New Medicines, Better Medicines, Better Use of Medicines

Drug Discovery & Development at the University of Strathclyde

University of Strathclyde

Glasgow, UK

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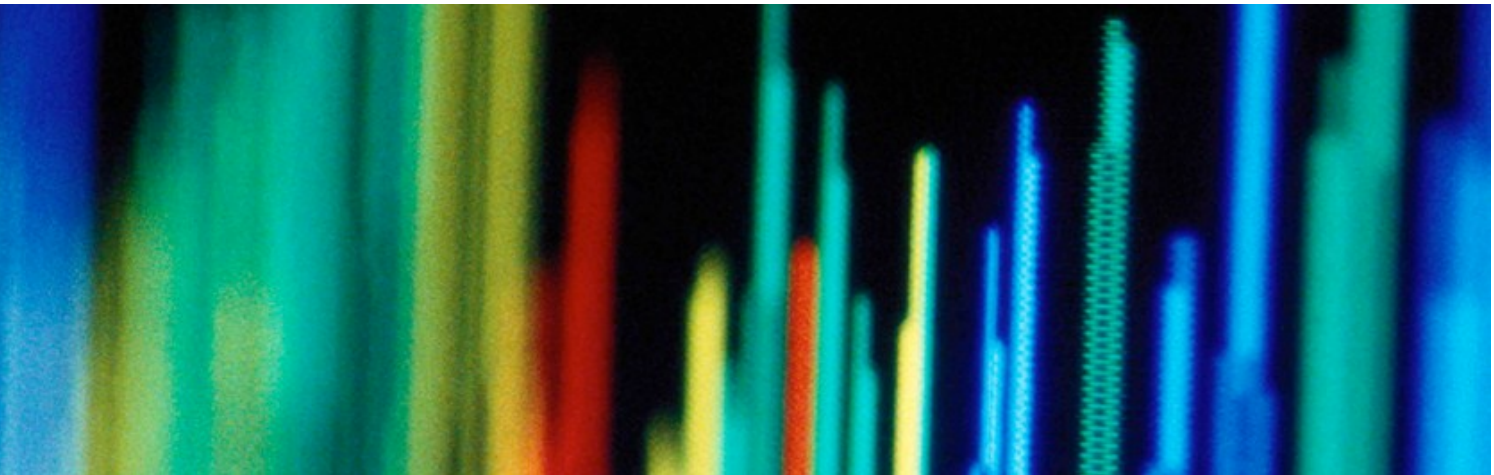

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Executive Summary

* The University of Strathclyde is a technological university that has identified Health as one of its strategic research priority areas. Drug discovery and development are highlighted within that priority with the mission statement: *New Medicines, Better Medicines & Better Use of Medicines.*
* The University is supporting drug discovery and development by co-ordinating the activities of relevant academic departments, in this case the Strathclyde Institute of Phramacy & Biomedical Sciences (SIPBS) and the Department of Pure & Applied Chemistry (P&AC) to have a focussed research profile with significant commercial potential.
* The contributing departments are equipped to internationally competitive standards and have a number of distinctive units and facilities including the Centre for Biophotonics, the Biological Procedures Unit, and the CRUK Formulation Unit (all in SIPBS) and Analytical and Spectroscopic Services (in P&AC). With respect to pharmaceutical manufacture, the University's Continuous Manufacturing and Crystallisation Centre is internationally renowned.
* The University has a track record of success in drug discovery and development as recently exemplified by anti-infective minor groove binders for DNA - the lead compound entering clinical trials in 2015; first-in-class IKKalpha selective inhibitors, which have high potential for treating prostate and other cancers; innovative non-invasive delivery methods for drugs and vaccines, a technology that has supported the formation of a new spin-out company; and the CRUK Formulation Unit, which has contributed to the success of several innovative medicines including temozolomide and abiraterone.
* The University welcomes partnerships in research, learning and knowledge exchange, both nationally and internationally, with other academic institutions and with industry. P&AC and SIPBS have a programme with GlaxoSmithKline (GSK) that enables GSK researchers to study for higher degrees and the University has been educating pharmacy students in partnership with the International Medical University in Malaysia for over 15 years.

