sciencescotland from The Royal Society of Edinburgh

Cutting Edge Research from Scotland

ISSUE 4 SPRING 2005

The Protein Code

The Nuts and Bolts of Cell Machinery

Bio-Mining

www.sciencescotland.org

Introduction

This issue of *Science Scotland*, a showcase for Scotland's scientific creative talent, illustrates well how the contest to sequence the human genome was a race to a starting line, not to a finishing post. It also highlights the world class work currently in progress in Scotland in the fields of proteomics and bioinformatics. Proteins are synthesised at the command of DNA and RNA and act as the intermediaries between genes and action. They are both numerous and complex, in that proteins interact with each other in different manners in varying conditions within cells. Understanding protein interactions in health and disease will open the way to earlier and more effective disease prevention and control, and also hopefully lead to specifically tailored, less toxic treatments for many diseases.

New technologies, in which Scotland leads the way, have made it possible for scientists to work at a level almost unimaginable 10 years ago, as is evident in the research described by Jonathan Cooper in which he studies the working of single heart cells. Understanding the exact nature and the timing of protein interactions in these cardiac cells will help expand our knowledge of factors controlling the health of the heart. This could help us to identify at an earlier stage in disease, the abnormalities within cells which lead to chronic heart disease, one of Scotland's current major health problems.

The work described by Walter Kolch and his group illustrates beautifully the need for collaboration in modern, high quality scientific research. These collaborations need to be between departments at University level, between Universities and Research Institutes at a national level, and between countries at the International level. Kolch and his colleagues are working at all these levels of collaboration with major grant funding from many bodies, including the European Union. It is encouraging for Scotland to note that this group makes the UK's contribution to the European Interaction Proteome project.

These new developments in understanding the differences in protein interactions in the cell, as it moves along the path from a normal cell to a fully malignant cancer cell, should open the door to specific treatment for the patients who need it at the time of their first surgery, and greatly reduce the burden of more toxic treatments.

The work described by Angus Lamond in Dundee and Matthias Mann in Denmark further illustrates Scotland's enthusiasm for collaboration across national boundaries. This work looks at the interaction of proteins in cells over time, a vital area for understanding how, why, and most importantly when, normal cells communicate with each other, and why breakdown in these communication pathways may cause disease states.

The importance of understanding protein-protein interactions is underlined by the work of Jean Beggs and David Tollervey, who are studying the proteins that are involved with the processing of the messenger RNA that 'transcribes' the information encoded in DNA sequences and enables cells to make their complement of proteins.

The human genome project has provided information about the sequence of the proteins found in cells but it does not reveal their complex three-dimensional architecture. Geoff Barton's work is concerned with predicting the likely structures of the proteins and in collaboration with colleagues in Dundee and in St Andrews, actually determining the structures of proteins that are good candidates for drug targets.

The articles in this exciting issue of *Science Scotland* together illustrate some of the world class scientific studies that are underway in Scotland in the protein field. In time, this work could lead to the acquisition of knowledge which will directly benefit the health and well being of people around the world.

Best wishes,

Professor Rona MacKie, CBE, FRSE

International Committee Convener,
The Royal Society of Edinburgh

Department of Public Health and
Health Policy

University of Glasgow

Contents

This magazine is produced by the Royal Society of Edinburgh, with the
support of the Scottish Executive, Scottish Development International and British Council Scotland.

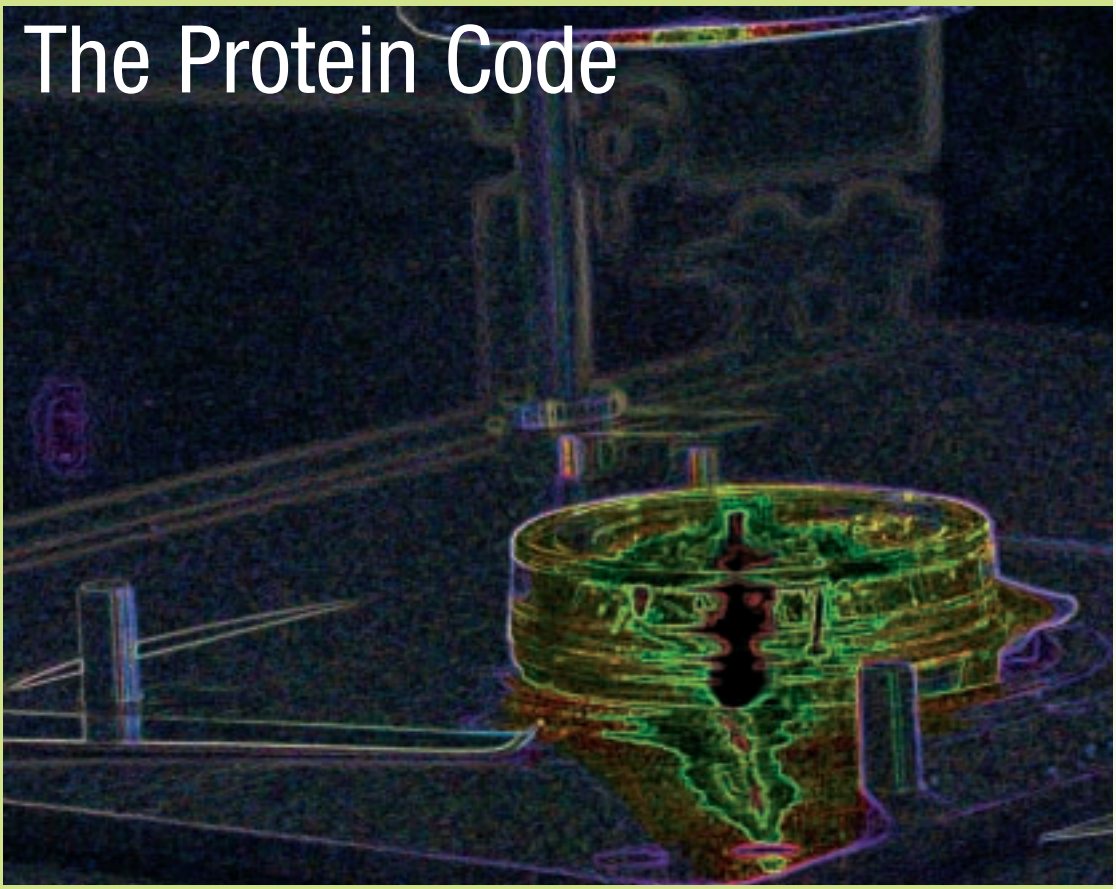
The Royal Society of Edinburgh
22-26 George Street
Edinburgh EH2 2PQ
Scotland

