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Q1 What led you to a research career focusing on diabetes, specifically exploring the multifaceted nature of the immunopathology of Type 1 diabetes (T1D) in the pancreas?

A career in research had never been something I had considered, and I came to it quite late: having had quite an itinerant youth, settling on being an artist in my mid-20s and then beginning my family, I did not begin formal study until I was 39. I began with a few short Open University (OU) courses and found that I loved learning academically! In a twist of fate, at this point, both my daughters' lives suddenly changed due to health issues, and as a working single parent with little time, I was faced with a stark choice: give up studying, or get a grant and a loan and commit fully. I talked to my daughters and picked the latter! So, I suppose back-handed serendipity led me toward a career in science, and to believe that anything can be possible, a belief I now share with my girls.

Within 18 months, I had attained a first-class honours BSc in human biosciences, developed a passion for immunology, and a love of being in the laboratory, chasing down my curiosity. So, when Noel Morgan (now of the University of Exeter, UK) advertised a funded PhD focusing on viruses in T1D degree, and having heard him lecture with what I know now is his distinctive warmth, humour, and clarity, I jumped at the chance to apply, little believing that the opportunity would develop into my dream job, and an exciting career! At the time, I knew very little about T1D, but the more I learned, the more I discovered in the pancreas, and the more I worked with the amazing researchers in the field, the more embedded and committed I have become.

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So, I guess abstract curiosity led me here, but the diabetes community and my amazing colleagues are what keep me in a career focused on exploring the immunopathology in T1D.

Q2 Your research team recently proposed that two distinct forms of T1D exist. Can you briefly explain the work that led to this discovery?

Diabetes is diagnosed when a person can no longer produce sufficient insulin to maintain their body's glucose homeostasis, and over the years, we have discovered that this can have many causes, including different genetic components, the impact of lifestyle choice, and initiating triggers of disease.

In T1D, this dysregulation is driven by an autoimmune-associated destruction of the insulin-producing pancreatic β-cell; however, studying these cells and the processes that destroy them *in situ* in living humans is not yet possible. This has hampered efforts to characterise the triggers and processes associated with the induction of T1D. To address this barrier to our understanding, and because the organ is challenging to access, pancreatic researchers mainly focus on samples collected

and preserved after a person's death (collected during an autopsy initiated to discover if diabetes is responsible or, if granted, at the time of organ donation). Thankfully, the samples collected close to diagnosis in children are now very rare, but they are critical for understanding how the condition manifests in humans, which we now know is significantly different to the model systems we also use to study T1D.

So, to answer your question, the work that led up to our discovery was facilitated by the privilege that we are the home of an archival biobank of the rarest of these pancreatic samples (the Exeter Archival Biobank [EADB] collection). These are so particularly rare because the collection was compiled many years ago by Alan Foulis, a Scottish pathologist, who had the foresight to collate pancreas samples collected from children who had sadly died at, or not long after, a diagnosis of T1D. Using these samples, the Morgan/Richardson laboratory devised a method of studying islets at different stages of β-cell loss in a given individual's pancreas by leveraging the fact that islets are not attacked simultaneously. The team used this phenomenon to piece together 'processes' in the fixed tissue in much the same way as you might think of making a stop-motion movie, ostensibly concatenating fixed 'time-points' of data collection along the trajectory of destruction in the islets before, during, and after the inflammatory process. The team pooled their data from several individuals, and, for the first time, could describe the influx and efflux of the immunological culprits involved during the targeted destruction of β-cells.

My first task as a PhD student was to examine if the immunological sequence of β-cell destruction observed in the EADB collection was mirrored in similar pancreas samples that were becoming available in geographically distinct cohorts (the USA and Norway).

However, I soon started spotting unexpected patterns in immune profiles and β-cell behaviour between individuals in each cohort, including the EADB collection. These observations then

became the focus of my PhD, in which I proposed the novel idea that two distinct immunological phenotypes of immunopathology occur in the pancreas of individuals with T1D. One is a B-lymphocyte enriched CD20 'hyper-immune'-profile, nearly always associated with an early age of diagnosis and very few β-cells at the time of diagnosis, where B cells appear to play a significant role in β-cell destruction, versus a second CD20 'pauci-immune' profile, which contains few B-lymphocytes at the islet margin, less β-cell destruction at diagnosis, and is much more often found in those diagnosed beyond their mid-teens.

At this point, heterogeneity in T1D was not discussed as much, but as probably the most extensive study of insulitis ever undertaken, this work highlighted the importance of B-lymphocytes as potentially key drivers of immune aggression in T1D, and has contributed to the growing awareness that immunological heterogeneity and the impact of age at diagnosis is critical when considering disease trajectory.

More recently, realising that some people (those with the CD20 pauci-immune-immunotype) still had significant β-cell mass at diagnosis, despite an absolute requirement for externally administered insulin, I became curious about the role that the islets themselves might play in their own survival between these two different 'forms' of immune attack. Inspired by differences in the staining patterns of insulin in our samples and by work done by Emily Simms (Indiana University School of Medicine [IUSM], Indianapolis, USA) on proinsulin signals in the blood, Clemens Ziller (a second year medical student and co-author on the paper) and I started looking at proinsulin processing in the pancreas, and in collaboration with our clinical colleagues at Exeter, we then found that the immunotypes correlated with phenotypically distinct errors in proinsulin processing between individuals.

Therefore, my recent proposal that endotypes exist in T1D is built on many years of studying the pancreas in these rare, beautiful, and tragic samples, which I believe still have much to tell us.

Q3 As a recipient of a Diabetes UK RD Lawrence Fellowship, where can we expect to see your focus lie in the near future?

