

# Adhesive Materials with Bioprotective/Biopromoting Functions

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Published online: 6 September 2014  
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**Abstract** Esthetic restoration using resinous materials has achieved great success in the past decade. A large part of this success is attributed to the significant advances in adhesive materials. Although refinement of existing adhesive materials is still required to improve bonding reliability and reproducibility, the development of innovative adhesives with bioprotective/biopromoting functions has been recognized as an important direction for future research. Until now, significant achievements have been made in the development of adhesives that can protect the bonded interface from extrinsic bacteria- or intrinsic enzyme-induced destruction, as well as

those that can promote the natural remineralization or regeneration process of the tooth tissue. In this review, the author will summarize the latest developments in these innovative bioactive adhesive materials.

**Keywords** Dental adhesives · Bioprotective · Biopromoting · Antibacterial · MMPs · Collagen cross-linking · Remineralization · Pulp regeneration

## Introduction

Dental caries remains a prevalent problem worldwide. Resin-based materials are now the primary choice for cavity restoration due to their superior esthetic properties and direct filling abilities [1]. However, the longevity of resinous restorations is limited and half of all restorations would fail within 10 years, mainly due to secondary caries and fracture [2–4]. Since the adhesive layer is the weak link in resinous restorations, refinement of the adhesive materials is necessary to improve the longevity of resinous restorations.

Adhesive materials with bioprotective functions are developed when attempts are made to protect the dentin–adhesive interface from extrinsic- or intrinsic-factor-induced degradation, and thus improve the longevity of resinous restorations. For instance, adhesives with antibacterial activities are expected to inhibit the destruction of the bonded interface caused by extrinsic bacteria, while adhesives with matrix metalloproteinase (MMP) inhibitory effects or collagen cross-linking properties attempt to protect against endogenous protease-induced degradation.

Adhesives with biopromoting functions should be able to promote the natural biofunctions of the tooth. With the purpose of mimicking or promoting the biomineralization process of dental hard tissue, plenty of research has been performed to develop adhesives with remineralization properties. Since the

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importance of vital pulp has been recognized, pulp preservation has become a hot focus in both experimental and clinical research. Accordingly, much time and effort has been devoted to developing adhesives that can promote the regeneration of the pulp.

In this article we will review the latest developments in adhesives with bioprotective and biopromoting functions.

## Adhesive Materials with Bioprotective Functions

### Adhesives with Antibacterial Functions

Production of adhesive materials with antibacterial functions could be beneficial in reducing the risk of secondary caries and improving the longevity of current resinous restorations. Basically, there are two approaches to provide antibacterial activity to adhesives—the agent-releasing approach and the non-agent-releasing approach. In the following sections, the authors will summarize the latest developments in these two approaches and discuss their advantages and disadvantages.

#### *Agent-Releasing Antibacterial Adhesives*

Various soluble antimicrobial agents, such as antibiotics, epigallocatechin-3-gallate, chitosan, chlorhexidine (CHX), and silver have been added to dental adhesives. The advantage of an agent-releasing approach is that the antibacterial effect can extend beyond the immediate region of the dental composite; however, the drawbacks are that the release kinetics are difficult to control, the long-term effect is not predictable, and mechanical properties of the carrier material can be degraded [5].

During the early days, CHX has been added to various dental materials to provide antibacterial activities [6, 7]. In recent years, CHX has also been incorporated in adhesives. However, the primary purpose is not to provide antibacterial activities, but to inhibit MMP-induced degradation of dentin collagen and thus improve the durability of the dentin–adhesive bond. As reported, CHX is added to adhesives at concentrations ranging from 0.01 % to 2 % [8•, 9–13]. According to the published results of Huang et al., the minimum inhibitory concentration of CHX against various oral pathogenic bacteria is around 5 µg/mL, which is approximately equal to 0.5 wt % if we estimate the density of the adhesive as 1 g/mL [14]. Thus, we can predict that adhesives containing 0.5–2 % CHX should exhibit some antibacterial activity when applied to dentin. This prediction has recently been proved by Hiraishi et al., who reported that the experimental self-etching primer containing 1 % CHX has inhibiting effects against *Streptococcus mutans* (*S. mutans*) [13].

Due to their strong antifungal and antiviral actions, silver ions have been considered for applications as an antibacterial

additive in dental adhesives. Direct incorporation of silver nanoparticles is a common and simple strategy. However, nano-sized silver ions tend to aggregate, and polymers directly filled with silver nanoparticles typically exhibit a ‘burst-type release’ of the ion. In 2011, a new technique coupling photo-initiated free radical polymerization of dimethacrylates with in situ silver ion reduction was introduced [15•]. Using this technique, silver nanoparticles were added to the primer and bonding agent of the Scotchbond Multi-Purpose bonding system at a concentration of 0.05 % or 0.1 %. Biofilm formation was significantly inhibited on the surface of the experimental material [16–21]. Furthermore, the total number of bacteria in the culture medium away from the experimental material was also reduced, indicating that nano-silver-containing adhesive has long-distance killing capability [21].

#### *Non-Agent-Releasing Antibacterial Adhesives*

Ever since Imazato et al. introduced the concept of the “immobilized bactericide” in 1994, non-agent-releasing antibacterial adhesives has become a hot research topic [22, 23••]. Immobilized bactericides are antibacterial components that can be chemically bonded to a carrier material. This technology is advantageous in terms of longevity of antibacterial effects and maintaining mechanical properties of the carrier materials. The first ‘immobilized bactericide’, methacryloyloxydodecylpyridinium bromide (MDPB), was synthesized by combining a polymerizable methacrylate group with an antibacterial quaternary ammonium group [23••](Fig. 1). Later, other researchers reported similar molecules with improved properties. Methacryloxyethyl cetyl dimethyl ammonium chloride (DMAE-CB) synthesized by Chen’s group exhibited significantly stronger bactericidal effect compared with MDPB [24] (Fig. 1). Recently, with the attempts to increase the amount of antibacterial quaternary ammonium monomers that can be incorporated in adhesives and subsequently enhance the antibacterial activity of the modified material without compromising biocompatibility, new antibacterial monomers with two polymerizable methacrylic moieties have been developed [14, 25, 26].