1 Drug Discovery & Development as an Institutional Strategic Priority

Strathclyde is a Technological University with a strong focus on using our research, knowledge and capability to meet current and future challenges. The University has identified Health as one of its priority research areas and we recognise the necessity and value of technological innovation and multidisciplinary approaches to meeting the challenges that global demographic change and economic pressure are generating on health delivery.

We place our research at the heart of health innovation and translation, combining knowledge of living systems with the application of advanced science and technology to generate products and interventions. To this end, our health research is consistent with the University's founding philosophy of being *a place of useful learning.* Furthermore, it is strongly affiliated to the University's Technology and Innovation Centre (TIC), a £90M investment that will be fully operational in 2014. The Centre will be a hub for collaborative research between the University and external partners and through interactions with health services, businesses and policy makers, will enable us to develop translational research shaped to the needs of stakeholders, advancing knowledge, healthcare and quality of life. Our strategy has been informed by UK Government and Department of Health reports including *Innovation Health and Wealth – Accelerating, Adoption and Diffusion in the NHS* (2012) and is aligned to key aspects of Research Council UK's cross-council *Excellence with Impact* agenda and the goals of the *Lifelong Health and Wellbeing* theme. Within Health, we have identified *New Medicines, Better Medicines & Better Use of Medicines* as a stimulus for closer co-operation between researchers from diverse disciplines that will advance our translational research and further develop the University's health research portfolio and global reputation. An example of our increasing global development is the recent signing of a memorandum of agreement with the International Prevention Research Institute (IPRI; Lyon, France) to form the Strathclyde Institute of Global Public Health.

Two departments are key to Drug Discovery & Development at the University:

Strathclyde's Institute of Pharmacy & Biomedical Sciences was formed in 2006 by the amalgamation of five departments covering pharmacy and life sciences, and advances Strathclyde's record of successful drug-related research. SIPBS has over 60 full-time academic staff; 74 postdoctoral researchers and 149 postgraduate PhD researchers supported by 47 technical staff.

Our Department of Pure & Applied Chemistry is part of WestCHEM, the joint research school of chemistry for the West of Scotland comprising researchers from the Universities of Strathclyde and Glasgow and now in its eighth year of continuous growth with respect to research income and researchers. The research grouping (one of five) that contributes significantly to Drug Discovery & Development at the University is Chemical Biology, Molecular Medicine & Synthetic Biology.

2 Strategy

We achieve impact in New Medicines by forming teams across SIPBS and Pure & Applied Chemistry supported by our Technology Transfer Office. Collectively, we have expertise in the commercialisation of drug discovery; target and companion biomarker identification and validation; creative medicinal chemistry; pharmacodynamics & kinetic assessment and formulation.

Furthermore, several members of staff hold joint appointments with NHS Boards including NHS Greater Glasgow & Clyde (GG&C) and NHS National Services Scotland. In these capacities they contribute to and hold membership of a number of senior strategic NHS / academic fora. For example, the Scottish Antimicrobial Prescribing Group, Farr Health Informatics Research Institute, Executive Governance Group and the MRC Scottish eHealth Research Centre Board. We are also represented on the Glasgow Biomedicine Board, which promotes translational research in the city and has oversight of all clinical trials in NHS GG&C.

3 Capabilities

SIPBS has fully equipped laboratories for state-of-the-art research across biomedical and pharmaceutical sciences, as well as pharmacoepidemiology and pharmacy practice, underpinning our focus on *New Medicines, Better Medicines, Better Use of Medicines*. SIPBS has Home Office-approved animal research facilities and GMP production facilities for specialist pharmaceutical products for phase l clinical trials. Specialist equipment for drug discovery & development includes a cell sorter, Next Generation gene sequencer, single crystal diffractometer and new tableting facilities. In addition to standard research laboratories we operate a number of specialised facilities:

- The Centre for Biophotonics: housing multiphoton confocal and fluorescent microscopes to facilitate our strong and increasing employment of bioimaging technologies.
- The Biological Procedures Unit: containing a wide range of animal species as well as gene-deficient, transgenic and reporter-gene mouse strains for the investigation of immunological aspects of disease through to testing of vaccine preparations and potential drugs.
- The CRUK Formulation Unit: a unique laboratory facility that produces anti-cancer drugs for clinical trials and projects in all 18 Experimental Cancer Medicine Centres in the UK and also elsewhere in the world (for example, in Australia and New Zealand).

