Division of Systems Biology

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NCTR, FDA

The views presented do not necessarily reflect those of the FDA.

Division Staff

- **Government Positions — Number of Full Time Employees (FTE)**
  - Research Scientists, Staff Fellows & Visiting Scientists : 23 FTE
  - Support Scientists : 11 FTE
  - Administrative : 3 FTE
  - FDA Commissioner Fellows: 0 FTE

- **ORISE Post Docs, Graduate Students, etc.:** 7 staff members

- **Total staff members** = 49

Outreach

- Collaborations with :
  - NCTR divisions
    - Biochemical Toxicology, Bioinformatics and Biostatistics, Genetic and Molecular Toxicology, Microbiology, Neurotoxicology
  - FDA regulatory centers
    - CDER, CDRH, CBER, CFSAN
  - Government agencies
    - NTP, NIH, VA
  - Universities
    - UAMS, MCW, Univ. Pitt., OSU, etc

Collaborations of Note

- CDER
  - Tyrosine Kinase Inhibitor (TKI) Systems Toxicology
  - Immune cell effects in a mouse obesity model
- CDRH
  - Aptamer technology
- CFSAN
  - Listeria detection and quantitation

Division of Systems Biology

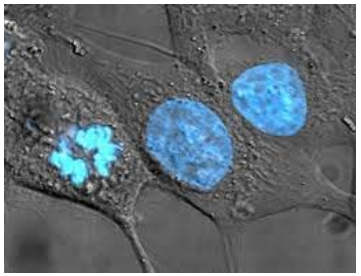
- Mission
  - *To address problems of food, drug, and medical product safety using systems biology approaches and innovative technology*

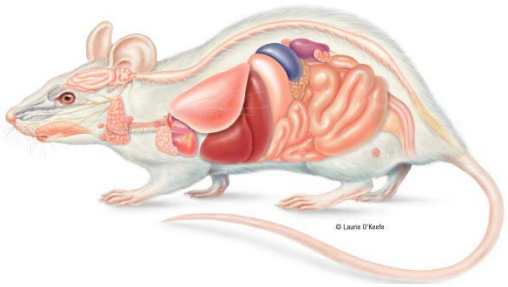
Why Systems Biology?

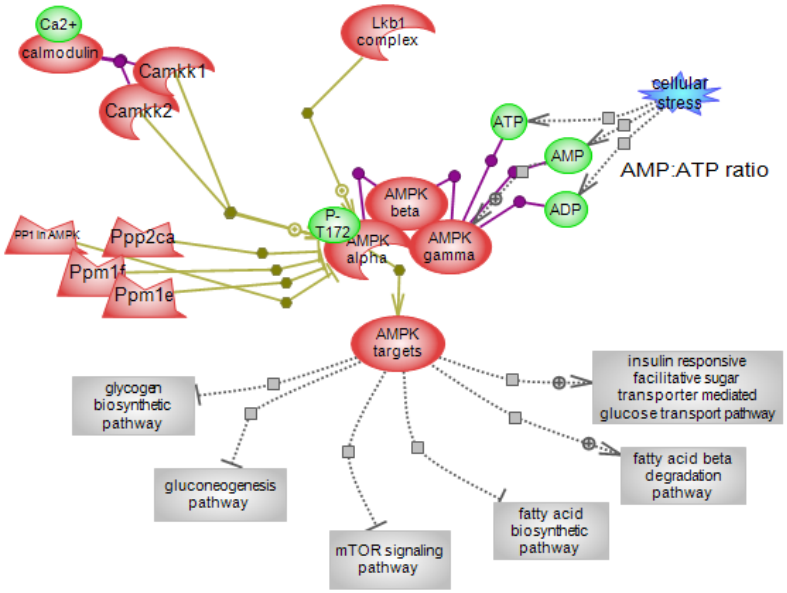
- Tools and approaches to bridge:
  - *Non-clinical models*
    - *adverse events and individual responses*

