

# Building Better Smiles, One Cell at a Time

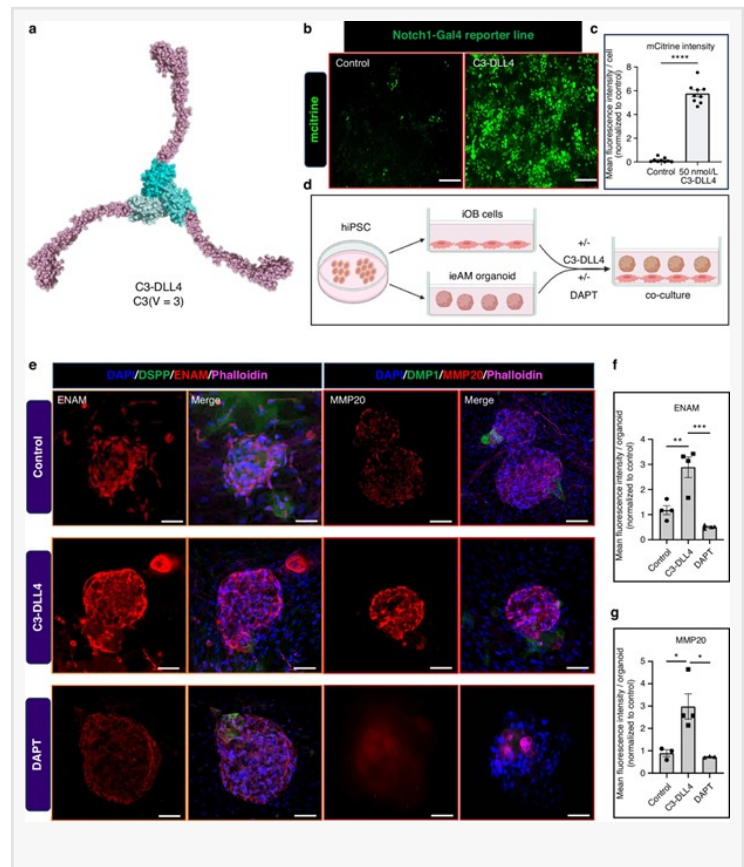
*Scientists explore the signals that transform stem cells into enamel-producing cells with regenerative potential*

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Tooth enamel is the hardest substance in the human body, yet once damaged, it cannot regenerate naturally. To overcome this limitation, scientists are investigating the biology of enamel-forming cells and the molecular signals that guide their development. In a new study, researchers combined cutting-edge stem cell and organoid technologies to explore these mechanisms, generating insights that could help pave the way for future biological approaches to tooth repair.

A bright, healthy smile is often associated with confidence, influencing self-esteem and everyday social interactions. Yet, enamel, the outermost protective layer of teeth, has a fundamental limitation. Once damaged, it cannot regenerate. This is because enamel is produced by specialized cells called ameloblasts, which are present only during tooth development and are lost after maturation. While modern dentistry can restore damaged teeth using fillings, crowns, or veneers, it cannot biologically regenerate true enamel. This long-standing gap in dental medicine has driven efforts to understand how enamel-forming cells develop and whether they can be recreated in vitro for regenerative therapies.

Against this background, researchers from the University of Washington investigated the molecular mechanisms governing ameloblast maturation, with a particular focus on the Notch signaling pathway and the transcription factor DLX3. Corresponding author Dr. Hannele Ruohola-Baker shares, "We sought to determine whether Notch-mediated communication from odontoblasts is responsible for promoting ameloblast maturation and whether artificial activation of this pathway could eliminate the need for odontoblast co-culture." The researchers



also examined whether DLX3 functions autonomously within ameloblasts to regulate terminal differentiation and enamel protein production. The study was made available online in the International Journal of Oral Science on March 2, 2026.

The researchers combined computational analysis with stem cell and organoid technologies to investigate how enamel-forming cells mature. They analyzed single-cell RNA sequencing data from developing human and mouse teeth to identify signaling pathways involved in enamel formation and pinpointed Notch as a likely mediator of communication between odontoblasts and ameloblasts. Human induced pluripotent stem cells (iPSCs) were then differentiated into these cell types and grown either together in co-culture or as three-dimensional ameloblast organoids. The team blocked Notch signaling using the inhibitor DAPT and activated it using an engineered DLL4-based protein scaffold called C3-DLL4. They also generated DLX3-deficient cell lines using CRISPR-Cas9 gene editing and evaluated maturation through gene expression analyses, protein studies, and transplantation experiments in mice.

