University of Pennsylvania
High-Throughput Screening Core

A Discovery Platform for Translation of Innovative Basic Science in Academia

David C. Schultz, Ph. D.
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Attrition in Drug Development

Phase II/III failures 2011-2012

Arrowsmith, Nat Rev Drug Disc. 12, 2013
Steps to Developing a New Drug

10-18 years

Drug

Clinical Development

Lead Optimization

Lead Discovery

Assay Development

Target Discovery

Disease

Steps:
- Target Discovery
- Assay Development
- Lead Discovery
- Lead Optimization
- Clinical Development
Mission

- To provide SOM investigators the ability to apply genetic approaches to identify cellular components of signaling pathways and study mechanisms of protein function in cellular models of human disease. – Target Identification/Validation

- To provide high-throughput screening of chemical libraries in high-density (i.e. 384) microtiter well plates to identify and assess the activity of organic small molecule modulators of protein function or disease biology. – Discovery

- Develop novel technology to support HTS at Penn (e.g. new assays, unusual cell types, unique biology)

- Seed collaborative research programs in thematic areas of unmet medical challenge.
SOM Screening Core Infrastructure

- **Automated pipetting workstations**
  - Janus Verispan 8-tip and MDT
  - Bulk Reagent Dispensers
  - ELx405 microplate washer

- **Detection Systems**
  - EnVision multi-mode microplate reader
  - ImageXpress Micro XLS
  - FLIPR Tetra screening system

- **BSL2 Tissue Culture** capabilities (hood & incubators)

- **Accessories** (Plate sealers, Barcode readers & Stackers)

- **Informatics**
SOM Screening Core Library Resources

Chemical Libraries

Bioactives, FDA approved, and FDA-like compounds
• SelleckChem Bioactives (~2100)
  • Kinase Inhibitors, Epigenetic Inhibitors, Cancer compounds, GPCR/Ion Channel, Metabolism, Microbiology, FDA approved/FDA-like
• LOPAC (1280): Library of Pharmacologically Active Compounds

Natural Products
• Microsource Purified Natural Products (800)

Diversity sets
• TBD (50,000-100,000) compounds
SOM Screening Core Library Resources

Genetic Libraries

siRNA
- human genome-wide, human drugable genome, human GO categories
- user-defined human and mouse

Non-coding RNAs
- IncRNAs (human)
- miRNA mimics/antagonists (human)

Human TRC 2.0 and Mouse TRC1.0 Lentivirus shRNA library
- Screening pools: GO categories; user-defined sets
- Order groups/individuals

MGC cDNA collection (CMV-driven)
- 18,000 full length, sequenced, mouse and human (arrayed);
- user-defined sets
- Order groups/individuals
What services can we provide?

› **Assay Development** (biochemical, cell, & high-content)
  › Consultation (technology assessment, assay design);
  › Optimization & miniaturization;
  › validation

› **High-throughput screening**
  › Pharmacologically active cmpds,
  › diversity collections,
  › focused libraries (e.g. annotated inhibitors),
  › siRNA, cDNA, shRNA

› **Pharmacological profiling**
  › Pathway inhibitor screening,
  › Structure-activity relationship studies,
  › synergism studies,
  › molecular mechanism of action

› **Grant preparation**
  › Letters of support, experimental design section
Assays

› **Enzymatic**
  › Luminescent and Fluorescence Intensity based
  › Radioactive
  › Fluorescence polarization (FP)

› **Protein: Protein, Protein: Nucleic Acid interactions**
  › ELISA
  › Fluorescence polarization (FP)
  › Alphascreen technology

› **Biophysical**
  › Thermal stability/Differential Scanning Fluorimetry (DSF)
  › Label-free SPR

› **Luciferase Reporter Gene Assays**

› **Metabolic Viability** *(Cell Titer Glo, MTS, Alomar Blue)*

› **AlphaLISA** *(biomarker expression - e.g. P-antigens, secreted proteins)*

› **Phenotypic/High Content Assays**
  › Live/Dead
  › Autophagy
  › EdU incorporation
  › Viral Infection
  › Migration/invasion
  › Lipid accumulation
Funding Opportunities

• NIH
• NCAT/TRND opportunities
• Foundations (e.g. Welcome Trust, Melanoma Research Foundation, Leukemia/Lymphoma Society, Gates, Cystic Fibrosis, StandUp2Cancer, Children’s Tumor Foundation)
• Commercial (e.g. Bayer Grants4targets, Astrazeneca Openinnovation)
• Institute/Center/Program Pilot project funds
  • Institute for Immunology
  • Center for Orphan Disease Research
  • Institute for Regenerative Medicine
Profiling and Sensitivities

• Phenotypic profiling of cell lines
  – FDA and FDA-likes
  – Annotated gene family (e.g. kinome)
  – Synthetic lethality screens
  – Synergy studies (combinations gene-gene; gene-drug; drug-drug)

• Across tumors (e.g. melanomas)

• Of a particular patient tumor line (to define responsiveness)
Targets for Melanoma Therapy

How can we better predict initial responses to molecular targeted therapies and/or design rational therapeutic combinations for durable responses?
Profiling Drug Activity

Meenhard Herlyn
Multiplex analysis of Cell Viability and Biomarker levels

WM164 (BRAF\textsubscript{V600E}, PTEN\textsubscript{WT})

Viability (resazurin)

AlphaLISA (pERK)

Grace Heck
Improving Clinical Efficacy with Combinations- Synergy screens

Drug combinations present opportunities to develop therapeutic strategies with clinical efficacy.

- A combination drug product (with low doses of each drug) may achieve a desired level of efficacy with a low side effects profile if each compound is associated with biologically different and independent side effects.

- A disease may have two biological pathways which each can be blocked by a different drug
  - Improved efficacy for altered physiology (asthma: bronchoconstriction and inflammation)
  - Improved management of infectious agents such as bacteria and viruses (HIV: HAART).
  - Improved kill rates for cancer cells/ reduce resistance.
Searching for Drug Synergy

Meenhard Herlyn
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