

## Beyond Lipid-Lowering and Cholesterol Control: Will Unleashing the Full Potential of NanoTech-Enhanced Statins Pave the Way for Next-Gen Innovative Oral and Dental HealthCare?

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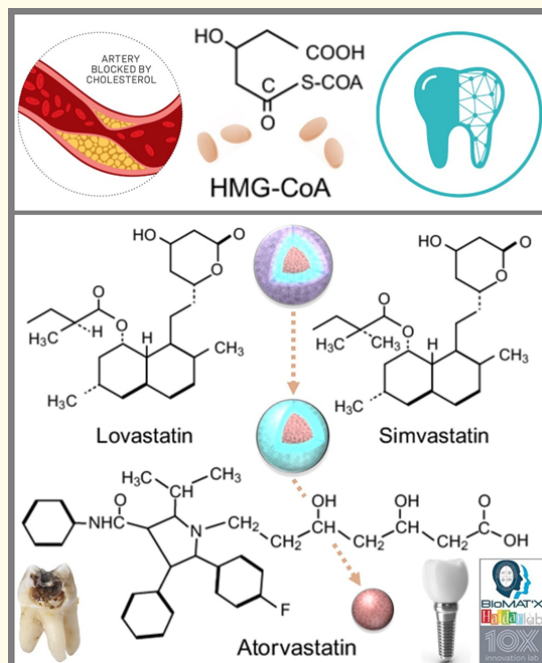
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### Graphical Abstract



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## Precis

Worldwide, oro-dental conditions, including dental caries, periodontal diseases, tooth loss, malocclusion, oral lesions (resulting from trauma, for example), and oral cancers (including extra-oral/cranio-maxilla-facial cancers such as oro-pharyngeal and salivary gland carcinomas), are prevalent and costly public health concerns. Indeed, these conditions can have a significant impact on the general health, well-being, and quality of life of the individual and furthermore may also be associated with systemic diseases such as cardiovascular disease, diabetes mellitus, human immunodeficiency virus/acquired immunodeficiency syndrome and adverse pregnancy outcomes. The burden is particularly high, in both developing and developed countries, with global treatment costs reaching hundreds of billions of dollars. In 2015, the cost of treating dental diseases amounted to a staggering USD\$544.41 billion worldwide, and this number is projected to increase to USD\$810.87 billion by 2030 due to population growth, aging, and changes in lifestyle habits. Therefore, designing and incorporating innovative, or novel preventive strategies and alternative yet effective therapeutic interventions are essential to improve oro-dental health and reduce the incidence of associated systemic disease(s).

Dentistry is an ever-evolving field that has seen significant advances in recent years. While traditional oral and dental treatments and procedures, including orthodontic movements, implants, bone regeneration and repair, are vital strategies and tools for maintaining optimal oral health, the significant impact on general health and quality of life fuels the need for discovering new, effective, and safe preventive and therapeutic agents to further enhance oral and dental health is indispensable. Herein, it is also essential to consider that the projected cost ensuring access to quality care remains affordable, for all. Statins, whether synthetic (atorvastatin, fluvastatin, pitavastatin and rosuvastatin) or semi-synthetic (pravastatin and simvastatin), are pleiotropic inhibitors of the 3-hydroxy-3-methylglutaryl enzyme originally developed to treat high cholesterol (reducing levels of low-density lipoprotein cholesterol biosynthesis often associated with arteriosclerotic cardiovascular disease), is a promising and growing area of R&D&I. Afar, statins have been shown to also have interesting protective, anti-inflammatory (particularly in individuals with periodontal disease)/-microbial (bactericidal, fungicidal, and anti-viral) and immuno-modulatory properties (by reducing the level of inflammatory interleukin 6 and inhibiting the enzymes involved with the

degradation of tissue such as MMPs, for example) as well as osseoregenerative, epithelization and wound healing potential capacity, via modulating bony turnover (relapse and remodelling) through affecting the involved mesenchymal stem cells (stimulating differentiation via increasing the bone morphogenic protein-2 gene expression), endothelial cells (and angiogenesis and fibrinogenesis via vascular endothelial growth factor stimulation), osteoblasts (promoting differentiation and mineralization and inhibiting the apoptosis of osteoblasts), and osteoclasts (i.e. anti-osteoclastic activity). In the available and accruing literature, statins demonstrated capability to enhance dental pulp and dentin regeneration, improve osseointegration and enhance the contact of dental titanium implant surfaces with an increased volume of the *de novo* bone, at the least in pre-clinical studies. In oncology, statins are suggested to have a role in inhibiting the growth, invasion, metastasis, cellular proliferation, differentiation, and cell cycle regulation of tumor cells. Nonetheless, more research remains needed to fully understand the potential benefits and control the potential favorable effects of using statins in all these contexts. This is especially true considering some of the known challenges, to date, that must be addressed before clinical use. Herein, one of the primary constraints is the potential (risk) for adverse side effects. Indeed, while statins can be generally considered safe and well-tolerated, they can cause a range of side effects, including muscle pain, liver damage, and digestive problems, amongst others. Henceforth, dentists, oral surgeons and other oral health professionals must carefully weigh the potential benefits of using statins against the potential risks and work closely with the patients and their families to monitor for any adverse reactions. Another challenge that can be highlighted is the cost of statins. While these drugs are widely used to lower cholesterol levels, they can be expensive, particularly for individuals who do not have insurance coverage. This may make it difficult for some patients to access the benefits of statins in dentistry. When thinking about dosage, concentration, safety, efficacy, and cost-effectiveness for the wide range of available statins, from a translational R&D&I point-of-view, in order to formulate an attractive solution, the recent advancements in nanotechnology open up exciting new possibilities for incorporating statins into oro-dental and maxillofacial applications. For example, nanoparticles, in general, and core-shell nanocapsules, in specific, developed at our BioMAT<sup>X</sup> R&D&I LAB, are designed to carry specific concentrations of bioactive statins directly to the affected area, maximizing the therapeutic effects of the encapsulated/released drug (at allow, safer and less expensive

dosages) while minimizing any potential side effects. These nano-scaled formulations can also be engineered to further control and modulate the release the drug over a pre-determined period of time, ensuring sustained linear delivery of the drug to the site of interest and action. Another promising application of nanoDentistry is the use of nanofibers to deliver statins. These fibers can be used to create scaffolds (interpenetrating porous network matrices) that support tissue regeneration and promote the growth of *de novo* bone and gum tissue, *in situ*. In addition, nanotechnology can also be used to improve the properties of traditional dental materials. For example, nano-systems can be added to dental composites to improve bio-mechanical strength and durability, while also incorporating statins to promote tissue regeneration and repair, locally. For such innovations, robust pre-clinical and clinical testing is vital to ensure the safety, efficacy, and suitability of the products for human use [1-20].

### Closing Remarks

In conclusion, statins, which were originally developed to treat high cholesterol, is a promising area of dental research, development, and innovation. The incorporation of nano-bio-technology into the development of statin-incorporated formulations and release-controlled drug delivery systems if/when included into our clinical and surgical armamentarium can improve oral and dental health care. By enhancing the bio-efficacy and -safety (and cost) of using statins in dentistry, we can help reduce inflammation, promote tissue regeneration, and improve the overall oro-dental health related quality of life of our patients. Ultimately, the decision to use statins should be made on a case-by-case basis, in consultation with a qualified oral health professional.

### Conflict of Interest

None.

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