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Application and Limitations of Biomimetic Supramolecular Protein Matrices in Tooth Enamel Regeneration

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Introduction

Tooth decay remains a widespread global issue, affecting 2.3 billion people worldwide (World Health Organization, 2022), with demineralisation of enamel being an irreversible trigger of tooth crystalline structure failure. Once the crystalline lattice dissolves under acidic conditions, its hydroxyapatite lattice is broken down and cannot naturally regenerate (Hasan et al., 2025). Existing dental treatments, such as fluoride varnishes and resin-coatings are limited to slowing the process of demineralisation but cannot regrow the basic hydroxyapatite crystalline lattice (Hasan N., et al, 2025). Researchers at the University of Nottingham developed an innovative treatment that aims to rebuild enamel lattice itself. Their creation of biomimetic protein matrices forms a gel designed to regrow enamel through controlled crystallisation growth (Hasan et al., 2025). This technique applies knowledge of the same biochemical conditions required in the process of enamel formation where protein-secreting cells direct calcium and phosphate ions into tightly packed hydroxyapatite enamel rods (Morse et al., 2016). The researchers aim to develop a clinically applicable alternative to current treatments which are limited to only slowing decay by weak surface sealants (Kassebaum et al., 2024). However, limitations such as in vivo testing under varying pH, salivary calcium/phosphate levels, mastication wear, and microbial biofilms need to be addressed before widespread application reduces the need for dental fillings (Hasan et al., 2025).

Chemical Background of Dental Enamel Formation

The protective outer layer of the dental crown, tooth enamel, is the hardest and most mineralised tissue in the human body (Hasan et al., 2025). Dental enamel forms through amelogenesis, where specialised cells called ameloblasts secrete amelogenin proteins that self-assemble into a highly ordered, and tightly bonded matrix through hydrophobic packing. Amelogenin molecules have hydrophobic parts that pack together through dispersion forces, forming β -

sheet structures (Fig. 2), while hydrophilic tails with charged groups remain exposed to bond calcium and phosphate ions from saliva through ionic attractions (Fig. 1) (Hasan et al., 2025).

Statherin-like domains in amelogenin with negatively charged regions stabilise calcium and phosphate ions to form calcium phosphate minerals, hydroxyapatite, that enamel consists of (Morse et al., 2016). Once these initial crystals form, hydroxyapatite grows further along the crystal's longest direction, the c-axis, creating elongated shapes that align parallel to another in highly organised layers, as shown in the fibril packing model (Fig. 2) (Raj et al., 2022).

This matrix is the basis of epitaxial crystal growth, where new hydroxyapatite crystals align with existing ones along the c-axis, producing organised enamel rods (Fig. 1), that resist chewing forces through their strongly bonded parallel lattice structure (Hasan et al., 2025). The ordered β -sheet ribbons and ion-binding prevent random precipitation, ensuring strong ionic bonding in the crystal lattice. The resulting properties of the enamel that produce a highly structured enamel tissue protect teeth throughout life by providing strength and anti-abrasive properties against physical, chemical, and thermal insults (Margiotta et al., 2025).

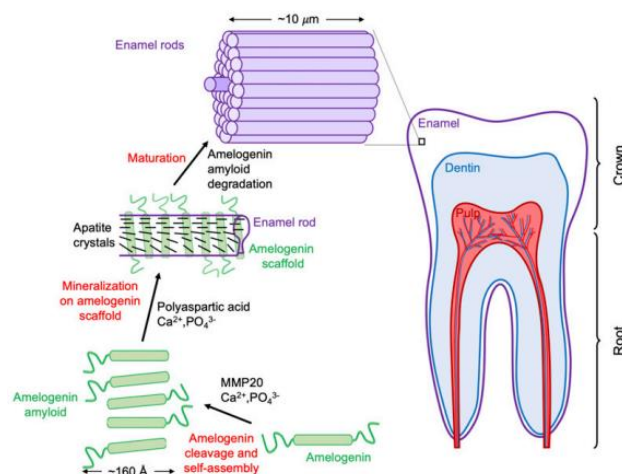


Figure 1: Diagram of amelogenin nanoribbons templating apatite crystal mineralisation into organised enamel rods (adapted from Bai et al., 2024).

Application & Limitations of Protein Engineering to Restore Dental Enamel

Affecting nearly half the global population, enamel damage is a major trigger of tooth decay. When enamel is lost, teeth become vulnerable to cavities and infections (Hasan et al., 2025). The body cannot regenerate enamel once lost, because ameloblast cells undergo apoptosis after tooth decay/demineralisation, resulting in dental care focussing on invasive treatments

or temporary sealants (Hebling et al., 2021).

Researchers from the University of Nottingham have applied knowledge of the amelogenesis process to develop a gel that mimics amelogenin's β -sheet scaffold and statherin ion-binding for clinical dental repair (Hasan et al., 2025). Researchers mimic this with a biomimetic supramolecular protein matrix using elastin-like recombinamers (ELRs), which form β -rich fibrils mimicking amelogenin (Hasan et al., 2025). Incorporated statherin mimics attract calcium and phosphate ions from saliva, increasing epitaxial remineralisation on eroded enamel or dentin surfaces (Fig. 1), restoring aligned apatite layers up to 10 μm thick. Scientists designed ELRs to form 2-5 μm coatings on eroded teeth, attracting calcium and phosphate ions from saliva to grow aligned apatite layers up to 10 μm thick, restoring the epitaxial crystal structure lost to acid erosion of enamel (Hasan et al., 2025). This addresses limitations of current, temporary dental treatments such as fluoride varnishes, without lattice continuity, unlike the ELR gel's organised crystal growth from the protein scaffold that templates ions into the precise enamel rod structure, resulting in weaker hydroxyapatite crystals which fracture under mastication forces (Angeles Martínez et al., 2026).