With a history in drug-related research, we also support a unique natural product extract library comprising 5,000 plant species representing >90% of plant families and facilities for *in silico* compound screening through our Drug Discovery Portal. This is a database of compounds for researchers to test virtually against biological targets identified as having a role in disease.

The Department of Pure & Applied Chemistry houses state of the art facilities for modern analytical and spectroscopic analysis. The NMR facility is purpose built unit, with a magnet room, technical support office, data processing laboratory and sample preparation and handling laboratory. At the heart of the facility are four Bruker NMR spectrometers (400 to 600 MHz) capable of a wide range of applications working from high-throughput fully automated mode using robotic sample handling and manual operation. HPLC is found in many research laboratories but a managed facility together with LCMS and microanalysis has a dedicated laboratory. Small molecule X-ray crystallography is routinely available using modern Oxford Diffraction Gemini and Xcalibur instruments fitted with variable temperature cryosystems. Both Mo and Cu sources are available so that a wide range of chemical types can be examined and that absolute structure determination is possible even for light atom structures

At the other end of the development pipeline, the first major health industry programme in the University's new TIC building will be our Continuous Manufacturing and Crystallisation Centre (CMAC). As the physical hub for research into the production of high value pharmaceuticals, CMAC illustrates the added value of industrial and academic collaboration in research. We aim to bring more of our research into translatable technologies and interventions that will return substantial health and economic benefits.

4 International Partnerships

We proactively seek partnerships in research and knowledge exchange, nationally and internationally. The University has strategic partner Universities – Stanford, NYU, NTU, Beijing, HKUST – as well as numerous interactions at Institute or personal levels. We also have very strong engagements with industry – international pharmaceutical companies through to local small-to-medium enterprises. These relationships cover not just research and knowledge exchange but extend into teaching: P&AC and SIPBS have a programme with GlaxoSmithKline (GSK) that enables GSK researchers to study for higher degrees (masters or doctorate). We are also wholly committed to the delivery of the best levels of undergraduate education in chemistry, pharmacy and biomedical sciences. Our programmes attract students from around the world – for example, we have been educating pharmacy students in partnership with the International Medical University in Malaysia for over 15 years. In all our research, knowledge exchange and teaching we are committed to the University of Strathclyde's ideal of being a place of useful learning.

5 Track Record of Success

5.1 Minor Groove Binders for Anti-infective Disease

Only the development of new classes of antimicrobials with novel mechanisms of action can fully address the burgeoning drug resistance in common pathogens. This need for novel classes of antimicrobials was emphasized in a recent report by the National Academy of Science's Institute of Medicine, which stated that, “The absence of new classes in the [pharmaceutical] pipeline ... is alarming when one considers the ever-increasing numbers of antibiotic-resistant organisms.”

Combining our medicinal chemistry expertise with our microbiological and clinical expertise has culminated in the development of the drug candidate MGB-BP-3, and the establishment of the Glasgow-based drug development company MGB BioPharma Ltd based entirely on IP generated at the University of Strathclyde.

MGB Biopharma successfully acquired an exclusive worldwide licence to develop and commercialise these drug candidates from the University who had used the royalty income from its previously marketed drug, leucovorin, to fund the development of this minor groove binder (MGB) platform of compounds.

A comprehensive set of *in vitro* and *in vivo* experiments performed by both the University and MGB Biopharma have confirmed MGB-BP-3’s very potent activity against C*. difficile* bacillus, superior to vancomycin, the current gold-standard drug for the treatment of *C. difficile* infection.

The UK MHRA has accepted all pre-clinical safety and efficacy data and agreed that MGB Biopharma is free to commence ‘first-in-man’ clinical studies in 2015.

