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Cutting Edge Research from Scotland

The search for new drugs

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Foreword

PROFESSOR ANNE GLOVER

Searching for new drugs

If there is one thing we can be sure of, it is that the human population will continue to suffer from disease and that we will need new, smarter, more tailored drugs to treat them.

This issue of *Science Scotland* focuses on searching for new drugs to improve treatment of existing diseases, as well as to explore opportunities of addressing treatment of diseases which have suffered from lack of attention up until now. A great example of this is captured in the philosophy of the Dundee Drug Discovery Unit (DDU). This is real innovation in the drug discovery landscape, where research scientists with academic and company backgrounds are brought together around world-class facilities to address the needs of big pharma and translate basic research into potential drug candidates. The DDU expertise is open for others to use and the satisfying twist in the tail is that as well as addressing the needs of big pharma, the DDU is also turning its attention to new drugs for neglected diseases which affect a large proportion of the world's poorest people and wouldn't normally be the target of big pharma. The activity in translational biology around Dundee is formidable, and demonstrates what you can achieve with great leadership, energy and the courage to focus and invest in your strengths.

It is hard for a country the size of Scotland to compete on the world stage in drug discovery and yet we do this, especially at the early research stage, by thinking differently. All around the globe, people know of "Dolly the sheep", the world's first cloned mammal, and much of our understanding of stem cells, which give rise to all the other cell types in the body, came from this pioneering research. This has delivered opportunities such as laboratory generation of blood cells so that erratic supplies of blood from donors can be addressed. This is a collaboration between the Scottish National Blood Transfusion Service and Glasgow University, along with Dundee, Heriot-Watt and Edinburgh Universities, bringing together a powerful combination of biological knowledge with engineering and bio-processing to scale up production. There is something of real importance to note here and that is that there is an appetite for collaboration, between universities, research institutes, big and small business and across disciplines, which opens up new possibilities for research and development. I believe the more we collaborate, the more we capitalise on our outstanding research in life sciences and take advantage of our small size and research-intensive nature in Scotland, the greater the economic and health impacts could be for Scotland.

There is a lot in this issue that will inspire you, such as reading the story of the University of Aberdeen spin-out company Haptogen and how that led its co-founder Andy Porter to help set up an angel investment firm to invest in other great ideas, as well as to develop a new teaching course at the university in biobusiness to stimulate the entrepreneurial spirit in the next generation of life scientists. This is the same sort of vision that Graham Coombs demonstrates in his leadership of the University of Strathclyde Institute of Pharmacy and Biomedical Science.

The future looks good for translating Scottish life science research into the drugs of the future. We need to keep working hard and embracing innovative approaches to make sure it happens.

Professor Anne Glover CBE FRSE FRSA
Chief Scientific Adviser for Scotland

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More everything...

Sir Philip Cohen, the director of the MRC-PPU (the Medical Research Council Protein Phosphorylation Unit) and SCILLS (the SCottish Institute for ceLL Signalling) at the University of Dundee, has been described as "one of the world's top scientists" and he is now the world's most cited biochemist, having published over 500 research papers during his career. His pioneering work on protein phosphorylation prepared the way for the discovery of some of the world's most important new drugs for the treatment of cancer. He has helped to put the city of Dundee on the biotechnology map. But as he approaches 'retirement' he says he is just reaching the exciting stage of life...

"It was 25 years before I received the first call from pharma," says Sir Philip Cohen. It took scientists several decades to prove that protein phosphorylation regulates most aspects of cell life, and it took even longer to convince the pharmaceutical industry that drugs which target protein kinases would help in the treatment of killer diseases such as cancer. As recently as 1998, the head of research and development at one pharmaceutical company (which no longer exists) told Sir Philip that there was "absolutely no future in kinase drug discovery," but later that same year researchers announced that a kinase inhibitor called Gleevec had proved remarkably successful in the treatment of chronic myelogenous leukaemia.

Today, according to Sir Philip, the market for drugs which target protein kinases is worth about $15 billion a year, and research on protein kinases accounts for about 30 per cent of the drug discovery programmes in the pharmaceutical industry and over 50 per cent of cancer R&D. Seventeen drugs targeting protein kinases have already been approved for the clinical treatment of cancer. And one of the remarkable aspects of protein kinases is that they often turn out to be useful in the treatment of multiple problems – for example, Gleevec is also effective in the treatment of gastrointestinal cancer.

> **"progress often comes from nibbling at the edges"**

Not many scientists can claim to have made such an impact, but having spent so many years investigating phosphorylation, Sir Philip then appeared to change direction when he announced that he was turning his attention to a very different branch of biochemistry called ubiquitination, inviting criticism by daring to suggest that phosphorylation and ubiquitination have many similar characteristics – and perhaps equal potential for providing drug targets. Until very recently, the conventional view among most biochemists was that ubiquitination was a mechanism mainly concerned with destruction (marking proteins for destruction by the proteasome), but Sir Philip points out that it also performs other key roles in cell regulation – for example, in immunity and how cells respond to DNA damage. Like phosphorylation, ubiquitination is also reversible and can therefore also act as a biological switch to alter protein function reversibly.

In Sir Philip's view, phosphorylation and ubiquitination are simply two biological systems which can't work without one another, and also help to regulate each other. And he wants to "popularise" further research in ubiquitination because our knowledge of this field is still rudimentary and in the future it will deliver many new drugs.

"I love looking at two processes that control everything," says Sir Philip. "And ubiquitination is another 'black box' – another system I would love to get a handle on."

SIR PHILIP COHEN

Although there are "striking parallels" between the histories of phosphorylation and ubiquitination, wrote Sir Philip and his co-author Marianna Tcherpakov in a recent article for the journal *Cell*, including a delay of many years before the fundamental science was translated into practical products, in recent years more drugs that target protein kinases have been approved for clinical use than drugs which target a component of the ubiquitin system. However, in 2003, a protease inhibitor (which stops a particular protease breaking down ubiquitinated proteins) called Bortezomib was the first to be approved for clinical use in the treatment of a fatal lymphoma.

Several other promising drugs that target components of the ubiquitin system have been developed since then, which are currently undergoing clinical trials, and Sir Philip welcomes the challenge ahead. He and Tcherpakov conclude in their paper: "Predicting the future is notoriously difficult. However, given the diverse approaches and avenues that remain unexplored in developing drugs targeted at the ubiquitin system, [we] would be surprised if ubiquitin drug discovery was not far more important in ten years' time than it is today. Nevertheless, only time will tell if ubiquitin drug discovery will eventually rival in its importance that of kinase drug discovery."

Q: What is protein phosphorylation?

A: Protein phosphorylation is a control mechanism that regulates most aspects of cell life. It involves the adding of a phosphate to a protein by a protein kinase or removal of a phosphate by a protein phosphatase, which activates or deactivates (switches on or off) many enzymes and other proteins, causing or preventing the mechanisms of diseases such as cancer and diabetes. Abnormal protein phosphorylation is a cause or consequence of cancer, diabetes and inflammatory disease, while defects in genes that encode protein kinases and phosphatases underlie a number of inherited disorders. Cyclosporin, the immunosuppressant drug widely used in organ transplantation, is a protein phosphatase inhibitor, while protein kinases have become the pharmaceutical industry's most important drug targets. Seventeen protein kinase inhibitors have been approved for clinical use as anti-cancer agents, including Gleevec, the drug that has transformed a previously fatal form of leukaemia into a manageable disease. (Gleevec was developed at Novartis by Nick Lydon, a former PhD student of the University of Dundee.)

Q: What is protein ubiquitination?

A: Protein ubiquitination was discovered in the late 1970s as a mechanism for marking proteins for destruction by the proteasome, but we now know it has many other functions and that it regulates almost all aspects of cell life. Ubiquitin is a small regulatory protein found in almost all tissues, and one of its key functions is recycling or degrading of unneeded proteins by binding covalently to the proteins and labelling them for destruction. As well as administering the "kiss of death" in proteins, ubiquitination also plays a key role in the control of the cell cycle, gene transcription and immunity. Abnormalities in this process are a cause of cancer as well as chronic inflammatory and auto-immune diseases.

Experiments, experiments, experiments

As well as having strong opinions on ubiquitination, Sir Philip also stresses that experiments are vital – and suggests the current emphasis on bio-informatics may be premature. He also says that many people get it wrong because of "weak" technologies and the use of "cheap and dirty" methods that are not sufficiently robust.

"We need to understand how complex biological systems are integrated," says Sir Philip. "There are hundreds of proteins to look at but I passionately believe in the importance of experiments – we are still only just scratching the surface."

To get the science right, Sir Philip thinks it's critical to invest in technologies such as mouse genetics – studying protein kinases in action by generating mice that carry a particular mutation. It can take a year to create 'knock-in' mice, at a cost of up to £40,000 per mutation, but according to Sir Philip, "without genetics, there is no proof." Biochemists can do very valuable work in the lab, testing specific pharmaceutical inhibitors, but it is only when they get the same answer in experiments with living mammals that there is "a good chance the hypothesis is correct."

What next?

Another key aspect of Sir Philip's research involves attempting to "unravel the signalling pathways in the innate immune system that control the production of pro-inflammatory cytokines and interferons during bacterial and viral infection." And rather than seeing ubiquitination as a separate sphere of research, he sees it complementing his earlier work in phosphorylation, studying "the interplay" between protein ubiquitination and protein phosphorylation.

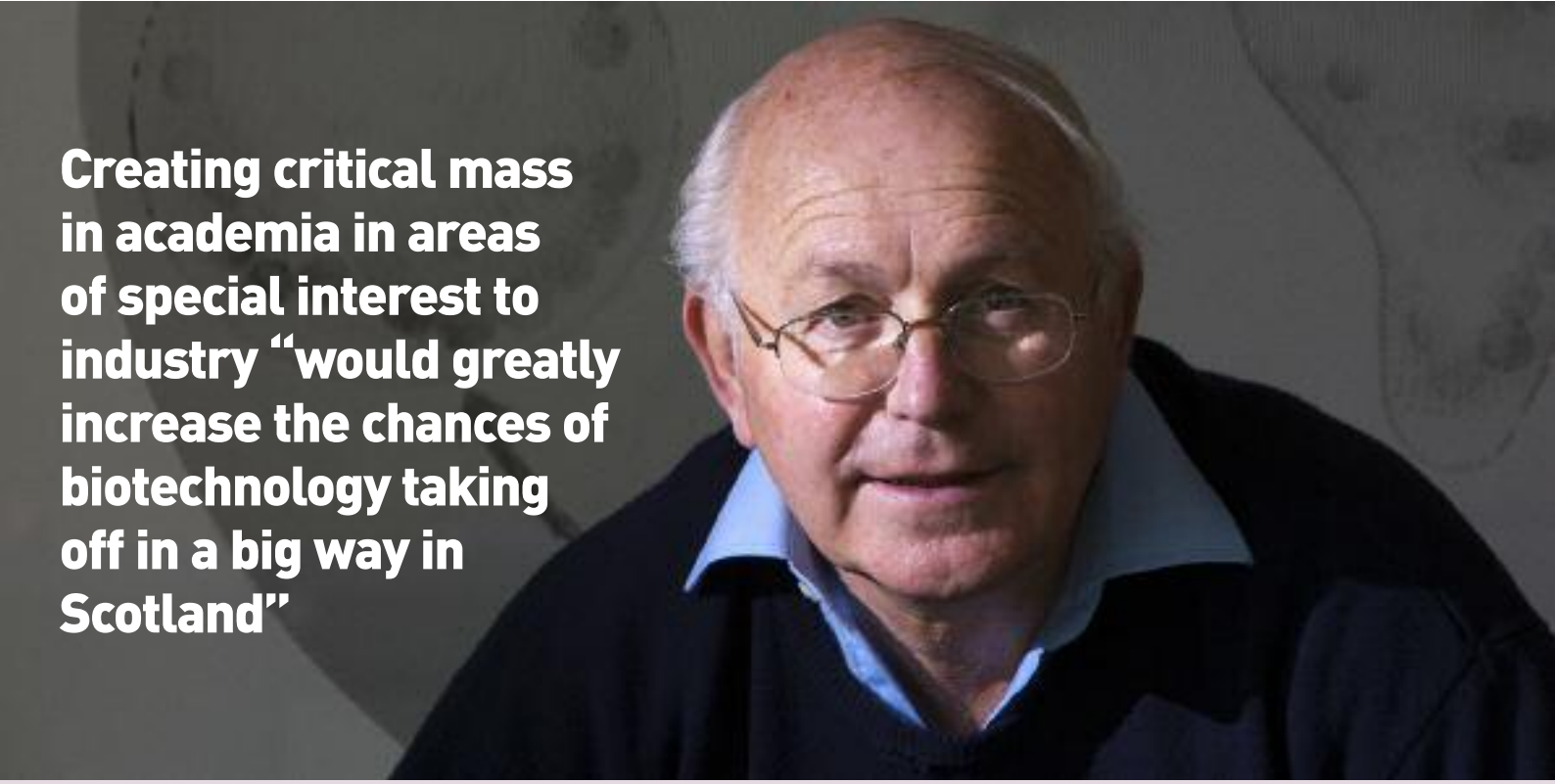
This journey to ubiquitination has taken many twists and turns already and Sir Philip admits he has "stumbled upon" many aspects of this new biological challenge, and now stands at another major crossroads in his career, just as he did years ago when he first got interested in phosphorylation.

