

# Current practicality of nanotechnology in dentistry. Part I: Focus on nanocomposite restoratives and biomimetics

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**Abstract:** First described in 1959 by physicist Richard P Feynman, who saw it as an unavoidable development in the progress of science, nanotechnology has been part of mainstream scientific theory with potential medical and dental applications since the early 1990s. Nanoparticles, nanospheres, nanorods, nanotubes, nanofibers, dendrimers and other nanostructures have been studied for various applications to biologic tissues and systems. While many layers of nanotechnologic capability have been envisioned for oral health in the last decade (eg, oral hygiene maintenance, local anesthesia, even whole-tooth replacement), few of these applications have been developed. Part 1 of a three-part series reviews the current clinical utility of nanotechnology's most tangible contribution to dentistry to date: the restoration of tooth structure with nanocomposites. Characterized by filler-particle sizes of  $\leq 100$  nm, these materials can offer esthetic and strength advantages over conventional microfilled and hybrid resin-based composite (RBC) systems, primarily in terms of smoothness, polishability and precision of shade characterization, plus flexural strength and microhardness similar to those of the better-performing posterior RBCs. Available comparative data for nanocomposites and organically-modified ceramic (Ormocer<sup>®</sup>) restoratives are also reviewed. Finally, plausible "next-phase" trends in current nanorestorative research are judiciously examined, including 1) calcium-, phosphate-, and fluoride-ion-releasing nanocomposites for anticaries applications and 2) restorative systems based on biomimetic emulation of the nanomolecular assembly processes inherent in dental enamel formation using nanorods, nanospheres, and recombinant amelogenins.

**Keywords:** nanostructure, dental restorative, resin-based composite, biomimetic, amelogenin

## Introduction

Nanotechnology in medicine has been recently reviewed (2002-present) from various perspectives relative to the human molecule-tissue interface.<sup>1-4</sup> A common trend in this ongoing discussion is the capability to operate on a scale small enough to interact with intracellular components including DNA.<sup>5-8</sup>

Operating on a stage this minute provides a perspective to envision restoring tooth structure at a level that offers progressively closer approximation of its individual anatomic structures. The ever-shrinking size of the nanoparticles in resin-based composite (RBC) ceramic restorative systems continues in a progression that might be envisioned as "mimicking" actual tooth structure.

Following this progression at the nanoscale, current laboratory-bench dental research is exploring designs for restorative systems that biomimetically approximate the very processes by which dental enamel is formed.<sup>9-12</sup> Admittedly, this progress is

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slower than might be considered desirable for clinicians wishing to put cutting-edge technology to clinical use.

## History of nanotechnology in dentistry

In the last 10 years numerous theoretical predictions have been made based on the potential applications for nanotechnology in dentistry, with varying levels of optimism.<sup>13,14</sup> In 2000, Freitas echoed the 1959 prediction in the popular lecture by the late physicist Richard P Feynman (who won the Nobel prize for physics in 1965). This prediction accompanied the birth of nanotechnology's definition and vision: that the atomic-level precision afforded by molecular devices operating at the nanoscale was an inevitable technologic eventuality.<sup>13</sup> Ironically, Feynman himself referred to the year 2000 in this same lecture, predicting a retrospective incredulity that serious focus on nanotechnology did not happen until 1960.<sup>15</sup> The theme of anticipated versus realized transition of emerging technology to actual practice is not new.<sup>16</sup> The pace of its applications to dentistry has been less than revolutionary. Even so, nanotechnology's impact on dental education has captured the interest of academicians, who are assessing its impact on dental curricula.<sup>17</sup>

This article will address the current major representation of practical nanotechnology in dentistry: restoration of tooth structure with RBCs that make use of nanoparticles. In addition, it will summarize dental biomimetic research contexts. Specifically, it will examine nanoscale processes currently being studied in dental research laboratories that bear striking resemblances to natural processes such as dental enamel formation.

## Overview of nanostructures for dental applications

### Nanoparticles

Nanoparticles (molecular units typically defined as having diameters of between 0.1 and 100 nm) of various composition represent the most widespread use of nanoscale units in dentistry. They are currently being used in RBC restorations; two-year clinical results have been published for several of them and will be discussed.<sup>18-21</sup>

Together with the evolution of nanoparticles for dental composites, sharper focus is being applied to reformulations of interfacial silanes. These have been used for many years to coat and bond inorganic fillers into RBC matrices in dental restoratives. Considerable research related to nanocomposites is focusing on tailoring newer types of silane bonding agents

for optimal use with nanoparticles in RBCs. Organosilanes such as allyltriethoxysilane have demonstrated good compatibility with nanoparticle fillers such as TiO<sub>2</sub>.<sup>22</sup> In addition, 3-methacryloxypropyltrimethoxysilane has also been demonstrated to enhance dispersion of silica nanoparticles (5–25 nm) within the restorative resin matrix.<sup>23</sup>

Silanization has been reported by Chan and colleagues<sup>24</sup> as one of several theoretical avenues for increasing fracture toughness of nanocomposites. Xu and colleagues also reported that silanization increased the strength of a novel ion-releasing calcium phosphate (CaPO<sub>4</sub>) composite, but decreased the level of release.<sup>25</sup> Another study by Karabela and Sideridou also found that different silane compositions used to bind composites containing silica nanoparticles had different effects on sorption of organic solvents and water by the RBC, as well as solubility of the RBC.<sup>26</sup> Nanoparticles and associated modifications of existing RBC systems have a considerable record of demonstrated clinical utility and widespread use. Nanohybrid RBCs are currently the most ubiquitous example of such technology.

### Nanorods

Nanorods are of particular interest in a restorative context. Chen and colleagues have synthesized enamel-prism-like hydroxyapatite (HA) nanorods that have exhibited self-assembly properties.<sup>10</sup> Since they are similar to the enamel rods that make up the basic crystalline structure of dental enamel, nanorods could contribute to a practical artificial approximation of such a naturally-occurring structure.

