

## Toward improving the health and longevity of transplanted organs <sup>[1]</sup>

Discovery <sup>[2]</sup>

**Author:** Elizabeth Dougherty

The ability to transplant an organ from one person to another is an incredible feat of medicine. It turns out, however, that transplanted organs aren't as durable as one might think.

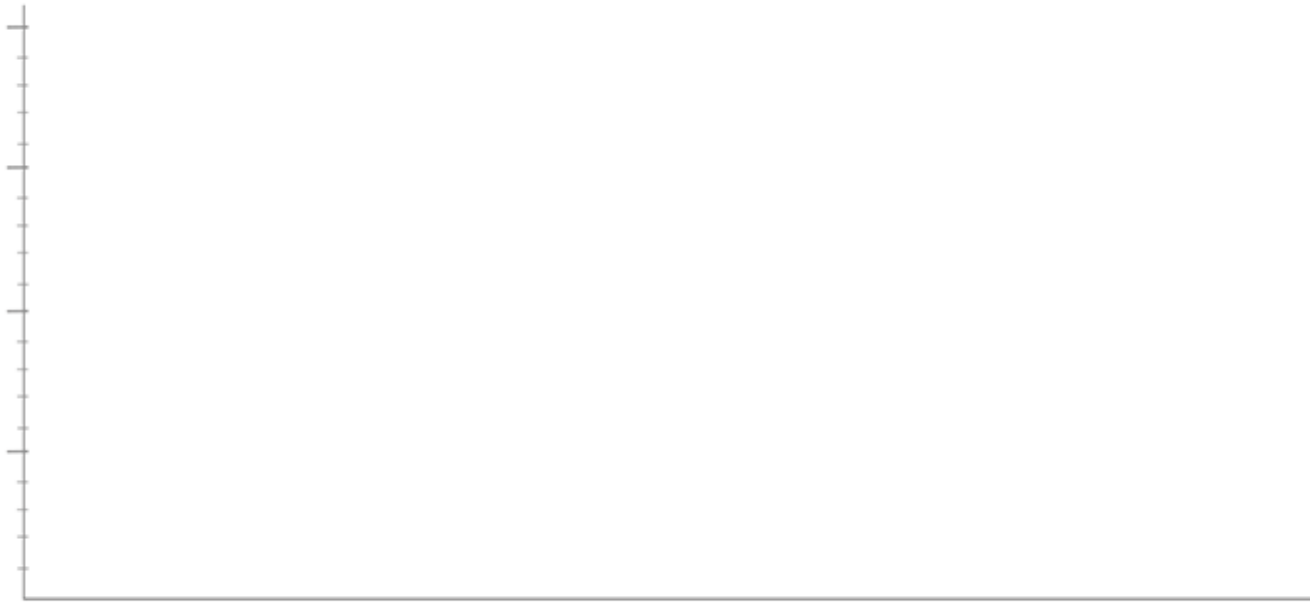
The very medicines that keep the body from rejecting the organ also slowly destroy it. A donated kidney, for example, may last five years. Most don't last 10. Some patients end up back on dialysis, visiting a clinic multiple times a week to have waste filtered from blood mechanically while waiting for a second donated kidney – in a queue that lasts between three and five years in the US.

Novartis researchers think they have an approach to transplant support that, if successfully developed, could make the promise of durable transplants a reality for many patients. In an analysis of patients participating in an early-stage clinical trial, 60% of transplant patients treated with an experimental compound called iscalimab (CFZ533) had transplanted kidneys that looked indistinguishable from healthy kidneys one year after transplant. In comparison, none of the patients in this trial taking standard therapies had normal-looking kidneys after a year. The findings appear in an [abstract](#) <sup>[3]</sup> for the American Transplant Congress in Boston, Massachusetts, in the US, on June 1 - 5, 2019.

Sandoz, one of the foundational companies of Novartis, introduced transplant-enabling drugs 35 years ago, answering a need for organ transplants. These drugs prevent the immune system from rejecting the new organ, which looks like a foreign invader to immune cells. Now Novartis researchers have a new goal in mind: transplants that last a lifetime.

“The idea is to protect organs in a way that gives someone a real life, not a downgraded life that continues to decline with the slow deterioration of the transplanted organ,” says Boerje Haraldsson, a nephrologist and Senior Global Program Head for Immunology, Hepatology and Dermatology in Novartis Global Drug Discovery (GDD).

# Kidney Transplant Loss After Three Years



Modified from Yilmaz et al 2003.

An unrelated study of over 600 kidney transplant patients showed that more damaged organs (as measured via biopsy at one year) are more likely to fail within three years of transplant. Kidneys that stay healthy are more likely to last. If iscalimab helps keep transplanted kidneys healthier, it could help them last longer. (J Am Soc Nephrol. 2003 Mar;14(3):773-9.)

The need for more durable transplants is strong, particularly for kidney transplants. Worldwide, approximately 3.2 million people are living with end-stage renal disease. That number is rising between 5% and 8% per year. Patients with the disease have two options: dialysis or transplant. An ever-expanding transplant waiting list tops 100 000 in the US alone, resulting in a chronic shortfall of donor kidneys.

