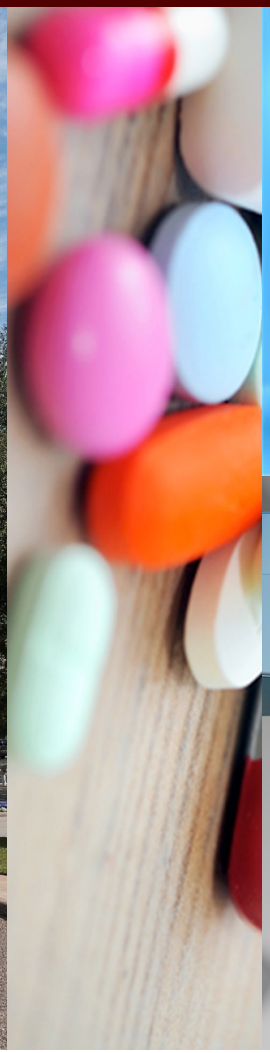
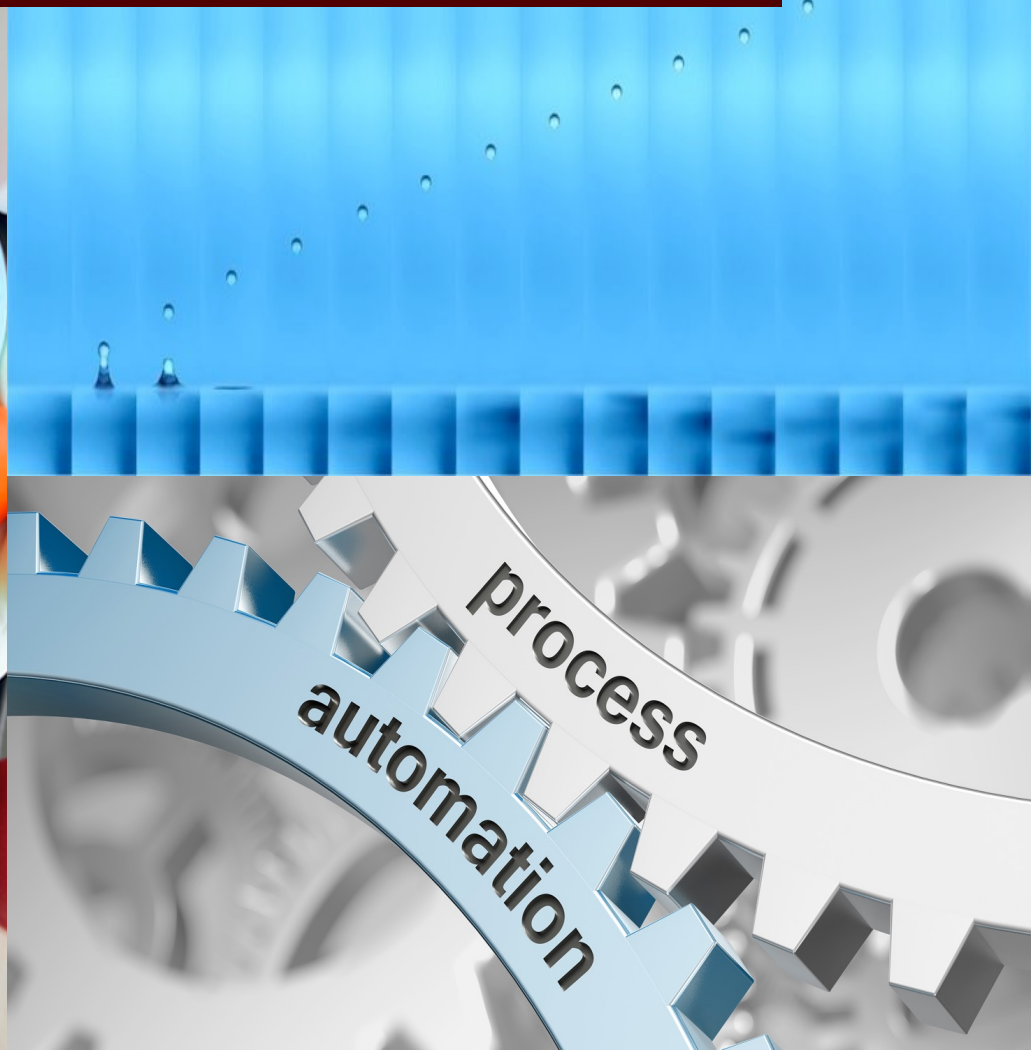
IBT High Throughput Research and Screening Core