### Nanospheres

In a similar direction, such a potential transition to restorative systems that also mimic nanoscale processes already inherent in natural tooth development will also be explored in this article. Specifically, nanosphere assembly in conjunction with calcium phosphate deposition and amelogenin nanochain assembly will be discussed in a restorative context.<sup>12</sup>

### Nanotubes

Nanotubes of various types have been investigated for dental applications in a number of interesting directions. Titanium oxide nanotubes have been shown *in vitro* to accelerate the kinetics of HA formation, mainly in a context of bone-growth applications for dental implant coatings.<sup>27</sup> More recently, modified single-walled carbon nanotubes (SWCNTs) have been shown to improve flexural strength of RBCs. These SWCNTs had silicon dioxide applied to them in conjunction with specialized organosilane bonding agents.<sup>28</sup>

## Nanofibers

Nanofibers and their uses for biomedical applications have been reviewed.<sup>29</sup> More recently, nanofibers have been used to generate ceramics containing HA and fluor-HA.<sup>30</sup> Nanofibrillar silicate crystals have also been recently studied in the capacity of reinforcement of dental composites, specifically a combination of the widely-used 2,2'-bis-[4-(methacryloxypropoxy)-phenyl]-propane (Bis-GMA) with triethylene glycol dimethacrylate (TEGDMA) added as a thinning agent.<sup>31,32</sup> Added in the correct proportions<sup>32</sup> and with uniform distribution of the fibers/crystals,<sup>31</sup> nanofibers were demonstrated to improve the physical properties of these composites.

## Dendrimers and dendritic copolymers

Dendrimers and dendritic copolymers have been studied, albeit less extensively than other nanostructures, in relation to dental composite applications. Combinations of specific polymers to optimize efficacy of restorative applications have been reported.<sup>33-35</sup>

## Restorative dentistry using nanocomposites

Evolution of direct RBC systems to the level of the nanofill composite has been recently reviewed by Puckett and colleagues.<sup>36</sup> The materials' physical properties have improved considerably (especially over the past five years). These changes have occurred in response to the persistent and daunting issues of polymerization shrinkage, and the dependable strength, microhardness, and associated wear resistance required in posterior occlusal applications. The ongoing challenge remains one of continuing to meet the esthetic demands of patients and clinicians.

## Nanoparticles and microfills from the 1970s forward

In the early 1970s, Johnson and Johnson (Langhorne, PA, USA) introduced the composite, Adaptic (which contained a resin matrix filled with ground quartz particles). This material was shortly followed by 3M's composite, Concise™ (3M ESPE, St. Paul, MN, USA). Both quickly gained wide acceptance as anterior restoratives. Their main drawback was the surface discoloration that resulted from the coarse quartz particles they contained. (Michl, pers comm) These materials have also been used extensively for crown core buildups for more than 25 years.

Since the beginning of the era of microfills in 1973 and their commercialization via the patent process in Germany

(Patentschrift DE 2403211 C3 filed January 1974) and the following year in the United States (US Patent 4,267,097 filed January 1975), RBCs have been increasingly used in place of amalgam as the filler-matrix technologies have improved.

Microfilled composites use silicon dioxide filler particles less than 100 nm in diameter in conjunction with prepolymerized organic fillers, aggregated by crushing them into larger filler particles. While this system produces consistently high-quality surface smoothness and has the longest clinical track record, these restorations lack the high strength needed to emulate amalgam.<sup>37</sup>

During this same period in which microfills were gaining popularity, nanomaterials were already available as titanium dioxide, aluminum oxide and silica oxide. These were used in dental products in small amounts (1%–5%) to improve powder flow. One of the nanosilica oxide products previously manufactured by Degussa in Germany (currently Dentsply International, York, PA, USA) was silanized with a methyl silan (Ox-50). This led to research attempts to fill the resin matrix with as much of the nanoparticle phase as possible, which resulted in the development of the restorative materials Isopast® and Heliomolar® by Ivoclar Vivadent (Schaan, Liechtenstein). This novel development was quickly emulated by 3M ESPE (Michl, pers comm).

The progressive development of RBCs to date, including microfilled and nanofilled restoratives, has been recently reviewed by Christensen.<sup>37</sup> Microfilled composites have the longest clinical track record, and provide a consistently smooth surface. However, microfills' lack of strength necessary for Class-I and -II occlusal applications has been a primary driver of the ongoing debate about progressive RBC use in applications typically – or perhaps traditionally – served by amalgam. The most commonly used RBCs currently comprise microhybrids and nanohybrids (virtually interchangeable terms). These materials use filler particles ranging from <100 nm to 600+ nm and have overcome most of the strength issue. Nanofills (such as Filtek™ Supreme Plus [3M ESPE] and Estelite® Sigma [Tokuyama America, Inc., Encinitas, CA, USA]) offer the combined advantage of less surface roughness than nanohybrids, with smoothness that approximates that of microfills, albeit with a much shorter clinical track record.<sup>37</sup>

Overall performance of RBCs for posterior applications has improved over the past two decades as systems have evolved to the use of nanofillers.<sup>36</sup> This has happened in parallel with a progressive decrease in filler-particle size, from a range of <100–600+ nm for nanohybrids and microhybrids to consistently less than 100 nm for nanofills and

microfills.<sup>37</sup> Nanocluster particles as small as 2–20 nm are currently being used as nanofilled restoratives.<sup>38</sup> A practical aim of this “paring down” of particle size to the nanoscale has been described by Mitra and colleagues in terms of critical length scale, a limit that applies to every physical property. By creating particles smaller than this limit, a material’s desirable performance (eg, optical properties, with a potential bearing on esthetics) can be maximized.<sup>38</sup>

## Top-down versus bottom-up manufacturing approach

Nanotechnology has redefined the focus on how newer and smaller materials are created. Traditional manufacture of filler particles for dental composites has required the comminution of larger particles of quartz, glass, or ceramics through grinding or milling. Since this process cannot effectively produce particles less than approximately 100 nm in diameter, direct molecular assembly, or “bottom-up” processes that involve synthetic chemical processes must be used.<sup>38</sup>

## Physical properties of nanocomposites and rationale for their advantages

Nanohybrid and nanofilled RBCs are generally the two types of composite restorative materials referred to under the term “nanocomposite”, usually in a context of particle size.<sup>16,39</sup> These are usually distinguished from their predecessors, microhybrids and the older conventional microfilled RBCs, mainly in terms of particle size combinations and distributions, which can vary greatly. Mean individual particle size of the older composites has exceeded 1  $\mu\text{m}$ , and experimental filler analyses in relation to physical properties of dental RBCs have involved filler particles as large as 15.5  $\mu\text{m}$ .<sup>40</sup> Comparative *in vitro* studies evaluating physical properties of the various types of RBCs are summarized in Table 1.

