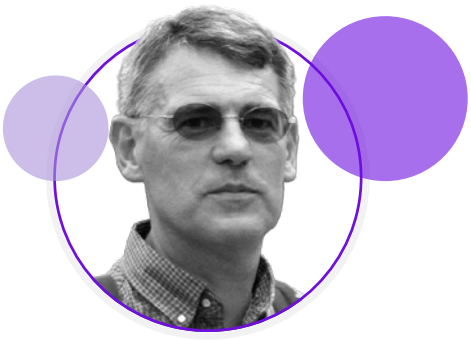


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Q1 A lot of your work has revolved around immunotherapy in Type 1 diabetes (T1D). How has immunotherapy for T1D progressed over the course of your career?

I started working in this field close to four decades ago now. In this period, our understanding of the disease has improved a lot.

A major change was confirming that T1D is an autoimmune disease. Many studies were published showing that it is a chronic autoimmune disease with a very long pre-diabetic period, which can last anywhere from months up to 20 years after autoantibodies are detected. This opened up the possibility of intervention.

The second change is that we used to think all the β cells had been killed by the time the disease started. From the studies on the pancreases of people who unfortunately passed away at different stages of the disease, we now know that many people still have 10–40% of their β cell mass when the disease starts. These cells are there, but they are not functioning. Again, this opens up the possibility of recovering them if the immune assault is stopped.

The third change is in how we perceive the role of the β cells themselves in the disease. They used to be seen as 'the corpse at a funeral': the object of much attention, but playing no role in the proceedings. This has changed, at least in part, through my own group's work since the 1990s. It is now well accepted that there is a dialogue between the β cells and the immune system. So, we need to do two things. First, we need to act on the immune system to reduce the immune assault and, if possible, "convince" the immune system to forget the β cells. Second, we need to make the β cells more resistant to the immune assault and reduce the signals they send to the immune system. For example, β cells release chemokines that attract more immune cells, and they overexpress the molecules involved in antigen presentation, which makes them easier for the immune system to recognise.

These are some of the main changes over the last 40 years of my research, and the pace is speeding up. More has happened in the last 5 years than in the previous 35, and I hope it keeps speeding up like this.

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Q2 At the European Association for the Study of Diabetes (EASD) Annual Meeting 2026, you chaired a session titled 'Protecting beta cells: stopping autoimmunity in its tracks'. What were the most interesting outcomes of that session, and how might they translate to better outcomes for patients?

This was mostly a basic research session, including abstracts, some of which were from my own group, on β cells and how to test drugs that protect them. There were also abstracts on T regulatory cells, which can dampen the autoimmune assault. The challenge is to get them to the islets so they can reduce the local autoimmune response and inflammation. There was also a very interesting abstract on how changes in the proinsulin

molecule make it more recognisable to the immune system, and how to stop this from happening.

My group presented two abstracts. The first was about delivering protective cargo directly to the β cells, so that you get a local effect without side effects. We identified a protein on the surface of the β cell and then developed nanocarriers that can deliver a small interfering RNA to block interferon signalling. We achieved this in human islets. We are now implanting human islets into immunodeficient mice to see whether we can stop interferon signalling there.

The second abstract came from a collaboration with a biotech company, InSphero, Schlieren, Switzerland, which is developing ways to screen new drugs that prevent β cell death *in vitro*. What is very interesting about their model is that they don't use only cytokines. They also co-culture the β cells with T cells that recognise them, which makes it a more relevant model. They validated two drugs already used in other autoimmune diseases: baricitinib, which is a JAK1/2 inhibitor and has already been through a clinical trial for T1D in Australia, and deucravacitinib, which is a tyrosine kinase 2 (TYK2) inhibitor used in psoriasis and psoriatic arthritis, and a clinical trial is being discussed in the USA.

Q3 You have also been involved in the INNODIA global network from the beginning. Since presenting the findings of the MELD-ATG and Ver-A-T1D trials last year, what has INNODIA been working on?

