INTERVIEW

Dr James Shapiro:
the hype, hope & reality of cell therapy for diabetes

Dr James Shapiro was born in Leeds, England, son of a family doctor. He studied Medicine in Newcastle and trained in Surgery in Bristol. He developed a longstanding interest in islet transplantation as a medical student. He has been on Faculty at the UofA since 1998. James led the team that developed and tested the "Edmonton Protocol" and was the lead author on their seminal NEJM paper in 2000. This protocol revolutionized the treatment for Type 1 Diabetes, as for the first time a series of patients were able to completely stop their life-sustaining insulin injections. He is currently leading a National Canadian project in ex vivo organ transplant repair and has active clinical trials in Edmonton evaluating caspase inhibitors and new subcutaneous devices for islet transplantation. He is leading diabetes clinical trials in stem cell transplantation and regenerative medicine.

Q Diabetes affects over 400 million people worldwide and represents a huge financial burden to healthcare. Insulin treatment has been the standard of care for many years now. Can you tell us about the limitations of this approach to disease management?

Insulin is a palliative treatment for a condition that would otherwise be fatal. It saves patients' lives and allows them to function in most day-to-day situations. But ultimately it doesn't cure the condition or prevent the secondary complications of diabetes, which are deadly: blindness, end-stage kidney disease that requires dialysis or kidney transplantation, possible amputations, heart disease and strokes. Diabetes still creates havoc for a patient long term, despite insulin therapy. There have been a number of improvements in insulin, particularly in the past 5 years or so for example in the way it's delivered through insulin pumps and through improved

monitoring with continuous glucose meters in select patients. There is a possibility that these two approaches could be combined to act as a bioartificial pancreas so that the amount of insulin needed more closely matches what the body requires; however, there is still much work required here and it is still very much an imperfect science. Normally the pancreas makes the exact amount of insulin you need when you digest food. If your blood sugar moves up a fraction, the pancreas makes the exact amount of insulin needed to bring it down. As soon as that's done, it shuts off. It's a very dynamic, real life circuit.

For someone with diabetes, suddenly you have this huge hysteresis. Unfortunately, when you inject insulin under the skin it is simply impossible to precisely match this release and quantity exactly to what the body requires over the course of a meal. The patient with diabetes will try to adjust their insulin based on what they eat and their exercise but it is such an imprecise science that it can be nearly impossible to get right. As a result, the hemoglobin A1c – which is a measure in the bloodstream of how close someone has control of their diabetes – is very rarely found to be equal to that of someone who has normal A1c. The higher above normal the more likely you are to get the secondary complications such as accelerated retinopathies or blindness complications.

Q Islet transplantation was first considered as a new therapeutic approach in the 1980s and you led the development of the Edmonton protocol in the 1990s for the use of this transplant treatment for type 1 diabetes. Could you provide us with an overview of this protocol?

Islet transplantation before the Edmonton protocol had been practised around 350 times and it wasn't very successful. Only 8% of patients were able to come off insulin for periods of time and virtually none were long lasting in duration. It wasn't a very exciting field to be in and people were not particularly enamoured by it.

I was asked if I wanted to lead the Edmonton team, back in 1998 when I came on staff as a transplant surgeon. In taking this on, I spent a PhD studying islet transplantation and my approach was to make a lot of changes all at once to the way things had been done previously in an attempt to really see if this approach could provide long-lasting solutions to diabetes patients.

The Edmonton protocol was not the most rigorously designed scientific study. Normally you would have a control group and a treatment group, changing a single variable. We changed around seven or eight variables all at once: adding fresh islets, not cultured, not frozen. They were immediately prepared and injected in the radiology suite by nonsurgical means to deliver the cells. We were prepared to give a second transplant and potentially a third very shortly after the first one if the patient needed it in order to provide enough cells to enable engraftment. Then we changed the anti-rejection drugs which at that time was unorthodox. The mainstay anti-rejection treatment was based on steroids and having reviewed all the experimental data we felt that a steroid would be bad for a patient with diabetes and with islets trying to work because

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the steroid actually makes you insulin resistant. They are also not very effective at preventing rejection. We changed the drug cocktail to include a compound that had very rarely been used in clinical practice: sirolimus/rapamycin. Our approach involved the administration of sirolimus and tacrolimus in combination, which was discouraged as both of those drugs act through very similar mechanisms.

