Enriching Phase I Studies for Better Decision Making

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Overview of Presentation

- What is driving the need for innovation in early clinical research?
- What are considered “game-changing” applications of emerging technology?
- How can these enriching technologies help answer troubling problems encountered in Phase I research programs?
- What are some examples?
- Summary

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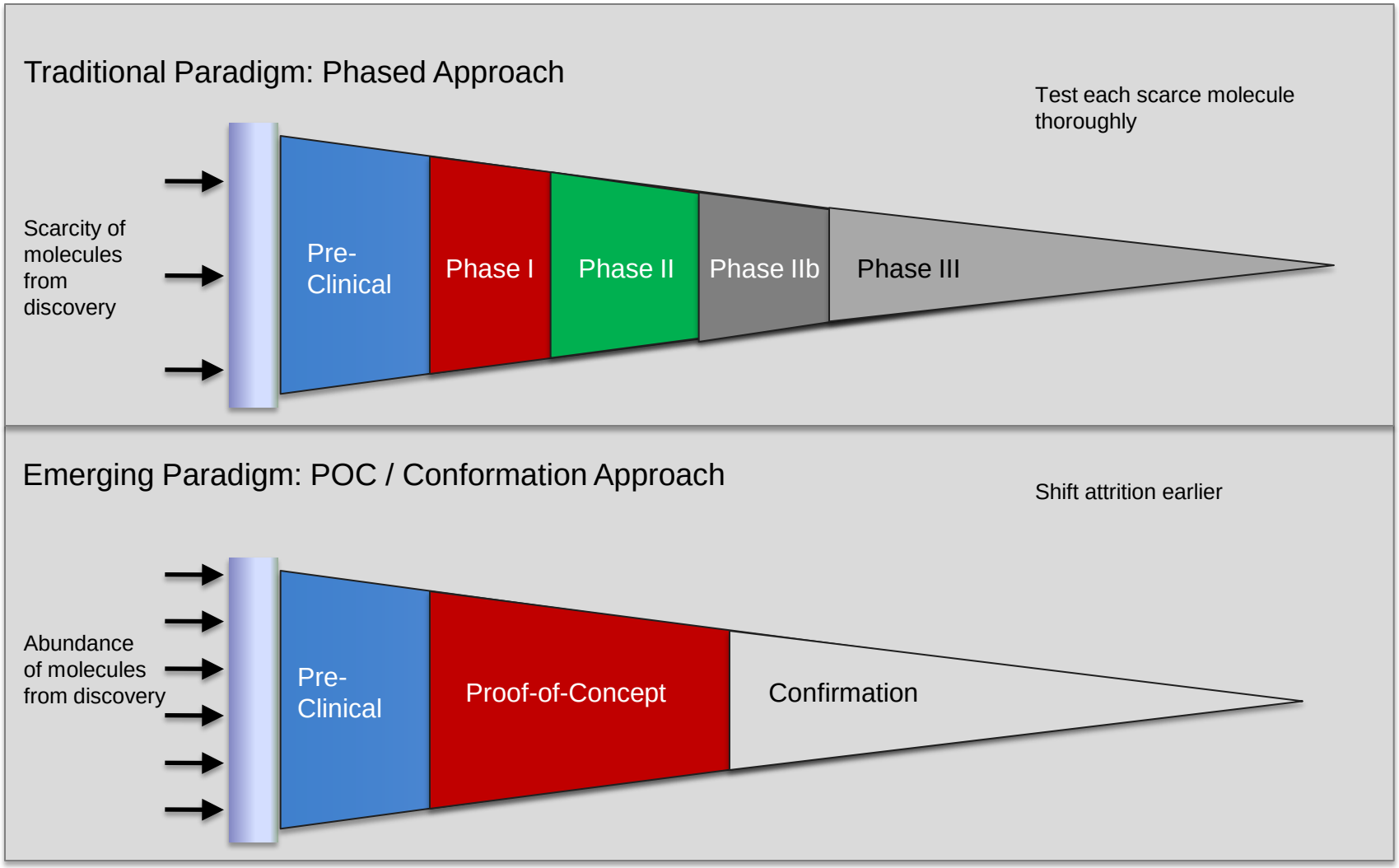
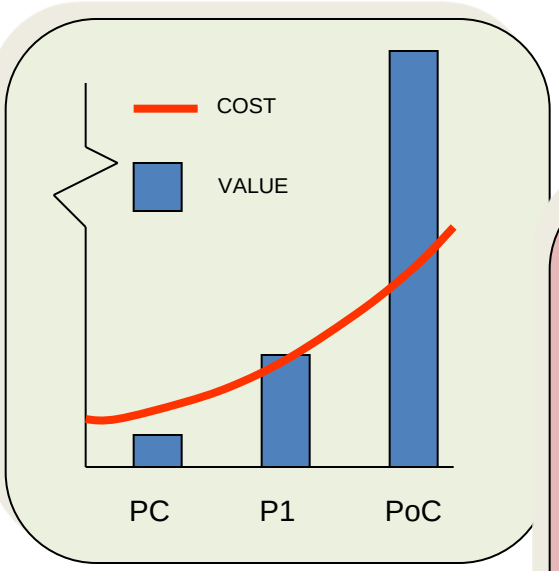
Clinical Development is Evolving



Source: William Blair & Company, (Bain and Company) Covance Investors Overview June 16, 2010

Importance of Proof-of-Concept Studies

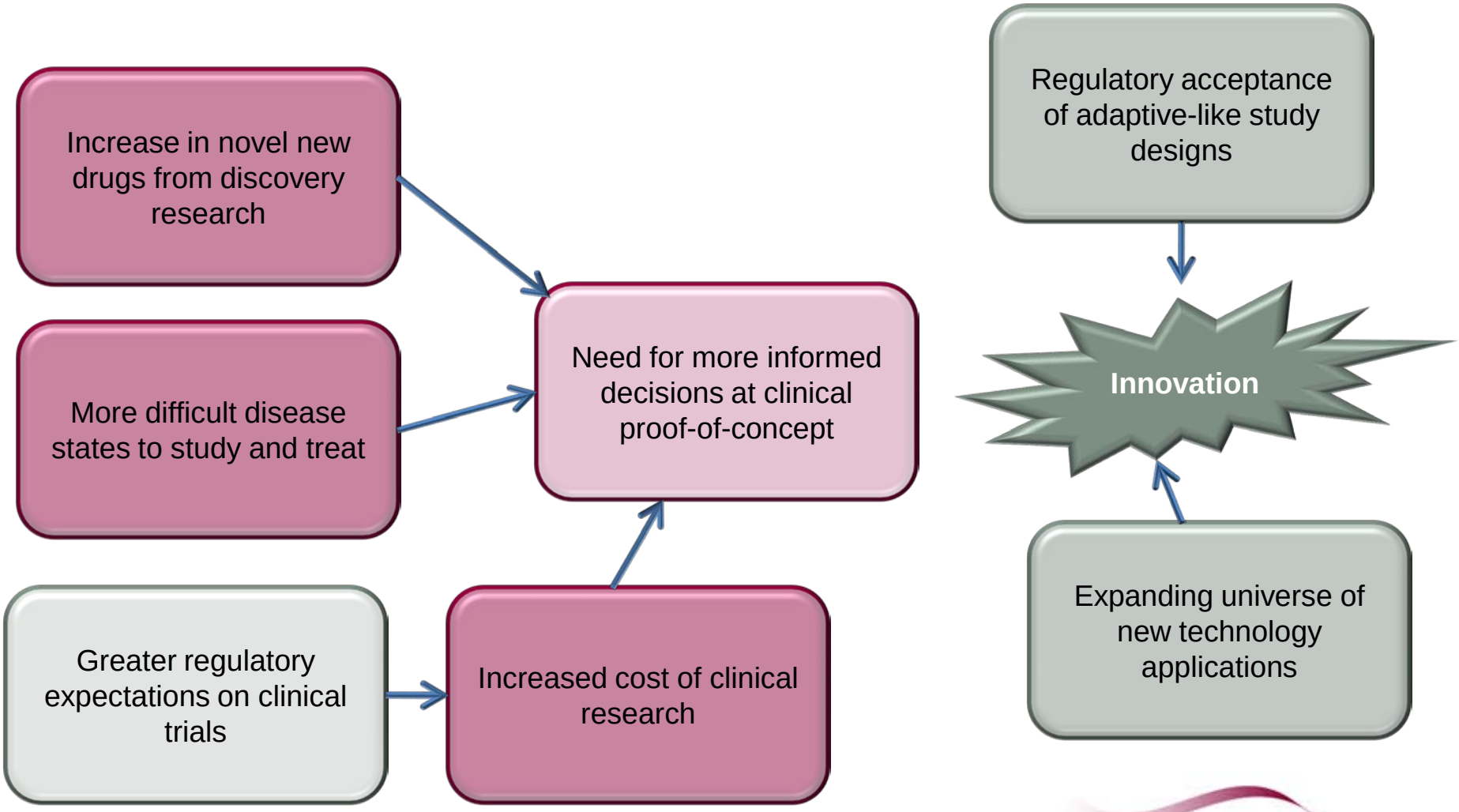
Defines Product Value For the First Time