The basics of phosphorylation were first understood in the mid 1950s, when it was shown to be a mechanism for controlling glycogenolysis (which produces glucose in the liver and energy for muscular activity), and gradually scientists unravelled more of its secrets. Sir Philip started doing his research into phosphorylation in the US in the late 1960s, and on returning to Dundee to set up his own laboratory in 1971, he set out to answer two major questions: how does insulin work and how are biological processes in cells regulated by phosphorylation?

His focus on how insulin works started in 1973, two years after he arrived in Dundee. Along the way, he learned about the mysteries of protein phosphorylation, with one discovery "cascading" into another as the pieces of the jigsaw fell into place. There were also many dead-ends, red herrings and wrong leads en route. For example, he once believed that phosphatases could be the key to insulin action, rather than protein kinases. As it turned out, this was wrong, but in the process he learned a lot about phosphatases – a fund of knowledge, which will also help in future research and drug development. For example, he discovered a phosphatase called calcineurin that was later found to be the target for cyclosporin, the immunosuppressant drug that has permitted the widespread use of organ transplantation.

According to Sir Philip, the discovery he is most proud of is working out how insulin stimulates glycogen synthesis in muscle – a quest which continued for more than two decades and culminated in the discovery of the "missing link" in this process, a kinase called PDK1, by Professor Dario Alessi, a Programme Leader in Sir Philip's Unit. In his autobiography, *For the love of enzymes*, Nobel Prize-winning biochemist Arthur Kornberg said that "There is no such thing as a boring enzyme," but with regard to PDK1, Sir Philip adds: "Some enzymes are more interesting than others."

Sir Philip's approach to phosphorylation involved "working backwards" – going from the final biological event (e.g. the synthesis of glycogen) to the root of the problem, step by step. He knew that insulin worked by removing a phosphate but then had to find out how it happened – a journey which led him to study a series of different events, including the discovery of different protein kinases and phosphatases and a myriad of phosphorylation "sites" on the enzyme, glycogen sunthase, where phosphorylation took place. Eventually, Sir Philip and his team of researchers began to understand how even very small amounts of insulin could amplify the signal by triggering a "cascade" of phosphorylation events to speed up the synthesis of glycogen, with PDK1 playing a critical role in the process.



Creating critical mass in academia in areas of special interest to industry "would greatly increase the chances of biotechnology taking off in a big way in Scotland"

One observer commented that Sir Philip's approach to research was like playing a game of chess – which happens to be one of his favourite games. The metaphor suggests that although you can plan several moves ahead, you can never predict every move or how the match will end, and have to be ready to respond to unexpected events, or "a logical system of continuations" which flows through the process.

Among Sir Philip's other key achievements are the classification and characterisation of serine/threonine-specific protein phosphatases and the elucidation of mitogen activated protein (MAP) kinase cascades.

With many big discoveries like these, Sir Philip says, scientists are tempted to think "this is it!" But progress often comes from "nibbling at the edges" – being persistent and patient enough to make the small incremental advances that hopefully lead to a breakthrough in knowledge.

In 1997, his pioneering work with insulin seemed to have answered in outline how this molecule worked. So he started exploring new fields of research, and eventually decided to tackle innate immunity and the role of ubiquitination in this process – a system which was "poorly understood" but had the potential to lead to the development of new anti-inflammatory drugs. "This is a chance to make a big contribution," Sir Philip declares – believing that the interplay between ubiquitination and phosphorylation, with its "increased potential for complexity," is going to become a dominant theme in the study of cell regulation in years to come.

Doing research on innate immunity – breaking open cells to find proteins of interest – is just as exciting for Sir Philip today as the study of insulin and phosphorylation was four decades ago, and he hopes that when it comes to deciding the future of the MRC-PPU, which he founded in 1990, and the Protein Ubiquitination Unit, a division of SCILLS, which opened in 2008, the two units will be integrated and continue to complement each other's work. SCILLS received initial funding worth £10 million over five years from the Scottish Government, while the current round of funding for the MRC-PPU will run out in April next year.

Doing the business

Sir Philip, who is also Co-Director of the Division of Signal Transduction Therapy (DSTT), "the UK's largest collaboration between a basic research institution and the pharmaceutical industry," has clear views on how to establish research units and attract funding.

What distinguishes Sir Philip's approach is that he seeks support for the team as a whole, rather than specific individual researchers or projects. In this way, strategic decisions can be made to put in place the support infrastructure that enables the team leaders to respond much more quickly to developments as they arise, because they have the money to do so. This set-up also enables post-doctoral researchers and PhD students to tackle the important aspect of their projects as soon as they arrive because the production of all the materials that they need has already been completed by the support staff.

The key to success, he repeatedly stresses, is "critical mass" – building up a team not only capable of doing broad research but also providing many aspects of technical support. This attracts biotechnology companies to Dundee to market reagents and services on the back of this infrastructure, which benefits the local economy, as well as basic fundamental research, and means "you also have much more to offer in collaborations with partners from industry." For example, the Unit generates 5,000 new DNA clones every year, as well as producing hundreds of proteins and antibodies.

The reinvention of Dundee

Sir Philip Cohen has played a major role in the emergence of Dundee as a major international centre for life sciences. As he himself puts it, the city is no longer famed for "jute, jam and journalism" but "biochemistry, biomedicine and biotechnology." Today, the sector employs over 8,000 people directly and indirectly and contributes an estimated 16 per cent to the local economy.

When Sir Philip arrived at the University of Dundee in 1971, the Biochemistry Department had only six members of staff, a handful of Ph.D. students and not a single postdoctoral researcher. The Biochemistry Department had started life in a converted stables for horses used in funeral processions and to carry the mail, but with the opening of a new building in 1970, the Medical Sciences Institute, Sir Philip was the first of several other academics who were recruited, and there was a surge of new appointments starting from the end of the 1980's.

The MRC-PPU was set up in 1990, at a time when the idea that protein kinases and protein phosphatases might be important drug targets was considered remote, but almost every pharmaceutical company now has a major programme in this area. Today, there are over 200 staff, working in 14 laboratories, and the Unit is involved in one of the largest-ever collaborations between the pharmaceutical industry and a UK University, currently in partnership with AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Merck-Serono and Pfizer.

SCILLS was set up in 2008 and, like the MRC-PPU, its facilities include a DNA Cloning Service, a Protein Production and Assay Development team, an siRNA screening facility and one of Europe's leading mass spectrometry centres. The Protein Ubiquitylation Unit is the first division set up in SCILLS and it already has eight Programme Leaders and a total of 60 scientific and support staff – and is about half the size of the MRC-PPU.

The College of Life Sciences at the University of Dundee now has a total of more than 1,000 scientific and support staff from over 50 countries, located in the Wellcome Trust Building, a £14 million facility which opened in 1997 and the Sir James Black Centre, a £21 million facility which opened in 2005. The actor Sir Sean Connery set the ball rolling in 1991 with a donation of £62,500 – a quarter of his fee for his walk-on part in *Robin Hood Prince of Thieves* – followed a few years later by £10 million from the Wellcome Trust, the largest-ever donation to a Scottish institution.

"In 1997," says Sir Philip, "I suddenly realised that what we're doing is important to the local economy."

Learning lessons from Upstate

In the mid-1990s, the MRC-PPU formed a close relationship with US-based biotechnology company Upstate, supplying reagents which Upstate sold to both academia and pharmaceutical companies all around the world. In 1998, the company's new CEO Sherry Snyder discovered that 12 per cent of its products were made in Dundee, and visited Scotland to find out more about his key supplier. Snyder sat in Sir Philip's spectacular "fund-raising room" overlooking the Tay Estuary and within 30 minutes decided to set up a new European division of Upstate in the nearby Technology Park.

The partnership continued to flourish, employing more than 100 people, and in 2004, Upstate was taken over by a company called Serologicals Corp for $205 million, later becoming a division of another pharmaceutical giant, now worth billions of dollars.

The University of Dundee and the MRC-PPU played a pivotal role in Upstate's success but did not directly benefit when it was sold because it didn't have any shares in the business.

Early last year, a new company called Ubiquigent Ltd was founded in Dundee in partnership with US biotechnology company Stemgent, to produce biological products and services generated by SCILLS, including reagents, assays and services. Sir Philip Cohen is excited to see the new company formed so quickly after the founding of SCILLS – and also pleased that SCILLS will benefit financially if the new company gets taken over or goes public in future, thanks to owning 20 per cent of the shares.

"The weakness of many departments," he says, "is too many individuals working alone, running their own little empires, with too many scientists focused on fine detail and not enough people looking at the big picture." Creating critical mass in academia in areas of special interest to industry "would greatly increase the chances of biotechnology taking off in a big way in Scotland," he adds.

The benefits of working very closely with the pharmaceutical companies also go far beyond money (the collaboration has so far attracted more than £40 million in funding, plus royalties). For example, says Sir Philip, researchers become more interested in clinical significance and have to work to more stringent industrial quality control standards. "I've come to learn how terrible quality control can be in academia," Sir Philip continues.

Having major pharmaceutical companies visit the unit for several days two or three times a year also challenges everyone to come up with important new findings and exposes students to the industry mindset.

Why life sciences?

Sir Philip's advice to young people thinking about a career in life sciences is to "do what you are passionate about." When he was at school, his passion was natural history, particularly bird watching, and when he went to study biochemistry at University College London, he was disappointed that it wasn't a cross between chemistry and ornithology. Two years later, however, when he started his first research project, he discovered the excitement of finding something "just around the corner" that no-one else had found before. Although he will step down as director of the MRC-PPU and SCILLS in April 2012, the passion still burns bright – Sir Philip has signed a new six-year contract to continue his research and says that his work on innate immunity is "just getting to the exciting stage." And unravelling the secrets of ubiquitination in this process is one of the passions which still drives him on.

Sir Philip loves to look at the processes that control everything – and judging by his appetite for science, he will never be happy to settle for less.

Further reading: *"Will the Ubiquitin System Furnish as Many Drug Targets as Protein Kinases?"* by Philip Cohen and Marianna Tcherpakov, *Cell* 143, November 24, 2010

DR JO MOUNTFORD

Blood on demand

Within the next two decades, every hospital may be able to source blood for transfusions on demand, thanks to new techniques being developed in the University of Glasgow, using embryonic stem cells to generate red blood cells...

Imagine the scene: A helicopter hovers over a battlefield in Afghanistan and lowers a piece of equipment the size of two washing machines, to make blood on the spot for wounded soldiers. This seems a million miles away from Dr Jo Mountford's laboratory in Glasgow, but that scenario has played a major role in helping inspire her research, in the quest to manufacture blood from embryonic stem cells – enough to meet demand in every hospital in Scotland and beyond.

Add to this the ability to generate other human cells such as heart tissue cells, for use in testing drugs, plus blood vessel cells and even neural cells, to replace or regenerate damaged or diseased tissues, and the scope of the research seems even more remarkable. For example, a total of 24 million people in the EU and USA who suffer from ischemic limb conditions could benefit from therapies which help to regenerate tissues either by replacing damaged or lost cells with new cells or by "helping the resident cells grow for themselves."

The idea of producing blood for use in transfusions was not Mountford's original aim, certainly not on the industrial scale that is currently being envisaged – up to two million units a year, using industrial bio-reactors. As often happens in science and scientific careers, the path to Mountford's current research project has taken a few twists and turns on the way – and under the surface there are several amazing surprises.

Mountford studied biological sciences at the University of Birmingham, where she also gained her PhD, specialising in blood development and working with progenitor cells from foetal livers and umbilical cords, before spending 12 months in Strasbourg studying molecular biology. She then spent two years in Oxford and returned to Birmingham again when she got a fellowship from the medical school, focusing on "intracellular signalling during haematopoietic differentiation."

In 2000, in the wake of the Alder Hey scandal, which involved the unauthorised removal, retention and disposal of human tissue, including children's organs, and made it much harder to get access to human tissue for research, Mountford moved to Memphis, Tennessee, where she worked at St Jude Children's Research Hospital. Human embryonic stem cells had first been isolated from very-early-stage embryos in 1998 and three years later they were shown to generate blood – and this revolutionised Mountford's ambitions for her research. In America at that time, she was able to experiment with adult stem cells, but US attitudes made it impossible to work with embryonic cells, and in 2002, Mountford headed back across the Atlantic to the faculty of medicine in Glasgow, to start research with human embryonic stem cells and continue her work on adult stem cells.

In Glasgow, thanks to funding from the Scottish National Blood Transfusion Service (SNBTS), Mountford was able to run her own research lab and that was when she started doing a collaborative project with her colleague Professor Tessa Holyoake, comparing aberrant leukaemia stem cells with normal stem cells to study how leukaemic stem cells resist death in response to targeted therapy. According to Mountford, blood stem cells are very difficult to obtain from normal individuals, so in search of a new source of these precious cells she started trying to make blood stem cells from embryonic stem cells (ESC), in the process making small amounts of red blood cells to demonstrate that these ESC-derived blood stem cells could become mature. "At that time, blood transfusion was not on the radar," says Mountford. But then the American Department of Defense (DARPA) appeared on the scene, looking for a new source of red blood cells for transfusion on the battlefield. They set a challenge to scientists across the world to develop a process suitable for emergency use in the field – offering significant funding to advance the research. Mountford and colleagues from the Scottish, Irish and National Blood Transfusion Services applied for the programme but the theatre of war was soon supplanted by the operating theatre as the main thrust of Mountford's research.

