Building a national capability for phenotypic screening

Prof Andrew L Hopkins
College of Life Sciences/ Nuffield Dept of Medicine
University of Dundee / University of Oxford

ELRIG Pharmaceutical Flow Cytometry & Imaging
GSK, Ware
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Black’s Rules

Sir James Black’s Requirements for a Drug Discovery Project

1. Is the project purged of wishful thinking?
2. Is a chemical starting point identified?
3. Are relevant bioassays available?
4. Will it be possible to confirm laboratory-specificity in humans?
5. Is a clinical condition relevant to the specificity in 4?
6. Does the project have a champion – someone with the necessary passion, conviction and energy?

Balancing ease with relevance

Organismal Level
- Patient
- Model Organism
  - Fungi
  - Parasite
  - Bacteria
  ...and more

Empirical Models
- Tissue & 3D Models
- Disease Models

Mechanistic Models
- Complex Cell models
- Simplistic Cell Models
- In Vitro Assays

Molecular Level
- Protein
- Nucleic acid

Highly Complex → Simplicity → Simple
More Physiological → Relevance → Less Physiological

Phenotypic Screening

Target–oriented Screening
Synaptic dysregulation in a human iPS cell model of mental disorders

Chemical Inhibition of NAT10 Corrects Defects of Laminopathic Cells

53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks
Phenotypic screening holds the promise to uncover new therapeutic principles and molecular pathways of currently untreatable diseases.

Use “target-centric chemical libraries” to discover additional pathway nodes for target-based therapeutic intervention or to enable the discovery of follow-on drugs.

Therefore, the goal will be to screen phenotypically in an efficient and effective manner and to combine phenotypic screening sensibly and productively with target-based drug discovery.

“Moreover, phenotypic screening is not just dependent on the use of many tools that have been established for target-based approaches; it also requires further technological advancements.”

Image analysis of *Schistosoma*

Each compounds will be tested against multiple larvae, which are automatically identified and characterized.

Whole Organism High-Content Screening by Label-Free, Image-Based Bayesian Classification for Parasitic Diseases
Paveley et al., PLOS Neglected Tropical Diseases (London School of Hygiene & Tropical Medicine)
Classification of Phenotype by Bayesian models

- Built 2 models phenotype purberbation
  - *Phenotypic model* (pixel intensities, morphological and texture properties)
  - *Motility* (larvae is moving or not)
- Model able to classify depending of the reference drugs (A)
- Model able rank correctly compounds for their in vivo effect (B)

Paveley et al., PLOS Neglected Tropical Diseases
What is the UK-NPSC? What are its aims?

- UK-NPSC is a new venture that aims to operate a world-class, industry-standard phenotypic drug discovery facility in academia.

- It will focus on using phenotypic approaches to identify new drug candidates that address unmet therapeutic needs, screening in a smart cost-effective way, predominantly using human cells and tissues with physiological relevance.

- It will have particular focus on complex multifaceted diseases where interrogating a single molecular target cannot model the disease state.
£8m infrastructure award to SULSA from Scottish Government to establish screening centres in Dundee and Oxford

- University of Dundee
  College of Life Science
  Ready
  Oct 2014

- University of Edinburgh
  Edinburgh Phenotypic Assay Development Hub (E-PAD)
  College of Science & Engineering and Medicine & Veterinary Medicine
  Open
  Feb 2015

- University of Oxford
  Target Discovery Institute
  Nuffield Dept of Medicine
  Ready
  Oct 2014

Aberdeen
Dundee
Edinburgh
Glasgow
St. Andrews
Strathclyde
What is SULSA?

