PEPTOIDS AS A NOVEL THERAPY FOR EARLY CHILDHOOD CARIES

By

Jacob Spencer

D.M.D. Candidate, University of Louisville School of Dentistry, 2026

A Thesis

Submitted to the Faculty of the

School of Dentistry of the University of Louisville

in Partial Fulfillment of the Requirements

for the Degree of

Master of Science in Oral Biology

in Oral Biology

Department of Oral Immunology and Infectious Disease

University of Louisville

Louisville, Kentucky

May 2026

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A Thesis Approved on

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by the following Thesis Committee:

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Thesis Director

Gill Diamond, Ph.D.

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Lisa Ryan, Ph.D.

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Matthew Ramsey, Ph.D.

DEDICATION

This thesis is dedicated to my family, whose support made this work possible, and to the mentors, faculty and friends at the University of Louisville School of Dentistry who encouraged and supported me along the way.

ACKNOWLEDGMENTS

Many thanks to thesis director Dr. Gill Diamond for his mentorship, guidance, and support throughout this project. Also, thanks to the many members of the Diamond Lab for technical assistance and collaboration, including Erika Figgins, Lisa Ryan, and Denny Gao.

Dr. Annelise Barron of Stanford University and Dr. Edward Rudnick of Maxwell Biosciences provided the CLAROMER® peptoid compounds tested in this work.

This work was supported by funding from the National Institutes of Health (R01 DE028883; R01DE031928; R21 DE028378; R21 AI146542), Colgate-Palmolive, the Chan Zuckerberg Initiative, and Maxwell Biosciences.

ABSTRACT

PEPTOIDS AS A NOVEL THERAPY FOR EARLY CHILDHOOD CARIES

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Early Childhood Caries (ECC) is a disease whose etiology is marked by a cross-kingdom biofilm formed by *Streptococcus mutans* and *Candida albicans.* This disease affects millions of children around the world. Current treatment options, including fluoride and chlorhexidine are insufficient against this virulent biofilm-mediated disease. Dual species biofilms were cultivated for extensive testing. Synthetic peptoids (CLAROMER® compounds, Maxwell Biosciences) were evaluated for antimicrobial and anti-biofilm efficacy using planktonic MIC assays, colony-forming unit (CFU) enumeration on selective media, LIVE/DEAD confocal microscopy, pH monitoring, and a 48-hour kinetic time-course assay. These tests resulted in three lead candidates from 16 screened compounds. At 50 μg/mL, Peptoid B reduced *S. mutans* and *C. albicans* viability by 83.5% and 80.4%, respectively, surpassing chlorhexidine. These findings support further investigation of synthetic peptoids as a novel antimicrobial class targeting the dual-species biofilm responsible for ECC.

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CHAPTER 1

INTRODUCTION

Dental caries is one of the most prevalent chronic diseases in humans, affecting individuals across all age groups and income levels worldwide (Tinanoff et al., 2019). Dental caries is a multifactorial disease but is primarily biofilm-mediated. Detectable caries does not result from a single event but rather from repeated cycles of demineralization and remineralization at the tooth surface. This cycle is constant and dynamic. Caries (or cavities) progresses when the mineral demineralization of the tooth structure over time outweighs remineralization. (Featherstone, 2008; Abou Neel, 2009). Figure 1 illustrates the anatomical context of this process, depicting the hydroxyapatite dissolution that begins when local pH falls below approximately 5.5 and the carious lesion that results from sustained mineral loss.

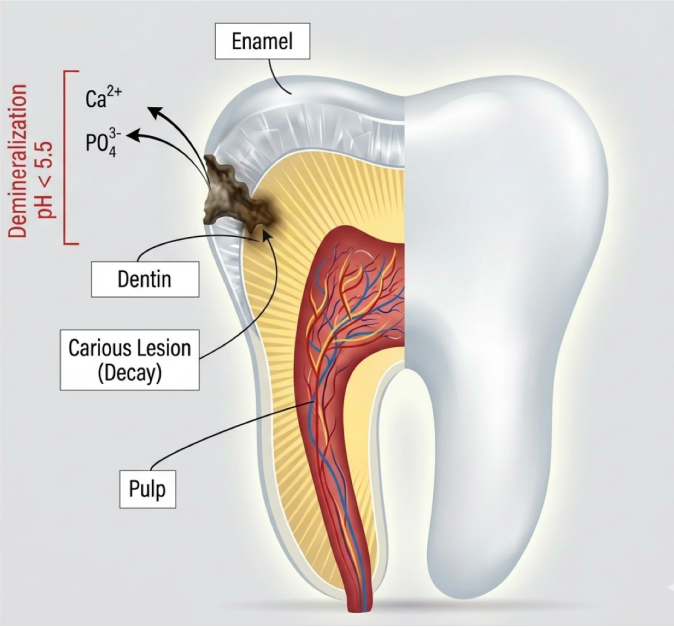

Figure 1. Cross-sectional illustration of a carious lesion in primary dentition. Net enamel demineralization begins when local pH falls below 5.5, driving release of Ca^{2+} and PO_4^{3-} from hydroxyapatite. (Original illustration generated by author.)

The pathogenesis of caries has long been studied, and different hypotheses for its cause have been proposed. The current and most supported framework is the "Ecological Plaque Hypothesis". The current understanding of this hypothesis proposes that caries is not solely due to the presence of a single bacterial species but by a shift in the ecosystem as a unit. It states that when the microbial community surrounding the hard tissues of the oral cavity are frequently exposed to fermentable carbohydrates and acids, there is a shift within the overall microbial community towards dysbiosis. (Takahashi & Nyvad, 2011; Chen et al., 2021). In this model, acid-tolerant, acidogenic species gain competitive advantage under low-pH conditions and come to dominate the biofilm. This results in an acidic local environment at the enamel surface, and which, over time, results in net mineral loss.

Early Childhood Caries (ECC) a manifestation of this oral disease in young children. The American Academy of Pediatric Dentistry defines ECC as the presence of one or more decayed, missing, or filled primary tooth surfaces in a child aged 71 months or younger (AAPD, 2023). ECC remains one of the most prevalent childhood infectious diseases globally (Tuan et al., 2023). Unfortunately, the disease disproportionately affects children from lower-income households and underserved populations in both high- and low-income countries (Martignon et al., 2024). ECC exists on a spectrum, from early white-spot lesions through severe coronal breakdown, as seen in figure 2.

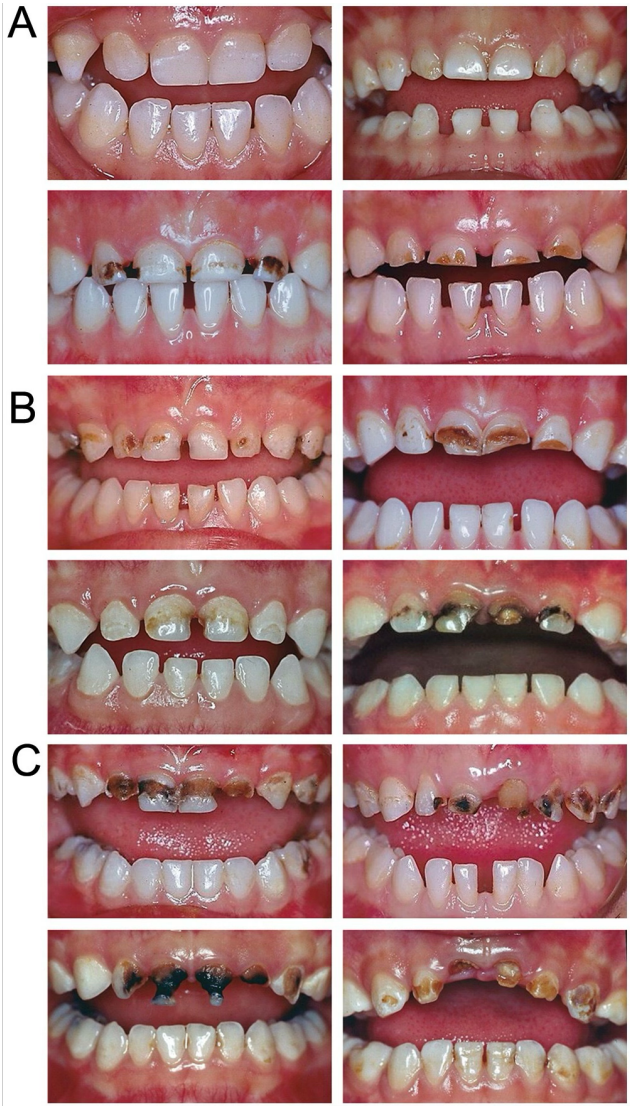

Figure 2. Representative clinical photographs illustrating the spectrum of ECC severity. (A) Early white-spot demineralization; (B) moderate cavitation; (C) severe S-ECC with extensive coronal destruction. (Adapted from Caufield, P.W., Li, Y., & Bromage, T.G., 2012. Journal of Dental Research, 91(6), 544–550.)

