >25% of the bacterial domain.

- a. He, X., JS. McLean, A. Edlund, S. Yooseph, A.P. Hall, SY. Liu, P. Dorrestein, E. Esquenazi, R. Hunter, G. Cheng, KE. Nelson, R. Lux and W. Shi. 2015. Cultivation of a human-associated TM7 phylotype reveals a reduced genome and epibiotic parasitic lifestyle. *Proc Natl Acad Sci USA* 112(1):244-9. PMID:PMC4291631
- b. Chipashvili, O., Utter, D.R., Bedree, J.K., Ma, Y., Schulte, F., Mascarini, G., Alayyoubi, Y., Chouhan, D., Hardt, M., Bidlack, F., Hasturk, H., He, X., McLean, J.S., and Bor, B. 2021. Ultrasmall episymbiotic *Saccharibacteria* suppresses gingival inflammation and bone loss through host bacterial modulation. *Cell Host & Microbe*. PMID:PMC8595704
- c. Tian, J., Utter, D.R., Cen, L., Dong, P-T., Shi, W., Bor, B., Qin, M., McLean, J.S. and He, X. 2022. Acquisition of the arginine deiminase system benefits epiparasitic *Saccharibacteria* and their host bacteria in a mammalian niche environment. *Proc Natl Acad Sci U S A* 119(2): PMID:PMC8764695
- d. Zhong, Q., Liao, B., Liu, J., Shen, W., Wang, J., Ma, Y., Dong, P-T., Bor, B., McLean, J., Shi, W., Li, Y., He, X*, and Le, S*. 2024. Episymbiotic *Saccharibacteria* TM7x modulates susceptibility of its host bacteria to phage infection and promotes their co-existence. *co-corresponding author. *Proc Natl Acad Sci U S A*. PMID:PMC11032452

2. Microbial-host interaction

Microbial host interaction plays a crucial role in human health and disease. I am particularly interested in understanding the process and mechanisms, such as host-derived small RNAs, in mediating host-microbial interactions.

- a. He, X., Li, F., Bor, B., Koyano, K., Cen, L., Xiao, X., Shi, W., Wong, D. 2018. Human tRNA-derived small RNAs modulate host-oral microbial interactions. *J Dent Res*. PMID:PMC 6151917
- b. Chipashvili, O., Utter, D.R., Bedree, J.K., Ma, Y., Schulte, F., Mascarini, G., Alayyoubi, Y., Chouhan, D., Hardt, M., Bidlack, F., Hasturk, H., He, X., McLean, J.S., and Bor, B. 2021. Ultrasmall episymbiotic *Saccharibacteria* suppresses gingival inflammation and bone loss through host bacterial modulation. *Cell Host & Microbe*. PMID:PMC8595704
- c. Yang, M., Dong, P.T., Cen, L., Shi, W., He, X*, and Li, J*. 2023. Targeting *Fusobacterium nucleatum* through chemical modification of host-derived transfer RNA fragments. *ISME J*. *co-corresponding author

3. Understanding oral microbiome associated with health and disease, and interspecies interaction within multispecies microbial communities

Oral cavity harbors more than 700 microbial species and is one of the most complex ecosystems ever described. While the majority of these inhabitants are considered commensal, some of them are responsible for oral infectious diseases such as dental caries, periodontitis, halitosis and stomatitis. Increasing lines of evidence suggest that these infectious diseases are often the result of the disturbed host homeostasis and imbalanced oral microbial ecology leading to overgrowth of otherwise low abundant opportunistic pathogens. One of my research interests is to better understand oral microbiome associated with health and disease, as well as investigate the impact of interspecies interaction on the physiology and virulence of key oral opportunistic pathogenic bacterial species.

- a. Agnello, M., Marques, J., Cen, L., Mittermuller, BA., Huang, A., Tran, N., Shi, W., He*, X., and Schroth*, RJ. 2017. Microbiome associated with severe caries in Canadian First Nations children. *J Dent Res* 96(12):1378-1385* Co-Corresponding author PMID:PMC5652857
- b. Xu, H., Tian, J., Zhang, Q., Zhou, Q., Shi, W., Qin, M., He, X*, and Chen, F. 2018. Oral microbiome shifts from caries-free to caries-affected status in 3-year-old Chinese children: A longitudinal study. *Front Microbiol* PMID:PMC6121080 * co-corresponding author.
- c. Liu, T., Liu, J., Liu, J., Yang, R., Lu, X., He, X., Shi, W. and Guo, L. 2020. Interspecies interactions between *Streptococcus* mutants and *Streptococcus agalactiae* in vitro. *Frontiers in Microbiology* PMID: PMC7358462
- d. Xiang D., Dong, P., Cen, L., Bor, B., Lux, R., Shi, W., Yu, Q*, He, X*, Wu, T*. 2023. Antagonistic interaction between two key endodontic pathogens *Enterococcus faecalis* and *Fusobacterium nucleatum*. *Journal of Oral Microbiology*. * co-corresponding author

4. Establishing in vitro multispecies microbial community model system to facilitate better understanding of ecological aspects of microbiome.

Human microbiome research revealed that every human body contains a variety of microbial communities on various mucosal surfaces that consist of thousands of different microbial species. Disturbance from host and environmental factors may alter the composition and abundance of these microbial species, leading to various polymicrobial diseases. One of my fields of interest is to study the ecology of human-associated microbial community using in vitro model system and, more importantly, examine the community role and function of individual species within a complex microbial community by knocking out or knocking down one particular species with a targeted antimicrobial and then tracking the impact on the rest of the species within the same community. Using in vitro oral community and *Streptococcus mutans* as a model system, we developed a proof of concept that we could potentially modulate the microbiome structure using targeted antimicrobials, allowing insights into the key community role of specific bacterial species.

- a. Tian, Y., X. He, R. Lux, J. McLean, G. Yu and W. Shi 2010. Using DGGE profiling to develop a novel culture medium suitable for oral microbial communities. *Mol Oral Microbiol* 25 (5): 357- 367
- b. He, X., W. Hu, J. He, H. Guo, R. Lux and W. Shi. 2011 Community-based interference against integration of *Pseudomonas aeruginosa* into human salivary microbial biofilm. *Molecular Oral Microbiology* 26: 1-16. PMID:PMC3327514
- c. Edlund, A., Yang Y, Y. Shibu, A. Hall, D. Nguyen, P. Dorrestein, K. Nelson, X. He, R. Lux, W. Shi, JS. McLean 2015. Meta-Omics Uncover Temporal Regulation of Pathways Across Oral Microbiome Genera during in vitro sugar metabolism. *The ISME Journal* doi: 10.1038/ismej.2015.72. [Epub ahead of print]. PMID:26023872
- d. Guo, L., JS. McLean, Y. Yang, R. Eckert, C.W. Kaplan, P. Kyme, O. Sheikh, B. Varnum, R. Lux, W. Shi and X. He. 2015 A precision-guided antimicrobial peptide as a targeted modulator of human microbial ecology. *Proc Natl Acad Sci USA* 112(24): 7569-7574. PMID: 26034276 PMID: PMC4475959

5. Developing novel therapeutics in preventing dental caries

Collaborating with researchers at ADAF, I have been actively involved in developing novel therapeutics, such as acid-activated antimicrobial compounds, probiotics, prebiotics in preventing dental caries.

- a. Guo, L., JS. McLean, Y. Yang, R. Eckert, C.W. Kaplan, P. Kyme, O. Sheikh, B. Varnum, R. Lux, W. Shi and X. He. 2015 A precision-guided antimicrobial peptide as a targeted modulator of human microbial

- ecology. Proc Natl Acad Sci USA 112(24): 7569-7574PMCID:PMC4575959
- b. Agnello, M., Cen, L., Nini Chaichanasakul Tran, Shi, W., McLean, JS. and He. X. 2017. Arginine Improves pH Homeostasis via Metabolism and Microbiome Modulation. J Dent Res96(8):924-930 PMCID:PMC5502959
 - c. Yang,Y., Reipa, V., Liu, G., Meng, Y., Wang, X., Mineart, K., Prabhu, V., Shi, W., Lin, N., He, X.*, Sun, J. 2018 pH-sensitive compounds for selective inhibition of acid-producing bacteria. ACS Applied Materials & Interfaces *Co-corresponding author. PMID29436821 DOI:10.1021/acsami.8b01089

Complete List of Published Work in MyBibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/111mBf10u98Ar/bibliography/public/>

BIOGRAPHICAL SKETCH

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NAME: Teles, Flavia Rocha Fonseca

eRA COMMONS USER NAME (credential, eg, agency login): TELES_FLAVIA

POSITION TITLE: Associate Professor

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable Add/delete rows as necessary*)

INSTITUTION AND LOCATION	DEGREE	END DATE	FIELD OF STUDY
Federal University of Rio de Janeiro (FURJ)	DDS	01/1997	Dentistry
Pontifical Catholic Univ Dental Institute (PCU)	Certificate	03/2000	Periodontology
State University of Rio de Janeiro (SURJ)	MS	02/2004	Periodontology
Harvard School of Dental Medicine, Boston, MA	DMSc	05/2007	Oral Biology

A. Personal Statement

I am a periodontist with training in Oral Biology and oral microbiology. For the past 18 years, I have been dedicated to clinical and translational research. During this period, I have recruited, sampled, treated and monitored patients for many NIH and industry-funded studies. During those years, my research activities included the microbiome of oral health and disease, including PD (please refer to bibliography), using microbial cultivation and “omics” approaches. My research program has been funded by NIH in the past several years (see below). In addition, I was a co-investigator in a large multicenter clinical study that aimed at identifying biomarkers of periodontal disease progression (U01-DE021127, PI: R Teles) and a collaborator and subcontract PI in a project (R01DE021553, PI: J Frias-Lopez) that analyzes the host-microbial Metatranscriptomic During Periodontal Disease Progression and Post Periodontal Treatment. My current R01 (DE-033033, PI: F. Teles) focuses on site-level analyses of dysbiosis in periodontitis progression and stability. I have not published or created research products under any other name. Some of the recent manuscripts I have authored/co-authored demonstrate my expertise and supports the premise and feasibility of Zoe’s K08 proposal.

1. Long-term dynamics of the human oral microbiome during clinical disease progression Duran-Pinedo A, Solbiati J, **Teles F**, Teles R, Zang Y, Frias-Lopez J BMC Biol 2021 Nov 6;19(1):240 doi: 10.1186/s12915-021-01169-z PMID: 34742306
2. Subgingival host-microbiome metatranscriptomic changes following scaling and root planing in grade II/III periodontitis Duran-Pinedo AE, Solbiati J, **Teles F**, Frias-Lopez J Clin Periodontol 2023 Mar;50(3):316-330 doi: 10.1111/jcpe.13737. PMID: 36281629
3. **Teles F**, Martin L, Patel M, Hu W, Bittinger K, Kallan MJ, Chandrasekaran G, Cucchiara AJ, Giannobile WV, Stephens D, Kantarci A. Gingival crevicular fluid biomarkers during periodontitis progression and after periodontal treatment. *J Clin Periodontol*. 2024 Sep 15. doi: 10.1111/jcpe.14061. Online ahead of print. PMID: 3927872.
4. **Teles FRF**, Chandrasekaran G, Martin L, Patel M, Kallan MJ, Furquim C, Hamza T, Cucchiara AJ, Kantarci A, Urquhart O, Sugai J, Giannobile WV. Salivary and serum inflammatory biomarkers during periodontitis progression and after treatment. *J Clin Periodontol*. 2024 Aug 5. doi: 10.1111/jcpe.14048. Online ahead of print. PMID: 39104016.

Ongoing Research Support

2025-30 NIH Grant #U54-AG-089323; The Oro-Respiratory-Gut Virome Axis Over Space and Time PD/PI: Ronald G Collman and Frederic D Bushman Role: **Co-investigator: Flavia Teles**.

2024-29 NIDCR/NIH Grant# R01 DE033033; Defining Dysbiosis and Mechanisms of Periodontitis Progression and Stability. Role: **PI: Flavia Teles** (MPI: Kyle Bittinger).

2024-29 NIDCR/NIH Grant# UE5DE029439; AADR Mentoring an Inclusive Network for a Diverse Research Workforce of the Future - MIND the Future. PI/Project Leader: Christopher Fox (AADOCR). **Flavia Teles** Role: Mentor.

2024 CiPD-IBI Artificial Intelligence in Oral Health Innovation Award. **Flavia Teles & Shefali Verma.**

2023-24 PennCHOP Microbiome Pilot and Feasibility Grant; Exploring Compositional and Functional Changes in the Oral Microbiome Linked to Periodontal Disease Progression. **PI: Flavia Teles (NCE).**

2021-26 NIDCR/NIH Grant# T90 DE030854; Advanced Training at the Interface of Engineering and Oral-Craniofacial Sciences. PI: Hyun (Michel) Koo, Kate Stebe. **Co-Investigator: Flavia Teles**

Completed Research Support (last 3 years)

2022 Office of the Vice Provost for Research's Bridge Funding Partnership Program Interkingdom Mechanisms of Oral Carcinogenesis Role: **PI: Flavia Teles**

2022 Josephine and Joseph Rabinowitz Research Award *Integrating Omics-Data via Deep Learning to Predict Periodontitis Progression* Role: **PI: Flavia Teles**

2022 Schoenleber Pilot Grant *Using the BPDP Biobank to Explore Genetic and Epigenetic Modulators of Periodontitis* Role: **PI: Flavia Teles**

2021-22 Center for Innovation and Precision Dentistry (CiPD) Pilot Funding Program Magnetic nanopore membranes for rapid detection of oral pathogens and biomolecules in human saliva

2017-22 NIDCR/NIH Grant # 1K99DE027086 Investigating the role of Tumor Necrosis Factor-Receptor Associated Factor 3 Interacting Protein 2 (TRAF3IP2), a critical adaptor in IL-17 pathway, in periodontal disease PI: Shaoping Zhang, **Co-Investigator (co-mentor): Flavia Teles**

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2025 - present	Professor of Microbiology (tenured), Department of Basic & Translational Sciences, University of Pennsylvania School of Dental Medicine, Philadelphia, PA
2017 - 2025	Associate Professor of Microbiology, Department of Basic & Translational Sciences, University of Pennsylvania School of Dental Medicine, Philadelphia, PA
2014 - 2024	Associate Research Investigator/Adjunct Faculty, Department of Applied Oral Sciences, The Forsyth Institute, Cambridge, MA
2014 - 2017	Research Associate Professor, Department of Periodontology, University of North Carolina at Chapel Hill School of Dentistry, Chapel Hill, NC
2011 - 2014	Assistant Member of the Staff, Department of Applied Oral Sciences (as of 2012), The Forsyth Institute, Cambridge, MA
2009 - 2014	Instructor in Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston, MA
2009 - 2011	Staff Scientist, Department of Periodontology, The Forsyth Institute, Boston, MA (Cambridge, MA in 2010)
2004 - 2004	Clinical Instructor in Periodontology, Harvard School of Dental Medicine, Boston, MA
2003 - 2009	Research Periodontist (non-tenured, full-time), Department of Periodontology, The Forsyth Institute, Boston, MA

Honors

2025	IAP/IADR Ricardo Teles Clinical Research Award
2025	American Academy of Periodontology (AAP) Clinical Research Award
2024	CiPD-IBI Artificial Intelligence in Oral Health Innovation Award (co-recipients: Flavia Teles & Shefali Verma)
2024	IDEA Prize Finalist Award; Colorimetric Sensing of Acetaldehyde towards Detection of Oral Squamous Cell Carcinoma PI: Shu Yang, Co-PI: Flavia Teles
2023	Tenenbaum Lectureship: <i>The Benjamin Tenenbaum Memorial Lecture in Periodontics</i> , Columbia University College of Dental Medicine, New York, NY
2022	IDEA Prize Finalist Award; Artificial Intelligence for Multimodal Data Integration in Periodontitis
2021	AADR Fellow (Selected)
2017	IADR Women in Science Award for Distinguished Research

2014	Krakov Harvard/Forsyth Endowed Endodontic Research Fund (Mentee: Dr A Andrada)
2014	Krakov Harvard/Forsyth Endowed Endodontic Research Fund (Mentee: Dr L Brito)
2012	Forsyth's Center for Discovery at the Host-Biofilm Interface Pilot Grant
2012	IADR Travel Grant for Young Investigators
2010	PCIR Junior Investigator Laboratory Support Award, Harvard University/Harvard Catalyst
2009 - 2011	Eleanor and Miles Shore 50 th Anniversary Fellowship Program for Scholars in Medicine - The Forsyth Institute/Harvard Medical School
2007 - 2013	NIH Loan Repayment Program Award
2006 - 2009	Forsyth Institute's Institutional NRSA Postdoctoral training grant (T32), sponsored by NIDCR, Boston, MA

Professional Activities

2025- present	Permanent Member, Oral, Dental and Craniofacial Sciences (ODCS) Study Section
2024 - present	University of Pennsylvania's Center for Precision Dentistry (CiPD) Executive Committee
2024 - present	American Academy of Periodontology (AAP) Diagnostic Technologies and Medicine Workgroup Member (appointed)
2024	NIH Ad hoc reviewer: Oral, Dental and Craniofacial Sciences (ODCS) Study Section
2024 - 2025	AADOCR MIND the Future Program (Invited Mentor)
2024	NIH Ad hoc reviewer: Special Emphasis Panel ZRG1-F07A M(20)
2023 - present	Editorial Board Member, Journal of Periodontology
2021 - present	Associate Editor, Journal of Clinical Periodontology
2021 - present	Editorial Board Member, JADA Foundational Science
2021 - present	Editorial Board Member, Journal of Oral Microbiology
2021 - present	Task Force on Design and Analysis in Oral Health Research Member
2020 - 2023	AAP Task Force on Future Science Strategy Member (appointed)
2020	ZDE1 YM16 Special Emphasis Panel
2020	ZRG1 MOSS C-02 Special Emphasis Panel
2019	Journal of Dental Research Editor- in-Chief Search Committee member
2019 - 2021	IADR/AADR Publications Committee Representative (elected)
2019 - 2020	Chair, AADR Edward H Hatton Awards Committee
2019	ZRG1 MOSS-S (02) - Dental, Microbiology and Oral Biology (June)
2019	Initiation and 5-year funding (provided by Colgate Palmolive) of the Women in Science Promising Talent Award
2019	Organizer, IADR Tenure x Non-Tenure: Which Career Track is Right for You? Hands-on workshop
2018 - present	University of Pennsylvania Forum for Women Faculty, Council Member
2018 - 2019	IADR/AADR Vice-President, Women in Science Network Group
2018	NIDCR ZRG1 BCMB-C (40) P PAR-17-340: Collaborative Program Grant for Multidisciplinary Teams (RM1)
2018 - 2019	Ad hoc abstract reviewer for the IADR/AADR, Women in Science Network Group
2018	IADR/AADR Workshop Organizer and Presenter: Priming Women for Success in Dental Research
2018	IADR Symposium Organizer : Gender bias in scholarly activity: An evidence- based approach
2018	ZRG1 MOSS-S (02): Dental, Microbiology and Oral Biology
2017 - present	Editorial Board Member: Journal of Dental Research
2017 - 2018	AADR Edward H Hatton Awards Committee Member
2017	IADR/AADR Group Program Chair, Women in Science Network Group
2017	NIH Ad hoc reviewer: Oral, Dental and Craniofacial Sciences Study (ODCS) Section
2017	NIH Ad hoc reviewer and Chair: Special Emphasis Panel/Scientific Review Group ZRG1 MOSS-S (02) Study Section
2017	IADR Symposium Organizer: What will it take to close the gender gap in dental academia?
2015	IADR Symposium Organizer, Chair and Presenter: Clinical Impact of Periodontal Research: The Legacy of Anne Haffajee

2015 - 2016	Initiation, fundraising and endowment of the "AADR Anne D Haffajee Fellowship for Women in Oral Research" (more than \$125,000 raised)
2016	NIH Ad hoc reviewer: Special Emphasis Panel/Scientific Review Group ZRG1 MOSS-S (02)
2015 - 2016	President-North Carolina Section of the AADR
2012 - present	IADR/AADR Women in Science Network Group
2011 - 2014	Member of Forsyth's Institutional Review Board (IRB)
2008 - present	IADR/AADR Periodontal Research Group
2006 -	ADEA, American Dental Education Association
2004 -	AADR, American Association for Dental Research

C. Contribution to Science

- One of my main contributions to periodontology has been the characterization of periodontal and peri-implant biofilms in vivo. We established the impact of clinical conditions and oral surfaces on microbial succession.
 - Teles FR, Teles RP, Uzel NG, Song XQ, Torresyap G, Socransky SS, Haffajee AD. Early microbial succession in redeveloping dental biofilms in periodontal health and disease. *J Periodontol Res*. 2012 Feb;47(1):95-104. doi: 10.1111/j.1600-0765.2011.01409.x. PMID: 21895662.
 - Teles FR, Teles RP, Sachdeo A, Uzel NG, Song XQ, Torresyap G, Singh M, Papas A, Haffajee AD, Socransky SS. Comparison of microbial changes in early redeveloping biofilms on natural teeth and dentures. *J Periodontol*. 2012 Sep;83(9):1139-48. doi: 10.1902/jop.2012.110506. PMID: 22443543.
 - Sanz-Martin I, Doolittle-Hall J, Teles RP, Patel M, Belibasakis GN, Hämmerle CHF, Jung RE, Teles FRF. Exploring the microbiome of healthy and diseased peri-implant sites using Illumina sequencing. *J Clin Periodontol*. 2017 Dec;44(12):1274-1284. doi: 10.1111/jcpe.12788. PMID: 28766745.
 - Herrera BS, Henz SL, Dua S, Martin L, Teles RP, Patel M, Teles FRF. Pursuing new periodontal pathogens with an improved RNA-oligonucleotide quantification technique (ROQT). *Arch Oral Biol*. 2023 Aug;152:105721. doi: 10.1016/j.archoralbio.2023.105721. PMID: 37196563.
- As a clinician-scientist and a trained periodontist, I emphasized the clinical and translational aspect of periodontal research and how our findings can ultimately improve patient care.
 - Furquim CP, Soares GM, Ribeiro LL, Azcarate-Peril MA, Butz N, Roach J, Moss K, Bonfim C, Torres-Pereira CC, Teles FR. The salivary microbiome and oral cancer risk: a pilot study in Fanconi Anemia. *J Dent Res*. 2017 Mar;96(3):292-299. doi: 10.1177/0022034516678169. PMID: 27827319.
 - Singh M, Teles F, Uzel NG, Papas A. Characterizing microbiota from Sjögren's syndrome patients. *JDR Clin Trans Res*. 2021 Jul;6(3):324-332. doi: 10.1177/2380084420940623. PMID: 32689841.
 - Feres M, Retamal-Valdes B, Fermiano D, Faveri M, Figueiredo LC, Mayer MPA, Lee JJ, Bittinger K, Teles F. Microbiome changes in young periodontitis patients treated with adjunctive metronidazole and amoxicillin. *J Periodontol*. 2021 Apr;92(4):467-478. doi: 10.1002/JPER.20-0128. PMID: 32844406.
 - Teles FRF, Lynch MC, Patel M, Torresyap G, Martin L. Bacterial resistance to minocycline after adjunctive minocycline microspheres during periodontal maintenance: a randomized clinical trial. *J Periodontol*. 2021 Sep;92(9):1222-1231. doi: 10.1002/JPER.17-0565. PMID: 33866555.
- Because periodontal diseases result from the cross talk between the host and the local microbiome, I also explored the immunological aspects of periodontitis. Our studies determined local and systemic cytokine profiles associated with periodontal diseases.
 - Teles FR, Teles RP, Martin L, Socransky SS, Haffajee AD. Relationships among interleukin-6, tumor necrosis factor- α , adipokines, vitamin D, and chronic periodontitis. *J Periodontol*. 2012 Sep;83(9):1183-91. doi: 10.1902/jop.2011.110346. PMID: 22181684.
 - Papathanasiou E, Teles F, Griffin T, Arguello E, Finkelman M, Hanley J, Theoharides TC. Gingival crevicular fluid levels of interferon- γ , but not interleukin-4 or -33 or thymic stromal lymphopoietin, are increased in inflamed sites in patients with periodontal disease. *J Periodontol Res*. 2014 Feb;49(1):55-61. doi: 10.1111/jre.12078. PMID: 23550893.
- Given recently identified associations between periodontitis and different types of cancer, I was sought by leaders in the field to collaborate with them in pivotal projects. My expertise in the microbial and

immunological analysis of clinical samples allowed me to help elucidate relationships between periodontal diseases and colon and lung cancers.

- a. Debertin J, Teles F, Martin LM, Lu J, Koestler DC, Kelsey KT, Beck JD, Platz EA, Michaud DS. Antibodies to oral pathobionts and colon cancer risk in the CLUE I cohort study. *Int J Cancer*. 2023 Jul 15;153(2):302-311. doi: 10.1002/ijc.34527. PMID: 36971101.
 - b. Ampomah NK, Teles F, Martin LM, Lu J, Koestler DC, Kelsey KT, Beck JD, Platz EA, Michaud DS. Circulating IgG antibodies to periodontal bacteria and lung cancer risk in the CLUE cohorts. *JNCI Cancer Spectr*. 2023 May 2;7(3) doi: 10.1093/jncics/pkad029. PMID: 37040077.
 - c. Zhao N, Teles F, Lu J, Koestler DC, Beck J, Boerwinkle E, Bressler J, Kelsey KT, Platz EA, Michaud DS. Epigenome-wide association study using peripheral blood leukocytes identifies genomic regions associated with periodontal disease and edentulism in the Atherosclerosis Risk in Communities study. *J Clin Periodontol*. 2023 Sep;50(9):1140-1153. doi: 10.1111/jcpe.13852. PMID: 37464577.
 - d. Mulvaney R, Pan Y, Zhao N, Teles F, Lu J, Platz EA, Kelsey KT, Michaud DS Blood Leukocyte DNA Methylation Markers of Periodontal Disease and Risk of Lung Cancer in a Case-Control Study Nested in the CLUE II Cohort. *Cancer Epidemiol Biomarkers Prev*. 2024 Aug 2. doi: 10.1158/1055-9965.EPI-24-0279. Online ahead of print. PMID: 39093033
5. I utilized the knowledge obtained in my studies of periodontal health and disease to help close the gaps in the etiology and pathogenesis of root canal infections.
- a. Tavares WL, Neves de Brito LC, Teles RP, Massara ML, Ribeiro Sobrinho AP, Haffajee AD, Socransky SS, Teles FR. Microbiota of deciduous endodontic infections analysed by MDA and Checkerboard DNA-DNA hybridization. *Int Endod J*. 2011 Mar;44(3):225-35. doi: 10.1111/j.1365-2591.2010.01805.x. PMID: 21083570.
 - b. Brito LC, Sobrinho AP, Teles RP, Socransky SS, Haffajee AD, Vieira LQ, Teles FR. Microbiologic profile of endodontic infections from HIV- and HIV+ patients using multiple-displacement amplification and checkerboard DNA-DNA hybridization. *Oral Dis*. 2012 Sep;18(6):558-67. doi: 10.1111/j.1601-0825.2012.01908.x. PMID: 22335194.
 - c. de Brito LC, Teles FR, Teles RP, Nogueira PM, Vieira LQ, Ribeiro Sobrinho AP. Immunological profile of periapical endodontic infections from HIV- and HIV+ patients. *Int Endod J*. 2015 Jun;48(6):533-41. doi: 10.1111/iej.12345.PMID: 25069888.
 - d. de Brito LCN, Doolittle-Hall J, Lee CT, Moss K, Bambirra Júnior W, Tavares WLF, Ribeiro Sobrinho AP, Teles FRF. The apical root canal system microbial communities determined by next-generation sequencing. *Sci Rep*. 2020 Jul 2;10(1):10932. doi: 10.1038/s41598-020-67828-3. PMID: 32616783.

Complete List of Published Work in MyBibliography:

<https://www.ncbi.nlm.nih.gov/sites/myncbi/flaviateles1/bibliography/49134379/public/>

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Bonham, Kevin

eRA COMMONS USER NAME (credential, e.g., agency login): kbonham

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
University of California, San Diego, La Jolla, CA	BS	06/2006	Biochemistry and Cell Biology
Harvard University, Immunology, Cambridge, MA	Ph.D.	2014	Immunology

A. Personal Statement

My diverse training and research background have provided me with broad expertise in computational and statistical methods rooted in deep understanding of molecular and cell biology. My undergraduate and graduate work was focused on experimental biology, using biochemical, molecular, and cell biological techniques to study fundamental mechanisms in biochemical signaling in immune cells. In addition to publishing my graduate work in Cell and Annual Reviews of Immunology, to fund this work, I applied for and received an NSF graduate research fellowship, and at the end of my PhD I was awarded the prestigious Jeffery Modell Immunology Award. Despite my early focus on experimental biology, my postdoctoral training turned towards computational genomics, and I have dedicated the last 11 years towards this expertise. During my first postdoc in Rachel Dutton's lab, I developed a python package to investigate horizontal gene transfer in cheese-associated microbes, and validated these findings with in vitro molecular experiments. I then joined the lab of Curtis Huttenhower, where I deepened my understanding of computational genomics, biostatistics, and software engineering by leading a project investigating the relationship between the human gut microbiome and inflammatory arthritis, and overseeing the development of computational infrastructure for a consortium of microbiome researchers investigating type-I diabetes. In the following six years in the Klepac-Ceraj lab at Wellesley College, I took the lead on a NIH/ECHO-funded project investigating the influence of the human gut microbiome on neurocognitive development, and developed a novel approach using machine learning to extract biological data from a large multi-'omic datasets. I also continued to develop research software, particularly in the julia programming language. In my independent lab, I will retain the perspective of an experimental biomedical scientist while pursuing breakthrough computational analyses to understand complex data. Through collaborations and teaching, I have seen the challenges that scientists and students that are focused on bench work have when attempting to perform computational analyses, and I will develop tools and learning resources that enable wet lab-focused scientists to use the power of advanced statistical modeling and machine learning on their multi-'omic datasets.

1. Bonham KS, Margolis ET, Fahur Bottino G, Sobrino AC, Patel F, McCann S, Zieff MR, Miles M, Herr D, Davel L, Bosco C, Huttenhower C, Pini N, Alexander DC, Jones DK, Williams SCR, Amso D, Gladstone M, Fifer WP, Donald KA, Gabard-Durnam LJ, Klepac-Ceraj V. Codevelopment of gut microbial metabolism and visual neural circuitry over human infancy. mBio. 2025 Aug 13;16(8):e0083525. PubMed Central PMCID: PMC12345167.
2. Matthew C. Woodruff, Kevin S. Bonham, Fabliha A. Anam, Tiffany A. Walker, Caterina E. Faliti, Yusho Ishii, Candice Y. Kaminski, Martin C. Ruunstrom, Kelly Rose Cooper, Alexander D. Truong, Adviteeya N. Dixit, Jenny E. Han, Richard P. Ramonell, Natalie S. Haddad, Mark E. Rudolph,

Srilakshmi Yalavarthi, Viktoria Betin, Ted Natoli, Sherwin Navaz, Scott A. Jenks, Yu Zuo, Jason S. Knight, Arezou Khosroshahi, F. Eun-Hyung Lee, Ignacio Sanz. Chronic inflammation, neutrophil activity, and autoreactivity splits long COVID. *Nature Communications*. 2023 July; 14(1). Available from: <https://doi.org/10.1038%2Fs41467-023-40012-7> DOI: 10.1101/2021.09.21.21263845

3. Bonham K, Kayisire A, Luo A, Klepac-Ceraj V. Microbiome.jl and BiobakeryUtils.jl - Julia packages for working with microbial community data. *Journal of Open Source Software*. 2021 November 17; 6(67):3876-. Available from: <https://joss.theoj.org/papers/10.21105/joss.03876> DOI: 10.21105/joss.03876
4. Bonham KS, Orzalli MH, Hayashi K, Wolf AI, Glanemann C, Weninger W, Iwasaki A, Knipe DM, Kagan JC. A promiscuous lipid-binding protein diversifies the subcellular sites of toll-like receptor signal transduction. *Cell*. 2014 Feb 13;156(4):705-16. PubMed Central PMCID: PMC3951743.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2025 -	Assistant Professor, Tufts Medical Center, Department of Medicine, Boston, MA
2019 - 2025	Senior Research Scientist, Wellesley College, Biological Sciences, Wellesley, MA
2017 - 2018	Postdoctoral Fellow, Broad Institute, Harvard T.H. Chan School of Public Health, Cambridge, MA
2009 - 2014	Graduate Research Assistant, Harvard Graduate School of Arts and Sciences, Boston Children's Hospital, Boston, MA
2006 - 2008	Research Assistant, The Scripps Research Institute, La Jolla, CA

Honors

2018 - 2019	Diversity and Inclusion Award, Sloan Foundation, NumFocus
2009 - 2013	Graduate Research Fellowship, National Science Foundation
2003 - 2006	Provost's Honor, University of California, San Diego
2002 - 2006	Millenium Scholarship, University of California, San Diego
2014	Jeffery Modell Immunology Prize, Harvard Immunology Program
2014	Harvard DMS Student Commencement Speaker, Harvard Medical School

C. Contribution to Science

1. I am deeply invested in scientific open source software, and have made several contributions in this domain. My first postdoctoral fellowship focused on horizontal gene transfer (HGT) among bacteria using a model of microbial communities developed by Rachel Dutton. Dr. Dutton had sequenced dozens of isolates from cheese rinds, a complex multi-species biofilm on the outer surface of traditionally aged cheeses, and we combined these with publicly available genomes of cheese-associated bacteria to investigate gene sharing. I designed and wrote an open-source python package to compare average nucleotide identity between genomes to pairwise similarities of individual genes, and reasoned that pairs of genes that were substantially more similar than their parent genomes were likely the result of HGT. Using this software, we showed that more than 4000 individual protein-coding genes appeared to be HGT across species boundaries, and many of these HGT genes were in large, multi-gene islands. We further showed that a substantial proportion of identified HGT were involved in the acquisition of nutrients, particularly iron, and experimentally confirmed that at least one of these large islands, shared amongst many Actinobacteria species, was an actively-mobile integrative and conjugative element (ICE). Since 2017, I have been an active contributor to the open source community of the julia programming language. I am the co-leader of the BioJulia organization, and actively maintain multiple packages in that organization as well as in JuliaData and EcoJulia, and have made contributions to dozens of packages and the julia language itself. In 2020 and 2022, I taught an introductory bioinformatics course at Wellesley College using julia, and am currently

building the BioTutorials package for BioJulia. In addition, I created and registered two packages for microbial community analysis (Microbiome.jl and BiobakeryUtils.jl), and published them in the Journal of Open Source Software. These packages are examples of "eating your own dogfood" -- I have actively used them in my own projects investigating the relationship between the gut microbiome and child brain development, and have made all analysis code and raw data public and open-source to the greatest extent permitted by IRB and consortium data use agreements. Finally, I have made advances in expanding the use of machine learning in biomedical research. I developed a method to score the importance of individual features in high-dimensional random forest models across multiple rounds of training, increasing the ability to derive biological insight from these models. I deployed this approach in work published in *Nature Communications* to rank the importance of individual blood proteins in categorizing patients with post-acute sequelae of COVID-19, and further adapted it to explore the contribution of individual microbial taxa to brain development in human infants.

