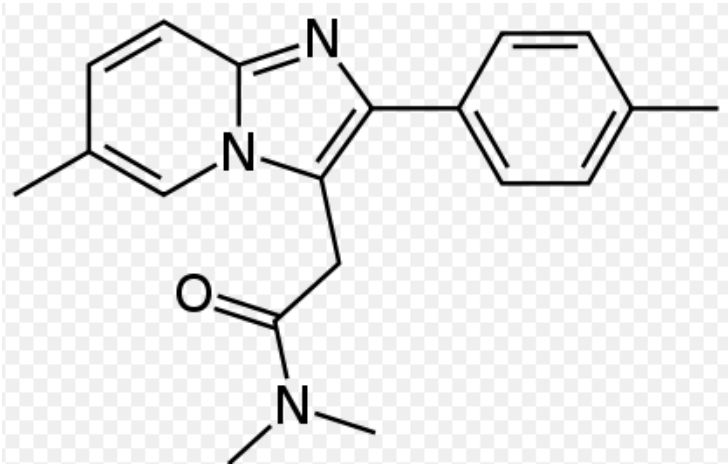
Liver Toxicity Knowledge Base – A knowledge base approach for drug-induced liver injury

Weida Tong, Ph.D

Division of Bioinformatics and Biostatistics, NCTR/FDA

http://www.fda.gov/ScienceResearch/BioinformaticsTools/default.htm


Zolpidem Sandoz® 10 mg
Zolpidemi hydras
30
SANDOZ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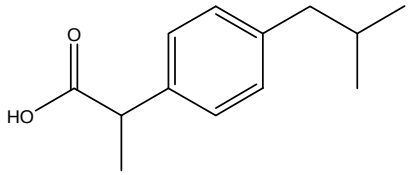
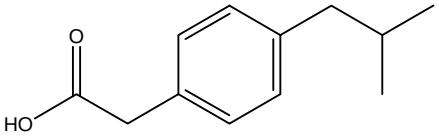
Some Drugs Are More Likely to Cause DILI



Ibuprofen – OTC drug
On the market >30 yrs with not much hepatotoxicity



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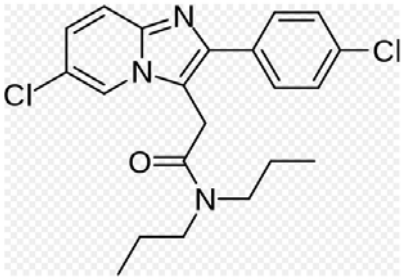
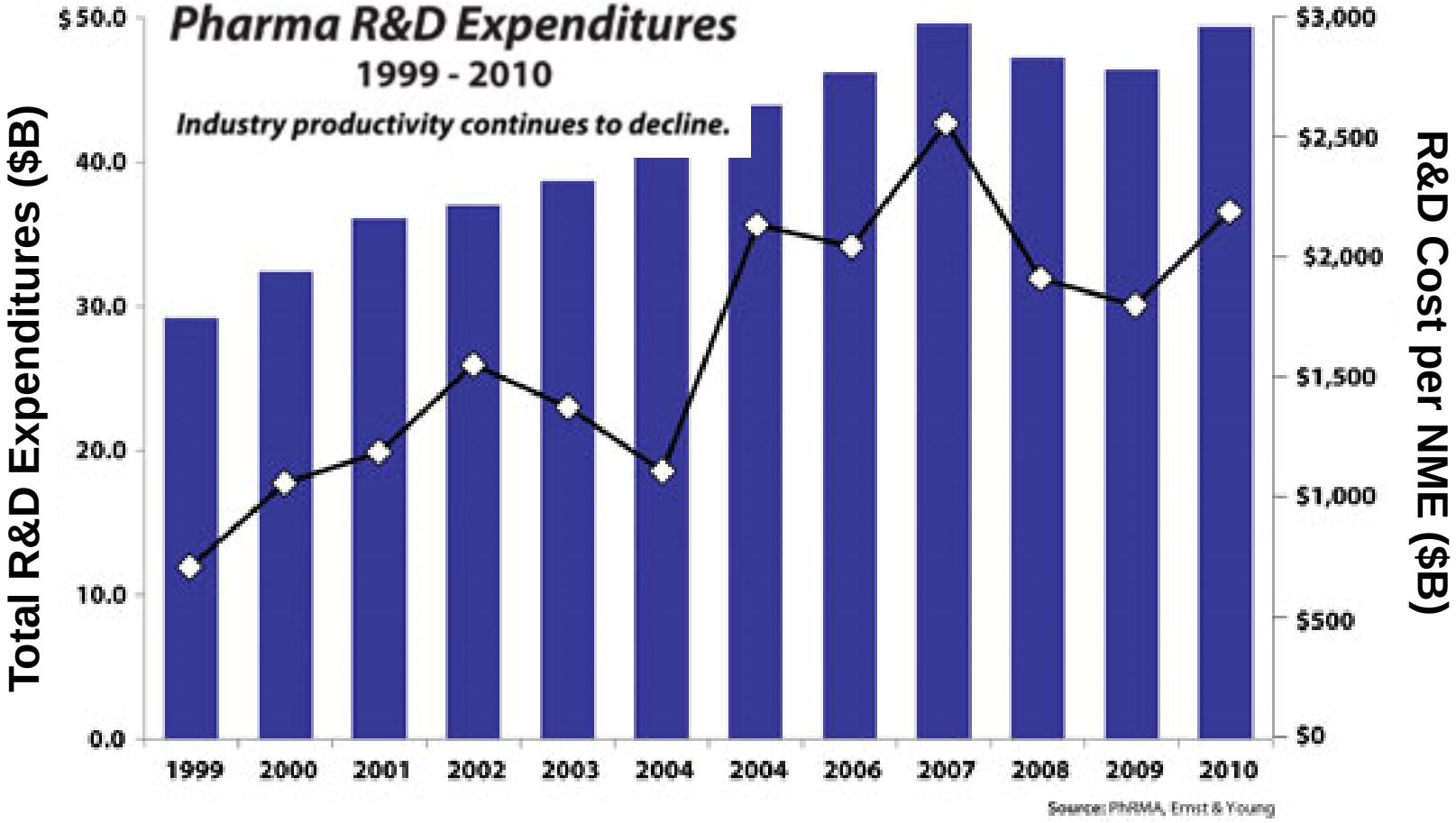


Alpidem – withdrawal
Withdrawn because of causing death or requiring liver transplantation