The results revealed that Notch signaling is a crucial driver of ameloblast maturation. Blocking the pathway sharply reduced the production of essential ameloblast maturation markers such as ENAM, AMELX, and MMP20, whereas activating it with the engineered C3-DLL4 scaffold promoted their expression and enabled stem cell-derived ameloblasts to mature even without support from odontoblasts. These treated organoids acquired molecular and structural features of mature enamel-producing cells, including proper epithelial polarity and elevated levels of additional maturation markers such as ODAM, KLK4, TUFT1, FAM83H, and WDR72. Remarkably, when transplanted beneath the kidney capsule of immunodeficient mice, the organoids produced enamel-like mineralized material, demonstrating functional potential in vivo.

The study further revealed that DLX3 is essential for terminal ameloblast maturation. "Although DLX3-deficient cells were capable of forming early ameloblasts and establishing polarity, they failed to activate the full enamel-secreting gene program even under strong Notch stimulation," shares Dr. Anjali P. Patni. She adds, "Key genes involved in enamel matrix formation and mineralization were markedly suppressed, indicating that DLX3 functions cell-autonomously to enable terminal differentiation and enamel protein production."

These findings represent an important advance for regenerative dentistry. Beyond identifying Notch signaling and DLX3 as central regulators of enamel formation, the study demonstrates that mature enamel-forming cells can be generated from human stem cells without requiring odontoblast co-culture. It also establishes a robust human organoid platform that can be used to investigate tooth development, inherited enamel disorders, and the molecular pathways governing enamel production.

Although the work remains at a preclinical stage, it lays a strong foundation for future biologically based approaches to enamel repair. The engineered C3-DLL4 scaffold could be adapted to better mimic natural developmental signals, while the organoid platform may enable disease modeling, drug screening, and the development of personalized therapies for conditions

such as amelogenesis imperfecta. Ultimately, these advances move the field closer to therapies that restore natural enamel rather than relying solely on synthetic dental restorations.

In conclusion, this study identifies Notch signaling as a central driver of human ameloblast maturation and demonstrates that engineered pathway activation can replace odontoblast-derived signals to generate functional enamel-forming cells. It further establishes DLX3 as an indispensable factor for terminal differentiation. Together, these findings provide a mechanistic framework for enamel regeneration and represent a significant step toward biologically based dental repair strategies.

#### Reference

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Website: <https://www.washington.edu/>

#### About Hannele Ruohola-Baker from the University of Washington

Hannele Ruohola-Baker is a Professor of Biochemistry and Institute for Stem Cell and Regenerative Medicine at the University of Washington. An internationally recognized leader in Stem Cell Biology, Developmental Biology, and Regenerative Medicine, Dr. Ruohola-Baker's laboratory investigates the molecular and cellular mechanisms that govern stem cell states, tissue regeneration, and disease modeling. Her team integrates AI-designed proteins, organoid systems, and advanced genomic technologies to pioneer strategies for repairing and rebuilding human tissues, with recent breakthroughs in tooth enamel regeneration, vascular stabilization, and direct reprogramming platforms. As a scientific leader, she champions cross-disciplinary collaboration, mentoring the next generation of scientists, and driving forward the vision of AI-Driven Foundational Regenerative Medicine to transform human health.

#### About Anjali P. Patni from the University of Washington

Dr. Anjali P. Patni is a PhD candidate and research assistant in the Department of Oral Health Sciences at the University of Washington School of Dentistry. Her research focuses on dental

biology, regenerative medicine, and oral health sciences. She employs single-cell genomics and CRISPR-based approaches to investigate tooth development and enamel regeneration with the aim of advancing regenerative therapies for dental diseases. Patni has co-authored several peer-reviewed publications spanning oral microbiology, dental caries, and microbial ecology. Her research also includes host-microbe interactions and sequencing-based studies of oral disease, contributing to collaborative efforts to improve preventive and regenerative dental care.

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