

SUMMARY STATEMENT
(Privileged Communication)

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Release Date: 03/13/2025
Revised Date:

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Application Number: 1K25DE035216-01

Principal Investigator

ELIAS, JEREMY

Applicant Organization: ADA FORSYTH INSTITUTE, INC.

Review Group: DSR
National Institute of Dental and Craniofacial Research Special Grants Review
Committee

Meeting Date: 02/25/2025
Council: MAY 2025
Requested Start: 07/01/2025

Opportunity Number: PA-24-191
PCC: L5R1

Project Title: Bacterial Bioprinting for Analysis of Oral Microbe Ecosystems and Antimicrobial Interactions
SRG Action: Impact Score:47
Next Steps: Visit https://grants.nih.gov/grants/next_steps.htm
Human Subjects: 10-No human subjects involved
Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Project Year	Direct Costs Requested	Estimated Total Cost
1	151,700	163,836
2	151,700	163,836
3	151,700	163,836
4	151,700	163,836
5	151,700	163,836
TOTAL	758,500	819,180

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1K25DE035216-01 Elias, Jeremy

RESUME AND SUMMARY OF DISCUSSION: This is a new K25 application from ADA Forsyth Institute in response to PA-24-191, "Mentored Quantitative Research Development Award (Parent K25 Independent Clinical Trial Not Allowed)". The goal of this application is to provide Dr. Jeremy Elias with protected time for supervised study and research, enabling productive professionals with quantitative and engineering backgrounds to integrate their expertise into NIH-relevant research. The proposed research aims to investigate bacterial bioprinting to analyze oral microbial ecosystems and antimicrobial interactions, focusing on optimizing *S. mutans* in 3D models, interspecies effects on biofilms, and antimicrobial efficacy in 3D environments. Mixed strengths and weaknesses were noted in the application. The candidate has a solid foundation in material science and biomaterials and demonstrates a strong commitment to career development through a well-structured plan emphasizing coursework, scientific networking, and communication. Additionally, the candidate benefits from an outstanding research environment with strong institutional support, well-equipped facilities, and a highly qualified mentorship team. The project takes an innovative approach by incorporating 3D printing technology for microbial modeling, presenting a novel direction. Furthermore, the interdisciplinary team brings together expertise in biomaterials and microbiology, ensuring alignment with the project's objectives. However, the application lacks clear biological context, with an unclear justification for the use of 3D printing. While the candidate has a solid background in material science, the publication record in microbiology is modest. The proposed research exhibits inconsistencies in design, with key microbiological factors, such as oxygen requirements and polymicrobial interactions, not adequately addressed. The measurement approaches for material characterization and bacterial interactions appear underdeveloped. The absence of preliminary data further weakens the study's feasibility and rationale, raising concerns about the overall scientific rigor of the proposed research. Additionally, the evaluation plan lacks strong assessment metrics for tracking candidate progress and project success, and potential gaps in expertise, such as the absence of a dentist or cariologist, may limit the project's clinical relevance. As a result, the panel expressed moderate enthusiasm for this application, leading to a medium Overall Impact score.

DESCRIPTION (provided by applicant): Dental caries is one of the most widespread chronic diseases, presenting a significant burden to human health and economy worldwide. Caries-causing bacteria and biofilms exist not only on substrates of tooth surfaces, but also in three-dimensional environments with varying architecture and porosity, making the modeling of these 3D architectures significant for the study and treatment of caries. This project aims to generate new information on single- and multi-species interactions involving *S. Mutans*, one of the primary caries-causing agents, using previously unexplored in vitro 3D architectures. To achieve this goal, we combine knowledge of caries microbiology and spatial behavior with control over 3D microstructure, bacterial aggregation, and spatial distribution through 3D bioprinting techniques. We will also utilize these techniques to evaluate pH-responsive antimicrobial agents and their efficiency against acid-producing bacteria in 3D environments. Three specific aims are designed to achieve this goal: Aim 1) Specifying our range of control over printability, viability, and proliferation of *S. Mutans* in a bioprinted bacteria-laden 3D model. This will be completed by adapting bacteria-laden hydrogels, which have been successful in supporting *S. mutans* proliferation and aggregation in preliminary studies. Aim 2) Assessing the impact of *S. mutans* interspecies interaction on biofilm formation and acid production in 3D hydrogels. This aim will utilize our knowledge of bacterial co-aggregation in caries environments, combined with our ability to control spatial positioning of bacterial aggregates, to evaluate spatial effects of interspecies interactions on biofilm formation and acid production. Aim 3) Evaluating the spatial specificity and pH-responsive potential of antimicrobial agents against acid-producing bacteria in 3D single-species and co-cultured environments. This aim will be achieved by integrating the engineering of pH-responsive antimicrobial agents into bioprinted systems to resolve antimicrobial efficiency at high resolution in three dimensions. During this K25 Mentored Quantitative Research Development Award, I will receive training in methods of bacterial culture, advanced imaging, and bioengineering needed to successfully complete my