Nanohybrid composites possess a wider range of particle sizes, and multiple filler compositions. For example, inorganic particles averaging 7 nm together with larger glass particles averaging <2000 nm are used in NANOSIT™ nanohybrid composite (Nordiska Dental, Angelholm, Sweden).<sup>41</sup> Nanofills have a more uniform particle size range (eg, 75 nm and 5–20 nm for translucent and nontranslucent shades of Filtek™ Supreme Plus [3M ESPE], respectively).<sup>42</sup>

The use of combinations of nanomeric particles and nanoclusters was introduced with Filtek™ Supreme (3M ESPE). The intent was to promote better wear patterns by using nano-sized primary particles (between 2 and 75 nm, depending on the shade) breaking off from the bottom-up designed larger

clusters (0.6–1.4  $\mu\text{m}$ ). This would result in a smoother surface than would breakage of the much larger, nonsubdivisible particles (produced via top-down manufacturing) contained in many hybrids.<sup>38</sup>

Materials with this cluster structuring have been reported to have distinct mechanical and physical properties compared with conventional RBCs, including better maintenance of biaxial flexural strength during six months of water immersion, in contrast to a microhybrid tested.<sup>43</sup>

Another study by Turssi and colleagues<sup>44</sup> found considerable variation among different nanocomposites in a three-body wear test conducted in an oral wear simulator, as well as flexural fatigue limit (FFL) analysis by the staircase method. Of these materials, a microfill control (Heliomolar®; Ivoclar Vivadent), a nanohybrid (Grandio®; Voco GmbH, Cuxhaven, Germany) and an agglomerated cluster/fine-particle nanofill (Filtek™ Supreme) showed significantly higher FFL than either an ormocer-based RBC (CeramX™ mono; Dentsply International, York, PA, USA), or another nanohybrid (Premise™; Kerr Corp., Orange, CA, USA). Ormocers are discussed below in greater detail.

The rationale for broader particle-size range of hybrids includes manufacturer statements of superior esthetics, surface and polishability.<sup>41,45</sup> While comparisons with older materials may prove the hypothesis, comparisons with nanofills tend to show that their esthetics are at least noninferior to those of nanohybrids. A comparative study by Yap and colleagues demonstrated that materials based on ormocer and nanomer technology were significantly smoother than those based on microfillers and nanoclusters. These composite materials, in turn, were significantly smoother than glass ionomers and compomers. For the material group that was finished and polished (as opposed to the group that received polymerization against a matrix strip only), roughness values observed for the ormocer and nanofill were significantly lower than those observed for the microfill and nanocluster composites.<sup>46</sup>

The ongoing hypothesis for the use of progressively decreasing filler particle sizes is a model of better dispersion and increased interfacial area between matrix and filler. This should translate into increased flexural strength, surface microhardness, and thus polishability of the finished restoration.

Tanimoto and colleagues published a computational approach that quantified an observed progressive decrease in flexural strength as the mean filler-particle diameter increased. This investigation was limited to silica fillers ranging from 3.3 to 15.5  $\mu\text{m}$ ,<sup>40</sup> which is considerably above the maximum particle size range of nanohybrids or nanofills.

However, a study by Beun and colleagues<sup>47</sup> compared the physical properties of nanofilled, universal hybrid and microfilled composites, and observed a higher elastic modulus with the nanofilled RBC than most of the hybrids tested. While all materials tested exhibited similar flexural strengths, microfills showed the poorest physical properties overall.

Glass-ionomer cements have been reported to have significantly poorer surface-finish and esthetic properties than the newer composites.<sup>46</sup> However, manufacturers have begun to incorporate nanoscale structuring to produce “nanoionomers,” in an effort to make their surface finish more closely approximate that of a hybrid composite. One recent *in vitro* study by Oxman and colleagues compared Ketac™ Nano (3M ESPE), a paste/paste nanoionomeric hybrid resin-modified glass ionomer (NHRMGI) with two fluoroalumosilicate RMGIs (Fuji II LC and Fuji Filling LC [GC America, Inc., Alsip, IL USA]) and a nanohybrid composite (Tetric EvoCeram®) by ANOVA with Tukey’s comparison at  $P < 0.05$ . Ketac™ Nano showed significantly higher gloss than the other RMGIs (initial polish numbers by gloss meter were  $36.5 \pm 1.3$  versus  $64.2 \pm 11.1$  for Tetric EvoCeram), with greater similarity to that of a hybrid composite (three-body wear depth at 80,000 cycles of  $21.8 \pm 1.3 \mu\text{m}$  versus  $6.8 \pm 0.4 \mu\text{m}$  for Tetric EvoCeram®). Wear rates for the other RMGIs were significantly higher than for Ketac Nano®.<sup>48</sup>

## Ormocers

Ormocer® is an acronym for organically modified ceramics, a registered trademark of Fraunhofer-Gesellschaft (Munich, Germany). Ormocers represent a new technology based on sol-gel synthesis using particles comprising silicones, organic polymers, and ceramic glasses that is applicable to dental composites.<sup>49</sup> Ormocer® composite technology is used in conjunction with nanoparticle fillers such as  $\text{ZrO}_2$  that are widely used in nanocomposite restorative systems. Some ormocers (such as CeramX™ [Dentsply International]) contain particles as small as 2–3 nm in diameter.<sup>50</sup>

Modifying ormocers with organic moieties such as methacrylate-substituted  $\text{ZrO}_2$  or  $\text{SiO}_2$  organosol nanoparticles was found by Moszner and colleagues to improve the mechanical properties of RBCs.<sup>51</sup> This study also describes ormocers as being more biocompatible,<sup>51</sup> a claim echoed by one manufacturer (Voco GmBh).<sup>52</sup> Ormocers also claim decreased surface roughness, which is supported by *in vitro* evidence involving a variety of polishing techniques (see Table 1).<sup>46,53</sup>

An *in vitro* study by Montanaro and colleagues examined the adhesion of *Streptococcus mutans* strain ATCC 25175

to the ormocer® Admira (Voco GmBh), glass ionomers including Fuji IXFAST (GC Amercia), a compomer, flowable composites, and microhybrids. Admira and Fuji IX™ FAST were more susceptible to *S. mutans* adhesion than a polystyrene control. The other materials showed adhesion similar to the control.<sup>54</sup> Clinical evaluations of ormocer-based composites compared with nanofills are discussed below.

## Esthetics of nanocomposites

An early goal of nanocomposite development was the introduction of materials that possessed the strength to function under the stresses of Class I and Class II occlusal applications, while at least replicating the esthetic standards of hybrids and microfills. With this objective, Mitra and colleagues used bottom-up manufacturing design to produce a nanocomposite that contained a combination of nanomeric-particle and nanocluster nanofillers that possessed physical properties comparable to hybrids and with esthetic properties comparable to microfills.<sup>38</sup> This formulation is currently used in Filtek™ SupremePlus nanocomposite (3M ESPE).

