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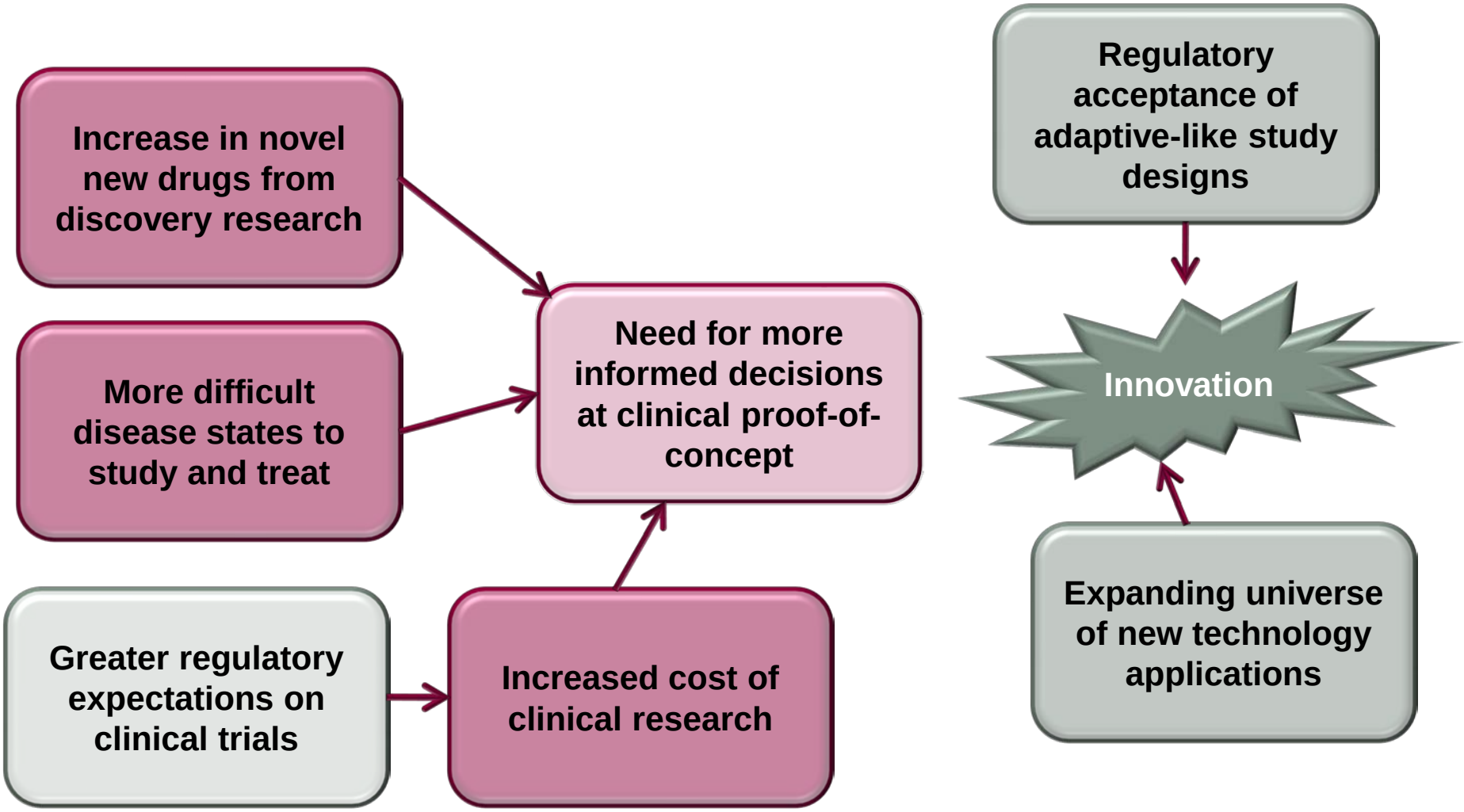
Solving Challenges Faced in Early Clinical Development