% Chance of Reaching Market	
Preclinical	0.1-1
FIH study	5-10
POC study	10-30

Typical Costs ($million)	
IND tox study	0.5 – 1.0
FIH study	0.7 – 1.4
POC study	2 - 20

The Pressure is On for Proof-of-Concept!



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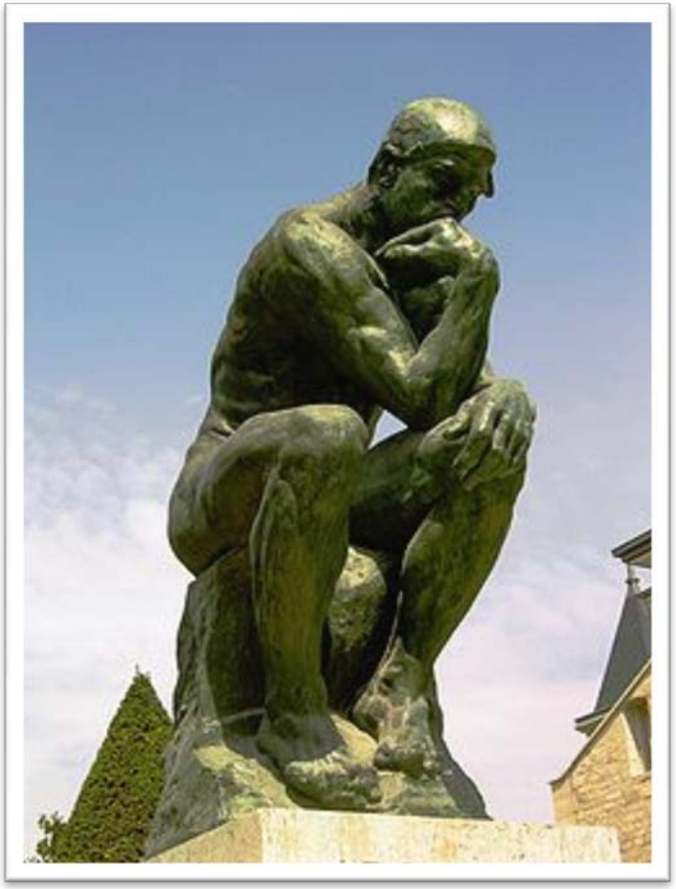
What is a better decision?



- One made earlier
- With greater confidence
- More efficiently

Better data, faster, cheaper

Game Changing Innovation

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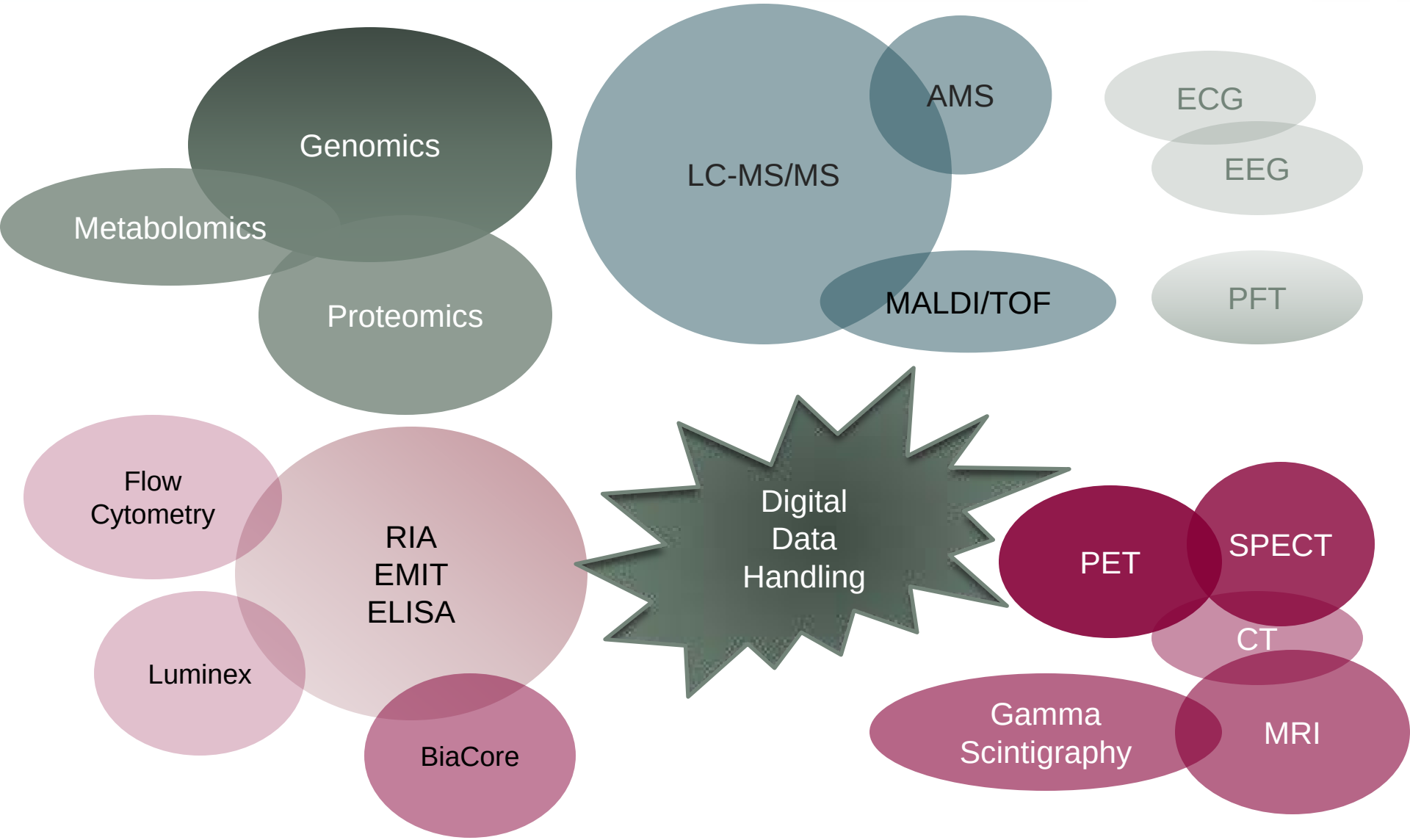
New Technology Drives Innovation

