CEO on Strategy

Open Briefing interview with MD & CEO Andrea Grant

Living Cell Technologies Limited
Level 3, Suite 302, 70 Pitt Street
Sydney, New South Wales 2000

In this Open Briefing®, Andrea discusses:

- Underlying science of products in clinical development: DIABECELL and NTCELL
- Product differentiation, potential market size
- Cash position, funding adequacy

Record of interview:

openbriefing.com
Living Cell Technologies Limited (ASX: LCT) has two products in or about to enter clinical trials, DIABECELL and NTCELL, based on implants of micro-encapsulated cells derived from pigs, to treat diabetes and neurodegenerative diseases respectively. What is the science behind the activity of the two products and what are their key attributes as agents for diabetes and neurodegenerative disease?

MD & CEO Andrea Grant
DIABECELL is conceptually simple: it's essentially a cell replacement therapy. A person with type 1 diabetes has lost the insulin producing capability of their pancreas because their immune system has destroyed the islet cells in their pancreas. Islet cells release either insulin when blood glucose rises or glucagon when blood glucose falls. With DIABECELL, we're using pig islets to replace the blood glucose regulatory system. We put the pig islets in a capsule in order to protect the cells from attack by the immune system. Normally, if you put an animal cell into the human body, the immune system would destroy it.

Although NTCELL is based on the same technology platform of encapsulated cells, it's not based on a replacement approach, but on a regenerative approach. Basically, NTCELL secretes a host of growth factors, immunomodulators and other proteins that promote survival and growth of new cells. We've shown that NTCELL has a powerful ability to regenerate cells and restore function in animal models of Parkinson's disease, stroke, Huntington's disease and hearing loss as well as non-neurological conditions such as chronic wounds. It's also potentially useful in a range of other degenerative conditions. The first indication for which we're taking NTCELL into clinical development is Parkinson's.

openbriefing.com
What is the estimated size of the targeted markets for DIABECELL and NTCELL?

MD & CEO Andrea Grant
The target patient profile for DIABECELL is commonly described as a person with brittle or unstable type 1 diabetes. Standard of care is not sufficient for these patients: despite intravenously injecting insulin frequently during the day and regularly checking their blood glucose levels, these people can't keep their blood glucose within safe levels. Five to 15 percent of people with type 1 diabetes find themselves in this situation. We estimate there are approximately 12 million people with type 1 diabetes globally, of whom 8 million are adults. Initially DIABECELL is being trialled in adults, so we're looking at a target market of five to 15 percent of 8 million, which is between 400,000 to 1.2 million patients. The global market for insulin replacement therapies in 2012 was estimated at US$16 billion, and about

an eighth of this is related to people with type 1 diabetes. So, the market for insulin alone for type 1 diabetics is about US$2 billion, and that's without including the devices and monitors required to support the insulin injections. We intend to take a healthy chunk of the market.

For NTCELL in Parkinson's our ideal target patient profile is someone with mid-stage Parkinson's, people who have had the disease for five to 10 years and whose response to standard of care is diminishing. In 2011, it was estimated that there were about 4 million men and women with Parkinson's disease in the seven major markets, and about 35 percent, or 1.4 million of these will be mid-stage. The current global market for small molecule dopamine replacement therapies is around US$2 billion, of which at least $700 million would be for mid-stage patients.

openbriefing.com
How does your cell implant technology differ from stem cell therapies, which are currently a major focus of the life science sector?

MD & CEO Andrea Grant
It's worth pointing out that there isn't a single "stem cell therapy" approach. There are lots of different methodologies being developed by companies big and small using widely different stem cells as starting materials, a host of different culturing techniques and a multitude of differentiation techniques to turn the stem cells into the cell of choice. So, it's almost impossible to compare different stem cell therapeutic approaches, let alone a xeno- or animal-based cell therapy and a stem cell approach.

Rather than comparing at a technology level, I think it's more valuable to consider: is there enough evidence that the product will be clinically safe and efficacious; can the product be manufactured in a quality controlled environment and with a cost of goods that will lead to decent profit margins; and finally can the product be cost-effectively marketed and distributed so that it can be used simply and easily and treatment standards can be reproduced by clinicians at point of care. For any cell therapy approach, regardless of the underlying technology, all of those things need to be true for it to be commercially and clinically viable.