Antibacterial adhesives containing quaternary ammonium monomers act as cavity disinfectant before curing. When the primer containing MDPB was kept in direct contact with planktonic bacteria, all bacteria were killed within 30 s [27]. Noticeably, these antibacterial adhesives are able to penetrate 500-µm-thick dentin block [28] and eradicate caries-related species inside the dentin [18, 29]. In vivo studies using beagle dogs also demonstrated that the MDPB-containing primer could inactivate *S. mutans* in the cavity [30].

After curing, antibacterial adhesives containing quaternary ammonium monomers can inhibit the growth of bacteria that comes into contact with the material and thus reduce bacterial microleakage at the dentin–adhesive interface. When

*S. mutans* is incubated in contact with the cured primer/adhesive surface containing various quaternary ammonium monomers, the number of viable bacteria was significantly reduced [31–33]. Similar results have also been found in clinical studies [34]. Notably, the antibacterial activity of the quaternary ammonium monomer-containing adhesives is long-lasting and does not fade after at least 3 months [35]. However, these antibacterial adhesives only exhibited bacteriostatic, rather than bactericidal, effects against the contacting bacteria. Furthermore, the bacteriostatic effects can be diminished when the material is covered by saliva pellicles [21, 36, 37].

In conclusion, both the agent-releasing and non-agent-releasing antibacterial adhesives have their advantages and disadvantages. The combination of these two techniques could show complimentary behavior for inhibiting bacteria. Indeed, several publications reported that adhesive containing both quaternary ammonium monomer and silver nanoparticles have enhanced antibacterial activities against both bacteria in contact with the material and those suspended in the culture medium away from the surface [17–20, 38, 39].

#### Adhesives with Anti-Matrix Metalloproteinase Functions

Although modern adhesives can achieve satisfying immediate bonding to dentin, they demonstrate a loss of bond strength over time. Enzymatic degradation of the collagen matrix by host-derived MMPs and cysteine cathepsins plays a major role in the destruction of the bonded interface [40]. One strategy to improve the durability of resin–dentin bonds is to use inhibitors that inactivate MMPs at the bonded interface.

The vast majority of the experiments aimed at improving the durability of dentin bonds using enzyme inhibition have been performed with CHX. The use of 2 % CHX for 60 s as a preliminary dentin treatment after acid-etching has reduced interfacial aging over time [41, 42]. However, this procedure adds an additional step to the bonding protocol, despite the clinician's need for simplification. Moreover, although large amounts of CHX remain bound to partially and completely demineralized dentin for at least 8 weeks, it may be exhausted over longer periods of time [43]. To provide a CHX reservoir that can release the agent in a relatively controlled manner, researchers have tried to incorporate CHX in adhesives. It has been demonstrated that the addition of CHX in concentrations up to 0.2 % to commercial etch-and-rinse adhesives provides controlled release of CHX in sufficient concentration to inhibit MMP activity without jeopardizing the materials' ultimate tensile strength, water sorption, and solubility [8•]. For etch-and-rinse adhesives, most studies demonstrated that the incorporation of CHX at concentrations ranging from 0.01 % to 1 % could reduce the degradation of the bonded interface [9, 10]. For self-etching adhesive, CHX incorporation has been shown to be effective in reducing the collagenolytic activity of

dentin powder [11]. However, when it comes to bond strength, the results are controversial. Zhou et al. demonstrated that when incorporated in the primer of Clearfil SE Bond, CHX preserved dentin bond as long as the concentration of CHX is higher than or equal to 0.1 % [44]. On the contrary, De Munck et al. found that the addition of 0.05 % CHX to the primer of Clearfil Protect Bond, adhesives of G-bond and Scotchbond 1 XT is not effective in protecting the bonded interface from degradation [10, 12]. The controversial findings may be attributed to the different chemical compositions of the adhesives to which CHX was included.

Very recently, quaternary ammonium antibacterial monomers have been reported to have potent inhibitory effects on MMPs. Tezvergil-Mutluay et al. [45] found that quaternary ammonium monomers, including MDPB, exhibited MMP inhibition behavior that was comparable with that of CHX [44]. Noticeably, MDPB at 5 %, which is the concentration utilized for the primer of commercial adhesive Clearfil Protect Bond, achieved 89 % inhibition of soluble rhMMP-9 and approximately 90 % inhibition of matrix-bound MMPs [45•]. Similarly, Liu et al. also reported the MMP-inhibitory effects of DMAE-CB [46]. Compared with CHX, which leaches out from bonded interfaces, quaternary ammonium monomers are advantageous in that they can co-polymerize with adhesive monomers and thereafter be retained in the hybrid layer for a long time. Indeed, several studies, including in vivo studies, revealed that Clearfil Protect Bond can achieve more durable bonding than conventional adhesives [47].

#### Adhesives Containing Collagen Protective/Cross-Linking Agents

Type I collagen accounts for 90 % of the organic matrix of dentin, and degradation of the unprotected collagen by endogenous proteases is the primary reason for the destruction of the adhesive–dentin bond. Besides the inactivation of endogenous proteases, another strategy to preserve the stability of dentin bond is to stabilize dentin collagen using cross-linking agents. Synthetic agents (glutaraldehyde and carbodiimide hydrochloride) and nature-derived agents (proanthocyanidins [PAs]) have been shown to effectively interact with type I collagen [48••]. Compared with synthetic agents, natural PAs have two attractive characteristics—very low toxicity and renewable/sustainable resources [49]. Using PA or PA-rich extracts as pre-conditioners before application of adhesives is effective in enhancing the mechanical properties of dentin and preserving bonding stability [50, 51]. However, this strategy adds an extra step to the bonding procedure and cannot achieve sustained release of PAs. Furthermore, according to the majority of published data, the application time of PA-containing pre-conditioner varied from 10 min to 1 h, which is not feasible in a clinical setting [52]. To solve these problems, PA has recently been incorporated directly into dental