- a. Matthew C. Woodruff, Kevin S. Bonham, Fabliha A. Anam, Tiffany A. Walker, Caterina E. Faliti, Yusho Ishii, Candice Y. Kaminski, Martin C. Ruunstrom, Kelly Rose Cooper, Alexander D. Truong, Adviteeya N. Dixit, Jenny E. Han, Richard P. Ramonell, Natalie S. Haddad, Mark E. Rudolph, Srilakshmi Yalavarthi, Viktoria Betin, Ted Natoli, Sherwin Navaz, Scott A. Jenks, Yu Zuo, Jason S. Knight, Arezou Khosroshahi, F. Eun-Hyung Lee, Ignacio Sanz. Chronic inflammation, neutrophil activity, and autoreactivity splits long COVID. *Nature Communications*. 2023 July; 14(1). Available from: <https://doi.org/10.1038%2Fs41467-023-40012-7> DOI: 10.1101/2021.09.21.21263845
 - b. Bonham K, Kayisire A, Luo A, Klepac-Ceraj V. Microbiome.jl and BiobakeryUtils.jl - Julia packages for working with microbial community data. *Journal of Open Source Software*. 2021 November 17; 6(67):3876-. Available from: <https://joss.theoj.org/papers/10.21105/joss.03876> DOI: 10.21105/joss.03876
 - c. Kevin S Bonham, Guilherme Fatur Bottino, Shelley Hoeft McCann, Jennifer Beauchemin, Elizabeth Weisse, Fatoumata Barry, Rosa Cano-Lorente, Curtis Huttenhower, Muriel M.K. Bruchhage, Viren D'Sa, Sean Deoni, Vanja Klepac-Ceraj. Gut-resident microorganisms and their genes are associated with cognition and neuroanatomy in children. 2020 February. DOI: 10.1101/2020.02.13.944181
 - d. Bonham KS, Wolfe BE, Dutton RJ. Extensive horizontal gene transfer in cheese-associated bacteria. *Elife*. 2017 Jun 23;6 PubMed Central PMCID: PMC5526665.
2. I have made substantial contributions towards understanding the gut-microbiome-brain axis, particularly in developing children, using a combination of statistical and machine-learning based methods. Previous work has demonstrated that gut microbes, and particular microbial products can have profound effects on human health, affecting the immune system, metabolic system, and even the central nervous system. In humans and in animal models, previous work showed the microbiome is associated with atypical neurodevelopment such as Autism spectrum disorder (ASD), and in adults microbial metabolism had been linked to disorders such as anxiety and depression. But very little is known about the relationship between microbial metabolism of neuroactive compounds during the critical early years of life, and the association between these molecules and typical development. In work published in *Science Advances* in 2023, we investigated the relationship between the microbiome and neuroanatomy and cognition of 381 healthy children in the US, demonstrating that differences in microbial taxa and genes were associated with overall cognitive function and the size of brain regions. I used both statistical and machine learning models to show that multiple microbial species were enriched or depleted in children with higher cognitive function scores. Microbial metabolism of short-chain fatty acids was also associated with cognitive function. In addition, machine models were able to predict the volume of brain regions from microbial profiles, and taxa that were important in predicting cognitive function were also important for predicting individual brain regions and specific subscales of cognitive function. In a separate study using the same cohort and in collaboration with researchers from Dartmouth investigating a different cohort, we showed that the early-life microbiome (at 3 or 12 months of age), particularly genes enabling the production of short-chain fatty acid were prospectively associated with behaviors at 3 years old measured by the Social Responsiveness Survey (SRS2), which are associated with risk for Autism. Because of the rapid

development of both the microbiome and the brain in the first years of life, identifying associations between the two can be challenging during this time. We addressed this in part by developing a normative model of early-life microbiome development across the globe. To do this, we developed a machine learning model to estimate child age using gut microbial taxonomic relative abundances from metagenomes. Using 3154 samples from 1827 infants across 12 countries, our model achieved high temporal resolution (achieving a root mean square error of 2.56 months) for the first 1.5 years of life. We identified key taxonomic predictors of age, including declines in *Bifidobacterium* spp. and increases in *Faecalibacterium prausnitzii* and *Lachnospiraceae*. We further showed conserved microbial succession patterns in infants from around the globe, suggesting universal developmental trajectories. Most recently, in work published in *mBio* we have shown that gut microbial genes encoding enzymes for the metabolism of neuroactive compounds are prospectively associated with neurodevelopment of the visual circuit in 197 infants from South Africa as measured by the visual evoked potential (VEP) as measured with electroencephalography (EEG). The VEP indirectly measures both neural structure as well as activity, and we measured both the VEP and the gut microbiome at up to 3 visits in the first 15 months of life. Genes for the metabolism of the neurotransmitters GABA and glutamate, the amino acid tryptophan, and short-chain fatty acids involved in myelination, including acetate and butyrate. Microbial gene sets around 4 months of age were strongly associated with the VEP from around 9 to 14 months of age and showed more associations than concurrently measured gene sets, suggesting microbial metabolism in early life may affect subsequent neural plasticity and development.

- a. Fahur Bottino G, Bonham KS, Patel F, McCann S, Zieff M, Naspolini N, Ho D, Portlock T, Joos R, Midani FS, Schüroff P, Das A, Shennon I, Wilson BC, O'Sullivan JM, Britton RA, Murray DM, Kiely ME, Taddei CR, Beltrão-Braga PCB, Campos AC, Polanczyk GV, Huttenhower C, Donald KA, Klepac-Ceraj V. Early life microbial succession in the gut follows common patterns in humans across the globe. *Nat Commun*. 2025 Jan 14;16(1):660. PubMed Central PMCID: PMC11733223.
 - b. Bonham KS, Margolis ET, Fahur Bottino G, Sobrino AC, Patel F, McCann S, Zieff MR, Miles M, Herr D, Davel L, Bosco C, Huttenhower C, Pini N, Alexander DC, Jones DK, Williams SCR, Amso D, Gladstone M, Fifer WP, Donald KA, Gabard-Durnam LJ, Klepac-Ceraj V. Codevelopment of gut microbial metabolism and visual neural circuitry over human infancy. *mBio*. 2025 Aug 13;16(8):e0083525. PubMed Central PMCID: PMC12345167.
 - c. Laue HE, Bonham KS, Coker MO, Moroishi Y, Pathmasiri W, McRitchie S, Sumner S, Hoen AG, Karagas MR, Klepac-Ceraj V, Madan JC. Prospective association of the infant gut microbiome with social behaviors in the ECHO consortium. *Mol Autism*. 2024 May 17;15(1):21. PubMed Central PMCID: PMC11101342.
 - d. Kevin S. Bonham, Guilherme Fahur Bottino, Shelley Hoeft McCann, Jennifer Beauchemin, Elizabeth Weisse, Fatoumata Barry, Rosa Cano Lorente, Curtis Huttenhower, Muriel Bruchhage, Viren D'Sa, Sean Deoni, Vanja Klepac-Ceraj. Gut-resident microorganisms and their genes are associated with cognition and neuroanatomy in children. *Science Advances*. 2023 December. DOI: 10.1126/sciadv.adi0497
3. My early career contributions involved biochemical and cell-biological characterization of signaling pathways in the immune system. In my first postbaccalaureate position, I characterized small-molecule inhibitors of protein arginine methyltransferases (PRMTs), which had previously been shown to play a role in T-helper cell differentiation. To do this, I performed in vitro biochemical experiments using radio-labeled substrates and purified PRMT enzymes. I also extracted naive T-cells from mice, and performed ex vivo differentiation experiments to assess the activity of these molecules. My graduate research was focused on the biochemistry and cell biology of innate immune signaling, particularly downstream of toll-like receptors (TLRs). The existing paradigm when I started my work suggested that an adaptor protein called TIRAP was exclusively localized to the plasma membrane of cells, and was unnecessary for TLRs such as TLR9 that primarily signal from endosomes. This paradigm was based on the observation that unmethylated CpG DNA, a TLR9 agonist, was able to induce inflammatory cytokine production in TIRAP-KO macrophages. In addition, TIRAP's localization domain was shown to bind PIP2, a plasma-membrane restricted lipid, and existing orthodoxy

suggested that PI-binding domains were highly specific. I showed that cells less phagocytic than macrophages, such as plasmacytoid dendritic cells and immortalized macrophages, were unable to respond to the endocytosis of a DNA virus (HSV) in the absence of TIRAP. In addition, I showed that TIRAP's native lipid binding domain was in fact promiscuous, and could enable localization to both the plasma membrane and endosomes. By replacing the localization domain with those of higher specificity, I showed that TIRAP could independently rescue signaling from the plasma membrane, or from endosomes, or from both locations depending on the specific lipid moiety targeted.

- a. Brubaker SW, Bonham KS, Zanoni I, Kagan JC. Innate immune pattern recognition: a cell biological perspective. *Annu Rev Immunol.* 2015;33:257-90. PubMed Central PMCID: PMC5146691.
- b. Bonham KS, Orzalli MH, Hayashi K, Wolf AI, Glanemann C, Weninger W, Iwasaki A, Knipe DM, Kagan JC. A promiscuous lipid-binding protein diversifies the subcellular sites of toll-like receptor signal transduction. *Cell.* 2014 Feb 13;156(4):705-16. PubMed Central PMCID: PMC3951743.
- c. Bonham Kevin, Hemmers Saskia, Lim Yeon-Hee, Hill Dawn M., Finn M. G., Mowen Kerri A.. Modulation of T-helper cell function by AMI-1. *FEBS Journal.* 2010; 277(9):2096-2108. Available from: <http://dx.doi.org/10.1111/j.1742-4658.2010.07623.x> DOI: 10.1111/j.1742-4658.2010.07623.x

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Panos N. Papapanou

eRA COMMONS USER NAME (credential, e.g., agency login): PapapanouP

POSITION TITLE: Professor of Dental Medicine; Section of Oral, Diagnostic and Rehabilitation Sciences; Division of Periodontics; Columbia University College of Dental Medicine

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
School of Dentistry, University of Athens, Greece	D.D.S.	1984	Dental Science
Columbia University School of Dental & Oral Surgery	D.D.S.	2001	Dental Science
Göteborg University, Sweden	Ph.D.	1989	Periodontology
Forsyth Dental Center, Boston, MA	Postdoctoral	1992-1993	Oral Microbiology

A. Personal Statement

I am a tenured Professor of Dental Medicine at Columbia University, with a long-standing research interest in the epidemiology and pathobiology of periodontitis, and the study of its effects on general health outcomes. I also serve as Editor-in-Chief of the *Journal of Clinical Periodontology*.

My research group has pioneered the study of gingival tissue transcriptomes to investigate the biologic basis of the classification of periodontitis, to study the association between bacterial subgingival colonization patterns and gene expression profiles in the gingival tissues and, ultimately, to develop a precision medicine-based approach to the diagnosis and management of periodontitis. With respect to the role of periodontitis as a systemic health stressor, we have conducted epidemiologic studies (cross-sectional, cohort and intervention trials) in the context of adverse pregnancy outcomes, diabetes mellitus, atherosclerotic vascular disease, and cognitive decline.

The proposed K08 award project fits naturally with my research interests on the role of periodontal infection/inflammation as a general health stressor.

Ongoing and completed projects that I would like to highlight include:

R01 AG076015

Papapanou (MPI); 09/30/21-06/30/26

A longitudinal study of periodontal infections and Alzheimer's disease: The WHICAP Ancillary Study of Oral Health.

R56 DE026487

Papapanou (PI); 09/01/17-08/31/20

A combined genetic/epigenetic approach to study periodontitis susceptibility and pathobiology.

R03 DE024735

Papapanou (PI); 04/01/15-03/31/18

A genomic approach to the pathobiology and classification of periodontitis.

R56 DE022568

Papapanou (MPI); (09/30/13-08/30/16)

Periodontitis exposure and risk of incident dementia.

Citations:

- a. Rubinstein, T., Brickman, A.M., Cheng, B., Burkett, S., Park, H., Annavajhala, M.K., Uhlemann, A.C., Andrews, H., Gutierrez, J., Paster, B.J., Noble, J.M., **Papapanou, P.N.** (2024) Periodontitis and brain magnetic resonance imaging markers of Alzheimer's disease and cognitive aging. *Alzheimer's and Dementia* 20: 2191-2208. DOI: 10.1002/alz.13683
- b. Yang, T., Cheng, B., Noble, J.M., Reitz, C., **Papapanou, P.N.** (2022) Replication of gene polymorphism associated with periodontitis-related traits in an elderly cohort: the Washington Heights/Inwood Community Aging Project Ancillary Study of Oral Health. *Journal of Clinical Periodontology* 49: 414-2427.
- c. **Papapanou, P.N.**, Park, H., Cheng, B., Kokaras, A., Paster, B., Burkett, S., Watson, C.W.-M., Annavajhala, M.K., Uhlemann, A.-C., Noble, J.M. (2020) Subgingival microbiome and clinical periodontal status in an elderly cohort: The WHICAP ancillary study of oral health. *Journal of Periodontology* 91: Suppl1, S56-S67.
- d. Demmer, R.T., Breskin, A., Rosenbaum, M., Zuk, A., LeDuc, C., Leibel, R., Paster, B., Desvarieux, M., Jacobs, D.R.Jr., **Papapanou, P.N.** (2017) The subgingival microbiome, systemic inflammation and insulin resistance: The Oral Infections, Glucose Intolerance and Insulin Resistance Study (ORIGINS). *Journal of Clinical Periodontology* 44: 255-265.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2015 - 2023	Chairman, Section of Oral, Diagnostic and Rehabilitation Sciences, Columbia University College of Dental Medicine (CDM)
2005	University Tenure
2003 - 2015	Chairman, Section of Oral and Diagnostic Sciences, Columbia University CDM
2003 -	Professor of Dental Medicine, Columbia University CDM
1999 - 2023	Director, Division of Periodontics, CDM
1998 - 2003	Associate Professor of Dentistry, Columbia University School of Dental and Oral Surgery
1997- 1998	Assistant Dean, Research Curriculum, Faculty of Odontology, Göteborg University, Sweden
1995 - 1998	Associate Professor, Department of Oral Microbiology, Faculty of Odontology, Göteborg University, Sweden
1992 - 1995	Associate Professor, Department of Periodontology, Faculty of Odontology, Göteborg University, Sweden
1992 - 1993	Visiting Scientist, Department of Oral Microbiology, Forsyth Dental Center, Boston, MA
1989 - 1992	Assistant Professor, Department of Periodontology, Faculty of Odontology, Göteborg University, Sweden

Honors

2021	International Research Prize; Swedish Society of Dental Medicine
2021 -	Editor in Chief; Journal of Clinical Periodontology
2018	Special Citation; American Academy of Periodontology
2017	Co-chair, World Workshop for the Classification of Periodontal and Peri-implant Diseases and Conditions
2017	Distinguished Scientist Award in Basic Research in Periodontal Disease; International Association of Dental Research
2016	The Yngve Ericsson Prize in Prophylactic Dentistry Research; Swedish Patent Revenue Fund for Prophylactic Odontology and European Organization for Caries Research (ORCA)
2015	William J. Gies Award; International Association of Dental Research
2012	Special Citation; American Academy of Periodontology
2009	International Award in Periodontal Medicine; Sunstar Foundation

- 2008 - 15 Councilor, Periodontal Research Group, International Association of Dental Research
- 2007 Clinical Research Award; American Academy of Periodontology
- 2007 Educator Award for Outstanding Teaching and Mentoring in Periodontics; American Academy of Periodontology
- 2007 Fellow; American College of Dentists
- 2007 Honorary Alumnus, Graduate Program in Periodontics, College of Dental Medicine, Columbia University
- 2005 - 06 President; Periodontal Research Group, International Association of Dental Research
- 2003 Life Honorary Member; Hellenic Society for Periodontology, Athens, Greece
- 1998 The Walther-Engel Prize; Academy of Graduate Dental Education, Karlsruhe, Germany
- 1996 The 1st Anthony A. Rizzo Young Investigator Award; Periodontal Research Group, International Association of Dental Research
- 1988 The Jens Waerhaug Research Prize; Scandinavian Society of Periodontology

Other Experience and Professional Memberships

Advisory Board Membership

European Research Group for Oral Biology (1995-2000); European Journal of Oral Sciences (1999-2006); Institute for Applied Mathematics and Statistics, Chalmers Institute for Technology, Göteborg, Sweden (1995-1998); Community Dentistry and Oral Epidemiology (2003-2005); Dentistry Today (2000-2005); Journal of Clinical Periodontology (*Associate Editor* 2009-2016); Journal of Dental Research (2005-2008 and 2017-2022); Journal of Periodontal Research (2000-2005); Journal of Periodontology (2002-2023)

Committees (selected)

Executive Committee, Columbia University College of Dental Medicine (CDM) (1999-present); Governance Committee, CDM, (2004-2013); Columbia University Health Sciences Conflict of Interest Committee, (2001-2023); Research Committee, CDM (1999-present); Research Strategic Planning Committee Chair, CDM (2002); Research, Science and Therapy Committee, American Academy of Periodontology (2006-present); Irving Center for Clinical and Translational Research Advisory Committee (2002-2018); Committee on Appointments and Promotions, CDM, Chair, (2012- 2023); Committee on Appointments and Promotions, Columbia University Irving Medical Center, Chair, (2018- 2021)

Ad hoc reviewer-Journals

Acta Odontologica Scandinavica; American Journal of Cardiology; Annals of Periodontology; American Journal of Epidemiology; Arteriosclerosis, Thrombosis, and Vascular Biology; Archives of Oral Biology; Community Dentistry and Oral Epidemiology; Compendium; Dentistry Today; e Cells and Materials Journal; European Journal of Oral Sciences; FEMS Microbiology Letters; Journal of the American Medical Association; Journal of Periodontal Research; Journal of Dental Research; Journal of Clinical Periodontology; Journal of Translational Medicine; Nature Medicine; Nature Communications; Oral Diseases

Ad hoc reviewer-Study Sections

Oral, Dental and Craniofacial Sciences Study Section, Center for Scientific Review, National Institutes of Health (2005, 2009); Heart Lung, and Blood Program Project Review Committee (2005, 2006, 2007); Michael Smith Foundation for Health Research, British Columbia, Canada (2006), New Zealand Dental Association (2007)

Reviewer- International Workshops

Epidemiology, 1st European Workshop in Periodontics, 1993; World Workshop in Periodontics, 1996; 5th European Workshop in Periodontics, 2005; 7th European Workshop in Periodontics, 2010; Co-Chair; World Workshop for the Classification of Periodontal and Peri-implant Diseases and Conditions, 2017.

C. Contributions to Science

1. One of my major research interests is the epidemiology of periodontal diseases and the identification of clinical, microbiological, serological and genetic risk factors/markers of periodontitis. Contrary to earlier studies indicating a universal prevalence of periodontal disease, our work demonstrated that (i) advanced periodontitis affects only a fraction of the population (10-15%), and (ii) its progression rate is in most instances low. We

were the first to demonstrate that baseline levels of periodontitis can serve as a strong predictor of periodontitis progression, and among the first group to show that levels of specific bacteria in the subgingival niche confer higher risk for disease progression. In recognition of my expertise in the epidemiology of periodontitis, I was invited to be the sole author of the position paper on the Epidemiology of Periodontal Diseases at the 1996 World Workshop on Periodontitis and, more recently (2017), to serve as one of the two American Academy of Periodontology Co-chairs that led the World Workshop for the Classification of Periodontal and Peri-implant Diseases and Conditions. Representative publications of this line of research are listed below:

- a. Papapanou, P.N., Baelum, V., Luan, W.-M., Madianos, P.N., Chen, X., Fejerskov, O., Dahlén, G. (1997) Subgingival microflora in adult Chinese: Prevalence and relation to periodontal disease progression. *Journal of Periodontology* 68: 651-666.
- b. Dye, B.A., Herrera-Abreu, M., Lerche-Sehm, J., Vlachojannis, C., Pikdoken, L., Pretzl, B., Schwartz, A., Papapanou, P.N. (2009) Serum antibodies to periodontal bacteria as diagnostic markers of periodontitis. *Journal of Periodontology* 80: 634-647.
- c. Papapanou, P.N., Sanz, M. et al: (2018) Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *Journal of Clinical Periodontology* 45: Suppl 20:S162-S170.
- d. Shariff, J.A., Cheng, B., Papapanou, P.N. (2020) Age-specific predictive models of the upper quintile of periodontal attachment loss. *Journal of Dental Research* 99: 44-50.

2. A multidisciplinary team at Columbia University has focused on the role of periodontitis as a systemic health stressor. We conducted epidemiologic studies on the role of periodontitis as a risk factor for atherosclerosis and stroke, and were the first to demonstrate that periodontal colonization by specific periodontal microbiota is associated with increased intima media thickness and hypertension. In recognition of my expertise in the field, I was one of only two dentists who served as co-authors in the American Heart Association Scientific Statement on the role of periodontitis in atherosclerotic vascular disease. In parallel, I served as the Columbia site Principal Investigator in the first NIH-funded multi-center study examining the role of periodontal therapy on adverse pregnancy outcomes, and have also participated in studies on the two-way relationship between diabetes mellitus and periodontitis. Representative publications of this line of research are listed below:

- a. Michalowicz, B.S., Hodges, J.S., DiAngelis, A., Lupo, V.R., Novak, M.J., Ferguson, J.E., Buchanan, W., Bofill, J., Papapanou, P.N., Mitchell, D.A., Matseoane, S., Tschida, P.A. (2006) Treatment of periodontal disease and the risk of preterm birth. *New England Journal of Medicine* 355: 1885-1894.
- b. Lalla, E. & Papapanou, P.N. (2011) Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. *Nature Reviews Endocrinology* 7: 738-748.
- c. Lockhart, P.B., Bolger, A.F., Papapanou, P.N., Osinbowale, O., Trevisan, M., Levison, M.E., Taubert, K.A., Newburger, J.W., Gornik, H.L., Gewitz, M.H., Wilson, W.R., Smith, S.C. Jr., Baddour, L.M. (2012) Periodontal Disease and Atherosclerotic Vascular Disease: Does the Evidence Support an Independent Association?: A Scientific Statement From the American Heart Association. *Circulation* 125: 2520-2544.
- d. Demmer, R.T., Trinh, P., Rosenbaum, M., Li, G., LeDuc, C., Leibel, R., González, A., Knight, R., Paster, B., Colombo, P.C., Desvarieux, M., Papapanou, P.N., Jacobs, D.R. Jr. (2019) Subgingival microbiota and longitudinal glucose change: The Oral Infections, Glucose Intolerance and Insulin Resistance Study (ORIGINS). *Journal of Dental Research* 98: 1488-1496.

3. Over the past 15 years, my group has pioneered the use of gingival tissue transcriptomes in the study of the pathobiology and classification of periodontitis. We have published the first comprehensive description of gene expression signatures in gingival tissues in states of periodontal health and disease. We further demonstrated that the subgingival microbial colonization patterns are strong determinants of the transcriptomic responses in the adjacent gingival tissues. In parallel, we demonstrated that periodontal therapy has discernible effects on the peripheral blood mononuclear cell transcriptome, compatible with a potential promotion of an anti-atherogenic phenotype. We proceeded with a molecular 'class validation' analysis of the then current classification of periodontitis and demonstrated (that gingival lesions from CP and AgP showed only limited differences on the transcriptional level. However, a 'class discovery' approach using the gingival tissue transcriptional profiles as a basis to form homogeneous clusters of periodontitis patients identified two fairly robust clusters that differed with respect to important periodontitis-related phenotypic characteristics. Using a systems biology approach in the pathobiology and classification of human periodontitis, we have used

genome-wide reverse engineering approaches to facilitate the identification of candidate genes that may distinguish between causal and associative interactions and may account for the emergence or the maintenance of pathological phenotypes in periodontitis (“Master regulators”). Our latest work focused at the computational decomposition of the gingival tissue transcriptome into cell-type specific signatures. Representative publications of this line of research are listed below:

- a. Demmer, R., Behle, J.H., Wolf, D.L., Handfield, M., Kebschull, M., Celenti, R., Pavlidis, P., Papapanou, P.N. (2008) Transcriptomes in healthy and diseased gingival tissues. *Journal of Periodontology* 79: 2112-2124.
- b. Kebschull, M., Demmer, R.T., Grün, B., Guarnieri, P., Pavlidis, P., Papapanou, P.N. (2014) Gingival tissue transcriptomes identify distinct periodontitis phenotypes. *Journal of Dental Research*, 93: 459-468.
- c. Sawle, A., Demmer, R.T., Kebschull, M., Papapanou, P.N. (2016) Identification of master regulator genes in human periodontitis. *Journal of Dental Research* 95: 1010-1017.
- d. Momen-Heravi, F., Friedman, R.A., Albeshri, S., Sawle, A., Kebschull, M., Kuhn, A., Papapanou, P.N. (2021) Cell type-specific decomposition of gingival tissue transcriptomes. *Journal of Dental Research* 100;549-556 doi: 10.1177/0022034520979614.

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/pubmed/?term=papapanou+p>

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Noble, James

eRA COMMONS USER NAME (credential, e.g., agency login): jn2054

POSITION TITLE: Professor of Neurology (in the Taub Institute for Research on Alzheimer Disease and the Aging Brain and GH Sergievsky Center) at CUMC

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Vanderbilt University, Nashville, TN	BS	05/1998	Chemistry and Math
Emory University School of Medicine, Atlanta, GA	MD	05/2002	
Mailman School of Public Health, Columbia University, New York, NY	MS	05/2008	Epidemiology
Columbia-Presbyterian Medical Center, New York, NY	Resident	06/2003	Preliminary Medicine Resident
Columbia University Medical Center, New York, NY	Resident	06/2006	Neurology Resident
Columbia University Medical Center, Taub Institute, New York, NY	Postdoctoral Fellow	06/2008	Aging and Dementia

A. Personal Statement

I am a Professor of Neurology at CUIMC in the Department of Neurology, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, and G.H. Sergievsky Center at Columbia University. My training included residency training in neurology, behavioral neurology/neuropsychiatry and neuroepidemiology fellowship (T32 NS007153), all based on work at Columbia University Irving Medical Center. I am driven to be an outstanding clinician in my field, educator to my peers and trainees, and leader of novel research and public health outreach endeavors. I have put my intense energy, focus, and enthusiasm into several areas connected by a) identifying and creating novel and innovative approaches to complex neurological problems, b) invested expertise in clinical fields and the communities they impact and c) identifying and mitigating significant health disparities. I began with being taught how to describe health disparities in communities facing pathological cognitive aging and have since made my own course towards identifying novel mechanisms for health disparities in that population and created innovative community outreach programs aiming to improve the burden of disease. My primary and active areas of research interest in Alzheimer's disease and related dementias (ADRD) include potentially modifiable risk factors (including the roles of infection and inflammation (PI: R01 AG076015) and multigenerational community-based education programs aiming to increase access to neurological care in minority communities (as PI: R01AG054536, as Co-I: R01 NS067443). I am the Cognitive Core leader of the Diabetes Prevention Program Outcomes Study (DPPOS) which has implemented UDS evaluations on nearly 1600 members of this aging cohort also assessed using multimodal biomarkers (U19 AG078558). Most relevant to this application, I am the clinical core leader and co-director of the Columbia ADRC (P30 AG066462, PI: Small) which is a central resource, supporting many other research projects towards a singular goal of improved understanding of pathobiology, diagnostic tests, and treatment for ADRD. Additionally, I am co-editor of the 14th edition of Merritt's Neurology (2021), an internationally recognized textbook, and am the author of the caregiver-directed book "Navigating Life with Dementia" (Oxford University Press/American Academy of Neurology, 2022). I also have a track record of mentorship, aiming to shepherd the next generation of inspired clinical neuroscientists through my longstanding and broad education roles in the College of Physicians & Surgeons (2009-2016: neurology clerkship director, 2013-present: founding co-director of the NIA-funded Brief Research in Aging and Interdisciplinary Neurosciences-BRAIN T35 AG044303, 2017-present: co-director of VP&S preclinical neuroscience course with Dr. Przedborski), Mailman School of Public Health, and Engineering programs at Columbia University and with the American Academy of Neurology. I collaborate with many local, national, and international investigators, to facilitate the work of our

center and supporting many others towards a singular goal of improved understanding of pathobiology, diagnostic tests, and treatment for ADRD.

Most relevant to this proposal is my expertise at the crossroads of oral health and dementia. As I published in JNNP in 2009, I was the first to identify an epidemiological association between *P. gingivalis* and cognitive impairment in aging US adults. Since then I have served as PI of the Ancillary Study of Oral Health in the Washington Heights Inwood Columbia Aging Project (WHICAP), a now 12-year community-based epidemiology study of oral health among its aging participants. I look forward to mentoring Dr. Zhu on this project and her K08 training grant.

Ongoing projects I would like to highlight include:

R01 AG076015, Noble (PI), 9/1/2021-4/30/2026

A Longitudinal Study of Periodontal Infections and Alzheimer's Disease: The WHICAP Ancillary Study of Oral Health

U19 AG078558, Luchsinger (PI), Role: Clinical Core leader, 9/1/2022-8/31/2027

Alzheimer's Disease and Alzheimer's Disease Related Dementias in Prediabetes and Type 2 Diabetes: The Diabetes Prevention Program Outcomes Study AD/ADRD Project (DPPOS)

P30AG066462, Small (PI), Role: Clinical Core Leader, 5/1/2020-4/30/2025

Alzheimer's Disease Research Center-Clinical Core

Citations:

1. Rubinstein T, Brickman AM, Cheng B, Burkett S, Park H, Annavajhala MK, Uhlemann AC, Andrews H, Gutierrez J, Paster BJ, Noble JM, Papapanou PN. Periodontitis and brain magnetic resonance imaging markers of Alzheimer's disease and cognitive aging. *Alzheimers Dement*. 2024 Mar;20(3):2191-2208. PubMed Central PMCID: PMC10984451.
2. Noble JM, Papapanou PN. With Teeth, Broken, or Fixed: The Challenges of Linking Periodontitis, Neuroepidemiology, and Biomarkers of Disease. *J Alzheimers Dis*. 2023;93(3):991-994. PubMed PMID: 37248907.
3. Noble JM, Scarmeas N, Celenti RS, Elkind MS, Wright CB, Schupf N, Papapanou PN. Serum IgG antibody levels to periodontal microbiota are associated with incident Alzheimer disease. *PLoS One*. 2014;9(12):e114959. PubMed Central PMCID: PMC4270775.
4. Shariff JA, Burkett S, Watson CW, Cheng B, Noble JM, Papapanou PN. Periodontal status among elderly inhabitants of northern Manhattan: The WHICAP ancillary study of oral health. *J Clin Periodontol*. 2018 Aug;45(8):909-919. PubMed Central PMCID: PMC6242775.

B. Scientific Appointments and Honors

Positions and Scientific Appointments

2024 -	Professor of Neurology (in the Taub Institute for Research on Alzheimer Disease and the Aging Brain and GH Sergievsky Center) at CUMC, Columbia University, New York, NY
2018 - 2024	Associate Professor of Neurology (in the Taub Institute for Research on Alzheimer Disease and the Aging Brain and GH Sergievsky Center) at CUMC , Columbia University, New York, NY
2017 - 2023	Chief Medical Advisor, NoMo Diagnostics, Chicago, IL
2010 -	President & Co-Founder (volunteer), Arts & Minds, Inc (501c3), New York, NY
2008 - 2018	Assistant Professor of Neurology (in the Taub Institute for Research on Alzheimer Disease and the Aging Brain and GH Sergievsky Center) at CUMC, Columbia University Medical Center, New York, NY

2007 - 2011 Assistant Attending Neurologist, Harlem Hospital Center, New York, NY

Honors

2023	Academy of Community and Public Service, Columbia University
2021	A. B. Baker Teacher Recognition Award., American Academy of Neurology
2018	Outstanding Recent Alumni Award, Mailman School of Public Health Alumni Association
2017	Fellow, American Academy of Neurology
2013	Virginia Apgar Teaching Academy, Columbia University
2012	Emerging Leaders Forum (Inaugural Class), American Academy of Neurology
2011	Stephen Q. Shafer Award for Humanism in Neurology, Department of Neurology, Columbia University Medical Center
2008	Anna C. Gelman Award for Excellence in Epidemiology, Columbia University, Mailman School of Public Health

C. Contribution to Science

1. Drawing from an interest in the associations between oral health (specifically periodontitis) and stroke, and stroke with dementia, all of which adversely affect aging populations, I have developed several novel research projects exploring associations between periodontitis and dementia. We were the first to identify a cross-sectional association between serum antibodies to a causal periodontal organism (*P. gingivalis*) and cognitive impairment among older US adults (NHANES-III). Next, we identified an association between another common oral pathogen (*A. naeslundii*) and incident Alzheimer disease, another novel finding. Subsequent work by other groups have supported these epidemiological associations in pathobiological links in rodent models and human autopsy and CSF data. Currently, we are studying the oral health of 1100 participants in the Washington Heights Columbia Aging Project (WHICAP), exploring serological evidence of host response to periodontal pathogens, as well as next generation sequencing of pathogen specimens obtained from whole mouth periodontal examinations in relation to MRI and clinical outcomes.
 - a. Rubinstein T, Brickman AM, Cheng B, Burkett S, Park H, Annavajhala MK, Uhlemann AC, Andrews H, Gutierrez J, Paster BJ, Noble JM, Papapanou PN. Periodontitis and brain magnetic resonance imaging markers of Alzheimer's disease and cognitive aging. *Alzheimers Dement*. 2024 Mar;20(3):2191-2208. PubMed Central PMCID: PMC10984451.
 - b. Noble JM, Papapanou PN. With Teeth, Broken, or Fixed: The Challenges of Linking Periodontitis, Neuroepidemiology, and Biomarkers of Disease. *J Alzheimers Dis*. 2023;93(3):991-994. PubMed PMID: 37248907.
 - c. Shariff JA, Burkett S, Watson CW, Cheng B, Noble JM, Papapanou PN. Periodontal status among elderly inhabitants of northern Manhattan: The WHICAP ancillary study of oral health. *J Clin Periodontol*. 2018 Aug;45(8):909-919. PubMed Central PMCID: PMC6242775.
 - d. Noble JM, Scarmeas N, Celenti RS, Elkind MS, Wright CB, Schupf N, Papapanou PN. Serum IgG antibody levels to periodontal microbiota are associated with incident Alzheimer disease. *PLoS One*. 2014;9(12):e114959. PubMed Central PMCID: PMC4270775.
2. Determinants of Alzheimer disease and related disorders are uncertain but are thought to be related to a mixture of modifiable risk factors across the lifespan, including education, diabetes and other factors associated with systemic chronic inflammatory response, as well as genetics including heterogeneity of mutation prevalence, differential penetrance or expression. To this end, I have led several research epidemiologic projects exploring the roles of education, diabetes, c-reactive protein and APOE as well as differential rates of diabetes on the incidence of cognitive impairment including Alzheimer disease in WHICAP.
 - a. Vonk JMJ, Arce Rentería M, Avila JF, Schupf N, Noble JM, Mayeux R, Brickman AM, Manly JJ. Secular trends in cognitive trajectories of diverse older adults. *Alzheimers Dement*. 2019 Dec;15(12):1576-1587. PubMed Central PMCID: PMC6925643.