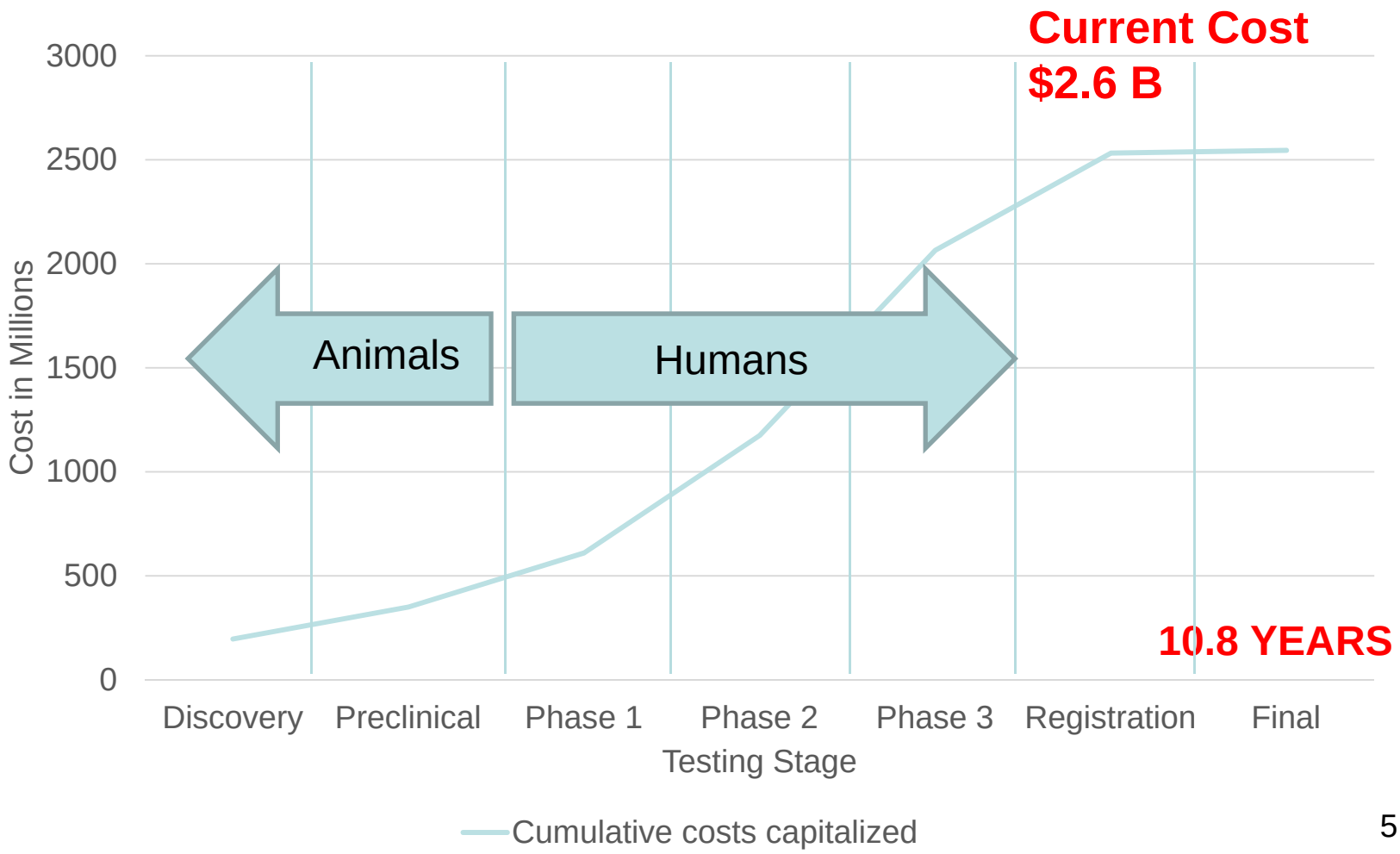
The Cost and Time to Bring a New Drug to the Market Increases Significantly



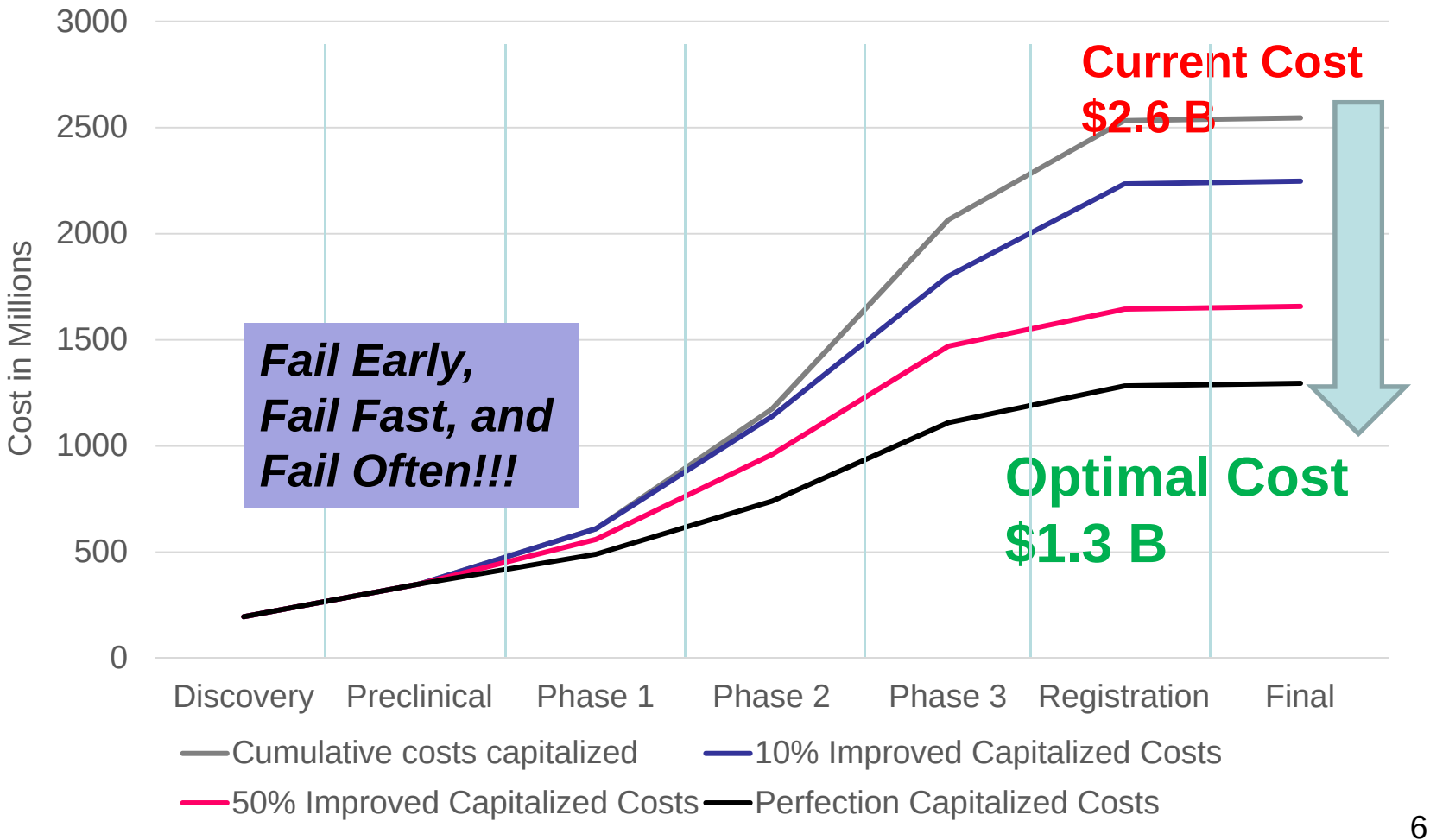
The R&D investment required to bring a new drugs to market has tripled, from $770M per NME in 1999 to $2.3B in 2010