J. Fred Pritchard, Ph.D.

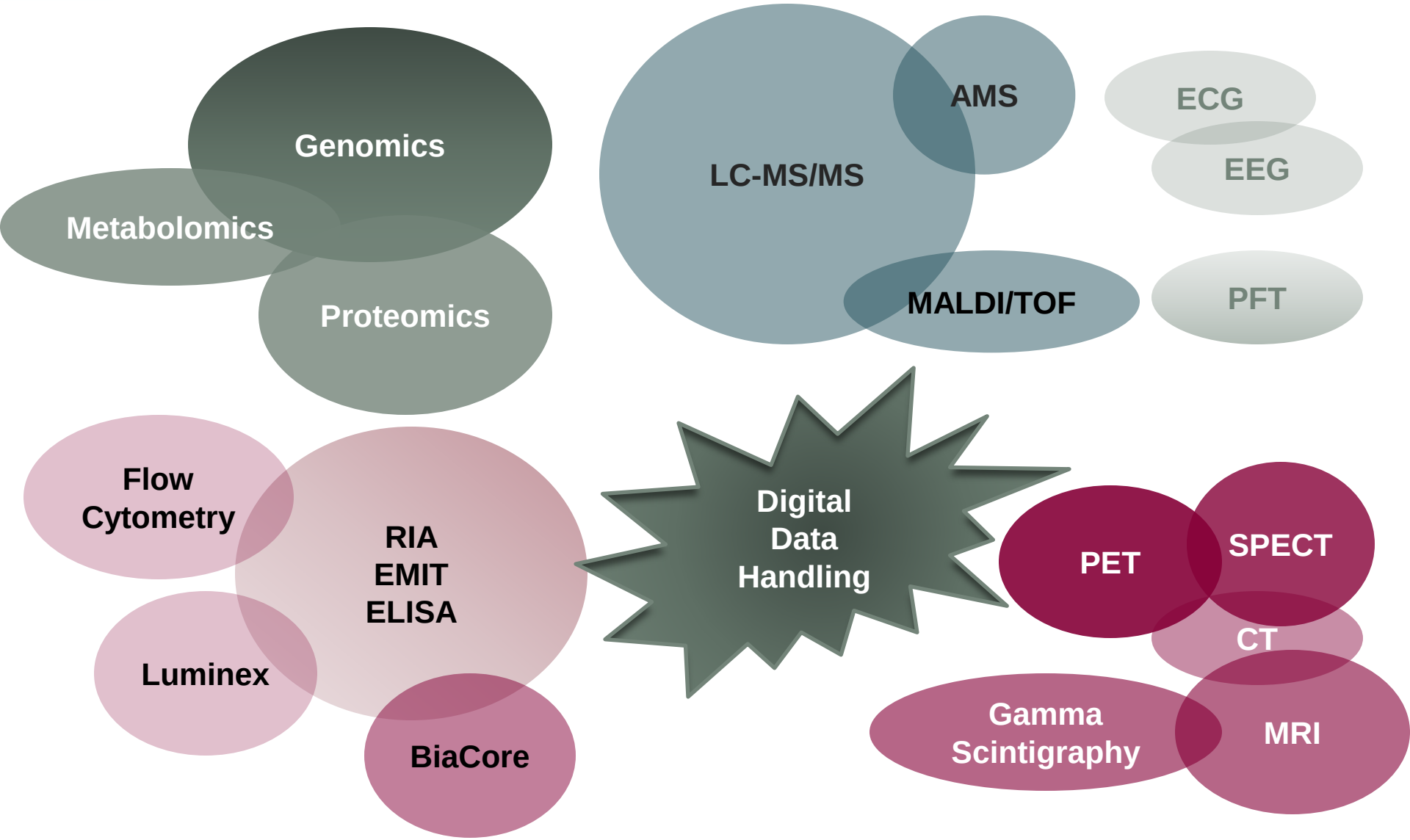
June 5, 2013

The Pressure is On for Proof-of-Concept!



New Technology Drives Innovation

So Many New Tools in So Little Time



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Understanding Relevance of Preclinical Signals Early in Clinical Development

- Focus of Presentation
  - Examples of common and uncommon problems faced by drug developers early in clinical development.
  - How to leverage new technologies to provide early answers to tough questions

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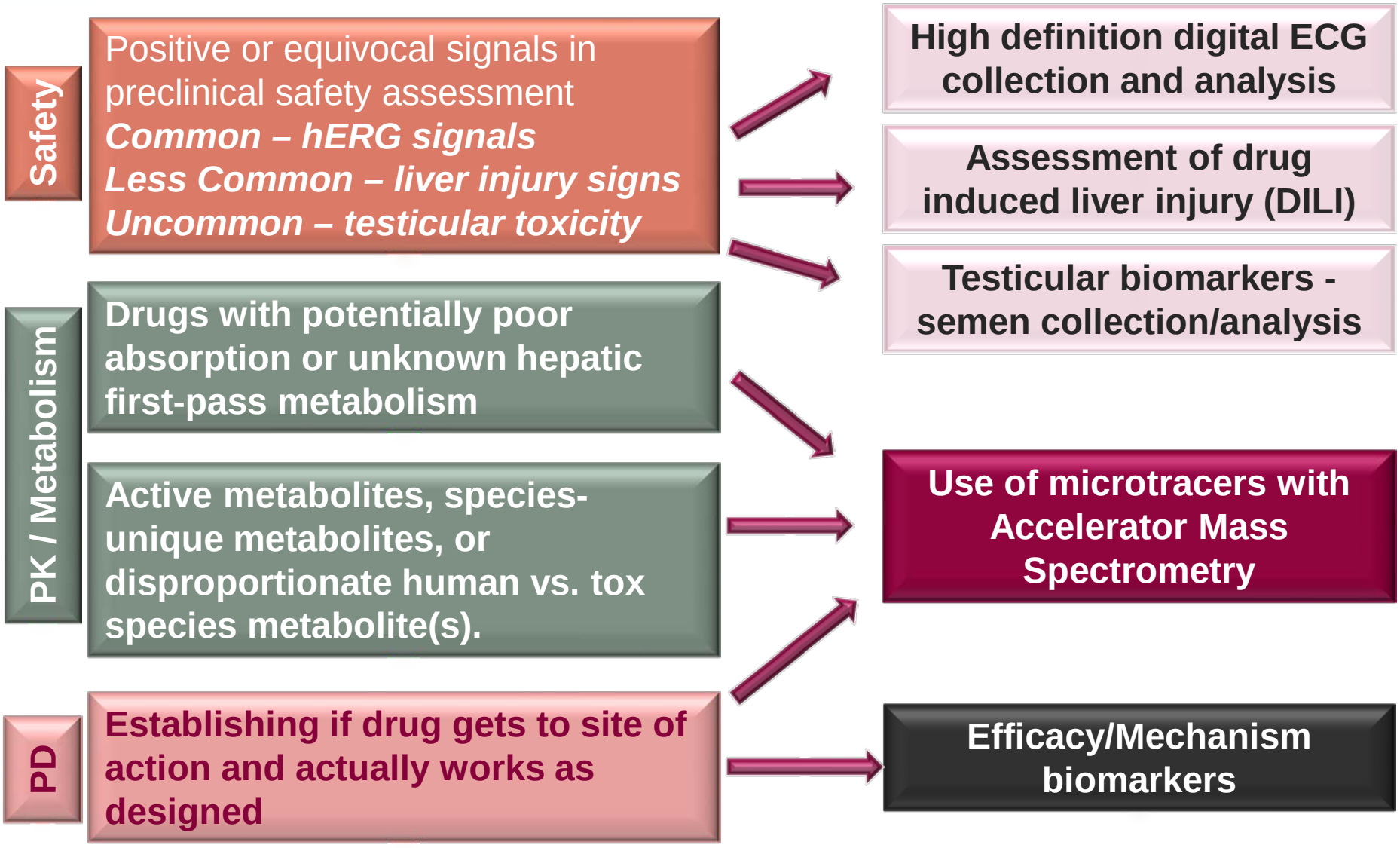
Troublesome Problems Encountered in Early Clinical Research



