New science and technology for understanding and predicting adverse drug events

Nancy Beck, PhD
RUF Public Meeting
May 15, 2015
What is it
• A PPP, led by RUF, aimed at improving drug safety assessment

Objective
• Apply “systems-biology”-based computational approaches
• Better understand the biological mechanisms leading to Adverse Events (AEs)
• Develop predictive models

Outcome
• Reduce AEs in patients
• Modernize drug safety assessment --- move from reactive to more predictive and proactive scientific approach
What is a “Systems Biology” Approach?

• Computational & mathematical modeling of biological systems
• Focuses on complex interactions within biological systems
• Holistic, rather than the more traditional reductionist approach

**Systems Approach** vs. **Reductionist Approach**

- **Systems Approach**
  - molecular
  - cellular
  - tissue
  - organ
  - patient

- **Reductionist Approach**
Systems Approach: Linking Across Scales of Complexity

Molecular Level → Patient Level
Drug → AE

Requires multi-scale modeling to connect events across “scales”
Multi-Scale Modeling to Predict AEs

- Used widely in several fields
  - Engineering, Computer Science, Physics, Chemistry, Meteorology
- Used less commonly in biology
- Technological & computational advances have made this approach possible in biology/medicine
- Only beginning to be used for drug safety/risk assessment
- PredicTox is pulling in expertise/thinking from the fields mentioned above
- Apply those skills to development of multi-scale biological models (molecular $\rightarrow$ patient) to predict drug-induced AEs
PredicTox Project Plan

Start with Proof of Concept/Pilot

• Tyrosine Kinase Inhibitors & Left Ventricular Dysfunction
• Potential to apply broadly

Conduct pilot in two major phase

• Build Knowledge management platform
  – Gather data from all those “scales”
  – Build platform/centralized knowledge base to house clinical, preclinical and molecular data

• Research Using data platform
  – Hypothesis-Driven Research (Clinical, Translational & Basic)
  – Methods Research (Multi-scale models to predict AEs)
PredicTox Framework

Preclinical Data
- Animal toxicity “package”
- Animal pharmacology “package”
- Cardiac imaging
- Cardiac biomarkers

Clinical Data
- Pharmacology “package”
- Cardiac risk factors
- Heart rate/blood pressure
- Cardiac AE reports
- Cardiac imaging
- Cardiac biomarkers

Phys-Chem Data
- Molecular weight
- Chemical structure
- Partition coefficient
- Dissociation constants
- Quantitative Structure Activity Relationships

Molecular Data
- Kinase/ligand binding
- Activity/functional assays
- Signaling pathways
- High Throughput/High Content Screens
- -Omics

Integrated Drug Safety Data Platform

Hypothesis-Driven Research

Clinical, Translational, Basic
- Incidence
- Severity
- Patient specific risk factors
- TKI fingerprint
- Signaling networks
- Mechanisms

Methods Research

Multi-scale Modeling
- Simulate effects
  - over time
  - different genetic backgrounds
  - different drugs/drug combos
  - different risk factors

Improved Patient Safety
Outcomes

• Better prediction of a drug’s potential to cause an AE
• Better preclinical screens to identify problems early on
• Better clinical risk prediction/diagnostics
• Treatment strategies to mitigate potential AEs
• Better understanding of individual patient risk (Precision Medicine)
• Biological/mechanistic insight will help evaluate validity of potential post-market safety signals (signals detected in Sentinel)
Current Project Activities

- Securing data sharing agreements with pharma companies
- Gathering publicly available data
- Building the centralized knowledge platform
- Computational Modeling Workshop planned for fall
- Presenting at scientific conferences
How to Get Involved

- Data, expertise, funding, and other resources
- There is no membership fee to participate
- For more info: contact nbeck@reaganudall.org