



Leveraging Biomarkers in Early Clinical Drug Development for Metabolic Disease Therapies

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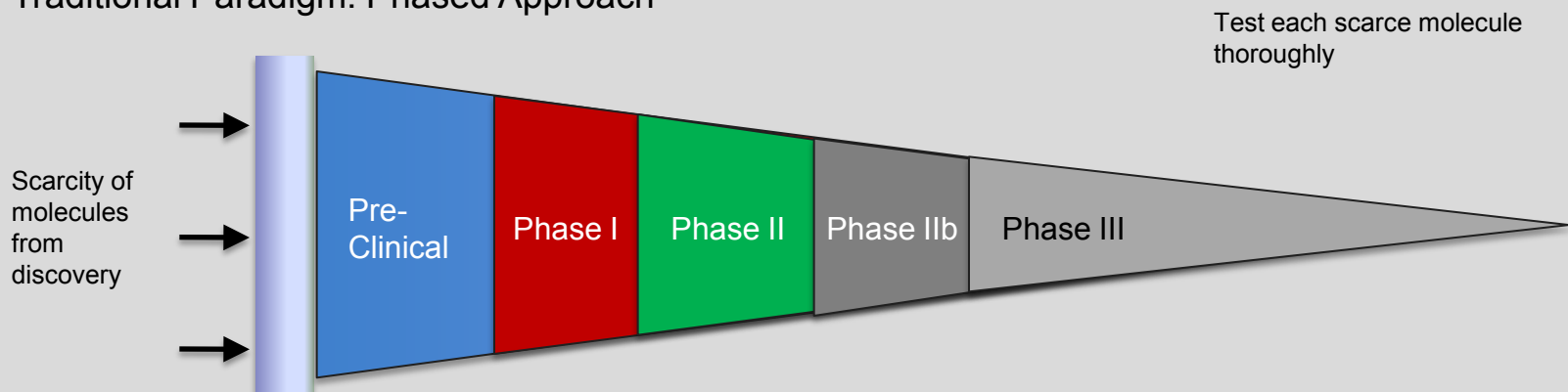
August 31, 2011

Overview of Presentation

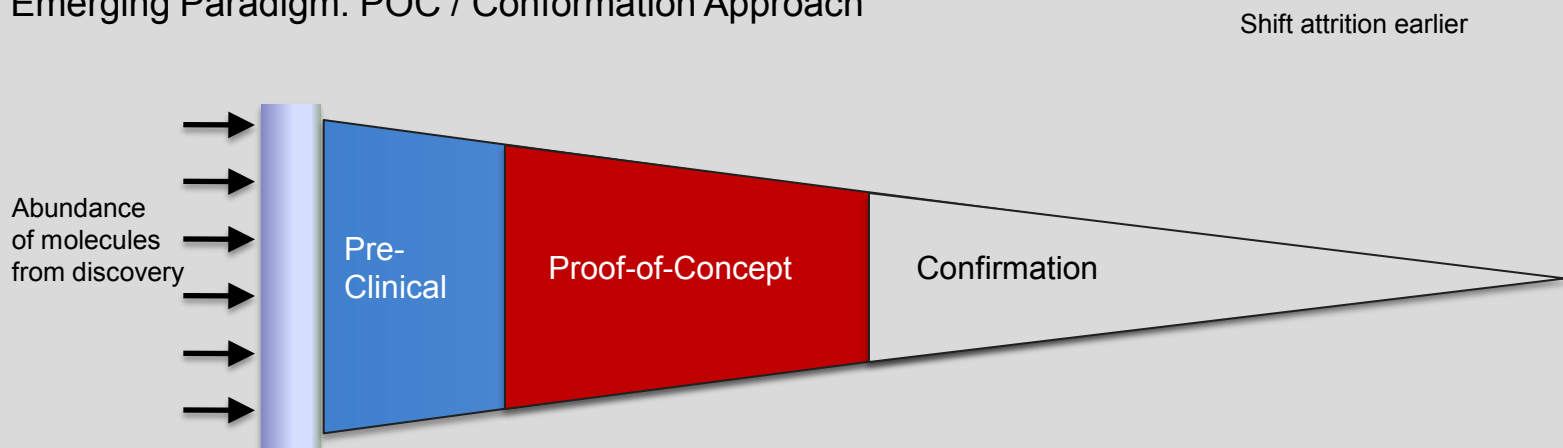
- What is driving the need for innovation in early clinical research?
- Are biomarkers new?
- Why include biomarkers in early drug development?
- What are some examples?
 - Type 2 Diabetes
 - Lysosomal Storage Diseases
- What are the challenges?
 - Novel Biomarkers
 - Analytical Issues
 - Complex Study Logistics
- Summary