QT Prolongation

QT Safety Biomarkers

- Nonclinical risk assessment:
  - In vitro IKr
  - In vivo QT

  Ref: ICH S7B

- Clinical risk assessment:
  - ECGs in Phase I - II
  - Thorough QT/QTc study

  Ref: ICH E14

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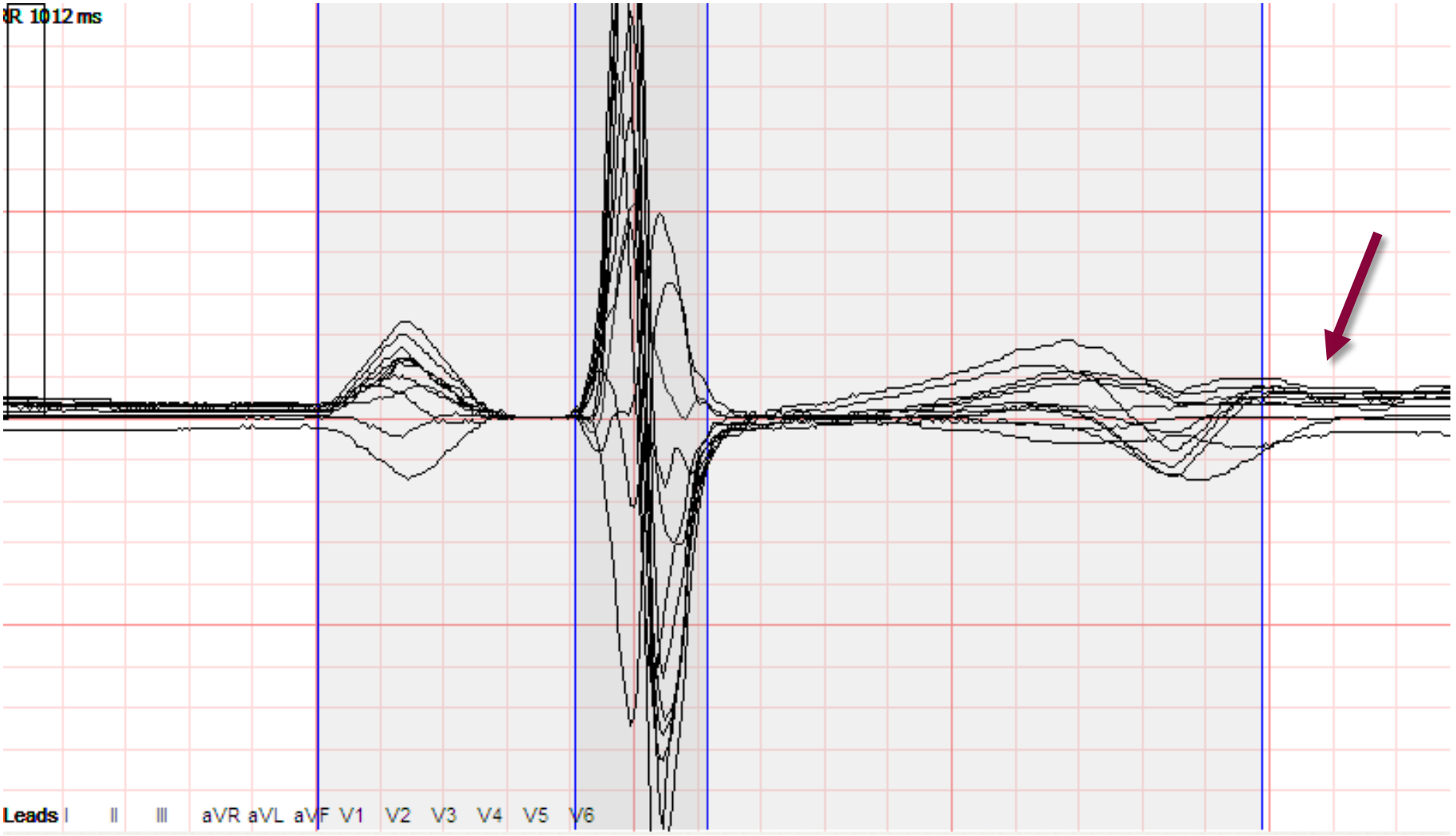
Comparing ECG Acquisition Modalities

