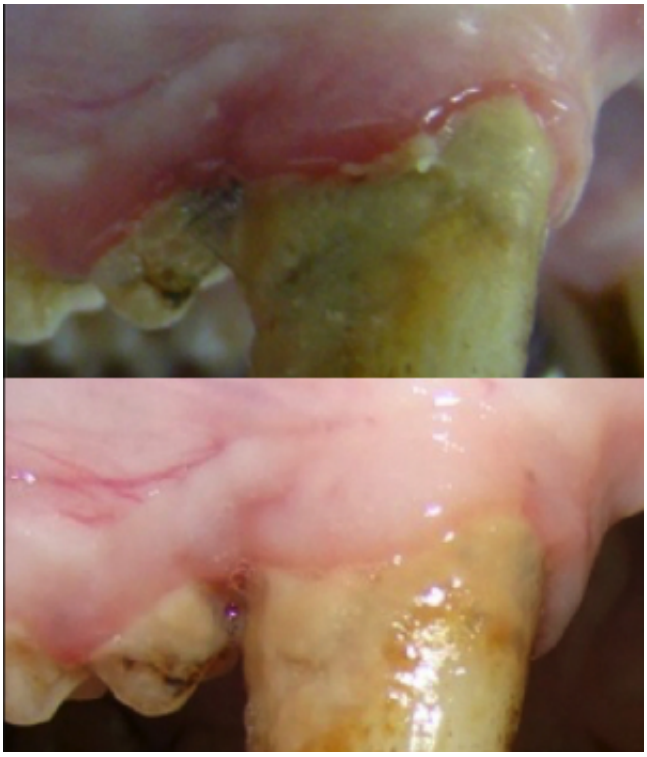
Penn team reverses signs of naturally occurring chronic periodontitis

March 7 2016



A tooth before (top) and after (below) six weeks of treatment shows noticeable improvements in redness and inflammation. Credit: University of Pennsylvania

Periodontitis, a gum disease present in nearly half of all adults in the United States, involves inflammation, bleeding and bone loss. In its severe form, it is associated with systemic inflammatory conditions such as atherosclerosis and rheumatoid arthritis. Few treatment options exist beyond dental scaling and root planing, done in an attempt to reduce

plaque and inflammation.

Now, with findings from a study led by University of Pennsylvania researchers, there is new hope that the disease can be effectively reversed.

The work, which appears in the *Journal of Clinical Periodontology*, employed an inhibitor of a protein called C3, a component of the body's complement system, which is involved in immunity and inflammatory responses. Delivering this inhibitor, Cp40, to the periodontal tissue just once a week reversed naturally occurring chronic periodontitis inflammation in a preclinical model.

George Hajishengallis, Thomas W. Evans Centennial Professor in Penn's School of Dental Medicine's Department of Biology, and John D. Lambris, Dr. Ralph and Sallie Weaver Professor of Research Medicine in the Perelman School of Medicine's Department of Pathology and Laboratory Medicine, were co-senior authors on the study, the result of years of collaboration.

"Even after one treatment, you could see a big difference in inflammation," said Hajishengallis. "After six weeks, we saw reversals in inflammation, both clinically and by looking at cellular and molecular measures of osteoclast formation and inflammatory cytokines."

"The results were so clean, so impressive," Lambris said. "The next step is to pursue Phase 1 trials in humans."

In addition to Hajishengallis and Lambris, the research team included lead author Tomoki Maekawa, Tetsuhiro Kajikawa and Evlambia Hajishengallis of Penn Dental Medicine; Sophia Koutsogiannaki and Daniel Ricklin of Penn Medicine; Ruel A. Briones and Cristina A. G. Garcia of Manila Central University and Ranillo R. G. Resuello and Joel

V. Tuplano of the Simian Conservation Breeding and Research Center.

This study builds on earlier work by Hajishengallis, Lambris and colleagues which identified C3 as a promising target for treating periodontal disease. C3, or the third component of the complement system, is a key part of signaling cascades that trigger inflammation and activate the innate immune system. Their previous research, which used an inducible model of periodontal disease, found that Cp40 could reduce signs of the disease.

To get closer to a natural scenario, however, the current work was conducted on animals that naturally had developed chronic periodontitis. Initially the research team tried administering Cp40 three times a week, but after seeing significant reductions in inflammation, they tried giving it only once a week to a different group and saw the same good results.

"Statistically, giving the drug only once a week was indistinguishable from three times a week," Hajishengallis said.

This study delivered the drug via a local injection to avoid any potential systemic effects from inhibiting a component of the immune system. There were no adverse effects reported.

"Some people have been concerned that blocking complement would lead to more infections but that is not the case here," Lambris said. "We're stopping the inflammation in the gums and thereby killing the bacteria that need inflammatory tissue breakdown proteins to survive."

The researchers are even more encouraged that this treatment worked well as a stand-alone therapy; in humans, they said, it would be given in addition to the standard of care scaling and planing. They are planning to pursue a Phase 1 safety and efficacy study in human volunteers.

More information: Tomoki Maekawa et al. Inhibition of pre-existing natural periodontitis in non-human primates by a locally administered peptide inhibitor of complement C3, *Journal of Clinical Periodontology* (2016). DOI: 10.1111/jcpe.12507