

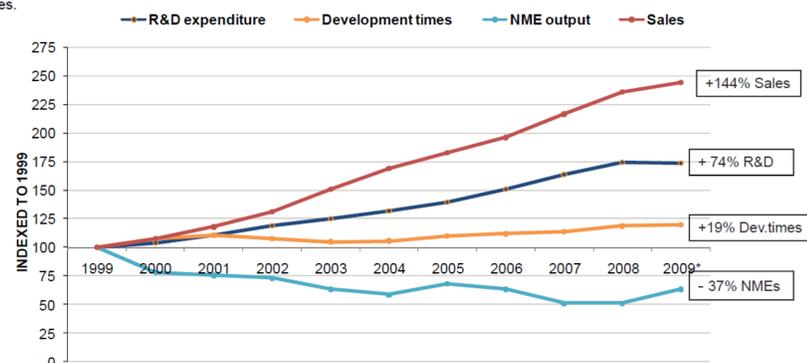
Translational Drug Discovery Group

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Background

Drug discovery is undergoing its biggest revolution for a generation. The traditional research model followed by big pharma has failed to produce sufficient numbers of new drugs to sustain historic investment levels. To reduce costs, companies are globalising research activities and outsourcing other activities. This is having a negative impact on UK-based research.

Although global sales of ethical pharmaceuticals continued to rise in 2009, R&D expenditure declined for the first time (0.3%). NME output increased in 2009, but numbers are still more than 30% lower than in 1999. Development times have risen slightly. The widening gap between the global sales and R&D curves may be attributable to the rise in generic drug sales.



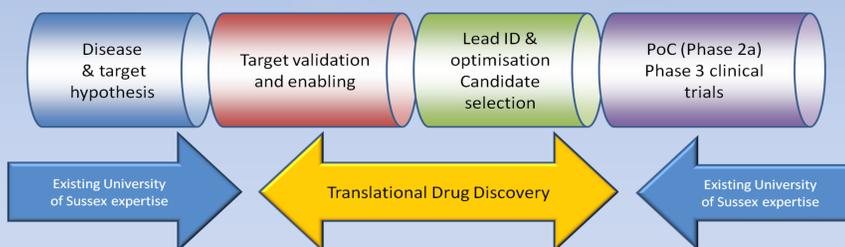
A new paradigm for UK-based translational research is needed. Capitalising on fundamental discoveries at the University of Sussex and exploiting the clinical excellence of the Brighton and Sussex Medical School, the Translational Drug Discovery Group is well positioned to translate those novel discoveries into candidate molecules for clinical evaluation.

Translational Drug Discovery Group

...is a new venture by the University of Sussex combining academic excellence with industrial experience to develop novel approaches to 'difficult to treat' diseases.

Our vision for a successful drug discovery organisation within the university is built on the fusion of:

- An in-depth understanding of the disease pathway biology, structure and function of the target protein.
- Insight from the practicing clinician into clinical need, patient selection, surrogate biomarkers, trial design and access to human tissue.
- Strong, existing platform of biophysical, biochemical and structural technologies.
- Proven track record within the members of the Translational Drug Discovery Group of prosecuting multiple drug discovery projects from target to clinic.



Our objectives are:

1. To target identification of clinical candidates for poorly treated diseases
2. To ensure sustainability of research group
 - **Grant funding** to prosecute LO projects for identified cancer targets (CRUK, MRCT, EU FP7)
 - **Develop mature portfolio** of oncology discovery projects
 - **Develop early portfolio** in neurodegeneration & infectious / developing world disease (Wellcome Trust, DNDi, Gates Foundation)
 - **Develop collaborative research** projects with external partners (e.g. Novartis)
 - **Out license** advanced projects or spin out as venture-funded company (Sussex Innovation Centre)
3. Develop medicinal chemistry & drug discovery courses to teach the next generation of drug hunters.

Laboratory Refurbishment

Early June 2011: A lab in need of renovation



August 2011: Laboratory is operational



The Group

The group started recruiting May 2011 and will be fully operational by January 2012. An experienced medicinal chemistry team has been recruited and this will be supplemented by an enzyme pharmacology and cell biology group. It will also provide an excellent training resource for MSc and PhD students.