I chaired the first INNODIA session at EASD 2026, which focused both on β cells and the immune system. There was an interesting presentation on a drug developed after verapamil that inhibits thioredoxin-interacting protein (TXNIP), with the aim of protecting β cells against endoplasmic reticulum stress. That was an interesting presentation.

At this INNODIA meeting, several companies, both big pharma and smaller ones, presented new drugs that they want to take into clinical trials with INNODIA's help. So there were no major trial results reported; it was more about which projects are being incubated.

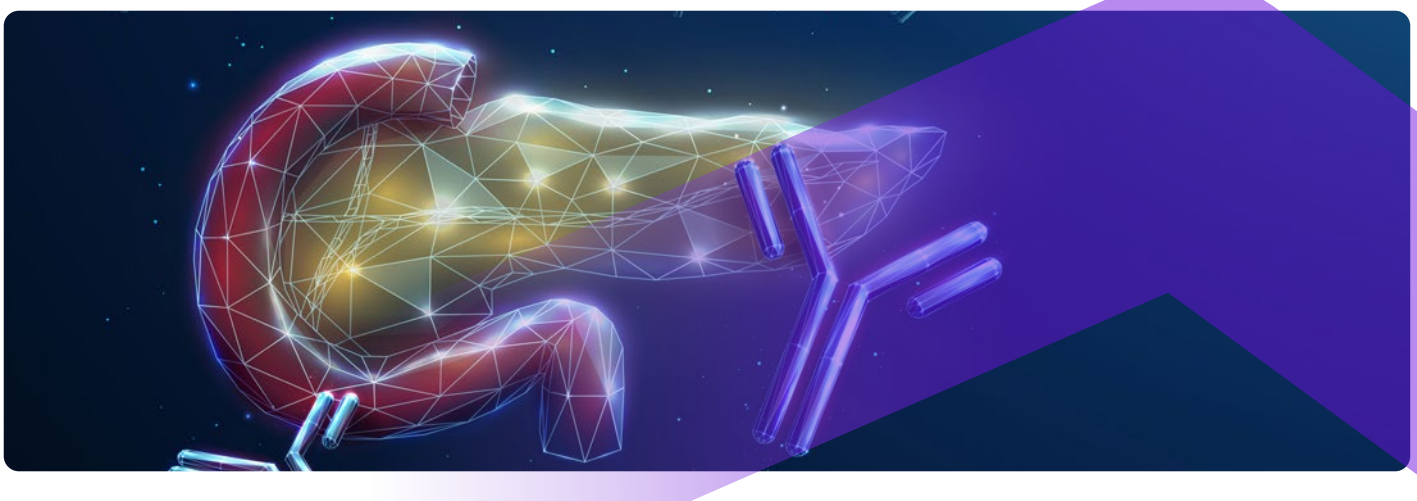
Q4 Were there any trials that particularly stood out to you at EASD 2026?

For me, it was the JAK1/2 trials, and I hope there will also be a TYK2 inhibitor trial.

One thing that was discussed quite a bit was why the disease doesn't stop once most treatments end. The most promising trials, such as anti-CD3 at Stage 2, delay the disease by 2–3 years, but the disease continues to progress afterwards. We don't really understand whether that's because the β cells have already reached an irreversible stage or other causes. New data suggest there is a class of stem-like CD8 T cells, probably in the pancreatic lymph nodes, that can travel to the pancreas and the islets and become more aggressive there. These cells may be a reservoir for the autoimmune disease, and they are very difficult to eradicate. There was a very interesting paper published on this a few weeks ago. If these cells really are proven to be the reservoir, they will be a new therapeutic challenge. You could draw a parallel with some types of leukaemia, where cells remain in the brain or bone in the skull, where treatment cannot reach them, and later restart the disease. This could represent a problem for therapy.

Q5 What's next for INNODIA?