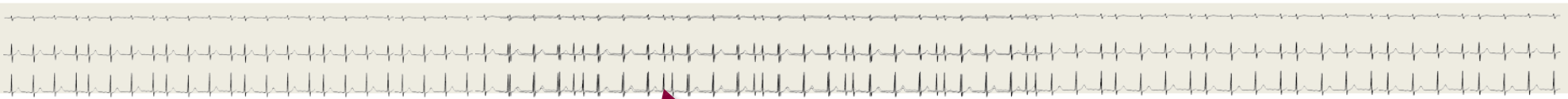
	Stand alone 12 Lead	Standard Holter	Telemetry System	Blue-tooth Holter
Continuous ECG Collection	NO	YES	YES	YES
Retrospective data collection	NO	YES	YES	YES
View Safety ECG	YES	NO	YES	YES
Data capture out of range	NO	YES	NO	YES
Transportable	YES	YES	NO	YES

Digital ECG Reading Enables Overlay of Lead Signals for Better Accuracy in Measurement of Intervals



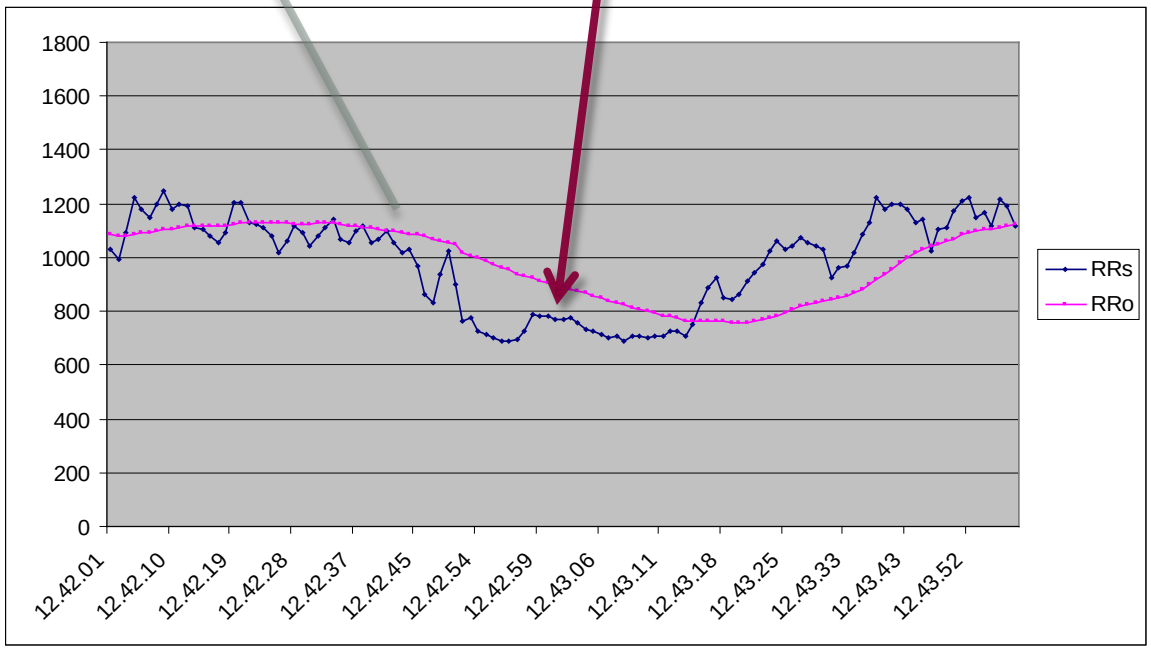
ECG Extraction: Find a Period of Stable Heart Rate and Reduced Noise

