Division of Systems Biology

Presented by: William B Mattes, PhD, DABT

NCTR, U.S. Food and Drug Administration

Division Staff

- Government Positions (# full time employees)
  - Research Scientists, Staff Fellows & Visiting Scientists : 21
  - Support Scientists : 9
  - Administrative : 3
  - FDA Commissioner Fellows: 0
- ORISE Post Docs, Graduate Students, etc.: 4

- Total = 37 staff members

Outreach

- Collaborations with
  - NCTR divisions
    - All
  - FDA regulatory centers
    - All
  - Government agencies
    - NTP, NIH (NCATS), VA, USDA, NIST
  - Universities
    - UAMS, MCW, UNC, Univ. Pitt., OSU

Collaborations of Note

- CDER
  - Refinement of iPSC-cardiomyocyte models for cardiotoxicity prediction
  - *In vitro* toxicity assessment of opioids on neural precursor cell development
- CBER
  - Microphysiological system (MPS) model of testis function
  - Metabolomics in MAIT knockout mice
- USDA
  - *E. coli* detection and quantitation

Division of Systems Biology

- **Mission:**

  To address problems of food, drug, and medical-product safety using systems biology approaches and innovative technology.

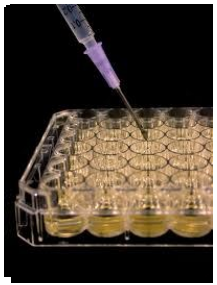
Why Systems Biology?

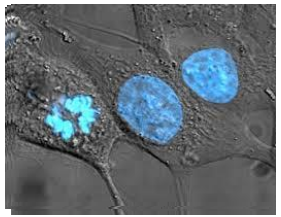
- Tools and approaches to bridge:
  - Non-clinical models
    - adverse events and individual responses

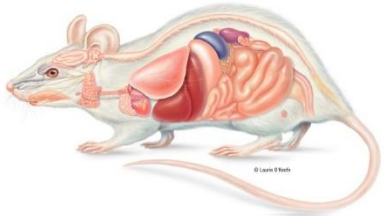
    -- with ---
  - Clinical settings
    - adverse events and individual responses

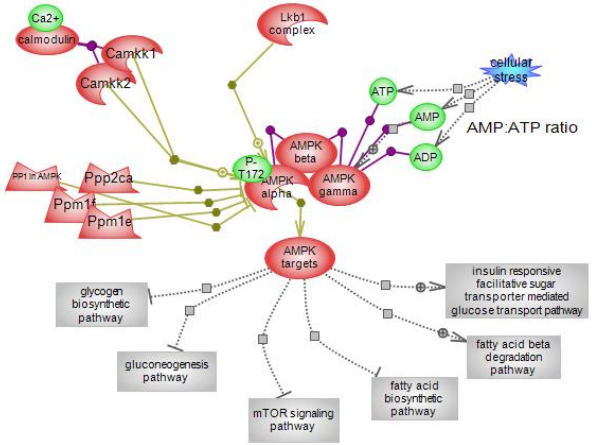
  - “Translational Toxicology”
  - “Precision Safety Assessment”