Although it never did become reality, the "extraordinary" idea of a military blood factory evolved into a method for producing blood on demand for use in hospitals – what Mountford now describes as a "more realistic, normal idea", with universal applications that would ensure a secure supply of blood for the future. Funding from the Wellcome Trust, SNBTS and, more recently, the Scottish Funding Council has allowed Mountford and her colleagues to advance this work, transferring laboratory protocols into clinically-usable processes and starting to look at the issues of scale.

This became the main theme in her research from 2008 onwards, with other applications such as blood vessel cells (for regeneration) and heart tissue cells (for testing the safety of new drugs) also in development.

"Manufacturing blood for transfusions is only one application," says Mountford. "By generating heart or liver cells, for example, researchers could avoid late-stage failures with drug trials and make drug development faster and safer." Theoretically, stem cells could also be used to develop regenerative medicines for diverse applications – including everything from solving the problem of hair loss to the replacement of neural cells in degenerative conditions such as Parkinson's. The level of complexity of some of these applications is much higher than for blood transfusion, says Mountford. For example, neural cells would have to integrate into the brain and re-establish the correct connections, whereas blood is administered directly into a vein and functions as a cell suspension rather than as complex structured tissue.

Red blood cells do not have a nucleus so have fewer safety concerns compared to muscle, nerve and liver cells generated from embryonic stem cells, for example. But if scientists can crack this first basic step, the possibilities are endless, with cost a major part of the equation. According to Mountford, every unit of blood for transfusions costs at least £140 to supply (even more with add-ons such as testing and public awareness campaigns) – and blood services account for a massive three per cent of the total NHS budget.

The biggest technical hurdle, says Mountford, is getting the nucleus out of the cell, "but we are making progress," she adds. This is what happens in nature, she explains, so the cells can carry oxygen more efficiently and travel through the narrow capillaries of the blood vessels. In addition to the fundamental science involved, the other major hurdle is to upscale production to industrial levels. One unit of blood contains about two trillion red blood cells and the NHS uses about two million units a year – "astronomical" amounts compared to current laboratory levels. The body is very efficient, says Mountford, and the bone marrow produces two million new red blood cells every second. So far, Mountford and her team have managed to produce a billion cells (10^9) or roughly a teaspoon from a single experiment. The number needed for trials is about 10^{15} cells, which would make about 500 – 1,000 units of red cells, while commercial-scale production would be at least 1,000 times greater.

"The other sticking point is numbers," Mountford explains. "Unlike the cells which develop in humans, cells which grow *in vitro* like low densities, about one million per millilitre. At that density the generation of a single unit of red blood cells would take 1,000 litres of growth medium at a cost of about £300 per litre." This is not economically viable, says Mountford, so new culture conditions will be needed that enable the cells to grow and mature at much higher density. The team in Glasgow is now working with colleagues at Heriot-Watt University to address these bio-processing challenges.

MOUNTFORD'S TEAM HAS MANAGED TO PRODUCE A BILLION RED BLOOD CELLS (10^9) OR ROUGHLY A TEASPOON FROM A SINGLE EXPERIMENT. THE NUMBER NEEDED FOR TRIALS IS 10^{15} CELLS, WHILE COMMERCIAL-SCALE PRODUCTION WOULD BE AT LEAST 1,000 TIMES GREATER.

> "equally important is the need to ensure that donors continue to give blood"

As well as quantity, the researchers also have to think about quality issues, including the use of animal products and the possibility of contamination during the manufacturing process. Foetal calf serum is used in the process to grow human cells simply because it is available in bulk, but there is a possibility of transmitting animal diseases or that some of the animal proteins may attach to the surface of human cells, risking cross-species immune responses if the cells were put into people. "In the early stages of the project, animal products were used, but we are eliminating these and replacing them with clinical-grade human or recombinant reagents to eliminate these risks," Mountford explained.

Another issue is the need to harvest cells – or separate the mature cells from immature cells. The engineering challenge this presents is not unlike a sewage works, says Mountford, potentially including very similar fluid dynamics and similar decisions – i.e. "How do we separate lighter erythrocytes from denser nucleated cells?" and "What is better: individual batch production or continuous flow systems?"

Typically, red blood cells live for 120 days in the body, so when a unit of blood is donated, cells of varying ages will be collected. However, *in vitro* generation should produce a more uniform product to maximise efficiency at the same time as achieving mass production. Blood donations can be stored for about 35 days, but scientists still argue about whether blood more than three weeks old is less effective than fresh blood. Mountford adds: "We don't know how long our blood will last, but our major advantage is that we will be able to supply on demand, evening out peaks and troughs of current supplies and theoretically supplying the NHS with universal donor (O-) red blood cells that have been freshly grown and distributed."

The stem cells themselves must meet the highest of quality standards, primarily the Good Manufacturing Practice (GMP) standard, and the project sources clinical-grade cells from Roslin Cells near Edinburgh, one of the only suppliers in Europe which produces "true" GMP cells. Mountford says: "We develop processes in the lab that will drive the embryonic stem cells to differentiate into red blood cells, but these processes need to be reviewed and amended to comply with GMP standards and to produce clinically-acceptable cells. This is a very different level of rigour that is not familiar to most academic labs, but Roslin Cells and the SNBTS have invaluable expertise in this area and are central to the overall project."

The newly-extended project brings together a multi-disciplinary team of biologists and engineers, and one of the most curious aspects is the role of social scientists. The use of embryonic stem cells is both novel and controversial, says Mountford, so it's vital to "manage public expectation" and consider the impact on society at large, especially in view of previous issues such as the Alder Hey "scandal" and fears generated by variant CJD and HIV Aids. People need to be reassured that the new kind of blood is perfectly safe as well as "ethical," but equally important is the need to ensure that donors continue to give blood and don't get carried away with the idea that blood will soon be easy to produce on demand – a prospect still more than a decade away.

"In seven years," says Mountford, "we will know whether it works or not. Clinical trials could begin in five to six years and it would be 10 years before it becomes widely used."

Embryonic Stem Cells

Most tissues in our bodies have a resident population of somatic stem cells (also called adult stem cells) that can repair the tissue in which they reside. Embryonic stem cells (ESC) have the truly remarkable capacity to generate all tissues in the body. Stem cells also have the unique ability to divide and renew themselves indefinitely.

Bloody Facts

- 1 unit of donated red blood cells contains about $2x10^{12}$ cells, and astronomers estimate there are only about 10^{11} stars in the Milky Way
- donated blood can be kept for up to 35 days
- only 4% of the people in the UK who are eligible to give blood are donors
- our bodies contain about five litres of blood – a total of about 20–30 trillion red blood cells
- more than two million units of blood are used each year in the UK
- blood costs about £140 per unit (roughly a pint)
- 95% of the population can be safely given O Rhesus negative (O-) blood in an emergency

PROFESSOR ANDY PORTER

Small molecules = big business

Professor Andy Porter is one of Scotland's most successful scientists – and one of our most successful entrepreneurs. The co-founder of Haptogen who pioneered a new way of targeting small molecules in the fight against the "superbugs" is also helping to create a new generation of biotech companies – and the next generation of biotechnologists trained in the commercial realities of biobusiness...

"I've had a few ideas in my time," says Andy Porter. "But I focus much more now on spotting ideas."

One of Porter's best ideas was helping set up Haptogen in 2002 and five years later selling it to one of the world's biggest pharmaceutical companies. And the ideas keep coming...

Porter, who is Professor of Biotechnology at the University of Aberdeen, is also teaching a new course in biobusiness and is one of a triumvirate at Grampian BioPartners (GBP), an angel investment firm which "talent spots" up-and-coming biotech firms.

Porter's story starts in the Rothamsted Research Institute, in Hertfordshire, where he specialised in plant genetics, trying to make oilseed rape more resistant to pests and disease. In 1991, Professor Bill Harris, the head of genetics in Aberdeen, persuaded him to head north to run his research lab, leaving a secure job to enter a completely different field of research. "I knew nothing about antibodies," Porter confesses. "But I could see the revolution was coming."

This was one of the first "educated risks" that punctuate Porter's career. He did have a training in molecular biology, but spent the eight-hour train journey to Aberdeen "mugging up" on antibody engineering to prepare for his interview.

Soon, however, Porter was established in Aberdeen and spent the next four years managing the output from Harris's lab. "It was an exciting place to be," he says. Moving from plants to medical science opened up a new world of commercial applications, and combining his backgrounds in physiology, biochemistry and molecular biology, Porter became a true biotechnologist rather than just a "gene jockey."

Porter's first venture into business was to help set up a company called Remedios, an environmental technology company spun out of the University of Aberdeen in 1999.

Three years later, this experience encouraged him to set up Haptogen with Dr Gillian Broadbent and Dr Keith Charlton, now his partners at GBP. According to Porter, they all had to decide at the time whether to accept offers to join the expanding biotech community in England or try and go it alone and set up a company in Scotland. "Our main driver initially was not really to deliver a commercial success but to stop the 'brain-drain' of antibody engineers from Aberdeen to Cambridge."

Serious science

The "big idea" at Haptogen was using human antibodies to target extremely small signalling molecules or "haptens" – aiming for targets "beyond the reach of other immunotechnologies." The overall aim was to develop more specific and safer drugs to fight infections, inflammation and liver disease, and improve diagnostics, in the process pioneering a new approach known as Haptomics.

One anti-infectives programme involved targeting the signalling molecules rather than the whole bacteria themselves – a new approach which made it harder for the bacteria to develop resistance. "The bacteria don't know they are under attack, and can even be encouraged to commit suicide," Porter explains. "It's actually hard for bacteria to infect us, so they divide and divide until there are enough of them to 'put on their armour and unsheathe their swords' and launch a co-ordinated and simultaneous attack. The antibodies stop communication by switching off the signalling function and counteract the attack mechanisms (the armour and weapons)."

"This was serious science," says Porter. "In antibody engineering, we were able to carve out a niche, making antibodies for difficult targets."

Porter and his team also used antibodies from sharks to develop new therapeutic solutions. These small and robust proteins had the potential to be delivered orally and "reach parts of the body other antibodies couldn't reach."

Porter continues his interest in developing new anti-infectives therapies through his role as an Investor/Director in the Aberdeen spin-out company, NovaBiotics. Through the efforts of its CEO, Dr Deborah O'Neil, NovaBiotics is one of only a handful of biotech companies in Scotland with a mid-stage clinical product. According to Porter, its anti-fungal biologics (protein-based) drug Novexatin® has the potential to deliver "blockbuster" revenues (over $1 billion per annum) when it completes its clinical development path, hopefully by 2014.

Business lessons learned

Porter's research in antibodies focused on a specialist area which still has enormous potential. According to Porter, there are two protein-based (big molecule) drugs in the Top Ten today and within the next three years, there could be as many as six. "The "biologics revolution" is starting to gather momentum – especially among the smaller companies. For now at least, protein therapeutics are the future, says Porter, with medicinal chemistry approaches increasingly being reduced or cut altogether from drug company pipelines.

Haptogen succeeded very quickly because it managed to deliver and commercialise its science, but Porter observes that although Scotland is "great at the science," we are not good at commercialisation. He also says companies have to take risks if they want to succeed – and be willing and able to ride out the bad times. "Most biotech start-ups are always only six months away from success," he explains, "and six weeks away from going bust."

Porter's career has evolved through a number of stages, from manager and scientist to entrepreneur and now includes his role as "biobusiness teacher." He strongly feels that to succeed in the commercial side of biotech, you need the basic science, but he also recognises that not every student is cut out for business, stressing that what matters most is to understand how the pharmaceutical industry operates.

The biobusiness course at Aberdeen is one way that Porter is trying to put something back into Scotland, drawing on his own experience in business, and he hopes the course will soon expand beyond its successful base in biological sciences and into other areas of science at Aberdeen.

Biotech companies are also beginning to send their "bench scientists" on to parts of the course. "Companies now realise it is important that their scientists, not just their business teams, need to be business savvy," says Porter. "Whilst small biotechs can see the benefits of the entire team understanding the industry, these same companies often don't have the time or structure to carry out this important training in-house ."

Research focus

Professor Andy Porter's central research theme is the application of antibody engineering to the solution of both medical and environmental problems.

Environmental:

Antibodies are one of the few molecules that can recognise specific targets present at concentrations as low as a few parts per trillion. Porter and his colleagues specialise in the selection of antibody structures specific for small molecular weight targets (haptens), generating highly sensitive diagnostic molecules and utilising anti-hapten antibodies in a number of exciting biotechnological projects. Currently, these projects include:

1. the development of a new test for water-borne bio-toxins that fully meet WHO guidelines on sensitivity and specificity
2. the development of antibodies for use "off-world". These antibodies are due to be sent to the planet Mars to help detect molecules that indicate primitive life may have once existed on the planet. Control antibodies for this mission have already been in space as part of the pay-load on a European space agency flight, returning safely and retaining function.

