

Small beginnings

Using zebrafish larvae to screen drugs, Paul Goldsmith has built up the Cambridge-based company DanioLabs. Meanwhile, Mark Carlton's company, Paradigm Therapeutics, has been investigating G-protein coupled receptors – proteins that, if controlled by drugs, could alter the progression of some diseases.

IN A NUTSHELL

- **Technology Transfer funding from the Wellcome Trust** backed the Cambridge-based companies DanioLabs and Paradigm Therapeutics during their early stages.
- **DanioLabs has used zebrafish larvae** to screen drugs.
- **Paradigm Therapeutics has used mice** to study the function of G-protein-coupled receptors.
- Both **DanioLabs and Paradigm Therapeutics were acquired by larger companies** in early 2007.

TAKING SCIENCE TO MARKET

From start-up to big business

The journey from start-up to big business is fraught with challenges. But two biotech companies backed by Wellcome Trust funding have recently been bought up for millions. Paul Goldsmith and Mark Carlton – the founders of DanioLabs and Paradigm Therapeutics, respectively – explain how they became science entrepreneurs.

Back in 1999, Paul Goldsmith was a respected and successful clinical neurologist at Addenbrooke's Hospital in Cambridge, UK. Today, he still works at the hospital but he's now also a science entrepreneur, a man who took a smart idea and turned it into a multimillion-pound biotech concern in a matter of just five years.

It was Dr Goldsmith's beginnings at the bench that set him onto the rollercoaster ride into the business world. He'd noticed something interesting. "There were lots of drugs being prescribed for indications they weren't invented for," he says. Gabapentin, for example, was a drug being used to control epileptic seizures. But it soon became clear that it had a more widespread and therefore more lucrative effect as a treatment for nerve pain.

"Time and again there was this story of a drug being developed for one reason but ending up being prescribed for another," says Dr Goldsmith. This gave him the idea of coming up with a quick and easy method of screening existing drugs for their ability to treat other conditions.

His first decision was to settle on a model organism, a vertebrate that might offer insights into the human condition, could be easily manipulated, was cheap to work with and had the potential to act as a compound screening system. In these regards, the zebrafish (*Danio rerio*) had a lot to commend it (see box, page 36).

This tiny, bright fish drew him towards Bill Harris, Professor of Developmental Biology at the University of Cambridge, and he began a PhD to explore ways of using larval zebrafish to identify new functions for old drugs. "He took me on as a bit of a risk," says Dr Goldsmith. "We saw a common opportunity, but hadn't really nailed it down or distilled it."

While most PhD students are happy to begin their academic career with their feet firmly rooted in the library, Dr Goldsmith spent the first few months out on the town. As a hub for the biotechnology industry, Cambridge was a perfect place to be. "I used the Cambridge network to meet people in the pharmaceutical industry," he says.

By Henry Nicholls, a science writer based in London.

It was at this point that he began to appreciate the appetite for such a screening system among the pharmaceutical companies. Not only could they use it to screen existing drugs for their potential to offer therapy in other areas but they could also revisit thousands of drugs that had been consigned to the development dustbin. Many of these had seen years of investment and had already been through toxicology tests, so the development time of promising leads would be very rapid.

At the same time, Dr Goldsmith realised he would have to develop his business skills. He made the idea more credible by coming up with a catchy name for the company: DanioLabs Ltd. He filed a patent to protect part of the zebrafish technology crucial to the screening system. Lawyers and accountants had taken a punt on him, prepared to run up a bill knowing that if DanioLabs didn't make it they would never see a penny. Financial consultants came in on a similar basis to smarten up projections of turnover and income. Dr Goldsmith put together a glossy commercial package, learned facts and figures to support his business case and honed its presentation. "It was an incredibly steep learning curve," he says.

This business preparation was done in his spare time and largely with his own money. "I paid my first recruit out of my own pocket," he says. But personal sacrifice was a necessary step towards the next big hurdle: persuading someone to stump up some serious financial backing.

Getting the interest of and the money from venture capitalists was a bit like driving a Formula One car with the very real possibility of running out of petrol before the next pit stop, says Goldsmith. "You've got to have a slight delusional element because if you really knew the chances of success you probably wouldn't do it."

On one occasion, he'd flown over to the USA to meet up with a major pharmaceutical company that had shown an interest, only to discover they'd cancelled without letting him know. "I found myself in a fairly remote area and they didn't so much as offer me a cup of tea," he says.

In the face of such setbacks, it would have been easy to give up. "You've got to be resilient," he says. Ultimately, his tenacity and energy pulled him through and in 2002, DanioLabs secured initial funding of £1.2 million from Catalyst BioMedica Ltd (what was then the technology transfer arm of the Wellcome Trust) and the Cambridge Angels, a group of local investors specialising in financing biotechnology start-ups.

This was enough to buy in the assets and the people. "I'm very proud of the team," says Dr Goldsmith. "We set out to get a particular ethos in the company right from the start, knowing that this would carry through and be extremely important." And the greatest determinant of success or failure is the quality of the management, he says.



Steve Wilson

WHY ZEBRAFISH?

Zebrafish (above) have great potential to act as a model for certain human diseases. The sequencing of the zebrafish genome has helped the field to move ahead rapidly, and there are plenty of tools for overexpressing, underexpressing or knocking out particular genes.