Nanocomposites have been reported for the past several years to offer desirable overall esthetics, function and biocompatibility for anterior restorations. A two-part series published in 2004 by Terry<sup>55,56</sup> provided initial clinical recognition of nanocomposites’ role in the esthetic dentist’s armamentarium. The series recaps the history of nanocomposite development and provides clinical guidance specifically for their use in anterior restorations.<sup>55</sup> A case report by Milnar also illustrates predictable replication of esthetics via combined use of a direct nanofill and calorimetric analysis for shade selection.<sup>57</sup> A study by Beun and colleagues that primarily highlights the elastic strength of nanofills comments on their esthetic utility in anterior restorations as well.<sup>47</sup> Favorable compatibility of nanofills with esthetic dentistry has also been reported by Ward.<sup>58</sup> However, larger-scale clinical colorimetric esthetic studies comparing nanocomposites with older-generation RBCs are lacking to date.

Significant improvement in surface smoothness/polish retention have been reported for nanofills compared with conventional microfills.<sup>59,60</sup> Yap and colleagues reported that a nanomer-based RBC (Filtek™ Supreme Translucent) as significantly smoother than nanocluster-based RBCs (Filtek™ Supreme [dentin]).<sup>46</sup> This is an interesting observation in view of a more recent study by Senawongse and Pongprueksa, in which the same nanocluster RBC system produced the smoothest overall finish after polishing or brushing, measured by both scanning electron microscope (SEM) and surface roughness tester.<sup>61</sup>

**Table 1** *In vitro* studies comparing physical properties of nanocomposite and other resin-based composite restoratives, 2004 – present

Author	Variables tested	Materials tested	Key findings
Oxman et al <sup>68</sup>	Polish gloss, three-body wear depth (AFM SEM micrographs) and esthetics of Ketac Nano, an NHRMGI, with two RMGIs and a nanohybrid composite	Ketac Nano (NHRMGI) Fuji II LC (RMGI) Fuji Filling LC (RMGI) Tetric Evo Ceram (nanohybrid)	NHRMGI showed significantly higher gloss compared to other RMGIs, closer to that of a hybrid composite and had a significantly lower wear rate compared with other RMGIs (ANOVA with Tukey's comparison; $P < 0.05$ ).
Yesil et al <sup>64</sup>	Three-body wear of restorations using oral wear simulator: relative abrasive wear, attrition wear, and roughness; attrition of opposing cusps	Filtek™ Supreme (nanofill) Premise (nanohybrid) Point 4 (microhybrid) Heliomolar RO (microfill)	RBC type did not significantly affect the amount of measured attrition ( $P = 0.15$ ) but did significantly affect abrasive wear ( $P = 0.02$ , one-way ANOVA and Tukey's multiple range post hoc test); no significant difference in the average size of the RBC-generated opposing enamel wear facet. Heliomolar RO produced a significantly rougher surface within the wear track than Premise or Point 4 but did not differ significantly from Filtek™ Supreme. Use of nanofillers in two RBCs tested did not significantly improve wear resistance or opposing cusp wear compared with traditional materials.
Senawongse and Pongprueksa <sup>61</sup>	Surface roughness (assessed by contact stylus profilometer and SEM) of unpolished RBC versus different polishing methods	Filtek™ Supreme XT Filtek™ Z350 (universal nanofill) Estelite® Sigma (submicron fill; 100–300 nm particles) Premise™ (nanohybrid) Tetric EvoCeram (nanohybrid) Filtek™ Z250; Tetric Ceram; Clearfil™ AP-X (microhybrids) CeramX™ (ormocer®, 2–3-nm particles)	After brushing, surfaces of all materials except Filtek™ Z350 and Filtek™ Supreme XT (dentin) were rougher than unpolished surfaces and those polished with abrasive disks or silicone devices. Nanofills with nanoclusters had the smoothest surfaces after polishing and brushing.
Beun et al <sup>67</sup>	Elastic moduli, flexural strength, Vickers microhardness, degree of conversion and depth of cure during polymerization with LED and halogen lamps, filler-particle weight and morphology (by SEM)	Filtek™ Supreme Grandio® and Grandio® Flow (nanohybrids) Point-4, Tetric Ceram, Venus, Z 100 (universal hybrids) Filtek™ A110, Durafill® VS (microfills)	Nanofilled RBCs showed mechanical properties at least as good as those of universal hybrids. Nanofills had higher elastic moduli than those of universal and microfilled composites, except Z-100. Microfills had the poorest mechanical properties. Flexural strength was not a discriminating factor. Polymerization degrees obtained with halogen lamp were higher than with LED lamp.
Korkmaz et al <sup>65</sup>	Surface roughness and microhardness of nanocomposites and microhybrid composite finished and polished with two different one-step polishing systems (240 samples)	Filtek™ Supreme XT; Aelite Aesthetic Enamel (nanofills) Grandio® (nanohybrid) CeramX™ Tetric EvoCeram Filtek™ Z250	Mylar strips produced smoothest surfaces in all composite groups ( $P < 0.05$ ). No statistically significant differences between polishing systems were observed in the Filtek™ Supreme XT, CeramX™, Aelite Aesthetic Enamel and Grandio® groups for surface roughness ( $P > 0.05$ ; 1-way ANOVA). In the Tetric EvoCeram group, Sof-Lex discs produced the greatest roughness. No statistically significant differences were observed between polishing systems ( $P > 0.05$ ); Mylar-strip-produced surfaces showed statistically significantly lower microhardness values than polished surfaces ( $P < 0.05$ ). Nanocomposites may be successfully polished using one-step polishing systems.