Medical:

Porter and his team also run the Scottish Biologics Facility (SBF) which is a joint University of Aberdeen and SULSA-funded laboratory, focused on the delivery of antibody and peptide-based tools and reagents for translational medicine. A varied range of projects is associated with the facility, including programmes in oncology, anti-infectives and cardiology. Techniques available include cloning and selection of antibodies and peptides from phage display libraries, recombinant protein expression and antibody characterisation by ELISA , BIAcore and bio-assays. The facility recently signed an MTA with Cambridge University to bring the "McCafferty library" to Aberdeen. This 100 billion clone human naive antibody library allows rapid and reliable selection of monoclonal antibodies to almost any target.

The 'hottest places' in biotechnology

Professor Andy Porter uses his experience in business to identify promising biotech companies, via the angel investment firm set up by him and his partners at Haptogen. Through Grampian Biopartners (GBP), he also sets out to demystify the science for other investors.

The company's approach to the business is simple: "Focus on what we understand, find the hot places and second-guess the market." Is it world-class science? But importantly is there also a significant market opportunity?

For GBP, the current "hot places" in biotech are:

1. biologics drug discovery
2. immunotechnologies & biomarker diagnostics
3. regenerative medicine tools

> "Biotechnology makes nothing, sells nothing and has no customers but this is not a barrier to commercial success."

At the start of one biobusiness class, Porter says to his students: "You've found a compound/bug at the bottom of the ocean that could be a cure for cancer, and in six weeks you will make a presentation to apply for a new round of funding. Now get on with it!"

Every year, Porter fears this "student-led" approach to the subject will be a "disaster" and every year the students produce what he describes as "brilliant projects." As well as teaching general communications skills and preparing the students in the art of the "elevator pitch" (selling your message in a couple of minutes), Porter also deals with basic business questions such as whether it is better to license a new technology or set up a new company, the different roles for technical and business skills and how to approach tasks by dividing them up into more manageable chunks.

Sometimes, the lessons are tough ones. To describe the commercial realities of drug discovery, Porter uses the example of lung cancer versus breast cancer. Sadly, people with lung cancer don't tend to live very long after diagnosis so if you test a new drug, it is easier and importantly quicker to measure its effectiveness. Breast cancer has typically longer survival rates, so you have to wait longer to see the results. The longer the drug development path, the more the 20-year period of protective patent life is eroded. Lung cancer thus offers "good" commercial potential for drugs, shortening the development path and extending the patent-protected revenue window – and that's a fact of business life which Porter passes on to all his students.

When he teaches biobusiness, Porter also likes to sum up the "madness" of the industry by telling his students: "Biotechnology makes nothing, sells nothing and has no customers." Yet as Porter himself has discovered, this is not a barrier to commercial success.

In the Scottish biotechnology sector, says Porter, most companies end up with a split business model, pursuing their core research at the same time as earning money from consultancy and other related activities. "Most Scottish companies are forced down the revenue route," Porter adds.

His perspective on the biobusiness also sheds light on the financial realities. For example, one company may have revenues of £100 million a year and be valued at £400 million, while another company has revenues of £50,000 and is worth over £1 billion, because it is based on a validated drug-engine and/or blockbuster drug pipeline.

So what is his advice to Scotland's budding biotech entrepreneurs? "Think global and promote yourselves globally," says Porter. "In Scotland, we have a tendency to be insular, but young companies have to get out there – decide what are the most important commercial conferences and don't just attend them but present from the platform. It's about building a brand and getting yourself noticed."

It is also a tough and some would say a crazy way to try and make make money, says Porter, who also advises new start-ups to get as much investment as they possibly can and "focus, focus, focus" the spend on key value-building milestones, like drugs into man. "I understand the fears they have," says Porter, "because I've been through it. The fear of failure's never far away but the thrill that comes from being at the forefront of your science is very seductive."

A new Golden Age of cell biology?

Ten years ago, the sequencing of the human genome promised many medical advances but, according to Professor Angus Lamond, there are still many steps to go on the scientific journey to decode the secrets of life...

PROFESSOR ANGUS LAMOND

For Professor Angus Lamond, head of the Wellcome Trust Centre for Gene Regulation & Expression at the University of Dundee, the prize is a big one – to study *all* the proteins in a cell and understand how the whole system behaves by "characterising the properties of all the proteins that the genome tells the cells to make."

Sequencing the genome was a great intellectual achievement and technological landmark which will help us to develop new and safer drugs, but it certainly wasn't the last word in biology, and Lamond's quest to understand the underlying chemistry of life and the "near infinite spectrum of proteomes" is part of the continuing story of science.

To understand Lamond himself and the serious nature of what he is seeking to do in his current research, it may be revealing to know that when he was an undergraduate, while other students may have spent their summer holidays picking strawberries or lying on beaches, he was rubbing shoulders with Nobel Prize winners and learning how to clone genes.

Nowadays, Lamond is pioneering new ways of analysing proteins to see what is happening inside cells, using the latest proteomics technologies (see **The Science**) and creating online databases to communicate the results (e.g. the human nucleolar proteome). Another fundamental aim of his work is to answer key questions such as "how long does a protein live?" and find out why the same protein lives for different lengths of time in different cells and under different growth conditions. But the intellectual curiosity that drives Lamond forward today is the same that he had as a student.

The story starts in Glasgow over 30 years ago. Lamond's father was a shop steward in a heavy engineering works and the young man was the first member of the family to go to university. At first, he thought of studying chemistry, but after borrowing a textbook on biology, he opted for a degree in molecular biology at the University of Glasgow. Lamond says his interest was to "try to understand living things at the chemical level," and he soon turned his attention to the world of cell biology and genetics, which "captured his imagination" and steered the course of his future career. "I always studied what interested me most rather than what other people thought I ought to be doing," says Lamond. Working on a research project for one of his tutors also exposed him to laboratory work, and at the end of his third year he applied for a summer job in Andrew Travers' laboratory in Cambridge. This was a pivotal moment for the 20-year-old Lamond – and his first "lucky break." As soon as he arrived, he "entered a completely different world" and realised this was what he wanted to do with his life.

During that extraordinary summer, Lamond met a lot of scientific VIPs, including Nobel Prize winner Francis Crick, who co-discovered the structure of DNA. One day, when Lamond was rummaging around in the freezer looking for some radioactivity to use in an experiment, he bumped into another Nobel Laureate, the biologist Fred Sanger – who had won the Prize in 1958 for his work in insulin and later that year (1980) won it for a second time for work that paved the way for sequencing the genome.
The young undergraduate did not know who Sanger was and imagined at first that he may be a janitor, but as Sanger started probing him with questions concerning his work, it dawned on him the "janitor" may know quite a lot about science.

Returning for his final year in Glasgow, Lamond helped his tutor, Professor David Sherratt, on a piece of research which was subsequently published in the journal *Nature*, and along with his summer work at Cambridge, he was able to co-author two research papers before he graduated with his BSc degree. "I enjoyed the freedom to create things and test my ideas," says Lamond, describing his "apprenticeship" in Glasgow with David Sherratt, where he studied transposons (sequences of DNA that move to new positions within the genome of a single cell) and how they develop resistance to antibiotics.

The Science

PROTEOMICS

Although the human genome has now been completely sequenced, we are still a long way from a full understanding of the proteins encoded by these genes and the complex biological systems in which they're involved. A new fundamental concept called the "proteome" (i.e. the full set of proteins present) has recently emerged, and proteomics is a new discipline that complements genomic DNA research, by comparing the proteomes of cell structures and systems under different conditions to further unravel biological processes.

SPLICING

The process of gene expression in the cell is carried out by a series of "protein machines." The process starts with DNA transcription (reading the "blueprint" for a protein on a particular gene) and carries through to production of that protein by ribosomes ("machines for making proteins").

The production of a protein begins with a ribonucleic acid (RNA) copy of the DNA blueprint. The RNA cannot be translated into protein by the cells until certain stretches of information which are not required to make the protein are removed – literally "spliced" out of it.

RNA Splicing is performed by a protein machine termed the "spliceosome", a complex of more than 50 proteins and small RNAs, acting together to catalyse this multi-step reaction. One of the Lamond group's research goals is to shed further light on the organisation of this structure and its regulation within the cell nucleus. Until we understand how it functions normally, we cannot understand what has gone wrong in disease states which affect this particular cellular process.

NUCLEOLUS

The nucleolus is a subnuclear organelle (self-enclosed unit with a specific function) – the factory in which specific genes are transcribed, processed and assembled to form ribosome subunits.

Recent studies suggest that the mammalian nucleolus may also play roles in events leading to the development of tumours, as well as in viral replication and cellular stress sensing. However, the precise mechanisms involved still remain largely unknown.

SUBNUCLEAR BODIES

The Lamond group studies the organisation of the cell nucleus, using fluorescently-tagged proteins and antibodies to "map" specific regions and structures. They also purify subcellular structures to identify as many of their protein components as possible (their 'proteomes'), hence obtaining important clues to the functions of these structures within the cell. Nuclear bodies play important roles in controlling cell functions and are often altered or disrupted by stress, viral infection or cancer. Understanding nuclear bodies can thus help to understand and treat many forms of human disease.

Before he returned to Cambridge to work for his PhD, Lamond spent three months in Zurich learning how to clone genes in the "highly disciplined" laboratory of Charles Weissmann, the scientist who first cloned interferon – a protein which was once the "great hope" for the treatment of cancer.

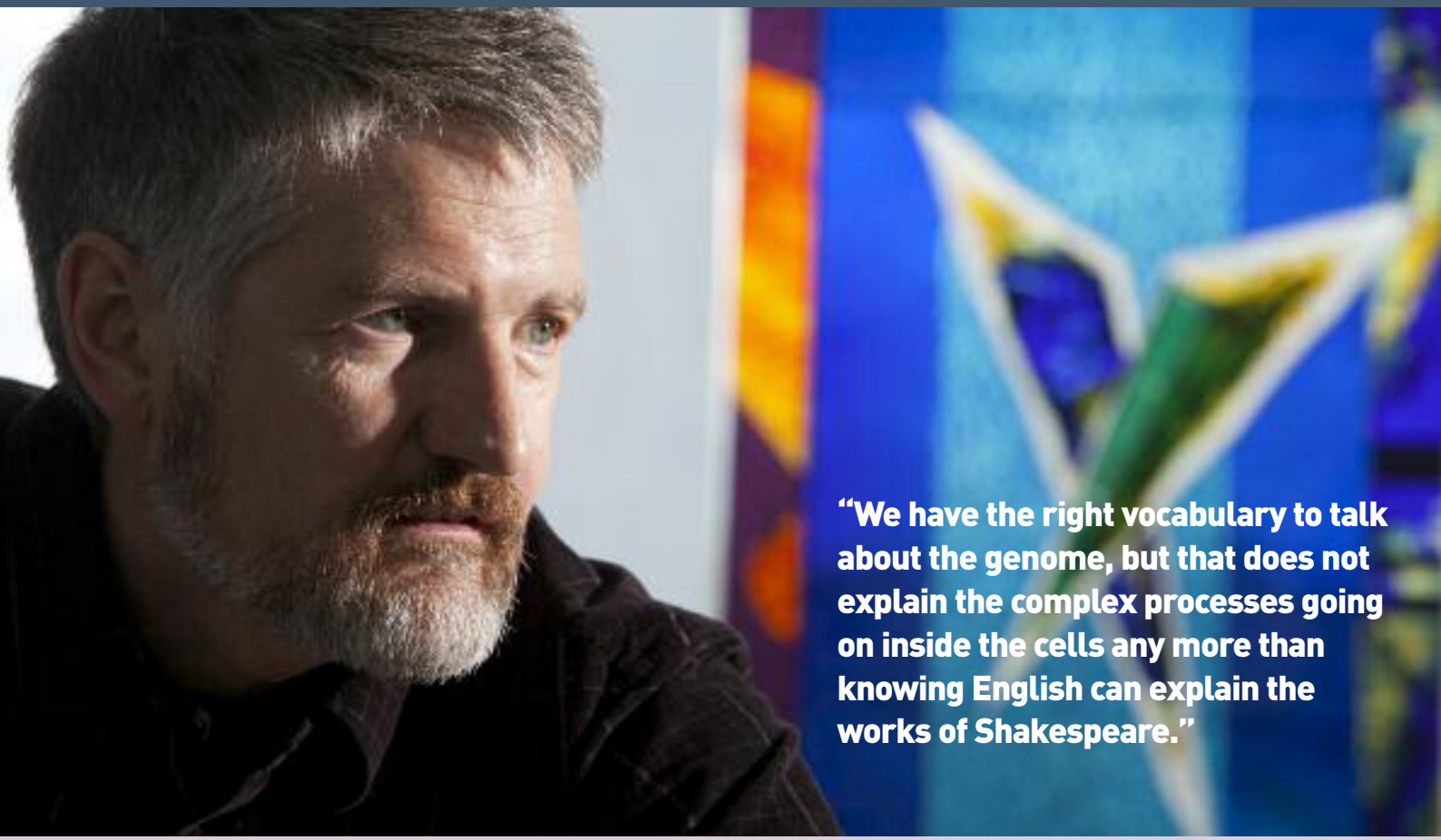
Back in Cambridge, Lamond completed his PhD studies in less than three years, with a thesis on the regulation of bacterial genes. What excited him most was the "adventure" of biology and the excitement of being the first person ever to know a new piece of information about how life works – such as how proteins interact and how drugs make our cells respond in different ways. "I was exploring how molecules behave," he explains, "working at the frontiers of molecular biology." In retrospect, he also thinks the fact that he didn't fear failure was down to the fact that he "didn't know enough not to do things." At the same time, he has always loved the "democratic" nature of science and how scientists don't pay attention to status and judge you by the quality of your ideas, rather than just your title or position. Lamond also stresses the importance of not being frightened of getting the "wrong" results in an experiment. "Research shouldn't be about 'end-gaming' – you have to learn from your mistakes."