- b. Noble JM, Schupf N, Manly JJ, Andrews H, Tang MX, Mayeux R. Secular Trends in the Incidence of Dementia in a Multi-Ethnic Community. *J Alzheimers Dis.* 2017 Oct 3;60(3):1065-1075. PubMed Central PMCID: PMC6084436.
 - c. Noble JM, Manly JJ, Schupf N, Tang MX, Luchsinger JA. Type 2 diabetes and ethnic disparities in cognitive impairment. *Ethn Dis.* 2012 Winter;22(1):38-44. PubMed Central PMCID: PMC3398739.
 - d. Noble JM, Manly JJ, Schupf N, Tang MX, Mayeux R, Luchsinger JA. Association of C-reactive protein with cognitive impairment. *Arch Neurol.* 2010 Jan;67(1):87-92. PubMed Central PMCID: PMC4426905.
 3. I have demonstrated in a novel capacity that young children are a) educable about stroke--an abstract health concept to them, b) can retain this information for as much as 15 months, c) can enact a stroke emergency action plan when witnessing an actual stroke d) and can improve the neurologic health literacy of their adult family members. We have demonstrated that not only can these programs be delivered in an interactive didactic approach but more recently we have identified simpler means of delivery of key educational concepts including through the use of classroom-based brief video game play. A study of this program's effectiveness statewide in New York is ongoing, a similarly modeled program in Alzheimer disease recently completed (R01 AG054536, PI: Noble), and another program focusing on early health choices and behaviors is ongoing (R01 NR017571).
 - a. Williams O, Leighton-Herrmann Quinn E, Teresi J, Eimicke JP, Kong J, Ogedegbe G, Noble J. Improving Community Stroke Preparedness in the HHS (Hip-Hop Stroke) Randomized Clinical Trial. *Stroke.* 2018 Apr;49(4):972-979. PubMed Central PMCID: PMC5871596.
 - b. Noble JM, Hedmann MG, Williams O. Improving dementia health literacy using the FLOW mnemonic: pilot findings from the Old SCHOOL hip-hop program. *Health Educ Behav.* 2015 Feb;42(1):73-83. PubMed PMID: 24893605.
 - c. Williams O, DeSorbo A, Noble J, Gerin W. Child-Mediated Stroke Communication: findings from Hip Hop Stroke. *Stroke.* 2012 Jan;43(1):163-9. PubMed Central PMCID: PMC3246577.
 - d. Williams O, Noble JM. 'Hip-hop' stroke: a stroke educational program for elementary school children living in a high-risk community. *Stroke.* 2008 Oct;39(10):2809-16. PubMed PMID: 18635851.
4. Through collaboration with Dr. Maryam Zolnoori and other colleagues, I have and continue to support several local, regional, and national projects which have utilized machine learning and natural language processing to help identify AD/ADRD and its progression using speech and language signals through voice recordings of persons with cognitive impairment as well as patient-clinician interactions as well as NLP of medical text records. I am currently co-investigator with Dr. Ying Wei which follows adapting this work of NLP and other techniques to EHR and large aging datasets aiming to establish phenome- and genome-wide associations (R01AG087496).
 - a. Zolnoori M, Vergez S, Xu Z, Esmaeili E, Zolnour A, Anne Briggs K, Scroggins JK, Hosseini Ebrahimabad SF, Noble JM, Topaz M, Bakken S, Bowles KH, Spens I, Onorato N, Sridharan S, McDonald MV. Decoding disparities: evaluating automatic speech recognition system performance in transcribing Black and White patient verbal communication with nurses in home healthcare. *JAMIA Open.* 2024 Dec;7(4):ooae130. PubMed Central PMCID: PMC11631515.
 - b. Ryvicker M, Barrón Y, Song J, Zolnoori M, Shah S, Burgdorf JG, Noble JM, Topaz M. Using Natural Language Processing to Identify Home Health Care Patients at Risk for Diagnosis of Alzheimer's Disease and Related Dementias. *J Appl Gerontol.* 2024 Oct;43(10):1461-1472. PubMed Central PMCID: PMC11368608.
 - c. Zolnoori M, Barrón Y, Song J, Noble J, Burgdorf J, Ryvicker M, Topaz M. HomeADScreen: Developing Alzheimer's disease and related dementia risk identification model in home healthcare. *Int J Med Inform.* 2023 Sep;177:105146. PubMed Central PMCID: PMC10529395.
 - d. Ryvicker M, Barrón Y, Shah S, Moore SM, Noble JM, Bowles KH, Merrill J. Clinical and Demographic Profiles of Home Care Patients With Alzheimer's Disease and Related Dementias: Implications for Information Transfer Across Care Settings. *J Appl Gerontol.* 2022 Feb;41(2):534-544. PubMed Central PMCID: PMC8450301.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Athanasios I. Zavras

eRA COMMONS USER NAME (credential, e.g., agency login): TZAVRAS

POSITION TITLE: Professor & Chair, Department of Public Health & Community Service

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Athens Dental School, Athens, GR	D.M.D.	06/1991	Dentistry
Tufts University School of Dental Medicine, MA	Certificate	07/1993	Pediatric Dentistry
Harvard University School of Public Health, MA	Sc.M	06/1994	Epidemiology
Harvard University School of Medicine, MA	Dr.M.Sc.	02/1999	Biology/ Epidemiology

A. Personal Statement

My career goal is to identify new innovative ways to improve the health status of the population, especially the most vulnerable ones. Following a dental degree and specialty training in Pediatric Dentistry, I pursued a Master in Epidemiology and a Doctorate in Epidemiology & Oral Biology. My doctoral studies in Dentistry and Epidemiology in the 90's and subsequent NIH K23-and K22-sponsored career development training provided a strong scientific foundation in translational and clinical research. Using this K08 award, we propose to mentor Zoe Zhu to explore the role of oral microbiome in the oral-systemic connections. As a co-mentor on Zoe's K08 application. I'll lend my expertise in clinical research for pilot study in Aim 3b of her proposal, regarding study design issues and control of bias, calibration of examiners, patient recruitment, IRB submission, patient consultations of laboratory results and in ensuring continuous support and troubleshooting. In addition, I'll also provide her my guidance on her career advancement.

Ongoing and recently completed projects that I would like to highlight include:

2023-2028 HRSA Predoctoral Training Grant in Special Needs P.I Maria Dolce
Co-investigator and member of advisory committee. The aim of the project is to develop resources and to re-organize the care at Tufts Dental School in order to improve the care of patients with complex medical issues and disabilities

2023-2025 Carequest Foundation P.I Athanasios Zavras
Transitioning Into a New System That Can (TRANSTC): Improving the Oral Health Related Quality of Life for People With Disabilities. The aim of the project is to pilot test novel delivery model of care for patients with intellectual and developmental disabilities that is based on WHO-ICD, teledentistry, case coordination and traveling hygienists to integrate care.

2023-2024 Commonwealth of Massachusetts P.I Athanasios Zavras
Providing technical expertise to the State to develop an incubator for tele-dentistry and mobile dentistry in an effort to expand access.

B. Positions, Scientific Appointments, and Honors**Positions and Scientific Appointments**

2000-07	Assistant Professor (full time, tenure track). Harvard University Medical School. Director, Cancer Research & Control. Harvard International Institute for the Environment and Public Health.
2007-09	Associate Professor (full time, tenure track) and Director for Dental Public Health Harvard University Medical faculty - School of Dental Medicine.
2008-17	Professor (adjunct) of Epidemiology. Harvard University School of Public Health.
2009-14	Professor of Dentistry and Epidemiology and Head of Div. of Oral Epidemiology. Columbia College of Dental Medicine and Mailman School of Public Health. Member; Herbert Irving Comprehensive Cancer Center.
2014-22	Chairman and Professor. Dept. of Pediatric Dentistry. Boston University Henry Goldman School of Dental Medicine.
2022-	Chairman and Professor. Dept. of Public Health & Community Service. Asst Dean for Faculty Advancement. Tufts University School of Dental Medicine
2000-07	Assistant Professor (full time, tenure track). Harvard University Medical School. Director, Cancer Research & Control. Harvard International Institute for the Environment and Public Health.
2007-09	Associate Professor (full time, tenure track) and Director for Dental Public Health Harvard University Medical faculty - School of Dental Medicine.
2008-17	Professor (adjunct) of Epidemiology. Harvard University School of Public Health.
2009-14	Professor of Dentistry and Epidemiology and Head of Div. of Oral Epidemiology. Columbia College of Dental Medicine and Mailman School of Public Health. Member; Herbert Irving Comprehensive Cancer Center.
2014-22	Chairman and Professor. Dept. of Pediatric Dentistry. Boston University Henry Goldman School of Dental Medicine.
2022-	Chairman and Endowed Professor. Dept. of Public Health & Community Service. Asst Dean for Faculty Advancement. Tufts University School of Dental Medicine

Honors

1998	IADR International Research in Prevention Award
1999	James Morse Dunning Postdoctoral Research Award, Harvard University, Boston
1999-04	K23 Mentored Career Development Award, NIDCR, NIH
2002-04	Executive Committee member (elect) & Director of the Americas, International Society for the Prevention of Tobacco Induced Diseases (ISPTID)
2004	President, International Society for the Prevention of Tobacco Induced Diseases
2005-08	K22 Career Transition Award, NIDCR, NIH
2007-10	Full member, Dana Farber / Harvard Cancer Center
2010-14	Full member, Herbert Irving Comprehensive Cancer Center
2013-15	Commission on Dental Accreditation (CODA) Consultant Site Visitor for Public Health
2016-	Director, Secretary Treasurer (2019-20), Vice President (2020-21) and President (2021-22) of the American Board of Dental Public Health

NIH Committee Service

2005	Member (ad hoc), Special Emphasis Panel to review NIDCR CREED pilot grants
2006	Member (ad hoc), NIDCR PBRN applications on Osteonecrosis of the Jaw
2006	Member (ad hoc), Special Emphasis Panel ZRG1 Fluoride Pharmacogenetics grant.
2007	Member (one time, Oct. 2007), Skeletal Biology Development and Diseases SBDD Study Section, National Institutes of Health, Bethesda, MD.
2007	Chair, Musculoskeletal, Oral and Skin Sciences Special Emphasis Panel – Pharmacogenetics of Fluoride ZRG1 MOSS-E(51)R. Nov. 1, 2007 National Institutes of Health, Bethesda, MD.

2008	Member (one time, Jun 2008), Skeletal Biology Development and Diseases SBDD Study Section, National Institutes of Health, Bethesda, MD.
2008	Member (ad hoc), Special Emphasis Panel, NIDCR R03 grants.
2008	Member (ad hoc), Special Emphasis Panel, NIDCR ZRG1 MOSS-E(51)
2009	Member (ad hoc), EPIC Study Section
2009	Chair, Special Emphasis Panel, NIH ZRG1
2010	Member (ad hoc), Special Emphasis Panel, NIH ZRG1
2013	Member (ad hoc), Special Emphasis Panel, NCI ZRG1

C. Contributions to Science

1. Pharmacogenetics and Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ)

My research program established foundational understanding of bisphosphonate-induced osteonecrosis of the jaw through large-scale epidemiological studies and pharmacogenetic investigations. Using medical claims data from over 714,000 individuals, I demonstrated the association between bisphosphonate use and adverse jaw outcomes, challenging earlier assumptions about the condition. My work identified critical genetic variants, including the role of RBMS3 through genome-wide pharmacogenetic analysis, and established temporal relationships between bisphosphonate exposure and osteonecrosis development. This body of work has influenced clinical guidelines for bisphosphonate prescribing and monitoring protocols.

- Zavras AI, Zhu S. Bisphosphonates treatment and risk of surgery of the jaw. Is it osteonecrosis? J Oral Maxillofac Surgery 2006 Jun;64(6):917-23
- Cartsos V, Zhu S, Zavras AI. Bisphosphonates use and adverse jaw outcomes: a medical claims study of 714,000 individuals. Journal Amer Dental Assoc 2008;139(1):23-30
- Nicoletti P, Cartsos VM, Palaska PK, Shen Y, Floratos A, Zavras AI. Genomewide Pharmacogenetics of Bisphosphonate-Induced Osteonecrosis of the Jaw: The Role of RBMS3. Oncologist 2012 Jan 20
- Palaska PK, Cartsos V, Zavras AI. Bisphosphonates and time to osteonecrosis development. The Oncologist 2009 Nov;14(11):1154-66

2. Genetic Epidemiology of Oral Cancer

I have conducted extensive research on gene-environment interactions in oral cancer etiology, with particular focus on alcohol metabolism genes and DNA repair mechanisms. My investigations demonstrated that single nucleotide polymorphisms in alcohol dehydrogenase genes modify oral cancer risk in the context of alcohol consumption, providing evidence for personalized prevention strategies. I further identified associations between metallothionein-1 genotypes, IGF2R polymorphisms, and ERCC5 DNA repair gene variants with oral squamous cell carcinoma risk and disease progression. This translational research has advanced understanding of molecular pathways in oral carcinogenesis.

- Zavras AI, Wu T, Laskaris G, Wang YF, Cartsos V, Segas J, Lefantzis D, Joshipura K, Douglass CW, Diehl SR. Interaction between a single nucleotide polymorphism in the Alcohol Dehydrogenase 3 Gene, alcohol consumption and oral cancer risk. International Journal of Cancer 2002;97:526-30
- Zavras AI, Yoon AJ, Chen MK, Lin CW, Yang SF. Metallothionein-1 Genotypes in the Risk of Oral Squamous Cell Carcinoma. Ann Surg Oncol 2011 May;18(5):1478-83
- Zavras AI, Yoon AJ, Chen MK, Lin CW, Yang SF. Association between Polymorphisms of DNA Repair Gene ERCC5 and Oral Squamous Cell Carcinoma. Oral Surg Oral Med Oral Path Oral Rad 2012 Sep 11
- Hwang PH, Lian L, Zavras AI. Alcohol intake and folate antagonism via CYP2E1 and ALDH1: effects on oral carcinogenesis. Med Hypotheses 2012 Feb;78(2):197-202

3. Nutritional Epidemiology and Cancer Prevention

My collaborative research established the role of dietary factors and specific micronutrients in oral cancer etiology and prevention. Through case-control studies, I identified protective effects of micronutrient intake and examined the prospective relationship between alcohol consumption and oral premalignant lesions. I also investigated the malignant transformation rate in patients with oral epithelial dysplasia through systematic

review and meta-analysis, providing evidence-based estimates for clinical risk stratification. This work has informed dietary recommendations for cancer prevention.

- a. Petridou E, Zavras AI, Diehl SR, Lefatzis D, Laskaris G, Segas J, Desypris N, Douglass C, Trichopoulos D. The role of diet and specific micronutrients in oral cancer. *Cancer* 2002;94(11):2981-2988
- b. Maserejian NN, Joshipura KJ, Rosner BA, Giovannucci E, Zavras AI. Prospective Study of Alcohol Consumption and Risk of Oral Premalignant Lesions in Men. *Cancer Epi Biomarkers Prev* 2006 Apr;15(4):774-81
- c. Shariff J, Zavras AI. Malignant Transformation Rate in Patients Presenting with Oral Epithelial Dysplasia—Systematic Review and Meta-Analysis. *Journal of Oral Diseases* 2015, Article ID 854636

4. Pharmacoepidemiology and Drug Safety Surveillance

I have pioneered research on adverse drug and device reactions affecting the oral cavity, establishing surveillance methodologies and reporting frameworks. My investigations of antiepileptic drugs during pregnancy identified associations with congenital jaw and oral malformations. I also conducted signal detection studies examining antiretroviral prophylaxis and cleft lip/palate risk using FDA adverse event databases. This pharmacovigilance research has contributed to improved drug safety monitoring and clinical decision-making protocols.

- a. Koo J, Zavras AI. Antiepileptic drugs during pregnancy and risk of congenital jaw and oral malformation. *Oral Dis* 2013
- b. Cartsos V, Palaska PK, Zavras AI. Anti-Retroviral Prophylaxis and the Risk of Cleft Lip and Palate: Preliminary Signal Detection in the FDA AERS Database. *Cleft Palate Craniofac J* 2012 Jan;49(1):118-21
- c. Zavras AI, Rosenberg G, Danielson JD, Cartsos V. Adverse drug and device reactions in the oral cavity: Surveillance and reporting. *JADA* 2013;144(9):1014-1021

PHS OTHER SUPPORT

Name of Individual: Jake Jinkun Chen
Commons ID: jchen14

ACTIVE

Title: A Long Noncoding RNA Ameliorates Periodontitis via Distinct Epigenetic Pathways

Major Goals: The major goals of this project are to use a long noncoding RNA, lncRNA recently identified and characterized in our lab as a therapeutic agent to treat periodontal disease and to understand the epigenetic mechanisms.

Status of Support: Active

Project Number: RO1 DE30074

Name of PD/PI: Chen, J.

Source of Support: NIH/NIDCR

Primary Place of Performance: Tufts University

Project/Proposal Start and End Date: 12/01/2020 - 11/30/2025

Total Award Amount (including Indirect Costs): \$3,515,795

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
3. [2023]	2.7 CM
4. [2024]	2.7 CM
5. [2025]	2.7 CM

Title: Roles of Noncoding RNA in Bone Regeneration

Major Goals: The major goals of this project are to understand the mechanisms and apply the noncoding RNA identified and characterized in our lab together with the novel nanoparticle materials to enhance bone regeneration in oral and craniofacial region.

Status of Support: Active

Project Number: RO1 DE25681

Name of PD/PI: Chen, J.

Source of Support: NIH/NIDCR

Primary Place of Performance: Tufts University

Project/Proposal Start and End Date: 09/01/2020 - 08/31/2025

Total Award Amount (including Indirect Costs): \$3,220,452

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
3. [2023]	2.7 CM
4. [2024]	2.7 CM
5. [2025]	2.7 CM

Title: Therapeutic Potentials of a New Long Noncoding RNA in Diabetic Bone Wound Repair

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

Name of Individual: Jake Jinkun Chen
 Commons ID: jchen14

Major Goals: The major goals of this project are to use our newly discovered long noncoding RNA DBD (lncR-DBD) to target the major etiopathogenesis of diabetic bone disease as a novel, efficient and effective therapeutic remedy.

Status of Support: Active

Project Number: R01 DK131444

Name of PD/PI: Chen, J.

Source of Support: NIH

Primary Place of Performance: Tufts University

Project/Proposal Start and End Date: 8/16/2022 – 7/31/2027

Total Award Amount (including Indirect Costs): \$2,977,300

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
1. [2023]	1.8 CM
2. [2024]	1.8 CM
3. [2025]	1.8 CM
4. [2026]	1.8 CM
5. [2027]	1.8 CM

Title: Potentials of Epigenetic Molecules in Attenuating the Phenotypes of Periodontitis

Major Goals: The major goals of this project are to use an elegantly designed and precisely synthesized nanoparticle (NP) system that will carry both JQ1 and miR-335-5p and specifically release them into major target cells in periodontitis, resulting in a block of the pathogenesis and activation of endogenous regenerative factors.

Status of Support: Active

Project Number: 1 R01 DE032006

Name of PD/PI: Chen, J.

Source of Support: NIH/NIDCR

Primary Place of Performance: Tufts University

Project/Proposal Start and End Date: 08/01/2023 - 07/31/2028

Total Award Amount (including Indirect Costs): \$4,133,912

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
1. [2023]	2.4 CM
2. [2024]	2.4 CM
3. [2025]	2.4 CM
4. [2026]	2.4 CM
5. [2027]	2.4 CM

Title: Enhancement of Diabetic Fracture Healing using a Modified Messenger RNA Approach

Major Goals: The major goals of this project are to use our newly chemically modified messenger RNA (cmRNA) encoding adiponectin (APN) encapsulated in our novel lipid nanoparticle (LNP) to

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

Name of Individual: Jake Jinkun Chen

Commons ID: jchen14

promote the fracture healing, followed by single-cell RNA-sequencing to determine the underlying mechanisms.

Status of Support: Pending

Project Number: R01 AR082500

Name of PD/PI: Chen, J.

Source of Support: NIH/NIDCR

Primary Place of Performance: Tufts University

Project/Proposal Start and End Date: 12/01/2023 - 11/30/2028

Total Award Amount (including Indirect Costs): \$4,044,232

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
1. [2023]	2.4 CM
2. [2024]	2.4 CM
3. [2025]	2.4 CM
4. [2026]	2.4 CM
5. [2027]	2.4 CM

IN-KIND

None.

Overlap (summarized for each individual):

None.

I, Jake Chen, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

*Signature: _____

Date: 09/30/2025 _____

PHS OTHER SUPPORT**For All Application Types – DO NOT SUBMIT UNLESS REQUESTED**

Name of Individual: Soha Hassoun

Commons ID: SHASSOUN

Other Support – Project/Proposal**ACTIVE****Title:** Faster, More Efficient, and Hybrid Computation in Microbial Bioelectronic Systems

Major Goals: The goal of our project is to develop new concepts and methods that span biology, materials science, and microelectronics to enable efficient, fast and precise communication that uses hybrid analog-digital computing. Here we will develop optimal material interfaces to efficiently couple charge transfer across the abiotic-biotic interface, discover new biological knowledge and tools to rapidly encode and decode information in biofilms, and develop new hybrid analog-digital (aka mixed-signal) microelectronic devices and algorithms. This work will create bacterial microelectronics systems that integrate biofilm communities and electronic materials enabling the full capabilities of electrobiology to be realized.

Status of Support: Active**Project Number:** RT210041P1**Name of PD/PI:** Caroline Ajo-Franklin**Source of Support:** William Marsh Rice University (DOD originating sponsor)**Place of Performance:** Tufts University, Medford Campus**Start and End Date:** 10/01/2022 – 09/30/2025**Total Award Amount:** \$2,050,000

Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##.##)
1. 2023	1.0 SM
2. 2024	1.0 SM
3. 2025	1.0 SM
4. 2026	1.0 SM

Title: Deep learning models for metabolomics analysis

Major Goals: Untargeted metabolomics using tandem mass spectrometry (MS) have attained substantial success in the discovery of biomarkers and advancing our understanding of cellular metabolism. Despite this success, only a small fraction of measured spectra can currently be annotated. This bottleneck can be attributed to the limitations of current annotation tools that have not yet exploited advances in deep learning and available data modalities (spectra, peaks, molecules, and fragments). The goal of this application is to advance the interpretation of spectra collected through untargeted metabolomics using deep learning techniques.

Status of Support: Active**Project Number:** 5R35GM148219**Name of PD/PI:** Soha Hassoun**Source of Support:** NIH**Place of Performance:** Tufts University, Medford Campus**Start and End Date:** 04/01/2023 – 03/31/2028**Total Award Amount:** \$1,942,425

Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##.##)
1. 2023	2.0 SM + 1.81 AM
2. 2024	2.0 SM + 1.81 AM
3. 2025	2.0 SM + 1.38 AM

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 01/31/2026)

Name of Individual: Hassoun, Soha
Commons ID: SHASSOUN

Year (YYYY)	Person Months (##.##)
4. 2026	2.0 SM + 1.38 AM
5. 2027	2.0 SM + 1.38 AM

Title: Draper Labs Fellowship - Giselle Ventura

Major Goals: This grant supports one student from the DRAPER lab in pursuing a project related to Draper Labs in the area of statistical machine learning and biological data.

Status of Support: Active

Project Number: PO001-0001075119

Name of PD/PI: Soha Hassoun

Source of Support: The Charles Stark Draper Laboratory, Inc.

Place of Performance: The Charles Stark Draper Laboratory, Inc., Cambridge, MA

Start and End Date: 06/01/2025 – 05/31/2026

Total Award Amount: \$81,378

Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##.##)
1. 2025	0.01
2. 2026	0.01

Title: Computer and Information Science and Engineering Graduate Fellowships (CSGrad4US)

- Madeleine van Zuylen

Major Goals: This grant...

Status of Support: Active

Project Number: G-4A-152

Name of PD/PI: Soha Hassoun

Source of Support: Computing Research Association (CRA); NSF originating sponsor

Place of Performance: Tufts University, Medford Campus

Start and End Date: 09/01/2025 – 08/31/2030

Total Award Amount: \$159,000

Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##.##)
1. 2026	0.01 SM
2. 2027	0.01 SM
3. 2028	0.01 SM
4. 2029	0.01 SM
5. 2030	0.01 SM

PENDING

Title: MetaboCure: End-to-End Automated Approaches for Curating Metabolomic Data

Major Goals: We develop MetaboCure, an AI-driven multi-agent system designed to automate and dynamically refine metabolomics data curation using advanced large language models.

Status of Support: Pending

Project Number: PAR-25-131

Name of PD/PI: Soha Hassoun

Source of Support: NIH

Name of Individual: Hassoun, Soha
Commons ID: SHASSOUN

Place of Performance: Tufts University, Medford Campus

Start and End Date: 07/01/2026 – 06/30/2030

Total Award Amount: \$1,522,654

Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##.##)
1. 2026	0.9 SM
2. 2027	0.9 SM
3. 2028	0.9 SM
4. 2029	0.8 SM

Title: Transcriptomics CoPilot: Automating and Democratizing Transcriptomic Data Analysis through Conversational AI

Major Goals: The proposed project aims to develop a multi-agent, AI-powered assistant, the "Transcriptomics CoPilot," to expedite transcriptomics analysis using natural language queries.

Status of Support: Pending

Project Number: N/A

Name of PD/PI: Soha Hassoun

Source of Support: NIH

Place of Performance: Tufts University, Medford Campus

Start and End Date: 04/01/2026 – 03/31/2028

Total Award Amount: \$400,642

Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##.##)
1. 2026	0.5 SM
2. 2027	1.0 SM

Title: Development of an Oral Microbiome Foundation Model for Non-Invasive Alzheimer's Disease Diagnosis and Prognosis

Major Goals: We propose to develop an Oral Microbiome Foundation Model (OMFM) by pretraining a transformer encoder on large-scale human OM data. We will then fine-tune this OMFM on carefully curated AD-labeled cohorts to detect AD-specific microbial signatures. Further, as a pilot study, we clinically validate our oral microbiome-based tool for AD screening in dental patients.

Status of Support: Pending

Project Number: N/A

Name of PD/PI: Zoe Zhu

Source of Support: DOD

Place of Performance: Tufts University, Medford Campus

Start and End Date: 07/01/2026 – 06/30/2030

Total Award Amount: \$680,000

Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##.##)
1. 2026	0.5 SM
2. 2027	0.5 SM
3. 2028	0.5 SM

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 01/31/2026)

Name of Individual: Hassoun, Soha
 Commons ID: SHASSOUN

Year (YYYY)	Person Months (##.##)
4. 2029	0.5 SM

Title: Molecular generation for the annotation of metabolomics data

Major Goals: The primary goal of this project is de novo molecular generation to annotate mass spectra, enabling chemical structures to be proposed even when no database matches exist.

Status of Support: Pending

Project Number: N/A

Name of PD/PI: Soha Hassoun

Source of Support: NSF

Place of Performance: Tufts University, Medford Campus

Start and End Date: 06/01/2026 – 05/31/2029

Total Award Amount: \$1,203,112

Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##.##)
1. 2026	0.5 SM
2. 2027	0.5 SM
3. 2028	0.5 SM
4. 2029	0.5 SM

IN-KIND

Summary of In-Kind Contribution: N/A

Status of Support: N/A

Primary Place of Performance: N/A

Project/Proposal Start and End Date (MM/YYYY) (if available): N/A

Person Months (Calendar/Academic/Summer) per budget period

*Estimated Dollar Value of In-Kind Information: N/A

***Overlap** (summarized for each individual): No overlap between any projects.

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

***Signature:** Soha Hassoun Digitally signed by Soha Hassoun
 Date: 2025.10.08 10:32:22 -04'00'

Date: 10/8/2025

PHS398 OTHER SUPPORT

*Name of Individual: Xuesong He
 Commons ID: xuesonghe2

ACTIVE

*Title: **Impact of Saccharibacteria and their bacterial hosts in Periodontal and Inflammatory Diseases**

Major Goals: The major goal of this project is to study the pathogenic nature and eukaryotic host interaction of newly characterized ultra-small Saccharibacteria (TM7) in mouse periodontal disease model.

*Status of Support: Active

Project Number: 1R01DE031274-01

Name of PD/PI: Bor, Batbileg

*Source of Support: NIDCR

*Primary Place of Performance: ADA Forsyth Institute, Inc.

Project/Proposal Start and End Date: 01/2022 –12/2026

* Total Award Amount (including Indirect Costs): \$2,503,070

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
4. 2024 - 2025	0.60 calendar
5. 2025 - 2026	0.60 calendar

*Title: **Domestication and Characterization of TM7-The Most Elusive Oral Phylum**

Major Goals: The major goal of this project is to study the ecology, evolution and pathogenesis of the first human oral TM7/Saccharibacteria isolate and only member of the Candidate Phylum Radiation cultivated to date.

*Status of Support: Active

Project Number: 2R01 DE023810-12

Name of PD/PI: MPI He (Contact PI) and McLean

*Source of Support: NIDCR

*Primary Place of Performance: ADA Forsyth Institute, Inc.

Project/Proposal Start and End Date: 09/1/2024-08/30/2029

Total Award Amount (including Indirect Costs): \$2,831,366

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
12. 2024 - 2025	1.80 calendar
13. 2025 - 2026	1.80 calendar
14. 2026 - 2027	1.80 calendar
15. 2027 - 2028	1.80 calendar
16. 2028 - 2029	1.80 calendar

*Title: **Preventing dental caries through targeted treatment of acid-producing bacteria**

Major Goals: The proposed research focuses on prevention of dental caries through targeted treatment

of acid-producing bacteria(t-TAB). Its goal will be achieved by formulating and developing a series of pH-sensitive quaternary pyridinium salts and empowering the traditional, non-pH-sensitive chlorhexidine with t-TAB capability. The successful candidates capable of preventing acid-induced tooth damage through achieving a healthy microbial community and maintaining environmental pH above 5.5 will be identified using a multispecies biofilm model that simulates human oral microbial community and further assessed for caries prevention *in vitro* using a microbial-caries model on human enamel and *in vivo* through a well-developed mouse caries model.

*Status of Support: Active

Project Number: 5R01DE029479-02

Name of PD/PI: MPI Sun (Contact PI), He

*Source of Support: NIH/NIDCR

*Primary Place of Performance: ADA Forsyth Institute, Inc.

Project/Proposal Start and End Date: 09/01/2021 – 08/31/2026

* Total Award Amount (including Indirect Costs: \$3,746,349

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
4. 2024 - 2025	1.80 calendar
5. 2025 - 2026	2.16 calendar

***Title: Host tRNA-derived small RNAs (tsRNAs) mediate interactions between host and oral microbes**

Major Goals: The goal of this application is two-fold: (1) To achieve mechanistic understanding of the cross-kingdom trafficking of host-derived *F. nucleatum* (Fn)-targeting tsRNAs and their modulating effect on Fn growth during NOKSI-Fn interaction, through exosome tracking and in- depth dissection of the tsRNAs transporter and intracellular targets in Fn; (2) To expand our work to profile and compare salivary tsRNAs between healthy and periodontitis subjects, with a focus on demonstrating the broad implication of host-generated tsRNAs as a conserved mechanism to achieve host-microbial homeostasis.

*Status of Support: Active

Project Number: 1R01DE030943-01A1

Name of PD/PI: He, X.

*Source of Support: NIH/NIDCR

*Primary Place of Performance: ADA Forsyth Institute, Inc.

Project/Proposal Start and End Date: 02/2022 – 01/2027

Total Award Amount (including Indirect Costs): \$2,448,988

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
3. 2024 - 2025	1.80 calendar
4. 2025 - 2026	1.80 calendar
5. 2026 - 2027	1.80 calendar

***Title: Caries resistance mechanisms in high-risk Indigenous children**

Major Goals: This study investigates potential caries protective mechanisms in Indigenous children from Manitoba, focusing on the small percentage of caries free children with high load of caries causing bacteria of *Streptococcus mutans*. The Specific Aims are Aim 1. Test whether and how *Rothia* and/or other oral species may mitigate the cariogenic effects of acidogenic bacteria. Aim 2. Test whether and how tooth properties

modulate susceptibility to acid dissolution of enamel and dentin. Aim 3. Test how tooth substrate or saliva affect acidogenicity and spatial structure of biofilms.

Status of Support: Active

Project Number: 1 R01 DE032834-01

Name of PD/PI: MPI: F. Bidlack (Contact), W. Shi, J. Starr

*Source of Support: NIH/NIDCR

*Primary Place of Performance: ADA Forsyth Institute, Inc.

Project/Proposal Start and End Date: 04/2023 – 03/2028

* Total Award Amount (including Indirect Costs): \$3,813,490

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
2. 2024-2025	1.08 calendar
3. 2025-2026	1.20 calendar
4. 2026-2027	1.20 calendar
5. 2027-2028	1.20 calendar

*Title: **Gut Microbiome and Salivary Gland Function: Protective Actions & Key Players**

Major Goals: To determine the impact of gut microbiome on salivary gland function, with a particular focus on the previously unexplored, salivary gland protective gut bacteria and the players and mechanisms that mediate their actions in Sjögren's syndrome.

*Status of Support: Active

Project Number: 1 R56 AI181002-01A1

Name of PD/PI: Yu, Q.

*Source of Support: NIH / NIDCR

*Primary Place of Performance: ADA Forsyth Institute, Inc.

Project/Proposal Start and End Date: 01/2024 – 12/2025 (NCE)

* Total Award Amount (including Indirect Costs): \$359,999

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2024	1.40 calendar

*Title: **Design Microbiome-Based Therapies to Prevent and Ameliorate Posttraumatic Stress Disorder**

Major Goals: The overarching challenge is that we do not fully understand the PTSD-gut microbiome relationship and hence lack rational design of microbiome-based therapeutics for the prevention or amelioration of PTSD. Our central hypothesis is that microbiome-based interventions can prevent and ameliorate PTSD. Our overall objective is to initiate a unique project to evaluate the PTSD-gut microbiome relationship and develop synbiotics (a combination of prebiotics and probiotics) to prevent or ameliorate PTSD, leveraging a population-based cohort and an etiologically relevant mouse model.

Status of Support: Active

Project Number: TP220055

Name of PD/PI: Liu, Y, Koenan

*Source of Support: DoD

*Primary Place of Performance: Brigham & Women's Hospital, Inc.

Project/Proposal Start and End Date: 09/2023 – 08/2027

* Total Award Amount (including Indirect Costs): \$358,200 (Forsyth TC)

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months
2. 2024-2025	0.96 calendar
3. 2025-2026	0.96 calendar
4. 2026-2027	0.96 calendar
5. 2027-2028	0.96 calendar

*Title: **Virtual Twin-Powered Rapid Development of Bioactive Multifunctional Dental Restorative**

Major Goals: Aim 1 is to create a self-improving dental adhesive that enhances its bond with the tooth substrate by facilitating mineralization at the interface. Aim 2 focuses on crafting bioactive dental composites with self-healing and antimicrobial properties, achieved by integrating innovative nanofillers. Aim 3 is to produce CAD/CAM restoratives optimized for digital dentistry, offering robust, biocompatible materials with excellent aesthetics and bonding strength to teeth. Ultimately, our integration of artificial intelligence and a virtual lab with the material development process in the physical lab will revolutionize and individualize dental care. This platform will provide materials precisely tailored to meet diverse patient needs.