The consequences of untreated ECC can be localized or become systemic. If left untreated, large ECC and result in dentoalveolar pain, abscess formation, and spread of odontogenic infection (Foláyan et al., 2023). In young children, more severe manifestations of these conditions can disrupt a child's nutrition, sleep, speech and cognitive development during important growth periods (Alazmah, 2017). At the health system level, Severe ECC

(S-ECC) often requires multi specialist treatment under general anesthesia, including pediatric dentists, oral surgeons and dental anesthesiologists. Treating this disease can be difficult and resource-intensive, and treatment under general anesthesia increases risk of adverse reactions. Overall, S-ECC places significant burden on patients, their families and dental/healthcare infrastructure (Goomer et al., 2013).

ECC rates have not declined substantially despite decades of preventive effort and a well-understood disease pathogenesis. There are multiple reasons for a lack of progress in ECC rates. Existing clinical agents are effective in certain contexts but fall short against the more aggressive, polymicrobial forms of disease that characterize S-ECC. The specific limitations of current therapies are discussed in more detail in Chapter 4. Overall, the epidemiology and clinical burden of this disease indicate the need for investigating new treatment strategies, especially modalities that target microbial etiology of the disease.

CHAPTER 2

MICROBIAL ETIOLOGY OF ECC AND THE ROLE OF BIOFILMS

Understanding the microbial etiology is critical for developing potential treatment options for ECC. As noted previously, the Ecological Plaque Hypothesis describes the key role microbial homeostasis plays in disease and in health. Dental caries is not caused by free-floating planktonic bacteria, but rather by microbes adhering to the tooth surface, known as dental plaque. Dental plaque is a structurally organized, polymicrobial biofilm formed within an extracellular matrix (ECM). This matrix is not simply a group of cells; it is a distinct habitat with the microbes contained within showing gene expression patterns, metabolic properties, and antimicrobial resistance characteristics, all of which differ from planktonic organisms (Bowen & Koo, 2011).

When dietary sugars and acid, such as sucrose, are introduced to the oral cavity, the sugar exposure drives a competitive shift within the plaque community. There is a marked shift in the composition of the oral flora, as increased levels of acidogenic and aciduric species, such as *S. mutans*, Lactobacillus species, and others that tolerate sustained acid levels, are found in higher numbers. This in turn can suppress competing commensal organisms (Marsh, 2003). These acid tolerant organisms metabolize the dietary sugar through glycolysis, producing fermentation products such as lactic acid. As this acid accumulates around the tooth, and within the biofilm matrix, high concentrations that salivary buffering cannot neutralize, result in a lower local pH at the tooth-biofilm interface. This marks the start of the demineralization process (Ray, 2024; Spatafora et al., 2024).

The outer, hard surface of teeth is made of enamel, along with an inner layer of dentin. These mineralized structures are mainly composed of a structure called hydroxyapatite (Hap). Hydroxyapatite is a calcium-based lattice which compose 90% of enamel and 70% of dentin. When local pH around the enamel drops below ~5.5, the surrounding fluid becomes undersaturated with respect to calcium and phosphate ions, and net mineral demineralization occurs (Featherstone, 2008; Wang et al., 2023). Calcium and phosphate dissociate from the hydroxyapatite crystal lattice and diffuse into the surrounding saliva (Abou Neel, 2009). If this mineral imbalance persists over a period of time due to frequent acid challenges without adequate remineralization, the result is mineral loss of the tooth structure. This creates structural deficiencies that are described as dental carious lesions (Featherstone, 2008).

A key aspect of cariogenic biofilms is their well-structured extracellular matrix (ECM). The ECM of cariogenic plaque is structural scaffolding that provides protection to resident microorganisms. The ECM is composed of a mix of microbial-derived exopolysaccharides (EPS), proteins, lipids, and extracellular DNA (eDNA) (Bowen & Koo, 2011). These products form a structure that helps block potential threats, such as antimicrobial agents, buffers, and ions from the surrounding saliva. This allows for a continuation of the acidic microenvironment.

Studies have shown that resident microbes play a key role in maintaining this biofilm matrix. *S. mutans* synthesizes glucosyltransferase (Gtf), which binds to the mannans on the cell wall of *C. albicans*. This interaction creates a dense scaffold that

allows future proliferation of the biofilm matrix. It also confers mechanical stability and enhances the virulence of the biofilm (Hwang et al., 2017). Additionally, the Gtfs produced by *S. mutans* result in water-insoluble glucan polymers that anchor bacteria to the tooth surface and to each other (Bowen & Koo, 2011). The net result of the ECM is a protected acidic microenvironment largely inaccessible to host defense or therapeutic intervention.

Microorganisms within mature biofilms exhibit greater antimicrobial resistance and virulence compared to planktonic cells via overlapping mechanisms. As noted, the structure of the ECM results in restricted diffusion and limited antimicrobial agent penetration. Cells in deeper biofilm layers often exist in slow-growth or dormant states that reduce the activity of agents targeting replicating cells (Kulis et al., 2025). These cells are labeled as "persister" cells due to their metabolically dormant state. This results in a subpopulation that is effectively refractory to antibiotics and can repopulate the biofilm following withdrawal of treatment (Leung & Lévesque, 2012). Taken together, these properties mean that biofilm-eradicating concentrations of most antibiotics are 100- to 1,000-fold higher than planktonic MICs.

CHAPTER 3

THE DUAL-SPECIES INTERACTION BETWEEN STREPTOCOCCUS MUTANS AND CANDIDA ALBICANS

The rapid progression of Severe Early Childhood caries (S-ECC) has been shown to be driven by a specific cross-kingdom interaction between *S. mutans* and *C. albicans* (Marsh, 1994; Zhu et al., 2022). *S. mutans* is a Gram-positive cariogenic bacterium, while *C. albicans* acts as an opportunistic fungal pathogen. Both of these organisms are co-isolated from S-ECC lesions at rates substantially above what chance co-occurrence would predict (Falsetta, 2014; Spatafora et al., 2024). High levels of these organisms correlate with more aggressive caries progression than either organism is capable alone. The molecular basis of this interaction is depicted in Figure 3.

A key component in the development of stable and virulent mixed biofilms is the GtfB enzyme secreted by *S. mutans*. After being synthesized and released by the bacteria, GtfB adheres onto mannans (polysaccharides composed of mannose sugar units) on the *C. albicans* cell wall (Hwang et al., 2017). Once bound to the fungal surface, these GtfB convert dietary sucrose into extracellular glucans (Bowen & Koo, 2011). This teamwork allows both organisms to become more stable and incorporated into the overall biofilm structure.

This molecular binding pattern allows for *C. albicans* to grow its hyphae through the developing biofilm, providing enhanced structural stability. That in turn benefits the

biofilm, by expanding the surface area available for *S. mutans* attachment. This pattern continues, resulting in a stable and widespread EPS matrix. This is evidenced by studies indicating that EPS production in dual-species biofilms exceeds that of *S. mutans* monocultures substantially. The resulting mixed biofilm is thicker, mechanically more robust, and structurally more resistant to disruption (Bowen & Koo, 2011; Hwang et al., 2017).

