Biomarkers for Drug Safety
(Really Biomarkers for Drug Toxicity)

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Biomarker Definition

- A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention

  NIH Biomarkers Definitions Working Group, Clin Pharmacol Ther 2001;69:89-95
Holy Grail of Drug Toxicity Biomarker Development

u Preclinical
  l Biomarker elevation predicts clinical toxicity
  l Absence of elevation predicts future safety

u Clinical
  l Individual biomarker elevation predicts
    w Individual toxicity?
    w Population risk?
    w Often assumed to be the same but is not
  l Absence of elevation predicts future safety
Why Identify Drug Safety Signals Early?

- Inform decisions on future drug development
  - Go/No Go decision
  - Risk assessment
  - Risk mitigation
- Sensitivity/Specificity issues
  - False negatives
    - Future development costs wasted
  - False positives
    - Potentially successful drugs lost
Fall in NMEs Submitted to FDA
We Can Ill Afford Misleading Signals

Frantz, Nature Reviews Drug Discovery 3:379, 2004
Success Rates in All Phases of Drug Development

Toxicity Biomarkers
Sensitivity/Specificity Tradeoffs

- Setting the sensitivity too high at expense of specificity – too many false positives
  - Will reject many safe and potentially useful drugs

- Conversely increasing specificity may increase clinical safety failures
  - Too many false negatives
Toxicity Biomarkers
Sensitivity/Specificity Tradeoffs

- All drugs are not equal
  - Sensitivity/specificity tradeoff varies by indication

- Nasal allergy therapy vs. oncology cure
  - Different tolerance for
    - Failure to detect toxicity
    - Calling toxicity where no clinical toxicity would occur
Tolerance For False Positives?

- 50 preclinical biomarker safety assays
  - 1% random false positive in each assay
  - 50% of drugs would be wrongly rejected in preclinical screening
- Same issue with false negatives
  - Large number of compounds fail in clinical

- Would we define this as success?
- How would we know?
Safety Biomarkers
Linear Reasoning vs. Pattern Recognition

u QT prolongation—linear reasoning
  | Mechanism understood
  | Linked to TDP (actual toxicity)
  | Linked to hERG channel
  | Linked to “at risk” genotypes
  | Manipulation of risk factors linked to toxicity
    w Low Potassium
    w Increased plasma concentration
    w Even QT prolongation by drug linked to TDP
Safety Biomarkers
Linear Reasoning vs. Pattern Recognition

- “Positive Array” with no underlying hypothesis
  - What will our comfort level be?
  - How do we avoid just replicating the “last war”
    - Drug XXX did this so it must be bad because it was
    - Real question is will this predict toxicity in a different molecule?
      - How will we know if we abandon compounds?
  - In the absence of mechanism what level of specificity will we/should we tolerate?
Knowledge of Mechanisms Helpful

- Kinase inhibitors in oncology
  - Cardiac toxicity
  - Is it mechanism (cardiac kinase) based
  - Defining specific cardiac kinase linked to toxicity
    - Would allow prediction of toxicity
    - Develop molecules devoid of inhibition of cardiac enzyme.
The Better Our Understanding of Mechanism

- Better our ability to predict toxicity
- Better our ability to exclude it
- Best hope for improved productivity
- Biomarkers may be an intermediate stop
  - Same non-competitive structures could also jointly define mechanisms
Safety Biomarkers
Limitations

- Likely success is predicting increased incidence of events that are very rare in background population
  - Hepatotoxicity
  - Nephrotoxicity
  - Torsades
  - Repro Tox
Public health problem is increased incidence of events common in background population
- MI and COX-2 inhibitors
- 4X risk produces thousands of cases
- Not easy to detect
  - Against background
  - From spontaneous reports
  - Preclinically
Developing Safety Biomarkers
Our Challenge for Today

- How do we do it?
- How do we measure success?
  - Improved clinical drug safety?
  - More drugs killed early?
    - What if we are wrong (specificity/sensitivity)
    - How will we know?
      - Positives will not progress
  - Spawning a new industry is not the same as success
    - If it just decreases the number of available drugs
Developing Safety Biomarkers
Our Challenge for Today

- How do we validate safety markers?
  - Across drugs
  - Across companies
  - Prospectively (when no one takes a drug forward with a signal)
  - Retrospectively looking back from evidence of toxicity
  - Different when there is a “linear relationship” like QT
  - Different if we can understand mechanisms
  - In most cases we won’t have
    - Linear relationship or mechanism
Developing Safety Biomarkers
Our Challenge for Today

- How do we engage all the stakeholders?
- How do we share data pre/noncompetitively?
- How do we share/interpret data on drugs stopped early in development?
- How do we make drugs safer without needlessly killing effective drugs in early development?