

Biomarkers of acute idiosyncratic hepatocellular injury within clinical trials

Paul B. Watkins

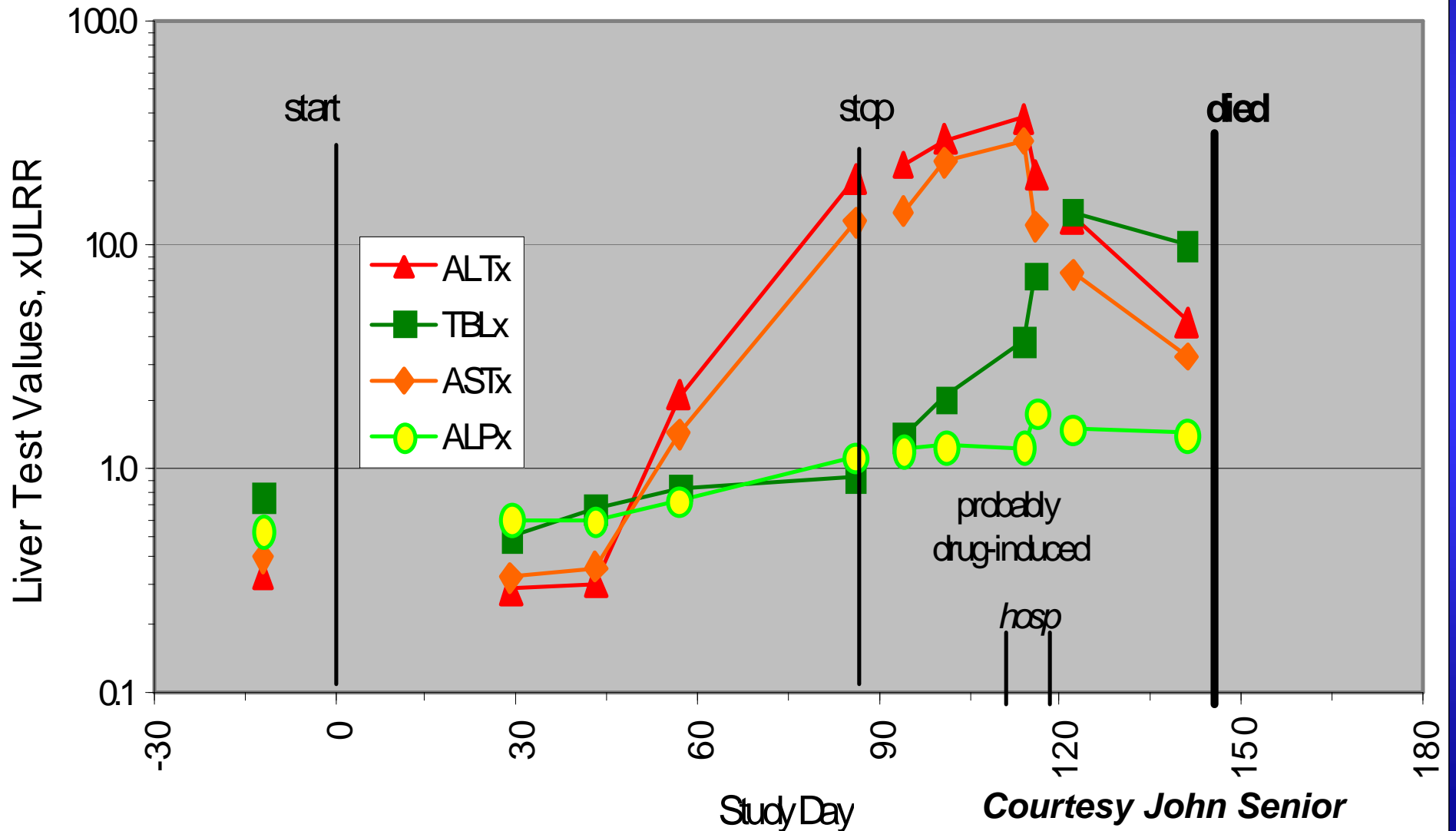
Hamner Center for Drug Safety Sciences

University of North Carolina

Chapel Hill, N.C.

Acute Idiosyncratic Hepatocellular Injury (AIHI)

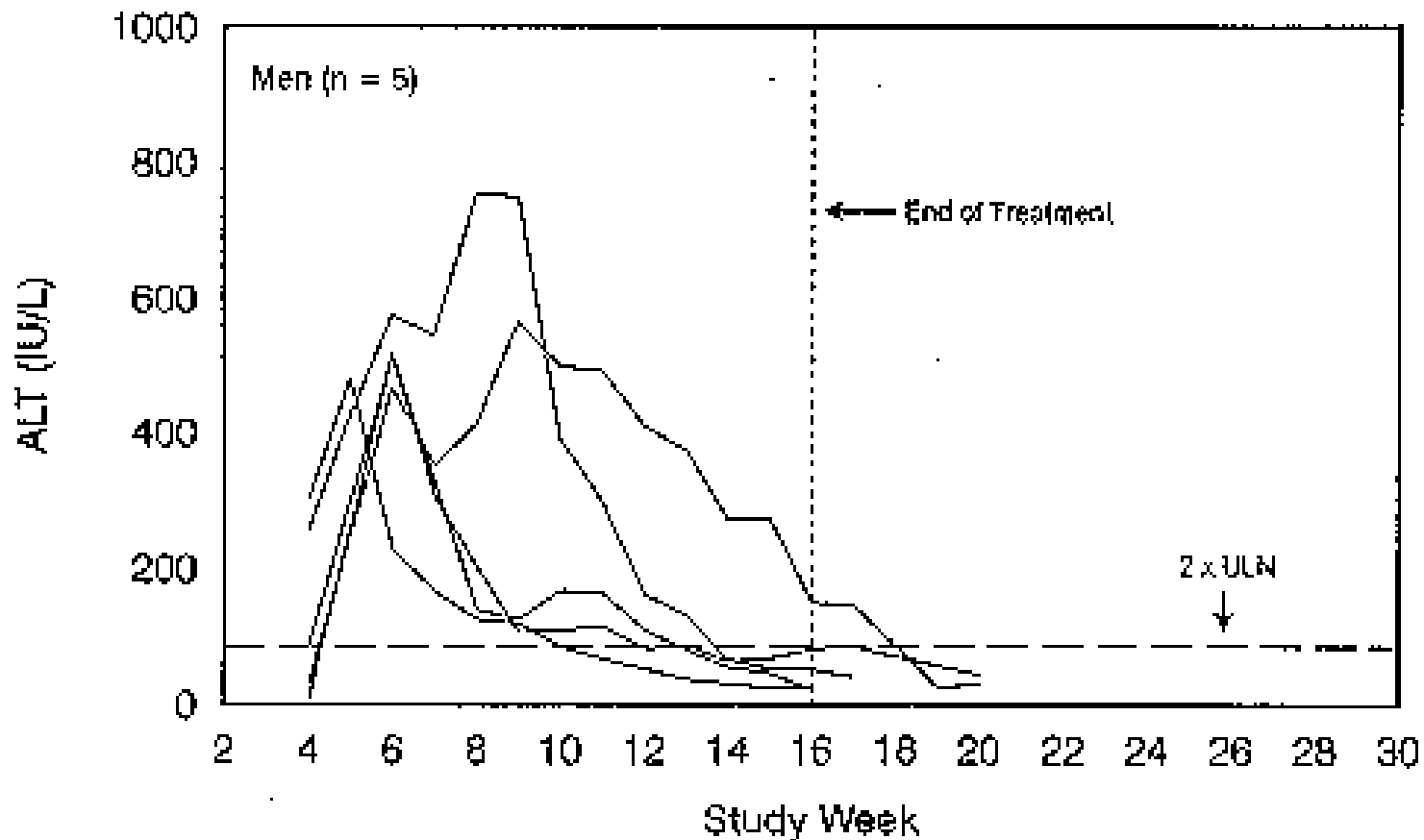
Patient #1234, caucasian male 80, Drug X



Problems with ALT as a biomarker for AIHI in clinical trials

- 1). Frequency and height of ALT elevations does not predict AIHI risk (eg. ALT > 20 X ULN observed in 2% of patients treated with tacrine and 0.2% of patients treated with troglitazone in clinical trials).
- 2). ALT elevations occur with many drugs, some of which do not appear to have risk of AIHI (eg. heparins, statins, aspirin, tacrine).

