Establishing a National Phenotypic Screening Capability in the UK

UK-NPSC National Phenotypic Screening Centre

SULSA Scottish Universities Life Sciences Alliance

UK-NPSC is a partnership between SULSA (BOX 1) and the University of Oxford that will operate a world-class phenotypic drug discovery facility. It will collaborate with a wider network of centres from across the UK, Europe and beyond, to bridge the gap between academia and pharmaceutical companies and drive innovation in the sector. The Scottish Government awarded £8M to SULSA to finance state-of-the-art robotics, instrumentation and computation at the Universities of Dundee and Oxford.

BOX 1 | SULSA: Scottish Universities Life Sciences Alliance (www.sulsa.ac.uk)
A highly successful partnership between the Universities of **Aberdeen, Dundee, Edinburgh, Glasgow, St. Andrews** and **Strathclyde** supported by the Scottish Funding Council. SULSA makes Scottish biosciences research more globally competitive by pooling resources from the leading universities.

UK-NPSC will focus on using phenotypic approaches (see BOX 2) to identify new drug candidates that address unmet therapeutic needs. Chemical libraries will be screened in a smart cost-effective way, predominantly using human cells and tissues. There is a special focus on complex multifaceted diseases where interrogating a single molecular target cannot model the disease state. UK-NPSC will work closely with industry, academia and disease-focused charities to translate fundamental biological research into novel drugs, and is optimally placed to provide new chemical starting points for further development.

BOX 2 | Phenotypic Screening
A phenotype is one or more observable features or traits that report changes in an organism's genotype, epi-genotype or a response to its environment. Phenotypic screening is therefore the systematic and quantitative analysis of changes in phenotype in the presence of absence of pertubagens such as siRNA or small molecules. Unlike a genotype, a phenotype can be described with different levels of complexity: either simply with a few measures or using hundreds or thousands of parameters. Phenotypes are temporally dynamic – this necessitates not only an in-depth knowledge of the biology but also the judicious development of assays that balance logistical feasibility with physiological relevance.

Why?

The financial viability of the pharma industry is endangered by high R&D costs to get drugs to market, and a faltering pipeline. In recent years identifying and validating the "targets" underlying disease has been a dominant *modus operandi* for the industry. The 'single-target' hypothesis, and hence the target itself, has become the driver for new drug discovery. Phenotypic screening is target-agnostic and better captures the complexity of living systems (see Fig. 1). Analysis of first-in-class drugs (Swinney & Anthony, 2011) has indicated that the majority are discovered by phenotypic methods rather than screening molecular targets, although followers came most often from target-based work. Whether, in the long term, more or less drugs will come from a target-based or from systems-based approaches (chemocentric or purely phenotypic) only time will tell. With renewed interest in phenotypes, in systems pharmacology and in polypharmacology, the 'one gene, one protein, one target, one drug' dogma is in need of revision. The development of the UK-NPSC is therefore timely.

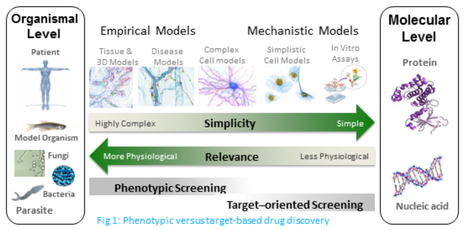
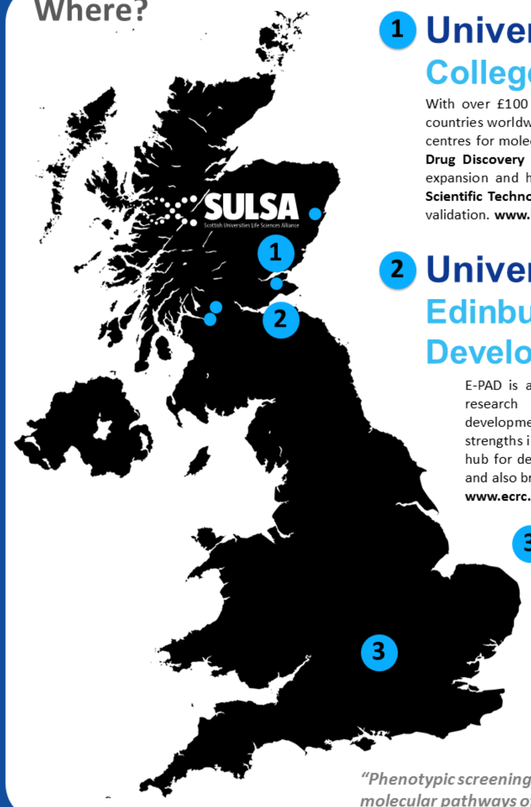


