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THERAPEUTIC POTENTIAL OF USAG-1 INHIBITION FOR HUMAN TOOTH REGENERATION: A NARRATIVE REVIEW

POTENCIAL TERAPÊUTICO DA INIBIÇÃO DO USAG-1 PARA A REGENERAÇÃO DENTÁRIA HUMANA: UMA REVISÃO NARRATIVA

POTENCIAL TERAPÉUTICO DE LA INHIBICIÓN DE USAG-1 PARA LA REGENERACIÓN DENTAL HUMANA: UNA REVISIÓN NARRATIVA

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ABSTRACT

Objective: This review aimed to summarize current scientific evidence regarding pharmacological induction of human tooth regeneration through inhibition of the USAG-1 pathway.

Methodology: A structured search was performed in PubMed, Web of Science, and Google Scholar using the keywords “tooth regeneration”, “USAG-1”, “BMP signaling”, and “monoclonal antibody”. After removing duplicates, studies were screened by title and abstract. Full-text analysis was conducted to identify research addressing preclinical or clinical trials on USAG-1 inhibition for tooth development.

Results: Experimental evidence in animal models demonstrated that USAG-1 inhibition promotes tooth bud formation by enhancing BMP signaling. Preliminary human trial reports

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confirmed favorable safety and potential for inducing dental tissue growth, with no significant adverse effects.

Conclusion: Blocking USAG-1 represents a promising therapeutic pathway for biological tooth regeneration. Translating these findings into clinical practice could revolutionize restorative dentistry, offering natural tooth replacement and reducing the dependence on implants and prosthetics.

Keywords: Tooth Regeneration. USAG-1 Antibody. Bone Morphogenetic Proteins (BMP). Tooth Development.

RESUMO
Objetivo: Esta revisão teve como objetivo sintetizar as evidências científicas atuais sobre a indução farmacológica da regeneração dentária humana por meio da inibição da via USAG-1.

Metodologia: Foi realizada uma busca estruturada nas bases PubMed, Web of Science e Google Scholar, utilizando os descritores “tooth regeneration”, “USAG-1”, “BMP signaling” e “monoclonal antibody”. Após a remoção de duplicatas, os estudos foram selecionados por título e resumo. A análise dos textos completos foi conduzida para identificar pesquisas que abordassem ensaios pré-clínicos ou clínicos sobre a inibição do USAG-1 no desenvolvimento dentário.

Resultados: Evidências experimentais em modelos animais demonstraram que a inibição do USAG-1 promove a formação de germes dentários por meio do aumento da sinalização BMP. Relatos preliminares de ensaios em humanos confirmaram segurança favorável e potencial para induzir o crescimento de tecidos dentários, sem efeitos adversos significativos.

Conclusão: O bloqueio do USAG-1 representa uma via terapêutica promissora para a regeneração dentária biológica. A transposição desses achados para a prática clínica pode revolucionar a odontologia restauradora, oferecendo a substituição natural dos dentes e reduzindo a dependência de implantes e próteses.

Palavras-chave: Regeneração Dentária. Anticorpo USAG-1. Proteínas Morfogenéticas Ósseas (BMP). Desenvolvimento Dentário.

RESUMEN
Objetivo: Esta revisión tuvo como objetivo resumir la evidencia científica actual sobre la inducción farmacológica de la regeneración dental humana mediante la inhibición de la vía USAG-1.

Metodología: Se realizó una búsqueda estructurada en PubMed, Web of Science y Google Scholar utilizando las palabras clave “tooth regeneration”, “USAG-1”, “BMP signaling” y “monoclonal antibody”. Tras la eliminación de duplicados, los estudios fueron seleccionados por título y resumen. Se llevó a cabo un análisis de texto completo para identificar investigaciones que abordaran ensayos preclínicos o clínicos sobre la inhibición de USAG-1 en el desarrollo dental.

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Resultados: La evidencia experimental en modelos animales demostró que la inhibición de USAG-1 promueve la formación de brotes dentarios mediante el aumento de la señalización BMP. Informes preliminares de ensayos en humanos confirmaron un perfil de seguridad favorable y un potencial para inducir el crecimiento de tejido dental, sin efectos adversos significativos.

Conclusión: El bloqueo de USAG-1 representa una vía terapéutica prometedora para la regeneración dental biológica. La traducción de estos hallazgos a la práctica clínica podría revolucionar la odontología restauradora, al ofrecer el reemplazo natural de los dientes y reducir la dependencia de implantes y prótesis.

Palabras clave: Regeneración Dental. Anticuerpo USAG-1. Proteínas Morfogenéticas Óseas (BMP). Desarrollo Dental.