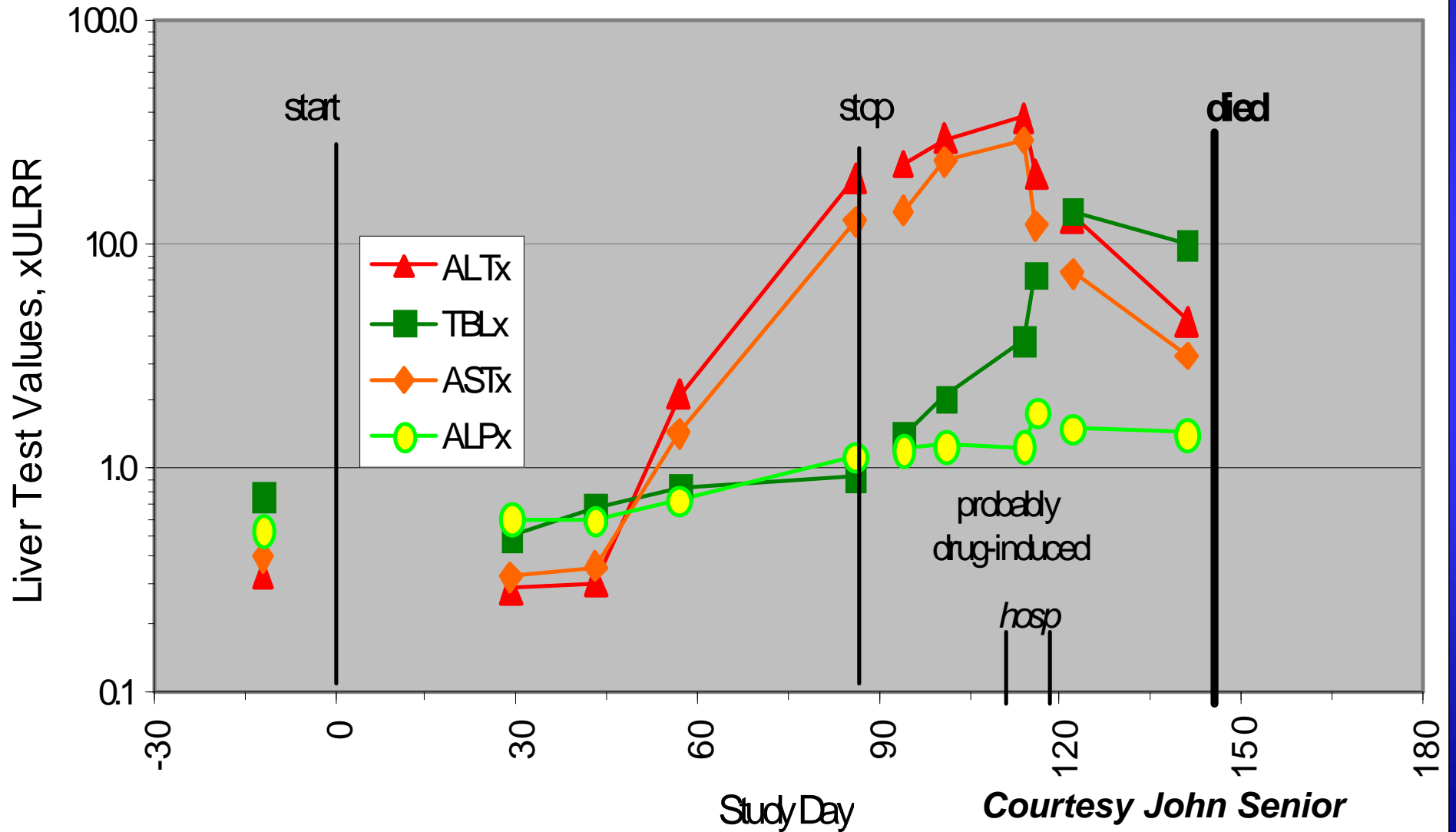
Treatment with tacrine through ALT elevations



Unpublished data

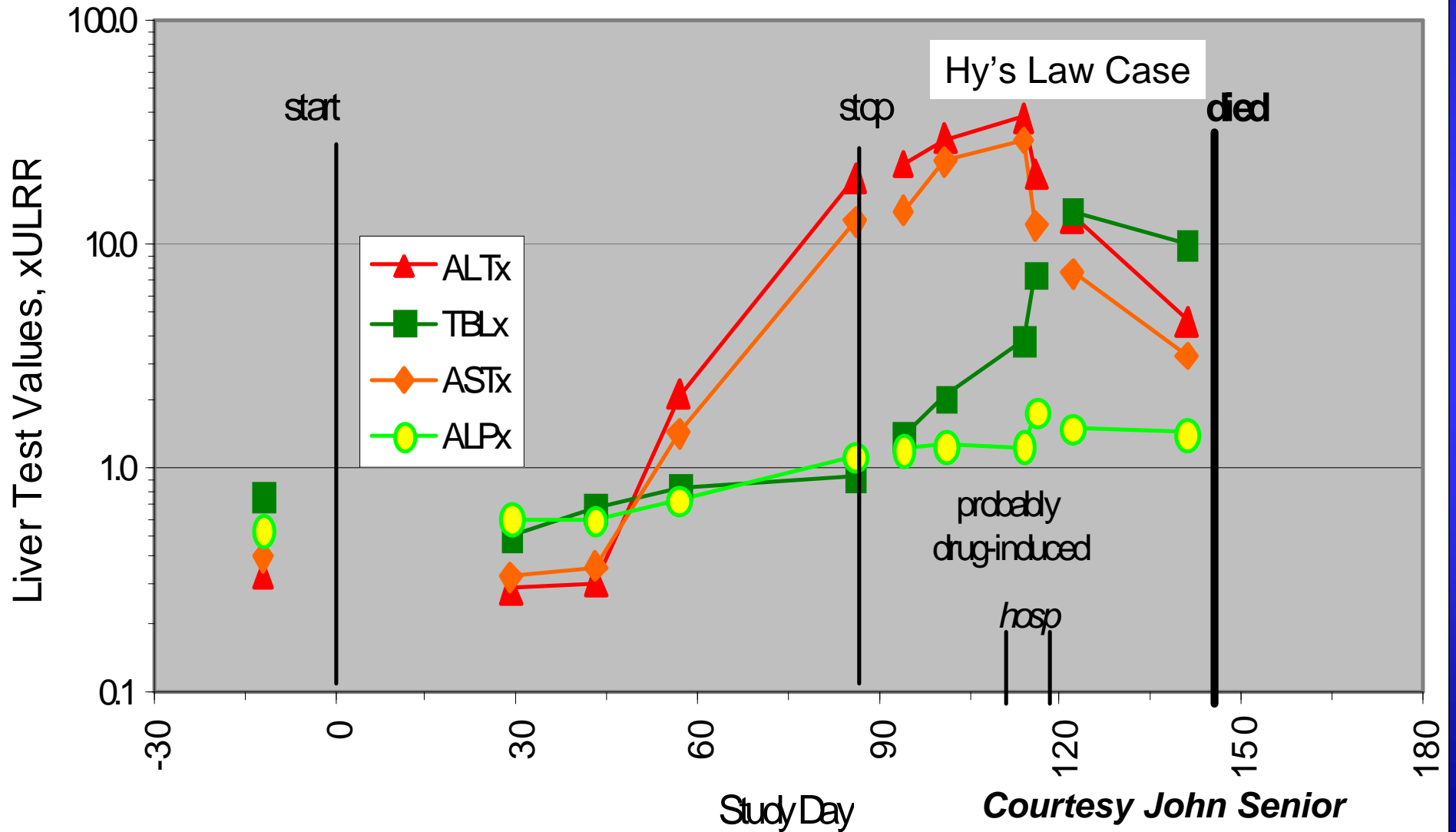
Acute Idiosyncratic Hepatocellular injury (AIHI)