Status of Support: Active

Project Number: 1RM1DE034233-01

Name of MPIs: Sun, Bidlack, Mimomen

Source of Support: NIH/NIDCR

*Primary Place of Performance: ADA Forsyth Institute, Inc.

Project/Proposal Start and End Date: 09/18/2024 – 06/30/2029

*Total Award Amount (including Indirect Costs): \$ 6,342,218

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2024-2025	1.20 calendar
2. 2025-2026	1.20 calendar
3. 2026-2027	1.20 calendar
4. 2027-2028	1.20 calendar
5. 2028-2029	1.20 calendar

*Title: **Impact of Diabetes hyperglycemia on peri-implantitis**

Major Goals: The goals of this study are to 1) determine cellular inflammatory responses to peri-implant microbiota from normal and diabetic mice in vitro, 2) to identify and characterize peri-implant microbial changes under normal vs. DM conditions in vivo, and 3) to investigate the peri-implant inflammation and bone loss after exogenous microbial transfer in germ-free mice in vivo.

Status of Support: Active

Project Number: 1R21DE032156-01A1

Name of MPIs: Xiaozhe Han

Source of Support: NIH/NIDCR

*Primary Place of Performance: Nova Southeastern University

Project/Proposal Start and End Date: 09/2023 – 08/2025

*Total Award Amount (including Indirect Costs): \$ 53,000 (Forsyth TC)

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
2. 2024-2025	0.24 calendar

***Title: Mechanistic investigation of multispecies interactions in clear aligner induced periodontal inflammation**

***Major Goals:** *Fusobacterium nucleatum*, *Actinomyces spp.* and *Saccharibacteria* (TM7) are frequently reported to have significantly increased abundance in inflammatory diseases, including clear aligner-associated gingival inflammation. This study investigates their interaction in relationship with gingival inflammation. It will provide molecular insight into these tri-species interactions and lay the foundation for therapeutic interventions against gingival inflammation.

***Status of Support:** Pending

Project Number: 1R03DE034509 - 01A1

Name of PD/PI: Tingxi Wu

***Source of Support:** NIH / NIDCR

***Primary Place of Performance:** ADA Forsyth Institute, Inc.

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/15/2025 – 07/14/2027

*** Total Award Amount** (including Indirect Costs): \$398,000

*** Person Months** (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2025 - 2026	0.60 Calendar
2. 2026 - 2027	0.60 Calendar

PENDING

Title: Periodontitis Role in Inflammatory Bowel Disease

Major Goals: This proposal investigates the causal role of periodontitis, oral bacteria, and host factors in promoting intestinal inflammation in IBD using mechanistic studies in pre-clinical models.

Status of Support: Pending

Project Number: 1R01DK140281-01A1

Name of PD/PI: Thumbigere-Math V

***Source of Support:** NIH/NIDDK

***Primary Place of Performance:** University of Maryland Baltimore

Project/Proposal Start and End Date: 04/2025 – 03/2030

*** Total Award Amount** (including Indirect Costs): \$290,720 (Forsyth TC)

*** Person Months** (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months
1. 2025-2026	0.60 calendar
2. 2026-2027	0.60 calendar
3. 2027-2028	0.60 calendar
4. 2028-2029	0.60 calendar
5. 2029-2030	0.60 calendar

Title: Developing Chemically Modified Host-Derived Small RNAs to Target Oral Pathobionts

Major Goals: Test the hypothesis that strategic chemical modifications of *Fusobacterium nucleatum*-targeting host-derived tsRNAs will provide insights into nucleotide-specific interactions critical for bacterial protein targeting, uptake, and antimicrobial effects, thereby enabling the development of **first-of-its-kind** species-specific antimicrobials.

Status of Support: Pending

Project Number: R01

Name of PD/PI: Li, J.

*Source of Support: NIH/NIDCR

*Primary Place of Performance: University of Michigan

Project/Proposal Start and End Date: 12/2025 – 11/2030

* Total Award Amount (including Indirect Costs): \$1,842,730 (Forsyth TC)

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months
1. 2025-2026	1.80 calendar
2. 2026-2027	1.80 calendar
3. 2027-2028	1.80 calendar
4. 2028-2029	1.80 calendar
5. 2029-2030	1.80 calendar

Title: Underscoring human oral host-pathogen interactions and modulation in an immunocompetent in vitro model of early dysbiosis

*Major Goals: we aim to investigate the underlying immune-driven events that play a major role in the homeostatic balance between host and microbial communities, providing stability in healthy conditions, while contributing to immune-inflammatory progression in periodontal disease states. Leveraging our team's expertise in human in vitro modeling, microbiology, mucin biophysics, biogeography, and clinical translation, we aim to leverage a 3D human oral tissue model to provide a mechanistic framework of oral host-microbial interactions and modulation in early dysbiosis to support future therapeutic interventions

*Status of Support: Pending

Project Number: 1102

Name of PD/PI: Ghezzi, CE

*Source of Support: NIH / NIDCR

*Primary Place of Performance: University of Massachusetts, Lowell

Project/Proposal Start and End Date: 07/2025 – 06/2030

*Total Award Amount (including Indirect Costs): \$883,972 (Forsyth TC)

*Person Months (Calendar/Academic/Summer) per budget period.


Year (YYYY)	Person Months (##.##)
1. 2025 – 2026	0.60 calendar
2. 2026 – 2027	0.60 calendar
3. 2027 – 2028	0.60 calendar
4. 2028 – 2029	0.60 calendar
5. 2029 – 2030	0.60 calendar

IN-KIND

None

***Overlap** (summarized for each individual): No scientific or effort overlap at this time. Should pending projects be awarded prior to the completion of Dr. He's active commitments his effort will be adjusted within sponsor acceptable parameters so as not to exceed 12 calendar months effort in total.

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Signature:  _____
Xuesong He (Aug 7, 2025 10:19:30 EDT)

Date: Aug 7, 2025

He_Other Support_08.07.25

Final Audit Report

2025-08-07

Created:	2025-08-07
By:	Abigail Oldham (aoldham@forsyth.org)
Status:	Signed
Transaction ID:	CBJCHBCAABAA3zJfpQ3FpCGRNHptYSBk0AqByNoP2nHA

"He_Other Support_08.07.25" History



Document created by Abigail Oldham (aoldham@forsyth.org)

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Document e-signed by Xuesong He (xhe@forsyth.org)

Signature Date: 2025-08-07 - 2:19:30 PM GMT - Time Source: server



Agreement completed.

2025-08-07 - 2:19:30 PM GMT

**Adobe Acrobat Sign**

PHS OTHER SUPPORT

*Name of Individual: FLAVIA R TELES
 Commons ID: TELES_FLAVIA

Other Support – Project/Proposal**ACTIVE**

*Title: Defining Dysbiosis and Mechanisms of Periodontitis Progression and Stability

*Major Goals: Determining microbial, immunological and metabolomic changes that lead of periodontitis progression or periodontal stability, which would better inform clinicians regarding diagnosis, prevention, treatment and monitoring of periodontitis patients.

*Status of Support: Pending

Project Number: R01-DE-033033-01A1

Name of PD/PI: FLAVIA R TELES

*Source of Support: NATIONAL INSTITUTES OF HEALTH/NATIONAL INSTITUTE OF DENTAL & CRANIOFACIAL RESEARCH

*Primary Place of Performance: University of Pennsylvania

Project/Proposal Start and End Date: (MM/YYYY) (if available): 05/2024 - 04/2029

*Total Award Amount (including Indirect Costs): \$3,026,992

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2025	2.7 Calendar
2. 2026	2.7 Calendar
3. 2027	2.7 Calendar
4. 2028	2.7 Calendar
5. 2029	2.7 Calendar

*Title: The Oro-Respiratory-Gut Virome Axis Over Space and Time

*Major Goals: To characterize the human virome and understand its nature over space and time in priority niches identified by the NIH Human Virome Initiative.

*Status of Support: Active

Project Number: U54-AG-089323

Name of PD/PI: Ronald G Collman and Frederic D Bushman

*Source of Support: NATIONAL INSTITUTES OF HEALTH

*Primary Place of Performance: University of Pennsylvania

Project/Proposal Start and End Date: (MM/YYYY) (if available): 02/2025 - 01/2030

*Total Award Amount (including Indirect Costs): \$20,213,896

*Person Months (Calendar/Academic/Summer) per budget period.

Name of Individual: FLAVIA R TELES

Commons ID: TELES_FLAVIA

Year (YYYY)	Person Months (##.##)
1. 2025	1.8 Calendar
2. 2026	1.8 Calendar
3. 2027	1.8 Calendar
4. 2028	1.8 Calendar
5. 2029	1.8 Calendar

PENDING

Title: Sex-dimorphism in periodontitis etiology: Does it matter?

Major Goals: To investigate the role of sexual dimorphism in periodontitis, an inflammatory gum disease that affects males more frequently than females.

*Status of Support: Pending

Project Number: NA

Name of PI: Effie Ioannidou

*Source of Support: NATIONAL INSTITUTES OF HEALTH/NATIONAL INSTITUTE OF DENTAL & CRANIOFACIAL RESEARCH

*Primary Place of Performance: University of Pennsylvania

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/2025 - 06/2030

*Total Award Amount (including Indirect Costs): \$96,245

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2026	0.6 Calendar
2. 2027	0.6 Calendar
3. 2028	0.6 Calendar
4. 2029	0.6 Calendar
5. 2030	0.6 Calendar

*Title: Tracking Host-Microbiome Interactions Over Time in Individual Periodontal Patients

*Major Goals: (a) develop profile-tree approaches to study the patterns of host-microbial cross-talk for each patient; (b) analyze our densely sampled longitudinal data to address various biological questions, including causal factors for disease progression and condition; (c) develop a library of software with our new approaches

*Status of Support: Pending

Project Number: NA

Name of MPI: SAYAKA MIURA

*Source of Support: NATIONAL INSTITUTES OF HEALTH

Name of Individual: FLAVIA R TELES

Commons ID: TELES_FLAVIA

*Primary Place of Performance: University of Pennsylvania

Project/Proposal Start and End Date: (MM/YYYY) (if available): 08/2025 - 07/2027

*Total Award Amount (including Indirect Costs): \$73,600

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2026	1.2 Calendar
2. 2027	1.2 Calendar

IN-KIND

NONE

***Overlap (summarized for each individual):**

NONE

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

*Signature: _____

Date: _____

Flavia Teles

Digitally signed by Flavia

Teles

Date: 2025.03.10 16:34:19

-04'00'

*Name of Individual: Bonham, Kevin
Commons ID: kbonham

Project/Proposal

*Title: NONE

*Major Goals:

*Status of Support:

Project Number:

Name of PD/PI:

*Source of Support:

*Primary Place of Performance:

Project/Proposal Start and End Date: (MM/YYYY) (if available):

* Total Award Amount (including Indirect Costs):

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. [enter year 1]	
2. [enter year 2]	
3. [enter year 3]	
4. [enter year 4]	
5. [enter year 5]	

PENDING

*Title: Stress adaptation in the infant-associated microbe Bifidobacterium infantis

*Major Goals: The goal of the project are to test the molecular responses to changes in osmotic stress and perform genomic and genetic investigation of high-salt response.

*Status of Support: Applied

Project Number:

Name of PD/PI: Kevin Bonham

*Source of Support: Charles C. Hood Foundation

*Primary Place of Performance: Tufts Medical Center

Project/Proposal Start and End Date: (MM/YYYY) (if available): 1/1/2026 – 12/31/2027

* Total Award Amount (including Indirect Costs): \$200,000

* Person Months (Calendar/Academic/Summer) per budget period. 2.4 Person Months

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 01/31/2026)

Name of Individual: Bonham, Kevin
Commons ID: kbongham

*Title: Salivary and Microbiome Biomarkers to Predict Outcomes in Opioid-exposed Infants

*Major Goals: The goal of the project is to identify the pro-inflammatory effects of the maternal opioid use on infant gut microbiome and NAS-related feeding dysregulation and morbidities in the first 6 months of age. Develop biomarker-based predictive models of NAS-related feeding dysregulation and other associated morbidities.

*Status of Support: Applied

Project Number:

Name of PD/PI: Elizabeth Yen

*Source of Support: NIH

*Primary Place of Performance: Tufts Medical Center

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/1/2026 – 03/31/2028

* Total Award Amount (including Indirect Costs): \$489,500

* Person Months (Calendar/Academic/Summer) per budget period. 2.4 Person Months

IN-KIND

N/A


***Overlap** (summarized for each individual):

N/A

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 01/31/2026)

Name of Individual: Bonham, Kevin
Commons ID: kbongham

*Signature: 

Date: 10/06/2025

*Name of Individual: Papapanou, Panos N.
Commons ID: PapapanouP

Other Support – Project/Proposal

ACTIVE

*Title: A Longitudinal Study of Periodontal Infections and Alzheimer's Disease: The WHICAP Ancillary Study of Oral Health

Major Goals: The main goal of this study is to further test the hypothesis that periodontitis is an unrecognized risk factor for incident cognitive impairment among the participants in the WHICAP Ancillary Study of Oral Health (R56 DE022568).

*Status of Support: Active

Project Number: 1R01AG076015-01

Name of PD/PI: Noble / Papapanou

*Source of Support: National Institute on Aging

*Primary Place of Performance: Columbia University Health Sciences

Project/Proposal Start and End Date: 09/30/2021 – 06/30/2026

* Total Award Amount (including Indirect Costs): \$3,970,497

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2025	2.40 CM
2. 2026	2.40 CM

PENDING

*Title: Intensive Periodontal Treatment to Improve Oral and Cardiometabolic Health in Patients with Prediabetes

Major Goals: We propose use a novel cohort multiple randomized controlled trial design to test whether comprehensive periodontal health care improves dysglycemia and prevents development of incident type 2 diabetes in persons with prediabetes.

*Status of Support: Pending

Project Number: Pending

Name of PD/PI: Ryan Demmer, Mayo University

*Source of Support: National Institutes of Health

*Primary Place of Performance: Columbia University Health Sciences

Project/Proposal Start and End Date: 04/01/2025 – 03/31/2030

* Total Award Amount (including Indirect Costs): \$413,807

* Person Months (Calendar/Academic/Summer) per budget period.

Name of Individual: Papapanou, Panos N.

Commons ID: PapapanouP

Year (YYYY)	Person Months (##.##)
1. 2026	2.10 CM
2. 2027	2.10 CM
3. 2028	2.10 CM
4. 2029	2.10 CM
5. 2030	2.10 CM

*Title: Comprehensive Periodontal Therapy to Improve Oral and Cardiometabolic Health in Prediabetes

Major Goals: We propose use a novel cohort multiple randomized controlled trial design to test whether comprehensive periodontal health care improves dysglycemia and prevents development of incident type 2 diabetes in persons with prediabetes.

*Status of Support: Pending

Project Number: Pending

Name of PD/PI: Ryan Demmer, Mayo Clinic

*Source of Support: National Institutes of Health

*Primary Place of Performance: Columbia University Health Sciences

Project/Proposal Start and End Date: 07/01/2025 – 06/30/2031

* Total Award Amount (including Indirect Costs): \$496,569

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2026	2.90 CM
2. 2027	2.90 CM
3. 2028	2.90 CM
4. 2029	2.90 CM
5. 2030	2.90 CM
6. 2031	2.90 CM

*Title: Advancing the Genomics Knowledge Base for Oral Diseases

Major Goals: The consortium will meta-analyze gene polymorphism data associated with oral phenotypes of dental caries and periodontitis that are derived exclusively from intra-oral clinical examinations. No self-reported phenotypes will be analyzed.

*Status of Support: Pending

Project Number: Pending

Name of PD/PI: John R. Shaffer, University of Pittsburgh

*Source of Support: National Institutes of Health

*Primary Place of Performance: Columbia University Health Sciences

Project/Proposal Start and End Date: 07/01/2025 – 06/30/2028

Name of Individual: Papapanou, Panos N.

Commons ID: PapapanouP

* Total Award Amount (including Indirect Costs): \$190,158

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2026	0.60 CM
2. 2027	0.60 CM
3. 2028	0.60 CM

*Title: The Oral Microbiome and Impaired Glucose Regulation

Major Goals: This renewal will examine immune-system mediated mechanisms underlying these relationships via the use of SomaScan, which will enable a test of specific concepts related to complement system disruption while also continuing to assess more classical inflammatory mediators (CRP, IL-6, and TNF-alpha).

*Status of Support: Pending

Project Number: Pending

Name of PD/PI: Demmer, Ryan, Mayo Clinic

*Source of Support: National Institutes of Health

*Primary Place of Performance: Columbia University Health Sciences

Project/Proposal Start and End Date: 09/01/2024 – 08/31/2029

* Total Award Amount (including Indirect Costs): \$117,374

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2025	0.20 CM
2. 2026	0.22 CM
3. 2027	0.24 CM
4. 2028	0.24 CM
5. 2029	0.30 CM

IN-KIND

NONE

***Overlap** (summarized for each individual):

NONE

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

Name of Individual: Papapanou, Panos N.

Commons ID: PapapanouP



*Signature: _____

Date: 3/12/2025

**For New and Renewal Applications – DO NOT SUBMIT UNLESS REQUESTED
PHS 398 OTHER SUPPORT**

There is no "form page" for reporting Other Support. Information on Other Support should be provided in the format shown below.

*Name of Individual: NOBLE, JAMES
Commons ID: jn2054

Other Support – Project/Proposal

*Title: Center of Excellence in Alzheimer Disease at Columbia University Medical Center/NYPH

Major Goals: The overarching central goal of the Center of Excellence in Alzheimer Disease at Columbia University Medical Center/NYPH is to strengthen the provision of integrated, comprehensive, specialty diagnosis, treatment and support for underserved New York City residents and their caregivers who have Alzheimer disease and related dementias. Broadly, there are two principal component goals: (a) education of practicing, and in-training, health care providers, patients, families and caregivers; and (b) specialty dementia care with diagnostic evaluations, treatment, coordinated management and support services.

Project Number: DOH01-C37268GG-3450000

Name of PD/PI: Honig

*Source of Support: New York State Department of Health

Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/2022 - 05/2027

* Total Award Amount (including Indirect Costs): \$2,663,333.00

*Title: Alzheimer's Disease Research Center

Major Goals: The general objective of the ADRC at Columbia University is to tackle the main barriers in the field of Alzheimer's disease and related disorders, which include early detection, prevention and intervention.

Project Number: P30AG066462

Name of PD/PI: Small

*Source of Support: NIH/NIA

Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/2020-04/2025

* Total Award Amount (including Indirect Costs): \$15,735,779

*Title: A Longitudinal Study of Periodontal Infections and Alzheimer's Disease: The WHICAP Ancillary Study of Oral Health

Major Goals: *The study aims to assess approximately 750 participants of the Ancillary Study of Oral Health who are still followed up to (i) a repeat periodontal examination, encompassing clinical and microbiological measures of periodontitis (including 16S rRNA and metagenomic sequencing of periodontal plaque samples), and (ii) an assessment of peripheral monocyte profiles and levels of systemic inflammation, to examine the effect of periodontitis on incident ADRD over an 8-year period, and to identify mechanistic associations between the two conditions.*

Project Number: R01AG076015

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 1/31/2026)

Name of Individual: NOBLE, JAMES
Commons ID: jn2054

Name of PD/PI: Noble

*Source of Support: NIH/NIA

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/2021 - 06/2026

* Total Award Amount (including Indirect Costs): \$3,970,497

*Title: National Alzheimer's Coordinating Center

Major Goals: The National Alzheimer's Coordinating Center (NACC) is a key program for integrating the efforts and data collection of the twenty-eight National Institutes on Aging (NIA)-funded Alzheimer Disease Centers (ADC). As part of this group of 32 funded ADCs, the Columbia ADC makes certain that it collects all core NACC required elements of the Uniform Data Set (UDS), and that it databases this data, and transmits it to NACC.

Project Number: U24AG072122

Name of PD/PI: Kukull

*Source of Support: University of Washington

*Primary Place of Performance: Columbia University Irving Medical Center

Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/2021 - 05/2026

* Total Award Amount (including Indirect Costs): \$133,900

*Title: Longitudinal imaging of microglial activation in different clinical variants of Alzheimer's disease

Major Goals: The objective is to determine how microglial activation, measured with PET imaging, is spatially and temporally related to tau pathology and neurodegeneration in AD.

Project Number: R01AG063888

Name of PD/PI: Small

*Source of Support: NIH/NIA

Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/2020-05/2025

* Total Award Amount (including Indirect Costs): \$4,775,355

*Title: Alzheimer's Disease and Alzheimer's Disease Related Dementias in Prediabetes and Type 2 Diabetes: The Diabetes Prevention Program Outcomes Study AD/ADRD Project.

*Major Goals: To carry out four research projects to elucidate the nature and predictors of cognitive impairment in persons with pre-diabetes and type 2 diabetes.

Project Number: 1U19AG078558-01

Name of PD/PI: Luchsinger [Contact], Temprosa, Nathan

*Source of Support: NIH/NIA

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/2022 - 08/2027

* Total Award Amount (including Indirect Costs): \$72,608,506.00

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 1/31/2026)

Name of Individual: NOBLE, JAMES
Commons ID: jn2054

*Title: Early Age-Related Hearing Loss Investigation (EARHLI): A Randomized Controlled Trial to Assess Mechanisms Linking Early Age-Related Hearing Loss and Alzheimer's Disease and Related Dementias

*Major Goals: This project aims to evaluate if hearing interventions can prevent or reduce cognitive decline in people with early-stage hearing loss at-risk for dementia. If successful, this application could yield a promising new non-pharmacologic intervention for a major Alzheimer's disease (AD) risk factor.

Project Number: R01AG075083-01A1

Name of PD/PI: Golub, J.

*Source of Support: NIA

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/2022 – 08/2027

* Total Award Amount (including Indirect Costs): \$5,896,247

*Title: Statistical Framework for Unraveling Age-Dependent Genetic Landscape in Age-Related Diseases and Multimorbidity: Harnessing Large-Scale EHR and DNA-Biobank

*Major Goals: This project aims to build a more comprehensive understanding of the genetic architecture of Alzheimer's Disease and related dementias, taking into account the complexities of age-related changes and diverse phenotypes. By leveraging large-scale biobanks, electronic medical records, and innovative machine learning techniques, we hope to uncover crucial insights that could lead to better understanding of disease progression, improved prevention strategies and novel therapeutic targets, representing a significant advancement in dementia research.

Project Number: 1R01AG087496-01

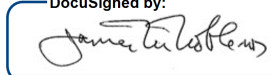
Name of PD/PI: Wei

*Source of Support: NIH/NIA

Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/2024-02/2029

* Total Award Amount (including Indirect Costs): \$3,638,845

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

DocuSigned by:

*Signature: _____
8CB12F91323843B
3/12/2025 | 11:34:54 PDT
Date: _____

PHS OTHER SUPPORT
For All Application Types – DO NOT SUBMIT UNLESS REQUESTED

There is no "form page" for reporting Other Support. Information on Other Support should be provided in the format shown below.

*Name of Individual: Athanasios Zavras
 Commons ID: TZAVRAS

Other Support – Project/Proposal

*Title: Transitioning Into a New System That Can (TRANSTC): Improving the Oral Health Related Quality of Life for People With Disabilities.

*Major Goals: The aim of the project is to pilot test novel delivery model of care for patients with intellectual and developmental disabilities that is based on WHO-ICD, teledentistry, case coordination and traveling hygienists to integrate care.

*Status of Support: Active

Project Number:

Name of PD/PI: Athanasios Zavras

*Source of Support: CareQuest Foundation

*Primary Place of Performance: Tufts University

Project/Proposal Start and End Date: (MM/YYYY) (if available): 2023-March 2025

* Total Award Amount (including Indirect Costs): 175,000

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	1.2CM
2. 2024	1.2CM
3. 2025	1.2CM

*Title: Commonwealth of Massachusetts

*Major Goals: Providing technical expertise to the State to develop an incubator for tele-dentistry and mobile dentistry in an effort to expand access to dental services and to improve oral health outcomes.

*Status of Support: Active

Project Number:

Name of PD/PI: Athanasios Zavras

*Source of Support: Massachusetts DPH

*Primary Place of Performance: Tufts University

Project/Proposal Start and End Date: (MM/YYYY) (if available): 2023-August 2025

Name of Individual:
Commons ID:

* Total Award Amount (including Indirect Costs): 134,939

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.6CM
2. 2024	0.6CM
3. 2025	0.6CM

IN-KIND

*Summary of In-Kind Contribution: Co-investigator and member of advisory committee on Dr. Maria Dolce's HRSA Training Grant. The aim of the project is to develop resources and to re-organize the care at Tufts Dental School in order to improve the care of patients with complex medical issues and disabilities.

*Status of Support: Active

*Primary Place of Performance: Tufts University

Project/Proposal Start and End Date (MM/YYYY) (if available): 2023-2028

*Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##.##)
1. 2023	0.6CM
2. 2024	0.6CM
3. 2025	0.6CM

*Estimated Dollar Value of In-Kind Information:

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

*Signature:



Date: _03/12/2025

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: C1F5LNUF7W86

Budget Type*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2026 End Date*: 06-30-2027 Budget Period: 1

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Zoe		Zhu		PD/PI		9.0			70,774.50	20,736.93	91,511.43
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	91,511.43

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							91,511.43

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: C1F5LNUF7W86
Budget Type*: ☒ Project ☐ Subaward/Consortium
Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2026 End Date*: 06-30-2027 Budget Period: 1

C. Equipment Description	
List items and dollar amount for each item exceeding \$5,000	
Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	
Total Equipment	0.00
Additional Equipment: File Name:	

D. Travel	Funds Requested (\$)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	11,736.00
2. Foreign Travel Costs	
Total Travel Cost	11,736.00

E. Participant/Trainee Support Costs	Funds Requested (\$)*
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	Total Participant Trainee Support Costs
	0.00

RESEARCH & RELATED Budget (C-E) (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: C1F5LNUF7W86
Budget Type*: ☒ Project ☐ Subaward/Consortium
Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2026 End Date*: 06-30-2027 Budget Period: 1

F. Other Direct Costs		Funds Requested (\$)*
1. Materials and Supplies		12,100.00
2. Publication Costs		
3. Consultant Services		1,000.00
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
Total Other Direct Costs		13,100.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	116,347.43

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC	8.0	116,347.43	9,307.79
Total Indirect Costs			9,307.79
Cognizant Federal Agency		DHHS, Darryl W. Mayes, 212-264-2069	
(Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	125,655.22

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	125,655.22

L. Budget Justification*	File Name: Budget_Justification.pdf
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: C1F5LNUF7W86
Budget Type*: ☒ Project ☐ Subaward/Consortium
Enter name of Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2027 End Date*: 06-30-2028 Budget Period: 2

A. Senior/Key Person													
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*	
1.	Zoe		Zhu		PD/PI		9.0			70,774.50	20,736.93	91,511.43	
Total Funds Requested for all Senior Key Persons in the attached file													
Additional Senior Key Persons:			File Name:								Total Senior/Key Person		91,511.43

B. Other Personnel									
Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*		
	Post Doctoral Associates								
	Graduate Students								
	Undergraduate Students								
	Secretarial/Clerical								
1	Other	0.6			2,250.00	659.25	2,909.25		
1	Total Number Other Personnel					Total Other Personnel		2,909.25	
								Total Salary, Wages and Fringe Benefits (A+B)	94,420.68

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: C1F5LNUF7W86
Budget Type*: ☒ Project ☐ Subaward/Consortium
Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2027 End Date*: 06-30-2028 Budget Period: 2

C. Equipment Description	
List items and dollar amount for each item exceeding \$5,000	
Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	
Total Equipment	0.00
Additional Equipment: File Name:	

D. Travel	Funds Requested (\$)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	550.00
2. Foreign Travel Costs	
Total Travel Cost	550.00

E. Participant/Trainee Support Costs	Funds Requested (\$)*
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	Total Participant Trainee Support Costs
	0.00

RESEARCH & RELATED Budget (C-E) (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: C1F5LNUF7W86

Budget Type*: ☒ Project ☐ Subaward/Consortium

Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2027

End Date*: 06-30-2028

Budget Period: 2

F. Other Direct Costs		Funds Requested (\$)*
1. Materials and Supplies		16,730.00
2. Publication Costs		2,000.00
3. Consultant Services		2,500.00
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Volunteer Subject Payments		2,200.00
9. Patient Recruitment		700.00
Total Other Direct Costs		24,130.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	119,100.68

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC	8.0	119,100.68	9,528.05
Total Indirect Costs			9,528.05
Cognizant Federal Agency	DHHS, Darryl W. Mayes, 212-264-2069		
(Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	128,628.73

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	128,628.73

L. Budget Justification*	File Name: Budget_Justification.pdf
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

UEI*: C1F5LNUF7W86
Budget Type*: ☒ Project ☐ Subaward/Consortium
Enter name of Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2028 End Date*: 06-30-2029 Budget Period: 3

A. Senior/Key Person													
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*	
1.	Zoe		Zhu		PD/PI		9.0			70,774.50	20,736.93	91,511.43	
Total Funds Requested for all Senior Key Persons in the attached file													
Additional Senior Key Persons:			File Name:								Total Senior/Key Person		91,511.43

B. Other Personnel									
Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*		
	Post Doctoral Associates								
	Graduate Students								
	Undergraduate Students								
	Secretarial/Clerical								
1	Other	0.6			2,250.00	659.25	2,909.25		
1	Total Number Other Personnel					Total Other Personnel		2,909.25	
								Total Salary, Wages and Fringe Benefits (A+B)	94,420.68

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

UEI*: C1F5LNUF7W86
Budget Type*: ☒ Project ☐ Subaward/Consortium
Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2028 End Date*: 06-30-2029 Budget Period: 3

C. Equipment Description	
List items and dollar amount for each item exceeding \$5,000	
Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	
Total Equipment	0.00
Additional Equipment: File Name:	

D. Travel	Funds Requested (\$)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	
Total Travel Cost	2,000.00

E. Participant/Trainee Support Costs	Funds Requested (\$)*
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	Total Participant Trainee Support Costs
	0.00

RESEARCH & RELATED Budget (C-E) (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI*: C1F5LNUF7W86

Budget Type*: ☒ Project ☐ Subaward/Consortium

Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2028

End Date*: 06-30-2029

Budget Period: 3

F. Other Direct Costs		Funds Requested (\$)*
1. Materials and Supplies		16,744.00
2. Publication Costs		2,000.00
3. Consultant Services		2,500.00
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Volunteer Subject Payments		1,000.00
9. Patient Recruitment		700.00
Total Other Direct Costs		22,944.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	119,364.68

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC	8.0	119,364.68	9,549.17
Total Indirect Costs			9,549.17
Cognizant Federal Agency		DHHS, Darryl W. Mayes, 212-264-2069	
(Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	128,913.85

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	128,913.85

L. Budget Justification*	File Name: Budget_Justification.pdf
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

UEI*: C1F5LNUF7W86
Budget Type*: ☒ Project ☐ Subaward/Consortium
Enter name of Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2029 End Date*: 06-30-2030 Budget Period: 4

A. Senior/Key Person													
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*	
1.	Zoe		Zhu		PD/PI		9.0			70,774.50	20,736.93	91,511.43	
Total Funds Requested for all Senior Key Persons in the attached file													
Additional Senior Key Persons:			File Name:								Total Senior/Key Person		91,511.43

B. Other Personnel							
Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Other	0.6			2,250.00	659.25	2,909.25
1	Total Number Other Personnel				Total Other Personnel		2,909.25
Total Salary, Wages and Fringe Benefits (A+B)							94,420.68

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

UEI*: C1F5LNUF7W86
Budget Type*: ☒ Project ☐ Subaward/Consortium
Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2029 End Date*: 06-30-2030 Budget Period: 4

C. Equipment Description	
List items and dollar amount for each item exceeding \$5,000	
Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	
Total Equipment	0.00
Additional Equipment: File Name:	

D. Travel	Funds Requested (\$)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	3,666.00
2. Foreign Travel Costs	
Total Travel Cost	3,666.00

E. Participant/Trainee Support Costs	Funds Requested (\$)*
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	Total Participant Trainee Support Costs
	0.00

RESEARCH & RELATED Budget (C-E) (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

UEI*: C1F5LNUF7W86

Budget Type*: ☒ Project ☐ Subaward/Consortium

Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2029

End Date*: 06-30-2030

Budget Period: 4

F. Other Direct Costs		Funds Requested (\$)*
1. Materials and Supplies		16,744.00
2. Publication Costs		2,000.00
3. Consultant Services		1,000.00
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Volunteer Subject Payments		1,000.00
9. Patient Recruitment		500.00
Total Other Direct Costs		21,244.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	119,330.68

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC	8.0	119,330.68	9,546.45
Total Indirect Costs			9,546.45
Cognizant Federal Agency	DHHS, Darryl W. Mayes, 212-264-2069		
(Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	128,877.13

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	128,877.13

L. Budget Justification*	File Name: Budget_Justification.pdf
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

UEI*: C1F5LNUF7W86
Budget Type*: ☒ Project ☐ Subaward/Consortium
Enter name of Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2030 End Date*: 06-30-2031 Budget Period: 5

A. Senior/Key Person													
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*	
1.	Zoe		Zhu		PD/PI		9.0			70,774.50	20,736.93	91,511.43	
Total Funds Requested for all Senior Key Persons in the attached file													
Additional Senior Key Persons:			File Name:								Total Senior/Key Person		91,511.43

B. Other Personnel							
Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Other	0.6			2,250.00	659.25	2,909.25
1	Total Number Other Personnel					Total Other Personnel	2,909.25
Total Salary, Wages and Fringe Benefits (A+B)							94,420.68

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

UEI*: C1F5LNUF7W86
Budget Type*: ☒ Project ☐ Subaward/Consortium
Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2030 End Date*: 06-30-2031 Budget Period: 5

C. Equipment Description	
List items and dollar amount for each item exceeding \$5,000	
Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	
Total Equipment	0.00
Additional Equipment: File Name:	

D. Travel	Funds Requested (\$)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	
Total Travel Cost	2,000.00

E. Participant/Trainee Support Costs	Funds Requested (\$)*
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	Total Participant Trainee Support Costs
	0.00

RESEARCH & RELATED Budget (C-E) (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

UEI*: C1F5LNUF7W86

Budget Type*: ☒ Project ☐ Subaward/Consortium

Organization: TUFTS UNIVERSITY BOSTON

Start Date*: 07-01-2030

End Date*: 06-30-2031

Budget Period: 5

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	16,744.00
2. Publication Costs	2,000.00
3. Consultant Services	2,500.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Volunteer Subject Payments	1,000.00
9. Patient Recruitment	700.00
Total Other Direct Costs	22,944.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	119,364.68

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC	8.0	119,364.68	9,549.17
Total Indirect Costs			9,549.17
Cognizant Federal Agency	DHHS, Darryl W. Mayes, 212-264-2069		
(Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	128,913.85

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	128,913.85

L. Budget Justification*	File Name: Budget_Justification.pdf
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION

A. Personnel

Zoe Zhu, D.D.S, PhD., Principal Investigator (9 CM). Dr. Zhu is an Assistant Professor in the Dept. Of Periodontology at Tufts University School of Dental Medicine and is committed to devoting 75% of her effort to research activities and career development trainings proposed in this K08 application. She will perform the majority of the experiments in the proposal, in particular those involving data processing, deep learning model design and training, clinical exam and sample collection, processing for sequencing.

