Special Issue Article

Reactions: Antibacterial and bioactive dental restorative materials: Do they really work?

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Abstract: Purpose: The study and development of antibacterial materials for use in dental applications is growing with the development of novel materials and procedures. Examination of the effects of such antibacterial materials on oral pathogens as well as on stability and longevity of dental restorations is of paramount importance to the field. **Results:** This review addressed the range of topics covered by the manuscripts presented at the Seoul symposium on antibacterial dental materials. (*Am J Dent* 2018;31Sp Is B:32B-36B).

Clinical significance: Based on the presented works, it seems that the emerging antibacterial and bioactive materials can potentially benefit restorative dentistry; however, like many other subjects in clinical dentistry, good quality evidence on their effectiveness under clinical situations is yet to be accumulated.

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Introduction

The general need for anti-microbials stems from the overall procedure of placing a dental restoration to treat an infectious disease; caries. An existing pervasive weakness of resin-based dental restorations lies in their ability to intimately adapt to the tooth structures on which they are placed, followed by polymerization shrinkage. Thus, even if complete adaptation is achieved initially, when the material is polymerized, gaps are produced as the materials shrink towards their center of gravity, away from the tooth surface. Both adhesives and composites are susceptible to polymerization shrinkage. The resulting gaps allow infiltration of bacteria, which thrive and flourish under the protection of the restoration and away from tooth brushing and brief oral rinses. It is for this very reason that the selection of antimicrobials requires careful consideration.

Antibacterial dental adhesives

Because of inherent polymerization shrinkage of resin-based composite materials, detachment of cured composite fillings from the cavity wall and formation of microgaps are almost inevitable. Although recently developed resin-based composite/adhesive systems bond to dentin with bond strength values greater than enamel (20 MPa) in vitro, recurrent or secondary caries along the microgap between restorations and cavity walls is still a major issue for resin-based composite fillings. Previous studies reported that resin-based composites tend to accumulate more bacteria or plaque than other restorative materials in vitro.

Antimicrobial agents available for dental adhesive systems

Although some commercially available resin-based composites/adhesive systems show antibacterial activity, this is normally only an adverse reaction of the components of the composites, and the inhibitory effect against bacteria is unlikely to be reliable. Besides developing stronger and more durable adhesive systems, incorporation of antibacterial agents into resin-based composite/adhesive systems has been investigated for decades. Attempts have been made to prevent plaque accumulation on the tooth and restorative surfaces by incorporation of antibacterial agents such as glutaraldehyde, chlorhexidine digluconate, and 12-methacryloyloxy dodecyl pyridinium bromide (MDPB) monomer into restorative materials. Certain synthesized monomers similar to MDPB also have shown antibacterial activity when immobilized in a resin-based composite material and their effectiveness has been supported by results from in vitro tests.

MDPB is a compound of quaternary ammonium plus a methacrylate group. In an unpolymerized state, this monomer acts only as a disinfectant. When the material is polymerized, the copolymerization of MDPB with other monomers from the composite material immobilizes the antibacterial agent in the polymer matrix, and inhibits the growth of bacteria with which it has direct contact. Through the advancement of dental adhesive systems, incorporation of the antibacterial monomer MDPB enhanced the antibacterial effect of a proprietary dentin primer before curing and showed no adverse influence on bond strength to dentin and polymerization of the adhesive system.

Particulate silver is well known for its low toxicity and good biocompatibility with human cells. Silver nanoparticles (AgNPs) have been extensively explored over the last decade and are a potent antibacterial agent. Incorporation of AgNPs alone or combined with synthesized quaternary ammonium dimethacrylates into either dental resins or adhesive systems has been observed to inhibit microcosm biofilm growth, metabolic activity, and lactic acid production. Biological methods are available for the synthesis of AgNPs with active antibacterial potency and to make AgNPs more biocompatible with human tissues and cells.

Propolis, a natural non-toxic beehive product, has been shown to reduce the incidence of dental caries in rats, and the accumulation of supragingival plaque in vivo. Two compounds, apigenin and tt-Farnesol, have been identified as potential anti-plaque/anti-caries agents. Apigenin and tt-farnesol, alone or in combination, showed cariostatic properties in rats without significant effect on microbial viability in the rats' mouths. Results

of a recent in vitro study revealed no changes in dentin bond strength, resin-dentin interfacial morphology, or total amount of protein and soluble polysaccharide with the additions of the above anti-caries agents.