Clinical Development is Evolving

Traditional Paradigm: Phased Approach

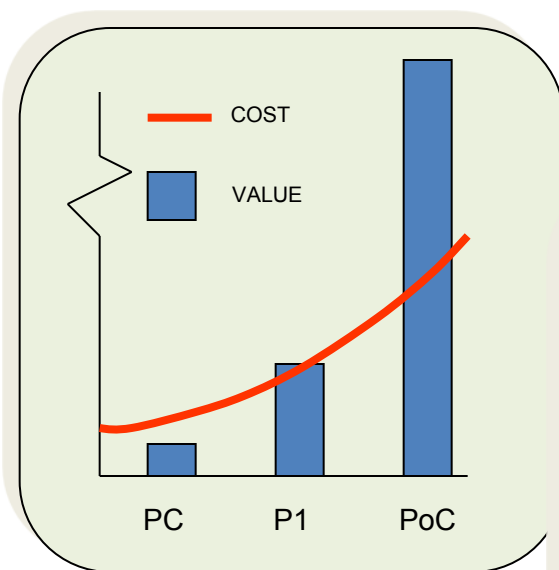


Emerging Paradigm: POC / Conformation Approach



Importance of Proof-of-Concept Studies

Defines Product Value For the First Time



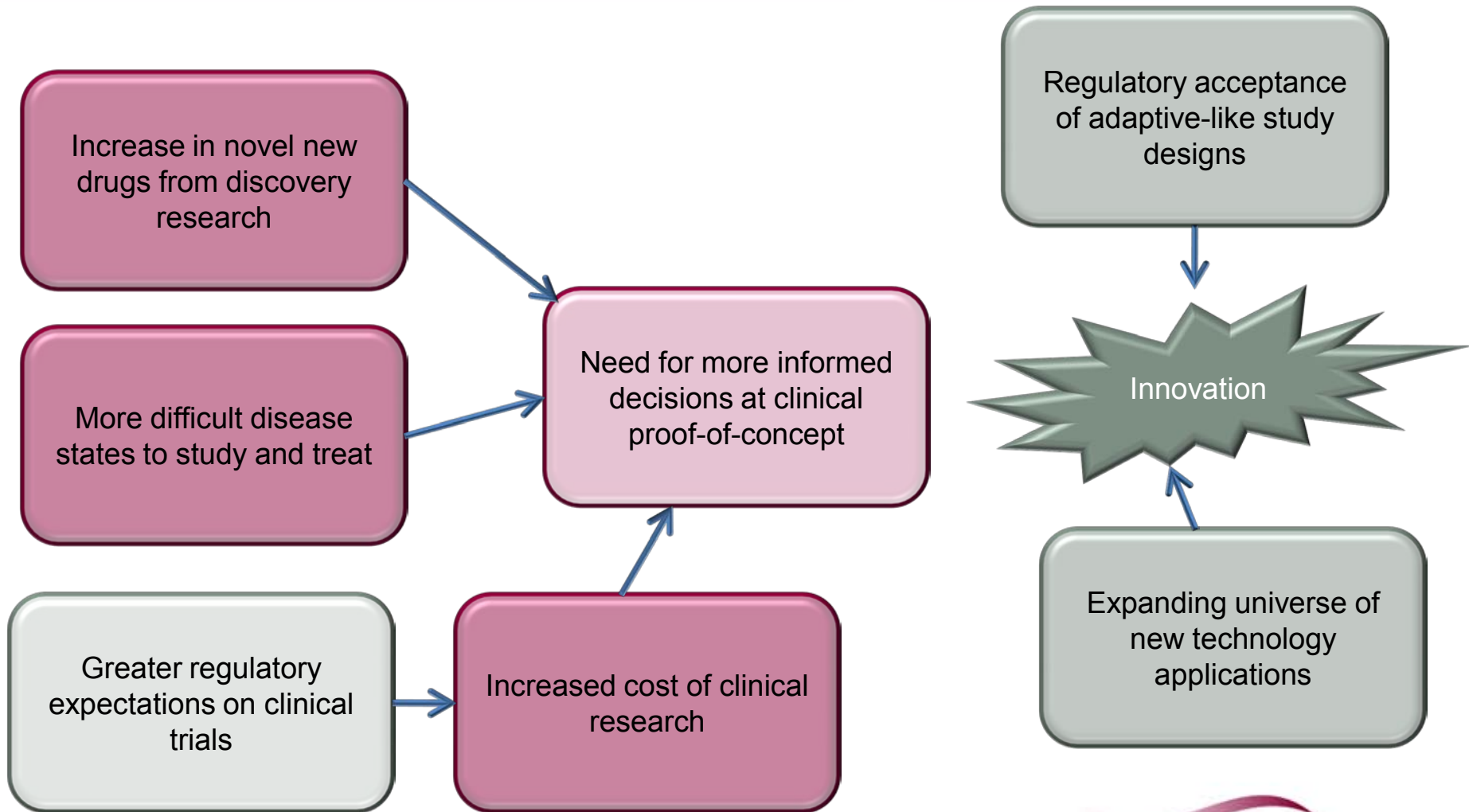
% Chance of Reaching Market

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

