

# Gene therapy and stem cells save limb

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Blood vessel blockage, a common condition in old age or diabetes, leads to low blood flow and results in low oxygen, which can kill cells and tissues. Such blockages can require amputation resulting in loss of limbs. Now, using mice as their model, researchers at Johns Hopkins have developed therapies that increase blood flow, improve movement and decrease tissue death and the need for amputation. The findings, published online last week in the early edition of the *Proceedings of the National Academy of Sciences*, hold promise for developing clinical therapies.

"In a young, healthy individual, hypoxia — low oxygen levels — triggers the body to make factors that help coordinate the growth of new blood vessels but this process doesn't work as well as we age," says Gregg Semenza, M.D., Ph.D., professor of pediatrics and [genetic medicine](#) and director of the vascular biology program at the Johns Hopkins Institute for Cell Engineering. "Now, with the help of gene therapy and stem cells we can help reactivate the body's response to hypoxia and save limbs."

Previously, Semenza's team generated a virus that carries the gene encoding an active form of the HIF-1 protein, which turns on genes necessary for building new blood vessels. When injected into the hind legs of otherwise healthy mice and rabbits that had been treated to reduce blood flow, the HIF-1 virus treatment partially restored blood flow.

People with diabetes have a 40 times higher risk of losing a limb to [amputation](#), says Semenza. To find out if HIF-1 gene therapy could

improve blood flow in a diabetic animal, the team then tested the same virus in diabetic and non-diabetic mice that had blood flow cut off to one hind leg. Twenty-one days after treatment, the HIF-1 virus-treated mice had 85 percent recovery of blood flow compared with 24 percent in the mock-treated mice. And, treated, diabetic mice had much less tissue damage compared to the untreated diabetic mice. These results were reported in the Nov. 3 issue of the [Proceedings of the National Academy of Sciences](#).

In the current study, the team asked if the same gene therapy treatment could improve reduced blood flow associated with advanced age. Comparing 13 month old mice to 3 month old mice, blocking the femoral artery in the hind leg causes all older mice to lose their legs while only about a third of younger mice have to lose their legs. The research team treated young and old mice with the HIF-1 virus and examined blood flow and tissue health. They found that while treatment improved young mice, it did not make a noticeable difference in the older mice.

But, it was known that when HIF-1 normally activates signals in the body to build new vessels, one of the many types of cells recruited to the site of new vessel growth is a population of [stem cells](#) from the bone marrow, which are called bone marrow-derived angiogenic cells. So the team isolated these cells from mice and grew them under special conditions that would turn on HIF-1 in these cells.

When the researchers treated the mice with both the HIF-1 virus and simultaneously injected bone marrow-derived angiogenic cells, treated, older mice were less likely to lose their legs compared to their untreated counterparts.

Further study of these [mice](#) showed that activating HIF-1 in the cells appeared to turn on a number of genes that help these cells not only

home to the ischemic limb, but to stay there once they arrive. To figure out how the cells stay where they're needed, the research team built a tiny microfluidic chamber and tested the cells' ability to stay stuck with fluid flowing around them at rates mimicking the flow of blood through vessels in the body. They found that cells under low oxygen conditions were better able to stay stuck only if those same cells had HIF-1 turned on.

"Our results are promising because they show that a combination of gene and cell therapy can improve the outcome in the case of critical limb ischemia associated with aging or diabetes," says Semenza. "And that's critical for bringing such treatment to the clinic."

Source: Johns Hopkins Medical Institutions

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