



Enriching Phase I Studies for Better Decision Making

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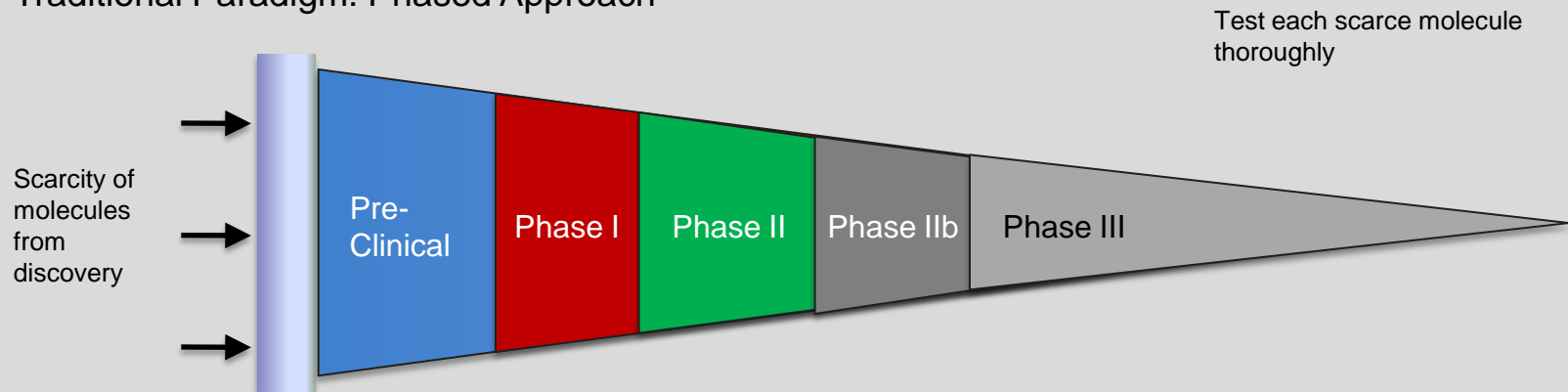
September 15, 2011

Overview of Presentation

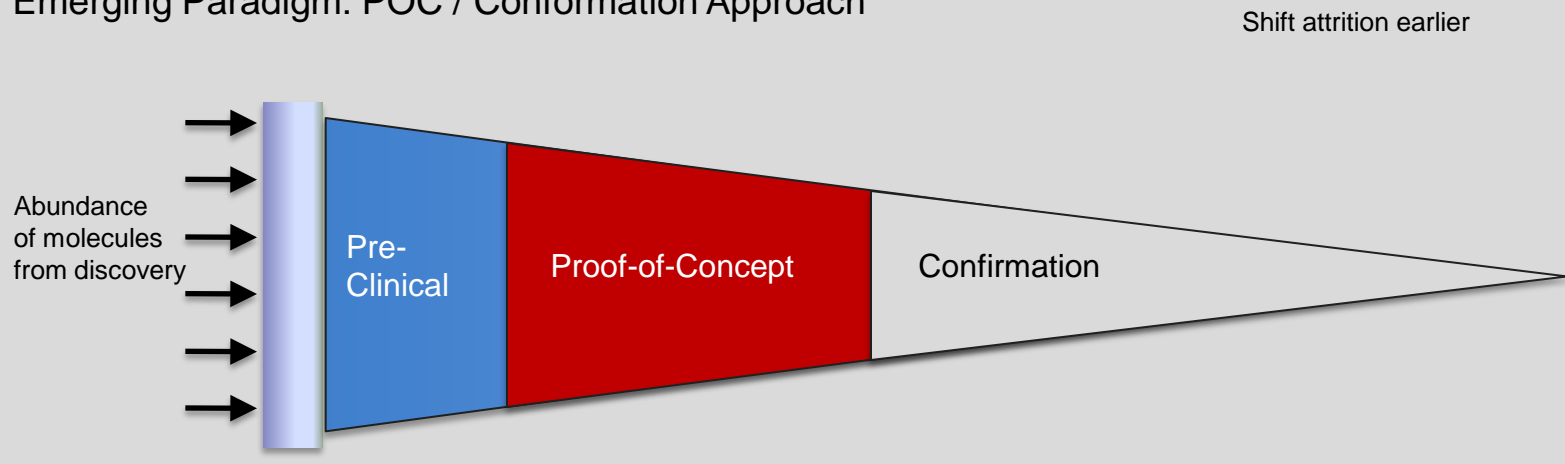
- What is driving the need for innovation in early clinical research?
- What are considered “game-changing” applications of emerging technology?
- How can these enriching technologies help answer troubling problems encountered in Phase I research programs?
- What are some examples?
- Summary