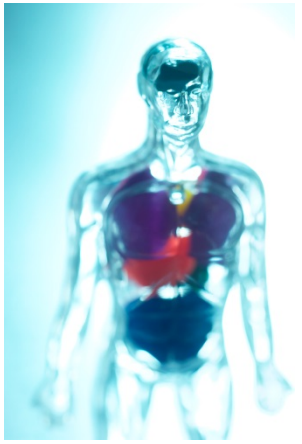
    -- with ---
  - *Clinical settings*
    - *adverse events and individual responses*
  - ***"Translational Toxicology"***
  - ***"Precision Safety Assessment"***

Systems Thinking

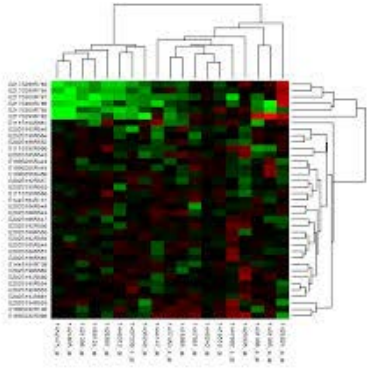




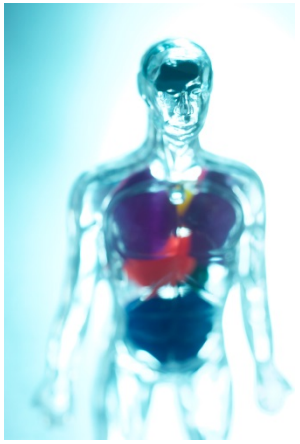


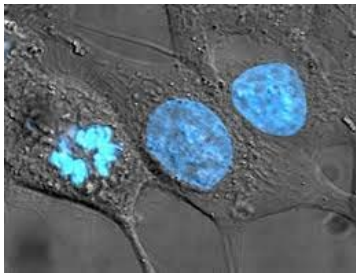


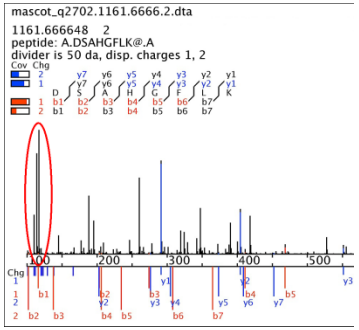
Systems Tools



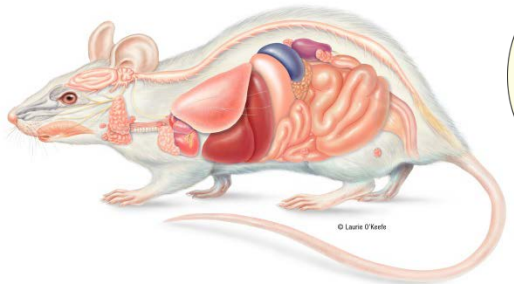
Transcriptomics

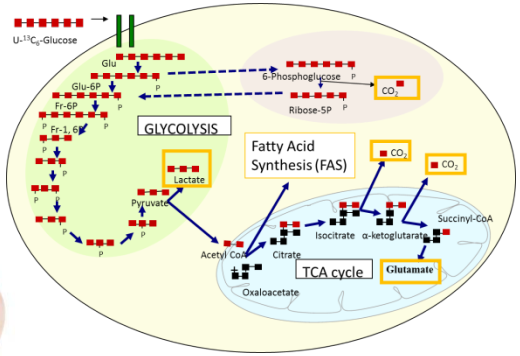






Proteomics





Metabolomcs

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 (MS and aptamer arrays)*
  - *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*

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Division of Systems Biology

- Model Systems
  - *In vitro*
    - Primary cell culture
    - Cell lines
    - Induced pluripotent stem cells (iPSC)
  - *In vivo*
    - Rodents
    - Specialized mouse models
  - Clinical
    - Blood, urine miRNA, protein, metabolite profiling