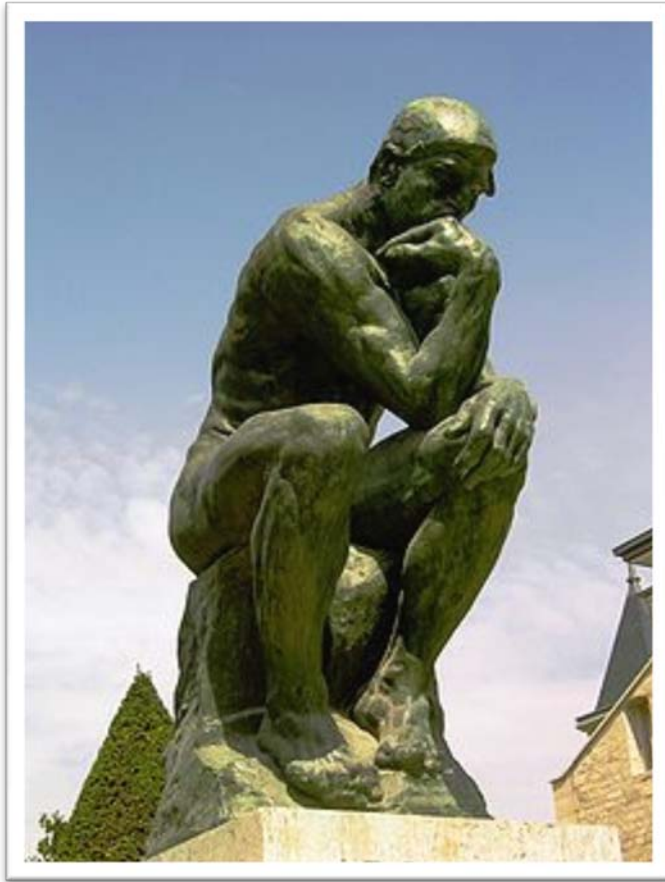
Typical Costs (\$million)

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?

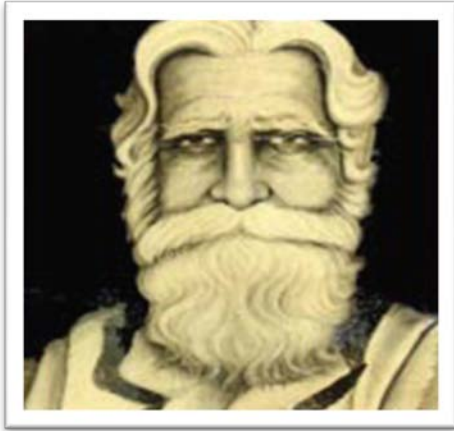


- One made earlier
- With greater confidence
- More efficiently

Better data, faster, cheaper

Q: Are Biomarkers New?

A. Biomarkers Are Not New.



Sushruta (clinician in India, 600 B.C.)