Research Coordinator TBD (0.6 CM YR2-5). The research coordinator will be responsible for recruiting patients and assisting with sample collection, data logging, patient reimbursement payments and organization of the clinical portion of the project.

In accordance with NIH definitions, the primary mentors (Dr. Jake Chen and Dr. Soha Hassoun), and the co-mentors (Drs. He, Teles, Bonham, Papapanou, Noble, Zavras) are considered as Other Significant Contributors to the K08 candidate and provide mentorship to the candidate on an as needed basis, in-kind, and at no cost to the grant award.

Fringe Benefits: The provision fringe benefits rate at Tufts University for FY26 and beyond of 28.5% has been applied for faculty and staff. Base salaries listed are for the current University fiscal year with a full-time (100%) appointment.

B. Research Support and Other Expenses Justification

Supplies: (\$79,062)

The amount requested for materials and supplies will cover 1) the cost of high-performance hardware, cloud computing services, 2) Regents and Kit for DNA extraction, 16s rRNA sequencing, 3) disposable dental exam and other needed protective equipment.

Y1	Y2	Y3	Y4	Y5
\$12,100	\$16,730	\$16,744	\$16,744	\$16,744

Educational and Training Expenses: (\$9,952)

Align with the primary training goals, the candidate requests this budget for taking formal courses, workshops, and short-term lab visits.

Year 1: 1) Advanced Bacterial in Genomics Course – Cold Spring Harbor Laboratory (<https://meetings.cshl.edu/courses.aspx?course=C-ABG>) (\$6,070), 2) CTS 500 study design (\$1,666), and 3) A visit to Columbia University for two weeks (hosted by Dr. Papapanou and Dr. Noble), to get hands on experience on oral health and AD clinical study through their ongoing project “Longitudinal Study of Periodontal Infections and Alzheimer’s Disease” (R01 AG076015). – Cost listed in travel.

Year 2: Microbial Genomics & Metagenomics Workshops - Lawrence Berkeley National Lab. (<https://mgm.jgi.doe.gov/>) (\$550)

Year 5: CTS 538 for grant writing. (\$1,666)

Y1	Y2	Y3	Y4	Y5
\$7,736	\$550	\$0	\$1,666	\$0

Participant Recruitment and Compensation Cost: (\$5,200)

The clinical pilot study in Aim3 requests this budget for advertising recruitment and the compensation of 80 participants in total for Year 2-5.

Y1	Y2	Y3	Y4	Y5
\$0	\$22,00	\$1,000	\$1,000	\$1,000

Consultancy: (\$9,500)

Dr. George Chen will be the consultant on oral microbiome 16s rRNA sequencing and data handling in Year 1-5. Dr. Meghan Short and the Tufts CTSI BERD will provide the statistical support for this study in Year 2,3 and 5.

Y1	Y2	Y3	Y4	Y5
\$1,000	\$2,500	\$2,500	\$1,000	\$2,500

Travel: (\$10,000)

A visit to Columbia University for two weeks (hosted by Dr. Papapanou and Dr. Noble) in Year 1. Travel for IADR annual meeting at \$2,000/visit in Year 3-5.

Y1	Y2	Y3	Y4	Y5
\$4,000	\$0	\$2,000	\$2,000	\$2,000

Publication: (\$8,000)

A total of seven papers is expected to be completed during the award period. We are requesting \$2,000/yr for publication costs in Year 2-5.

Y1	Y2	Y3	Y4	Y5
\$0	\$2,000	\$2,000	\$2,000	\$2,000

Data Management and Sharing:

75% of Dr. Zhu's effort is inclusive of the 2 hours per month effort dedicated to overseeing data management and repositories.

C. Total Indirect Costs, (\$47,480.63)

Y1	Y2	Y3	Y4	Y5
\$9,307.79	\$9,528.05	\$9,549.17	\$9,546.45	\$9,549.17

Facilities and Administration

F&A rate is calculated at 8% of the modified total direct costs in accordance with the FOA.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)	
Section A, Senior/Key Person		457,557.15
Section B, Other Personnel		11,637.00
Total Number Other Personnel	4	
Total Salary, Wages and Fringe Benefits (A+B)		469,194.15
Section C, Equipment		0.00
Section D, Travel		19,952.00
1. Domestic	19,952.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		104,362.00
1. Materials and Supplies	79,062.00	
2. Publication Costs	8,000.00	
3. Consultant Services	9,500.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	0.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	5,200.00	
9. Other 2	2,600.00	
10. Other 3	0.00	
11. Other 4	0.00	
12. Other 5	0.00	
13. Other 6	0.00	
14. Other 7	0.00	
15. Other 8	0.00	
16. Other 9	0.00	
17. Other 10	0.00	
Section G, Direct Costs (A thru F)		593,508.15
Section H, Indirect Costs		47,480.63
Section I, Total Direct and Indirect Costs (G + H)		640,988.78
Section J, Fee		0.00
Section K, Total Costs and Fee (I + J)		640,988.78

PHS 398 Cover Page Supplement**1. Vertebrate Animals Section**

Are vertebrate animals euthanized? ☐ Yes ☐ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

☐ Yes ☐ No

If "No" to AVMA guidelines, describe method and provide scientific justification

.....

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

☐ Yes ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount (\$)	*Source(s)
----------------	--------------------------	------------

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ☐ Yes ☒ No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Human Fetal Tissue Section

*Does the proposed project involve human fetal tissue obtained from elective abortions? ☐ Yes ☒ No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

5. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ☐ Yes ☒ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ☐ Yes ☐ No

6. Change of Investigator/Change of Recipient Organization Section

☐ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

☐ Change of Recipient Organization

*Name of former organization:

PHS 398 Career Development Award Supplemental Form

OMB Number: 0925-0001

Expiration Date: 12/31/2027

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	
Candidate Section	
2. Candidate Information and Goals for Career Development	CandidateInformation_GoalsCD.pdf
Research Plan Section	
3. Specific Aims	Specific_Aims.pdf
4. Research Strategy*	Research_Proposal.pdf
5. Progress Report Publication List (for Renewal applications)	
6. Training in the Responsible Conduct of Research	Training_in_the_RCR.pdf
Other Candidate Information Section	
7. Candidate's Plan to Provide Mentoring	
Mentor, Co-Mentor, Consultant, Collaborators Section	
8. Plans and Statements of Mentor and Co-Mentor(s)	PlansandStatementsofMentors.pdf
9. Letters of Support from Collaborators, Contributors, and Consultants	Combined_LOS.pdf
Environment and Institutional Commitment to Candidate Section	
10. Description of Institutional Environment	DescriptionofInstitutionalEnvironment.pdf
11. Institutional Commitment to Candidate's Research Career Development	InstitutionalCommitment_CRCD.pdf
12. Description of Candidate's Contribution to Program Goals	
Other Research Plan Section	
13. Vertebrate Animals	
14. Select Agent Research	
15. Consortium/Contractual Arrangements	
16. Resource Sharing	ResourceSharing_K08.pdf
17. Other Plan(s)	DataManagementAndSharingPlan_K08.pdf
18. Authentication of Key Biological and/or Chemical Resources	Authentication_Key_Biological_Chemical_K08.pdf
Appendix	
19. Appendix	

PHS 398 Career Development Award Supplemental Form

Citizenship*:

20. U.S. Citizen or Non-Citizen National?* ☒ Yes ☐ No

If no, select most appropriate Non-U.S. Citizen option

- ☐ With a Permanent U.S. Resident Visa
- ☐ With a Temporary U.S. Visa
- ☐ Not Residing in the U.S.

If you are a non-U.S. citizen with a temporary visa applying for an award that requires permanent residency status, and expect to be granted a permanent resident visa by the start date of the award, check here: ☐

CANDIDATE INFORMATION AND GOALS FOR CAREER DEVELOPMENT

A. CANDIDATE'S BACKGROUND

As a dentist-scientist dedicated to health-oriented research, I work at the intersection of biology and computational science to understand oral diseases and their links to systemic health. This five-year mentored K08 award will provide me the necessary training in machine learning, microbiology and oral-systemic connections, putting me on track for an independent research career.

Early Research Training. My journey into research began in dental school, supported by the National Student Innovation Research Program (China), where I explored the attachment characteristics of oral pathogenic bacteria on various dental implant surfaces. This initial research experience laid the foundation for my aspirations in dental research. Subsequently, my postgraduate training combined an Oral and Maxillofacial Surgery (OMFS) residency and a Ph.D. program at the prestigious Shanghai 9th People's Hospital, Shanghai Jiao Tong University, under Dr. Steve Guofang Shen's supervision. This period provided exceptional clinical training alongside a solid research background, fostering my understanding of oral disease mechanisms and their systemic connections. My PhD projects focus on alveolar bone regeneration mechanisms during orthodontic treatment, resulting in first-author papers and comprehensive training in molecular and cellular biology techniques and animal surgery models. This pivotal period solidified my ambition to pursue a dual role as a dentist-scientist.

Postdoctoral Research. Pursuing deeper scientific inquiry, I started my postdoc research fellowship at Tufts, under Dr. Jake Chen's supervision. I conducted several projects on host-microbial interaction, periodontitis and its correlation with Alzheimer's disease (AD), and non-coding RNA therapeutics for periodontal disease. Through single-cell RNA sequencing of inflamed gingiva samples, I demonstrated an aggravated host immune response driven by epigenetic regulation and identified novel biomarkers of periodontitis. These projects enabled me to master next-generation sequencing and bioinformatics for processing complex datasets in oral disease analysis.

Current Position and AI Integration. Since joining the Department of Periodontology at Tufts Dental Medicine (TUSDM) as a full-time junior faculty member, I have further expanded my research methodology by integrating AI techniques into oral health research. Leveraging my programming skills and bioinformatics expertise, I have been actively involved in Tufts' AI community through training courses and workshops. I am collaborating with my mentor, Dr. Soha Hassoun (Tufts CS), to design a Copilot for the axiUm Electronic Dental Record system using large language models (LLMs) (a pending R21 project on which I serve as co-PI). Additionally, my role as a clinical investigator in multiple studies at TUSDM is enhancing the clinical research experience vital for my K08 project and future R01 grants.

In August 2024, I was selected as a mentee in the NIH-funded AADOCR MIND the Future Program, where mentorship from Dr. Flavia Teles (UPenn) has enhanced my research and grant writing skills and fostered a new collaboration developing an RNN model to predict periodontitis progression using longitudinal biomarker data.

Recognition and Leadership. My work has been recognized through multiple awards, including first prize at the IADR CTSN Outstanding Award, the Tufts DO-IT Grant, the ASBMR Young Investigator Award, and the FASEB Mentored Presenter Award. I have published 27 peer-reviewed papers, delivered 13 conference presentations, and hold 2 issued and pending patents. I am actively engaged in scientific community service, serving as Vice President of the AADOCR Boston Section, Program Chair of the Society of In Vitro Biology, and committee member on AADOCR Fellowship committees. I have served as an Early Career Reviewer for NIH Center for Scientific Review (CSR) and reviewer for prestigious journals including Journal of Dental Research, Journal of Clinical Periodontology, and Bone Research.

Recent AI Research Funding. In March, I received 2025-2026 Colgate Award for Research Excellence (CARE) Program funding (\$30k, 2-3 awards granted nationwide annually) for developing a machine learning model for home-based periodontal assessment using ensemble methods that achieved over 80% accuracy. In September, I was awarded the highly competitive Tufts Institute for Artificial Intelligence (TIAI) Seed Fund, which provides funding support (\$10k/yr) and, more importantly, the dedicated effort of a senior data scientist at 0.5 FTE (20 hours per week) for two years to collaborate on my AI research in oral health. These funding awards not only provide critical funding and expert collaborative support for my AI work in oral health but also enhance my credibility as an emerging independent investigator, reinforcing the potential impact of my K08 project advancing AI-driven diagnostics in oral and systemic health.

B. CAREER GOALS AND OBJECTIVES

My long-term research career goals, as an independent dentist-scientist, revolve around **leading a translational research team** dedicated to **advancing early intervention and treatment of oral diseases**, and exploring the **links and shared pathogens between oral and systemic conditions** such as AD. I aspire to

collaborate with clinicians, researchers, biostatisticians, and machine learning scientists to employ a **multidisciplinary approach** to transform the oral-systemic connections into practical clinical and research tools. For example, leveraging the oral microbiome as a non-invasive, cost-effective tool to assess and preliminarily diagnose AD or other diseases associated with oral health. **My vision** includes developing clinically deployable AI-driven screening tools that can be implemented in both clinical and home-based settings, expanding access to early detection of oral and systemic diseases. Alongside these research endeavors, I am dedicated to dental education and mentoring, aiming to guide and inspire the forthcoming generation of dental researchers.

In the short-term scope of this proposal, as an early-stage investigator, my objective is to build my multi-faceted research skillset for the K08 project and begin to forge my collaborative networks. My prior research and training have laid a solid groundwork for my current proposal. My recent successes in developing ML tools for periodontal assessment and my ongoing collaboration on using LLMs and RNN models have demonstrated my growing competence in AI applications for oral health. However, to advance my skills in sophisticated deep learning architectures like Transformers, which are essential for my K08 project, I **require support from the K08 award in four key areas**: **1)** formal training in advanced machine learning with an online master program, **2)** training in microbiology through formal courses, workshops, and hands-on involvement in Dr. He's (microbiology mentor) projects, **3)** clinical research training through observation of the WHICAP study and independent execution of a pilot clinical study. **4)** career development and professional skills training.

C. CAREER DEVELOPMENT / TRAINING ACTIVITIES

Primary Training Goal 1: Obtaining advanced training in AI

Justification: My ML experience so far includes the classic machine learning methods (e.g., Logistic Regression and Random Forest, Histogram Gradient Boosting, Support Vector Machine) and pre-trained LLMs (GPT, Llama), with recent exposure to the RNN models. To better handle complex data such as our 16s rRNA sequencing data at a large-scale and train the transformer, I need to expand my skills in deep neural networks. These advanced techniques are crucial for improving our model development [Aim1b, 2c and 3c].

Training activities:

• Coursework

I will complete the following specific courses in the Applied Machine Intelligence master's program:

- Year 1:
EAI 6000: Fundamentals of AI (Fall) - Neural network architectures, backpropagation, optimization
ALY 6110: Data Management and Big Data (Fall) - Handling large-scale sequencing datasets
EAI 6020: AI System Technologies (Spring) - HPC, GPU acceleration for model training
- Year 2:
EAI 6060: Healthcare Information Processing (Fall) - Deep learning for healthcare applications
ALY 6040: Data Mining Applications (Fall) - Advanced ML techniques for pattern discovery
ALY 6150: Healthcare Data and Applications (Spring) - Clinical data integration

• Mentorship

Ongoing weekly code review sessions with **Dr. Kevin Bonham** on model development; bi-weekly 1on1 mentoring meetings with **Dr. Soha Hassoun**.

• Hands-on Training

- **Laboratory Training (Months 6-9):** A 3-month immersive training in **Dr. Soha Hassoun's** Computer Science Lab will focus specifically on: (1) implementing self-attention mechanisms for OTU sequence processing (Aim 1b), (2) developing position encodings for microbial taxonomic hierarchies (Aim 2a), and (3) optimizing training strategies for imbalanced AD/control datasets (Aim 3c).
- **TIAI Collaborative Support (Years 1-2):** Two years of dedicated support from the Tufts Institute for Artificial Intelligence (TIAI) through partnership with a senior scientist, facilitating ongoing collaboration on transformer model development, implementation optimization, and integration of advanced deep learning techniques throughout the project.

Milestones:

- Month 6: Complete EAI 6000 and ALY 6110; demonstrate competency by implementing basic Transformer encoder that achieves >70% accuracy on toy dataset
- Month 12: Complete domain-specific courses; begin OMFM pretraining on 10% of data
- Month 18: Finish master's program; complete full-scale OMFM pretraining
- Month 24: Fine-tune OMFM for AD prediction; submit first manuscript

Primary Training Goal 2: Developing the expertise in microbiology

Justification: Despite my strong background in oral biology, my experience in oral microbiology is limited, particularly regarding its links to systemic diseases. To enhance the data interpretation and clinical relevance of our model outputs, I need to deepen my knowledge of microbiology, including microbial interspecies interactions, microbial ecology, and host-microbial interactions. Additionally, gaining more hands-on experience in a microbiology lab for sample collection, extraction and sequencing is essential for the pilot clinical study [Aim 3a].

Training activities:

- **Coursework**

I will attend the workshop and course below, which offer advanced training in microbial metagenomics, equipping participants with cutting-edge techniques in bacterial sequencing and data interpretation.

- **Microbial Genomics & Metagenomics Workshops** at Lawrence Berkeley National Lab. (3 days)
- **Advanced Bacterial in Genomics Course** – Cold Spring Harbor Laboratory. (20 days)
- **Advanced course/workshop on batch effect correction and meta-analysis methods for microbiome data** (e.g., through CTSI or online platforms like Coursera) (~2 days)

- **Mentorship**

Co-mentor **Dr. Flavia Teles** at UPenn offers targeted training in oral microbiology through monthly virtual meetings and AADOCR MIND the Future Program in-person events, for any questions I have regarding oral pathogenic bacteria and host-microbial interaction and potential ML applications in this field.

- **Hands-on training in Oral Microbiology Lab.**

Co-mentor, **Dr. Xuesong He**, will involve me in his ongoing R01 projects (R01DE023810 and DE030943) at ADA Forsyth, focusing on microbial interspecies interactions.

Months 6-12: Monthly visits (2-3 days each) to Dr. Xuesong He's lab to:

- Master saliva sample collection and DNA extraction protocols for pilot study (Aim 3b)
- Learn quality control procedures for 16S rRNA sequencing
- Understand batch effect considerations in multi-site microbiome studies

Months 12-36: Quarterly hands-on sessions focusing on:

- Processing pilot study samples under Dr. He's supervision
- Interpreting sequencing quality metrics and troubleshooting failed samples
- Understanding biological vs. technical variation in microbiome data

Milestones:

1) I will attend the designated workshop and course in the Year 1 and Year 2, and then meet with my mentors to review what I have learned and integrate these insights into our research project. 2) Dr. Teles has provided 1-on-1 mentoring since August 2024 through MIND the Future, leading to our collaboration on an RNN model for periodontitis progression. I am confident that continued mentorship will deepen my expertise in oral microbiology, benefiting my K08 project and generating new publications and grant proposals. 3) Hands-on experience in Dr. He Lab will enhance project deliverables and refine my microbiome sample processing techniques. At Month 24, I will successfully process at least 20 pilot samples independently with Dr. He's quality oversight.

Primary Training Goal 3: Obtaining advanced training in translational and clinical study.

Justification: Although I have a strong background in clinical training and basic research, my experience in clinical study design and execution is limited. To address this gap and effectively conduct proposed external and clinical validation and pilot study [Aim 2d and 3a], I have completed training in GCP, CITI, and IRB protocol development and I am currently serving as an examiner in two clinical studies at TUSDM. With the support of this K08, I will further enhance my skills by learning from mentors who specialize in translational and clinical studies.

Training activities:

- **Coursework:** I will complete CTSI courses in translational research training, such as **CTS 500 - Study Design**.

- **Hands-on training**

Two-week WHICAP Training Visit (Month 18-20): Co-mentors - **Dr. Panos Papapanou** and **Dr. James Noble** are leading a large clinical study on periodontal infections and AD. I will spend two weeks with their research team to gain hands-on experience in implementing dental and neurological clinical studies.

- Week 1: Shadow and calibrate periodontal examinations; learn standardized AD cognitive assessment protocols; observe data management systems
- Week 2: Participate in team meetings on recruitment challenges; review IRB protocols for vulnerable populations; understand longitudinal data collection strategies

- **Mentorship**

After visiting the WHICAP team, I'll work with co-mentor **Dr. Athanasios Zavras** and neurologist consultant **Dr. Laudate** at Tufts on clinical research design for [Aim 3b], including study design, bias control, examiner calibration, participants identification, and AD assessment methods.

- **Institutional support in training**

- I will work with our Dental Research Administrator, **Ann-Marie Billig** on IRB approval for this project, and conduct the pilot study with well-trained research coordinators at the TUSDM Clinical Research Center.
- I will enhance my research ethics and patient communication skills. (Consultant: **Dr. Ellen Patterson**)
- I will collaborate with **Noe Duenas** and/or **Angelique Santiago** in the Recruitment and Retention Support Unit (RRSU) at CTSI and my research coordinator at TUSDM Clinical Research Center on recruitment.
- I will consult with **Dr. Meghan Short** from BERD (Biostatistics, Epidemiology, and Research Design) on statistical questions through the limited biostatistical mentorship provided by the K08 program.

Milestones:

Key milestones include 1) completing essential CTSI coursework in Year 1; 2) participating in a two-week hands-on training visit with the WHICAP clinical team in Year 2; 3) apply learned protocols to develop and execute Aim 3a pilot study guidance from expert mentors and institutional support at Tufts in Year 3-5. These sequential outcomes will enhance my expertise in clinical study implementation.

Primary Training Goal 4: Professional Development and Grant writing of an R01 proposal.

Justification: To pursue my independent research career and long-term goals, I need to develop my professional skills and sharpen my grant writing to prepare for my future R01 grant.

Training activities:

- **Coursework:** I will complete the **CTS 538** course for grant writing.
- **Mentorship:** **Dr. Jake Chen** (primary mentor) and **Dr. Athanasios Zavras** (career development mentor), will host in-person meetings with me and provide invaluable guidance on advancing my career, ensuring timely research progress, a strong publication record, effective networking, and a smooth transition to greater independence.
- **Institutional support and NIH study section reviewer experience**
 - TUSDM Faculty Mentorship Program and CTSI Junior Faculty Research Career Development Forum
 - I will complete the advanced grant writing course, CTS 538 - Grant Writing.
 - I will enroll in the CTSI mock grant review to get feedback and improve my R01 application.
 - I participated in NIH Early Career Reviewer Program and attended a study section in Washington D.C., gaining firsthand insight into grant review process and key criteria that make an application competitive.

Milestones: These training activities will build the skills essential for independent research. I will begin R01 preparation in Year 4.5 and submit the initial application early in Year 5. The remaining award period allows for incorporation of reviewer feedback and resubmission if necessary, strategically positioning me for a successful transition to independent investigator status.

Time Allocation

During the K08 award period, I will commit 100% of my full-time professional effort to achieve my career development goals, allocating 75% to research and 25% to other professional duties. These include teaching and mentoring dental students and residents, as well as serving in academic organizations and committees that support professional growth and networking in my scientific field.

<i>Proposed Time Commitment</i>						
Description of Activities	Type	Y1	Y2	Y3	Y4	Y5
Coursework (AI part-time master, CTS 500, CTS 538)	K08 (included in 80%)	25%	15%	5%	5%	5%
Conferences and seminars	K08 (included in 80%)	10%	10%	10%	10%	10%
Research activities	K08 (included in 80%)	35%	35%	40%	40%	35%
Meeting/consultation with mentors and consultants	K08 (included in 80%)	10%	10%	10%	10%	10%
Manuscript/Grant writing	K08 (included in 80%)	5%	5%	10%	10%	15%
Total K	K	75%	75%	75%	75%	75%
Other activities – teaching (dental students and residents)	Other (10%)	10%	10%	10%	10%	10%
Other activities – mentoring student's research	Other (5%)	10%	10%	10%	10%	10%
Other activities – community services & administrative	Other (5%)	5%	5%	5%	5%	5%
Total other	Other	25%	25%	25%	25%	25%

Skills and Abilities Required to Achieve My Research and Career Development

We have identified the essential skills needed to achieve my research and career development goals, and the associated training activities and mentoring/consulting requirements are summarized in the table below.

Skills/Abilities needed for primary goals	Career Development/Training Activities (mentors and consultants)
Large-scale data management and processing	<ul style="list-style-type: none"> • Courses ALY 6110 (Data Management and Big Data) and EAI 6020 (AI System Technologies) • Protocol setup, data collection, access the databases (G. Chen, A. Tai) • Data preprocessing and quality control (S. Hassoun, X. He)
Deep learning and Transformer architectures	<ul style="list-style-type: none"> • Part-time master program of AI in healthcare • Hands-on training in CS lab implementing Transformer models (S. Hassoun), and from TIAI senior data scientist (R. Batorsky) • Code review sessions for troubleshooting and debugging complex models (K. Bonham)
Understanding of strengths and limitations of different AI algorithms	<ul style="list-style-type: none"> • Attending TAP Pilots Review biweekly and improve the designed model with machine learning experts (S. Hassoun)
Model interpretability and comprehend its AD clinical significance.	<ul style="list-style-type: none"> • Integrating the knowledge of oral microbiome and AD to interpret the model output and discover the novel pathogenic mechanisms of AD (J. Chen, F. Teles, P. Papapanou, J. Noble)
Reproducible research practices	<ul style="list-style-type: none"> • Version control (Git/GitHub) • Documentation and code sharing (S. Hassoun)
Training on translational and clinical study design	<ul style="list-style-type: none"> • Complete the CTSI courses, such as CTS 500 - Study Design. • Guidance from mentors with expertise in clinical and translational study. (J. Chen, J. Noble)
Experience in recruitment and enrollment of participants	<ul style="list-style-type: none"> • Utilize the service offered by the RRSU at CTSI to optimize the workflow and recruitment process (N Duenas at RRSU) • Work with research coordinator at TUSDM Clinical Research Center. • Recruitment through TUSDM, TMC Memory Care Clinic (T. Laudate) • Recruitment through other sources if needed (e.g., Facebook groups)
Conducting the clinical pilot study	<ul style="list-style-type: none"> • Complete related training, such as GCP, and CITI. – Completed • IRB approval and compliance (A. Zavras, E. Patterson) • Data security and compliance (HIPAA, patient privacy) (T. Laudate, E. Patterson) • Adverse event monitoring/reporting (even if minimal risk) (A. Zavras)
Research ethics and patient communication skills	<ul style="list-style-type: none"> • Ethical considerations will be integrated into every phase of the pilot study. E. Patterson (consultant) will guide me with her expertise in ethics and patient communication.
Understanding and working knowledge of statistical bioinformatics	<ul style="list-style-type: none"> • Biostatistical mentorship at CTSI: Dr. M Short, a biostatistician with expertise in microbiome and AD, provided her advice on this proposal and agreed to be my biostatistical mentor on this K08 for power analysis and sample size calculations for microbiome studies.
Effectively collaborate with a multidisciplinary team.	<ul style="list-style-type: none"> • Communication with different specialists and departments (A. Zavras) • Program management: timeline, resources and personnel (J. Chen) • Annual group meeting with all mentors to assess my progress
Grant writing training	<ul style="list-style-type: none"> • Complete the advanced grant writing courses, CTS 538 - Grant Writing • Enroll in the CTSI mock grant review session to get feedback and improve my K08 application
Professional skills (present, publish and disseminate my work)	<ul style="list-style-type: none"> • Presentation at conferences and seminars (e.g., IADR annual meeting). • Complete > two peer-reviewed manuscripts for publication each year. • Continue participating in the CTSI Junior Faculty Research Career Development Forum (enrolled since 2022)
Collaborations with core facilities and researchers both within and outside Tufts	<ul style="list-style-type: none"> • Leverage mentors' network at large. (all mentors) • Create opportunities for de-novo collaborations

Mentoring Team and Consultants

Below is a table summarizing the mentors and consultants along with their roles, specialties, and commitment levels. A detailed description of the mentoring team, including two primary mentors and co-mentors, is provided in the **Plans and Statements of the Mentors** section. **Letters of support** from all 6 co-mentors are attached; consultant letters have been obtained but are not included in the application package due to the 6-page limit for the LOS section, with their roles and commitments detailed in the table below and in the **Research Plan**.

Name	Role	Specialty	Commitment	Primary Affiliation
Jake Jinkun Chen, DMD, MDS, PhD, FACD	Primary Mentor	<ul style="list-style-type: none"> Oral Biology Translational research in oral-systemic health 	Weekly 1on1 meetings; Coordinating the group meetings	Tufts University School of Dental Medicine
Soha Hassoun, MS, PhD	Primary Mentor	<ul style="list-style-type: none"> Computer science – focusing on ML models for biological data analysis and disease prediction 	Bi-weekly 1on1 meetings; Coordinating the group meetings	Computer Science, Tufts University School of Engineering
Xuesong He, DDS, PhD	Co-mentor	<ul style="list-style-type: none"> Oral microbiology – microbial interspecies interactions 	Monthly 1on1 meetings; Annual committee meeting	ADA Forsyth Institute
Flavia Teles, DDS, MS, DMSc	Co-mentor	<ul style="list-style-type: none"> Oral microbiology Periodontal diseases Host-microbe interactions 	Mentorship through AADOCR MIND the Future, Monthly 1on1 meetings; Annual committee meeting	Penn Dental Medicine
Kevin Bonham, PhD	Co-mentor	<ul style="list-style-type: none"> Computational biology – focusing on microbiome and brain function 	Bi-weekly 1on1 meetings; Annual committee meeting	Tufts University School of Medicine
Panos N. Papapanou, DDS, PhD	Co-mentor	<ul style="list-style-type: none"> Pathobiology of periodontitis and its role in Alzheimer's Disease and Atherosclerosis 	Year 1-2: quarterly meetings; Year 3-5: Monthly 1on1 meetings; Annual committee meeting	Columbia University College of Dental Medicine
James M. Noble, MD, MS	Co-mentor	<ul style="list-style-type: none"> Neurology: Aging and Dementia Link Between AD and Periodontitis 	Year 1-2: quarterly meetings; Year 3-5: Monthly 1on1 meetings; Annual committee meeting	Columbia University Medical Center
Athanasios Zavras, DMD, MS, DmedSc	Co-mentor	<ul style="list-style-type: none"> Clinical dental research Faculty Career Development 	Quarterly 1on1 meetings; Annual committee meeting	Tufts University School of Dental Medicine
Ellen Patterson, MD, BA, MA	Consultant	<ul style="list-style-type: none"> Psychiatry and Behavioral Science 	Consultation for ethical considerations and patient communication for a pilot study in Aim 3	Tufts University School of Dental Medicine
Thomas Laudate, PhD	Consultant	<ul style="list-style-type: none"> Clinical Neurology: AD Diagnosis 	Consultation for AD assessment and AD label noise in Aim 2 and Aim 3	Memory Care Clinic, Tufts Medical Center
George Chen, PhD	Consultant	<ul style="list-style-type: none"> Bioinformatics - focusing on oral microbiome data 	Consultation for bioinformatics and human oral microbiome database	ADA Forsyth Institute
Albert Tai, PhD	Consultant	<ul style="list-style-type: none"> Bioinformatics - focusing on sequencing data processing 	Consultation for 16s rRNA sequencing data processing	Tufts Genomic Core
Meghan Short, PhD	Consultant	<ul style="list-style-type: none"> Biostatistics 	Consultation for biostatistical questions	Tufts Clinical and Translational Science Institute
Rebecca Batorsky, PhD	TAI support	<ul style="list-style-type: none"> Senior Data Scientist 	0.5 FTE (20 hr/wk) effort for 2 years (2025-2027)	Tufts Institute of AI

SPECIFIC AIMS

Oral and systemic health are deeply interconnected. Growing evidence indicates that oral microbiome dysbiosis not only accompanies oral diseases (e.g., periodontitis, caries), but also contributes to systemic disease progression, including neurodegenerative disorders, diabetes, and cardiovascular disease. Extensive efforts have produced large-scale oral microbiome sequencing datasets that enable high-throughput identification and quantification of microbes (e.g., 16S rRNA and shotgun metagenomics), yet these face critical limitations: 1) Data limitations and bias: disease-specific datasets have limited reusability for other conditions, and small single-study controls create biased population baselines; 2) Methodological constraints: traditional biostatistical approaches require dimensionality reduction, overlooking fine-grained microbial interactions essential for understanding oral-systemic relationships. To address these limitations, we **propose** leveraging advanced machine learning (ML) techniques to develop a Transformer-based Oral Microbiome Foundation Model (OMFM). Trained on extensive unlabeled 16S rRNA data, OMFM will learn contextualized microbial representations and serve as a scalable platform for studying the oral microbiome with population-level baselines. The model is readily extendable to diverse downstream tasks through fine-tuning, such as predicting Alzheimer's disease (AD).

AD is a progressive neurodegenerative disorder characterized by cognitive decline. **Emerging evidence suggests oral microbiome dysbiosis plays a crucial role in AD pathogenesis**. Oral bacteria influence neurodegeneration through multiple pathways, entering the bloodstream through daily activities and contributing to systemic inflammation characteristic of AD. Our recent study demonstrates that periodontal pathogens exacerbate AD pathology. Notably, preclinical AD individuals exhibit distinct oral microbiota profiles, offering potential for early detection before symptom onset. However, no deep learning model currently exists for oral microbiome-based AD prediction. Our novel OMFM approach directly addresses this critical gap.

We **hypothesize** that the OMFM will learn complex microbial interaction patterns and generalize to downstream tasks such as systemic disease prediction, enabling clinically-viable AD screening in dental clinics.

Aim 1: Build a deep learning foundation model for the oral microbiome. *Working hypothesis:* Training OMFM on a large, integrated oral microbiome 16S rRNA dataset will yield embeddings capturing nuanced taxa interactions, establishing a pioneering platform for oral microbiome research. *Aim1a:* Curate and process the data of 187,145 oral microbiome samples from public sources (e.g., HMP, SRA) with standardized pipeline and cross-study harmonization to create AI-ready dataset. *Aim1b:* Leveraging ELECTRA framework, pretrain OMFM through rigorous hyperparameter tuning to learn intricate microbial patterns and interactions. *Aim1c:* Evaluate model performance and quality through replaced-token detection, robustness testing, attention analysis. Benchmark against BERT, TabTransformer, and MGM 2.0 to ensure OMFM is robust and generalizable.

Aim 2: Develop and benchmark predictive models for AD using oral microbiome data. *Working hypothesis:* Fine-tuned OMFM will achieve clinically meaningful prediction accuracy and outperform baseline models. *Aim 2a:* Curate an AD-labeled dataset pairing oral 16S rRNA data with clinical diagnoses from ~3,000 samples, while addressing diagnostic heterogeneity. *Aim 2b:* Establish traditional ML baselines (logistic regression, random forests, SVM, gradient boosting) and fine-tune OMFM with LoRA for AD classification. *Aim 2c:* Evaluate model performance and implement explainability techniques (SHAP and IG) to reveal biologically meaningful associations. *Aim 2d:* Externally validate on WHICAP cohort (750 participants, 2 visits) to assess generalizability.

Aim 3: Explore clinical implementation of OMFM-based AD screening tool. *Working hypothesis:* Oral microbiome profiles differ significantly between AD patients and controls, and OMFM can capture these differences to enable non-invasive detection and risk prediction with clinical utility. *Aim 3a:* Conduct an IRB-approved pilot study at Tufts (80 participants: 40 AD, 40 controls; 2 visits) comparing diagnostic accuracy across multiple oral sites to optimize sampling strategies. *Aim 3b:* Train OMFM on WHICAP longitudinal data (Aim2d) to predict one-year cognitive decline and validate the model on our independent Tufts cohort (Aim 3a), demonstrating the oral microbiome's capacity to forecast AD progression.

