Scotland’s universities have a long tradition of excellence in biomedical and life sciences research. This issue highlights how this expertise has underpinned the development of many innovative Scottish biomedical companies, turning exciting ideas into new drugs and other pharmaceutical solutions, which have major international impact.

These are challenging times for the pharmaceutical industry. The difficulty of producing safe new drugs that can meet stringent safety regulations and be brought to market has resulted in high risks and hugely increased costs. As a result, pharma has severely cut back on its in-house research and development, and looks to reduce costs and risk by outsourcing many aspects of the drug discovery pipeline. Thus pharma increasingly looks to identify promising new drug candidates developed by smaller biomedical and biotechnology firms that can test the feasibility of new methods and technologies. This provides a great opportunity for the biotechnology sector in Scotland, thanks to the strength of basic research in Scottish universities and the resulting pool of highly trained and well educated personnel able to staff new biomedical companies. If we are willing to invest in innovation, and are willing to take risks and not insist on short-term financial returns, many Scottish companies can flourish, effectively filling a gap in the market created by the financial and technological realities of modern pharma.

While Scotland is exceptionally well placed to take advantage of the changing face of pharma, we should never be complacent. Professor Roland Wolf, while noting that “Research collaborations between universities, the pharmaceutical industry and biotechnology companies are an integral and highly successful component of all Scottish universities,” suggests that there has been a slowdown in the rate of forming new companies, and that “new ways are needed to support academics as founders of companies in achieving the correct balance between academic and commercial work.” (see Profile of CXR Biosciences on Page 20 and Viewpoint on Page 27).

The new Chief Scientist for Scotland, Professor Andrew Morris, highlights the many advantages in Scotland for conducting healthcare research, thanks to the strength of basic research and excellent healthcare and the efficient organisation of healthcare informatics. However, Professor Morris also argues that Scotland must be careful to avoid damaging internal competition and continue to improve efficiency in the face of increasing external competition [see Profile of Aridhia on Page 8 and Viewpoint on Page 26].

NovaBiotics (Page 4) is a good example of an innovative company making a name for itself in a specialist area of biotechnology, backed by investors who are willing to wait for returns. The Aberdeen-based company is developing a range of drugs based on antimicrobial peptides, including a new treatment for nail fungus – a market worth billions of dollars a year. “We design the drugs and license the recipe to pharma,” says chief executive Deborah O’Neil. Biomedicine is not only about drugs – it is also about outcomes. Aridhia (Page 8) is a highly successful company using informatics as a powerful tool to fight chronic diseases, developing solutions for healthcare – and self-care – based on intelligent analysis of healthcare data. For drugs to be effective, it is critical that they are delivered efficiently to their site of action and in the right doses. This is where Glasgow-based XstalBio (Page 11) comes to the fore, developing delivery solutions for new therapeutic proteins, vaccines and peptides.

There is no simple formula for success in the biotechnology sector, as our Profile of MD Biosciences (Page 14) suggests. “We had no intellectual property (IP),” says co-founder Professor Paul Garside. “But who says that you need IP to spin out a successful biomedical company?” MGB Biopharma (Page 17) is not just developing new anti-bacterial drugs, but a new way of doing pre-clinical research – and a new way of building a drug development business.

Aberdeen’s Antoxis (Page 23) is developing a chemical platform, based on the flavonoids found in fruit and vegetables, to develop a new range of powerful drugs to treat established diseases such as cancer, and provide novel small molecules for use in the regenerative medicine industry.

This issue of Science Scotland demonstrates the huge potential in Scotland for combining academic excellence with commercial opportunity. Biomedicine already plays an important role in the Scottish economy and offers the prospect for huge growth potential in future.
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ANY VIEWS EXPRESSED IN THIS PUBLICATION DO NOT NECESSARILY REPRESENT THOSE OF THE ROYAL SOCIETY OF EDINBURGH, NOR ALL OF ITS FELLOWS.
Inspired by nature

Core business: Drug development
Location: Aberdeen
Founded: 2004
Number of employees: 15

Aberdeen-based NovaBiotics is on the brink of a significant breakthrough in drug development – and hopefully a much-deserved return for its investors in the not-too-distant future...

According to the Chief Executive of NovaBiotics, Deborah O’Neil, the company she founded eight years ago has no products, customers or revenues – yet. But it has already attracted investments of £10 million and has completed clinical trials for a drug which could generate £1.5 billion in sales in a market worth an estimated £3 billion a year.

Novexatin® is designed to cure an ugly and painful condition that affects about 12 per cent of the world’s population: onychomycosis, or “nail fungus.”

According to O’Neil, the company is considering raising a further £10 million in funds to further progress this revolutionary new drug towards commercialisation, along with two other potential best-sellers – drugs to fight cystic fibrosis (Lynovex® now has ‘orphan’ approval in Europe) and candidaemia, a potentially fatal bloodstream infection. In parallel, the company is also in discussions with potential strategic pharmaceutical partners with a view to out-licensing Novexatin® and thereafter jointly developing it for the clinic.

As well as having various patents for Novexatin® and at least 80 other applications pending, O’Neil believes communication is essential to win the support of investors. “We have to keep them updated with all and any tangible technical progress within the company,” she says, explaining that this is important if investors are to “keep the faith” in the longer-term value of the company’s platform and pipeline products – recognising that development life-cycles tend to be much longer for biotechnology than for most other sectors.
The industry model has moved on, but the majority of the investment community hasn’t caught up yet – an exception being our investors, who have stepped into the breach to support us and get us further down the development track than originally planned.

“Raising funds in this sector often feels like being on a treadmill,” says O’Neil. “Rather than moving on from Round A to Round B and so on in the traditional sense, we’ve been more focused and leaner in our financing model, but this has meant going from A to Z and round again.

“This is true for most early to mid-stage biotechnology companies and their need for cash,” she adds. “The industry model has moved on, but the majority of the investment community hasn’t caught up yet – an exception being our investors, who have stepped into the breach to support us and get us further down the development track than originally planned.”

O’Neil identifies three “key pieces of data” which investors rely on:

1. effectiveness of drug candidates over the competition and key differentiators
2. safety of the drug over competition – marketed and in development
3. good market research to support claims of commercial potential of each product candidate

With Novexatin®, it’s also important that it penetrates the nail, so the drug reaches the target fungi.

The market leader in nail fungus treatments [Lamisil tablets] only offers a success rate of 38 per cent in patients with mild to moderate disease, relapse is common, and this and other systemic antifungal treatments are associated with well-described side effects and safety issues. The currently available topical [brush-on] treatments have even worse efficacy profiles than Lamisil. But according to O’Neil, Novexatin® (which is also a topical treatment) acts ten times faster than the “best of the bunch” of these products and has a ten times better success rate, according to studies conducted so far. In addition, it only needs to be applied once a day for a month.

The other key products in the company’s pipeline are Novamycin® and Lynovex® (see sidebar). The latter recently gained “orphan drug status,” so it can be fast-tracked to clinical trials on the basis that it treats a relatively rare condition – cystic fibrosis – which only affects about 70,000 people worldwide. Other products in the portfolio are designed to treat conditions such as MRSA, acne and dandruff.

Lynovex®, says O’Neil, is a classic example of serendipity in science. While investigating compounds which might assist in getting drugs to penetrate nails, as part of the development of Novexatin®, the research team discovered a compound which could disrupt bacterial biofilms that are the major issue with the lung infections associated with cystic fibrosis.