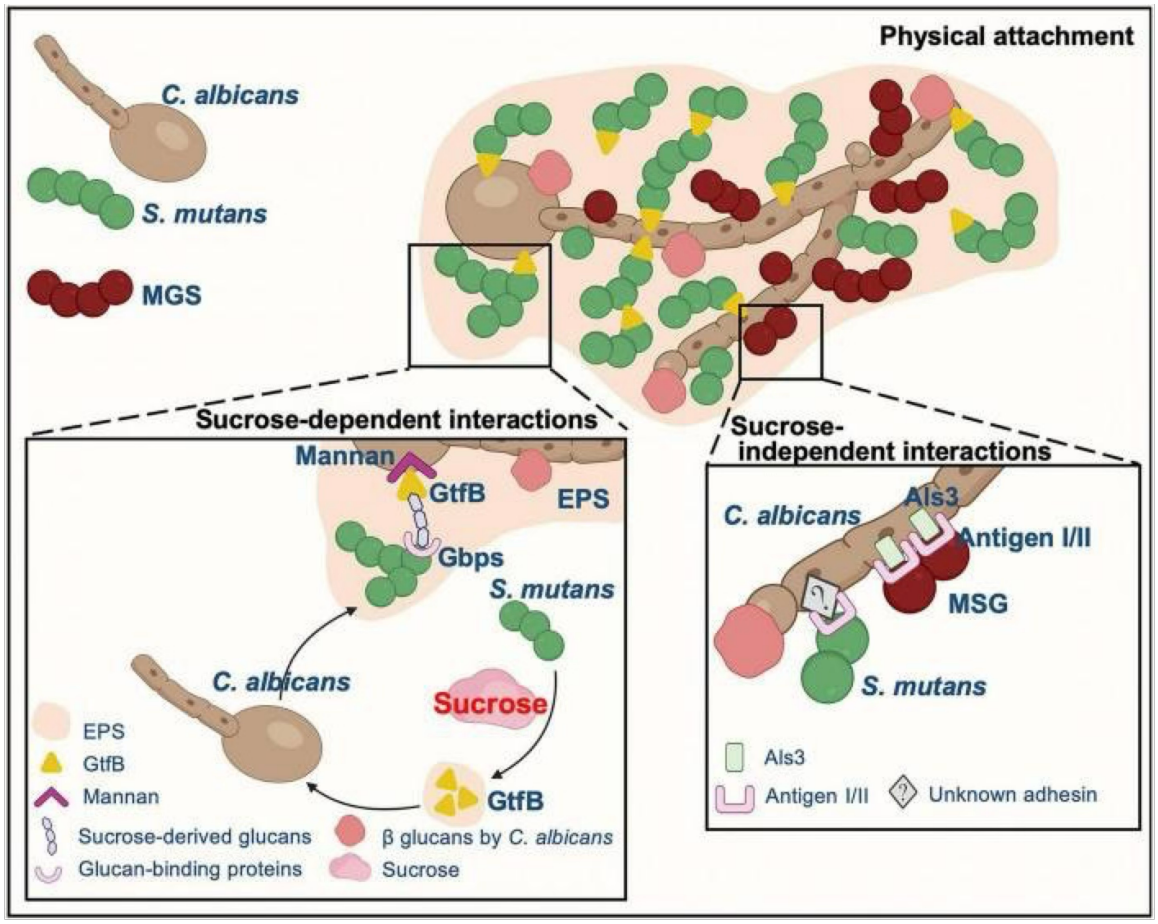

Figure 3. Attachment mechanisms underlying the S. mutans–C. albicans cross-kingdom interaction. Left: sucrose-dependent GtfB binding to fungal mannans driving glucan (EPS) synthesis. Right: sucrose-independent adhesin-mediated attachment. (Adapted from Frontiers in Microbiology, 2022. PMCID: PMC9668886.)

Another virulence factor of this dense ECM of the dual-species biofilm is it creates a more effective acid trap. Lactic acid produced by *S. mutans* gets trapped at the biofilm-

enamel interface with greater efficiency than in single-species biofilms. This allows for longer periods of an acidic pH below the critical demineralization threshold, accelerating the loss of hydroxyapatite structure. This sustained acidification helps explain the rapid caries progression seen clinically in S-ECC (Hwang et al., 2017; Zhu et al., 2022).

The clinical implication of this cross-species interaction is that an antimicrobial agent capable of killing *S. mutans* alone may be insufficient against S-ECC biofilms. Disrupting both components of the is a vital for successful biofilm eradication and effective treatment.

CHAPTER 4

LIMITATIONS OF CURRENT PREVENTIVE AND THERAPEUTIC APPROACHES

Decades of microbial and caries research has provided a clear understanding of the etiology of early childhood caries (ECC); however, current preventive and therapeutic treatments remain inadequate. A focus of pediatric dentistry is on prevention. Carious lesions can be restored, but it's much better to prevent their formation through preventative methods. In children who are high caries risk, the two primary agents in clinical use today are topical fluoride and chlorhexidine. These agents have proven to be beneficial, however have not been able to effectively limit or prevent the effects of these damaging biofilms in high-risk patients (Featherstone, 2011).

Fluoride has been the standard of care for caries prevention for over 50 years. It primarily functions by inhibiting demineralization and promoting the remineralization of enamel (Cury & Tenuta, 2014). Used topically via toothpaste or varnishes, it results in the incorporation of fluorapatite into partially demineralized enamel, which reduces the critical pH threshold required for subsequent acid dissolution (Cury & Tenuta, 2014; Featherstone, 2011). While useful for remineralization on clean enamel surfaces, fluoride does not kill cariogenic organisms at clinically applied concentrations and lacks meaningful antifungal activity. Resistance to fluoride by cariogenic organisms is possible, as recent studies have shown that the presence of fluoride-resistant *S. mutans* limits the anti-caries efficacy of fluoride. (Sun et al., 2024). In short, fluoride targets the consequence of the disease—mineral loss—without addressing its microbial etiology.

Chlorhexidine (CHX) is a commonly used antiseptic rinse that is broad-spectrum, targeting both bacteria and fungi (Twetman & Dhar, 2015). It is commonly identified as the gold standard for oral disinfection and is commonly used to treat gingivitis and reduce bacteria. Chlorhexidine's mechanism is via disruption of the bacterial cytoplasmic membrane by binding to the negatively charged cell wall, resulting in intracellular leakage and cell death. However, bacterial resistance to CHX has been noted, as bacteria are capable of the upregulation of efflux pumps, limiting the amount of antiseptic agent actually targeting the biofilm (Kampf, 2016). Recent systematic reviews show no clear evidence that CHX is more effective long-term for managing ECC than a placebo (Twetman & Dhar, 2015). A key reason for this finding is that CHX is sequestered by the dense EPS matrix of the dual-species biofilm characteristic of ECC, preventing deep matrix penetration. In fact, at suboptimal concentrations, CHX may paradoxically stabilize the biofilm by inhibiting natural biofilm detachment, allowing pathogenic communities to persist (Jain et al., 2022). A major red flag for long-term clinical use by clinicians is the potential for staining of teeth and taste perception alteration, both of which can reduce compliance in pediatric patients (James et al., 2017).

Other conventional agents, such as systemic antibiotics and antifungals are not appropriate first-line options for ECC management. Widespread use of these agents carries risk of selection of drug-resistant strains while having limited effects on mature biofilms. Thus, there is a critical limitation in current treatment options, and no established therapy specifically targets the *S. mutans*-*C. albicans* interaction that is responsible for the most aggressive and severe forms of ECC (Koo et al. 2017).

CHAPTER 5

PEPTOIDS AS A NOVEL ANTIMICROBIAL STRATEGY

Antimicrobial peptides (AMPs) are a class of antimicrobials who show broad-spectrum activity and membrane disruptive mechanisms. These peptides are naturally occurring, playing a role in innate mucosal immunity. They are present in saliva, gingival crevicular fluid, and the secretions of oral epithelial surfaces (Diamond et al., 2009). They have multiple antimicrobial targets, including membrane disruption, EPS and eDNA degradation, and interference with quorum-sensing pathways that coordinate biofilm assembly (Figure 4). This Mult mechanistic profile is pharmacologically attractive because it increases the barrier to resistance development as compared to antimicrobial agents with a single molecular target (Yasir, 2018).