So Many New Tools in So Little Time



Troublesome Problems Encountered in Early Clinical Research

Positive or equivocal signals in preclinical cardiovascular safety assessment → **High definition digital ECG collection and analysis**

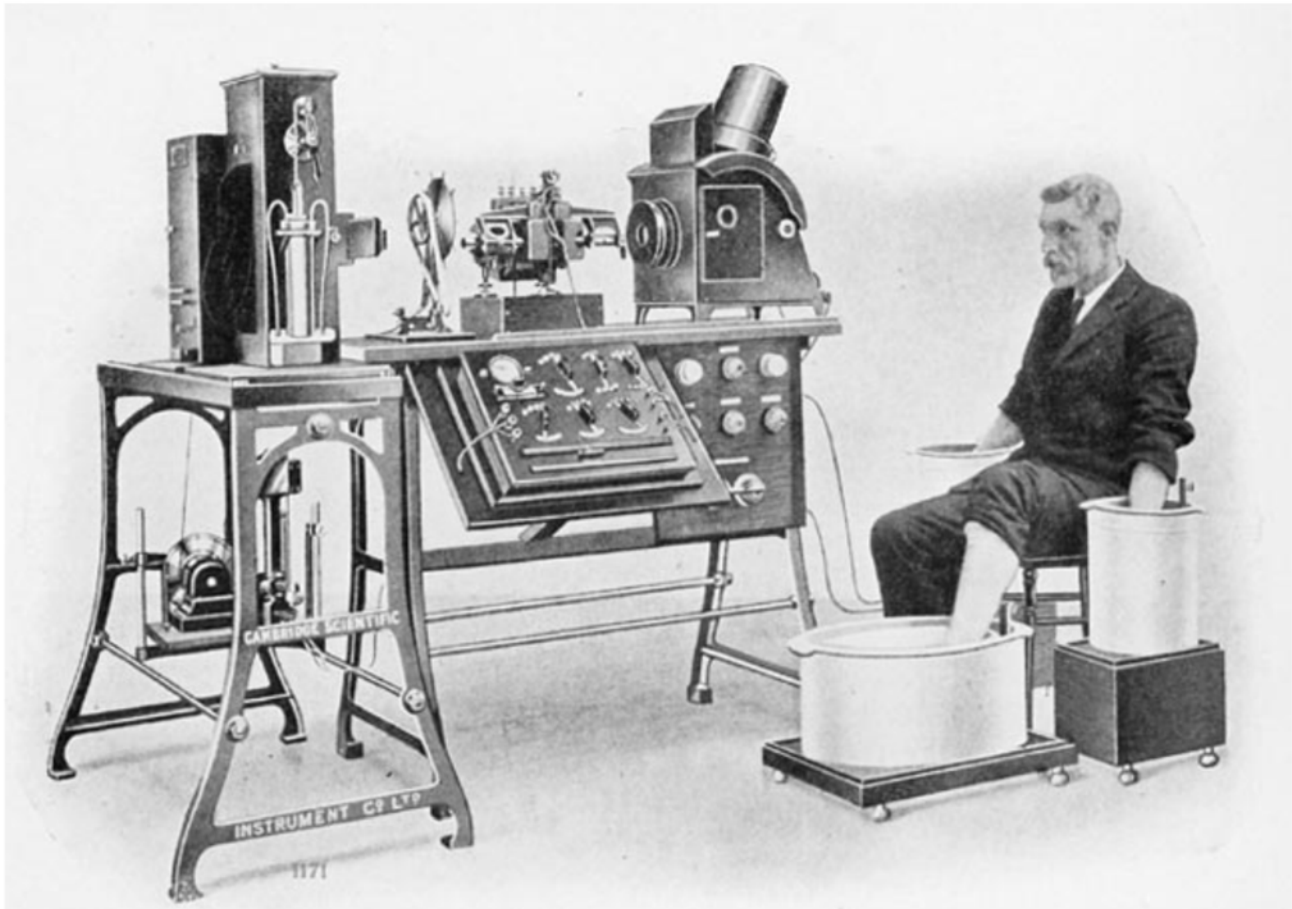
Drugs with potentially poor absorption or unknown hepatic first-pass metabolism

Active metabolites, species-unique metabolites, or disproportionate human vs. tox species metabolite(s).

→ **Use of microtracers with Accelerator Mass Spectrometry**

Establishing if drug gets to site of action → **Efficacy/Mechanism biomarkers**

An Early ECG Device



PHOTOGRAPH OF A COMPLETE ELECTROCARDIOGRAPH, SHOWING THE MANNER IN WHICH THE ELECTRODES ARE ATTACHED TO THE PATIENT, IN THIS CASE THE HANDS AND ONE FOOT BEING IMMERSED IN JARS OF SALT SOLUTION

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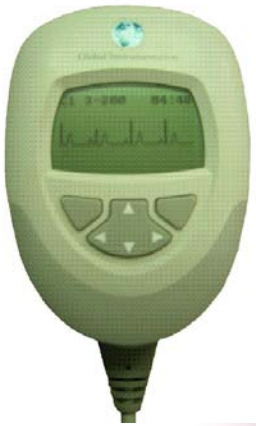
Holter Monitor

- Developed for Mercury space program
- Evolved far beyond early devices
- Now continuous 12 lead ECG acquisition
- Most TQT studies in ECG Warehouse are collected using Holter monitors

1971



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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

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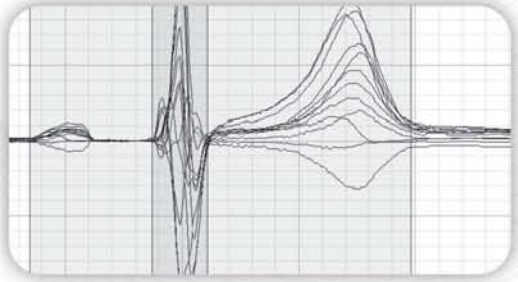
The Hybrid Phase I/ ECG Core Laboratory

- Phase I focus only
- Single vendor with unified functionality
- Single database
- Single PM, DM, stats