However, it turned out to be much more successful than we had ever dreamt. We performed the islet transplantation in seven patients and at the end of the initial follow up period, all seven patients were insulin free which had virtually never happened before with islet transplantation. At the time, I was busy starting a clinical practice as a transplant surgeon and was busy up all night performing surgeries and as such I don't think that I fully understood the implications of what we had achieved. We published the data and procedure in the *New England Journal of Medicine* and it generated a great deal of interest. The switchboard in the hospital was jammed for three days with patients calling from all around the world wanting to get on the transplant list. It immediately changed all of our lives as people were suddenly interested in this little city that no one had heard of before – Edmonton.

Q What have been the main outcomes of this implementation today and how has it been evolved over the last 15 years?

The procedure has evolved enormously. The first step was to expand the experience locally, nationally and internationally. We worked with the immune tolerance network, which was a government-funded organization in the USA and we carried out a 10-center replication of the original Edmonton trial. We observed a spectrum of outcomes. Some centers that had experience in making islets and with administering the antirejection drugs did very well; however, some centers had never really seen an islet before and didn't know how to dose the drugs, and as such we saw poorer outcomes. The centers with the most experience had identical results to those we had achieved.

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The second phase was to convince the government in Alberta that this was a treatment that could be transitioned over for use in highly selected patients with unstable type 1 diabetes, and they immediately agreed to fund it as part of clinical care exactly the same way they have funded liver or kidney transplants. We were very fortunate in 2001 when the government invested in islet transplantation as a non-research tool. It doesn't mean that we haven't continued to do research, we have intensively in fact, but it's been

very helpful to have the islet manufacture covered and the patient care cost covered for the standard treatment approach.

More recently, other groups have continued to develop and improve the Edmonton protocol, for example Bernard Herring in Minnesota published results from islet transplantation in a series of patients in which they achieved much better single donor to recipient combinations through use of a drug called thymoglobulin which acted as the induction antibody, together with sirolimus and tacrolimus. We also worked with the NIH to carry out a registration trial with the FDA. Working with all the centers involved and with the islet transplant consortium, our endpoint goal was to keep A1c levels at 7% in unstable type 1 diabetes patients. The FDA didn't require patients to be off insulin, they felt it was more important that the A1c levels were stabilized, thus demonstrating that we could potentially reduce the risk of complications and protect patients from severe hypoglycemia which they faced on a daily basis. We successfully met the criteria the FDA required and a registration trial has been completed now, CIT07, and another trial after kidney transplantation is also nearing completion. The FDA is reviewing that data now and we'll very likely provide a biological license for islets in the USA. That's important because many of the centers in the USA have been very dependent on research funding to move forward. While we've continued in Edmonton and carried out over 516 islet transplants now, since 1999, some of the centers in America were able to participate in these trials for a while but then have slowed down on activity based on the lack of funding. The biological license will be an important key to unlock routine funding in the USA which will allow more routine islet transplants to be carried out.

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Q Recent research is looking at the defining the ideal implantation site. What are your thoughts on some of the outcomes we are seeing from alternative sites?

We are definitely interested in identifying the ideal implantation site and have been involved in a number of these studies. The portal vein has been tried and tested since the 1970s as the one site that can allow islets to engraft and function, thus enabling patients to come off insulin. With the portal approach, almost 60% of patients remain insulin-free with our newer protocols after 7 years.

The reason as to why we are now looking at other sites is two-fold. We know that when we transplant the islets into the portal vein, a large proportion of the cells do not survive the first few hours of implantation. All the success and function we see is based on the

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small number of cells that actually end up engrafting. Therefore, if we were able to get more cells to engraft at the outset then we would have even better outcomes.

If we have new cells, such as embryonic stem cells that have an unknown safety record or a safety record that is in evolution, what's the risk of a teratoma, malignant transformation, or uncontrolled hypoglycemia developing? It would be unwise to put those first-in-human cells into a place in the body that didn't facilitate easy removal if required. If you want to take out cells from the liver you have to do a liver resection or a liver transplant. That would be a big operation for somebody who didn't need it.

When we look towards the future and towards alternative cell therapies, we think that it's probably important to find other sites that at least can be a testing bed before we go back into the liver. I actually think the liver is quite a good site and I think it could be improved further but there clearly are other alternative sites. For example we've been looking at the lining of the stomach, the gastric submucosa, in collaboration with the University of Pittsburgh although it is too early to say whether this will be successful or not.