www.royalsoced.org.uk
www.sciencescotland.org
ISSN 1743 - 6222 (Science Scotland Print)
ISSN 1743 - 6230 (Online)

If you would like more information please contact
sbrown@royalsoced.org.uk

Issue 5 of 'Science Scotland' to be published this autumn will focus on energy

The Protein Code



Cells

All living things are made of cells, from the simplest single-celled organisms, such as bacteria, to complex, multi-celled organisms such as plants and animals. Humans are made of billions of individual cells of many different types, including skin, muscle and nerve cells, each of which has specialised roles in the body. Cancer and other major human diseases result in various ways from basic defects in the normal working of healthy cells.

Understanding the proteins encoded by the genome and interpreting their behaviour within human cells will be important in developing more detailed knowledge of what is happening in diseased cells. After all, it is the many types of protein molecules that actually do most of the work in cells.

Professor Angus Lamond of the University of Dundee, together with his collaborator, Professor Matthias Mann at the University of Southern Denmark in Odense are advancing our understanding of the dynamic processes that take place within human cells. The focus of their research is on proteins and the proteome (see italicised explanations). Working with their international teams, Professors Lamond and Mann are using new techniques to study in unprecedented detail how proteins move inside human cancer cells.

Biologists have known for many years that the cells of animals and plants have a complex internal structure that is subdivided into specialised compartments, termed "organelles". It was also understood that many types of protein molecules could move between these different compartments within the cell. However, knowing exactly which proteins move under which conditions has proved difficult to measure in detail and even harder to quantify.

The Lamond and Mann groups have pioneered the combined use of mass spectrometry, stable isotope labelling of human cells grown in culture and time-lapse fluorescence microscopy to characterise how the levels of hundreds of different human proteins change over time within organelles under different cell growth conditions. The location of proteins also changes over time and these new techniques allow snap shots to reveal the changes as they occur. Lamond refers to this as "time-lapse proteomics".

"The results we have obtained using our new 'Time-Lapse Proteomics' approach have shown just how dynamic and extensive protein movements between subcellular compartments can be," says Professor Lamond. "We didn't expect the flux to be so dramatic and to involve so many proteins moving in such a complex fashion.

Time-Lapse Proteomics

The 'Time-Lapse Proteomics' studies described here rely upon a procedure to repeatedly identify and measure the levels of each protein within a specific cell compartment. To do this, cultures of human cells are grown in the laboratory in media containing different chemical isotopes that label the proteins in each culture by changing their mass. The separate cultures are then treated differentially with specific drugs and the compartment under study biochemically purified from the cells. The proteins in the compartment are identified using a mass spectrometer - an instrument that can separate and measure molecules based on their mass. Because the proteins from each culture are labelled with isotopes that subtly change their mass, the mass spectrometer allows the relative levels of each type of protein in the organelle to be compared.

Proteins

Proteins are both the building blocks and the machine tools of living cells. While DNA is famous as the molecule that stores genetic information, it is the many different types of protein molecules encoded by our genes that actually do most of the work in cells. The failure of proteins to perform their allotted role correctly is a main cause of disease. Some proteins have structural roles. For example, the fibres that make up muscle are made of protein. Enzymes are also proteins – they catalyse the chemical reactions that break down food and provide cells with energy (metabolism). Other types of proteins are regulators that bind to specific regions of DNA to control how genes work.

The Proteome

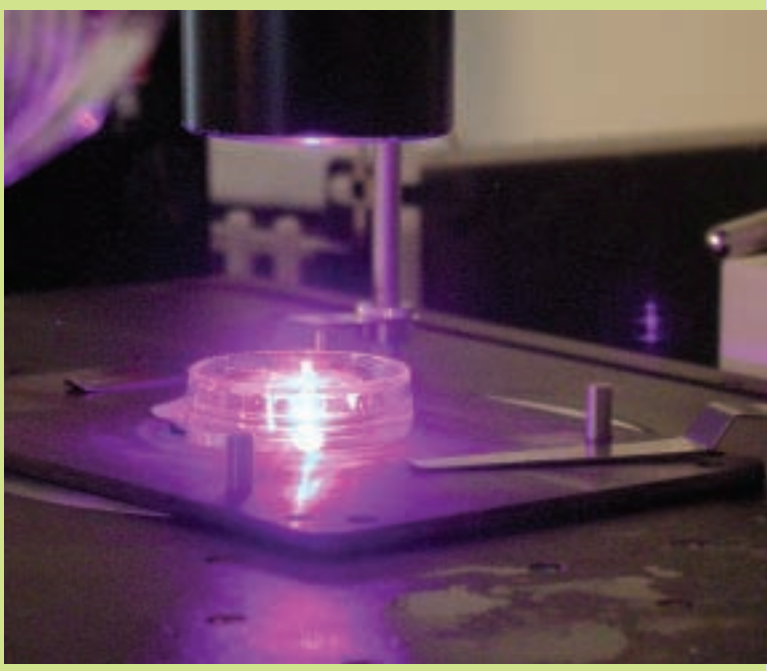
In the same way that the complete chemical sequence of DNA for all genes in organisms is termed the 'genome', the full set of proteins encoded by the genome is called the 'proteome'. Proteomics can be described as the new art of identifying proteins en masse and studying their structure and function. It is already established as an important area of science for the key task of interpreting the genome.