GEN, 32(9), 18, 2012

Where $ Goes – the Cost Across Various Stages of Drug Development



Small Improvement in Preclinical Space Will Lead A Large Saving in Clinical Success



Not Every Organ Is Created Equal

Phase	Preclinical		Phase I-III		Phase-IV
#Drugs	156	88	63	82	47
Cardiovascular:	24%	27%	35%	21%	45%
Hepatotoxicity:	15%	8%	29%	21%	32%
Haematology/BM:	3%	7%	3%	4%	9%
Nervous system:	12%	14%	2%	21%	2%
Immunotox; photosensitivity:	7%	7%	10%	11%	2%
Gastrointestinal:	5%	3%	2%	5%	2%
Reprotox:	9%	13%	5%	1%	2%

The drug attrition in other toxicity domains not mentioned above are less than 9%

1-9% **10-19%** **>20%**

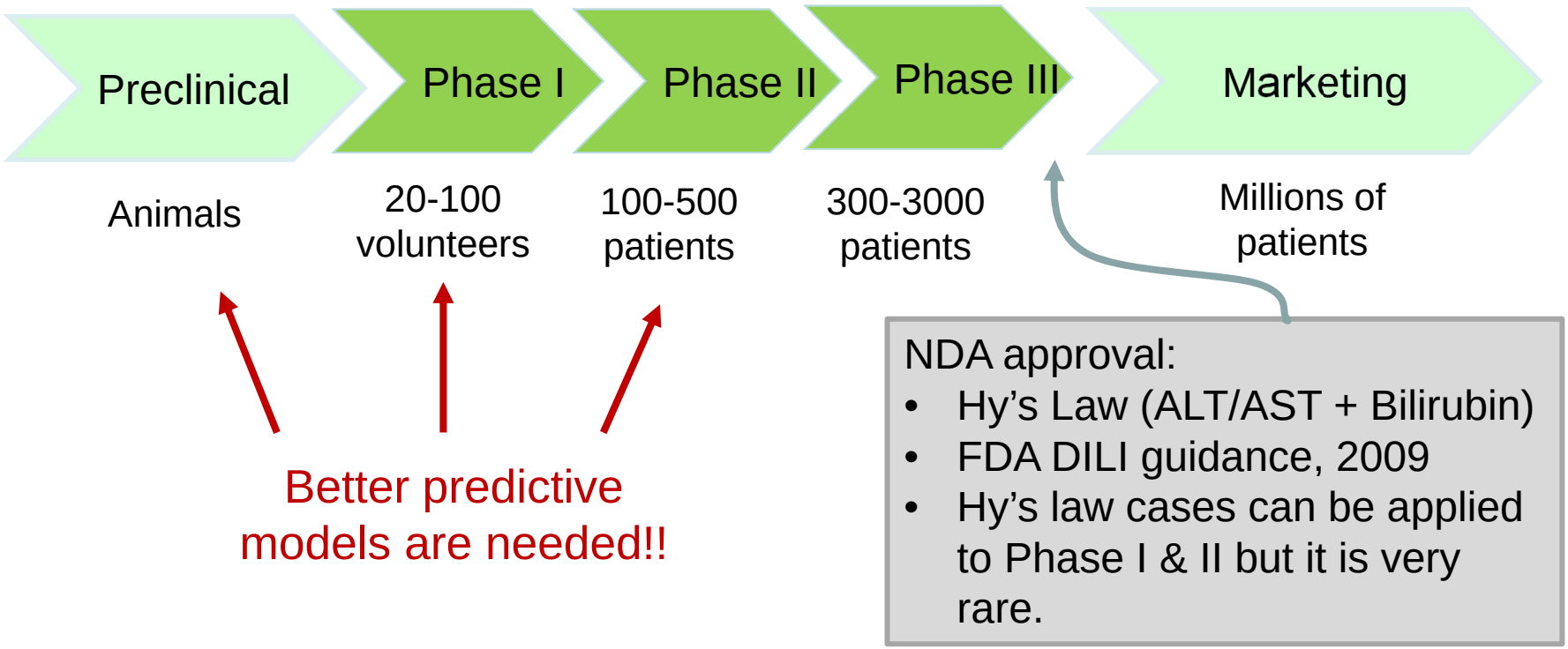
Adapted from Redfern WS et al. The Toxicologist 2010; 114 (S-1), 1081.

A Recap ….

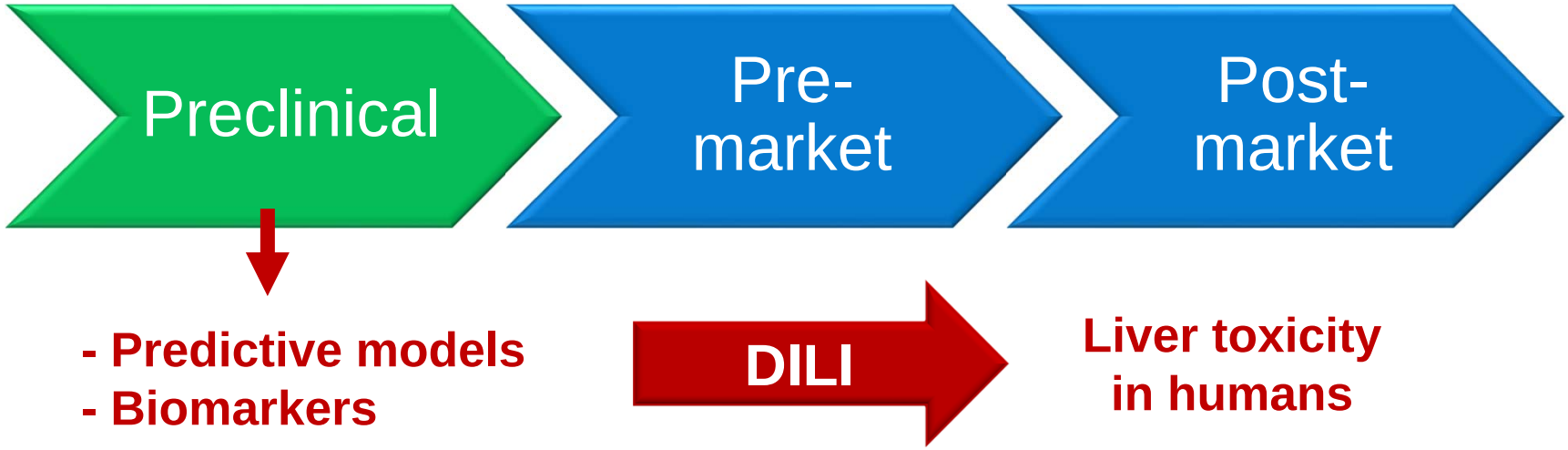
- If we are able to stop the bad drug candidates proceeded to the clinical trials, we would be able to improve the success in drug development
  - False positives are of most concern!!!