Lamond spent the next two years at Christ's College, Cambridge, as a junior research fellow, and when he was inducted, he was asked to sign the Fellows' book, which previously Milton and Darwin had signed. During his time there, he also met his fellow Glaswegian, Lord Todd, who won the Nobel Prize for Chemistry in 1957.

Next stop was postdoctoral studies in Cambridge, USA, and after receiving his BSc and PhD he was able to get his 'BTA' (Been To America). In America, he switched his research from studying bacterial to human genes, working at the Massachusetts Institute of Technology (MIT) in the Centre for Cancer Research, where he continued his training. At MIT Lamond studied RNA processing (the splicing of RNA in eukaryotic cells), under the guidance of future Nobel Laureate Phillip Sharp, seeking to "understand how the molecular machinery interprets genetic information to assemble proteins."

Lamond got "lucky" again when he moved back to Europe and the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, where he "became a born-again cell biologist". At EMBL he continued to study RNA splicing in human cells and it was at this point that he first got his hands on a new type of fluorescence microscope, called a 'confocal', which enabled him to see more clearly the structures inside a living cell, "and how the nucleus of the cell is organised." He was also introduced at EMBL to mass spectrometry technology and its new application for the identification of proteins, literally by weighing individual fragments of purified cell proteins.

For eight years working in Germany at EMBL and the last 16 years in Dundee, Lamond's work has therefore evolved from analysing the chemical process of splicing to studying the proteins in the nucleus, and now he is taking full advantage of the latest technology to look at all the proteins in cells – the "nuts and bolts" of how cells develop and respond to their environment.



"We have the right vocabulary to talk about the genome, but that does not explain the complex processes going on inside the cells any more than knowing English can explain the works of Shakespeare."

"It's hard to study the proteins in living cells," Lamond explains, "because you can't see them." To solve this problem, scientists fuse human genes with genes which originally came from bright-coloured jellyfish, and the jellyfish genes colour the proteins so they can be seen in a fluorescence microscope– a process known as green fluorescent protein (GFP) tagging. Lamond also compares this "revolutionary technique" to putting a siren on the roof of a police car so people can hear it in the midst of the traffic.

How proteins behave is a key part of Lamond's research – measuring, for example, where they are located within the cell and how they bind to other proteins and affect them – and he enjoys the detective work involved in measuring and identifying thousands of proteins. "Mass spectometry has changed the way we do experiments," Lamond explains, "doing things we couldn't imagine before."

In his view, advances in technology have ushered in a new Golden Age for cell biology, as the science itself evolves from cloning genes to sequencing the genome and beyond. Sanger, for example, made enormous breakthroughs, but most of his ground-breaking methods have now been replaced with more efficient new technologies.

"For 25 years, we've been spending much of our time trying to solve technological problems, but now we have the tools to study what we really want – how cells work," says Lamond. Bacteria and viruses were the focus of attention in the 1950s and '60s, with "simple experiments driven by clever ideas." This was followed by a phase where experimental methods became more complex, with many of the breakthroughs coming from unexpected discoveries, rather than clever ideas. Nowadays, says Lamond, there is "an interplay of ideas and technologies" which is changing the way we do science once again.

Lamond thinks decoding the genome was a major advance but, alone, it has not delivered the host of new drugs and medicines many people expected. He feels instead that proteomics is increasingly important in the drive to understand how cells work and thereby to discover new drug targets and new and safer medicines. Proteomics enables us to study cells at very high resolution, to identify all the proteins and observe what happens to them inside the cell after drug treatments.

"We know what the genome is," Lamond continues, "so now we have to find out how it works."We have the right vocabulary to talk about the genome, but that does not explain the complex processes going on inside the cells any more than knowing English can explain the works of Shakespeare. When you also add the "overload of data" involved, the picture gets more and more complex, but recent breakthroughs in biological computing, including new techniques for data visualisation, are helping biologists to cope with the huge data volumes, says Lamond,.

Lamond's work can sometimes seem quite complex, but the aims are quite simple – if also ambitious. "I want to understand how complex chemistry changes over time," he explains, "and pioneer the intellectual framework so we can measure the responses and properties of cell proteins and understand what's happening inside the cell when it responds to its environment." It's a long way from his student days in Glasgow but exactly the same sense of wonder and the same determination to understand the "Big Bang" of biology.

An answer to cancer?

Every day (or so it seems), the media announce another "cure" for the disease that kills an estimated eight million people a year. But the reality is that cancer is many diseases, with many different targets for researchers to aim for. For Dr Martin Drysdale and his team at the Beatson Institute for Cancer Research in Glasgow, the challenge is even more daunting. They are after targets that other researchers have described as "undruggable" – in a series of ground-breaking projects that may take more than ten years to come to fruition...

DR MARTIN DRYSDALE

"We are challenging the dogma that some targets are undruggable," says Dr Martin Drysdale, the head of the Drug Discovery Programme at the Beatson Institute for Cancer Research in Glasgow. "They are only 'undruggable' because of what has happened in the past. And this is where FBDD plays a critical role – pushing the limits to find potential starting points to help validate targets and de-risk future research."

Finding novel compounds which may become drugs for the treatment of diseases such as cancer is one of the major challenges in drug discovery. FBDD (fragment-based drug discovery) is a new approach to looking for the molecules which could become new candidates for drugs. Instead of screening relatively large, complex compounds, FBDD focuses on very small, less complex fragments with a very low molecular weight – typically screening about 1,000 –1,500 fragments. Because these tiny fragments are not very potent (i.e. do not bind very strongly), they are hard to find using traditional methods, but using biophysical techniques such as X-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy, combined with the latest computational methods, the fragments are more easily detected and enable researchers to understand better how the fragment binds to the target or relevant protein, so the "hits" are more likely to turn into "leads" – and ultimately drugs. In simple terms, this means discovering a very tiny clue which leads to the arrest of a serial killer – in Drysdale's case, cancer.

Not every researcher is convinced that FBDD is the "answer to cancer" or other diseases, but more researchers are becoming more positive now, says Drysdale. "There are many targets in cancer which are amenable to FBDD and structure-based methods, but FBDD is also therapeutically agnostic," he adds. "It is capable of targetting any disease, and it is at its most powerful when you combine it with structure-based methods."

The road to Glasgow

Drysdale, who comes from Edinburgh and studied chemistry at the University of St Andrews, did his PhD in an "esoteric" area of chemistry called FVP (flash vacuum pyrolysis) – subjecting molecules to very high temperatures and low pressure to transform them into new compounds.

At this stage, his career could have led him in several directions – including petrochemicals – but what inspired him to go into drug discovery was a TV documentary on the Scottish pharmacologist Sir James Black, who developed beta blockers and won the Nobel Prize in Medicine in 1988 for the development of the anti-ulcer drugs propranolol and cimetidine. Drysdale was so excited by the programme that he wrote to Sir James to "ask him for a job." Unfortunately, nothing resulted from this but Drysdale persevered and eventually got a post-doctorate post at the pharmaceutical company Parke-Davis (now part of Pfizer), based in Cambridge, where he worked on the development of anti-anxiety agents. This experience also exposed him to a multi-disciplinary environment and a relatively small team of about 25 chemists and 50 biologists who worked and played together and exchanged expertise. "It was a good working model," says Drysdale. "I have always been a keen sportsman, and Parke-Davis was not unlike being part of a sports team."

Two years later, Drysdale moved on to Wellcome in Beckenham, joining a medicinal chemistry team led by Dr Allen Miller, formerly of the University of Dundee. At that time, says Drysdale, Wellcome was the "ivory tower of pharma," famous for the work of luminaries such as Sir John Vane, its former R&D Director, who shared the Nobel Prize in Medicine in 1982 for his work on prostaglandins. At Wellcome, Drysdale also learned researchers cannot work in isolation – it is better to share a small percentage of something important than have 100 per cent of nothing.

"There is nothing more exciting than drug discovery. It is almost a privilege to be in a position to make a real difference."

Drysdale initially continued research in central nervous system (CNS) drugs, then shifted his focus to "the science around nitric oxide," a chemical compound which is an important cellular messenger involved in many physiological and pathological processes in the CNS, as well as anti-inflammatory and cardiovascular areas – and *Science* journal's "molecule of the year" in 1992. Drysdale then became a project leader and also coordinated the chemistry across two teams developing synthase inhibitors – one of the company's most valuable assets. It was an enjoyable time for Drysdale which also led to practical results by delivering candidates for clinical trials – and exposed him to the commercial pressures of the pharmaceutical industry.

Two years after Glaxo merged with Wellcome in 1995, an opportunity arrived to join a new biotechnology company in Cambridge called Ribo Targets, which later merged with Vernalis. Drysdale's work involved building up the research group from scratch, including designing and building the lab, and after focusing on anti-infectives, he moved into cancer research, using FBDD, and became the company's deputy research director.

His experience in Cambridge was a good preparation for his current position at the Beatson Institute, not just in technical terms but also in collaborative methods of working. "It was very dynamic," says Drysdale. "People talked to each other and got things done."

FBDD was pioneered in the US by the pharmaceutical company Abbott. It was "a great idea", but Drysdale and others at Vernalis wanted to take FBDD in a different direction, focusing on ligands rather than proteins, to identify where the binding to atoms takes place, using X-ray crystallography and NMR.

Drysdale also started to focus on cancer. "In recent years, there have been remarkable advances in our understanding of what cancer is and how to treat it, but I became increasingly aware of the unmet needs in cancer research," he explains. "When I started working in oncology, I quickly realised that was what I wanted to do."

We now know that cancer is many diseases and the old way of thinking of cancer as organ-based (e.g. lung or liver) is no longer the best way to describe it, says Drysdale. "We also have the potential to target cancer more specifically than ever before," he adds. And the Drug Discovery Programme at the Beatson Institute, where Drysdale has gathered together a team of about 20 people, is a great opportunity not just to prove the scientific worth of FBDD, but also make significant breakthroughs in cancer research.

Focus on FBDD

FBDD is beginning to produce practical results, says Drysdale. Thanks to FBDD, there are 18 compounds now in clinical trials, including one discovered by a company called Plexxikon and developed by Roche for the treatment of melanoma, which is close to reaching market registration.

Reaching this stage can be an extremely slow process, says Drysdale – and may lead nowhere. "Drug discovery is no good if you choose the wrong target," he says. "The target may be promising but after years of research, you may find out it is not involved in the etiology of the disease. The biggest challenge is to identify targets, and in cancer there are many, many targets, as well as many types and classes of proteins to deal with."

Major Targets

The Drug Discovery Programme at the Beatson Institute for Cancer Research has a number of targets including:

1. c-Myc – a hub transcription factor which regulates many important processes in the development of cancer. Many upstream and downstream oncogenes are regulated through Myc and it therefore represents an attractive pleiotropic target for the treatment of cancer.
2. RAS – RAS mutations may be one of the initiating mutations in many cancers. They are found in up to 30 per cent of human cancers and are particularly common in pancreatic, colon and lung adenocarcinoma. It is one of the most challenging "undruggable" targets in cancer research.

Cancer Worldwide (Source: WHO)

- there are more than 100 types of cancers (Source: WHO)
- cancer accounts for about eight million deaths every year – over ten per cent of all deaths – and this is expected to increase to about 12 million deaths by 2030
- the five most common types of cancer that kill men are (in order of frequency): lung, stomach, liver, colorectal and oesophagus
- the five most common types of cancer that kill women are: breast, lung, stomach, colorectal and cervical
- about 72 per cent of all cancer deaths in 2007 occurred in low- and middle-income countries
- the World Health Organisation (WHO) estimates that 30 per cent of cancers can be prevented – mainly by avoiding tobacco, having a healthy diet and being physically active – while a third could be cured if detected early and properly treated
- 20 per cent of all cancers are caused by a chronic infection – e.g. human papillomavirus (HPV), which causes cervical cancer, and hepatitis B virus (HBV), which causes liver cancer.

Cancer in Scotland (Source: NHS)

- just over 28,600 new cases of cancer were diagnosed in 2008
- over 15,100 people died of cancer in 2009
- for males, the most common cancers are prostate, lung and colorectal
- for females, the most common cancers are breast, lung and colorectal – 56 per cent
- the main causes of death for both sexes are lung cancer (29% of cancer deaths in males, and 26% in females), followed by colectoral, prostate, oesophagus and stomach (males) and breast, colectoral, ovary and pancreas (females)

FBDD, says Drysdale, has a key role to play. "Many targets are regarded by the industry as 'undruggable' because they've failed to reach the start point, and FBDD helps us find more start points to validate."