Koh et al <sup>86</sup>	Surface roughness after polishing with four different polishing systems	Gradia <sup>®</sup> Direct (microhybrid) Filtek <sup>™</sup> Supreme	There was no significant difference in roughness between RBCs for individual polishing systems ( $P = 0.3991$ ). Filtek <sup>™</sup> Supreme was smoother than Gradia <sup>®</sup> after baseline roughening. Sof-Lex <sup>™</sup> provided the smoothest final surface with either composite. Astropol produced a rough surface with Gradia <sup>®</sup> specimens.
Jung et al <sup>60</sup>	Average roughness (RA) and profile-length ratio (LR) after finishing of four nanoparticles and one hybrid RBCs with different rotary-instrument protocols, assessed by SEM and optical laser stylus profilometry (60 samples)	Premise Tetric EvoCeram Filtek <sup>™</sup> Supreme CeramX <sup>™</sup> Duo Herculite XRV <sup>™</sup> (hybrid)	The materials and finishing methods had a significant effect on surface roughness ( $P < 0.001$ for Ra and LR; two-way and one-way ANOVA and Scheffe post-hoc tests). Significant interactions occurred between the RBCs and the finishing methods ( $P < 0.001$ for Ra and LR). Three of the nanocomposites were significantly smoother than Herculite XRV <sup>™</sup> with all finishing methods. CeramX <sup>™</sup> Duo and Herculite XRV <sup>™</sup> had similar Ra and LR. SEM showed that use of a 30 $\mu\text{m}$ diamond caused detrimental surface alteration on all RBC types tested.
Jung et al <sup>59</sup>	Average roughness of four nanoparticles and one hybrid RBCs after finishing and polishing with three different techniques (one-step and multi-step); assessed by SEM and optical laser stylus profilometry (60 samples)	Premise Tetric EvoCeram Filtek <sup>™</sup> Supreme CeramX <sup>™</sup> Duo Herculite XRV <sup>™</sup>	Surface roughness after polishing was significantly influenced by three factors: composite material ( $P < 0.001$ ); three-way and two-way ANOVA and Scheffe post-hoc tests), finishing protocol ( $P < 0.001$ ) and polishing method ( $P < 0.001$ ). Strong interactions were seen between finishing and polishing methods ( $P < 0.001$ ). Two of the nanocomposites were significantly smoother ( $P \leq 0.001$ ); the other two were similar in surface quality to a hybrid. Astropol produced the lowest average roughness on all composites.
Basert <sup>53</sup>	Effect of several finishing and polishing procedures on the surface roughness of nanofill and nanohybrid RBCs and ormocer-based restoratives	Filtek <sup>™</sup> Supreme Grandio <sup>®</sup> Admira (ormocer <sup>®</sup> )	Mylar strip produced the smoothest surface on all materials. The ormocer (Admira) had the least variability in initial surface roughness.
Yap et al <sup>46</sup>	Surface finish, eight different types of aesthetic restoratives	Fuji II LC (FL; RMGI) Fuji IX GP Fast (FN; highly viscous glass ionomer cement) F2000 (FT; compomer) Z100 (ZO; minifill) A110 (AO; microfill) Admira (AM) Filtek <sup>™</sup> Supreme Translucent (FST; nanomer) Filtek <sup>™</sup> Supreme (FS; nanocluster)	Ra values observed for finished/polished AM and FST were significantly lower (ANOVA/Scheffe's test; significance level of 0.05) than for AO and FS. Surface finishes of glass ionomers and compomer were significantly poorer than composites. Ormocer <sup>®</sup> - and nanomer-based composites were significantly smoother than those based on microfillers and nanoclusters.

**Abbreviations:** AFM, atomic-force microscopy; NHRMGI, nano-hybrid resin modified glass ionomer; RBC, resin-based composite; RMGI, resin-modified glass ionomer; SEM, scanning electron microscopy; LED, light-emitting diode.

Additional comparative studies show that the physical properties of nanocomposites are comparable to or better than those of the later-generation microhybrids,<sup>43,62</sup> including a two-year clinical assessment by Ernst and colleagues that compared a nanofilled RBC with a fine-particle hybrid and showed similar performance.<sup>19</sup> Studies of this type are perhaps the best initial clinical predictor of nanocomposites' evolving track record.

## Clinical studies: the first two years of nanocomposite performance data

Terry's early review of the evolution of the nanocomposite in 2004 made assessments regarding increased strength, durability and longevity of nanocomposites.<sup>56</sup> To date, the predominant trends in studies comparing two-year data for the various gradations of nanocomposites to those of conventional composites have shown clinical acceptability and noninferiority, but probably not a clearly revolutionary advantage in terms of actual clinical performance, at least not at the current time point.

Several clinical studies published in the last three years have begun to benchmark the clinical record of nanocomposites. Results across these studies are similar and consistent, which is a positive sign for the clinician making greater use of nanocomposites in restorative practice. Similarly, a comprehensive summary of such similar results is important from a benchmarking perspective. Retrospective evaluation may identify nuances in study design that have a bearing on the continued evolution and specific utility of such restoratives.

As stated above, Ernst and colleagues<sup>19</sup> compared the nanofill Filtek™ Supreme with a conventional fine hybrid (Tetric Ceram, Ivoclar Vivadent) in Class-II applications. Each of 50 patients received one restoration with each material in a split-mouth design. After two years there was no statistically significant difference in durability between the two materials as measured by Ryge criteria. A summary of studies involving the longest-term clinical evaluations to date for nanocomposite performance is presented in Table 2.

Eighteen-month results of a clinical study comparing the nanofill Filtek™ Supreme (3M ESPE) with the nanohybrid Grandio® (Voco GmbH) to restore carious lesions in combination with an antibacterial adhesive by Ergucu and Turkun<sup>63</sup> were also favorable. The only statistically significant difference was greater surface roughness with Grandio® than with Filtek™ Supreme ( $P < 0.05$ , see Table 2).

Additional clinical studies reporting two-year data for performance of nanofills, nanohybrids, and ormocers

compared with conventional microhybrid RBCs used in occlusal restorations have been published by Mahmoud and colleagues<sup>64</sup> and Efes and colleagues.<sup>18,65</sup>

Mahmoud and colleagues analyzed 140 restorations (Admira [Voco GmbH] an ormocer® RBC; Tetric EvoCeram®, a nanohybrid; Filtek™ Supreme, a nanofill; Tetric Ceram®, a microhybrid RBC) in 35 patients, each of whom received 1 restoration of each type. After two years, all three types of the newer composites performed similarly to the microhybrid RBC tested, with no statistically significant difference ( $P > 0.05$ ) in United States Public Health Service (USPHS) modified Ryge scoring criteria.<sup>64</sup>

Efes and colleagues compared two types of newer RBCs: the ormocer® Admira and the nanofill Filtek™ Supreme with Renew (a conventional hybrid). Over a two-year period, they evaluated 90 Class-I maxillary restorations in 90 patients, with specific endpoints of hypersensitivity and secondary caries. Except for one ormocer® restoration, which had failed at two years, no secondary caries or hypersensitivity was evident for any RBC tested ( $P > 0.05$ ). All materials' performance was clinically acceptable (see Table 2).<sup>65</sup> An additional study by Efes and colleagues also showed excellent two-year performance by the same nanofill and ormocer®. Two previously calibrated dentists evaluated the two restoratives using the same criteria with regard to secondary caries, marginal adaptation, surface texture and other variables. This study also evaluated the use of a flowable liner with each of these materials; it offered no additional benefit for either one.<sup>18</sup>

