Progenitor Labs Ltd

For stem cells, business models differentiate

Business models for regenerative medicine are in transition. A recent report by the Science and Technology Committee of the UK House of Lords noted that it wasn't possible for a small company with new technology to survive without a broader network of support from funders and public institutions.

This concept of shared responsibility – otherwise known as open innovation – is being tested at a site in Stevenage, UK, not far from London. This is the location of a new bioscience park – the Stevenage Bioscience Catalyst – which has been jointly funded by the government, GlaxoSmithKline Plc (GSK) and the Wellcome Trust.

Among the first tenants at the SBC are the stem cell companies Plasticell Ltd and Progenitor Labs Ltd. Here, the two companies are developing new science and new business models.

The situation is unusual in that the founder of the two companies, Yen Choo, already has a formal relationship with GSK, which has a major research facility at the site.

In March, GSK's venture capital arm, SR One, awarded £4 million in seed funding to Progenitor Labs, the younger of the two companies. Through informal contacts dating back more than five years, Dr Choo established relationships with both the oncology and stem cell divisions of GSK whilst doing proof-of-principle tests for his technology platform. This relationship looks set to flourish in the biocatalyst setting.

The question now is whether this will also spur development in the wider regenerative medicine community. A serial entrepreneur, Dr Choo has a distinct take on regenerative medicine.

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>
> *Yen Choo*

"It is fairly clear that in regenerative medicine some indications are best pursued through a cell therapy route and some through a drug therapy route," he said in an interview with *MedNous*. Those medical indications that are uniquely suited to the use of *cells as therapy* are acute injuries to the skin or damage to the blood. The drug therapy route, on the other hand, can be used in a wide variety of medical indications – mostly non-critical.

Dr Choo founded Plasticell in 2002 in order to develop a screening technology for stem cell research applications. The technology is a combinatorial screening platform that can direct the differentiation of embryonic, induced pluripotent, or adult stem cells into a variety of somatic lineages as well as into progenitor cells. Progenitor cells are cells that are at an advanced state of differentiation but not fully differentiated. In other words, they are short of their final destination. One of the applications for this technology is to produce progenitor cells for platelets – something that could be stockpiled in the event of a medical emergency.

Progenitor Labs, the second company, was spun out of Plasticell in 2011 in order to develop a different technology. Using the Plasticell screening platform, Progenitor is able to produce synthetic progenitor cells that resemble those which lie dormant in human tissue. It then conducts screens of small molecule compounds in order to identify those compounds capable of instructing the progenitor cells to reach their final destination, or therapeutic endpoint. This endpoint could be the repair or restoration of organ function. Dr Choo refers to these compounds as 'small molecule regenerative drugs'.

Although he is the founder of both companies, Dr Choo has retreated from the direct management of Plasticell in order to devote his energies to developing Progenitor Labs. He is currently executive chairman of Plasticell and chief executive officer and chief scientific officer of Progenitor Labs. Dennis Saw is CEO of Plasticell.

The reason for having separate managements is that the business models of the two companies are different: Plasticell is focused on cell therapy, while Progenitor is focused on small-molecules that will lead to regeneration.

"The skills that you are going to need in the two different companies, as well as possibly the relationships with collaborators and also the levels of funding, are going to be very different," Dr Choo commented.

Having said this, there are licensing and service agreements between the two companies and they both work side-by-side in the Stevenage Bioscience Catalyst's 'open innovation' setting along with GSK. Dr Choo describes the synergies this way:

First as a spin-out, Progenitor Labs uses technology from Plasticell. "Experienced Plasticell scientists are engaged in the [Progenitor] projects, and indeed lead two out of three discovery projects. Plasticell obtains revenue from Progenitor, and as a shareholder, will share in the upside if the programmes are successful," the executive commented.

Second, GSK is contributing resources and expertise to the projects. Progenitor consults GSK experts on assay development and screening and has access to GSK's drug discovery resources. For its part, GSK's stem cell unit has an insight into Progenitor's research strategy and technology.

Finally, through SR One, GSK shares in the risk and the upside of Progenitor. Progenitor is able to take advantage of SR One's network of contacts to meet other pharmaceutical companies and financial investors.

Plasticell and Progenitor Labs were not Dr Choo's first companies. In fact, his first entrepreneurial venture was Gendaq Ltd, a company that he co-founded with Timothy

Brears in 1999 to exploit the research of Aaron Klug, a Nobel laureate in chemistry. Dr Choo worked with Professor Klug on his PhD in molecular biology at the University of Cambridge.

When he and Dr Brears spun out Gendaq from the UK Medical Research Council's Laboratory of Molecular Biology, Prof Klug had already moved from his post as director of the laboratory to become president of the Royal Society.