NovaBiotics designs and develops novel drugs, but manufacturing and marketing will be handled by its commercial partners – major pharmaceutical/biopharmaceutical companies – who will pay licensing and development milestone fees to NovaBiotics, as well as royalties for every product sold once the drugs reach the market. This will leave NovaBiotics to focus on what it does best. “We design the drugs and license the recipe to pharma,” says O’Neil.

According to O’Neil, revenue from these alliances will be “returned to the shareholders and re-invested into pipeline development, to facilitate expansion and maximise even greater investor returns.”

The science

NovaBiotics focuses on the design and development of novel anti-infective therapies for difficult-to-treat infectious fungal and bacterial conditions, including life-threatening infections such as candidaemia and cystic fibrosis, using its “unique patented peptide anti-infective technology” – drugs based on the antimicrobial peptides produced in our bodies “as the first line of defence against any infectious challenge.”

Peptides are simple chains of amino acids. And insulin is another example of a peptide drug.

NovaBiotics’ technology is not only “more effective and safer than conventional antimicrobials”, but also kills rather than merely inhibits the pathogens that it targets and, in so doing, minimises or even rules out the risk of antibiotics drug resistance developing.

To develop drug candidates ready for clinical trials, NovaBiotics uses an approach called “rational drug design” which fast-tracks the process by working back from knowledge of the molecules that nature uses to fight infections and turning them into therapies, rather than screening hundreds of thousands of chemical compounds to find one that works. This can cut the time it takes to get a drug to market by up to 75 per cent – down to only five years in the case of Novexatin®.

Says O’Neil: “It can take 12 years and at least $2–$7bn to get a drug to market – unless you do it the NovaBiotics way, which gives you more years of sales whilst the drug is still on patent.”
“The big pharmaceutical companies no longer focus on R&D,” she continues, “and don’t tend to licence or acquire technology until the later stages of clinical development.” In recent years, there’s been a global cull of research in pharma, she adds. The blockbuster drugs developed in the 1980s will soon drop off the patent cliff and there is not much in the pipeline to replace them. As a result, pharma is turning more and more to biotech to come up with the new drug classes and real innovation – but it tends not to adopt these new candidates until they are sufficiently ‘de-risked’ in their development cycle.

The development cycle for Novexatin® has been longer than anticipated when the business was first spun out, says O’Neil, mainly because pharma wanted later-stage assets, and as a result of the failure of three potential rival products in the course of their development, which created a greater degree of scepticism in the industry. “This is understandable,” says O’Neil.

“Nail fungus is a very tough clinical problem to solve, but our completely differentiated approach is certainly succeeding so far.”

In the early days of NovaBiotics, Scottish Enterprise saw the potential of the technology, but believed it was “too close to market” for proof-of-concept funding. NovaBiotics co-founder John Pool, as Business Biotechnology Advisor for Scottish Enterprise, saw the huge market potential of focusing the platform on one very large commercial opportunity and put his finger on the button when he asked O’Neil if her new technology could tackle nail fungus.

O’Neil admits that if Pool hadn’t shaped the strategy at this point, things could have been very different: “I may have been more interested in other applications for the technology, particularly life-threatening conditions like MRSA.”
NovaBiotics has three key products in the pipeline:

**Novexatin®** is a brush-on treatment for fungal nail infections (onychomycosis). It not only addresses the underlying cause of the problem by killing the fungi but also improves cosmetic appearance of the nail. Market potential: $3 billion per year.

**Lynovex®** tackles both of the major clinical problems in cystic fibrosis (CF) by breaking down excessive mucus in the lungs, killing the bacteria responsible for the chronic recurrent airway infections associated with CF and also preventing formation of the slimy biofilms which these bacteria form to protect them against antibiotic effects and immune system clearance. The market is expected to be worth $2 billion by 2014 and individual treatments currently cost about $20,000 per patient per year. Lynovex® received orphan drug designation for the treatment of CF in Europe in October 2011.

**Novamycin®** is an antifungal peptide for the treatment of the bloodstream and deep-tissue infections caused by Candida and other yeasts and moulds. Novamycin® is also being developed as a treatment for oral pharyngeal Candida infections and vulvo-vaginal infections. The cost of current treatments for bloodstream Candida infections can run to tens of thousands of pounds per patient, with survival rates as low as 20 per cent and drug resistance also a problem. The global market is forecast to be worth $5.7 billion by 2014. Novamycin® was developed from the same technology platform as Novexatin® and therefore has already been significantly de-risked.
Better outcomes for all

Core business: Health informatics
Date incorporated: 2007
Location: Edinburgh
Annual revenues: About £3 million
Number of employees: 60
Major customers: UK, Kuwait, Australasia

In health care, better outcomes are the target that everyone aims for. And Aridhia not only promises better outcomes for patients and healthcare providers, but also for its own stakeholders and the economy...

In 2007, David Sibbald was sitting in his Edinburgh office, analysing vast amounts of data, trying to puzzle out better solutions for his clients. How can we improve the telecoms network? How can we deliver better results for the bank?

Meanwhile, in Dundee, Professor Andrew Morris was trying to understand why diabetes was spreading so quickly in Scotland and how to improve patient care, analysing vast amounts of data sometimes going back to the early 1950s.

Then the two men had dinner (Sibbald claims he paid the bill) and founded one of Scotland’s most successful biomedical companies, specialising in health informatics.

Today, Aridhia employs 60 people, including software developers, life scientists and clinicians, and has revenues of £3 million a year. Its client base is also growing fast around the world, including major contracts in the Middle East and beyond.

In 2007, Morris already had extensive experience in diabetes, using data to develop solutions for patients and healthcare providers, and realised the obvious next step was to apply this highly specialised knowledge to other common chronic diseases, and ultimately also in other countries. Sibbald was used to looking at data “whizzing around the infrastructure,” and saw a lot of parallels between commercial clients and the medical sphere – everyone wants high-performance solutions, integration, analysis, scalability, robustness, reliability and good presentation of data. Everyone wants to ask “what-if” questions. In medicine, there are lots of “domain-specific” data (including thousands of parameters for diabetes, covering everything from lifestyle to genetics) but also lots of general data, too. In fact, the worlds of informatics and medical research are not as different as they may first appear. Customer service and patient care are also very similar, and lower costs are always near the top of the wish list in any enterprise – including a healthcare provider.
... the company’s mission is simple: To support the management of chronic diseases through the use of health informatics.

In healthcare, some diseases are more common – and more costly – than others. Common chronic diseases such as cancer, diabetes and respiratory and cardiovascular problems are a huge and growing problem all around the world. They are not just the leading causes of mortality, but are also forecast to double in prevalence by 2030. In a global “market” where the healthcare bill is expected to rise to $30 trillion by the year 2030, the business potential is also enormous – because of the growing demand for more cost-effective approaches. “And when you apply informatics to medical problems,” says Morris, “better can also be cheaper.”

Rising to the challenge

Aridhia’s solutions are designed to address three main aspects of health care: patient outcomes, costs and individual engagement. And the company’s mission is simple: To support the management of chronic diseases through the use of health informatics.

Health informatics is the integration of computer and medical science to analyse data – including observational and genetic data – so that healthcare providers can improve their understanding of trends in the wider population, as well as provide better, more personalised care for individual patients by studying risk factors and the impact of treatment and public health programmes. Morris says it’s also important to “stratify risk” – grouping patients according to their individual risk profiles.

Aridhia also stresses the need to use health informatics to engage individuals in their own care – for example, self-monitoring. “There is an enormous asymmetry,” Sibbald explains, “between the data held by the healthcare provider and the information available to individuals. Most industries use informatics to transfer responsibility back to individuals, so why should healthcare not do the same?”

