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Small Molecule Discovery in Oncology and Beyond: Challenges and Opportunities

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TRACO Lecture
September 30, 2024

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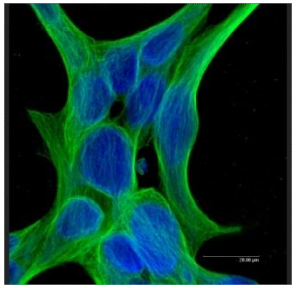
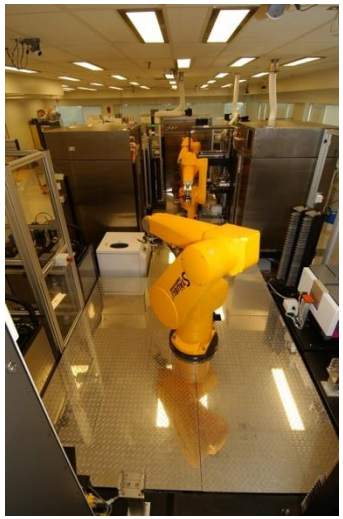
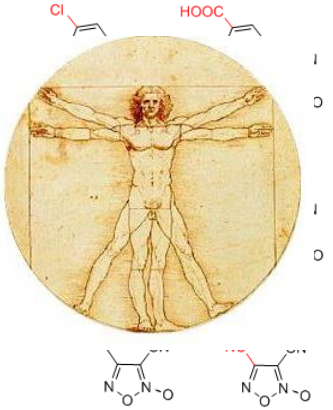
Steps in the Drug Discovery Process

Identify target → Create testing system (aka, "assay" → Test >100,000 chemicals for activity on target → Make modifications to active chemicals to make suitable for human use → Test in animals for safety, effectiveness → Test in humans for safety, effectiveness







"Assay Development"

"HTS"

"Medicinal Chemistry"

"Preclinical Development"

"Clinical Development"

Basic research

Target to Lead

Lead to First-in-Human

Biopharma, NIH CC, CTSAs

$50-500K

$500K-2M

$5-20M

$50-200M

(Per project cost)

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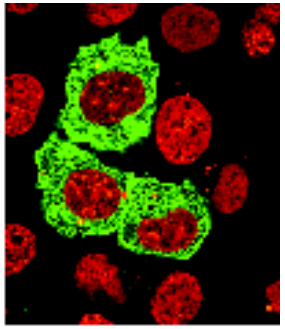
Range of Screening Assays

Extent of reductionism

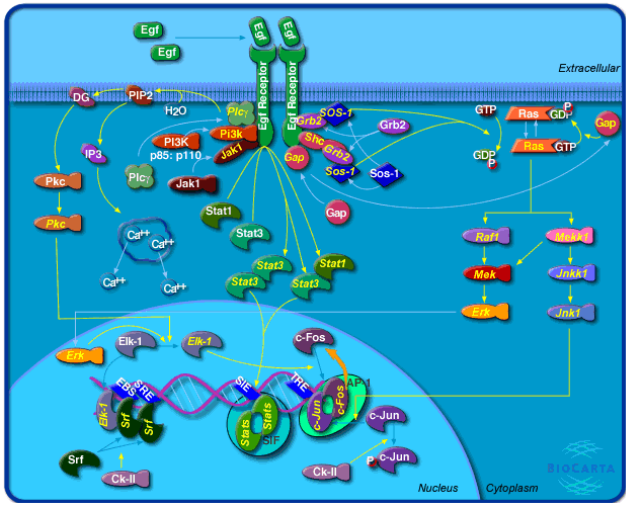
Phenotype

(Image-based HCS, GFP, etc)



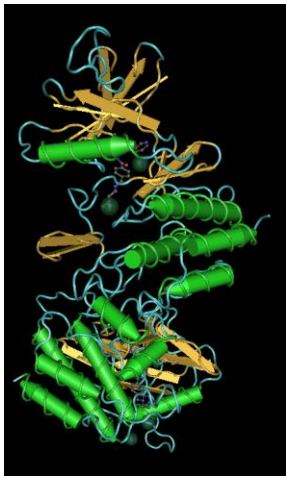
Pathway

(Reporters, e.g., luciferase, β-lactamase)

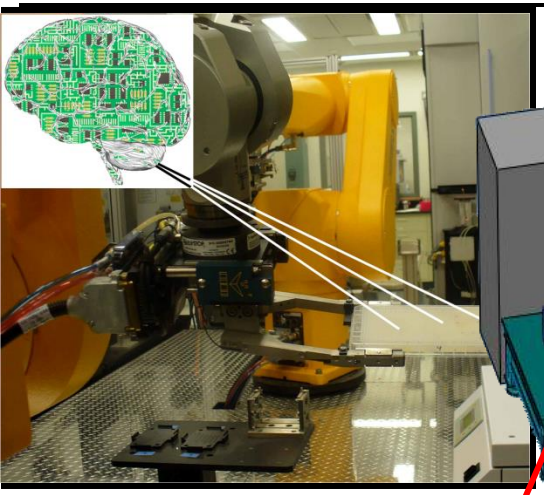


Protein

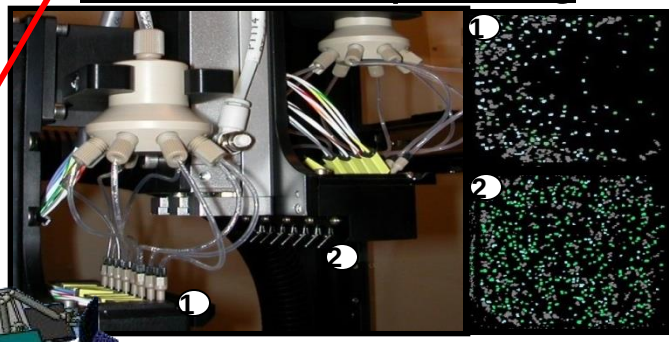
(Enzyme readouts, interactions, etc)



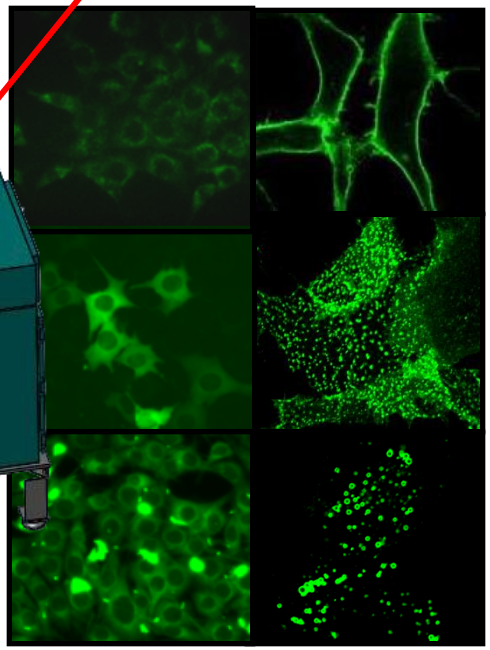
Robotics & Informatics



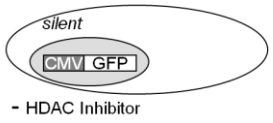
Microliter Dispensing

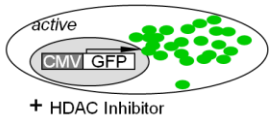


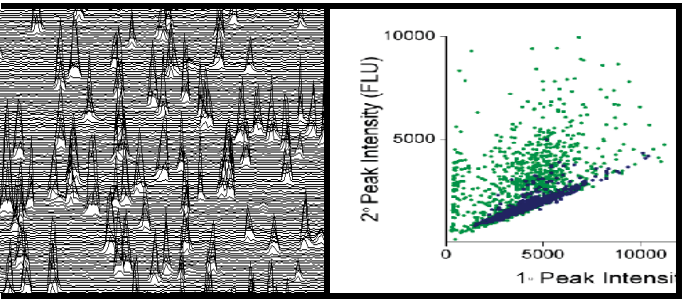
Microscopy



Laser Cytometry







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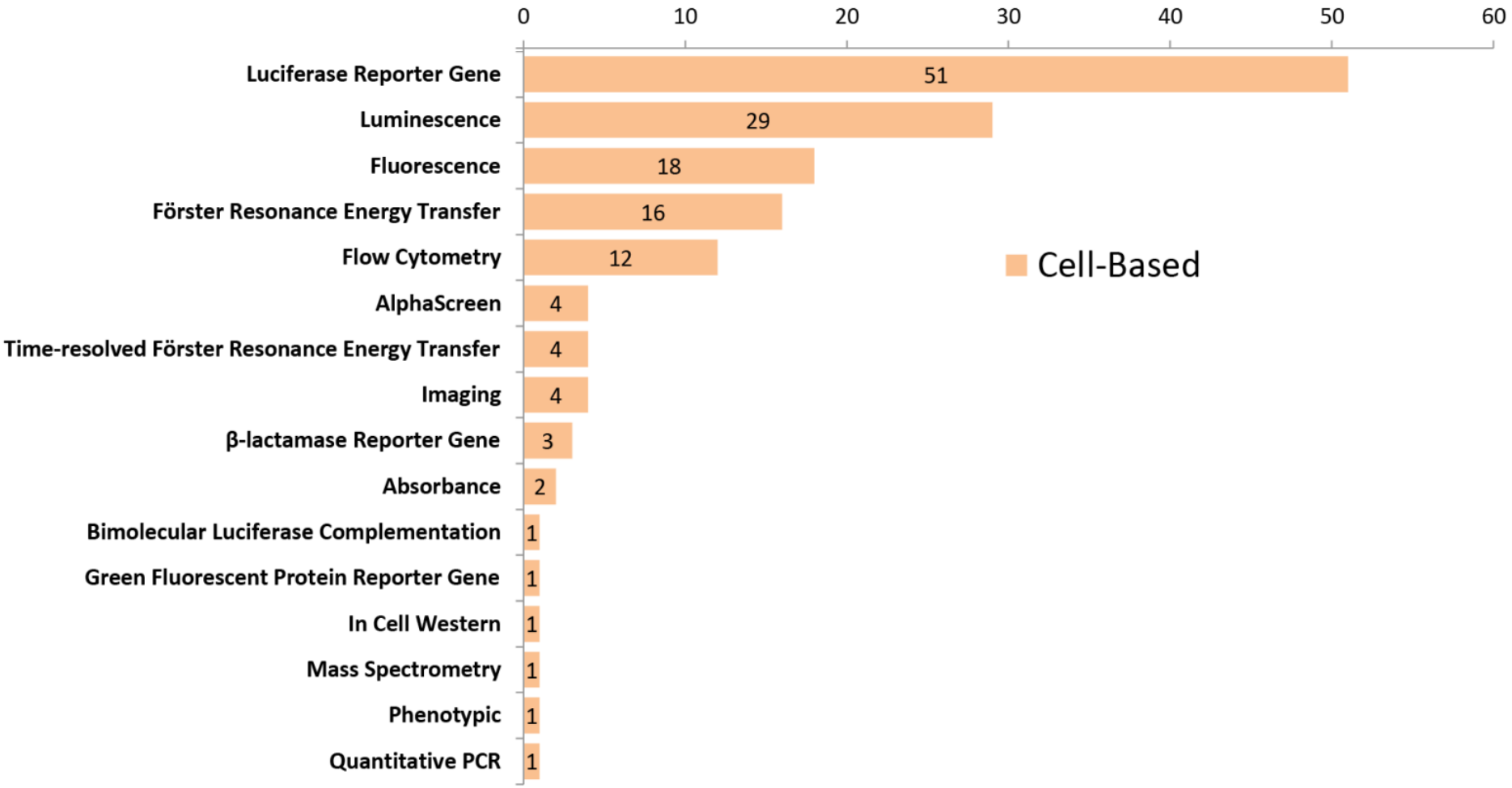
149 Cancer Relevant Cell-Based HTS Assays from PubChem



