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Living Cell Technologies: Finding a path to market for xenotransplantation therapy

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Living Cell Technologies: Finding a path to market for xenotransplantation therapy

Case Profile

This case examines the research commercialisation process of biotech company Living Cell Technologies (LCT). The case outlines the process of pre-clinical and clinical trials undertaken by the company as they moved towards commercialising their pig islet cell treatment for Type I diabetes including the R&D and manufacturing capabilities the firm has developed. Also, the case describes the challenges in bringing a sometimes controversial biotech product to market, including regulatory hurdles; rapid changes to legislation; the impact of public opinion; and the difficulties in raising capital, maintaining cash flow and developing a pipeline of opportunities over a long period of commercialisation.

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Introduction

Living Cell Technologies (LCT) was established in 1987 by businessman David Collinson and Paediatric Professor Bob Elliott to commercialise Elliott's research into the use of pig islet cells as a treatment for Type I diabetes. The pair met when Collinson's son was diagnosed with the disease. Elliott's research into a diabetes treatment had, to that point, been unsuccessful. Yet, Collinson offered financing to continue the project. The pair founded a company, Diatranz, with NZ$8 million in start-up capital provided by Collinson. Elliott called Collinson a 'mentor' who pushed him to consider the financial and commercial applications of his work.[1] After developing a technique for successful xenotransplantation, regulatory changes postponed human clinical trials and the progression of research commercialisation. LCT found opportunities to continue their research internationally, shifted their headquarters to Australia and listed on the Australian Stock Exchange. LCT also entered agreements and research collaborations in the US, Russia and China, and established a joint venture firm with Japan-based Otsuka Pharmaceutical Factory, Inc., who provided significant funding for DiabeCell research and commercialisation. LCT eventually successfully trialled their Type I diabetes treatment DiabeCell and obtained approval for Phase I and Phase II clinical trials for their Parkinson's disease treatment NTCell.

Background

Type I diabetes is an autoimmune disease in which the body attacks the insulin-producing cells of the pancreas, preventing it from controlling blood sugar levels. High blood sugar levels cause hyperglycaemia, resulting in erratic behaviour and damage to nerve cells and blood vessels. Low blood sugar levels cause hypoglycaemia, which causes the person with diabetes to drop into a coma. Type I diabetics must monitor their blood sugars and inject themselves with insulin multiple times per day. Pig insulin injections were the first established treatment for the disease in 1922. It was a close enough match to human insulin to be an effective treatment, albeit with side effects like skin rashes. In 1963 scientists invented chemically synthesised insulin however they were unable to produce enough to meet demand. Doctors treated Type I diabetes with pig and cattle-derived insulin until the early 1980s, when researchers were able to manufacture enough synthetic insulin through biotechnology.[2]

[1] Professor Bob Elliott (2011). *New Zealand Management*. 58 (3). p. 25.

[2] Retrieved from www.diabetes.co.uk.

Elliott was Australian-born and trained as a paediatrician at the University of Adelaide. He moved to New Zealand in 1970 as Foundation Professor of Paediatrics at The University of Auckland, becoming Professor of Child Health Research in 1978. During his research, Elliott developed a new method of testing new-born infants for cystic fibrosis which was adopted internationally.[3] Elliott also began to research the use of islet cells for the treatment of Type I diabetes, inspired by the work of diabetes researchers Dr Paul Lacy and Dr George Maxwell. In 1961, Elliott transplanted cells into the eye chamber of diabetic rats, and inserted rat islet cells into a semipermeable chamber under the skin of diabetic rabbits, with no success. In 1976, Elliott injected human foetal islet cells intramuscularly into Type I diabetic patients, also with no success.

In 1987, Elliott met Collinson who encouraged him to continue his research. Elliot recalled that 'for an untutored businessman [Collinson] understood a lot [about science]. When I told him the problem was with the cells, he said, 'can't you put some new ones in?' I explained that my research had been a failure until then, and he said he'd like me to continue and pulled out his chequebook."[4] Elliot continued his research but, in 1995, transplants of new-born pig islet cells into the peritoneal cavity of Type I diabetics also failed. In all instances, the implanted foreign cells were rejected by the recipients.

In 1995, after discussion with a European colleague, Elliott came up with the idea of encapsulating the islet cells in a permeable seaweed-derived alginate (a seaweed-derived resin). Researchers at the University of Perugia, Italy, had pioneered an encapsulation technology that allowed cells to survive and nutrients to pass through the skin that protected them. The encapsulation process blocked the body from identifying the islet cells as foreign cells and allowed the islet cells to access the blood and nutrients they required to stay alive.[5]

Early Stages

In May 1996, Diatranz undertook human clinical trials on six Type I diabetic patients in North

[3] Kea New Zealand. (2011). *World Class New Zealand Award Winners*. Retrieved from http://www.keanewzealand.com/global/2011-winners

[4] Professor Bob Elliott. (2011). *New Zealand Management*. 58 (3). p. 25.

[5] NZ Bio. (2007). *Journal Endorses LCT Therapy*. Retrieved from http://www.nzbio.org.nz/default.aspx?page=20&news=1585

Shore Hospital, Auckland. The subjects had 1.3 million capsules of alginate injected into their abdomens. Each capsule contained around 500 insulin-producing islet cells taken from the pancreas of newborn piglets. The alginate capsules were designed to let insulin out of the capsule while allowing nutrients in, and most importantly to shield the cells from rejection without the need for immunosuppressant drugs.[6] Trial participants reported no major adverse effects and their insulin requirements dropped by up to 40% immediately after the implant, although the effectiveness of the treatment gradually faded over the following two years.[7] Diatranz researchers monitored the participants and reported to the US Centre for Communicable Diseases no changes in blood screening results, demonstrating the safety of the treatment.

In January 1997, the New Zealand Ministry of Health (MoH) ordered an immediate halt to the trial after the publication of a report by British scientist Clive Patience, which 'proved' the theoretical possibility that Porcine Endogenous Retrovirus (PERV) could be transferred from animals to humans. The report cited a pig kidney cell which was held in culture for ten years before being combined with various human organ cells. Traces of PERV were subsequently found in the human cell DNA and the discovery was reported in a US FDA (US Food and Drug Administration) report warning that xenotransplantation carried the risk of transferring animal retroviruses to humans.[8]US, UK, Europe and New Zealand authorities immediately halted xenotransplantation trials. The New Zealand Medicines and Medical Devices Safety Authority (MedSafe) followed the guidance of the FDA and the MoH asked the Health Research Council Ethics Committee and the Gene Technology Advisory Committee to make recommendations on the future of xenotransplantation in New Zealand.

Diatranz diverted staff and financing to disproving the possibility of virus transfer. The company tried to replicate Patience's finding by transferring the virus to live rabbits, mice, dogs, baboons, monkeys and chimpanzees with no success, and a subsequent international study of 164 people who had received live pig cell transplants of any nature found that no patients had contracted the disease.[9] Patience subsequently published work on the use of cells from miniature pigs which showed no evidence of infection. As a result of the latest published data, Diatranz made an application to the MoH to continue their research under the Medicines

[6] Coghlan, A. (2007). Man's pig cells implants still active 10 years on. *New Scientist. 194* (2598), p. 8.

[7] Chisholm, D. (1999, April 25). Warehouse boss sets up diabetes team. *Sunday Star Times*. p. A3.

[8] Tyler, V. (1997, January 19). Ministry bans pig cell insulin. *Sunday News*. p. 2.

[9] Langdon, C. (2002, February 28) Insulin patients lose out in treatment plan. *The Dominion Post*. p. 9.

Act, which considered encapsulation as a medicine. MoH referred the application to the MoH/Health Research Council subcommittees for consideration. While waiting for the ruling, Diatranz set up a laboratory at a disused pharmaceutical factory in South Auckland. In 1999, New Zealand entrepreneur Stephen Tindall provided $3 million worth of angel investment to the company, which allowed them to recruit and continue to pay eleven new staff members from The University of Auckland Medical School paediatrics department, taking Diatranz' headcount to 25. Diatranz also used the funding to continue refining the alginate cell coating. Elliott reported that previous coating materials allowed for implantation of only one million cells, but with newer coating, this could increase up to three million cells.[10]

Diatranz also invested in a new source of pig cells. In January 1999, the New Zealand Rare Breeds Society spent $100,000 catching and shipping 17 endangered pigs from the remote Auckland Islands, 465km south of New Zealand's South Island. The pigs had been released on to the islands in 1807 to provide a food source for shipwrecked seal and whale hunters, but with the demise of the whaling industry the islands were increasingly uninhabited and the pigs reverted to the wild.[11] The pigs' isolation meant they were uninfected with PERV and other pathogens prevalent in pig populations and were the only herd in the world designated free of Porcine Circovirus 2.[12] The pigs were kept in quarantine in Southland with financial support from the Invercargill City Council and expanded to a herd of sixty. Diatranz contacted the Invercargill Council to take over the housing of the pigs, moving some to a sterile custom-built facility in Auckland while others remained in quarantine in Southland.