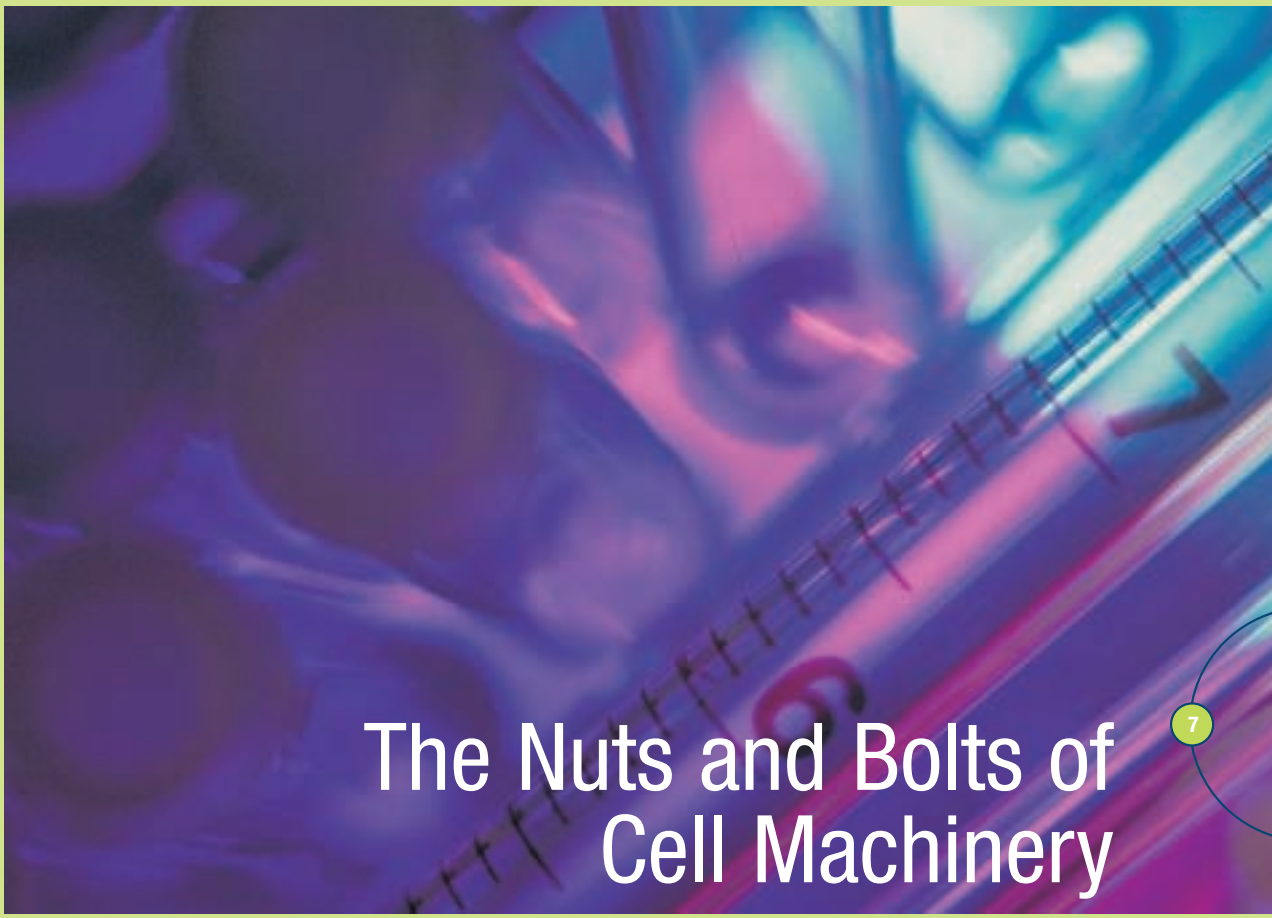
Now that we have a way to measure these changes accurately for hundreds of proteins in a single experiment, we aim to build a detailed picture of the changes that can occur in diseased cells."

Lamond comments on the work at his lab: "Using high sensitivity mass spectrometry techniques, we have so far identified around 700 human proteins in the cellular organelle called the nucleolus. We determined the kinetics of over 400 nucleolar proteins after exposing cells to various drug treatments and thereby demonstrated that there is no unique, complete proteome for the nucleolus, but rather an overlapping set of proteomes that are relevant to different cell states or conditions."

This ground-breaking work demonstrates how biologists are recruiting new technologies and working across disciplines to advance our understanding of the human genome and its protein products. It should provide valuable new insights in the future into the molecular mechanisms involved in a range of human diseases.

Further details on the latest results from the Lamond and Mann groups can be viewed online at **www.lamondlab.com/nopdb/**





The Nuts and Bolts of Cell Machinery

Walter Kolch, Professor of Molecular Cell Biology and Scientific Director of the Sir Henry Wellcome Functional Genomics Facility at Glasgow University, is intent on explaining the interactions between proteins to provide new levels of detail in our understanding of disease.

"Almost paradoxically the success of the genome projects has highlighted the need to analyse the proteome" says Kolch. "The genome may be the blueprint for life; however, it is the proteins encoded by the genes that are the nuts and bolts of all the cellular machinery." The modest number of approximately 40,000 genes in the human genome gives rise to a bewildering variety of an estimated 1 million different types of proteins, due to the processes of RNA splicing and editing, proteolytic processing and posttranslational modification. These modifications can alter the function of a protein and change its interactions with other proteins.