Clinical Development is Evolving

Traditional Paradigm: Phased Approach

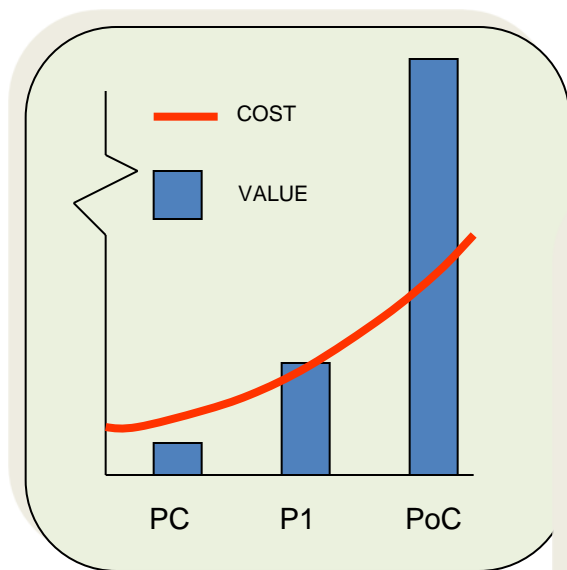


Emerging Paradigm: POC / Conformation Approach



Importance of Proof-of-Concept Studies

Defines Product Value For the First Time



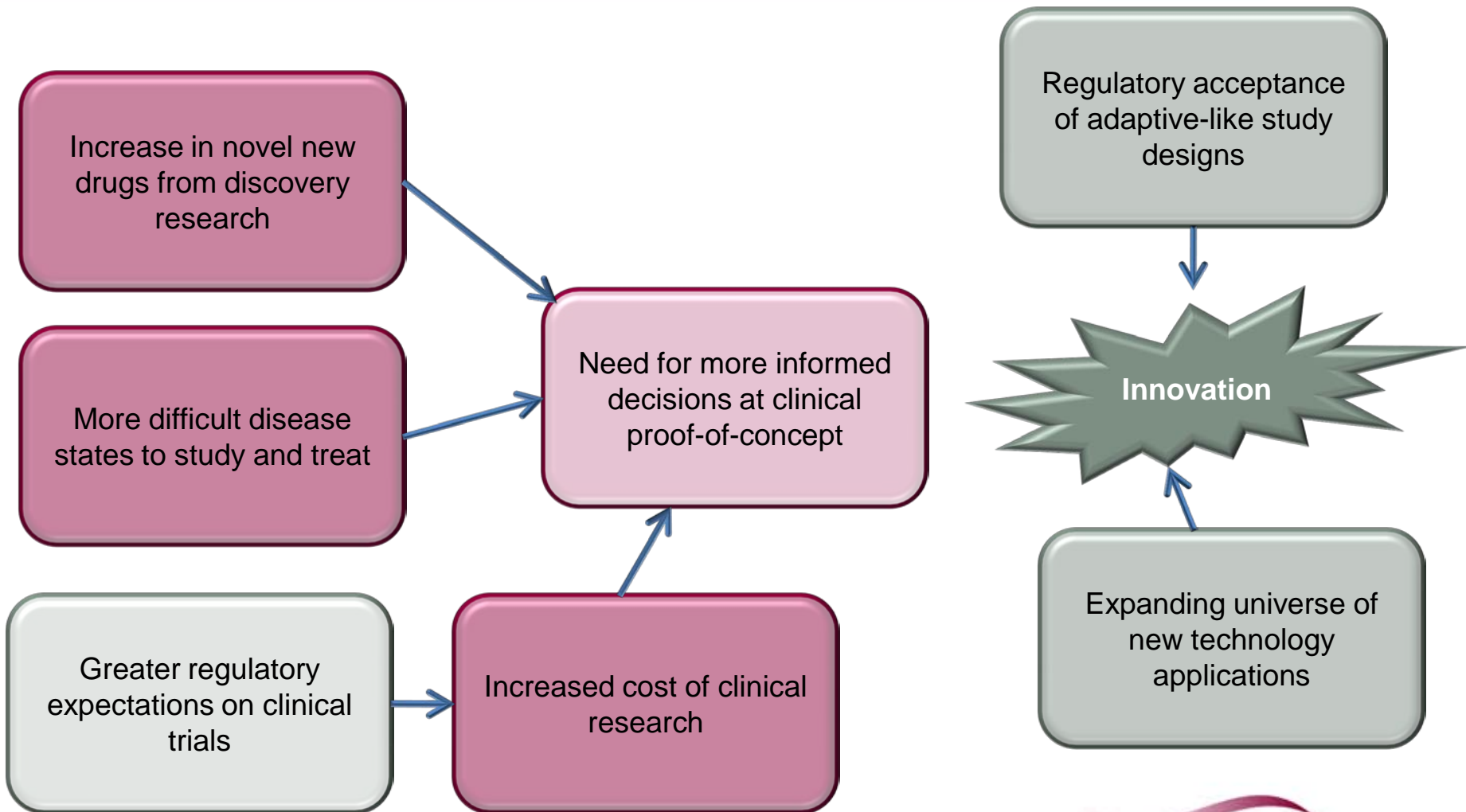
% Chance of Reaching Market

Preclinical	0.1-1
FIH study	5-10
POC study	10-30

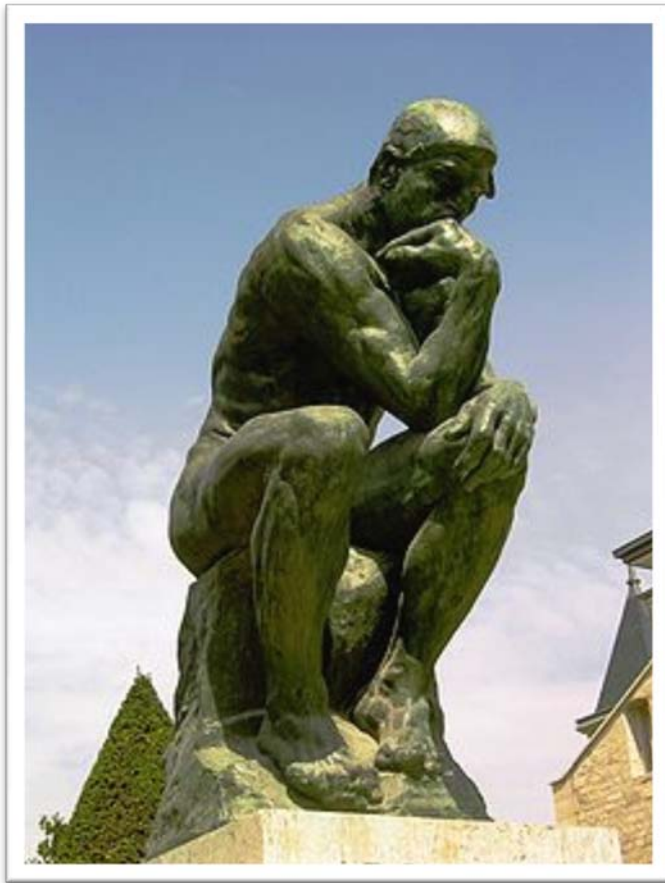
Typical Costs (\$million)

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!



What is a better decision?



- One made earlier
- With greater confidence
- More efficiently

Better data, faster, cheaper

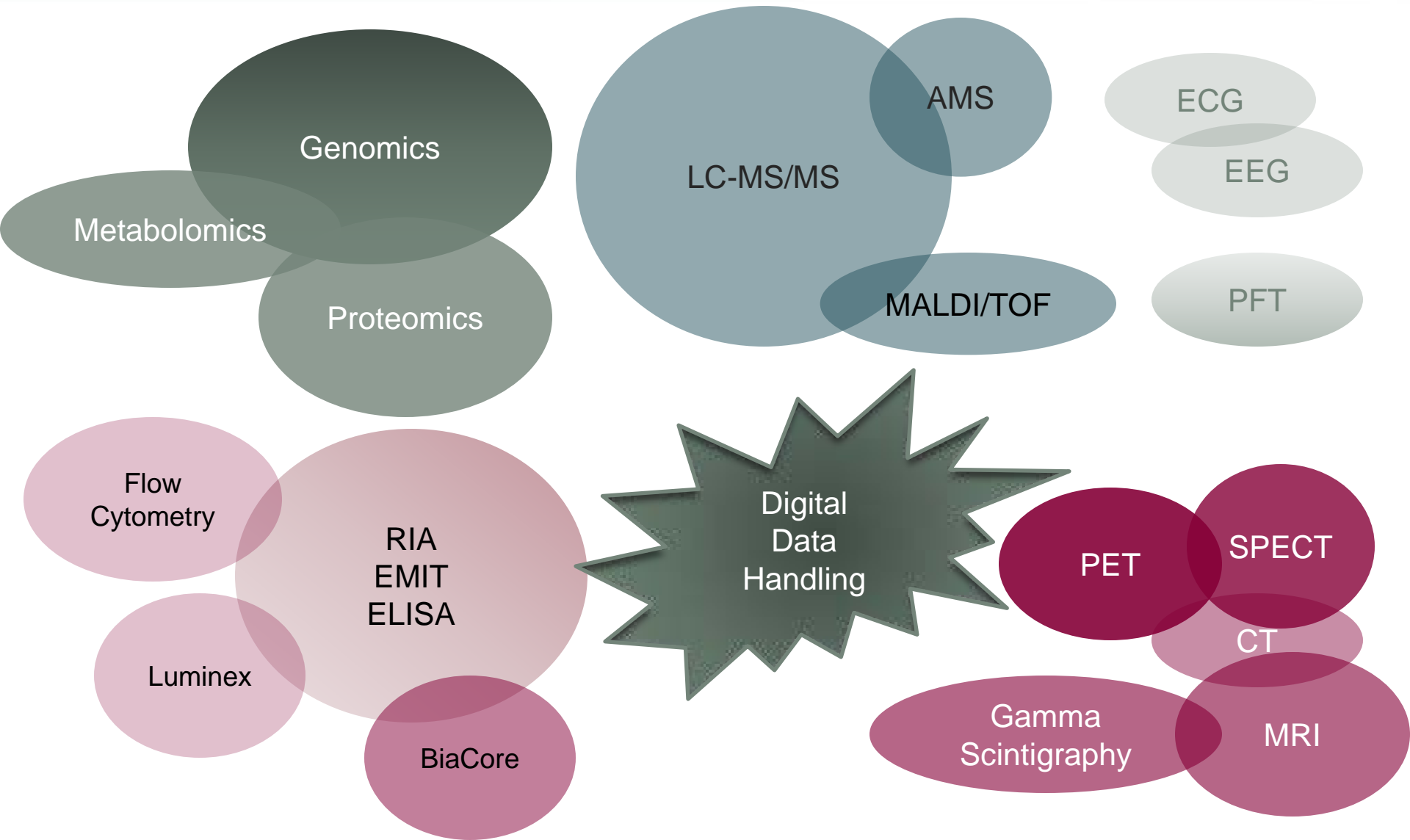
Game Changing
Innovation

Game Changing Innovation in Medical History

- 600 BC – Sushruta (India) reported ants attracted to urine of diabetics
- 1555 – Józef Struś first measured blood pressure (by placing increasing weights on the skin over an artery until the pulse no longer lifted the weight)
- 1895 – Wilhem Roentgen discovered x-rays → imaging biomarkers
- 1896 – Henri Becquerel discovered radioactivity → radiodiagnostics
- 1901 – Willem Einthoven invented the first ECG apparatus