In December 1999, the MoH denied Diatranz their application to continue clinical trials. Director-General of Health Karen Poutasi based her decision on advice from the Gene Technology Advisory Committee, which required more evidence of primate trials before it would allow resumption of human trials.[13] Diatranz appealed the ruling, but the MoH upheld the initial decision citing the precautionary principle. Under that principle, if an action or policy has a suspected risk of causing harm to the public or environment, in the absence of scientific consensus that the action is harmful, the burden of proof that it is not harmful falls on those taking action. Trials could not re-start until more evidence on the safety of the procedure could

[10] Chisholm, D. (1999, April 25). Warehouse boss sets up diabetes team. *Sunday Star Times*. p. A3

[11] Pincock, S. (2008, August 14). Pigs Might Fly. *Australian Doctor*. (14 August 2008). p. 21.

[12] Living Cell Technologies. *Annual Report 2005/2006*. Auckland, New Zealand.

[13] 'Diabetes plan dashed'. (1999, December 23). *The Press*. p. 31.

be established.[14] Beyond Diatranz' application, the Royal Commission on Genetic Modification recommended a moratorium on xenotransplantation until safety and ethical issues were resolved.[15] Elliott said that Diatranz were unlikely to apply to the MoH for a third time due to a lack of funding, and questioned why the practice of xenotransplantation was being assessed by a Commission whose explicit purpose was to evaluate genetic modification in New Zealand, not xenotransplantation.[16] Instead, they applied to conduct human clinical trials in Italy, citing studies from the preceding five years which failed to find a single instance of pig retrovirus transfer to humans.[17] In 2002, Diatranz decided to again appeal the decision by the Director-General, on the basis that there was no mention of the 'precautionary principle' in the Medicines Act, under which Poutasi had made the decision[18].

In November 2001, Diatranz announced their contribution to a human clinical trial in Mexico. The trial had begun 18 months previously when Elliott met Mexican transplant surgeon Dr Rafael Valdes-Gonzalez. Valdes-Gonzalez was planning a clinical trial using a technology similar to Diatranz[19] and Elliott offered the use of islet cells harvested from the Auckland Island pigs, which were transported to Mexico City in the hand luggage of Diatranz staff. Diatranz was contracted to monitor the results of the trial and share some of the data, but not to run the trials themselves, which followed Mexican health guidelines and had approval from the Mexican Ministry of Health and the University of Mexico.[20] Twelve children had pig islets cells implanted in their abdomens, and all recipients reported a drop in their insulin requirements. Three children reduced their insulin intake by 40% and one was taken off insulin completely.[21]

In 2002, Diatranz applied to conduct a 24-person clinical trial in the Cook Islands,

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[14] Birnie, L. (2001, August 8). Research Firm Gives up on NZ. *The Dominion Post*. Retrieved from Australia/New Zealand Reference Centre.

[15] Birnie, L. (2001, August 8). Research Firm Gives up on NZ. *The Dominion Post*. Retrieved from Australia/New Zealand Reference Centre.

[16] Wong, G. (2002). Bob Elliott's Last Stand. *Metro*. *(251)*. Retrieved from Australia/New Zealand Reference Centre.

[17] Napp, B. (2001, August 4). Think pig: diabetes trials hit snag. *The Dominion Post*. p. 1.

[18] Langdon, C. (2002, February 28) Insulin patients lose out in treatment plan. *The Dominion Post*. p. 9

[19] Valdes-Gonzales et al. (2005). Xenotransplantation of porcine neonatal islets of Langerhans and Sertoli cells: a 4-year study. *European Journal of Endocrinology*. (153). pp. 419-427.

[20] Wong, G. (2002). Bob Elliott's Last Stand. *Metro*. *(251*). Retrieved from the Australia/New Zealand Reference Centre.

[21] Purdy, K. (2001, November 11). Trial fires up Transplant Lobby. *Sunday Star Times*. p. A6.

which would take place under US FDA guidelines.[22] Diatranz made a series of presentations to Islanders explaining the process, which Prime Minister Dr Robert Wooton supported.[23] However, the International Xenotransplantation Association (IXA) wrote to the New Zealand Minister of Health expressing concerns about the trial in Mexico, citing the lack of international regulation and the use of children as trial subjects. They had similar concerns about the potential Cook Islands trials.[24] International guidelines also stipulated that medical research should not take place in a country with less regulation than the researchers' home country.[25] Minister of Health Annette King asked Wooton to wait for the results of the New Zealand medical review on xenotransplantation and in March 2002 Wooton deferred the trials.[26] Elliott said that the Cook Islands trials had been in discussion for two years previously and were not an attempt to circumvent regulation.[27]

Xenotransplantation also remained banned in New Zealand, pending the MoH review. After Poutasi declined Diatranz' second application for clinical trials in 2001, the MoH added an amendment to the Hazardous Substances and New Organisms Bill (HASNO), banning xenotransplantation until the 30th of June 2003 without special consent. If Diatranz re-commenced trials without consent, they could be fined $200,000 or be imprisoned for six months. Elliott applied for an exemption for Diatranz from the amendment, because their third appeal was already in process and could not be banned retrospectively under law, but the select committee rejected the application in March 2002.[28] In May 2002, the New Zealand Parliament imposed a further two-year ban on xenotransplantation in New Zealand through the passing of the HASNO amendment. The law allowed exceptions to the ban, but any exceptions required

[22] Archer, K. & McLellan, F. (2002). Controversy Surrounds Proposed Xenotransplant Trial. *Lancet. (359),* (9310), p. 949.

[23] Ibid.

[24] Ibid.

[25] Archer, K. & McLellan, F. (2002). Controversy Surrounds Proposed Xenotransplant Trial. *Lancet. (359),* (9310), p. 949.

[26] 'Cooks PM defers pig cell research. (2002, March 28). *New Zealand Herald*. Retrieved from Australia/New Zealand Reference Centre.

[27] Wong, G. (2002). Bob Elliott's Last Stand. *Metro*. *(251*). Retrieved from the Australia/New Zealand Reference Centre.

[28] Wong, G. (2002). Bob Elliott's Last Stand. *Metro*. *(251*). Retrieved from the Australia/New Zealand Reference Centre.

the Minister to consult with the public and MoH officials.[29] Elliott announced that Diatranz would explore the possibility of running clinical trials in Australia and, in 2003, the company moved their head office to Adelaide, although 25 of the company's 30 staff remained in Auckland.[30] In 2004 they also established a US subsidiary, LCT BioPharma, Inc. to experiment with pig cell encapsulation technology as a treatment for stroke. A US presence was also intended to help the company gain international presence and credibility.[31]

Diatranz needed significant capital to maintain the pig herd and pay staff wages, but also to complete pre-clinical trials and gain regulatory approval for human trials in Australia and elsewhere. The company could no longer rely on the private funding they had used previously as New Zealand private investors were unwilling to invest in a project which had not received government regulatory approval and was associated with the controversial practice of genetic modification.[32] The Australian Stock Exchange (ASX) was performing strongly and Australia had recently released draft guidelines on xenotransplantation for public consultation, so the possibility of running trials in the country looked promising.[33] Collinson and Elliott decided to list on the ASX to raise expansion capital and give them access to a wider pool of Australian investors. The company registered on the ASX through a 'backdoor listing'. In December 2003, mining company Weymouth Resources listed on the National Stock Exchange of Australia, several days after acquiring 13.9% of Diatranz for $1.13 million. Weymouth acquired the remaining 86.1% of LCT in January 2004; the same day the directors of Weymouth resigned and the LCT directors were appointed before Weymouth announced that it had changed its name to Living Cell Technologies (LCT).[34] Weymouth acted as a shell company, with few assets aside from a shareholder base. The backdoor listing meant that LCT was able to avoid the expense, time and extra requirements (including underwriting and legal fees, and certain listing rules) needed for an initial public offering, although they still had to comply with takeover rules and gain shareholder approval.