While the challenges posed by the complexity of the proteome are enormous, its analysis opens the door to understanding cellular processes that govern health and disease, with huge ramifications for basic research and medicine. The key to this door is the new discipline of proteomics that has emerged thanks to technical breakthroughs in the fields of mass spectrometry and bioinformatics (see “The Protein Code” p4-6 and “Bio-Mining” p10-12). These developments have allowed the identification and analysis of new proteins with unprecedented speed and sensitivity.

Professor Kolch explains, "It used to take many months to identify a single cellular protein. However, the important recent advances made in mass spectrometry and related methods mean that hundreds of proteins can now be identified in one afternoon – 15 years ago, this would have been seen as the work of centuries."

The next step, beyond identifying individual proteins, is to study how they interact and function within a cell. Professor Kolch explains, "Proteins assemble into complexes that carry out a particular function, so you can think of such protein complexes as a machine with a purpose. Many proteins are assembled into molecular machines that either generate energy, or else maintain and control the cell's shape and movement. The protein complexes may be quite dynamic and their life-span can vary greatly." Studying these molecular machines raises many questions. As is so often the case in modern science, the answers lie in bringing different disciplines together to work on the complex problems.

Professor Walter Kolch

Facility Unique in Europe

The Sir Henry Wellcome Functional Genomics Facility (SHWFGF) in Glasgow has been established to respond to this challenge. The Centre is embedded in the Biomedical Faculties of the University of Glasgow and uniquely in Europe brings together a raft of core skills – Proteomics, Gene Arrays, DNA Analysis, Robotics, Bioinformatics and Laser Micro-dissection. It is both a service facility and a research centre. The proteomics unit is equipped with state-of-the-art instrumentation for protein separation, identification and analysis. Kolch comments, "The provision of the specialist facilities demands the involvement of experts and it is therefore appropriate that the facility also undertakes its own research, ensuring that its services remain at the cutting edge of requirements in this field."

A constant challenge is to work with ever smaller samples. It is important to isolate and study individual cells and to analyse the interactions of proteins within these cells. Laser micro-dissection, another of the disciplines represented at SHWFGF, is used to recover individual cells or groups of cells, either from cultures grown in the laboratory or from tissue sections. Combined with parallel clinical studies this provides a powerful tool for detecting molecular changes associated with disease.

In future, the need to study smaller and smaller amounts of protein complexes will require the development of micro-devices for protein analysis. The lab-on-a-chip concept (see "Lab-on-a Chip" p13-14) is an important route for isolating a single copy of a protein complex, which can then be analysed using a highly sensitive mass spectrometer.

Scotland at Forefront of Proteomics

Scotland has a longstanding reputation as a leader in protein analysis, built on her strengths in biochemistry and structural biology. Scotland is now also at the forefront of the new discipline of proteomics. According to Professor Kolch, "Our strength in Scotland lies in applying these recent breakthroughs in protein analysis to the understanding of cancer, heart disease and infection and inflammation. This is not an esoteric study, but one which is expected to bring real benefit in terms of medical developments in the coming years".

The Molecular Pathology of Cancer

Professor Kolch also leads a research group at the Cancer Research UK's Beatson Institute, Scotland's leading Cancer Research facility, which is located on the Bearsden Campus of the University of Glasgow. "Employing methods spanning molecular cell biology, biochemistry, bioinformatics and proteomics, we are analysing multi-protein signalling complexes and working at understanding their function in signalling networks. Our aim is to understand the molecular mechanisms of cancer development."

"Cancer can be considered a disease of communication at the molecular level. Cellular communication uses biochemical networks that receive and integrate extracellular cues into specific cellular responses. We try to understand how a communication pathway can convert numerous input signals into specific responses that control such diversified functions as cell growth, survival and differentiation."

Image by Thomas McGuire courtesy of The Beatson Institute

The Beatson Institute is one of 11 European institutions, collaborating on Interaction Protome, an integrated project to establish Europe as the international scientific leader in the analysis of protein-protein interactions. Major objectives include the establishment of a broadly applicable platform of routine methods for the analysis of protein interaction networks.

EU funding under the Framework Programme has been provided for five years to enable Interaction Proteome to develop novel technology, including a high-end mass spectrometer with a large dynamic range, high-density peptide arrays, and improved visualisation technology for light and electron microscopy. Using the novel technology, the interaction partners of more than 100 relevant protein domains and more than 3,000 peptides will be characterised.

The particular contribution of the Beatson scientists to this project will be to field test the application of these new technologies in the biology laboratory and develop them into useful tools for untangling the complicated wiring of the "signal transduction pathways" that control cell differentiation, proliferation and death. Kolch's team will be involved at many levels in the project from identifying the protein components of the molecular machines that drive these pathways by mass spectrometry, to visualising the subcellular localisation of proteins using novel microscopic techniques, and to the computational modelling of the signalling pathways. This project aims to set an experimental paradigm for how we can obtain comprehensive understanding of complex biological processes and will be a contribution to the new field of "Systems Biology".

Bio-Mining

Professor Geoff Barton

Professor Geoff Barton holds the first Chair in Bioinformatics created in Scotland. Since 2001 he has been based at the School of Life Sciences at the University of Dundee, where he and his team are contributing sophisticated computational techniques to post-genomic studies.

"The term 'Bioinformatics' began to be used in the early 90s," says Professor Barton. "Before that I would probably have been called a 'computational molecular biologist' – significantly more of a mouthful." The development of this discipline has been a key element in enabling biologists to handle the huge amounts of data involved in projects such as the mapping of the human genome.

Bioinformatics really represents a confluence of computer scientists, mathematicians, statisticians and biologists. Professor Barton's research centres around the development and application of computational techniques to predict the structure and function of proteins from their amino acid sequence.

"We face challenges of both scale and of complexity," says Barton. "It is not just that we may need to manage data that would fill a whole stack of telephone directories, but that the actual data are substantially more complex than that!"