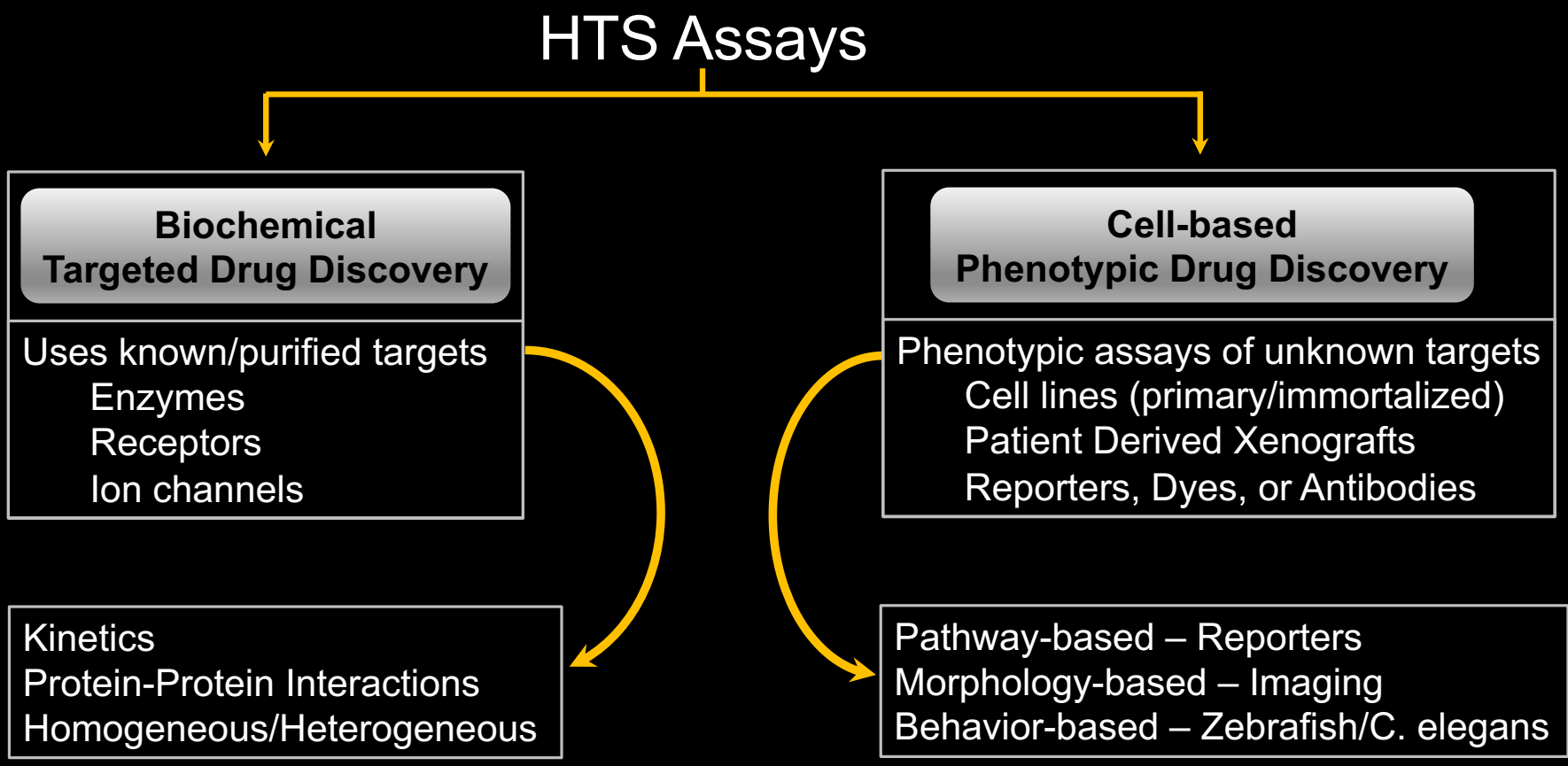
What is High Throughput Screening (HTS)?

