

# **Biomarkers of Drug Safety**

## *How a Preclinical Program Can Translate into the Clinic*

**Jerry M. Collins, Ph.D.**

**Developmental Therapeutics Program**

**DCTD, NCI, NIH, HHS**

# **PRIVATE CITIZEN**

**ADMINISTRATIVE DISCLAIMER:  
Not Necessarily Policy  
of the U.S. Government**

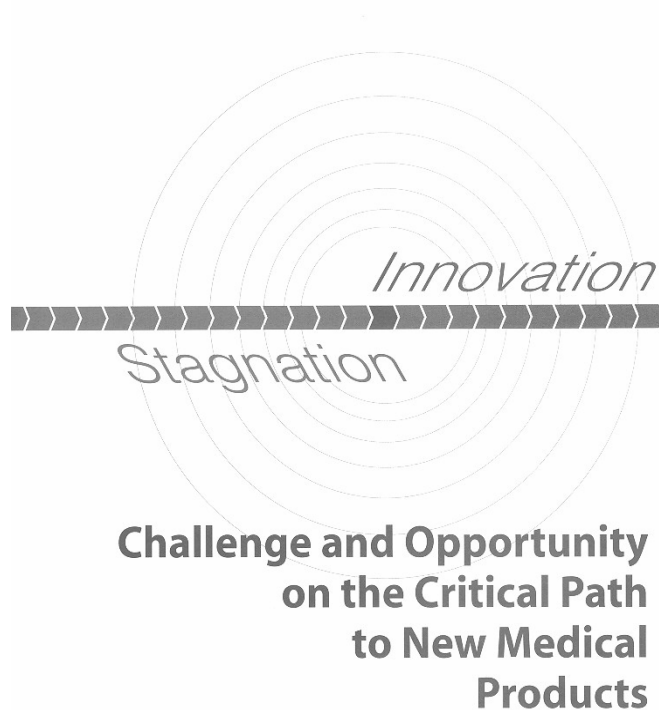
**PROFESSIONAL DISCLAIMER:  
My Primary Experience Is with  
Biomarkers of Efficacy, not Safety**