Patient #1234, caucasian male 80, Drug X



Acute Idiosyncratic Hepatocellular Injury (AIHI)

Patient #1234, caucasian male 80, Drug X



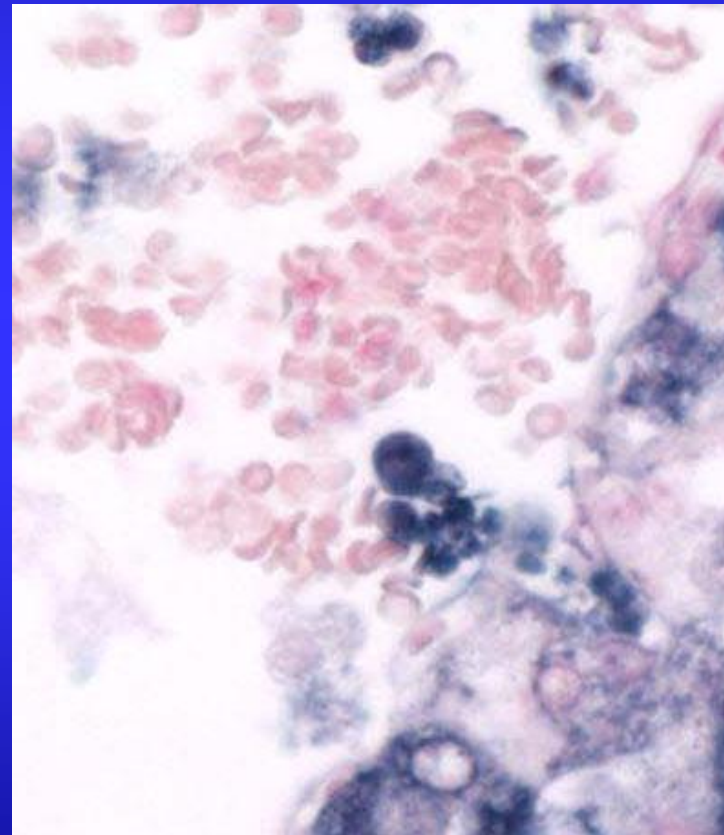
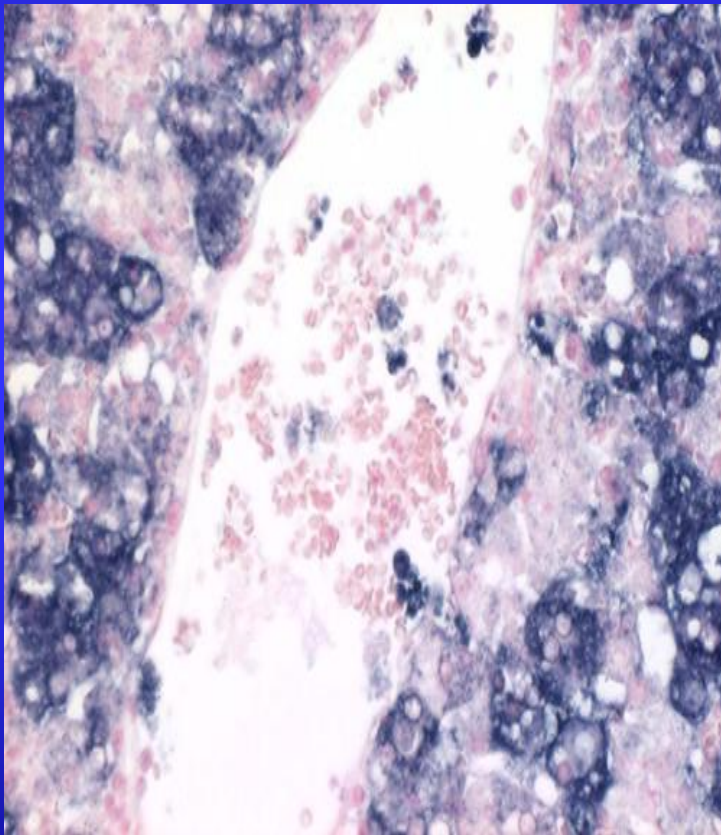
Liver Safety Biomarker Efforts

- 1). Drug Induced Liver Injury Network
(DILIN)**
- 2). Serious Adverse Events Consortium**
- 3). InnoMed Pred Tox**
- 4). ILSI HESI Biomarker Technical
Committee**
- 5). Predictive Safety Testing Consortium**

Non-protein avenues for biomarker discovery

- 1). Liver specific mRNA transcripts are present in blood during liver injury.**