- It is an experimental process

- A way of performing drug discovery research that:
  - ✓ Uses robust but simple experimental methods
  - ✓ Uses automation for highly repetitive activity
  - ✓ Typically run against a specific biological target
  - ✓ Used as an 'activity' filter
  - ✓ Quickly generates Big Data sets & Data management issues

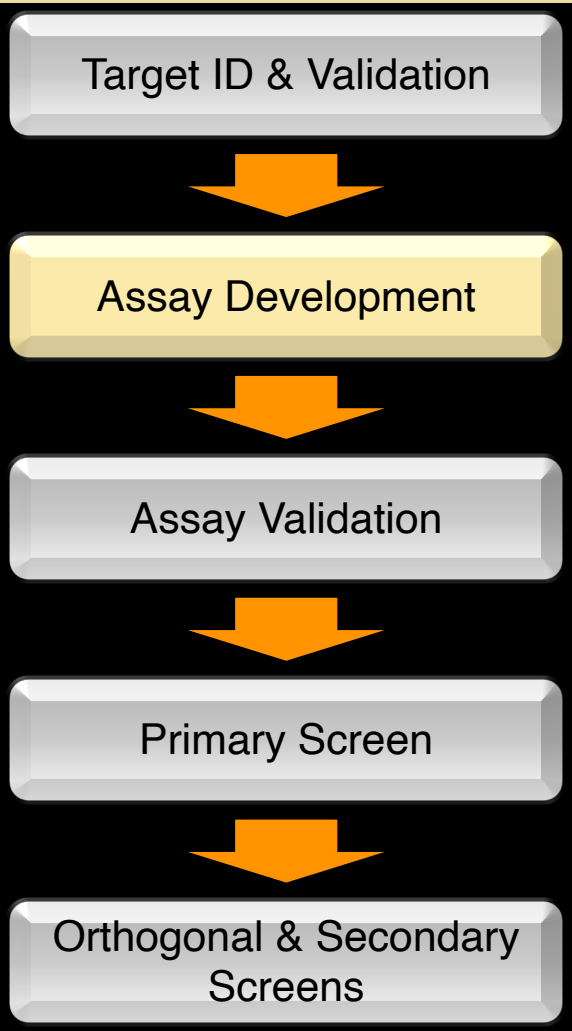
- Primary goal: Eliminate most of test agents that do not affect the biological target.
- HTS can identify a starting place for a new probe or drug
- HTS can identify a new purpose for an approved drug

Assay Design: Types of Assays



The Deliverable = Identify compounds that modulate activity

Common Steps for any Screening Campaign



What is going to be screened?
Agonist, antagonist, or modulator?

How will it be screened?
Appropriate assay controls?
Rigor and Reproducibility

How good is the screening assay?

Were any ‘Hits’ identified?

Validate the hits as against the target?

Assay Development

- Relevance: Does the readout unequivocally relate to the target?
- Specificity/Sensitivity: Is the readout specific for the target, sensitive enough?
- Reliability/Robustness: Are results reproducible inter- & intra-assay and statistically significant?
- Practicality: Do time, reagents, and effort correlate with quality and quantity of results?
- Feasibility: Can assay be run with resources at hand?
- Automation: In order to screen large numbers of compounds, can assay be automated and run in highly parallel format?
- Cost: Does cost of the assay permit scale-up for high-throughput screening?

The quality of an assay determines the quality of data i.e., compromising on assay development can have substantial downstream consequences.

Eckstein, Jens. ISOA/ARF Drug Development Tutorial.

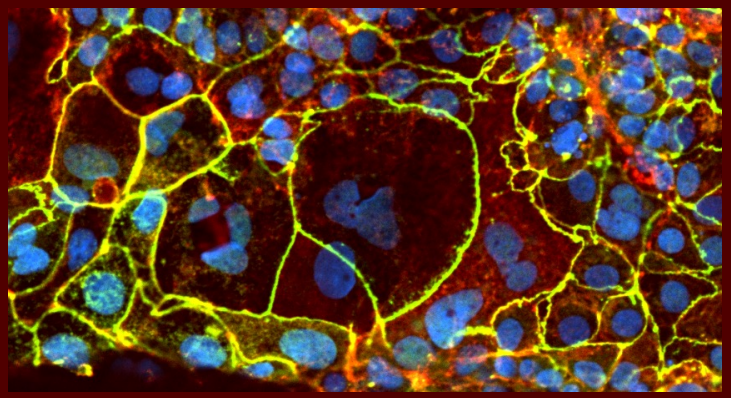
Assay Development

Key factors that must be addressed prior to screening:

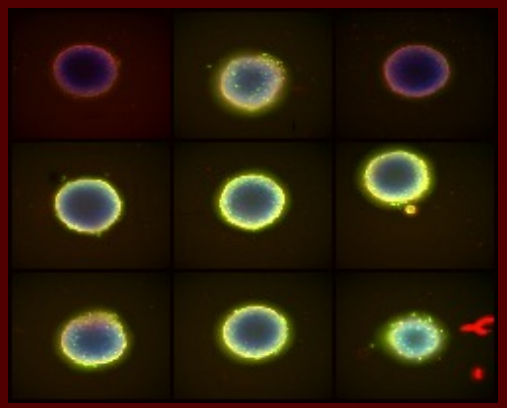
- Appropriate controls
  - Positive Control – Gives a response similar to what is expected from the screen
  - Negative Control – Provides an indication of the baseline for the assay
  - The difference between them is the dynamic range of the assay
- Assay rigor, reproducibility, and signal stability
- Miniaturization and adaptation to automation
- Available secondary assays to test biological relevance and mechanisms of action

Model Systems Screened in the Core

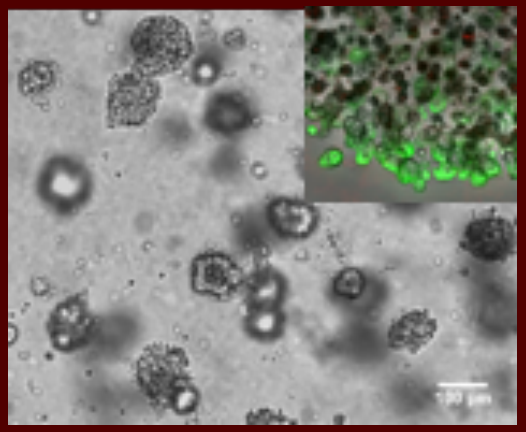
Proteins (enzymes)



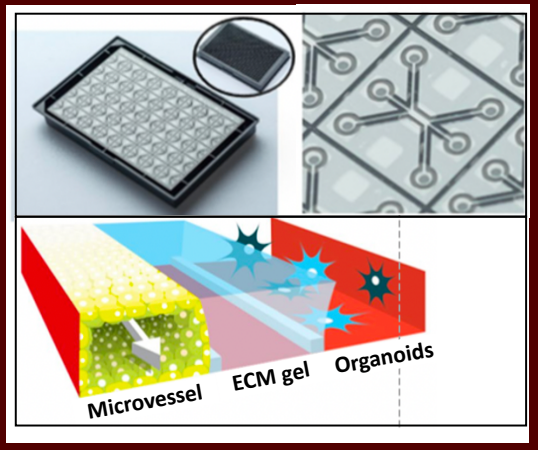
Cell Lines and PDX-derived



Spheroids



Organoids



Tissue Chips

Simple model organisms

High Throughput Research and Screening Center Resources

Stand alone liquid handling

- Multidrops

- Multiflow

- Mantis

Automated liquid handling platforms + TC Incubators

- Plate washers

- Tecan Evo

- Labcyte Echo

Robotically integrated Detection systems

- ImageXpress Micro confocal & IN Cell 6000

- MP-FLIM

- ZE5 flow cytometer

- Neo Synergy2 & Tecan M1000 readers

Data & Image processing and secondary analysis

- Biovia Pipeline Pilot

- Deep Learning Studios

- Python

- Fiji/ImageJ

- CellProfiler

Current Drug and Compound Collections

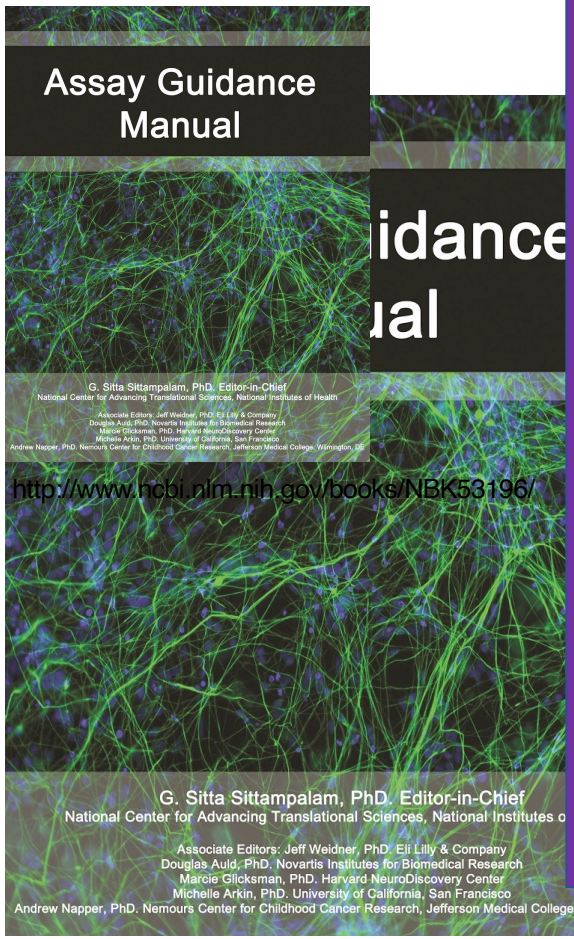
Library Focus		Library Focus
Approved Drug Library		Stem cell Differentiation Compound Library
		Cell cycle related compound Library
Oxidation-Reduction Compound Library		Apoptosis Compound Library
Anti-Metabolism disease Compound Library		Autophagy Compound Library
Mitochondrial Targeting Compound Library		DNA Damage _ Repair Compound Library
Epigenetics Compound Library		Ion Channel Inhibitor Library
		Endocrinology-Hormones Library
PI3K-AKT-mTOR Compound Library		Neuronal Signaling Compound Library
MAPK Inhibitor Library		
Tyrosine kinase inhibitor library		JAK STAT Compound Library
		Wnt_Hedgehog_Notch Compound Library
Selleck Bioactives Collection		
		Fluorochemical Library
Prestwick/Microsource Collections		Natural Compound Library