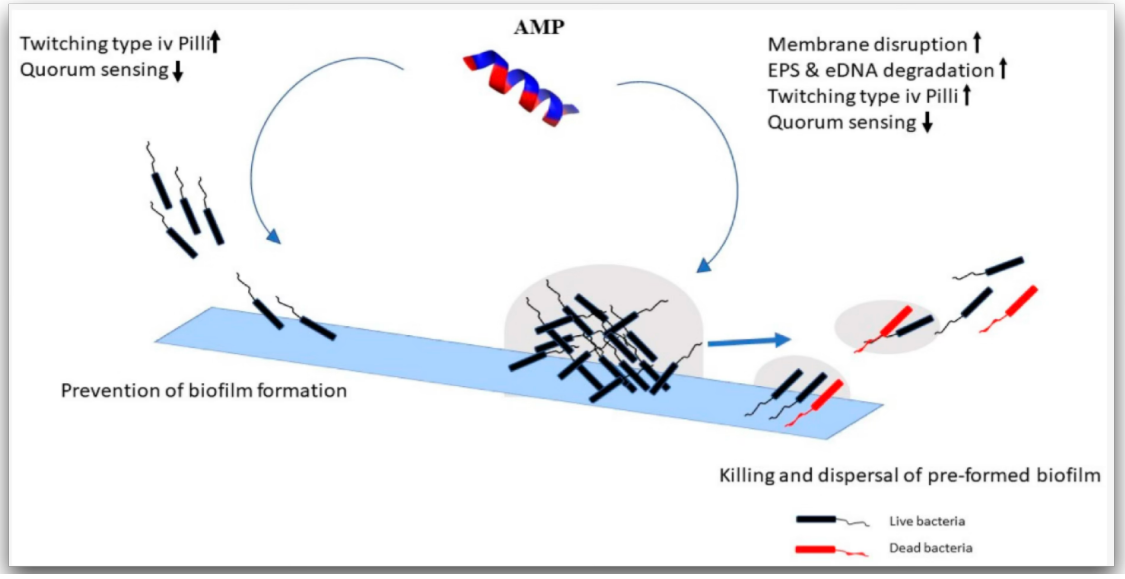

Figure 4. Mechanisms of anti-biofilm activity of antimicrobial peptides (AMPs), including prevention of attachment, membrane disruption, EPS and eDNA degradation, and quorum-sensing interference. (Adapted from Yasir, M., Willcox, M.D.P., & Dutta, D., 2018. Materials, 11(12), 2468.)

However, for all their proposed pharmacological potential, clinical use of natural AMPs has been limited by proteolytic instability. When applied orally, salivary and tissue proteases cleave peptide amide bonds at rates that render the treatment ineffective (Dohm et al., 2011). Additionally, natural AMPs are limited by high manufacturing costs and formulation challenges in the enzyme-rich oral environment.

Peptoids (oligo-N-substituted glycine polymers) are synthetic analogs of peptides. These were designed to preserve the antimicrobial function of AMPs while limiting the proteolytic degradation. The key structural modification is the relocation of R groups (amino acids) from the alpha-carbon to the amide nitrogen (Figure 5). This eliminates the backbone N-H hydrogen bond donors, which are required for substrate recognition by most proteases. The structural change renders the backbone more resistant to the enzymes that rapidly degrade natural AMPs (Zuckermann et al., 1992).

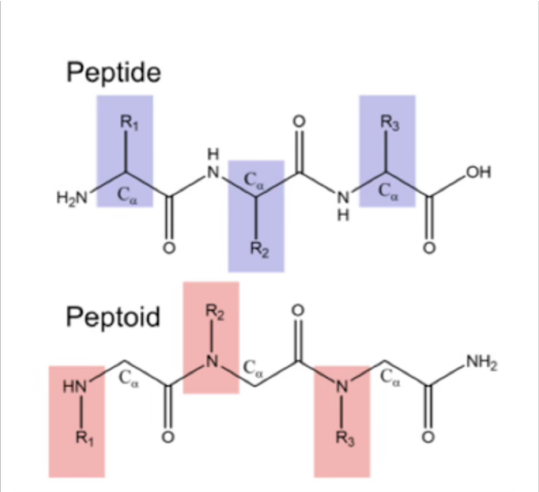

Figure 5. Structural comparison of a peptide (upper) and a peptoid (lower). Side chains in the peptoid are appended to the backbone amide nitrogen rather than the alpha-carbon, eliminating backbone N-H donors and conferring protease resistance. ("Next Generation Virucides – Peptoids," Maxwell Biosciences.)

The specific peptoid compounds evaluated in this study are Maxwell Biosciences synthetic peptoids (CLAROMER®). These have been formulated to replicate the mechanism of the human cathelicidin LL-37. Like natural AMPs, these peptoids work via cationic (positive) charge and amphipathic structure to promote binding to negatively charged microbial membranes, which can destabilize the membrane and lead to cell death (Ghosh et al., 2023). Once the peptoid binds to the surface, its hydrophobic region inserts directly into the lipid bilayer. This either forms distinct physical pores or induces large-scale membrane thinning, which causes essential intracellular contents like potassium ions and ATP to rapidly leak out, shutting down the cell's metabolism (Chongsiriwatana et al., 2008).

Preclinical safety data on CLAROMER® compounds have been favorable. In cell line and small animal model studies, the compounds were tolerated at concentrations well above the therapeutic range with minimal cytotoxicity to oral keratinocytes and pulmonary epithelial cells (Diamond et al., 2021). While not yet tested in the oral cavity, mechanistically, the target of these compounds adds in additional compatibility. *S. mutans* has a cell wall that contains negatively charged acids and *C. albicans* contains mannans that also carry a negative charge. In contrast, human epithelial cells have much less negative charge on their surface; this difference in charge between host and pathogen results in cationic peptoids being more likely to interact with microbial cells than with host tissues (Chongsiriwatana et al., 2008). Overall, the favorable safety profile, resistance to salivary degradation and targeted mechanism of action, makes these synthetic peptoids

ideal candidates for evaluating against the *S. mutans* and *C. albicans* biofilms seen in severe early childhood caries.

CHAPTER 6

SPECIFIC AIMS

The objective of this study was to evaluate the antimicrobial and anti-biofilm activity of novel synthetic peptoids against in vitro dual-species biofilms of *S. mutans* and *C. albicans*.

Aim 1: Establish a reproducible dual-species in vitro biofilm model combining *S. mutans* and *C. albicans* under cariogenic conditions, including sucrose-supplemented media.

Aim 2: Assess the efficacy of peptoid candidates against mature dual-species biofilms using quantitative colony-forming unit (CFU) enumeration on selective media and LIVE/DEAD confocal laser scanning microscopy.

Aim 3: Characterize species-specific susceptibility patterns within the dual-species system to distinguish the bacterial and fungal responses to peptoid treatment and identify primary targets for S-ECC biofilm disruption.

CHAPTER 7

MATERIALS AND METHODS

7.1 Study Design and Overview

This study utilized an in vitro experimental design to evaluate synthetic peptoid antimicrobials against dual-species *S. mutans–C. albicans* biofilms. Sixteen peptoid candidates were first screened against planktonic cultures of each organism using minimum inhibitory concentration (MIC) methodology. Compounds with the most potent and balanced dual-species activity were then advanced to biofilm testing. Anti-biofilm efficacy was characterized across four complementary assays: quantitative CFU enumeration on species-selective agar, LIVE/DEAD confocal laser scanning microscopy (CLSM), supernatant pH monitoring following sucrose challenge, and a kinetic time-course viability assay over 48 hours. Untreated wells containing growth medium served as negative controls. Chlorhexidine gluconate (CHX) at 50 μg/mL was used as a positive control in all biofilm assays.

7.2 Antimicrobial Susceptibility Testing

MIC determination was performed following CLSI reference broth microdilution methods, as shown in Figure 6(CLSI M27, 2017; CLSI M07, 2018). This initial assay was done using 96 well microtiter plates. Microbial growth of each organism was assessed by OD600 after overnight incubation. For *C. albicans,* a single colony was suspended in sterile PBS, and the optical density was adjusted to OD600 = 1.0, and the suspension was diluted

1:1000 into RPMI-MOPS. For *S. mutans,* a colony was suspended in BHI broth to OD600 = 1.0 (~1.3×10^8 CFU/mL); 4.62 µL of this suspension was added to 6 mL BHI to achieve working inoculum. Peptoid stocks were prepared at 256 µg/mL and serially diluted twofold across plate columns. The MIC was recorded as the lowest concentration producing complete growth inhibition. The final column was absent of any peptoid, serving at the negative control. Aliquots from clear wells were sub cultured onto species-appropriate solid media to determine minimum bactericidal (MBC) and minimum fungicidal (MFC) concentrations: BHI agar for *S. mutans*, YPD agar for *C. albicans*.