- Hepatotoxicity is one of top 2 trouble organs in safety study for preclinical success:
  - 40-50% DILI cases are not detected in preclinical studies
  - DILI contributes 20-30% drug failure in both pre-market (Phase 1-3) and post-market phases (Phase 4)
  - Being the cause of > 50 drug withdrawals from worldwide market
  - A major reason of premature termination of drugs in development
  - *Frequently encountered in the review process*

The Management of DILI Risk in the Review Process



Liver Toxicity Knowledge Base (LTKB)



- LTKB Components:
  - Determining human DILI with a systematic approach
  - Collecting diverse datasets (most are from emerging technologies) associated with marketed drugs
  - Developing DILI predictive models; assessed individually and in combination

Chen M, et al. *Drug Discov Today*, 2011, 16: 697
Chen M, et al. *Drug Discov Today* ,2016, 21(4), 648

LTKB DILI Models

- The “rule-of-two” model – high daily dose (DD>100mg) and high lipophilicity (logP>3) predict DILI, *Chen et al. Hepatology, 58(1): 388, 2013*

- Computational models:
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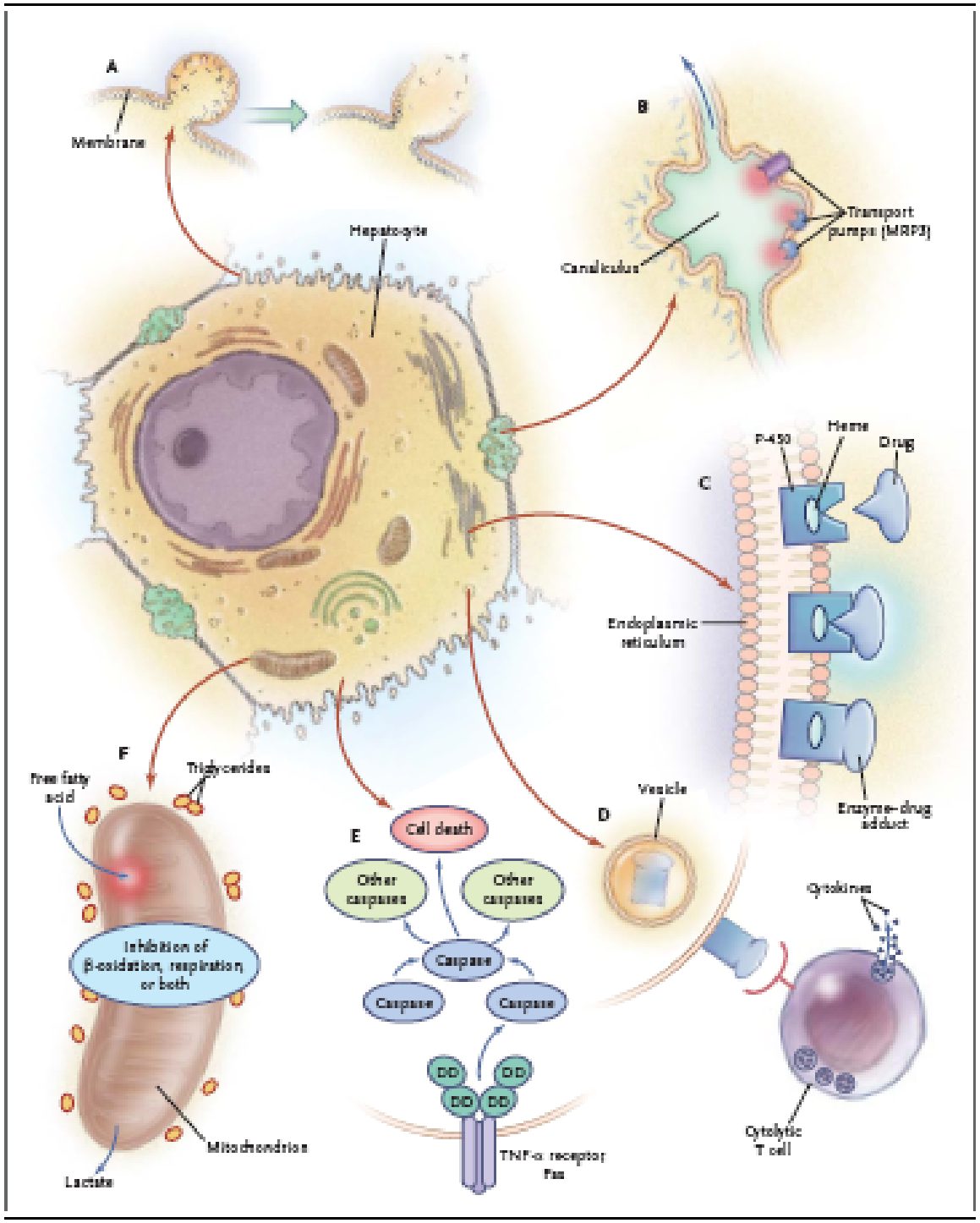


The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

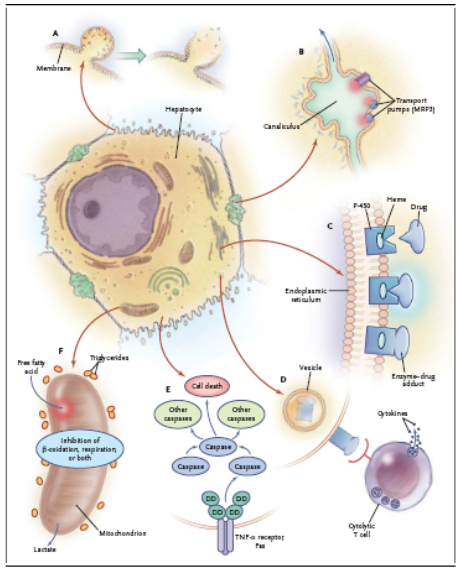
MEDICAL PROGRESS

Drug-Induced Hepatotoxicity

William M. Lee, M.D.