BLUETOOTH HOLTER

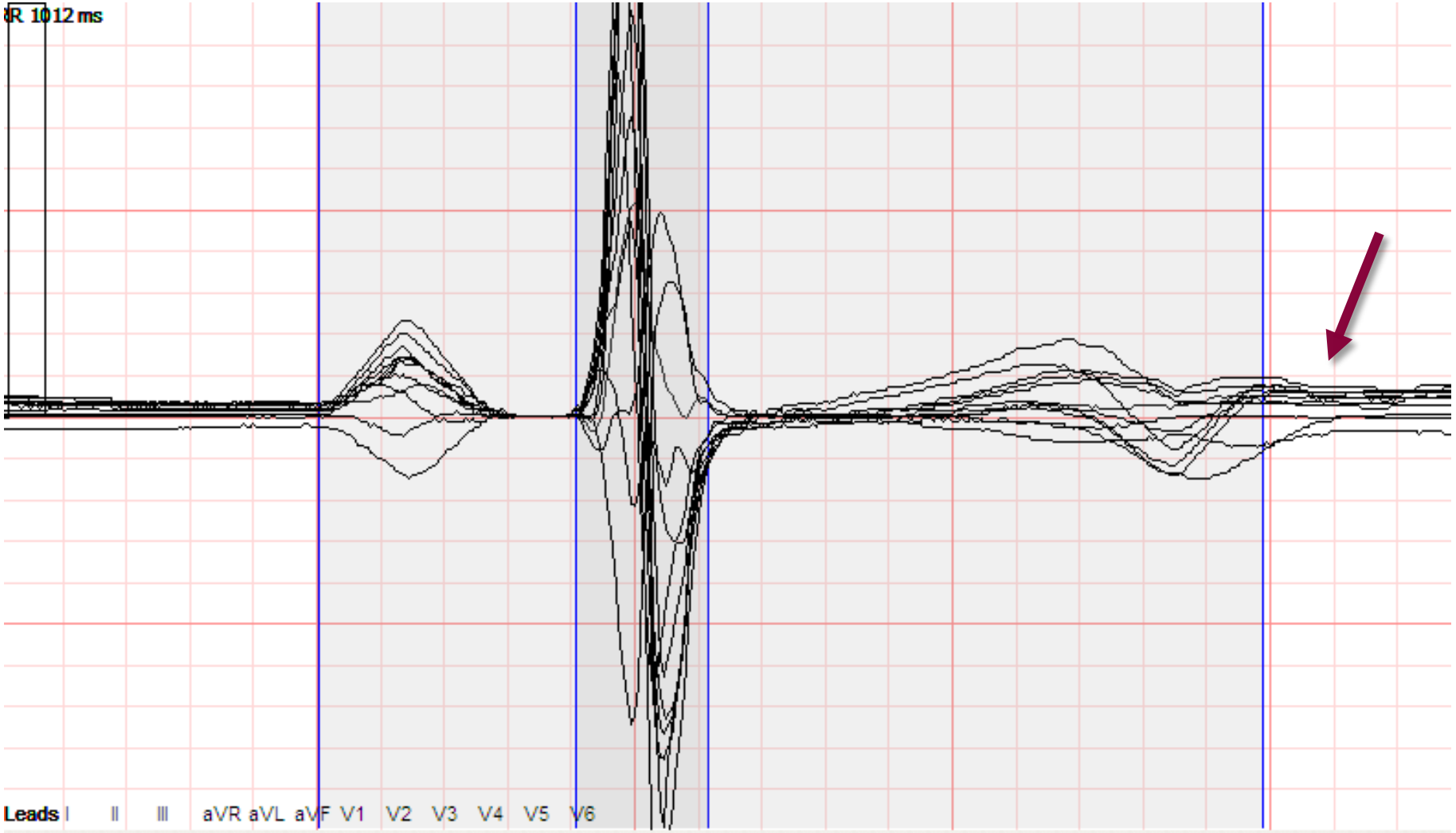
- Instant ECG review
- Computer generated date/time stamp
- Preconfigured demographics
- Single device to acquire safety ECGs during Holter recording
- 1000 sample/second acquisition
- Up to 48 hours ECG collection

HIGHLY AUTOMATED ECG PROCESSING

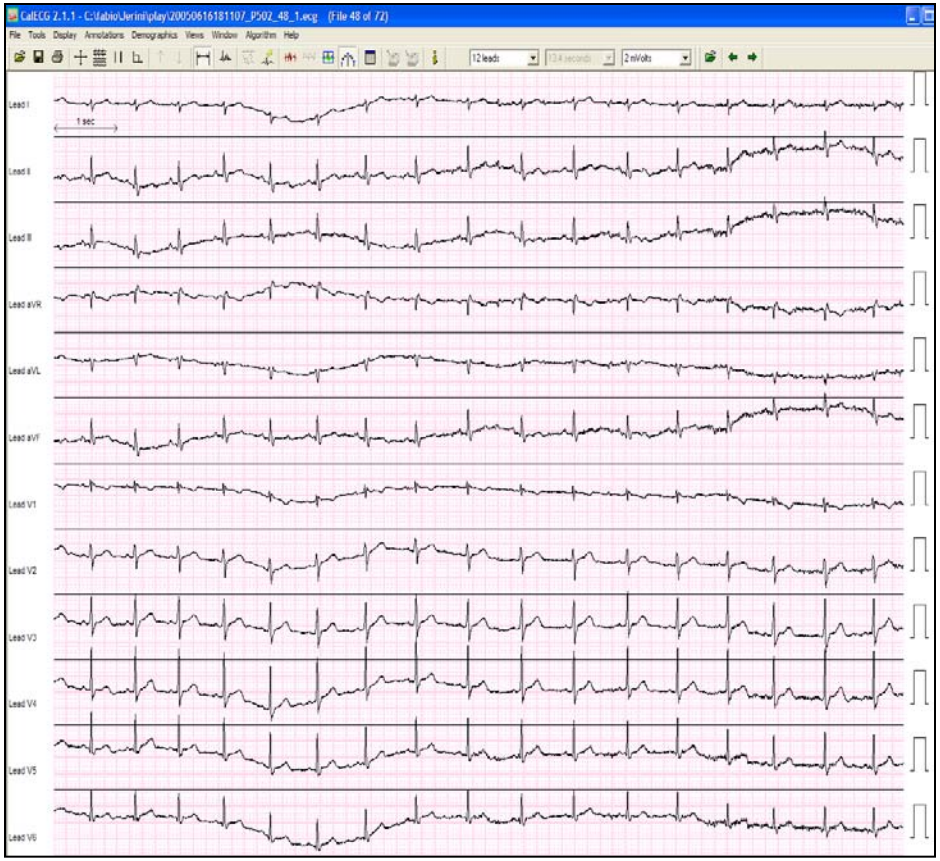


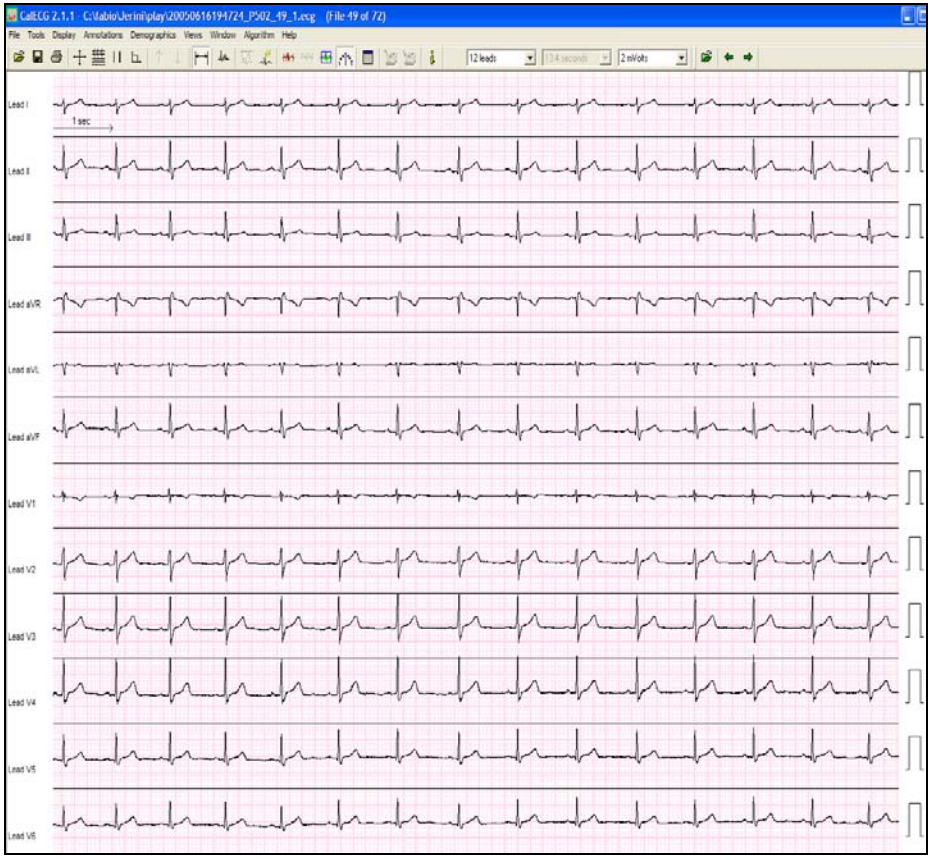
- Automated, optimized ECG extractions from Holter
- Normal ECGs measured automatically providing lower variabiliy=better data
- Cardioloigst only review approximately 10-20%
- Faster data turnaround