Coussens, N. P., Braisted, J. C., Peryea, T., Sittampalam, S. G., Simeonov, A. and Hall, M. D. **Small Molecule Screens: A Gateway to Cancer Therapeutic Agents with Case Studies of FDA-Approved Drugs** *Pharmacological Reviews*, October 2017, 69 (4) 479-496

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Important Considerations for Choosing an Assay

- **Assay expense**
  - Cost per well
  - Disposal cost(s)

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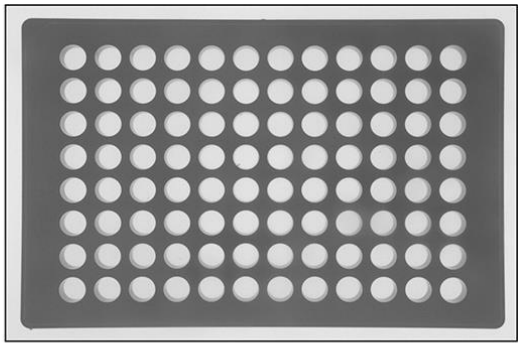
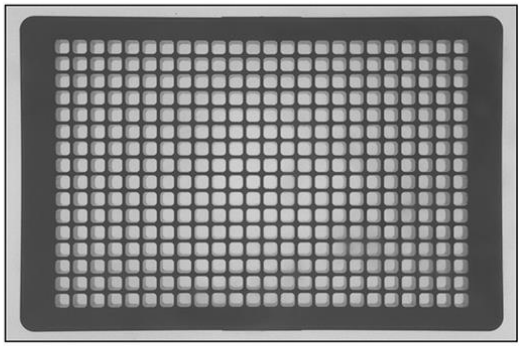
Assay Miniaturization Saves Time and Reagents

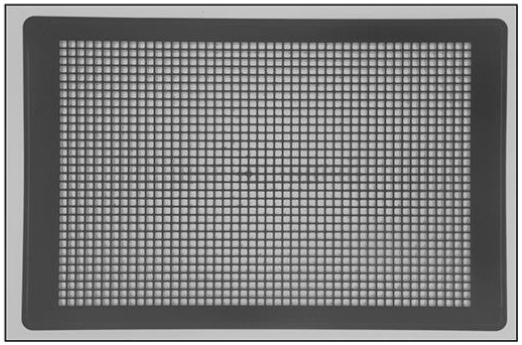
96-well
~50,000 cells/well

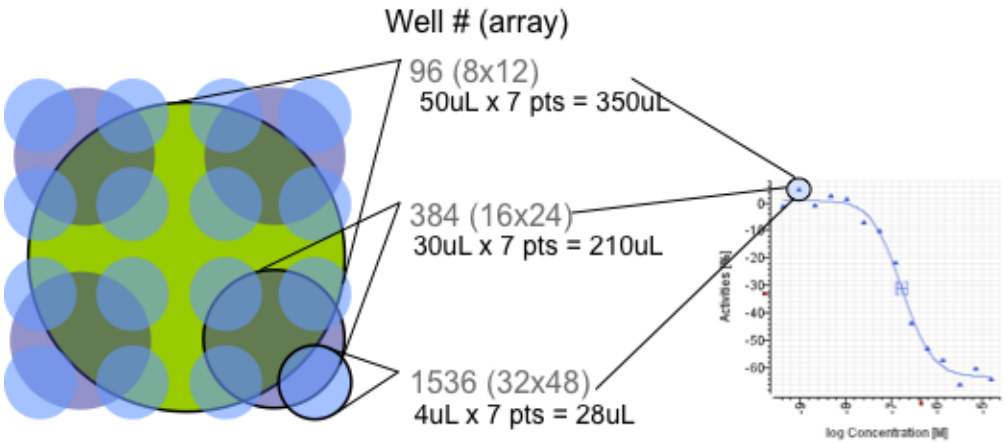


384-well
~5,000 cells/well



1536-well
~500 cells/well





	96	384	1536
Plates per 100,000 compounds:	1,042	261	66
Assay volume (uL):	50-200	30-50	2-8
Adherent cell seeding density:	~10,000	~2,000	~500

Horman, Shane R. "Complex High-Content Phenotypic Screening." Special Topics in Drug Discovery. InTech, 2016.

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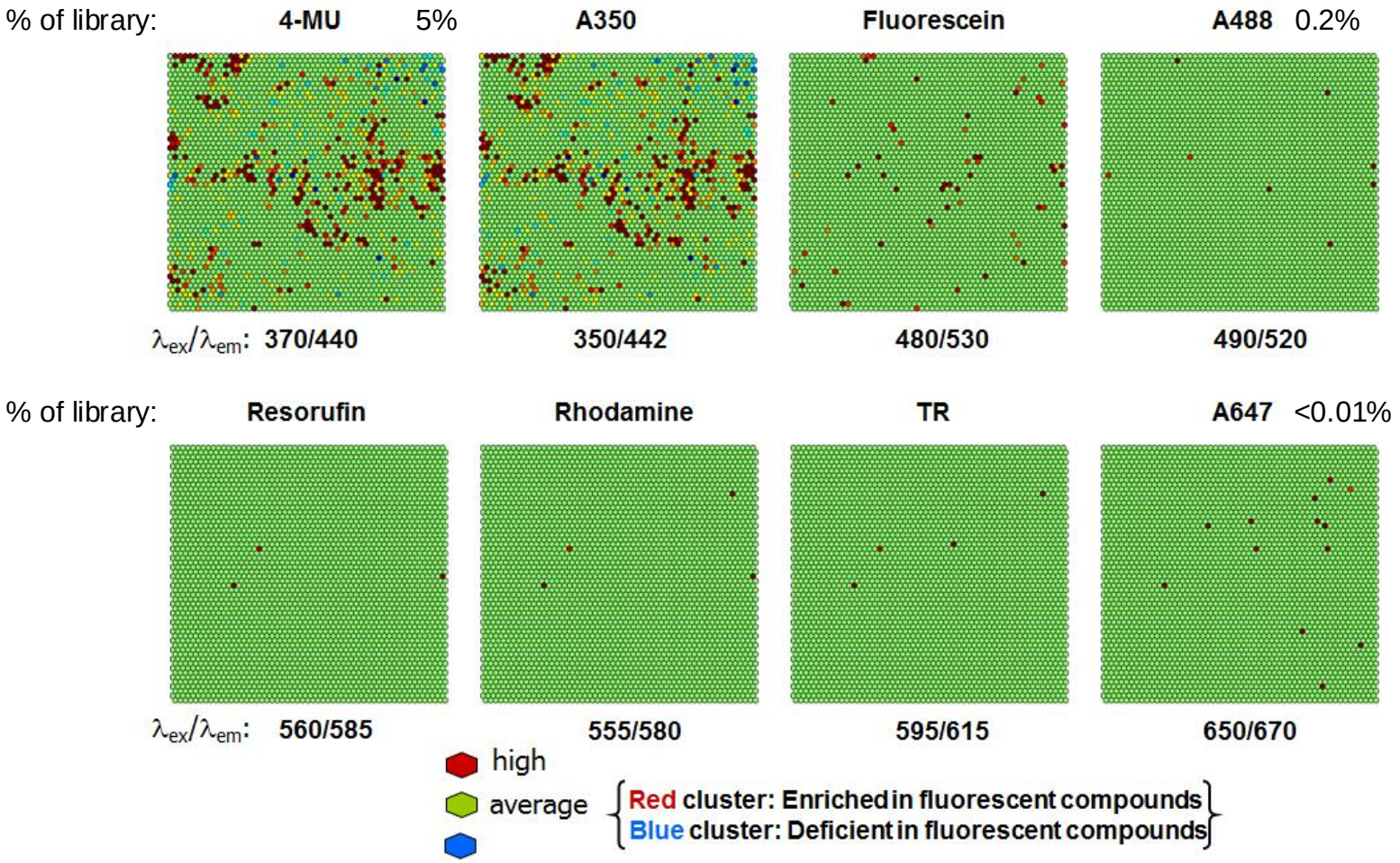
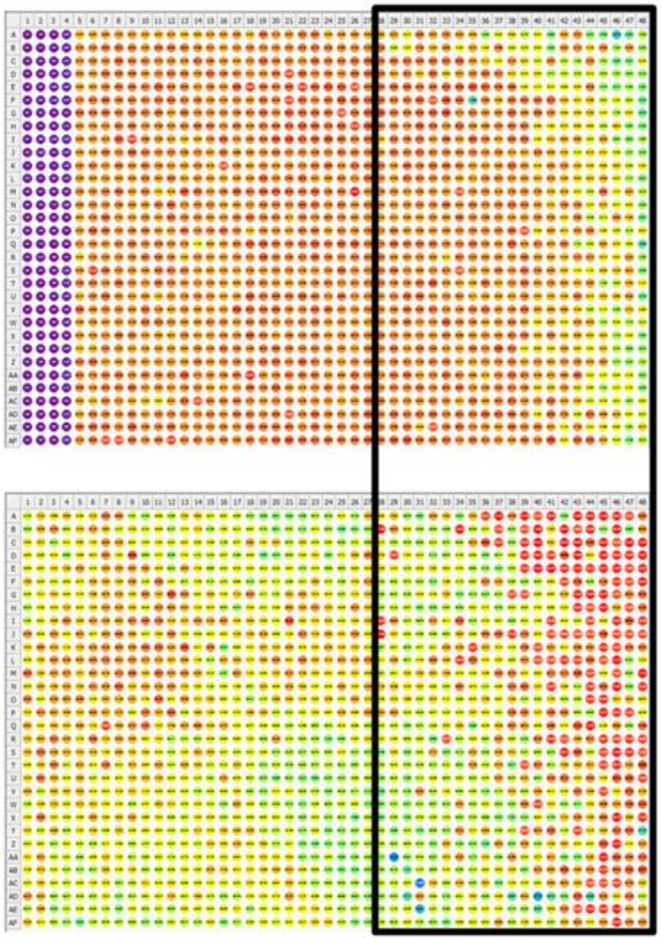
- **Potential for assay interference**
  - Fluorescent compounds can interfere with fluorescent readouts
  - Colored compounds might interfere with luminescence