Accurate QTc require a stable preceding heart rate



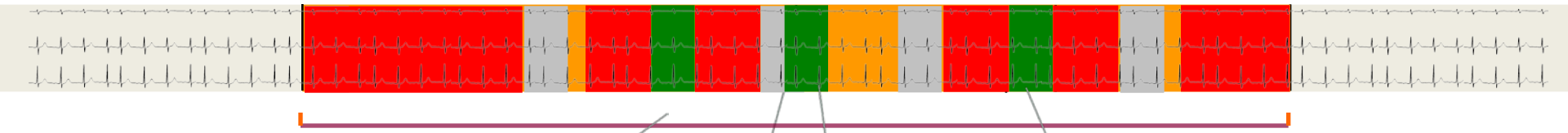
Extracted time point

Nominal time point



Antares Optimal ECG Extraction: Decreases Variability

Searching for best extraction, noise and HR stability criteria…



OPTIMUM WINDOW

Second extraction

Nominal Timepoint

Third extraction

Best ECG! First extraction

F Badilini, Vaglio, Sarapa, A.N.E 2009;14(Supp1):22-29

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Better data, faster, cheaper

Drug Induced Liver Injury

Regulatory Action on Marketed Drugs due to DILI (1995-2010)**

**Partial List

Withdrawals (US* &/or other countries+)

troglitazone*
bromfenac*
trovofloxacin*
tilbroquinol+
pemoline+
tetrabamate+
ebrotidine+
nefazodone+
tolrestat+
droxicam+
niperotidine+
chlormezanone+
ximelegatran+
lumaricoxib+
gemtuzumab+

Boxed Warnings (US)

lamividine
leflunomide
propylthiouracil
lapatanib
pazopanib
sunitimib
tenofovir
tipranavir
tolcapone
bosentan
deferasirox
ambrisentan
acitretin
cytarabine
maraviroc
eltrombopa
acetaminophen (Rx)

Restricted (US)

trovofloxacin
felbamate
pemoline

Drug-Induced Liver Injury Biomarkers

- Classic serum chemistry tests include total bilirubin (TBL) and enzyme activities of ALP, AST and ALT.
  - “Validated” by more than 60 years of clinical use
  - Serum enzyme activity are NOT tests of liver function
  - TBL and prothrombin time ARE tests of liver function
  - ALT high sensitivity; TBL high specificity
- Problems:
  - Don’t discriminate between drug and non-drug etiologies
  - Are not early predictors of DILI outcomes
    - Resolvable versus serious acceleration of injury
  - Normal ranges not agreed upon

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Drug-Induced Liver Injury Biomarkers

- There is a need for DILI biomarkers to predict
  - Clinical resolution vs progression at an early stage of mild liver injury
  - Which drugs can cause idiosyncratic DILI
  - Which patients are susceptible to develop DILI

From Mark Avigan, CDER, FDA, presentation at FDA/C-Path/PhRMA HepTox Steering Committee Meeting, 15 March 2012

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Novel Biomarkers of Drug-Induced Liver Injury

- Liver-enriched microRNAs were shown to be promising serum biomarkers of acetaminophen-induced acute liver injury in mice1 and humans2
- miR-122 and miR-192 were detected earlier than ALT and at lower doses.
- miR-122 had improved liver tissue specificity vs ALT.
- There is a high degree of cross-species conservation of microRNA sequences

1Wang K et al. Proc Natl Acad Sci USA 106: 4402-4407 (2009)
2Starkey Lewis et al. Clin Pharmacol Ther 92: 291-293 (2012)

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Better data, earlier to address potential toxicity

Other Exploratory Biomarkers of DILI Currently under Investigation

- Albumin mRNA
- α-glutathione S-transferase
- High-mobility group box 1
- Cytokeratin 18
- Glutamate dehydrogenase
- Sorbitol dehydrogenase
- F-protein

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Assessing Potential for Testicular Toxicity in Men

Male Reproductive Safety – Preclinical Evaluation

- Preclinical toxicology studies may demonstrate testicular histopathological abnormalities in one species or in multiple species at high doses.
  - Histopathological changes – degeneration of spermatocytes, dilation of seminiferous tubules
  - Decrease in fertility, spermatagonia, increase in abnormal sperm in rodent reproductive toxicology studies
- There is no single species that is best for prediction of human risk.
- Abnormalities in any species may be a cause for regulatory concern leading to clinical holds.

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Testis is a Dual Organ in Function and Structure

Interstitial Compartment

- Endocrine Function
- Leydig cell
- Low metabolic rate
- Fibroblast stem cells
- Resistant to toxicity
- Functional serum biomarkers are testosterone and LH

Seminiferous Compartment

- Exocrine Function
- Sertoli and germ cells
- Active turnover rate
- Spermatogonial stem cells
- Exquisitely sensitive to toxicity
- Functional serum biomarker is FSH (highly variable) and Inhibin B (needs further clinical validation)

Semen analysis still best choice to evaluate effects on sperm production despite challenges in collecting good samples

Strategy for Assessing Testicular Safety in Men

- Conduct Phase I multiple dose safety/PK study in a healthy volunteer population of vasectomized males and postmenopausal women.
  - Data used to select dose for testicular safety study, ensuring adequate safety margins.
- Conduct study in healthy men after single dose or short term treatment where a “responder” is defined as someone who has >50% reduction in sperm concentration from baseline.
  - Needs to cover at least 90 days after dosing – full spermatogenesis cycle (e.g. semen collections at baseline - predose, 65 days, 95 days, 125 days after dosing)
  - Power study to test non-inferiority (no increase in number of responders in treated group compared to placebo-treated group) – usually 100-150 participants

