Division of Systems Biology

William B Mattes, PhD, DABT
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

Metabolomics
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• 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
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• 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
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• 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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• 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

Palmitoyl carnitine (µM) vs ALT (IU/L)

- 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.

RAPID-B *Listeria* Detection

Non-Listeria Bacterial Species
Tyrosine Kinase Inhibitor (TKI) -Induced Cardiotoxicity Using iPSC- Cardiomyocytes

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

**Early Injury Markers of Toxicity**

<table>
<thead>
<tr>
<th>SOMA ID</th>
<th>Target Full Name</th>
<th>UniProt</th>
<th>Fold ratio (Dox/Sal)</th>
<th>Doxorubicin Effect</th>
<th>Drug exposure in weeks (cumulative dose in mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>2 (6) 3 (9) 4 (12) 6 (18) 8 (24)</td>
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<tr>
<td>SL005703</td>
<td>Neurogenic locus notch homolog protein 1</td>
<td>P46531</td>
<td>1.72  1.59  1.67  1.53  1.59</td>
<td>No cardiotoxicity</td>
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<tr>
<td>SL000017</td>
<td>von Willebrand factor</td>
<td>P04275</td>
<td>1.60  1.62  1.97  1.92  2.20</td>
<td>Myocardial Injury</td>
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<tr>
<td>SL016563</td>
<td>Mitochondrial glutamate carrier 2</td>
<td>Q9H1K4</td>
<td>1.19  1.17  1.32  1.30  1.21</td>
<td>Pathology</td>
<td></td>
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<tr>
<td>SL004652</td>
<td>Wnt inhibitory factor 1</td>
<td>Q9Y5W5</td>
<td>1.33  1.11  1.36  1.23  1.18</td>
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<tr>
<td>SL008909</td>
<td>Legumain</td>
<td>Q99538</td>
<td>1.30  1.02  1.20  1.23  1.24</td>
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<tr>
<td>SL011049</td>
<td>Mannan-binding lectin serine protease 1</td>
<td>P48740</td>
<td>1.35  1.17  1.30  1.23  1.24</td>
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</tbody>
</table>

**Markers of Toxicity**

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<td></td>
<td>2 (6) 3 (9) 4 (12) 6 (18) 8 (24)</td>
</tr>
<tr>
<td>SL001761</td>
<td>Troponin I, cardiac muscle</td>
<td>P19429</td>
<td>1.61  1.52  1.95  3.50  3.59</td>
<td>No cardiotoxicity</td>
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<tr>
<td>SL005233</td>
<td>Tumor necrosis factor receptor superfamily member 27</td>
<td>Q9HAV5</td>
<td>1.21  1.20  1.39  1.50  1.65</td>
<td>Myocardial Injury</td>
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<tr>
<td>SL003328</td>
<td>Complement factor I</td>
<td>P05156</td>
<td>0.96  0.88  0.86  0.82  0.83</td>
<td>Pathology</td>
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<tr>
<td>SL007502</td>
<td>Carbohydrate sulfotransferase 15</td>
<td>Q7LFX5</td>
<td>0.94  0.81  0.75  0.78  0.72</td>
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<tr>
<td>SL003303</td>
<td>C-C motif chemokine 28</td>
<td>Q9NRJ3</td>
<td>0.73  1.10  0.79  0.68  0.54</td>
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<td>SL004857</td>
<td>Desmoglein-2</td>
<td>Q14126</td>
<td>0.76  0.77  0.61  0.39  0.26</td>
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<td>SL004791</td>
<td>Tumor necrosis factor receptor superfamily member 25</td>
<td>Q93038</td>
<td>0.80  0.87  0.74  0.55  0.45</td>
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<td>SL007464</td>
<td>Anti-Muellerian hormone type-2 receptor</td>
<td>Q16671</td>
<td>0.87  0.84  0.65  0.44  0.41</td>
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<tr>
<td>SL010390</td>
<td>Coiled-coil domain-containing protein 80</td>
<td>Q76M96</td>
<td>1.03  0.83  0.91  0.89  0.69</td>
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<tr>
<td>SL008178</td>
<td>Dermatopontin</td>
<td>Q07507</td>
<td>0.99  0.83  0.88  0.85  0.72</td>
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<tr>
<td>SL002508</td>
<td>Interleukin-18-binding protein</td>
<td>O95998</td>
<td>1.16  0.98  1.12  1.23  1.38</td>
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<tr>
<td>SL000462</td>
<td>Insulin-like growth factor-binding protein 1</td>
<td>P08833</td>
<td>1.23  0.85  0.96  1.10  2.81</td>
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<tr>
<td>SL003679</td>
<td>Cation-independent mannose-6-phosphate receptor</td>
<td>P11717</td>
<td>1.13  0.95  0.91  0.85  0.79</td>
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<tr>
<td>SL009324</td>
<td>Follistatin-related protein 3</td>
<td>Q95633</td>
<td>1.02  0.86  0.85  0.86  0.77</td>
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<tr>
<td>SL004676</td>
<td>Insulin-like growth factor-binding protein 5</td>
<td>P24593</td>
<td>1.13  0.94  0.94  0.96  0.83</td>
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</tr>
</tbody>
</table>

False Discovery Rate <0.1
Spectral Data Activity Relationships

SAR and SDAR* are Fundamentally Different

Molecular physical and structural properties correlated to biological activity

Q SAR

Biological Activity

Molecular quantum mechanical properties correlated to biological activity

Q SDAR

*Patented
SDAR Modeling of hERG and PLD

hERG toxicophore

PLD toxicophore

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 tyrosine kinase inhibitors (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
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?