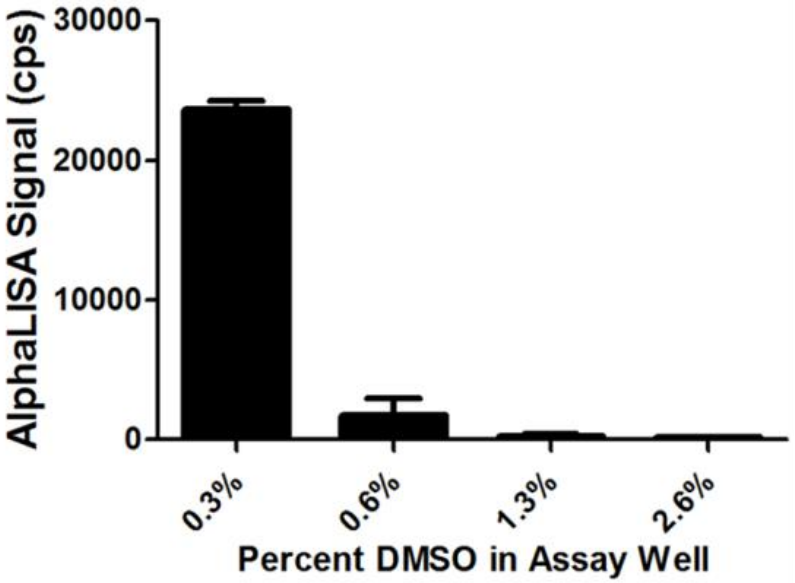
Fluorescence Spectroscopic Profiling of Compound Libraries



Simeonov, A., Jadhav, A., Thomas, C.J., Wang, Y., Huang, R., Southall, N.T., Shinn, P., Smith, J., Austin, C.P., Auld, D.S. and Inglese, J., 2008. **Fluorescence spectroscopic profiling of compound libraries.** *Journal of Medicinal Chemistry*, 51(8), 2363-2371.

Determination of Assay Tolerance to DMSO/Vehicle is Important





Yasgar A., Jadhav A., Simeonov A., Coussens N.P., **AlphaScreen-Based Assays: Ultra-High-Throughput Screening for Small-Molecule Inhibitors of Challenging Enzymes and Protein-Protein Interactions**. *Methods Mol Biol*. 2016;1439:77-98.

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Important Considerations for Choosing an Assay

- **Homogenous assay format is preferred for screening**
  - Add reagents, mix and measure (no solution removal or wash steps)
  - Automation friendly
  - Reduces variability
  - Decreases hands-on time
  - Improves reproducibility

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  - Time required for data analysis and record keeping

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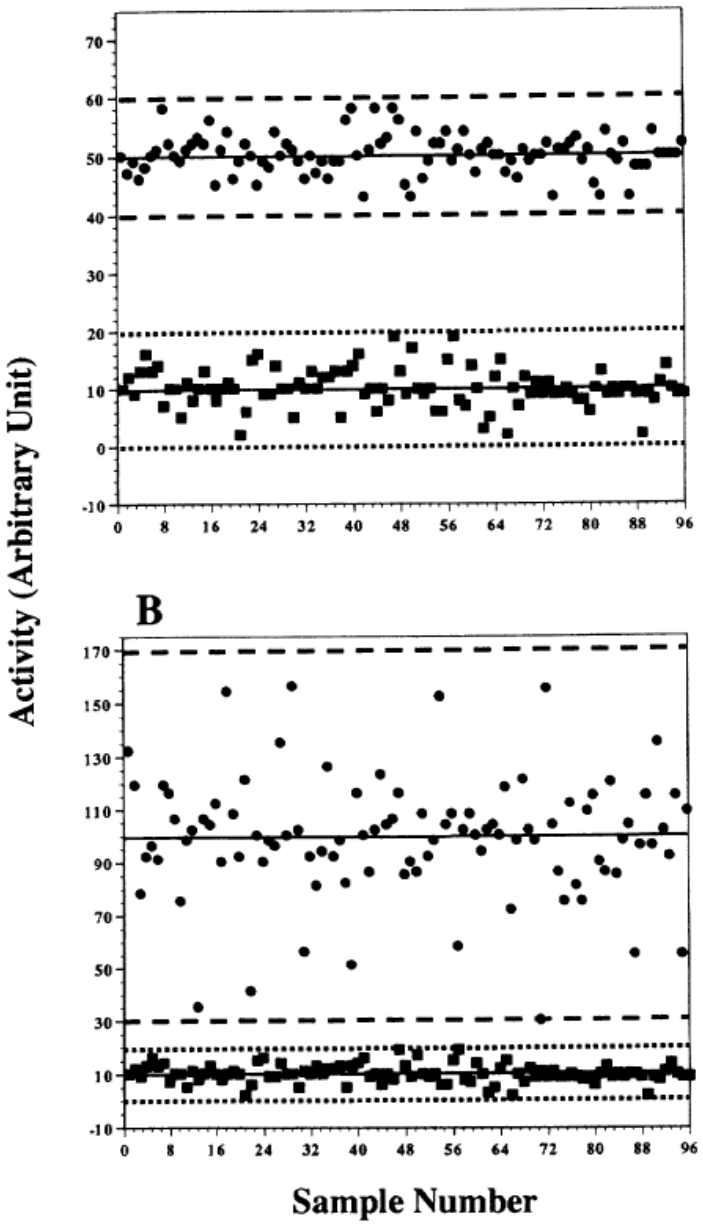
  - Longer signal stability minimizes differences among stacks of plates
- **Assay Sensitivity**
  - Choice of readouts is important
    - Colorimetric<fluorescent<luminescent

Evaluating Assay Suitability for Screening



S/N = 12

S/B = 5

z = 0.5

S/N = 27

S/B = 10

z = 0.1

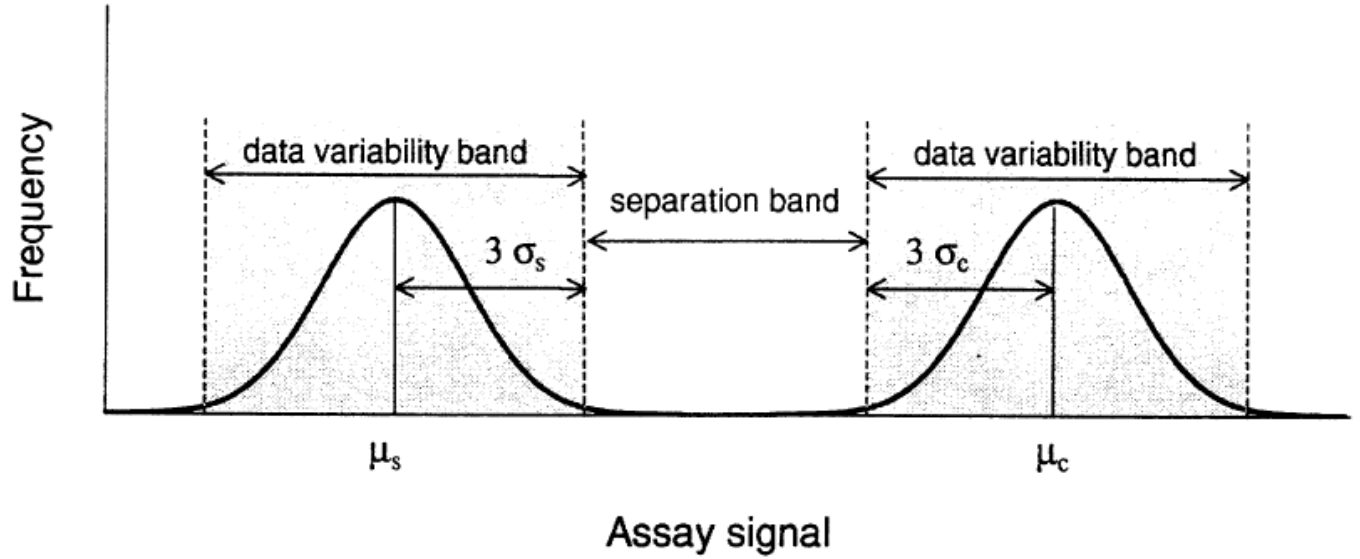
$$S/N = \frac{\text{mean signal} - \text{mean background}}{\text{standard deviation of background}}$$

$$S/B = \frac{\text{mean signal}}{\text{mean background}}$$

$$Z = 1 - \frac{3SD \text{ of sample} + 3SD \text{ of control}}{|\text{mean of sample} - \text{mean of control}|}$$

A Simple Statistical Parameter for Use in Evaluation and Validation of High Throughput Screening Assays. Zhang JH, Chung TD, Oldenburg KR. J Biomol Screen. 1999;4(2):67-73.

Evaluating Assay Suitability for Screening

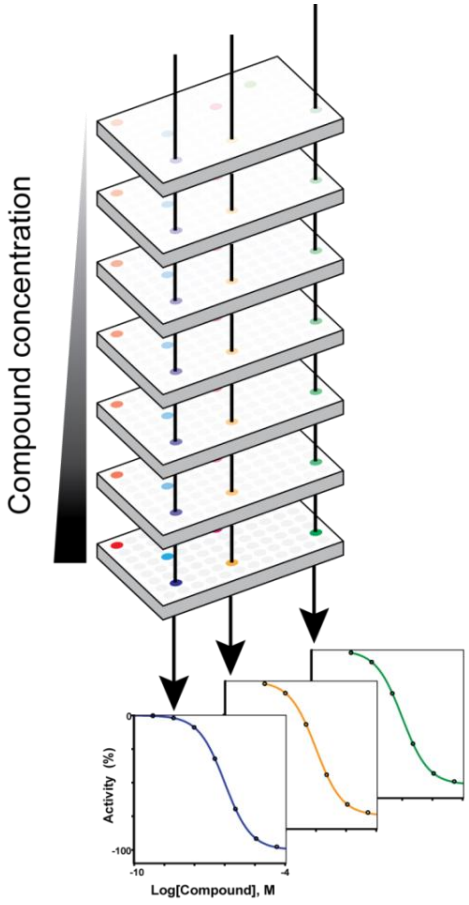


$$Z = 1 - \frac{3SD \text{ of sample} + 3SD \text{ of control}}{|\text{mean of sample} - \text{mean of control}|}*$$

Z-factor value	*Structure of assay*	*Related to screening*
1	SD = 0 (no variation), or the dynamic range → ∞	An ideal assay
$1 > Z \geq 0.5$	Separation band is large	An excellent assay
$0.5 > Z > 0$	Separation band is small	A double assay
0	No separation band, the sample signal variation and control signal variation bands touch	A "yes/no" type assay
<0	No separation band, the sample signal variation and control signal variation bands overlap	Screening essentially impossible

A Simple Statistical Parameter for Use in Evaluation and Validation of High Throughput Screening Assays. Zhang JH, Chung TD, Oldenburg KR. J Biomol Screen. 1999;4(2):67-73.