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[29] Springall, L. (2002). Government officials clobber Diatranz. *Independent Business Weekly*. p. 2.

[30] Collins, S. (2004, October 11). Biotech Shares Double in Value. *New Zealand Herald*. Retrieved from Australia/New Zealand Reference Centre.

[31] Collins, S. (2004, October 11). Biotech Shares Double in Value. *New Zealand Herald*. Retrieved from Australia/New Zealand Reference Centre.

[32] Ex-Kiwi Research Firm bound for ASX. (2004, June 21). *New Zealand Herald*. Retrieved from Australia/New Zealand Reference Centre.

[33] Diabetes research to move to Aussie. (2002, July 11). *The Dominion Post*. p. A9.

[34] Living Cell Technologies. *Annual Report 2003/2004*. Auckland: New Zealand.

LCT was organised into three departments: research and production, based in Auckland and led by Dr Paul Tan; product development, based in Rhode Island and led by Alfred Vasconcellos; and head office in Adelaide. CEO Collinson remained based in Auckland. In August 2004, the Australian Securities Commission approved LCT's A$6.8 million prospectus and the company listed on the ASX on the 1st of September 2004. The new public company posted a loss of A$10.3m from March 2003 to June 2004. LCT shares were listed at the minimum amount of A$20c, but six weeks later had doubled to A$42.5c, and the company's market capitalisation became A$34 million.[35] In September 2004, the Australian National Health and Medical Research Council banned xenotransplantation for a five year period, due to concerns about retrovirus transfer between pigs and humans.[36] However, in October 2004, LCT released the results of their pre-clinical studies of NeurotrophinCell (NTCell) for treating Huntington's disease where animals showed 86% less damage to the brain.[37]

LCT continued to refine their technology and, in 2005, entered into a letter of intent with Theracyte, a subsidiary of Baxter Inc, to obtain their technology, IP and manufacturing materials. Theracyte patents involved a "family of small, thin, pillow-shaped devices which could be filled with cells and placed under the skin to deliver drugs and therapeutic factors," and would partner with LCT's encapsulation technology.[38] The device had FDA approval for clinical trial cell applications. LCT acquired all Theracyte's assets in return for 300,000 LCT shares, a small royalty on future product sales, and three million options to acquire unissued shares once the first Theracyte product gained regulatory approval.[39] The purchase "provided LCT with an alternative cell delivery system with FDA clinical trial approval [and] expanded LCT's ability to supply live cell products to the international market."[40]

Development

[35] Collins, S. (2004, 11 October). Biotech Shares Double in Value. *New Zealand Herald*. Retrieved from Australia/New Zealand Reference Centre.

[36] Dean, T. (2009). Xenotransplantation Ban Lifted In Australia. *Australian Life Scientist*. Retrieved from Australia/New Zealand Reference Centre.

[37] Living Cell Technologies. (2004, October 11). LCT treatment protects the brain from damage by Huntington's disease. Australian Securities Exchange. Retrieved from http://www.asx.com.au/asx/statistics/displayAnnouncement.do?display=pdf&idsId=00467215

[38] Living Cell Technologies. *Annual Report 2003/2004*. Auckland: New Zealand.

[39] Living Cell Technologies. *Annual Report 2005*. Auckland: New Zealand.

[40] Living Cell Technologies. *Annual Report 2003/2004*. Auckland: New Zealand.

In 2005, LCT identified DiabeCell (their diabetes treatment) and NTCell (NeuroptrophinCell, initially planned to develop a treatment for Huntington's disease) as their key strategic priorities. They undertook primate trials for NTCell in Singapore. Cells were taken from a piglet's choroid plexus, the part of the brain which produced cerebrospinal fluids, hormones and proteins essential for brain cell function. The cells were encapsulated and transplanted into the striatum, the area of the brain affected by Huntington's disease. Results showed that brain cell damage in the primates after treatment was five times less than cell damage in the control animals (50% cell death versus 10%). LCT met with the US FDA to discuss requirements for the first human clinical trial of the product before submitting an Investigational New Drug (IND) application. That year LCT also applied to list on the American Depository Receipt (ADR) Programme on the International Over-the-Counter Quality Exchange (OTCQX) to increase their exposure to US investors, and to raise their international profile.[41] OTCQX International was a platform that enabled foreign companies to access the US public market if they met the requirements including being sponsored by a professional third-party advisor.[42]

The xenotransplantation debate in New Zealand appeared to be shifting, and LCT again tried to push for clinical trials of DiabeCell in the country. Despite the regulatory struggle, the company wanted to pursue clinical trials in New Zealand due to the fragility of the pig cells, which needed to be prepared and delivered quickly after harvesting. Delivering the cells outside of New Zealand would be expensive and time-consuming. New Zealand was also considered to be prime site for clinical trials due to relatively low costs and a skilled and capable workforce.[43]

The moratorium on xenotransplantation lapsed in 2004, and in 2005 the Bioethics Council called for public submissions on a discussion document which considered cultural, spiritual and ethical issues to do with xenotransplantation.[44] In May 2006, LCT was granted $2.73 million by the Foundation of Research, Science and Technology (FRST) to develop manufacturing operations and cell bioprocessing expertise. The grant was subject to the company gaining approval for clinical studies and achieving other capital raising targets.

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[41] Living Cell Technologies. (2008). LCT Prepares to List on the International OTCQX. [Press Release.] Retrieved from http://www.lctglobal.com/Media-And-News/Press-Releases/.

[42] OTC QX. http://www.otcqx.com/qx/home

[43] NZ Bio. (2009). *Driving Economic Growth Through Bio Based Industries*: *The 2009 Bioeconomy Industry Summit Report*. Auckland: New Zealand. Retrieved from http://www.nzbio.org.nz/portals/3/files/NZBIOSummitReport07-12-09website.pdf

[44] MacDonald, N. (2005, February 1). Views sought on animal transplants. *The Dominion Post*. p. a4.

MedSafe issued LCT with a license to manufacture animal cell products for use in human therapeutics, the first step towards the resumption of clinical trials. LCT indicated to MedSafe that it intended to apply to resume Phase I trials in Auckland.[45] In September 2007, the New Zealand regional ethics committee approved clinical protocols of LCT Phase I/IIa trials. In October 2008, after two years of consultation with several committees, Health Minister David Cunliffe gave conditional approval for trials. The Minister imposed strict conditions: all results had to be held in an archive at Middlemore Hospital, Auckland, where the trials would be run; trials had to be overseen by an independent safety management board, and the process had to be reviewed by an international expert before they could begin.

In anticipation of beginning clinical trials, in 2007 LCT raised A$6 million in a capital placement, following a US$2 million placement by US company NaviGroup Management, who maintained the option of an additional $6 million worth of shares. In October 2007, LCT also undertook Phase I/IIa clinical trials of DiabeCell at the Sklifosovsky Institute in Moscow, Russia, under the guidance of Professor Nikolai Skaletsky.[46] The Institute was willing to fund the trials in return for their staff gaining experience and instruction from LCT staff, and the trials were overseen by a US-based contract research organisation. Elliott noted the added expense of running the trials in Russia, due to the costs of transporting staff and cells from New Zealand, and communication difficulties.[47] Phase I and IIa trials were run concurrently to "fast track the commercial potential in one market, as well as optimise dosing before the pivotal study."[48] In June 2007, two of an anticipated eight patients had 5000 encapsulated pig islet cells injected into their abdomens, followed by a second implant six months later. Initial results were promising and the first two patients cut their insulin doses by up to a quarter.[49] The results also had a positive effect on the share price, which increased from A$8.2c in August 2007 to

[45] Pig Cell Treatment Two Steps Away. (2006, December 2). *New Zealand Herald*. Retrieved from Australia/New Zealand Reference Centre.

[46] National Health and Medical Research Council. (2009). *Discussion Paper: Xenotransplantation, a review of the Parameters, Risks and Benefits*. Canberra: Australia. Retrieved from http://www.nhmrc.gov.au/_files_nhmrc/file/about/committees/expert/gtrap/nhmrc_xeno_discussion_paper_website.pdf

[47] Making Pigs of Ourselves. (2008, October 24). *The Herald Sun (Melbourne)*. Retrieved from Australia/New Zealand Reference Centre.