outlined aims, facilitated by engineering and microbiology experts at ADA Forsyth. With the skills acquired through the successful completion of my aims during this period, I plan to continue research on microbial interactions, using more complex material models and microstructural control to answer new questions regarding caries environments and oral health at a larger scale.

PUBLIC HEALTH RELEVANCE: The goal of the proposed research is to advance the understanding and treatment of widespread and costly oral diseases such as dental caries through bacteria-laden bioprinting. I will achieve my goal by establishing a 3D bioprinted hydrogel model that is simple, versatile, and possesses tailorable material chemistry to manipulate bacterial aggregation and biofilm formation. The results of this project will establish novel in vitro models to investigate new aspects of bacteria-material and bacteria-bacteria interactions.

CRITIQUE 1

Candidate:	3
Career Development Plan/Career Goals /Plan to Provide Mentoring:	4
Research Plan:	6
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):	3
Environment Commitment to the Candidate:	2

Overall Impact: The candidate has a good foundation in materials science and a goal for applying this expertise to biomedical research, particularly in the context of oral microbiology and biomaterials. The career development plan is well-structured, with an emphasis on mentorship, training, and scientific communication. However, the candidate will need to rapidly acquire new skills in microbiology and bioengineering to successfully transition into this interdisciplinary field. Additionally, the candidate should consider broadening the research scope to increase its impact and ensure long-term career success. Overall, the candidate is positioned to achieve the career goals with the support of the mentoring team and the resources available at ADA Forsyth. The research plan is somewhat innovative, leveraging 3D bioprinting to replicate the complex microenvironments seen in situ. Its study framework, outlined hypotheses, and application of imaging methods to track microbial spatial distribution in bio-surfaces promise new perspectives to oral microbiology and materials science if relevant to in vivo situations. The main limitations revolve around materials choice (acrylamide), the lack of acknowledge of inherent complexity of oral biofilms and their interactions with biomaterials, and ensuring robust reproducibility in the 3D printing process, which limits the significance of this application.

Candidate:

Strengths

- Committed postdoctoral fellow with strong interest in working in the topic interfacing both material and biology.

Weaknesses

- Lack of publication track record in the pursued topic of materials and microbiology, overall publication record is modest.

Career Development Plan/Career Goals & Objectives:

Strengths

- Focused career development plan on developing skills in the pursuit of biology and material interface.

- Clear short- and long-term career goals of becoming proficient in required knowledge and skills in biology and material interfaces and becoming independent investigator and pursue R grant investigation.

Weaknesses

- Lack of evidence that the training and career development activities will lead to the anticipated outcomes for a successful transition.

Research Plan:

Strengths

- Developing a new 3D printed model for studying microbe-materials interactions.
- Application of polymicrobial interactions in the study design.
- Exploring therapeutic efficacy of pH sensitive compounds that target polymicrobial interactions.

Weaknesses

- Lack of scientific rigor and rationale in many study designs and experiments, lack of proof of principle studies in supporting current proposal, choice of pH sensors for imaging, selection of microbes for polymicrobial studies.
- Lack of details on physiological relevance of biomaterials, broader microbial contexts, and no back up plan for pH sensitive compounds if they do not work with polymicrobial system.