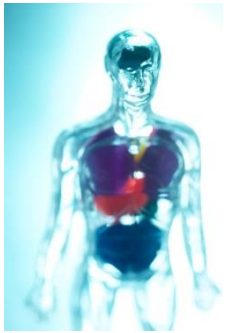
Systems Thinking



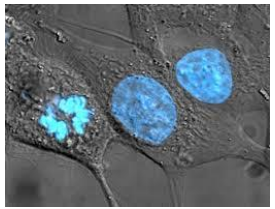


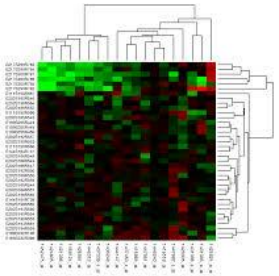




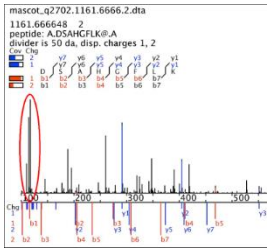


Systems Tools

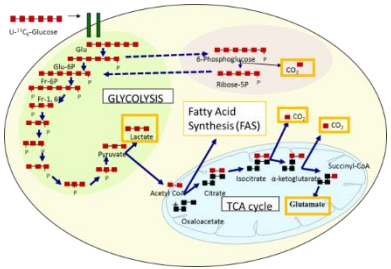




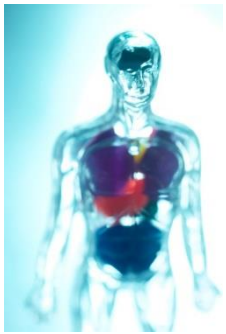
Transcriptomics



Proteomics



Metabolomics



Division of Systems Biology

- Goals
  - Translational prognostic and/or predictive biomarkers of hepatotoxicity and cardiotoxicity
  - Mechanistic basis for species, tissue, sex, and sub-population specificity in drug toxicity
  - *In vitro* models for better evaluation of reproductive, developmental, and clinical toxicity
  - *In silico* models for predicting relevant toxicities
  - Robust technologies for pathogen detection and outbreak characterization

Division of Systems Biology

- Strategies
  - Explore classes of drugs with known toxicities: such as anthracyclines, acetaminophen, tyrosine kinase inhibitors
  - Characterize systems biology effects with state of the art tools: mRNA and miRNA transcriptomics, epigenomics, metabolomics, proteomics
  - Integrate data with systems biology informatics accounting for species, tissue, sex, and sub-population differences
  - Incorporate innovative *in vitro*, computational and instrumental technology

Division of Systems Biology

- General Themes
  - Translational Safety Biomarkers and Mechanisms
  - Alternative Models to Assess Drug Safety
  - Technology to Assess Food Safety
  - Computational Modeling
  - Cross-Species Predictions

With an eye toward application in use and evaluation of FDA-regulated products

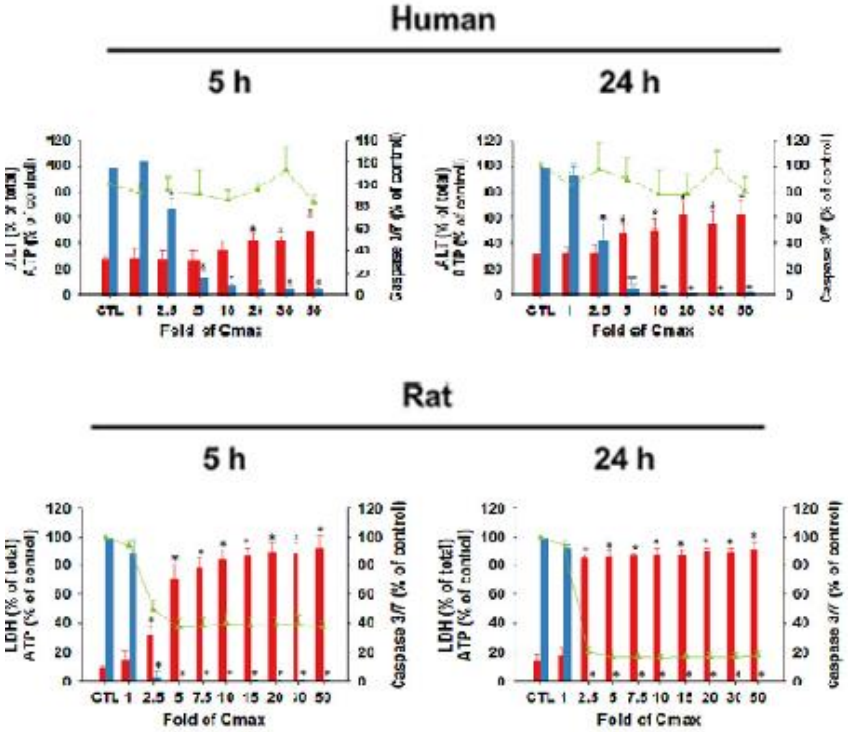
Top Accomplishments During the Last 5 Years

- Cytotoxicity of 34 FDA approved small-molecule kinase inhibitors in primary rat and human hepatocytes
    - Zhang, J., et al. (2018). *Toxicol Lett* **291: 138-148.**
- Immune response proteins as predictive biomarkers of doxorubicin-induced cardiotoxicity in breast cancer patients.
    - Yu, L. R., et al. (2018). *Exp Biol Med (Maywood)* **243(3): 248-255.**