The technology underpinning Gendaq involved regulating genes by engineering transcription factors found inside cell nuclei called zinc finger DNA-binding proteins. The goal was to discover and validate new drug targets. In 2001 Sangamo BioSciences Inc[1] of the US acquired Gendaq and Drs Brears and Choo left for other ventures. In 2002 Dr Choo founded Plasticell with a view to focusing on cells.

"I wanted to focus on engineering, not proteins but cells, and thought of a way in which you could do that with stem cells using combinatorial approaches. That is how Plasticell was born.

"There are two things that you want to fiddle with in cells. One is the genotype and the zinc finger technology is probably the leading method for engineering the genotype of a cell nowadays. The other thing you want to fiddle with is the phenotype. In order to fiddle with the phenotype you probably have to culture the cells and treat them and manipulate them in a way that causes them to change their phenotype without the genotype having been altered. That is what Plasticell does in its most basic form," the executive said.

The screening technology

To accomplish this double act, it was necessary to observe how stem cells differentiate and then to work backward to identify the combination of growth factors that produced a specific result. Dr Choo and colleagues seeded small microscopic beads with stem cells (eg embryonic, induced pluripotent, or adult stem cells) and then split the beads into different samples. Each of the samples was fluorescently labelled and incubated under different conditions. Borrowing from combinatorial chemistry, the researchers sampled all the different combinations of conditions in order to find out what the cells required in order to differentiate. And then they carried out screens on all of the beads to find out which displayed a particular cell type. Antibodies were used to identify the cell type.

"Once you have isolated the beads with the cell type that you are after, then you look individually on each bead for the fluorescent tags that they picked up along the way. That way you can trace the cell culture history," Dr Choo commented.

At the end of the day, the experiments throw up many protocols. The art is to select the most suitable protocol for the task at hand. In the early years, Plasticell offered services to pharmaceutical companies that needed cell lines for research. More recently the company has been moving away from services to focus on making cell therapies.

Progenitor Labs was spun out of Plasticell in 2011. But years before that Dr Choo had begun to think about a way to use the Plasticell technology to make 'small molecule regenerative drugs'. The idea came from an analysis of erythropoietin (EPO), the hormone that controls red blood production. Too little erythropoietin in the body means too few red blood cells and anaemia. The drug, Epogen, is a synthetic erythropoietin used to treat anaemia caused by chronic kidney disease.

The analysis revealed that erythropoietin has its effect by working on red blood *progenitor* cells rather than on haematopoietic stem cells, or the stem cells that form blood and immune cells.

"I had the idea that if you had a bucket of these red-blood cell progenitors you could use them in a screen to discover either EPO itself, or the next EPO," Dr Choo recalled. To test this hypothesis Dr Choo's group, together with researchers at GSK, used the Plasticell screening technology to pick out an agonist of granulocyte colony-stimulating factor (GCSF) using cell material that had been derived from stem cells.

Needless to say, Dr Choo filed a patent on his invention and also held conversations with other practitioners in the field, namely Fate Therapeutics Inc in the US which was working on similar technology. One upshot is that Paul Grayson, the former CEO of Fate, is currently on Progenitor's board of directors.

Rediscovering Promacta

Dr Choo also approached GSK to discuss doing a proof-of-principle experiment to rediscover Promacta (eltrombopag), a small molecule drug to treat abnormally low platelet counts that was approved by the US Food and Drug Administration in 2008. "After having done mouse experiments I said to them: let us show you, this time using human embryonic stem cells, that we can rediscover Promacta." And they did it.

"The importance of this was, that if you discover one of these small molecule drugs that can generate one particular organ you can probably do that for other organs as well… This is how GSK first became interested in what we did," the executive said.

Plasticell and Progenitor officially took up residence at the Stevenage Bioscience Catalyst on 10 June. As an 'open innovation' centre, SBC aspires to be a hub for cell therapy and regenerative medicine in the UK.

Dr Choo said that many different business models will likely co-exist on the site. In regenerative medicine this could be regenerative drugs or cell therapies. "For example, do you want to develop generic EPO to increase red blood cell count, or do you want to develop synthetic red blood cells from hESC (human embryonic stem cells) for blood transfusion… The two therapies are suitable for different indications, and have different business models," he said. At the end of the day the question is: which market does a company wish to pursue?

Reference:

1. Sangamo BioSciences announced on 17 July 2013 that its technology had been used to 'silence' the extra copy of chromosome 21 which is the root cause of Down syndrome. This was accomplished by using zinc finger DNA-binding protein technology. http://investor.Sangamo.com.

The editors of *MedNous* prepared this article on the basis of a literature search and an interview with Dr Yen Choo at the Stevenage Bioscience Catalyst in May 2013.