Fig 1: Phenotypic versus target-based drug discovery

Where?



1 University of Dundee
College of Life Sciences

With over £100 million of research income in 2013 and nearly 900 staff from over 60 countries worldwide, the College has a reputation as one of the most dynamic international centres for molecular cell biology. Co-location of UK-NPSC within the same complex as the **Drug Discovery Unit** will assist in taking phenotypic hits forward into hit-validation, hit expansion and hit-to-lead chemistry. The range of facilities in the **Centre for Advanced Scientific Technologies (CAST)** will strengthen follow up work for target identification and validation. **www.lifesci.dundee.ac.uk**

2 University of Edinburgh
Edinburgh Phenotypic Assay Development Hub (E-PAD)

E-PAD is a new initiative launched in July 2014 that will maximize the wealth of research expertise across the University of Edinburgh in phenotypic assay development and phenotypic profiling technologies. E-PAD will leverage Edinburgh's strengths in cell biology, informatics, regenerative and clinical medicine. It will act as a hub for developing novel biological assays for transfer to the UK-NPSC for screening and also bring into play its world-class Reverse Phase Protein Array Facility.
www.ecrc.ed.ac.uk/discovery-unit/capabilities.html

3 University of Oxford
Target Discovery Institute (TDI)

TDI is a major new collaborative research initiative led by Professor Sir Peter Ratcliffe FRS. The TDI has grown to encompass several groups alongside the HTS Facility, including Chemical Biology, Epigenetics, Proteomics and Mass Spectrometry and Medicinal Chemistry. The work in the TDI is an exemplar of Oxford's work in translational medicine. – **www.tdi.ox.ac.uk**

"Phenotypic screening holds the promise to uncover new therapeutic principles and molecular pathways of currently untreatable diseases" - Jorg Eder, Novartis

Please contact us: we are actively seeking partners to collaborate on assay development and screening projects
www.uknpsc.org uknpsc@sulsa.ac.uk @UKNPSC

How?

A series of technical advances have radically changed the utility of phenotypic screening approaches. The three main components of the process: the cellular/physiological context, the approach to phenotypic analysis, and the organization/annotation of chemical (small molecule) libraries, are the subject of major new developments that enhance the potential for informative phenotypic screening.

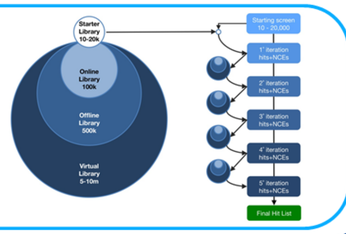
- The complementary power of **iPS cell technology** (to derive relevant material from specific patient groups) and **genome engineering** e.g. CRISPR technologies to engineer relevant genetic changes and reporter systems into the endogenous biological circuitry (BOX 3).
- Increasing speed and capabilities of **high-content imaging and analysis** systems will permit the interrogation of increasingly sophisticated cellular properties, including behaviour in co-cultures, 3D and organotypic systems (BOX 4)
- Increasingly dense annotation of small molecular libraries, developments in **chemo-informatics** and their use in 'informed' iterative moderate-scale screening strategies that avoid the need for ultra-high throughput approaches and can feasibly be combined in high content screens (BOX 5).
- Sophisticated **phenotypic profiling and fingerprinting** technologies: at the cellular/tissue level through quantitative imaging and analysis; at the protein/pathway level e.g. Reverse Phase Protein Arrays (RPPA) and at the gene expression level e.g. the LINCS approach, for compound classification, structure-activity relationship and triaging.