Top Accomplishments During the Last 5 Years

- Why are most phospholipidosis inducers also hERG blockers?
  - Slavov, S., et al. (2017). *Arch Toxicol* **91(12): 3885-3895.**
- Sex and age differences in liver microRNAs expression during the life span of F344 rats
  - Kwekel, J. C., et al. (2017). *Biol Sex Differ* **8: 6.**
- Level 2 validation of a flow cytometric method for detection of Escherichia coli O157:H7 in raw spinach
  - Williams, A. J., et al. (2015). *Int J Food Microbiol* **215: 1-6.**

Human vs. Rat Hepatotoxicity

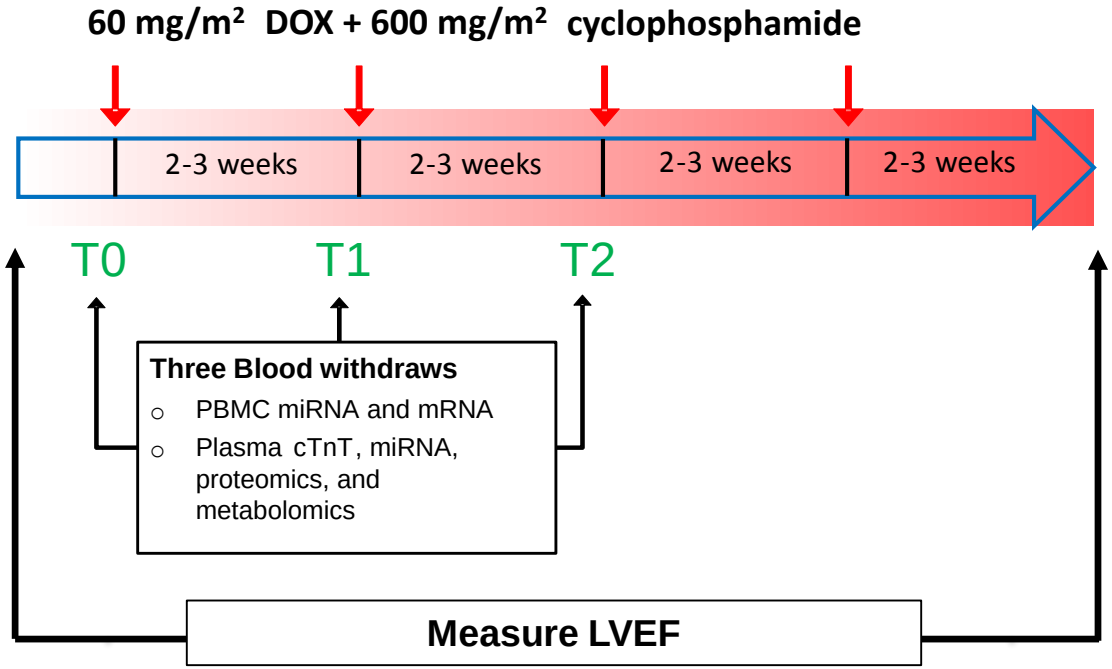


The tyrosine kinase inhibitor (Tki) Sorafenib is more toxic to rat hepatocytes than human hepatocytes

