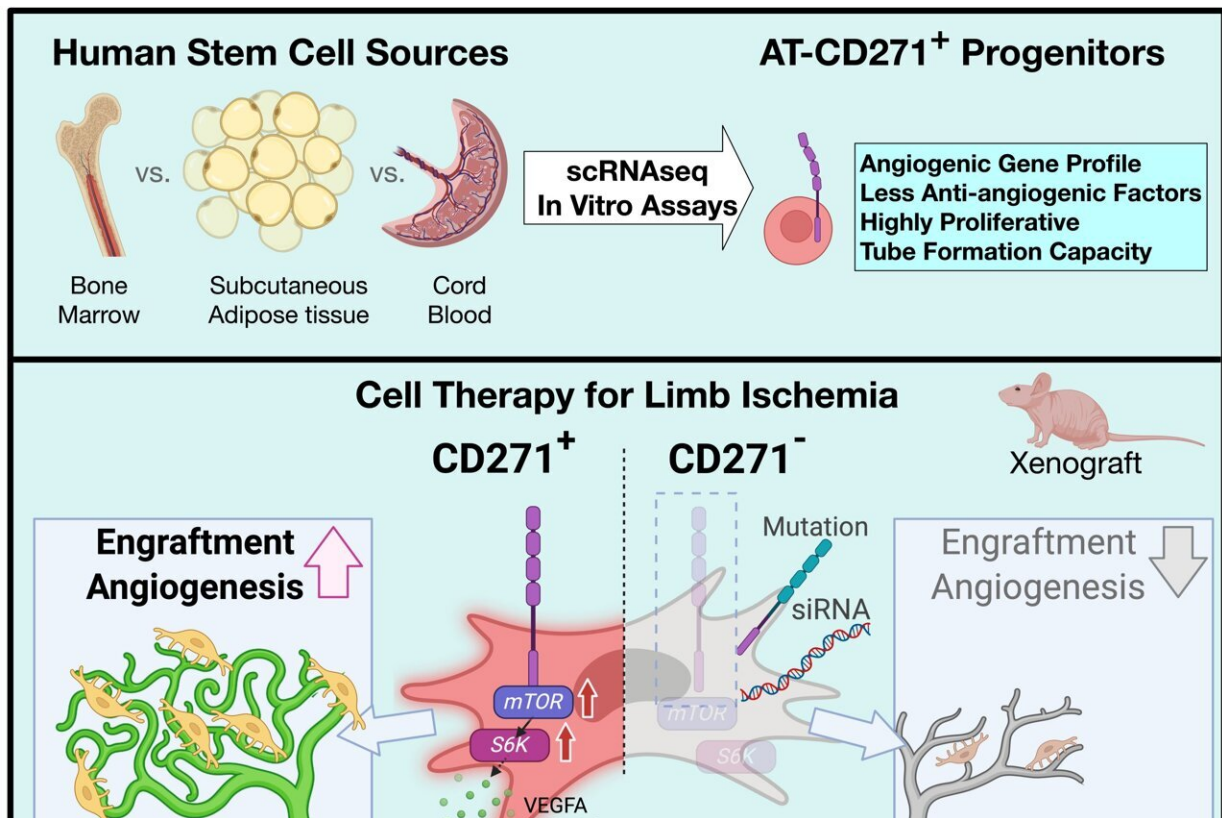


# New way to prompt blood vessel growth shows promise for rescuing limbs at risk

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Critical limb ischemia (CLI), the end-stage condition of peripheral artery disease (PAD), is increasing worldwide. Diabetes, smoking (Buerger disease), and autoimmune diseases all can cause CLI. A new study led by experts at Cincinnati Children's and Kanazawa University in Japan shows, in mice, that transplanting human stem cells from fat tissue that are CD271-positive can restore blood flow by prompting new blood vessel growth. This graphic abstract illustrates the process. Credit: Cincinnati Children's and *Cell Reports Medicine*

Across the United States, about 2 million people are living with an amputation and another 185,000 amputations occur every year, [according to the Amputee Coalition](#), a Washington DC-based support group. About 54% of these lost limbs were caused by vascular disease, including diabetes and peripheral arterial disease (PAD).

And as more people are diagnosed with diabetes in the US and worldwide, the number of amputations keeps rising.

Now, experts at Cincinnati Children's in collaboration with colleagues from Kanazawa University in Japan, have uncovered a new way to prompt blood vessel growth that shows promise as a treatment for preventing ischemia-induced amputations. Their discoveries were based on achieving a deeper understanding of why two patients in a clinical trial in Japan walked away with fully recovered limbs that appeared destined for amputation.

