Foreword

The College of Life Sciences is committed to ensuring that our research has a real and significant impact on the quality of people’s lives – their health, the economy and the environment.

Nurturing our scientific talent is central to our ability to translate our world-class research into local, national and global therapeutic and healthcare benefits. This brochure highlights some recent examples of how research in the College of Life Sciences is making a difference.

Professor Doreen Cantrell CBE FRS FRSE FMedSci
Vice-Principal and Head of the College of Life Sciences
The Open Microscopy Environment: Share and share alike

Led in Dundee by Professor Jason Swedlow, the Open Microscopy Environment is an international consortium that has revolutionised the ability of researchers and industrial partners to handle, analyse, share and interpret vast amounts of image data.

Share and share alike is the core philosophy of the Open Microscopy Environment (OME) that is delivering software solutions for life sciences research. From identifying biological structures in cells to examining animal behaviour, high-resolution imaging has become a critical technology across all of Biomedical and Life Sciences. The amount of imaging data generated in research labs in academia, pharma and biotech has reached gargantuan proportions. The explosion in the quantity and quality of data is further complicated by variation in file formats and size.

Founded by Professor Jason Swedlow FRSE at the University of Dundee in 2000, the Open Microscopy Environment is an open source, community-led consortium that is now a leading provider of software solutions for biological image management. When Professor Swedlow initiated this project he had two ambitious aims “First - whatever technology we developed would be open source, allowing us to share applications, tools, and know-how to the largest possible number of users, developers and scientists, all around the world. The second - we should build the most powerful and innovative software we could and ensure that it worked and could be used for as many different problems as possible.”

The OME Consortium (http://openmicroscopy.org) developed a software tool called Bio-Formats that can be used for converting images and metadata from different platforms to a standardised open format. Bio-Formats is currently the most comprehensive scientific image file format translator available and is used in >60,000 sites worldwide.

OME also developed OMERO, a data management system that enables access, sharing, analysis and publication of complex multi-dimensional image data. Scientists in >3,000 sites worldwide use OMERO to securely access their data from anywhere and apply whatever methods they need to analyse their image data.

A major impact is the uptake of OME image software and management tools by multinational companies, which is provided to them through the Glencoe Software spin-out (http://www.glencoesoftware.com/), founded in late 2005 by Professor Swedlow. Examples of companies currently distributing software platforms developed by OME and provided by Glencoe Software include Applied Precision Inc, PerkinElmer and Rockefeller University Press. The latter incorporated a customised version of OMERO in the world’s first web-based publication system for original multi-dimensional image data (http://jcb-dataviewer.rupress.org).

The impact of Professor Swedlow’s work and the OME team was recognised in 2011 when he was named BBSRC “Innovator of the Year” for its economic and social impacts.

www.openmicroscopy.org

“The technology built by the Open Microscopy Environment has been invaluable in powering the JCB DataViewer, the world’s first browser-based system for presenting, sharing and archiving the raw image data that are an essential part of many scientific publications.”

Liz Williams • Executive Editor of The Journal of Cell Biology
Influencing water safety policy to reduce the risk of blue-green algal toxins

Scientists at the University of Dundee applied their knowledge to inform worldwide health agencies, and governmental and regulatory policy on cyanotoxins, among the most hazardous natural poisons in the aquatic environment.

Cyanobacteria (blue-green algae) occur globally and produce a wide range of potent toxins in such concentrations that they poison and even kill animals and humans. Some cyanobacterial toxins can cause death by respiratory failure while others target the liver and nervous system. In the late eighties/early nineties, documented effects on human and animal health following exposure to cyanobacterial blooms, including in the UK, caused increasing public concern. Suitable techniques for the analysis of cyanotoxins in recreational lakes and drinking water supplies were not available, and there were insufficient toxicological data to set health-based guidelines for cyanotoxin control.

In 1990, Professor Carol MacKintosh together with Professor Geoff Codd FRSE uncovered the biochemical mechanism of action of the microcystins, a family of potent hepatotoxins produced by cyanobacteria. These toxins act by binding irreversibly to essential enzymes named protein phosphatases. This work led to microcystins becoming valuable research reagents for studying the roles of protein phosphatases in health and disease.

Moreover, their biochemical insights enabled the Dundee teams to develop new detection methods for the toxins and to explain their wider health risks. Advice provided by Professor MacKintosh resulted in new analytical methods being applied to maintain drinking water safety during a period of cyanobacterial blooming in reservoirs in the Thames area. A key report made by Professor Codd with medical colleagues established that the death of 60 patients in a haemodialysis unit in Caruaru, north-east Brazil, could be attributed to exposure to highly toxic microcystins in the water supply from a lake with a massive growth of cyanobacteria.