Effect of antibacterial dental adhesives on oral pathogens

Recent studies have examined the effects of the above antibacterial adhesive systems primarily on *Streptococcus mutans* bacteria. The majority of initial effectiveness studies were conducted in vitro using the agar diffusion method. The applied commercial adhesive had MDPB incorporated into the primer and demonstrated an antibacterial effect on infected cavities in dog teeth as well as reduction of enamel demineralization around orthodontic brackets after 30 days. The current trend in this area of study is the use of a microcosm model because it offers the advantage of coming closer to the physicochemical, microbiological and nutrient conditions of in vivo plaques, in addition to maintaining complexity and heterogeneity. However, the only in situ study of these commercial adhesive systems demonstrated that none of the antibacterial materials tested reduced caries formation in dentin.

What have we learned from published studies?

Most studies that aim to develop new antibacterial agents are in vitro studies that focus mainly on caries-related oral pathogens. However, the geometric factor of the actual adhesive layer including primer and bonding agent for resin-based composite restorations may not be designed correctly in most of these in vitro studies. According to examination by scanning electron microscope of the resin-based composite/ adhesive systems' bond to dentin, the adhesive layer or hybrid layer is usually only 2 to 5 μm-thick between the dentin wall and the bonding surface of resin-based composite restoration. This thin layer of adhesive exists rarely at the cavosurface and proximal enamel margin, but mostly at the gingival margin on the root surface of composite restorations. This means that only a very limited surface area of dental adhesive is exposed to the oral cavity in clinical situations. The antimicrobial effectiveness results observed in some bench studies therefore could be misinterpreted due to improper design, specifically due to the surface area mismatch between specimen and in situ clinical condition. In particular, the antimicrobial effect is overestimated and magnified by the high surface area design of specimen exposure to high agent concentration, especially by the direct contact test method. If an in vitro test will be conducted to determine the efficacy of an antibacterial agent, the most correct testing methodology will present a clinically relevant design for the tested specimens. Such a procedure should be developed and adopted accordingly in future studies.

When antimicrobial agents are added to primer solution or to a self-adhesive system, the final adhesive layer will be polymerized which results in the added agent being trapped inside the cross-linked network of polymer matrix. Many parameters, such as permeability of the resinous matrix, and driven force factors determine the releasing rate of some releasing agents such as chlorhexidine and AgNPs. In order to achieve efficacy and reaction longevity for the antimicrobial agent, the antimicrobial mechanisms and the releasing factors of each agent must be verified.

Future perspectives

As the world's population ages, an increasing incidence of root caries will be observed among the elderly who retain more of their teeth and who are at a higher risk for root caries. Gingival recession leads to increased exposure of tooth root surfaces, which have a higher solubility to biofilm acids than does coronal enamel. Root surface restorations with subgingival margins are difficult to clean and may develop pockets that facilitate periodontal bacterial growth. Thus, the need exists to develop antibacterial dental adhesives that can inhibit cariogenic and periodontal pathogens at root surface restorations. To validate these materials for this application, periodontitis-related bacteria such as *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Fusobacterium nucleatum*, etc. must to be tested in relevant research studies, in addition to the cariogenic bacteria already tested.

Finally, in vivo studies are absolutely necessary to validate the efficacy of antibacterial dental agents applied to the dynamic environment of the living oral cavity, rather than to the limited static environment simulated by in vitro studies. In addition, optimization of the microecologic regulative effects of antimicrobial materials has received little attention to date and should be further examined.

Antibacterial dental restorative materials

Chen et al[1] conducted a literature review of published information in a single online database, PubMed, restricting the search criteria to publications issued within a very recent 4-year period, from 2012-2016. Journal entries were limited to publications written in English, and although the majority of scientific publications are presented in the English language, valuable and clinically relevant research is presented in the non-English native language of the study authors. Of particular note are publications recently coming from Eastern Europe, specifically from Turkey and Hungary. Because of high research costs in the U.S. and other mature scientific markets, some clinical research is favored in these or other locations where oversight and/or cost of research is not as substantial and the universal adoption or education of the scientific community to English is not fully established, yet the quality and reliability of the research is sound and trustworthy. Accordingly, some clinically relevant information may have been omitted by restricting the search parameters to only publications presented in English.

