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## TODAY'S HEADLINES

January 2, 2004

### REGENERATIVE MEDICINE

## CELLULAR U-TURN

Small molecule induces cells to revert to progenitor cells

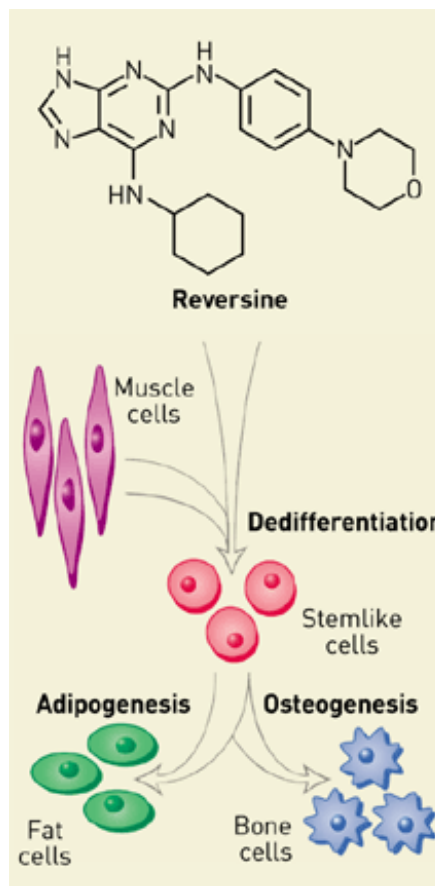
**CELIA HENRY**

Scientists at [Scripps Research Institute](#) have identified a synthetic small molecule that can turn differentiated cells back into progenitor cells. The molecule, dubbed reversine, represents a first step toward regenerative medicine.

Organisms such as salamanders that regrow their damaged tails use cellular dedifferentiation as part of the tissue regeneration process. Extracts from the regenerating limbs of amphibians previously have been shown to induce mammalian cells to dedifferentiate. Such extracts are essentially cocktails, however, and nobody knows what molecules actually induce the process or the mechanism by which dedifferentiation proceeds.

Although the signaling pathway for dedifferentiation is unknown, kinases (enzymes that catalyze phosphorylation) are thought to be involved. Therefore, the Scripps team, led by assistant chemistry professor Sheng Ding and chemistry professor [Peter G. Schultz](#), screened a

combinatorial library composed of heterocyclic compounds that might be expected to interact with kinases. The team found reversine, a synthetic substituted purine that can by itself induce dedifferentiation on a type of muscle cell known as a myoblast [*J. Am.*



**REGENERATION** Reversine causes mouse muscle cells to dedifferentiate into progenitor cells that can then redifferentiate into fat or bone cells.

COURTESY OF SHENG DING

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Reversine works specifically with mouse myoblast cells to turn them into multipotent progenitor cells that can differentiate into a variety of cells, such as fat, bone, muscle, or cartilage. Mouse cells were first treated for four days with each of 50,000 different compounds to induce dedifferentiation. The dedifferentiated cells were then assayed for their ability to differentiate into bone cells or fat cells in the presence of known osteogenic- or adipogenic-inducing agents.

The researchers don't know whether the progenitor cells they form have the same molecular signature as those that are formed naturally, which are known as mesenchymal stem cells, but they know that the cells have similar abilities to form different cell types.

Every cell type will probably require a different molecule to induce dedifferentiation. "Different cells have distinct molecular signatures and microenvironments," Ding notes. "We don't believe there is one such molecule that can work in every cell type." The team is currently trying to find molecules that cause dedifferentiation in other cell types.

Ding sees small molecules like reversine as a significant step toward regenerative medicine. "Stem cells can be used to generate a variety of cell types, but there are problems facing the practical use of stem cells, including methods for controlling their proliferation and differentiation, as well as cell sources and the rejection problem," he says. "We think that small molecules that can induce dedifferentiation of differentiated tissue represent an alternative approach to regenerative medicine." Potentially, easily accessible cells could be harvested, dedifferentiated, and then redifferentiated into less accessible cell types.

Shannon J. Odelberg of the University of Utah Health Sciences Center, one of the scientists who initially reported that amphibian extracts can cause mammalian cells to dedifferentiate, calls the work "quite significant" both in its confirmation of previous work and the new avenues that it opens.

Odelberg points out that the work suggests ways to generate a large supply of progenitor cells in vitro. He believes that with more research, such approaches may lead to a way to promote regeneration in mammals through in vivo cellular dedifferentiation.

Now, Ding and his coworkers are studying the process of dedifferentiation and the mechanism of action of reversine. "If we can figure out the binding partner of this molecule, then we can probably figure out the signaling pathway," he says. "If we have a defined protein target, we can further optimize this molecule. We can apply other approaches to that pathway that can improve the efficiency of dedifferentiation."

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