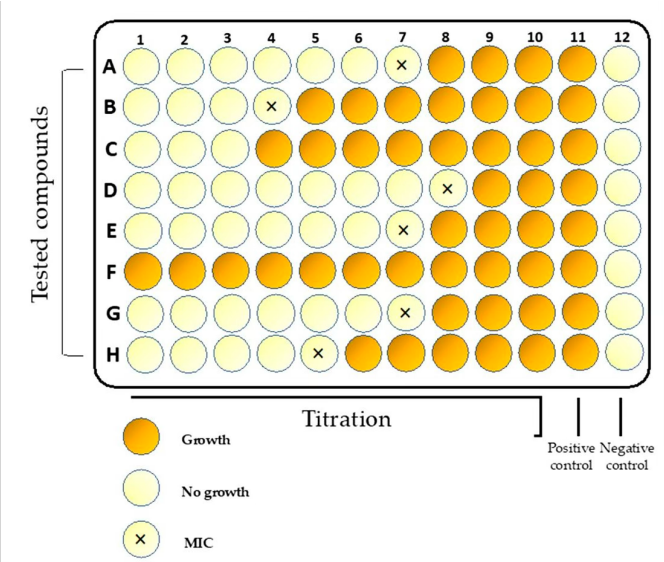

Figure 6. Representative 96-well microtiter plate for MIC determination. Orange wells indicate visible growth; clear wells indicate complete growth inhibition. X marks identify the MIC for each peptoid concentration series. (Hielscher Ultrasonics MIC Assay Protocol.)

7.3 Dual-Species Biofilm Model and Treatment

The dual-species biofilms were grown by combining cultures of *S. mutans* and *C. albicans* in BHI broth (pH 7.1) with 1% sucrose to support Gtf-mediated EPS synthesis, simulating a cariogenic oral environment following a protocol provided by the Koo Laboratory at the University of Pennsylvania (Liu & Koo, 2023; Hwang et al., 2017). To create the dual-species inoculum, 1 µL of *S. mutans* (grown to an OD600 of 1.0) and 2.63 µL of *C. albicans* (grown to an OD600 of 0.8) were added per 1 mL of medium, producing a starting suspension of 10^6 CFU/mL for *S. mutans* and 10^4 CFU/mL for *C. albicans* (a 100:1 bacterial-to-fungal ratio).

The biofilms were cultured in chamber slide wells (0.8 mL per well; Figure 7). For each well, 800 µL of the inoculated BHI and sucrose medium was added directly to the chamber. The slides were incubated statically at 37°C for 24 hours to allow biofilm maturation. Following maturation, the medium was aspirated and replaced with fresh medium containing the peptoid at a concentration of 50 µg/mL. This standardized testing concentration was selected based on planktonic MIC results (Table 1) to provide a uniform dose that exceeds the baseline inhibitory thresholds, accounting for the increased resilience and EPS matrix protection of the mature biofilm. Treated biofilms were incubated statically for an additional 24 hours prior to analysis prior to analysis.

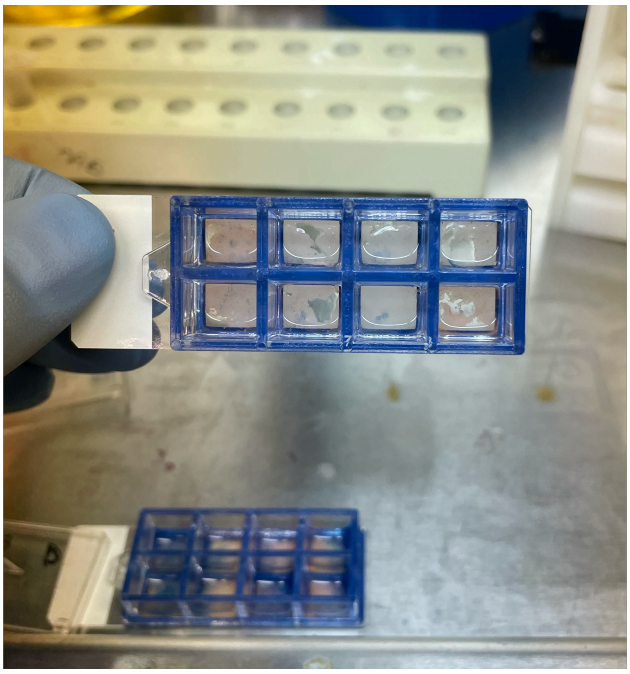

Figure 7. Chamber slide wells (0.8 mL per well) used for dual-species biofilm cultivation and treatment. Following 24-hour maturation in sucrose-supplemented BHI medium was replaced with peptoid compound at the indicated concentration. (Original photograph by author.)

7.4 Confocal Microscopy and Biofilm Viability Analysis

Dual-species biofilms were cultivated utilizing the standardized protocol as described in Section 7.3. Following the 24-hour treatment period, LIVE/DEAD staining was performed using a SYTO 9 / propidium iodide (PI) dual-fluorescence protocol (Stiefel et al., 2015). The dual fluorescence staining allows for identifying membrane integrity of the treated biofilm. SYTO 9 labels all cells with intact membranes green, PI penetrates only cells with damaged membranes and stains them red. A working stain solution (3 µL SYTO 9 + 3 µL PI per 1 mL sterile water) was prepared and 100 µL applied to each chamber well. A cover slip was placed over the treated and stained biofilms, and fixed into

place. Z-stack image acquisition was performed using a Leica SP8 Laser Inverted Confocal Microscope. Images were analyzed using Imaris and ImageJ pixel-quantification software to calculate the % of red and green biomass within each image stack. These software's also allowed for 3D modeling of the treated and stained biofilms.

7.5 pH Analysis of Biofilm Acidification

Dual-species biofilms were cultivated utilizing the standardized protocol as described in Section 7.3. Then, the mature dual-species biofilms were treated with 1% sucrose solution to stimulate cariogenic acid production. One hour after the sucrose challenge, peptoid treatments were applied to designated wells with untreated wells serving as negative controls. Supernatant aliquots were collected at 0, 1, 12, and 24 hours post-treatment and pH was measured immediately using a calibrated micro-pH electrode. This assay was conducted as a single replicate at the screening stage.

7.6 Quantitative Biofilm Viability Assay (CFU Enumeration)

Dual-species biofilms were cultivated utilizing the standardized protocol as described in Section 7.3. After 24 hours of treatment with at 50 μg/mL, wells were washed once with 1 mL sterile PBS to remove non-adherent organisms. An additional 1 mL PBS was added per well, and adherent biofilm was mechanically detached by scraping with a sterile cell scraper. Suspensions were vortexed and serially diluted to 10^{-5}. This final dilution was plated on species-specific selective media to evaluate whether the peptoids

demonstrated preferential antimicrobial activity against either organism. Mitis Salivarius (MS) agar with bacitracin for *S. mutans* enumeration, and CHROMagar™ Candida for *C. albicans* enumeration. Plates were incubated 48 hours at 37°C and counted. This experiment was run and tested in triplicate (n = 3 independent chamber wells per group) for statical analysis.

7.7 Time-Course Viability Assay

Dual species biofilms were established and treated with peptoids as described in Section 7.3. Individual wells were harvested at seven time points (0, 1, 2, 4, 8, 24, and 48 hours post-treatment), washed, scraped, and resuspended in PBS as described in Section 7.6. Total viable counts were determined by plating onto non-selective BHI agar, enabling quantification of combined bacterial and fungal cell levels at each time point. This assay was conducted in biological duplicate.

7.8 Statistical Analysis

Statistical comparisons between treatment groups and the untreated negative control were performed in Microsoft Excel. For biological triplicate assays, data are reported as mean ± standard deviation. A p-value threshold of < 0.05 was used to define statistical significance. pH monitoring and confocal microscopy were conducted as single-replicate exploratory assays; data from these experiments are presented descriptively

without inferential statistics. The time-course experiment was conducted in biological duplicate and is likewise treated as preliminary data.