A. Disruption of the hepatocyte
B. Disruption of the transport protein
C. Active metabolites and enzyme-drug adduct
D. Cytolytic T-cell activation
E. Apoptosis of hepatocytes
F. Mitochondrial dysfunction

Injury and Recovery



Propagation and Amplification
- **Cell toxicity**
- **Inflammatory cell infiltration**
- **Immune activation**

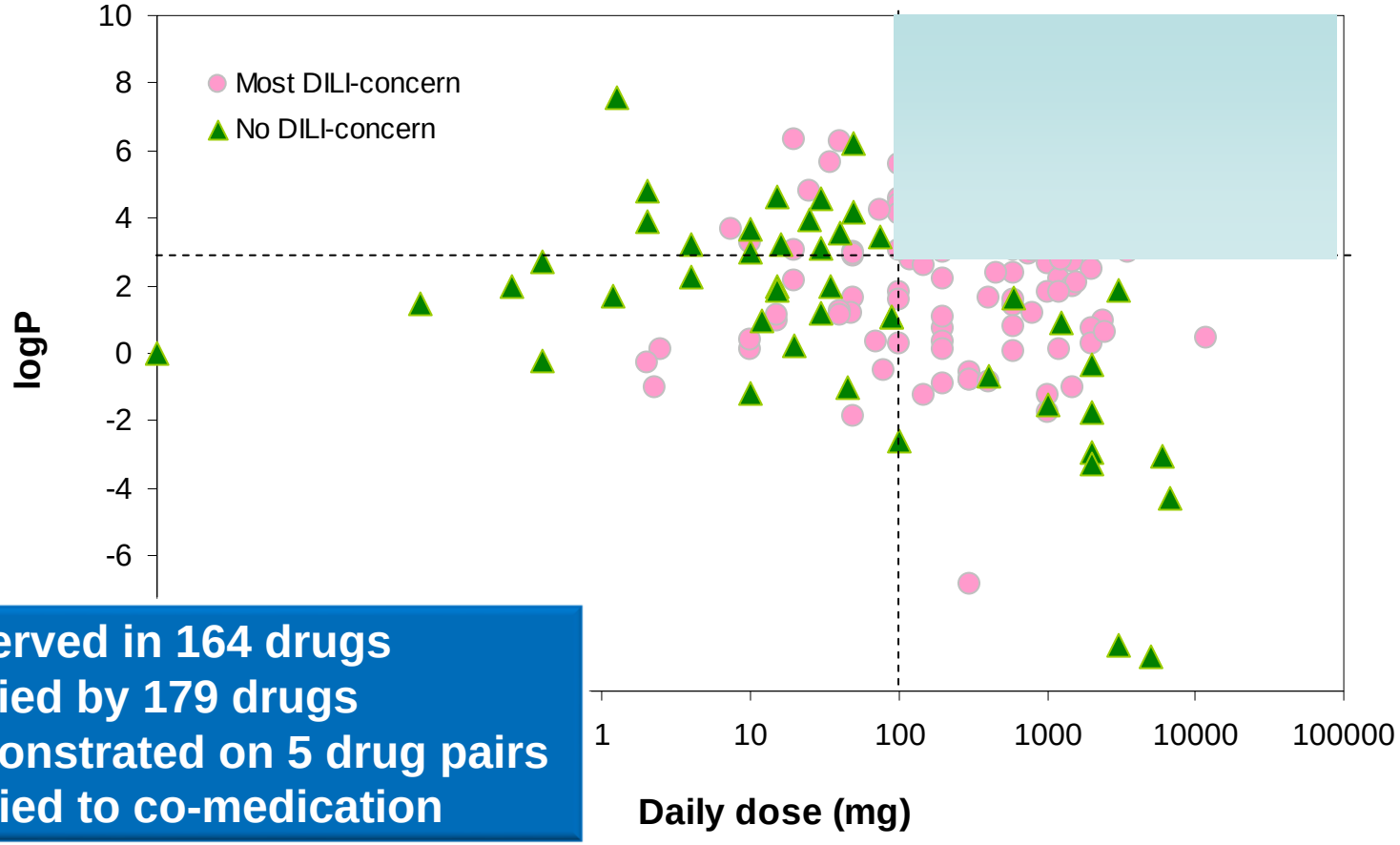
Injury

Individual variability
- Genetic predisposition
- Environmental factors
- Age, sex …

Protection and Resolution
- **Chemical detoxification**
- **Cell repair**
- **Tissue repair**

Recovery

Rule-of-Two (RO2): High Lipophilicity (logP>3) + High Daily Dose (DD>100 mg) Predicts severe DILI



- **Observed in 164 drugs**
- **Verified by 179 drugs**
- **Demonstrated on 5 drug pairs**
- **Applied to co-medication**

Chen et al. Hepatology, 58(1): 388, 2013

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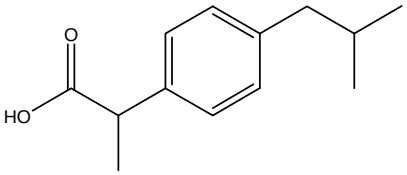

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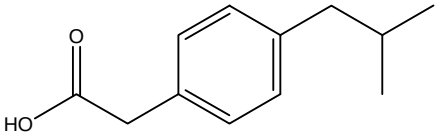

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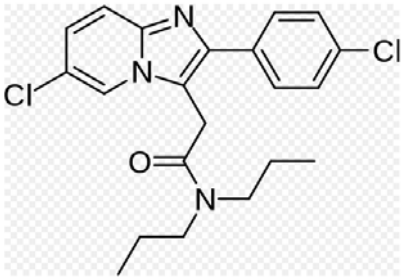