adhesives. However, the presence of PA during light-curing might interfere with polymerization of adhesive monomers. After all, PAs are known as radical scavengers that may exert detrimental effects to the light-curing process [53]. In addition, the release of PA could lead to resin breakdown and reduce integrity of the bonding interface. Not surprisingly, when Green et al. examined the hybrid layer formed with experimental adhesive containing 5 % PA, they found that it presented more porous morphology compared with its PA-free counterpart, presumably due to a lower degree of conversion of adhesive resins [52]. In addition, Hechler et al. found that when PA was directly mixed with the adhesive, the microtensile bond strength (immediately, or after 1 year of collagenase digestion) was lower than when PA was used as a pre-conditioner [54]. Similar results have also been reported by Epasinghe et al. [55]. In addition, due to its brownish color, the incorporation of PA into adhesives can hamper the esthetic performance of resinous restorations. Thus, the direct application of PA in dental adhesives merits further investigation.

## Adhesive Materials with Biopromoting Functions

### Adhesives with Remineralization Functions

Resin-dentin bonding is a unique form of tissue engineering in which a demineralized dentin collagen matrix is used as the scaffold for resin infiltration to produce a hybrid layer that couples adhesive/resin composites to the underlying mineralized dentin. However, the resin–dentin bonds created by infiltration of hydrophilic resin monomers into the demineralized dentin matrix are imperfect, resulting in the presence of mineral-depleted, resin-sparse, water-rich collagen fibrils along the bonded interface [41]. Thus, how to imitate the biomineralization process of dentin, reproduce its natural hierarchical structure of mineralized tissues, protect them from external challenges against degradation, and restore their mechanical strengths to normal level is thought to be a prime strategy to improve the dentin bonding stability [55, 56]. Based on this concept, different modifications have been made on adhesives to provide them with the dentin remineralization function.

### Fluoride-Containing Adhesives

Fluoride-releasing restorative materials have been widely used for caries prevention [57]. Dental adhesive systems containing fluoride in composition have been suggested in order to inhibit the action of secondary caries arising from enamel cracks or microleakage in the tooth/restoration interface [58]. Some researchers have extensively demonstrated the significant cariostatic and antibacterial effect of fluoride-releasing

restorative materials [59, 60]. One such material is Clearfil Protect Bond, a two-step, self-etching primer adhesive system that contains an antibacterial monomer (MDPB) in the primer and sodium fluoride in the adhesive [5, 23••]. Apart from the functions mentioned above, fluoride ions penetrating into the dentin have been shown to enhance mineralization of the dentin [61–63]. This applies especially to the improved dissolution resistance initiated by epitaxial deposition of fluorapatite over remnant apatite crystallites in the hybrid layer [64]. In this conventional remineralization strategy, fluoride requires the presence of some apatite crystals in the partially demineralized dentin to initiate deposition of new mineral [65]. The deposition of minerals in this way is known as interfibrillar mineralization, which cannot reproduce the hierarchical structure and mechanical strength of the natural dentin. In addition, with this traditional strategy, remineralization does not occur in locations where seed crystallites are absent [65]. Thus, the classical ion-based crystallization concept may not be applicable for remineralizing completely demineralized dentin within hybrid layers created by etch-and-rinse adhesive systems or the superficial part of a caries-affected dentin lesion left behind after minimally invasive caries removal, due to the unavailability of seed crystallites in those regions for accomplishing homogeneous nucleation of apatite crystallites [66].

### Fluoride-Free Adhesives

Different from conventional remineralization, biomimetic remineralization represents a different approach to improve bonding stability by attempting to backfill the demineralized dentin collagen with liquid-like amorphous calcium phosphate (ACP) nanoprecursor particles that are stabilized by biomimetic analogs of non-collagenous proteins [67–69]. This strategy reproduced both intrafibrillar and interfibrillar minerals and recapitulated the dimension and order of the apatite crystallites that are found in natural dentin [70–73]. Using this biomimetic remineralization strategy, both hybrid layers created by etch-and-rinse adhesives [68, 74, 75] and moderately aggressive self-etch adhesives [65, 74, 76], as well as 250- to 300- $\mu\text{m}$ -thick completely demineralized dentin lesions, can be remineralized [77–79]. This bottom-up remineralization strategy does not rely on seed crystallites, and may be considered as a potentially useful mechanism in extending the longevity of resin–dentin bonds [80] via restoring the dynamic mechanical properties of the denuded collagen within the hybrid layer to approximate those of mineralized dentin [81].

Although the biomimetic remineralization strategy is considered to be the most promising way to remineralize the denuded collagen in the hybrid layer lacking of seed crystallites, this system is still in the in vitro experimental level. To date, studies published by various research groups utilized



sectioned dentin slabs of the resin–dentin interface or artificially-created carious lesion, and not the whole tooth, for remineralization [69–71]. These slabs were immersed in a metastable remineralization solution containing supersaturated calcium and phosphate ions, as well as the biomimetic analogs responsible for generating fluidic ACP nanoprecursors. Whereas poly(anionic acid)-stabilized ACP nanoprecursors can readily infiltrate sideways into the interfacial defect in a sectioned slab, this is not possible clinically because the area occupied by the bonded dentin or carious dentin is segregated from the oral environment by a restorative material and only a very small part of the interface is exposed along the cavosurface margin. It is unrealistic for biomimetic remineralization to be accomplished through the use of a mouth rinse or a topically applied delivery system such as a remineralization paste or gel, wherein the polymer-stabilized-ACP nanoprecursors have to diffuse thousands of micrometers into the adhesive or caries-affected dentin within a restoration. For effective remineralization, the critical components of the biomimetic scheme (i.e. calcium and phosphate source and biomimetic analog/analog) have to be incorporated into a dentine adhesive or restorative material [82••]. These critical components should be able to be released from polymerized resins. This necessitates incorporation of hydrophilic resin monomers in the adhesive or resin composite to facilitate water, ion, and nanoparticulate diffusion. To increase the durability of the restorations, there should also be sustained release of these critical components to remineralize tooth-restoration interfaces that have been subjected to secondary caries. These requirements impose considerable challenges to the translation of a scientifically-sound concept into a