Morris also talks about the “journey of care,” pointing out that patients with common chronic diseases tend to see multiple professionals (podiatrists, cardiologists and dieticians, etc.). “We are not good at joining up the different parts of the story,” he says. “Health informatics is a very simple idea, but it makes a big difference. We also want it to encourage more self-care – pushing information to the patient. The focus is always on the patient.”

Computers vs Cancer

One of the most challenging projects undertaken by the Aridhia team is a study of the seven main types of cancer, developing new software to improve our understanding of the disease and how to deliver better patient care. There are 15,000 new cases of cancer in Scotland per year, and by combining different methods, including analysis of observational data as well as biopsies, a clearer picture should emerge not only of the general trends but also of highly individual factors. Like many other common chronic diseases, cancer is a “cocktail” of problems and pre-existing conditions, and the optimum treatment is usually different for different patients.

The project, which involves NHS Lothian, NHS Tayside and cancer centres in the Universities of Edinburgh and Dundee and is funded to the tune of £1 million by the Technology Strategy Board (a sum matched by Aridhia), is scheduled for completion by the end of 2013. “It is the first and most significant study of its type in the world,” says David Sibbald, “and the results could dramatically change our approach to the treatment of cancer.” Sibbald also believes that it will not just provide a solution for Scotland, but also have an international impact.

This international outlook is what drives the two founders on. “We want to grow a successful company in Scotland that exports solutions, bringing benefits back to Scotland”, says Morris. “And for that we need to align our clinical research and knowhow with informatics and the knowledge of how to commercialise what we are doing.”
The company journey

When Aridhia was formed, what Sibbald brought to the table was his knowledge of commercialisation and productisation, as well as industrial-strength informatics. He was able to combine this with Morris’s medical expertise and knowledge of informatics, gained in his own research projects over the years.

For example, in 1996, Morris and his team in Dundee received £100,000 from the Chief Scientist Office at the Scottish Government Health Department to build a multi-disciplinary team to analyse data to improve patient care for diabetes, focusing on the area around Dundee. In those days, there were about 7,500 people with diabetes in Tayside. Today, says Morris, there are 21,000, and it is estimated that people with diabetes are responsible for more than 10% of healthcare expenditure, or approximately £1.5 billion in Scotland alone. The total number of people with diabetes in Scotland is currently running at just over 250,000. “The technology has evolved a lot over the years,” Morris says, “and the scale of the problem has also increased.”

Morris, who was recently appointed Chief Scientist at the Scottish Government Health Department, is a Director of Aridhia. He is also Governor of the Health Foundation, and Convenor of Health Science Scotland, but despite all this he still sees patients every week, to keep in touch with healthcare in the real world.

The company also draws great strength from its other major shareholders, NHS Tayside and the University of Dundee, who provide raw data and expertise, and play a major role in the “collaborative partnership” between the different organisations.

Sibbald’s company, Sumerian, and Scottish Equity Partners are the largest private investors.

Before Aridhia was formed, Sibbald ran a company specialising in high-performance computing, and as soon as he and Morris started working together, he saw the “huge opportunity to bring diverse domains together.”

The “good chemistry” between the two founders has been the driving force behind the company’s growth. “The key to health informatics is cross-domain skills,” Sibbald explains. “People tend to stick with their communities, but we wanted to bring them together.”

The future

The logical next step for Aridhia’s technology is the extension to genomic and genetic data. There are multiple parameters in every disease – e.g. cancer is not one disease, but a combination of factors and pre-existing conditions – and the application of genomics will provide more precise diagnosis and treatment of individual conditions.

The ultimate goal of Aridhia and every healthcare provider is better patient care and lower costs. But the “journey” is only beginning. “Many healthcare systems don’t capture data in real time,” says Morris, “parly because there are so many factors involved. There is a disconnect between activities and costs.”

Morris is also concerned about a waste of resources, duplication and harm: “Knowledge through data is key,” he adds. “We have to drive knowledge to the front line, in real time, to personalise patient care.”

Health informatics, in its current form, is a relatively new approach to health care. It is hard to measure the benefits of any advance, including health informatics, because healthcare is an ever-changing, ongoing process and the populations and the individuals change over time. But there is little doubt that health informatics will soon become a cornerstone of healthcare, because the pressures on the system are so great and the benefits of more intelligent data analysis promise to relieve at least some of the pressure.

“Current models of healthcare provision are not sustainable,” Morris concludes. “If the bill for healthcare starts to increasingly erode GDP, as current projections suggest, then we’re in trouble – not just in terms of health but also the economy.”

Case study: Kuwait

One of Aridhia’s most notable projects to date is the Kuwait Scotland eHealth Innovation Network (KSeHIN), a collaboration between Kuwait’s Ministry of Health (MOH), the Dasman Diabetes Institute in Kuwait and a Scottish consortium consisting of the University of Dundee, NHS Tayside and Aridhia.

The collaboration with Kuwait (population 3.1million) involves using a package of solutions to do in-depth research into diabetes, including a “smart learning environment” for 105 MSc students, plus clinical network development, exported by the NHS research interactions and informatics platforms developed by Aridhia for data analysis.
The formulation for success

Core business: Drug delivery of biological molecules
Date incorporated: August 2001
Location: Glasgow
Annual revenues: About £600,000
Number of employees: 12
Major customers: Top 20 pharmaceutical companies, including vaccine and biotech companies

It may seem odd that XstalBio does not name its clients on its website, but its CEO and founder, Marie Claire Parker, explains: “We help provide formulation solutions for many of the world’s leading pharmaceutical companies. Our clients and the projects that we work on are confidential and this is primarily because if our technology provides an ‘edge’, solves a technical problem or is potentially game-changing, then it’s logical to limit what other companies know. Although we can’t say who we work with, which would be good for our business, the flip-side is that we have developed a number of long-term relationships with some clients and as their challenges have changed, we’ve been responsive to this and this has helped us to innovate.”

Founded in 2001, XstalBio focuses on “advanced drug delivery,” developing solutions that enable bio-pharmaceuticals to get inside the body as efficiently as possible – an area that can be overlooked in the initial stages by many companies developing new therapeutic proteins, vaccines and peptides. According to Parker, some drugs can lose more than half of their potency during their journey from laboratory to body, and this not only adds to costs but makes them less reliable. The reason, she explains, is that biomolecules are large, complex three-dimensional structures which can be very sensitive to their environment. “Our job,” she says, “is to get them into the body in the right dose in an easily-delivered stable form, effectively and safely. The challenge set by clients may be different every time, but nine times out of ten, our technology solves it.”

The technology

The technology that led to XstalBio being founded was jointly developed by researchers at the University of Glasgow and the University of Strathclyde in the late 1990s and was patented by Parker and her colleagues, Johann Partridge, Barry Moore and Peter Halling.

The protein-coated microcrystal system (PCMC) was a breakthrough that enabled protein-based drugs to be delivered by inhaler instead of by injection, and serendipity was almost as important as the science involved. As Parker describes it, quoting science fiction writer Isaac Asimov, “The most exciting phrase to hear in science and the one that heralds most discoveries is not ‘Eureka!’ but ‘that’s funny.’”
The “funny” thing that happened was that Parker and her colleagues were expecting to prepare an amorphous mix of particles (formulating enzymes for biocatalysis with different common salts) when they discovered that the particles were in fact not amorphous but crystalline and had unique properties – a water-soluble, crystalline core (amino acid, sugar or salt) which provided an efficient form of transport for bioactive molecules, enabling them to be prepared in a dry powder format for delivery via inhaler in the appropriate particle-size range. Solving these technical challenges not only kept the drug stable but also made it easy to control the dose and the release rate, combining several different protein nanoclusters on the same surface.