Recorded that urine of diabetic patients attracted ants

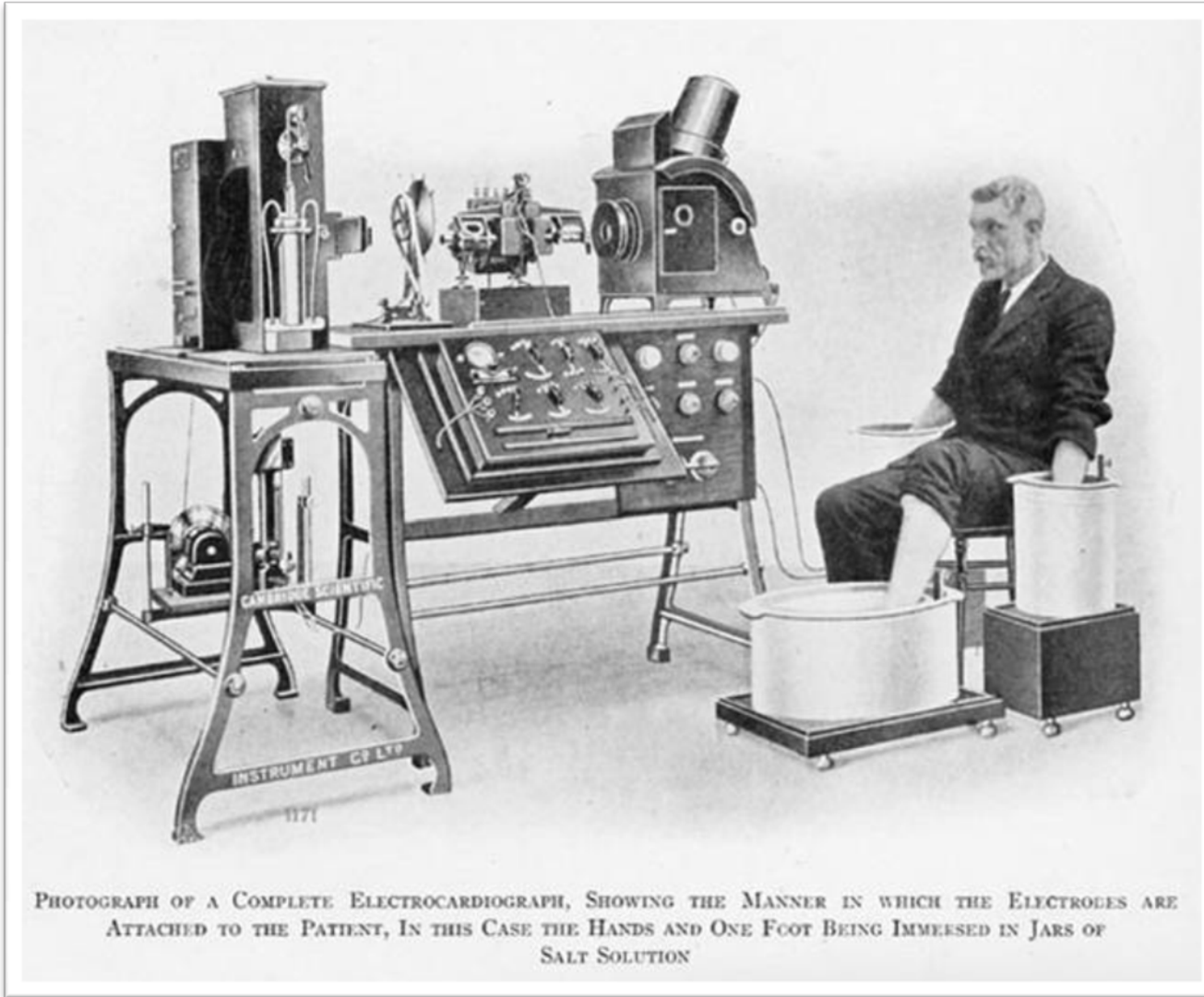


= Diagnostic biomarker for diabetes

Other Early Milestones in Biomarker Development

- **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** **Wilhelm Röntgen** discovered x-rays
→ imaging biomarkers
- **1896** **Henri Becquerel** discovered radioactivity
→ radiodiagnostics
- **1901** **Willem Einthoven** invented the first ECG apparatus

An Early ECG Device



The Hybrid Phase 1/ ECG Core Laboratory

- Phase 1 focus only
- Single vendor with unified functionality
- Single database
- Single PM DM stats