The Core maintains a collection of drugs and investigational agents approved for use in humans, bioactive compounds, natural products, and some small molecules. The Core maintains > 35,000 testable agents.

Useful Resources

Site	Site URL
The Assay Guidance Manual	https://www.ncbi.nlm.nih.gov/books/NBK53196/
PubChem	https://pubchem.ncbi.nlm.nih.gov
Cancer Therapeutics Response Portal (CTRP)	https://portals.broadinstitute.org/ctrp.v2.1/
Wellcome Sanger Institute Genomics of Drug Sensitivity in Cancer (GDSC)	https://www.cancerrxgene.org
Center for Cancer Genomics (CCG)	https://www.cancer.gov/about-nci/ organization/ccg
Human Metabolome Database	https://hmdb.ca
Drug Bank	https://go.drugbank.com
Probes and Drugs	https://www.probes-drugs.org/home/

The Assay Guidance Manual



http://www.ncbi.nlm.nih.gov/books/NBK53196/

HTS Assay Validation

Philip W. Iversen, Benoit Beck, Yun-Fei Chen, Walthere Dere, Viswanath Devanarayan, Brian J Eastwood, Mark W. Farmen, Stephen J. Iturria, Chahrzad Montrose, Roger A. Moore, Jeffrey R. Weidner, and G. Sitta Sittampalam.

Published May 1, 2012; Last Update: October 1, 2012.

Assay Operations for SAR Support

Benoit Beck, Yun-Fei Chen, Walthere Dere, Viswanath Devanarayan, Brian J. Eastwood, Mark W. Farmen, Stephen J. Iturria, Phillip W. Iversen, Steven D. Kahl, Roger A. Moore, Barry D. Sawyer, and Jeffrey Weidner.

Published May 1, 2012; Last Update: November 20, 2017.

Minimum Significant Ratio – A Statistic to Assess Assay Variability

Joseph V. Haas, Brian J. Eastwood, Philip W. Iversen, Viswanath Devanarayan, and Jeffrey R. Weidner.

Published November 1, 2013; Last Update: November 20, 2017.

References

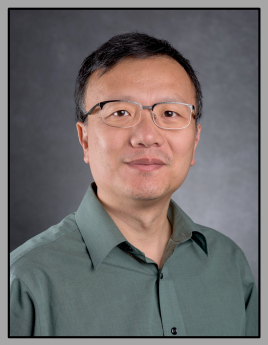
http://www.ncbi.nlm.nih.gov/books/NBK53196/

IBT High Throughput Research and Screening Center

"Our Team"





Specialized Expertise – "*The Heart of the Core*"

Scientific and Technical Staff:
Industry level HTS, Imaging and Data Analysis, Informatics, Robotics, Automation, Tissue culture




INSTITUTE OF BIOSCIENCES AND TECHNOLOGY
TEXAS A&M HEALTH SCIENCE CENTER

The IBT High Throughput Research and Screening Center for Probe and Drug Discovery

Peter Davies, MD, PhD
Program Director
pdavies@tamu.edu

Clifford Stephan, PhD
Scientific Director
cstephan@tamu.edu

INSTITUTE OF BIOSCIENCES AND TECHNOLOGY
TEXAS A&M UNIVERSITY

IBT Roundtable 6 Aug 2021