Different versions of PCMC are developed for specific pharmaceuticals – for example, proteins such as insulin. XstalBio’s PCMC system is also very effective for treating diseases such as cystic fibrosis, because it can be delivered as a dry powder straight to the lungs.

The company

XstalBio was one of the first companies in Scotland to spin out from two universities (Strathclyde and Glasgow), but Parker and her colleagues needed more than good science to get it established, setting up their operation in the Centre for Integrated Diagnostic Systems (CDIS), a bio-incubator facility in the University of Glasgow. After the initial excitement of discovery, they had to validate the new technology and fund their research by working with a major pharmaceutical company. At first, they also looked for venture capital (VC) investment, but this proved to be a distraction. “Many potential investors were very positive about the new technology,” says Parker, “but they thought we were too early-stage and told us to come back when we’d signed our first licence agreement.” Several people also advised Parker to try and limit involvement from VC investors because “they seek returns over a timescale that often isn’t aligned with that of the life-science industry.”
We have developed a number of long-term relationships with some clients and as their challenges have changed, we’ve been responsive to this and this has helped us to innovate.

In the pharmaceutical industry, product and technology timescales tend to be longer than in most other sectors. Even if the science is already proven, says Parker, negotiations with potential clients (over budgets and priorities, etc.) can in the most extreme cases go on for up to two years from the first point of contact “before you even lift a pipette.”

Because they believed in the science, Parker and her colleagues decided to go ahead anyway, and took three years, from 1999 to 2002, to prove the technology worked, working with the company’s first pharmaceutical partner, Boehringer Ingelheim in Germany. “It is rare in science to find new technology working so quickly,” says Parker, “but we met all our targets and we were all very keen to exploit it.”

In 2004, she then secured the licence for PCMC, after reaching agreement with Strathclyde and Glasgow, and the client list steadily grew. “Intellectual property (IP) is worthless if it sits on the shelf,” Parker says.

The CEO and founder has always refused to let barriers get in her way, combining scientific discipline with a talent for business and a passion for getting things done. “For some academics, the safe option is to do nothing, but I was fired up from the start,” she explains. Other scientists spin out too early, she cautions, but XstalBio managed to fund its research from the start on its earnings, primarily from Boehringer Ingelheim, supplemented by grants and awards, including several SMART: SCOTLAND awards, plus funds from private shareholders. “We aimed to grow organically,” says Parker.

From 2005 onwards, XstalBio started to build up a much broader client portfolio among the Top 20 pharmaceutical giants, along the way developing new PCMC solutions and building up its scientific data. In addition, in collaboration with Boehringer Ingelheim, PCMC can be manufactured for clinical batches of material under licence.

“You have to be proactive,” says Parker, “but you also have to realise that individual clients can be very different and have to be carefully managed. One size does not fit all.”

There are lots of companies who specialise in formulation, says Parker, but most of them are focusing on incremental problems rather than on the new “game-changing” solutions which XstalBio is developing in Glasgow today. The delivery of drugs by inhalation is only one aspect of the company’s work now and Parker’s team is looking to the future by focusing on methods to deliver very high concentrations of drugs – in a single shot – in doctors’ surgeries and even in the home, so patients do not need to go to hospital for treatments that can often take several hours. Although the underlying technology is still based on PCMC, the company is currently developing a much broader platform to meet more diverse therapeutic needs, at the same time as working with a wide range of clients.

So, what is the next step for XstalBio?

In Parker’s view, the target is a trade sale within the next two or three years – a plan that has been in the back of her mind since the company started. This will mean becoming part of a large drug delivery company, or the drug delivery division of a large pharmaceutical firm.

“We’re determined to make it all happen,” says Parker. “Our success is based on constant innovation and listening to customers. We can’t be sure that what we develop today will be tomorrow’s new technology, but we have to embrace risk and never let anything get in our way.”

How can we encourage entrepreneurs?

“Instead of focusing on students who are doing well, we should encourage students who are failing – because they will be the entrepreneurs of the future,” says XstalBio CEO and founder, Marie Claire Parker. “Students should be helped to find out what they’re good at, and role models can also help to inspire, but real entrepreneurs often tend to be born out of hardship. Successful people seem to have a spark in them, while others complain and get nowhere, the difference being that they act on their ideas rather than bemoan circumstances around them that conspire for failure.”

In Parker’s view, it’s important to develop resilience – learn how to bounce back from failure. “Schools and universities should focus more on problem solving, rather than learning by rote, with open-book exams in many cases paving the way for a different, more rewarding form of learning for both pupil and teacher,” she explains.

According to Parker, many scientists are held back in business by the impossible quest for perfection. “New solutions don’t need to be perfect,” she says, “just good enough. Does it tick most of the boxes? Are some boxes less important than others? Is it innovative enough? Will it be useful and straightforward to implement? Will it integrate with clients’ existing solutions and be marketable, and is it better than what’s out there?”

Parker also thinks it’s important to get the right people around you to build up the business and considers she’s been very lucky so far, with a core management team of five people who work very well together, have complementary skills and benefit from a range of personal styles.
Profile **MD Biosciences**

For more details...

Core business: **Preclinical research**

Date incorporated: **2004**

Location: **Glasgow (parent company headquartered in Zurich with offices in Minnesota and Tel Aviv)**

Employees: **6**

Major customers: **Leading pharmaceutical companies**

"We had no intellectual property (IP)," says MD Biosciences co-founder Professor Paul Garside. "But who says that you need IP to spin out a successful biomedical company?"

While most other spin-outs are based on scientific or technological breakthroughs, MD Biosciences (MDB) Inflammation Discovery Services was based on the realisation that a small group of scientists working at the University of Glasgow had the expertise and the resources to provide a valuable service to the pharmaceutical industry – screening new drug candidates to identify which ones are likely to work best.

At first, some people doubted that a spin-out was the right way to go, says Garside, but it soon became clear that setting up a new company, specialising in preclinical research for drugs designed to treat inflammatory diseases, was the best approach to running the new operation – and generating revenues for everyone involved.

"At that time," says Garside, "there was no mechanism for doing that kind of commercial research within the university environment, but we were convinced it would work as a spin-out." In those days, it was also very hard to win research grants for more than a few months at a time, which made it hard to market research as a business. More predictable cash flow and longer-term funding were needed – plus regular contracts.

With financial and operational backing from Eddie Moradian, the CEO and founder of Morwell Diagnostics, the new joint-venture company was founded in 2004 and quickly grew to 18 people. And despite the economic recession, which has seen the pharmaceutical industry cut back its spending significantly in recent years, it has proven a major success. MDB IDS has also been supported by the University of Glasgow’s Innovation Network Programme and its First Step Awards, which offer up to £5,000 per project to help create long-term collaborations between SMEs and university researchers. Scottish Enterprise has also backed MDB.

Before the company was formed, Garside and co-founder Professor Ian McInnes had been approached by a number of big pharmaceutical companies over the years to provide specialised preclinical research, but it was not until they went to a biomedical conference in the US in 2004 that the business began to take shape.
What makes MDB different, according to Garside, is that it provides a much more detailed picture of a candidate drug’s mode of action in terms of the immune response, going beyond standard tests not only to see how the drug works, but also what it may be capable of doing.

“I think we were invited to the conference as agents provocateurs,” Garside recalls. “We were asked to comment on the methods used for screening new drug candidates, and were able to suggest ideas which seemed to be of interest to the industry.”