“A Advance Scotland's Excellence in Life Sciences Research and Innovation”

Aberdeen, Dundee, Edinburgh
Glasgow, St. Andrews
Strathclyde

- 9 Professors
- 6 Readers
- 7 Lecturers
- 90 PhD students
- 22 Facilities and 25 Technologists

A network of collaborations and opportunities in 6 Universities that involves 11,000 researchers

Biology areas
- Cell
- Systems
- Synthetic
- Translational
- Imaging

Significant Leveraged funds over 6 years

£27M

£379M
Human Cell Biology Focus

- Patient-derived cells
- Complex co-culture models
- 3D cell and tissue models
- Stem cell technology
  - Patient-derived iPS for disease-relevant models
  - ES/iPS derived cells for new or difficult-to-obtain cell types
  - ES/iPS derived cells for predictive toxicology assays
  - ES/iPS for tissue and organoid assay development
- Precision engineering using CRISPR/Cas9
  - Disease modelling - isogenic lines
  - Reporter line creation
- Haplogen KO lines
Environment for Cell and Assays Initiatives

Public Initiatives

- MRC Regenerative Medicine Hubs
- Pharma Partners
- Academic Stem Cell Labs
- Commercial Suppliers
- Commercial Collaborators
Infrastructure Current Status

- **£8M capital award to SULSA** from Scottish Government in 2014
  - State-of-the-art automation – purchased & being built in USA
  - Wide range of imagers and readers - purchased
  - nL liquid handling capabilities & compound storage – purchased
  - Wet lab and Cell culture lab equipment - purchased
  - Enterprise-level IT infrastructure expansion/enhancement – currently in design phase, operational by Feb 2015.

- **Dundee screening centre** - University of Dundee
  - Refurbishment of lab space underway
  - Operational by Feb 2015

- **Oxford facility** at the University of Oxford
  - Embedded in the HTS laboratory at the Target Discovery Institute

- **Establishment of E-PAD** phenotypic assay development group at the University of Edinburgh
Dundee Laboratory
Imagers, Readers and HTS FACS

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

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

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

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

Tecan Infinite
M1000Pro
Multimode reader

Intellicyt
iQue Screener
2 laser 6 parameter
High throughput
Flow cytometer
High Res Bio Integration & Build
Dundee Laboratory Automation and liquid handling

6 Station Microstar

9 Station Microstar (BSL2)

Labcyte Echo 555
Labcyte Echo 550
Cybio FeLix
Agilent Bravo
Tecan Evo 100

AmbiStores
SteriStore D
TundraStore D
Formulatrix Tempest

Thermo Multidrop Combi
BioTek ELX405 plate washers
Agilent PlateLoc
Brooks Xpeel
Additional Facilities at College of Life Sciences

- **hES & hiPS cell culture/cell line generation/banking facility**
  Established July 2014 with Wellcome Trust-funding. Managed by senior researcher Dr. Lindsay Davidson (ex-Cellartis). Supports cell production for WT-funded hiPSC i proteomics work (Angus Lamond) and other Life Science researchers across the University.

- **Drug Discovery Unit:** Full range of HTS, Cat-3 HTS, Medchem, ADME/DMPK

- **Centre for Advanced Scientific Technologies (CAST)**
  - *FingerPrints* Proteomics Facility
  - Advanced Light and Electron Microscopy Unit
  - OMX Blaze Super-resolution Microscopy Facility
  - Next Generation Genomic Sequencing Unit
  - Crystallography and NMR Facility
  - Cloning Service
  - DNA Sequencing Service
  - Flow Cytometry Core Facility
Oxford TDI Laboratory

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

Brooks Xpeel

AmbiStores
SteriStore D
Echo 555
Read Out Technologies - Summary

- Fast Confocal HCS (dual spinning disc)
- Confocal HCS (line scanning)
- Wide-field Deconvolution HCS
- Wide-field Epifluorescence HCS
- High Throughput Flow Cytometry
- Label-free read-outs
  - Transmitted light – true phase contrast
  - EPIC™ technology
- Multimode plate readers
- Live cell timelapse – cell tracking and kinetics
- Cell-by-cell data & population data
Increasingly dense annotation of small molecular libraries combined with developments in chemo-informatics lead to the ability to perform ‘informed’ iterative moderate-scale screening that avoid the need for ultra-high throughput approaches and can feasibly be combined in high content screens.
Collaboration

- UK-NPSC intends to collaborate with a wider network of centres from across the UK, Europe and beyond, to bridge the gap between academia and pharmaceutical companies and help drive innovation in this emerging discipline.