[48] Living Cell Technologies. *Annual Report 2006/2007*. Auckland: New Zealand.

[49] Pig Cell Trials Get Exciting Results. (2007, October 9). *New Zealand Herald*. Retrieved from Australia/New Zealand Reference Centre.

A$47c in October 2007.[50] By 2009, LCT was able to report that the trials had successfully "demonstrated safety and tolerability. Also, the trial showed proof of principle of efficacy in humans with insulin-dependent diabetes."[51] Six of the eight patients ultimately demonstrated improvements in blood glucose control and reduced their daily insulin requirements and two patients were able to discontinue insulin injections completely for up to 32 weeks.[52] In July 2008, the company established a Russian subsidiary, LCT Biomedical Ltd, to lead commercial development of the product.[53] In this arrangement, LCT would manufacture DiabeCell using the Auckland Islands pig herd and partner with clinical service providers who would administer the product under LCT guidelines.[54]

The possibility of the next round of clinical trials and eventual commercialisation meant that LCT had to work on refining their encapsulation technology for DiabeCell in larger doses, as well as upscale their manufacturing capacity for the product to include clean rooms and establishment of Good Manufacturing Practice (GMP) standards. LCT built a state of the art manufacturing and diagnostic facility in South Auckland and, in 2007, gained GMP certification for their manufacturing facilities, and international accreditation (IANZ) for their molecular diagnostic laboratory and systems. The certifications ensured that LCT's clinical data was accepted in 49 countries, including the US, UK and Australia.[55] GMP certification also meant the company could manufacture animal cell therapeutics for human use internationally.

LCT committed capital to building an NZ$2.5 million new piggery in Invercargill, which was opened in May 2009 and had space for fifty breeding sows. Two pig facilities were necessary to guarantee security of supply, in the case of pig loss at one facility due to infection or natural disaster. Also, the new piggery was necessary to grow their supply of islet cells. Elliott estimated that twenty neonatal piglets would be required per patient, to treat a Type I diabetic for a lifetime.

With around 20 million people suffering from Type I diabetes internationally; for

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[50] Investors Happy to Find Life is a Living Cell. (2007, October 23). *The Age (Melbourne)*. Retrieved from Australia/New Zealand Reference Centre.

[51] Living Cell Technologies. *Annual Report 2009/2010*. Auckland: New Zealand.

[52] Living Cell Technologies. *Annual Report 2009/2010*. Auckland: New Zealand.

[53] Living Cell Technologies. *Annual Report 2008/2009*. Auckland: New Zealand.

[54] Living Cell Technologies. *Annual Report 2008/2009*. Auckland: New Zealand.

[55] Living Cell Technologies. *Annual Report 2008/2009*. Auckland: New Zealand.

clinical trials alone, hundreds of piglets were required. In 2007 LCT predicted they would need 100 – 200 breeding sows for the anticipated New Zealand clinical trials and in the longer term aimed to build sterile housing for 1000 breeding sows. Their planned breeding programme would enable commercial market entry within three years following the clinical trials, with 100 sows in year one, 600 sows in year two, and 3600 sows in year three, who would provide 36,000 piglets. Of those 36,000 piglets, 18,000 would be used as breeding sows, with the 18,000 male piglets used for harvesting cells. LCT filed patents covering the breeding techniques and housing of the pigs and began to investigate ways of maximising value from the piglets, who did not survive the harvesting of their pancreas. Their options included "exploring the potential for the pig tissues to be used in other established markets for pig-derived biomaterials, which would enable earlier revenue opportunities for the company."[56]

At the same time, LCT was going through changes in their senior management team. In 2007, David Collinson stepped aside as Group CEO due to health issues, though he remained a non-executive director until his death in 2009. LCT New Zealand CEO Dr Paul Tan took on the Group CEO role in 2007. Tan was a former Associate Professor of Immunology who had also worked as CEO of CenTech and deputy director of biotech firm Genesis Research and Development. However, in July 2008, Board Member Dr Robert Caspari was appointed Group CEO and Tan reverted to CEO of LCT New Zealand. Caspari was Colorado-based and had previously held senior executive roles in pharmaceutical companies including Myogen and Novo Nordisk. Caspari's appointment was in line with the company's strategy to expand their shareholder base, particularly in the US market. However, he stepped down from the role in September 2009 after the global financial crisis impacted on LCT's capital raising and expansion plans in the US, and Paul Tan resumed the position.

Financially the company was similarly unsettled and in 2009 LCT posted a loss of $6.12 million.[57] By mid-2009 the New Zealand government had still not ruled on LCT's application to begin trials, and the company was spending $600,000 per month maintaining the pig herd and research facility including 15 tonnes of sterilised grain per week to feed the pigs,[58] and paying wages to their 43 staff members. Finally, in June 2009, Health Minister Tony Ryall authorised the trials with revised conditions: they must only involve eight 'severe' diabetics and patients would be provided with more information on the process and results than legally

[56] Living Cell Technologies. *Annual Report 2006/2007.* Auckland: New Zealand.

[57] Living Cell Technologies. *Annual Report 2008/2009.* Auckland: New Zealand.

[58] Milne, A. (2009, July 4). Pig Cell Trials Likely to Take Six Months. *Southland Times*. p. A5.

required.[59] The trials were to be run by Dr John Baker, the clinical director at Middlemore Hospital, and the participants would be monitored for eight weeks before the implants.[60] Four people with diabetics would receive injections of 10,000 islet cells, and four would receive 15,000 islet cells. The first patient was injected with pig cells in October and by December had reduced the daily insulin dose by 30%. In March 2010, LCT announced initial results from the first two patients, who had “reduced or eliminated” incidents of hypoglycaemic unawareness (a sudden drop in blood sugars, resulting in impaired consciousness). In August 2010, the Government approved the inclusion of four more patients to the initial trial, to add “additional rigour.”[61] By 2011, the company reported that no patients had experienced adverse reactions and that LCT was focused on "optimising the patient results" through experimentation with dosage size and frequency.[62]

In December 2010, LCT received registration from the Russian government to sell DiabeCell commercially. The company intended to establish distribution networks and form partnerships with health care providers, as well as inform the Russian public about the technology. This would include “managing expectations” of the market as to the effectiveness of the treatment; while DiabeCell had reduced insulin requirements for the majority of test subjects, it was also “not a cure-all” for Type I diabetes and could not be marketed as such.[63] The company noted that, in an ‘ideal’ world, LCT would have started establishing distribution networks earlier, but couldn't afford to spend the money without confirmation of registration. At that stage, the company anticipated starting Phase III trials in 2011 and had begun building relationships with "leading health centres around the world" to conduct the trials.[64] Eventually, LCT intended to partner with those same health centres in multiple markets to create ‘Centres of Excellence’ and sell DiabeCell when it was commercialised.[65] The company believed that LCT’s “fully integrated proprietary supply and manufacturing capabilities" would easily be

[59] Milne, A. (2009, July 4). Pig Cell Trials Likely to Take Six Months. *Southland Times*. p. A5.

[60] Milne, A. (2009, December 5). Pig cell trial patient cuts insulin dose by 30 percent. *Southland Times*. Retrieved from Australia/New Zealand Reference Centre.

[61] Living Cell Technologies. (2010). LCT receives approval to expand DiabeCell trial. [Press Release.] Retrieved from http://www.lctglobal.com/Media-And-News/Press-Releases/

[62] Living Cell Technologies. *Annual Report. 2010/2011*. Auckland: New Zealand.

[63] Living Cell Technologies. *Annual Report. 2010/2011*. Auckland: New Zealand.

[64] Living Cell Technologies. *Annual Report 2010/2011*. Auckland: New Zealand.

[65] Living Cell Technologies. *Annual Report 2010/2011*. Auckland: New Zealand.

scalable when demand for the product grew.[66] In November 2010, LCT announced positive results trialling the use of NTCell to treat Parkinson's disease in rodents. Choroid plexus cells from new-born piglets were implanted in the nigrostriatum of affected rats. The trial rats experienced 56% fewer abnormalities in the affected part of the brain than the control rats, and 'marked' repopulation of the dopamine- producing cells which were depleted with Parkinson's disease.