**Concept of Therapeutic Index:  
Ratio of Therapeutic Benefit to  
Adverse Events**

**No One Can Be Interested Solely  
in Efficacy or Toxicity**

**Bottom Line: you need to know  
both in order to assess the ratio**

# *Dimensions of the Critical Path*



View from The U.S. Food and Drug Administration



## Dimensions

- Assessing safety
- Demonstrating medical utility
- Industrialization

<http://www.fda.gov/oc/initiatives/criticalpath/>

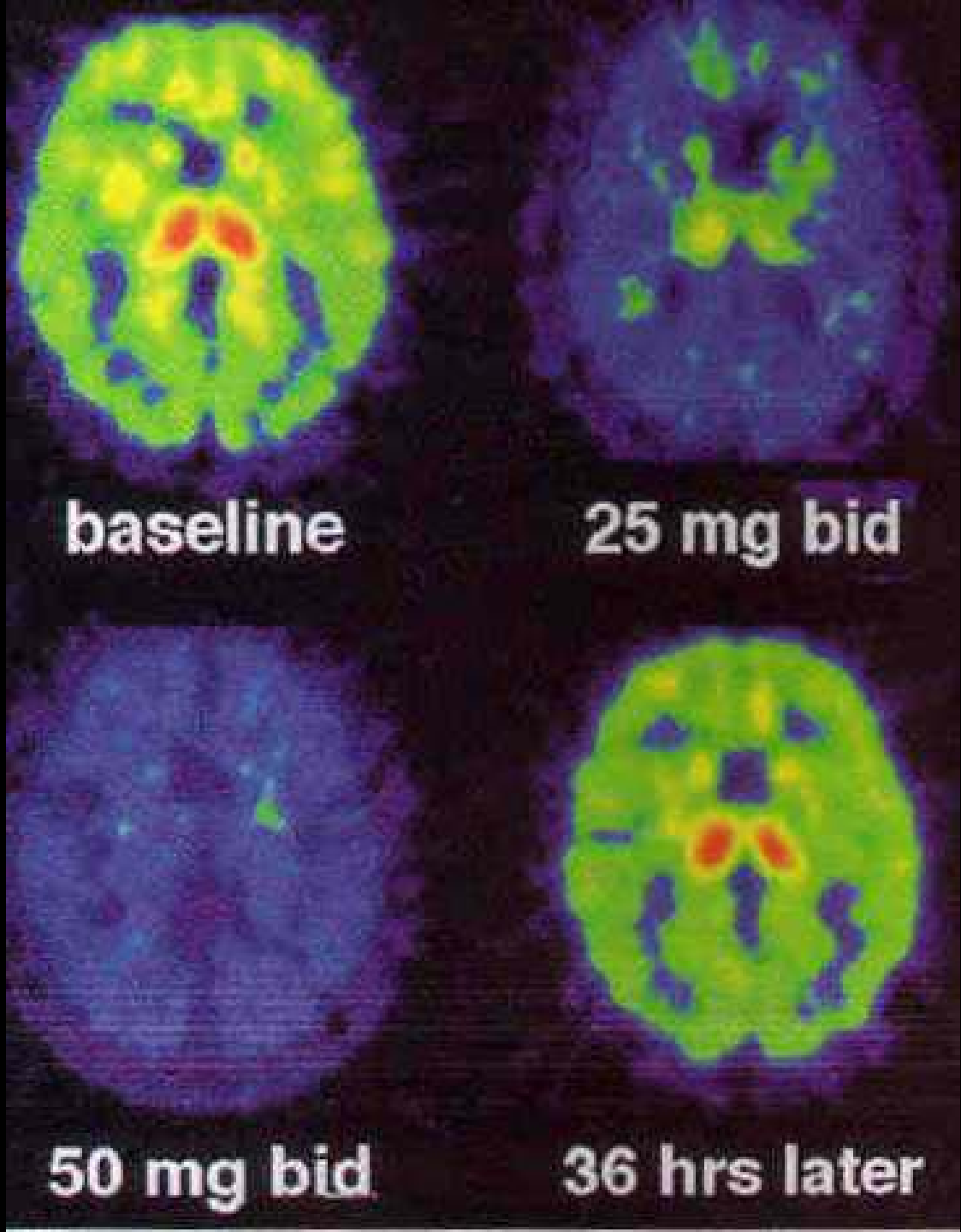
# Possible candidates

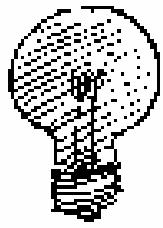
- Genotype
  - BRCA1 and 2
- Phenotype
  - Tyrosine kinases
  - PSA/CA125/CEA
- Imaging
  - Bone density; proliferation (FLT?); apoptosis (annexin?)
- Hormonal
  - E.g., estradiol

**Reversible  
MAO-B  
Inhibition by  
Lazabamide**

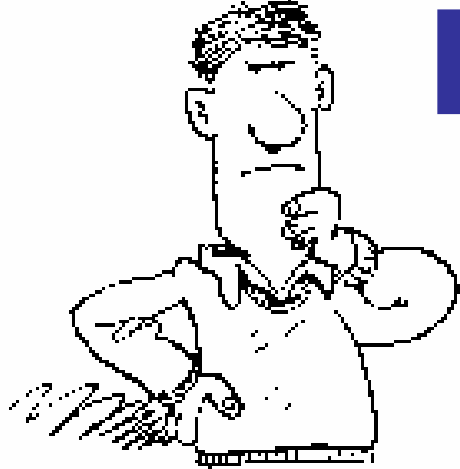
**J.Fowler,  
N.Volkow**

**BNL  
Neurology(93)**





# What Time Is It For Imaging-Based Biomarkers?



**Time to  
Seize The Moment!**

**Especially For Drug Development**

# **Can We Find and Use Biomarkers for Clinical Safety?**

## **PREVIEW**

**If Adverse Event Is Common - - YES  
Failure to Gain Marketing Approval  
due to safety is usually based on  
relatively frequent events**

**If Adverse Event Is Rare - - NOT LIKELY  
Drug Withdrawal from Market usually  
based on rare and/or late events**

**Pharmacogenetics & pharmacogenomics  
in drug development and regulatory  
decision making: report of the first  
FDA-PWG-PhRMA-DruSafe Workshop.**