New Technology Drives Innovation

So Many New Tools in So Little Time



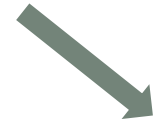
Troublesome Problems Encountered in Early Clinical Research

Positive or equivocal signals in preclinical cardiovascular safety assessment



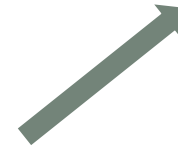
High definition digital ECG collection and analysis

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



Use of microtracers with Accelerator Mass Spectrometry

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

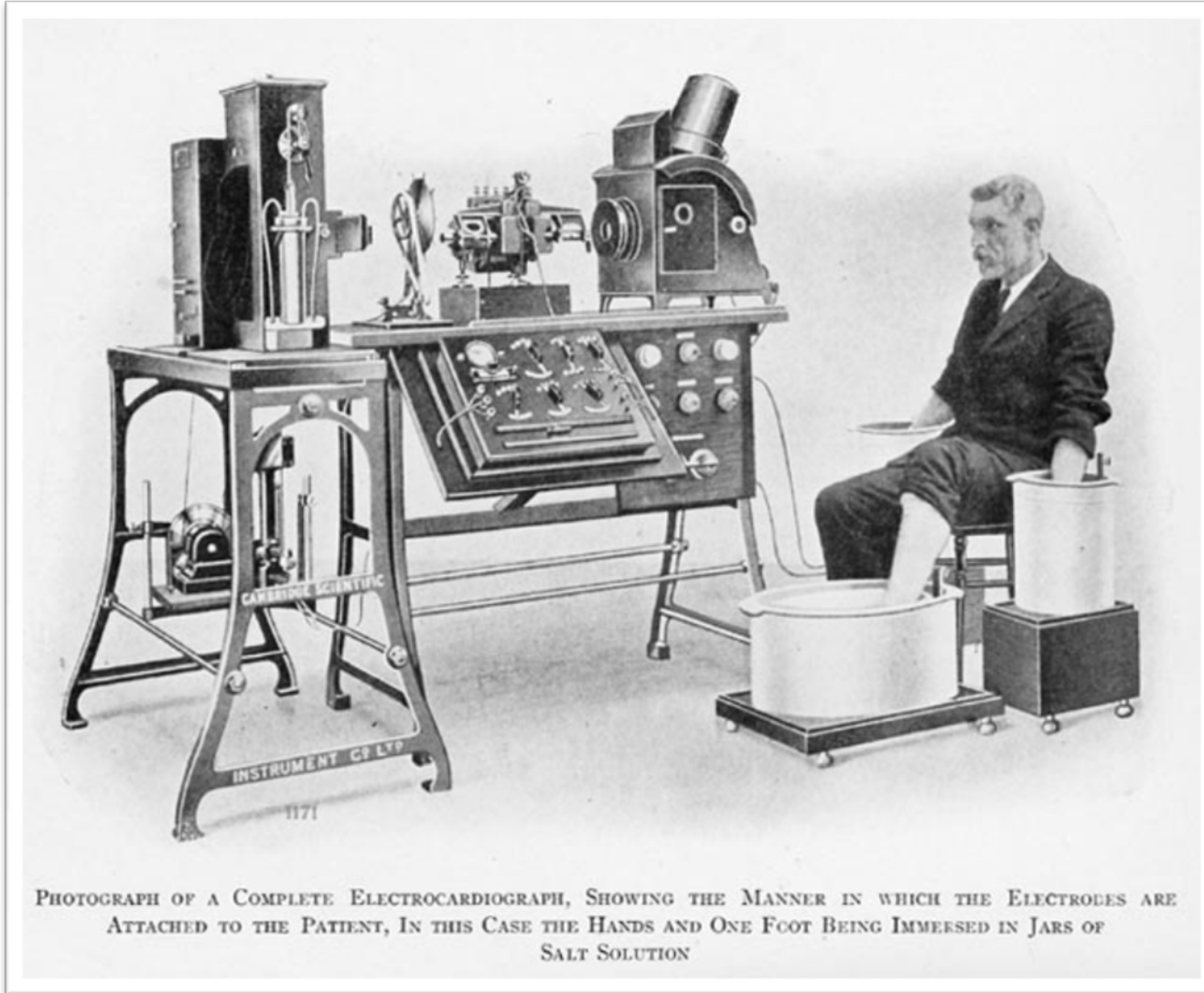


Establishing if drug gets to site of action



Efficacy/Mechanism biomarkers

An Early ECG Device



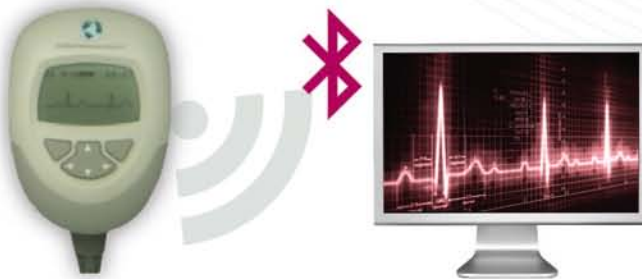
PHOTOGRAPH OF A COMPLETE ELECTROCARDIOGRAPH, SHOWING THE MANNER IN WHICH THE ELECTRODES ARE ATTACHED TO THE PATIENT, IN THIS CASE THE HANDS AND ONE FOOT BEING IMMERSED IN JARS OF SALT SOLUTION

The Hybrid Phase I/ ECG Core Laboratory

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

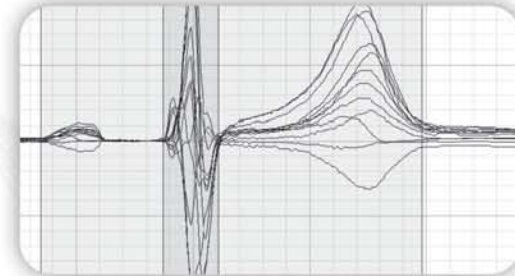


BLUETOOTH HOLTER



- 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 variability=better data
- Cardiologist only review approximately 10-20%
- Faster data turnaround