This study will advance understanding of oral microbiome dysbiosis by leveraging our novel OMFM both for AD prediction and as a platform for investigating other systemic diseases. My background in oral-systemic health research, including studies on oral pathogens in AD, along with bioinformatics skills in large-scale sequencing data processing and analysis, and ML model development for oral disease prediction, provides a strong foundation for this research. Through this K08 award and with a dedicated multidisciplinary mentoring team covering all required expertise, I will receive comprehensive training through regular mentorship meetings, formal coursework in deep learning and microbiology, and hands-on experience conducting translational and clinical studies. This training will establish my expertise in oral biology, advanced AI in healthcare, and clinical translation, positioning me to pursue R01 funding to expand OMFM for broader clinical applications and launch an independent career as a dentist-scientist bridging computational and clinical oral health research.

RESEARCH STRATEGY

A. Significance

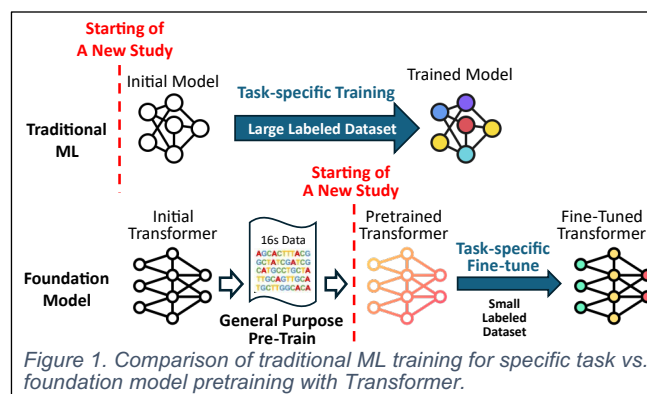
The link between oral and systemic diseases is well-established and supported by extensive research. Oral diseases, particularly periodontal disease, are implicated in the etiology of systemic conditions such as diabetes, cancer and Alzheimer's disease (AD)^{1,2}. Recent studies indicate that dynamic shifts in the oral microbiome are not merely consequences of local oral diseases but actively contribute to systemic disease progression³. An imbalance in this complex microbial community, known as dysbiosis, plays a key role in driving these pathological processes⁴. For example, *Porphyromonas gingivalis* (*Pg*), a main pathogen that causes periodontitis, can enter the bloodstream through inflamed periodontal tissues leading to systemic inflammation^{5,6}. Understanding the composition and function of the oral microbiome is thus essential for exploring its role in systemic health.

Next-generation sequencing technologies, like 16S rRNA amplicon sequencing and shotgun metagenomic, have greatly advanced research on microbiomes, especially the roles of microbes in disease etiology. They provide high-throughput identification and quantification of microbes for biostatistical and bioinformatics analysis. However, **this body of research still faces several key limitations:** 1) **Data Limitations.** The datasets from traditional workflows, designed for a specific disease, have limited reusability in future studies, especially on other diseases. The healthy control sample size is also small due to cost and logistics, which is less representative of the healthy population. 2) **Analysis Method Limitations.** Both biostatistics and bioinformatics have limited capabilities in handling high dimensional data requiring dimensionality reduction, like variable selection⁷. These techniques primarily focus on selected taxa and fail to capture fine-grain microbial interactions and the broader ecological environment, which could be key to new insights into the oral-systemic relationship. To address these limitations, we **hypothesize** that an **oral microbiome foundation model (OMFM)** can 1) serve as a scalable platform to study oral microbiome with a healthy baseline, 2) enable the identification of relationships between microbial dysbiosis and diseases, including its temporal response in systemic diseases.

A **foundation model** is a machine learning (ML) model trained on vast unlabeled datasets to learn general patterns of the data, which can be fine-tuned for specific tasks with minimal labeled data compared with traditional ML models (Fig. 1). Large language models (LLMs) exemplify this approach, which are trained to understand natural language. In my recent work, I have gained skills in utilizing and fine-tuning pretrained LLMs for dental applications, including Copilot for the axiUm electronic dental record (EDR) system (a pending R21 with my AI mentor [Dr. Soha Hassoun](#), role: co-PI). Transformers, the underlying architecture of LLMs, efficiently process sequential data and have been widely used for biological data (e.g., AlphaFold, DNABERT⁸⁻¹⁰). In this study, we will develop a **Transformer-based OMFM** using large-scale oral microbiome data to capture intricate microbial patterns and interactions, analogous to decoding the "language" of microbes (**Aim 1**).

OMFM offers significant advantages: 1) **Holistic Pattern Understanding** – capturing intricate microbial patterns and relationships beyond traditional methods. 2) **Reusability and Generalizability** – providing a robust, low-bias baseline for future studies across diseases, populations, and study designs. 3) **Extensibility** – adaptable to downstream tasks including disease prediction, anomaly detection, and sequencing error correction through fine-tuning with task-specific heads. These features make OMFM a powerful tool for investigating the complex relationships between oral and systemic health. In the current phase of this project, we focus on exploring the extensibility of the OMFS for AD prediction by fine-tuning the model with an additional classification head to learn unique profiles of AD patients' oral microbiome and distinguish them from the non-AD population (**Aim 2**).

AD is a progressive neurodegenerative disorder characterized by cognitive decline¹¹. The microbiota-gut-brain axis links the gut microbiome to cognitive health, with studies showing gut microbiome profile differs among elders with AD, no dementia, and other dementia types¹², and its composition shifts progressively across AD stages^{13,14}. In oral health research, emerging evidence suggests **oral microorganisms dysbiosis plays a crucial role in AD pathogenesis**¹⁵⁻¹⁷ and offers strong predictive potential for AD detection. The oral cavity's proximity to the brain and gastrointestinal tract provides multiple pathways for oral microbial influence on neurodegeneration. For example, oral bacteria and their toxins enter bloodstream through daily activities like chewing, brushing¹⁸, with *Pg* bacteremia increasing blood-brain barrier permeability and triggering neuroinflammation¹⁹. Recent studies have identified *Pg*-produced lipopolysaccharide²⁰, and oral pathogens (*Actinomycetales*, *Bacteroidales*²¹, and *Treponema*²²) in AD brain tissue. Furthermore, periodontal bacterial infections contribute to systemic inflammation and neuroinflammatory processes characteristic of AD²³⁻²⁷. Under the supervision of [Dr. Jake Chen](#) (primary mentor), our recent study on 5XFAD mice demonstrated that *F.*



nucleatum leads to increased beta-amyloid deposition, Tau phosphorylation, and worsened cognitive impairment²⁸. Other studies reported *Pg*^{29–31} and *A. actinomycetemcomitans*^{32,33} exacerbate AD pathogenesis. Intriguingly, **preclinical AD individuals exhibit increased oral microbiota diversity**, with dominant genera like *Haemophilus* and *Neisseria*³⁴. Thus, we believe **oral microbiome bears strong predictive power for AD**.

However, quantitative assessment of cognitive impairment from oral microbiome data remains challenging. The aforementioned limitations of current analytical methods yield inconsistent results, for example, some studies report decreased periodontitis-associated bacteria in AD¹⁸, whereas others show increases^{35,36}. These conflicting findings underscore the need for larger datasets and more powerful analytical methods. While the deep neural networks (DNNs), including transformers, have successfully predicted diseases from gut microbiome data (e.g., inflammatory bowel disease³⁷), such methods remain underutilized for oral microbiome-AD research. To date, only one study has used traditional ML³⁸, with no DNN-based models reported. This gap motivates our proposed OMFM approach, which leverages deep learning's capacity for handling high-dimensional, sparse data. My prior work on ML models for periodontitis³⁹ and RNN models for progression prediction—the latter developed in collaboration with Dr. Flavia Teles (MIND the Future Program mentor)⁴⁰—provides the foundation for this work.

Finally, oral microbiota is increasingly recognized as a **non-invasive and cost-effective** method for detecting health issues, such as gastric⁴¹, pancreatic⁴² and laryngeal cancers⁴³. We propose to pilot OMFM-based AD screening in clinical settings, optimizing sampling strategies and predicting AD risk from longitudinal data (**Aim 3**). Since oral microbiome is also associated with cardiovascular disease, colorectal cancer, and diabetes, this work establishes a foundation for extending OMFM to other systemic diseases.

B. Innovation

This project introduces three innovations: **1) Methodological**: We develop the first Transformer-based foundation model for oral microbiome. The OMFM captures complex microbial interactions beyond traditional methods' reach. **2) Clinical**: We create the first deep learning model for AD prediction from oral microbiome data and the first use of longitudinal oral microbiome changes to forecast AD risk, addressing critical gaps in early detection. **3) Translational**: OMFM is highly extensible to multiple downstream tasks through parameter-efficient fine-tuning. Unlike traditional single-use models, OMFM can be readily adapted for other systemic conditions with minimal additional data. Combined with non-invasive, low-cost testing (~\$45/sample) deployable in dental clinics, this creates a scalable, versatile platform for oral-systemic health research with broad clinical applications.

C. Approach

Specific Aim 1: Build a deep learning foundation model for oral microbiome (OMFM). We will use the Transformer architecture⁴⁴, chosen for its scalable self-attention mechanism, on a large oral microbiome dataset. This will be a pioneering effort to create a generalized foundation model for future oral microbiome research.

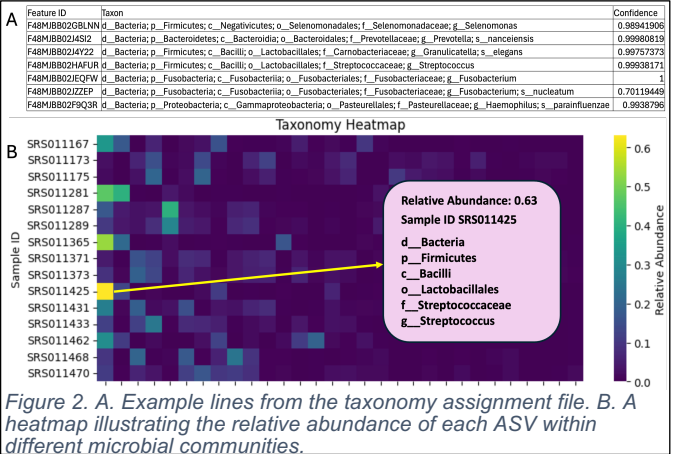
Aim1a. Data collection and processing. Under *Dr. Xuesong He's* (microbiology co-mentor) supervision, I have

	HMP	FMD	SRA	ENA	NHANES	WHICAP	Total
oral rinse			22,871	7,107	9,997		39,975
dental plaque	1,392	1,275	14,071	5,186		739	21,271
tongue	466	449	9951	2,119			12,519
palatine tonsil	466		284	150			434
buccal mucosa	465	433	4,760	447			5,640
throat	463		7,601				7,601
hard palate	462		561	20			581
saliva	435	3,163	85,309	6,503			94,975
	4,149	5,320	145,408	21,532	9,997	739	187,145

Table 1. Oral Microbiome Datasets for OMFM Training.

curated oral microbiome 16S rRNA seq data from public sources, such as Human Microbiome Project (HMP), Forensic Microbiome Database (FMD), Sequence Read Archive (SRA), and recently available NHANES oral microbiome 16S data⁴⁵. Our dataset totals **187,145** samples (Table 1), nearly 10 times larger than the 18,480 gut microbiome samples used in previous Transformer study³⁷. Samples include both healthy individuals and patients with various diseases, collected from multiple oral sites (e.g., dental plaque, saliva, tongue, buccal mucosa). This diverse dataset captures full spectrum of microbial patterns in oral cavity, thereby enhancing the robustness and generalizability of the OMFM.

Data processing pipeline. To ensure data integrity and consistency, we have developed and validated a standardized processing workflow on 1,292 HMP samples with promising results (Fig. 2). The pipeline includes three key steps: **1) Data Format Standardization**: FASTQ files are standardized by converting quality score encodings to uniform format and harmonizing metadata annotation (age, sex, oral site, medical conditions) using FASTQC and custom scripts. **2) Quality Filtering and Denoising**: QIIME2's DADA2 plugin performs quality filtering, chimera removal, and generation of Amplicon Sequence Variants (ASVs). **3) Taxonomic Assignment**: A naïve-Bayes classifier⁴⁶ trained on HOMD reference sequence assigns taxonomy to ASVs at species-level resolution.



Cross-study harmonization strategy. To address variability from different sequencing platforms, DNA extraction protocols, and hypervariable regions, we will implement a multi-step normalization approach adapted from MMUPHin⁴⁷, which has been validated on integrating microbiome data from 10 IBD studies: **1)** Transform raw ASV counts into relative abundances by normalizing to total sequencing depth. **2)** Collapse individual ASVs to genus level to minimize technical differences caused by varying primer sets and target regions. **3)** Apply quantile-based binning to discretize each genus-level abundance into five ordinal bins (Bin0-4) based on empirical distribution across samples. This enables

GenusIndex	Genus	Abundance	Bin	Token (assignment)
0	Streptococcus	0.31	4	982 (Strep_Bin4)
1	Veillonella	0.0008	1	281 (Veill_Bin1)
2	Actinomyces	0	0	143 (Actino_Bin0)
...
9999	GenusX	0.05	3	7382 (GenusX_Bin3)

Table 2. Preparation for transformer training, where each (genus, abundance bin) pair is mapped to a unique token in model vocabulary.

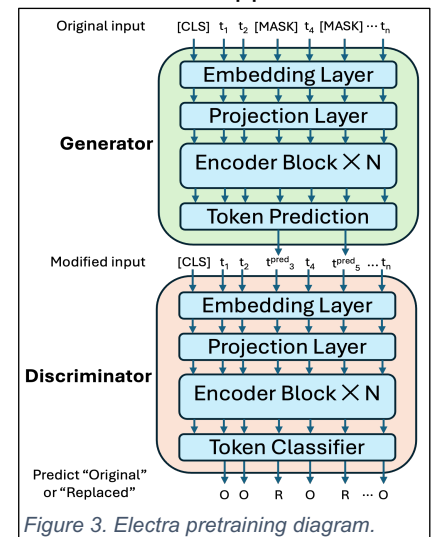
consistent abundance encoding for transformer input while minimizing study-specific bias (Table 2).

Metadata variables integration. To control for confounding factors and address incomplete metadata, we will prepend each sample with **metadata tokens** encoding demographics (age, sex, race/ethnicity), clinical variables, lifestyle factors, and technical characteristics (hypervariable region, study source, oral site, sequencing batch). Example: [AGE_65-74], [SEX_F], [DIABETES_Yes], [SMOKING_Never], [REGION_V4], [SITE_Saliva]. For missing values, we will supplement with study-specific author-provided data and apply statistical imputation. These variables enable the model to 1) learn which patterns are confounded versus disease-specific, 2) ensure balanced representation through stratified sampling, and 3) identify potential biases across demographic and clinical subpopulations through subgroup analyses.

Preparation for transformer training. The normalized, binned abundance data will be converted to fixed-length token sequences where each position corresponds to a genus, and each value represents its abundance bin (Table 2). Technical and clinical metadata tokens are prepended as described above. The AI-ready dataset will then be split into training, validation, and test sets (80%/10%/10%), stratified by study source, sequencing platform, hypervariable region, oral site, and health status to ensure proportional representation of all conditions.

Aim1b. Design, train, and validation of OMFM. Transformers are ideal for 1D sequence data and have been applied to DNA and protein sequence data^{10,48–51}. **ELECTRA**⁵² is a Google-developed Transformer architecture, has shown success on microbiome data⁵² through its sample-efficient, replaced-token detection approach. Under supervision of [Dr. Hassoun](#), and in direct collaboration with [Rebecca Batorsky](#), [senior data scientist at Tufts Institute of AI \(TIAI\)](#) through [TIAI Seed Fund](#) recently awarded to the candidate, we will pretrain the Transformer encoder using ELECTRA. Unlike masked language models (e.g., BERT), ELECTRA learns from all input tokens, leading to faster convergence and superior performance on high-dimensional, sparse microbiome data. ELECTRA involves training two Transformers: a Generator, which predicts masked tokens (t^{pred}) to create modified input, and a Discriminator, which is trained as a binary classifier to identify whether each token is “Original” or has been “Replaced” by the Generator (Fig. 3). The loss functions for the Generator and Discriminator are $\mathcal{L}_G = \mathbb{E}(\sum_{i \in m} p_G(x_i | x^{\text{msk}}; \theta_G))$ and $\mathcal{L}_D = \mathbb{E}(\sum_{t=1}^n BCE(\mathbb{I}[t \in \mathbf{m}], \hat{m}_t | \theta_G, \theta_D))$, where \mathbf{m} is the list of masked token indices; x^{msk} is the masked input tokens; x_i is the i^{th} input token to the model; \hat{m}_t is the predicted probability of the t^{th} token being masked by the discriminator. The Generator and Discriminator are trained alternately with their loss functions during training, and a hyperparameter λ is introduced to balance the learning rate between the two models. The tokens are direct inputs to the embedding layer of ELECTRA, where the embedding layer transforms each token into a dense vector for downstream processing by self-attention layers. The Generator’s softmax layer within the token prediction function outputs a probability distribution over the fixed vocabulary, thus ensuring that the Generator produces only valid microbiome tokens.

Pretrain and hyperparameter tuning. We pretrain the model on microbiome abundance data using the replaced-token detection objective, in which a small generator predicts masked (genus, bin) tokens and a larger discriminator learns to classify each token as original or replaced. Following best practices from the ELECTRA paper, we use a masking rate of 15%, where a subset of input tokens is masked and substituted with predictions from the generator. The generator is initialized with fewer layers and hidden units than the discriminator to maintain efficiency and prevent overfitting. Stratified validation set is used for hyperparameter tuning and early stopping, and the held-out test set provides unbiased estimate of pretraining effectiveness for downstream tasks. The Generator and Discriminator will be trained jointly using the Adam optimizer⁵³, with a linear warmup and inverse square root decay schedule, applying dropout and weight decay for regularization. We will perform a structured hyperparameter search on a 10% stratified subset of the training data to optimize key parameters (e.g., embedding dimension, number of layers), evaluating configurations on replaced-token detection accuracy with early stopping to prevent overfitting. The optimal configuration will then be used for full-scale pretraining.



Aim1c. Evaluate and benchmark the model performance. We will **evaluate** the pretrained OMFM's quality using replaced-token detection accuracy on a held-out test set. To assess robustness against data sparsity, we will conduct dropout simulations measuring embedding stability and prediction confidence. We will also analyze self-attention mechanisms, quantifying attention entropy and diversity to ensure the model learns biologically meaningful microbial interactions. Together, these evaluations will validate the quality, robustness and interpretability of the model before it is used for downstream tasks. To rigorously **benchmark** our approach, we will compare ELECTRA-based OMFM against three state-of-the-art architectures using the same data and optimization settings, including : **1) BERT-based model**^{10,50}, to contrast replaced token detection with generative token prediction; **2) TabTransformer**^{54,55}, to compare token-level versus column-wise self-attention; **3) Microbial General Model (MGM) 2.0**^{56,57}, to evaluate against other microbiome-specific pretrained models. Benchmarking against these established and specialized models will provide a clear assessment of the OMFM's performance, with final model selection also informed by success on the downstream AD classification task in **Aim 2**.

Cross-Modality Validation. We acknowledge that 16S rRNA sequencing lacks the strain-level resolution and functional annotation capabilities of **shotgun metagenomics**. However, the scale of existing oral 16S data far exceeds available oral metagenomes (~10k samples), making 16S the only current viable option for large-scale foundation model pretraining. To validate that our 16S-trained OMFM generalizes to metagenomic data, we will conduct a small validation study using paired 16S and metagenomic samples of same individuals (HMP cohort) and evaluate the model's replaced-token detection accuracy on metagenomics test set. If the model maintains comparable accuracy, this will demonstrate that the learned representations capture underlying biological patterns, supporting future extension of the OMFM to strain-level and functional metagenomic analyses.

Expected results and future directions. **1)** We expect OMFM to train successfully, demonstrated by high replaced-token detection accuracy confirming effective learning of microbial patterns and interactions. **2)** We will confirm biological interpretability through attention and embedding analyses showing the model captures known microbial co-occurrence patterns. **3)** We expect OMFM to achieve competitive or superior performance compared to benchmarking models. **Future work** will extend the OMFM to metagenomic data via transfer learning, enabling strain-level taxonomic resolution and functional gene annotation. Additionally, we will explore hybrid generative-discriminative pretraining strategies to refine the architecture.

Potential problems and alternative strategies. **1)** Acquiring large, high-quality data is a major challenge for model training. We have curated 187,145 samples from multiple sources, representing the largest oral microbiome dataset for model training. Additionally, synthetic datasets generated by tools like CAMISIM⁵⁸ can augment training data, particularly during early-stage training to address cold start challenges. **2)** Overfitting is another risk given the high dimensionality of the input space; in response, we will employ early stopping, dropout, and weight decay, and can reduce model complexity or adopt parameter-efficient tuning methods (e.g., adapters) if necessary. **3)** If ELECTRA underperforms compared to the benchmarked models, we will explore adapting best-performed model, or ensemble approaches that combine strengths from multiple pretraining paradigms.

Specific Aim 2: Develop and benchmark predictive models for AD using oral microbiome data. We will assess the feasibility of using oral microbiome for AD prediction by establishing baseline models and fine-tuning OMFM with AD prediction head. Comparing the models will reveal whether OMFM improves prediction performance for disease-specific tasks.

Aim2a. AD-labeled Oral microbiome dataset curation. We will curate a labeled dataset pairing 16S rRNA data with clinical AD diagnoses, incorporating **2,095** AD-labeled samples from previous studies (Table 3). **Additional 1,015** samples from the recently completed MIVAS III Study will be added once available⁵⁹. To address diagnostic heterogeneity across studies, we will: **1)** systematically review and document the diagnostic criteria and severity staging for each study in consultation with my neurology co-mentor (Drs. Noble), **2)** flag studies using non-standard or poorly documented diagnostic methods for sensitivity analyses, and **3)** prioritize studies with biomarker-confirmed diagnoses (CSF, PET). The data will be split into training, validation, and test sets (8:1:1), stratified by study source and diagnostic rigor.

Aim2b. Develop and fine-tune models for AD prediction. To evaluate OMFM's predictive power and generalizability in low-data regimes, we will establish **baseline models** using traditional ML. Since no prior work has applied ML to AD prediction using oral microbiome, we will develop low-complexity baselines with *Dr. Kevin Bonham* (computational biology mentor) to quantify the added value of deep representation learning. We will train logistic regression, random forests, support vector machines and gradient boosting models with PCA

Authors/organization	Journal	Year	Control	AD
Xi-Xi Liu et al.	J Alzheimers Dis	2019	39	39
Haiying Guo et al.	Oral Dis	2023	26	26
Lili Chen et al.	Geriatr Nurs	2022	0	66
Alba Troci et al.	PNAS NEXUS	2023	17	46
Yi-Fan Wu et al.	Int J Environ Res Public Health	2021	18	17
Na HS et al.	Research Square preprint	2020	14	15
Mihai S Cirstea et al.	J Alzheimers Dis	2022	54	45
Kuan-Lun Fu et al.	Oral Dis	2022	20	20
Haiying Guo	Oral Dis	2021	26	26
Irene Yang et al.	Exp Gerontol	2021	34	34
Majid Taati Moghadam et al.	J Clin Lab Anal	2022	15	15
Jacob Holmer et al.	J Oral Microbiol	2021	63	132
Lili Chen	Front Cell Infect Microbiol	2022	40	132
Hee Sam Na et al.	J clinical perio	2023	14	15
Argul Issilbayeva et al.	Pathogens	2024	71	64
Che Qiu et al.	Alzheimers Res Ther	2024	32	64
Yannick N Wadop et al.	bioRxiv	2024	15	17
Yiyi Zhang et al.	Mol Psychiatry	2023	35	19
Lili Chen et al.	J Clin Periodontol	2024	40	125
Tom Rubinstein et al.	Alzheimers Dement	2024	407	78
Joanna E L'Heureux et al.	PNAS NEXUS	2025	60	60
Total			1040	1055

Table 3. AD-labeled Oral microbiome 16S rRNA sequencing datasets identified from the published studies.

dimensionality reduction (20 components capturing 87% of variance; Fig. 4), optimizing hyperparameters via stratified cross-validation to **benchmark** transformer-based representations.

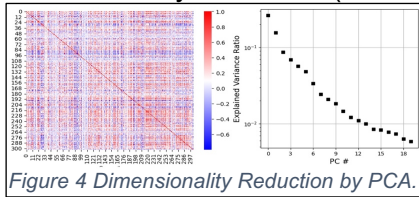


Figure 4 Dimensionality Reduction by PCA.

Adaptation (LoRA)⁶¹, inserting trainable adapter matrices (rank=4-16) parallel to frozen self-attention layers (Fig. 5). Only adapter weights are updated while the pretrained encoder remains fixed. Hyperparameters (hidden layer size, LoRA rank) will be optimized via validation set.

Aim2c. Models evaluation and explainability. We will evaluate OMFM performance on the held-out test set against traditional ML baselines and alternative transformer architectures (BERT, TabTransformer, MGM), each fine-tuned using the same protocol. We will report AUROC, accuracy, precision, recall, and F1-score. An AUROC exceeding 75% will be considered clinically meaningful⁶², with Δ AUROC > 10% indicating significant performance differences. To ensure model's **biological interpretability**, we will also implement explainability techniques. For tree-based models, we will apply SHAP⁶³ to quantify individual taxa contributions. For OMFM, we will compute integrated gradients (IG) to estimate token-level attribution, identifying influential genera while respecting contextual embeddings. Both methods provide interpretability on sample-level feature importance and population-level AD signatures, enhancing clinical trust by revealing biologically meaningful associations.

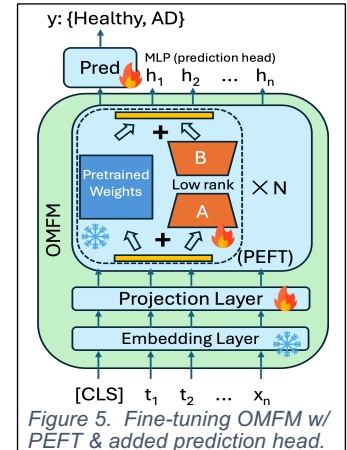


Figure 5. Fine-tuning OMFM w/ PEFT & added prediction head.

Aim2d. External validation in the WHICAP Cohort. We will further validate model generalizability on WHICAP cohort data, which was not used during training or hyperparameter tuning. Led by my mentors, *Dr. Panos Papapanou* and *Dr. James Noble*, the NIH-funded study of periodontal infections and AD on WHICAP Cohort⁶⁴ (R01 AG076015) collects longitudinal data, inducing clinical and oral microbial 16S rRNA seq data from a multi-ethnic cohort of aging adults (750 participants, 2 visits). I've obtained access to this high-quality dataset. We will preprocess WHICAP data using the same pipeline, and evaluate OMFM's performance (e.g., AUROC, accuracy).

Expected results and future directions. 1) We anticipate that our model will be benchmarked against traditional ML models, and achieve clinically meaningful performance (e.g., AUROC > 0.75) on both internal test-set and WHICAP external validation. 2) SHAP and IG are expected to highlight biologically plausible microbial signatures, supporting local and global interpretability and enabling validation against known disease-associated taxa. **Future directions.** 1) Enhance OMFM through multi-view contrastive learning, integrating co-abundance structure and taxonomic hierarchies during pretraining to better align representations with microbial ecology. 2) Incorporate uncertainty quantification methods (e.g., Monte Carlo dropout⁶⁵⁻⁶⁷, deep ensembles⁶⁸) into the classifier head to estimate confidence in AD predictions, which is critical for clinical deployment.

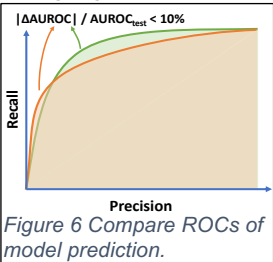
Potential problems and alternative strategies. 1) Population differences or label noise: We will perform sensitivity analysis to exclude ambiguous cases, control confounding with clinical metadata, and apply domain adaptation (CORAL⁶⁹, adversarial training⁷⁰). 2) If ELECTRA underperforms, we will investigate alternate pretraining objectives (contrastive learning, domain-adaptive masking), multi-task fine-tuning with auxiliary tasks (oral site prediction), and ensemble methods. We will use linear probes to assess embedding transferability. 3) We acknowledge that oral microbiome alone may have modest predictive performance given AD's multifactorial etiology. However, even a 5-10% improvement when integrated with clinical risk scores would have substantial public health impact given AD's prevalence. Our long-term vision is a multi-modal screening tool combining oral microbiome with clinical predictors and blood biomarkers.

Specific Aim 3: Explore clinical implementation of OMFM-based AD screening tool. While studies suggest altered oral microbiome in AD patients^{16,35,71}, detection feasibility and clinical potential remains unclear. This aim validates the AD prediction model clinically and explores early risk detection on longitudinal data.

Aim3a. Clinical feasibility study of oral microbiome-based AD detection. To evaluate the feasibility of using oral microbiome samples for non-invasive, cost-effective (~\$45/test) AD detection. Importantly, unlike previous studies listed in Table 2 that typically collected samples from a single site (e.g., saliva, dental plaque, or buccal mucosa), our approach will compare the diagnostic prediction accuracy of samples from different oral cavity sites within the same individual. This will help optimize sampling strategies for future study and clinical applications.

We will conduct this pilot study at the Clinical Research Center at Tufts Dental School. With guidance from *Dr. Noble* (neurology co-mentor, we will obtain the IRB approval and recruit 80 participants (40 AD patients and 40 cognitively healthy, gender- and age-matched individuals). Power analysis based on similar oral microbiome

studies⁷² (assuming AUROC=0.93) indicates that n=40 per group provides adequate precision (95% CI half-width ≤ 0.05) for pilot feasibility assessment. The inclusive and exclusive criteria will mirror those of the WHICAP study (aged ≥ 60 , >7 natural teeth, no other dementias, and no recent antibiotic use, cancer, or autoimmune diseases). We preliminary reviewed TMC patient records up to Feb 1, 2025, and identified 647 AD patients who meet these criteria, and established connection with Tufts Memory Care Clinic and Alzheimer's Association local chapter. Diagnoses and consent capacity will be verified via medical records before enrollment. Ethic: all participants will undergo a detailed informed consent process, with proxy consent^{73,74} for those with diminished capacity, and will be informed of their rights to receive or decline the results of their Montreal Cognitive Assessment (MoCA), dental exam, and model prediction outcomes. Exam and sample collection: Participants will be evaluated during two visits, 12 months apart. At each visit, they will complete a medical history form and be evaluated with a MoCA administered by Dr. Laudate (consultant) (healthy controls w/ score >26). I'll perform the dental exam and collect oral microbiome samples from saliva, dental plaque (and subgingival plaque if periodontitis is present), dorsum of the tongue, buccal mucosa, throat, and hard palate. Sample processing and sequencing: Genomic DNA will be extracted from samples using a GenElute Bacterial Genomic DNA Kit, stored at -20°C , and processed for sequencing via Illumina 16S Metagenomic Sequencing Library Preparation workflow on MiSeq v3 at Tufts Genomics Core. The data will be processed as described in **Aim 1** and used for AD diagnostic prediction. Performance evaluation: We will compare the predictive power across oral sites and validate against the test split from **Aim 2** (stratified by site). Model validation is defined as performance difference ($|\Delta\text{AUROC}|/\text{AUROC}_{\text{test}} < 10\%$ (Fig. 6).



Aim3b. Longitudinal AD Risk Longitudinal Risk Forecasting with the OMFM. While studies have shown that the gut microbiome changes significantly during the progression of Alzheimer's diseases^{75–77}, it remains unknown if similar dynamic changes occur in the oral microbiome. This critical research gap exists primarily due to the scarcity of longitudinal, time-series oral microbiome data linked to cognitive assessments. Our invaluable access to two distinct longitudinal datasets—the large, existing WHICAP cohort (**Aim2d**) and our newly collected Tufts cohort (**Aim3a**)—provides us an unprecedented opportunity. We will **leverage WHICAP data (~550) to develop a new downstream task for OMFM**. We will compare normalized cognitive assessment scores between visits and designate the top 25%⁷⁸ with steepest decline as "high-risk progression". By adding an MLP classification head, we will fine-tune OMFM on first-visit microbiome data to predict future high-risk status. We will then **externally validate this model on the independent Tufts cohort (80)**, evaluating its ability to predict 12-month cognitive trajectories in new participants. This will provide the first demonstration that longitudinal oral microbiome data can forecast AD risk, establishing critical proof-of-concept and preliminary data for future clinical applications focused on monitoring disease progression and treatment response.

Expected results, potential problems and alternative strategies. We anticipate rigorously clinically validating our model's ability to distinguish AD from non-AD cases with AUROC > 75 . Our feasibility study will optimize oral sampling strategy for AD prediction accuracy. Even if the model underperforms, the sample data from different oral sites remain valuable for identifying the best representations of oral samples for other systemic diseases. Furthermore, leveraging longitudinal data, we will predict AD risk by correlating temporal changes in oral microbiome profiles with cognitive decline, underscoring their potential for early detection. **Future work** includes a subsequent R01 large-scale clinical oral microbiome and AD study based on our pilot study and expanding this approach to other diseases. **Challenges** include recruiting a representative sample of AD patients with varying severity, especially early stage. **To address this**, we will review de-identified records and evaluate cognitive impairment with my neurology mentor and cnsultant. In addition, ethical considerations and human subject protection will be monitored by Dr. Athanasios Zavras (co-mentor) and Dr. Ellen Patterson (consultant).

D. Future directions

Research- This work establishes OMFM as a platform for oral-systemic health with three extensions: **1)** integrate metagenomic data for strain-level and functional resolution, **2)** conduct large-scale clinical research in OMFM-based AD screening, and **3)** extend OMFM to other systemic conditions as a versatile diagnostic platform. **Career-** This K08 positions me for independent research at the intersection of oral health, AI, and translational medicine. I will develop expertise in multi-modal data integration, establish interdisciplinary collaborations, and pursue NIH R01 funding for large-scale clinical studies. My goal is to lead a research program developing AI-driven diagnostic tools that transform oral health into a window for early detection of systemic diseases.



Training in the Responsible Conduct of Research

The RCR training was a significant part of my postdoc research training. I have completed a formal **Responsible Conduct of Research (RCR) Training** offered by Research Integrity, Office of the Vice Provost for Research (OVPR) at Tufts University. Training in the Responsible Conduct of Research (RCR) is an ongoing process at Tufts University. Trainees receive informal training from faculty and mentors, and formal training through the Tufts RCR course. This course currently meets NSF and NIH requirements, and all individuals covered by these mandates and working under eligible grants must attend this course. The course is administered by Tufts University Office of the Vice Provost for Research, which is responsible for administration of grants and contracts, management of intellectual property, oversight of human subject and laboratory animal research, and implementation of the university's policies on research and scholarship.

See <https://viceprovost.tufts.edu/responsible-conduct-research-rcr-training> for more details.