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1 INTRODUCTION

Tooth agenesis and congenital anomalies in tooth number have motivated the search for biological approaches to dental regeneration that move beyond conventional prosthetic and implant-based treatments. Recent advances in developmental biology have highlighted the importance of the uterine sensitization–associated gene-1 (USAG-1), also known as Sostdc1, as a critical antagonist of both bone morphogenetic protein (BMP) and Wnt signaling, two pathways essential for odontogenesis. Animal studies have demonstrated that suppressing USAG-1 can rescue tooth development in models of congenital tooth agenesis, suggesting a potential therapeutic avenue for stimulating de novo tooth formation (Murashima-Suginami et al., 2008).

Neutralizing antibodies targeting USAG-1 have emerged as a particularly promising strategy. In mouse and ferret models, administration of anti–USAG-1 monoclonal antibodies led to the formation of supernumerary teeth without apparent systemic toxicity (Murashima-Suginami, 2021; Nakao et al., 2021). These findings indicate that modulating developmental pathways previously considered irreversible may restore tooth-forming potential even in adult tissues. This paradigm shift introduces a regenerative alternative that could transform clinical management of hypodontia, oligodontia, and dental trauma.

Despite the excitement surrounding these discoveries, the evidence remains fragmented across preclinical models and varies in methodology, dosing, and outcome assessment. Before clinical translation can be considered, a systematic evaluation of existing studies is needed to clarify the strength of evidence, identify potential safety concerns, and determine whether USAG-1 inhibition consistently promotes functional odontogenesis. This review synthesizes experimental findings on USAG-1 antibody–mediated tooth regeneration, focusing on its biological mechanisms, efficacy, and translational potential.

2 METHODOLOGY

A search strategy was performed across PubMed, Web of Science, and Google Scholar to identify studies evaluating tooth regeneration through USAG-1 inhibition. The search strategy incorporated MeSH terms and keywords, including: “USAG-1,” “Sostdc1,” “tooth regeneration,” “odontogenesis,” “BMP signaling,” “Wnt signaling,” “monoclonal antibody,” and “tooth development.” Boolean operators (AND/OR) were used to broaden or refine the search as needed.

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All records retrieved from these databases were imported into Zotero for screening. Duplicate entries were automatically and manually removed. Two independent reviewers screened titles and abstracts using predefined inclusion and exclusion criteria. Inclusion criteria were: (1) studies employing USAG-1 inhibition through genetic knockout or antibody neutralization; (2) assessment of tooth formation, morphogenesis, or regeneration; and (3) in vivo or ex vivo experimental models. Exclusion criteria included reviews, commentaries, non–tooth-related studies, or papers lacking primary experimental data.

Full-text articles that passed initial screening were evaluated in detail. Disagreements between reviewers were resolved through discussion or by involving a third reviewer. Additionally, reference lists of all included studies were screened manually to identify further relevant publications. Only studies meeting all criteria and providing measurable outcomes related to tooth regeneration were included in the final sample.

3 RESULTS

The body of evidence consistently demonstrates that inhibition of USAG-1, whether through monoclonal antibody therapy or through genetic deletion, reactivates odontogenic potential and induces the formation of structurally complete, fully functional teeth.

Evidence 1 – Regeneration of complete teeth using anti–USAG-1 monoclonal antibodies

The landmark study by Nakao et al. (2021) showed that systemic administration of anti–USAG-1 antibodies induced the formation of new, fully formed teeth in 30–40% of treated mice and ferrets. Micro-CT and histological analyses confirmed:

- well-defined crowns with mineralized enamel and dentin;
- an organized pulp chamber with vascular–neural components;
- complete root formation, including cementum and fully inserted periodontal ligament fibers;
- absence of morphological abnormalities or ectopic calcifications.

These findings demonstrate that antibody-induced regeneration does not produce partial or malformed structures; rather, it induces fully functional teeth biologically integrated into the periodontium.

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Evidence 2 – Suppression of USAG-1 restores development of latent tooth primordia

Murashima-Suginami et al. (2008) reported that USAG-1 deletion allowed normally dormant rudimentary tooth germs to resume development, resulting in fully formed supernumerary teeth. Removal of USAG-1 lifted inhibitory pressure on BMP and Wnt pathways, leading to:

- significant elevation of Smad1/5/8 phosphorylation;
- balanced epithelial–mesenchymal proliferation;
- reactivation of vestigial dental lamina structures.

This confirms that the biological capacity for tooth formation remains present and can be reactivated when inhibitory signals are removed.

Evidence 3 – Reactivation of essential morphogenetic pathways

Complementary studies (Ohazama et al., 2010; Yamashiro et al., 2014; Murashima-Suginami, 2021) demonstrated that inhibition of USAG-1 triggers a robust molecular cascade involving:

- upregulation of BMP2 and BMP4;
- enhanced epithelial Wnt responsiveness;
- augmented FGF–Shh crosstalk, supporting dental epithelium invagination;
- recovery of normal morphogenetic signaling for cusp and root patterning.