People	Role	Experience
Simon Ward	Professor of Medicinal Chemistry & Director of Translational Drug Discovery Group	Chiroscience, Knoll, Cerebrus, GlaxoSmithKline
TBA	Chair of Molecular Pharmacology	
Richard Angell	Project leader & medicinal chemistry research fellow	GlaxoSmithKline, Arrow Therapeutics, AstraZeneca
Michael Paradowski	Chemistry laboratory manager & research fellow	Ecole Nationale Supérieure d'Ingenieurs (Caen), Pfizer
Lewis Pennicott	Synthetic chemistry research fellow	University of Sussex, Susschem, Evotec
Gareth Williams	Assay design & development	Pfizer
TBA	Research Fellow: Functional & cell-based screening	

Drug discovery track record: we are an experienced drug discovery group who are inventors on over **55 patents**, have made **significant contributions** to 3 projects that have made it to successful launch, 3 projects currently in phase 2 clinical trials and 4 projects in phase 1.

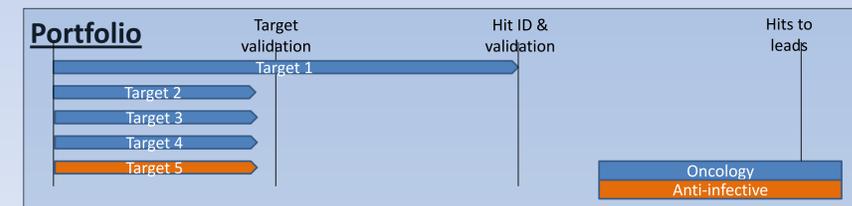
Commercial track record: due diligence in support of in/out licensing deals, collaborative deals, company spinout/start-up, company sale.

Project Portfolio – Initial Oncology Focus

Despite the major investment in cancer therapeutics, many research groups are targeting overlapping signalling pathways via kinase inhibition. Whilst recognising the importance of these approaches, the opportunity presented from targets identified in the Genome Damage & Stability Centre (GDSC) is to capitalise on the unique existing expertise to directly target DNA repair pathways to generate attractive 'druggable' targets with the potential to generate synthetic lethality in tumours of different DNA repair defective genetic backgrounds. The paradigm for this is the promising utility of PARP inhibitors as single agents in tumours that lack efficient homologous recombination repair (e.g. BRCA1, BRCA2). Whilst this is the most advanced example of clinical synthetic lethality, the inter-relationships and connectivity the GDSC has established between other cellular pathways for DNA damage repair and genome maintenance awaits clinical exploitation.

Initial targets have been identified for which disease validation is well progressed, reagents are available for biochemical and cell-based functional assays and determination of the protein crystal structure is completed or underway. Additionally, Peter Schmid (Prof Cancer Medicine) is providing further target validation through the use of clinical tumour samples.

Collaborations in progress with Prof Keith Caldecott, Dr Sherif El-Khamisy, Dr Helfrid Hoegger, Prof Laurence Pearl, Dr Tony Oliver, Prof Tony Moore, Prof Peter Schmid, Prof Guy Richardson, Prof Corne Kros..



Collaborations in other therapeutic areas are being established with Prof Tony Moore, Prof Peter Schmid, Prof Guy Richardson & Prof Corne Kros.

Research Methodology – Fragment-based Drug Discovery

Once a therapeutic target has been identified, the first step in modern drug discovery is to find a starting compound that binds to it. Identifying novel compounds as starting points for optimisation is one of the major challenges in drug discovery research. The methods of fragment-based drug discovery provide a potentially superior alternative to high throughput random screening, and involve screening about 1,000 to 1,500 low molecular weight fragments using biophysical techniques (NMR, thermal shift) with the experimental binding mode to be established by X-ray crystallography. Fragments are then grown to form new interactions as shown schematically. Although fragment hits have low potency due to their small size, they form high quality interactions and can be readily optimised into potent lead molecules, and ultimately clinical candidates.

Methodology in collaboration with Dr Iain Day, Dr Peter Varnai, Dr Mark Roe

Summary



- An experienced drug discovery group capitalising on scientific discoveries at the University of Sussex and integrating science across multiple disciplines
- A highly differentiated portfolio of novel targets & approaches to difficult to treat diseases
- Opportunities for collaboration with biotech, big pharma and funding organisations
- Potential for major impact across multiple areas to translate fundamental science & create value