Format: The course consists of face-to-face instruction through a mixed format of slide presentations, didactic and small group discussions, and selected readings.

Subject Matter: The course includes (but is not limited to) the following instructional areas:

- a) Policies regarding human subjects and live vertebrate animals in research
- b) Data management practices, including acquisition, recording, archiving, disposal, etc., and associated laboratory tools
- c) Data ownership and sharing, and Open Access
- d) Responsible authorship and publication practices
- e) Peer review obligations and responsibilities
- f) Research misconduct and policies for handling misconduct
- g) Conflict of interest: personal, professional, and financial
- h) Financial management in the laboratory
- i) Collaborative research, including collaborations within an institution, between multiple institutions (including international collaborations), and with industry
- j) Mentor/mentee relationships and responsibilities
- k) The scientist as a responsible member of society, contemporary ethical issues in biomedical research, and the environmental and societal impacts of scientific research

Faculty Participation: The course is taught by a group of Tufts senior faculty and staff with experience in the relevant subject matter. Faculty in charge of and participating in research training programs frequently contribute to presentations and discussions.

Duration of Instruction: Instruction consists of a minimum of 12 one-hour sessions, typically three sessions per week over four weeks. Sessions are grouped according to theme when appropriate (e.g., Data management/Data ownership and sharing/Open Access; Responsible authorship/Peer review).

Frequency of Instruction: Trainees must participate in RCR training at the earliest opportunity during their employment at Tufts, at least once every career stage, and at least once every four years. Once the course is completed, the trainee receives a dated "certificate of completion."

How Participation in RCR Instruction Will Be Monitored

Participation in the Tufts RCR course will be monitored in two ways: attendance and class participation. Trainees enrolled in the RCR course will be expected to attend all sessions. The attendance will be the primary way to ensure that trainees have received adequate training. In addition to attendance, trainees are expected to be actively involved in class discussions. Because research is being done in a multitude of disciplines at Tufts, obtaining input from all trainees through sessions led by faculty and staff with a diversity of expertise is essential to lead to engaging discussions from multiple perspectives.

In addition, I also have completed the **Collaborative IRB Training Initiative (CITI)** program and the **Good Clinical Practice (GCP)** training and obtained the certificates.

Plans and Statements of Mentors

Given the multidisciplinary nature of the proposed work, we assembled an extensive mentoring team that exceeds the usual scope, drawing on experts from multiple relevant fields. The team includes co-primary mentors, Dr. Chen and Dr. Hassoun; co-mentors, Dr. He, Dr. Teles, Dr. Bonham, Dr. Papapanou, Dr. Noble and Dr. Zavras. Each mentor brings the specific expertise this proposal requires and is fully committed to their mentoring roles.

A. Co-Primary Mentors - Dr. Chen and Dr. Hassoun

We are truly delighted to express our strongest support for Dr. Zoe Zhu's K08 application and to affirm our commitment as her primary mentors, providing guidance for her career development and coordinating her esteemed research mentoring team. As her co-primary mentors, we confirm that Dr. Zhu will commit a minimum of 75% full-time effort to this K08 and related research activities. We are fully committed to protecting this dedicated time and ensuring she has the resources necessary to focus on her career development goals.

Dr. Zhu has effectively leveraged her expertise in basic research, clinical experience, and artificial intelligence to tackle critical gaps in dental research, with her work focusing on the high-priority NIDCR theme of oral-systemic disease connections. As senior PIs, we recognize the significant scientific impact of her proposed work from both dental research and computational biology perspectives. She has an impressive publication record, including 27 papers in high-impact journals, with four as first author and three as co-first author, as well as 2 issued and pending patents. Her work has been widely recognized by the scientific community. She recently applied machine learning for home-based periodontitis assessment using ML ensemble methods, achieving over 80% accuracy without overfitting. This work resulted in a published paper, won first prize at the IADR CTSN Outstanding Award, and secured funding from the 2025 Colgate CARE Program to advance this AI-driven tool toward clinical application. In September 2025, she was awarded the highly competitive Tufts Institute for Artificial Intelligence (TIAI) Seed Fund, which provides both funding support and the dedicated effort of a senior data scientist at 0.5 FTE (20 hours per week) for two years to collaborate on her AI research in oral health. Additionally, she has received the Tufts DO-IT grant, the ASBMR Young Investigator Award, the FASEB Mentored Presenter Award.

Dr. Zhu is a selected mentee in the NIH-funded AADOCR MIND the Future Program, where she has actively participated in group mentoring sessions, and received one-on-one mentorship from Dr. Flavia Teles, a leading expert in AI applications for oral research. This mentorship led to a collaboration developing an RNN model that predicts periodontitis progression, demonstrating her ability to integrate AI with clinically relevant dental research.

Beyond her research and professional skill development, Dr. Zhu is deeply engaged in scientific community service. She serves as the Vice President-elect of AADOCR Boston Chapter, Program Chair of the Society of In Vitro Biology, and as a committee member of the AADOCR Fellowship Committee. She also serves as Guest Editor for two special issues in *Frontiers in Oral Health*: "AI Applications in Dentistry" and "Diabetes and Oral Health." Additionally, she has contributed as an Early Career Reviewer for the NIH Center for Scientific Review and as a reviewer for prestigious journals, such as *Journal of Dental Research*.

Building on this strong foundation, we are honored to serve as Dr. Zhu's co-primary mentors with tremendous enthusiasm. Her development plan uniquely integrates oral-systemic health, machine learning, and microbiology, positioning her at the forefront of Dental-AI research. We will work closely with her co-mentors, providing targeted guidance and training in our areas of expertise to support her research and career advancement. Our goal is to help her establish an independent niche in this emerging field and address a critical oral health challenge.

• Scientific Qualifications as Mentor

Dr. Chen – I hold the positions as Director of Oral Biology Division and Professor of Periodontology Department at Tufts University School of Dental Medicine (TUSDM). My extensive research background in translational studies discovering connections between oral and systemic diseases, coupled with my mentoring experience, strongly qualifies me to mentor Dr. Zhu. I received exemplary training in Oral Pathology at University of Connecticut Health Center and reviewed numerous disease cases across all major bodily systems at the Armed Forces Institute of Pathology, providing me with vast knowledge of human diseases. I earned my Ph.D. in Periodontal Physiology at University of Toronto in 1993. Since 1994, I have consistently been funded by NIH and am currently leading four active R01 projects funded, providing substantial resources to support Dr. Zhu's proposed research beyond the allowable costs of this K08 award. Our recent research focuses periodontal diseases linked to systemic conditions such as diabetes and Alzheimer's disease. Dr. Zhu is a main contributor

to two of our recent papers. Dr. Zhu's K08 research proposal aligns well with our work on oral-systemic connections and takes an innovative turn by expanding into disease prediction using advanced ML techniques.

Dr. Hassoun - My lab focuses on developing novel ML models to advance biological and biomedical discovery. We have extensive experience with deep learning neural networks and have created multiple software tools to investigate issues related to metabolomics and microbiome-drug interactions. My research is well-funded by the NIH, NSF and DoD, ensuring adequate computational resources and expertise to support Dr. Zhu's machine learning research activities. My collaboration with Dr. Zhu began last year on a project using Large Language Models (LLMs) for dental record retrieval. We submitted an R21 proposal on this topic together as Co-Principal Investigators. I am very impressed by Dr. Zhu's ability as a quick learner who effectively applies AI methods to solve dental research questions. With the training opportunities provided by this K08 award, including formal ML courses and direct supervision from me (we propose Dr. Zhu work in my lab for three months to enhance her AI skills), I strongly believe she will make significant scientific contributions to this field.

• Previous Mentoring Experience

Dr. Chen - In addition to my research and clinical work, I am also an experienced teacher and mentor. Since 1982, I have taught a broad range of dental and craniofacial courses and mentored approximately 97 predoctoral and postdoctoral individuals.

Five representatives of the mentees:

- a. Qisheng Tu, MD, PhD. (3 years, 2002-05), Professor, Department of Periodontology, TUSDM
- b. En Luo, DDS, PhD. (1.5 years in 2010-11), Professor, West China Hospital of Stomatology, Chengdu, China
- c. Shu Li, DDS, PhD. (1.0 year in 2008), Professor and Director, School of Stomatology Shandong University, China
- d. Jin Zhang, MD, PhD. (1.5 years in 2013-14), Professor, Guangzhou University of Chinese Medicine, China
- e. Ling Li, PhD. (1.0 year in 2003), Professor and Deputy Director of the National Experimental Teaching Demonstration Center of Basic Medical College, Southern Medical University, Guangzhou, China.

Dr. Hassoun - My mentoring experience includes supervising 9 PhD students (currently 8 in AI/ML for biological engineering) and over 30 MS and undergraduate projects. I have also mentored new faculty at Tufts and other institutions in grant writing, collaboration, and navigating departmental politics. Additionally, I have consulted on ML approaches for challenges such as gut microbiome analysis, biosensing applications, and metabolomics.

Five representatives of the mentees:

- a. Xinmeng Li, Ph.D. (5 years, 2017-2022), Machine Learning Scientist, Montai, Cambridge, MA
- b. Sara Amin, Ph.D. (6 years, 2013-2019), Data Scientist, Amazon, Bellevue, WA
- c. Neda Hassanpour, Ph.D., (5 years, 2013-2018), Principal Data Scientist, Takeda, Cambridge, MA
- d. Ehsan Ullah, Ph.D. (6 years, 2009-2014), Research Software Engineer, Qatar Computing Research Institute, Qatar
- e. Guatham Sridharan, Ph.D. (5 years, 2008-2013), Associate Director, Alnylam Pharmaceuticals, Cambridge, MA

• Mentoring Role of the Co-Primary Mentors

As co-primary mentors on Dr. Zhu's K08 grant, we will oversee the project's progress and provide comprehensive guidance on both scientific research and career development. We will also coordinate the mentoring team to synchronize efforts, evaluate Dr. Zhu's overall progress, provide constructive feedback, and offer redirection as needed through mentoring committee meetings, and annual assessment of Individual Development Plan (IDP).

Dr. Chen - Dr. Chen will leverage his extensive expertise in translational and clinical dental research by meeting with Dr. Zhu weekly to review data, troubleshoot challenges, and offer insights into oral-systemic disease connections. He will also oversee Dr. Zhu's studies on oral pathogens, monitor the conduct of the proposed research, and review future grant proposals and manuscripts. With her laboratory space in the Division of Oral Biology, Dr. Zhu benefits from daily access to Dr. Chen. Furthermore, Dr. Chen will guide her transition from a mentored researcher to an independent investigator while expanding her professional network in dental research.

Dr. Hassoun - Dr. Hassoun will oversee the Computer Science and AI aspects of this K08 proposal. She will hold bi-weekly meetings with Dr. Zhu, via Zoom or in-person, to mentor her in applying advanced ML techniques to oral microbiome data. Specifically, Dr. Hassoun will work closely with Dr. Zhu on developing the OMFM (Aim 1) and its application for oral and systemic disease prediction (Aim 2), discussing model training progress and troubleshooting challenges to secure impactful publications and presentations. Additionally, with K08 support, Dr. Zhu will spend three months in Dr. Hassoun's lab to further enhance her deep learning skills.

B. Co-Mentors - Dr. He, Dr. Teles, Dr. Bonham, Dr. Papapanou, Dr. Noble and Dr. Zavras

In addition to the primary mentors overseeing Dr. Zhu's research and training, the co-mentors will offer targeted guidance on specific aspects of this K08 proposal.

Dr. Xuesong He (ADA Forsyth) - Oral Microbiology

- **Qualifications as Mentor.** As a dentist and microbiologist, Dr. He has been in the oral microbiology field for over 17 years, with extensive expertise in bacterial inter-species interactions, microbial ecology and oral microbiome-systemic links which are integral to this proposed K08 study (Aim 1 and 2). Currently, Dr. He is the contact PI of two active R01s and Co-PI of a multiple-PI R01 grant, which focuses on different aspects of human oral microbiome research, including microbial-host interaction.
- **Mentoring Experience.** Over the past 10 years, Dr. He has mentored 8 predoctoral and 12 postdoctoral trainees, many of whom received F or K99 awards; several have advanced to faculty roles while others have joined the biotech industry.
- **Mentoring Role.** Dr. He will host monthly 1on1 meetings, via Zoom or in-person, and involve Dr. Zhu in his ongoing projects on microbial interspecies interactions at ADA Forsyth, providing her with intensive training in sample collection, extraction, and processing to deepen her understanding of the physiological mechanisms underlying microbial dysbiosis and disease.

Dr. Flavia Teles (UPenn Dental School) - AADOCR MIND the Future Mentor, Host-microbial Interactions

- **Qualifications as Mentor.** Dr. Teles is a periodontist with extensive training in oral biology and oral microbiology, and she has dedicated the past 18 years to clinical and translational research. Her work in the oral microbiome of health and disease, spans microbial cultivation and multi-omics approaches. Currently, she serves as contact PI and Co-I on multiple NIDCR grants. With a strong publication record and proven expertise in studying periodontal dysbiosis, Dr. Teles is exceptionally well-qualified to mentor Dr. Zhu.
- **Mentoring Experience.** Dr. Teles has extensive mentoring experience, serving on a T32 grant and the AADOCR MIND the Future Program. In these roles, she has guided numerous trainees in oral microbiology and dental research, helping them secure competitive funding and advance their careers.
- **Mentoring Role.** As the assigned mentor through MIND the Future Program, Dr. Teles has provided Dr. Zhu with invaluable guidance in research design, grant writing, and the application of AI to dental research through monthly 1-on-1 sessions and group mentoring. This effort significantly enhanced Dr. Zhu's K08 proposal and sparked a new collaboration to develop a neural network model that uses longitudinal gingival crevicular fluid biomarker data to predict periodontitis progression. During the K08 phase, Dr. Teles will continue to mentor Dr. Zhu by offering targeted training in oral microbiology, and clinical dental research methods, as well as career development mentoring, through the MIND the Future Program and monthly virtual meetings.

Dr. Kevin Bonham (Tufts Medical School) - Computational Biology, AI in Microbiome and Brain Function

- **Qualifications as Mentor.** Dr. Bonham has a diverse background spanning experimental biology and computational genomics, he specializes in developing advanced ML techniques to analyze large-scale biological datasets, focusing on the interplay between microbial communities and brain function.
- **Mentoring Experience.** Although this is Dr. Bonham's first time serving as a mentor, he was profoundly shaped by the mentorship of Dr. Curtis Huttenhower, his postdoctoral supervisor and a leader in computational genomics and the Human Microbiome Project. Dr. Bonham will adopt a similar mentoring approach with Dr. Zhu, providing detailed guidance on machine learning techniques for microbiome research.
- **Mentoring Role.** As a co-mentor for this K08 award, Dr. Bonham will provide comprehensive, hands-on training in data preprocessing, normalization, and the fine-tuning of Transformer-based models for oral microbiome analysis. His mentoring plan includes monthly one-on-one sessions in person. Additionally, as Dr. Zhu enrolls in a formal ML course, Dr. Bonham will be available to answer her questions and provide guidance, ensuring she effectively integrates and applies the course material to the K08 research projects.

Dr. Panos Papapanou (Columbia Univ. Dental School) - Oral-Systemic Health and Dental Clinical Research

- **Qualifications as Mentor.** Dr. Papapanou has extensive expertise in the epidemiology and pathobiology of periodontitis and its systemic impacts. As the Multiple PI of the ongoing WHICAP Periodontal Infections and AD study (NIH R01 AG076015), Dr. Papapanou has demonstrated leadership in clinical trial design and execution. His pioneering work on periodontal infections and AD in the elderly population, including studies

on subgingival microbial colonization, has significantly advanced our understanding of the oral-systemic connection, particularly regarding AD.

- **Mentoring Experience.** Dr. Papapanou has a longstanding record of mentoring emerging dental researchers, both formally through NIH training grants and informally through national advisory committees. He has guided numerous investigators who have secured independent funding and achieved prominent academic positions, reflecting his deep commitment to developing the next generation of dental scientists.
- **Mentoring Role.** Dr. Papapanou will provide targeted guidance on integrated oral and systemic health research, refining clinical study designs, and interpreting clinical findings, through quarterly meetings in Year 1-2, transitioning to monthly virtual meetings in Year 3-5. During a two-week visit to Columbia University (Year 2), Dr. Zhu will gain firsthand experience in clinical trial operations, including participant recruitment, standardized assessment protocols, data collection procedures, and regulatory compliance, directly preparing her for the pilot clinical study in Aim 3b. Dr. Papapanou and Dr. James Noble, as MPIs on a WHICAP sub-study, have committed to sharing their longitudinal data - including AD-related and oral 16S rRNA data - for the clinical validation and further training on AD risk evaluation of the AD prediction model.

Dr. James Noble (Columbia Univ. Medical Center) - Clinical Neurology and Alzheimer's Disease

- **Qualifications as Mentor.** Dr. Noble is an internationally recognized expert in neurodegenerative diseases, neuroepidemiology, and clinical research. As a key leader at the Taub Institute for Research on Alzheimer's Disease, he is the leading PI of 4 ongoing NIH-funded projects, examining cognitive outcomes and systemic factors that influence dementia, including periodontitis.
- **Mentoring Experience.** Dr. Noble has a strong track record mentoring emerging clinical neuroscientists through his roles at Columbia University and with the American Academy of Neurology. He has served as neurology clerkship director, founding co-director of the NIA-funded Brief Research in Aging and Interdisciplinary Neurosciences-BRAIN T35, and co-director of the VP&S preclinical neuroscience course.
- **Mentoring Role.** Via quarterly meetings in Year 1-2, transitioning to monthly virtual meetings in Year 3-5, and during Dr. Zhu's visit at Columbia, Dr. Noble will provide targeted mentorship in several critical areas: 1) cognitive assessment and AD stage labeling to ensure that diagnostic criteria reflect clinical consensus, 2) evaluation of reliability and clinical relevance of Dr. Zhu's model outputs ensure they can translate into meaningful clinical practice, 3) rigorous clinical validation to ensure that the model's predictions align with real-world patient care, 4) providing experience in clinical neurology research, 5) helping her convert the model into actionable insights that advance non-invasive AD diagnostics.

Dr. Athanasios Zavras (TUSDM) - Career Development and Clinical Study Design

- **Qualifications as Mentor.** Dr. Zavras has a robust background in epidemiology, translational research, and clinical trial design, he has successfully advanced his own career through NIH K awards and now brings over 30 years of Mentoring Experience to support young investigators.
- **Mentoring Experience.** Over his career, Dr. Zavras has mentored more than 80 students and junior faculty, guiding them toward independent research careers through formal mentorship programs and individual coaching as Assistant Dean for Faculty Advancement at TUSDM. Since 2024, Dr. Zavras has served as Dr. Zhu's career development mentor through the TUSDM Faculty Mentorship Program.
- **Mentoring Role.** As a co-mentor on Dr. Zhu's K08 application, Dr. Zavras will provide guidance on clinical research design, including study design, bias control, examiner calibration, and patient recruitment. He will also mentor Dr. Zhu in her overall career development through quarterly in-person meetings and the TUSDM Faculty Mentorship Program. His extensive experience in clinical research will be pivotal in helping Dr. Zhu transition to an independent research career and secure future R01 funding.

C. Consultants

Along with the mentoring team, Dr. Zhu will also receive support from consultants with specialized expertise.

Consultant: *Dr. Thomas Laudate* (Tufts Medical Center) - Clinical Neurology and Alzheimer's Disease

In addition to Dr. Noble, who provides neurology expertise from outside Boston, Dr. Laudate serves as our local neurology consultant at Tufts. Dr. Laudate is a Clinical Neuropsychologist in Memory Care Clinic at TMC. His clinical work and research experience include a focus on Alzheimer's disease and other neurodegenerative disorders. Dr. Laudate has been working closely with Dr. Zhu on the development of the research proposal Aim

2 and 3, regarding the potential participants identification and AD assessment methods in the clinical pilot study. He will guide Dr. Zhu on recruitment, AD patient communication and conducting the MoCA assessment.

Consultant: *Dr. Ellen Patterson* (TUSDM) - Ethics and Patient Communication in Clinical Study

Dr. Patterson is a board-certified psychiatrist and the TUSDM Director of Behavioral Science Education. She will serve as a consultant, focusing on ethical considerations, plain language health communication and ethical information consent process. In this K08 proposal, her role is to ensure that participants are involved in the study both effectively and ethically. Regular meetings will be held with her to receive guidance on the clinical pilot study.

Consultant: *Drs. George Chen* (Forsyth) and *Albert Tai* (Tufts) - Oral Microbiome Sequencing and Database

Dr. Chen is the Director of Forsyth Bioinformatics Core and Forsyth Oral Microbiome Core (FOMC), and Dr. Tai is the Director of Tufts Genomic Core. With extensive expertise in 16S rRNA sequencing and data processing, they will serve as bioinformatics consultants, and sample sequencing will be conducted at their core facilities.

Biostatistical consultant: *Dr. Meghan Short* (Tufts CTSI) – Statistical Plan and Data Analysis

Dr. Short, a statistician specializing in microbiome research and Alzheimer's & Neurodegenerative Diseases, offered invaluable input on my proposal development and has agreed to serve as my biostatistical consultant.

D. Mentoring Plan

We have developed a dedicated mentoring plan that reflects our unwavering commitment as co-primary mentors. This plan provides comprehensive, individualized guidance and ensures Dr. Zhu receives targeted training in both scientific and professional areas to support her transition to an independent research career.

Mentoring team assembly. Given the multidisciplinary nature of the proposed work, we have worked with Dr. Zhu to assemble an extensive mentoring team that exceeds the usual scope, to include experts from multiple relevant fields. In addition to the co-primary mentors (Dr. Chen and Dr. Hassoun), Dr. Zhu will receive mentoring from Dr. Bonham to guide the application of ML models to microbiome data, and Dr. Noble and Dr. Laudate to provide expertise in AD clinical study. Further, Dr. He will train her on microbial interspecies interactions, and Dr. Papapanou and Dr. Teles will mentor her on the role of periodontal pathogens in AD. Finally, Dr. Zavras will serve as a career development mentor, with additional consultation from Dr. Ellen Patterson (Clinical Ethics), Dr. Meghan Short (Biostatistics), and Dr. Albert Tai and Dr. George Chen (Next-Generation Sequencing). This diverse team ensures comprehensive support for both the scientific and professional development of the project.

Setting goals. Dr. Zhu has accumulated significant expertise in molecular and computational biology, dental research and clinical practice, through her extensive prior training. The primary goal of her K08 phase is to provide her with formal training in advanced machine learning and microbiology, and to further enhance her skills in translational and clinical research. This training will accelerate her progress towards scientific independence and establish her as a leading researcher in the field of dental AI. (see development plan for detailed primary training goal 1-4)

Funding and resource support. Funding- Both of our laboratories are well-funded. Dr. Chen's four active NIH R01 grants and Dr. Hassoun's NSF and DoD funding provide continuous support throughout the entire five-year K08 award period, covering research costs beyond those supported by the K08 mechanism. Additionally, Dr. Zhu has secured research funding from the Colgate Care (2025-2026) and TIAI Seed Fund (2025-2027). Dr. Zhu is requesting a small supply budget for research on this K08, which will provide essential funds and offer her the valuable experience of managing a budget. Resource- We have sufficient resources to support Dr. Zhu in carrying out the proposed studies, including high-performance hardware for large deep learning model training and the necessary infrastructure for microbiome sequencing and conducting clinical pilot studies. Additionally, The TIAI Seed Fund also provides the dedicated effort of a senior data scientist at 0.5 FTE for two years to support her AI research development, further strengthening the computational resources available during the critical model development phase (Year 1-2).

Training and evaluation. Working together with Dr. Zhu, we have meticulously crafted a K08 training plan, which encompasses intensive mentorship from an exceptional mentoring team, combined with didactic and independent study (e.g. formal courses for machine learning, microbiology and translational study), thorough training in the responsible conduct of research, participation in seminars and national scientific conferences, as

well as enhancing the impact of Zoe's research and her networking. *(For detailed training plan, please refer to the Career Development - Training Activities section).*

We will provide annual evaluations of Dr. Zhu's progress with the input of other mentors as part of the annual assessment of the Individual Development Plan (IDP). Since working in the same department, Dr. Chen meets with Dr. Zhu every Tuesday afternoon, to review data and progress, and he is available for daily consultation. Dr. Hassoun will hold formal bi-weekly meetings with Dr. Zhu, via Zoom or in person, to discuss model training progress and troubleshooting. All other mentors will also monitor the research and training progress of Dr. Zhu through regular mentoring sessions, to ensure she meets training milestones in machine learning, oral microbiome analysis, and clinical research. Her performance will also be assessed by her contributions to project deliverables, publications, grant submissions, and participation in professional development activities, ensuring her transition to an independent research career. Lastly, the primary mentors are committed to coordinating progress report meetings with all mentors every year, which will serve as platforms for synchronizing efforts, evaluating progress, discussing challenges, providing feedback, and offering redirection when necessary.

Career development. We have developed a framework for the faculty position that Dr. Zhu holds at TUSDM and secured institutional support *(please refer to the Institutional Commitment Letter from Dean Karimbux)*. The plan allocates 75% effort to the proposed research and career development activities in this K08 Award, 10% to active teaching, 10% to mentoring dental students and residents in research, and 5% to community service and administrative duties, such as department meetings, committee services, and faculty development activities. Given Dr. Zhu's dentist-scientist background with multidisciplinary training and her career goals, our objective is to ensure her success as an aspiring dental academician. We are aware of the challenges and opportunities that face junior faculty with research and teaching activities, and with the support from this K08 award, we will be able to protect Dr. Zhu's 75% effort to the proposed plan.

Independence. Dr. Zhu's diverse training and experience position her as a future leader in dental research, particularly in the emerging field of dental-AI. Through this K08 award, we aim to maximize her growth and prepare her for an independent research career. A key advantage of her proposal is that the necessary sources and datasets for her model training have already been identified, and data processing methods have been tested on her preliminary data, which allows her project to commence without delays. Consequently, we anticipate that Dr. Zhu will begin publishing results early in her award period. We foresee Dr. Zhu submitting a competitive R01 application by the end of her K08 tenure, ensuring a smooth and well-coordinated transition towards greater independence. Given her demonstrated perseverance and proven track record, this timeline appears both achievable and realistic.

In summary, our mentoring plan provides Dr. Zhu with a robust, multidisciplinary support network that spans oral biology, advanced machine learning, and clinical research. Through regular one-on-one meetings, formal coursework, and hands-on training at mentors' institutions, she will gain the technical, professional, and leadership skills needed to transition to an independent research career. Our strong institutional resources and comprehensive evaluation framework ensure that Dr. Zhu is well-prepared to secure future R01 funding and emerge as a leader in the emerging field of dental-AI research.

Sincerely,



Jake Chen, DMD, MDS, PhD, FACD
Director, Division of Oral Biology
Professor, Department of Periodontology
Tufts University School of Dental Medicine

Date: Sep 9, 2025



Soha Hassoun, Ph.D.
Professor, Department of Computer Science (Primary)
Adjunct Professor, Dept of Chemical and Biological Engineering
Adjunct Professor, Dept of Electrical and Computer Engineering

Date: Sep 18, 2025



Sep 18, 2025

Re: Letter of Support for Dr. Zhu's K08 Application

Dear Members of the Review Committee,

I am writing to strongly support Dr. Zhu's K08 award application, titled "Development of an Oral Microbiome Foundation Model for Systemic Diseases Assessment." I'm Dr. Xuesong He, a Professor in the Department of Microbiology at the ADA Forsyth Institute. My research focuses on the oral microbiome, particularly on microbial-host interactions and microbial ecology, demonstrating how dysbiosis contributes to oral and systemic diseases. This extensive background uniquely qualifies me to mentor Dr. Zhu on microbiology for this K08 training grant.

Dr. Zhu's proposed approach aims to improve microbiome analysis by integrating microbial interactions and ecological context. Currently biostatistical and bioinformatic methods use dimensionality reduction, which can miss critical interactions within the microbial communities. In contrast, Dr. Zhu's self-supervised oral microbiome foundation model (OMFM), trained on large-scale unlabeled 16S rRNA data, generates contextualized taxa representations that capture intricate structures and patterns while reducing bias from small control groups. Furthermore, by incorporating a prediction head fine-tuned with AD patient data, Dr. Zhu's OMFM shows substantial potential applications, including the prediction of systemic conditions like Alzheimer's disease. If success, this groundbreaking work will not only deepen our understanding of oral-systemic connection but also paves the way for innovative disease diagnostic and assessment strategies.

As a co-mentor on this K08 training grant, I will offer comprehensive guidance through monthly 1-on-1 mentorship meetings as well as in-person, hands-on wet lab training covering the following aspects:

Data collection and processing: I have guided Dr. Zhu in identifying available high-quality oral microbiome 16S rRNA sequencing datasets from public sources and experts in my network, and I will continue to provide guidance throughout this process (**Aim 1a**). My familiarity with microbiome sequencing data source, broad collaborative network, and experience in handling and processing large-scale microbiome data will be instrumental in ensuring good quality and quantity of the data.

Bioinformatics and data interpretation: Leveraging my expertise in microbial ecology and bioinformatics, I will provide insights into the development of the baseline and model compression (**Aim2b and 2d**). Give Dr. Zhu the necessary training to improve her understanding of microbial interactions and community dynamics and assist with data interpretation.

Involvement in Ongoing Projects and Laboratory Skill Development: I will involve Dr. Zhu in my ongoing projects which focus on investigating microbial interspecies, microbial-host interactions and elucidating the impact of oral microbial ecology on human health and disease. Dr. Zhu will gain a deeper understanding of the underlying physiological and biological mechanisms driving host immune responses, microbial signaling, and community dynamics. Additionally, she will receive intensive training in microbiome sample collection, extraction, and processing for her **Aim 3**, thereby developing both the technical expertise and scientific insight required to contribute meaningfully to this field.

Dr. Zhu's interdisciplinary skill set, combining basic research, dental training, and artificial intelligence, enables her to create revolutionary methodologies for exploring the oral microbiome's role in systemic diseases and further applying them in translational and clinical studies. With the support of this K08 award, I am confident that Dr. Zhu will achieve her research goals, profoundly impact the discovery of oral-systemic connections, and prepare herself to pursue future R01 funding in this field. I wholeheartedly support Dr. Zhu's K08 application and am excited to contribute my expertise to help her succeed. Thank you for considering this application. Please feel free to contact me if you require any further information.

Sincerely,

A handwritten signature in black ink, appearing to read "Xuesong He".

Xuesong He, PhD. DDS.
Professor
The ADA Forsyth Institute
Phone: (617) 892-8228
Email: xhe@forsyth.org

Sep 12, 2025

Dear Members of the K08 Grant Review Committee,

I am delighted to offer my unwavering endorsement for Dr. Zoe Zhu's NIH/NIDCR K08 award application. As a co-mentor on this grant and as Zoe's mentor through the NIH-funded AADOCR MIND the Future program since September 2024, I have had the privilege of working closely with Zoe through monthly one-on-one Zoom meetings and dedicated training sessions. Our interactions have covered both scientific challenges and career development, including intensive guidance on grant writing, which has been instrumental in developing this application.

I have had the opportunity to closely observe Zoe's professional development. I have been consistently impressed by her dedication, ingenuity, and the rapid progress she has made in applying artificial intelligence (AI) to dental research. I am confident that Zoe is a truly outstanding candidate for this award, with the potential to make transformative contributions to the field of periodontal health.

Zoe exemplifies innovation and diligence, quickly adopting new technologies to tackle diverse challenges in oral health research using machine learning. In our recent collaboration, she designed a study employing a recurrent neural network to predict periodontitis progression from longitudinal data on gingival crevicular fluid biomarkers—an impressive integration of advanced computational methods into clinically relevant research.

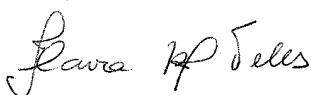
Zoe has demonstrated exceptional communication skills, regularly presenting her work at prestigious international and national conferences such as IADR and AADOCR. Her achievements, including receiving the IADR CTSN Outstanding Award, Colgate Award for Research Excellence, and Tufts Institute for Artificial Intelligence Seed Fund for AI applications in oral health, underscore her academic excellence. Furthermore, her selection as Early-Career Reviewer for an NIH grant review session in Washington, D.C., and as a mentee in the NIH-funded AADOCR MIND the Future highlights her potential as a rising leader in dental research.

As Professor in the Department of Basic and Translational Sciences at the University of Pennsylvania School of Dental Medicine with expertise in oral microbiology and clinical periodontal research, I am well positioned to mentor Zoe on this K08 grant and in her career trajectory. I am confident that my continued guidance will equip her with skills and insights needed to make significant contributions to our field.

In my role as co-mentor, I will continue to provide comprehensive guidance throughout her K08 training via monthly mentoring meetings and additional discussions tailored to her needs. Leveraging my expertise in oral diseases, microbiology, and clinical research, I will train her to integrate high-throughput 16S rRNA sequencing data and machine learning techniques with clinical insights to characterize multi-species oral biofilms and identify novel oral pathogens. Additionally, I will mentor her in developing robust clinical research designs aimed at elucidating the dynamic relationships between the oral microbiome and systemic diseases, such as Alzheimer's disease, while optimizing oral sampling strategies to enhance predictive accuracy. This mentorship will equip her with the technical expertise and translational skills necessary to launch her future independent research projects and drive innovative advancements in oral health.

Thank you for considering this application. Please do not hesitate to contact me if you require any further information.

Sincerely,

A handwritten signature in black ink that reads "Flavia Teles".

Flavia Teles, DDS, MS, DMSc

Professor of Microbiology Department Basic and Translational Sciences University of Pennsylvania
School of Dental Medicine Levy Building 422
240 South 40th Street Philadelphia, PA 19104 Email: fteles@upenn.edu

September 18, 2025

Dear Members of the NIH K08 Review Committee,

I am writing to express my strong support for Dr. Zoe Zhu's K08 application, "Development of an Oral Microbiome Foundation Model for Systemic Diseases Assessment." My name is Kevin Bonham and I am an assistant professor in the Department of Medicine at Tufts University School of Medicine and Tufts Medical Center. My expertise in applying advanced machine learning techniques to large-scale biological datasets, with a focus on the interplay between microbial communities and brain function, uniquely qualifies me to guide Zoe in this critical domain. I am also a former postdoctoral fellow of Dr. Curtis Huttenhower - a preeminent researcher in computational biology, a leading scientist in the Human Microbiome Project, and creator of many foundational software methods for microbial multi-'omics - I have been deeply involved in cutting-edge gut microbiome research and continue to collaborate on Dr. Huttenhower on multiple cohort-analysis and software development projects. This background reinforces my ability to mentor in the integration of computational methods with biological research.

As we both work at the Tufts Health Science Boston campus, I have had the opportunity to work closely with Zoe on her K08 grant application. Through our discussions, I have seen that she has a keen understanding of the challenges of microbial data processing, pathological changes of microbiome during cognitive impairment, and the integration of computational methods with biological insights. In our mentoring sessions, I have provided detailed guidance on how to leverage advanced ML techniques to analyze complex oral microbiome datasets, and I am committed to continue mentoring her on this K grant, with a specific focus on modeling the interplay between the oral microbiome and Alzheimer's disease.