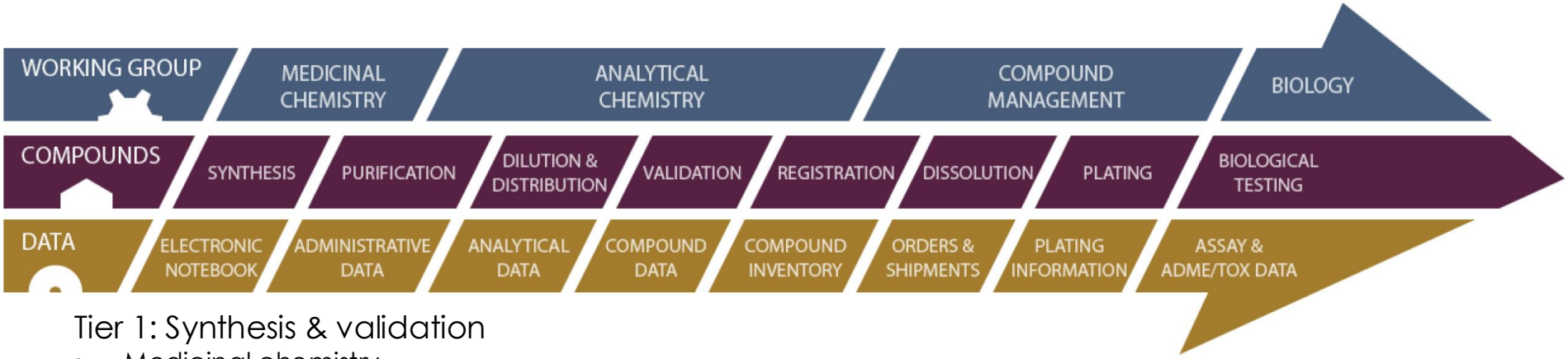
Improving the Process of Early Discovery: Quantitative High-Throughput Screening (qHTS)



- Conventional screening done at one concentration
  - Not appropriate for potency testing – "dose makes the poison"
- qHTS tests compounds assayed at multiple concentrations (range: 4 logs)
- Enabled by miniaturized assay volumes (2-8 µL per test) and informatics pipeline
- Generates *pharmacological actives* instead of statistical "hits"
  - Dramatically increases reliability
  - Dramatically reduces false positives and false negatives
- *To date, several hundred million datapoints from several hundred screens have been generated and deposited in the public domain.*

PNAS 103:11473

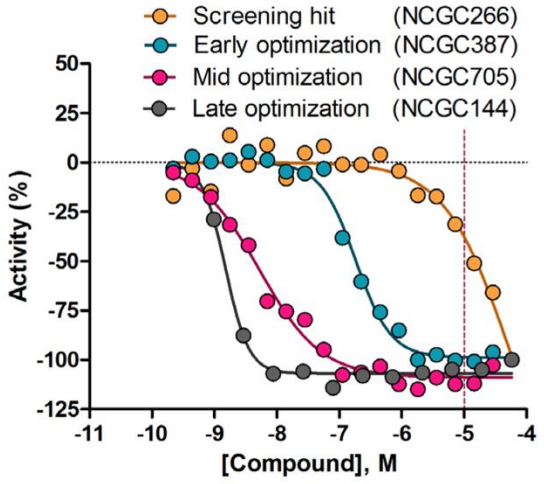
Medicinal Chemistry, an Integrated Process

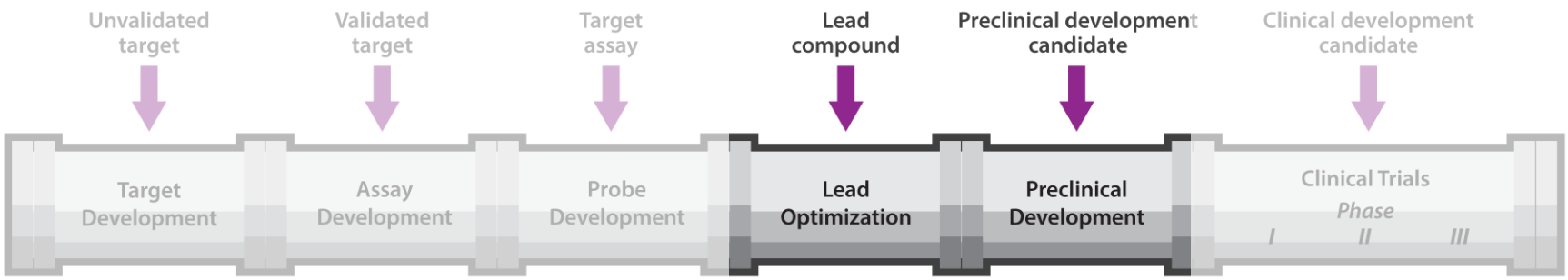


Tier 1: Synthesis & validation
- Medicinal chemistry
- Purification
- In vitro ADME

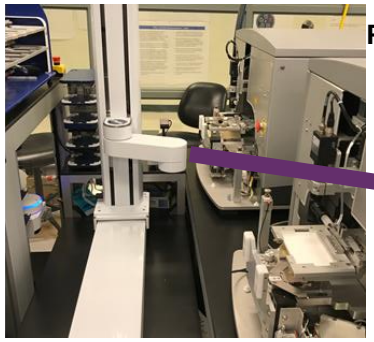
Tier 2: Compound profile expansion
- Met ID/CYP studies
- In vitro toxicology

Tier 3: Advanced Preclinical studies
- Formulation
- Scale-up
- In vivo PK/PD
- Preclinical toxicology

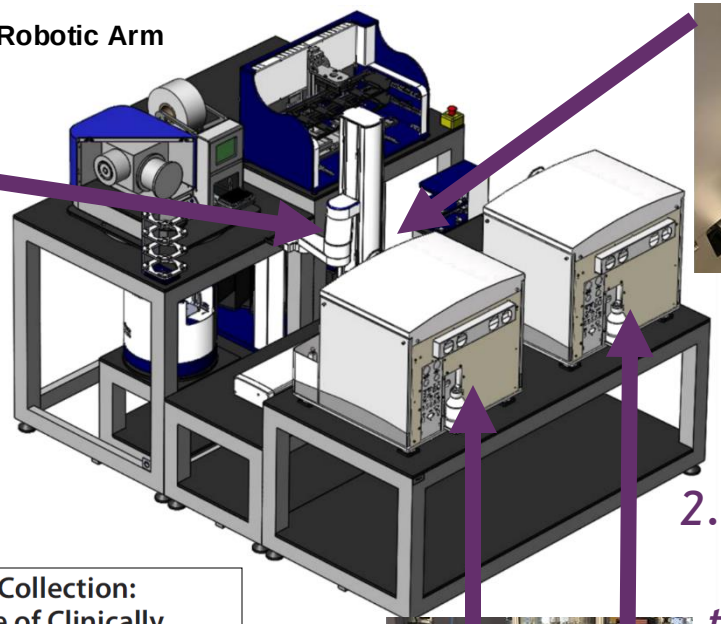


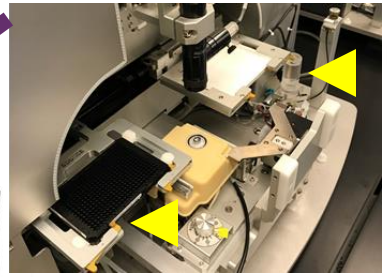


Translation Challenge: Rapid Discovery of Drug Combinations



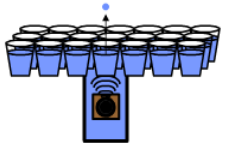
Robotic Arm





Destination Plate
(1536, screening)

Source Plate
(384, compounds)



1. Appropriate libraries

2. Automation/ screening technologies

3. Informatics platform

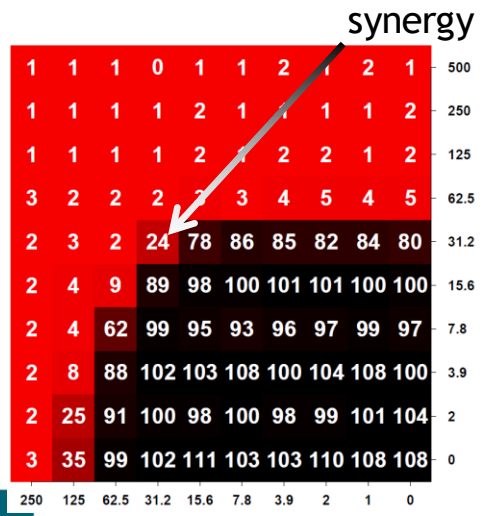
The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

Ruili Huang,* Noel Southall,* Yuhong Wang, Adam Yasgar, Paul Shinn, Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin†

Small-molecule compounds approved for use as drugs may be "repurposed" for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across human diseases, particularly for rare and neglected diseases, for which the cost and time required for development of a new chemical entity are often prohibitive. Previous efforts to build such a comprehensive collection have been limited by the complexities, redundancies, and semantic inconsistencies of drug naming within and among regulatory agencies worldwide; a lack of clear conceptualization of what constitutes a drug; and a lack of access to physical samples. We report here the creation of a definitive, complete, and nonredundant list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules amenable to high-throughput screening.