In Situ Hybridization for Albumin in Rat Liver after Toxic Injury

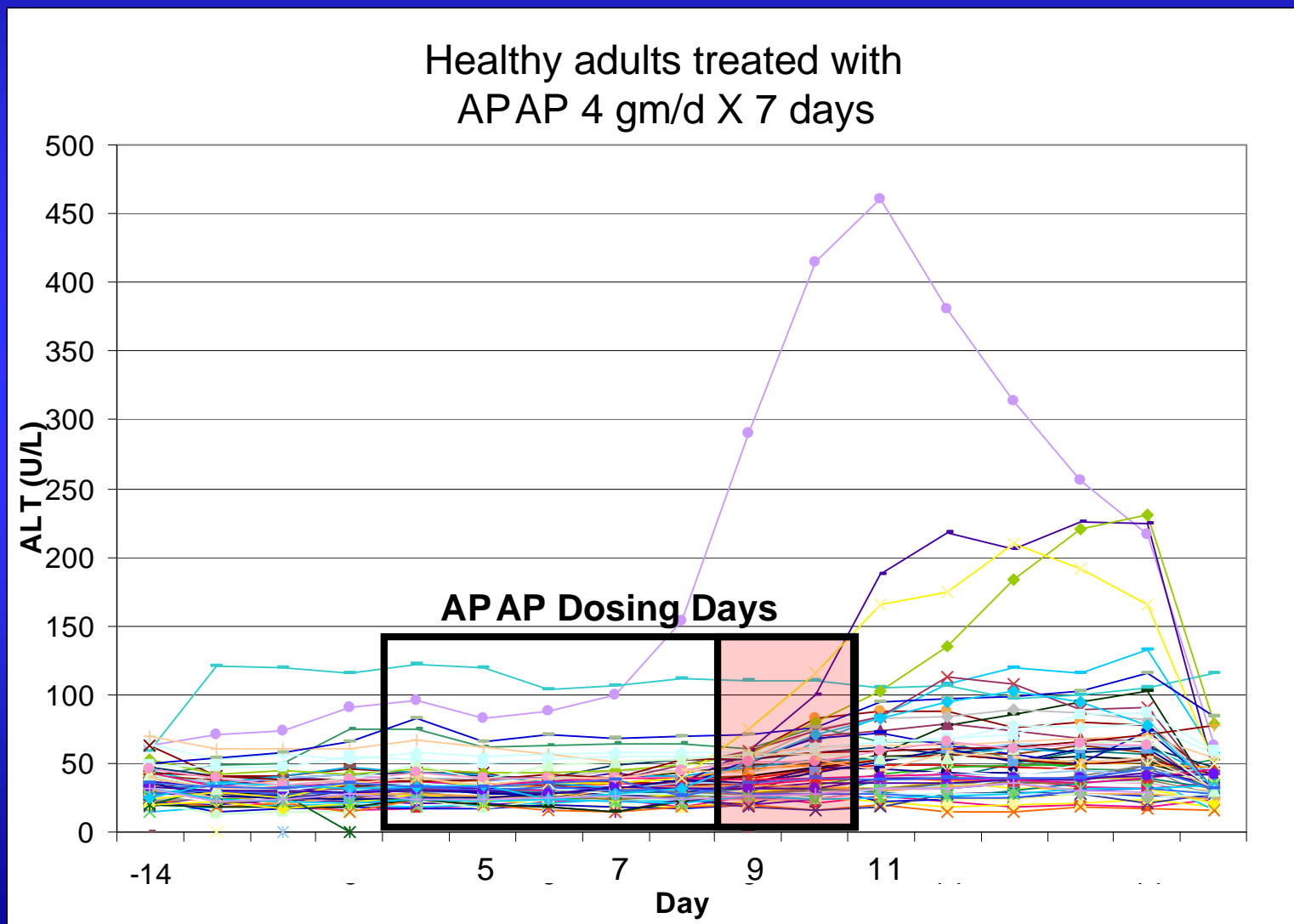


From Pfizer Scientists

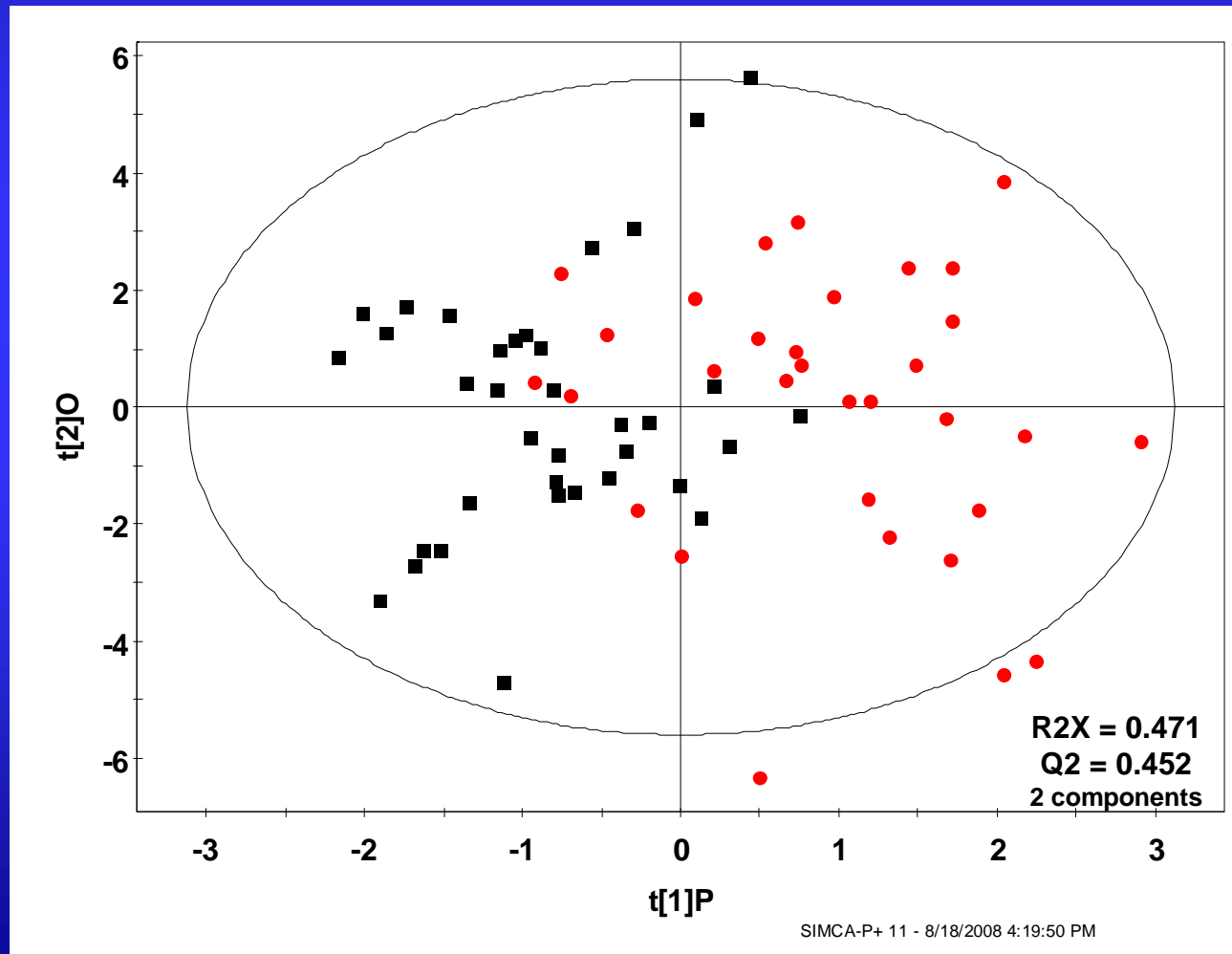
Other promising avenues for biomarker discovery

- 1). Liver specific mRNA transcripts are present in blood during liver injury.
- 2). Metabolomic approaches are promising.

Can Metabolomics Distinguish Responders from Non-Responders?