- UK-NPSC aims to build a strong multi-partner industry consortium as well as embrace the wealth of academic excellence across the UK by working closely with governmental and charitable funding bodies and networks to facilitate the translation of fundamental biological research into novel, more effective, drugs.
Establishing a Phenomics Consortium

- Building an industry funding in a consortium model to support phenotypic assay development and screening “free-at-the-point-of-use”
  - Akin to the European Lead Factory
    - Simpler IP model
  - Currently in advanced negotiation with several major pharma companies:
    - First company committed (October 2014)
    - Companies committing cash and compounds
    - Non-proprietary annotated and diversity libraries
  - Expected launch in 1Q2015
- Full IP ownership and publication rights to academics with milestone for any assays used by industry. Non-exclusive
Propose a basic research idea to be developed into an assay under guidance of UK-NPSC staff

Fit assay remit: range from simple to complex phenotypic assays

Perform Pilot with non-proprietary compound sets

Perform iterative or conventional library screens to find hits and progress to leads

Perform phenotypic profiling & pathway analysis for molecular mechanism of action studies and target identification

Routes to further funding: MRC DPFS, WT Seeding Drug Discovery...

Open-access academic IP model or commercial collaboration model
Drivers for Academia

- Develop a research idea into an industry-standard assay
- Perform Pilot screen as proof-of-concept for funding applications
- Perform chemical biology probe screens for target validation and biology exploration
- Perform diverse library screens to find hits for further drug development
- Screen Open Innovation collections
- Perform phenotypic profiling & pathway analysis for MMOA studies and target identification
- Routes to further funding: MRC DPFS, WT Seeding Drug Discovery and others
- Use open-access or industry collaboration models
- UK-NPSC bridges gap to facilitate industry collaboration
- Wider networking opportunities
Drivers for Industry

- Access to academic expertise in relevant areas of biology and a global network of collaborators and special interest groups
- De-risk complex but high-value assay development
- Co-develop advanced platform technologies
- Access to cutting-edge high content screening facilities and competencies
- Utilise SULSA-managed project selection: online application and peer review process; project monitoring and reporting
Assays: Offering different calls for proposals

- **Industry-proposed Assay**: co-developed and screened by UK-NPSC.
- **Academic-proposed Assay funded by Govt/charity** that will be developed and executed directly by UK-NPSC – outcomes open for partnering?
- **Grand Assay Challenge Fund** (that may respond to an unmet bioassay need – mixed funding depending on area)
- **Blue Skies Fund**: open call for high-risk but innovative ideas for new bioassays (as above)
- **Innovation in Technology and Platform Development (ITPD) Fund** (Engineering, informatics, optics, sensors)
- **Pro-active recruitment of assays** by head-hunting the best team to deliver it – this could be interdisciplinary and international.
New Biology Tools and Technologies
3D, iPS, tissue/organotypic, co-culture, CRISPR engineering

Advanced Imaging Technology, Image analysis and Mathematical Modelling and Statistics

Chemoinformatics
iterative screening
Polypharmacology
Activity Profiling

UK-NPSC

UK-NPSC
National Phenotypic Screening Centre

SULSA
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Consultant & Associate Staff Member,
University of Dundee

**Dr. Den Barrault**
Executive Director of SULSA

**Professor Jason R. Swedlow FRSE**
Group leader Quantitative Imaging,
Founder Open Microscopy Environment,
College of Life Sciences, University of Dundee

**Prof. Sir Peter Ratcliffe FRS**
Director of TDI, University of Oxford
Head of Nuffield Dept. of Clinical Med.
Nuffield Professor of Clinical Medicine

**Dr. Daniel Ebner**
Group Leader – Cellular High Throughput Screening and HTS Operational Cell Screening Officer
TDI, University of Oxford

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

**Dr. Jarek Tomczak**
Director & Consultant
Informatics Unlimited, Cambridge
web: www.uknpsc.org
Email: uknpsc@sulsa.ac.uk
Email: a.hopkins@dundee.ac.uk
@UKNPSC