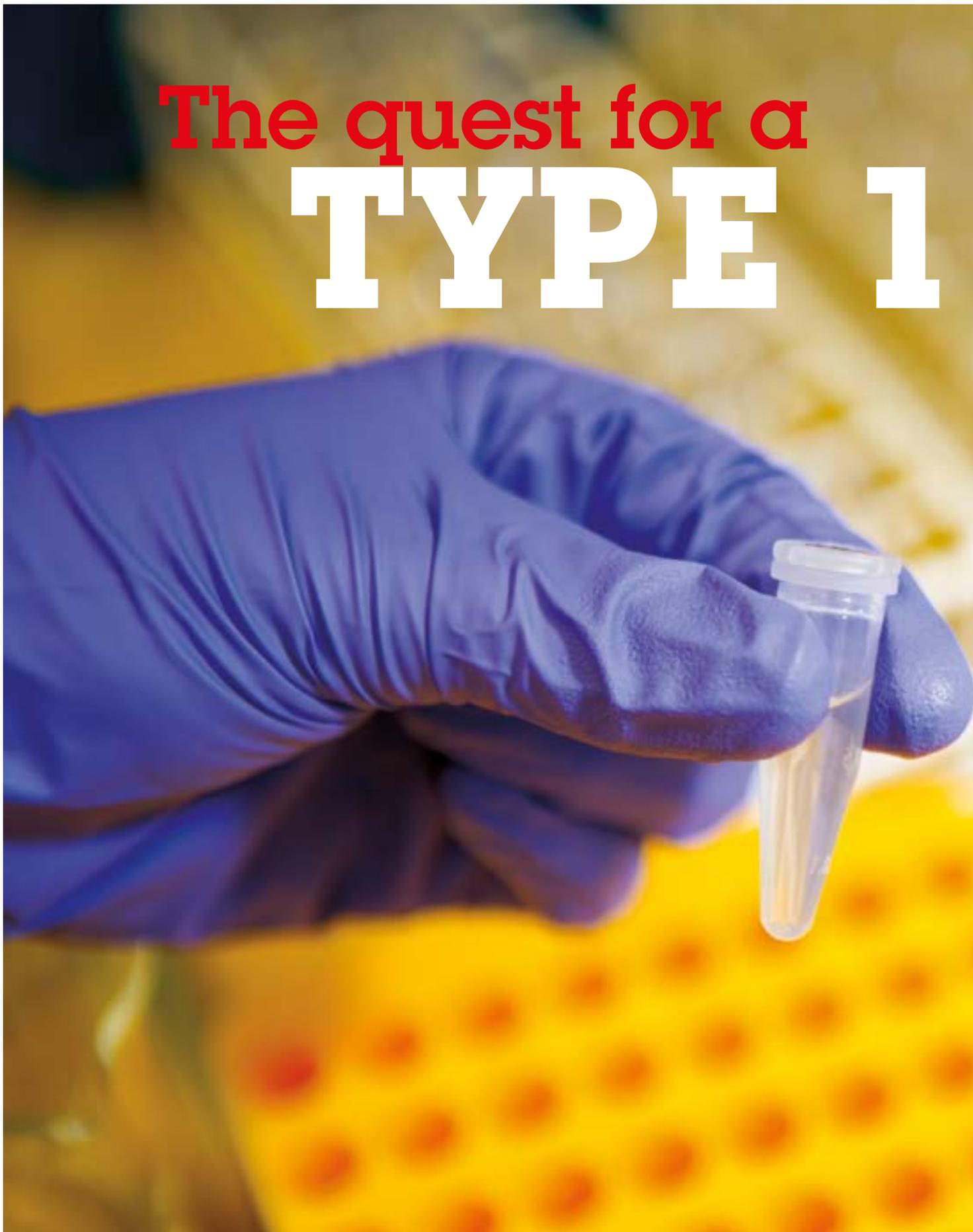


The quest for a **TYPE 1**



CURE

A cure for the autoimmune attack that destroys the beta cells in Type 1 diabetes is a distant goal, but one which could be achieved through the combined efforts of clinicians and researchers.

Colin Dayan, Professor of Clinical Diabetes & Metabolism at Cardiff University, introduces the UK Type 1 Diabetes Immunotherapy Consortium which is leading research into new immune-based therapies for the condition

Type 1 diabetes is caused by the immune system damaging the insulin-producing cells of the body. It is not known why this autoimmune process happens, but the evidence points to a combination of being born with slight changes in many immune system genes that make this kind of reaction more likely, with some events in the first year or two of life that trigger this reaction. It then takes many months or years for the damage to the insulin cells to happen – in some people 20 years or more. Researchers can detect that this process is happening and, in many cases, predict who will develop Type 1 diabetes by measuring blood levels of antibodies to the insulin-making cells.

A treatment that could slow, or even halt, the autoimmune process could delay the age at which diabetes is diagnosed. Being diagnosed at the age of 20 or 25, rather than 5 or 10 years old, would certainly have significant

“A treatment that could slow, or even halt, the autoimmune process could help to delay the age at which diabetes is diagnosed”

advantages, for the person would not have to live for so many years with diabetes and the possibility of health complications. And, if the treatment were given after diagnosis, it could make the ‘honeymoon period’ (see box, page 28) last longer, thereby protecting the patient’s long-term health.