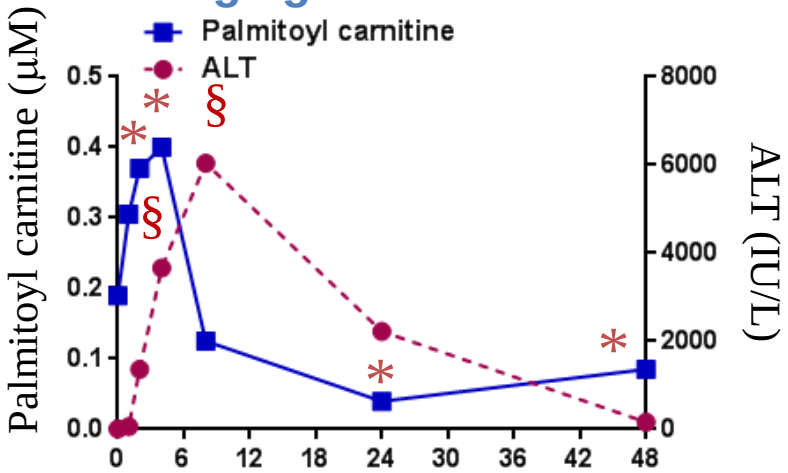
Top Accomplishments

1. Translational biomarkers of liver injury
2. Rapid-B flow detection of *listeria*
3. Demonstration of mitochondrial injury in cardiomyocytes after tyrosine kinase inhibitor treatment
4. Identification of protein changes in mouse plasma very early after doxorubicin treatment
5. 3D-SDAR model showing that the toxicophore for phospholipidosis is similar to that hERG binding

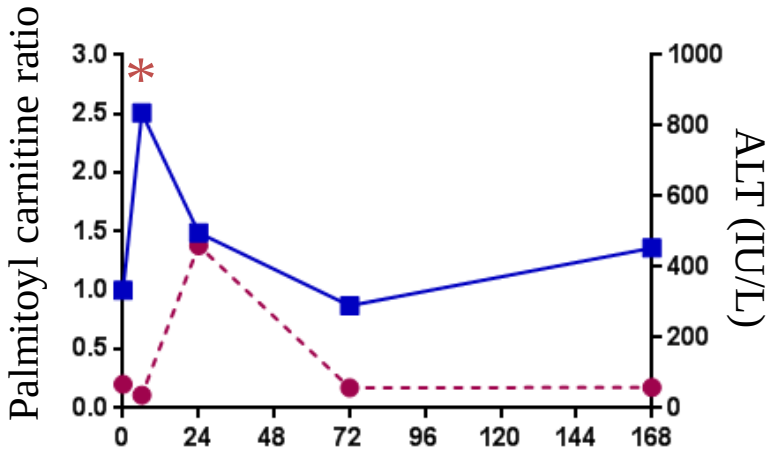
Translational Kinetic Response of Palmitoyl Carnitine vs ALT