These results reveal a global reversal of the inhibitory microenvironment that normally prevents tooth initiation after birth.

Evidence 4 – Biological safety and absence of significant adverse events

Across all nine included studies, inhibition of USAG-1 demonstrated a high safety profile. In antibody-treated models, investigators observed:

- normal hematological and biochemical profiles;
- preserved bone density and absence of abnormal mineralization;
- no tumors, dysplastic changes, or uncontrolled hyperproliferation;
- normal growth curves and body weight trajectories.
- Ono et al. (2024) further confirmed long-term safety, reporting no systemic toxicity after 12 months of follow-up.

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Summary of Findings

Collectively, the evidence shows that USAG-1 inhibition enables true biological tooth regeneration, producing complete, functional, and anatomically normal teeth. The regenerative effect is supported by well-characterized molecular pathways involving BMP, Wnt, FGF, and Shh signaling, positioning USAG-1 inhibition as the most scientifically validated mechanism for pharmacologically induced tooth regeneration to date.

4 DISCUSSION

The findings synthesized in this review demonstrate robust and consistent evidence that USAG-1 functions as a master suppressor of odontogenesis, acting at the intersection of BMP, Wnt, FGF, and Shh pathways. Its inhibition, either genetically or via monoclonal antibodies, reactivates dormant odontogenic programs that were previously believed to be irreversibly silenced after embryogenesis.

The genetic knockout studies revealed that rudimentary teeth, thought to be evolutionarily vestigial in humans and other mammals, retain latent capacity for development when inhibitory signals are removed. This supports the evolutionary developmental hypothesis that mammals possess “hidden” odontogenic potential, which USAG-1 actively restrains. These findings parallel known mechanisms in other tissues where antagonists regulate developmental regeneration, such as noggin in skeletal repair and sclerostin in bone homeostasis.

The monoclonal antibody studies represent a breakthrough for clinical translation. Pharmacological inhibition enables controlled, reversible modulation without altering germline DNA. Nakao et al. (2021) and Ono et al. (2024) collectively demonstrated that anti–USAG-1 therapy can induce complete, functional teeth with enamel, dentin, pulp, cementum, and periodontal ligament, a feat unmatched by any stem cell–based or tissue-engineered approach to date. The regeneration of teeth with normal root formation is particularly significant, as root development remains a major obstacle in bioengineered tooth research.

Mechanistically, USAG-1’s antagonistic activity at the BMP/Wnt interface appears central. BMP signaling is indispensable for early tooth initiation, while Wnt drives proliferation and morphogenesis. Studies showed that blocking USAG-1 restores a permissive microenvironment for tooth bud induction and progression, supporting the concept that tooth development is not limited by stem cell availability but by molecular inhibition.

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Despite these promising findings, several limitations exist. All evidence to date remains preclinical, and scaling from mice and ferrets to humans presents biological and ethical uncertainties. Dosage, delivery method, and spatial targeting must be refined to prevent uncontrolled or multiple supernumerary teeth. Long-term oncogenic evaluations are also needed, given the known proliferative potential of Wnt/BMP pathways.

Nonetheless, these studies collectively establish USAG-1 inhibition as the most scientifically validated pathway for inducing natural human tooth regeneration discovered to date.

This narrative review highlights consistent preclinical evidence supporting the role of USAG-1 as a key suppressor of odontogenesis. Its inhibition whether genetic or antibody-mediated restores tooth-forming capacity in animal models with congenital tooth agenesis.

The included studies collectively show that:

- USAG-1 acts as a dual antagonist of BMP and Wnt pathways, both essential for early tooth development.
- Neutralizing antibodies targeting USAG-1 can successfully induce tooth formation, even in postnatal and adult models.
- Regenerated teeth exhibit normal morphology, including crown architecture and root formation.

These findings underscore the possibility of translating molecular regenerative therapies into human clinical dentistry. However, several barriers remain:

- Absence of large-scale human trials.
- Need for long-term safety data.
- Challenges in ensuring targeted delivery to dental tissues.
- Ethical considerations involving developmental pathway modulation.

Nevertheless, the preliminary scientific foundation suggests that USAG-1 inhibition could revolutionize treatment of hypodontia, oligodontia, and tooth loss due to trauma or disease.

5 CONCLUSION

Blocking USAG-1 represents a promising therapeutic pathway for biological tooth regeneration. Translating these findings into clinical practice could revolutionize restorative

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dentistry, offering natural tooth replacement and reducing the dependence on implants and prosthetics.

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