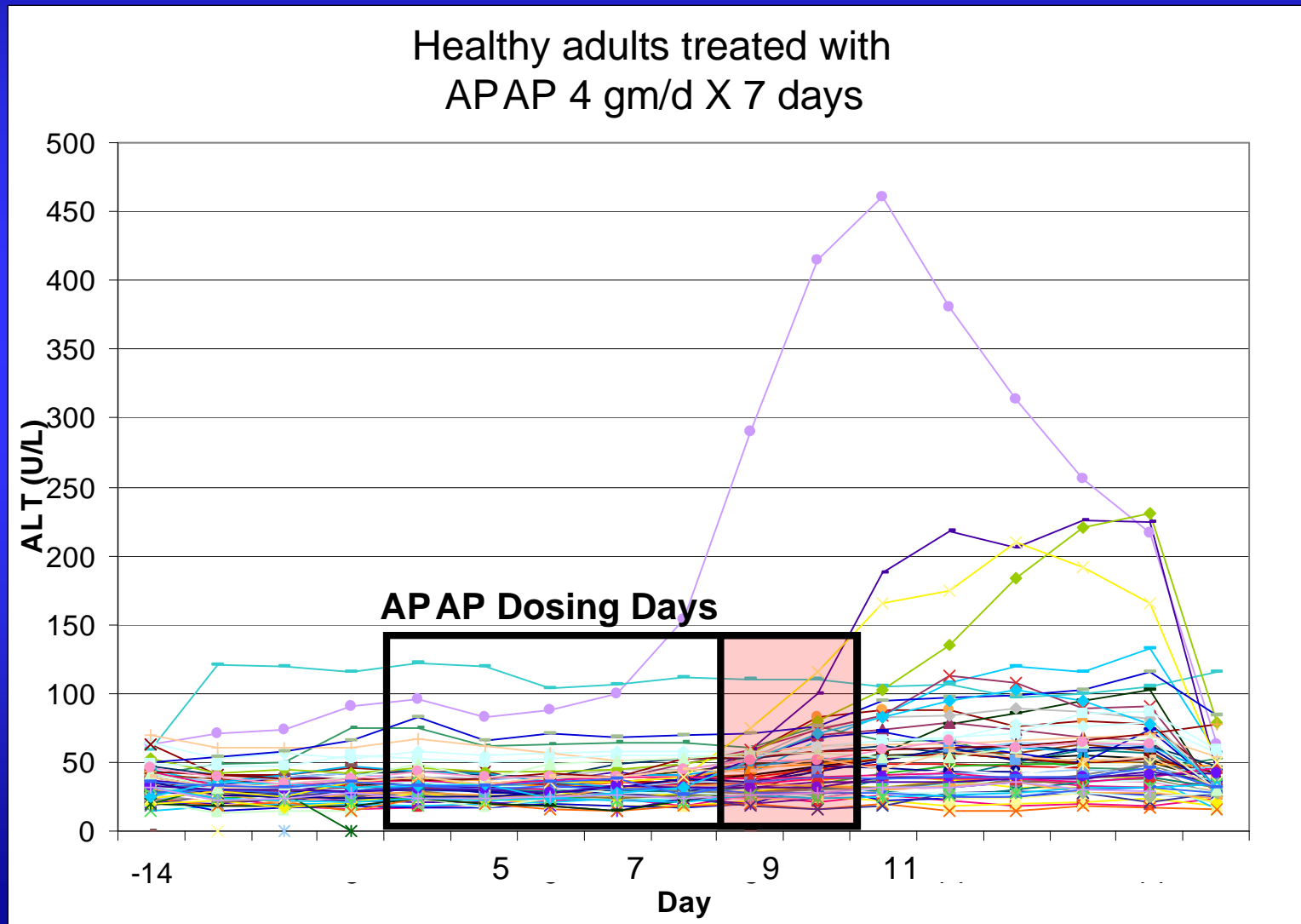


OPLS Analysis of Responders vs. Non-responders at Days 9-10

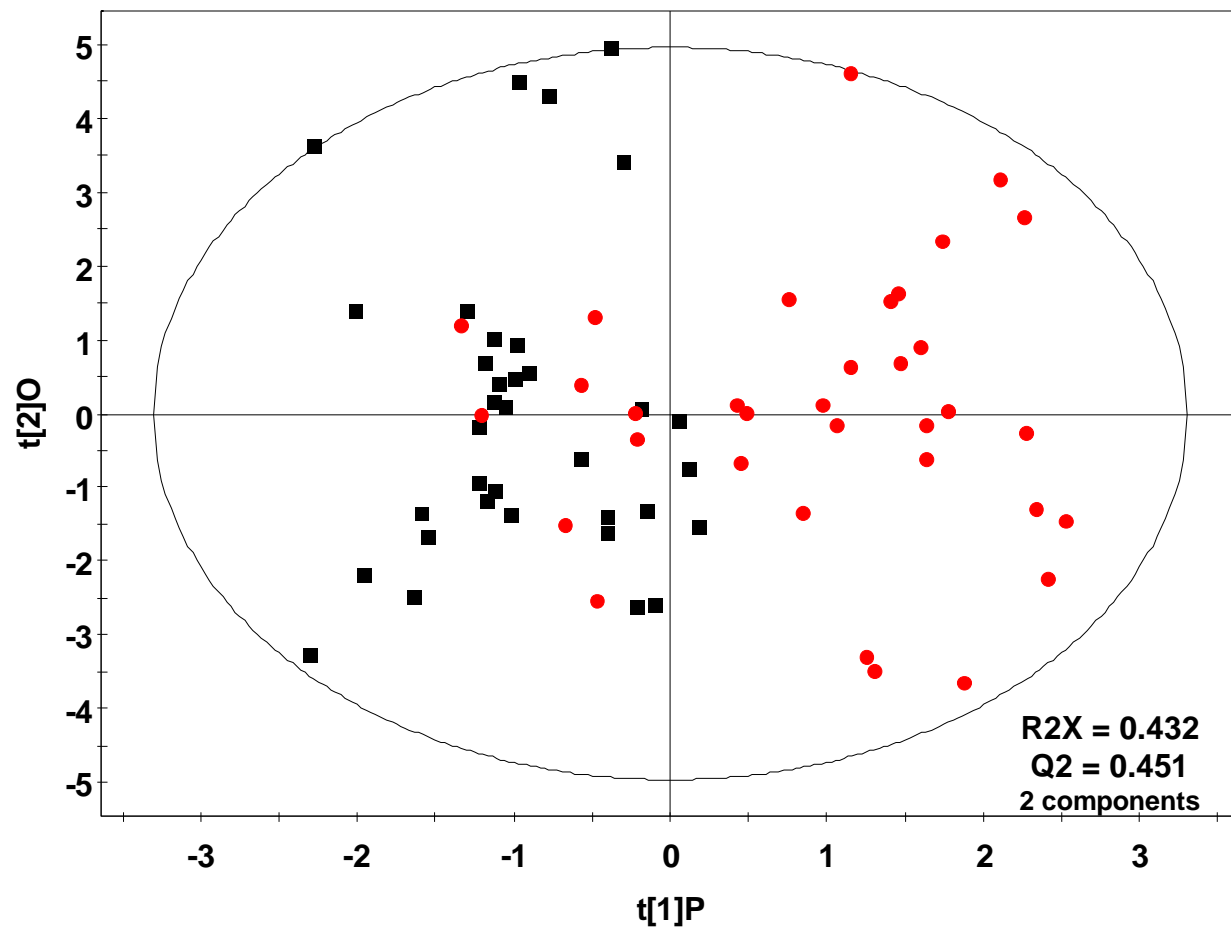


Unpublished data

Metabonomic Prediction of Hepatotoxicity Prior to ALT Rise



OPLS Analysis of Responders vs. Non-responders at Days 5-6

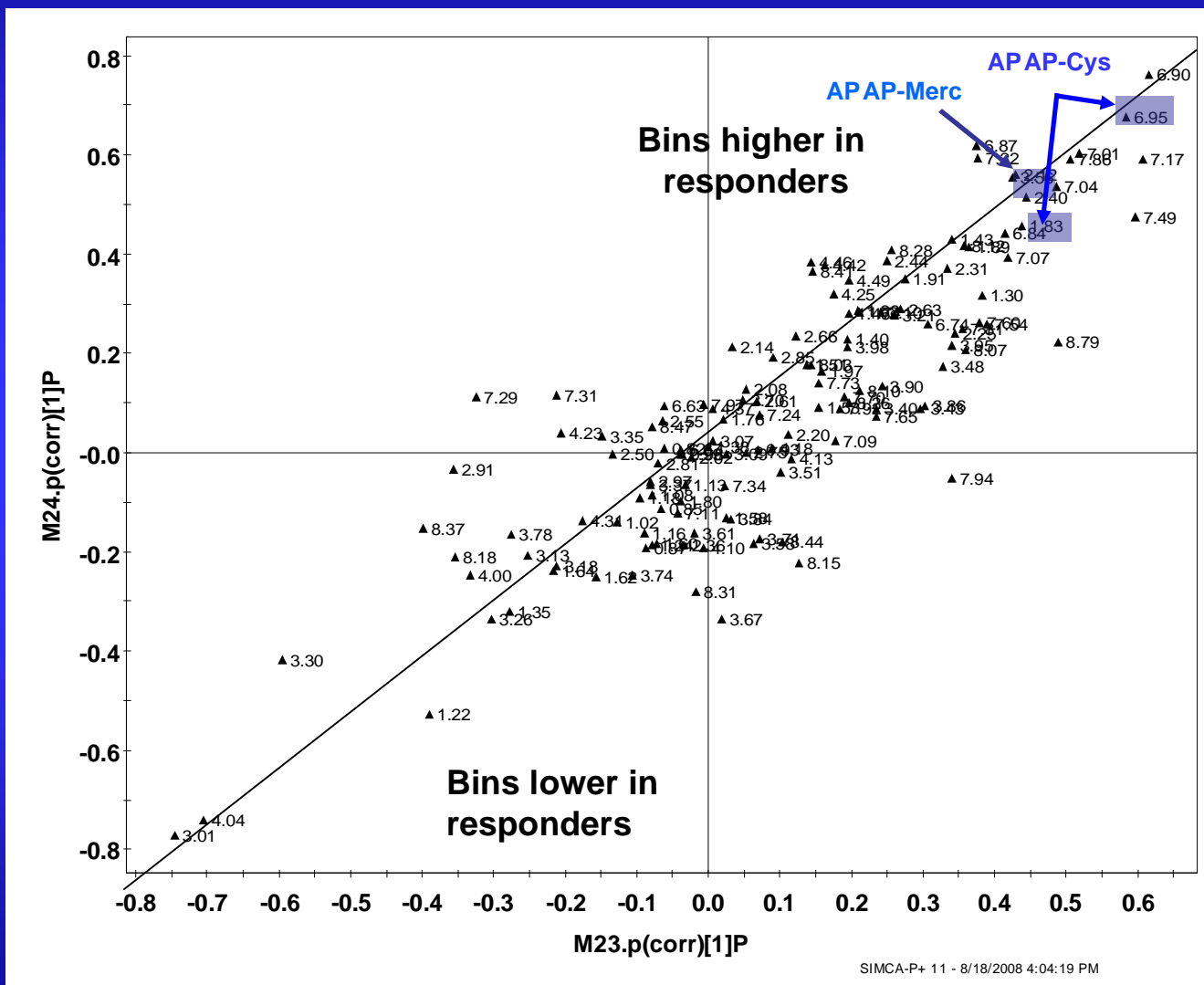


SIMCA-P+ 11 - 8/18/2008 4:25:05 PM

Unpublished data

Correlation Between Biomarkers for Days 5-6 vs Days 9-10

Coefficients from Days 5-6



Coefficients from Days 9-10

Unpublished data

Summary

A bottleneck for progress is the availability of prospectively collected human biospecimens with complete phenotype data.

Three target clinical populations for discussion

- 1). Hy's Law Cases.
- 2). Prospective, controlled clinical trials with established, well-characterized AIHI agents such as isoniazid.
- 3). Phase 3 clinical trial subjects receiving a drug known to cause ALT elevations but not yet known to cause AIHI.

Thanks

Jack Bloom, Chris Hunt

Dominique Larrey (Montpelier, FR),

Neil Kaplowitz (USC),