FDA

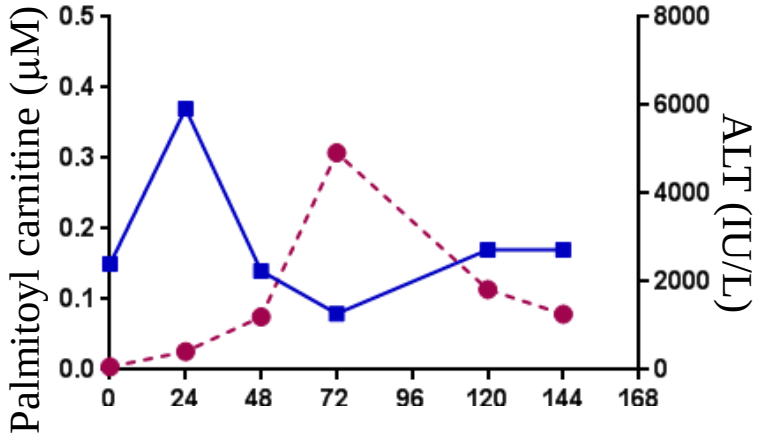
200 mg/kg APAP in mice



1250 mg/kg APAP in SD rats



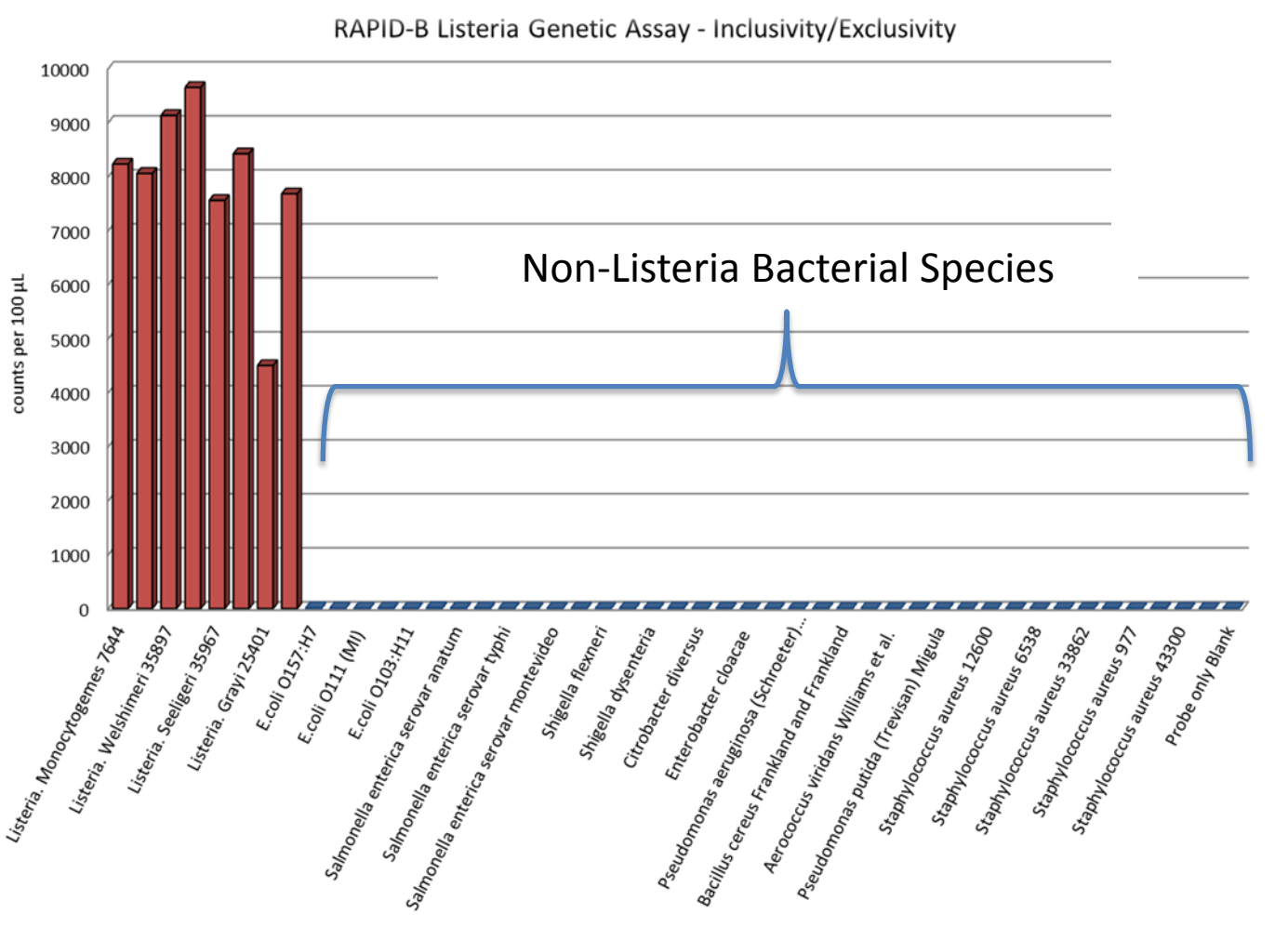
Human APAP overdose (Late NAC)



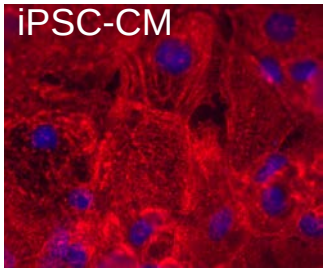
Palmitoyl (16:0) carnitine peak appears before ALT peak in rodents and humans when NAC treatment is delayed.