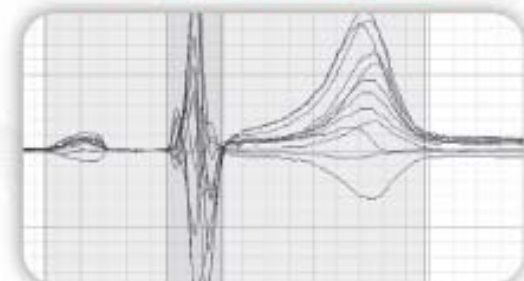


BLUETOOTH HOLTER



- 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

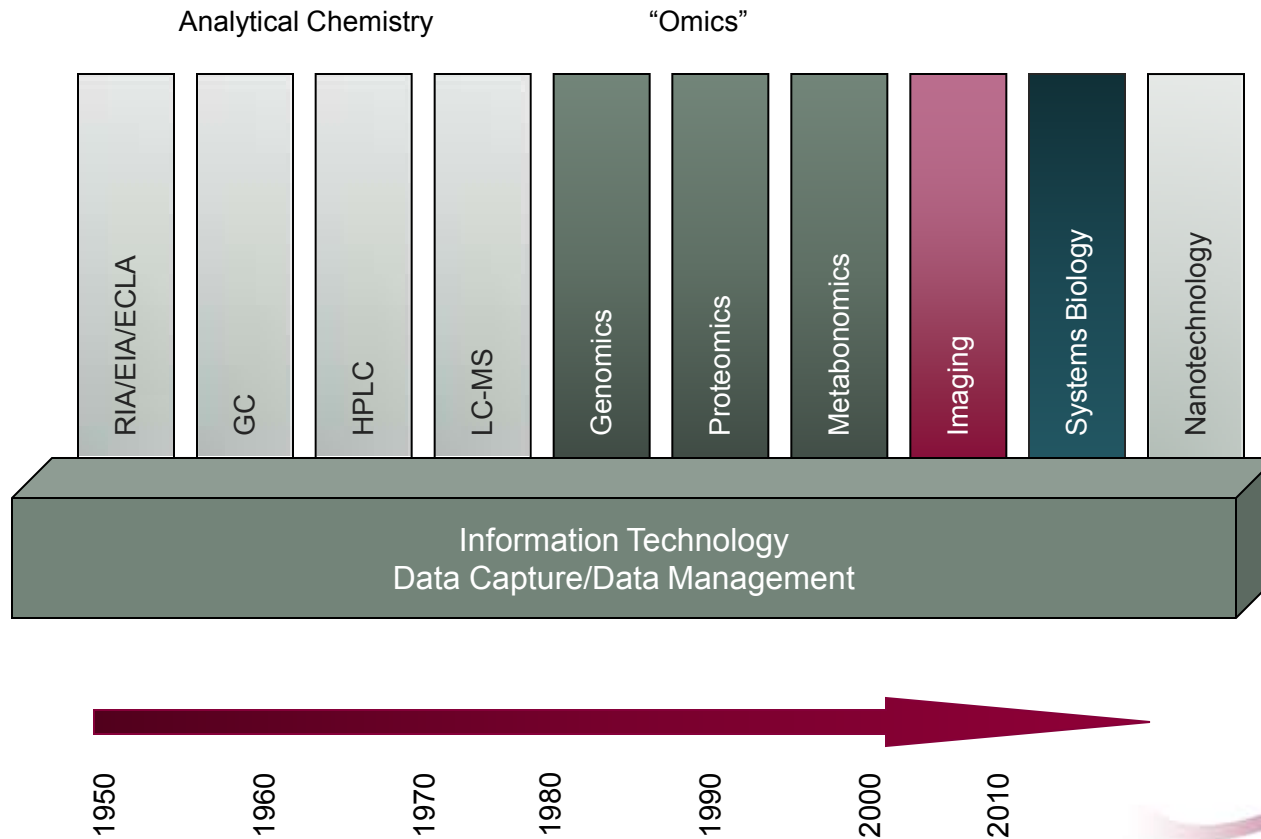
HIGHLY AUTOMATED PROCESSES



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

Modern Era of Biomarkers – New Technology Drives Innovation

1950s to present day



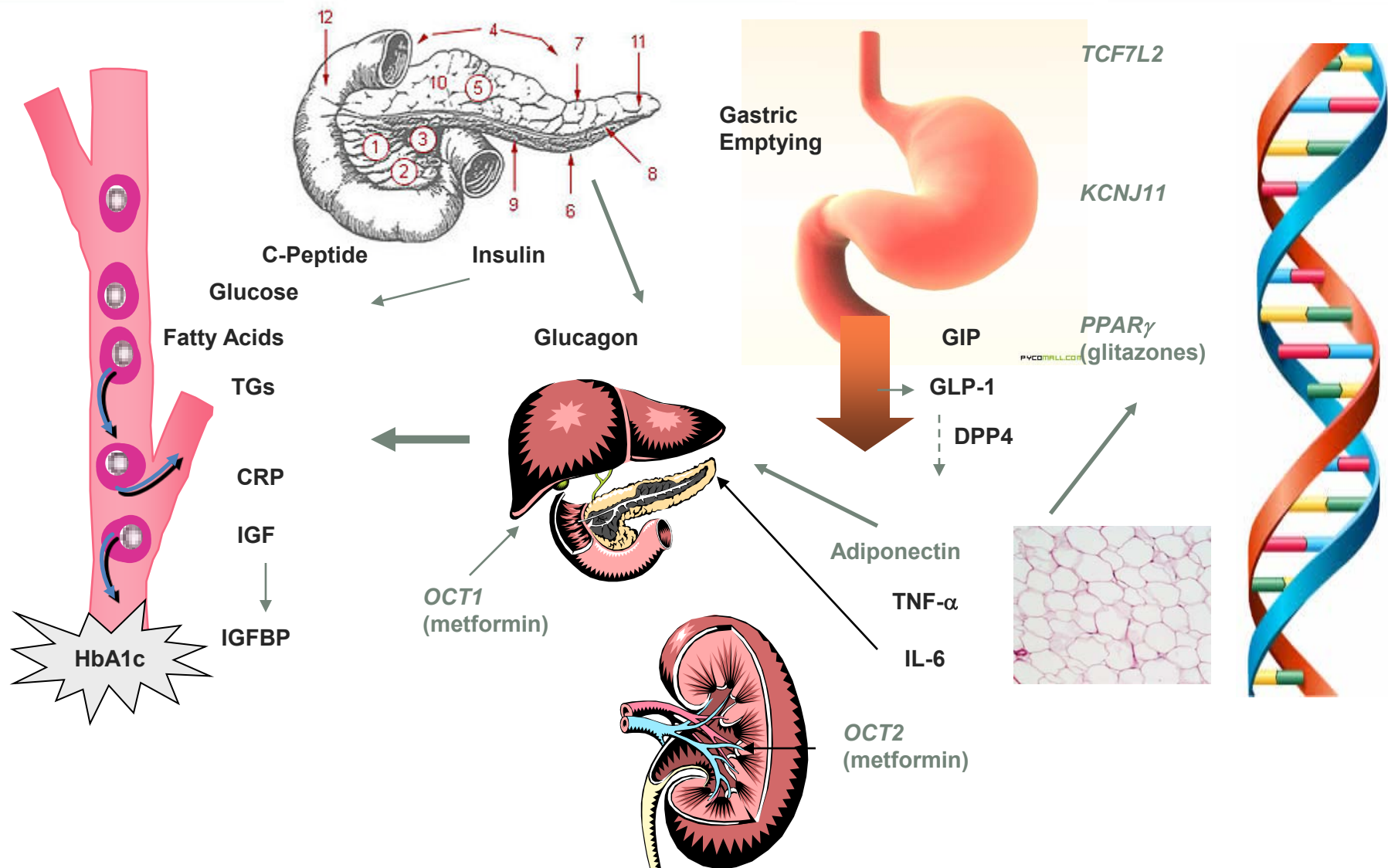
Biomarkers and Decision-Making

- Key question: How will the biomarker(s) advance the drug's development?
- Primary purpose of biomarkers is to enable better decisions

Diabetes

- Diabetes affects nearly 25.8 million people (8.3% of the population) in the U.S.
 - 18.8 million diagnosed
 - 7.0 undiagnosed
- > 35% of U.S. adults > 20 years have pre-diabetes
- > 50 of U.S. adults > 65 years have pre-diabetes
- Leading cause of kidney failure, nontraumatic limb amputations and new cases of blindness
- Major cause of heart disease and stroke
- 7th leading cause of death