Holter Monitor

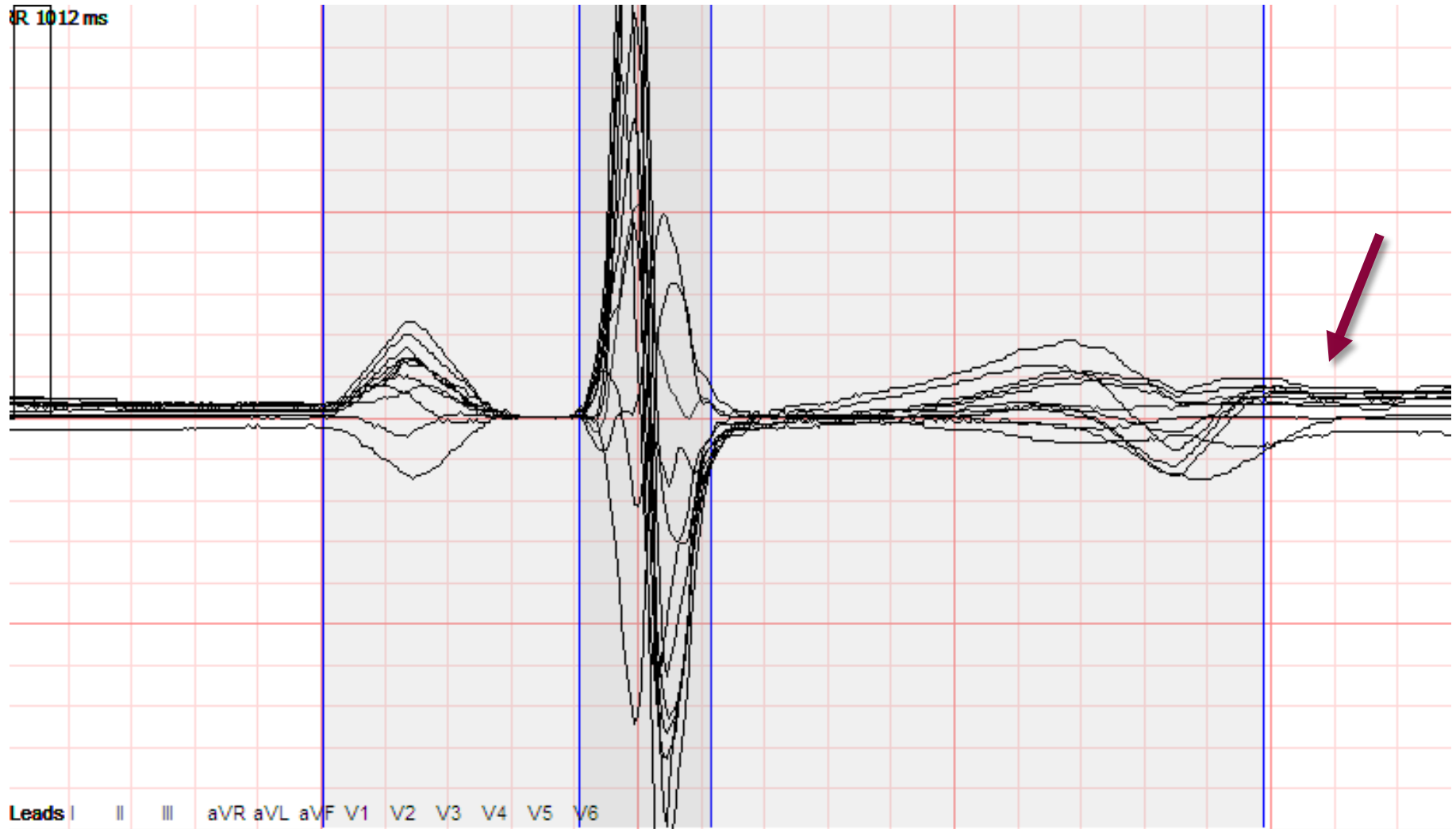
- Developed for Mercury space program
- Evolved far beyond early devices
- Now continuous 12 lead ECG acquisition
- Most TQT studies in ECG Warehouse are Holter



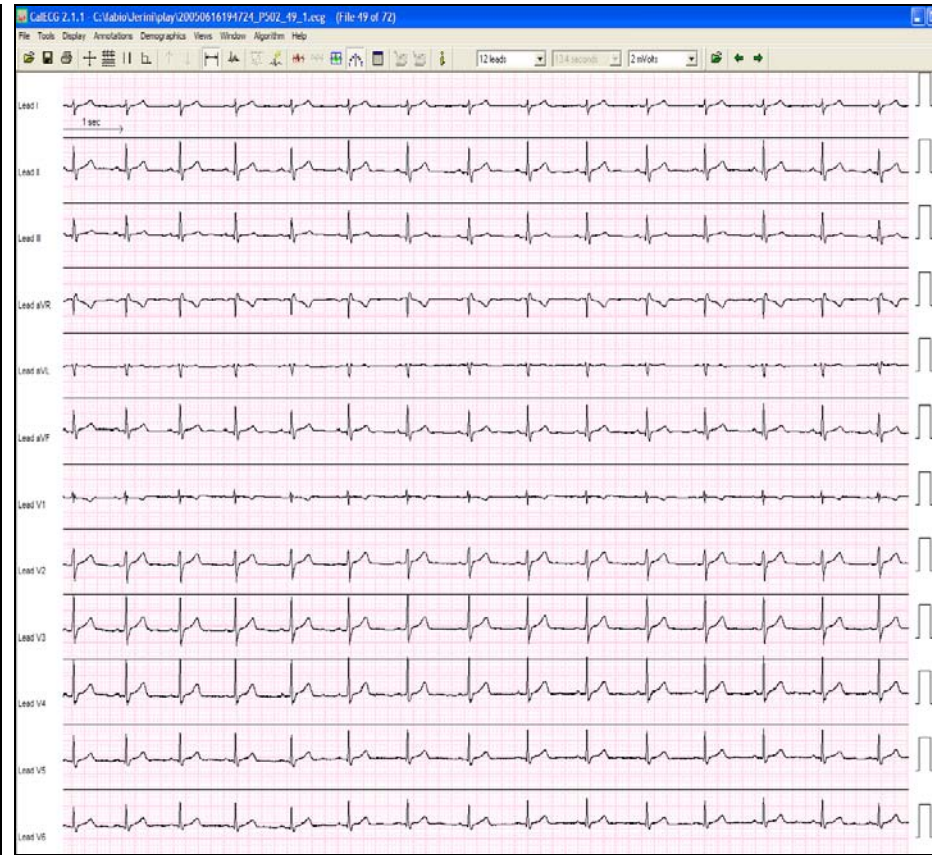
Comparing ECG Acquisition Modalities

	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

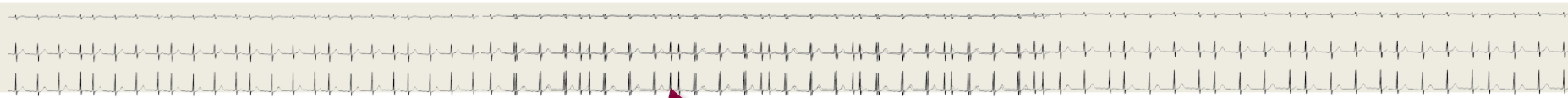


ECG Extraction: Artifacts Are a Problem



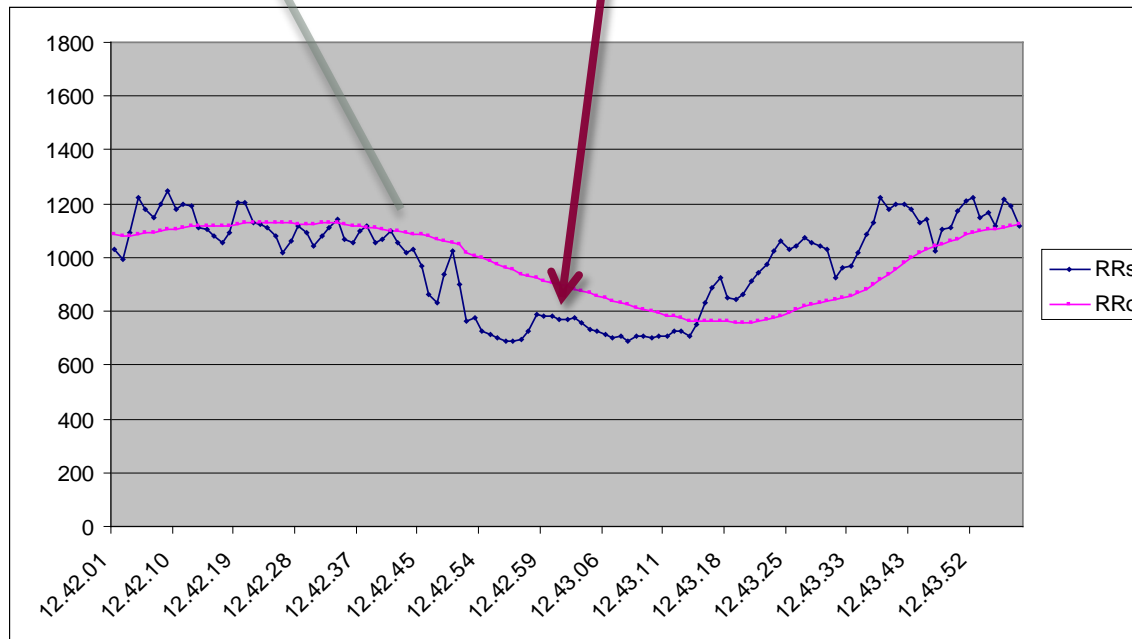
ECG Extraction: Find a Period of Stable Heart Rate and Reduced Noise

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...