Beger et al. Arch Toxicol (2015) 89:1497–1522

RAPID-B *Listeria* Detection

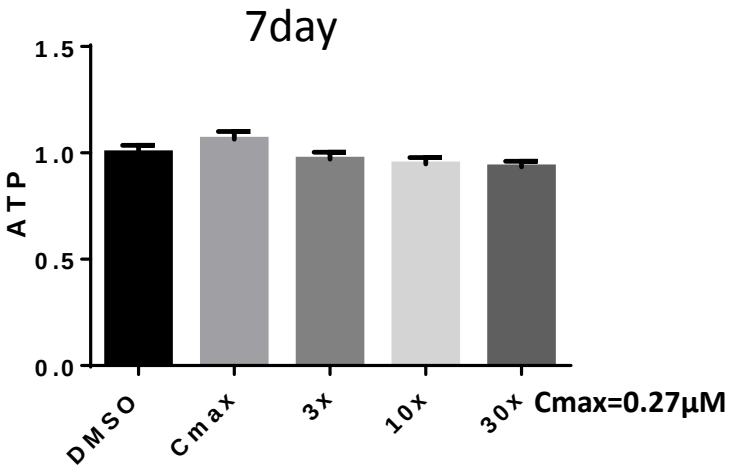


Tyrosine Kinase Inhibitor (TKI) -Induced Cardiotoxicity Using iPSC- Cardiomyocytes

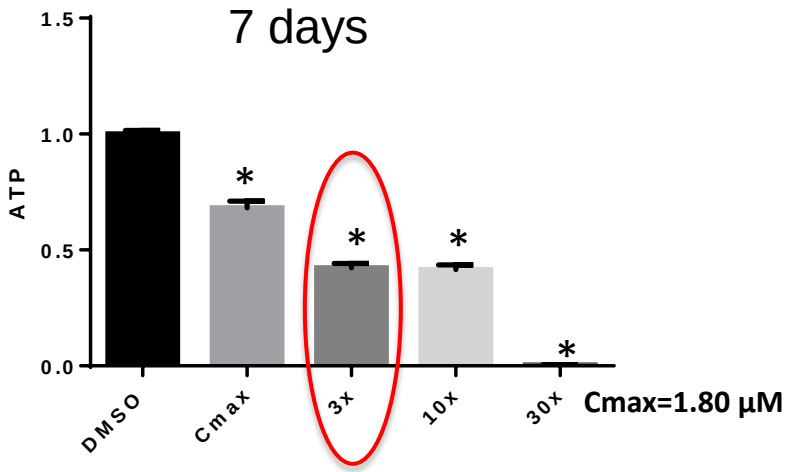


cTNT / DNA

Gefitinib
Cardiac safe



Vandetanib
Black Boxed Warning



Chronic treatment in human iPSC- cardiomyocytes confirm the structural cardiotoxic effects of vandetanib, consistent with previous clinical reports. Conversely, gefitinib was not cytotoxic.

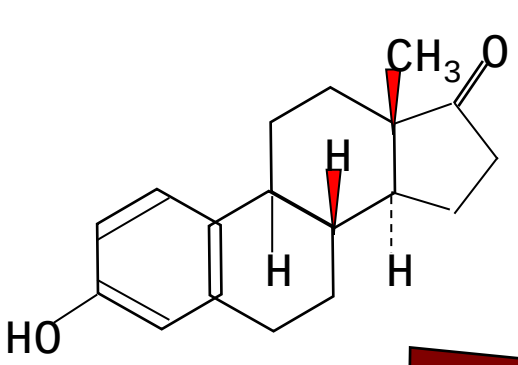
Circulating Protein Markers of DOX Toxicity