Finally, Schirrmeister and colleagues<sup>21</sup> compared the ormocer RBC CeramX™ with the microhybrid TetricCeram, with a potentially confounding variable of the use of K-0127 primer/adhesive for both RBCs; 31 of 43 patients (each of whom had received one Class-I or Class-II molar restoration with each RBC) returned for the two-year recall visit. One CeramX™ restoration had failed (removal was necessary due to pulpitis and need for root canal treatment). While some marginal discoloration was noted for both RBCs, no statistically significant changes were noted for surface texture, and no sensitivity or recurrent caries occurred ( $P > 0.05$ ).<sup>21</sup>

In summary, the comparative clinical performance to date among the various types of nanocomposites as well as in comparison with older hybrids does not yet show a clear advantage for nanofills. Continued systematic benchmarking of longevity and clinical acceptability data from this type of comparative study are essential for any such advantage to be noted as RBCs continue to evolve. Nevertheless, consistent clinical acceptability and low failure rates evident from these studies are encouraging.

## **In vitro nanotechnologic dental research approaching clinical feasibility**

### **Nanofibrillar reinforcement**

Two recent *in vitro* studies by Tian and colleagues<sup>31,32</sup> have provided interesting insights based on the theme of nanofibers and nanocrystals. Nanofibrillar silicate crystals can be used either alone<sup>31</sup> or in conjunction with nanofibers, to reinforce bis-GMA/TEGDMA-based nanocomposites.<sup>32</sup> Both studies found that the addition of such nanostructures in smaller amounts up to an effective threshold improved mechanical properties of the experimental RBC.

### **Caries prevention**

Optimal delivery of molecules that facilitate tooth structure remineralization and forestall caries is an active area of nanostructure-based research. Much of this work involves nanoparticles in conjunction with RBC systems.

Xu and colleagues recently published *in vitro* data on a stress-bearing, fluoride (F)-releasing nanocomposite whose flexural strength ( $110 \pm 11$  MPa) matched that of a commercial non-F-releasing RBC ( $108 \pm 19$  MPa). This material contains novel  $\text{CaF}_2$  nanoparticles in a whisker-reinforced resin matrix, and had sustained F-release values exceeding those of conventional and resin-modified glass ionomers. This study's results are summarized in Table 3. Such an RBC could offer the previously unavailable combination of the strength of a hybrid, and the F-releasing capacity of an RMGI that by itself is not suitable for high-stress occlusal restorations.<sup>66</sup> Whisker reinforcement of RBCs has been known for some time to offer reduced brittleness and increased fracture toughness compared with conventional composites.<sup>67</sup> Its use with nanoparticles as in the study described above could reduce rates of restoration fracture and secondary caries (see Table 3).

In a similar direction, several other recent studies by Xu and colleagues<sup>25,68,69</sup> have evaluated the incorporation of nanosized  $\text{CaPO}_4$  particles into RBCs, with a resulting improvement in stress-bearing capacity as well as ion release that could inhibit caries.<sup>68</sup> Further investigation of this model using dicalcium phosphate anhydrous (DCPA) incorporated with nanosilica-fused whiskers found that it increased the strength of the RBC by as much as threefold while releasing  $\text{CaPO}_4$ . This release was greater with decreasing  $\text{CaPO}_4$  particle size.<sup>25</sup> The authors hypothesize that such a system could provide a desirable combination of caries prevention and increased restoration strength.<sup>25,69</sup> Lee and

colleagues found a similar trend with reducing the particle size of a zirconia-amorphous calcium phosphate RBC filler, ie, good release properties were observed in addition to an increase in biaxial flexural strength.<sup>70</sup> Finally, HA and fluorapatite bioceramic nanoscale fibers have been studied, with the interesting finding that nanostructure solubility could be manipulated to produce effective release of fluorine ions from fluorhydroxyapatite.<sup>30</sup> When envisioned as part of a nanocomposite restorative or sealant system, such a process could have important applications in caries prevention.

### **Biomimetics: amelogenins, hydroxyapatite, enamel replication and repair**

Perhaps the most tempting venue for speculation on the next phase of nanorestitution of tooth structure is that of nanotechnology mimicking processes that occur in nature (biomimetics), such as the formation of dental enamel. Salient research over the last six years on the theme of studying and replicating enamel formation is summarized in Table 3.

The central theme in the study of ways to mimic nature's already-efficient use of nanotechnology surrounds the cooperative interaction between self-assembled nanospheres of the proline-rich protein amelogenin (the most abundant protein in dental enamel), and the formation and directional orientation of HA crystals that compose enamel's hard-tissue mineral phase. Spanning a period between publication of earlier work by Fincham and Moradian-Oldak<sup>71,72</sup> and Fincham and colleagues<sup>73,74</sup> from the early 1990s to the present, studies of various types of amelogenins continue to elucidate this protein's cooperational versatility among processes that occur at the nanoscale during the formation of dental enamel.<sup>75,76</sup>

A recent *in vitro* study by Wang and colleagues has further elucidated mechanisms of interaction among amelogenin nanospheres, nanoparticles and nanorods at critical points during the HA crystal-growth process. The results offer further evidence for cooperativity in interfacial matching between organic and inorganic nanophases that may resemble processes that occur in actual enamel formation.<sup>77</sup> In another attempt to mimic enamel formation, Uskokovic' and colleagues also recently described such a synergy among protein self-assembly, proteolysis (through a pivotal role of matrix metalloprotease-20 [MMP-20], also known as enamelysin) and crystallization. They used an *in vitro* model with full-length human amelogenin (rH174) in a saturated aqueous calcium solution.<sup>78</sup> Tarasevich and colleagues have described

Table 2 Clinical studies comparing nanocomposite and other resin-based composite restoratives