This research has had a major impact on the recognition, toxicity-assessment and risk-management of cyanobacterial blooms and cyanotoxins in waterbodies worldwide. Professor Codd has been involved in the safety assessment and protection of numerous waterbodies affected by cyanobacteria throughout the British Isles beyond and has played a major role in preparing World Health Organisation guidelines on the public health consequences, monitoring and management of toxic cyanobacteria in water. These guidelines represent the current position of ‘UN Water’, the body that coordinates programmes concerned with water issues amongst the 24 United Nation agencies. This research has provided primary guidance in the formulation and adoption of safety plans by several governmental and regulatory authorities for health protection against cyanobacterial in human drinking water supplies, aquaculture, agriculture and veterinary practice. Further benefits of the research include current programmes for the sharing of best practices for cyanobacterial and toxin monitoring and control throughout Europe.

www.lifesci.dundee.ac.uk/people/carol-mackintosh
www.lifesci.dundee.ac.uk/people/geoffrey-codd

"This work has had an enormous impact on how world health authorities (including the World Health Organisation) have approached mitigation of the poisonous effect of this important class of aquatic toxin."

Professor Charles Holmes • University of Alberta
As sophisticated proteomics methodologies are increasingly embraced by both academics and industry across the globe, growth in this area is set to explode. **Professor Angus Lamond FRS FRSE FMedSci** at the College of Life Sciences has been at the forefront of developing sophisticated proteomics technology to allow comprehensive analysis of the components of human macromolecular complexes, organelles and cells. During this work, Professor Lamond and his postdoctoral fellow at the time **Dr Paul Ajuh**, quickly recognized that a major stumbling block was access to high quality and reliable reagents needed for these studies as well as access to appropriate proteomics platforms and expert data analysis. Dundee Cell Products (DCP) was created in 2006 to fill this niche in the market, taking advantage of the expertise in cell biology, proteomics and mass spectrometry developed in the University. The main strengths (and selling point) of the company were to be the quality of their products and the high level of expertise of the individuals involved in the company.

Now in its eighth year, DCP provides new cutting edge technology services to biotech, pharma and academic customers throughout the UK and worldwide. Researchers in Europe, North America and Asia, as well as multinational biotechnology companies are using products and services from DCP. Links with Professor Lamond and the company have continued and this has brought benefit to the portfolio the company can offer. For example, the laboratory of Professor Lamond was the first in the UK and one of the first worldwide to adopt and optimise a procedure called SILAC, a technique based on mass spectrometry that detects differences in protein abundance among samples using non-radioactive isotopic labeling. It was quickly realised that there was commercial demand for expertise and reagents associated with this powerful and reliable workflow and as a result, provision of this technology was adopted in the products and services offered by Dundee Cell Products to the biotechnology community.

The company continues to grow and has been able to recruit highly skilled staff from the College of Life Sciences, providing jobs for postgraduate and postdoctoral researchers from the University. **Dr Francesco Rao**, a former CLS postdoctoral fellow, is now the Chief Scientific Officer of DCP.

www.lifesci.dundee.ac.uk/people/angus-lamond

www.dundeecellproducts.com

---

**I have been dealing with Dundee Cell Products for the past two to three years both as a postdoc and as an independent investigator. I would highly recommend their services to anyone. I would especially recommend them to young investigators who have limited personnel, and limited funds as a cost effective and rapid way to progress projects.”**

Dr Lee Hamilton • Lecturer at the University of Stirling
Harnessing early stage drug discovery to drive the translation of biomedical research towards new therapeutics

The massive, yet largely untapped bank of University derived, internationally competitive life sciences discovery and innovation has the potential to provide solutions for unmet medical need and jobs. Created in 2006, The Drug Discovery Unit at the University of Dundee performs early stage drug discovery to translate ideas for new medicines from basic biomedical research into prototype drugs ready for partnering with industry. This greatly enhances the impact of biomedical research by providing a mechanism for the translation of academic innovation into patient benefit.

The DDU draws on the best of both worlds, employing over 75 highly skilled, experienced scientists from academic and pharmaceutical industry backgrounds. It is the only fully operational and integrated drug discovery team within UK universities working across multiple disease areas, with the full range of disciplines required to produce novel drug candidates.