Drysdale also explains that although the work done by his Drug Discovery Programme may not lead to instant results, it does de-risk the process of developing new therapies by industry and also helps to increase understanding by "proving we can target a particular molecule."

Drysdale has applied the same rigour to his work at the Beatson as he used to do in industry. "It's an industry-standard programme," he says. Academia is good at coming up with ideas but when it comes to drug discovery, industry simply does the job better – and Drysdale wants the Beatson to reproduce those same high standards, using basic biology to identify and validate targets.

"We have an opportunity to move into the drug discovery paradigm," Drysdale explains. "My programme acts as a bridge between the basic research and the clinicians. You can't do translational research without this – it's an interesting collaborative environment."

In Drysdale's new lab, chemists and biologists work side by side. The chemists make a compound and deliver it to the biologists only a few yards away, then watch it being tested. This is not just highly unusual in research of this nature but symbolic of the way the Beatson operates.

The gap between academia and industry is also beginning to close, according to Drysdale, blurring the edges between them. "The industry model has changed," he continues. "As more facilities close down, commercial companies consider new options for doing research like not-for-profit institutes and universities. There are also more people available with industry experience."

Future targets

Five years from now, says Drysdale, the objective is to build up a portfolio of drug discovery programmes at various stages – hit validation, hits-to-lead and optimisation of leads. And over the next five years, he wants to see evidence of de-risked high-profile targets and collaborations leading to the development of clinical products.

He also sees an opportunity to use FBDD to investigate targets in difficult areas such as invasion and metastasis (when a disease spreads from organ to organ), and move into entirely new areas like 3D fragment libraries. "This is a challenging space," he explains. "It is an area of research outwith industry timescales, and if we can de-risk it, then pharma can take up the challenge from there. In the commercial arena, researchers can't always go after the most important targets. We have the opportunity to lay down the infrastructure for future research and prove we're adding value."

Cancer research isn't just all about science – it's also about human beings. "Patient benefit is key," says Drysdale. And like it or not, it's also all about money – "a numbers game" as costly and as time-consuming as putting a man on the moon.

Drysdale relishes the challenge, however: "There is nothing more exciting than drug discovery. It is almost a privilege to be in a position to make a real difference. With FBDD, we are pushing the limits. Not every start point will lead to a clinical trial, but we have to start somewhere."

City of drug discovery

PROFESSOR MIKE FERGUSON

Dundee is called the "City of Discovery" in honour of the ship built in a local yard on Tayside, used by Captain Scott and Ernest Shackleton on their successful scientific expedition to the Antarctic (1901–04). In the future, however, the nickname may change to recognise the pioneering work done by the Drug Discovery Unit in the University of Dundee, set up five years ago and already producing exciting results...

They are not called "neglected tropical diseases" for nothing. But if Professor Mike Ferguson and his colleagues in the University of Dundee's Drug Discovery Unit succeed in their mission, killer diseases such as sleeping sickness and malaria may not be so neglected in the future.

According to Ferguson, Professor of Molecular Parasitology and Dean of Research, neglected tropical diseases were "not in the lexicon" of the pharmaceutical industry only a few years ago. They are a problem which affects the poorest people in the world and simply don't receive the same attention as more 'profitable' problems such as cancer. In addition, major killers such as malaria present other problems – treatments must be inexpensive and must be delivered to the millions of people who need them, and the parasites which spread the disease can develop resistance to many new drugs.

This lack of interest is beginning to change now, however, and Ferguson says "pharma is engaging at all levels" of the problem, with philanthropic organisations such as the Bill and Melinda Gates Foundation funding projects at the point of delivery and the Wellcome Trust and other bodies such as the Drugs for Neglected Diseases Initiative and Medicines for Malaria Venture funding the translation of basic research – including Dundee's Drug Discovery Unit (DDU), where a team of researchers is developing lead compounds for diseases such as trypanosomiasis (sleeping sickness), Chagas' disease, leishmaniasis, malaria and other protozoan pathogens.

The DDU was first conceived in 2002, when Ferguson and his colleague Professor Alan Fairlamb, now head of the Biological Chemistry and Drug Discovery Division, were "frustrated that the drug targets being identified could not be translated into therapeutics." The pharmaceutical industry had all the resources they needed, but they realised they would need industry expertise in-house to design new medicinal compounds themselves, rather than waiting for pharma to pick up their leads. As Ferguson puts it: "If we couldn't go to pharma, then we would bring pharma to us."

At about this time, the new Sir James Black Centre was being created, with one floor set aside for the new DDU. Even before it was opened, Ferguson and Fairlamb started raising the funds required to buy new equipment and hire key people, including Ian Gilbert, now Professor of Medicinal Chemistry and deputy head of the Division of Biological Chemistry and Drug Discovery, and Professor Julie Frearson, recruited from the Cambridge-based drug discovery company BioFocus.

This commitment to the DDU was one of the first "gambles" taken by Ferguson over the next few years – recruiting leading scientists without being sure where the next wave of funding would come from. Ferguson then spoke to Dr Mark Walport, the Director of the Wellcome Trust, and persuaded him the DDU could represent a timely opportunity. When the Trust reviewed the DDU's application, it agreed the unit needed to bring in more industry experts, and gave it more than £8 million over five years to pursue its new mission.

One of the first key appointments was Paul Wyatt, now Professor of Drug Discovery and Director of the Drug Discovery Unit – part of a team with over 170 years of industry experience in the pharmaceutical and biotechnology sector. According to Wyatt, "The unit was created to respond to a lack of capacity in the UK for early-stage drug discovery in the academic sector," and its mission is "to translate basic science into lead compounds to validate putative drug targets, to use as tools to investigate disease pathways and, when appropriate, advance to pre-clinical drug candidates."

IN 2013, THE DDU WILL EXPAND INTO A NEW HOME, THE CENTRE FOR TRANSLATIONAL AND INTERDISCIPLINARY RESEARCH (CTIR).

The unit today is still the only one of its kind in the UK – a drug discovery research lab in the heart of a university campus. Other research labs are "virtualised" among several locations, but the DDU is fully integrated, bringing together assay development, high-throughput small-molecule screening, cell biology, medicinal chemistry, structural biology, computational chemistry and DMPK (drug metabolism and pharmacokinetics).

Sometimes a great notion...

The DDU's ultimate aim is to find "effective targets and pathways" that eventually lead to the development of cures for killer diseases, in-house and in partnership with leading pharmaceutical companies. Sometimes, says Ferguson, this noble quest can be highly frustrating. Academic researchers doing good basic science can come up with what look like promising targets, but some "great molecules" or prototypical drugs may turn out to be nothing more than interesting "notions" and never become actual products. One moment, you might imagine you have found a cure for cancer, and the next you are getting a nasty surprise. "There is no shame in that, however," Ferguson adds, pointing out that only one or two out of every ten candidate targets proves to be valid. "We must expect attrition in the course of our research."

Parallel worlds

When the DDU opened in 2006, Ferguson was delighted to "train our guns" on neglected tropical diseases, but he also recognised that in order to make the new unit sustainable over the long term, it would need a broader remit, so from the start it also focused on innovative targets and pathways for other diseases such as cancer, diabetes and eczema, through collaboration with local experts in these areas. With tropical diseases, the idea is to validate drug targets and to develop new drug candidates, which would then go for clinical trials. With innovative targets, the idea is to make the validated targets "more tempting to pharma" by de-risking the basic research – reducing a large number of 'potential targets' to a small number of 'druggable targets' which pharma translates into drugs.

One of the benefits of this approach, apart from the promise of future financial returns, is the economies of scale which it enables, with researchers in the two "parallel worlds" sharing expensive equipment which could otherwise be idle for some of the time – e.g. robotics for compound screening and analytical equipment for chemistry. Ferguson stresses the need to avoid any conflict between the two spheres of research, so that money intended for one project does not go into another. It's an unusual model, he says, but it's helped to attract over £30 million in funding so far. The first £4 million was spent on the laboratory, with generous contributions from the Wolfson Foundation and the European Regional Development Fund, followed by almost £10 million from the Wellcome Trust and the Scottish Funding Council on equipment and recruitment to build the tropical diseases team and establish a Scottish compound screening facility – and significant progress has already been made.

The road to Dundee

Ferguson himself has dedicated most of his career to neglected tropical diseases, since he chose this as the topic of his PhD Thesis in 1979 at London University, before he went to New York's Rockefeller University to continue his research. At one time he believed that he would do research on cancer, but tropical diseases soon became his primary focus, specialising in membrane biochemistry – which plays a crucial role in cellular activities, with the membrane surrounding the cell acting as a barrier between the intracellular and extracellular environments, and as a site for diverse biochemical activities.

Neglected tropical diseases were an intellectual challenge which also satisfied Ferguson's need to do something "good for mankind." And as his work in membrane chemistry progressed, he made a breakthrough which would have an impact not just on the study of parasites and tropical diseases but also on our basic understanding of cells, working out how a whole group of proteins are anchored to cells – not just in parasites but in all eukaryotic cells (all cells except bacteria). This pioneering work in GPI membrane anchors (GPI = glycosylphosphatidylinositol) occupied Ferguson for several years, and gave him a solid grounding in the "nitty-gritty" of science, including five years working out the "partial and then complete structure" of the anchors, studying billions of possible options. "It was a long gestation period," says Ferguson, but later he started to dream of translating these ideas into druggable products.

His work in membrane biochemistry is now in the text books, but Ferguson confesses that it was not quite what he expected – or hoped for: "At first, I was bitterly disappointed that I hadn't discovered something unique to the parasites – an obviously druggable target," he says. "But then I realised that this was an important discovery in fundamental science, creating a framework for future biological research."

Ferguson then faced a choice: should he build on this discovery and specialise in GPI membrane anchors in general or continue to focus on neglected tropical diseases?

In recent years, he's also faced more difficult decisions and come out of his "comfort zone" to push for the creation of the DDU, so his dream of curing tropical diseases can come a few steps closer to reality.

DDU to double

In 2013, the DDU will expand into a new home, the Centre for Translational and Interdisciplinary Research (CTIR) – doubling the number of staff in the unit to 70 people.

As well as advancing the quest for new druggable targets, Ferguson believes the CTIR will also be an "experiment" in how such research centres work and evolve. The mission of the new centre is "to enhance translational research by expanding drug discovery capacity and to enhance computational and mathematical biology and informatics to meet the future of biomedical research" but the emphasis on interdisciplinary research is also a critical part of the project.

Dundee is very strong in imaging, mathematical biology and bioinformatics, says Ferguson, and when we hire new recruits, including biophysicists as well as astrophysicists, this will make for an interesting 'marriage,' allowing physical and computational scientists to "interact with experimental biologists" in a 'dry science' environment which allows them to work side by side, helping scientists "see different ways of doing things" and gain new respect for other disciplines at the same time as helping solve each other's problems. Mathematics, physics and computing are becoming more important in biology, for instance, and scientists with these skills know biologists are struggling with fast-increasing mountains of data and the need for predictive models in the quest to understand biology and to discover new drugs.

"The interface between biology and chemistry creates all sorts of new applications," he says. "In the CTIR, we will also have physicists and engineers, mathematicians and computer scientists, helping biochemists and molecular biologists. I don't think different disciplines should stay in their separate silos. It's our job to break down the madness."

Ferguson also believes that it's time to end single degree courses and start to teach the 'science of endeavour', regarding each discipline as part of a continuum. "The critics say you have to learn to walk before you run, and that you need a good grounding in a specialist subject, but I think we should take a more interdisciplinary approach – e.g. spend a third of the time on biology, one third on chemistry and one third on physics." Ferguson admits this is a cultural and also a "tribal" debate which will rage on for years, but hopes the new facility will blaze a trail for interdisciplinary research.

"It's time to end single degree courses and start to teach the 'science of endeavour'"

MEDICINAL CHEMISTS IN THE DDU DESIGN AND SYNTHESISE NEW MOLECULES TO TACKLE UNMET MEDICAL NEEDS.

Progress so far

The DDU has already made some significant breakthroughs. In tropical diseases, it has delivered two series of lead compounds that could lead to new drugs to treat sleeping sickness, and Ferguson says they could be ready for the first clinical trials within the next year. Another team in innovative targets and pathways has helped translate a potential drug target for skin disorders, discovered by Professor Irwin McLean and colleagues, which is generating interest from a number of leading pharmaceutical firms. This builds on a discovery four years ago that about 50 per cent of the people who suffer from severe eczema carry mutations in the filaggrin gene, and is another good example of "de-risking" research to reach the stage where targets have commercial potential. "To show that a great scientific discovery has real therapeutic potential through early-stage drug discovery is the target de-risking paradigm that the innovative targets and pathways team are working to," says Ferguson.