Immunotherapy or insulin?

Over the last 20 years, a vast array of new drugs that treat the immune system have been developed and been proved effective in diseases such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and psoriasis. So why does progress on similar immune therapies seem so slow in Type 1 diabetes? The answer is that drugs that affect the immune system often also carry an increased risk of infections and possible long-term increased risk of cancer. In other autoimmune diseases, there is no other treatment, but in Type 1 diabetes, there is insulin. As is well known, many people with Type 1 diabetes live very full lives on insulin treatment for 50 or more years. So, the bar is much higher for treating the immune system in Type 1 diabetes. In short, any treatment must prove itself to be better than insulin. This is especially true of any treatment that might be given to patients in the early stages, before they actually develop diabetes.

Some progress has already been made in developing immunotherapy for



Type 1 diabetes. In the 1980s, it was shown that drugs used for kidney transplants – such as ciclosporin – could slow the loss of insulin production by the body, including in children. However, side effects, such as vulnerability to infection and reduced kidney function, meant that all the children came off the treatment within five years and the benefit was lost.

Since then, over 20 newer treatments have been tried and at least four of these have shown some beneficial effect in preserving insulin production. These include the new monoclonal antibody treatments: anti-CD3, rituximab, abatacept and alefacept. However, although almost all of these drugs are used routinely in other conditions, concerns about safety compared with insulin and a diminution of their therapeutic effect over time have delayed their introduction into routine clinical care. Lower doses have been tried to avoid side effects, with some negative results being reported in the last few years, which has inevitably led to disappointment.

The challenge

What are the barriers to making faster progress in diabetes immunotherapy? There appear to be three key obstacles. First and foremost – money. Clinical trials are very expensive. Early-stage trials, involving less than 120 patients, cost anything between £2m and £10m and the larger studies required for a drug to obtain a licence, involving 300–400 people, can cost up to £50m or even more. These sums exceed what

charities like Diabetes UK can afford and require significant government and industry investment. And, it is also becoming apparent that the requirement for careful dose adjustment and combinations of treatment to ensure the therapy is safe, and has prolonged therapeutic effects, will require many more studies to get right.

Second – these clinical trials need patients. Around 6,000 children and adults are diagnosed with Type 1 diabetes each year in the UK. To be effective, current treatments need to be started within three months of diagnosis, when there is still quite a lot of insulin being made by the body. At present, less than 5 per cent of newly diagnosed adults and children are taking part in clinical trials of new treatments – around 300 people each year – enough for two or three small studies or one large one. For more rapid progress, we need to make it possible for many more patients to take part in the research programme.

Finally, there is a need for more ‘joined-up’ working. At present, many research teams and companies are working independently, hoping that their approach will be the first to work. This means that specialised immune lab and genetic tests to determine which treatments do (or don’t) work are not always shared. There may be obstacles to drugs from different teams being used in combination, as well as competition for patients to include in clinical trials.

The Consortium

This year, a major new initiative was funded by Diabetes UK, with support

“Clinical trials are very expensive. Early-stage trials cost anything between £2m and £10m, and the larger studies can cost up to £50m or even more”

from Tesco and JDRF, to begin to bring these efforts together, overcome the obstacles and accelerate progress – the UK Type 1 Diabetes Immunotherapy Consortium. This initiative brings together five of the major centres for Type 1 diabetes research in the UK – namely, King’s College London, Queen Mary University of London, Cambridge, Bristol and Cardiff – as well as the UK Diabetes Research Network. The funding will provide for a coordination centre in Cardiff to bring together 15 highly committed hospital centres for adults and children around the UK to become expert centres for clinical trials in immune treatments for type 1 diabetes (see table, below right).

The Type 1 Diabetes UK team will train clinical staff in these areas on the risks and benefits of immune treatments and taking part in clinical trials so they can explain these to their patients, with the aim of increasing the number of newly diagnosed adults and children who take part in clinical trials by two- to three-fold in the next three years. In each centre, there will be a lead nurse who has particular expertise in immunotherapy and can support, advise and train his/her colleagues. Experience in earlier studies shows the importance of building trust between the patient and their healthcare team when recruiting into clinical trials. Well informed explanation by trusted carers is the most effective way of increasing recruitment.

Running the studies in 15 centres around the country, rather than just in the centres where the research laboratories are, will allow many more people to take part without having to travel long distances. Increasing the number of patients at each centre taking part in trials will make clinical trials both quicker and cheaper – as a lot of the cost is in setting up a centre. Cheaper and quicker studies will attract pharmaceutical companies to make use of the opportunity offered in the UK and increase the overall number of studies being performed. Coordinating Type 1 diabetes immunotherapy studies across the country will aim to ensure that all centres are operating to capacity all of the time, with one study seamlessly following on from the next.