Plethora of Biomarkers for Diabetes



Considerations in Evaluating a Candidate Biomarker

- Clinical relevance
 - Ideally, should be related to MoA of the drug and the clinical endpoint
- Sensitivity and specificity to treatment effects
 - Ability to detect the biomarker or change in biomarker in the target population
- Reliability
 - Ability to measure the biomarker analytically with accuracy, precision, robustness and reproducibility
- Practicality
 - Is the biomarker non-invasive? Is it suitable to implement in multi-site trials?
- Simplicity
 - Simpler is better for translating a biomarker from lab bench to bedside

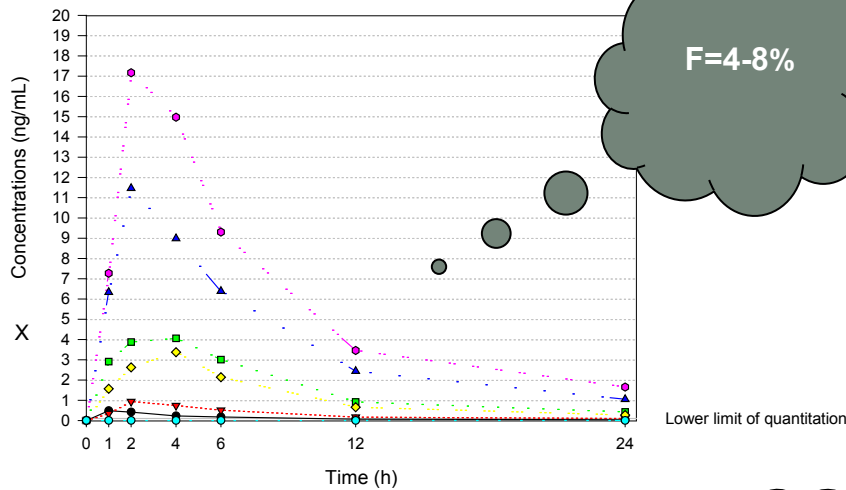
SAD Study of a Novel DPP-4 Inhibitor in Mild Diabetic Patients

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

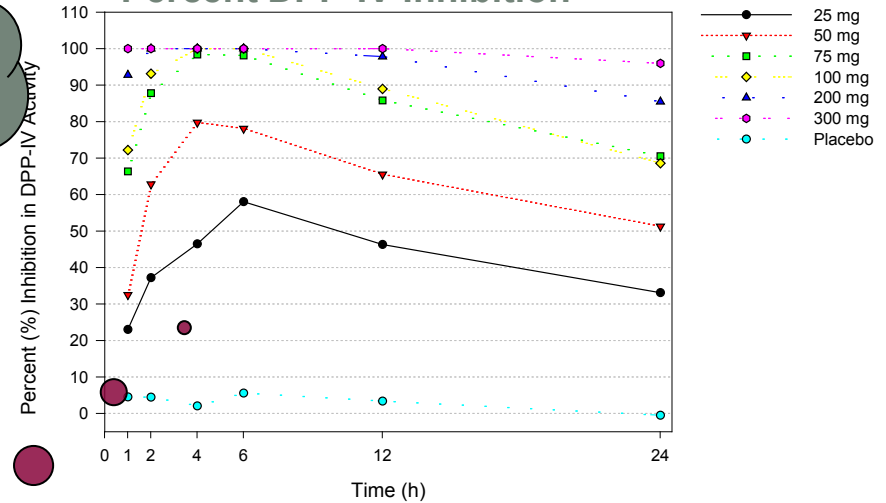
Sequence	Patients	Treatment Periods		
		P'1	P'2	P'3
4	N = 5	PLA	100 mg	300 mg
5	N = 5	50 mg	PLA	300 mg
6	N = 5	50 mg	100 mg	PLA