**J Clinical Pharmacology, April 2003**

**L.Lesko, R.Salerno, B.Spear, D.Anderson,  
T.Anderson, C.Brazell, J.Collins, et al.**

# Pharmacogenomics Strategy Applied to Drug Dosing

- Determine alleles of polymorphic CYP enzymes to determine dose and dosage regimen



The Pharmacogenomics Journal (2002) 2, 20-24  
© 2002 Nature Publishing Group All rights reserved 1470-269X/02 \$25.00

www.nature.com/tpj

EELS (Ethical, Economic, Legal & Social) ARTICLE

Pharmacogenomic-guided drug development: regulatory perspective

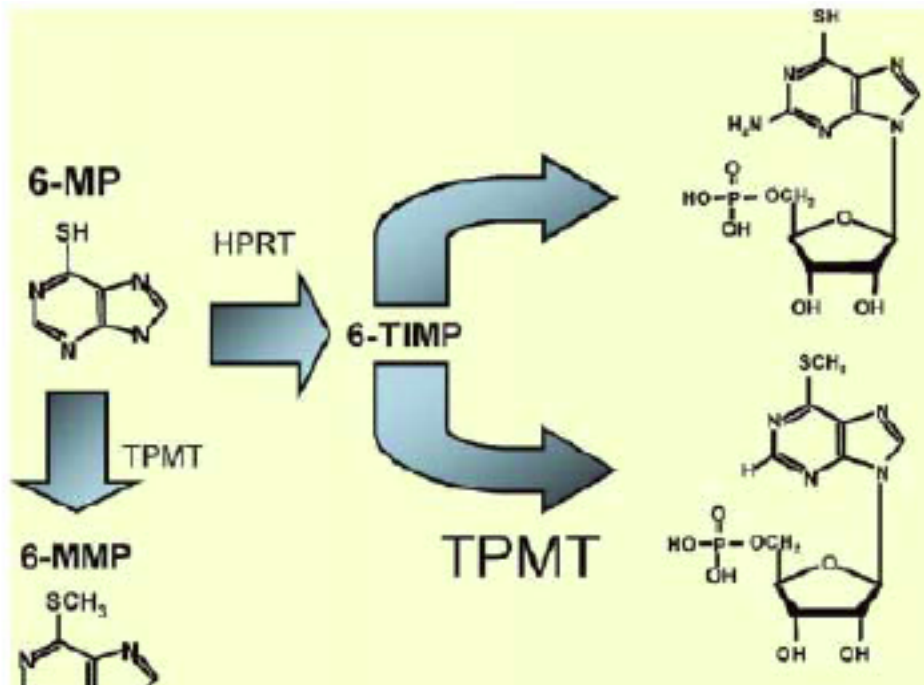
LJ Lesko<sup>1</sup> and J Woodcock<sup>2</sup>

<sup>1</sup>Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD, USA; <sup>2</sup>Office of the Center Director, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD, USA

**“We continue to be concerned that despite the widespread availability of simple PG tests to determine a patient’s genotype with regard to CYP 450 enzymes, there has been little use of this information to tailor drug dosing...”**