CHAPTER 8

RESULTS

8.1 Antimicrobial Susceptibility Testing (Planktonic MIC/MBC)

To identify the most promising therapeutic candidates, the 16 available peptoid candidates went though MIC screening assays. Results of these tests identified a range of potency against planktonic *S. mutans* and *C. albicans*. Results for the most active compounds are compiled in Table 1.

	S. mutans		*C. albicans*	
peptoid	MIC (µg/ml)	MBC	MIC	MFC
A	4	16	8	32
B	8	32	16	32
C	16	32	64	64
D	4	16	32	64
E	1	4	32	64
F	32	64	16	64
G	4	16	16	32
H	2	8	8	32

Table 1. Planktonic MIC, MBC, and MFC values (µg/mL) for screened peptoids against S. mutans and C. albicans. Peptoids A, B, and H showed the strongest dual-species profiles and were selected for biofilm testing. (Experimental data, author.)

Peptoid B was the strongest overall candidate with an MIC of 2 µg/mL and MBC of 8 µg/mL against *S. mutans*; MIC of 8 µg/mL and MFC of 32 µg/mL against *C. albicans*. **Peptoid H** also showed comparable dual-species coverage, with MIC and MBC/MFC values of 4 µg/mL and 32 µg/mL for both organisms. **Peptoid A** was the most potent antibacterial (MIC 1 µg/mL; MBC 4 µg/mL) but required substantially higher

concentrations to inhibit *C. albicans* (MIC 32 µg/mL; MFC 64 µg/mL). It was critical to consider the activity of a peptoid against both organisms because an effective treatment must effectively target both species. Peptoids A, B, and H were chosen for further biofilm testing, with Peptoid B identified as the primary candidate of interest.

8.2 Confocal Microscopy and Biofilm Viability

Confocal laser scanning microscopy (CLSM) with LIVE/DEAD staining was used to visualize the impact of peptoid treatment on biofilm membrane integrity. In short, it provides a visual inference to the effects of the peptoid on the membrane of the organisms in the mixed biofilm. Untreated controls consistently showed widespread green fluorescence visually, and when image tested, membrane-compromised cells (red biomass) accounted for only 19.3% of the total volume.

At the 50 µg/mL concentration, the peptoids demonstrated efficacy comparable to the positive control, which was 0.12% Chlorhexidine (CHX). Upon analysis, CHX-treated biofilms yielded ~45% red biomass. The three tested peptoids showed a similar amount of red, fluorescence, with Peptoid A (45.1%), Peptoid H (46.9%), and Peptoid B (48.7%) all matching or exceeding the positive control value.

This test, done in single replicate, precludes formal statistical analysis. However, the red shift (towards membrane compromise) observed at the 50 µg/mL concentration is consistent across all three peptoids. These results, even qualitatively, provide visual evidence of membrane disruption observed in the initial quantitative CFU assays (Section

8.4).

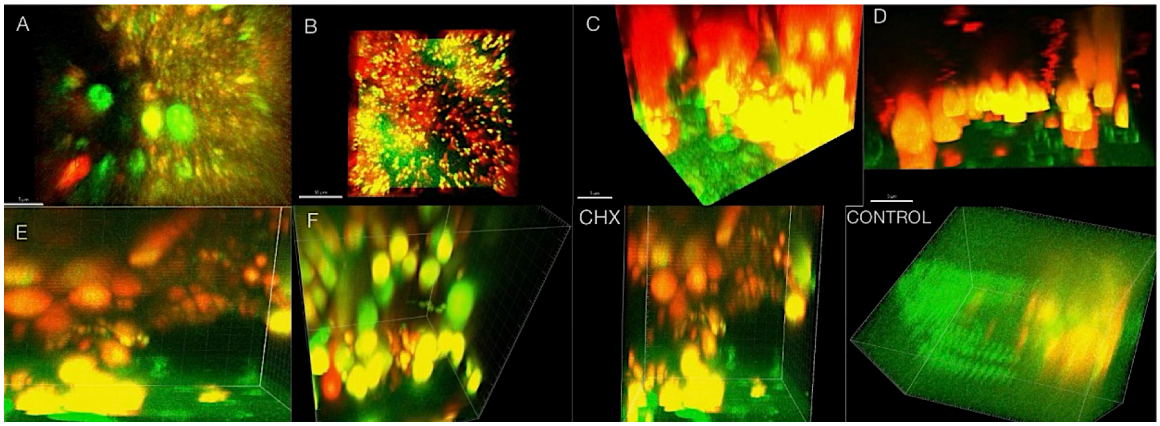

Figure 8. Three-dimensional LIVE/DEAD confocal images of dual-species biofilms. Green: viable cells (intact membranes, SYTO 9). Red/orange: membrane-compromised cells (propidium iodide). Left: peptoid-treated biofilm with extensive cell death. Right: CHX-treated and untreated controls. (Original confocal data, author.)

8.3 pH Analysis of Biofilm Acidification

To assess metabolic disruption, the pH of the biofilm supernatant was monitored following a sucrose challenge. In untreated controls, the pH fell rapidly from an initial 4.8 to 4.3 within the first hour. The supernatant remained acidic, holding at 4.4 after 24 hours. Notably, these values remained consistently below the critical threshold for enamel demineralization (~5.5), confirming the sustained acidogenic potential of the untreated dual-species community (Figure 9).

Biofilms treated with Peptoid A or Peptoid B at 50 µg/mL showed reduced acid accumulation. By 24 hours, supernatant pH in Peptoid A– and Peptoid B–treated wells had recovered to 4.9 and 4.8, respectively, indicating reduced cariogenic metabolic activity in the surviving community. This test was done in single replicate, again precluding formal statistical analysis, thus findings are descriptive.

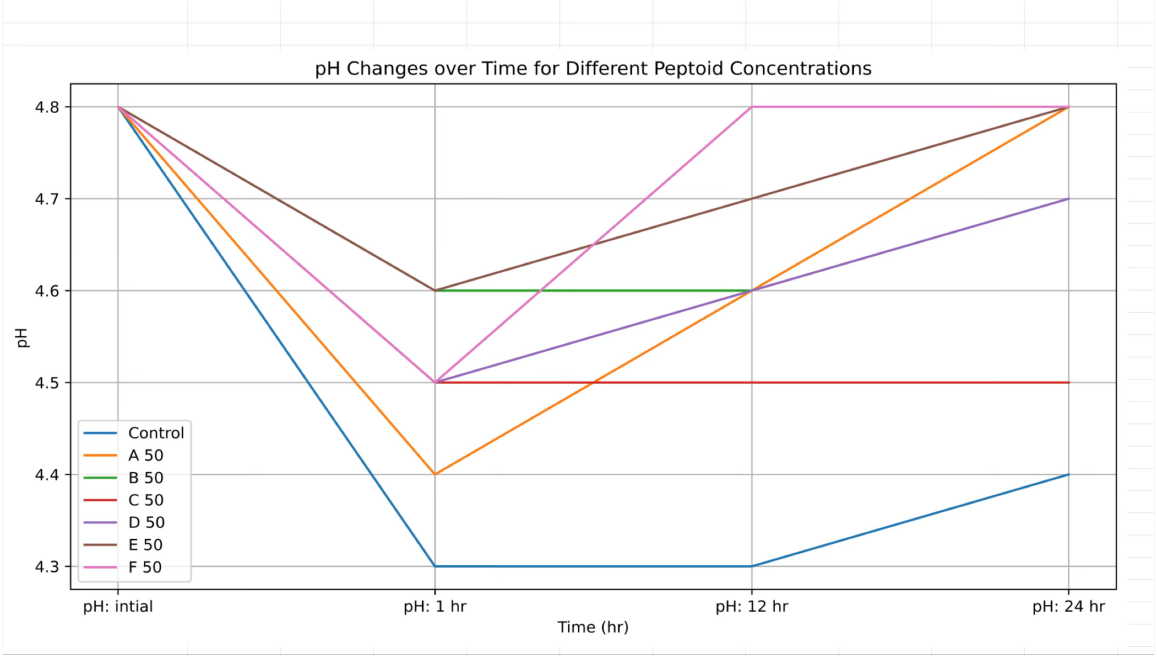

Figure 9. Biofilm supernatant pH over time following 1% sucrose challenge. Untreated controls dropped rapidly below the enamel demineralization threshold of pH 5.5. Peptoid-treated biofilms maintained substantially higher pH values at all measured time points. Data are from a single exploratory replicate. (Experimental data, author.)