I am so grateful to Diabetes UK, and their donors and supporters, for this opportunity to develop a team that will continue to strive to unravel at least some of the heterogeneity we see in T1D, and develop the skills to make this complex-sounding science accessible to people living with the condition. I hope that by further targeted exploration of the pancreatic landscape and employing new tools and technologies, we can unveil some of the drivers that ultimately lead to a diagnosis, maybe even suggesting paths to try to prevent them.

We live in exciting times for research, where new technology and data capacity can be employed to integrate all sorts of research modalities, meshing studies that are undertaken in more malleable systems, such as rodent, zebrafish, and cell models, with the work being done with human samples providing tools to deliver an ever more detailed understanding of the biological processes that contribute to T1D, and potential to halt them. I hope that I will also have a voice in advocating to improve our understanding of T1D in the pancreas in all communities; for example, we do not know what diabetes looks like in the pancreas in Africa, which may be important when we consider that the early initiating environmental triggers are likely very different.

Q4 What were the main conclusions of the highly cited paper that you co-authored, called 'Detection of a Low-Grade Enteroviral Infection in the Islets of Langerhans of Living Patients Newly Diagnosed with Type 1 Diabetes?'

Because the pathology in the pancreas starts so long before we can detect the dysregulation of glucose homeostasis, we are still looking for triggers in T1D. In this particular paper, our main observations in the pancreas were that a viral infection is more evident in the β-cells of people diagnosed with T1D than those without diabetes but, rather than an acute and aggressive lytic β-cell infection by virus, the authors proposed that the infection may be a slow and persistent low-grade infection, potentially explaining the protracted, peripherally undetectable pre-

diagnostic β-cell loss from the islets. One clue that this protracted viral insult is ongoing can be seen in histopathological investigations (such as that undertaken by Sarah Richardson, University of Exeter, and her colleagues), where the hyperexpression of human leukocyte antigen-1 (a protein that is critical in our immunological tolerance to self, and our battles with intracellular pathogens) is upregulated in all pancreatic samples from individuals who had a diagnosis of T1D and who retained some β-cells. However, this normal antiviral response may also be responsible for recruiting and activating the army of aberrant auto-immune cells that wreak havoc in the islets, ultimately leading to β-cell loss and diabetes onset.

With the recent news from the co-authors of this paper in Norway that antiviral therapies can delay the progression of T1D, I think there is still much to unravel in the virus story, particularly if the virus may be a trigger in some people but not in others.

Q5 You are committed to improving societal equity and education, while supporting a growth mindset for students and colleagues. How do you bring these qualities to your role at the University of Exeter?

Idealistically, societal equity, access to healthcare, and education for all are key aims for any society, and maybe naïvely, I also see having a positive, hopeful growth mindset as critical for creative problem-solving. But many of our communities are battling anxiety and mental health concerns. With budgets shrinking, and the world seemingly becoming an increasingly more complex environment to navigate, I try to offer a space for anyone who needs to be seen, heard, and cheered on to come and talk to me. I truly believe and advocate for the idea that a diverse but cohesive population, combined with a growth mindset based on kindness, hope, and curiosity is our best way forward, particularly if we hope to solve some of our seemingly most intractable problems.

I think my eclectic life journey has given me an unusual perspective, and the advice, or space to explore, that I offer often includes taking some time each day to just look at the sky, or a leaf, or your loved one's face, and invite the question: "Anything is possible. You just have to remember to ask: is worth it?" Mostly, I try to remain cogent that everyone's story is different, and, when I am asked for my thoughts and opinions, I try to hold the space for an understanding that we are all trying our best to navigate our lives, and each has something meaningful to contribute to the biggest pictures.

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Q6 What do you believe to be the current gaps in diabetes research, and which topics merit greater attention?

With the advent of the teplizumab licence, there is so much to celebrate. The first U.S. Food and Drug Administration (FDA)-approved therapy proven to slow (and maybe, in some people, even prevent) the progression of T1D, with the newly released news showing that it is safe to use in young people, and can slow the progression of the condition. People affected by T1D have waited so long for this win.

However, there are still gaps in our understanding of what makes T1D so heterogeneous, the trigger(s) that lead to β-cell targeting and loss, and why some people seem to have lots of residual β-cells, but none of their own circulating insulin. Is the environment impacting differently on individuals? Is the age at which a person encounters, or succumbs to, the initiating trigger the differentiator? Or is there something more fundamentally different in the biology of subgroups of individuals? When we understand this, we can start looking for diagnostic markers in a much more focused way.

Q7 You also specialise in microscopy imaging and data analysis. How important are these skills in your research career?

The significance of the technical advances in research methodologies, data capture, data science, and data sharing cannot be understated, and the recent step changes in the microscopy and imaging field have been huge in the last few years. We are now garnering rich and complex histology-derived datasets with thousands of data points from each individual staining experiment. These advances also offer the potential for cross-disciplinary research, which is increasingly commonplace. I am fortunate to be now working with and learning from image-data specialists and mathematicians, to pull apart the nuances in my ongoing observations.

But it all starts with the staining, the pictures, and the pattern spotting; and so, microscopy remains at the heart of my work.

Q8 Over the years you have been researching within the field of diabetes, what are the most significant changes you have observed in the field?

As I said, teplizumab, of course, is huge, as are the huge advances in the technology available for people to use to manage their condition, such as continuous glucose monitoring and closed-loop systems.

It has also been deeply powerful to increasingly hear the voices of lived experience in research settings, conferences, and grant panels. This feels incredibly important.

And, although nowhere near as significant, I am also told by the people who live with T1D, that it truly matters when they discover their personal heterogenous 'version' of T1D may be responsible for the clinical differences that they experience, rather than something that they are doing better or worse than their peers. I am sure this was happening long before I started my PhD, but this is what keeps me going. It is a really exciting time to be a researcher in T1D. I continue to feel incredibly privileged and grateful for my days.