Making the most of Laboratory Time

"Much of our work is about prediction. We can help molecular biologists to identify which experiments are really worth doing." Dundee is a leading centre for research into microbial pathogens, in particular those that cause the parasitic diseases malaria and African sleeping sickness. Barton explains "There is a pressing need to study the biological chemistry of these organisms and develop new drugs against them. Prediction is an important tool in identifying how these pathogens behave in the body and this is where Bioinformatics can deliver." Rapid computational techniques can be used to filter through all the possible experiments that could be done to decide on the few that are most critical, so that time in the laboratory is not wasted.

In recent years computational approaches have become an integral part of the biologist's repertoire. Barton has been responsible for developing new tools and techniques that have changed the way non-specialists make use of computing and a number of his developments are widely used around the world.

Alscript is a particularly widely-used tool that Professor Barton developed during his time at Oxford and the European Bioinformatics Institute. The software is used for making sense of sequences and its applications include protein linear sequences and 3-D structures. Before coming to Scotland, Barton's group was also amongst the first to pick up on the value of the web. He is keen to stress the importance of sharing knowledge by this route and of making new data and new techniques freely available to others.

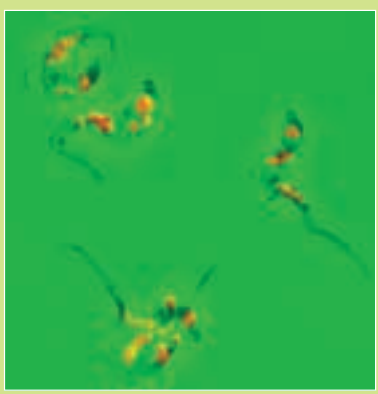
World-Renowned Centre of Excellence

The Group was established at the University of Dundee with the appointment of Geoff Barton to the first Chair of Bioinformatics in Scotland (appointments in Glasgow and Edinburgh followed shortly after). The School of Life Sciences is a world-renowned centre of excellence in life sciences research and received the highest (5) rating in both of the previous UK Research Assessment Exercises. The development of biological research over recent years as a data-intensive science led to the recognition that a significant research presence in computational methods was needed in the School. Funding to establish this area came from two sources, a Joint Infrastructure Fund (JIF) Post Genomics and Molecular Interactions Centre initiative, and a Scottish Higher Education Funding Council Research Development Grant (RDG) to create the Scottish Informatics, Mathematics, Biology and Statistics (SIMBIOS) Centre, a joint venture with the University of Abertay Dundee.*

At Dundee, the importance of Bioinformatics and other related studies has been recognised with the establishment of the Centre for Post Genomic Studies, where Professor Barton is the co-director. The Centre was opened two years ago with a massive remit to work towards interpreting the huge body of data produced by the Human Genome Project. Computational approaches will play a key role in mining the data to extract useful new insights into diseases such as African Sleeping Sickness, tuberculosis, cancer, diabetes and malaria.

Bioinformatics is also one of the key disciplines at the Scottish Structural Proteomics Facility (SSPF), a new joint venture between the Universities of St Andrews and Dundee. Last year, £5 million of funding was awarded to the facility, by the Biotechnology and Biological Sciences Research Council (BBSRC). One of the exceptional aspects of the SSPF is the way in which scientists from different disciplines are able to work alongside one another and bioinformatics is a central theme of many of these activities. Geoff Barton and his group play an important role, carrying out novel bioinformatics research that will speed up the process of solving new protein structures and improving the ability to interpret structural data.

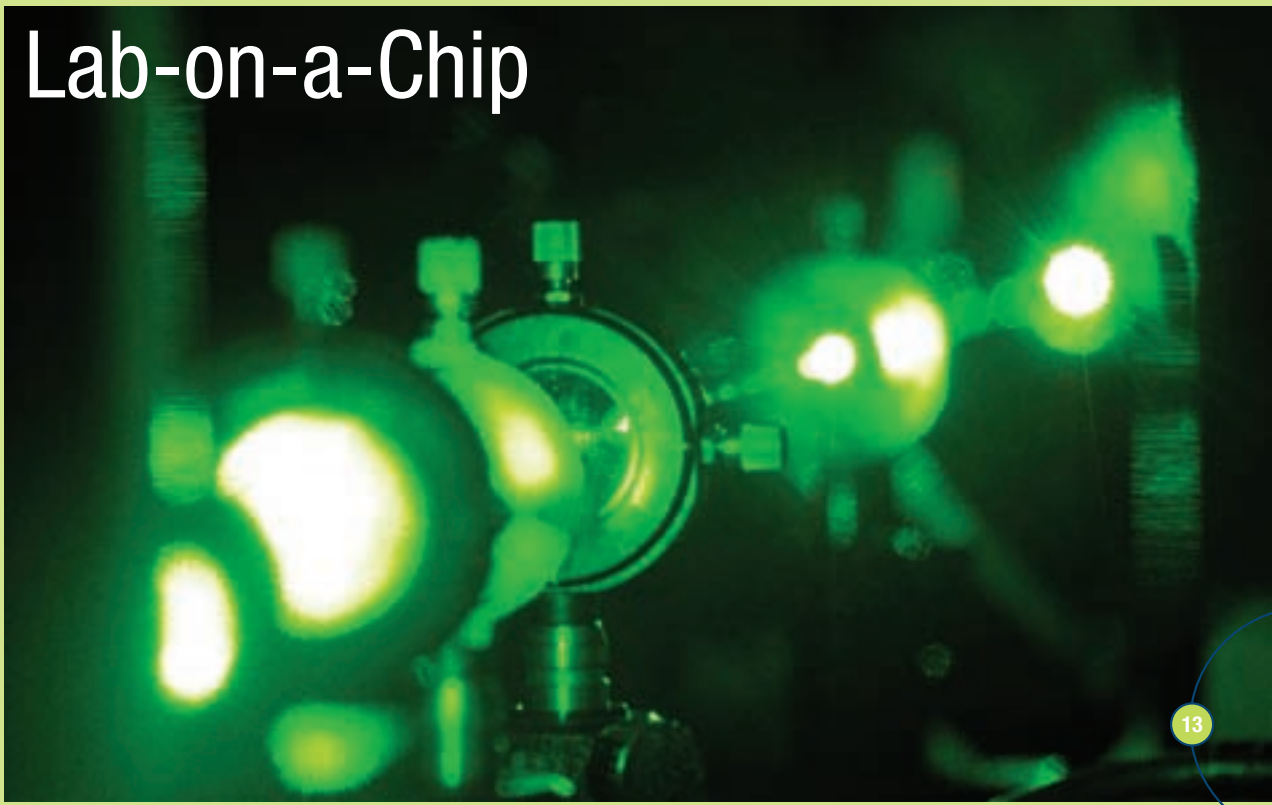
"Proteomics represents a very significant step forward in understanding life and the SSPF provides a key opportunity to integrate structural and computational studies with biology and enhance our understanding of fundamental life processes." The facility is designed to streamline the process of drug design, from the identification of novel therapeutic targets in drug-resistant bacteria to producing candidate lead compounds.