Author	Variable tested	N		Key findings
		Patients	Restorations	
Mahmoud et al <sup>64</sup>	USPHS modified Ryge criteria; two independent examiners	35	140	After two years, no statistically significant differences in clinical performance were detected ( $P > 0.05$ ; Friedman and/or Wilcoxon signed rank tests) among ormocer <sup>®</sup> , nanohybrid, and nanofill RBCs (all had acceptable clinical performance similar to microhybrid). One ormocer and one microhybrid composite restoration had failed after two years. No failures observed in nanohybrid or nanofill. Significant differences were observed in marginal adaptation and color match of Filtek <sup>™</sup> Supreme restorations and marginal discoloration of Dyract <sup>®</sup> eXtra and Filtek <sup>™</sup> Supreme restorations between baseline and 24 months ( $P \leq 0.05$ ; Friedman and Wilcoxon signed rank tests). Filtek <sup>™</sup> Supreme had a significantly higher retention rate (100%) than Dyract <sup>®</sup> eXtra (96%; $P \leq 0.05$ ). Dyract <sup>®</sup> eXtra restorations had significantly better color match than Filtek <sup>™</sup> Supreme. Significant differences were observed in marginal adaptation and color match of Filtek <sup>™</sup> Supreme restorations, and in marginal discoloration of both materials between baseline and 24 months ( $P \leq 0.05$ ).
Turkun and Celik <sup>67</sup>	USPHS criteria for color match, marginal discoloration, marginal adaptation, caries formation, anatomic form, postoperative sensitivity, surface roughness, and retention in noncarious Class-V restorations at baseline, 6, 12, and 24 months	24	100	Grandio <sup>®</sup> showed significantly more superficial surface roughness than Filtek <sup>™</sup> Supreme ( $P < 0.05$ ; Cochran Q test and the McNemar test). Otherwise, posterior restorations using novel nanocomposites plus antibacterial self-etching system showed satisfactory results at 18-month recall.
Ergucu and Turkun <sup>63</sup>	Color stability, marginal discoloration, marginal adaptation, caries formation, anatomic form, postoperative sensitivity, surface roughness, retention	30	49 Class I and 47 Class II	No statistically significant differences were observed ( $P > 0.05$ ). After two years, 96.8% of CeramX <sup>™</sup> + K-0127 and 100% of Tetric Ceram + Syntac Classic restorations were intact and showed acceptable clinical performance.
Schirmeister et al <sup>21</sup>	Sensitivity, recurrent caries, surface roughness, failure rate	43	86	POS was present in 26.3% of cases, with a statistically significant difference between days 1 and 3, days 5 and 30, and days 7 and 30 (Wilcoxon signed rank test, $P < 0.05$ ). Pressure-dependent POS was most prevalent (15.78% $\pm$ 4.209%). Rapidly-disappearing POS (within one week) had the highest percentage: 7.5% $\pm$ 9.934%.
Manchorova et al <sup>68</sup>	Postoperative sensitivity (POS) at days 1, 3, 5, 7, 14 and 30 after Class-I and -II restorations to treat medium and deep caries	34	76	

Ernst et al <sup>19</sup>	Ryge criteria (marginal adaptation, anatomic form, secondary caries, marginal discoloration, surface, color match); postoperative sensitivity	50	112	Filtek™ Supreme Terric Ceram (microhybrid) (both used with Scotchbond I adhesive)	After two years, no statistically significant difference (Wilcoxon–Mann–Whitney test) was observed between the two restoratives. The nanofill demonstrated efficacy for clinical use in stress-bearing posterior cavities.
Efes et al <sup>65</sup>	USPHS modified Ryge criteria	90	90	Admira Filtek™ Supreme Renew (hybrid)	None of the three materials exhibited secondary caries or postoperative sensitivity at six-month, one-year or two-year recall ( $P > 0.05$ ; Friedman and/or Wilcoxon signed rank tests). After two years, except for the one failed Admira restoration, no other criterion was clinically unacceptable.

**Abbreviations:** USPHS, United States Public Health Service; POS, postoperative sensitivity.

a process of disassembly or “shedding” of a variety of smaller substructures from nanospheres onto various organic and inorganic substrates, including those with methyl- and carboxyl-group functionality as well as crystal fluoroapatite. The authors hypothesize that amelogenin may have different functional and surface-interactive specificities.<sup>79,80</sup> The emergence of an amelogenin-interactive role in macromolecular self-assembly and enamel mineralization for a second protein, enamelin, also has been reported recently by Fan and colleagues.<sup>81</sup>

A study of rat enamel organ by Brookes and colleagues suggests that nanospheres formed *in vivo* (through interaction with amelogenin) appear to be a basic assembly unit of enamel formation. Secretion and assembly of monomeric subunits likely results in mature nanospheres that contain full-length amelogenins.<sup>9</sup> Hence, nanosphere assembly probably occurs intracellularly as a precursor to secretion of the enamel matrix. Self-assembly of synthesized and modified nanorods into an enamel prism-like structure has also been successfully done for human and rat enamel by Chen and colleagues.<sup>10</sup> Regularity of amelogenin nanosphere assembly into microribbons was also observed by Du and colleagues, who hypothesized amelogenin’s pivotal role in directing and ordering apatite crystal growth.<sup>11</sup>

Thus, pivotal roles for various nanostructure types appear inherent in dental enamel formation in nature. These lines of research suggest that such modes of assembly in nature are not dissimilar to the artificial assembly of nanostructures. The next logical step in this process would be successful emulation of “nature’s use of nanotechnology” to develop a restorative that could be delivered practically as a tooth-structure replacement.

Other recent studies by Fan and colleagues show perhaps the greatest advancement in this direction. One describes the development of an amelogenin-apatite composite.<sup>12</sup> produced by electrolytic deposition of calcium phosphate simultaneously with the self-assembly of amelogenin nano-chain structures, using a full-length recombinant amelogenin (rP172). Induction of parallel bundles of calcium phosphate nanocrystals was also evident. The authors noted that use of the full-length amelogenin (as compared with a truncated one) was critical to the optimal self-assembly of the apatite composite. The strength of the resulting composite was also dependent on use of the full-length amelogenin. They hypothesize that the organized-bundle morphology of such an amelogenin-assembled composite has important potential for its use as a restorative.

Fan and colleagues also found that dose-dependent enamel remineralization (via HA crystal growth) occurred

**Table 3** *In vitro* studies with relevance to caries prevention and the development of enamel/dentin restoratives involving biomimetic processes and nanostructures

