ADORAble implants

By Kai-Jye Lou, Staff Writer

Researchers at the **New York University Langone Medical Center** have found a way to ward off a leading cause of joint implant failure.¹ The group has shown that adenosine A_{2A} receptor agonists can block the inflammation and bone destruction that stems from debris particles flaking off the implants. The group now needs to translate the findings into a product that companies can test in the clinic.

Bruce Cronstein, a professor in the Departments of Medicine, Pathology, and Biochemistry and Molecular Pharmacology, said joint implant failure is a bigger problem than in previous decades because the average age of implant recipients today is lower.

“Prosthetic joint implants usually last 10–15 years before they began to fail, so if you put a replacement hip in a 65-year-old patient, it would probably last for the life of that patient,” said Cronstein. “But it’s much more common these days to see joint implants in younger age groups such as 50-year-old patients, and such patients are probably going to need a revision surgery once their first implant fails. The problem is that this surgery is going to be much more difficult to carry out, and the second implant is more likely to fail.”

Factors contributing to the increasing number of joint implant procedures in younger age groups include high obesity rates and increasing demand from patients themselves to improve the quality of their active lives.^{2,3} Moreover, processes that lead to implant failure also could weaken the bone at the site of the implant, which could make subsequent implants more likely to fail.

Cronstein’s group has been looking for ways to prolong the life of the initial implant. The team had previously studied adenosine signaling in rheumatoid arthritis (RA) and focused on the adenosine A_{2A} receptor (ADORA $_{2A}$) because agonizing it has anti-inflammatory effects.⁴

In November, Cronstein’s team added another puzzle piece with a paper showing that activation of ADORA $_{2A}$ suppressed the formation of osteoclasts, which carry out bone resorption.⁵

The group recognized the overlap between processes that lead to joint implant failure and those modulated by ADORA $_{2A}$, and thus they sought to determine whether an ADORA $_{2A}$ agonist could help prevent the inflammation and bone destruction triggered by debris particles (see Figure 1, “Processes that lead to debris particle-induced osteolysis”).

In wild-type mice injected with polymeric particles in a pouch above their skulls, injection of an ADORA $_{2A}$ agonist decreased bone loss,

inflammation and osteoclast levels compared with injection of saline. Those effects did not occur in particle-injected Adora $_{2a}$ knockout mice treated with the same agonist.

The polymeric particles model debris particles caused by implant wear.

In human bone marrow samples, an ADORA $_{2A}$ agonist inhibited osteoclast differentiation compared with no treatment. Results were published in *Science Translational Medicine*.

“The most interesting aspect of the findings reported in this paper is in identifying a new target for preventing implant failure, as nobody has really explored the role of the adenosine A_{2A} receptor in the debris-induced osteolysis setting,” said Edward Schwarz, director of the Center for Musculoskeletal Research at the **University of Rochester Medical Center**. “What the researchers need to do now is develop a product that

would be practical to test in the clinic, such as an oral drug.”

Nadim Hallab, an associate professor at **Rush University Medical Center**, said the findings reveal a clear effect against processes that cause implant loosening and failure.

“I think the key concerns going forward are not going to be whether A_{2A} agonists can prevent osteolysis but whether such an agonist could be developed in a manner that will contain or limit its anti-inflammatory effects,” said Hallab, who also is CEO at **Bioengineering Solutions Inc.** and **Orthopedic Analysis LLC**.

“As many of the patients experiencing joint implant failure are in the higher age groups, their immune systems may not be as robust, so persistent systemic immunosuppression from the anti-inflammatory effects could be risky.”

Bioengineering Solutions carries out implant debris analysis and particle production for companies developing prosthetic implants. Orthopedic Analysis tests for metal allergies in prospective implant recipients.

Practical options

Cronstein said his group is working with the **NIH** to translate the findings into a viable product.

One idea, he said, is to incorporate an ADORA $_{2A}$ agonist into the cement used to fix an implant in place or as a device coating on the implant itself.