Moradian, who was also attending the conference, was impressed by the two academics and asked them if they’d ever thought of working commercially. This initial conversation quickly gathered momentum and Moradian promised to fly over to Glasgow the following week to explore the possibility of spinning out a contract research organisation (CRO) from the University of Glasgow. While Moradian provided the majority of finance and also had a ready-made customer base to put on the table, Garside and his team provided the expertise and the technology, enabling the new company “to investigate the immune response in a more detailed manner.”

What makes MDB different, according to Garside, is that it provides a much more detailed picture of a candidate drug’s mode of action in terms of the immune response, going beyond standard tests not only to see how the drug works, but also what it may be capable of doing. From the start, Garside strongly believed that the ability to design bespoke studies for drugs would also be key to its long-term success. Some of the more advanced research models used would not seem out of place in a university environment, because academic researchers are often exploring new frontiers of drug design where the industry may not desire to go, but Garside saw the potential of using these techniques on an industrial scale, rather than just in speculative research.
“Persuading the big pharmaceutical companies to use a new model can be a challenge,” says Garside. “They know they need to do all the conventional studies, in order to compare results with similar competitive products, but the ability to look at the immune response in much more detail also gives them a major advantage.”

The science

Garside explains that when the body is attacked by an infection, two kinds of cells interact: T lymphocytes (or T cells) and B lymphocytes (or B cells). By “talking to each other,” these cells produce antibodies to counter infection. They are also adaptive – they learn from their experience (including their encounter with a vaccine) in order to respond to a future attack.

Instead of just showing that a drug is effective, Garside and his colleagues can demonstrate why it’s effective by showing how the T Cells and B cells respond to the drug by producing the right antibodies. Some cells may be encouraged by the drug to produce more antibodies and thus fight the infection, or the drug may help to multiply the number of cells that produce the antibodies. T cells also have specific receptors for specific infections, and it’s hard to identify these different T cells because they all appear to be so similar. The proteins they’re designed to fight are also highly complex. Once researchers understand what happens in detail, however, the pharmaceutical companies can then fine-tune the drug to make it more effective. And according to Garside, the trick is to detect the receptors and help the cells to recognise the nature of the challenge they face from specific infections – the “what, where, when, why and how” of diseases. For example, MDB IDS may study a new anti-inflammatory drug, and its job is to find out how it works and ask if it may also be used to treat other diseases.

MDB IDS researches the effects of drugs in vivo – i.e. looking at samples from living organisms – but is also exploring new “dynamic imaging” methods to extend its capabilities. This enables researchers to detect biomarkers inside the body and is therefore non-invasive and greatly speeds up the research. Generally, the immune response provoked by most infections can be measured from the very early stages to predict how it is likely to progress, so this means researchers can reach their conclusions more quickly, thus speeding up development of more effective drugs.

The focus of Garside’s research has been “to investigate the fundamentals of immune regulation in vivo and apply any findings to infectious and auto-immune disease scenarios.” And, ultimately, this means understanding the basic interactions of the immune response – what happens in the body when we’re threatened by different diseases, and what turns the immune response on and off. A major aspect of his work is using advanced imaging techniques (a multi-photon laser scanning microscope) to see how cells move in living tissue in real time; what Garside describes as the difference between looking at still photographs and looking at a film.

Garside developed his interest in immunology while still an undergraduate at Salford University, where he “happened to do” a project in parasitic infections. This led to a PhD in intestinal parasites, which in turn fuelled Garside’s interest in the immune response, and brought him to Glasgow in 1989 to work as a post-doctoral researcher for five years under Professor Allan Mowat. He later won a Wellcome Trust Career Development Fellowship to study at the University of Minneapolis and then returned to Glasgow to run his own research lab and teach, becoming Professor of Immunobiology in 2002. This was followed by four years as Director of the Centre of Biophotonics at the University of Strathclyde, before returning to Glasgow again to continue his research.

During the last decade, Garside and McInnes spent a lot of time working to make MDB IDS a success, meeting clients and advising researchers. Both are still shareholders, but are no longer involved on a day-to-day basis.

Garside is proud of his role in establishing one of Scotland’s most successful spin-outs. He is also happy to be back in the research lab. But would he do it all over again?

“If the opportunity did come along and it was an innovative project, then definitely yes,” he replies.
It may be walking in the footsteps of Alexander Fleming, who discovered penicillin in 1928, but Glasgow-based MGB Biopharma is not only developing a new class of anti-bacterial drugs but also a new way of doing pre-clinical research – and a new way of building a drug development business.

The new class of anti-bacterial drugs, which will soon be ready for clinical testing, was discovered by Professor Colin Suckling of the University of Strathclyde, and MGB Biopharma (MGB) was the company formed to take the new technology onto the next stage, aiming to develop and commercialise a drug which is expected to prove more effective against hospital-acquired diseases than currently available therapies.

DNA minor groove binders (MGB) are the small molecules that inspired the new company name and they were discovered by a team of medicinal chemists, molecular modellers and microbiologists at the University of Strathclyde, led by Suckling. The initial development was funded by the University of Strathclyde and Scottish Enterprise’s Proof of Concept Programme, with help from royalties from Leucovorin®, an anti-cancer drug which emerged from research at Strathclyde in the 1980s, also led by Suckling.

The new drug, now known as MGB-BP-3, has demonstrated “very significant in vitro and in vivo activity against Gram positive bacteria, including MRSA, VRE and Clostridium difficile.” And MGB Biopharma CEO Miroslav Ravic says the market for such drugs could be worth at least $6 billion a year.

Ravic, who was born and educated in the former Yugoslavia, and worked as a Consultant in Belgrade University Hospital before coming to the UK 25 years ago to complete his PhD at St Bartholomew’s Hospital in London, has a very clear vision for the new class of drugs – and how to advance it through pre-clinical and clinical research.
His experience on “both sides of the fence” as a practising physician and in clinical research (he has been involved in more than 100 clinical studies) has shaped Ravic’s attitude to drug development and enabled him to take a very different approach to the business. He also spent almost ten years as the European Director of Clinical Research at Eisai – an experience which ultimately convinced him that there must be a “better, quicker and cheaper” way to develop new drugs. “Old habits die hard,” Ravic says. “But I wanted to develop drugs my way.”

After leaving Eisai, Ravic then spent three years at Antisoma, where he learned what life was like at a small drug development company. Whilst there, he helped to restructure the company’s clinical drug development group and also played a key role in the development of a new anti-cancer drug which was later licensed to Novartis in a deal worth $900 million.

This industry experience has taught Ravic several lessons and inspired his current approach to research. The big pharmaceutical companies dominate late-stage research and tend to use standardised methods – the same protocols again and again – rather than take any shortcuts. When they’re aiming to show that the new drug is “active,” having already proved it is safe, researchers may engage in several studies one after another, each costing millions of dollars. That is why it can take 8–15 years to develop new products, and meanwhile many people may be dying for lack of the more active drugs.

“Time is money,” says Ravic, who says that the conventional drug development cycle contains too much “dead space” – not just waiting for final approval but also in the earlier stages. And the answer, he says, is what is called “adaptive design,” combining various aspects of the drug development process, treating it as one continuum and designing bespoke studies tailored to candidate drugs. “Current drug development is very fragmented and, as a result, instead of integrating the development process from beginning to end, there is often little communication amongst those involved in pre-clinical research and even less between them and the clinical development teams,” says Ravic.

As well as having firm views about how to develop new drugs, Ravic had a clear idea of what kind of drugs he would like to develop, when he set up his own drug development business.