For DIABECELL, we're now in late-stage clinical trials so we've got reasonably high confidence that the product is going to be efficacious and safe. We have a GMP manufacturing process that meets the regulatory requirements of the New Zealand regulatory authorities, which are mutually recognised across the EU. We also understand our cost of goods and point of care administration, so we're confident DIABECELL as a cell therapy technology has a robust business model and meets the requirements for business profitability.

NTCELL for Parkinson's is at an earlier stage clinically, so of course the clinical risk is higher. However, the manufacturing process will again meet the regulatory requirements in New Zealand and the production process for NTCELL means the potential to scale up for high patient volumes is potentially even greater than for DIABECELL.

Overall, our cell therapy technology platform is as advanced in terms of commercial and clinical usefulness as any stem cell technology out there.

openbriefing.com
Given the basis of your technology is implanting cells derived from pigs, how do you mitigate the risk of zoonotic infections?

MD & CEO Andrea Grant
We use "clean pigs" derived from a herd that spent over 200 years in isolation from humans and other mammals on a small sub-Antarctic island 300 miles south of New Zealand. The pigs are naturally free of many of the diseases and viruses found in other pig herds. Importantly, the pigs are "null" for the virus that regulators are most concerned about, pig

endogenous retrovirus (PERV). We're the only company in the world with access to this herd, and we also have IP protecting its use for xenotransplantation therapies.

We house these clean pigs in a specific pathogen free (SPF) grade bio-isolation facility, so the risk of them becoming infected today is very low. We're also the only company in the world with an in-house molecular diagnostics capability that screens the pig herd three times per year, screens all products going out of the manufacturing facility as part of our quality control and quality assurance, and screens trial patients at one, two and five yearly intervals.

openbriefing.com
Both NTCELL and DIABECELL are encapsulated using your proprietary IMMUPEL technology. What is the importance of this to the activity of the cell implants and are there other applications in which the IP could be used?

MD & CEO Andrea Grant
IMMUPEL is very important to protect the pig cells from attack by the immune system. It's worth also noting that as well as animal cells most "allogenic" (stem) cell therapies derived from other species or other humans will also require immunosuppressants. IMMUPEL allows us to deliver our product without needing to administer immunosuppressants which can have long-term complications and challenges for patients. This protection from the immune system is central to our unique selling point but also central to our products' efficacy.

We also believe the IMMUPEL technology has other applications. As I said, any allogenic cell therapies will need to be protected from an immune response, as the starting material is from a different patient. We're targeting the development of this IP and formation of partnerships around the technology as an area for business development in the next 12 months.

openbriefing.com
Both DIABECELL and NTCELL are being developed by Diatranz Otsuka Limited (DOL), a 50:50 joint venture between LCT and Otsuka Pharmaceutical Factory Inc. What is the development strategy for the products and how will your clinical trial strategy position the products in the major markets such as the US and Europe?

MD & CEO Andrea Grant
Just to clarify: only DIABECELL is being developed by DOL at present. At this stage, for NTCELL in Parkinson's, we have a co-development agreement with Otsuka for the Phase I study. Under the agreement, Otsuka pays all the expenses we incur in relation to the Phase I study, as well as a A$5 million fee for the option of transferring NTCELL into DOL if the Phase I study is successful.

With DIABECELL, we were the first company to have sought and gained regulatory approval for clinical trials of a xeno-based cell therapy product. To do that, we had to overcome some significant ethical and regulatory issues: it took four years to get New Zealand regulatory approval to run the first human clinical trial of DIABECELL. Because we were "trail blazing" with DIABECELL, we focused very much on New Zealand and developing a strong relationship with the regulators here. Now Otsuka is involved, we're starting to address our clinical development strategy for DIABECELL in the major European and US markets in earnest.