However, the company had also gone through another series of changes at the executive level. In August 2010, as the company "escalated efforts to prepare for the commercialisation of DiabeCell," pharmaceutical executive Dr Ross MacDonald was appointed to the new role of Managing Director to work alongside Group CEO Paul Tan. One month later Tan resigned from his role, remaining as external advisor for the clinical development of DiabeCell's clinical and regulatory strategy. McDonald moved into the role of Group CEO and Managing Director of the LCT Group but resigned seven months later in June 2011. Co-founder Elliott became Acting Group CEO until December 2011, when Dr Andrea Grant was appointed to the position. Grant formerly held senior roles at Roche Products New Zealand and was Managing Director of biotech company Galapagos NV.

Financially the period of clinical trials was uncertain. In 2009, LCT offered 1800 New Zealand and Australian shareholders up to A$15,000 in shares at A$25c each, which raised A$6.87 million. In June 2010, LCT announced that $9.5m worth of unlisted options would be underwritten to add at least $2 million to their cash reserves.[67] In 2010, LCT recorded a loss of A$5.6 million, mostly due to staff and research and development costs, and in 2011 reported a loss of A$6.9 million, despite receiving funding of US$500,000 from the US Juvenile Diabetes Foundation towards the New Zealand Phase II trial of DiabeCell. The company had also gained revenue from a two-year exclusive research licensing deal for their encapsulation technology with Johnson & Johnson subsidiary Centodor, who intended to use the encapsulation technology with other human cells. The agreement meant that Centodor would pay for all of LCT's research to do with encapsulation technology during a two-year period. At the end of the two years, Centador had the option of licensing the technology for another two years, with

[66] Living Cell Technologies. *Annual Report 2010/ 2011*. Auckland: New Zealand.

[67] Living Cell Technologies. (2010). LCT options expiring on the 30th of June 2010 to be Underwritten on the 22nd of June 2010 - $2.0 million working capital secured. [Press Release]. Retrieved from http://www.lctglobal.com/Media-And- News/Press-Releases/.

LCT gaining upfront annual and royalty payments.[68] LCT also granted a license to US start-up company CytoSolv, to use their choroid plexus IP to develop treatments of diabetic ulcers and other wounds; LCT provided a restricted supply of choroid plexus cells from the Auckland Islands pigs.[69] However, to undertake Phase III trials in Auckland and continue the process of commercialising DiabeCell, the company estimated they would need significantly more cash than the $2 million they had available.[70]

In March 2011, LCT received A$1.7 million in funding from Chinese-based Jiangsu Aosaikang Pharmaceutical Co., Ltd (ASK), in return for 14% of the company. Also, LCT and ASK agreed to undertake collaborative research, and LCT gave ASK first right of refusal to negotiate a license to commercialise and become the sole provider of DiabeCell in China, once the product was tested and registered.[71] The following month LCT received A$4 million in funding from Otsuka Pharmaceutical Company, the research and manufacturing arm of Japanese conglomerate Otsuka Group, in return for shares to the value of A$3 million and a research and commercialisation collaboration agreement. The investment was in two instalments and would be used by LCT to fund Phase III clinical trials.

Otsuka provided further funding in October 2011, investing A$25 million in return for a 50% share in the DiabeCell project, which would be run as a joint venture named Diatranz Otsuka Ltd (DOL). LCT investors retained a 50% ownership in DOL fixed assets and a 50% share of downstream DiabeCell profits. The company wanted to "secure a major pharmaceutical partner" to co-develop new products through commercialisation. LCT would realise revenues through sharing the ownership of 'downstream' product profits[72] and retained a perpetual, exclusive license to exploit the IP outside the diabetes field, full ownership of research and development knowledge to exploit assets, and full ownership of encapsulation IP. Elliott estimated that LCT was still at least two to three years away from bringing DiabeCell to market and that the company would have been out of business within three months without

[68] McKnight, S. (2010, January 2). US giant signs seaweed human cells research deal with NZ firm. *Dominion Post*. p B6.

[69] Living Cell Technology. (2010). Living Cell Technologies Receives 10% of CytoSolv. [Press Release]. Retrieved from http://www.lctglobal.com/Media-And-News/Press-Releases/.

[70] Rotherham, F. (2010.) Funding crucial to future of pig cell diabetes treatment. *Dominion Post*. p. C3.

[71] Living Cell Technology. (2011). LCT receives funds from Pharmaceutical investor. [Press Release]. Retrieved from http://www.lctglobal.com/Media-And-News/Press-Releases/.

[72] Living Cell Technologies. (2011). Portfolio Summary 2011. [Press release]. Retrieved from http://www.lctglobal.com/Media-And-News/Press-Releases/

the Otsuka capital. Furthermore, the Otsuka deal around DiabeCell enabled LCT to free up capital to accelerate their NTCell trials in the coming year.

In 2011 LCT, also announced Phase IIb clinical trials to be held in Argentina: eight patients would be given two low dosages of DiabeCell over a period of three months. The New Zealand and Russian trials had established that lower dosages of islet cells were more effective than larger dosages, and the Argentinian trials would help refine the dosage level for maximum effect.[73] The first two patients were enrolled in the trials in June 2011 and received their first implant containing 5000 islets equivalents per kilogram of body weight in August. By 2012, LCT was able to present positive results in pre-clinical primate trials of NTCell for Parkinson's disease. The trials were conducted on animals who had been induced into a state similar to Parkinson's disease. In all of the studies, the transplantation reduced movement disorders and neurological defects associated with the disease; improvements were seen within two weeks and lasted up to six months.[74] LCT was preparing an application to MedSafe to hold Phase I human clinical trials for NTCell and MedSafe granted ethical approval in December 2012.[75]

A few days after ethical approval was obtained to proceed with Phase I clinical trials for NTCell, LCT entered a second agreement with Otsuka. The deal included a total funding of A$7 million, which would be paid out in three instalments and partially be dependent on meeting certain milestones. The money would be used to cover the estimated A$2 million for completion of Phase I trials of NTCell for Parkinson's disease. All pay-outs were expected to be made during 2013, concluding with the successful implantation of the product into a human patient.[76] In return, Otsuka obtained the exclusive option to co-develop and subsequently commercialise NTCell for the treatment of Parkinson's and other neurological diseases. Development and commercialisation would be through the existing joint venture, DOL, and would include an additional investment of A$20 million by Otsuka. LCT would then transfer its IP for therapeutic use of the product into DOL. However, only IP related to neurological

[73] Living Cell Technologies. Annual Report 2010/2011. Auckland: New Zealand.

[74] Living Cell Technologies (2012). LCT presents novel Parkinson's Disease treatment results. [Press Release]. Retrieved from http://www.lctglobal.com/Media-And-News/Press-Releases/

[75] Living Cell Technologies. (2012, November 16). Ethical approval for LCT's NTCell® Phase I trial. Retrieved from http://www.asx.com.au/asxpdf/20121116/pdf/42b7lfkllnk1sw.pdf

[76] Living Cell Technologies. (2012, December 17). LCT and Otsuka to co-develop NTCell® for Parkinson's disease. Retrieved from http://www.lctglobal.com/html/blob.php/121217%20LCT%20and%20Otsuka%20to%20codevelop%20NTCELL%20for%20Parkinsons.pdf?attach=0&documentCode=4808&elementId=20084

diseases and hearing loss would be included. Any NTCell-related IP for treatment of non-neurological diseases would not be affected and retained exclusively by LCT.[77]

To continue funding its research, LCT had to fundraise several times. In February 2016, LCT completed the placement of 54 million shares at AU$0.05063 to wholesale investors resident in New Zealand, raising AU$2.8. The company announced that the funds were being used as working capital to carry out the Phase IIb clinical trial of NTCell associated with Parkinson's disease and to apply for provisional consent to treat paying patients in New Zealand in 2017.[78] Further, in April 2016, LCT completed its share purchase plan with the issue of 9,532,034 fully paid ordinary shares, raising an additional $0.5m. The share purchase plan gave all shareholders in Australia and New Zealand the opportunity to participate in the success of the company on the same basis as the AU$2.8m private placement, which was completed in February. The AU$3.3m total raised is projected to provide funding to complete implants in the Phase IIb clinical trial of NTCELL for Parkinson's disease which commenced in March.[79] Just two weeks after, LCT raised additional AU$0.4M increasing the total fundraising to AU$3.7M.

