Inhibitors Design for matrix metalloproteinase's A molecular view for Dental Restoration

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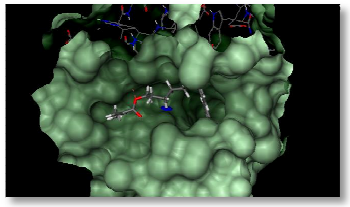
Adhesive resins are the most common human-synthetic material interface. Its widespread applications enables the reproduction of esthetics and mechanical resistance of native tooth as well as it repair from dental caries. This disease that affects 90% of the entire world's population and causes many other co-morbidities. Clinical application of restorative materials has encountered limitations due to the complexity and dynamics of tooth-resin interface. In the restoration process the adhesive resin is attached to collagen fibers that are exposed after acid etching of the hydroxyapatite surface [1]. Dental adhesives contain resin monomers that bond to dentin and enamel [2]. During the following years after restoration, pulp pressure infuses liquid in the dentinal channels defining an intricate frontier of wettability. In the long term this interface allows free acid monomers to dissolve hydroxyapatite [3], and activates matrix metalloproteinases (MMPs) that degrade collagen fibers [4], inducing failure of the restoration. The presence of endogenous
MMPs have been identified has a main cause for restoration failure. Furthermore different family types MMP in the human body are important for a number of diseases and particular important for cancer therapy. The search for new types of selective inhibitors towards different MMP is crucial for widespread medical applications.

In this project we aim to create a molecular tailored inhibitors collagen fibers by matrix metaloproteinases that can be directly applied to adhesive interface that can prevent tooth



The global work plan include

1 Computational studies to define the most promising candidates for synthesis

2 Organic chemistry synthesis of novel compounds

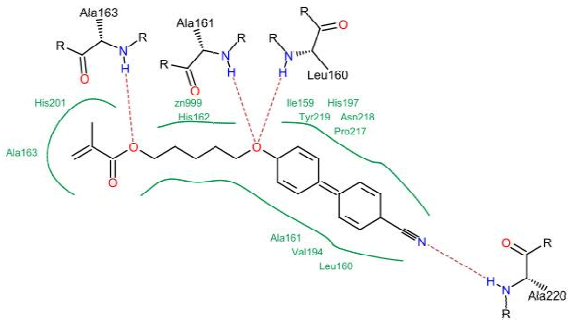
3 Biochemical and atomic force microscopy testing of the compounds towards different MMPs

4 Tensile resistance of the hybrid tooth resin and their fracture analysis by ultra microscopy

5 Cell toxicity evaluation of the synthesized compounds

6 Pre-clinical trials

This proposal focus on the two initials steps of the global work plan which are central to the overall success of this project.



The computational studies include the design of molecules capable:

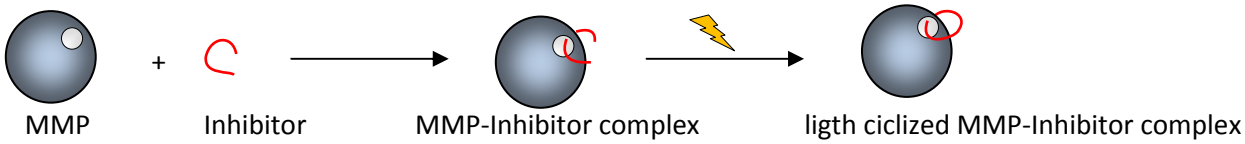
- Affinity docking towards specific MMP active site
- Prediction of chemical properties (solubility and partition coefficient)
- Study of the permeability of blood brain barrier (crucial for toxicity)

The design of new molecules is guided by the following principles:

- High affinity toward MMP active site;
- Differential specificity for different MMPs enzymes types.
- Co-polymerizable with the monomers present in commercial restoration resins.

In the framework of the global work plan the original ideas are proposed

The original idea of this proposal relay in a novel design and synthesis of inhibitors for MMPs.
In silico studies aim to determine the most promising molecules capable of preserving collagen fibers against degradative action of metalloproteinases present in the tooth or other human tissues.
Affinity docking towards MMP active site enables to predict the inhibitory effect and establish a rational strategy for further developments. Since these studies was done in parallel regarding the affinity toward different MMP's types valuable information regarding potential selectivity to different MMPS is extracted. This is particularly important in the context of more general applications (cancer therapy) since they can inhibit a specific MMP present in a particular tissues.
Complementary the prediction of chemical properties (solubility and partition coefficient) and other properties was obtained to filter the initial several hundreds of possible molecules to a subset of dozens of synthesizable molecules in the laboratory.
The chosen strategy based on previous experience is based on central moiety with a two hydroxyl groups that are stepwise substituted with two side groups to yield the final molecule.
Since one the side groups can have a vinyl sunstituint this enable the iinhitor molecule to be co polimerizable with the current dental resins.
The copolymerization of the inhibitor with the resin is a strategy than limits its potetential toxity since inibithos will be in direct contact with the human tissue but simultaneously covalently attached to the resin restricting dramatically their contact and diffusion with the biological tissues.
This approach creates a resin with covalently attached inhibitors
Furthermore taking advantage of the possibility of synthesizing bi vinyl inhibitors and the presence of a tunnel at some MMP active site it is possible do design photo cyclized MMP – Inhibitor complex, that can be light activated and be eventually important in anti cancer therapy since it inhibitory properties can be locally (tissue/organ) triggered by light.



Production of in situ, light activated, irreversible MMP-inhibitor complex

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