Rebuilding a better bone

By Tracey Baas, Senior Editor

A team from the **University of California, Davis Medical Center** has designed a chimeric molecule that could treat osteoporosis by increasing the homing of transplanted mesenchymal stem cells to bone surfaces in mice.¹ The next step is showing the method works in large animal models of bone diseases.

Mesenchymal stem cells (MSCs) occur in a variety of adult tissues including bone marrow, in which they help regenerate bone by differentiating into osteoblasts. The number of endogenous MSCs decreases with age, leading to a decreased ability to regenerate bone and increased potential for developing osteoporosis and other bone diseases.

A potential solution for age-related bone disorders is MSC transplantation, but in preclinical studies the cells do not home to bone surfaces and show limited long-term engraftment unless the cells are first genetically modified²⁻⁵ or delivered after bone injury.^{3, 6, 7}

The UC Davis Medical Center team addressed some of those limitations by designing a chimeric molecule that binds integrin $\alpha_4\beta_1$ (CD49D/CD29), which is highly expressed by MSCs undergoing osteoblast differentiation, and brings the MSCs to the bone surface to increase bone mass.

One portion of the chimeric molecule is LLP2A, a peptidomimetic ligand that binds integrin $\alpha_4\beta_1$. The other portion is Ale, better known as Fosamax alendronate, an osteoporosis drug that has intrinsic bone-seeking properties.

Merck & Co. Inc. markets Fosamax to treat and prevent osteoporosis and to treat Paget's disease. Merck declined to comment on the work.

The researchers characterized LLP2A-Ale in three different mouse models of bone disease.

In immunodeficient mice, a single i.v. injection of LLP2A-Ale plus human MSCs resulted in MSCs at bone surfaces at 24 hours postinjection. Those MSCs differentiated into osteoblasts and became embedded within the bone matrix at three weeks postinjection.

For the second model, the researchers looked at whether LLP2A-Ale could direct endogenous MSCs to the bone surface and thus increase bone mass in the absence of MSC transplants.

In mice with age-related bone loss, i.v. injection of LLP2A-Ale alone increased bone mass, vertebral maximum load and maximum bone

stress compared with injection of LLP2A or Ale alone. Also in the mice, a single i.v. injection of LLP2A-Ale significantly prevented age-related bone loss for up to eight weeks compared with saline injection ($p < 0.05$).

In an acute estrogen-deficient mouse model of osteopenia, which is less severe than osteoporosis, i.v. injection of LLP2A-Ale two weeks after ovariectomy prevented bone mass loss and increased bone formation compared with LLP2A or Ale injection alone. The chimeric molecule injection had effects similar to those of a four-week treatment with the anabolic agent parathyroid hormone (PTH).

Results were published in *Nature Medicine*.

Breaking barriers

Wei Yao, corresponding author on the paper and an assistant professor at the **UC Davis Center for Healthy Aging**, hopes to start toxicity studies beginning August 2012 and Phase I and II trials of LLP2A-Ale as early as 2014 in osteoporosis patients ages 50 and higher.

Yao's group is part of a larger Osteoporosis Disease Team, which recently received \$110,000 from the **California Institute for Regenerative Medicine** (CIRM). The larger disease team will use the seeding money to put together an IND application to the FDA, a critical component needed to apply for a larger Disease Team Therapy Development Award from CIRM, worth up to \$20 million. That money would be used to fund future clinical trials.

Other key members of the Osteoporosis Disease Team are Nancy Lane, director of the UC Davis Center for Healthy Aging; Jan Nolte, director of the Stem Cell Program and Institute for Regenerative Cures at the **University of California, Davis School of Medicine**; and Kit Lam, chair of the Department of Biochemistry and Molecular Medicine at the UC Davis Medical Center.

"The next steps needed are to show how this regeneration is occurring, especially in the situation where LLP2A-Ale is delivered on its own," said Anna Spagnoli, associate professor of pediatrics at **The University of North Carolina at Chapel Hill**. "It is interesting to speculate that the compound is acting upon

endogenous MSCs, but that possibility has not yet been proven by experiment. The experiments that will need to be done to show those specific mechanisms will be quite challenging."

Those challenges have to do with the technical limitations of tracking endogenous MSCs without affecting the characteristics of stem cells or the subsequent osteoblasts.

David Scadden wanted "to see more long-term studies that show details of the magnitude and durability of repair these cells [MSCs] are capable of, especially in disease models" that are not immunodeficient.

Scadden is professor of medicine at **Harvard University**, director of the **Massachusetts General Hospital Center for Regenerative Medicine and Technology** and co-director of the **Harvard Stem Cell Institute**.

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**—Anna Spagnoli,
The University of North Carolina
at Chapel Hill**

“We have already done additional experiments with the combination therapy in an aged mouse model of osteoporosis and have extended our characterization of bone mass formation out to three months. The work will be published in the near future,” Yao told *SciBX*.

Instead of osteoporosis, Scadden thinks orthopedic indications or osteogenesis imperfecta could be a better initial indication for LLP2A-Ale plus MSC transplants. Osteogenesis imperfecta—brittle bone disease—has no cure and is caused by a mutation in the *collagen* gene.

“Mouse models of osteogenesis imperfecta are available, so it would be possible to see how the method translates. Ultimately, one could envision MSCs being harvested from the patient, genetically corrected for the collagen mutation, and then directed back toward the bone,” said Scadden.

Spagnoli wanted to see the approach tried in nonunion fractures. These nonhealing fractures are treated mostly with bone autografts harvested from the back of the pelvis. A small number of pilot clinical studies have shown positive results for MSC transplants.^{8–11}

“If the MSCs that the team delivered are truly acting as osteoblasts and integrate to promote healing in a fracture nonunion model, that would be a most interesting situation,” she said.

The work described in the paper is patented by the **University of California** and is available for licensing. Yao said her team has had “some informal discussions with two big pharmas that really want to see large animal and toxicology studies before they’re ready to hold discussions with us.”

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COMPANIES AND INSTITUTIONS MENTIONED

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