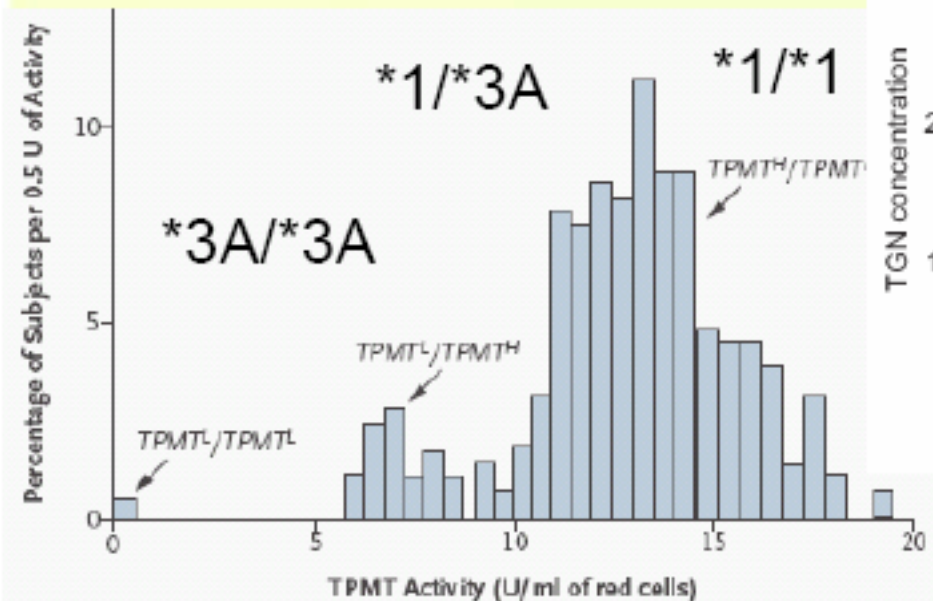
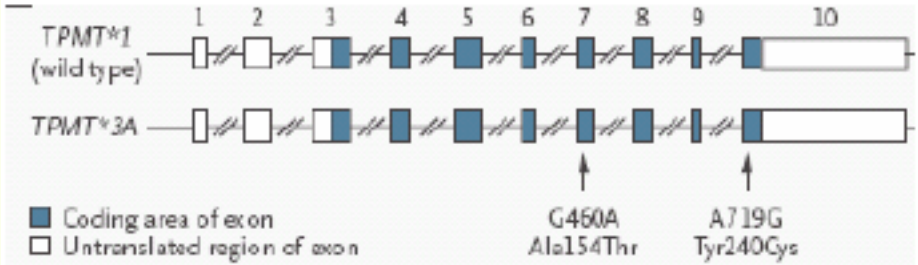
# Adverse drug reactions and PGRN

- TPMT, irinotecan
- Statin-induced myopathy
- Long QT-related arrhythmia
- Tamoxifen-related thrombosis
- Drug-induced kidney disease
- Traditional focus on drug metabolism; often require multicenter efforts to ascertain cases and controls, e.g. DILIN

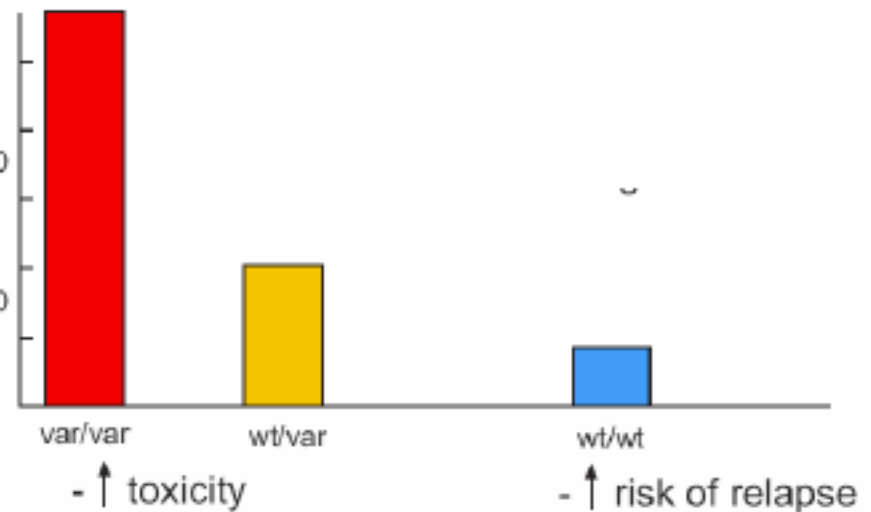


## 6-thioguanines (6-TGNs)

**cytotoxic**



TGN concentration



D.Roden; NIH Roadmap; not ADME

# Example of Specific Genes That Modify Drug Response

- **P450 CYP2D6 metabolizes the following drugs: amitriptyline, desipramine, fluoxetine, haloperidol, risperidone, venlafaxine, and >90 others**
- **Poor metabolizers: 6% of Caucasian and 2% of African-American populations**
- **Rapid metabolizers: 20% of Ethiopian and 2% of Scandinavian populations**

# International Warfarin Pharmacogenetics Consortium

- Variants in *CYP2C9* and in *VKORC1* associated with variable efficacy and toxicity
- “pooling” of warfarin datasets, each including 100s of subjects, each with outcomes and DNA and/or genotypes
- Goals
  - Short-term: develop a warfarin dosing algorithm, including ethnicity, other drugs, and genotypes
  - Medium term: genome-wide association
- Coordinated by and all data deposited at PharmGKB
- Currently 21 datasets, >5500 subjects



"Here's my sequence..."