Author	Material/process tested	Key findings
Xu et al <sup>66</sup>	Fluoride-releasing, stress-bearing nanocomposite containing novel CaF <sub>2</sub> nanoparticles in a whisker-reinforced dental resin	Flexural strength (mean ± SD; n = 6) was 110 ± 11 MPa for the composite containing 30% CaF <sub>2</sub> and 35% whiskers by mass (equivalent to 108 ± 19 MPa for stress-bearing, nonreleasing commercial composite; Tukey's at 0.05). The composite containing 20% CaF <sub>2</sub> had a cumulative F release of 2.34 ± 0.26 mmol/L at 10 weeks. This formulation may reduce the occurrence of secondary caries and restoration fracture.
Zhou et al <sup>89</sup>	Synthesis and antibacterial activity of a nanohydroxyapatite (n-HA)/zinc oxide (ZnO) complex	Two phases of ZnO and n-HA combined closely; this complex possessed strong antibacterial capability (99.45% to <i>Staphylococcus aureus</i> and 95.65% to <i>Escherichia coli</i> under light, respectively).
Zhou et al <sup>83</sup>	Genetically engineered peptides for inorganics (GEPIs)	Since an ideal dental restorative would mimic natural tooth structure, an analog of dental hard tissue (ie, hybrid of GEPIs and hydroxyapatite crystals), might be engineered using the recognition properties between GEPIs and HA crystal. GEPIs can be used in the assembly of functional nanostructures.
Fan et al <sup>82</sup>	Amelogenin (recombinant rPI72 at concentrations above or below 33 µg/mL) used with a modified biomimetic deposition method in the presence of fluoride to remineralize etched enamel	At a concentration of 33 µg/mL rPI72 and 1 mg/L fluoride, amelogenin initiated oriented bundle formation of fused needle-like fluoridated hydroxyapatite crystals from enamel surface in a dose dependent manner. Restorative/repairative dental biomaterial could be developed using an amelogenin fluoridated hydroxyapatite nanocomposite.
Fan et al <sup>12</sup>	Preparation of a material mimicking developing enamel (comprising calcium phosphate mineral, water, and enamel matrix proteins, mainly amelogenins); simultaneous assembly of amelogenin and calcium phosphate precipitates by electrolytic deposition	Formation of organized bundles in amelogenin-apatite composites results from amelogenin nanochain assembly; such materials have potential applications as dental restorative materials.
Brookes et al <sup>9</sup>	Investigation of specific intracellular/secretory processes/locations of <i>in vivo</i> assembly of amelogenin nanospheres using rat enamel organs using a bifunctional cross-linker, dithio bis succinimidyl propionate and gel electrophoresis/ western-blot probing	Intracellular amelogenin monomers are in close neighbor contact, forming complexes comprising up to six individual amelogenin monomers; authors suggest that these initial complexes are prefabricated intracellularly before secretion; post-secretion the prefabricated subunits assemble into full-size nanospheres containing numerous individual amelogenins (as in enamel matrix).
Du et al <sup>11</sup>	<i>In-vitro</i> formation of birefringent microribbon structures that were generated through the supramolecular assembly of amelogenin nanospheres	Authors observed growth of apatite crystals orientated along c-axis and parallel to long axes of the microribbons <i>in vitro</i> . Chains of self-assembled amelogenin nanospheres observed as intermediate states before microribbon formation suggest a key role for amelogenin in controlling the oriented apatite crystal growth during mineralization of enamel.
Beniash et al <sup>90</sup>	Clarification of the role of amelogenin (the most abundant protein in dental enamel) in enamel mineralization	Amelogenin's larger hydrophobic portion is involved in inhibition of crystal growth. Importantly, its 13-amino-acid hydrophilic C-terminal domain is essential for the alignment of crystals into parallel arrays, which only occurs with full-length monomeric amelogenin. Enamel is formed through cooperative interactions between forming crystals and assembling proteins.
Bouropoulos and Moradian-Oldak <sup>71</sup>	Investigation of interactions of recombinant mouse amelogenin nanospheres with hydroxyapatite crystals in solution using a Langmuir model of adsorption site specificity of amelogenin-hydroxyapatite binding	Authors described a numerical relationship between number of amelogenin nanospheres and hydroxyapatite crystal surface area covered by each population of nanospheres at maximum adsorption. They hypothesized that amelogenin binding onto apatite surface is selective and probably occurs only at certain sites.

**Abbreviations:** GEPI, Genetically engineered peptides for inorganics; HA, hydroxyapatite; SD, standard deviation.

under the direction of rP172 amelogenin (at a concentration of 33  $\mu\text{g}/\text{mL}$ ) in the presence of fluoride (F) at a concentration of 1  $\text{mg}/\text{L}$ . These results further emphasize the pivotal implications of amelogenin F-HA nanocomposite development for the restorative setting.<sup>82</sup>

Finally, genetically engineered peptides for inorganics (GEPs) have recently been hypothesized by Zhou and colleagues to have practical implications for tooth repair, if they can be engineered to recognize inorganic HA and form a hybrid with it (see Table 3).<sup>83</sup>

If some commercially viable combination of these processes could be developed into an amelogenin-nanosphere-based, HA-replicating, F-releasing, enamel-replicating restorative, its clinical implications would be significant. A conservative estimate might still place commercial availability of such a restorative system one to two decades away. However, a progression of improving technology systems based on biomimetic use of nanostructured materials is not an unreasonable expectation.

## Conclusion

Restorative dentistry relies on time-tested methods. Currently, nanotechnology has had its greatest impact on restorative dentistry by offering refinements to already clinically proven RBC systems.

Esthetic dentistry has from its inception attempted to recreate the natural appearance of tooth structure. So, perhaps if the clinician can envision tooth development as a long-standing natural process to be emulated by human technology, tooth-structure restoration becomes a continuum encompassing nature itself, rather than just the stepwise advancement of chemical and physical technology.

Esthetic intent (and incorporation of greater strength) has driven the use of RBCs for an expanding range of applications, and has met with increasing clinical acceptance over the past 30 years. Such acceptance has embraced nanotechnologic restorative techniques on a number of esthetic restorative fronts, including nanofilled RBCs and nanoionomers.

In parallel with this, research over the last 15 years has categorized many nanotechnologic processes inherent in the natural formation of tooth structure. The perspective of emulating nature's appearance revolutionized esthetic dentistry through to the present mainstream use of nano-RBCs. This same perspective could supply the impetus for introduction of HA-F-amelogenin nanochain restorative technology into mainstream dentistry. Made practical and durable (as RBCs gradually evolved to be), such nanorestorative biomaterials could very credibly be the next transformative clinical leap.

Using retrospect – or perhaps hindsight – this leap is at least comparable in magnitude to today's widespread use of nano-hybrid and nanofilled RBCs, compared with composites in use three decades ago.

## Acknowledgments

The author reports no financial disclosures or conflicts of interest in this work. The author would like to thank Gordon J Christensen, DDS, MSD, PhD of The Scottsdale Center for Dentistry, Scottsdale, AZ, USA; Rudolf J Michl, PhD of Chemichl AG Vaduz, Liechtenstein; and William K Deal, DMD of Bryn Mawr Dental Health Group, Inc., Bryn Mawr, PA USA, for their invaluable critical review of this article.

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