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



ECG Extraction: Artifacts Are a Problem





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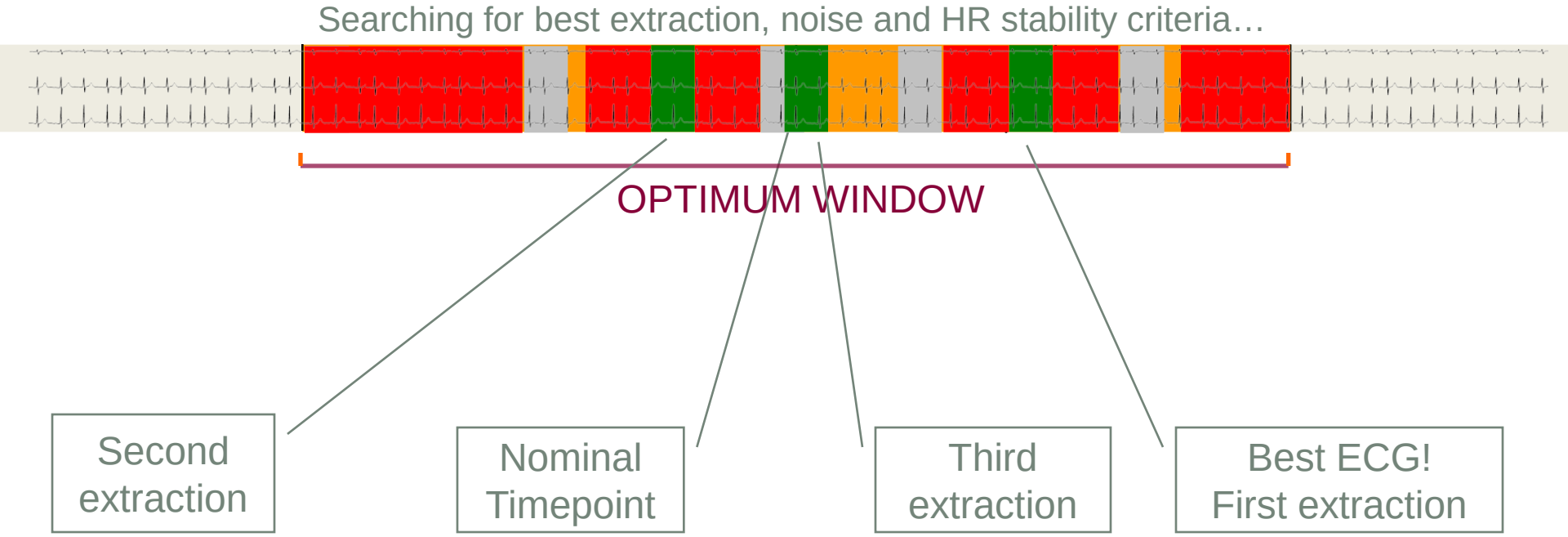
Antares Optimal ECG Extraction: Decreases Variability



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

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ECG Measurement Modalities

- Semi automated: standard process in most labs
  - aka “manually adjudicated”
  - Computer performs measurements
  - Every ECG confirmed by cardiologist
- Fully automated: “Black Box”
  - Machine read only
  - Consistent in normal ECG recordings
  - Recording characteristics can cause inaccurate measurements
  - Moxifloxacin produces abnormal ECGs
- Highly automated
  - Cardiologist reviews only questionable ECGs
  - Decreases variability

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Traditional vs. the Hybrid ECG Core Lab

Traditional ECG Core Lab	Hybrid ECG Core Lab
Two contracts (clinic+core lab)	One contract
Two study teams (clinic+core lab)	One study team
Large infrastructure supports late stage trials	Supports only Phase I clinics
Little to no Core lab visibility on clinic conduct	Direct visibility of clinic conduct
Cardiologist reviews all ECGs	Cardiologist reviews 10-20% of ECGs
ECG turnaround 4-6 weeks after LPLV	ECG turnaround 2 weeks after LPLV

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Celerion Hybrid Phase I/ECG Core Lab

- Optimal client interactions
- Data
  - Better
  - Faster
  - Cheaper
    - ~50% decrease in ECG costs

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Accelerator Mass Spectrometry

Measures isotope ratios – can detect ultra low levels of ^{14}C radioactivity

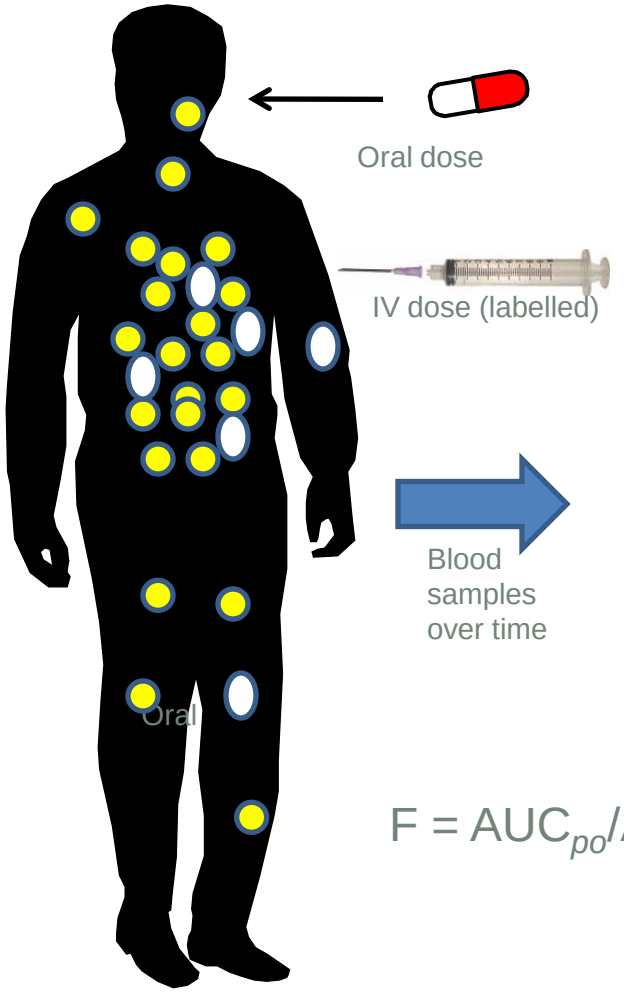
Technology used in carbon dating of antiquities

First biological application in 1989

Applications in Pharmaceutical Research (since 1998)

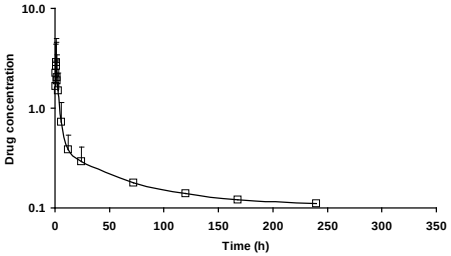
Preclinical:	Special bioanalysis (proteins, monoclonal antibodies, interfering RNA); Phase 0 (subtherapeutic dose) clinical studies
Early Clinical:	**MIST (Metabolism in Safety Testing) solution, metabolic profiling, absolute bioavailability**
Clinical:	Bioanalysis of high potency drugs

Isotopic Tracers: Determination of Absolute Bioavailability (F)