For NTCELL, we had the precedent and learnings from our clinical development of DIABECELL, and it only took us six months to get regulatory approval for clinical trials of the product in New Zealand. Also, because we have a major partner on board so early, we're likely to be more aggressive in terms of trialling NTCELL in the major markets early in the development process. We'd hope that we'd be in Europe and the US at the Phase II trial stage, rather than at a later stage as we are with DIABECELL.

openbriefing.com
Can you provide an update on the current clinical trial progress of DIABECELL and NTCELL?

MD & CEO Andrea Grant
We completed an interim analysis of our ongoing Phase I/IIa study of DIABECELL in Argentina in November last year. That analysis showed us that at higher doses of DIABECELL there was a clear clinical benefit: a significant reduction in glucose levels, the dose of insulin patients needed to inject was less and the incidence of unaware hypoglycaemic events was down.

We've now started a Phase IIb study of DIABECELL in Argentina, with 20 patients due to receive the higher dose and the first three patients having already been transplanted.

For NTCELL, we're hoping to transplant the first patient in the Phase I trial next month.

openbriefing.com
As at 31 December, LCT had cash of A$2.3 million, down from A$2.9 million at 30 September, and in the current quarter you're due to receive a A$3 million option fee from Otsuka to jointly develop and commercialise NTCELL. Given cash burn of A$0.8 million in the December half (implying cash burn of A$1.6 million pa), do you have adequate funding for your planned activities over the next 12 to 18 months?

MD & CEO Andrea Grant
Yes! This quarter we've received the A$3 million option fee from Otsuka, so as at today we have a cash balance above A$5 million. Then there's the additional option payment of A$2 million which will be paid by Otsuka after the first patient has been transplanted safely with NTCELL. We'd hope that will be paid by the end of the September quarter, at which point we'd expect our cash balance to be around the A$7 million mark.

Our cash burn going forward will be a lot less than in the December half of 2013, because Otsuka is now paying all of the costs associated with NTCELL R&D and the Phase I clinical trial. If the trial is successful – and we'd expect the trial to end around June 2014, 12 months after the first transplant – Otsuka has the option to move the IP into DOL, at which point Otsuka will transfer A$20 million into DOL for NTCELL's future development. DOL already has approximately A$15 million cash, which we're still confident is sufficient to complete clinical trials of DIABECELL and bring it to market.

Essentially, the clinical development around both these products is fully funded by our partner, so we don't need to raise further funds from our shareholders or use our own cash to run those two programmes. On the basis of our current operations and our non-NTCELL and DIABECELL activities, we're expecting cash burn of approximately A$1 million pa, so if we do nothing other than develop the two products for the two indications, we have about seven years of cash, which is well within the time frame of bringing the two products to market.

However, we're more ambitious than that. We've got some business development projects we want to kick off this year, which we're just working up the details of. Once we have some more clarity on those projects, we'll be able to provide more information.

openbriefing.com
Given Otsuka will fund the ongoing development of DIABECELL and NTCELL within DOL, what will be LCT's involvement in and ability to influence management of DOL?

MD & CEO Andrea Grant
One of the great things about our partnership model is that we have true 50:50 control of DOL with Otsuka. DOL is a privately held New Zealand company, with only LCT and Otsuka

as shareholders. Both companies have two directors on the board, and so decision making needs to be unanimous.

Likewise, DOL's scientific advisory panel and commercial advisory panel are made up of equal numbers of representatives from both companies' executive management, which gives LCT real influence in decision making and control of the product. That contrasts with many biotech-pharma licensing deals, where companies tend to lose control to the "bigger" partner.

openbriefing.com
What are the opportunities for LCT outside the areas of diabetes and neurodegenerative diseases?

MD & CEO Andrea Grant
There's published data in small animal studies showing NTCELL can improve outcomes in wound healing, so we're planning work in that area. We have work underway in diseases of the peripheral nervous system, such as retinopathy, which aren't part of the Otsuka option agreement. We also have a number of other programmes and partnerships underway or in planning, but for commercial and confidentiality reasons, I'm unable to discuss them as yet.

openbriefing.com
Thank you Andrea.

For more information about Living Cell Technologies, visit www.lctglobal.com or call Andrea Grant on (+64 9) 276 2690.

For previous Open Briefings by Living Cell Technologies, or to receive future Open Briefings by email, visit openbriefing.com