In May 2016, LCT initiated a research collaboration with the Centre for Brain Research (CBR) at the University of Auckland. The research collaboration intended to explore how LCT's products could reverse human brain neurodegenerative processes associated with pericytes (and other brain cells), which help sustain the blood-brain barrier and other homeostatic and haemostatic functions in the brain. The agreement had two primary goals. The first was to extend the pipeline for LCT's lead product NTCell by examining the effects of NTCell on cell cultures derived from human brains with Alzheimer's disease and Huntington's disease. The second was to identify other encapsulated cell therapies which may have had potential to treat these neurodegenerative disorders by examining whether they could promote neuroprotective effects in the brain.

The research will be undertaken by Auckland UniServices Limited (UniServices), the commercial research company of the University of Auckland, using the breakthrough drug testing and drug target validation platform, Neurovalida. Neurovalida, developed by Professor

[77] Ibid

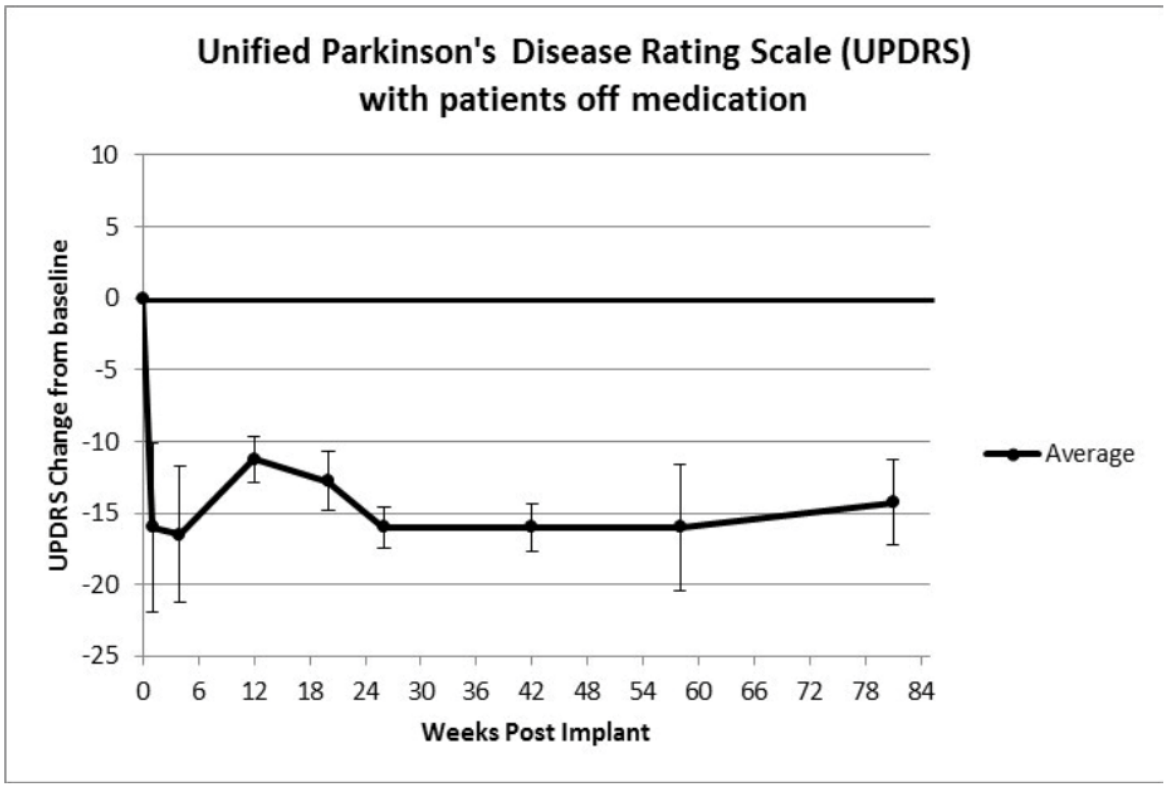
[78] Company's announcement. Retrieved from http://www.4-traders.com/LIVING-CELL-TECHNOLOGIES-10353909/news/Living-Cell-Technologies-LCT-Completes-2-8M-Private-Placement-and-Announces-SPP-21863170/

[79] Company's announcement. Retrieved from http://www.4-traders.com/LIVING-CELL-TECHNOLOGIES-10353909/news/Living-Cell-Technologies-Share-purchase-plan-raises-0-5m-22113341/

Mike Dragunow, Distinguished Professor Sir Richard Faull and Associate Professor Maurice Curtis from the CBR, provides human brain-based neuroscience research collaborations, partnerships and services.

In June 2016, Dr Barry Snow presented 81 weeks' worth of data on the safety and clinical effects of NTCell in patients with Parkinson's disease at the 20th International Congress of Parkinson's Disease and Movement Disorders in Berlin. 81 weeks after treatment all four patients who took part in LCT Phase I/IIa clinical study of NTCell for Parkinson's disease showed reversal of the progression of Parkinson's disease as measured by globally accepted and validated Unified Parkinson's Disease Rating Scale (UPDRS).

As the chart below shows, results were encouraging. After 81 weeks there is a clinically and statistically significant improvement in the patients' neurological scores from their pre-implant baseline.



Parkinson's disease progression is measured by a neurological rating scale, UPDRS. The UPDRS score increases by approximately 4 to 5 points each year as Parkinson's disease progresses. NTCell's ability to decrease UPDRS by an average of 14 points after 81 weeks was clinically significant, representing a 2.8 to 3.5-year reversal of neurological deterioration. In the first patient, the improvement was sustained at 130 weeks after NTCell implant. All four patients remain well and there are no safety concerns.

At the end of 2016, LCT completed all treatments for six patients in group 2 of the Phase IIb clinical trial of NTCell for Parkinson's disease, at Auckland City Hospital. Four patients had 80 NTCell microcapsules implanted into the putamen on each side of their brain, and two patients had sham surgery with no NTCell implanted. No safety issues were encountered in any of the six patients. Dr Ken Taylor, CEO of LCT mentioned that "Our goal, subject to continued satisfactory data, is to obtain provisional consent and launch NTCell as the first disease-modifying treatment for Parkinson's disease early in 2018".[80]

On the 8th of February 2017, LCT received permission from the Data Safety Monitoring Board to commence treating the patients in group 3. Four patients were to have 120 NTCell microcapsules implanted into the putamen on each side of their brain, and two patients were to have sham surgery with no NTCell implanted. Treatment of the group 3 patients at Auckland City Hospital planned for February has been delayed by a month due to having to wait for Quality Assurance (QA) clearance of the batch of NTCell prepared for group 3.[81]

In June 2017, LCT announced additional clinical results. 130 weeks after treatment all four patients who took part in LCT Phase I/IIa clinical study of NTCell for Parkinson's disease remained well and there were no safety concerns. The primary clinical endpoint of this initial open clinical study, involving the implantation of 40 NTCell capsules into the putamen on one side of the brain only, was deemed safe. In all patients, NTCell treatment continued to show improvement over baseline, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS). Efficacy was most evident in the measurement of motor function. The Principal Investigator, Dr Barry Snow of Auckland City Hospital, said that the sustained improvement was interesting and encouraging. "The results to date certainly validate the Phase IIb dose-ranging study in progress, in which higher doses of NTCell are implanted into the putamen on both sides of the brain and which includes a sham surgical-controlled placebo group."[82]

Conclusion

[80] Company's announcement. Retrieved from http://www.4-traders.com/LIVING-CELL-TECHNOLOGIES-10353909/news/Living-Cell-Technologies-Group-2-Parkinson-rsquo-s-Trial-Patients-rsquo-Treatment-Completed-23590517/

[81] Company's announcement. Retrieved from http://www.4-traders.com/LIVING-CELL-TECHNOLOGIES-10353909/news/Living-Cell-Technologies-Insights-February-2017-23952337/

[82] Company's announcement. Retrieved from http://www.lctglobal.com/upload/news/2017/170606%20130%20weeks.pdf

Initially founded as Diatranz in 1987, LCT did come a long way. Although first clinical trials that were conducted about 20 years ago looked promising, regulatory changes led the company to look for research opportunities abroad, resulting in the establishment and public listing of LCT in Australia. Attracting international investors and research collaborations enabled LCT to explore different avenues but also increased the pressure for showing positive results. LCT developed proprietary encapsulation technology, established two registered piggeries, and obtained GMP certification. While still focusing on the original market opportunity that drove the founders, i.e. to address Type I diabetes, LCT also investigated further applications for neurological diseases. Two joint ventures funded the next stages of development for DiabeCell and NTCell respectively, giving the company some financial certainty for the period. At the same time, other things remain unchanged. The uncertainty surrounding LCT's technologies remained high and financing for DiabeCell, NTCell, and other products relied on positive clinical trials outcomes. Funding of high-risk technological entrepreneurship remained challenging, and for a publicly-listed company, demonstrating positive results is as important as ever.