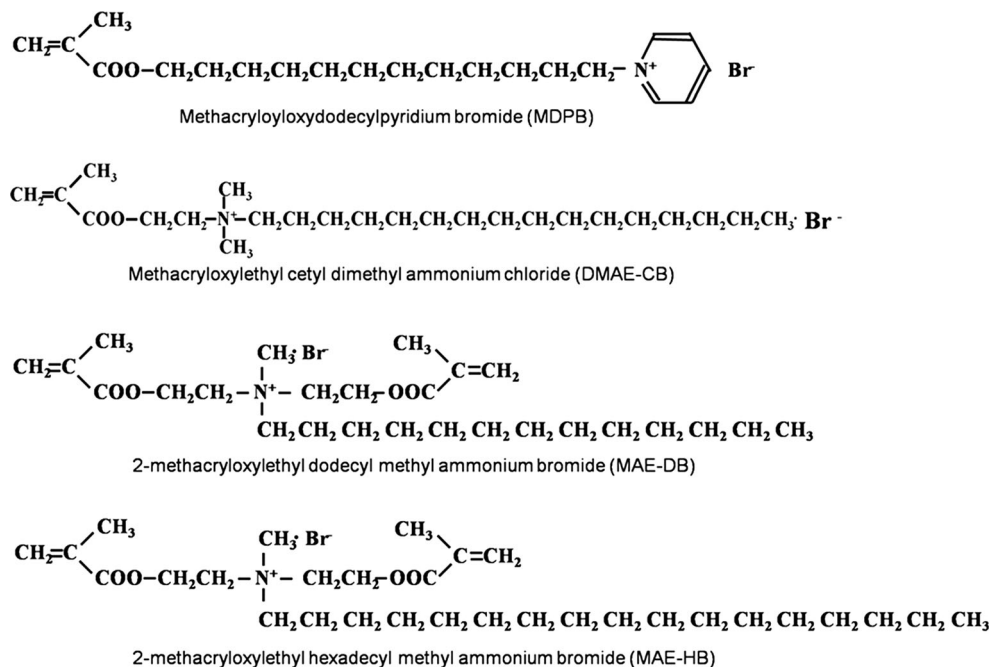
clinically-applicable approach, without adding extra steps into current bonding/restorative protocols.

The idea of incorporating calcium phosphate particles into resins to develop composites with remineralizing capabilities has been explored by different researchers [83–86]. However, the use of ACP nanoparticle-containing dentin adhesive is innovative. These experimental adhesives are very likely to be able to remineralize partially-demineralized dentin by epitaxial deposition of calcium and phosphate phases over remnant apatite seed crystallites. However, the use of solid-state ACP nanoparticles is not compliant with the non-classical theory of particle-based crystallization. To date, intrafibrillar remineralization of dentin collagen has not been reported with the use of experimental adhesives containing solid ACP nanoparticles. A potential delivery strategy is to produce poly(anionic) acid-stabilized ACP pre-nucleation clusters and store them as ‘cargos’ in mesoporous silica nanofillers. These mesoporous silica nanofillers may be incorporated in dentin adhesives as controlled release devices for the delivery of the ACP pre-nucleation clusters, or coalesced ACP fluidic polymer-induced liquid-precursors (PILP) phases, into faulty hybrid layers or caries-affected dentin [82••]. Research in the development of these novel nanotechnologies for clinical translation of the concept of biomimetic remineralization of dentin is in order.

#### Adhesive Materials with Pulp Regeneration Functions

In the case of accidental pulp exposure, the direct pulp-capping procedure may be the most important factor for successfully preserving dental pulp. Calcium hydroxide [Ca(OH)<sub>2</sub>] is the most eligible candidate for direct pulp

**Fig. 1** Chemical structures of quaternary ammonium monomers. MDPB and DMAE-CB are conventional antibacterial monomers with one methacrylate group. The new antibacterial monomers—MAE-DB and MAE-HB—have two methacrylate groups to enhance polymerization



capping because of its superior ability to form a dentine bridge [87, 88]. However, Ca(OH)<sub>2</sub>-based materials have no adhesive properties toward either dentin or overlaid resins, and they provide poor sealing of the exposed site. In addition, they are prone to dissolution by acid-etching and demonstrate low durability due to their low physical properties [89, 90]. As an alternative to Ca(OH)<sub>2</sub>-based materials, the use of resinous adhesives for vital pulp therapy has been proposed [91]. Resinous adhesive systems have the advantage of providing excellent sealing of the pulp exposure site and surrounding dentin, which contributes to the prevention of bacterial leakage and subsequent pulpal inflammation in the case of direct pulp capping [91, 92]. Dr. Katoh's laboratory has been studying adhesive resin systems for direct pulp capping [93, 94]. They found that adhesive resin systems applied to exposed pulp demonstrated no irritation to the pulp, but the dentin bridge formation with the adhesive resin systems was significantly slower than that using Ca(OH)<sub>2</sub>-based materials. This delayed dentin bridge formation may provide a critical situation in which pulp is exposed to bacteria through the resin–dentin interface. To solve this problem, they further developed an experimental adhesive resin system containing 10 wt % calcium chloride (CaCl<sub>2</sub>), 10 wt % hydroxyapatite, and a 10 wt % compound of ESQES peptide and QESQSEQDS peptide which mimic the sequence of dentin matrix protein 1, for direct pulp capping in cooperation with Kuraray Medical Inc. It was reported that the new experimental adhesive resin system was fairly effective in promoting dentin bridge formation. Nevertheless, the fact that there are contradictory experimental data and a lack of well-controlled clinical data suggests that the consideration of dentine adhesives as capping materials needs to be investigated further, in both experimental and clinical studies.