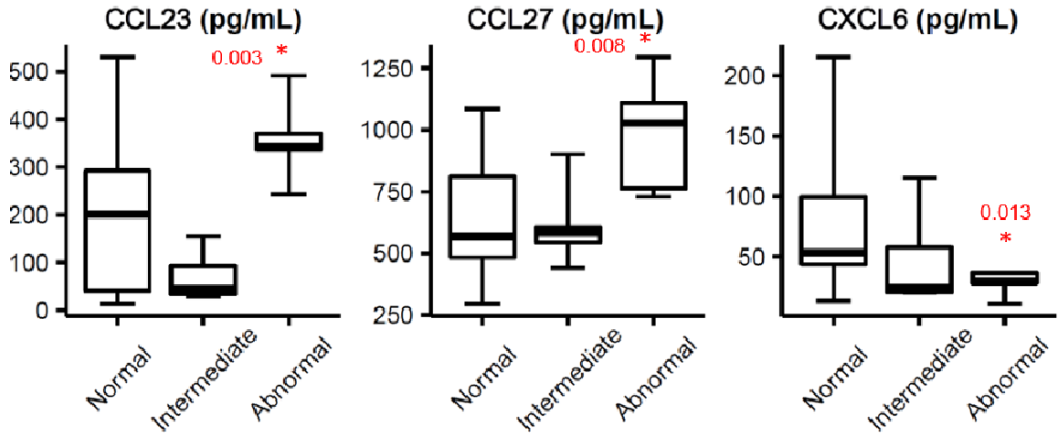
ALT ATP

Doxorubicin Study Design

100 breast cancer patients receiving DOX

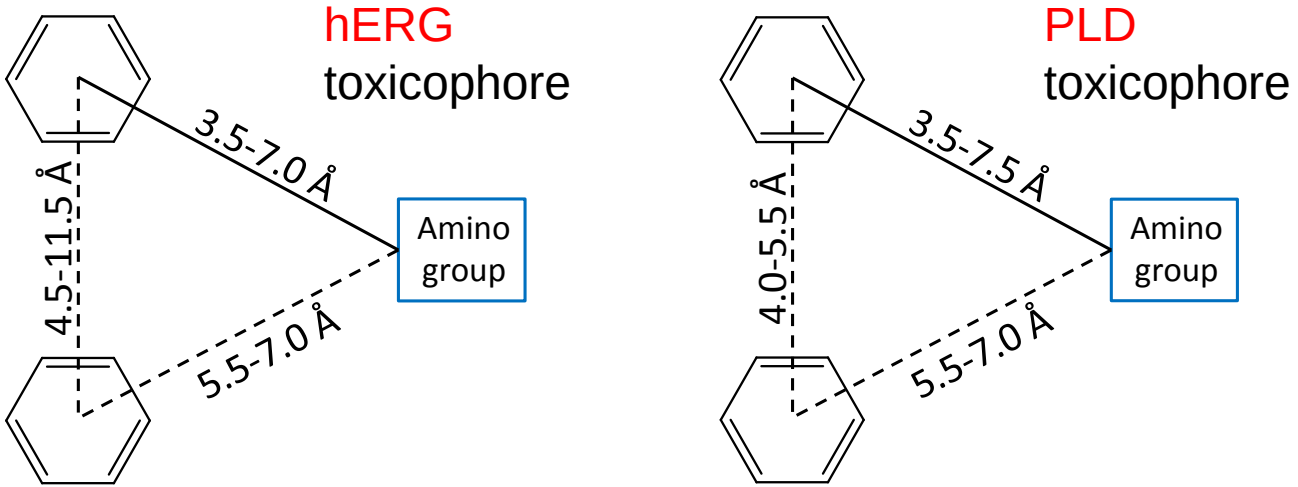


Plasma Proteins Predictive of Doxorubicin Cardiotoxicity



The levels of these three cytokines (CCL23, CCL27, and CXCL6) measured at time 0 (before treatment) are predictive of a patient's potential for treatment – induced cardiac dysfunction

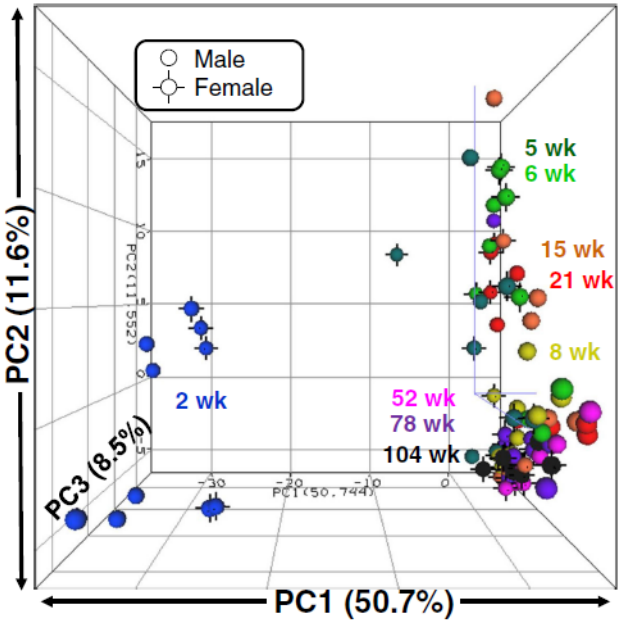
SDAR Modeling of hERG and PLD



hERG and PLD toxicophores.

