What initially inspired you to work in the emerging discipline of stem cell biology?

My doctorate thesis attempted to establish how the liver progenitor cell (also referred to as the hepatic oval cell) becomes activated into proliferation and differentiation. As I was working on this, Dr Julie Goff – a close friend and colleague of mine at the University of Pittsburgh – and I were working on another project, and she was teaching me the ins and outs of the haematopoietic stem cell world. At some point we started to notice the similarities between the two cell populations in terms of their expression profiles and asked each other: “Could they be the same cell, or at least come from a similar source?” We set out to test that theory, and several years and experiments later were fortunate to be the first ones to publish it.

You have spent most of your career studying the liver, how easy has the transition into pancreas and diabetes research been?

The transition to the pancreas has been fairly easy, but understanding diabetes and all that goes with it has been somewhat challenging, particularly the immune response brought on by the disease. Maybe that’s why I think our islet homeostasis protein (IHoP) is so important, because I don’t have the preconceived notions that a person in the field might have. I’m looking at it from the outside-in and in some cases a new perspective is what it takes to move the field forward.

One of your research projects is investigating anti-fibrotic drugs; what are the mechanisms by which connective tissue growth factor (CTGF) stimulates liver repair, and how is this knowledge contributing to these efforts?

CTGF is a strong player in the TGF-β pathway and our previous research has shown that it is required to activate the hepatic oval stem cell compartment. However, its importance is more for the fibrotic side of things, and by attacking this protein we hope to break the extracellular matrix production in this process, thereby allowing the liver to repair in a normal fashion. The liver is an extremely exceptional organ when it comes to regenerating itself, not in the way a salamander does when it regenerates its tail, but a type of regeneration called hyperplasia. The liver will grow back to the same weight and size, but it will not look quite the same. If we can block the fibrotic pathway, the liver will take care of the rest and repair itself.

What have been some of your biggest career challenges and highlights?

Our data show that type 1 diabetes uses the immune system as a secondary reaction brought on by the overexpression of IHoP, causing the insulin-producing β-cells to die (a process termed apoptosis). This potentially game-changing concept challenges the 60-year-old dogma that type 1 diabetes is an autoimmune disease, and as such getting our IHoP paper accepted has been my greatest challenge.

This might sound a bit altruistic, but every student I have graduated and walked across the stage for their hooding ceremony and every postdoctoral researcher that has come to me after getting their first faculty appointment is what I get the most gratification from. The science is what it is, but giving the next generation of researchers the tools for success is my ultimate goal and greatest pleasure.

Do you see any of your work being translated into clinical practice for patients with diabetes or liver disorders in the near future?

I remember reading or hearing that less than 1 per cent of all research being done today will make it to the clinics. With this in mind, having a portion of my research make it that far is the eventual objective.

Our IHoP and CTGF work could make it there sooner rather than later (maybe within the next two or three years), because there are drugs on the market that could be used in an off-label fashion, but time will tell. In addition, I hope that the bioengineering project I have underway makes it there within the next five years or so, but there are still a lot of hurdles to overcome. Meanwhile, our gene therapy approach is already in trials; using the stem cell component is a new twist, but our previous reports show promise.
DESPITE HUMANITY’S ENORMOUS progress in technology and medicine, in many areas we remain bettered by biological systems. Through being inspired by, and making use of, solutions originally found in nature, numerous disciplines are making great progress, including nanotechnology and materials design. This situation is especially pertinent in medicine, as the human body’s incredible capacity for self-repair remains vastly superior to many of the most advanced medical techniques.

Clearly, a huge step forward could be taken in medical care if researchers could intelligently co-opt the self-healing capacity of the human body and direct this powerful mechanism to repair damage that it is unable to naturally.

INSPIRATION FROM BIOLOGY

The most exciting work being done on this front is in stem cell research. Stem cells are the body’s natural reconstruction mechanism—they are able to proliferate and specialise to do one of many possible jobs in the body, becoming anything from spermatozoa to heart muscle cells. Professor Bryon Petersen is a leading researcher in this field, heading a group at the University of Florida that is currently pursuing an array of ambitious projects. Petersen made his name in 1999 with a paper published in Science that demonstrated the plasticity of bone marrow cells—showing it is possible for them to differentiate into epithelial cells. This was one of the key papers in the development of modern stem cell research, as it indicated that stem cells are able to transcend their bodily source and develop into cells of an entirely unrelated type; its 3,000 citations are testament alone to its impact.

Petersen has since built upon this success, and currently heads four active stem cell initiatives. The first is a combination of stem cell research with another very exciting field of medical research: gene therapy. This area is based on the idea of transporting new genes into the nucleus, through the use of a packaging vector, in order to replace mutated genes and encode new proteins that are expressed in a therapeutic way. Gene therapy has only recently taken on clinical relevance, with the first treatment approved for full use as recently as 2012. Petersen’s team aims to use these novel techniques to modify stem cells and treat liver diseases such as Crigler-Najjar syndrome and glycogen storage disease. Both are incredibly damaging conditions, and this Florida group is aiming to develop the first effective treatments for them, short of full liver transplantation.

The second project involves work on diabetes. Returning to the earliest theme of his work, Petersen is investigating whether bone marrow stem cells can be differentiated into the insulin-producing cells needed by diabetes patients. The team has already had some success in using this method to fully cure hyperglycaemic mice within 35 weeks of treatment, and in doing so discovered a new protein termed islet homeostasis protein (IHoP), which could be a future target for potential type 1 diabetes treatments.

PSEUDO-LIVERS

The team’s third work packages exemplifies the idea of medical techniques inspired by biology. They have developed a novel technique for decellularising porcine liver tissue in which a series of detergents are added to living tissue, disrupting cell membranes and causing them to burst. The remnants of these cells are then washed away by the further addition of detergents. This process leaves behind the extracellular matrix, a system that supplies cells with structural support and transports chemicals between them. This matrix can be
Stem cells in action

The adaptable nature of stem cells means that the work being undertaken in Professor Bryon Petersen’s lab has the potential to treat a great selection of truly debilitating diseases, especially those affecting the liver – an organ often noted for its complexity.

**FIGHTING FIBROSIS**

The fourth goal of Petersen’s lab involves the treatment of alcoholic liver disease through targeting fibrosis – the formation of excess fibrous connective tissue in the liver that often results from excessive alcohol intake. This condition develops after alcohol has damaged the liver, and can progress onto liver cancer and cirrhosis if left untreated. It is therefore important to treat fibrosis while it is still reversible. The researchers discovered the role of connective tissue growth factor (CTGF) in liver repair. This biochemical was found to regulate transforming growth factor (CTGF) signalling pathway, and thus slow fibrosis. This project is only in its early stages, but initial tests are positive.

Three decades in, stem cell research still generates a huge amount of excitement, both in mainstream media and within the scientific community. Taken as a microcosm of the field, the work done by Petersen’s lab demonstrates why this is. Each of this group’s projects provides promising avenues to potential treatments for complex diseases that currently lack satisfactory treatments. These diseases range from those that are widespread and relatively manageable to rarer conditions that are nevertheless highly deleterious to quality of life. Petersen says his main ambition is for this research to become clinically realised and, with such a range of exciting projects in the pipeline, it seems likely that his dream could soon become a reality.