8.4 Quantitative Biofilm Viability (CFU Enumeration)

CFU enumeration assays were performed in triplicate on selective media to provide the primary quantitative efficacy data (Figure 11). These results allow us to assess species specific survival and viability following peptoid treatment.

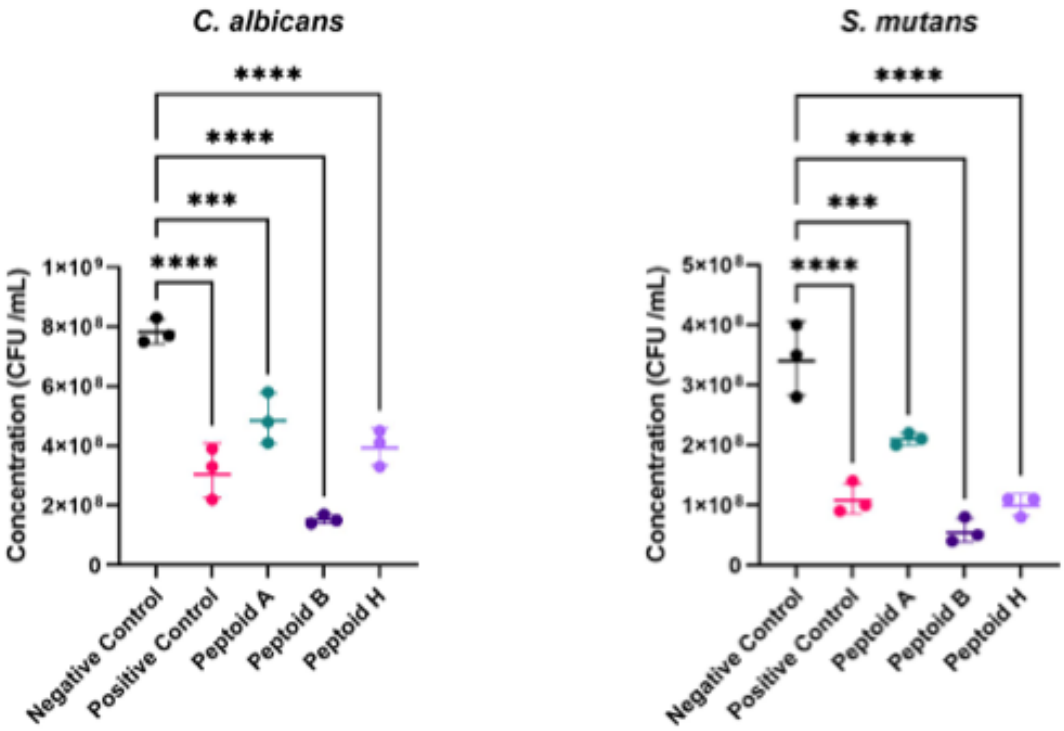

*Figure 10. Species-specific CFU recovery following 24-hour peptoid treatment at 50 µg/mL. Left: C. albicans on CHROMagar; Right: S. mutans on Mitis Salivarius agar. Biological triplicate; error bars = ± SD. ***p<0.001; ****p<0.0001 vs. untreated control. (Experimental data, author.)*

C. albicans counts in untreated controls averaged 78.33 ± 4.16 CFU (7.83×10^7 CFU/mL). CHX treatment reduced fungal counts to 31.33 ± 8.62 CFU ($p = 0.001$), a 60.0% reduction. Peptoid B reduced *C. albicans* to 15.33 ± 1.53 CFU ($p = 0.0001$), an 80.4% reduction, exceeding CHX. Peptoid H produced a 49.4% reduction to 39.67 ± 6.11 CFU ($p = 0.0008$); Peptoid A reduced fungal counts to 49.0 ± 8.54 CFU, a 37.4% reduction ($p = 0.0059$).

S. mutans counts in untreated controls averaged 34.33 ± 6.03 CFU (3.43×10^7 CFU/mL). CHX reduced bacterial counts to 11.0 ± 2.65 CFU ($p = 0.0036$), a 67.9%

reduction. Peptoid B reduced *S. mutans* to 5.67 ± 2.08 CFU ($p = 0.0015$), an 83.5% reduction. Peptoid H achieved a 70.9% reduction to 10.0 ± 1.73 CFU ($p = 0.0026$). Peptoid A showed limited antibacterial effect, with counts of 21.0 ± 1.0 CFU representing a 38.8% reduction ($p = 0.0194$).

Kill efficiency was balanced across species for the best performing treatment, Peptoid B (83.5% vs. 80.4%), while CHX showed greater selectivity toward bacteria over fungi (67.9% vs. 60.0%).

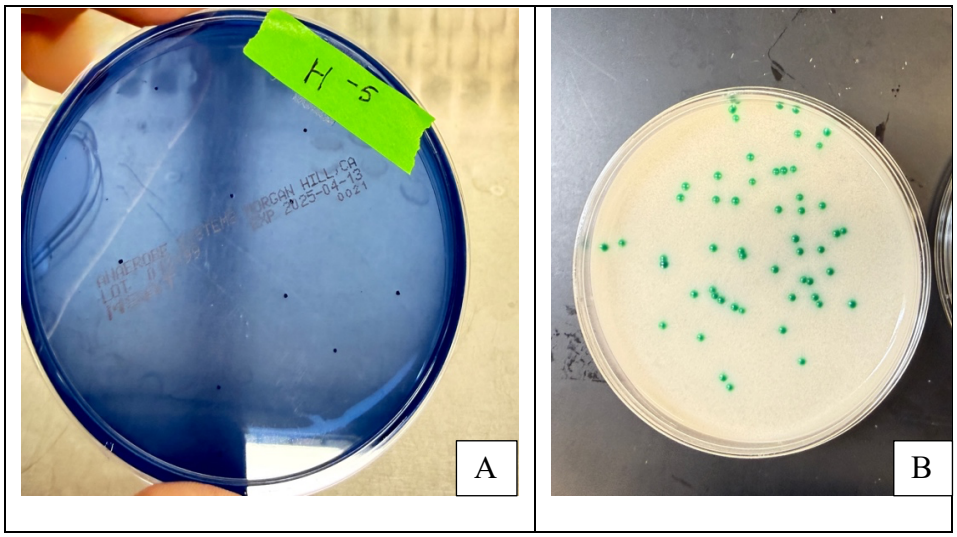

Figure 11. Comparison of microbial recovery of dual-species biofilm components on selective media. demonstrating the efficacy of the peptoid treatment in reducing colony-forming units (CFUs).
(A) S. mutans growth on selective Mitis Salivarius-Bacitracin (MSB) agar (H-5 dilution),
(B) C. albicans growth on CHROMagar, showing green colonies. (H-5 dilution)

8.5 Kinetic Time-Course Viability Assay

A time-course assay was conducted over 48 hours to measure total surviving biofilm biomass on non-selective BHI agar (results in Figure 12). Untreated (negative) controls remained stable at approximately 600 CFU across all time points, confirming biofilm viability over 48 hours. CHX (positive control) reduced total counts gradually: 26.7 CFU at 24 hours, 17.3 CFU at 48 hours.