Under my mentorship, Zoe will receive comprehensive, hands-on training in cutting-edge computational methodologies, including data preprocessing, normalization, and fine-tuning of transformer-based models. Our training plan will include monthly one-on-one sessions, participation in advanced seminars in my department, and collaborative research projects that emphasize the integration of microbiome data with predictive modeling for systemic diseases. I am confident that this tailored training will equip her with the skills necessary to develop and validate a robust Oral Microbiome Foundation Model (OMFM), ultimately advancing the field of Dental AI and non-invasive disease diagnostics.

Zoe's innovative approach, which combines large-scale unlabeled oral microbiome data with high- quality disease-specific datasets and state-of-the-art deep learning methods, promises to overcome the limitations of traditional analytical techniques. I believe her work has the potential to transform our understanding of oral-systemic health and pave the way for new diagnostic tools in Alzheimer's disease and beyond.

I fully support Zoe's K08 application and am enthusiastic about the opportunity to mentor her as she develops into an independent investigator in this emerging interdisciplinary field. Please do not hesitate to contact me if you require any additional information.

Sincerely,



Kevin Bonham, PhD
kevin.bonham@tuftsmedicine.org Assistant
Professor
GI Division | Tufts Medical Center



COLUMBIA UNIVERSITY
College of Dental Medicine

PANOS N. PAPAPANOU, DDS, PhD
*Professor of Dental Medicine Section of Oral,
Diagnostic and Rehabilitation Sciences
Division of Periodontics*

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New York City, September 5, 2025

Re: Letter of Support for Dr. Zhu's K08 Application

Dear Members of the Review Committee,

I am writing to express my enthusiastic support for Dr. Zhu's K08 application titled "Development of an Oral Microbiome Foundation Model for Systemic Diseases Assessment". As a multiple principal investigator on the WHICAP Ancillary Study of Oral Health, I recognize the significant potential of Dr. Zhu's proposal to advance our understanding of the role of the oral microbiome in Alzheimer's disease (AD). Dr. Zhu's innovative approach — using deep neural networks to develop a foundation model for oral microbiome analysis — represents a critical advancement over traditional statistical and bioinformatics methods. Her proposal, which seeks to utilize the existing datasets to predict AD risk, not only addresses a significant gap in the current research but also holds promise for the development of non-invasive, cost-effective diagnostic tools in dental and clinical settings.

As a seasoned researcher in periodontology and a key contributor to the WHICAP Ancillary Study of Oral Health examining the relationship between oral health and systemic diseases in a diverse elderly population — based on a longitudinal investigation that has been underway for over 25 years — I have devoted a good part of my career to investigating the links between periodontal infections and systemic diseases. My work, currently supported by an R01 grant from the National Institute on Aging, investigates how periodontal pathogens trigger systemic inflammation and contribute to cognitive impairment and AD. Through these studies, we have collected critical data on oral microbiome dynamics in AD, and I have successfully mentored investigators in this field. I am well qualified to guide Dr. Zhu in exploring the oral microbiome's predictive power for AD.

As a co-mentor on Dr. Zhu's K08 training grant, I am fully committed to providing comprehensive guidance throughout her training. I will share my extensive expertise in periodontal infections, as well as my experience in clinical study implementation, with a particular focus on supporting her **Aims 2 and 3**. In addition to monthly mentoring sessions for research supervision and troubleshooting, our research team is also committed to making the extensive WHICAP Oral Health 16S rRNA sequencing data available to Dr. Zhu for the oral microbiome foundation model and AD prediction model training. Furthermore, the clinical study and longitudinal data collected in our ongoing R01 "A Longitudinal Study of Periodontal Infections and Alzheimer's Disease" provides a unique resource that will support the external validation of the AD prediction model and examining temporal microbiome changes during AD development and progression.

Moreover, I am delighted by the prospect of collaborating with Dr. Zhu on our ongoing studies in periodontitis and AD. Her expertise in advanced computational methods and deep learning will undoubtedly complement our work and enhance the translational impact of our research. I am confident that her contributions will play a pivotal role in shaping future interdisciplinary studies at the intersection of oral health and neurodegeneration.

I strongly support Dr. Zhu's application and believe that her proposed research will significantly advance the oral and systemic diseases research. Please feel free to contact me if you require any further information.

Sincerely,

Panos N. Papapanou, DDS, PhD

September 19, 2025

Re: Zoe Zhu, DDS, PhD, K08 Applicant

Dear K08 Award Review Committee Members,

It is my pleasure to write this letter in strong support of Dr. Zhu and her K08 application, “Development of an Oral Microbiome Foundation Model for Systemic Diseases Assessment”. I am a Professor of Neurology at Taub Institute for Research on Alzheimer's Disease and the Aging Brain and G.H. Sergievsky Center, Columbia University Medical Center. My research interests center on aging, dementia, and cognitive outcomes in older adults, and I currently serve as Principal Investigator on NIH-funded research projects examining the role of periodontal disease, diabetes, inflammation, and microbial exposures on cognitive trajectories.

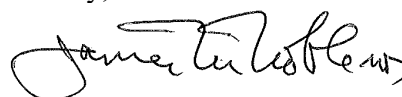
I have reviewed Dr. Zhu's proposal and am enthusiastic about her innovative approach to applying machine learning and explainable AI methods to Alzheimer's disease (AD) staging and outcome prediction. As a neurologist specializing in neurodegenerative conditions, I recognize the importance of detecting subtle, early biological changes that may signal AD development and progression. My laboratory and clinical teams have encountered similar challenges in parsing multifaceted patient data to identify risk factors and intervention opportunities. This background positions me well to provide meaningful guidance to Dr. Zhu on:

- **AD Stage Labeling and Data Processing:** I will advise on the most appropriate diagnostic criteria and neuropathological confirmations to ensure that Dr. Zhu's data alignment reflects cutting-edge clinical consensus.
- **Data Interpretation and Explainability:** I will help assess the reliability and clinical relevance of her models' outputs, ensuring the data-driven methodologies and algorithmic decisions translate meaningfully into clinical practice.
- **External Validation of the OMFM for AD prediction:** External Validation of the OMFM for AD prediction: Dr. Zhu will have access to de-identified data from our WHICAP study, which focus on periodontitis and AD will providing a real-world dataset for the model's important external validation.
- **Regular Mentorship and Collaboration:** As a co-mentor, I will meet monthly with Dr. Zhu to review progress, address challenges, and guide her toward successful publications and presentations. Our ongoing R01 project in periodontitis and AD, co-led by Dr. Papapanou (also a mentor of Dr. Zhu) and me, provides natural synergy with this K08 proposal. I look forward to offering both scientific insights and professional mentorship.

Dr. Zhu has proposed an ambitious yet feasible plan that leverages advanced computational tools in the service of improving the care of patients with, or at risk for, AD. Her passion for translational science is evident, and I am confident that her dedication—combined with our collective mentorship—will yield impactful findings and help shape her development into an independent investigator.

I strongly endorse Dr. Zhu's K08 application and am fully committed to supporting her progress throughout the award period. Please feel free to contact me if you have any questions regarding my role as co-mentor and collaborator.

Sincerely,



James M. Noble MD, MS, CPH, FAAN
Professor of Neurology at CUIMC
Taub Institute for Research on Alzheimer's Disease
and the Aging Brain
GH Sergievsky Center
Department of Neurology
Columbia University Irving Medical Center



School of Dental Medicine

Athanasios Zavras, DDS, MS, DrMedSc

Professor and Chair of the Department of Public Health and Community Service

Associate Dean for Community and Global Affairs, Dental School Administration

September 14th, 2025

RE: K08 Applicant, Zoe Zhu, D.D.S, Ph.D.

Dear Review Committee Members,

I am writing to express my unwavering support for Dr. Zhu and her K08 award application, which seeks to advance our understanding of the interaction and ecological environment of the oral microbiome and exploring its novel application in systemic diseases assessment like Alzheimer's disease, using cutting-edge deep learning technology. In addition, the proposed project has the potential to advance Dr. Zhu, a promising junior faculty at TUSDM with training as oral surgeon and with a PhD in molecular biology, as well as research experience on computational biology (a rare trait among dentists) to independent translational researcher.

As the Delta Dental of Massachusetts Professor and Department Chair of Public Health and Community Service at Tufts University School of Dental Medicine (TUSDM), and with my clinical research experience, I recognize the potential impact of Dr. Zhu's proposal. Having being a beneficiary of two NIH K awards in my past (K23 and K22), I particularly recognize the impact that the proposed training in Dr. Zhu's academic career. In my case, it allowed me protective time over several years to "develop" my academic skills beyond molecular epidemiology to become a clinical researcher that is able to design, direct, analyze and lead Phase 3 and 4 clinical trials. I wholeheartedly believe that the K08 program will offer similar opportunities to the applicant.

As a mentor of over 80 students in the past 30 years, I wish to emphasize my enthusiasm in mentoring junior colleagues to reach their potential. This enthusiasm translates into an active mentorship plan for Dr. Zhu. In my previous institutional capacity as Assistant Dean for Faculty Advancement at the School of Dental Medicine, I had the opportunity to mentor Dr. Zoe Zhu through our TUSDM Faculty Mentorship Program in career development and translational research since late last year. Now serving as Associate Dean for Community and Global Affairs, I continue to actively mentor junior faculty and remain deeply committed to Dr. Zhu's professional development. It quickly became apparent to me that Dr. Zhu's unwavering dedication and innovative approach are exactly the kind of driving forces needed to advance the field. During the K08 award period, I commit to provide guidance on Dr. Zhu's career development through monthly meetings, and ensuring she possesses the resources and opportunities necessary to emerge as an independent researcher.

Additionally, in my mentoring role guiding the integration of external and clinical validation of the prediction model with the WHICAP study led by Dr. Papapanou and overseeing the clinical pilot study, I will lend my expertise in study design, bias control, examiner calibration, patient recruitment, IRB submission, and patient consultation regarding laboratory results, ensuring continuous support and troubleshooting throughout the process. A key focus of this pilot study is to explore and optimize the sampling strategy for future studies in this field, by assessing the AD prediction power of the microbiome samples collected from various sites in the oral cavity. At the end of the K08 and if successful with the main Aims, Dr. Zhu will have enough preliminary results to support an R01 submission.

I wholeheartedly endorse Dr. Zhu's application for the K08 award and pledge my full support to ensure the success of this impactful research. Should you require additional information or clarification regarding my support for this project, please feel free to reach out to me.

Sincerely,

A handwritten signature in black ink, appearing to read "A. Zavras", written in a cursive style.

Prof. Athanasios Zavras

Description of Institutional Environment

The scientific environment at Tufts University fosters synergy and collaboration among investigators, students, and faculty, supporting Dr. Zhu's research training and career development to achieve her goal of becoming an independent investigator.

Mentoring and consulting resources. Dr. Zhu's mentoring team consists of established scientists primarily from Tufts. Dr. Chen, an expert in oral-systemic translational studies, and Dr. Hassoun, a specialist in machine learning applications in healthcare, from the Dental School and Computer Science, respectively, will provide extensive training in oral-systemic connections and machine learning. They are well-funded by NIH and DOD. Additional mentors and consultants further strengthen her support network: Dr. Noble (co-mentor, Neurology, Columbia Univ.) and Dr. Laudate (consultant, Clinical Neurology, Tufts Medical Center) will contribute expertise in Alzheimer's Disease (AD) clinical research; Dr. Kevin Bonham (co-mentor in computational biology, Tufts Medical School) will guide the application of ML models to study cognitive function; Dr. Papapanou (Columbia Dental College, mentor on periodontal pathogens and AD) and Dr. Teles (University of Pennsylvania, mentor in microbiology and clinical periodontology) will provide insights into oral pathogens in AD; and Dr. He (ADA Forsyth) is the co-mentor on microbial interspecies interactions. Dr. Zavras (Tufts Dental School, career development co-mentor) will support her clinical research and professional growth, while consultants Dr. Ellen Patterson (Tufts Dental School, clinical ethics), Dr. Meghan Short (Tufts CTSI, biostatistics), and Dr. Albert Tai (Tufts Genomic Core, next-generation sequencing) offer specialized expertise.

In addition to this strong mentoring team, Dr. Zhu is an active participant in the Tufts Faculty Network Mentoring Program, which provides access to senior faculty mentors across different schools and departments, fostering interdisciplinary collaboration and broadening her institutional perspective beyond her immediate research area.

Institutional Funding and Technical Support on Dr. Zhu's AI work. Dr. Zhu was recently awarded the highly competitive Tufts Institute of Artificial Intelligence (TIAI) Seed Fund (Nov 2025 - Nov 2027), which provides strong support for her AI research. This award includes an annual budget of \$10,000 for project costs. More importantly, TIAI has assigned a senior data scientist to work directly with Dr. Zhu on her research projects at 0.5 Full-Time Equivalent (FTE), equivalent to 20 hours per week. This data scientist will serve as a hands-on collaborator and mentor, providing real-time guidance on machine learning methodologies and ensure that Dr. Zhu masters AI and computational skills throughout the first two years of the K08 training period, including advanced machine learning techniques, algorithm development, model validation, and best practices in AI-driven research. This support will facilitate Dr. Zhu's progressive independence in applying AI and ensure successful completion of the proposed research aims, underscoring Tufts' institutional commitment to her development as an independent dentist-scientist with AI expertise.

Core Facilities and Resources

- The **Clinical Research Center at Tufts Dental School** provides an excellent clinical setting for conducting research, with clinical research coordinators assisting investigators with patient recruitment, data collection, and study organization. Dr. Zhu has successfully collaborated with the CRC team on previous projects.
- Dr. Zhu has access to Tufts' High-Performance Compute (**HPC**) cluster with over 200 nodes and ~6,504 CPU cores, supporting deep learning and bioinformatics analysis.
- The Tufts University Genomics Core (**TUGC**) provides key instruments including Illumina NovaSeq 6000, HiSeq 2500, NextSeq 550, and MiSeq sequencers, along with services for NGS library preparation, sample QC, and data processing. Dr. Zhu has successfully collaborated with the TUGC team on previous projects.
- The **Tufts Dental School Technology Services Team** offers a strategic support for health information management and security tailored for the school, ensuring data integrity and compliance with regulations.

Support from Tufts CTSI and OVPR Office. The Tufts Clinical and Translational Science Institute (CTSI) and the Office of the Vice Provost for Research (OVPR) offer substantial support for career development. Tufts CTSI provides resources for interdisciplinary research, including access to collaborative networks, mentoring programs, and training in clinical and translational science. The OVPR office offers workshops and seminars on grant writing, research ethics, and career development, helping early-career investigators like Dr. Zhu to enhance their research skills and professional growth.

Institutional Commitment to Candidate's Research Career Development

RE: Dr. Zoe Zhu, K08 Mentored Clinical Scientist Research Career Development Award Application

Dear Reviewers,

As Dean of Tufts University School of Dental Medicine (TUSDM), I am delighted to provide the following information regarding our commitment to Dr. Zoe Zhu's research and career development training.

Founded in 1868, TUSDM is a leader in education, patient care, research, and community service. We have a robust support system for junior faculty seeking external grant applications. Our TUSDM Faculty Mentorship Program, provides senior PI mentorship for junior PIs, assisting with research, career development, and NIH grant preparation. Dr. Zavras, our Associated Dean for Community and Global Affairs, is Zoe's mentor in this program. We offer well-equipped Clinical Research Centers and dedicated teams to support faculty in their translational and clinical studies. The school continually invests in cutting-edge technology to ensure access to the latest advancements in oral healthcare, underscoring our commitment to fostering innovation and excellence in research and education.

Dr. Zoe is currently a full-time assistant professor at TUSDM. Dr. Zhu was promoted to assistant professor from her postdoctoral fellow position in July 2022 in recognition of her outstanding performance. She joined Tufts with an impressive resume as a dual-trained dentist-scientist and has excelled in research, teaching, and service. To support her next career steps, an advisory oversight committee has been established, including mentors Dr. Jake Chen (TUSDM) and Dr. Soha Hassoun (Tufts Computer Science), co-mentors Dr. Brent Forester (Tufts Medical Center), Dr. Xuesong He (Forsyth), Dr. Kevin Bonham (Tufts Medical Center), Dr. Flavia Teles (UPenn), Dr. Panos N. Papapanou (Columbia), Dr. James Noble (Columbia), Dr. Athanasios Zavras (TUSDM), and consultants Dr. Albert Tai (Tufts Genomics Core), Dr. Ellen Patterson (TUSDM), and Dr. Meghan Short (Tufts CTSI). Dr. Zhu successfully completed an internal pilot grant (DO-IT grant, \$5k) and was recently awarded the Colgate Award for Research Excellence (\$30k) to advance her research on AI applications in dentistry.

TUSDM is committed to providing Dr. Zhu with office space (M&V811OS), laboratory space (dedicated bench space in Dr. Chen's lab), equipment, and other resources for her research and career development. She has a dedicated laptop with necessary software for data analysis and access to the Tufts axiUm electronic database. Additionally, she has full access to all core facilities and the high-performance computing hardware available at Tufts Analytics Platform (TAP). Faculty and staff overseeing these cores are committed to supporting Dr. Zhu with her research project and training.

As a member of Tufts University, Dr. Zhu participates in numerous faculty development programs and seminar series offered by the Office of the Vice Provost for Research (OVPR) and Tufts Clinical and Translational Science Institute (CTSI). This allows her to network, collaborate, and communicate with other scientists and clinicians in the Tufts scientific community.

TUSDM will ensure Dr. Zhu devotes at least 75% protected time to developing her research career. We are fully committed to her retention, development, and advancement during the award period. TUSDM will provide Dr. Zhu with all necessary resources to complete her research project, achieve her career development goals, and transition to a productive and independent dentist-scientist investigator.

Sincerely,



Nadeem Karimbux, DMD, MMSc
Dean
Professor of Periodontology

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 12/31/2027

Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data *

☒ Yes ☐ No

Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.

Are Human Subjects Involved

☒ Yes ☐ No

Is the Project Exempt from Federal regulations?

☐ Yes ☒ No

Exemption Number

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8

Other Requested Information

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	The clinically validation our fine-tuned OMFM on AD diagnostic prediction, as a non-invasive and economical approach, a pilot study.	No

Section 1 - Basic Information (Study 1)

1.1. Study Title *

The clinically validation our fine-tuned OMFM on AD diagnostic prediction, as a non-invasive and economical approach, a pilot study.

1.2. Is this study exempt from Federal Regulations *

☐ Yes

☒ No

1.3. Exemption Number

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?

☒ Yes

☐ No

1.4.b. Are the participants prospectively assigned to an intervention?

☐ Yes

☒ No

1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?

☐ Yes

☒ No

1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?

☐ Yes

☒ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- the individuals diagnosed with Alzheimer's Disease

2.2. Eligibility Criteria

The participants will be required to meet the following criteria: (1) identify English as their preferred written and spoken language; (2) age 50 years or older; (3) ability to read, understand and complete questionnaires independently or with their proxies; and (4) no use of antibiotics and probiotics in the last 3 months.

2.3. Age Limits	Min Age: 60 Years	Max Age: 100 Years
2.3.a. Inclusion of Individuals Across the Lifespan	Individualsacrossthelifespan_zz.pdf	
2.4. Inclusion of Women and Minorities	Inclusion_Women_Minorities_zz.pdf	
2.5. Recruitment and Retention Plan	RecruitmentandRetention_zz.pdf	
2.6. Recruitment Status	Not yet recruiting	
2.7. Study Timeline	STUDY_TIMELINE_zz.pdf	
2.8. Enrollment of First Participant	01/01/2026	Anticipated

INCLUSION OF INDIVIDUALS ACROSS THE LIFESPAN

Scientific/Ethical Rationale for Age Range of Participants:

The primary focus of this study is on Alzheimer's Disease (AD), which predominantly affects older adults. Therefore, the age range of participants will be from 50 years and above. This inclusion is justified for the following reasons:

- **Scientific Rationale:** AD primarily affects individuals aged 60 and above, who constitute the majority of our study population. Including individuals aged 50-59 allows us to capture data on the early onset and progression of AD, providing valuable insights into the disease's development stages. By setting the minimum age at 50, we ensure that our study is both scientifically relevant and focused on the population most at risk.
- **Ethical Rationale:** Excluding individuals under 50 years of age is justified due to the very low prevalence of AD in younger age groups. Including such young participants would not be scientifically relevant to the study's objectives and may pose unnecessary risks.

Expertise and Experience Working with Included Age Groups:

- **Investigating team:** Dr. Zhu, the principal investigator, and all our co-ordinations and staff have experience in working with older adults. Dr. Laudate is a clinical neurologist has extensive experience working with older adults and individuals at risk of AD. He will provide necessary training to the team prior the pilot clinical study.
- **Institutional Resources:** Our TUSDM clinical research center regularly conducts studies involving older adults, providing a supportive environment with necessary expertise.

Appropriateness of Facilities Available for Age Range of Participants: Our institution is well-equipped to accommodate the needs of older adult participants, including **Accessible Research Facilities** designed to be elder-friendly, with features that cater to mobility issues and other age-related challenges, and **Data Privacy and Security** with robust protocols ensure the privacy and confidentiality of sensitive health data, particularly for vulnerable older adult populations.

Age Distribution and Meaningful Analysis: The inclusion of a wide age range allows for meaningful analysis relative to the study's purpose:

- **Early Onset Detection:** By including participants aged 50-59, we can identify early signs and progression patterns of AD, contributing to early intervention strategies.
- **Progression and Impact:** Studying participants aged 60 and above provides insights into the disease's later stages, aiding in developing comprehensive treatment and management plans.

INCLUSION OF WOMEN AND MINORITIES

No study subject will be excluded based on gender or race/ethnicity. Research has shown that minorities and women are particularly vulnerable to Alzheimer's disease (AD). Women have a higher incidence of AD at later ages and relative to Caucasians, the threat of AD is even more substantial in the African-American and Hispanic communities. Based on these known demographics of Alzheimer's Disease, we expect the study population to be inclusive of a diverse demographic representation.

Gender Inclusion:

We anticipate that approximately 50% of the study participants will be female. This estimation aligns with the prevalence of Alzheimer's Disease, which affects women at higher rates than men. Including a balanced gender representation is critical for understanding the disease's impact across genders and ensuring that our findings are applicable to both men and women.

Racial and Ethnic Inclusion:

We aim to achieve a diverse racial and ethnic composition in our study population. Based on the demographics of the patient populations at our study sites, we expect the following approximate distribution:

White: 50%

Black or African American: 40%

Other races (including Asian, American Indian/Alaska Native, and Native Hawaiian/Other Pacific Islander): 10%

Regarding ethnicity, we anticipate that approximately 95% of our study participants will identify as non-Hispanic, with the remaining 5% identifying as Hispanic or Latino. This distribution reflects the demographics of the populations most affected by Alzheimer's Disease and those served by our healthcare facilities.

Recruitment Strategies:

To achieve these inclusion goals, we will employ targeted recruitment strategies, including: 1) Outreach through community centers and organizations that serve diverse populations. 2) Collaboration with healthcare providers to identify and refer eligible participants from underrepresented groups. 3) Utilization of culturally appropriate recruitment materials and methods to engage diverse communities.

By implementing these strategies, we aim to ensure robust participation from women and minority groups, thereby enhancing the scientific validity and impact of our research.

RECRUITMENT AND RETENTION PLAN

This study will recruit up to 40 AD patients, and 40 age- and sex- match cognitively healthy control participants. The AD patients will be recruited from the Department of Adult Neurology at Tufts Medical Center. The recruitment of age-matched and cognitively healthy control participants will be conducted through a search of the TUSDM axiUm system for active dental patients who have no record of dementia or other conditions that meet our exclusion criteria.

For both groups, a Telephone Screening Script will be utilized to inform potential participants about the research study, and evaluate eligibility based on the selection criteria. If the patient/control is interested in participating in the study, they will be asked to come to the TUSDM research clinic for a study visit. All participants will be informed that they are free to decline participation and that no participating will have no effect on their status in the clinical facility. Considering cases when AD participants may have a diminished capacity to give consent, we will accept participant assent accompanied by proxy consent from a surrogate decision maker as a valid form of informed consent. In addition, all participants will be made aware of their rights to both receive and decline the results of their MoCA test, dental exam, and ML model outcomes.

The participants will be required to meet the following inclusion criteria: (1) identify English as their preferred written and spoken language; (2) age 50 years or older; (3) ability to read, understand and complete questionnaires independently or with their proxies; and (4) no use of antibiotics and probiotics in the last 3 months.

Subjects who meet any the following criteria will be excluded: (1) diagnosed with other types of dementia, such as vascular dementia, Lewy body dementia and alcoholic dementia; (2) For healthy controls only: Participants must have a MoCA score of 26 or higher, which is the MoCA cut-off for “normal”. (This will be tested during their visit. Samples will not be collected and sequenced if score < 26. Participants will still receive compensation.) (3) teeth number less than 7; (4) receiving supragingival scaling, subgingival scaling and root planning and other periodontal surgery treatments during the 6 months before sampling; (5) having open surgical treatments of head and/or mouth; (6) a history of cancer, autoimmune diseases, radiotherapy and chemotherapy; and (7) taking antibiotics, immunomodulators, cytokines and probiotics within the last 3 months.

STUDY TIMELINE

Conducting the study on a **rolling basis** allows for continuous **participant recruitment** and data collection, enhancing flexibility and improving participant retention. This approach addresses the challenges of recruiting a diverse and representative sample over time, allows for early data analysis and integration, and ensures efficient use of resources throughout the study period.

There're some key milestones on the timeline:

Month 12: IRB approval, staff training.

Month 15: Initiate recruitment, baseline data collection.

Month 18: DNA sequencing and preliminary data analysis.

Month 24-54: rolling recruiting, patient visits, sample collection and process.

Month 55-58: data interpretation.

Month 60: Final reporting and dissemination of results.

2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	Tufts University School of Dental Medicine

Inclusion Enrollment Report 1

1. Inclusion Enrollment Report Title* : The clinically validation our fine-tuned OMFM on AD diagnostic prediction, as a non-invasive and economical approach, a pilot study.
2. Using an Existing Dataset or Resource* : ☐ Yes ☒ No
3. Enrollment Location Type* : ☒ Domestic ☐ Foreign
4. Enrollment Country(ies): USA: UNITED STATES
5. Enrollment Location(s): Tufts University School of Dental Medicine
6. Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	2	2	0	0	4
Asian	2	2	0	0	4
Native Hawaiian or Other Pacific Islander	2	2	0	0	4
Black or African American	14	14	0	0	28
White	18	18	2	2	40
More than One Race	0	0	0	0	0
Total	38	38	2	2	80

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects

Protection_of_Human_Subjects_zz.pdf

3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?

☐ Yes ☒ No ☐ N/A

Single IRB plan attachment

3.3. Data and Safety Monitoring Plan

Data_Safety_Monitoring_Plan.pdf

3.4. Will a Data and Safety Monitoring Board be appointed for this study?

☐ Yes ☒ No

3.5. Overall structure of the study team

Overall_Structure_of_the_Study_Team_zz.pdf

Protection of Human Subjects

1. Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

- **Overall Study Design:** This is a cross-sectional study focused on validating the performance of our OMFM model in Alzheimer's Disease (AD) prediction. Participants will undergo cognitive assessments, demographic surveys, periodontal examination, and biological sample collection (subgingival and saliva).
- **Subject Population:** The study will include individuals aged 50 and above, 50% of them are diagnosed with AD. Approximately 50% of the subjects will be female, and we expect a diverse racial and ethnic composition (50% White, 40% Black or African American, 10% other races; 5% Hispanic or Latino).
- **Site:** Research will be conducted at the Clinical Research Center at Tufts University School of Dental Medicine.

b. Study Procedures, Materials, and Potential Risks

- **Research Procedures:** Participants will undergo cognitive assessments, demographic surveys, and biological sample collection. DNA will be extracted from the subgingival and saliva samples.
- **Materials and Data Collection:** Private identifiable information will be collected and stored securely. Previously collected biospecimens may be used if they can be linked with living individuals by authorized personnel only.
- **Potential Risks:**
 - **Psychological Risks:** Anxiety during cognitive assessments.
 - **Privacy Risks:** Potential breach of confidentiality concerning personal health information.
 - **Other Risks:** Social and legal risks if sensitive information is disclosed.

2. Adequacy of Protection Against Risks

a. Informed Consent and Assent

- **Informed Consent Process:** Consent will be obtained by trained research staff in a private setting, explaining the study's purpose, procedures, risks, and benefits. For participants unable to consent, consent will be obtained from legally authorized representatives (LARs). Documentation will be maintained securely.
- **Children and Vulnerable Populations:** The study does not involve children or other vulnerable populations.

b. Protections Against Risk

- **Minimizing Risks:** Oral microbiome sample collection and periodontal exam will be performed by licensed dentist. Cognitive assessments will be conducted with sensitivity to participants' comfort. Data will be de-identified and stored in encrypted databases, with access limited to authorized personnel.
- **Medical Interventions:** Emergency protocols will be in place for adverse events, with immediate medical intervention available.
- **Handling Incidental Findings:** Any incidental findings will be reviewed by the principal investigator and communicated to participants following ethical guidelines.

c. Vulnerable Subjects

- This study does not involve special vulnerable populations such as fetuses, neonates, pregnant women, children, or prisoners.

3. Potential Benefits of the Proposed Research to Research Participants and Others

- **Benefits to Participants:** Participants may benefit from early detection for AD, as well as access to health information and resources.
- **Benefits to Others:** The study aims to enhance understanding of AD, potentially leading to better diagnostic tools and treatments, benefiting the broader community.

4. Importance of Knowledge to be Gained

- **Scientific Importance:** This research will provide critical insights into the genetic and cognitive factors influencing AD, contributing to the development of predictive models and personalized interventions.
- **Reasonable Risks:** The anticipated benefits to participants and the knowledge gained justify the minimal risks involved, ensuring that the research is both ethically and scientifically sound.

DATA AND SAFETY MONITORING PLAN

A Data Safety Monitoring Board will not monitor this study because this is a minimal risk and non-therapeutic protocol. There is no research study intervention. The principal investigator and study team will review any unanticipated problems related to data safety or adverse events, and the principal investigator or study personnel will report unexpected adverse events according to TUFTS IRB policy. Any serious adverse event will lead to a cessation of enrollment until the relationship between the adverse event and the study conduct is determined. All serious adverse events will be reported to the IRB within 48 hours and other adverse events will be reported on an annual basis at time of continuing review by the IRB.

Overall Structure of the Study Team

For this study, “The clinically validation our fine-tuned OMFM on AD diagnostic prediction, as a non-invasive and economical approach, a pilot study”, we assembled a strong research team.

Investigating team:

PI - Dr. Zhu, assistant professor at TUSDM, has experience in working with older adults. Dr. Zhu will take the MoCA training to become a certified MoCA examiner for cognitive dysfunction screening. The MoCA assessment will be performed by Dr. Zhu, under the supervision by Dr. Thomas Laudate, a member on Dr. Zhu’s advisory team.

Advisor – Dr. Laudate, a clinical neuropsychologist at Department of Adult Neurology, Tufts Medical Center. Dr. Laudate has extensive experience in AD clinical diagnosis and in working with older adults and individuals at risk of AD. He will provide necessary training to the team prior the pilot clinical study.

Research Coordinators - Joseph Cimmino and Natalie S. Sadek, at the TUSDM Clinical Research Center. They have extensive experience in clinical studies and experience in working with older adults. They will assist Dr. Zhu on conducting patient recruitment, screening, providing inform consent, recording the data at visits, creating case reports, keeping study data/files organized and available throughout the study. In addition, together with Dr. Zhu, the coordinator will undergo an official MoCA training to become a certified examiner for administering the MoCA test. This process will be supervised by Dr. Thomas Laudate, a clinical neuropsychologist.

In addition, I would like to highlight our TUSDM clinical research center, which regularly conducts dental studies, as well as the studies involving older adults, providing a supportive environment with necessary expertise for this study.

Section 4 - Protocol Synopsis (Study 1)

4.1. Study Design

4.1.a. Detailed Description

4.1.b. Primary Purpose

4.1.c. Interventions

Type	Name	Description
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4.1.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ☐ Yes ☐ No

4.1.e. Intervention Model

4.1.f. Masking ☐ Yes ☐ No

☐ Participant ☐ Care Provider ☐ Investigator ☐ Outcomes Assessor

4.1.g. Allocation

4.2. Outcome Measures

Type	Name	Time Frame	Brief Description
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4.3. Statistical Design and Power

4.4. Subject Participation Duration

4.5. Will the study use an FDA-regulated intervention? ☐ Yes ☐ No

4.5.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.6. Is this an applicable clinical trial under FDAAA? ☐ Yes ☐ No

4.7. Dissemination Plan

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

RESOURCE SHARING PLAN

In our software and data sharing plans, we aim to provide means for replicating all our results.

Software Sharing Plans

This research will generate validated computational models and scripts written in python. The OMFM model will be publicly shared under a BSD open-source license. Such a permissive and widely used license will enable software dissemination and modifications by the open-source community. Results will be stored in appropriate file formats (e.g., tabular data in .csv files, or xml or json files). Models will be made available through the PIs website and on GitHub. All released code will have sufficient documentation and seeded with (synthetic) example data to allow easy use of our code. Researchers in this area will be able to use our code to explore their own data and advance their applications. A website hosted at Tufts University will give access to the tools developed within this proposal.

Data Sharing Plans

- Our models will use training datasets from publicly available datasets. We will avoid replicating data already in the public domain and respect licensing agreements. We will provide a listing and date of specific data used from databases. We will also specify how data is partitioned for training, validation, and test to ensure the ability to replicate our results.
- The pilot study in Aim 3 will generate novel data. We will endeavor to release our results and de-identified data rapidly, as detailed in the Data Management and Sharing Plan.

Plan for Dissemination of Research Finding

Once completed, methodologies and results developed from this proposal, will be disseminated via preprint server (arxiv and/or medRxiv.org) and peer-reviewed publications. Example journals for submission include: Journal of Dental Research, International Journal of Oral Science, and Journal of Dentistry. To further share our methods and approaches with the scientific community, we submit the work for publications at conferences, including AI in Health Conference, and Digital Health AI and Data, and annual meeting of International Association of Dental Research.

NIH Generated message:

The Other Plan(s) attachment included with the application is not evaluated during the peer review process but will be evaluated prior to a funding decision. Although part of the official submission, the attachment is maintained as a separate document in eRA Commons viewable by authorized users and is not part of this assembled application.

Authentication of Key Biological and Chemical Resources

1. We will purchase the GenElute™ Bacterial Genomic DNA Kit (Sigmaaldrich) for DNA extraction.
2. We will purchase the Nextera XT DNA Library Preparation Kit (illumina) for library construction.
3. We will purchase the MiSeq Reagent Kit v3 (illumina) for sequencing.

The purchased resources of chemicals will be authenticated prior to ordering and after receiving the chemicals to ensure that the authentication data provided by the vendors meets our needs in terms of how the product will be used. If the chemicals are going to be used long-term, we will assess the stability of the chemicals by assaying the activity of the chemicals periodically using methods as we described in our preliminary studies. Most of the chemicals will be used in this proposal have been validated and confirmed their specificity and efficiency in our preliminary studies. We generally order new reagents every 6 months.