Jack Uetrecht (Ontario, CA).



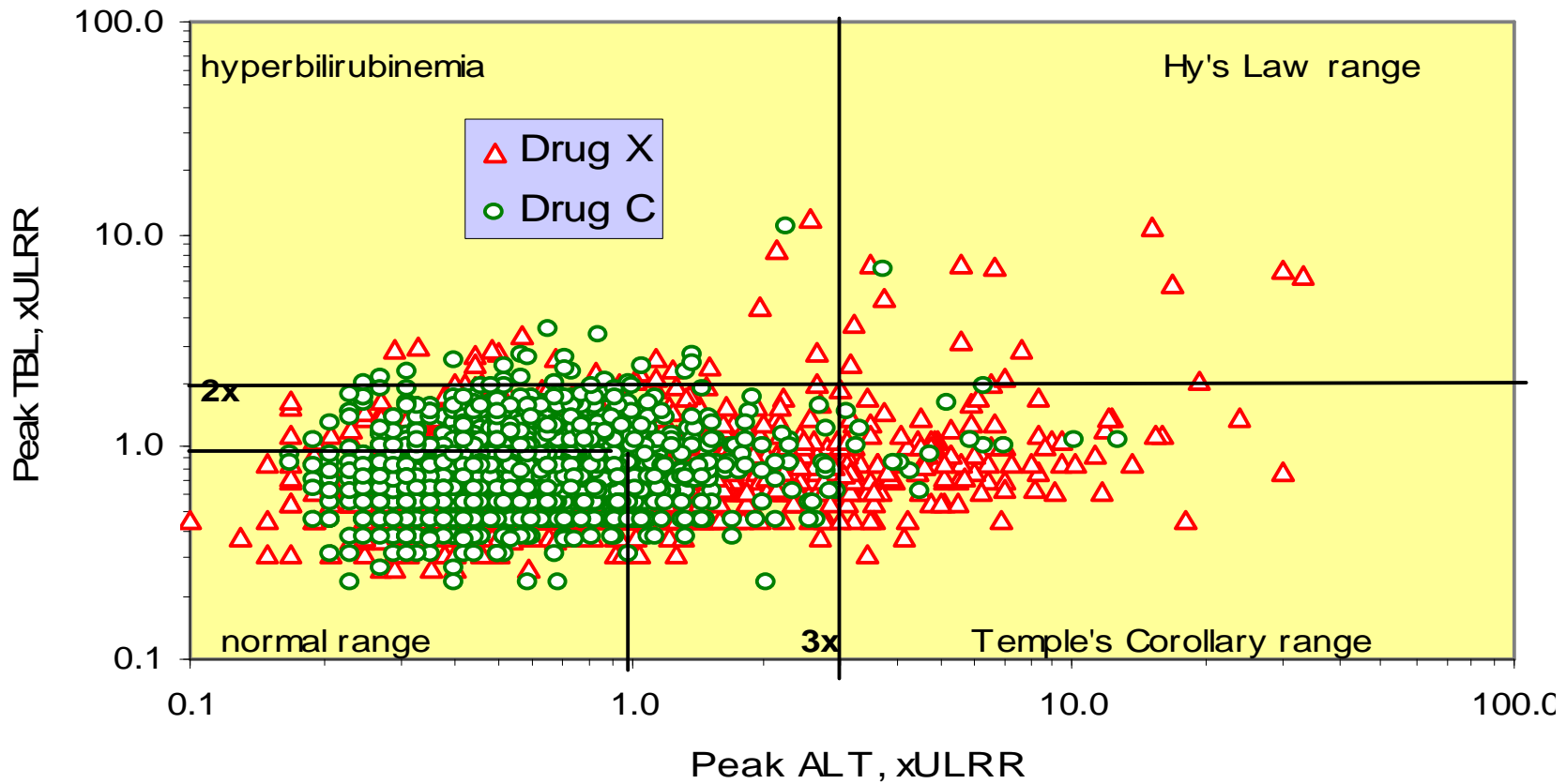
Conclusion

The data suggest that metabolomic approaches may be able to distinguish susceptibles from non-susceptibles prior to development of ALT elevations.

What did we learn about APAP hepatotoxicity?

- 1). Innate immune involvement suggested
- 2). NAPQI supported as reactive metabolite
- 3). Mitochondria is a target for toxicity.

eDISH format for display of clinical trial liver safety data



www.fda.gov/cder/livertox/presentations2008/D-GelperinGuo2.pdf

Studying Liver Toxicity in Humans

Aminotransferase Elevations in Healthy Adults Receiving 4 Grams of Acetaminophen Daily A Randomized Controlled Trial

Paul B. Watkins, MD

Neil Kaplowitz, MD

John T. Slattery, PhD

Connie R. Colonese, MS

Salvatore V. Colucci, MS

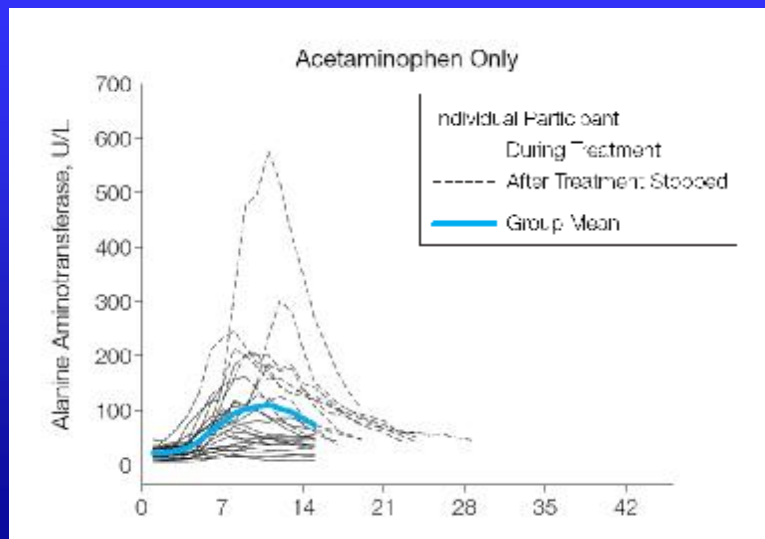
Paul W. Stewart, PhD

Stephen C. Harris, MD

Context During a clinical trial of a novel hydrocodone/acetaminophen combination, a high incidence of serum alanine aminotransferase (ALT) elevations was observed.