SOMA ID	Target Full Name	UniProt	Fold ratio (Dox/Sal)				
			Doxorubicin Effect				
			Drug expsoure in weeks (cumulative dose in mg/kg)				
			2 (6)	**3 (9)**	**4 (12)**	**6 (18)**	**8 (24)**
			No cardiotoxicity			**Myocardial Injury**	**Pathology**
Early Injury Markers of Toxicity							
SL005703	Neurogenic locus notch homolog protein 1	P46531	1.72	1.59	1.67	1.53	1.59
SL000017	von Willebrand factor	P04275	1.60	1.62	1.97	1.92	2.20
SL016563	Mitochondrial glutamate carrier 2	Q9H1K4	1.19	1.17	1.32	1.30	1.21
SL004652	Wnt inhibitory factor 1	Q9Y5W5	1.33	1.11	1.36	1.23	1.18
SL008909	Legumain	Q99538	1.30	1.02	1.20	1.23	1.24
SL011049	Mannan-binding lectin serine protease 1	P48740	1.35	1.17	1.30	1.23	1.24
Markers of Toxicity							
SL001761	Troponin I, cardiac muscle	P19429	1.61	1.52	1.95	3.50	3.59
SL005233	Tumor necrosis factor receptor superfamily member 27	Q9HAV5	1.21	1.20	1.39	1.50	1.65
SL003328	Complement factor I	P05156	0.96	0.88	0.86	0.82	0.83
SL007502	Carbohydrate sulfotransferase 15	Q7LFX5	0.94	0.81	0.75	0.78	0.72
SL003303	C-C motif chemokine 28	Q9NRJ3	0.73	1.10	0.79	0.68	0.54
SL004857	Desmoglein-2	Q14126	0.76	0.77	0.61	0.39	0.26
SL004791	Tumor necrosis factor receptor superfamily member 25	Q93038	0.80	0.87	0.74	0.55	0.45
SL007464	Anti-Muellerian hormone type-2 receptor	Q16671	0.87	0.84	0.65	0.44	0.41
SL010390	Coiled-coil domain-containing protein 80	Q76M96	1.03	0.83	0.91	0.89	0.69
SL008178	Dermatopontin	Q07507	0.99	0.83	0.88	0.85	0.72
SL002508	Interleukin-18-binding protein	O95998	1.16	0.98	1.12	1.23	1.38
SL000462	Insulin-like growth factor-binding protein 1	P08833	1.23	0.85	0.96	1.10	2.81
SL003679	Cation-independent mannose-6-phosphate receptor	P11717	1.13	0.95	0.91	0.85	0.79
SL009324	Follistatin-related protein 3	O95633	1.02	0.86	0.85	0.86	0.77
SL004676	Insulin-like growth factor-binding protein 5	P24593	1.13	0.94	0.94	0.96	0.83

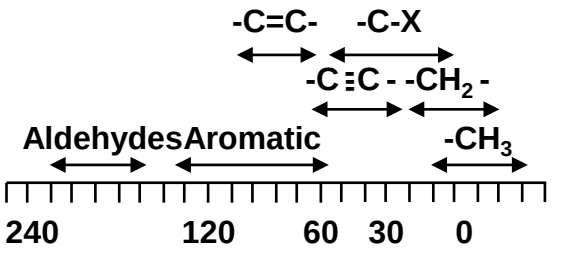
Plasma protein measurements performed using aptamer-based technology by SOMALogic, Inc. **False Discovery Rate <0.1**

Spectral Data Activity Relationships

SAR and SDAR* are Fundamentally Different



Spectroscopy



^{13}C NMR Spectrum (ppm)