Among the unit's other notable achievements are:

- More than 50 assays developed or optimised
- 45 hit discovery campaigns plus one SBDD (structure-based drug design) project
- 3,000 compounds made in-house
- Ten projects taken into hits to leads
- Two projects in lead optimisation – with cures in animal models of African sleeping sickness on oral dosing

Apart from these encouraging results, the DDU plays a key role in increasing the chance of success in developing candidate compounds by reducing the risks for pharmaceutical producers. A few years ago, when the genomics explosion got everyone very excited, the industry was "trapped in the headlights," says Ferguson, thinking every protein in the human genome could be a target, but screening every compound against every target was not very practical. "What got lost then was the deep biological science. We want the druggable golden nuggets – we don't want a great drug that doesn't cure anything," Ferguson adds.

Ten years from now, the hope is that more of the DDU's and their collaborators' science will be in the clinic, and whether that means all the work on the druggable target is done in Dundee or in partnership with pharma, Ferguson would see it as an equal success. "We're just happy to be part of the translational pipeline," he says.

The rational lottery

"Rational drug design" sounds like a perfectly sensible method in the quest to understand small molecules and proteins, and identify the compounds which could lead to cures for killer diseases. But in the history of translational medicine, fashions come and go, so who is to say which approach will produce results faster? Serendipity is also a significant factor. Professor Malcolm Walkinshaw believes there is a place for many different approaches (including serendipity), and his experience in industry and academia has taught him that these different methods complement each other – for very good reasons...

PROFESSOR MALCOLM WALKINSHAW

Things have changed a bit since Professor Malcolm Walkinshaw was a young man studying chemistry at the University of Edinburgh. Now the Director of the Centre for Translational and Chemical Biology in Edinburgh, Walkinshaw is well known for his work in a number of areas, including structure-based drug design, database development and virtual screening, but in the early 1970s, the technology was not quite as advanced.

For his PhD, Walkinshaw used X-ray crystallography to study the structures of small molecule sugars, and this laid the foundations of his gradual move into structural biology. His post-doctoral work involved the use of X-ray fibre diffraction methods to study polysaccharides and DNA structures, to understand how molecules recognise and communicate with each other, "using basic techniques like crystallography to understand, in atomic detail, the building blocks of biological macromolecules and begin to explain the energetics and thermodynamics of their interactions. The hope was that these insights and principles could be applied to bigger biological systems." This in turn led to his later work in protein production and characterisation, studying how proteins unfold, bind and interact, as well as studies of protein-protein interactions.

Walkinshaw's early research involved a lot of complex and tedious calculations, but in those days to use a computer – which was housed in its own special room – you had to load three or four trayfuls of punchcards (used to compile the program and read the data) into the computer, then wait 24 hours to get the result. The next day, a van would arrive with the answer, and if a single punchcard had been bent or damaged in some way, you would have to run the program all over again.

"It was primitive computing," says Walkinshaw. "Today, the process is infinitely faster – it only takes a couple of minutes on a laptop. And as a result, the pace of research has increased."

The technology used to generate data has also advanced out of all recognition. For example, in the past, to "solve" a crystal structure, the diffraction patterns were collected on photographic film. The films were then developed and scanned in order to calculate the 3D protein structure. Such a process took weeks and months, but nowadays, all this is done in real-time to generate a complete dataset in just a few minutes, and processes that used to take up to a year can be completed in a day.

As Walkinshaw's career progressed, various other trends also emerged. "By the late 70s," he says, "it was clear that protein crystallography was going to be the major method to answer questions about molecular recognition in biological systems."

Rational Research

Professor Malcolm Walkinshaw's Research Group at the University of Edinburgh focuses on two main areas:

1 Protein – Ligand Interactions

A database-mining program called LIDAEUS (LIgand Discovery At Edinburgh UniverSity) – 3D databases of available molecules can be searched to select potential ligands for protein binding pockets. "A number of novel ligands that bind with micromolar dissociation constants have been discovered. As a general strategy we select ligands suitable for combinatorial chemistry and we have synthesised families of tightly binding ligands for cyclophilin," states the Group's website. The Research Group also has a major collaboration with the Dundee-based biotech company Cyclacel Ltd, and the databases are available to all researchers looking for bioactive compounds.

2 Protein Structures of Medical Targets

A Signal Transduction Pathways

A study of the interactions between large immunophilins and Hsp90 and the structures of cyclophilin-40 have been determined. Other targets include CDKs and PCNA.

B Antiparasitic Drug Targets in Leishmania, Trypanosomes and Plasmodium

Studying enzymes in the parasite glycolytic pathway, including phosphofructokinase, pyruvate kinase and phosphoglycerate mutase, as well as plasmodial targets including DHFR-TS, in collaboration with Linda Gilmore and Paul Michels.

Walkinshaw has always been interested in classifying the properties of molecular structures to find out why the molecules behave the way they do and this later led to his focus on rational drug design. According to Walkinshaw, in fields such as biochemistry and translational medicine, fashions come and go. Through the years, rational drug design has fallen in and out of favour, but in its latest incarnation it is healthier than ever. In the late 1970s and 1980s, the focus was on protein crystal structures and the challenge was to design small drug-like molecules using a structural (or 'rational') approach. The development of molecular graphics also occurred around the same time and opened up new possibilities of being able to visualise molecules in three dimensions. The availability of numbers of protein structures, coupled with the newly available computational and molecular graphics techniques, allowed structure-based design to take centre stage.

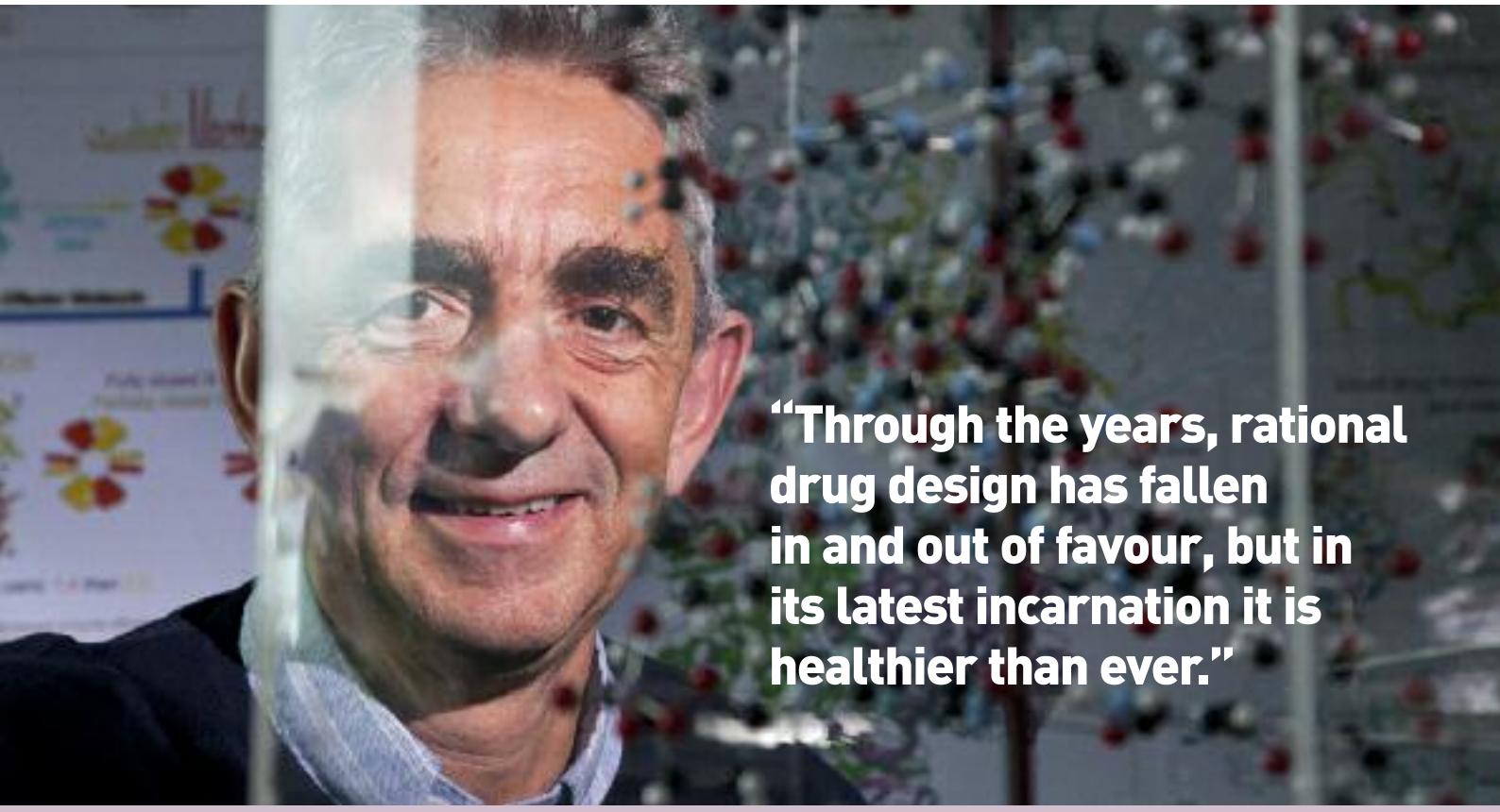
This emphasis on rational drug design steered the research of the big pharmaceutical companies for a number of years, but then began to lose favour to the newer combinatorial chemistry and screening approaches. In the mid-1990s, says Walkinshaw, the use of protein crystallography and structure-based design was not producing drugs as fast as pharma desired, and the fashionable new approach was high-throughput screening.

The big pharmaceutical companies were producing and cataloguing millions of compounds and looking for the one in a million that may eventually produce a working drug. But in recent years, huge advances in technologies to solve 3D structures of proteins, along with much more powerful computers, have also improved the hit-rates in structure-based or 'rational' approaches. "Rational drug design is alive and well," says Walkinshaw, "and it works best in conjunction with other complementary approaches including biophysical studies, sophisticated computing techniques and high-throughput screening."

Walkinshaw describes the scale of the drug-discovery problem by comparing the number of possible drug-like molecules that could be synthesised to the number of molecules in all the world's oceans – something in the region of 10^{50} – against that we only have about five to 10 million molecules available for screening, or as Walkinshaw puts it, "literally a drop in the ocean."

But we are making progress, he adds. Of the 30,000 proteins in the human body, we can now visualise 3D structures for about two-thirds of the total. Many of these proteins are potential drug targets and using computational techniques to screen integrated databases containing the details of millions of potential drug-like compounds, we can carry out 'virtual screening' tests more quickly than ever before. For example, once a target protein has been selected we can now use programs to identify a binding pocket and study its charge and its shape and use that information to identify a potential inhibitor, sampling up to one million compounds every two hours. Finding a compound which "docks" with a particular protein is never simple, adds Walkinshaw. "And you should always treat the results with healthy scepticism," he explains. "Predictions are seldom completely correct but they point you in the right direction for getting a hit. Our suite of virtual screening programs is now producing a 30 per cent success rate which is very encouraging."

The Walkinshaw lab currently works on a range of medically important targets. Of particular interest are antiparasitic targets, for example, in the search to cure parasitic diseases such as leishmaniasis and sleeping sickness. The computational and structural work is being carried out in Edinburgh and the biological and screening studies in collaborators' laboratories in Glasgow, Brussels and Maryland. Walkinshaw explains that in all living organisims there are ten steps involved in the conversion of glucose to pyruvate (a process called glycolysis). The aim is to intervene in that process by knocking out a pathway in such a way that you kill the parasite, not the host. "If we could hit a few of these targets, it would be even better," says Walkinshaw. "This could lead to the development of an effective 'cocktail' approach for drug therapy."



Lighthouse to ligands

Walkinshaw's career so far has followed a few twists and turns and has now come "almost full-circle." While still a student, he worked as a lighthouse keeper in his summer holidays and was tempted to go full-time after he got his degree. He also considered joining the Merchant Navy. Like many biologists today, his first degree was in chemistry, but he was persuaded to change tack and enter the "now fashionable field of structural biology," focusing on sugar structures. He then won a Fellowship in Wolfram Saenger's lab in Goettingen and "managed to solve my first protein structure, a snake neurotoxin – one of the relatively few structures available at that time," before returning to a full-time post in the Chemistry Department back home in Edinburgh, focusing again on small molecule crystallography, with an emphasis on molecular recognition and biological activity.

By the mid '80s the larger pharmaceutical companies were convincing themselves (prematurely, he says) that "rational drug design" was a fast and efficient way to new and more specific drug molecules. And in 1985, his next port of call was the Swiss pharma company Sandoz (now merged with Ciba to become Novartis), when rational drug design based on 3D molecular structures was becoming all the rage. For the next ten years he built up a multi-disciplinary team using crystallography, NMR and modelling in what is now called "structure-based ligand design."

One of his major contributions during this period was helping in the development of a drug called cyclosporin, an immunosuppressant drug widely used in organ transplants, now also being used for HIV/AIDS and Hepatitis.

Cyclosporin binds to a ubiquitous protein called cyclophilin, a member of a family of 18 such proteins found in our bodies, and according to Walkinshaw, "the role of cyclophilin is still a mystery we are only beginning to understand."