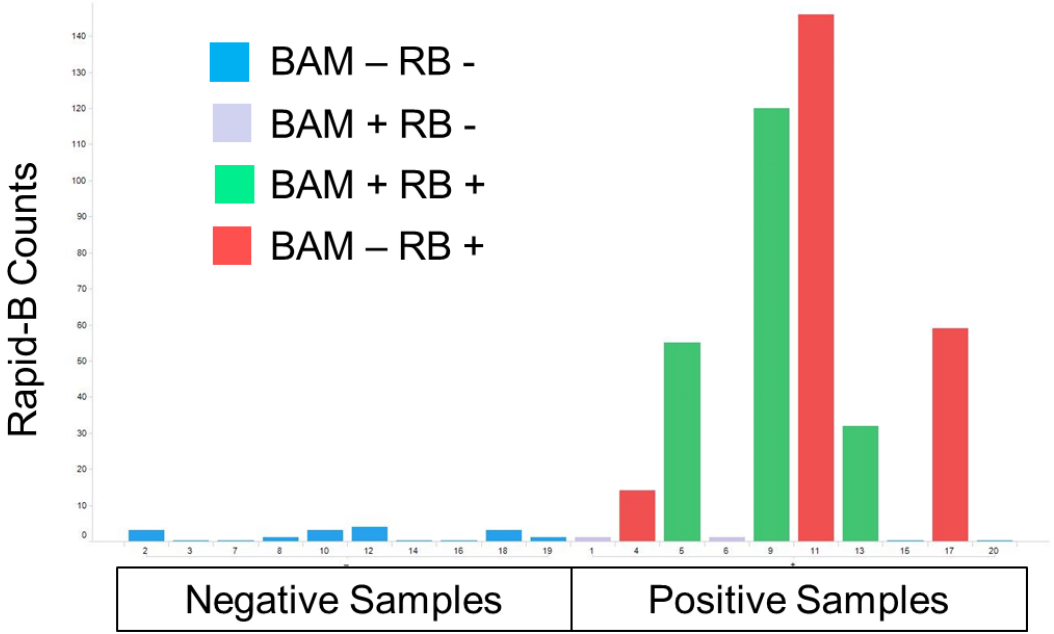
The PLD toxicophore is a subset of the hERG toxicophore!

Sex and Age-Specific Liver miRNAs



Rats of different sex and ages have distinct populations of certain microRNAs, which predict functional pathways that may underlie individual susceptibilities to liver toxicity and disease.

Rapid-B Detection of *E. coli* O157:H7 in Raw Spinach



Examples of Current Projects

- Rat model of transient and adaptive responses to hepatotoxicity
  (collaboration with CDER, UNC, Lilly)
- Evaluation of biomarkers predictive of anthracycline-induced cardiotoxicity in pediatric cancer patients
  (collaboration with CDER and ACH)