The study [published](#) in the journal *Cell Reports Medicine*, was led by first author Oto Inoue, MD, Ph.D., a cardiologist from Japan and a research fellow with Cincinnati Children's, and Juan Sanchez-Gurmaches, Ph.D., Division of Endocrinology.

Their team reports that a specific subset of stem cells isolated from [adipose tissue](#) (fat) that also carry the cell surface marker CD271 outperformed all other similar cell types at inducing blood vessel formation. The study also details key molecular mechanisms involved in the process.

The scientists confirmed these findings by transplanting this population of human stem cells into mice with limb ischemia. In every case, the treatment rescued limbs that otherwise would have required amputation.

Then, the team analyzed data from a clinical trial to provide initial

evidence that such a [cell transplant](#) may have already worked in humans. In this case, people with foot ulcers were treated with a generalized mix of stem cells collected from the patient's own tissues.

Of the small number of patients analyzed, the two patients with fully recovered limbs received high numbers of CD271-positive stem cells. Those results, in combination with the highly consistent benefits found in the mouse testing, appear to justify further work to launch a formal clinical trial, the co-authors say.

"Critical limb ischemia is one of the most severe outcomes for PAD and undertreated diabetes. This research shows hopeful results that this new subset of progenitors may have positive therapeutic value," Inoue says. "It was quite inspiring to see that one of the patients has recovered enough to return to work."

## **A race to address a widespread health problem**

With rising rates of obesity plaguing the United States, diabetes incidence has been rising for years, leading to a host of cardiovascular complications, including PAD, leading to critical limb ischemia.

Doctors treat PAD by using medications to slow the disease while performing bypass surgeries or catheter-based procedures to open clogged arteries in the limbs. However, many of the arteries that need treatment in the limbs are too small and difficult to access with surgery.

As a result, at least a third of the people who need revascularization therapy are not eligible for surgical interventions. Those who lose their limbs go on to experience significant pain and disability, while their underlying cardiovascular disease makes them increasingly likely to experience potentially fatal heart attacks, strokes, and other problems.

Once seen as a purely adult health problem, researchers at Cincinnati Children's and other centers have been finding early signs of vascular disease in teens and even younger children who struggle with severe obesity and diabetes.

## **Emerging alternatives from international collaboration**

Inoue, 40, has studied PAD in Japan for over a decade. He came to Cincinnati in 2021 to further study the emerging area of induced angiogenesis through cellular transplantation as a member of the Sanchez-Gurmaches lab.

Many researchers have explored the idea of transplanting [progenitor cells](#) to jump-start the body's own tissue-repair capabilities. However, the major limitation has been finding the right cells to use.

To solve this, the team used single-cell transcriptomics to hunt through a haystack of different types of progenitor cells to find the right population of cells. While many stem cells reside naturally in the [bone marrow](#), this study found the strongest trigger of blood vessel formation lurking within fat tissue. These cells carry the marker CD271, which has been shown in other studies to play important roles in tissue growth.

The team transplanted these human CD271-positive cells into mice to confirm their abilities. The human CD271 cells were 100% effective at prompting enough [blood vessel growth](#) in the mice to restore normal blood flow to the diseased limbs.

Evidence that this new cell population may work in human disease also was provided. The authors found that among people who received progenitor cells self-transplanted from fat, those who recovered better

and saved their limbs had higher numbers of CD271 progenitor cells present.

"The positive correlation between recovery and the number of CD271+ progenitors injected in the affected area of these patients was striking," Sanchez-Gurmaches says.

## Challenges ahead

The co-authors emphasize that the findings so far are preliminary. The therapeutic value of adipose tissue CD271-positive cells should be evaluated in larger numbers of patients through a formal clinical trial.

One significant issue to resolve is how to obtain enough CD271 progenitor cells to use as treatment. The new paper reports that the number of CD271 progenitors found in the fat of people with [insulin resistance](#) can be as much as 75% lower than people without insulin resistance. Also, the cells that are found tend to be less active in generating new vessels.

"Unfortunately, the people living with insulin resistance who face elevated risk of [limb](#) ischemia are the same people with low numbers of CD271-positive progenitor cells, which could make self-transplantation more difficult," Inoue says.

More research is needed to determine if these cells can be multiplied in the lab before transplantation.

**More information:** Oto Inoue et al, Single-cell transcriptomics identifies adipose tissue CD271+ progenitors for enhanced angiogenesis in limb ischemia, *Cell Reports Medicine* (2023). [DOI: 10.1016/j.xcrm.2023.101337](https://doi.org/10.1016/j.xcrm.2023.101337)

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