The DDU’s progress has been tremendous. In 2010, the DDU published the identification of new drug leads for human African trypanosomiasis, or ‘sleeping sickness’ in the leading scientific journal Nature. Funded by the Wellcome Trust, a partnership with GlaxoSmithKline is developing safe and affordable treatments for Chagas’ disease and leishmaniasis. These neglected tropical diseases kill tens of thousands of people around the world every year. The partnership has developed three compound series with efficacy in animal models of these diseases comparable to clinically used drugs and aims to select a pre-clinical candidate for leishmaniasis during 2014. A partnership with the Global Alliance for Livestock Veterinary Medicines (GALVmed) has discovered compounds that are in field trials in Africa for African animal trypanosomosis in cattle.

Malaria is a debilitating parasitic disease killing around one million people each year, mostly children under the age of 5. Through iterative design cycles the DDU produced, within a partnership with Medicines for Malaria Venture (MMV), a new prototypic drug that is curative in a mouse model of malaria. In 2014, this compound was accepted into MMV’s clinical development pipeline, affording hope that a safe, affordable, new medicine will be available to replace current treatments that are becoming ineffective due to drug resistance.

The DDU has also been instrumental in partnering projects in genetic skin diseases and Huntington’s disease with GlaxoSmithKline through their Discovery Partnerships with Academia (DPAc) scheme.

The DDU is a successful paradigm for translating basic, innovative life science research, with a portfolio of many exciting and innovative projects.

www.drugdiscovery.dundee.ac.uk

The Lancet 2012

“Something very special is taking place in Dundee... (where) a drug discovery unit has torn down disciplinary walls to put chemists next to biologists, industry scientists beside academics. The result is a portfolio of promising new medicines for malaria, trypanosomiasis, and other diseases.”

The Lancet 2012
In the late 1980s, Professor Grahame Hardie FRS FRSE FMedSci at the University of Dundee provided key insights into the regulation, composition and downstream targets of an enzyme called AMP-activated protein kinase (AMPK). Professor Hardie established that this protein was an energy sensor in the body, making it a key target in studies of obesity, metabolism and diabetes.

In 2003, a major puzzle was the identity of the upstream regulator of AMPK. Also based at the University of Dundee and just along the corridor, Professor Dario Alessi FRS FRSE FMedSci was working on a tumour suppressor protein called LKB1 and searching for its downstream targets. In many spontaneous cancers LKB1 is mutated, resulting in a loss of tumour suppressor function. Preliminary experiments soon led to the two researchers realizing that each held the solution to the other’s problem and, like fitting two halves of a jigsaw together, they discovered that AMPK was activated and controlled by LKB1. This provided a link between a key regulator of cellular metabolism (AMPK) and a protein involved in cell proliferation and cancer (LKB1). When LKB1 function lost, it no longer able to activate AMPK, resulting in increased tumour formation by removing the restraining influence that this pathway has on cell growth and proliferation.

The link between AMPK and LKB1 was intriguing, since it was already known that the drug metformin, already in use to treat type-2 diabetes, activated AMPK. Collaborative research between Professor Alessi and Professor Andrew Morris FRSE FMedSci (at the time Professor of Diabetic Medicine at the University of Dundee) went on to test the hypothesis that metformin could decrease the incidence of cancer by activating AMPK. Results of the subsequent epidemiological study showed that people with diabetes taking metformin were 30% less likely to develop any form of cancer than those on other medications.

This work has had a major impact on the cancer field, especially as metformin is orally available, has no long-term safety issues and is available as a generic drug. This has led to at least 52 case-controlled clinical trials worldwide examining the effect of metformin in a variety of cancers such as pancreatic, prostate, colorectal, and breast cancer. These kinds of trials will establish whether the stratification of patients with AMPK-inactivation in their cancers will benefit from AMPK-activating drugs. This knowledge has also led to several drug discovery campaigns to develop novel activators of this pathway, for the treatment of both diabetes and cancer.

Metformin may have already saved more people from cancer deaths than any drug in history”

Lewis Cantley • Director of Beth Israel Cancer Centre, Harvard Medical School
The pharmaceutical Industry is facing serious pressures, not least by the loss of $64-100 billion of revenue as key drugs lose patent protection and as the number of new approved drugs decreases steadily. Many drugs fail at the phase 2 and 3 stages, primarily because of a lack of efficacy and the risk of failure is higher if the drug has a novel mechanism of action. The high rate of drug attrition suggests that new approaches are needed to improve and expedite the drug discovery process. One approach to tackle this problem is to harness chemical, pharmacological and biological data for automated drug design. Professor Andrew Hopkins FRSC FLSW at the University of Dundee has been at the forefront of this research by combining chemoinformatics, chemogenomics and structural bioinformatics methodologies to tackle questions of target identification, polypharmacology and de novo compound design. In 2012, Professor Hopkins published the delivery of a new automated, adaptive methodology for designing drug ligands to multi-target profiles in the journal Nature (doi:10.1038/nature11691) and the technology received significant coverage in the press.