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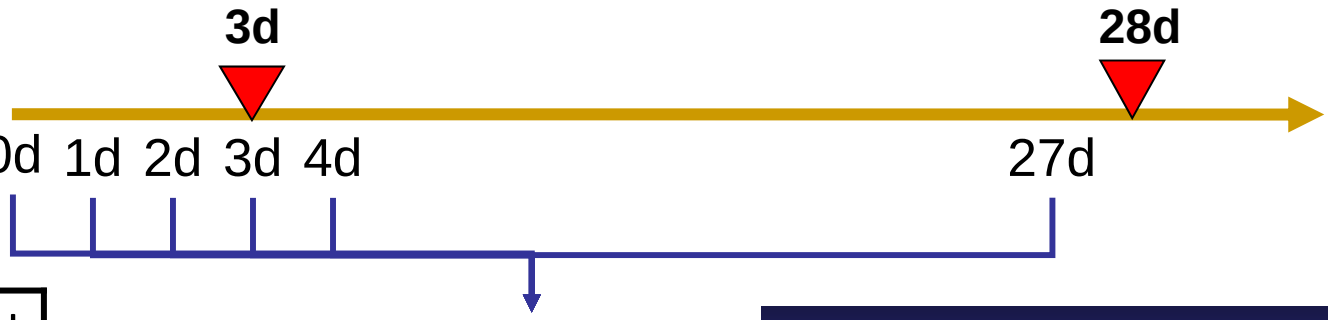
Entacapone (E) vs Tolcapone (T)



Dose		3d	28d
V		x	x
E	L		x
	M		x
	H	x	x
T	L		x
	M		x
	H	x	x

Urine → **Metabolomics (NMR)**

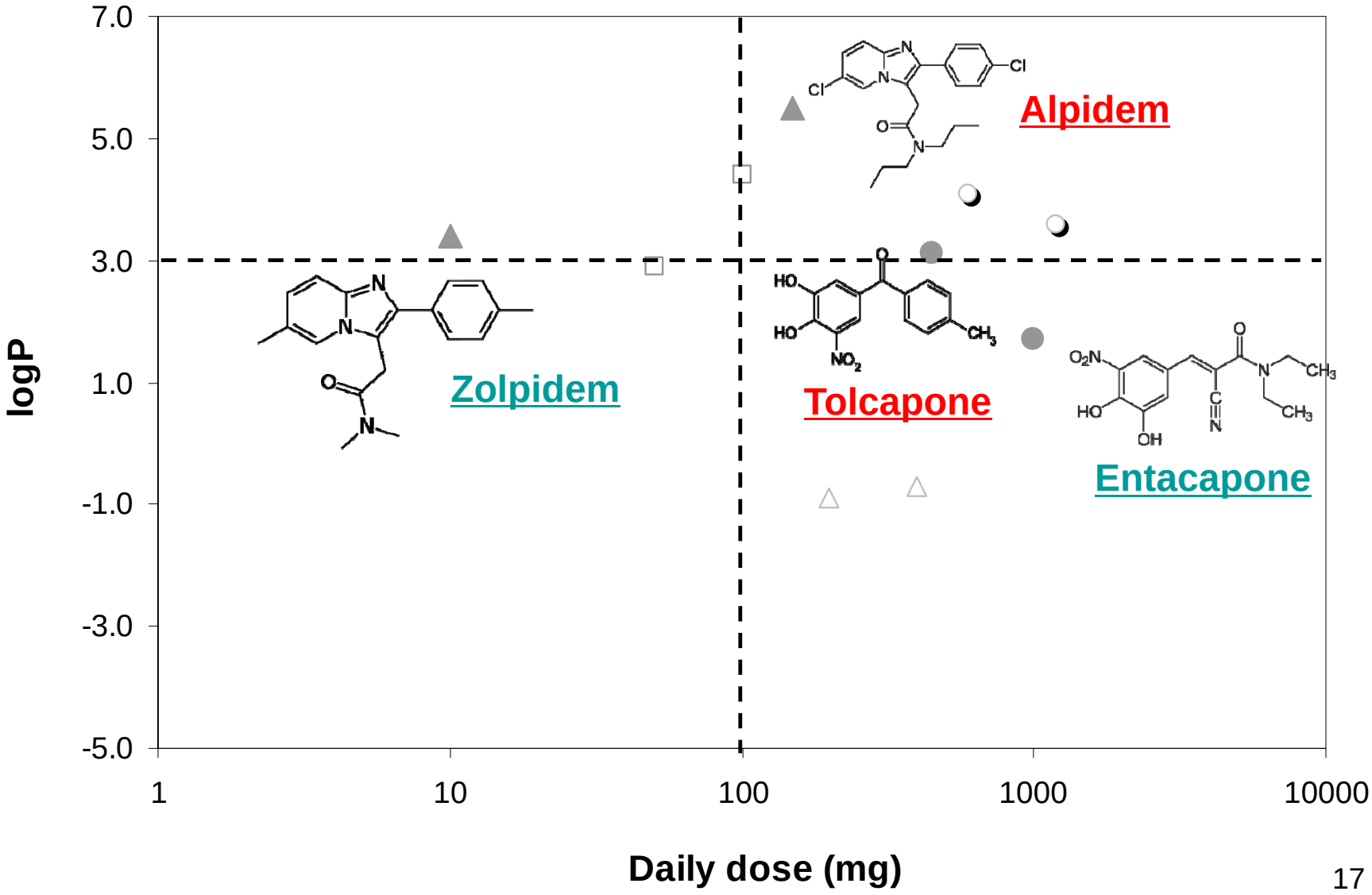
Plasma → **Blood chemistry**
Proteomics
Metabolomics

12 animals → Liver → **Genomics**
Proteomics
Metabolomics
Histopathology

Total 120 animals

MCBURNEY et al. *Toxicologic Pathology,* 37: 52-64, 2009[16]

Drug Pairs in the RO2 Space



FDA Use of RO2

	Cases (year)	Reason for consulting	RO2 Results	Follow-up study
NDA	Case 1 (2015)	DILI concern	+	2 Hy's law cases + 60 general DILI cases from ~ 6000 patients
NDA	Case 2 (2014)	Signs of DRESS and liver toxicity	+	Withdrawn by the sponsor
Phase I	Case 3 (2014)	High concern of its DILI risk	+	DILI damage found in 15% patients during clinical trial
Phase I	Case 4 (2015)	Concern of DILI risk observed for patients with liver disease	-	Still in clinical test **(no results)**
IND	Case 5 (2014)	Mitochondrial toxicity found	+	Still in clinical test **(no results)**
IND	Case 6 (2014)	Mitochondrial toxicity found	-	Still in clinical test **(no results)**

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DILI Prediction System (DILIps) - Rule-Of-Three (RO3)

- Hypothesis: there exists a distinct set of liver specific side effects that can be used to characterize the DILI risk of drugs in humans

- 13 HepSEs were identified using MedDRA, which yielded 91% accuracy to distinguish DILI drugs from non-DILI drugs
  - Since side effect data can not be directly used for screen drug candidates, QSAR models were developed for each of 13 HepSEs
  - Overall performance is below 70%

- RO3: any combination of three HepSEs predicts DILI at 95% positive predictivity