Three classes of antimicrobials were reviewed by Chen et al:[1] leachables, suspended particles, and polymerizable monomers. In addition to the drawbacks mentioned by the authors, other negatives should be mentioned for each of these three types. For leachables, a concern exists where the antimicrobial, in escaping the dental restoration, becomes a systemic compound that can be ingested, absorbed into the circulatory system, or otherwise have reactive effects with other tissues in other locations of the body. The risk of systemic effects to the patient bears consideration. Generally, these effects are mitigated by the dilution effect of the leached compound relative to the sheer size of the human body. Suspended particles by nature have a limited physical reach - only colonization directly on the surface of the particle is disrupted. Growth adjacent to the particles, up to a respectable inhibition zone, is still expected. Thus, suspended particles are better described as microbial

static - preventing further growth against the restoration. Polymerizable agents, which may be better defined as bacteriocidal ligands, experience the same weaknesses as the other two groups with potential additional limitations. If the ligand is capable of detaching from the monomer chain after polymerization, then the ligand is in reality a leachable although an advantage may exist in that the detached lingand bound within the polymer might take more time to migrate to the surface of the dental material and thus prolong the overall activity of the ligand added to the dental material. If the ligand remains bound to the polymer, then the ligand itself acts as a captured particle with the added disadvantage that numerous ligands would be wholly bound within the polymer, unable to interact with the microbes at the polymer surface. Further, unless the monomer is relatively small or short-chained, the ratio of active ligands to overall polymer may be less than the presented surface area of bound particles, providing a lowered anti-microbial effect. This behavior is noted by the authors, where the activity of only the monomer is noted as effective.

The authors present several anti-microbial agents indicated in the searched literature. Some, such as benzalkonium chloride and chlorhexidine have a well-known record of use. Other suggested compounds are relatively unknown in dentistry and certainly unknown to us, particularly the referenced use or research into urushiol and copper iodide. Urushiol is an oily extract obtained from several plants of the *Toxicodendron genus*, whose members include poison oak, poison sumac, and the Japanese urushi tree. The literature suggests a rapid onset of dermal edema when the compound is absorbed into the skin, and also suggests that a large portion of the population would present some level of allergic reaction to the compound. Urushiol is also reported to oxidize to a black-colored compound, which would further make the compound unsuitable for use in dental restorations. Copper iodide also may be subject to a similar concern. Some oral bacteria have demonstrated a reducing effect on metal ions. For example, ferric ions left over from some hemostatic preparations are known to reduce to metallic iron, producing a black discoloration. Copper ions are expected to do the same, reducing to an unsightly black-to-brown discoloration. Likewise, our experience with zinc compounds provides further evidence of metal redoxoxidation reactions in which zinc compounds (not necessarily zinc oxide) were observed to react in the presence of saliva to produce a gray color.

Because gaps are produced due to polymerization shrinkage, the selection of antimicrobials requires careful consideration. Leachables can quickly fill a marginal gap to achieve short-term, effective protection. However, this margin also provides a conduit for the leachable compound to escape and, in time, the situation becomes the same as if the leachable were never present to begin with. This marginal gap also limits the effectiveness of particles or active ligand polymers. Microbes may be inhibited at the surface of the dental material, but if the gap is sufficient the microbes may thrive on the tooth surface regardless, and the effectiveness of these materials is nullified. If a marginal gap cannot be addressed, then the ideal antimicrobial is a suspended compound with a zone of inhibition large enough to exceed the common distance of the marginal gap. Any efforts to pre-cleanse the treatment site may achieve a short-term reduction in microbial activity, but so long as the margin exists, a pathway is available for subsequent infiltration of microbes long after the restoration is placed. Little debate exists regarding effective materials and strategies for microbial control up to 1-2 years, however the ideal would be to achieve long term (5-10 years and more) microbial control.

Bioactive dental adhesives

The topic of bioactive dental adhesives has been discussed in the past and the development of new generations of multi-functional dental adhesives is still an area of great interest to many dental clinicians as well as dental materials researchers. This interest is reflected in Fujimura's article[2] which reviews the development of antibacterial bioactive dental adhesives from the manufacturer Kuraray Noritake Dental Inc., since the 1970s. Supporting literature for the review ranges from the 1990s to 2011. Although the focus of this article[2] is the review of Kuraray's developments, newer generations of bioactive dental adhesives have been studied in the past 5 years and are worth reviewing as well as comparing against Kuraray's products.