It was quickly realised that the computational technology platform invented by Professor Hopkins offered a highly scalable system to discover drugs against pharmacogenomic profiles of multiple drug targets. In addition to being a valuable new tool in drug discovery, the technology was also of interest for the potential repurposing of established drugs or anticipation of adverse drug reactions. e'scientia Ltd (www.exscientia.co.uk) was created in 2012 in partnership with Frontier IP as a technology platform company operating at the IT/healthcare interface with the goal of revolutionising productivity by the use of data analytics and machine learning in drug design and pharmacogenomics. Three proof of concept agreements have already been signed and overall the company has signed deals worth $6.25 million (excluding milestones and licensing payments), with no dilution of equity.

www.lifesci.dundee.ac.uk/groups/andrew_hopkins
www.exscientia.co.uk

**Automated drug design technology for the life science industry**

Pioneering automated drug design methodologies developed by researchers at the University of Dundee led to the spin out of e'scientia Ltd in 2012. The company provides technologies to enhance the efficacy and the efficiency of drug discovery for the pharmaceutical industry.

“This new automated, adaptive methodology by Dundee mimics the design process of human chemists but runs it on a very large scale at a faster rate. This technology could make significant advances in discovering and designing complex drugs.”

Douglas Kell CBE • Professor of Bioanalytical Science, University of Manchester
Keratinocyte cells, found in the outer layer of the skin, maintain the skin’s integrity and help it withstand the mechanical and chemical forces it is subjected to every day. Much of this strength comes from a dense meshwork of a family of proteins called keratins. Cutting edge genome wide and candidate gene linkage analysis led by Professor Irwin McLean FRS FRSE FMedSci and Professor Birgit Lane FRSE FMedSci at the University of Dundee directly showed that mutations in several keratin proteins cause a variety of skin fragility conditions including Weber-Cockayne Epidermolysis Bullosa Simplex, Bullous Congenital Ichthyosiform Erythroderma. Painful blistering, overgrowth or scaling of the epidermis are some of the symptoms of these diseases and can significantly impact upon the patient’s life. Prior to identification of the causative mutations, diagnosis was often based upon clinical classification and hindered by significant variability in patient symptoms, even within the same family. The discovery that these skin disorders were due to mutation of a particular keratin protein has circumvented the ambiguity of diagnosis and enabled the ability to provide accurate genetic testing. It has also allowed the creation of accurate care and treatment plans, enabled targeted therapeutics to be developed, as well as providing the opportunity for prenatal genetic testing in suitable cases. This research was instrumental in making available UK-wide genetic testing for Epidermolysis Bullosa Simplex since 2007.

A further skin disease that has been transformed by the work of the University of Dundee is pachyonychia congenita (PC). PC is an inherited skin disorder characterised by thickened toenails, calluses, blistering, thickened skin, and plantar pain. As well as identification of causative mutations in this disease, the laboratory of Professor McLean currently provides worldwide genetic testing for PC with funding from the charity the Pachyonychia Congenita Project (www.pachyonychia.org). Moreover this research directly resulted in the creation of an approved patient registry for Pachyonychia Congenita in 2004. Lastly, collaboration between Professor McLean and researchers in Utah has led to the development of an siRNA therapy for PC, which entered clinical trials in January 2008. This is the first clinical trial for a skin condition and for specific silencing of a mutant gene to successfully demonstrate the efficacy and safety of siRNA treatment.

www.lifesci.dundee.ac.uk/people/irwin-mclean
www.dgem.lifesci.dundee.ac.uk

The genetic testing provided for patients diagnosed with Pachyonychia Congenita has been an enormous help, both to individual patients and to the effort to learn more about PC in order to develop effective treatments. Through the work at Dundee, nearly 100 mutations have been identified in genes causing PC and new differential diagnosis guidelines have been drafted as a result.”

Mary E. Schwartz • Director of the Pachyonychia Congenita Project
Most aspects of cellular life, such as immune responses, the decoding of genes and the control of metabolism are regulated by the attachment and removal of phosphate from proteins which is performed by enzymes called kinases and phosphatases. Abnormalities in this process, cause of many diseases, such as arthritis, cancer, hypertension, lupus and Parkinson’s disease. A major challenge in this area is to develop drugs that suppress the activity of one, or at most a few, of the 500 kinases encoded by the human genome.

