INTERVIEW

# The Promise of a Diabetes Cure
# A Conversation with Dr. Melanie Graham



In a quiet lab in Minnesota, cutting-edge science is inching closer to freeing millions of diabetics from their daily insulin routines. Dr. Melanie Graham, a pioneering researcher in transplant immunology at the University of Minnesota, believes that xenotransplantation – the use of animal-derived cells – holds the key to revolutionizing diabetes care. In this exclusive interview with «l'express», she explains how pig islet cells, immune system engineering, and carefully managed primate models are converging to deliver safer, longer-lasting treatments – and perhaps, one day, a true cure...

**Why do you believe that xenotransplantation is key to the future of diabetes therapy?**

For millions of people living with diabetes, daily life revolves around managing blood sugar. That often means constant monitoring, strict diets, changes to daily routines, and, for many, regular insulin injections. It's a heavy burden that affects nearly every part of their lives.

In diabetes, whether type 1 or advanced type 2, the insulin-producing cells in the pancreas, called islet cells, have been damaged, exhausted, or destroyed. But we can replace those cells. Islet cell transplants have already helped more than 4,000 people, and many of them have been able to live without needing insulin injections. The challenge is that we don't yet have enough islet cells to offer this therapy to everyone who could benefit from it. That's a problem we're working to solve.

New sources of islet cells, whether derived from stem cells or from pigs (known as xeno-islets), could provide an almost unlimited supply of transplantable cells. Pigs are considered ideal donors because their islet cells function similarly to humans' and because they have a long-standing role in both medical and food production systems. These new sources are crucial for the future of diabetes therapy because they overcome a major barrier: access. By unlocking a reliable supply of cells, we move closer to regenerative, personalized treatments that don't just manage diabetes but restore insulin-independence and freedom from disease.

**How close are we to achieving immune tolerance without lifelong immunosuppressive drugs?**

We and others are exploring a variety of approaches, such as engineering transplanted cells to be "invisible" to the immune system, developing immune-modulating therapies that are highly specific or retrain the body's defenses, and using specialized transplant sites that naturally protect the cells. Several promising strategies have demonstrated success in primate models, are poised for clinical translation, and some have already entered early clinical trials.

We are truly in the era of a cure, where therapies that significantly reduce or even eliminate the need for lifelong immunosuppression are emerging. These advances are making islet transplantation, and transplantation in general, safer and longer-lasting than ever before.

**Your lab works extensively with primates. What are the scientific advantages and ethical boundaries you observe in this model?**

Nearly all science today relies on a combination of models, both new approach methodologies and animal studies, because different questions require different approaches. For transplantation research, we use non-animal models like immune cell profiling, perfusion cell culture, and organoids to study many important questions. However, when it comes to understanding rejection and immune tolerance, primates remain indispensable because their immune systems closely resemble ours. Studies in primates have been fundamental to the major breakthroughs in transplant immunology and therapy, including the development of new drugs that help transplanted organs survive longer while improving patient safety.

Primates are used only when absolutely necessary, guided by strict ethical standards and oversight. We are deeply committed to our animal welfare program, which focuses on reducing the number of primates used, refining every procedure to minimize stress or discomfort, and continually improving their quality of life. These animals have played a vital role in advancing therapies that change patients' lives, and caring for them is a responsibility we hold just as seriously as the science itself.

**Could extrahepatic islets redefine long term graft survival?**

Currently, islet cells are transplanted into the liver, a method called intraportal transplantation. It works, but the liver isn't their natural environment, which can limit long-term success. We're developing new transplant sites outside the liver, what we call extrahepatic sites, that are specifically designed to better mimic the natural environment of the pancreas. By giving islets a more supportive home, we believe we can improve long-term survival of the graft and bring durable, insulin-independence for more people with diabetes.

**What have been the biggest obstacles in translating preclinical results into human clinical trials?**

One of the biggest challenges in moving promising therapies from the lab to clinical trials is ensuring they will actually work, and be safe, in people. No single model can fully predict that, which is why we rely on a combination of tools – new approach methodologies, small animal studies, and primates, whose immune systems closely resemble our own.

Many transplant therapies in use today, such as alemtuzumab, belatacept, and immune toleranceprotocols, were first validated in primate models. Others, like anti-CD40 antibodies, showed strong results in non-human primates and are now enabling groundbreaking human trials, including the first successful heart and kidney xenotransplants. While no model is perfect, using them together allows us to move into clinical trials with the highest level of confidence, ensuring that our science is not only innovative, but also responsible.

**How do you respond to scrutiny from animal rights groups – and what reforms do you believe are necessary for public trust in translational research?**

We share important goals with animal advocacy groups, working to replace or reduce animal use in research and ensuring that, when animals are involved, their welfare is a top priority. This commitment is central to our scientific work, and we openly publish our efforts to improve animal welfare to maximize their positive impact. While we all hope for a future where animals are no longer needed in research, human biology is incredibly complex. Organoids offer valuable insights but lack an immune system, and artificial intelligence depends heavily on the quality of the data it learns from. Animal models provide dynamic, system-level responses, including metabolism, behavior, aging, and long-term effects, that remain essential until technology advances further. Supporting initiatives that combine these methods will accelerate progress in translational research.

Building public trust depends on openness and accountability in how animals are cared for and how research is conducted. Alongside the important voices of animal advocates, it is equally vital to hear from patients who live daily with the burden of disease, as their experiences and needs are at the heart of why we do this work. Together, these perspectives guide us to advance science responsibly, ethically, and with shared purpose.

**What role do regulatory bodies like the NIH or FDA play in shaping the feasibility and timing of your innovations?**

The NIH plays a vital role by funding all stages of discovery, from early research through clinical development, and by creating targeted programs that accelerate translation of promising therapies. The FDA works closely with scientists to adapt regulatory review processes, enabling innovative treatments to be evaluated efficiently and safely. Together, these agencies create an environment where cutting-edge science can be responsibly developed, thoroughly tested, and brought to patients as quickly as possible.

**Looking ahead, what new tools (AI, CRISPR, etc) are you integrating or observing with interest in your research pathway?**

CRISPR technology offers precise ways to edit donor cells to reduce immune rejection. Combined with sophisticated immune profiling, these tools enable us to develop more personalized and effective transplant therapies.

**Do you foresee a future where immunosuppression free transplantation becomes mainstream in other chronic diseases beyond diabetes?**

Yes, we see a future where transplant patients won't need lifelong immunosuppressive drugs, not just for diabetes, but for many chronic diseases. In our research, we learn from both cell-based therapies and solid organ transplants, with breakthroughs in one helping to advance the other. We've already shown in complex primate models that long-term transplant survival without chronic immunosuppression is possible. That gives us the confidence to begin moving these approaches into clinical trials, bringing us closer to safer, more lasting treatments for patients.

**Finally on a personal note – what drives you to stay committed to this long, uncertain path of translational science?**

I see translational science as a way to honor how deeply interconnected we all are, patients, animals, families, and researchers, working toward a future where healing is possible, and compassion guides every step.

■ Nad SIVARAMEN