## Conclusions

Tremendous efforts have been devoted to the development of novel adhesive materials with various bioprotective/biopromoting functions, and great progress has already been made in this field. However, there are still limits in almost all the present experimental biofunctional adhesives. Continuous research work is needed in the future to further improve the present experimental adhesives and extend their application from bench-top to actual clinical situations.

**Acknowledgements** This study was financially supported by Program for Changjiang Scholars and Innovative Research Team in University (No. IRT13051), the Major Program of National Natural Science Foundation of China (No. 81130078), and grants from the Natural Science Foundation of China (Nos. 81300909 51373198 and 81100772).

## Compliance with Ethics Guidelines

**Conflict of Interest** Franklin R. Tay and Satoshi Imazato declare that they have no conflict of interest. Jihua Chen, Ling Zhang, Ming Fang, Fang Li, Sai Ma, and Lina Niu have each received a grant from the National Natural Science Foundation of China.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by the authors.

## References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Bagramian RA, Garcia-Godoy F, Volpe AR. The global increase in dental caries. A pending public health crisis. *Am J Dent.* 2009;22:3–8.
2. Sakaguchi RL. Review of the current status and challenges for dental posterior restorative composites: clinical, chemistry, and physical behavior considerations. *Dent Mater.* 2005;21:3–6.
3. Demarco FF, Correa MB, Cenci MS, Moraes RR, Opdam NJ. Longevity of posterior composite restorations: not only a matter of materials. *Dent Mater.* 2012;28:87–101.
4. Ferracane JL. Resin composite: state of the art. *Dent Mater.* 2011;27:29–38.
5. Imazato S. Antibacterial properties of resin composites and dentin bonding systems. *Dent Mater.* 2003;19:449–57.
6. Takahashi Y, Imazato S, Kaneshiro AV, Ebisu S, Frencken JE, Tay FR. Antibacterial effects and physical properties of glass-ionomer cements containing chlorhexidine for the ART approach. *Dent Mater.* 2006;22:647–52.
7. Orug BO, Baysallar M, Cetiner D, Kucukkaraaslan A, Dogan B, Doganci L, et al. Increased antibacterial activity of zinc polycarboxylate cement by the addition of chlorhexidine gluconate in fixed prosthodontics. *Int J Prosthodont.* 2005;18:377–82.
8. Stanislawczuk R, Reis A, Malaquias P, Pereira F, Farago PV, Meier MM, et al. Mechanical properties and modeling of drug release from chlorhexidine-containing etch-and-rinse adhesives. *Dent Mater.* 2014;30:392–9. *This paper evaluated the effects of chlorhexidine addition into simplified etch-and-rinse adhesives on the ultimate tensile strength, water sorption, solubility, and the rate of chlorhexidine release over time. The authors demonstrate that the incorporation of chlorhexidine to commercial adhesive is a feasible method to provide a controlled release of CHX over time without jeopardizing the mechanical properties of the adhesives.*
9. Stanislawczuk R, Pereira F, Muñoz MA, Luque I, Farago PV, Reis A, et al. Effects of chlorhexidine-containing adhesives on the durability of resin-dentine interfaces. *J Dent.* 2014;42:39–47.
10. De Munck J, Van den Steen PE, Mine A, Van Landuyt KL, Poitevin A, Opendakker G, et al. Inhibition of enzymatic degradation of adhesive-dentin interfaces. *J Dent Res.* 2009;88:1101–6.
11. Zhou J, Tan J, Yang X, Xu X, Li D, Chen L. MMP-inhibitory effect of chlorhexidine applied in a self-etching adhesive. *J Adhes Dent.* 2011;13:111–5.