Liu et al. PLoS Computational Biology 2011

DILIps – A Real-World Validation

- 7 drug candidates (new molecule entity)
  - Provided by a pharmaceutical company in a blind fashion (e.g., Drug1-7)
  - At different stage of clinical trials (Phase I-III) by different pharmaceutical companies
    - 5 in clinical trial and 2 are the candidates for clinical trial
    - None of them exhibit a sign of liver toxicity in the preclinical phase (rat, mouse and/or monkey)
    - None of them reach to the market
  - Only chemical structure information was provided to us

DILIps Results for 7 Drug Candidates

- High risk group (three drugs)
  - Drug1: failed in Phase I due to liver toxicity; two patients in critical condition, both experienced hepatitis and one with jaundice; these two DILI manifestations were predicted by DILIps
  - Drug7: failed in Phase I due to liver toxicity
  - Drug2: a drug candidate for clinical trial

- Safe group (one drug)
  - Drug4: moved to Phase III but failed due to a reason not related to DILI

- “Uncertain” group (three drugs)
  - Drug5: finished in Phase III; no DILI
  - Drug6: one patient showed DILI in Phase I, but the causality was not established. For the safety concern, the drug was took out from the pipeline
  - Drug3: a drug candidate for Phase I

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QSAR Modeling Strategy

- In-house tools were used
  - Chemical descriptors were generated with Mold2 (777 descriptors)
  - Decision Forest (DF) was used for QSAR

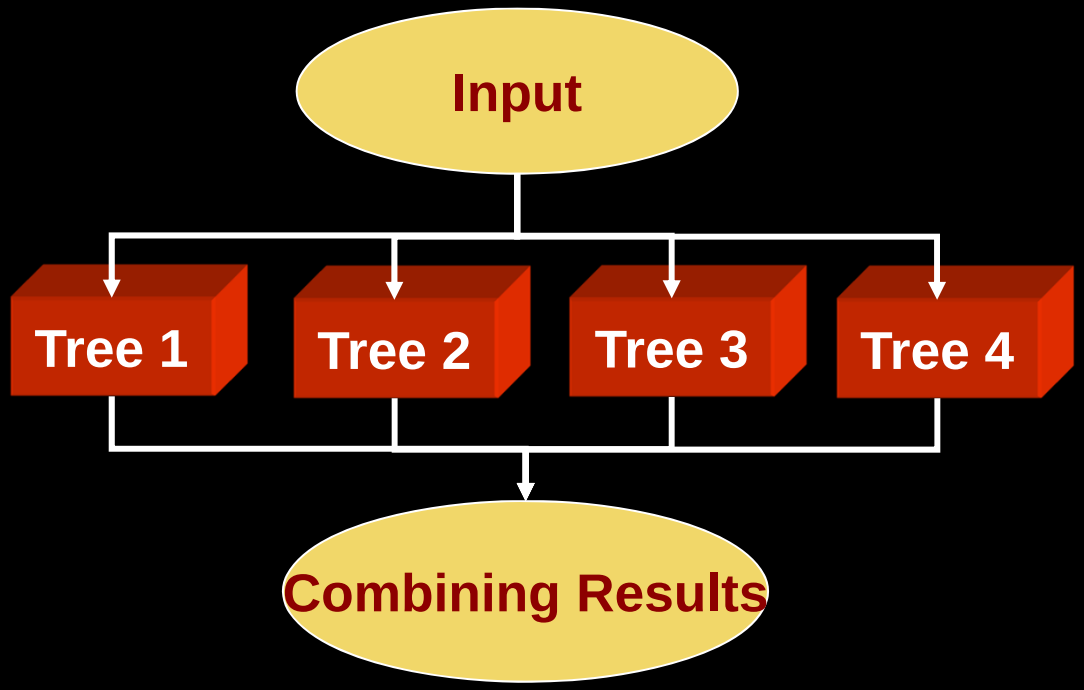
- The rationale behind this strategy: making the model freely available to the public

Hong et al., J Chem Inf Model, 2008, 48(7):1337

Tong et al., J Chem Inf Comput Sci, 2003, 43(2):525

Decision Forest

Assumption: A better classification can be reached by combining the results from several individual models.



Key points

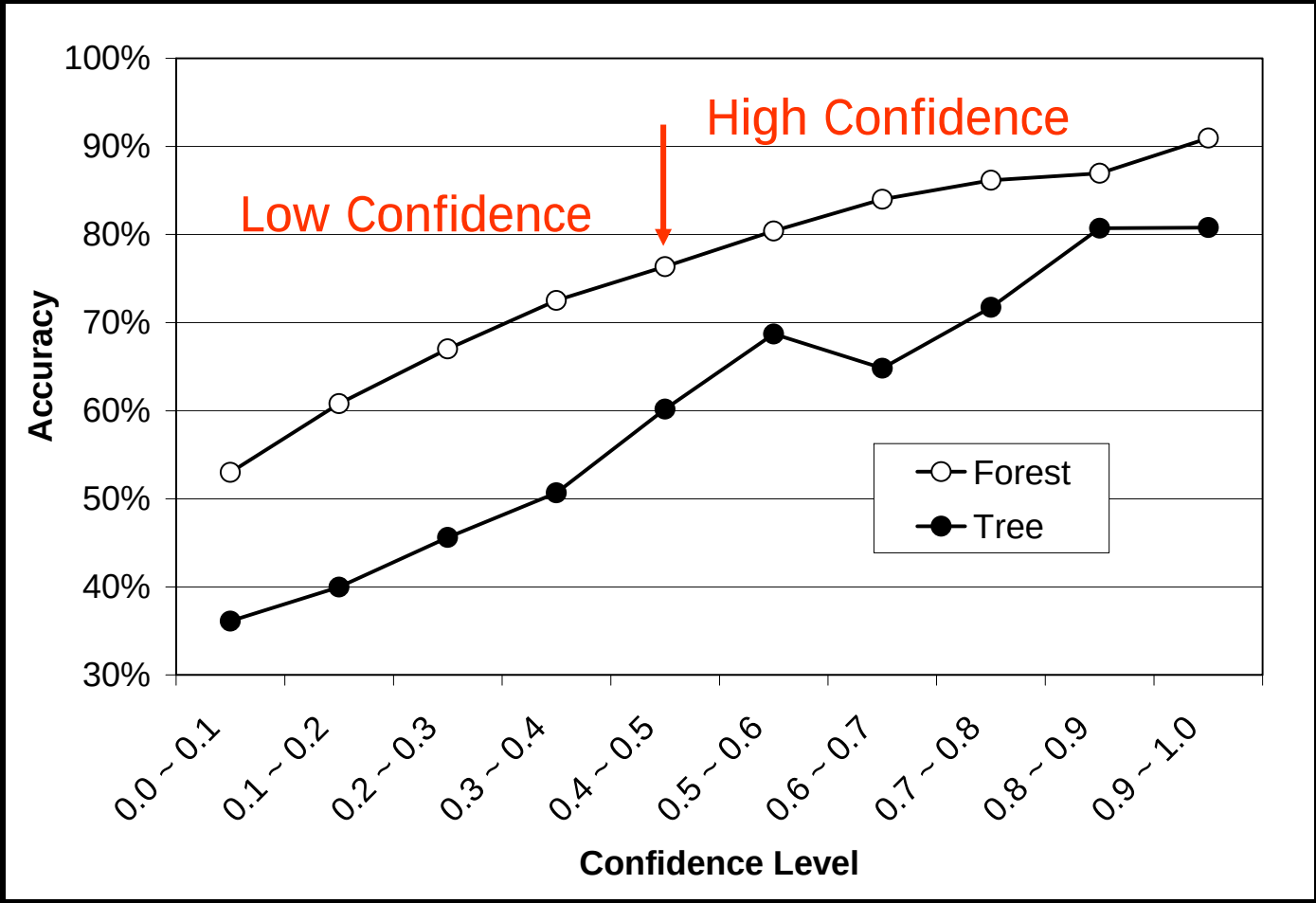
- Combining several identical trees produce no gain
- Combining several highly correct trees that disagree as much as possible

