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[Health System](#) > [Newsroom](#) > UC Davis investigators develop method of directing stem ...

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UC DAVIS INVESTIGATORS DEVELOP METHOD OF DIRECTING STEM CELLS TO INCREASE BONE FORMATION AND BONE STRENGTH

Successful testing in mice paves the way toward human trials for osteoporosis

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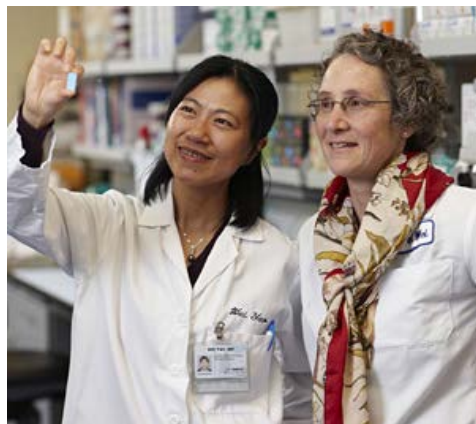
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(SACRAMENTO, Calif.) — A research team led by UC Davis Health System scientists has developed a novel technique to enhance bone growth by using a molecule which, when injected into the bloodstream, directs the body's stem cells to travel to the surface of bones. Once these cells are guided to the bone surface by this molecule, the stem cells differentiate into bone-forming cells and synthesize proteins to enhance bone growth. The study, which was published online today in *Nature Medicine*, used a mouse model of osteoporosis to demonstrate a unique treatment approach that increases bone density and prevents bone loss associated with aging and estrogen deficiency.



Researchers Wei Yao (left) and Nancy Lane (right)

"There are many stem cells, even in elderly people, but they do not readily migrate to bone," said Wei Yao, the principal investigator and lead author of the study. "Finding a molecule that attaches to stem cells and guides them to the targets we need is a real breakthrough."

Researchers are exploring stem cells as possible treatments for a wide variety of conditions and injuries, ranging from peripheral artery disease and macular degeneration to blood disorders, skin wounds and diseased organs. Directing stem cells to travel and adhere to the surface of bone for bone formation has been among the elusive goals in regenerative medicine.

The researchers made use of a unique hybrid molecule, LLP2A-alendronate, developed by a research team led by Kit Lam, professor and chair of the UC Davis Department of Biochemistry and Molecular Medicine. The researchers' hybrid molecule consists of two parts: the LLP2A part that attaches to mesenchymal stem cells in the bone marrow, and a second part that consists of the bone-homing drug alendronate. After the hybrid

molecule was injected into the bloodstream, it picked up mesenchymal stem cells in the bone marrow and directed those cells to the surfaces of bone, where the stem cells carried out their natural bone-formation and repair functions.

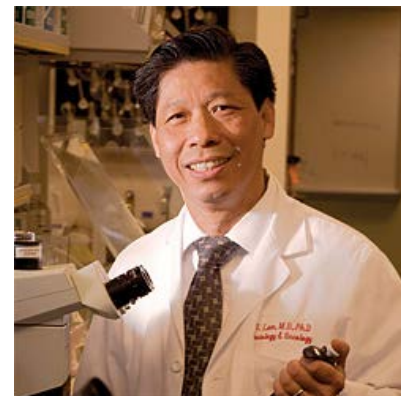
"Our study confirms that stem-cell-binding molecules can be exploited to direct stem cells to therapeutic sites inside an animal," said Lam, who also is an author of the article. "It represents a very important step in making this type of stem cell therapy a reality."

Twelve weeks after the hybrid molecule was injected into mice, bone mass in the femur (thigh bone) and vertebrae (in the spine) increased and bone strength improved compared to control mice who did not receive the hybrid molecule. Treated mice that were normally of an age when bone loss would occur also had improved bone formation, as did those that were models for menopause.

Alendronate, also known by the brand name Fosamax, is commonly taken by women with osteoporosis to reduce the risk of fracture. The research team incorporated alendronate into the hybrid molecules because once in the bloodstream, it goes directly to the bone surface, where it slows the rate of bone breakdown. According to Nancy Lane, a co-investigator on the study and director of the UC Davis Musculoskeletal Diseases of Aging Research Group, the dose of alendronate in the hybrid compound was low and unlikely to have inhibited the compound's therapeutic effect.

"For the first time, we may have potentially found a way to direct a person's own stem cells to the bone surface where they can regenerate bone," said Lane, who is an Endowed Professor of Medicine and Rheumatology and an expert on osteoporosis. "This technique could become a revolutionary new therapy for osteoporosis as well as for other conditions that require new bone formation."

Osteoporosis is a major public health problem for 44 million Americans. One in two women will suffer a fracture due to osteoporosis in their lifetime. Although effective medications are available to help prevent fracture risk, including alendronate, their use is limited by potential harmful effects of long-term use.



Kit Lam



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UC Davis Health System's 2011-2016 Strategic Plan

The major causes for osteoporosis in women include estrogen deficiency, aging and steroid excess from treatment of chronic inflammatory conditions such as rheumatoid arthritis. Generally, the osteoporosis generated by these metabolic conditions results from change in the bone remodeling cycle that weakens the bone's architecture and increases fracture risk.

Mesenchymal stem cells from bone marrow induce new bone remodeling, which thicken and strengthen bone.

The authors noted that the potential use of this stem cell therapy is not limited to treating osteoporosis. They said it may prove invaluable for other disorders and conditions that could benefit from enhanced bone rebuilding, such as bone fractures, bone infections or cancer treatments.



Jan Nolte

"These results are very promising for translating into human therapy," said Jan Nolte, professor of internal medicine, an author of the study and director of the UC Davis Institute for Regenerative Cures. "We have shown this potential therapy is effective in rodents, and our goal now is to move it into clinical trials."

Funding for the study came from the Endowment on Healthy Aging and the National Institutes of Health. The California Institute for Regenerative Medicine has given the team a planning grant to develop a proposal for human clinical trials.

"This research was a collaboration of stem cell biologists, biochemists, translational scientists, a bone biologist and clinicians," said Lane. "It was a truly fruitful team effort with remarkable results."

The *Nature Medicine* article is titled "Directing mesenchymal stem cells to bone to augment bone formation and increase bone mass." Min Guan, who is affiliated with the UC Davis Department of Internal Medicine, was co-lead author of the paper. Other UC Davis authors were Ruiwu Liu, Junjing Jia, Liping Meng, Ping Zhou and Mohammad Shahnazari, from the departments of Internal Medicine, and Biochemistry and Molecular Medicine, as well as the UC Davis Institute for Regenerative Cures. Authors Brian Panganiban and Robert O. Ritchie are with the Department of Materials Science and Engineering at UC Berkeley.

UC Davis is playing a leading role in regenerative medicine, with nearly 150 scientists working on a variety of stem cell-related research projects at campus locations in both Davis and Sacramento. The UC Davis Institute for Regenerative Cures, a facility supported by the California Institute for Regenerative Medicine (CIRM), opened in 2010 on the Sacramento campus. This \$62 million facility is the university's hub for stem cell science. It includes Northern California's largest academic Good Manufacturing Practice laboratory, with state-of-the-art equipment and manufacturing rooms for cellular and gene therapies. UC Davis also has a Translational Human Embryonic Stem Cell Shared Research Facility in Davis and a collaborative partnership with the Institute for Pediatric Regenerative Medicine at Shriners Hospital for Children Northern California. All of the programs and facilities complement the university's Clinical and Translational Science Center, and focus on turning stem cells into cures. For more information, visit www.ucdmc.ucdavis.edu/stemcellresearch.