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Molecule prompts blood stem cells to help repair heart damage in animal model

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Researchers at UT Southwestern Medical Center have for the first time used drug-treated blood stem cells to repair heart damage in an animal model, results that might point to methods for healing injuries from heart attacks or disease.

In the study, researchers screened about 147,000 molecules to find one that could transform human blood stem cells into a form resembling immature heart cells. When they implanted blood stem cells activated by this compound into injured rodent hearts, the human cells took root and improved the animals' heart function.

"The clinical potential is enormous," said Dr. Jay Schneider, assistant professor of internal medicine and senior author of the study, which appears online this week and in a future issue of the *Proceedings of the National Academy of Sciences.*

Despite medical advances in treating and preventing heart attacks, once the heart is damaged it cannot repair itself, said Dr. Schneider, a cardiologist.

"Heart attack is a man-made problem," he said. "It's a function of increased longevity and atherosclerosis, which have occurred at no other time in human evolution."

In the first stage of the current study, which involved mouse stem cells, the researchers screened some 147,000 compounds in UT

Southwestern's Small Molecule Library to see which ones would activate genes known to be at work in the early stages of heart development.

This initial screening sifted out about 1,600 compounds, but the researchers narrowed their focus to a related group of molecules, among the most potent and easy to make, called Shz for sulfonyl-hydrazone.

The researchers then tested the effects of one Shz compound, Shz-3, a molecular variant synthesized by chemists at UT Southwestern, on human blood stem cells. These cells, called PBMCs for peripheral blood mononuclear cells, were cultured with Shz-3 for three days, then for seven days without the drug.

Tests showed that the Shz-treated cells began to create RNAs and proteins found only in heart cells. They were then implanted into the hearts of rats with heart damage. After a week, the function of the rats' hearts had significantly improved, and after three weeks, the organs contracted as strongly as they did before the damage. Tests showed that the human cells were alive and had incorporated themselves into the heart tissue, although the researchers could not tell whether the human cells had become fully functional, contracting heart cells.

"This functional test is a good first step," Dr. Schneider said "What this shows is that this drug can act on blood stem cells that are already being used in other clinical trials. This may speed its movement into clinical trials for heart repair."

Shz compounds do not appear to be toxic in mice, and because the human blood stem cells are washed for seven days after treatment, the compounds are likely not to be harmful to humans, although further tests are needed, Dr. Schneider said.

Further studies will examine precisely what the Shz drugs are doing to

the cells, and to identify additional chemical signals that might drive the cells toward a more mature form of heart cell, the researchers said.

Source: UT Southwestern Medical Center

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