By replicating natural biomineralization with the ELR gel, it regenerates enamel rather than just temporarily protecting.

Scientists monitored mechanical properties to analyse performance by using a diamond tip driven into apatite crystals to test hardness that simulate oral conditions (Angeles Martínez et al., 2026). Eroded enamel demonstrated low Young's modulus—stiffness testing, $E = 37 \text{ GPa}$ and hardness $H = 1.1 \text{ GPa}$, after ELR treatment, enamel stiffness rises back to $E = 76 \text{ GPa}$ and $H = 3.1 \text{ GPa}$, matching or native enamel hardness due to denser nanocrystals created by ELRs (Fig. 4) (Hasan et al., 2025).

These tests validate durability, with low friction and wear rates, returning to natural levels (Angeles Martínez et al., 2026). These tests provide evidence that ELR growth creates durable enamel, unlike fragile current treatments (Hasan et al., 2025). The 2.3 billion people affected by enamel decay could receive treatments that extend tooth life, reducing the need for fillings or invasive oral surgery, especially for low-income socioeconomic groups (Kassebaum et al., 2024).

However, current research is only limited to in vitro testing, with no in vivo human trials yet, due to factors such as varying saliva pH levels, biofilms, and ion levels may disrupt growth or cause uneven crystal formation (Hasan et al., 2025). Long-term ELR biocompatibility across various populations, i.e., allergies or genetic variations need assessment, as uncontrolled variables could limit reliability until clinical validation (Hasan et al., 2025).

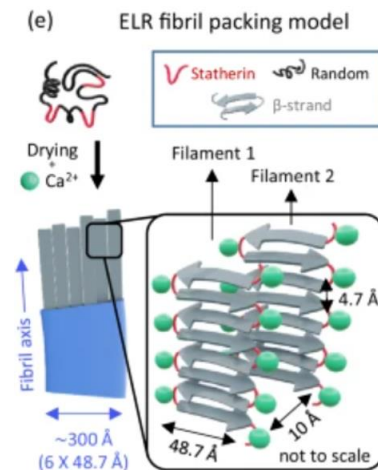


Figure 2: Fibril packing model of ELRs showing β -strands (grey arrows) and Statherin-mimicking loops (red) templating calcium ions (green) into organised filaments (Hasan et al., 2025).

Potential Impacts

If current biochemical limitations are resolved, in vivo trials are successful, and ELR gels reach clinics, they can cut global dental costs by billions, as enamel regeneration avoids 50-70% of fillings and crowns that cost AUD\$725-750 billion yearly worldwide (FDI World Dental Federation, 2023). ELR reduces the need for repeat fillings and costs for public dental clinics (FDI World Dental Federation, 2023). Public health systems like Medicare Dental save on procedures (\$200-1000 each), reducing waitlists and freeing materials for emergencies, directly benefiting low-income families who avoid dental care due to high expense (Australian Government Department of Health, 2025).

Longer lasting lattice repair reduces the risks of bacterial growth and inflammation, due to the ordered crystalline structure, creating tighter barriers that block bacteria from reaching dentine which could result in lowering associated cardiovascular and diabetes related risks (World Health Organization, 2023).

Unlike resin alternatives, ELRs can biodegrade without microplastic pollution, aligning with WHO goals to reduce dental waste and carbon dioxide from manufacturing/transport (World Health Organization,

2022). However, high starting production costs could limit access in developing countries where caries 80% prevalence, with more inequality unless subsidised by government funding (Hebling et al., 2021). Ethical concerns include over-reliance on gels decreasing the need for hygiene education (Margiotta et al., 2025).

Conclusion

Existing treatments for the repair of damaged tooth enamel include fluoride varnishes and resin coatings, which function primarily as surface sealants (Hasan et al., 2025). However, these techniques are limited by their inability to regenerate the original mineral structure, often resulting in barriers that fail under mechanical loading (Angeles Martínez et al., 2026). University of Nottingham researchers created a new gel that applies knowledge of dental enamel chemistry to create biomimetic ELR matrices, which regenerate hydroxyapatite lattices, restoring them to baseline strength and hardness ($E = 76 \text{ GPa}$, $H = 3.1 \text{ GPa}$). This breakthrough enables scientists to offer valid explanations for lattice repair and design action for sustainability by reducing the need for invasive, repeat surgeries (Hasan et al., 2025). However, this technology is limited by complex variables like oral pH and biofilms, which require careful monitoring and assessment of risk (Hasan et al., 2025). Successful in vivo testing through clinical trials is needed to include this innovation into clinical practice, ultimately providing opportunities for innovation that will benefit people globally across all socioeconomic groups (Kassebaum et al., 2024).

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