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Strategy for Assessing Testicular Safety in Men

- Primary Endpoint
  - Concentration of viable sperm in semen
- Secondary Endpoints
  - Sperm motility in semen
  - LH, FSH, testosterone and Inhibin B in serum at timepoints shortly after drug dosing and at periods of semen sampling
- Controlling variability is critical to obtain statistical valid results
  - Limit number of sites (ideal one or two)
  - Limit number of laboratories doing sperm testing (ideal just one with same team that sets up at clinical site during sampling periods)
  - Multiple samples per time period (ideal is 3 over 24 hours after 48 hour abstinence)

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Better data early to address potential serious toxicity

Use of Accelerator Mass Spectrometry

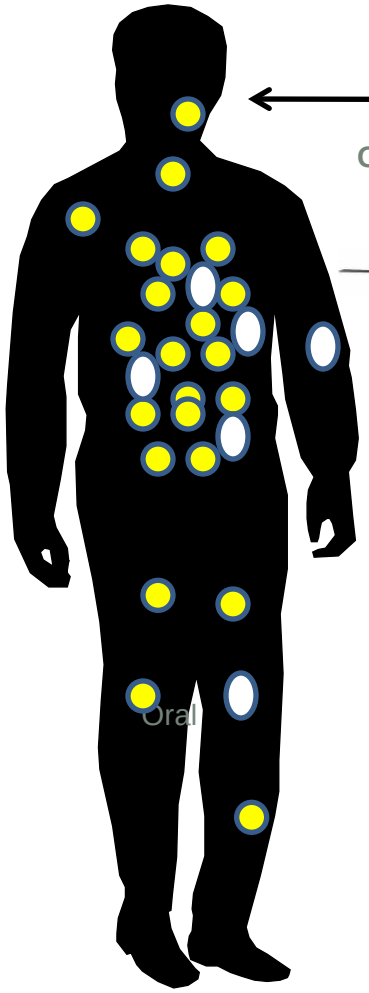
Accelerator Mass Spectrometry

- Measures isotope ratios – can detect ultra low levels of ^{14}C radioactivity
- Technology used in carbon dating of antiquities
- First biological application in1989

Applications in Pharmaceutical Research (since 1998)

Preclinical:	Special bioanalysis (proteins, monoclonal antibodies, interfering RNA); Phase 0 (subtherapeutic dose) clinical studies
Early Clinical:	**MIST (Metabolism in Safety Testing) solution, metabolic profiling, absolute bioavailability**
Clinical:	Bioanalysis of high potency drugs

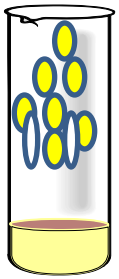
Isotopic Tracers: Determination of Absolute Bioavailability (F)



Oral dose

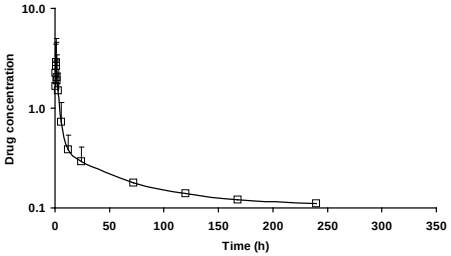
IV dose (labelled)

Blood samples over time



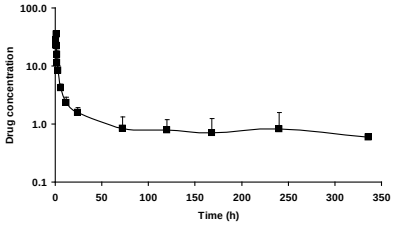
LC-MS measures total drug

Providing the ^{14}C-drug concentration is very small this = oral dose



HPLC-AMS measures ^{14}C-drug

This = IV dose



$$F = AUC_{po}/AUC_{iv} \times Dose_{iv}/Dose_{po}$$

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When AMS Provides Enriched Data?

- Poor or variable bioavailability
  - Is absolute bioavailability too low?
  - Is it influenced by formulation?
  - Role of gut absorption/metabolism vs. hepatic metabolism and efflux
- Different metabolic profiles between species used in toxicology
  - Which species reflect human metabolic profile qualitatively and quantitatively?
- Exposure in tissues
  - Cerebral spinal fluid (CSF) exposure for CNS-acting drugs?
  - Systemic exposure for dermal, inhaled, optical, etc. drug delivery
- High potency drugs
  - Ultra-low concentration measurements