The Fujimura et al[2] review article focused primarily on the properties of methacryloyloxydodecylpryridinium bromide (MD PB), a newly developed monomer in dental adhesives and supported Kuraray's findings with a review of in vitro studies which evaluate antibacterial properties, long-term durability and post-operative sensitivity. Providing more details about these studies in terms of groups compared, time ranges and comercially available and commonly used adhesives would be useful for clinicians and readers to better understand and evaluate the capabilities of Kuraray's products.

The biggest challenge in the development of antibacterial dental adhesives is leakage at the interface between tooth surface and restorative material because such leakage is the primary cause of secondary caries and failure of the tooth due to structural weakness. Moreover, bonding of dentin to the restoration has been shown to be even more challenging in addressing the successful restoration.

In the review article,[2] Fujimura highlights three important properties of Kuraray's dental adhesives: (1) antibacterial properties of MDPB before polymerization, (2) MDPB long-term durability and (3) no post-operative sensitivity. Bacterial inactivation has been studied with a number of bacteria and results have indicated inhibition of different types of bacteria compared to other adhesives. However, the article does not specify differences between other adhesives compared or the duration of inhibition of bacterial growth.

In general, one of the most important needs addressed by Kuraray's products is the bonding of dental adhesive to dentin, which throughout the years has proven to be one of the biggest challenges to achieving a successful restoration. With the development of MDPB, long term durability was demonstrated to exceed that of the other adhesives when compared in several in vitro and in vivo studies. As explained in the review, this property was the result of polymerization of the adhesive as well as the inhibition of matrix metalloproteinases which lead to degradation and subsequently affect bonding at the interface. Finally, post-operative sensitivity was reported to be improved over a 6-week period and over 1 year in two different studies. However, no further details were given regarding factors that might have influenced this effect and the differences between

the two studies that led to such discrepancies.

Several antibacterial dental methods have been investigated over the past decades. One such approach was the incorporation into dental materials of silver particles and other antibacterial agents proven to be highly effective in inhibiting bacterial growth in many applications. Kuraray has maintained interest on multifunctional adhesives capable not only of achieving antibacterial activity by bacteriolysis, but also by polymerizing and sealing the area of interest. This underscores the advantages of Kuraray's adhesives by eliminating the addition of multiple components and by having one component platform with multiple capabilities.

Although the studies mentioned in the Fujimura et al article[2] highlighted the antibacterial properties of Kuraray's adhesives, literature in the field still addresses the concern of a long-term antibacterial effect and the stability of the current commercially available adhesives in the market. With current commercially available adhesives attributed to more than half of all restorations failing within 10 years, the studies mentioned in the review article did not address or demonstrate longer survival of their adhesives. Additionally, the effect of remineralizing agents also needs to be considered.

Synthesis of novel antibacterial dental monomers

Antibacterial monomers bear various disadvantages in the field of dental materials. Firstly, antibacterial monomers tend to exhibit antibacterial activity only in the uncured state and only show bacteriostatic activity in the cured state. Secondly, monofunctional antibacterial monomers tend to weaken the mechanical properties of the cured resin at the higher concentrations needed for strong antibacterial effect. Wang et al[3] sought to develop new, more effective antimicrobial monomers and to improve the performance of these antibacterial monomers by increasing chain length for increased antibacterial activity and increasing monomer functionality to allow crosslinking with the resin to prevent the deterioration of mechanical properties.

Wang et al[3] synthesized five new antibacterial monomers, characterized them using NMR, IR and HRMS, tested their in vitro biocompatibility using a human gingival fibroblasts cytotoxicity assay, and determined their in vitro antibacterial activity against *Streptococcus mutans*, *Lactobacillus casei*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The differences among these monomers include alkyl chain length and the number of reactive vinyl groups (mono- vs. dimethacrylate). The study found that none of the monomers was cytotoxic compared to BisGMA; that longer alkyl chains and dimethacrylates tended to produce stronger antibacterial effects; and that ammonium salts containing the dimethylbenzyl moiety had stronger antibacterial effects than structures containing 1,4diazabicyclo[2.2.2]octane (DABCO).