We are also testing the skin as a potential implantation site. We have conducted a trial with Sernova Corporation (Ontario, Canada) to assess their implantation device. Their device goes under the skin leaving rods under the skin for about a month where new blood vessels form, after which you take out the rods from the middle and put the islet cells in. We can get cells to survive in there, but it is not clear yet as to whether they are functioning quite as well as they would in the portal vein.

Experimentally in the lab, we have developed a further modification of this approach with what we call the device-less approach whereby we place a simple plastic catheter, that's already in routine clinical use, under the skin and leave it there for a month. After which time, we remove the catheter and find that there lots of new blood vessels that have grown into that space and we can put islets or stem cells in there, and they engraft very efficiently. We haven't tried that in patients yet but it would be very easy to move this approach forward.

Q You mentioned a little about new emerging cell therapies with the advent of human embryonic stem cells and now, more recently, iPSCs. What are the new opportunities arising for different cells types in diabetes?

There's a lot of hype, a lot of real hope and a lot of hard work ahead to move therapies that look very promising into clinical practice. There are hESCs that have been coaxed into essentially being islet precursors: polyendocrine cells; this has been carried out by at least three groups – Doug Melton (Harvard University, USA), Tim Kieffer (University of British Columbia, Canada) and the company Viacyte (California, USA) with whom we have worked very closely over the last 12 years.

The Viacyte cells are now in clinical trial and testing and we are fortunate enough to be one of the clinical centers involved. The idea with this approach is that the cells are encapsulated in bio-membrane that prevents cell-to-cell contact. The hope is that we could carry out a successful transplant without needing the antirejection drugs. That's one of the key drawbacks to islet transplantation that remains today: the need for antirejection drugs. Anti-rejection drugs have a number of side effects, they suppress the immune system, they slightly increase the risk of certain cancers, certain infections and, in theory, could be life threatening. As such, we don't routinely offer islet transplants in children or patients who have good control of their diabetes; however if we could remove anti-rejection drugs from the equation, that would be a huge advance.

The big question is whether it's the right thing to move forward with cell encapsulation technology that prevents cell-to-cell contact, coupled with the use of stem cells. Yes it creates an opportunity but it also creates challenges because you now have two unknowns in the treatment approach. If it all works it will be fantastic but I suspect it will require a lot of iterations to refine the first-in-human trials to drive forward with this potential cure.

Q Has there been much interest and investment from Big Pharma and biotech companies within this particular field?

There is certainly interest but not so much in the islet cell transplantation side of things. That might well be a reflection of our decision early on to make the protocols for islet transplantation freely available. We were very open with our techniques for implanting the islets and the clinical protocols involved.

I think Big Pharma recognized early on that if we were just concentrating on islet transplantation for diabetes there wasn't going to be a huge market. It wasn't going to be applied all 400 million patients with diabetes. There wasn't going to be a treatment like that, it was going to be seen as an orphan indication for a selected number of patients with difficult-to-control diabetes, so about 5–10% of the population with type 1 diabetes.

If you look at stem cells and the possibility of applying that across the board in all forms of diabetes – type 1 and 2 – and if you could do that without anti-rejection drugs then suddenly the market explodes and becomes huge. There is enormous interest in the investment space in stem cell technologies that are currently available. There are companies popping up all over the place that have a potential cell which may have some capacity to make insulin. The key is whether these groups can generate robust data and demonstrate wheter these cells are really capable of making sufficient amounts of insulin needed to cure a patient with diabetes; if they are they safe – are they going to generate teratomas or some other adverse effect

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that we weren't expecting; are they going to cause hypoglycemia – uncontrolled release of insulin. All of these need to be tested in clinical trials so we need pharma and investment in this now because the clinical trials moving forward are expensive.

Viacyte, for example, has had enormous support from the California Institute for Regenerative Medicine and the Juvenile Diabetes Research Foundation as well as additional private investors. I think several companies are in the same boat right now. There is enormous opportunity ahead and these really are very exciting times - finally, I can say after watching this space for 15–20 years or so, I've seen islet transplantations move forward from experimental to routine care for highly selected patients.

With stem cells, we are finally seeing a move into the clinical arena and the very early results in patients look promising. It's still too early to say whether it will work at this point but there's real hope there.

AFFILIATION

Prof. James Shapiro,
Clinical Islet Transplant Program,
University of Alberta and Capital Health Authority,
Edmonton, Alberta, Canada.