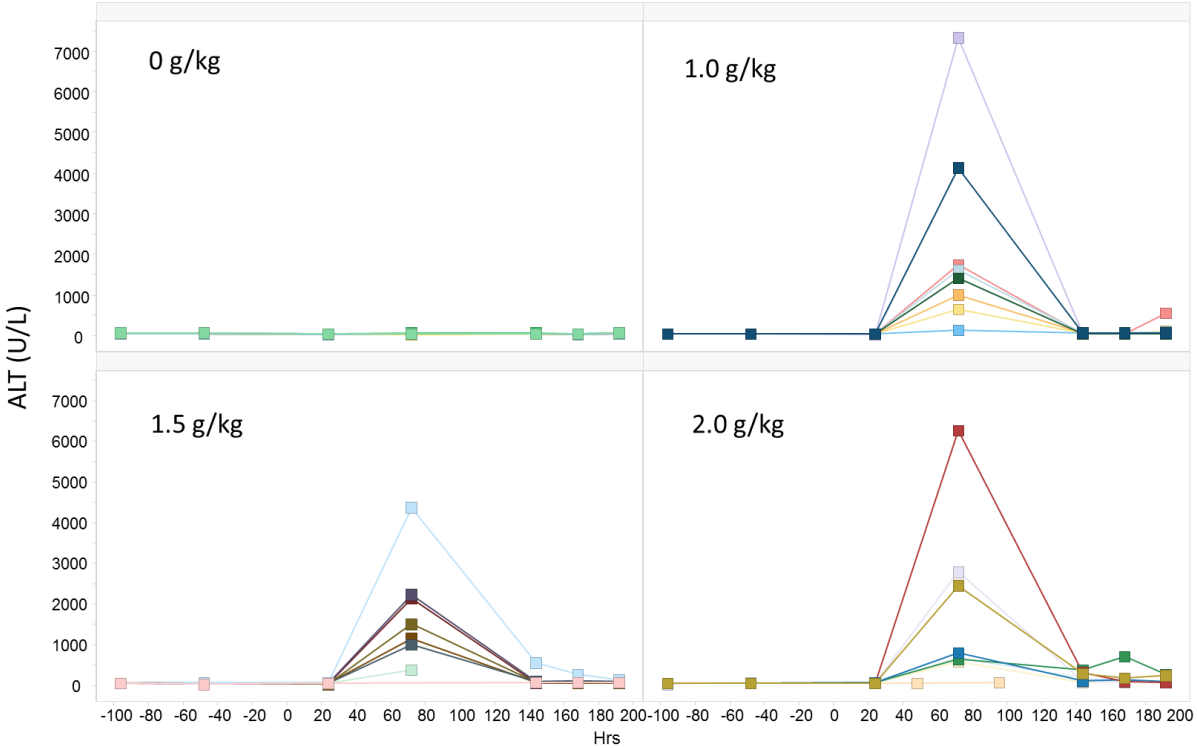
Examples of Current Projects

- Matrix-assisted laser desorption ionization imaging mass spectrometry (MALDI IMS) of opioids and neurotransmitters in rat brains
- Prediction of tyrosine kinase inhibitor (TKI) induced cardiotoxicity using induced pluripotent stem cell derived cardiomyocytes (collaboration with MCW)

Examples of Current Projects

- Exploration of a microfluidic system (MPS) with luminal structure for *in vitro* mouse spermatogenesis (Collaboration with CBER)

Rat Model of Transient Hepatotoxicity



Serum ALT

Transiently and idiosyncratically increased by acetaminophen treatment in Sprague-Dawley rats (Coloring by individual animal ID)

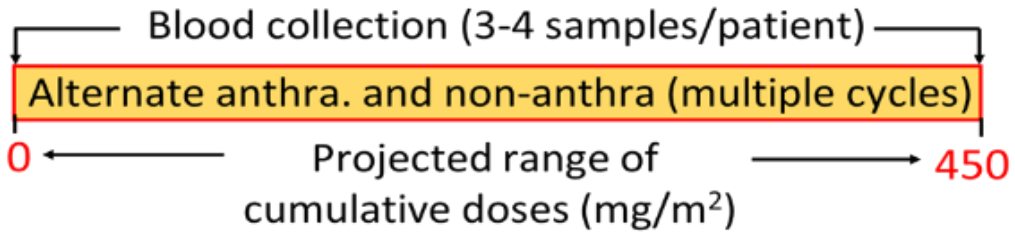
Replicates what is seen clinically

Most treated rats had only mild liver necrosis after sacrifice

Biomarker Study in Pediatric Patients

Proposed Study Design

- Twenty pediatric oncology patients (< 20 years of age)
- Any malignancy
- Any anthracycline (anthra.), any stage of therapy, any level of prior anthra. exposure
- Blood sample (3 mL) collected at the beginning and at the end of anthra. and non-anthra. treatment cycle