His home town exerted its pull yet again, and he came back to take up a new Chair in Structural Biochemistry in Edinburgh in 1995. His work since then has taken "a mainly medical slant," including the study of protein structures that provide targets for drugs against parasitic infections. In collaboration with his colleague Paul Taylor, he has also developed a database mining program called LIDAEUS (Ligand Discovery At Edinburgh UniverSity) which searches small molecule databases for potential inhibitors, to provide a starting point for combinatorial synthetic approaches."

Walkinshaw also collaborates with the chemistry department where he got his first degree – for example, he's involved in a project to generate compound libraries based on database hits to produce some genuine "lead"molecules for protein targets.

Fifteen years ago, it was unusual to leave industry for academia, but Walkinshaw today observes more researchers following a similar path. In many ways, the aims of industry and academia can be extremely different, but one thing is the same: whether the objective is science or profit, and whether or not you use rational drug design, serendipity will always have a role to play, combined with the passion which Walkinshaw believes is essential to success in any branch of science or business.

PROFESSOR GRAHAM COOMBS

Changing the subject

Scientists today often do research in esoteric areas, but even though this may divide them in terms of their specialist knowledge, they need to work closer and closer together and not just learn new skills but relearn their old subject over and over again – in an environment which also changes year after year...

The fact he's not a pharmacist may actually have been a big advantage for Professor Graham Coombs in undertaking his role as the head of the School of Pharmacy at the University of Strathclyde. "Instead of training pharmacists for the job as it is," he explains, "we want them to be able to adapt and ask, what if it changes?"

Coombs, who until April was also head of SIPBS (the Strathclyde Institute of Pharmacy and Biomedical Science), has seen dramatic changes in the course of his own academic career, in terms of scientific knowledge, drug development and the technologies used in research. He has also collaborated with numerous colleagues in the UK and beyond, in academia and industry, and this experience was crucial in preparing him for his role at the Institute, which was formed by the amalgamation of five departments from the Faculty of Science and also works in partnership with some of the biggest names in pharmaceuticals.

SIPBS was founded in 2006 and the idea behind it was simply to make it easier for scientists in different disciplines to work with each other and learn from each other. Its research projects focus on everything from mental health to cancer, and according to Coombs, with the construction of its new building, costing some £36 million, nearing completion, work at the Institute is "coming to fruition" and already making headlines for its breakthroughs in research (see sidebar).

The next generation of pharmacists will therefore emerge from an environment which emphasises the importance of multi-disciplinary teamwork and practical research, rather than a school which simply teaches them how to dispense a prescription.

Infectious enthusiasm

As well as being head of SIPBS, Coombs is the Professor of Biochemical Parasitology, and his own research focuses on two unicellular parasitic protozoa – *Leishmania*, which causes the killer disease leishmaniasis, and *Trichomonas*, a sexually transmitted pathogen which causes vaginitis and urethritis and may also have a role in HIV transmission. According to Coombs, both these diseases cause widespread suffering and the long-term aim of his work is to "underpin the development of novel therapies, either drugs or vaccines, which exploit unique biochemical aspects of the parasites."

Coombs developed his interest in parasitic protozoa during his studies at University College London (UCL), and later at the University of Kent, where he did his post-doctoral research on the mode of action of anti-malarial drugs. His general aim was to understand the parasites at the molecular level and "how they are adapted to their environment and live in the host," which enables biochemists to identify drug targets and develop vaccines.

"I was enthralled with these organisms," Coombs says, "because they tell us a lot about evolution as well as how they cause diseases." Studying protozoan cells, he explains, allows you to see the huge differences between them – for example, *Leishmania* and *Trichomonas* – and how they have adapted over time in the fight for survival.

Fundamental science is important, says Coombs, but the quest to cure killer infectious diseases continues to drive his research. "I always felt that doing biochemistry had very clear aims," he adds. "It was not just clever science but had applications."
The international "community" of parasitologists also appealed to Coombs – because there are relatively few of them compared to many other disciplines, it is easier to get to know other parasitologists in countries all over the world and therefore work together beneficially.

New trends

Since moving to the University of Glasgow in 1974 to establish his own research group specialising in biochemical parasitology, Coombs has focused on "elucidating biochemical adaptations of a range of parasitic protozoa, including pioneering studies on Leishmania amastigotes and peptidases of trypanosomatids," publishing more than 200 original papers, five books and several patents. In 1986, he was awarded the Seymour H. Hunter Prize by the Society of Protozoologists, and in 1993 he was elected a Fellow of the Royal Society of Edinburgh.

During his career in biochemistry, Coombs has seen dramatic technological advances and the emergence of various trends. There was a time, he says, when biochemical approaches in parasitology "went into a dip" as genetics began to attract greater interest. "The ability to manipulate genes makes it easy to create mutants to investigate the roles of the parasite's proteins and processes," Coombs explains, but the focus on genomics can also lead to the neglect of other studies and applications. Whatever is current or "sexy" will always attract lots of funding and followers, but the integration of different approaches, and collaboration of biochemists with other scientists with complementary expertise, is the key to long-term progress. In some ways, says Coombs, cloning is actually simple. "I like to do difficult things and take on challenges," he continues.

In recent years, Coombs has developed an interest in another new technology called metabolomics, using mass spectrometry to produce "super-accurate" measurements of metabolites. For example, to understand the mechanisms used by a parasite such as Leishmania to become resistant to drugs, mass spectrometry techniques are used to study the metabolome – very rapidly and in great detail – of parasites isolated from patients with leishmaniasis. The data generated show the differences between the isolates of drug-resistant parasites compared with drug-sensitive parasites, and this helps to point towards possible cures.

School of schools

The motto of the Strathclyde Institute of Pharmacy and Biomedical Science (SIPBS) is: "New medicines, better medicines and better use of medicines." Professor Graham Coombs, the first head of the SIPBS, describes the work of the Institute as "research intensive," focusing on themes including:

- pharmaceutical sciences
- cardiovascular sciences
- infection, immunity and microbiology
- cell biology
- cancer
- neuroscience and mental health

The Institute was formed from the bringing together of five different departments and Coombs describes this as "unique breadth in a single site," with medicinal chemistry and drug discovery taking place side by side with pharmacy practice, to realise the vision of an interactive and collaborative, multi-disciplinary school that "breaks down the barriers" between different branches of science such as pharmacology and immunology. According to Coombs, this leads to a subtle change in culture as well as in the flow of information, and creates new opportunities for specialists in niche areas to work much more closely with colleagues in other disciplines – and transfer their skills to partners round the world in countries such as Nepal where leishmaniasis is common.

The SIPBS' flagship undergraduate course is the four-year MPharm degree (Master of Pharmacy), and its other courses include Biomedical Science as well as post-graduate courses in both Clinical Pharmacy and Pharmaceutical Analysis, plus programmes in Drug Delivery Systems.

The Institute is also home to various facilities and research initiatives, including:

The Centre for Innovative Manufacturing

The new Centre will "revolutionise the way pharmaceuticals and other chemicals are made," with researchers and academics working together to develop new continuous manufacturing approaches for products such as medicines, foodstuffs, dyes, pigments and nanomaterials. Led by SIPBS Professor Alastair Florence, who headed a consortium that won £6.7 million in funding for the new facility, including £4.9 million from the EPSRC, the Centre will bring together existing teams at Strathclyde and house a suite of reactors for continuous manufacturing and crystallisation.

Cancer Research UK Formulation Unit

The Unit has a remit to pharmaceutically research and develop putative anti-cancer drugs to a level suitable for patient administration in early clinical trials. This requires "a mixture of blue sky and applied pharmaceutical research" across a range of drug types, and the Unit has handled about 100 new compounds, several of which (e.g. temozolomide, DMXAA, abiraternone) have been passed to pharmaceutical companies for further development.

CeNsUS

CeNsUS (Centre for Neuroscience University of Strathclyde) brings together PsyRING (the Psychiatric Research Institute of Neuroscience in Glasgow), SIPBS and the departments of Psychology, Bioengineering and Mathematics to build strategic partnerships between academia, the NHS and industry.

Simple intrasequence difference (SID) analysis

The development of software tools to probe the 3D structure of macromolecules looking for tell-tale topological motifs that are likely to be functional allosteric regulatory sites – which may offer new and better ways to control the functioning of therapeutic targets.

MGB Biopharma

A start-up company that has developed a group of novel synthetic polyamides that specifically bind to the minor groove of DNA. The DNA compounds are licensed for use as selective antibacterial agents and pre-clinical trials are expected to be completed by the end of 2011.

Recent breakthroughs

Among the Institute's recent achievements was the Life Science Innovation Award at the 2010 Nexxus Annual Life Science Awards, for a new technology developed by Dr Mike Mattey, an Honorary Lecturer in SIPBS. Dr Mattey's work focused on bacteriophage – a virus that "eats" bacteria – and could lead to a better way of fighting and preventing hospital "superbugs" such as MRSA. The treatment, which could also be used in veterinary medicine, food, agriculture, horticulture, decontamination and packaging, has been patented and will be commercialised by a spin-out company called Fixed Phage. Graeme Boyle, Director of Nexxus, commented: "This innovation is a significant breakthrough in the escalating fight against bacterial disease. Once again, Scottish scientists are at the forefront of world-class scientific developments and our universities are producing potentially world-class companies."

Dr Gail McConnell of SIPBS also recently won an award worth almost £1 million from the EPSRC for a project designed to improve the resolution of existing laser scanning microscopes, which could lead to important biomedical discoveries. The project will be carried out in the Centre for Biophotonics in SIPBS in conjunction with Professor Gian-Luca Oppo of Strathclyde's Department of Physics.

Researchers in the ROLEST lab have developed a novel high intensity narrow spectrum light (HINS-light) disinfection system for the inactivation of MRSA and other hospital pathogens. Extensive clinical evaluations of the new system, carried out at Glasgow Royal Infirmary, have demonstrated significant reductions in environmental bacterial levels, including MRSA, within sensitive areas of the hospital including isolation rooms in the Burns Unit and Intensive Care Unit. Studies are also exploring the application of HINS-light as a new method to inactivate food-borne pathogens and spoilage microorganisms, including bacterial pathogens belonging to the *Listeria, Staphylococcus, Salmonella, Shigella, Campylobacter, Bacillus* and *Clostridium* groups as well as yeast and mould fungi.

Killer diseases

Professor Graham Coombs has done research on the causative agent of various parasitic diseases, including leishmaniasis and trichomoniasis.

Leishmaniasis is caused by a parasite called *Leishmania*, one species of which, *L. donovani*, claims the lives of several thousand people and infects about half a million people every year in countries such as India and Nepal. Existing treatments (including antimonial drugs) are becoming less effective because the parasites have developed resistance to them, so it's important to improve our understanding of the mechanisms used by the parasite to adapt to drugs and achieve resistance – using new techniques such as metabolomics – in order to develop future treatment strategies.

Trichomoniasis is a sexually-transmitted infection of the urogenital tract which affects an estimated 180 million people worldwide every year, according to WHO. The most common site of infection is the urethra and the vagina. Men with the infection rarely exhibit symptoms but recent research suggests a link with prostate cancer. The complications in women include preterm delivery, low birth weight and increased mortality, as well as a predisposition to HIV, AIDS and cervical cancer.

Research in biochemistry does not always directly lead to new drugs, but does provide a better understanding of the mechanisms involved.

According to a recent paper co-authored by Coombs, "Research at the metabolic level is particularly relevant for parasite biology, where metabolic processes are among the major drug targets. Metabolic biomarkers could ultimately be reliable predictors of treatment outcome... because the concentration of metabolites integrates changes happening at both the genomic and environmental level."

Metabolomics is playing an increasingly critical role in research, but all these new technologies have key roles to play in the fight against killer diseases. Ultimately, Coombs says, the integration of genomics (the study of genes), proteomics (the study of proteins) and metabolomics (the study of metabolites) will lead to major breakthroughs in research and understanding of pathogens and the development of cures for infectious diseases.

"I'm a great believer in collaboration," says Coombs, suggesting that all successful research needs the right combination of skills. "We still need broad experience and knowledge – a better understanding of the organisms opens up a better possibility of targeting them with vaccines and drugs."

Research in biochemistry does not always directly lead to the development of new drugs *per se,* but does provide a better understanding of the mechanisms involved, which will ultimately lead to new therapies, usually working in collaboration with industry. "There needs to be industry involvement," Coombs says. "We are primarily doing the science, working at the fundamental level, but we also develop candidate vaccines and diagnostics which industry can then take to fruition of the product."

Much of the focus of SIPBS is on helping industry improve existing products and discover new ones but Coombs also feels very strongly that the Institute should also help pharmacists prepare to play a new and changing role in society – for example, more clinically focused on patients. "There is also a need for many pharmacists to become involved in research, to provide the evidence base for better use of therapies," says Coombs. And by creating an environment which brings together different disciplines and is also engaged in internationally-leading research, Coombs hopes the next generation of pharmacists will also be more aware of the need to collaborate – and more aware of the challenges faced by researchers.

NEXT ISSUE:

Knowledge Transfer (KT)
Engineering & IT

The next issue of Science Scotland (to be published in winter 2011) will focus on knowledge transfer (KT) within the Engineering and IT community, as well as other significant knowledge exchange (KE) activities between the academic and industrial sectors – looking at selected spin-out companies and small to medium-sized enterprises (SMEs).

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