QSAR

Molecular physical and structural properties correlated to biological activity

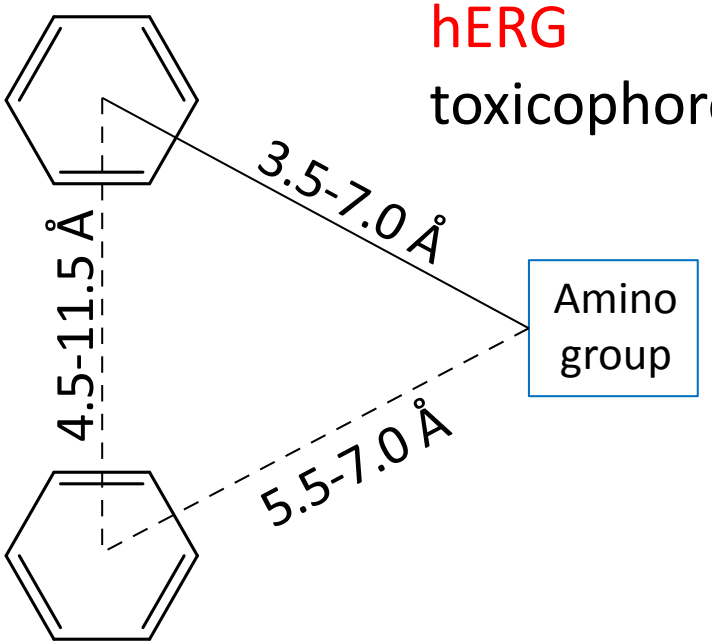
QSDAR

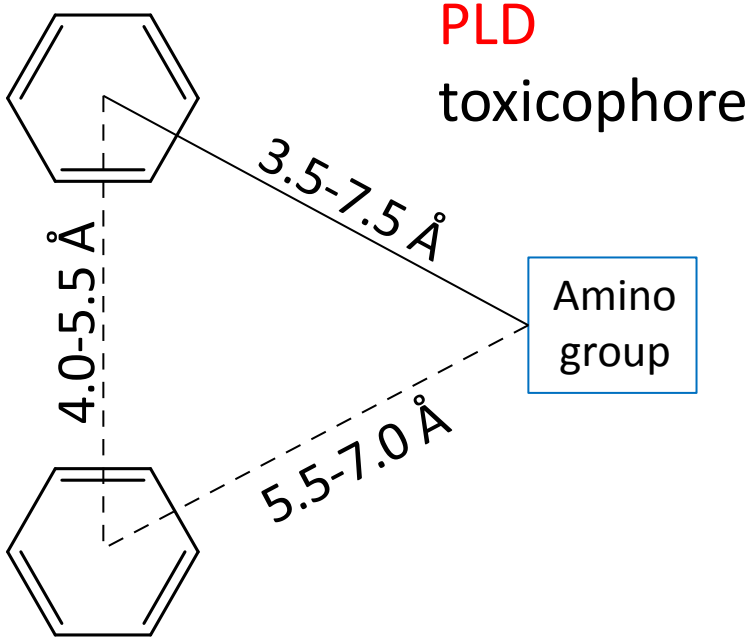
Molecular quantum mechanical properties correlated to biological activity

Biological Activity

*Patented

SDAR Modeling of hERG and PLD





hERG and PLD toxicophores.
The PLD toxicophore is a subset of the hERG toxicophore!

Examples of Current Projects

1. Evaluation of potential serum metabolic biomarkers that predict severity of acute kidney injury (AKI) in critically ill patients
2. Cell free microRNA (miRNA) as improved clinical biomarkers of drug-induced liver injury
3. Evaluation of an *in vitro* testis organ system as an alternative model for male reproductive toxicology
4. Comprehensive examination of tyrosine kinase inhibitor toxicity

Details of Projects

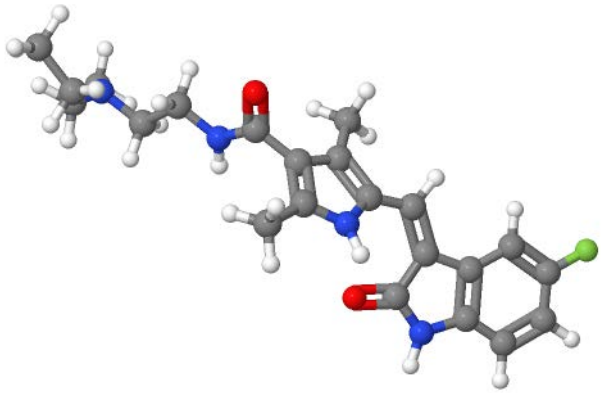
- Clinical AKI biomarkers
  - Collaboration with Univ. of Virginia Medical School
  - Examining plasma using SomaLogic aptamer technology

- Clinical miRNA DILI biomarkers
  - Examining urine miRNAs in patients from Acute Liver Failure Study Group
  - Results are suggestive for prognostic miRNAs