“Extending the life of a kidney transplant is so important. Not only does that keep people from going on dialysis, which is miserable, it keeps them from needing another transplant. This makes more transplant organs available for other people,” says Haraldsson. “This is important not only for the individual but for all of the people on transplant waiting lists.”



Boerje Haraldsson, Novartis drug developer. Photo credit: Laurids Jensen

The idea is to protect organs in a way that gives someone a real life, not a downgraded life.

**Boerje Haraldsson**, Senior Global Program Head, Immunology, Hepatology and Dermatology, Novartis Global Drug Discovery

## **Not too much immune suppression, not too little**

It was already clear that patients needed new approaches to long-term transplant support when James Rush started working on iscalimab a decade ago in the autoimmunity, transplantation and inflammation disease area in the Novartis Institutes for BioMedical Research (NIBR). He and his colleagues wanted to find a way to damp the immune system enough to prevent rejection of a transplanted organ, but not so much as to compromise a patient's health.

“We’re trying to develop the transplant drug equivalent of baby bear’s porridge,” says Rush. “Just the right amount of immunosuppression as opposed to too much or too little. This will hopefully enable long-term survival and function of the transplanted organ without compromising the ability of the patient to respond to infection.”

Standard therapy includes a medicine called a calcineurin inhibitor that shuts down large swaths of the immune system to prevent organ rejection. Calcineurin inhibitors are so heavy-handed that they can cause a range of side effects. Doses of these medicines have to be kept low enough to be tolerable for patients.

At tolerable doses, calcineurin inhibitors do prevent rejection, but they appear to leave a low level of inflammation smoldering inside the transplanted kidney. Inflammation is a sign that the immune system is still attacking the foreign tissue even if it’s not acutely rejecting it. Immune cells infiltrate the transplanted kidney and eat away at it, slowly turning healthy tissue into scar

tissue that isn't capable of doing the complex work of filtering waste out of the blood.

Rush and his colleagues had an alternative approach in mind. They were interested in selectively targeting the inflammation involved in organ rejection. The research team set their sights on targeting a signaling molecule called CD40. The immune response CD40 induces can cause organ rejection and the smoldering inflammation that damages kidneys over time.

When Rush and his team started experimenting with iscalimab, a monoclonal antibody that blocks CD40 signals, they discovered they needed a high dose to quash that smoldering inflammation. The team hypothesized that a high dose would be tolerable. The selectivity of their experimental medicine could enable them to deliver it safely and potentially strike that sought-after Goldilocks balance.

“This new approach is more selective so it should cause fewer side effects,” says Haraldsson. “If we have fewer side effects, we can be more aggressive in the dosing so that we have a better blockade against the immune reaction we want to stop.”

Evidence from preclinical experiments and an early-stage clinical trial supports the idea, but further testing in human clinical trials is required to establish the safety and efficacy of this approach.



James Rush, a Novartis scientist. Photo credit: Laurids Jensen

We're trying to develop the transplant drug equivalent of baby bear's porridge.

**James Rush**, Director, Autoimmunity, Transplantation and Inflammation, Novartis Institute for BioMedical Research

## Advancing care for transplant patients

In the early-stage clinical trial, iscalimab protected transplanted organs from rejection during the first year as effectively as a traditional calcineurin inhibitor. An important hurdle, since any new approach must perform at least as well as existing therapies.

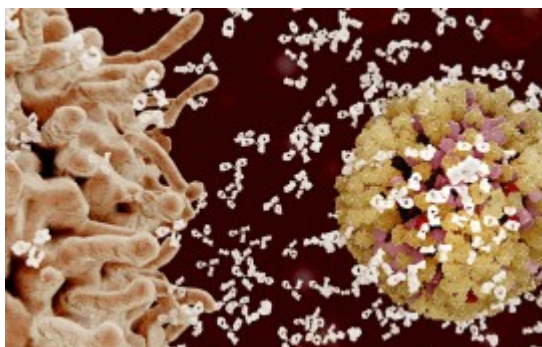
But were the transplanted organs healthier over that time? To find out, the drug development team biopsied the kidneys of patients enrolled in the trial. To Haraldsson, who has worked with kidney transplant patients for a quarter century, the results were promising.

The team evaluated the biopsied tissue and calculated a chronic allograft damage index (CADI). A healthy CADI score is between 0 and 1.0; scores higher than 1.0 indicate inflammation or tissue damage. The average CADI score for patients in the clinical trial taking standard therapy was 5.1 – compared with 1.6 for those taking iscalimab, with several trial patients in the healthy range.

“I’m used to seeing pathology slides that show inflammation after a transplant. But this data shows a completely new pattern in transplantation. We’re not just seeing normal transplanted organs, but normal healthy organs,” says Haraldsson.

The next step will be to test the regimen in a larger group of patients. Haraldsson and his drug development team are recruiting 325 kidney transplant patients to participate in a Phase II clinical trial to determine if this novel approach to immune suppression for transplant could benefit patients. A similar trial is underway for liver transplant patients.

Time will tell if the approach will be successful. “The existing drugs are very good and have improved life tremendously,” says Haraldsson. “The next drug must do even better if we want to transform solid organ transplantation and provide durable solutions for patients.”



Patient Perspectives [4]

## Targeting the roots of Sjögren’s syndrome [5]

*Main image: Photo credit, Laurids Jensen*

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