Several drawbacks of this study are noteworthy. Wang et al[3] did not attempt to test the ability of their new monomers to form polymers with dental resins, and no mechanical tests were done on dental resins containing these monomers. This is important, especially given the disadvantages of current antibacterial monomers. Only one antibacterial test was presented in this study, and this was with monomers only. Many monomers so-called antimicrobial are not actually bactericidal but only bacteriostatic once cured; therefore, the antibacterial activity of polymers cured from these new monomers must be tested, otherwise no improvement over what is already in the literature has been presented. A ring of inhibition assay could have been done with resin discs cured from these monomers, or better yet, dental resins cured with different concentrations of these monomers.

Even when just testing monomers, which would be more potent than the cured form, the author states, "Compound 6 has an inhibitory effect against *P. aeruginosa* at 10^{-4} M and 10^{-5} M concentrations, but the bacterium grows after a significant delay (although to a much lesser extent compared to the control). Monomer 5 causes an extended lag in growth for P. aeruginosa at 10^{-4} M concentration, but after 24 hours the total growth is equal to that of the control." These results indicate that when a biofilm begins to form, these monomers, and most likely the polymers made from or with these monomers, were not as antibacterial. It can thus be extrapolated that when cured, these monomers may not be effective once the surface is covered with proteins and/or biofilm. This is one of the disadvantages of antibacterial monomers upon which the authors were trying to improve.

Finally, the authors of this article[3] state, "The results indicate that the lipophilicity of the monomers plays a significant role in the antibacterial activity, with the highest activity shown for the most lipophilic monomer 6." However, the lipophilicity of these specific monomers was never determined, thus this statement cannot be corroborated until the authors test it.

A strong need exists to develop novel antimicrobial materials, and this study is intriguing in that regard. However, based on this presentation, it is not clear that the authors have indeed improved upon the disadvantages of antibacterial monomers. It seems that a combination of the use of antimicrobial monomers/polymers and releasing antibacterial agents may be needed. Furthermore, while a severe disadvantage of releasing antimicrobial agents is their limited time of efficacy, some publications have shown that the antimicrobial activity of Ag+ ions released from Ag nanoparticles in dental resins can last 4 weeks. However, whether the Ag+ ions would be depleted if the surface is bonded to dentin or enamel is unknown. Their release may be delayed until a marginal gap is formed and their release is needed, but this will need to be tested.

Anti-demineralization activity of cements

Turkistani et al[4] report on the possible inhibition of demineralization around a restoration made with a so-called bioactive new glass ionomer cement that releases calcium and fluoride. Of special note in the study by Turkistani et al[4] is the authors' application of optical coherence tomography (OCT) in their research. OCT is an optical diagnostic tool based on interferometers, and uses a low coherence broadband near-infrared light source. Excellent spatial resolution (~20 μm) and real-time images are obtained by OCT. Application of OCT in dentistry has become very popular, especially for early detection of caries, periodontal disease and oral cancer which are quite difficult to detect early (and often with ambiguous results) based on clinical examination or radiographs alone. OCT is a noninvasive, nondestructive, non-radiated, and real-time monitoring method with three-dimensional imaging ability that can help clinicians locate problem areas accurately and rapidly.

OCT is not without limitations, however. Firstly, cost and availability of the instrument can be a drawback, and even with

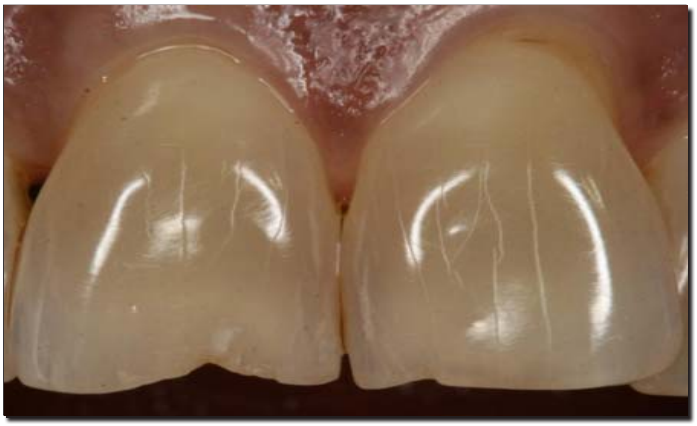

Fig. 1. Physical craze lines or cracks on the surface of anterior central incisors. Cracks are defined as gaps in the tooth surface, such as enamel cracks. OCT can be applied for non-invasive detection of cracks (fractures) and microleakage.

access to the instrument, OCT has limited penetration depth and scanning range. Because the scanning range is usually several millimeters, hundreds or thousands of pictures may be necessary to visualize a whole lesion. Wavelength choice may be another important consideration for specific types of tissue substrates.