www.ScienceTranslationalMedicine.org 27 April 2011 Vol 3 Issue 80 80ps16

Acoustic Dispensers



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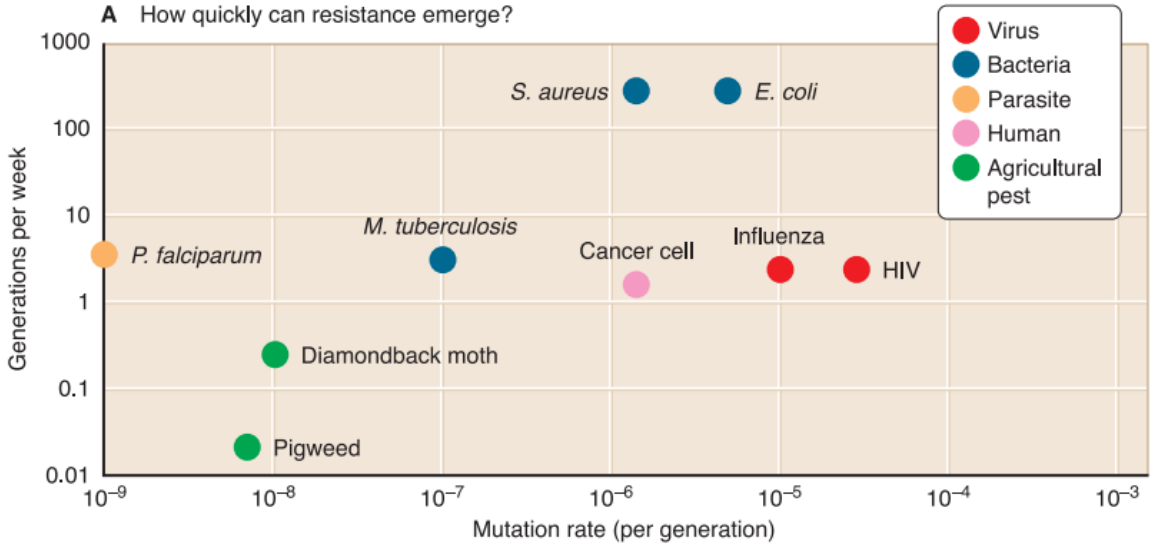
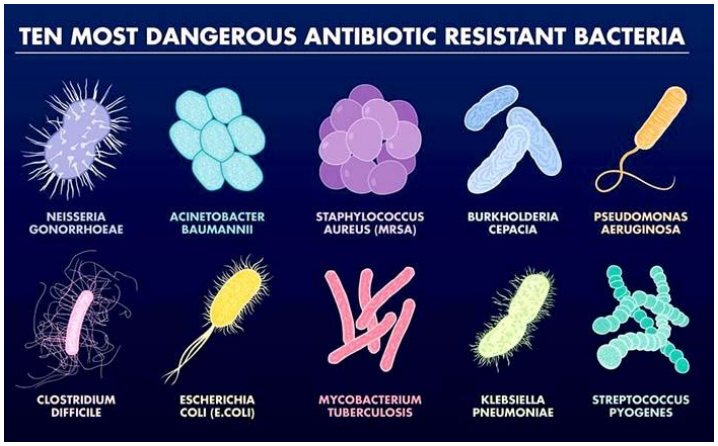
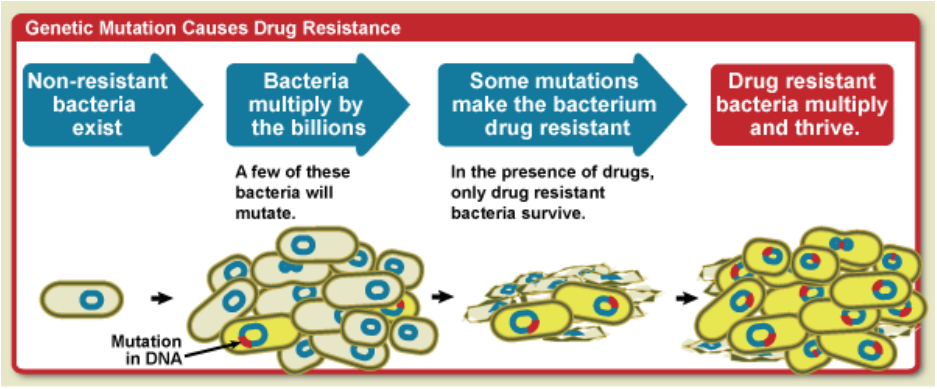
Application of Drug Combinations to Address Resistance







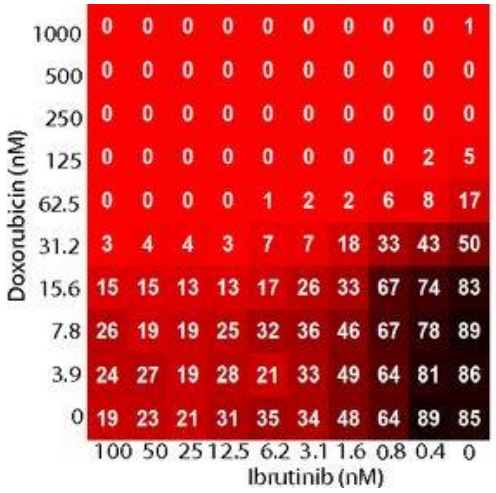
Dissemination of technology: combination screening to overcome drug resistance in cancer cells

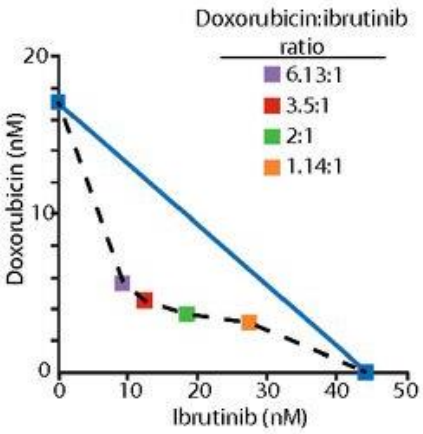
- Applied to ABC subtype of Diffuse Large B-Cell Lymphoma (ABC-DLBCL)
- Ibrutinib is a BTK inhibitor that has activity against ABC DLBCL
- Lead investigators: Craig Thomas (NCATS) and Louis Staudt (NCI)
- Study evaluated 459 drugs *in combination* with Ibrutinib
  - » 6 x 6 concentration-response "matrix blocks", validation in 10 x 10 concentration-response matrix blocks
- DNA-damaging agents identified as synergizing with Ibrutinib in killing ABC DLBCL cell lines
- **Dissemination:**
  - » Protocols
  - » Source code for dispense

High-throughput combinatorial screening identifies drugs that cooperate with ibrutinib to kill activated B-cell–like diffuse large B-cell lymphoma cells

Lesley A. Mathews Griner[a,1], Rajarshi Guha[a,1], Paul Shinn[a,1], Ryan M. Young[b,1], Jonathan M. Keller[a], Dongbo Liu[a], Ian S. Goldlust[a], Adam Yasgar[a], Crystal McKnight[a], Matthew B. Boxer[a], Damien Y. Duveau[a], Jian-Kang Jiang[a], Sam Michael[a], Tim Mierzwa[a], Wenwei Huang[a], Martin J. Walsh[a], Bryan T. Mott[a], Paresma Patel[a,c], William Leister[a], David J. Maloney[a], Christopher A. Leclair[a], Ganesha Rai[a], Ajit Jadhav[a], Brian D. Peyser[d], Christopher P. Austin[a], Scott E. Martin[a], Anton Simeonov[a], Marc Ferrer[a], Louis M. Staudt[b,2], and Craig J. Thomas[a,2]

[a]Division of Preclinical Innovation, National Institutes of Health Chemical Genomics Center, National Center for Advancing Translational Sciences, [b]Metabolism Branch, Center for Cancer Research, and [d]Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892; and [c]Basic Science Program, SAIC-Frederick, Inc., Chemical Biology Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD 21702



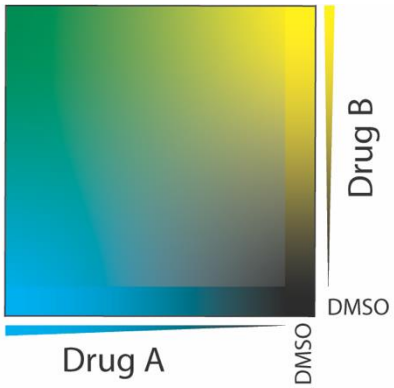


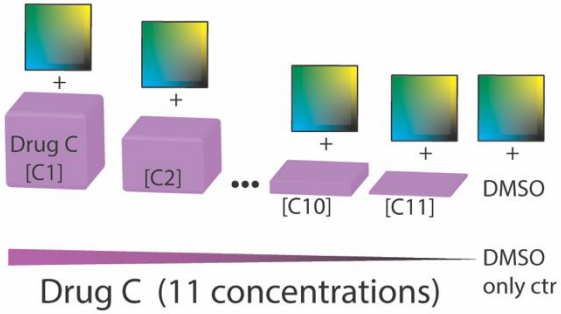
PNAS 111, 2349-2354

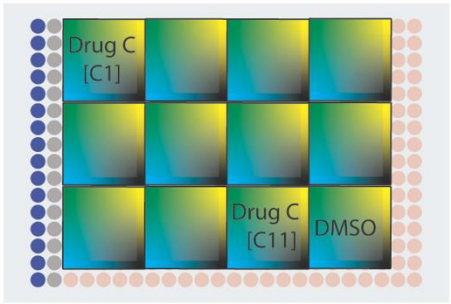
National Center for Advancing Translational Sciences

Example: triple drug combination screening to tackle resistance against artemisinin-based combination therapies in malaria

ACS Pharmacol. Transl. Sci. 2020, https://dx.doi.org/10.1021/acsptsci.0c00110?ref=pdf



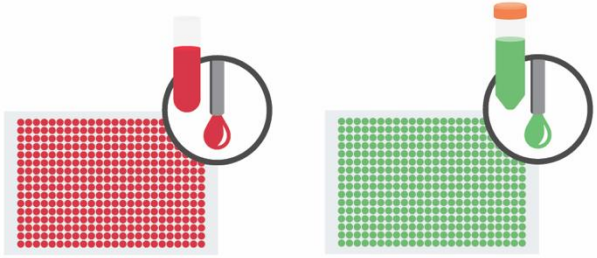


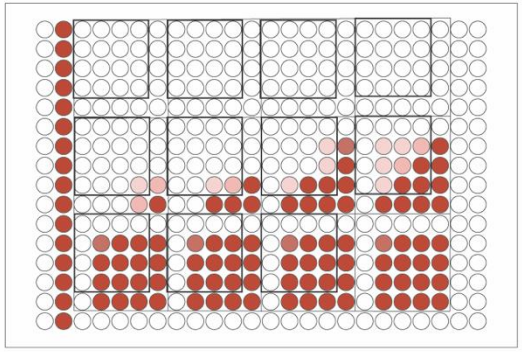


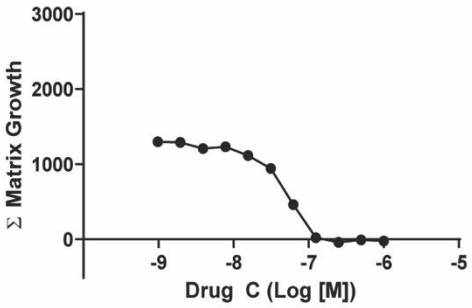
① Drugs A and B are acoustically dispensed in a 10x10-well matrix,12 replicate blocks per plate. Single drug resonses, bottom row (Drug A) and right column (Drug B).

② To each replicate block, serial dilutions of Drugs C is acoustically dispensed, with the final block serving as a DMSO control

③ Plate view of triple combination screening plate with positive control (artesunate, blue) and neutral controls (DMSO, grey) also shown.







④ Dispense *P. falciparum* and erythrocytes, incubate 72 hr

⑤ Dispense 2 μL of SYBRGreen1 and lysis solution, incubate overnight. Fluorescence quantified

⑥ Parasite proliferation response is normalized to artesunate and DMSO controls. For each concentration Drug C block, response of Drug A + Drug B wells is summed.

⑦ Triple drug response is analyzed as a function of Drug C concentration.

Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Revlimid (ViPOR) in Relapsed/Refractory B-cell Lymphoma

ClinicalTrials.gov Identifier: NCT03223610

Recruitment Status : Recruiting
First Posted : July 21, 2017
Last Update Posted : July 7, 2022

See Contacts and Locations

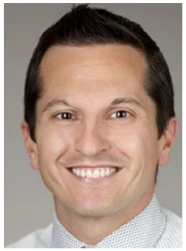
Sponsor:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
National Institutes of Health Clinical Center (CC) (National Cancer Institute (NCI))

ViPOR Regimen Is Safe, Shows Impressive Activity in Relapsed/Refractory DLBCL

December 21, 2020
Gina Mauro

December 21, 2020 — The 5-drug regimen of venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide showed a tolerable safety profile and encouraging antitumor activity with complete responses in patients with relapsed/refractory diffuse large B-cell lymphoma.


Christopher J. Melani, MD

The 5-drug regimen of venetoclax (Venclexta), ibrutinib (Imbruvica), prednisone, obinutuzumab (Gazyva), and lenalidomide (Revlimid; ViPOR) showed a tolerable safety profile and encouraging antitumor activity with complete responses (CRs) in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), according to phase 1b/2 findings that were presented during the 2020 ASH Annual Meeting and Exposition.

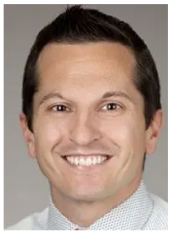
Results showed that of 52 evaluable patients, the best overall response was 71%, with a complete response (CR) rate of 52% and a 19% partial response (PR) rate. Specifically, in relapsed patients (n = 30), the objective response rate (ORR) was 83% with a 70% and 13% CR and PR rate, respectively. The ORR was 55% in refractory patients (n = 22), with a 27% CR rate and a 27% PR rate.

https://www.onclive.com/view/vipor-regimen-is-safe-shows-impressive-activity-in-relapsed-refractory-dlbcl

ViPOR Regimen Signals Benefit in Patients With Mantle Cell Lymphoma

February 7, 2022
Nichole Tucker

In an interview with Targeted Oncology, Christopher Melani, MD, discussed the ongoing ViPOR study exploring a Bruton's tyrosine kinase inhibitor and BCL2 inhibitor, and NF-κB survival pathway activating combination.


Christopher Melani, MD

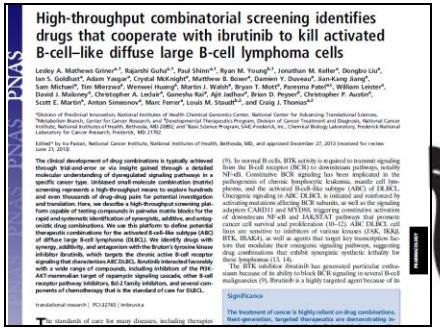
Treatment with the ViPOR regimen consisting of venetoclax (Venclexta), ibrutinib (Imbruvica), prednisone, and lenalidomide (Revlimid), has thus far appeared safe for use in patients with mantle cell lymphoma (MCL) and has demonstrated preliminary activity.

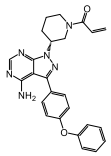
Results from the phase 1 portion of the ViPOR study (NCT03223610) were presented during the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition. Of the 11 patients who were treated, the ORR was 100% and the complete remission (CR) rate was 80%. Nine patients were evaluable for safety and no dose-limiting toxicities were observed. There were few grade 3 and 4 adverse events (AEs), but the hematologic grade 3/4 AEs included neutropenia (13%), anemia (11%), and thrombocytopenia (9%). The non-hematologic grade 3/4 AEs included hypokalemia (33%) along with fatigue, hypomagnesemia, elevated bilirubin, atrial fibrillation, lung infection, and syncope occurring in 11% of patients each.

https://www.targetedonc.com/view/vipor-regimen-signals-benefit-in-patients-with-mantle-cell-lymphoma

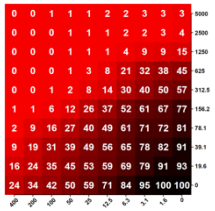
First matrix screen enables a translation journey in lymphoma

1st Matrix Paper
Feb, 2014

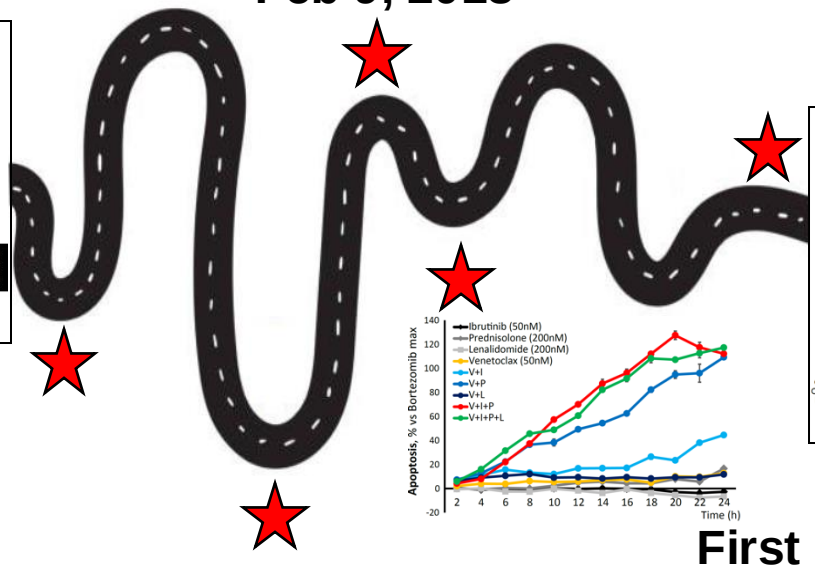




Ibrutinib
BTK
Inhibitor



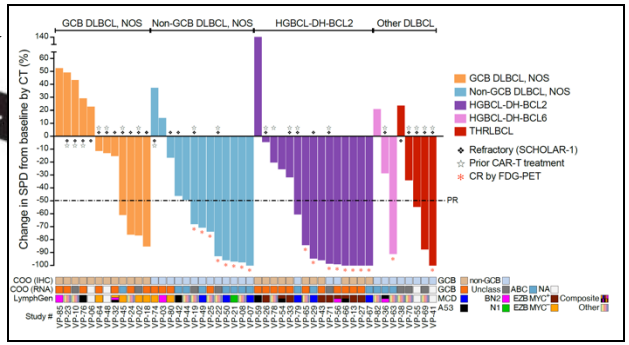
VIPOR Trial
Initiated
Feb 9, 2018



DA-TEDDI-R
Clinical Report
Published
June 2017

First MCTC
Experiment
March, 2020

VIPOR Clinical Study
Accepted for Publication
April 8, 2024



VIPOR: Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, Revlimid

The NEW ENGLAND JOURNAL of MEDICINE

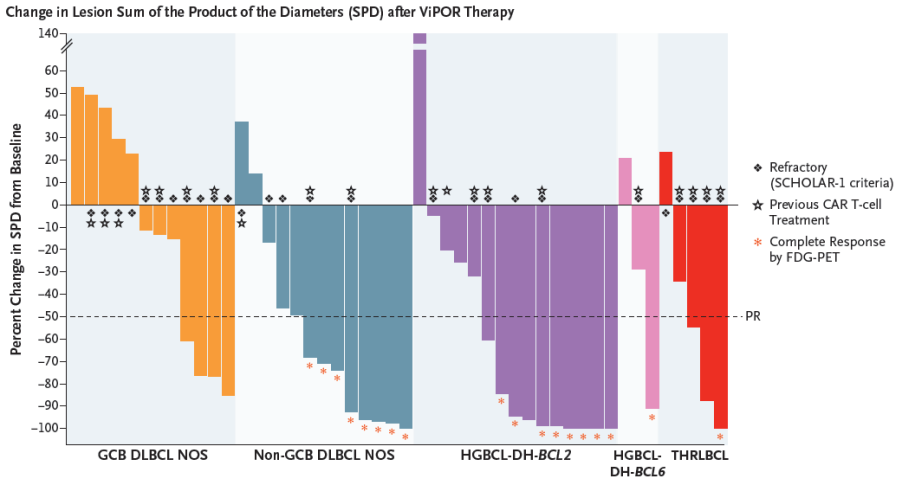
ESTABLISHED IN 1812 JUNE 20, 2024 VOL. 390 NO. 23

Combination Targeted Therapy in Relapsed Diffuse Large B-Cell Lymphoma

C. Melani, R. Lakhotia, S. Pittaluga, J.D. Phelan, D.W. Huang, G. Wright, J. Simard, J. Muppidi, C.J. Thomas, M. Ceribelli, F.A. Tosto, Y. Yang, W. Xu, T. Davies-Hill, S.D. Pack, C.J. Peer, O. Arisa, E. Mena, L. Lindenberg, E. Bergvall, C.A. Portell, R.J. Farah, S.T. Lee, A. Pradhan, C. Morrison, A. Tadese, A.M. Juanitez, C. Lu, A. Jacob, H. Simmons, W.D. Figg, S.M. Steinberg, E.S. Jaffe, M. Roschewski, L.M. Staudt, and W.H. Wilson

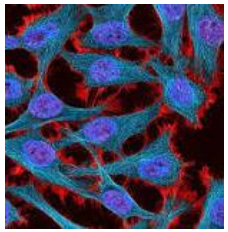
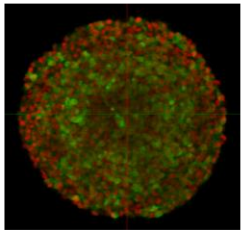
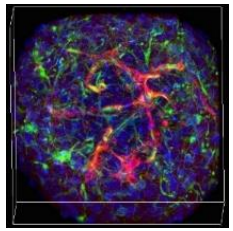
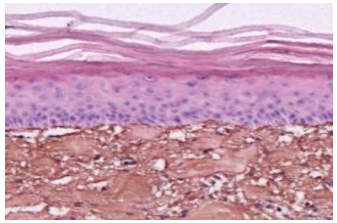
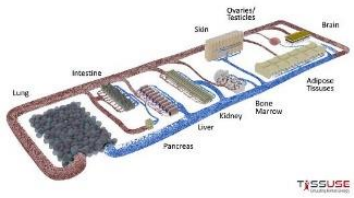
CONCLUSIONS

Treatment with ViPOR was associated with durable remissions in patients with specific molecular DLBCL subtypes and was associated with mainly reversible adverse events. (Funded by the Intramural Research Program of the National Cancer Institute and the National Center for Advancing Translational Sciences of the National Institutes of Health and others; ClinicalTrials.gov number, NCT03223610.)