I was one of the founders of INNODIA, together with Chantal Mathieu, KU Leuven, Belgium, and the late David Dunger. I oversaw the basic research, so the project covered both clinical trials and basic research. It was a very rewarding long-term project. We received 5 years of funding from the Innovative Medicines Initiative (IMI) and then



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3 more years, and we built a real network of people doing both basic research and clinical trials.

When the project ended, the basic research arm effectively ended too, because there was no more funding for it. INNODIA has since become mostly a structure for running clinical trials. They also advise on how to design trials and provide outstanding immunological support, with Tim Tree, King's College London, UK, Roberto Mallone, Université Paris Cité, France, and others.

INNODIA is now mainly a structure that supports, organises, and runs clinical trials, mostly sponsored by pharma, although some are also supported by T1D charities. It goes beyond consultancy, though they can do that too. They recruit patients, design and run the trial, and analyse the samples. They look not only at whether C-peptide was preserved, but also at the impact on the immune system. Very few groups can do this. They also have a network of labs across Europe that take part.

The samples are also stored in a common repository. If you want to study them, you just apply, and a small committee evaluates the request. When we started, this looked nearly impossible. It was thanks to Mathieu and Dunger that this fantastic network of clinical centres in Europe, which is still standing was created.

Q6 Where would you like to see immunotherapy for T1D in the next 5–10 years, and what role might cell therapies play?

For immunotherapies and therapies that protect β cells, I think the key issue will be combination therapies, again similar to what we see with leukaemia and cancer. I don't think any single therapy will solve the problem; we will need different therapies for different stages of the disease and to combine them. For example, one approach would be to start with anti-CD3 at Stage 2, then move to baricitinib or a TYK2 inhibitor for maintenance, and consider adding a drug to protect the β cells. That could be verapamil or one of the new drugs with a similar effect that are being developed. This will need more work.

Looking a little further ahead, I would consider targeted therapies that deliver cargo to the β cells, like we are trying to do. For this, we will need long-acting messenger RNAs or small interfering RNAs. For example, if we could block interferon signalling in the β cells only, there would be no systemic side effects such as susceptibility to viral infections, which may be a problem with long-term baricitinib use.

Cell therapy has also seen some very exciting developments. Islets from deceased donors have been transplanted into people with T1D for many years. But there are not nearly enough donors. If I'm not wrong, fewer than 5% of people with T1D in developed countries could receive a transplant. You also need immunosuppression, and the transplanted islets gradually lose function, even if they work well at first (though even a small amount of remaining function is enough to reduce hypoglycaemia).

An emerging development in this field is stem cell-derived islets. A company called Vertex Pharmaceuticals, Boston, Massachusetts, USA, has now done about 20 transplants in which stem cell-derived islets were placed in the recipients' livers under immunosuppression. In China, there was one autologous transplant: the team took cells from the patient, reprogrammed them into stem cells, turned these into β cells, and transplanted them back into the same patient. Their group gave a fascinating lecture on this at EASD 2026. The patient had already had a liver transplant, so she was fully immunosuppressed, and the team used that existing immunosuppression to implant the islets. They have been working for 1 year, and I believe they are still functioning, and the group plans to treat more patients.

"I don't think any single therapy will solve the problem; we will need different therapies for different stages of the disease and to combine them"

There is also a group led by Per-Ola Carlsson at Uppsala University, Sweden, that worked with a company in the USA to modify adult human islets so they are more resistant to the immune system. This was experimental, not curative, but the islets are still surviving 1 year later and still secreting C-peptide, as shown at EASD 2026. The amounts are small because only a few islets were transplanted, but they plan to increase the number of transplanted islets in the future.

The advantage of stem cell-derived islets is that you are not limited by the number of donor islets. You can produce very large amounts, and you can try to modify them so they are less recognisable to the immune system. I think this will be very interesting, and this is where I think the future will go. You may still need mild immunosuppression, but mild immunosuppression is much better than what we had when I was starting out.