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- The mentor and co-mentor have complementary expertise in the pursued topics of biomaterials and microbiology.
- Additional advisor, a former postdoctoral mentor, provides additional expertise in studying mineralized teeth or bone tissues.

Weaknesses

- Overly focuses on the development of the candidate's research skills.
- It is not clearly explained why the candidate switched his postdoctoral mentor.

Environment and Institutional Commitment to the Candidate:

Strengths

- Outstanding scientific environment at ADA-Forsyth Institute for planned studies in biology and materials, and career development of becoming an independent investigator.

Weaknesses

- 100% salary support requested by the candidate, no institutional support in salary is evident.

Protections for Human Subjects: Not Applicable (No Human Subjects).

Inclusion Plans: Not Applicable (No Human Subjects).

Vertebrate Animals: Not Applicable (No Vertebrate Animals).

Biohazards: Not Applicable (No Biohazards).

Training in the Responsible Conduct of Research: Acceptable

Comments on Format (Required):

- *[Not addressed by reviewer].*

Comments on Subject Matter (Required):

- *[Not addressed by reviewer].*

Comments on Faculty Participation (Required; not applicable for mid- and senior-career awards):

- *[Not addressed by reviewer].*
- Comments on Duration (Required):
- *[Not addressed by reviewer].*
- Comments on Frequency (Required):
- *[Not addressed by reviewer].*

Select Agents: Acceptable.

Resource Sharing Plans: Acceptable.

Authentication of Key Biological and/or Chemical Resources: Acceptable.

Budget and Period of Support: Recommend as Requested.

CRITIQUE 2

Candidate:	4
Career Development Plan/Career Goals /Plan to Provide Mentoring:	3
Research Plan:	5
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):	2
Environment Commitment to the Candidate:	2

Overall Impact: The PI is a postdoc in the ADA Forsyth Institute, and has previous experiences in materials (inorganic), which are aligned with dental materials in this project. The PI has accepted decent training, but productivity is not high. Two major mentors have outstanding records in research and training, and their backgrounds are solid for the proposed project. The career plans are generally acceptable although some parts need more details. The research topic is interesting, however, lacking the solid rationale for 3D printing and detailed and deep investigation of the proposed works make the plan weak. The research environment is excellent.

Candidate:

Strengths

- The PI is a Postdoctoral at the ADA Forsyth Institute and received the PhD in 2022 in Univ of Florida. The PI has previous training in material science related to the bone.
- The PI started to work on dental biomaterials during the postdoc.

Weaknesses

- The PI 's productivity is not high.
- The provided biosketch contains many errors (minor).

Career Development Plan/Career Goals & Objectives:

Strengths

- The long-term goal of the PI is to be an independent researcher in leading research institutes, and a short-term goal is to submit a R01 at year 3.
- The development plan includes mentor meetings, training in Biological Study and Bioengineering as well as courses, writing, and conferences.

Weaknesses

- Some parts of the development plan lack detailed methodology to strengthen the PI's research, teaching, and writing.

Research Plan:

Strengths

- Establishing in vitro bacterial models to study interactions between biofilm and tooth is an interesting idea.
- The preliminary data exhibited printing feasibility and bacterial survival.

Weaknesses

- The rationales to 3D printing bacterial/gel model are not solid. Such printing material and techniques and printing bacterial are not novel.
- In aim 1, S mutans bacterial will be tested for 3D printing, and the V. parvula is not included. But V Parvula will be printed in the Aim 2.
- The measurements for printed bacteria are not sufficient.
- Aim 2 and Aim 3 measurements are limited. The expected knowledge achieved from this model and interactions are not clear and deep.

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- Two major mentors, Dr. He and Dr Sun have two collaborative NIH projects. Dr. Sun is an expert in dental biomaterials, and Dr. He is an expert in oral microbiology with bacterial research. Their combination will provide solid background for the project and training.
- Primary mentor Dr. Sun has extensive experience for postdoc training.

Weaknesses

- None

Environment and Institutional Commitment to the Candidate:

Strengths

- The research environment and listed facilities and equipment are adequate for this project and training.
- The institute has provided strong commitment to the PI for research support.

