CEDARS-SINAI MEDICAL CENTER NEWS

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Citation: *Journal of Urology*, July 2005, "Bladder Reconstitution With Bone Marrow Derived Stem Cells Seeded on Small Intestinal Submucosa Improves Morphologic and Molecular Composition."

HIGHLIGHTS:
Because options are limited when a bladder needs to be surgically removed or repaired, efforts are underway to engineer tissue that would "reconstitute" the bladder with cells that resemble and function as the bladder's own cells. Now, according to results of an animal study, "scaffolds" seeded with bone marrow-derived stem cells regenerate bladder tissue relatively quickly and the cells appear genetically similar to natural bladder cells. The research is described in the July issue of the *Journal of Urology*.

STEM CELLS SPUR ENGINEERED BLADDERS TO GROW MORE QUICKLY, APPEAR MORE GENETICALLY CORRECT

LOS ANGELES (June 6, 2005) – When a patient's bladder is damaged by disease, injury or malformation, surgical removal or repair may be required, but scientists have yet to find the ideal replacement material. Now, according to results of an animal study conducted at Cedars-Sinai Medical Center, "scaffolds" seeded with bone marrow-derived stem cells produce new cells that appear genetically similar to host cells.

"Tissue engineering with stem cells is emerging as a potential treatment option for urologic conditions. If these early studies do translate into therapies, they could have a significant impact on patient outcomes and quality of life issues," said Gerhard J. Fuchs, M.D., director of Cedars-Sinai's Minimally Invasive Urology Institute and senior author of an article appearing in the July issue of the *Journal of Urology*.

According to Steve Y. Chung, M.D., lead investigator of the study and first author of the article, this research builds on earlier work in two significant ways. "This appears to be one of the first studies to report on the use of stem cells in bladder reconstitution, and we took our analysis a step further by looking at gene expression to determine what kinds of cells are actually being made," he said.

Since about the middle of the last century, a patient having the whole bladder removed would typically have an ostomy, an opening in the abdomen through which a tube carries urine into an external collection pouch. In recent years and in certain instances, surgeons have begun to fashion new bladders and repair or enlarge existing bladders using segments of either the large or small intestine. But normal bladder tissue has a unique impermeability and contractility, so while these newly constructed bladders often are able to serve as

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reservoirs, they do not function as well as a natural bladder and they are prone to infections and other complications.

Research has been underway, therefore, to engineer tissue that would "reconstitute" the bladder with cells that more closely resemble and function as the bladder's own cells. Several types of tissue, including small intestinal submucosa (SIS), have been used as scaffolds to support cell growth. SIS has been used in humans for many years and is approved by the Food and Drug Administration.

But while initial results of animal studies on bladder reconstitution looked promising, the scaffolds deteriorated to fibrous tissue that compromises the bladder's compliance and capacity. Researchers then started growing smooth muscle cells and urothelial cells – cells that comprise a normal bladder – on the scaffolds. Again, early results looked good but long-term results are proving inconsistent.

The Cedars-Sinai researchers augmented the scaffolds with stem cells taken from bone marrow. The experiments were conducted on the bladders of laboratory rats, using the SIS of pigs as scaffolds. Four groups, consisting of eight rats each, were studied.

A control group underwent a sham operation in which the bladder was not disturbed. In another group, about 40 percent of the bladder was removed and the surgical site was sewn closed. A third group had the same amount of bladder removed and replaced with scaffold material that had not been seeded. The fourth group had the same surgery and scaffold that had been seeded with bone marrow-derived stem cells that are known to differentiate into a variety of tissue cells. Bladder tissues from rats in each group were analyzed at one month and three months after surgery.

Chung said many studies reported to date have performed histological and functional analyses. "We looked at gene expression, too, because specimens may look fine histologically, but when you look at gene expression you see what kinds of cells are actually being made," he said. "Interestingly, at three months, the histology of the unseeded SIS looked very good, consistent with previous reports, but when we looked at the gene expression, they were expressing a high level of collagens type I and III – the properties of fibrosis or scar tissue. The gene expression appears to be preceding what researchers have been finding histologically in long-term follow-up."

Chung said the stem cell-seeded specimens allowed the bladders to reconstitute relatively quickly and the resulting cells had gene expression levels similar to those in the control group.

"From both histology and gene expression, it appears that the stem cells are either helping or actually differentiating into the host cells," he said. "It looks very promising, but this is a very early study that needs to be confirmed through larger studies. We expect to see further progress in this field in the near future."

Researchers from Cedars-Sinai's Minimally Invasive Urology Institute, Department of Surgery and Department of Pathology conducted the study in collaboration with the Department of Biostatistics at the University of Pittsburgh.

One of only five hospitals in California whose nurses have been honored with the prestigious Magnet designation, Cedars-Sinai Medical Center is one of the largest nonprofit academic medical centers in the Western United States. For 17 consecutive years, it has been named Los Angeles' most preferred hospital for all health needs in an independent survey of area residents. Cedars-Sinai is internationally renowned for its diagnostic and treatment capabilities and its broad spectrum of programs and services, as well as breakthroughs in biomedical research and superlative medical education. It ranks among the top 10 non-university hospitals in the nation for its research activities and was recently fully accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP). Additional

information is available at www.cedars-sinai.edu.

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