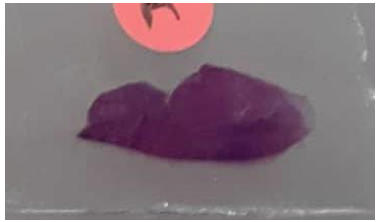


Clinical Markers to Explore

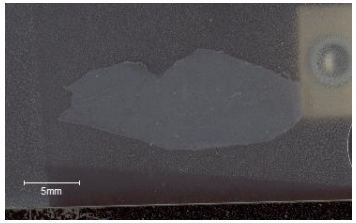
Literature	Canonical Name	UniProt
NT-prBNP	natriuretic peptides B preproprotein	P16860
PIGF	phosphatidylinositol glycan anchor biosynthesis class F	Q07326
GDF-15	growth differentiation factor 15	Q99988
sFlt1	fms related tyrosine kinase 1	P17948
hs-CRP	C-reactive protein	P02741
H-FABP	fatty acid binding protein 3	P05413
galectin-3 (Gal-3)	galectin 3	P17931
soluble ST-2	interleukin 1 receptor like 1	Q01638
myeloperoxidase	myeloperoxidase	P05164
CCL23	C-C motif chemokine ligand 23	P55773
BSP	Bone sialoprotein 2	P21815
CD177	CD177 antigen	Q8N6Q3
vWF	von Willebrand factor	P04275
TnI	troponin I3, cardiac type	P19429
NOTCH1	NOTCH1	P46531