Decision Forest - Two Premises

- Each tree was developed using a distinct set of descriptors that was explicitly excluded from other trees to ensure its *unique* contribution in prediction
- All trees were statistically comparable to ensure their *equal* weight in combining prediction

1. Tong et al. Decision Forest – Combining multiple independent models for prediction, JCICS, 43(2):525-531, 2003
2. Tong et al. Assessment of prediction confidence and domain extrapolation of two structure-activity relationship models for predicting estrogen receptor binding activity, EHP Tox, 112(12):1249-1254, 2004

Prediction Accuracy vs Confidence Level



Confidence Level = $|P - 0.5| \; / \; 0.5$

QSAR Modeling Approaches

1. **Cross-validation** to assess whether a robust model can be developed based on this dataset
2. **Permutation test** to ensure the observation is not due to chance
3. **Validation set 1** to assess the performance of the model derived from the training set
4. **Additional two validation sets** from the literature to further validate the model
5. **Applicability domain** assessment to identify the drug categories for which the model will perform better

Foretelling toxicity:

FDA researchers work to predict risk of liver injury from drugs

By Cassandra Willyard

In December 2014, the US Food and Drug Administration (FDA) approved a new drug cocktail, from the Chicago-based pharmaceutical company AbbVie, to treat hepatitis C infection. Less than a year later, the agency warned that the cocktail, Viekira Pak, and another, newer AbbVie hepatitis C therapy could cause serious liver injury in individuals with advanced liver disease. The agency noted that it had received reports of at least 26 cases of liver injuries that might have been caused by the drugs. Of these, ten patients experienced liver failure so severe that they either needed a transplant or died.

The news came as a shock to many people, and AbbVie's share prices tumbled. However, Weida Tong, a researcher at the FDA's National Center for Toxicological Research (NCTR) in Jefferson, Arkansas, could have predicted this outcome. He and his colleagues had recently developed an algorithm to assess a drug's potential for causing liver injury. Tong's team had not assessed these particular drugs before they were approved, but after the agency issued its warning, the researchers entered the data for Viekira Pak into their algorithm and found that it predicted the drug cocktail might have toxic effects on the liver.

When a drug receives FDA approval, the presumption is that it is safe. However, liver injury can be hard to predict, and animal studies do not always identify compounds that might harm human livers. Even human safety studies can miss the signs, in part because the potential for injury can depend on an individual's genetic makeup. "In the area of liver safety, I don't believe there's been any progress whatsoever in the last 30 years," says Paul Watkins, a toxicologist and director of the Institute for Drug Safety Sciences, a joint venture between The Hamner Institutes for Health Sciences and the University of North Carolina at Chapel Hill. Tong and his four-member team hope to change that by developing models that can predict which medicines might cause trouble, before drugmakers embark on costly clinical trials and dangerous drugs reach the public.

Researchers have devised many ways of assessing whether a drug will harm the liver. Watkins and his colleagues have constructed an *in silico* liver called DILIsym to model liver injury. Other researchers are creating three-dimensional mini-livers or seeding liver tissue onto plastic chips to identify toxic drugs, and some groups have bioengineered mice to carry human liver tissue. Tong is taking a less sensational approach by devising mathematical models to predict the risk of liver injury, but he is doing it from within the walls of the world's largest national drug regulatory agency.

Model student

Tong, a bioinformatics buff, began to work on drug-induced liver injury, or DILI, eight years ago. Although there was a wealth of information on the topic, he noticed that the data were scattered. So he became a collector, combing the literature for information that might be useful for building predictive models. As part of this effort, Tong knew that he would first need to develop a scheme for classifying existing drugs according to their potential for causing liver injury. So he and his colleagues turned to the drugs' full labeling information, which is found in the US National Library of Medicine's DailyMed database. These labels are dozens of pages long and contain more than a dozen sections, but the researchers homed in on just three: boxed warning, warnings and precautions, and adverse reactions. The team searched the labels for key words that might indicate liver harm, such as 'hepatitis' or 'fatty liver'. This methodology enabled them to sort nearly 300 FDA-approved drugs into three DILI categories: of 'most concern', of 'less concern' and of 'no concern' (*Drug Discov. Today* **16**, 697–703, 2011). "Even though FDA drug labels are not almighty perfect to address

Toxicological Knowledge Base Development

"Knowledgebase" development involves (1) data collection and (2) predictive modeling (e.g., QSARs):

- Endocrine Disruptor Knowledge Base (EDKB): ~8000 chemicals
- Liver Toxicity Knowledge Base (LTKB): ~2000 drugs
- Liver Cancer Knowledge Base (NCTRlcdb): ~1000 chemicals
- Tobacco Constituents Knowledge Base (TCKB): ~9000 tobacco constituents

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- Hong Fang (OSC)
- Wen Zou (Biostatistics)
- Dong Wang (Biostatistics)
- Vivian Huang (Biostatistics)
- Joshua Xu (R2R)

Other collaborators:

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- Larry Lesko (U of Florida)

FDA DILI Interest Group:

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- Marc Stone (CDER)
- Shashi Amur (CDER)
- Tina M Burgess (CVM)
- Ruyi He (CDER)
- Victor Crentsil (CDER)
- Jane Bai (CDER)
- John Senior (CDER)
- Mark Avigan (CDER)
- Andrew Mulberg (CDER)
- Ruby Mehta (CDER)
- Lara L Dimick (CDER)
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- Lilliam Rosario (CDER)

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