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 dispensors
  - ELx405 microplate washer
- **Detection**
  - EnVision multi-mode microplate reader
  - ImageXpress Micro
  - FLPR screening system
- **BSL2 Tissue Culture capabilities**
- **Informatics**
  - Screensaver, ChemAxon, CeuticalSoft-OpenHTS,

EnVision

Dispensor

Janus

Image Express

SOM Screening Core Library Resources

Chemical Libraries

Bioactives, FDA approved, and FDA-like compounds

- Selleck Chem Bioactives (~2000)
- 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

- lncRNAs (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’

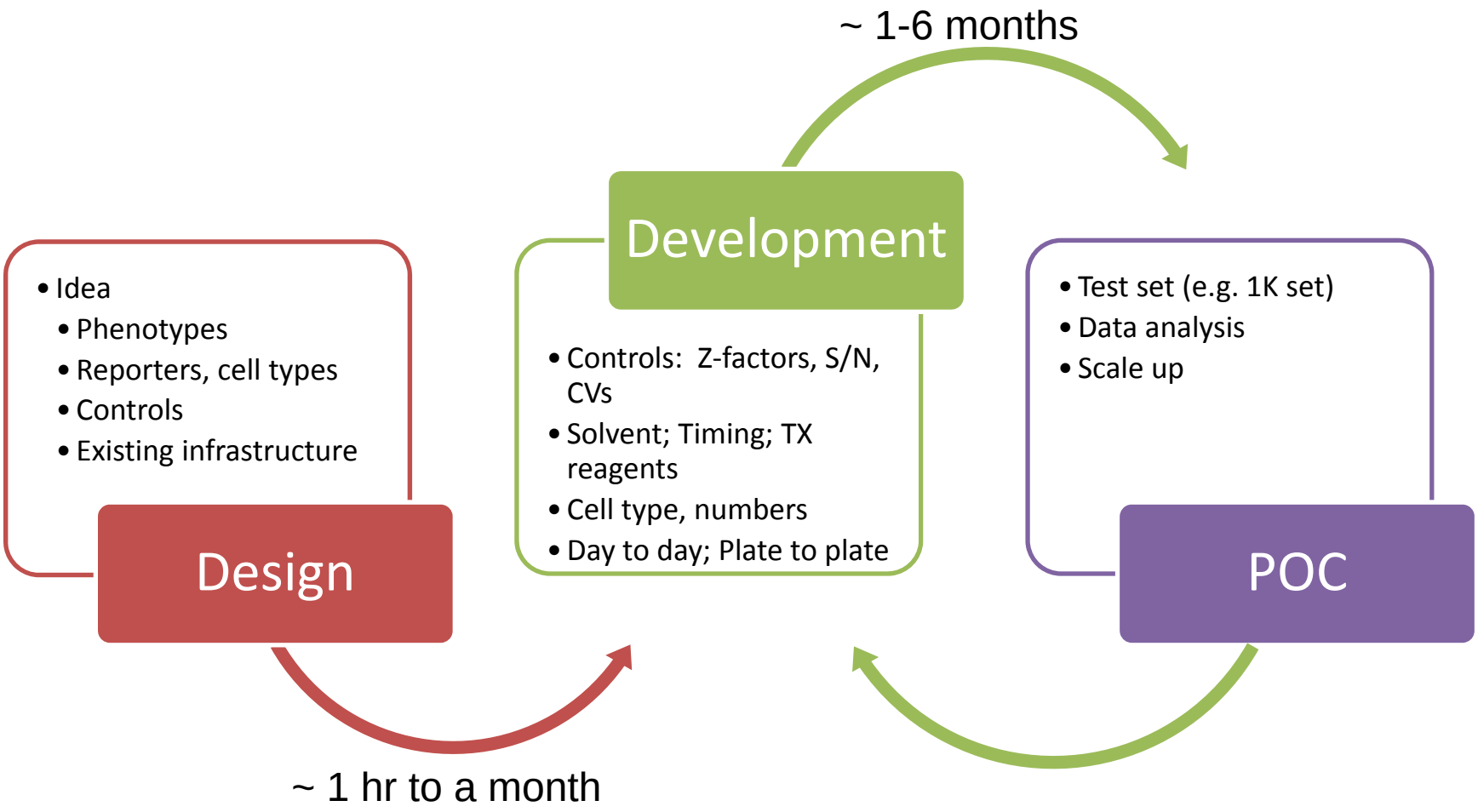
Assays

- 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



Automation: Screening

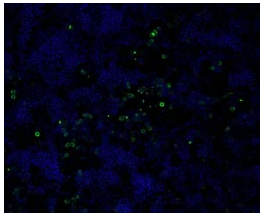
Automated
pippeting station

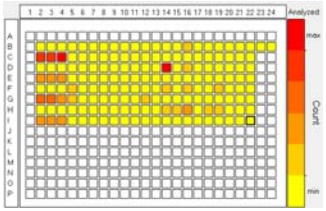
384w plates spotted
with cDNAs or siRNAs

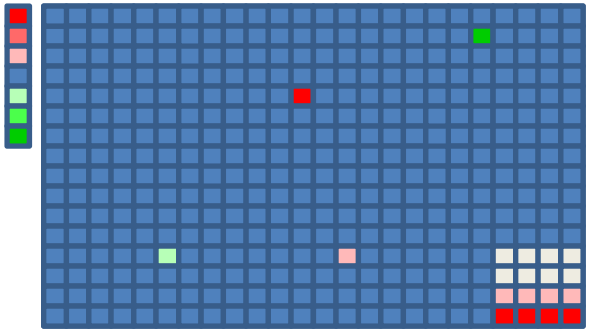
Dispenser

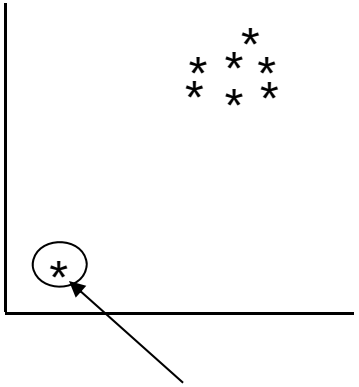
HT Multimode Reader

Automated Microscopy









"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-13-049/PAR-13-048, Drug Discovery for Nervous System Disorders (RO1/R21)
  - 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!