D.Roden; NIH Roadmap;2007



"Here's my sequence..."

This is not going to be easy!

It is straightforward to list obstacles (and there are many), but...

It is clear that variable drug responses are (1) a huge problem (2) include a genetic component

It is unconscionable that we continue to prescribe drugs empirically when this knowledge base is or can be available.



## Disconnect Between Biomarker Work and Product Labeling

Although hypersensitivity is a “Black-Box” warning for abacavir, and a wonderful scientific story revolving around HLA, not a single word about it in the labeling.

### **ANIMAL TOXICOLOGY**

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

Often no statements about animal toxicology in labeling. Only statement in Human Labeling; not relevant

# **Guidance for Industry**

## **Drug-Induced Liver Injury: Premarketing Clinical Evaluation**

***DRAFT GUIDANCE***

**Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**October 2007**

**Drug Safety**

# Prediction of Liver Toxicity in Humans as a Paradigm for Clinical Biomarkers of Safety

Ironically, the World's Leading Researchers on Human Liver Toxicity Are Meeting This Week in Boston

**American Association for the Study of Liver Diseases**

**2-6 November 2007, Boston**

**Office of Testing and Research  
Laboratory of Clinical Pharmacology**

**Hepatotoxicity Research Initiative**

**John Strong, Project Leader**

**Extending our work with human liver  
metabolism into the toxicity  
dimension.**

# Hepatotoxicity Research Initiative

## Acute Onset vs. Delayed Onset

### Human Hepatocytes *In Vitro*

- readily-available
- no inter-species issues
- but short-term culture only

# Which Molecule Produces Toxicity?

- **Drug as Direct Toxin**
- **Metabolite as Direct Toxin**
  - **Ability to Selectively Block Individual Enzymatic Pathways**
- **Indirect Mechanisms**
  - e.g., Depletion of GSH**

# Searching for Rare Events

- as in animal tox expts, some compensation by  $\uparrow$  concentration
- for pharmacogenetically-based events, can “enrich” the population of hepatocytes by genotyping
- also a role for phenotyping

**FDA / PhRMA / AASLD**

***Drug-Induced Liver Disease:  
A National and Global Problem***

**Feb 12-13, 2001**

**Chantilly, Va.**

**WORKSHOP HELD EACH YEAR:**

**[www.fda.gov/cder/livertox](http://www.fda.gov/cder/livertox)**

# Hepatotoxicity = Toxicity #1

Through the years, hepatotoxicity has been the most common single adverse effect causing major drug problems, including withdrawals and refusals to approve.

## **Withdrawal**

Marsilid (iproniazid)	1956
Ticrynafen	1979
Benoxaprofen	1982
Bromfenac	1998
Troglitizone	2000

## **Non-Approval**

Ibufenac (Eur)	1920's
Perhexiline (Fr)	1980's
Dilevalol (Port, Ir)	1990
Tasosartan	1998

# Hepatotoxicity

In addition to NA's and withdrawals, many drugs are explicitly second-line or bear serious warnings because of liver toxicity, including (partial list)

## **Second Line**

Pemoline

Tolcapone

Trovafloxacin

Felbamate

## **Moderate W/P**

Zileuton

Tacrine

Labetalol

Diclofenac

## **Strong Warning**

Valproic Acid

Ketoconazole

Nicotinic Acid

Acetaminophen

Chlorzoxazone

Isoniazid

Dantrolene

Rifampin

[www.fda.gov/cder/livertox](http://www.fda.gov/cder/livertox); R.Temple,'01

**Hepatotoxicity Problem is Clear,  
and We All Want to Fix It!**

**No Quick or Easy Answers**

**There Are Research Leads**

**AND**

**Concerted Effort Underway**