Whilst working as an industry consultant, he started searching for a new class of molecules which “ticked all the boxes” in terms of design and targeted acute diseases rather than chronic diseases, thus promising faster financial returns. He was also keen to focus on a drug that works on well-defined targets. “Another key factor,” says Ravic “is that the new drug is designed to target severe diseases that are difficult to treat – an area of high unmet need.” And the quest soon led Ravic to Glasgow, where Professor Suckling and his team had already tested new anti-bacterial compounds in vitro and were looking for a partner to help them move on to pre-clinical testing and turn the candidate molecule into a commercial product. Ravic felt convinced that some of these compounds had the potential to meet all of his criteria.

By this time, Ravic had also teamed up with his colleague Gavin Clark who, with 25 years’ experience in commercial roles at Johnson & Johnson, Bayer, NoVartis and GSK, had coincidentally been one of Suckling’s chemistry students in the late ’70s, and the two of them negotiated with the University of Strathclyde to license the technology. After due diligence, Ravic brought in Raymond Spencer, a highly experienced Chief Financial Officer from Antisoma and, together with Clark, founded MGB Biopharma and approached the new business with the same kind of radical outlook that Ravic applied to research. Rather than hiring a team of researchers and setting up a dedicated new facility, Ravic has created what he calls a “semi-virtual” company.
The solution devised by MGB was to build a “virtual” team of top researchers and experienced advisors who already knew each other from previous projects.

The basic development process involves proving safety (i.e. the drug is not toxic) and then demonstrating activity (the new drug has an effect on its target) and efficacy (how well it performs), followed by clinical testing to confirm these results and demonstrate compliance with all the required regulations. Last year, MGB-BP-3 was formally selected as a candidate for clinical testing after demonstrating “potent and rapid activity” against a range of Gram positive bacteria including MRSA, VRE, Streptococcus and C. difficile. This was what triggered the investors to inject the second tranche of fresh funds to move on to the next stage of development.

MGB presented its findings last year at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Chicago, USA, and in April this year it announced that it had published the results of activity of MGB-BP-3 against Gram positive bacteria, including MRSA and vancomycin-resistant enterococci, presenting those data at the 22nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) in London.

For MGB and its backers, this creates exciting possibilities. Clinical testing can be highly expensive, so either they fund this themselves, license the technology or sell it to a partner, providing a relatively early exit for the existing investors. Future sales could be significant, with similar new products being purchased for considerable sums of cash over the remainder of the development and the commercialisation, but the new drug will require much more additional investment before it is ready for hospital use.

“I deeply appreciate all those individuals who have put all the money together,” says Ravic. “If they exit now, that will be well deserved, and if we go on to the next stage, the returns could be even greater.” In addition, Ravic believes that the compound will make it “with or without our investment,” simply because it has so much potential in such a “needy” market.

“The results so far are promising,” adds Ravic. “While the problem of MRSA is not increasing as fast as previously, the cost of treating Clostridium difficile continues to rise, and MGB-BP-3 promises not only to treat the disease but also to prevent its recurrence – thus saving even more lives and money.”

The company’s business model may change in future, says Ravic, but being semi-virtual has delivered very real results so far for him and the rest of his team – and could lead to a made-in-Scotland anti-bacterial drug that will not only save many lives but ultimately generate billions of dollars in sales.
Profile **CXR Biosciences**

The business of science

| Core business: | **Drug development solutions and investigative toxicology services** |
| Date incorporated: | **2002** |
| Location: | **Dundee** |
| Number of employees: | **30–40** |
| Major customers: | **60+ pharmaceutical, biotechnology, agrochemical and chemical companies including GlaxoSmithKline, AstraZeneca, Pfizer, Procter & Gamble and Dow Agrochemical** |

Roland Wolf describes how a team of scientists in the University of Dundee joined forces with investors to create one of the city’s most successful biomedical spin-outs – and shares his thoughts on what is needed to encourage the growth of the sector in Scotland...

Reflecting on the last 11 years since he helped to start up CXR Biosciences, Roland Wolf has much to be proud of – including the fact that the company has an anti-cancer agent that has recently completed a Phase 1 clinical trial, and has developed a number of unique models for drug development, toxicology assessment and chemical risk assessment.

The company has also created employment for 30–40 people over the years, boosting the local economy in the process and gaining an international reputation for world-class research.

But Wolf is not content to rest on his achievements so far and also has strong opinions on the biotechnology sector in Scotland, believing that the formula for business success is not always in tune with the needs and motivations of academic researchers.

“We need to develop a new business model which translates commercial success back into research,” says Wolf. “Academics have to understand the motivations of investors, and investors need to understand the scientists as well as the science involved. It’s nice to make money, but most academics have very different objectives and also tend to have more altruistic reasons for doing what they do.”

Every board needs the right mix of people, he adds, including managers who balance and reflect the two different cultures of business and science.

Wolf also thinks that Scotland has tremendous intellectual resources, but could do much better when it comes to translating that wealth into profits. “How many spin-outs have been truly successful in terms of global impact, profits and employment?” asks Wolf. “How many start-ups have moved on to the next level? And how can we help them to do so?”
Academics have to understand the motivations of investors, and investors need to understand the scientists as well as the science involved.

In the years since then, the idea has turned into a reality, as the large pharmaceutical companies increasingly use the services of contract research organisations to handle their most difficult projects.

The services provided by CXR “improve the clinical predictability of drug discovery ADMET (absorption, distribution, metabolism, excretion and toxicity) screens, reduce late-stage product attrition, rescue chemicals and drugs that may otherwise be abandoned and transform human risk assessment of drugs and chemicals.” It has developed a range of novel pre-clinical models, including genetically “humanised” mice which help to predict how the drug will affect human beings, plus a range of mechanistic assays and bespoke assays and screens tailored to client requirements. It also offers microarray services “to provide a detailed understanding of the cellular responses to compounds”, which is useful in a variety of ADMET applications, especially investigative toxicology.

Before setting up CXR, Wolf led research that resulted in another spin-out called Cypex, which also emerged from the University of Dundee, as part of a project in partnership with 15 pharmaceutical companies, specialising in the development and manufacture of in vitro drug metabolism systems. The company released its first recombinant protein in 2000 and now has a portfolio of over 100 products to help in drug development, including human drug-metabolising enzymes, fine chemicals and antibodies.
Wolf came to Dundee in 1992 after 11 years at the University of Edinburgh, where he headed the laboratories at the Imperial Cancer Research Fund’s Medical Oncology Unit and subsequently headed the ICRF Molecular Pharmacology Unit in the Biochemistry Department in George Square. In 1998, he made a major discovery concerning the role played by a single gene in protection against cancer, and today he is the Director of the University of Dundee Medical Research Institute and Honorary Director of the Cancer Research UK Molecular Pharmacology Unit.

Before CXR was set up at the Dundee Technopole building, it operated for three years as the Centre for Xenobiotic Research, based at Ninewells Hospital & Medical School. In its first round of funding, it attracted £4 million from private and public investors, including the Edinburgh-based Archangel group and Scottish Enterprise Tayside, and its other shareholders were the founding scientists and the University of Dundee. The company also received funding from the European Regional Development Fund, a Regional Selective Assistance award and private sector bank finance.

“The work at CXR was very challenging,” says Wolf, “and we achieved a lot with relatively little investment. Our research programme, in collaboration with Scottish Enterprise through the ITI Life Sciences initiative (based in Dundee), has also been fantastically successful, and helped to sustain the business over the years.”

CXR was set up with two main objectives, focusing on contract research and drug discovery. First, it aimed to use its cutting-edge technologies to help in drug development, providing solutions to advance pre-clinical research, including innovative and bespoke models. And secondly, it was also on a quest to develop new drugs – concentrating on a molecule which Wolf says has considerable potential right across the spectrum of cancer.