Second
extraction

Nominal
Timepoint

Third
extraction

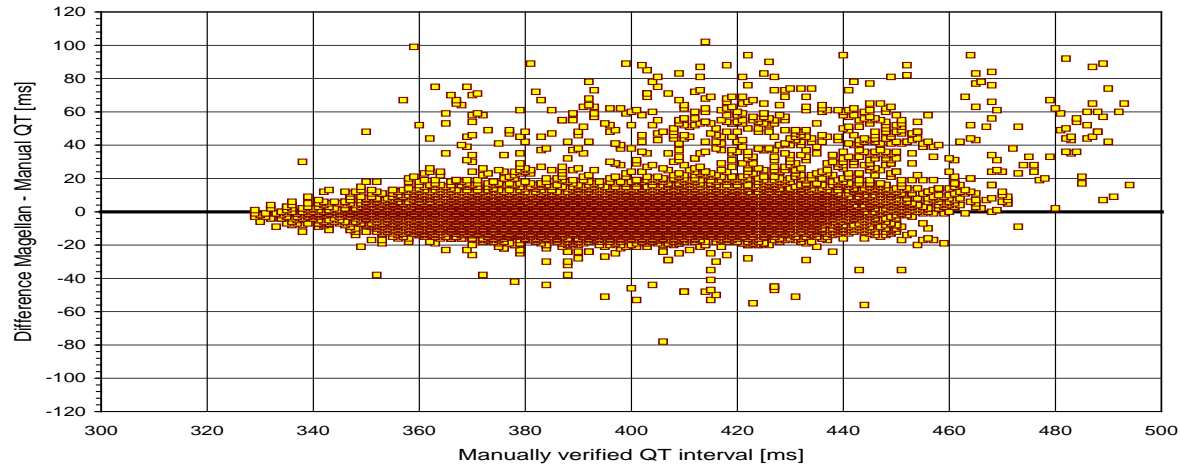
Best ECG!
First extraction

ECG Measurement Modalities

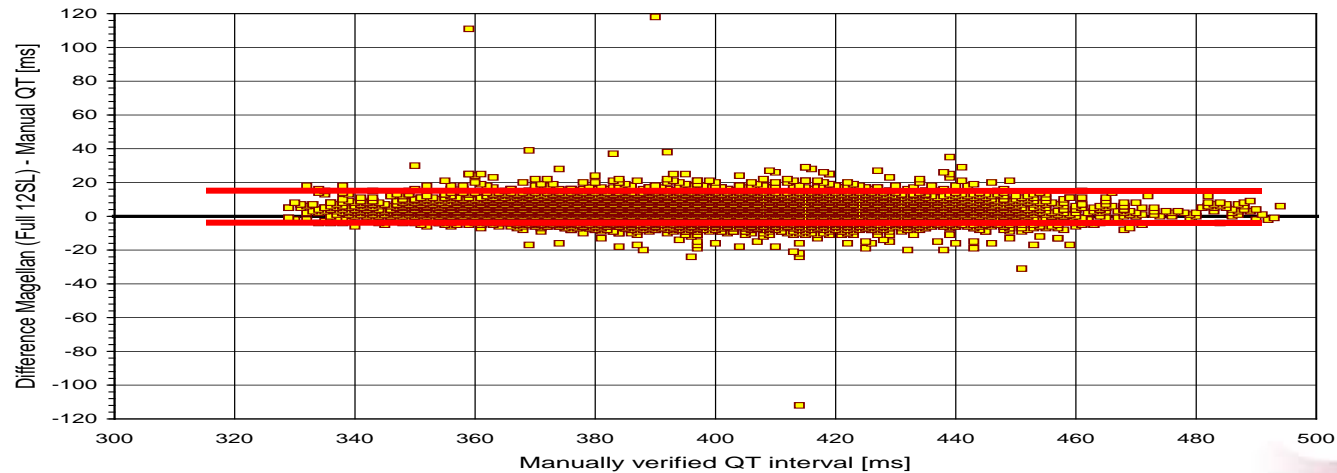
- Semi automated: standard process in most labs
 - aka “manually adjudicated”
 - Computer performs measurements
 - Every ECG confirmed by cardiologist
- Fully automated: “Black Box”
 - Machine read only
 - Consistent in normal ECG recordings
 - Recording characteristics can cause inaccurate measurements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