Objective To characterize the incidence and magnitude of ALT elevations in healthy participants receiving 4 g of acetaminophen daily, either alone or in combination with selected opioids, as compared with participants treated with placebo.

Design, Setting, and Participants A randomized, single-blind, placebo-controlled, 5-treatment, parallel-group, inpatient, diet-controlled (meals provided), longitudinal study of 145 healthy adults in 2 US inpatient clinical pharmacology units.



Study found that 30-40% of subjects experienced ALT elevations > 3X ULN

Watkins, et al., JAMA, 296 (1), 87, 2006

Industry SAE Priorities 2006

Rank Order [1 highest to 5 lowest]

| | Overall Priority | Variance | |
|---------------------------|------------------|------------|--|
| Hepatotoxicity | 1.1 | low | |
| QT Prolongation | 2.6 | moderate | |
| Rhabdomyolosis | 3.3 | moderate | |
| Serious Skin Rashes [SJS] | 3.5 | high | |
| Edema | 4.4 | high | |

SAE Consortium Survey – courtesy of Arthur Holden

Regulatory actions on approved due to hepatotoxicity (1995-2008)

Withdrawals

bromfenac

troglitazone

pemoline

Second Line

felbamate

tolcapone

trovafloxacin

Warnings

acetaminophen

leflunomide

nefazodone

nevirapine

pyrazinamide/rifampin

terbinafine

valproic acid

zifirlukast

atomoxetine

interferon 1b –1b and 1a

saquinavir

infliximab

bosentan

telithromycin

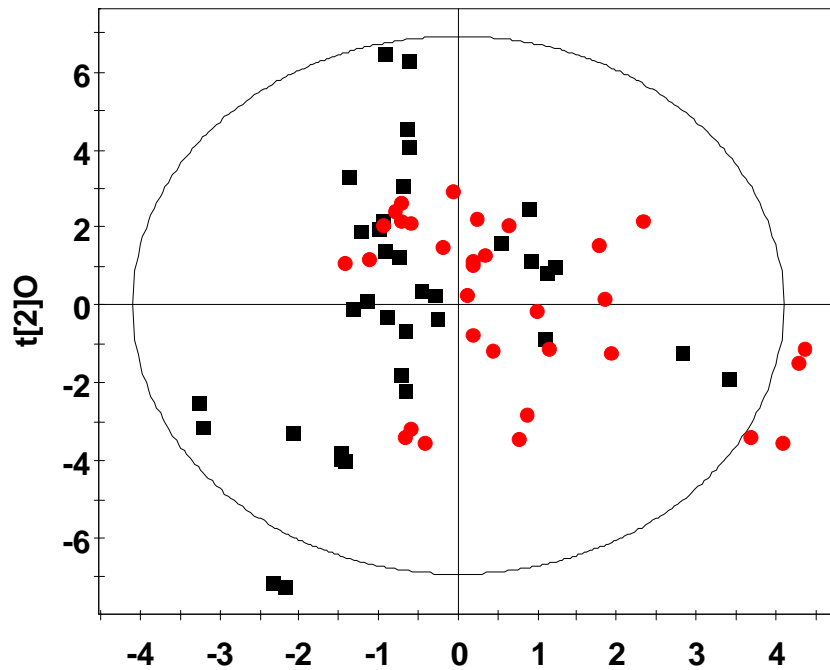
(kava, lipokinex)

<http://www.fda.gov/medwatch/safety.htm>

Characteristics of AIHI

- 1). Current preclinical screens not very sensitive or predictive.
- 2). Appear to occur with drugs that produce elevations in serum alanine aminotransferase (ALT)