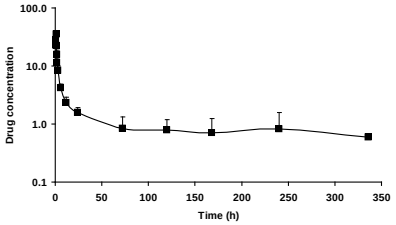
LC-MS measures total drug

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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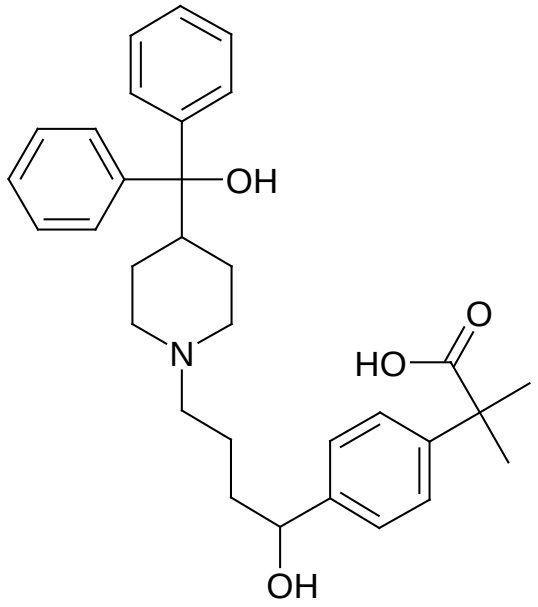
Example: Fexofenadine

- Fexofenadine HCl is a histamine H1-receptor antagonist used to treat allergies
- It is a PgP and an OATP substrate
- Fexofenadine is not substantially metabolized
- It has been on the market for over 12 years
- Although fexofenadine is a well established drug, it has never previously been administered intravenously



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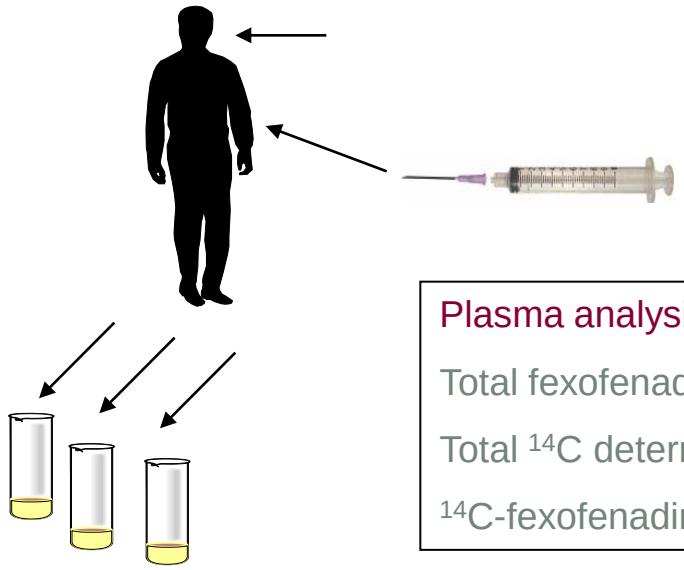
Study Design

6 healthy male volunteers

Single oral dose
120 mg non-labelled fexofenadine



Simultaneous IV dose of
100 μg, 200 nCi ^{14}C-fexofenadine

Plasma collected over 24 h

Plasma analysis

Total fexofenadine determined by HPLC-fluorescence

Total ^{14}C determined by AMS

^{14}C-fexofenadine determined by HPLC and AMS

Acknowledgement:
This research study was funded by the European Commission grant number LSHG-CT-2005-018672

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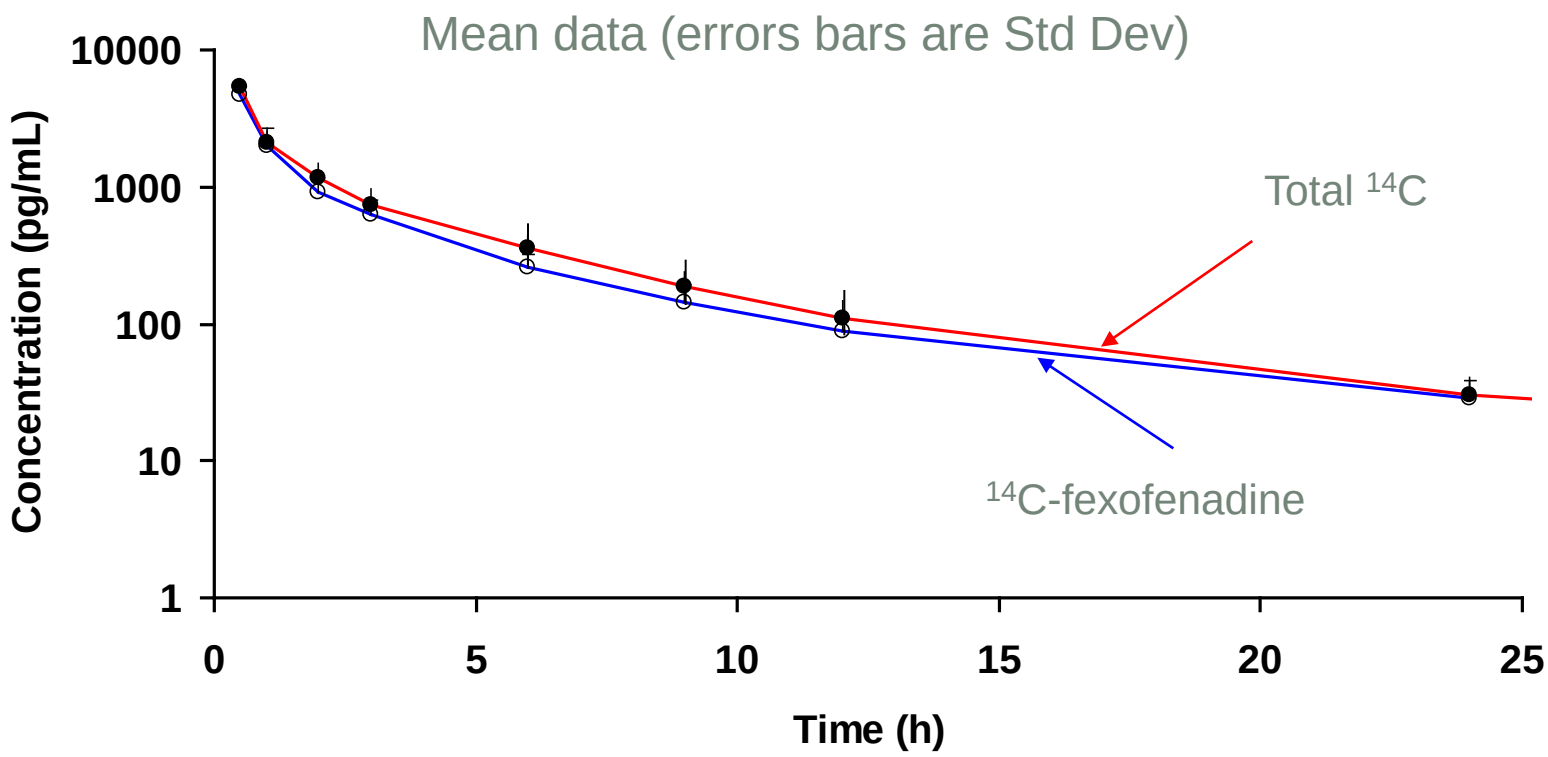
Total 14C vs. Parent IV Dose