Given that OCT is a relatively new technology, comparison of its results with those of other dental diagnostic methods is important to assist researchers in interpreting results. In the results presented by Turkistani et al,[4] we would have preferred to see images from both OCT and CLSM from all groups including the control, but results for only three groups were shown.

Other limitations of the tests performed by Turkistani et al[4] included choice of tooth substrate and in vitro demineralization as a means to simulate the actual carious process. Holding demineralized test specimens at pH 4.5, for example, may not accurately represent the condition of the oral cavity condition, even though it does result in somewhat accelerated demineralization progress. Demineralization and remineralization is a cyclic process which could result from the presence of ions not only in dental cement, but also from ions in saliva.

What are the future perspectives?

As evidenced by Figs. 1 and 2, physical cracks and gaps can be aptly evaluated by OCT, but bioactivity of antibacterial dental materials around restorations may not be as evident with this technique. Nonetheless, such effects can be indirectly observed under clinical situation using this technology.

Conclusion

The investigation of anti-microbials in dental restorative materials is not new. Whether intrinsically present in metal amalgams that have been in use for a century, or in resin-based restoratives that have found wide acceptance for over 30 years, the topic of anti-microbial properties in dental restoratives has been foremost on the minds of researchers and manufacturers for decades. Many technologies and additive compounds that have been in use for decades continue to be in use today.

A contemporary challenge that researchers face in the development of antibacterial dental adhesives is the need for more accurate and robust in vitro and in vivo models that can provide reliable information and matching to clinical scenarios. This implies the need to collect data from studies with longer durations (up to 10 years) in order to fully address concerns on survival of restorations and persistence of antibacterial activity.

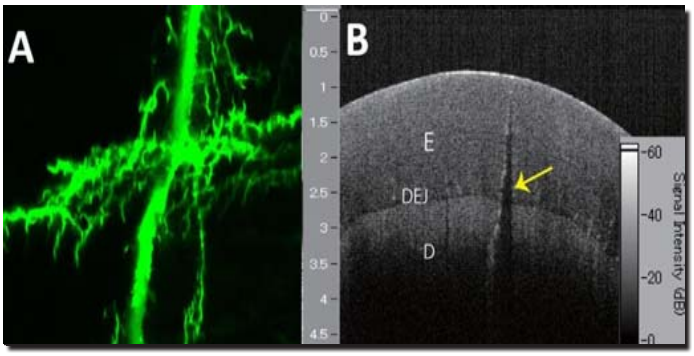

Fig. 2.**A.** CLSM from a central incisor specimen with an invisible crack. Fluorescein dye penetration revealed the presence of a major crack and of lateral cracks. **B.** A SS-OCT image of a sample visualized as a deep enamel crack transillumination. This crack extended beyond the DEJ.

Current research on minimally invasive dental restorations suggests the use of composite materials that are typically bio-inert to replace missing volume. Future developments should focus on dental adhesives with synergistic effects that will not only replace missing volume but also will have bioactive and therapeutic properties. More robust and longer studies proving information about the properties and their mechanisms of action are required both in vitro and in vivo. Inclusion of optimization studies for antimicrobial materials will be required to fully understand possible induction of drug resistance. Through multidisciplinary efforts, the development of antimicrobial dental adhesives promises tremendous advances in oral health.

Identification of compounds that have long-term bacterial inhibition effect and that are compatible with restorative agents like adhesives and cement is a challenging task. When such a material is applied to the restorative interface, bacteria will not grow at the dental structure and a long term antibacterial effect will be achieved. Advances from different groups as well as collaborations among different groups and technologies will result in truly long-term antimicrobial dental materials that are biocompatible and capable of preventing secondary caries and restoration failure. With efforts from the community, we expect this to be accomplished in the near future.

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