12. De Munck J, Mine A, Van den Steen PE, Van Landuyt KL, Poitevin A, Opendakker G, et al. Enzymatic degradation of adhesive-dentin interfaces produced by mild self-etch adhesives. *Eur J Oral Sci.* 2010;118:494–501.
13. Hiraishi N, Yiu CK, King NM, Tay FR. Effect of chlorhexidine incorporation into a self-etching primer on dentine bond strength of a luting cement. *J Dent.* 2010;38:496–502.
14. Huang L, Xiao YH, Xing XD, Li F, Ma S, Qi LL, et al. Antibacterial activity and cytotoxicity of two novel cross-linking antibacterial monomers on oral pathogens. *Arch Oral Biol.* 2011;56:367–73.
15. Cheng YJ, Zeiger DN, Howarter JA, Zhang X, Lin NJ, Antonucci JM, et al. In situ formation of silver nanoparticles in photo crosslinking polymers. *J Biomed Mater Res B.* 2011;97:124–31. *This paper described the preparation of methacrylate polymers containing silver nanoparticles by coupling photo-initiated free radical polymerization of dimethacrylates with in situ silver ion reduction. They demonstrate that, with this technique, nanocomposites with substantial antibacterial effect and acceptable mechanical properties can be synthesized.*
16. Cheng L, Zhang K, Melo MA, Weir MD, Zhou X, Xu HH. Antibiofilm dentin primer with quaternary ammonium and silver nanoparticles. *J Dent Res.* 2012;91:598–604.
17. Zhang K, Melo MA, Cheng L, Weir MD, Bai Y, Xu HH. Effect of quaternary ammonium and silver nanoparticle-containing adhesives on dentin bond strength and dental plaque microcosm biofilms. *Dent Mater.* 2012;28:842–52.
18. Cheng L, Zhang K, Weir MD, Liu H, Zhou X, Xu HH. Effects of antibacterial primers with quaternary ammonium and nano-silver on *Streptococcus mutans* impregnated in human dentin blocks. *Dent Mater.* 2013;29:462–72.
19. Zhang K, Cheng L, Imazato S, Antonucci JM, Lin NJ, Lin-Gibson S, et al. Effects of dual antibacterial agents MDPB and nano-silver in primer on microcosm biofilm, cytotoxicity and dentine bond properties. *J Dent.* 2013;41:464–74.
20. Li F, Weir MD, Fouad AF, Xu HH. Effect of salivary pellicle on antibacterial activity of novel antibacterial dental adhesives using adental plaque microcosm biofilm model. *Dent Mater.* 2014;30:182–91.
21. Li F, Weir MD, Chen J, Xu HH. Comparison of quaternary ammonium-containing with nano-silver-containing adhesive in antibacterial properties and cytotoxicity. *Dent Mater.* 2013;29:450–61.
22. Imazato S, Torii M, Tsuchitani Y, McCabe JF, Russell RRB. Incorporation of bacterial inhibitor into resin composite. *J Dent Res.* 1994;73:1437–43.
23. Imazato S, Ma S, Chen JH, Xu HH. Therapeutic polymers for dental adhesives: loading resins with bio-active components. *Dent Mater.* 2014;30:97–104. *This review summarized the latest achievements in the development of therapeutic dental adhesives. Adhesives with antibacterial activities or remineralization effects were thoroughly discussed in this paper.*
24. Ma S, Izutani N, Imazato S, Chen JH, Kiba W, Yoshikawa R, et al. Assessment of bactericidal effects of quaternary ammonium-based antibacterial monomers in combination with colloidal platinum nanoparticles. *Dent Mater J.* 2012;31:150–6.
25. Huang L, Sun X, Xiao YH, Dong Y, Tong ZC, Xing XD, et al. Antibacterial effect of a resin incorporating a novel polymerizable quaternary ammonium salt MAE-DB against *Streptococcus mutans*. *J Biomed Mater Res B Appl Biomater.* 2012;100:1353–8.
26. Antonucci JM, Zeiger DN, Tang K, Lin-Gibson S, Fowler BO, Lin NJ. Synthesis and characterization of dimethacrylates containing quaternary ammonium functionalities for dental applications. *Dent Mater.* 2012;28:219–28.
27. Imazato S, Kuramoto A, Takahashi Y, Ebisu S, Peters MC. In vitro antibacterial effects of the dentin primer of Clearfil Protect Bond. *Dent Mater.* 2006;22:527–32.
28. Schmalz G, Ergücü Z, Hiller KA. Effect of dentin on the antibacterial activity of dentin bonding agents. *J Endod.* 2004;30:352–8.
29. Imazato S, Walls AWG, Kuramoto A, Ebisu S. Penetration of an antibacterial dentine-bonding system into demineralized human root dentine in vitro. *Eur J Oral Sci.* 2002;110:168–74.
30. Imazato S, Kaneko T, Takahashi Y, Noiri Y, Ebisu S. In vivo antibacterial effects of dentin primer incorporating MDPB. *Oper Dent.* 2004;29:369–75.
31. Imazato S, Kinomoto Y, Tarumi H, Ebisu S, Tay FR. Antibacterial activity and bonding characteristics of an adhesive resin containing antibacterial monomer MDPB. *Dent Mater.* 2003;19:313–9.
32. Li F, Chai ZG, Sun MN, Wang F, Ma S, Zhang L, et al. Anti-biofilm effect of dental adhesive with cationic monomer. *J Dent Res.* 2009;88:372–6.
33. Li F, Chen J, Chai Z, Zhang L, Xiao Y, Fang M, et al. Effects of a dental adhesive incorporating antibacterial monomer on the growth, adherence and membrane integrity of *Streptococcus mutans*. *J Dent.* 2009;37:289–96.
34. Brambilla E, Ionescu A, Fadini L, Mazzoni A, Imazato S, Pashley D, et al. Influence of MDPB-containing primer on *Streptococcus mutans* biofilm formation in simulated class I restorations. *J Adhes Dent.* 2013;5:431–8.
35. Xiao YH, Ma S, Chen JH, Chai ZG, Li F, Wang YJ. Antibacterial activity and bonding ability of an adhesive incorporating an antibacterial monomer DMAE-CB. *Biomed Mater Res B Appl Biomater.* 2009;90:813–7.
36. Imazato S, Ebi N, Takahashi Y, Kaneko T, Ebisu S, Russell RR. Antibacterial activity of bactericide-immobilized filler for resin-based restoratives. *Biomaterials.* 2003;24:3605–9.
37. Muller R, Eidt A, Hiller KA, Katzur V, Subat M, Schweikl H, et al. Influences of protein films on antibacterial or bacteria-repellent surface coatings in a model system using silicon wafers. *Biomaterials.* 2009;30:4921–9.
38. Cheng L, Weir MD, Zhang K, Arola DD, Zhou X, Xu HH. Dental primer and adhesive containing a new antibacterial quaternary ammonium monomer dimethylaminododecyl methacrylate. *J Dent.* 2013;41:345–55.
39. Zhang K, Li F, Imazato S, Cheng L, Liu H, Arola DD, et al. Dual antibacterial agents of nano-silver and 12-methacryloyloxydodecylpyridinium bromide in dental adhesive to inhibit caries. *J Biomed Mater Res B Appl Biomater.* 2013;101:929–38.
40. Breschi L, Mazzoni A, Ruggeri A, Cadenaro M, Di Lenarda R, De Stefano DE. Dental adhesion review: aging and stability of the bonded interface. *Dent Mater.* 2008;24:90–101.
41. Hebling J, Pashley DH, Tjäderhane L, Tay FR. Chlorhexidine arrests subclinical degradation of dentin hybrid layers in vivo. *J Dent Res.* 2005;84:741–6.
42. Carrilho MR, Geraldini S, Tay F, de Goes MF, Carvalho RM, Tjäderhane L, et al. In vivo preservation of the hybrid layer by chlorhexidine. *J Dent Res.* 2007;86:529–33.
43. Carrilho MR, Carvalho RM, Sousa EN, Nicolau J, Breschi L, Mazzoni A, et al. Substantivity of chlorhexidine to human dentin. *Dent Mater.* 2010;26:779–85.
44. Zhou J, Tan J, Chen L, Li D, Tan Y. The incorporation of chlorhexidine in a two-step self-etching adhesive preserves dentin bond in vitro. *J Dent.* 2009;37:807–12.
45. Tezvergil-Mutluay A, Agee KA, Uchiyama T, Imazato S, Mutluay MM, Cadenaro M, et al. The inhibitory effects of quaternary ammonium methacrylates on soluble and matrix-bound MMPs. *J Dent Res.* 2011;90:535–40. *This research investigated the influences of quaternary ammonium methacrylates on MMPs and proved that*