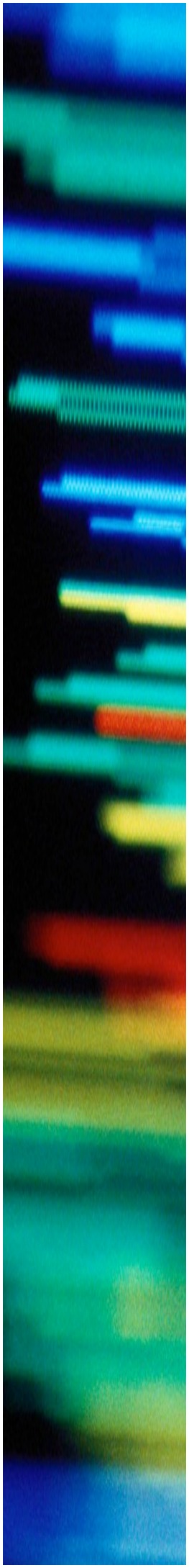
5.2 First-in-class IKKalpha Selective Inhibitors

The pharmaceutical industry has devoted considerable effort to generating NF-κB pathway inhibitors and a leading approach has been to target the IκB kinases (IKK). Reported inhibitors have either been pan-IKK inhibitors or IKKβ selective and to date there have been no reports of IKKα selective compounds. Despite being proposed as a target for treating inflammation, inhibition of IKKβ has more recently been associated with a number of side effects including development of inflammatory skin disease and sensitisation of colonic epithelium to a range of insults. Given the growing evidence that IKKα has an important role in a number of cancers the development of selective IKKα inhibitors is an attractive approach and selectivity over IKKβ may help facilitate use of such compounds clinically.

SIPBS and P&AC scientists have identified a major cohort of prostate cancer patients with a specific molecular marker who have a significantly worse prognosis and in which an IKKα inhibitor could be of therapeutic benefit and have generated first-in-class IKKalpha selective compounds with:

- Potency (sub 10nM), selectivity (>30 fold over IKKβ) and chemical tractability
- Broad selectivity (>100 fold) against a panel of 40 representative kinases
- Low molecular weight (250 - 350) and good ligand efficiency
- Orally bioavailable compounds
- Appropriate ADME properties (permeability, plasma stability, plasma protein binding, CYP450/HERG profile

This programme has been awarded ~£5m by Cancer Research UK and Prostate Cancer UK to date.



5.3 Innovative non-invasive delivery method for drugs and vaccines

Non-ionic surfactant vesicles (NIVs) have a synthetic bilayer that mimics naturally derived cell membranes. These make them chemically stable in a biological environment, with very low toxicity. The Strathclyde research into NIVs led to Inhalosomes—an inhaled formulation to deliver drugs directly to the site of therapeutic need and Bilosomes—an orally-available formulation that also negates the need for injections; removes cold chain storage and enables lower doses of drug to be used therapeutically, increasing treatment options and reducing manufacturing costs, all of which are desirable attributes for both consumers and the pharmaceutical industry.

Inhalosomes permit delivery of small molecule therapeutics, initially encapsulating Cisplatin for the treatment of non-small cell lung cancer, but with potential for other therapeutics for lung cancers and other respiratory diseases. The development of bilosomes as an oral vaccine allows for absorption of the pharmaceutically active ingredients into the blood stream from contact with the mucous membranes of the gastrointestinal tract, providing greater effectiveness of the vaccine. A further beneficial impact is the "green synthesis" of the vaccine removing the need for the use of chloroform in its preparation.

In addition both delivery systems allow the therapeutic to be given by a non-invasive method, reducing the need for trained staff (which is a requirement for intravenous delivery). This will reduce healthcare costs and increase patient compliance, particularly with those who are reluctant to take injectable medication.

The University has collaborated with Biovaxpharma Ltd to create a new biotechnology spin out Inhalosome-C Ltd, which was awarded a £196k TSB grant in December 2012 to manufacture the NIV/cisplatin combination for inhalation delivery in lung cancer. In collaboration with Respironics Respiratory Drug Delivery Inc. a subsidiary of Philips Healthcare, the researchers are also investigating how nebulisers can be used to improve pulmonary delivery.

5.4 Improved survival rates for malignant brain and prostate cancer

The Formulation Unit is funded directly by Cancer Research UK to conduct pure and applied research across a range of chemical drug and formulation types, which culminates in the manufacture of an investigational medicinal product for patient administration in clinical trial, compliant with EU regulatory requirements.