trypanosomes

High performance computing (HPC) is central to bioinformatics research. Dundee Life Sciences has established an HPC facility that is equivalent to over 200 PCs working together in parallel. Here, Geoff is inspecting the high speed networking that enables this facility to communicate and share data with researchers throughout Scotland and the World.

Lab-on-a-Chip

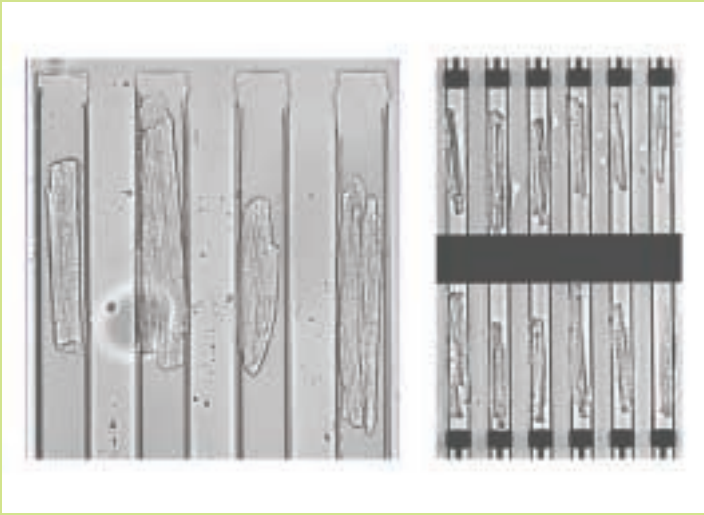


Glasgow's tradition of excellence in the miniaturisation of electronics equipment provides the foundation for Professor Jonathan Cooper's interest in studying individual living cells.

"In some cases one is the ideal number. It can be informative to study cells one at a time, in order that their behaviour can be observed without influence from their neighbours" he explains. "Currently there is a considerable interest in using microfabricated sensors, integrated with microfluidics, for single-cell analysis. These micro-scale lab-on-a-chip devices will have applications in pharmaceutical research, both for new medicine discovery, as well as for the toxicological assessment of compounds."

Amongst the different types of cells in the human body, heart cells have become a particular area of interest for Professor Cooper. There are many reasons to focus on the heart cell; according to British Heart Foundation statistics, 40% of UK deaths in 2001 resulted from heart disease. While there are medicines available to treat the symptoms of heart disease, there are currently no drugs with which to treat its cause.

Professor Jonathan Cooper is Professor of Bioelectronics at the University of Glasgow. He is intent on improving our understanding of disease through his work in micro- and nanotechnologies.



A series of single cardiomyocytes in microchamber arrays (volume less than a fraction of a drip of a tap) being stimulated by microelectrodes.

Professor Jonathan Cooper, FRSE, FREng

Cooper and his team, working closely with Godfrey Smith, Professor of Cardiovascular Science in Glasgow, have demonstrated a lab-on-a-chip system that can provide clinicians and the pharmaceutical industry with a better understanding of the mechanism of heart disease and allow them to work towards new therapeutic compounds. The device is designed in such a way that individual cells can be positioned in arrays of microelectrodes. The cells can then be electrically stimulated, controlling the rate at which each cell beats.

Local manipulation of the environment is provided by microfluidic connections so that it is possible to study the individual cells in a variety of conditions, including under reduced oxygen which is a good model for ischaemia. At the same time the cell can be imaged and a number of important parameters associated with both its electrical and mechanical activities can be measured. The microfluidic chambers have also been adapted to allow the measurement of metabolites, such as lactate, as well as electrophysiological ion channel activities. In one series of experiments, the team are correlating the frequency of beating with the rate of lactate production and the generation of the membrane potential, under both 'normal' and ischaemic conditions.

Professor Cooper continues: "we now have two potential routes of investigation, both of which are of immense scientific interest. We can either study the cells as healthy, viable systems, by electrically pacing the muscle filaments, and preventing them from de-differentiating, or we can deliberately put them in an environment which is more akin to a diseased state, and observe the processes leading to cell damage and death."

Single heart cells are not the only objects of interest to Professor Cooper. The current focus on proteomics has led to the development of complex nanotech sensors that can accurately measure proteins. For example, by further manipulation of the applied potentials across each cell, coupled with careful positioning of the electrodes, Cooper has been able to selectively permeabilise the ends of the cells, enabling the introduction of intracellular nanosensors. He would now like to develop a range of new optical probes that could be used to explore protein-protein interactions within many types of cell. Much of his current focus is therefore on methods for safely introducing these sensors into the cells, and ensuring that they do not adversely damage the intracellular mechanisms. The work is currently being supported through the IRC in Nanotechnology, a collaboration between the Universities of Glasgow and Oxford, and the National Institute of Medical Research.

