University of Pennsylvania
Perelman School of Medicine
High-Throughput Screening Core

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Mission

- Provide the PSOM community with HTS resources to identify genes or organic small molecule modulators of signaling pathways, cellular phenotypes, and protein function in models of human disease.
  - To educate and assist with HTS assay development, optimization, miniaturization, and validation
  - To provide laboratory robotics infrastructure and technically trained staff for HTS
  - To provide libraries of small molecule and genetic tools for HTS
  - To facilitate small-scale screens from user-defined gene-sets
- 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.
- Educate the SOM on utility and uses of HTS
SOM Screening Core Equipment

- **Automated pipetting workstations**
  - Janus MDT/Verispan 8-tip
  - Bulk reagent dispensers
  - ELx405 microplate washer

- **Detection**
  - EnVision multi-mode microplate reader
  - ImageXpress Micro
  - FLPR screening system

- **BSL2 Tissue Culture capabilities**

- **Informatics**
  - Screensaver, ChemAxon, CeuticalSoft-OpenHTS,
SOM Screening Core Library Resources

**Chemical Libraries**
*Bioactives, FDA approved, and FDA-like compounds*
- Microsource Spectrum Collection (2000)
- LOPAC (1280)
- The Prestwick Chemical Library (1120)
- NIH Clinical Collection (~800)

**Diversity sets**
- TBD

**Genetic Libraries - Large scale and user-defined**

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

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

**Lentivirus shRNAs**
- Screening pools: genome-wide; 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 will we provide?

- **Assay Development** (biochemical, cell, & high-content)
  - Consultation, technology assessment, assay design, optimization, miniaturization

- **Small-scale screening**
  - User-defined sets of genes
  - User-defined cell-types across small libraries of bioactive compounds/inhibitors
  - Synergy screening with smaller libraries

- **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, mechanism of action

- **Grant preparation**
  - Letters of support, experimental design section
Small scale screening

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

• Functional studies of ‘OMICs gene sets
  – Over-expression of gene-sets
  – Loss-of-function of gene-sets

• Validation of GWAS ‘hits’ or Exome ‘hits’
Assays

• Reporter Gene Assays (e.g. luciferase)
• Signaling
• Survival
• Microscopy (cell biology)
• Infection
• Anything you can read in a plate reader or microscope
Cell types

• Transformed lines
  – almost all routinely used cell lines
• Primary cells
  – macrophages, DCs, epithelial, etc
• Not lymphoid cells
  – hard to transduce
• BUT…can mix cells where perturb one cell and read out in another
  – eg. siRNA in macrophage but read T cell biology out
The Assay Development Process

Design
- Idea
- Phenotypes
- Reporters, cell types
- Controls
- Existing infrastructure

Development
- Controls: Z-factors, S/N, CVs
- Solvent; Timing; TX reagents
- Cell type, numbers
- Day to day; Plate to plate

POC
- Test set (e.g. 1K set)
- Data analysis
- Scale up

~ 1 hr to a month

~ 1-6 months
Automation: Screening

Automated pippeting station → 384w plates spotted with cDNAs or siRNAs → Dispenser

"Hit"
Services

• **Consultations** (per hour)
  – Assay development
  – Assay optimization
  – Assay validation
  – Grant submissions

• **Equipment usage** (per hour)
  – With help
  – Without help

• **Small scale screens**
  – User-defined (siRNAs, shRNAs, cDNAs, chemicals)
  – Library plates (e.g. kinome)

• **Large scale screens**
  – Library plates

• **Data Analysis**
  – Normalization, annotation
  – HCA analysis sequence dev.
  – Screen reports

• **Reagents**
  – Transfection
  – Plastics
  – Tips
  – Arraying

• **siRNAs, shRNAs, cDNAs**
  – User defined small sets
  – Individual clones
Funding Opportunities

- **NIH**
  - PAR-13-364, Development of Assays for High-Throughput screening for use in Probe and Pre-therapeutic Discovery (R01)
  - PAR-14-283/PAR-14-284, High Throughput Screening (HTS) to Discover Chemical Probes (R21/R01)
  - PAR-14-279, Discovery of *in vivo* Chemical Probes (R01)
  - PAR-14-006, Seeding Collaborations for Translational Research to Discover and Develop New Therapies for Diseases and Conditions within NIDDK's Mission (RO1)
  - PAR-13-267, Novel NeuroAIDS Therapeutics: Integrated Preclinical/Clinical Program (P01)
  - PAR-15-041, Targeting Persistent HIV Reservoirs (TaPHIR) (R21/R33)

- **NCAT/TRND opportunities**

- **Foundations** (e.g. Welcome Trust, Melanoma Research Foundation, Leukemia/Lymphoma Society, Gates)

- **Institute/Center Pilot project funds**
HOW TO GET STARTED?

- Contact David Schultz at dschultz@mail.med.upenn.edu for an initial consultation
  - Define the project
  - Determine if the facility has relevant expertise/technology to pursue the project
  - Develop a management plan
  - Set expectations
  - Get started!