Current key facts (2017)

Living Cell Technologies (LCT) is an Australasian biotechnology company improving the wellbeing of people with serious diseases worldwide by discovering, developing and commercialising regenerative treatments which use naturally occurring cells to restore function.

The business

LCT is listed on the Australian (ASX: LCT) and US (OTCQX: LVCLY) stock exchanges. The company is incorporated in Australia, with its research and development, and operations based in New Zealand. LCT is developing NTCell for the treatment of neurodegenerative diseases.

Product pipeline and key milestones

In June 2015 LCT completed a Phase I/IIa clinical study of NTCell in Parkinson's disease. The study met the primary endpoint of safety. NTCell also improved clinical features of Parkinson's in the four patients studied.

A Phase IIb study commenced in March 2016. Upon successful completion, the company intends to apply for provisional consent to treat paying patients in New Zealand in

2017.

LCT is also investigating applications for NTCell in other neurodegenerative conditions, including Huntington's, Alzheimer's and motor neurone diseases.

The science

LCT's product pipeline consists of cell therapies developed from cells sourced from a unique herd of designated pathogen-free pigs bred from stock originally discovered in the remote sub-Antarctic Auckland Islands.

LCT's proprietary technology, IMMUPEL, coats cells with protective capsules that prevent them from being attacked by the patient's immune system. This allows the use of cell therapies without the need for co-treatment with drugs that suppress the immune system, which often has negative side effects.

Leadership

CEO Dr Ken Taylor joined LCT in February 2014. Before joining LCT he had a prestigious international career in both academia and business including many years with Roche.

NTCell

NTCell is a cell therapy with the potential to halt disease progression in people with Parkinson's disease. It is estimated that more than 7 million people worldwide have Parkinson's disease. The global market for the current standard treatment for Parkinson's disease – dopamine replacement – is approximately A$2 billion per annum. The Phase I/IIa clinical study of NTCell showed it was safe and well tolerated.

At 58 weeks post-implant, NTCell reversed the progression of Parkinson's disease, as measured by validated neurological rating scales and questionnaires, by 3-4 years. A Phase IIb clinical study commenced in March 2016. The primary endpoint will address the efficacy of NTCell as a treatment for Parkinson's disease. NTCell has also demonstrated a powerful ability to regenerate damaged tissue and restore function in preclinical studies of other neurodegenerative diseases.

Joint venture with Otsuka

In 2011, LCT formed the New Zealand 50:50 joint venture company Diatranz Otsuka Limited (DOL) in partnership with Otsuka Pharmaceutical Factory, Inc. (OPF). The joint venture aimed to accelerate the development of DIABECELL, a cell therapy which, in

clinical trials, has been shown to improve some of the symptoms of type 1 diabetes significantly. DOL has licenced OPF to use DIABECELL in the United States and Japan and OPF are developing an improved product in the United States. DOL has the right to commercialise the US product in the rest of the world.

Timeline of key events

Year	Event
1987	Collinson and Elliott establish Diatranz Limited with NZ$8 million start-up capital provided by Collinson
1996	Diatranz undertakes clinical trials on six Type I diabetic patients in Auckland
1997	Clinical trials discontinued due to theoretical risk of porcine endogenous retrovirus transfer
1999	Diatranz takes over housing of pathogen-free Auckland Islands pigs
1999	Diatranz secures NZ$3 million angel investment from Tindall and staff number grows to 25
1999	Application to continue clinical trials is denied by Ministry of Health (MoH)
2000	Diatranz contributes to human clinical trials in Mexico
2001	MoH deny application
2001	Application for clinical trials lodged in Italy
2002	Application for human clinical trial in the Cook Islands, which is deferred
2003	Diatranz moves head office to Adelaide and explores possibilities for clinical trials in Australia
2004	Listing of Living Cell Technologies (LCT) on Australian Stock Exchange (ASX)
2004	Australian National Health and Medical Research Council bans xenotransplantation for a five year period
2004	Release of pre-clinical study results on NTCell
2004	Establishment of US-based subsidiary LCT BioPharma, Inc.
2005	Letter of intent signed with Theracyte
2005	Primate trials for NTCell in Singapore

2005	Application for American depositary receipt (ADR) to be able to list on Over-the-Counter Quality Exchange (OTCQX)
2006	LCT receives NZ$ 2.73 million from the Foundation of Research, Science and Technology (FRST)
2007	LCT raises US$2 million through capital placement by US-based NaviGroup Management
2007	LCT raises A$6 million through capital placement
2007	Phase I/IIa clinical trials of DiabeCell at the Sklifosovsky Institute in Moscow, Russia
2007	David Collinson steps down as CEO and LCT NZ CEO Dr Paul Tan takes over as Group CEO
2007	LCT gains Good Manufacturing Practice (GMP) certificate for manufacturing facilities earns international accreditation (IANZ) for their molecular diagnostic laboratory and systems
2008	LCT lists on International OTCQX
2008	Caspari is appointed Group CEO and Tan reverts to CEO of LCT New Zealand
2008	LCT establishes Russian subsidiary LCT Biomedical Ltd
2008	LCT starts collaborating with Centocor Research & Development, Inc.
2009	Opening of new piggery in Invercargill worth NZ$2.5 million
2009	Human clinical trials approved by MoH with trials starting at Middlemore Hospital, Auckland
2009	Establishment of LCT Biomedical Limited (Russia)
2009	Reporting of ‘successful’ results of Phase I/IIa trials
2009	LCT reports loss of $6.12 million with ongoing monthly costs of $600,000
2009	LCT raises $6.87 million through offering to 18000 New Zealand and Australian shareholders
2010	MacDonald is appointed Managing Director to work alongside Tan
2010	Tan resigns and MacDonald becomes Group CEO
2010	LCT announces positive results from trials on rodents in the use of NTCell
2010	LCT registers in Russia to sell DiabeCell commercially

2010	LCT receives US$500,000 from the US Juvenile Diabetes Foundation
2011	LCT announces a second product line based on transplanting choroid plexus brain cells. NTCell has the potential to treat neurodegenerative diseases, including Parkinson's.
2011	LCT enters two-year license agreement with US-based Centodor
2011	LCT grants license to CytoSoly to develop treatments of diabetic ulcers
2011	LCT receives A$1.7 million funding from Jiangsu Aosaikang Pharmaceutical Company in exchange for a company 14% stake and collaborative research agreement
2011	LCT receives A$4 million funding from Otsuka Pharmaceutical Company
2011	MacDonald resigns as Group CEO and Elliot becomes Acting CEO
2011	Joint venture with Otsuka Pharmaceutical Factory, Inc resulting in the establishment of Diatranz Otsuka Limited (DOL).
2011	Settlement of $A50 million for DOL to commercialise DiabeCell
2011	Grant is appointed CEO
2012	Pre-clinical studies for NTCell completed
2012	Snow is appointed to lead NTCell trial
2012	Tan re-joins LCT as Chief Science and Medical Officer, leading the clinical trials for DiabeCell and NTCell
2012	MedSafe approves Phase I clinical trials for NTCell
2013	A four patient Phase I/IIa clinical trial of NTCell in Parkinson's disease commenced.
2016	LCT raised AU$3.7M in fresh capital to conduct the Phase two trial.
2016	LCT initiated a research collaboration with the Centre for Brain Research.
2016	Positive results for the Phase I/IIa clinical trial were announced.
2017	A Phase IIb clinical trial of NTCell is currently underway in Auckland, New Zealand. Trial's results are expected by the end of 2017.

Stock price and trading volume (June 2007 – June 2017)

Teaching note for the Living Cells Technologies (LCT) case.