This interest of Professor Cooper in protein-protein interactions ties in closely with the interests of Professor Kolch (see page 7). This research will be greatly facilitated by an injection of funding for proteome research in Scotland that has just been announced by the Biotechnology and Biological Sciences Research Council (BBSRC). £9.6 million is to be spent in support of a new Interdisciplinary Research Collaboration in Proteomic Technologies (IRColl) involving the Universities of Glasgow, Dundee and Edinburgh. This collaborative project, which will be led by Walter Kolch, is called Radical Solutions for Researching the Proteome (RASOR). It will directly benefit the research of all the groups mentioned in this issue of *Science Scotland*. In addition, a new doctoral training centre, led by Professor Cooper, funded at £2.3M over the next six years, will seek to train up to eight PhD students a year on the impact of new engineering technologies in proteomics.

Refining the Message

Professors Jean Beggs and David Tollervey of the Wellcome Trust Centre for Cell Biology, University of Edinburgh, are using a combination of proteomics and genetics to study how RNA is made and how it functions in yeast cells.

RNA molecules are crucial for the function of all types of cells. While genes store genetic information in the chemical sequence of DNA molecules, for this information to be used it must be copied into the related molecules called RNA. Many types of RNA thus act as genetic messengers, termed "mRNAs", which carry information from the genes that instruct the cell how to assemble the many different types of proteins needed for life. This process of making RNA is highly complex and involves many separate events that are carried out by a wide array of protein factors.

These processing events are important control steps in gene expression and can also increase the coding potential of the genome, as individual mRNAs can be processed in different ways, giving rise to the capacity to encode more proteins.

Professors Jean Beggs and David Tollervey

Professors Jean Beggs' and David Tollervey's work is largely funded by the Wellcome Trust, and is based at the Wellcome Trust Centre for Cell Biology at the University of Edinburgh. This provides state-of-the-art facilities, supplemented by mass spectrometry equipment provided by the Edinburgh Protein Interaction Centre (EPIC) http://www.epic.ed.ac.uk/ and funded by a Joint Infrastructure Fund (JIF) award from the Wellcome Trust. To promote integrated systems analyses, Edinburgh University is establishing a new Centre for Systems Biology, and recently made two appointments in this area; Professor Andrew Millar (formerly from Warwick University) has taken up the Chair of Systems Biology, and Professor Igor Goryanin (formerly GlaxoSmithKline) is the Henrik Kacser Professor of Computational Systems Biology. A third Chair in this area will be filled in the near future.

Professor Jean Beggs FRS, FRSE

The common baker's yeast *(Saccharomyces cerevisiae)* is widely used by biologists to analyse complex processes in cells because it is easy to grow and study in the laboratory. All of the DNA in yeast cells has been sequenced and therefore all the yeast genes are now known. As yeast and human cells are very similar at the single cell level, results obtained through studying yeast cells, which is usually easier than studying human cells, can help us to understand how human cells function. Therefore, yeast has been used to reveal the complex pathways of RNA production within cells and especially to reveal the interactions between different proteins involved in this process.

Two particular techniques have been used by Beggs and Tollervey that provide valuable insights into how RNA is produced.

The first involves clever *in vivo* screening methods to detect protein-protein and protein-nucleic acid interactions. Jean Beggs comments, "I have collaborated recently with Dr Pierre Legrain and colleagues (formerly working in the Institut Pasteur) to use the so-called "two-hybrid" screening strategy to identify interactions between yeast proteins involved in critical steps in the production of RNA. In this way we identified many novel proteins and uncovered unexpected links between different pathways affecting RNA molecules."

This screening methodology can now be carried out using robots to automate and thereby greatly speed up the laboratory procedures. In this way very large numbers of genes can be analysed, hence revealing vital clues about which proteins interact with which partners.

The second approach employed by Beggs and Tollervey involves using mass spectrometry to study yeast proteins in a similar way to that used in the study of human cell proteins (see articles by Lamond and Kolch). As Professor Tollervey explains, "We first use DNA technology to add a small chemical "tag" (known as a Tandem Affinity Purification (TAP) peptide) to the protein we want to study and then use this tag as a hook for purifying the protein along with all of the other proteins that bind to it. These interaction partner proteins are then identified using mass spectrometry."

These two approaches have produced large amounts of important new data that have helped improve our understanding of RNA production and other cell processes involving complex protein assemblies. These strategies have been exploited in a recent large international collaboration funded by the European Union and coordinated by Beggs and Tolllervey together with four other European research groups. For further information see; www.eurnomics.org.

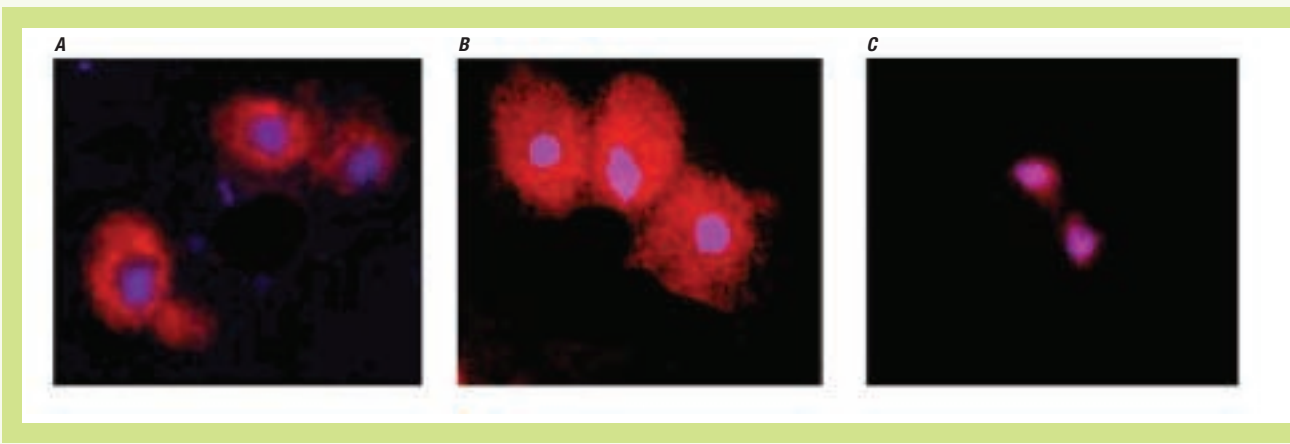


Figure showing the use of fluorescence to detect the localization of different proteins in yeast cells. Red represents protein; blue shows nuclear DNA. Protein A is exclusively in the cytoplasm, protein B is present throughout the whole cell and protein C is exclusively nuclear. The different locations of the proteins reflects their associations with different RNAs in the cells