“In Scotland, we have invested hundreds of millions of pounds in academic research and we want that activity to translate into better drugs and treatment of disease,” says Wolf. “For this to occur there needs to be a clear understanding of the motivation of the investors and the academics.”

In terms of corporate ethos, Wolf also has clear views, stressing the importance of creating an esprit de corps that makes every member of staff feel involved and “excited” about what the company does.

Wolf also feels very strongly that academics should not get embedded in the day-to-day issues of corporate life and says that scientists rarely give up their commitment to research. It should be possible, he adds, to design research studies and engage in them without spending all of their time in the everyday details. “We should try to avoid squeezing scientists into a mould,” he continues. And judging by the way he describes his vocation, Wolf will never be squeezed into anyone’s mould.

Roland Wolf left CXR in October 2012 to focus on his academic activities.
Doing things naturally

Core business: Drug development – diseases of oxidative stress and mitochondrial dysfunction

Location: Aberdeen

Company founded: 2006

Number of full-time employees: 2

The next time you bite into an apple, eat raspberries or blueberries, or knock back a glass of red wine, you will be treating yourself to some of nature’s most effective therapies – the antioxidants or flavonoids that help to protect against the development of major illnesses such as cardiovascular disease, neurodegenerative conditions and certain cancers. And a small company in Aberdeen is using these natural “remedies” as a chemical platform to develop a new range of more powerful drugs to treat established disease and provide novel small molecules for use in the regenerative medicine industry...

A major focus of this work was to establish the mechanisms by which certain members of the flavonoid family could act as antioxidants, thereby protecting cells from free radical attack. Free radicals are atoms or molecules that contain an unpaired electron, making them highly reactive and damaging towards cell membranes and a host of important biomolecules necessary for maintaining health. They are continually produced in the body as a by-product of the conversion of oxygen to energy. This ‘oxidative stress’ is controlled by the body’s elaborate antioxidant defence mechanisms. However, these are not fool-proof and a level of damage inevitably occurs, which can result in disease and the degenerative changes seen in ageing. The paradox is that we need oxygen to live, but ultimately it can also lead to our demise.

There is now a substantial body of epidemiological evidence that diets high in polyphenol antioxidants – for example, apples, red berries and certain vegetables, as well as tea, coffee and wine (in moderation) – are associated with a reduction in a range of chronic illnesses. These include cardiovascular disease, inflammatory disorders, Type 2 diabetes, neurodegenerative conditions such as Parkinson’s disease, and certain forms of cancer.

However, once the disease is established, much higher levels of oxidative stress can be generated that overwhelm the body’s natural defences and result in cell death. So the challenge for scientists is how to amplify the therapeutic properties of flavonoids and get them into the cells to have beneficial effects – increase the bioactivity and target specific, susceptible locations inside the cell.
Antoxis describes this as “the rational design and synthesis of entirely new flavonoid-like molecules which demonstrate a step change in activity compared with the natural compounds.”

A chemist by background, McPhail has developed a range of techniques (using electron spin resonance spectroscopy), to determine the antioxidant potency of foodstuffs such as wine, tea, berry juices and even whiskies. “Although there has been a great deal of interest in identifying dietary sources high in antioxidants, it was understanding the complex relationships between molecular structure, antioxidant activity and bio-potency which really intrigued me,” McPhail says. “By understanding these effects, the logical next step was to design new synthetic molecules that combine antioxidant potency along with the additional molecular features needed to produce drug-like characteristics.

Developing a successful therapeutic is not just about a molecule’s ability to destroy free radicals; it is dependent on many factors, including stability, accessing the disease site and the ability to be absorbed by the cell and target key locations, such as the mitochondria, where oxidative stress occurs.”

It is this valuable know-how that lies at the heart of Antoxis and the company was recently granted its second patent in the US and beyond, covering over 100 million molecular variants of the flavonoid family.

Using this rational design approach, compound libraries have now been developed that combine antioxidant potency with rapid cell uptake and targeting of key areas involved in oxidative stress and free radical damage.

McPhail explains: “Our goal is to design in drug-like characteristics to these novel product scaffolds that will make them suitable for use in clinical conditions which the natural compounds are not optimised for – for example, by increasing the amount of compound that can cross from the bloodstream into the brain and slowing its rate of metabolism.”

Of particular interest are antioxidants within the company’s pipeline that target the energy ‘power house’ of the cell – the mitochondria. “This would allow us to intervene in the cycle of oxidative stress, free radical damage and mitochondrial dysfunction that is a major component of many diseases such as Parkinson’s, Huntington’s and sepsis,” adds McPhail.

The company is also looking at wider applications for its compounds and is undertaking studies in the field of regenerative medicine. “Results indicate that several of our proprietary molecules can effectively preserve stem cell viability in situations where they are exposed to high levels of oxidative stress, and once the compounds are incorporated into the cell, there is a good time window of protection, which is of huge benefit clinically.

After transplantation, therapeutic cell therapies are exposed to reperfusion and immune response effects that can result in significant generation of oxygen-derived, free radical species (which in layman’s terms means that over 80% of the transplanted cells can die within 24 h). As recent evidence has shown that treatment with dietary antioxidants can help reverse this loss of viability and functionality, the company believes its antioxidants have far better characteristics to improve treatment outcomes, as they are almost 1000 times more potent than their natural cousins.

Early evidence in a number of regenerative medicine applications would tend to support this view.

The use of Antoxis’ compounds in regenerative medicine is seen as a quicker route to market because it’s likely that the compounds would not be given as a drug but be categorised as a medical device (cells loaded with protective agents outside the body and pre-implantation), thereby reducing the long and costly regulatory development pathway associated with mainstream therapeutics. This would provide the company with a much earlier income stream, potentially within two years, that would then be re-invested into higher-value, but longer-term drug development programmes.
Although there has been a great deal of interest in identifying dietary sources high in antioxidants, it was understanding the complex relationships between molecular structure, antioxidant activity and bio-potency which really intrigued me.

The business plan
The key to commercial success for Antoxis, according to McPhail, will be the “patent space” the company controls – and this is what will ramp up the company’s value over the next few years. Antoxis now has patents protecting over 100 million synthetic variants of the natural flavonoid scaffold. These patents are not just about a single product – they encompass a platform technology from which different molecular variants can be optimised for specific clinical and stem cell applications.

The ‘on-the-bench’ data is very encouraging, so far. According to McPhail, the lead compounds provide an “exceptional ability” to keep a wide range of cell types alive, including neuronal cells, when they are exposed to otherwise lethal levels of oxidative stress. The company is now undertaking in vivo disease models to identify which particular clinical indications and compound combinations are most suitable to move into clinical trials. McPhail says he is also confident that Antoxis’ products out-perform the natural products, and also other antioxidant molecules in clinical trials or on the market.

Alliances
For McPhail, swapping the white coat for the business world has been an interesting experience, and one he is enjoying. “Setting up the company has been very exciting – especially the prospect of taking the science to market and, hopefully, of providing some kind of health benefit. I was fortunate in securing a Royal Society of Edinburgh/Scottish Enterprise Enterprise Fellowship, prior to company formation, which was of immense benefit.”

Like many other biomedical start-ups, Antoxis operates as a semi-virtual company. When the company needs to produce any chemical compounds or undertake pre-clinical research and development, it simply sub-contracts the project to a specialist firm, thus avoiding costly overheads. This makes for greater flexibility and enables the company to respond rapidly to new challenges, rather than being locked into an infrastructure that may not be appropriate a few years down the line. “Unlike large pharma, biotechs need to be highly-adaptable, with a more dynamic business model,” says McPhail.