1. **Synopsis of the case**

The case is about the key decisions faced by the management of Living Cells Technologies (LCT) in the commercialisation of their intellectual property. The history of LCT's expertise lies in their patents around a solution to Type I diabetes through the use of pig cells. Over the course of some ten years, the company's expertise has evolved to include a proprietary encapsulation technology, a herd of pigs certified for manufacturing and a swath of patents regarding the use of pig islet cells for human health solutions. In the face of less-than-ideal phase-II clinical trial results for *Diabacell*, LCT Type I diabetes product, development of competing for novel solutions for Type I diabetes, and shifting investment priorities by venture capitalists and large pharma, LCT management faced some tough choices. What commercialisation pathways to pursue in the light of the uncertain market for biotechnology knowledge?

The case is set in New Zealand and Australia, a small industrialised economy geographically distant from the key financial, customer and regulatory markets typically associated with biotechnology. Over the course of the case, LCT established business partnerships in Australia (securing early-stage funding), Italy, Russia (for R&D collaborations and sites for its early-stage human trials), and Japan (for an equity joint venture with Otsuka) as it endeavours to commercialise its products. During the early years of LCT, societal concerns about genetic modification and weak capital markets led to complex background conditions. These conditions affected the decisions the management made at that time and provided a second set of issues around the firm's current trajectory.

2. **Target group/Positioning**

The case is aimed at postgraduate and executive students. It is written for audiences interested in the business challenges of science-based research commercialisation in light of the high uncertainty and long timeframes associated with biotechnology. We gained experience by using the case with research and executive students in bioscience and commercialisation programmes and PhD students from STEM subjects taking research commercialisation electives. It would be equally useful for executive audiences in strategy / strategic management / strategic innovation / corporate venturing courses where strategic decision-making and markets for knowledge are important topics.

3. **Learning objectives and key issues**

The overall objective of this case is that students can recommend a commercialisation pathway and a business model for to support LCT's NTCell technology.

Since this is a significant task, we break it down into some learning objectives:

- Assess the market for knowledge around LCT's NTCell technology
- Discuss viable commercialisation pathways LCT's NTCell technology and the different value creation and capture mechanisms associated with each pathway.
- Discuss regulatory challenges and IP/legal determinants.

Note: it might be that the case is used for one or some of the smaller learning objectives. Alternately, the case can be re-visited over multiple sessions addressing the smaller objectives and working towards the overall objective.

To achieve the learning objectives, key issues that require discussion include:

- Who are the customers in the market for knowledge that LCT is trading in?

  Often students do not distinguish between the seller that LCT is seeking to trade with, which is an organisational buyer of some sort (a pharma and biotech firm or potential of VC) as opposed to the customer of the final product (the insurance or private or public health purchaser), or the end-consumer (people whose condition can be treated with NTCell applications). It is important to make these distinctions. The information asymmetries are caused by all three but understanding the (potential) buyer is most important in assessing the market for knowledge. It is equally important to clarify what value is potentially created for that buyer and what value potentially can be captured by LCT.
- Where do the firm's (and to some extent the entrepreneurial founders) preferences fit?

  Often students, particularly executive students with strategy or entrepreneurship backgrounds, privilege the firm's or the founder's preferences about commercialisation pathways that support those goals. Regarding working out what commercialisation pathways are viable, it is important that students focus on understanding the issues related to information asymmetry, tacitness, specialised investment and IP protection that determine the market for knowledge first. Unless a market for knowledge can be established, then the goals of the firm/entrepreneur

are meaningless. I.e. if a firm cannot establish a market for its knowledge and business model, it will experience difficulties to find a buyer and to capture value from its knowledge.

4. **Teaching strategy**

We start by asking students what they think about LCT's main challenges abo ut commercialising Diabacell. Subsequently, we ask if those are the same challenges they're facing with commercialising NTCell. From here students usually establish that there are some common commercialisation challenges that matter – which relate to the market for knowledge – while there are some situational and learning challenges that are not (or less) pertinent.

We encourage students to describe the market for knowledge that leads LCT to list on the stock market to raise capital for Diabacell, prompting them to consider all facets. Since we use Pisano's (2006) model, we point toward information asymmetries, tacitness, and specialised investment and IP protection. We ask students what other pathways they would consider (e.g. seed capital, VC, JVs, licensing out, sell off the patents) and why they think those weren't pursued (see Bellavitis, Filatotchev, Kamuriwo, and Vanacker 2017 for a discussion of trends in entrepreneurial finance). Explain that certain buyers were discouraged by the high uncertainty, and others were not attracted because they couldn't capture value from LCT's research in a timely manner.

Once that line of questioning is exhausted, we ask how the market for knowledge changed to enable LCT to secure the equity joint venture, prompting students to clarify whether uncertainty had increased and decreased. Once we have exhausted this line of questioning, or students are demonstrating competence with key concepts, we move on to ask about the market for knowledge for NTCell.

Discussion of NTCell is harder since there are several 'unknown unknowns' (true uncertainty in Knightian terms) and students have to grapple with making reasonable assumptions to consider the relevant market for knowledge. We continue the questioning, focussing on what are viable commercialisation pathways given what is known and what are the reasonable assumptions in the face the uncertainties. At this point, it is useful to have a student scribe/map the ideas on a whiteboard so that different ideas are captured and refined. Also, in situations where students start making a lot of unrealistic assumptions, we probe them about how they think their hypothesis could be tested. How (and if) an answer would change the market for knowledge, and what are the most important hypotheses

(those using Steve Blank's key hypothesis testing concept might couch their questioning in those terms). Once two or three commercialisation pathways have emerged, we ask students which path they'd recommend and why. Often there is a lively debate.

5. **Background reading**

We suggest the following as pre-reading:

On markets for knowledge:

Pisano, G. (2006) Chapter 8: Organizational strategies and business models in *Science business: the promise, the reality, and the future of biotech*. Boston, MA: Harvard Business School Press.

Teece, D. J. (2013). Profiting from Innovation. In E. H. Kessler (Ed.), *Encyclopedia of Management Theory* (pp. 622–625).

Gans, J. S., & Stern, S. (2003). The product market and the market for "ideas": commercialization strategies for technology entrepreneurs. *Research Policy*, 32(2), 333–350

Arora, A., & Gambardella, A. (2010). Ideas for rent: an overview of markets for technology. *Industrial and Corporate Change*, 19(3), 775–803

On commercialisation pathways:

Pattnaik, P., & Pandey, S. (2014). University Spinoffs: What, Why, and How? *Technology Innovation Management Review*, 4(12), 44–50. (NB: although it is about university spin-offs, the introduction of commercialisation pathways is useful private commercialisation contexts too)

Lubik, S., & Garnsey, E. (2016). Early Business Model Evolution in Science-based Ventures: The Case of Advanced Materials. *Long Range Planning*, 49(3), 393–408.

On entrepreneurial finance:

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6. Experience of using the case

We have used the case four times with research students in a research commercialisation course that has a bioscience focus and four times with executive students in a science-based entrepreneurship course that have a science commercialisation focus. Also, we have used it as part of two-day workshops for STEM PhD students interested in commercialising their research.

In previous instances, the students have had multiple experiences of case-based analysis and classes are three-hours in duration. Because they are more skilled at preparing for and discussing cases, the discussion can easily run for 2-3 hours. In the research commercialisation course, we have used the case as the basis for a team assessment requiring students to undertake additional desk research into prospective buyers, potential competing solutions and the types of deals that LCT might benchmark against to estimate the financial and non-financial value the firm might expect. This extension is a substantial task (worth 30% of the course mark) and involved ¼ of the course time.

In the latter, students have neither prior experience nor skills in case discussion. Often their reading is superficial, so we revise the learning objectives to achieve lower-order outcomes such as identifying, labelling and illustrating key concepts that are important to the workshop.

In preparing for the case in all these instances, we find it is useful for students to:

- Draw themselves a timeline of key events of the firm's history and decisions made by the management to date. This is a long case and covers some 20 years, so it helps students to depict what they think is important.
- When we specify other pre-readings, we direct students to complete pre-work to illustrate and apply the models to the case, so they have some ideas to share.

7. Multimedia

An explanation of what LCT does from the CEO. The interview was from 2013 when the case was initially written. This is useful for a non-science audience as the nature of the

health issues and procedures are explained in lay terms https://www.youtube.com/watch?v=4fYHqWr47mU

An interesting video about NTCell, the cell therapy for the treatment of Parkinson's Disease and other neurodegenerative disorders can be found https://vimeo.com/145458852.