BOX 3 | New Paradigms in human biological assays
- Patient-derived cells
- Complex co-culture models
- 3D cell and tissue models
- Pluripotent stem cell technology
- Precision engineering with CRISPR/Cas9
  - Disease modelling - isogenic lines
  - Reporter line creation
- Haplogen haploid KO lines

BOX 4 | Advances in Imaging and Informatics
- Fast Confocal High Content Screening (HCS)
- Wide-field Deconvolution/Epifluorescence
- High Throughput Flow Cytometry
- Label-free read outs
- Live cell imaging – cell tracking and kinetics
- Cell-by-cell data & population data
- Decision analytics-based screening
- Advanced phenotypic profiling/fingerprinting
- Statistical analysis tools and application of advanced algorithms in hit discovery

BOX 5| Smart Iterative Screening

Bespoke diversity set
Open-access functionally-annotated sets
Private Commercial sets



Who?


Professor Andrew Hopkins FRSC FSB FLSW
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SULSA Research Professor of Translational Biology


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Executive Director of SULSA


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Associate Staff Member, University of Dundee


Dr Neil Carragher
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Nuffield Professor of Clinical Medicine


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Professor Jens Rittscher
Group Leader
Quantitative Image Informatics
TDI, University of Oxford


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Consultant &
Associate Staff Member, University of Dundee

When? Operational timeline

UK-NPSC Oxford Q4 2014
UK-NPSC Dundee Q1 2015

Oxford Laboratory

The investment from SULSA will add to the HTS lab at the TDI. The entire screening system is contained within a BSL2 safety enclosure.

6 Station Microstar (BSL2)

GE IN Cell 6000
Confocal imager
1 x 5.5 MP sCMOS camera
Live cell imaging and dispensing

PE EnVision
Multimode reader with label-free EPIC technology

BioTek ELX405 plate washers

Agilent PlateLoc

Formulatrix Tempest


HRB AmbiStore


HRB SteriStore D


Labcyte Echo 555


Brooks Xpeel

Dundee Laboratory

The Dundee Screening Laboratory comprises >250m² of bespoke laboratory space. The facilities will have an interconnected cell and tissue culture suite. two fully equipped wet labs and three office spaces located adjacent to the Screening and Cell culture suites. There is also a co-located purpose-designed utilities store for freezers, fridges and cryostorage. The instruments will be integrated into 2 state-of-the-art modular robotic Microstar systems (one 9-sided and one 6-sided) from HighRes Biosolutions (Woburn, MA, USA), with a Biological Safety Level 2 Enclosure around the larger system. Key instruments will be integrated on removable carts for flexibility and rapid system reconfigurations.


6 Station Microstar


Labcyte Echo 555
Labcyte Echo 550


Cybio FeLix


Agilent Bravo

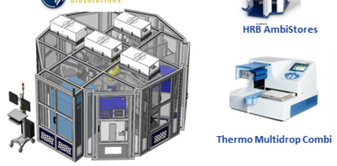

Tecan Evo 100


HRB AmbiStores


HRB SteriStore D


HRB TundraStore D


Formulatrix Tempest



9 Station Microstar (BSL2)

Thermo Multidrop Combi


BioTek ELX405 plate washers


Agilent PlateLoc


Formulatrix Mantis


Brooks Xpeel

Automation and Liquid Handling


Yokogawa CV7000
Dual spinning disk confocal HCS
3 x 5.5 MP sCMOS cameras
Live cell imaging and dispensing modules


Perkin Elmer EnSpire
Multimode reader with label-free Corning EPIC™ technology


GE IN Cell 2200
3D deconvolution HCS
1 x 5.5 MP sCMOS camera
Live cell imaging and dispensing modules


Tecan Infinite M1000Pro
Multimode reader

Molecular Devices Image Xpress Micro XLS
Epifluorescence and True Phase Contrast, 1 x 5.5 MP sCMOS camera
Live cell imaging module

Intellicyt iQue Screener
2 laser 6 parameter
High throughput
Flow cytometer

Imagers, Readers and HTS FACS