Pioneering research at the University of Dundee led by Professor Sir Philip Cohen FRS FRSE, developed the first systematic assays to analyse the selectivity of kinase inhibitors, which, has proved crucial for the development of new therapeutic drugs targeting kinases. This procedure, termed “kinase profiling” greatly helped the pharmaceutical industry causing kinases to become their most important class of drug target. Kinase drug discovery accounts for 30% of industry’s total R&D budget and over 50% of global cancer drug discovery. In 2013 over 25 kinase inhibitors were undergoing Phase III clinical trials.

In 1998, Sir Philip and Professor Pete Downes OBE FRSE FMedSci (now University Principal) together set up the Division of Signal Transduction Therapy, a unique collaboration between academic researchers and the world’s leading pharmaceutical companies. The aim was to initiate and accelerate the development of potent and specific drugs that modulate kinases and phosphatases for the treatment of disease. A further aim was to develop research tools for academic scientists to understand the regulation of normal cell functions. The consortium is now entering its 17th year and is one of the largest and longest running collaborations between academia and the pharmaceutical industry. Pharmaceutical companies (currently AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Serono, Pfizer and Janssen Pharmaceutica NV) have made a significant investment in the consortium and in return benefit from access to unpublished results, technology, know-how and reagents in the participating academic laboratories, and have first rights to license intellectual property generated. The integration of expertise in protein ubiquitylation in 2012 was of particular interest to the corporate partners.

A key ingredient to the success of the consortium has been the critical mass of leading academic researchers prepared to work together under a binding legal agreement in a field of industrial interest. This type of collaboration is vital for the development of new treatments, that bring benefits for patients and the economy.

www.lifesci.dundee.ac.uk/people/philip-cohen
www.ppu.mrc.ac.uk/overview/DSTT.php
Insight into an anti-cancer drug target and tools for life sciences research

A key regulator of cell growth and survival called PKB (also called AKT) is the focus of numerous anti-cancer drug clinical trials. The role of this protein and how it is switched on was uncovered by researchers in Dundee and has stimulated pharmaceutical companies to undertake drug development campaigns focused on PKB as a target molecule. Moreover, this research led several life sciences companies to generate research tools to accelerate academic and industry research in this area.

The protein PKB regulates many cellular functions including metabolism, growth, and proliferation. PKB was identified in the early 1990s and interest was sparked by the finding that increased PKB expression and activity was detected in aggressive cancers, such as gastric, breast, prostate, ovarian and brain tumors. In 1995, the laboratory of Professor Sir Philip Cohen FRS FRSE at the University of Dundee identified a protein called GSK3 as the first physiological substrate of PKB. Shortly after, Professor Dario Alessi FRS FRSE FMedSci in a series of seminal papers uncovered the mechanism by which PKB was activated, demonstrating that it involved the attachment of phosphate to particular sites on the protein. Moreover, he identified the protein called PDK1 that switched on PKB activity. Subsequent structural studies at the University involving Professor Daan van Aalten FRSE provided important insights for the design of small molecules permitting targeted inhibition of PDK1.

Clinical studies measuring PKB activity in tumours have used the phosphorylation sites identified by Professor Alessi as a marker of its hyperactivation. For example, in breast cancer patients, hyper-activation of PKB is associated with poor prognosis and increased probability of relapse accompanied by distant metastases. PKB is a firmly established focus for pharmacological intervention and there has been a huge effort by numerous academic groups worldwide to understand better the complex signaling pathways that involve PKB, particularly in cancer. The work in Dundee has contributed to this effort. Several clinical trials are underway testing the antineoplastic activity of PKB inhibitors in a variety of cancers. This research has also stimulated biotechnology companies to develop reagents to help researchers probe this signaling pathway in normal and diseased tissue. Antibodies specific to the key sites on PKB are used to measure its activation, and kits to measure the effects of PKB on downstream targets are sold by many life science companies as a direct result of discoveries made by researchers in the College of Life Sciences.

Work at Dundee to dissect this signalling pathway helped establish PKB as a firm focus for pharmacological intervention in cancer.”

Malcolm Skingle CBE • Director - Academic Liaison, GlaxoSmithKline

www.lifesci.dundee.ac.uk/people/philip-cohen
www.lifesci.dundee.ac.uk/people/daan-van-aalten
www.lifesci.dundee.ac.uk/people/dario-alessi