MALDI IMS of Neurotransmitters from a Mouse Brain

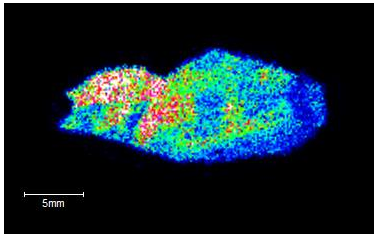
H&E



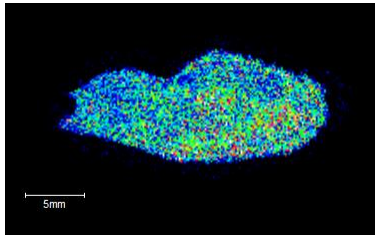
Optical Image



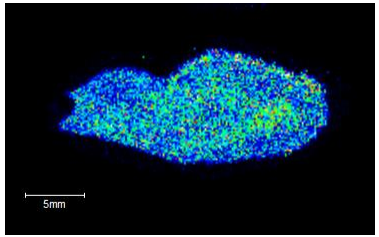
GABA m/z 104.18



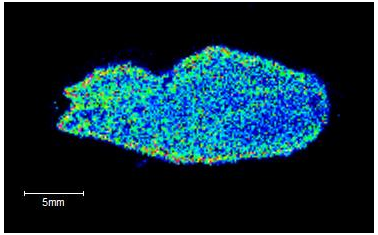
Glutamate m/z 148.06

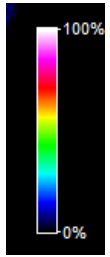


Acetylcholine m/z 147.17

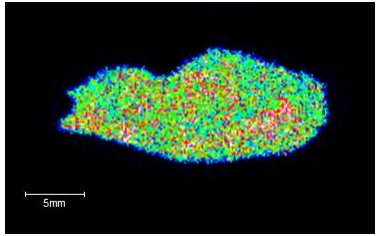


Epinephrine m/z 184.05

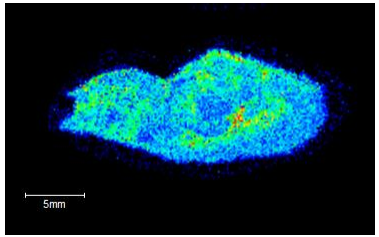




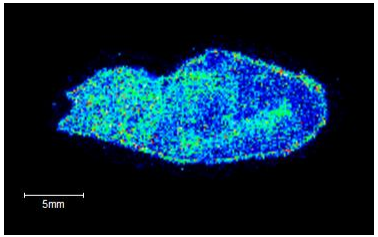
Norepinephrine m/z 170.01



Tryptophan m/z 205.23



Isoleucine/leucine m/z 132.13



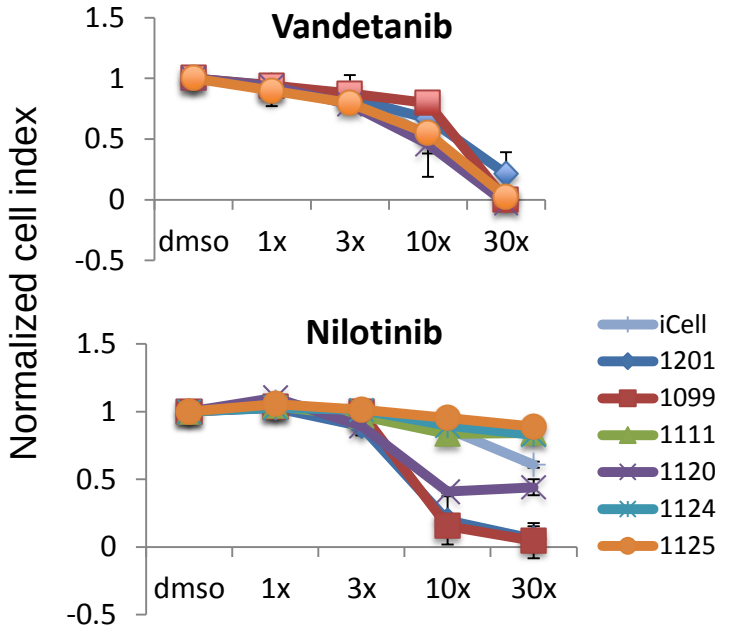
Human Stem-Cell Model of Individual Sensitivities to Chemotherapy

HyperGEN – NHLBI Family Blood Pressure Program:

250 iPSC lines and Cardiomyocytes (iPSC-CMs)

- African-American and Caucasian Cohort
- Phenotyping: Cardiovascular phenotypes and risk factors
- Family-based ascertainment
- Whole Exome Sequencing data available

- Several chemotherapeutic kinase inhibitors (KIs) tested in cell lines from different individuals
- Some KIs are similarly toxic to all cell lines
- Other KIs (e.g., Nilotinib) are toxic only to certain cell lines
- Potential for facilitating precision medicine!



Testis – Microphysiological System

A Microfluidic Method to Mimic Luminal Structures in the Tumor Microenvironment

José A. Jiménez-Torres, David J. Beebe, and Kyung E. Sung

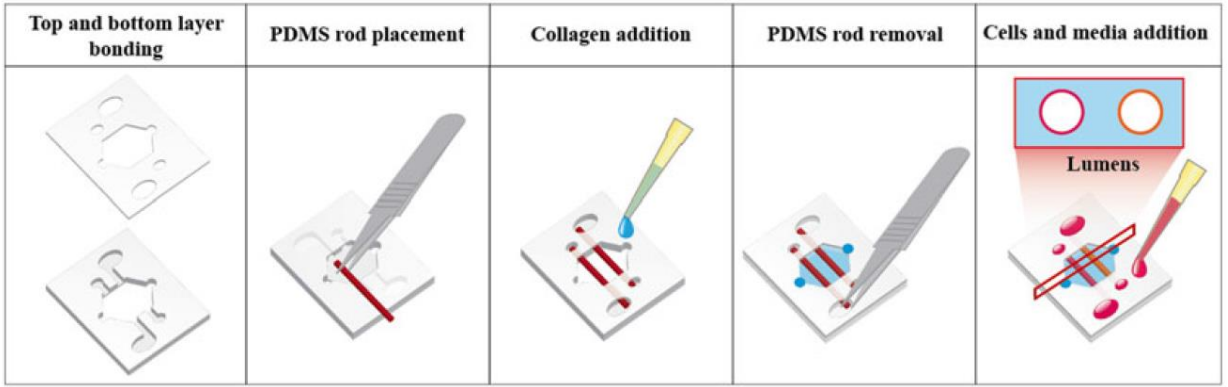


Fig. 3 Device assembly. First the device top and bottom layers are bonded together, followed by PDMS rods placement in the chamber. After performing the coatings described in Subheading 3.3, **step 5**, ECM gel is added and polymerized. PDMS rods are removed revealing the lumens that are lined with cells

Future Directions

- Further development of:
  - MALDI-IMS for detecting neuropharmacology impact
  - Expansion of transient hepatotoxicity model for biomarker discovery
  - Characterization of individual iPSC-CM lines for screening

- Single-cell RNAseq analysis?
  - Differences in individual cell responses to drugs
    - Explanation for focal lesions?

Feedback Requested

- For the approaches we are currently advancing (e.g., MALDI-IMS, MPS, iPSC-cells) are there areas we should explore other than those mentioned?
  - E.g. Whole-body MALDI imaging of drug / metabolites in rodents and/or zebrafish

- What developments (e.g., technology) on the horizon that would impact FDA are we missing?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