- these monomers have comparable MMP inhibitory activity to chlorhexidine.*
46. Liu N, Li F, Chen YJ, Zhang L, Lu S, Kang JJ, et al. The inhibitory effect of a polymerisable cationic monomer on functional matrix metalloproteinases. *J Dent.* 2013;41:1101–8.
  47. Donmez N, Belli S, Pashley DH, Tay FR. Ultrastructural correlates of in vivo/in vitro bond degradation in self-etch adhesives. *J Dent Res.* 2005;84:355–69.
  48. Bedran-Russo AK, Pauli GF, Chen SN, McAlpine J, Castellan CS, Phansalkar RS, et al. Dentin biomodification: strategies, renewable resources and clinical applications. *Dent Mater.* 2014;30:62–76. *This review provides an overview of key dentin matrix components, targeting effects of biomodification strategies, the chemistry of renewable natural sources, and current research on their potential clinical applications.*
  49. Han B, Jaurequi J, Tang BW, Nimni ME. Proanthocyanidin: a natural crosslinking reagent for stabilizing collagen matrices. *J Biomed Mater Res A.* 2003;65:118–24.
  50. Fang M, Liu R, Xiao Y, Li F, Wang D, Hou R, et al. Biomodification to dentin by a natural crosslinker improved the resin-dentin bonds. *J Dent.* 2012;40:458–66.
  51. Liu R, Fang M, Xiao Y, Li F, Yu L, Zhao S, et al. The effect of transient proanthocyanidins preconditioning on the cross-linking and mechanical properties of demineralized dentin. *J Mater Sci Mater Med.* 2011;22:2403–11.
  52. Green B, Yao X, Ganguly A, Xu C, Dusevich V, Walker MP, et al. Grape seed proanthocyanidins increase collagen biodegradation resistance in the dentin/adhesive interface when included in an adhesive. *J Dent.* 2010;38:908–15.
  53. Liu Y, Wang Y. Effect of proanthocyanidins and photo-initiators on photo-polymerization of a dental adhesive. *J Dent.* 2013;41:71–9.
  54. Hechler B, Yao X, Wang Y. Proanthocyanidins alter adhesive/dentin bonding strengths when included in a bonding system. *Am J Dent.* 2012;25:276–80.
  55. Epasinghe DJ, Yiu CKY, Burrow MF, Tay FR, King NM. Effect of proanthocyanidin incorporation into dental adhesive resin on resin-dentine bond strength. *J Dent.* 2012;40:173–80.
  56. Liu Y, Tjäderhane L, Breschi L, Mazzoni A, Li N, Mao J, et al. Limitations in bonding to dentin and experimental strategies to prevent bond degradation. *J Dent Res.* 2011;90:953–68.
  57. Shen C, Zhang NZ, Anusavice KJ. Fluoride and chlorhexidine release from filled resins. *J Dent Res.* 2010;89:1002–6.
  58. Mukai Y, Tomiyama K, Shiiya T, Kamijo K, Fujino F, Teranaka T. Formation of inhibition layers with a newly developed fluoride-releasing all-in-one adhesive. *Dent Mater J.* 2005;24:172–7.
  59. Torii Y, Itota T, Okamoto M, Nakabo S, Nagamine M, Inoue K. Inhibition of artificial secondary caries in root by fluoride-releasing restorative materials. *Oper Dent.* 2001;26:36–43.
  60. Preston AJ, Mair LH, Agalany EA, Higham SM. Fluoride release from aesthetic dental materials. *J Oral Rehabil.* 1999;26:123–9.
  61. Itota T, Torii Y, Nakabo S, Tashiro Y, Konishi N, Nagamine M, et al. Effect of fluoride-releasing adhesive system on decalcified dentin. *J Oral Rehabil.* 2003;30:178–83.
  62. Shinohara MS, De Goes MF, Schneider LF, Ferracane JL, Pereira PN, Di Hipólito V, et al. Fluoride-containing adhesive: durability on dentin bonding. *Dent Mater.* 2009;25:1383–91.
  63. El-Deeb HA, Al Sherbiney HH, Mobarak EH. Bond durability of adhesives containing modified-monomer with/without-fluoride after aging in artificial saliva and under intrapulpal pressure simulation. *Oper Dent.* 2013;38:48–56.
  64. Klont B, ten Cate JM. Remineralization of bovine incisor root lesions in vitro: the role of the collagenous matrix. *Caries Res.* 1991;25:39–45.
  65. Kim YK, Yiu CK, Kim JR, Gu L, Kim SK, Weller RN, et al. Failure of a glass ionomer to remineralize apatite-depleted dentin. *J Dent Res.* 2010;89:230–5.
  66. Liu Y, Mai S, Li N, Yiu CK, Mao J, Pashley DH, et al. Differences between top-down and bottom-up approaches in mineralizing thick, partially demineralized collagen scaffolds. *Acta Biomater.* 2011;7:1742–51.
  67. Tay FR, Pashley DH. Guided tissue mineralisation of partially demineralised human dentine. *Biomaterials.* 2008;29:1127–37.
  68. Tay FR, Pashley DH. Biomimetic remineralization of resin-bonded acid-etched dentin. *J Dent Res.* 2009;88:719–24.
  69. Kim J, Arola DD, Gu L, Kim YK, Mai S, Liu Y, et al. Functional biomimetic analogs help remineralize apatite-depleted demineralized resin-infiltrated dentin via a bottom-up approach. *Acta Biomater.* 2010;6:2740–50.
  70. Niederberger M, Cölfen H. Oriented attachment and mesocrystals: non-classical crystallization mechanisms based on nanoparticle assembly. *Phys Chem Chem Phys.* 2006;8:3271–97.
  71. Balooch M, Habelitz S, Kinney JH, Marshall SJ, Marshall GW. Mechanical properties of mineralized collagen fibrils as influenced by demineralization. *J Struct Biol.* 2008;162:404–10.
  72. Bertassoni LE, Habelitz S, Kinney JH, Marshall SJ, Marshall JR, Marshall GW. Biomechanical perspective on the remineralization of dentin. *Caries Res.* 2009;43:70–7.
  73. Bertassoni LE, Habelitz S, Marshall SJ, Marshall JW. Mechanical recovery of dentin following remineralization in vitro—an indentation study. *J Biomech.* 2011;44:176–81.
  74. Mai S, Kim YK, Toledano M, Breschi L, Ling JQ, Pashley DH, et al. Phosphoric acid esters cannot replace polyvinylphosphonic acid as phosphoprotein analogs in biomimetic remineralization of resin-bonded dentin. *Dent Mater.* 2009;25:1230–9.
  75. Mai S, Kim YK, Kim J, Yiu CK, Ling J, Pashley DH, et al. In vitro remineralization of severely compromised bonded dentin. *J Dent Res.* 2010;89:405–10.
  76. Kim J, Vaughn RM, Gu L, Rockman RA, Arola DD, Schafer TE, et al. Imperfect hybrid layers created by an aggressive one-step self-etch adhesive in primary dentin are amendable to biomimetic remineralization in vitro. *J Biomed Mater Res A.* 2010;93:1225–34.
  77. Kim J, Mai S, Carrilho MR, Yiu CK, Pashley DH, Tay FR. An all-in-one adhesive does not etch beyond hybrid layers. *J Dent Res.* 2010;89:482–7.
  78. Liu Y, Li N, Qi Y, Niu LN, Elshafiy S, Mao J, et al. The use of sodium trimetaphosphate as a biomimetic analog of matrix phosphoproteins for remineralization of artificial caries-like dentin. *Dent Mater.* 2011;27:465–77.
  79. Qi YP, Li N, Niu LN, Primus CM, Ling JQ, Pashley DH, et al. Remineralization of artificial dentinal caries lesions by biomimetically modified mineral trioxide aggregate. *Acta Biomater.* 2012;8:836–42.
  80. Kim YK, Mai S, Mazzoni A, Liu Y, Tezvergil-Mutluy A, Takahashi K, et al. Biomimetic remineralization as a progressive dehydration mechanism of collagen matrices—implications in the aging of resin-dentin bonds. *Acta Biomater.* 2010;6:3729–39.
  81. Ryou H, Niu LN, Dai L, Pucci CR, Arola DD, Pashley DH, et al. Effect of biomimetic remineralization on the dynamic nanomechanical properties of dentin hybrid layers. *J Dent Res.* 2011;90:1122–8.
  82. Niu LN, Zhang W, Pashley DH, Breschi L, Mao J, Chen JH, et al. Biomimetic remineralization of dentin. *Dent Mater.* 2014;30:77–96. *This paper reviewed the changing concepts in calcium phosphate mineralization of fibrillar collagen, and summarized the latest findings on the remineralization of resin-dentin bonds and artificial caries-like lesions. The problems and progress associated with the translation of a scientifically sound concept into a clinically applicable approach were also discussed.*
  83. Skrtic D, Antonucci JM, Eanes ED, Eichmiller FC, Schumacher GE. Physiological evaluation of bioactive polymeric composites