A single pair of adults will breed once a week, producing up to 200 offspring at a time. A moderate-sized aquarium can therefore generate tens of thousands of experimental animals every year. They grow rapidly, with their basic body plan mapped out within just 24 hours, so within days it's possible to study most of the organs.

This makes zebrafish far cheaper than other experimental vertebrates. "The cost ratio of husbandry compared with mice is between 1 in 100 and 1 in 1000," notes Paul Goldsmith. More importantly, hatchlings can live in as little as 50 microlitres of fluid, so can be tested against minute amounts of drugs, which might be expensive to synthesise. Finally, of course, they don't raise ethical hackles to the same extent as other, more complex experimental animals.

This was an area in which Dr Goldsmith did not imagine he'd excel. "I assumed that as soon as the company was up and running and the people were in place, I'd return to the bench as a research scientist," he says. That never happened and, increasingly, he found himself in a management role. "It was these aspects I found most interesting and did much more of than I expected," he says.

In March 2007, with two products in clinical development, one in preclinical development and plenty of others showing promise, leading UK biotechnology company VASTox plc (now Summit plc to reflect its 'evolved' status) acquired DanioLabs for £15m.

"Going back four or five years, if you'd said we'll use small, silver fish to find drugs, a lot of people would have wondered what was going on," says Richard Seabrook, Head of Business Development at the Wellcome Trust. The Trust's decision to support DanioLabs in its earliest days was a bold one. But the recent takeover shows it was clearly sound, says Dr Seabrook.

For Dr Goldsmith, the acquisition of DanioLabs is by no means the end of the road. "I try to think of each stage as an instar in development," he says. "The journey continues, but it's a different journey."

A paradigm business

This experience is mirrored by that of Mark Carlton, another Cambridge-based scientist-turned-entrepreneur. "The first meeting was held at my house to discuss the applications of the techniques we were working on academically to an industrial setting," he says.

The goal of Paradigm Therapeutics Ltd, as Dr Carlton's company became known, was to use mouse models to explore the function of novel G-protein-coupled receptors (GPCRs) identified during the human and mouse genome sequencing projects. These are receptors that sit in the membrane of cells and that play a key role in many signalling pathways, so finding drugs to bind to them could be useful for manipulating the progression of certain diseases (see box, right).

With guidance from local venture capitalists and a £543 379 award from the Wellcome Trust, Paradigm began to demonstrate the principle before it could be turned into a commercial operation. Then in a succession of funding rounds, the company raised some £25m over the course of about five years. All this was new to Dr Carlton, who brought a retired venture capitalist onto the board to get an insight into how their minds work. "That was very good training," he says.

In addition to financing a steady improvement of the technology underlying the business, the new money allowed Paradigm to establish a secondary branch of the operation in Singapore. "This increased our capacity and built in an element of security to the business," says Dr Carlton.

By the end of 2004, Paradigm's scientists had identified hundreds of promising GPCRs. The next strategic move, says Dr Carlton, was to acquire Amedis Pharmaceuticals Ltd, a company with the chemistry know-how to begin synthesising drugs.

In June 2005, Paradigm struck up lucrative commercial partnerships with two large pharmaceutical companies, allowing them to test their own drugs on Paradigm's expanding database of potential targets. One of these companies – Takeda Pharmaceutical Company Ltd, the largest pharmaceutical firm to come out of Japan – obviously liked what it saw because in March 2007, it acquired Paradigm's considerable biological nous. Dr Carlton remains modest. "It's going well," he says.

Both he and Dr Goldsmith are prepared to offer up a few nuggets of advice to any would-be science entrepreneurs. "Ideas come cheaply but doing something about it is a big hurdle," says Dr Carlton. Putting together a team with a broad range of talents is the way to make progress, he says.

Dr Goldsmith agrees that networking and team building are crucial. "Get involved with a team made



RECEPTIVE IDEAS

In the run-up to takeover, Paradigm Therapeutics had developed a promising pipeline of novel drugs targets that might be of therapeutic value in areas where new treatments are urgently needed.

Their approach has been to use mice to study the function of G-protein-coupled receptors (GPCRs), a large family of transmembrane receptors that sense molecules outside the cell and trigger intracellular responses. Once they've identified a GPCR that could play a role in disease, they can begin to think about how drugs might alter its function and benefit the patient.

For example, Paradigm scientists knocked out a particular GPCR in mice and found the animals never went through puberty. This suggested that the receptor – known as GPR54 – might be needed to stimulate the hypothalamic-pituitary-gonadal axis, a crucial step in the synthesis of reproductive hormones. Indeed, it turned out that people with a mutant form of GPR54 suffer from idiopathic hypogonadotropic hypogonadism and do not experience pubescence.

With a sound understanding of the fundamental function performed by GPR54, the Paradigm scientists were quick to spot its potential for the treatment of cancers that rely on sex hormones to grow. A drug that can bind irreversibly to GPR54 will effectively switch off the HPG axis, stop the synthesis of testosterone and oestrogen in the gonads, and prevent the growth of the tumour.

up of people with different skills," he says. Both men also stress the importance of a willingness to change, compromise and accommodate. "But if you want to be involved in business then go for it," says Dr Goldsmith. "And keep at it."

Above: The first meeting of Mark Carlton's company – now Paradigm Therapeutics – took place in his house. But having raised £25 million over about five years and developed a promising pipeline of novel drugs, the company was taken over in 2007.

Paradigm Therapeutics