What you need to know about RNA processing:

RNA is produced in the nucleus of the cell. The mRNA (messenger RNA) has to be processed and transported to the cytoplasm to produce proteins.

Introns and RNA Splicing

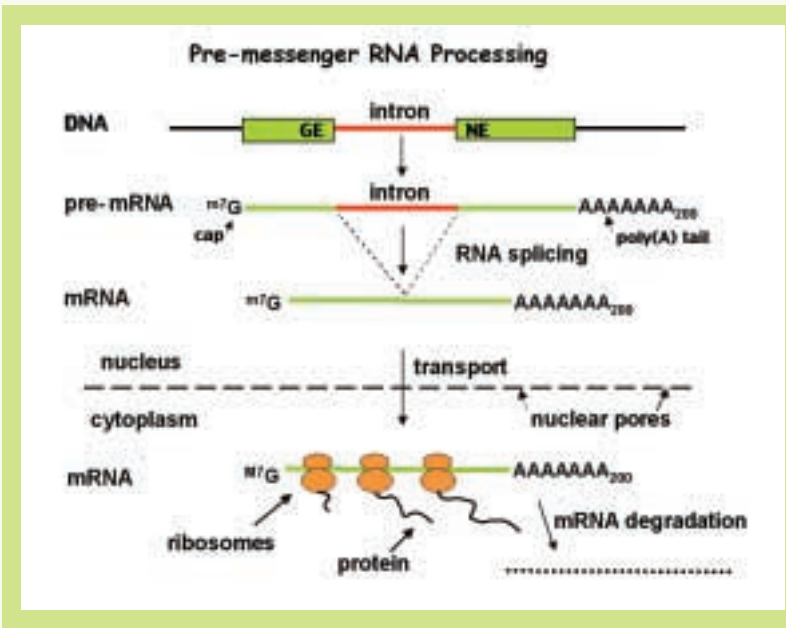
Some genes have their protein-coding information interrupted by non-coding sequences called introns. The intron will also be present in the RNA copy of the gene and must be removed by a process called RNA splicing before proteins can be produced. (see www.ed.ac.uk/~jeanb/).

Spliceosomes and RNA splicing

Spliceosomes are complexes that contain around 80 to 100 proteins and 5 small RNAs in addition to the pre-mRNA. The spliceosome is only one of many RNA-protein machines in the cell. In the splicing process, spliceosomes remove introns from messenger RNA precursors (pre-mRNAs). These are highly dynamic complexes and will undergo many rearrangements and changes in composition during the course of the splicing.

Ribosomes

Ribosomes are the molecular machines that produce the protein products encoded by genes and messenger RNAs (mRNAs); they contain about 80 proteins and four ribosomal RNAs (rRNAs). The synthesis of ribosomes is one of the major metabolic pathways in all cells.



This work points to the future directions of biological research. The more traditional, small-scale projects using the "bottom-up" approach - i.e. with individual research groups studying only one or two factors in isolation –are now being supplemented by "top-down" methods, which attempt to simultaneously analyse hundreds or even thousands of different proteins at once. These large-scale projects are often referred to as "Systems Biology", because their aim is to explain how the entire system of protein interactions within a cell operates.

Beyond the Human Genome: Deciphering Biology and Disease

Caledonian Research Foundation (CRF) International Conference

Organised by and to be held at The Royal Society of Edinburgh (RSE)

27-28 April 2006

The sequencing of the human genome is a truly historic scientific achievement that offers huge promise for the future of medicine and drug discovery. How can this information best be exploited in the years ahead? What is the future for genome research and what will its impact be on science, healthcare and society? These are key questions for planning the direction and funding of biomedical science in the UK for the next generation and will be addressed at this major international conference. We invite you to attend and learn directly about the excitement of the latest genome research and how it may change our lives.

The Royal Society of Edinburgh

For further information please visit: www.calres.co.uk www.royalsoced.org.uk

To register please contact: dwelsh@royalsoced.org.uk Tel: 00 44 (0) 131 240 5000

Science Scotland, bringing you the best of Science and Technology from Scotland, is a publication from the Royal Society of Edinburgh, with support from:

SCOTTISH EXECUTIVE

The Scottish Executive is the devolved government for Scotland. It is responsible for most of the issues of day-to-day concern to the people of Scotland, including health, education, justice, rural affairs, and transport.

BRITISH COUNCIL Scotland

The British Council Scotland enhances Scotland's international reputation and contributes to building an internationally-oriented, outward-looking Scotland.

SCOTTISH DEVELOPMENT INTERNATIONAL

Scottish Development International works to broaden Scotland's international appeal as a first choice source of knowledge from which to develop and exploit innovative technologies and ideas.

Register online at **www.sciencescotland.org** for regular updates, or complete and return this form to:
The Royal Society of Edinburgh, 22-26 George Street, Edinburgh, EH2 2PQ, United Kingdom

Title

Forname

Surname

Job Title

Organisation Name

Address

Town/City

Region/State

ZIP/Postcode

Email address

Please tick if you would like to receive a copy of our regular newsletter:

☐ By Email ☐ By Post ☐ or Both