Increasing the predictivity of *in vitro* assays: a continuum of 3D models of healthy and diseased tissues

2D | **Spheroids** | **Organoids** | **Printed Tissues** | **Organ-on-a-chip**

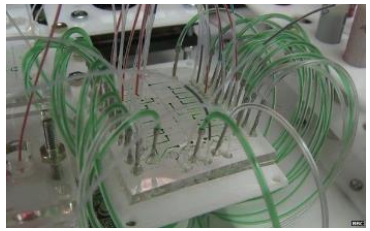






Physiological complexity

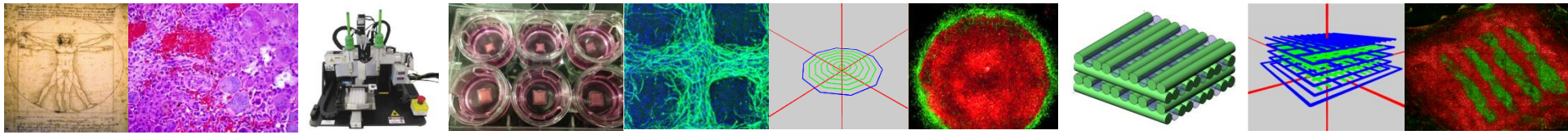
HTS compatibility







3D Tissue Bioprinting



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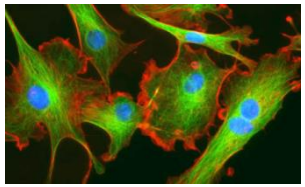
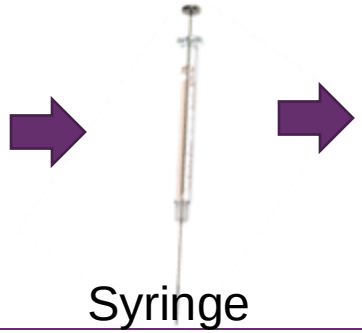
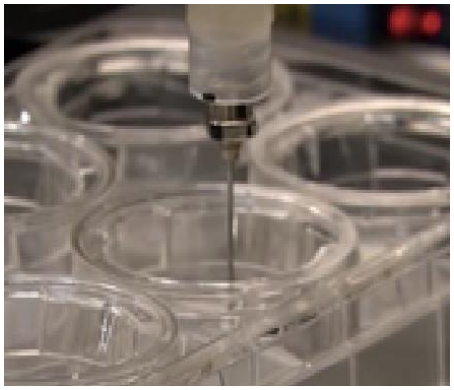
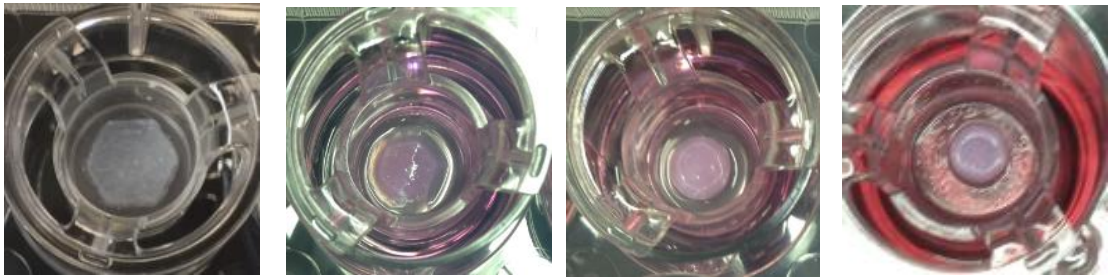




Gel Cells Syringe Printer

Hydrogel polymer is mixed with cells and loaded into syringe.





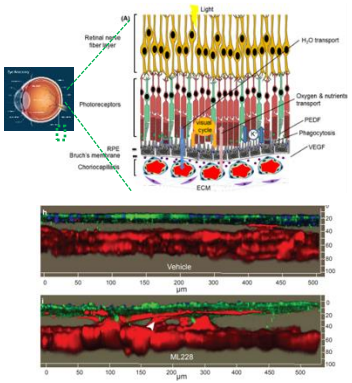
Printed construct 1 day 1 week 2 weeks

The printer “3D prints” the cell/gel mixture in a layer by layer approach.

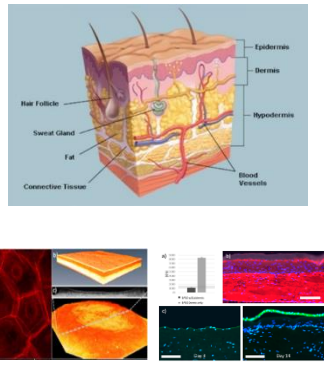
The printed construct is incubated to allow the cells to form a tissue, and to enable proper cell differentiation.

Current portfolio of engineered 3D tissue models

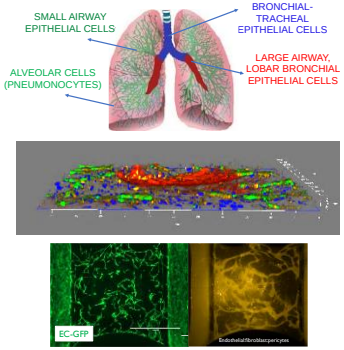
Retina



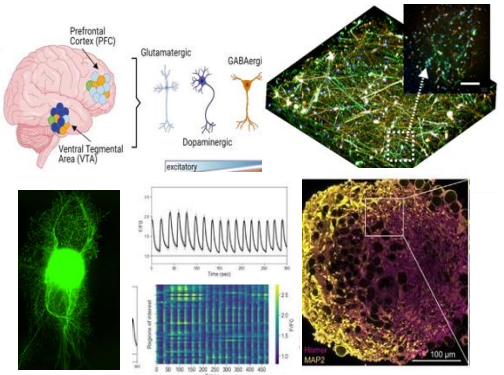
Skin



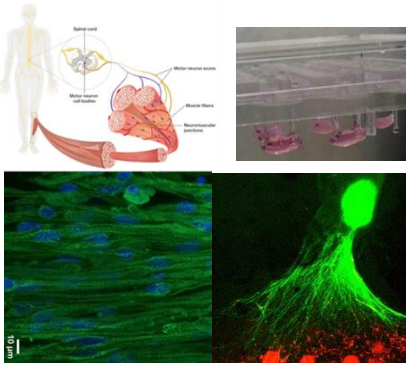
Lung



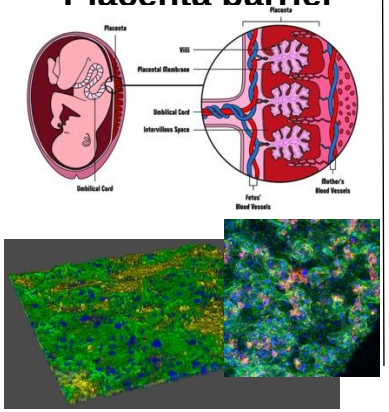
CNS/PNS



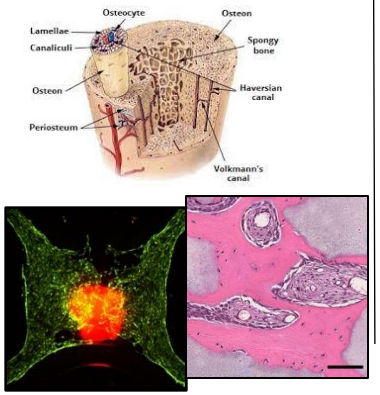
Muscle/ Neuromuscular Junction



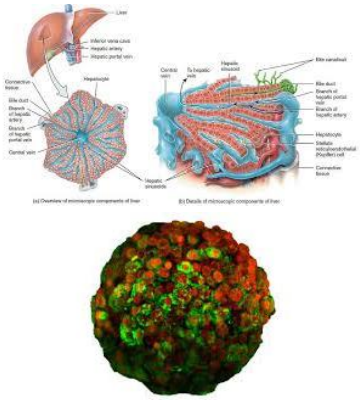
Placenta barrier



Bone



Liver

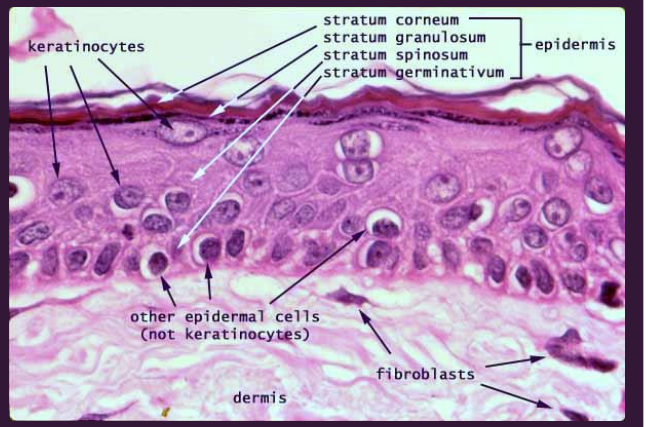


Program Director Marc Ferrer, Ph.D. https://ncats.nih.gov/bioprinting

National Center for Advancing Translational Sciences

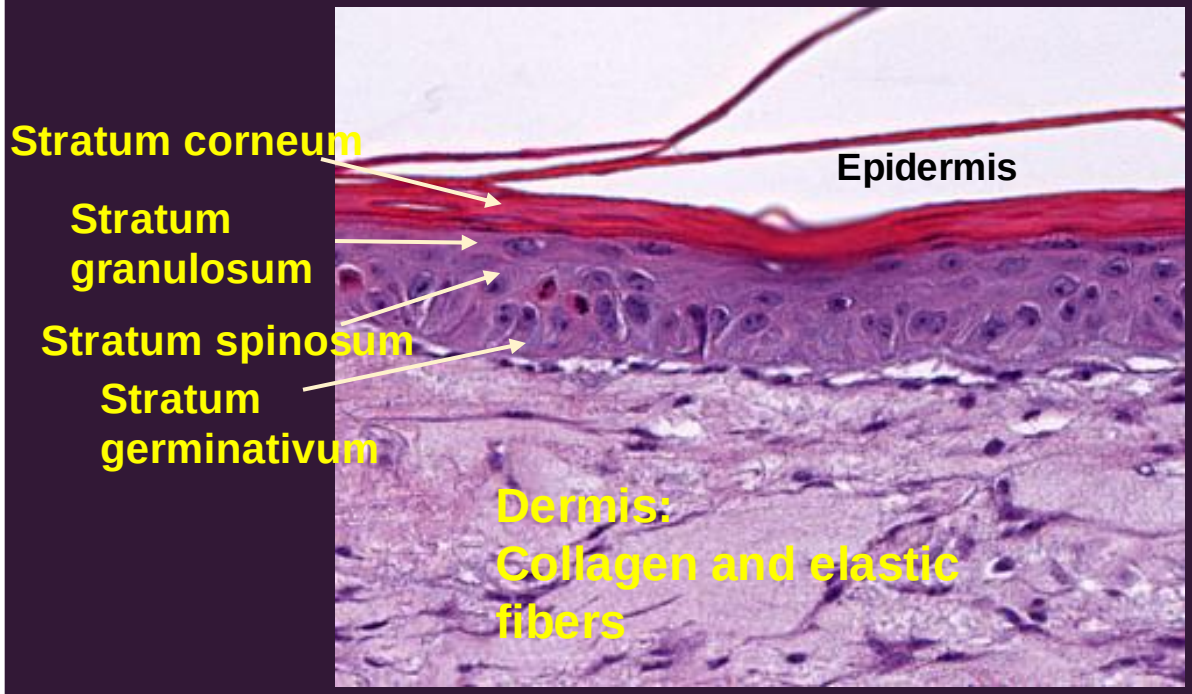
Skin biofabrication

Native Skin



http://www.siumed.edu/~dking2/intro/IN005b.htm

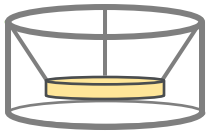
3D-Bioprinted Skin



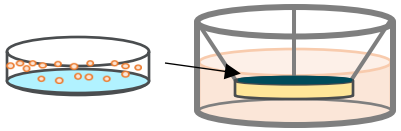
Generation of bioprinted skin tissues

Reconstructed human epidermis (RhE)