“The nice thing about adenosine A_{2A} agonists is they are generally not very heat labile and will probably survive the cement setting process, which is an exothermic event,” Cronstein told SciBX. “As for developing a long-term coating for the prosthetic itself, that is going to require more ingenuity.”

Hallab said the success of either approach will hinge on the ability to develop a product that retains its activity after 10–15 years. “Nearly all implants are still doing fine at 5 years, and it’s the problems that begin after 10–15 years that need to be addressed,” he said.

Schwarz added that companies developing medical implants have no

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Figure 1. Processes that lead to debris particle-induced osteolysis. As joint implants wear, debris triggers processes that lead to inflammation and osteolysis. Together, these processes cause the implant to loosen and fail.

Macrophages are the primary target of debris particles from an implant. These cells take up debris via phagocytosis and secrete cytokines and chemokines in response [a]. One of these secreted cytokines, macrophage colony-stimulating factor 1 (CSF1; M-CSF), activates colony-stimulating factor 1 receptor (CSF1R; C-FMS; CD115) on osteoclast precursors [b].

When M-CSF is present with another factor, receptor activator of NF- κ B ligand (RANKL; TNFSF11), osteoclast precursors differentiate into bone-resorbing osteoclasts [c]. RANKL activates tumor necrosis factor receptor superfamily member 11a (TNFRSF11A; RANK; CD265) and is produced by other cells such as T lymphocytes.

In addition to promoting osteoclast generation, the cytokines and chemokines secreted by the macrophage also attract additional macrophages, osteoclast precursors and other proinflammatory cells to the area [d].

As reported in Mediero *et al.*, adenosine A_{2A} receptor (ADORA_{2A}) agonists can block the inflammation- and osteolysis-promoting effects of wear debris particles and thus have the potential to prevent joint implant failure.

appetite for the risks associated with developing a long-term coating for joint implants and will not want to run a 10-year clinical trial to evaluate the safety and efficacy of such a product.

“These companies have shied away from long-term coatings because they won’t know the long-term effects until much later and could be liable if the coating does end up causing problems,” he said. “At this time, implant companies are only considering coatings with short half-lives, such as antimicrobial coatings.”

Thus, Schwarz thinks the focus instead should be on patients who are showing signs of implant failure but are not candidates for a revision surgery or those who choose not to have such a surgery. “An oral A_{2A} agonist could be beneficial and help delay implant failure in such patients,” he told *SciBX*.

Yousef Abu-Amer, a professor in the Department of Orthopedics and the Department of Cell Biology and Physiology at the **Washington University in St. Louis School of Medicine**, said it will be important to determine how tissue-specific deletion of ADORA_{2A} affects various cellular compartments and to identify the molecular mechanism by which the receptor regulates osteoclasts. He noted that such studies could provide the researchers with useful insights on specificity, drug design and potential side effects.

He also said it will be important to study the effects of candidate agonists on fracture repair, bone formation and integration of an implant with bone and to carry out studies that evaluate both systemic

and local application.

At least one orally delivered ADORA_{2A} agonist is in clinical trials. BVT.115959, which is being developed by **CBT Development Ltd.**, **Ergomed Group** and **Swedish Orphan Biovitrum AB**, is in Phase II testing to treat diabetic neuropathic pain.

Moreover, at least three injectable ADORA_{2A} agonists have already progressed into or through the clinic as vasodilators for use in myocardial perfusion imaging (MPI). These include Lexiscan regadenoson, which is marketed by **Gilead Sciences Inc.** and **Astellas Pharma Inc.**; **Pfizer Inc.**’s binodenoson, which is in registration; and **Forest Laboratories Inc.**’s apadenoson, which is in Phase III testing.

Last month, a team at the **University of California, San Francisco** published data showing that ADORA_{2A} agonists could promote β cell regeneration, suggesting a potential application in diabetes.^{6,7}

NYU has a patent covering medical implants containing adenosine receptor agonists and methods for inhibiting medical implant loosening. The work is available for licensing from the university’s Office of Industrial Liaison.

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COMPANIES AND INSTITUTIONS MENTIONED

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