- based on hybrid amorphous calcium phosphates. *J Biomed Mater Res B Appl Biomater.* 2000;53B:381–91.
84. Dickens SH, Flaim GM, Takagi S. Mechanical properties and biochemical activity of remineralizing resin-based Ca-PO<sub>4</sub> cements. *Dent Mater.* 2003;19:558–66.
  85. Xu HHK, Sun L, Weir MD, Antonucci JM, Takagi S, Chow LC, et al. Nano dicalcium phosphate anhydrous-whisker composites with high strength and Ca and PO<sub>4</sub> release. *J Dent Res.* 2006;85:722–7.
  86. Xu HHK, Weir MD, Sun L, Takagi S, Chow LC. Effect of calcium phosphate nanoparticles on Ca-PO<sub>4</sub> composites. *J Dent Res.* 2007;86:378–83.
  87. Brännström M, Nyborg H, Strömberg T. Experiments with pulp capping. *Oral Surg Oral Med Oral Pathol.* 1979;48:347–52.
  88. Stanley HR. Criteria for standardizing and increasing credibility of direct pulp capping studies. *Am J Dent.* 1998;11:17–34.
  89. Cox CF, Suzuki S. Re-evaluating pulp protection: calcium hydroxide liners vs. cohesive hybridization. *J Am Dent Assoc.* 1994;125:823–31.
  90. Taira Y, Shinkai K, Suzuki M, Kato C, Katoh Y. Direct pulp capping effect with experimentally developed adhesive resin systems containing reparative dentin-promoting agents on rat pulp: mixed amounts of additives and their effect on wound healing. *Odontology.* 2011;99:135–47.
  91. Lu Y, Liu T, Li X, Li H, Pi G. Histologic evaluation of direct pulp capping with a self-etching adhesive and calcium hydroxide in beagles. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2006;102:78–84.
  92. Kitasako Y, Ikeda M, Tagami J. Pulpal responses to bacterial contamination following dentin bridging beneath hard-setting calcium hydroxide and self-etching adhesive resin system. *Dent Traumatol.* 2008;24:201–6.
  93. Koliniotou-Koumpia E, Tziafas D. Pulpal responses following direct pulp capping of healthy dog teeth with dentine adhesive systems. *J Dent.* 2005;33:639–47.
  94. Silva GAB, Lanza LD, Lopes-Júnior N, Moreira A, Alves JB. Direct pulp capping with a dentin bonding system in human teeth: a clinical and histological evaluation. *Oper Dent.* 2006;31:297–307.