Antoxis does not operate alone, however, and has partnerships and collaborative agreements with several other organisations, including large pharma and mid-sized bio-pharma. In particular, the company has fostered excellent links with Scotland’s universities, including Aberdeen, Edinburgh and Glasgow and, in some respects, is replicating the ‘open innovation’ model that is becoming more common in big pharma.

Aberdeen University is a shareholder in the company, while Glasgow University provided the medicinal chemistry expertise needed to generate the first-generation, flavonoid-like molecules, supported by funding through the Scottish Enterprise Proof of Concept scheme. Antoxis has also been supported through SULSA (the Scottish Universities Life Sciences Alliance) with post-doctoral posts in oncology and regenerative medicine at the University of Edinburgh.

“The key in Scotland,” says McPhail, “is to create an environment where academics can be more commercially focused as well as do blue-sky research.” Thanks to Scottish Enterprise, funding initiatives that encourage high-tech SMEs and the universities to work together, along with an excellent investor network (in Antoxis’s case, Genomia Fund, Grampian BioPartners, TriCap and Kapital Assets), the blue-sky thinking which led to the birth of Antoxis, and continues to power its commercial development programme, will not just lead to better medical treatments, but also to a healthy return on investment.
Healthcare systems internationally are under great strain. Despite increased spending on healthcare (8% of GDP in the UK and 17.4% in the US), the pressure continues to mount every year – with increasing life expectancy, new technologies, enhanced patient and public expectations and a “rise and rise” of chronic or non-communicable disease, major challenges in all countries.

The facts about chronic disease are particularly stark: up to three quarters of people over 75 years of age currently suffer from a chronic disease, and the incidence of chronic disease in the over 65s will double by 2030. Last year, a UN summit declared chronic diseases to be a global threat to the future sustainability and affordability of healthcare, and the World Economic Forum estimates that chronic diseases will cost the world economy $47 trillion over the next 20 years.

The quest for better quality at reduced cost remains elusive, but in many countries such as Singapore and Australia, for example, they are focusing on closer integration of science with healthcare provision and public health, facilitating the convergence of research with healthcare, not only to accelerate clinical innovation, but also as a vehicle of economic growth.

Scotland is a relatively small market in terms of global healthcare delivery. Annual expenditure on healthcare provision is about £12 billion for five million people. In life sciences research, however, Scotland has a disproportionate impact. It hosts the UK’s second-largest Life Sciences cluster and one of the most sizeable in Europe, with an annual turnover worth £3.1 billion. Scotland also competes well in health science research, attracting 11.5% (£189M) of the total £1,618M of the health-relevant research expenditure in the UK in the recently published UK Clinical Research Collaboration report.

As a location for research and clinical trials, Scotland has a number of advantages over many other countries, including internationally-competitive universities where academics undertake clinical service as well as research. We also have a stable and improving healthcare system, an emerging nationwide clinical research infrastructure (NHS Research Scotland), and an informatics capability that exploits electronic patient records, linkable through a unique NHS patient identifier, enabling clinical trials, stratified medicine and genetic studies.

But more needs to be done to ensure Scotland remains a powerful player as part of a UK biomedical science cluster. We need to think global and act locally. Speed, efficiency and costs are three key metrics. We have ground-breaking initiatives such as SULSA, Generation Scotland and the Scottish Patient Safety Programme, and the recent announcement of Scottish Funding Council Innovation Centres is also highly promising, but it is time to create new alliances before we find ourselves spectators on the global stage.

Four key developments would potentially add value:

1. Structured NHS/academic collaborations focusing on education, research and quality clinical care delivery.
2. A focus on health and biomedical informatics, using electronic patient records to support better treatment, safety and research.
3. A commitment to harmonisation of NHS Caldecott Guardian activities and university governance, costing and contracting, so institutions can become a single point of contact.
4. Greater collaboration between the biotechnology, pharmaceutical, computer science and medical devices industries, embracing principles of open innovation.

This would not only help position Scotland as a single research site, but also enhance our global competitiveness and help us face the challenges of chronic disease.

There is a fundamental shift taking place in the geography of science. Collaborative research networks are expanding all over the world, particularly in the emerging economies, and the influence of more established research centres such as the UK may be waning. Researchers here will need to step out of their comfort zones to keep up with the dynamism of the new players, but there are some optimistic signs that individuals and institutions are willing to take risks, concede a little sovereignty and work across boundaries.

On a recent trip to Sydney, I walked along Macquarie Street, named after Lachlan Macquarie, a Scot who played a leading role in shaping the development of Australia in the early 19th Century. Two hundred years later, there is an opportunity for Scotland to shape the health science agenda – and have a major international impact on chronic disease management and health system design.

Andrew Morris is Professor and Dean of Medicine at the University of Dundee, Chief Scientist (Health) at the Scottish Government and co-founder of Aridhia Informatics.
Exploiting the scientific excellence of Scottish universities in the commercial sector

Research collaborations between universities, the pharmaceutical industry and biotechnology companies are an integral and highly successful component of all Scottish universities. There are numerous examples of how such scientific/commercial interactions have resulted in improved health care and have contributed to the Scottish economy. In the distant past, such collaborations may have been frowned on by academics, but they are now a key component of their research portfolio. However, translating academic excellence and university research into the creation of successful spin-out companies has slowed down over the last few years. We need to understand the reasons behind this slowdown and to develop new approaches to regain momentum in an area where Scotland has world-class expertise and that has the potential to make a major contribution to the Scottish economy.

Academics are judged by the international competitiveness and impact of their research. Their goal is to perform research of the highest standard to benefit mankind. This is reinforced by government through the Research Excellence Framework (REF), which assesses academic research output and provides financial support to universities based on their performance. Although the REF takes commercial activity into account, university researchers are extremely concerned about any new commitments that risk damaging their basic research careers. Given the large amount of time needed and the uncertain rewards, setting up a new company is often perceived as a very risky commitment for academics.

New ways are needed to support academics as founders of companies in achieving the correct balance between academic and commercial work. Universities, and their funding systems, need to give appropriate recognition and reward to academics who invest precious time in commercialisation, and investors need to understand that academic founders are generally motivated by translating science into either public or patient benefit, rather than by short-term financial return or making money per se. The latter is, of course, essential to any successful business, but the balance between vision, innovation and commercial return must be dynamic to navigate the complex landscape to significant growth and success.

Understanding motivations is also fundamental in the relationship between founders, the CEO, the board and the investors. Generally speaking, founders should do what they do best and be concerned with the intellectual and scientific development of the company and not with its day-to-day management. A biotechnology company cannot operate like a major pharmaceutical company, and a balance between running a commercial business and innovation, entrepreneurship and motivation is needed. The company’s CEO and board must have an in-depth knowledge of all aspects of the business it is running, including the science and the market-place, otherwise competitiveness will be lost and the company will not realise its potential.

Finally, the relationship between the founder, the CEO and the chairman of the board is pivotal to the success of a spin-out company. This must be based on mutual respect, transparency and trust. There must be a high level of commitment from all parties; simply turning up for board meetings is not enough. Everyone must subscribe to a common vision and goal.

Scotland’s universities spend hundreds of millions of pounds on outstanding innovative research every year, yet are still not exploiting efficiently the best of the significant economic benefits that this should create. There are many possible reasons for this and we are still searching for a model that both encourages and reduces the pressures on founders. More effective new initiatives are urgently needed to try and bridge this gap, as current approaches have been largely ineffectual. It is critical that we re-evaluate our approach and that government, higher education funding councils and investors all listen to what the academics are saying. Academics in Scotland are up for this!

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