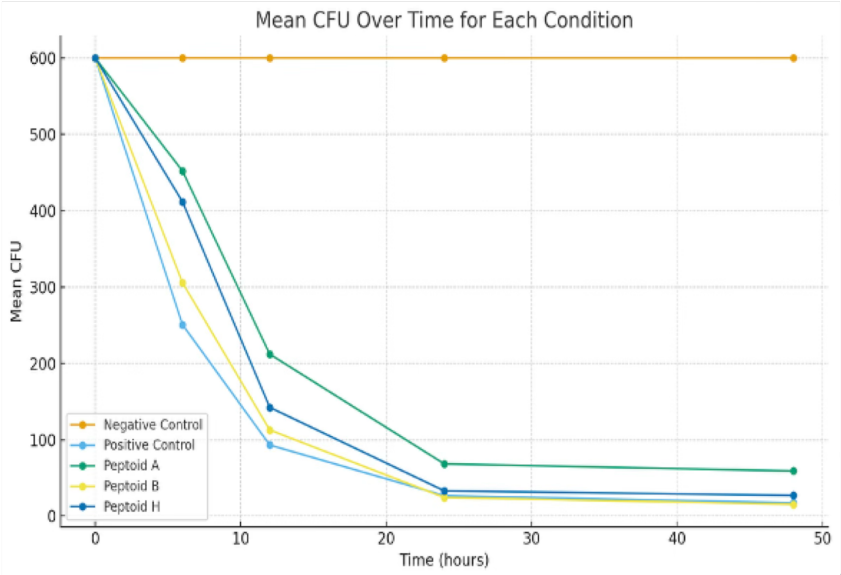

Figure 12. Kinetic time-course total viable CFU counts on non-selective BHI agar over 48 hours at 50 µg/mL. Untreated controls remained stable. Peptoid B demonstrated faster onset and greater kill magnitude than chlorhexidine at all late time points. (Experimental data, author.)

Peptoid B again was the best performing peptoid, seen by a steeper and faster kill curve. Counts dropped to 112.7 CFU by 12 hours and continued declining to 24.3 CFU at 24 hours and 15.3 CFU at 48 hours—below the CHX 48-hour value. The difference between Peptoid B and CHX was most pronounced in the 1–12 hour window.

CHAPTER 9

DISCUSSION

The primary objective of this study was to evaluate the antimicrobial efficacy of novel synthetic peptoids against the dual species biofilm responsible for ECC. The overall results indicate that these compounds possess potent, broad-spectrum activity against *S. mutans* and *C. albicans*. The best performing compound, Peptoid B, reduced viable counts of both *S. mutans* and *C. albicans* by more than 80% within mature dual-species biofilms at 50 μg/mL. Compared to the clinical gold standard-CHX- which achieved 60–68% reductions under identical conditions. Thus, these early testing results establishes a meaningful difference in efficacy against the cross-kingdom target relevant to S-ECC. The result was consistent across CFU enumeration and confocal microscopy, and the kinetic data indicate that the kill advantage of Peptoid B over CHX is apparent within the first 12 hours of exposure.

The biofilm-effective concentration of 50 μg/mL for Peptoid B represents a 25-fold increase over its planktonic MIC of 2 μg/mL against *S. mutans*. This ratio is substantially lower than the 100- to 1,000-fold MIC escalation typically required for biofilm eradication by conventional antibiotics (Koo et al., 2017). Given the potency, some degree of EPS matrix penetration is implied by these results, though the extent and mechanism of that penetration would be a priority for follow-up studies.

When considering the safety profile of the peptoids, the proposed mechanism of action relies on charge-based selectivity. At a neutral pH, the positively charged

(cationic) peptoids are electrostatically attracted to the negatively charged (anionic) surfaces of *S. mutans* and *C. albicans* (Chongsiriwatana et al., 2008). In contrast, healthy host cells and beneficial oral bacteria maintain a lower net negative surface charge, which reduces the likelihood of interaction. This suggests pathogen selectivity, meaning a potential peptoid treatment could target the disease-causing biofilm while leaving commensal and healthy tissue alone (Ghosh et al., 2023).

CHX's comparatively poor antifungal performance — 60.0% fungal reduction versus 67.9% bacterial reduction — is consistent with its known weak activity against *C. albicans*. The 80.4% fungal reduction by Peptoid B is a meaningful improvement with direct mechanistic relevance. *C. albicans* is not simply a passenger in the dual-species biofilm; it serves as the structural scaffold through which Gtf-mediated glucan synthesis amplifies *S. mutans* virulence. Preserving the fungal component while reducing bacterial counts allows EPS synthesis to continue and the matrix scaffold to remain intact, facilitating bacterial recolonization. Disrupting both species simultaneously is a mechanistic requirement for durable biofilm eradication in this context, not an incidental finding.

9.1 Limitations

These results, while encouraging, do have some limitations when sharing the results of their effectiveness. The primary methodological limitation is reduced replication across several assays. CFU enumeration was conducted in biological triplicate and supports statistical inference; the 80.4% and 83.5% reductions in *C. albicans* (p =

0.0001) and *S. mutans* ($p = 0.0015$) by Peptoid B provide a statistically robust proof-of-concept. pH monitoring and confocal imaging were single-replicate exploratory experiments and must be interpreted accordingly. Increasing replication of these protocols for statistical analysis is important.

Another limitation is the substrate. Polystyrene (the chamber used to cultivate the biofilms) does not replicate the surface chemistry or mineral content of enamel or dentin. Transitioning to saliva-coated hydroxyapatite (sHA) discs within a dynamic flow-cell system would more accurately simulate the mineralized tooth surface and evaluate peptoid activity under realistic oral conditions. Also, the two-species system used in these assays is a simplification. The oral cavity contains a massive variety of different organisms, the cariogenic microbiome includes Actinomyces, Lactobacillus, Bifidobacterium, and other organisms whose interactions with peptoids are unknown. A multispecies system incorporating these organisms is a logical next step.

While these compounds are not ready for clinical testing, using the data we have and knowledge of peptoids mechanisms, suggest these could be incorporated into professional and home dental care. Because the N-substituted peptoid backbone lacks the amide N-H groups required for protease recognition, these compounds are expected to maintain structural integrity in enzyme-rich oral environments (Zuckermann & Kodadek, 2009). This property supports formulation of various methods of delivery, such as topical varnishes, deep-fissure gels or rinses (Anderson et al., 2022).

CHAPTER 10

CONCLUSION

This study set out to address a critical limitation in pediatric dentistry: the gap in effective antimicrobials to manage Severe Early Childhood Caries (S-ECC). This disease, driven by a cross-kingdom partnership between *S. mutans* and *C. albicans*, lacks an available clinical agent that directly targets both components of this interaction within a mature, EPS-protected biofilm matrix. This gap in treatment options is the clinical problem this study addresses.

The data presented here indicate that Peptoid B reduces viable populations of both *S. mutans* and *C. albicans* by more than 80% within mature dual-species biofilms at a single dose of 50 μg/mL, outperforming chlorhexidine in measured outcome. Peptoid H also showed strong anti-biofilm activity and warrants continued characterization.

Translating these results toward clinical application will require additional lab testing. Validating the antibiofilm properties of these peptoids within a multispecies biofilm models, sHA substrate-based biofilm systems, and in vivo animal caries models are the next steps for preclinical assays. Additionally, formulation development for pediatric oral delivery would need to happen in order to find the most effect route of administration appropriate for results and effective for use in children.

The evidence presented here supports the argument that effective intervention requires simultaneous targeting of both *S. mutans* and c albicans. Synthetic peptoids, with their protease-resistant structure, broad-spectrum membrane activity, and selectivity for

anionic pathogen surfaces, make for uniquely suited antimicrobials. Dental research is constantly investigating alternatives to current therapeutics, and the compounds described here may ultimately offer a clinically viable option to treating prevalent and damaging disease.

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CURRICULUM VITA

NAME: Jacob Spencer

ADDRESS: Department of Oral Immunology and Infectious Disease

School of Dentistry, University of Louisville

Louisville, Kentucky 40202

EDUCATION & TRAINING:

D.M.D. Candidate, Class of 2026

University of Louisville School of Dentistry, Louisville, Kentucky

M.S., Oral Biology (in progress)

University of Louisville School of Dentistry, Louisville, Kentucky

B.S., Microbiology, 2022

Brigham Young University, Provo, Utah

RESEARCH EXPERIENCE:

Graduate Research Assistant, Diamond Laboratory

Department of Oral Immunology and Infectious Disease

University of Louisville School of Dentistry, 2023–2026

MENTOR:

Gill Diamond, Ph.D.

Professor, Department of Oral Immunology and Infectious Disease

University of Louisville School of Dentistry

NATIONAL MEETING PRESENTATIONS:

Spencer, J. *Peptoids as a Novel Therapy for Early Childhood Caries.*

University of Louisville School of Dentistry Research Day (Research!Louisville) 2023, 2024, 2025

FUNDING SOURCES:

NIH R01 DE028883; R01DE031928; R21 DE028378; R21 AI146542

Colgate-Palmolive Company

Chan Zuckerberg Initiative

Maxwell Biosciences, Inc.