Getting to the root of periodontitis

By Michael J. Haas, Senior Writer

Current periodontitis therapies do not target the underlying immune response that drives the disease. A team from the U.S. and Brazil is looking to change that and has shown that microparticles loaded with chemokine CC motif ligand 22 recruited T_{reg} cells to the gingiva and slowed periodontitis progression in mice and dogs.[1]

Future studies will need to determine whether the microparticle-based therapy can help treat patients with more advanced disease who already have substantial loss of tooth-supporting alveolar bone.

Periodontitis results from a chronic inflammatory response to bacterial plaque and tartar deposits on the teeth, and the condition damages the gingiva (gums) and alveolar bone, leading to tooth loss. Treatment involves lengthy scaling and root-planing procedures to remove the deposits and may include local use of antibiotics to kill the bacteria and/or systemic treatment with low doses of the generic antibiotic doxycycline to inhibit tissue-damaging matrix metalloproteinases (MMPs) in the gingiva.

In devising a strategy to actually modulate the disease, a team led by Steven Little connected two key pieces of information. The first was a series of studies in patients with periodontitis[2–4] and disease models[5] that showed that insufficient numbers of T_{reg} cells in the gingiva may enable the chronic inflammation that drives disease progression.

The second piece came from a study that showed that chemokine CC motif ligand 22 (CCL22) secreted by ovarian tumors recruited T_{reg} cells to the tumor microenvironment, thus enabling immune evasion by the tumors.[6]

Little and colleagues put the two pieces together and hypothesized that tissue-specific delivery of CCL22 could recruit T_{reg} cells and help treat diseases involving destructive inflammation.

Last year, Little's team took the first step in investigating this hypothesis by showing that poly(lactic-co-glycolic) acid (PLGA) microparticles loaded with mouse Ccl22 released their cargo and recruited T_{reg} cells to the injection site in the hind leg muscles of normal mice.[7]

The microparticles did not migrate far from the injection site because they were too large to be taken up by phagocytic cells or cross the vascular endothelium.

Now, Little's team has tested the PLGA-based technology in animal models of periodontitis. "It is the most prevalent disease of destructive inflammation, and it has a massive market size, making it an obvious target," he told *SciBX*.

Little is chair of chemical and petroleum engineering and a faculty fellow in the Department of Bioengineering and Department of Immunology at the **University of Pittsburgh**. He also is a fellow at the university's **McGowan Institute for Regenerative Medicine** and cofounder of **Qrono Inc.**, a company that develops long-acting, injectable formulations of drugs. Qrono was not involved in the PLGA studies.

In mouse models of periodontitis, saline solution of the Ccl22-loaded PLGA microparticles injected into the gingiva recruited T_{reg} cells, thereby lowering levels of proinflammatory cytokines and MMPs and decreasing alveolar bone loss compared with injections of empty microparticles.

The team also delivered the microparticles as a dry powder to subgingival pockets—spaces between the gums and teeth that deepen as periodontitis progresses—in dog models of the disease. That mode of administration would be simpler and less painful than injection and thus more likely to be used in the clinic.

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> ***—George Hajishengallis, University of Pennsylvania***

The dry powder microparticles decreased pocket depth, gingival inflammation and alveolar bone loss compared with empty microparticles.

The powder was well retained in the subgingival pockets and did not dissipate when the dogs ate or drank, which Little said was probably because saliva hydrated the powder and allowed it to swell and remain in place.

Collectively, the findings suggest that CCL22-loaded microparticles applied as dry powder to subgingival pockets could treat periodontitis in patients, Little said. "We expect that this would most likely be given as an adjunct to normal scaling and root-planing procedures that are performed by a clinician during regular maintenance of the disease," he added.

Data were reported in the *Proceedings of the National Academy of Sciences*.

The team included Gustavo Garlet, an associate professor of biological sciences at the **University of São Paulo**'s School of Dentistry.

Back to the bone

Little said that his team has run safety studies of the CCL22-loaded microparticles in an undisclosed animal model and observed no side effects, even at a dose 40-fold higher than that required for a therapeutic effect. Ongoing work includes testing the microparticles in a second, undisclosed model.

"Since periodontal tissue destruction is ultimately inflicted by the host inflammatory response, a therapy that effectively modulates that response should have advantages over the current standard of care," said George Hajishengallis, professor of microbiology at the **University of Pennsylvania**'s School of Dental Medicine. "Local, topical delivery of CCL22-loaded microparticles could be a promising approach."

He added that "complete inhibition of inflammation may not be required, as the homeostatic mechanisms of the host may operate effectively when excessive inflammation is under control" as a result of the therapy.

Hajishengallis agreed with Little that the microparticles were likely to complement, not replace, the current standard of care in periodontitis because removing bacterial plaques remains a critical aspect of treatment.

"Bacteria cause inflammation, which fosters more bacterial growth, which in turn can cause even more inflammation," said Hajishengallis. "The whole thing is a vicious cycle."

Hajishengallis thinks that the microparticles could deliver other host-modulating therapeutics to treat periodontitis, including regulatory chemokines, lipoxins and resolvins, complement inhibitors and integrin antagonists such as EGF-like repeats and discoidin I-like domains 3 (DEL1; EDIL3).[8,9]

However, Takuro Yuge, senior manager of R&D strategic planning at **Kaken Pharmaceutical Co. Ltd.**, thinks that the microparticle technology would have to be supplemented.

"Host immune responses are important drivers of periodontitis, and the recruitment of T_{reg} cells by CCL22 may be effective at preventing the production of proinflammatory cytokines in the periodontal tissues that initiate alveolar bone resorption," he said. "But most patients with periodontitis already have alveolar bone loss and require therapies that promote bone formation, not just prevent its resorption."

"Regulation of homeostasis with T_{reg} cells may not be enough to increase bone formation in patients with significant bone deterioration," said Katsumi Nogimori, Kaken's executive corporate officer and deputy chief officer of R&D.

Kaken's KCB-1D is in Phase III testing to treat periodontitis. The company has not disclosed the target or therapeutic modality of the therapy.

But Little disagreed, noting that his team's mouse model studies showed that the Ccl22-loaded microparticles upregulated multiple factors involved in bone growth and regeneration, including bone morphogenetic protein 4 (Bmp4), Bmp6, transforming growth factor-β (Tgfb; Tgfβ), collagen type I α2 (Col1a2) and several osteoblast transcription factors.

"I think that these findings suggest that recruiting T_{reg} cells promotes not only a prohomeostatic environment but a proregenerative one as well," he said. "Thus, our treatments could indeed promote bone regeneration in patients who already have significant alveolar bone loss."

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> ***—Katsumi Nogimori, Kaken Pharmaceutical Co. Ltd.***

The team has not yet tested that possibility because it would require a lengthy and expensive preclinical study, he said. "We aren't ruling out this kind of study," but the team is currently considering the best way to translate the technology to the clinic.

Little said that the team also is testing the technology in models of other diseases that involve destructive inflammation. "We have recently obtained very promising data in animal models that suggest these microparticle formulations could stave off transplant rejection and even induce tolerance of the transplant," he said.

The University of Pittsburgh has patented the findings, and the IP is available for licensing or partnering, Little said.

He added that the **NIH**'s **National Institute of Dental and Craniofacial Research** and the **Wallace H. Coulter Foundation** funded the *PNAS* study.

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