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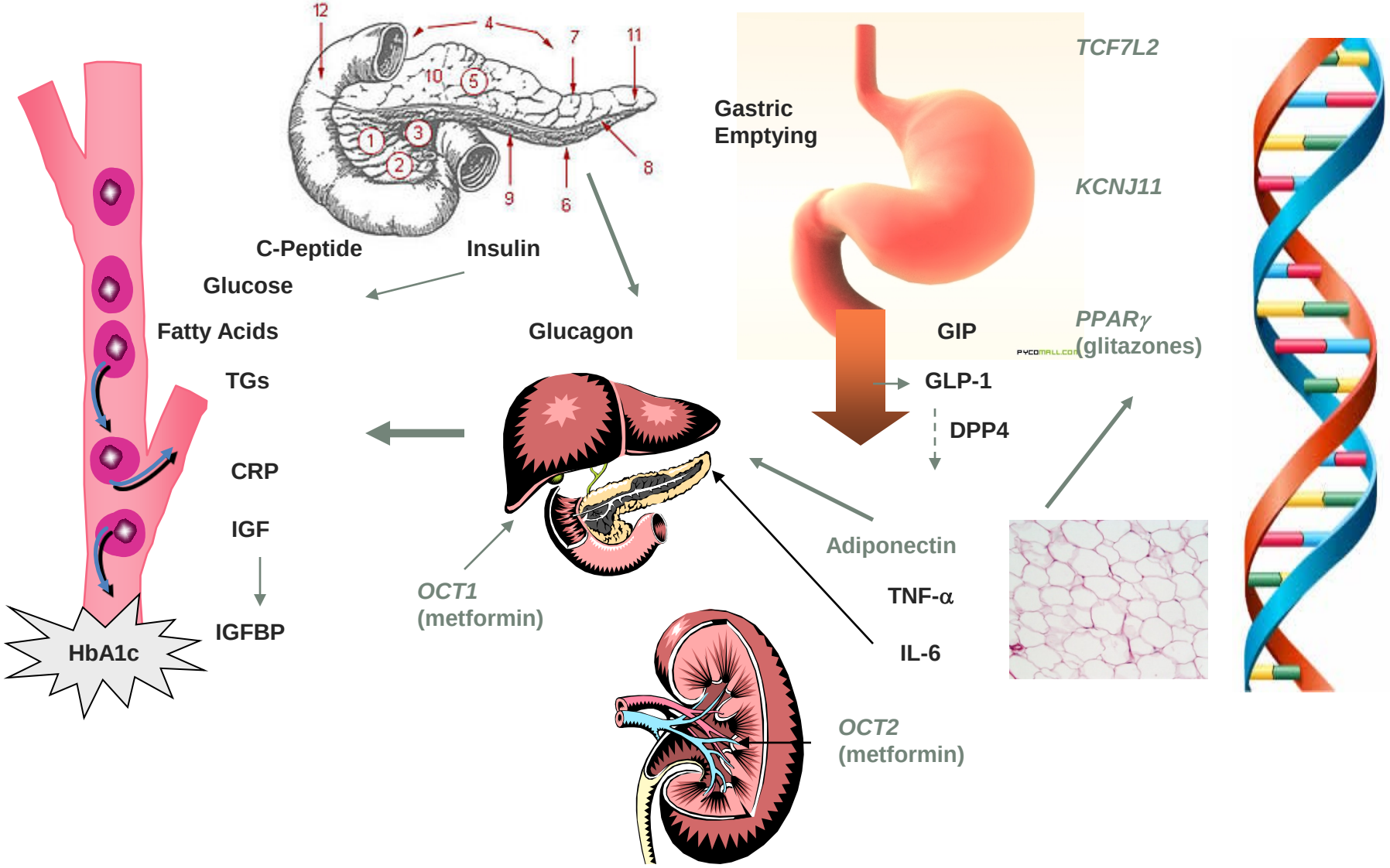
Use of Mechanism/Efficacy Biomarkers in Early Clinical Development

Plethora of Biomarkers for Diabetes



SAD Study of a Novel DPP-4 Inhibitor in Mild Diabetic Patients

Sequence	Patients	Treatment Periods		
		P1	P2	P3
1	N = 5	PLA	75 mg	200 mg
2	N = 5	25 mg	PLA	200 mg
3	N = 5	25 mg	75 mg	PLA

Sequence	Patients	Treatment Periods		
		P'1	P'2	P'3
4	N = 5	PLA	100 mg	300 mg
5	N = 5	50 mg	PLA	300 mg
6	N = 5	50 mg	100 mg	PLA