There is also renewed funding for the ADDRESS-2 (After Diagnosis Diabetes REsearch Support System) study, supported by the UK Clinical Research Network, which currently identifies newly diagnosed adults and children from over



130 hospitals in the UK. The extensive ADDRESS-2 network will work closely with the 15 trial centres to ensure that almost all adults or children newly diagnosed with Type 1 diabetes across the UK are offered a trial they can take part in if they want to. This part of the initiative will be led by Professor Des Johnston and Helen Walkey.

A second key part of the new funding is to establish a network of the leading laboratories in the UK to share blood samples from patients in trials and ensure that all possible state-of-the-art tests of the immune system are performed on these samples. This will mean that, even if a treatment in a clinical trial is not effective or only partly effective, we will be able to understand reasons why and improve in the future.

Thus, we will be learning from failure and building on success. This mechanistic core of the UK T1D Consortium will be led by Dr Tim Tree, King's College London. These tests will be offered to pharmaceutical companies as well as university researchers performing trials, so that we learn from every man, woman and child taking part in every study.

Finally, the Consortium will train a new generation of clinical researchers and scientists in the latest approaches to immunotherapy, so that the effort will go on until the job is done.

Looking to the future?

Is effective immunotherapy for Type 1 diabetes really possible? Experience does suggest that where sufficient



T1D UK immunotherapy consortium – recruitment

Table 1: Proposed T1D Research Centres		
London (Guy's)	Birmingham	Sheffield
London (QMUL)	Chester	Swansea
London (UCL)	Liverpool	Exeter
Cambridge	Oxford	Dundee
Cardiff	Newcastle	Bristol

Table 1: T1D Research Centres that will run studies locally and recruit from regional PIC sites. Colour coding is below:

Adults	Children	Adults & Children
--------	----------	-------------------

The Big Collection helps fund Type 1 research



Professor Colin Dayan



resources are well targeted, remarkable results can be achieved. For instance, treatment of acute leukaemia and other childhood cancers and HIV/AIDS have been transformed in recent years from universally fatal diseases into long-term manageable, or even curable, conditions. In fact, new cases of acute leukaemia in children are rarer than new cases of Type 1 diabetes. As a result of a large number of studies that recruited high numbers of patients with acute leukaemia, more than 80 per cent of children with this once fatal disease can now expect to be cured.

We say that if this can be achieved in one condition (leukaemia), then it can be done in another (Type 1 diabetes). We can also take heart from the fact that the UK is not alone in this quest. There are initiatives in Type 1 diabetes immunotherapy in other countries – most notably the Diabetes TrialNet network in the USA, which has centres in Europe (www.diabetestrialnet.org). The UK has the advantage of being ‘small, but perfectly formed’ – small enough to move live cell samples for studies between centres within the same day, making it possible to do complex immune studies that are difficult to do on frozen samples. By bringing us all together to maximise our effort – patients, families, doctors, nurses, scientists, universities, funders and companies – we have an excellent chance of developing new treatments that can make the honeymoon for patients with diabetes last longer and longer.

PHOTOS: DIABETES UK

“We can also take heart from the fact that the UK is not alone in this quest. There are initiatives on Type 1 diabetes immunotherapy in other countries”

TARGETING THE HONEYMOON PERIOD IN TYPE 1 DIABETES

A major focus of Type 1 diabetes immunotherapy research is the ‘honeymoon period’ experienced by those newly diagnosed with the condition. Controlling blood glucose in Type 1 diabetes is not easy. Although there have been major advances in blood testing and insulin delivery technology, it still requires a lot of effort and dedication to achieve tight control of blood glucose levels. Indeed, it is so hard to achieve this control that, across the world, less than 30 per cent of people with Type 1 diabetes are able to achieve ideal levels of blood glucose. How can we make it easier?

In the first few months after diagnosis, many people with Type 1 diabetes find that blood glucose control is not so difficult and more than twice as many people manage to obtain their blood glucose targets then, than later after diagnosis. This is because most people still have some of their own insulin production capacity from the pancreas left at this time. Although it is only a small amount, it is released after a meal and switches off automatically when the blood glucose is low. It is rather like power-assisted steering in a car – you still have to steer, but it is a lot easier and smoother than if there was no assistance. However, over the next few months and years, almost all of this last part of insulin production by the pancreas is lost, and blood glucose control becomes more difficult, with more lows and highs. This period soon after diagnosis has been referred to as the ‘honeymoon period’, and some people may even not need any insulin injections for a short time. In diabetes immunotherapy research, a major goal is to make the honeymoon last longer, both by understanding it better and targeting patients for treatment when they are still in this state.

NEW

QUALITY you can trust

QuickLink™
Download to
Free App



The Only Sub £10 Test Strip with:

- Accuracy Exceeding all International Standards
- Contactless Download for Better Diabetes Management
- The Finest Ultra-Thin Lancet
- Best in Class Features, including DVLA Memory

GlucoMen®
AREO



30 YEARS IN DIABETES CARE

UK wide support for HCPs and patients

Call: **0800 243667 (0118 9444128)**
Email: **glucomen@menarinidiag.co.uk**

Or speak with your local
GlucoMen Diabetes Support Specialist