Compounds are selected by the Cancer Research UK New Agents Committee, which does not operate with a traditional drug development pipeline. The Unit, therefore, has to be capable of covering pharmaceutical research ranging across analytical methods and techniques, utilization of these techniques to understand and limit chemical degradation and assist stabilization, and the final development of formulations.

The Unit collaborates with multiple clinical cancer centres in the UK, and nationally and internationally with multiple cancer drug discovery groups. As the only UK academic centre capable of conducting this formulation research, the Unit's research input has played a vital role in the formulation research, clinical testing and eventual marketing of two anti-cancer drugs:

Temozolamide

Malignant brain cancer accounts for 2% of all new UK cancer cases. There are around 4,800 new malignant brain tumour cases per annum in the UK with 3,700 deaths and around 240,000 new cases per annum, world-wide. Before the availability of temozolomide, approximately 29% of adult patients with malignant brain tumours survived one year after diagnosis and 13% at five years.

By making temozolomide available orally, it is easier to administer than standard chemotherapy regimes and, in relapsed cases, increased progression-free survival at 6 months has increased from from 8% on previous therapy to 21%, and survival from 44% to 60%. In addition, temozolomide significantly improves quality of life prior to disease progression.

Abiraterone

Prostate cancer causes 258,000 worldwide deaths annually with around 50,000 being from the castrate resistant form of the disease. Hormone treatment will increase median survival by around two and a half years and provide symptomatic relief. However, metastatic prostate cancer will nearly always become castrate resistant with the only remaining treatment option being chemotherapy, with docetaxel and steroids only recommended for robust patient groups. In metastatic castrate resistant patients who have progressed after chemotherapy, abiraterone significantly increased median survival from 10 to 15 months and median prostate specific antigen progression from 6 to 10 months.

Wider benefits of these anti-cancer drugs: The use of temozolomide in other malignancies, for example melanoma, is currently under active research. The clinical use of abiraterone is also expanding with potential extension into third or even second line metastatic prostate cancer therapy. In addition the method of action of abiraterone is applicable in certain breast cancers, and clinical studies in this indication are on-going.

5.5 Transformative Research Training for GSK

The University has established a unique collaborative programme in *Synthetic and Medicinal Chemistry* which enables GSK employees to work towards a higher research degree (as registered MPhil/PhD students) through their work-based research projects. Under rigorously-established intellectual property agreements, GSK-based drug discovery programmes are proposed and, in turn, tuned by Strathclyde academics. Research projects are conducted within GSK laboratories with an Industrial/ GSK Supervisor and Academic Supervisors (and an Internal Examiner) from Strathclyde.

In 2010 the programme was the subject of a Scottish Parliamentary Motion on the establishment and delivery of this ground-breaking initiative:

"*… the Parliament congratulates the University of Strathclyde and GSK on the first ever initiative in the UK to deliver a bespoke postgraduate chemistry degree programme; recognizes that this unique research programme will be geared towards identifying and developing novel treatments for a range of diseases; acknowledges the potential that this will have to deliver considerable benefits for patients and public health; commends this innovative initiative as a tangible demonstration of the benefits of collaboration … between academia and industry, and notes that the programme … aims to benefit society as a whole*."

Scottish Parliamentary Motion S3M-05519

"*The Academic Supervisors have exposed both the GSK Chemist and Industrial Supervisor to a series of alternative research strategies and methods, complementing the available skills and expertise at GSK. This programme has led to enhanced levels of project-relevant scientific knowledge, advanced thinking, and overall scientific rigour within the Medicinal Chemistry research teams, through the associated academic peer review and collaboration. Furthermore, the quality of reporting and depth of literature coverage by the GSK chemists have clearly advanced through the programme. The established collaborative framework has had a positive impact on and is now contributing extensively to overall organisational learning within GSK, and has now been extended into the areas of Drug Metabolism and Pharmacokinetics, Biological Sciences, and Analytical Chemistry, more latterly with international interest and participation.*"

David Allen, Senior Vice-President, Respiratory Therapy Area, and Global Chief Chemist, GSK

In summary, these specific partnerships with GSK have been created and are founded upon the research track record and outputs of the associated academics and have led to unique, beneficial, and amended research training practices within this internationally-leading pharmaceutical company.