Confirms fexofenadine undergoes very limited metabolism

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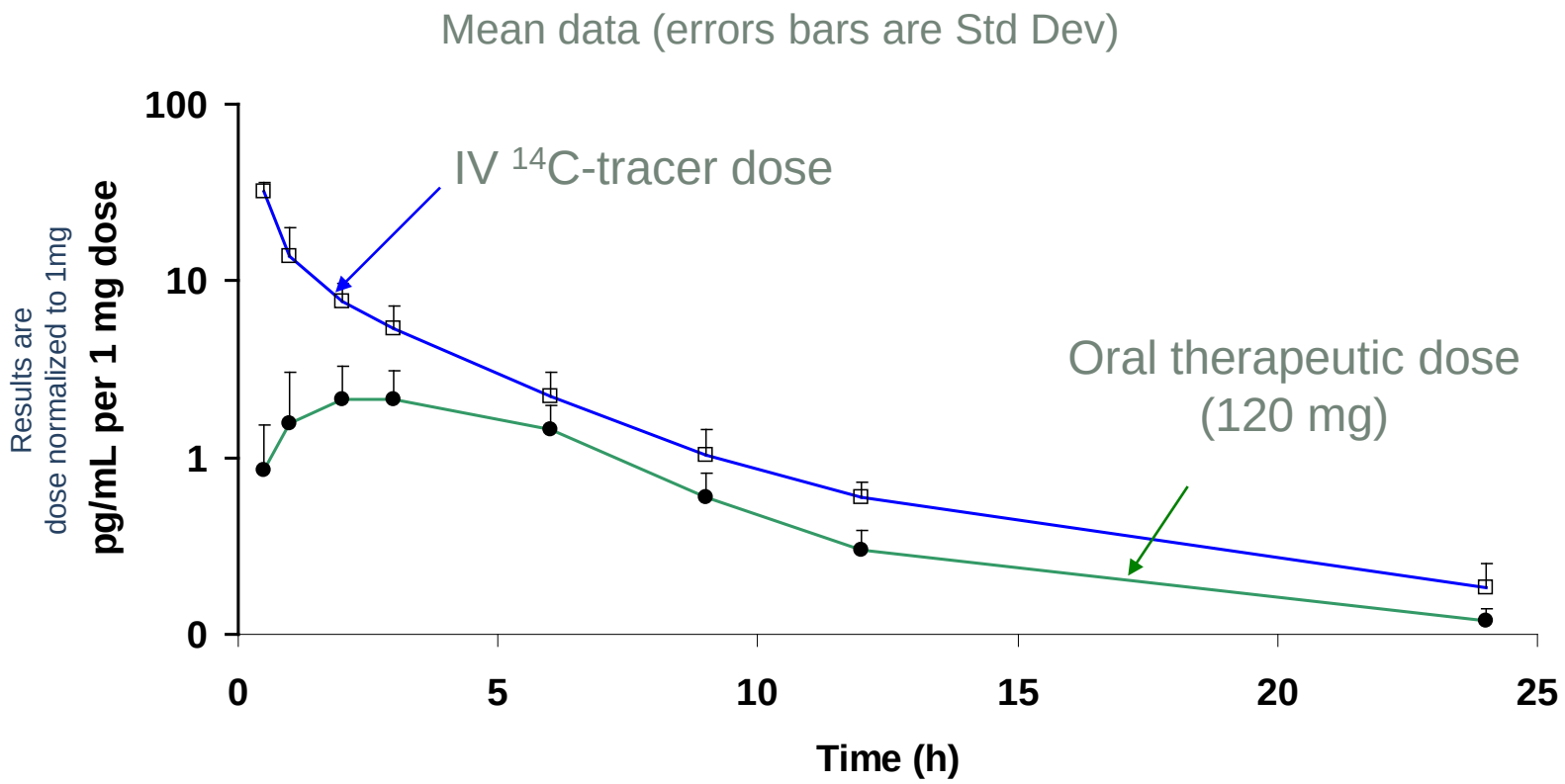
Absolute Oral Bioavailability of Fexofenadine



Mean oral absolute bioavailability 28%

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PK Parameters for Fexofenadine

Parameter	Microtracer data (%CV, n= 6)	Literature data
$t_{1/2}$ (h)	10 (27)	14
CL (L/h)	17 (23)	4.2*
V (L)	245 (17)	85
F(%)	28 (26)	? 10*

*** Minimum based on excretion of unchanged drug in urine**

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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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Biomarkers and Decision-Making

Human Biomarker : *a measure of biochemical or physiological function, anatomical structure, genetic characteristics or pharmacological activity primarily used to identify or predict changes in the human body brought on by disease or therapy*

Biomarkers in Drug Development: A Handbook of Practice, Application, and Strategy Ed: Michael R. Bleavins , Claudio Carini, Mallé Jurima-Romet, Ramin Rahbari; John Wiley & Sons.c. 2010

How will the biomarker(s) advance the drug's development?

- Primary purpose of biomarkers is to enable better decisions

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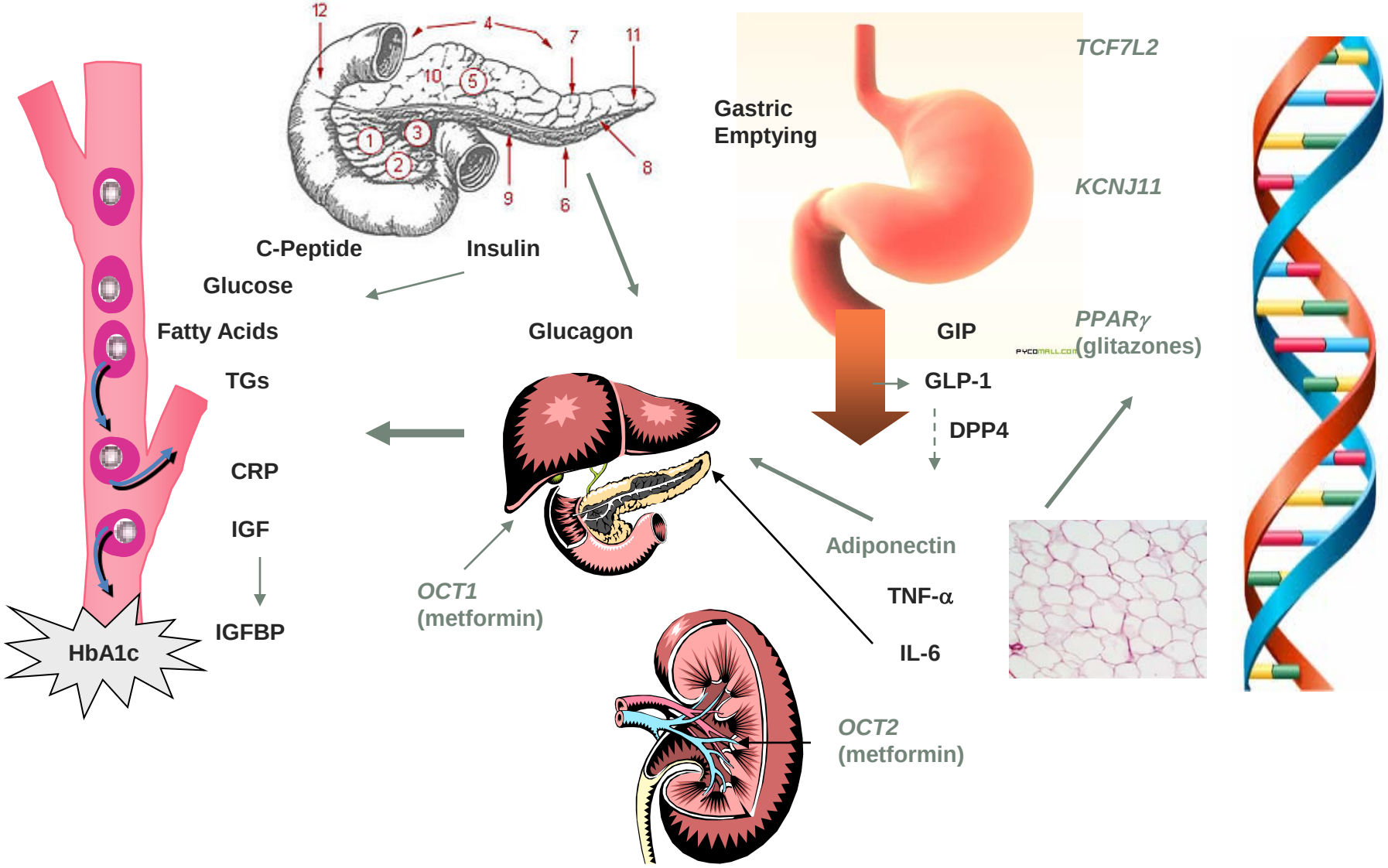
Plethora of Biomarkers for Diabetes