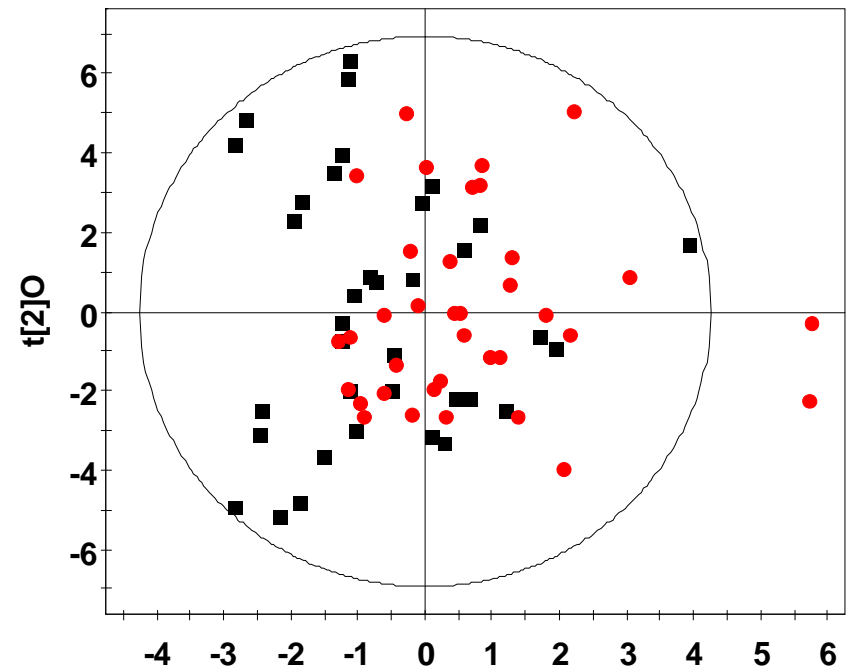
OPLS Days Using Only APAP Metabolites



Day 9-10

t[1]P
SIMCA-P+ 11 - 8/21/2008 11:52:33 AM

$R^2X = 0.91$
 $R^2Y = 0.16$
 $Q^2 = 0.09$



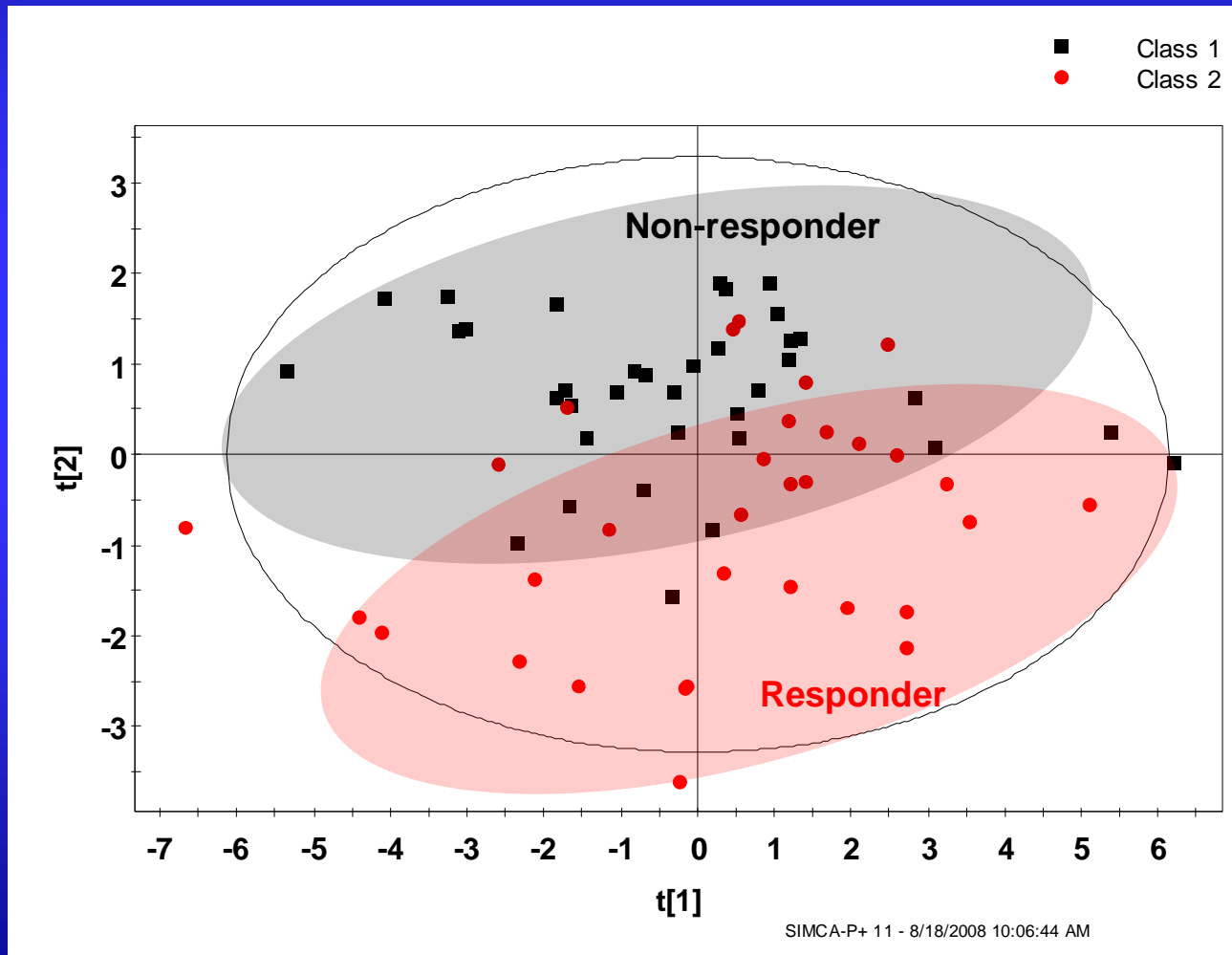
Day 5-6

t[1]P
SIMCA-P+ 11 - 8/21/2008 11:53:37 AM

$R^2X = 0.88$
 $R^2Y = 0.16$
 $Q^2 = 0.11$

Unpublished data

PCA Analysis of Responders & Non-responders at Days 9-10

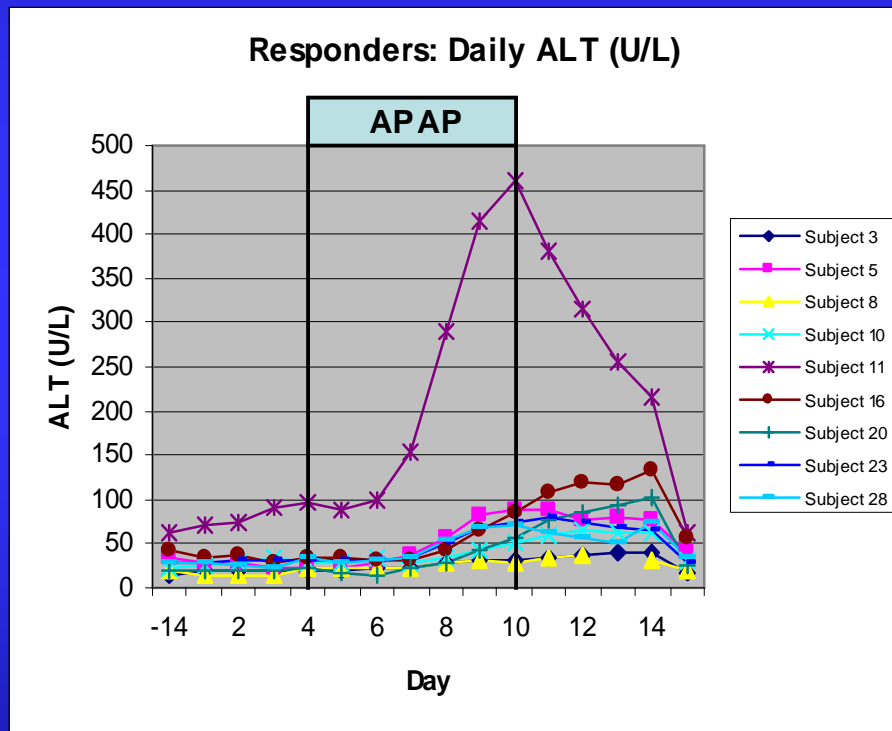


Unpublished data

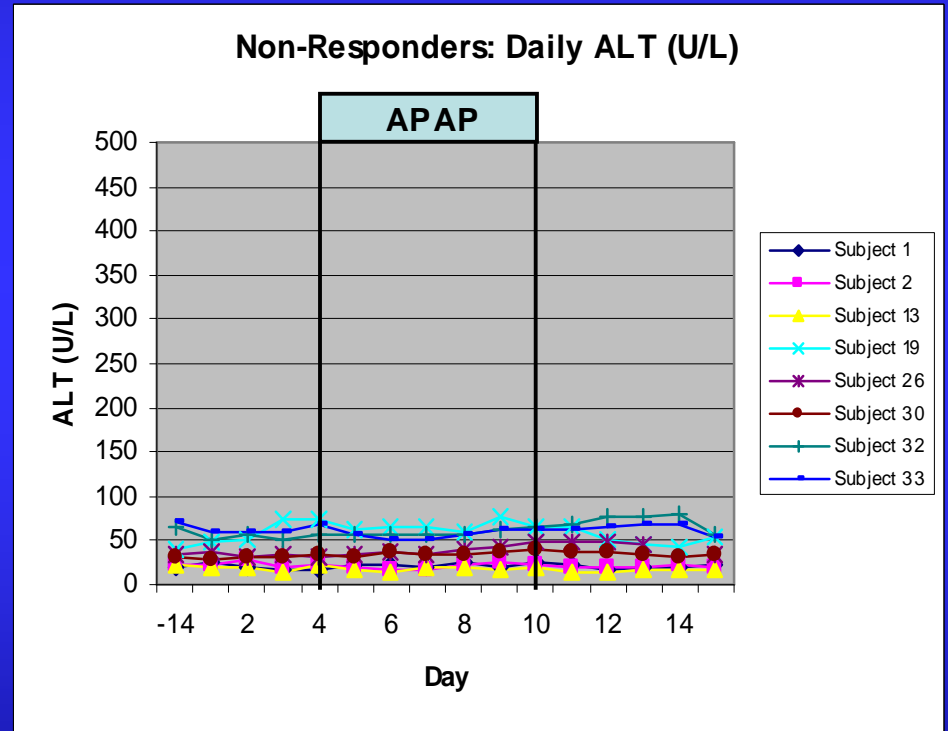
Non-protein avenues for biomarker discovery

- 1). Liver specific mRNA transcripts are present in blood during liver injury.**
- 2). Metabolomic approaches are promising.**

Responders and Non-Responders in a two week acetaminophen (4gm/d) Study



Peak ALT levels > 2.0 x baseline



Peak ALT levels < 1.5 x baseline