Algorithm Evolution

“Old” QT algorithm



“New” QT algorithm



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

Celerion Hybrid Phase I/ECG Core Lab

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

Accelerator Mass Spectrometry

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

Technology used in carbon dating of antiquities

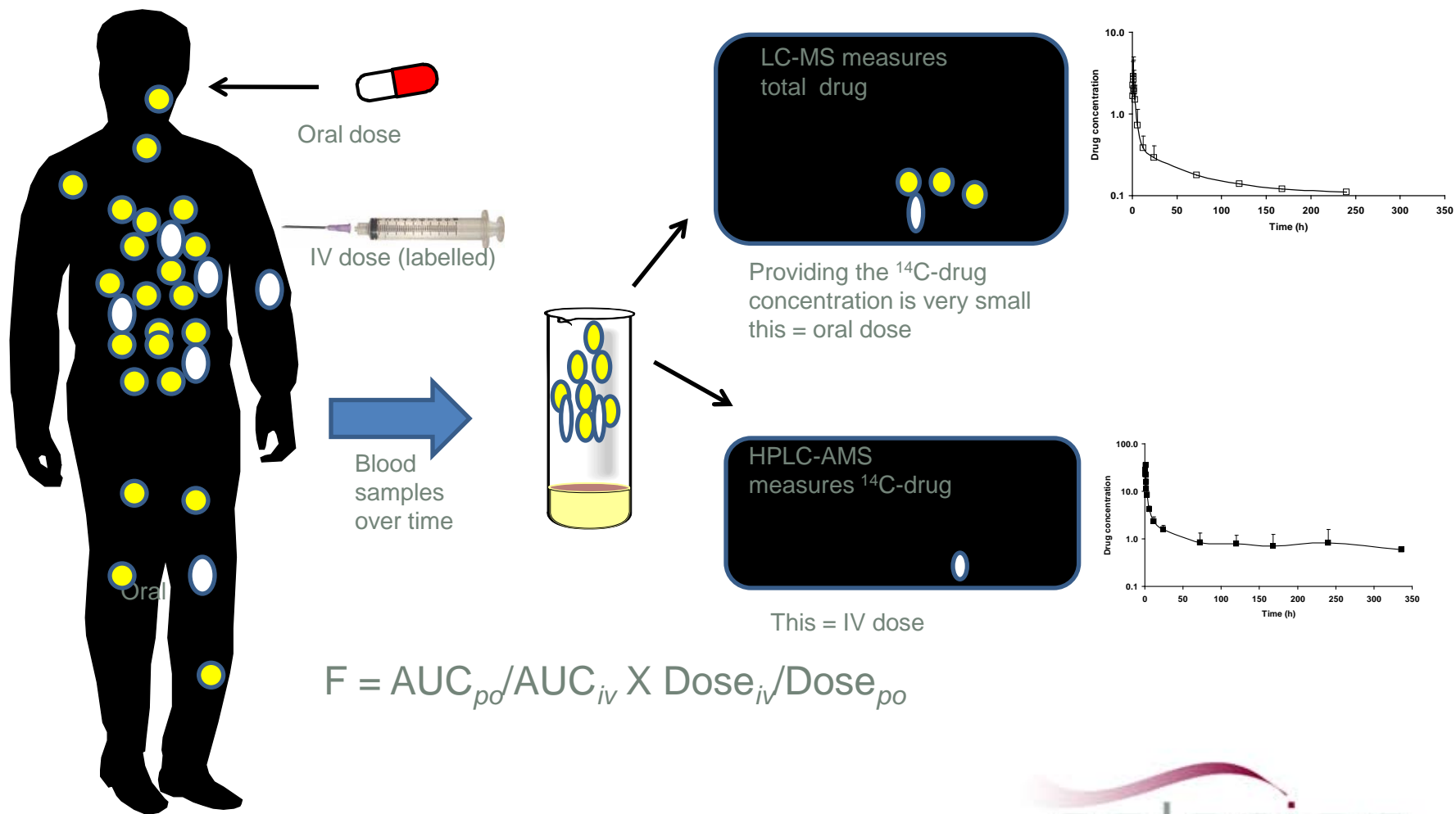
First biological application in 1989



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

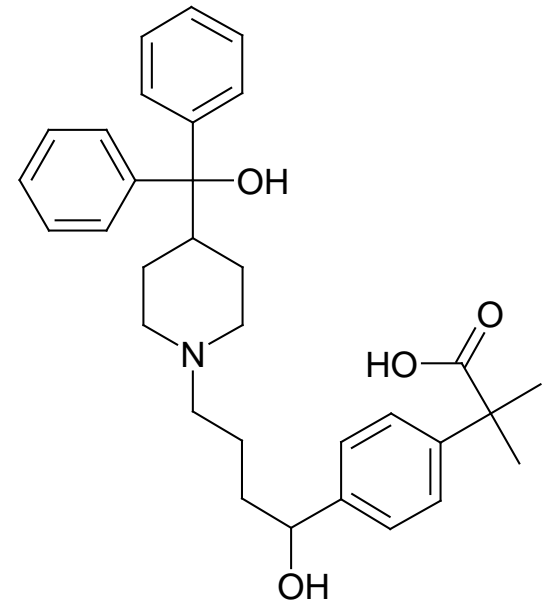
Isotopic Tracers: Determination of Absolute Bioavailability (F)



$$F = \text{AUC}_{po} / \text{AUC}_{iv} \times \text{Dose}_{iv} / \text{Dose}_{po}$$

Example: Fexofenadine

- Fexofenadine HCl is a histamine H1-receptor antagonist used to treat allergies
- It is a P-gP 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



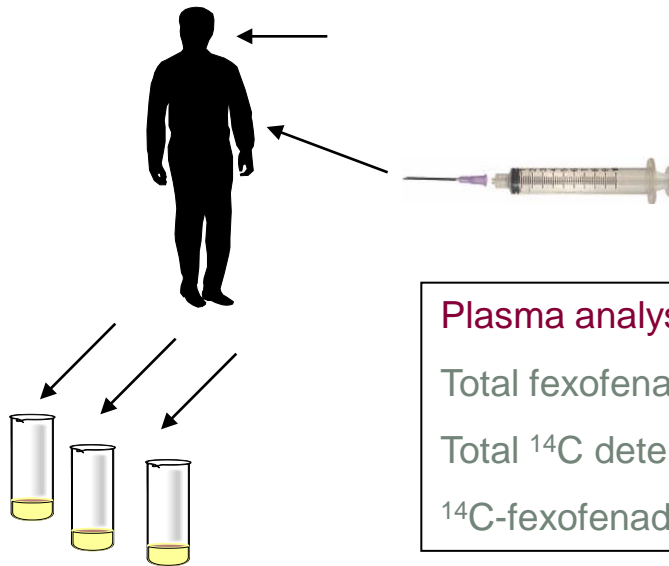
Study Design

6 healthy male
volunteers

Single oral dose
120 mg non-labelled
fexofenadine

Simultaneous IV dose of
100 μ g, 200 nCi 14 C-fexofenadine

Plasma
collected over
24 h



Plasma analysis

Total fexofenadine determined by HPLC-fluorescence

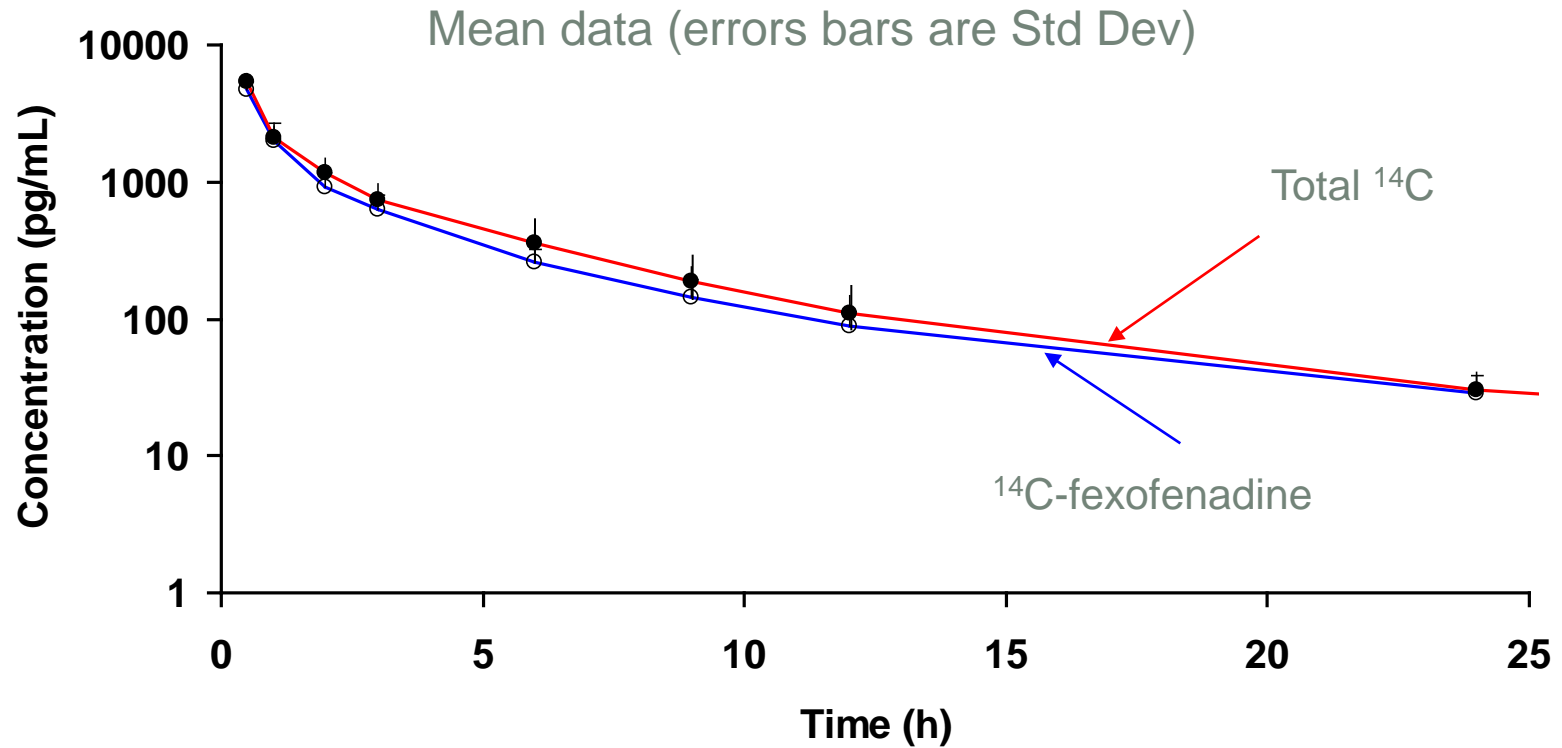
Total 14 C determined by AMS

14 C-fexofenadine determined by HPLC and AMS

Acknowledgement:

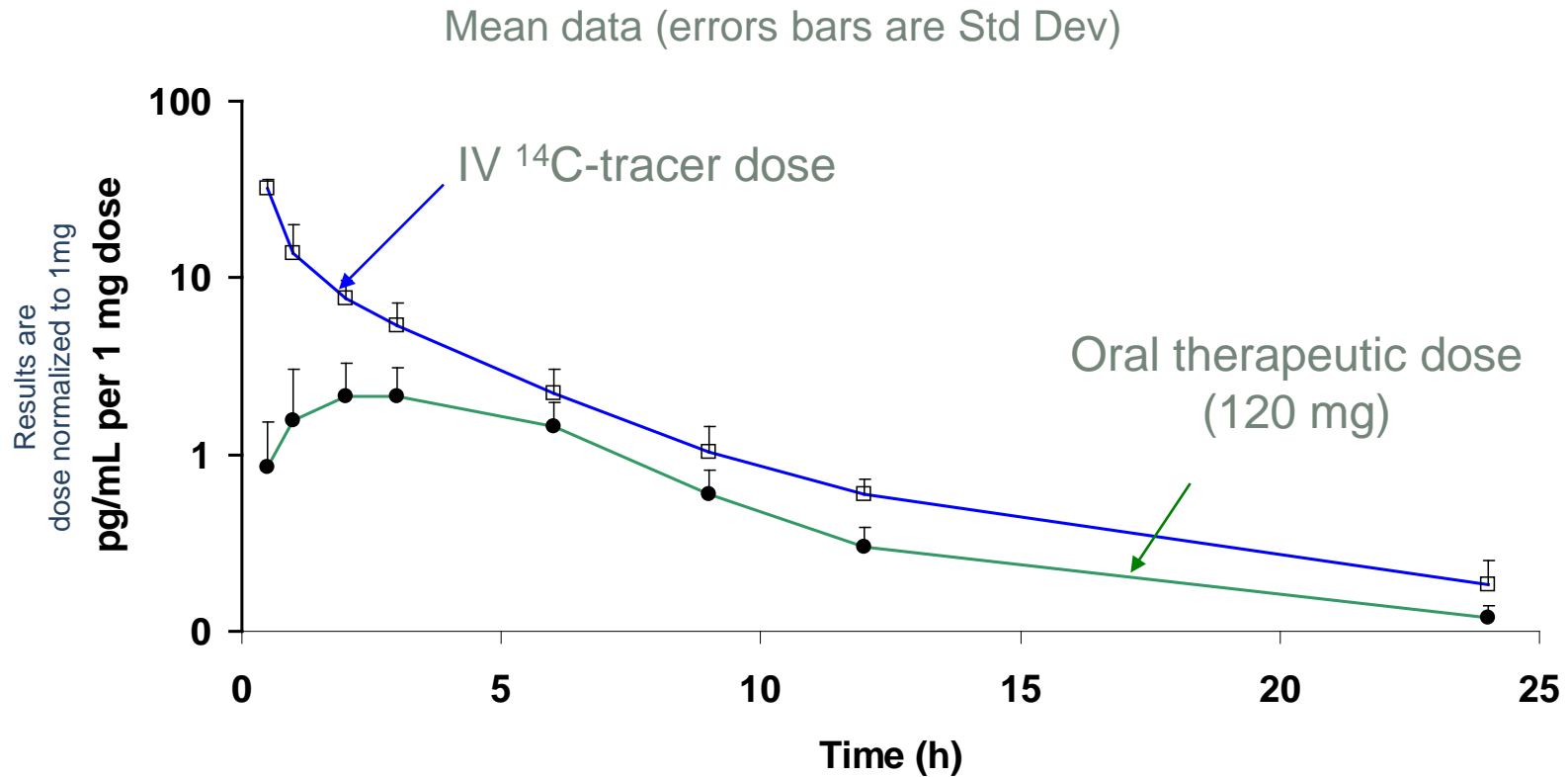
This research study was funded by the European Commission grant number LSHG-CT-2005-018672

Total ¹⁴C vs. Parent IV Dose



Confirms fexofenadine undergoes very limited metabolism

Absolute Oral Bioavailability of Fexofenadine



Mean oral absolute bioavailability 28%

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

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

Biomarkers and Decision-Making

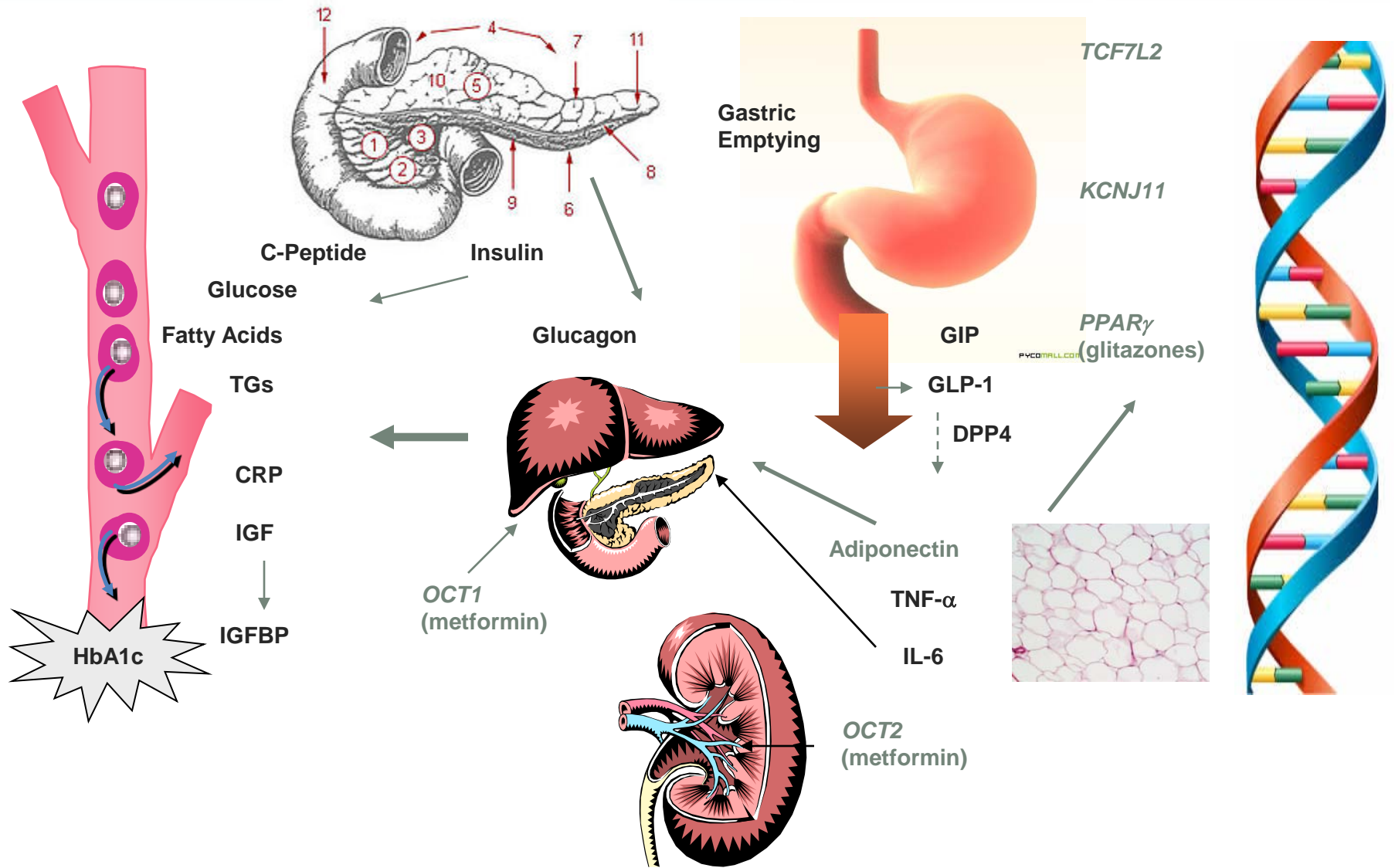
Human Biomarker : *a measure of biochemical or physiological function, anatomical structure, genetic characteristics or pharmacological activity primarily used to identify or predict changes in the human body brought on by disease or therapy*