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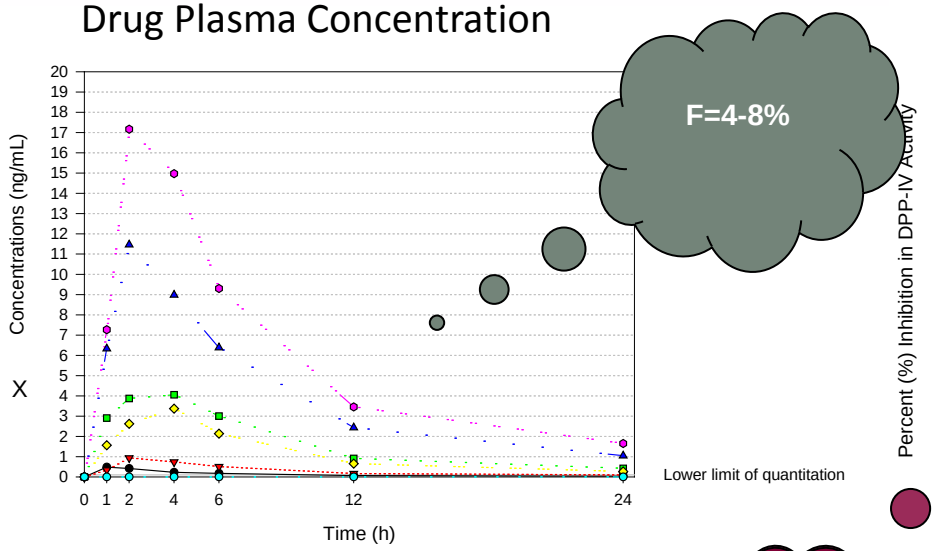
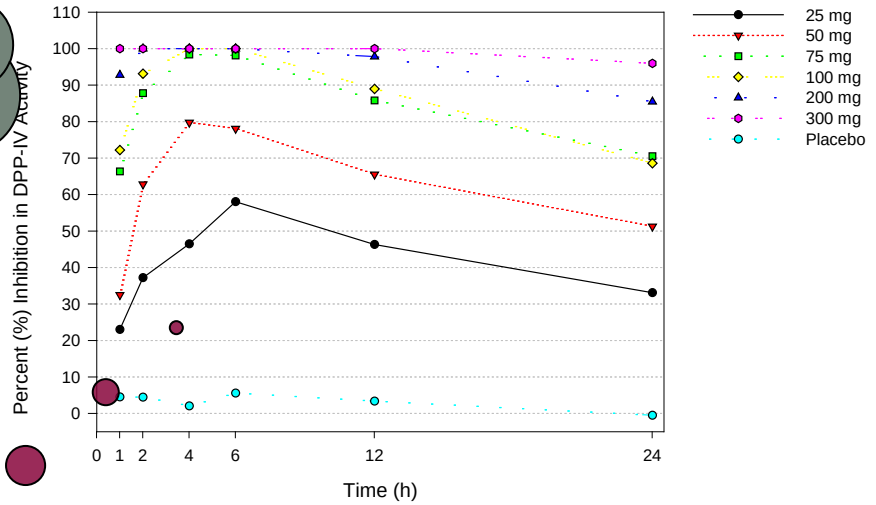
Results of SAD Study in Mild Diabetic Patients: *Early Evidence of Efficacy*

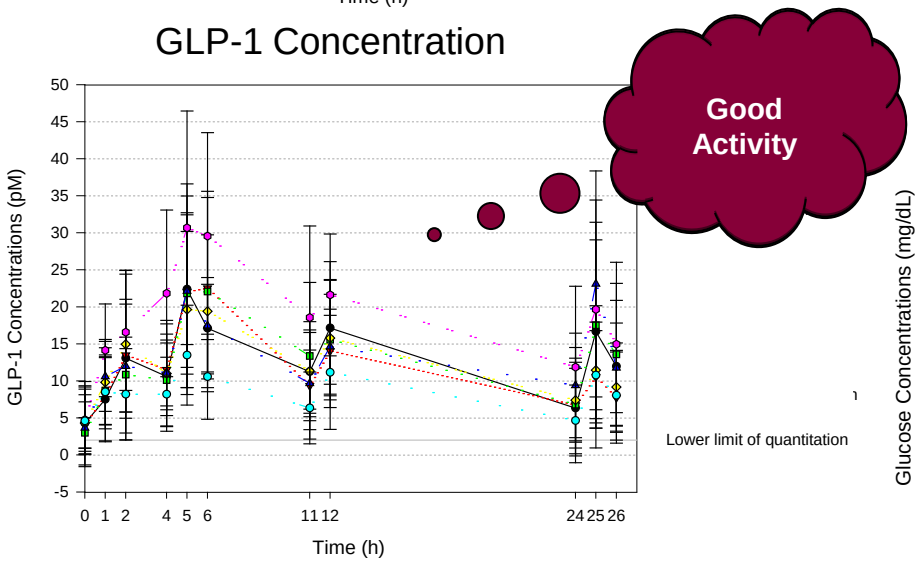
Drug Plasma Concentration



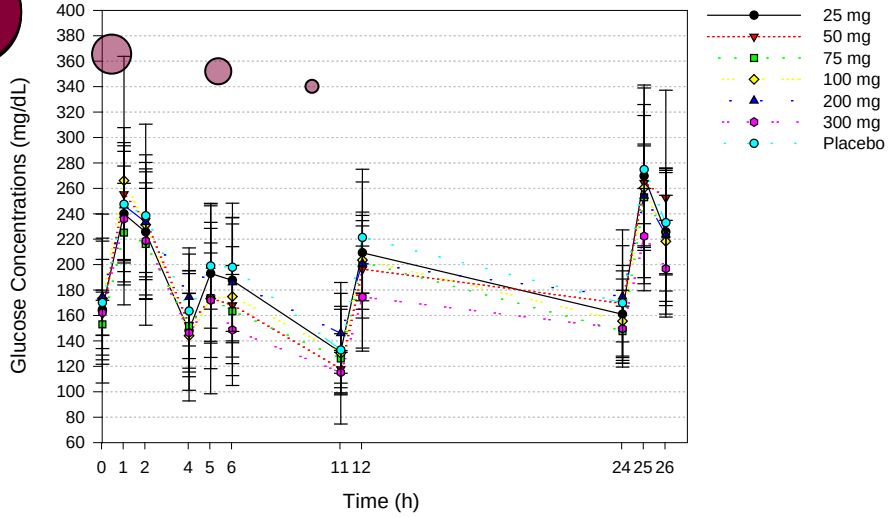
Percent DPP-IV Inhibition



GLP-1 Concentration



Glucose Concentration



Summary

- Opportunities
  - New technologies enrich early clinical pharmacology studies by providing better data, faster and cheaper.
  - Regulators are open to new and creative approaches
- Challenges
  - Technologies must be effectively deployed and properly validated
  - Study designs and logistics more complex

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Q & A

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