Details of Projects

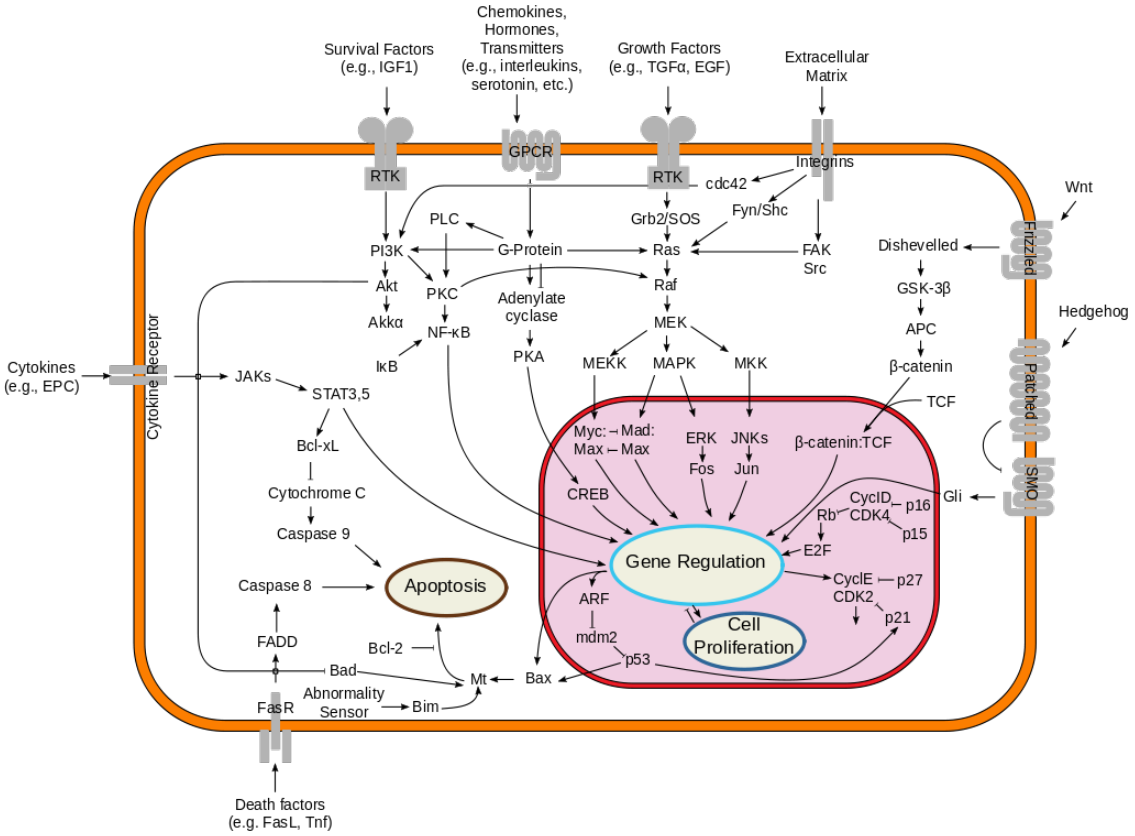
- Comprehensive examination of **t**yrosine **k**inase **i**nhibitors (TKIs)
  - Data mining of mouse, rat and human kinome for species, sex, and organ differences in targets
  - *In vitro* comparisons of hepatotoxicity in primary hepatocytes and iPSC – derived cardiomyocytes
  - *In vivo* systems biology study of sunitinib in a mouse model of cardiomyopathy

Sunitinib
Sutent, SU11248



Details of Projects

- TKIs – multiple targets and pathways



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Future Directions

- Stem cell models for hepatocytes and cardiomyocytes
  - Collaboration with outside laboratories (e.g., MCW, Stanford)
  - Potential for monitoring inter-individual variability
- Adaptation in DILI
  - *In vivo* and *in vitro* studies to investigate models for adaptation to therapeutic doses of APAP

Feedback Requested

- I have considered the area of TKI toxicity as a good “systems biology” problem:
  - Is this truly relevant to FDA regulation?
  - What aspects might I consider?
  - What toxicities are relevant?

Feedback Requested

- Clinical collaborations:
  - How important are these?
  - I have considered the non-clinical <> clinical connection important for biomarkers and mechanistic work – is this correct?
  - What other directions might be considered?

Feedback Requested

- How might interactions between Systems Biology and other FDA Centers be enhanced?
- What emerging sciences/technologies can you advise me to pursue?
- What future directions do you recommend for this division that would impact the FDA?