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.

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

- Primary purpose of biomarkers is to enable better decisions

Plethora of Biomarkers for Diabetes



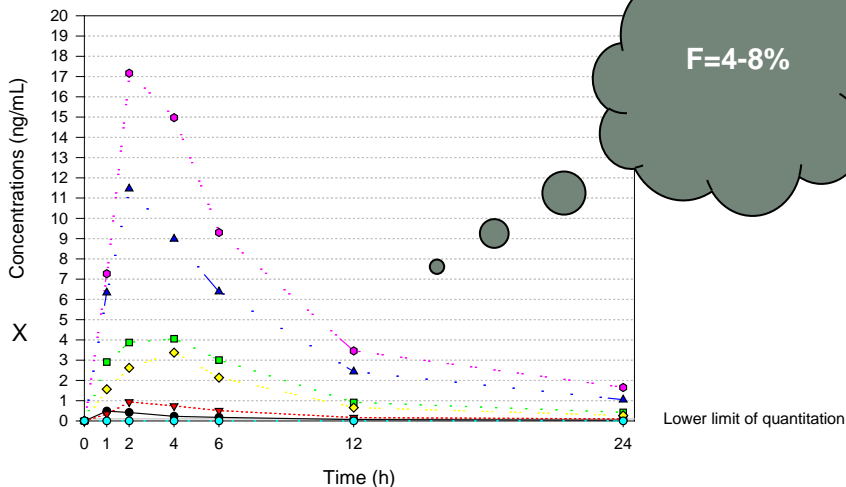
SAD Study of a Novel DPP-4 Inhibitor in Mild Diabetic Patients

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

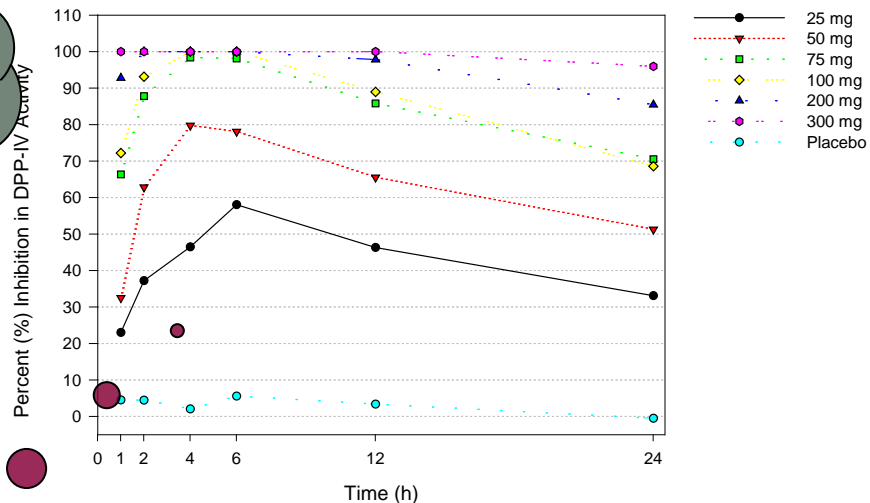
Sequence	Patients	Treatment Periods		
		P'1	P'2	P'3
4	N = 5	PLA	100 mg	300 mg
5	N = 5	50 mg	PLA	300 mg
6	N = 5	50 mg	100 mg	PLA

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

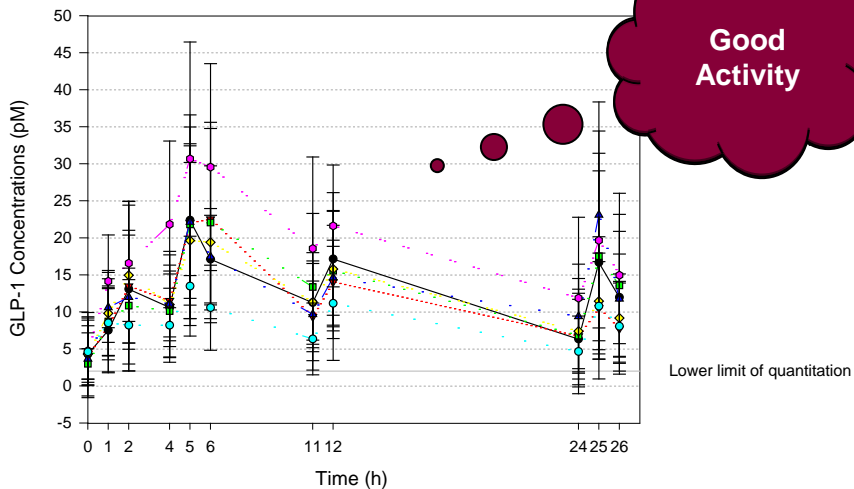
Drug Plasma Concentration



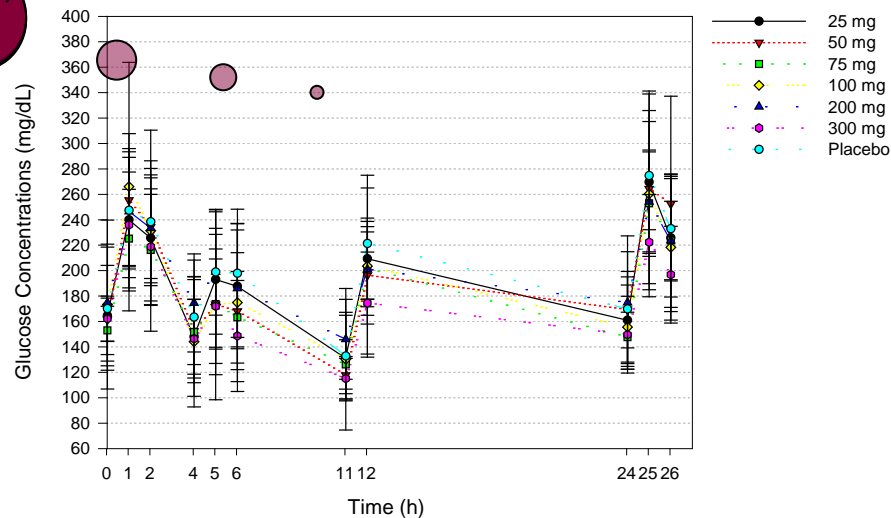
Percent DPP-IV Inhibition



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

Q & A