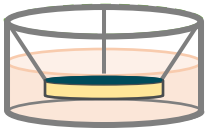
1. Coat the 96-well transwell insert membrane with collagen



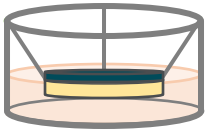
2. Add keratinocytes



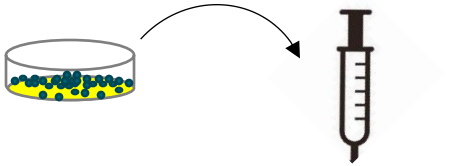
3. Submerge culture for 3 days



4. Air-liquid interface culture for 8 days



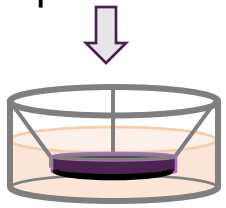
Full thickness skin tissue (FTS)



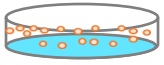
1. Suspend fibroblasts in bioprinting gel

2. Bioprint fibroblast bioink to a 3-layer U shape on bottom side of 96-well transwell insert membrane

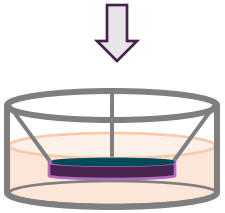
3. Add bioprinting gel to cover the U shape

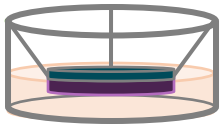


4. Submerge bioprinted tissue in medium for 7 days



5. Add keratinocytes and submerge culture for 3 days





6. Air-liquid interface culture for 8 days

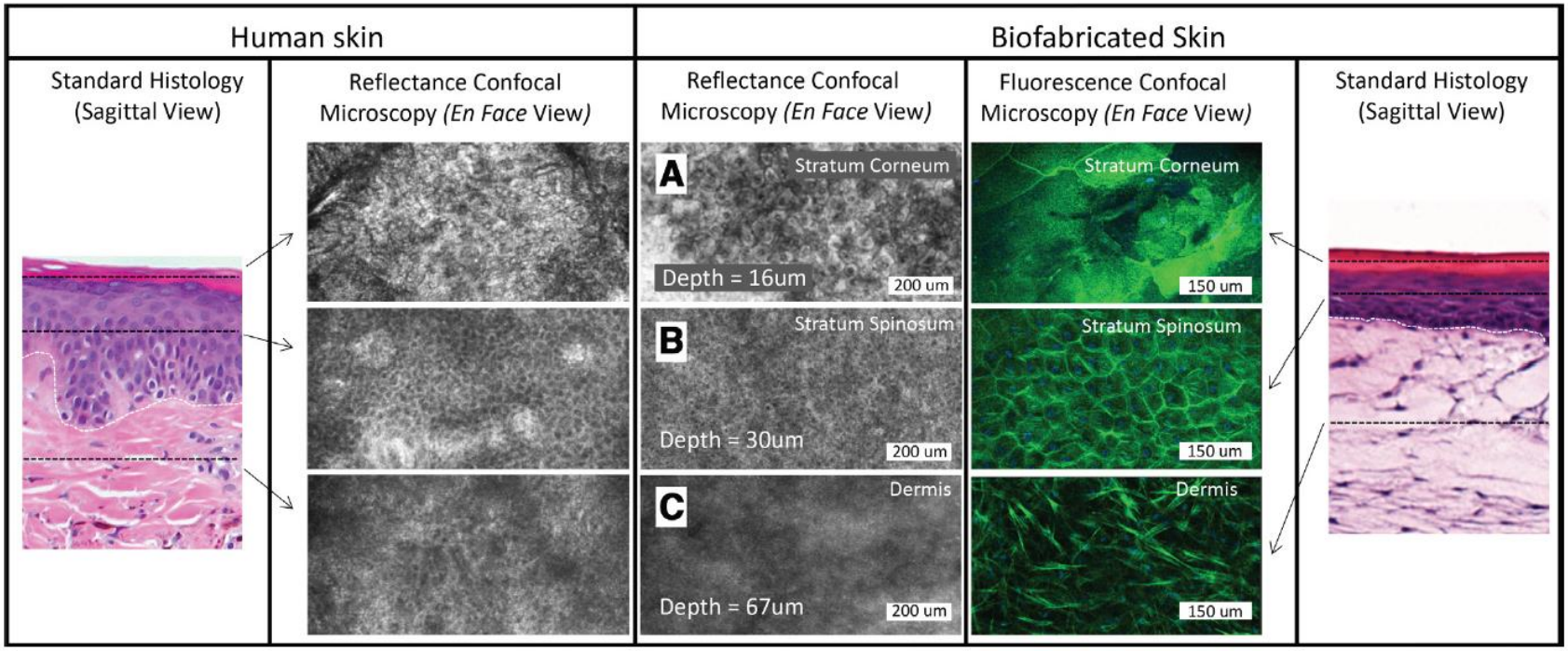
Z Wei and X Liu et al., Frontiers in Bioengineering and Biotechnology (2020)

NIH National Center for Advancing Translational Sciences

www.oncotarget.com Oncotarget, 2020, Vol. 11, (No. 27), pp: 2587-2596

Research Paper

A 3D biofabricated cutaneous squamous cell carcinoma tissue model with multi-channel confocal microscopy imaging biomarkers to quantify antitumor effects of chemotherapeutics in tissue



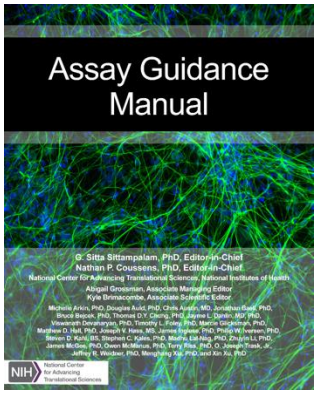
Collaboration between NCATS (Marc Ferrer) and Rockefeller University (Daniel Gareau)

National Center for Advancing Translational Sciences

Where do I go for more information about assay development?

National Center for Advancing Translational Sciences

Sharing internal know-how: Assay Guidance Manual (47 chapters/ 1,338 printed pages)



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Website: https://ncats.nih.gov/expertise/preclinical/agm

Email us: NCATS_AGM_Editors@mail.nih.gov

Facebook: www.facebook.com/assayguide

Linkedin: www.linkedin.com/groups/7437344

https://ncats.nih.gov/agm-video

August 7th Videos

1. Austin, CP: **Welcome to the Assay Guidance Manual (AGM) Workshop**
2. Coussens, NP: **Strategies for Assay Selection & Robust Biochemical Assays**
3. Riss, T: **Treating Cells as Reagents to Design Reproducible Screening Assays**
4. Trask, OJ: **Assay Development Considerations for High Content Imaging**
5. Auld, DS: **Studies in Mechanisms and Methods in Assay Interferences**
6. Dahlin, JL: **Assay Interference by Chemical Reactivity**
7. Chung, TDY: **Basic Assay Statistics, Data Analysis & Rules of Thumb**
8. Devanarayan, V: **Reproducibility & Differentiability of Potency Results**
9. Sittampalam, GS: **Avoiding Artifacts & Interferences in Assay Operations**

March 26-27th Videos

1. Austin, CP: **Welcome to the Assay Guidance Manual (AGM) Workshop**
2. Coussens, NP: **Robust Assays Define Success in Preclinical Research**
3. Lal-Nag, M: **Target Identification & Validation in Translational Discovery**
4. Foley, TL: **Development & Validation of Cell-Based and Biochemical Assays**
5. Riss, T: **Treating Cells as Reagents to Design Reproducible Screening Assays**
6. Trask, OJ: **Assay Development for HCS & Best Practices for 3D HCS**
7. Roth, KD: **Mass Spectrometry for Drug Screening and Lead Optimization**
8. Dahlin, JL: **Bioassay Interference by Aggregation and Chemical Reactivity**
9. Patnaik, S: **Lead Selection and Optimization by Medicinal Chemistry**
10. Xia, M: ***In Vitro* Toxicological Testing Using a qHTS Platform**
11. Xu, X: ***In Vitro* Assessment of ADME Properties of Lead Compounds**
12. Kahl, SD: **Statistical Design of Experiments for Assay Development**
13. Guha, R: **Pharos Application to Target Evaluation and Drug Discovery**
14. Weidner, JR: **Assay Operations: Keeping Assays Robust and Reproducible**

NIH National Center for Advancing Translational Sciences

Assay Guidance Manual Training Workshops

- Online Training Modules
- Upcoming Workshops
- Past Workshops

NCATS offers a variety of Assay Guidance Manual (AGM) training workshops throughout the year designed to share best practices and advice on robust assay design, development and implementation for researchers involved in the drug discovery process.

Online Training Modules

NCATS offers an online AGM training workshop in addition to the in-person AGM workshops held throughout the year. The online training workshop also features experts sharing best practices and expert advice on assay design, development and implementation. View the video modules.

NIH National Center for Advancing Translational Sciences

Assay Guidance Workshop on 3D Tissue Models for Antiviral Drug Development

Tue Jun 7, 11:00 AM - Wed Jun 8, 5:15 PM (EDT)

Zoom

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THIS EVENT HAS ENDED

Video of the workshop is available at the links below:

Assay Guidance Workshop on 3D Tissue Models for Antiviral Drug Development (Day 1) (June 7, 2022)

Assay Guidance Workshop on 3D Tissue Models for Antiviral Drug Development (Day 2) (June 8, 2022)

About the Workshop

The National Center for Advancing Translational Sciences (NCATS) Assay Guidance Manual (AGM) program is hosting a two-day workshop that will cover a broad range of critical concepts, including practical approaches and best practices, for developing standardized 3D cellular assays with the hope of helping the community to successfully develop therapeutics for future pandemic threats. This workshop is jointly organized by NCATS, the National Institute of Allergy and Infectious Diseases (NIAID) and the Bill & Melinda Gates Foundation. The overall goal of this workshop is to help scientists establish robust, reproducible, scalable, consistent, advanced 3D tissue models to study pandemic threat viruses.

https://ncats.nih.gov/expertise/preclinical/agm/training

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