Weaknesses

- None.

Protections for Human Subjects: Not Applicable (No Human Subjects).

Inclusion Plans: Not Applicable (No Human Subjects).

Vertebrate Animals: Not Applicable (No Vertebrate Animals).

Biohazards: Acceptable.

Training in the Responsible Conduct of Research: Acceptable.

Comments on Format (Required):

- Acceptable

Comments on Subject Matter (Required):

- Acceptable

Comments on Faculty Participation (Required; not applicable for mid- and senior-career awards):

- Adequate

Comments on Duration (Required):

- Adequate

Comments on Frequency (Required):

- Adequate

Select Agents: Not Applicable (No Select Agents).

Resource Sharing Plans: Acceptable.

Authentication of Key Biological and/or Chemical Resources: Acceptable.

Budget and Period of Support: Recommend as Requested.

CRITIQUE 3

Candidate:	1
Career Development Plan/Career Goals /Plan to Provide Mentoring:	3
Research Plan:	4
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):	2
Environment Commitment to the Candidate:	2

Overall Impact: Dr. Elias is a highly trained materials scientist who is proposing a well-conceived training plan to expand his expertise into printed materials containing cariogenic bacteria that can be probed for activity using spatially defined printed structures. The data generated may add to the understanding of interspecies communication, however a weakness is the relevance of these printed matrixes to tooth structure.

Candidate:

Strengths

- Dr. Elias is an outstanding candidate for this award, having comprehensive training in material science and engineering.

Weaknesses

- None.

Career Development Plan/Career Goals & Objectives:

Strengths

- Excellent plan for coursework and experimental training.

Weaknesses

- None.

Research Plan:

Strengths

- Development of a 3D hydrogel containing cariogenic bacteria that are spatially arrayed is an interesting concept to study their acidogenic properties within defined spatial locations and concentrations.
- The research plan lays out well defined aims that assess the effects of proximity and aggregation/concentration of bacteria on each other as well as acid production and resulting pH changes.

Weaknesses

- The special arrays seem to be far removed from the actual physical context of enamel and dentinal channels where these interactions occur in vivo. More consideration of creating a model of tooth structures in this printing is missing.

- Much of the constructs of approximation of bacterial partners through bio printed filaments seem artificial in that this is done in the absence of a context of caries models.
- Many of the proposed aims are fine tuning what is already known to occur (pH and sucrose mediated acid production for example), so that data generated to be seems incremental.

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- A very strong group of mentors with outstanding expertise in biomaterial and bioprinting.

Weaknesses

- A dentist/cariologist would be helpful to bring a clinical context to this work.

Environment and Institutional Commitment to the Candidate:

Strengths

- Outstanding

Weaknesses

- None

Protections for Human Subjects: Not Applicable (No Human Subjects).

Inclusion Plans: Not Applicable (No Human Subjects).

Vertebrate Animals: Not Applicable (No Vertebrate Animals)

Biohazards: Not Applicable (No Biohazards).

Training in the Responsible Conduct of Research: *[Not addressed by reviewer].*

Comments on Format (Required):

- *[Not addressed by reviewer].*

Comments on Subject Matter (Required):

- *[Not addressed by reviewer].*

Comments on Faculty Participation (Required; not applicable for mid- and senior-career awards):

- *[Not addressed by reviewer].*

Comments on Duration (Required):

- *[Not addressed by reviewer].*

Comments on Frequency (Required):

- *[Not addressed by reviewer].*

Select Agents: Not Applicable (No Select Agents).

Resource Sharing Plans: Acceptable.

Authentication of Key Biological and/or Chemical Resources: Acceptable.

Budget and Period of Support: Recommend as Requested.

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1K25DE035216-01; PI Name: Elias, Jeremy

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-18-197 at <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-197.html>. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

National Institute of Dental and Craniofacial Research Special Grants Review Committee NATIONAL INSTITUTE OF DENTAL & CRANIOFACIAL RESEARCH DSR

02/25/2025 - 02/26/2025

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-22-044 at <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-044.html>, including removal of the application from immediate review.

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* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.