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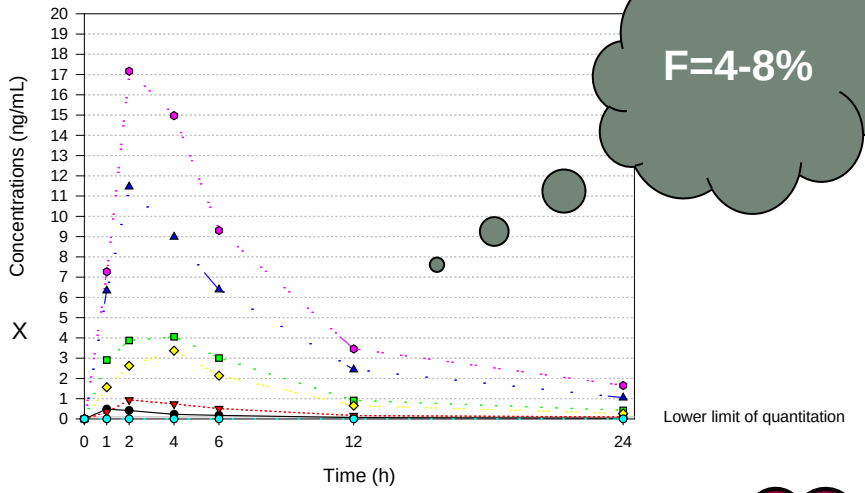
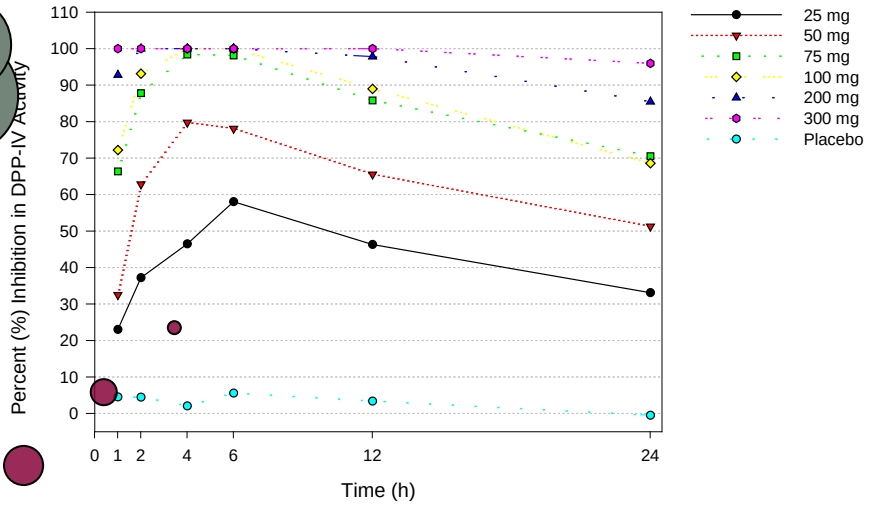
Results of SAD Study in Mild Diabetic Patients: *Early Evidence of Efficacy*

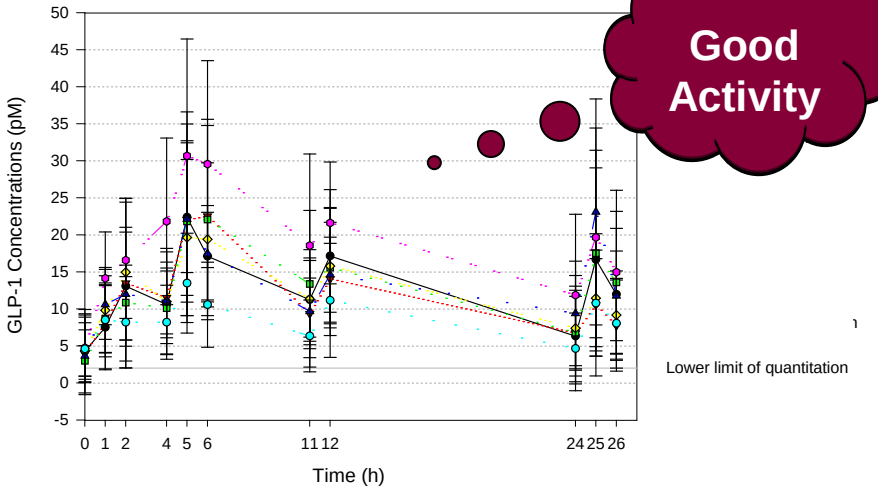
Drug Plasma Concentration



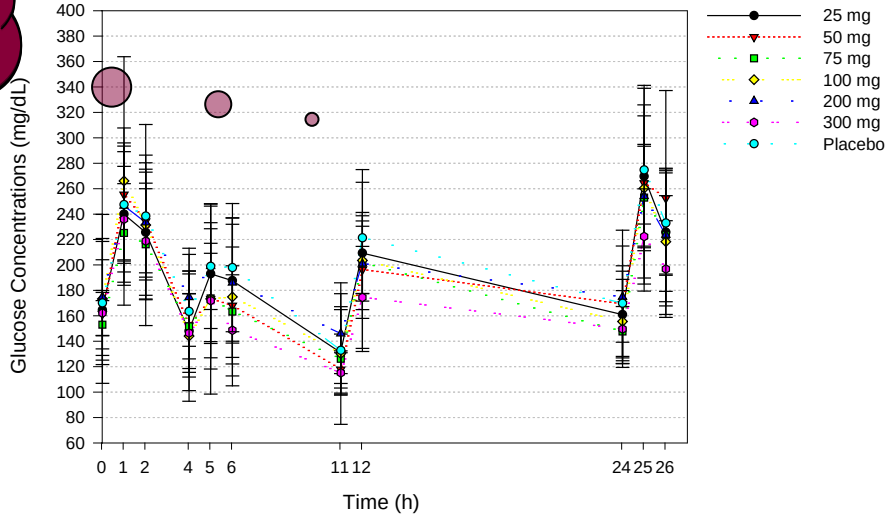
Percent DPP-IV Inhibition



GLP-1 Concentration



Glucose Concentration



Takeaways

- Solutions to Troublesome Problems in Early Clinical Development
  - New technologies, properly applied
  - Creative study designs – answer more questions in each study
  - Focus on reducing variability in key indicators of safety and efficacy

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