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

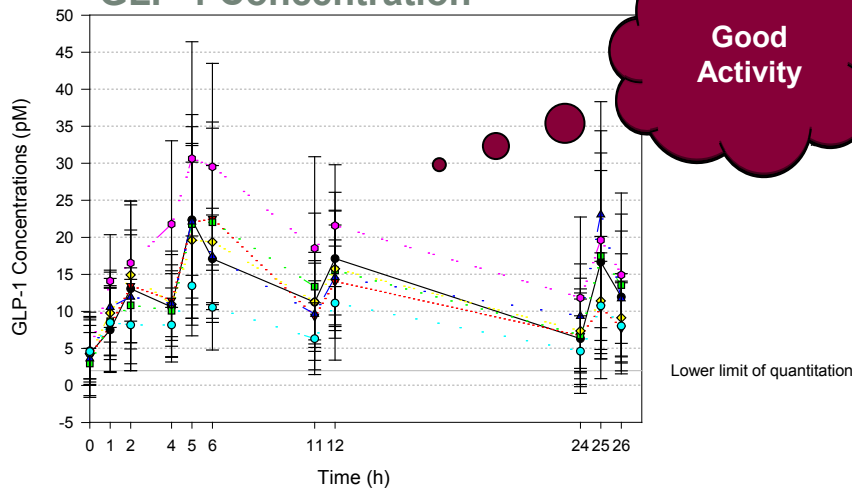
Drug Plasma Concentration



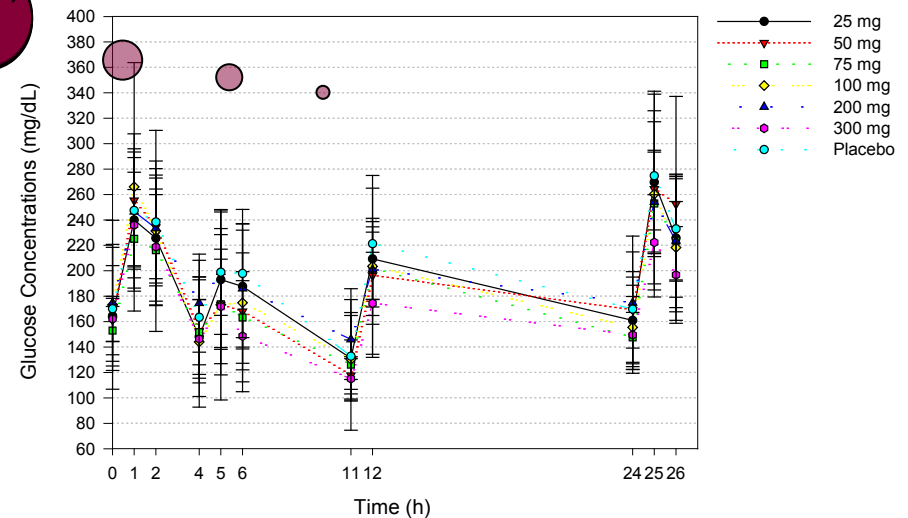
Percent DPP-IV Inhibition



GLP-1 Concentration

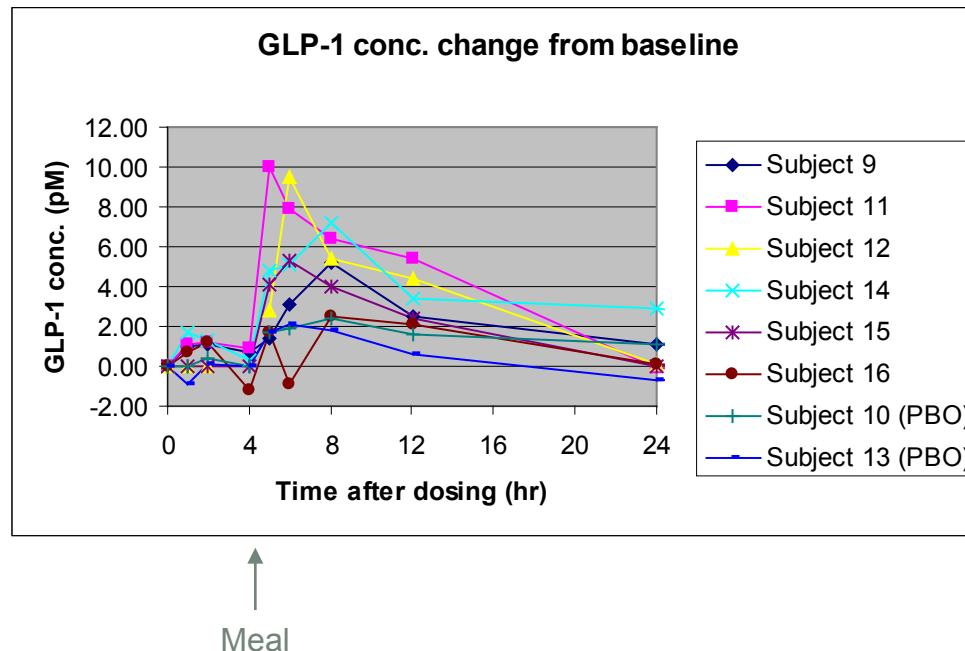


Glucose Concentration



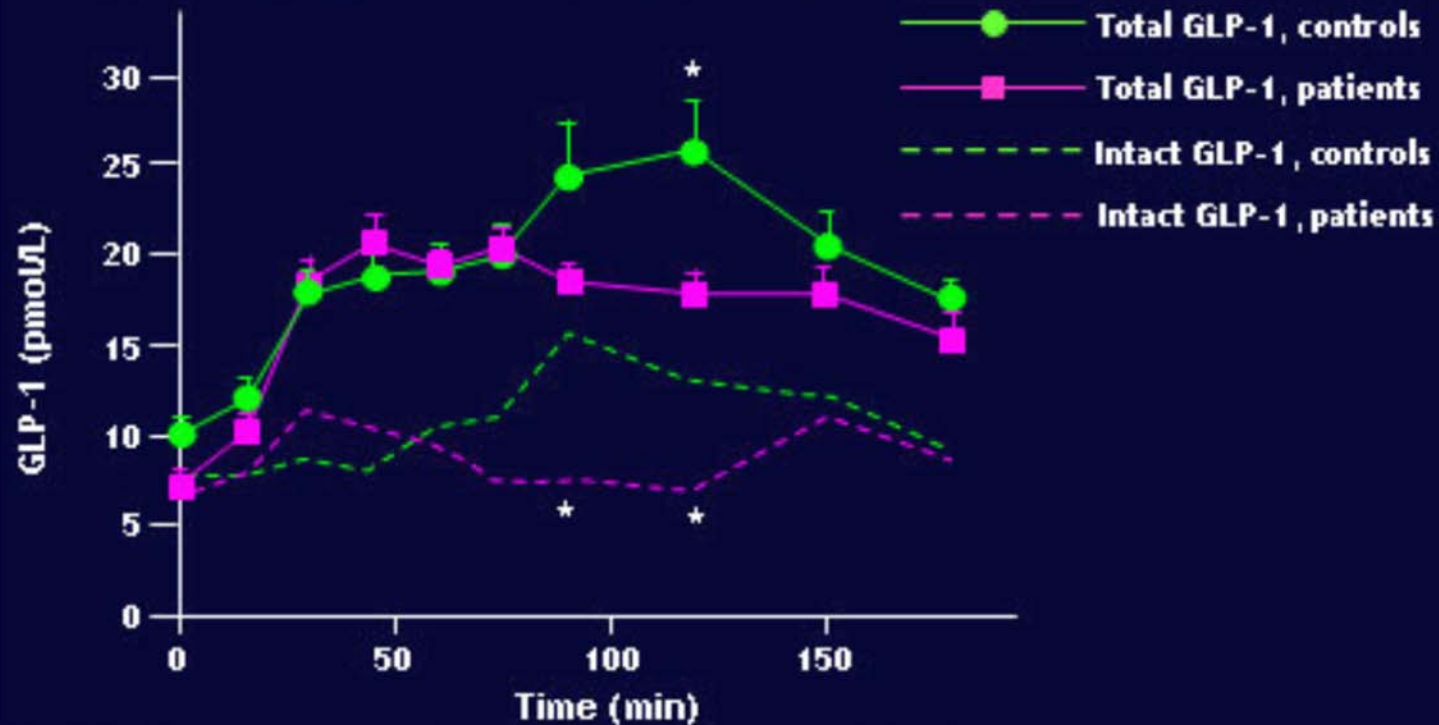
SAD Study of Novel DPP-4 Inhibitor in Healthy Volunteers

High Inter-subject Variability in Postprandial GLP-1



GLP-1 Response to Meal is Different Between Healthy Volunteers and Type 2 Diabetics

Modest but Significant Decrease in Meal-Stimulated Intact GLP-1 in Type 2 Diabetes



* $P < .05$ for difference between type 2 patients with diabetes and healthy subjects.

Misbell T et al. Diabetes. 2001;50:609-613.

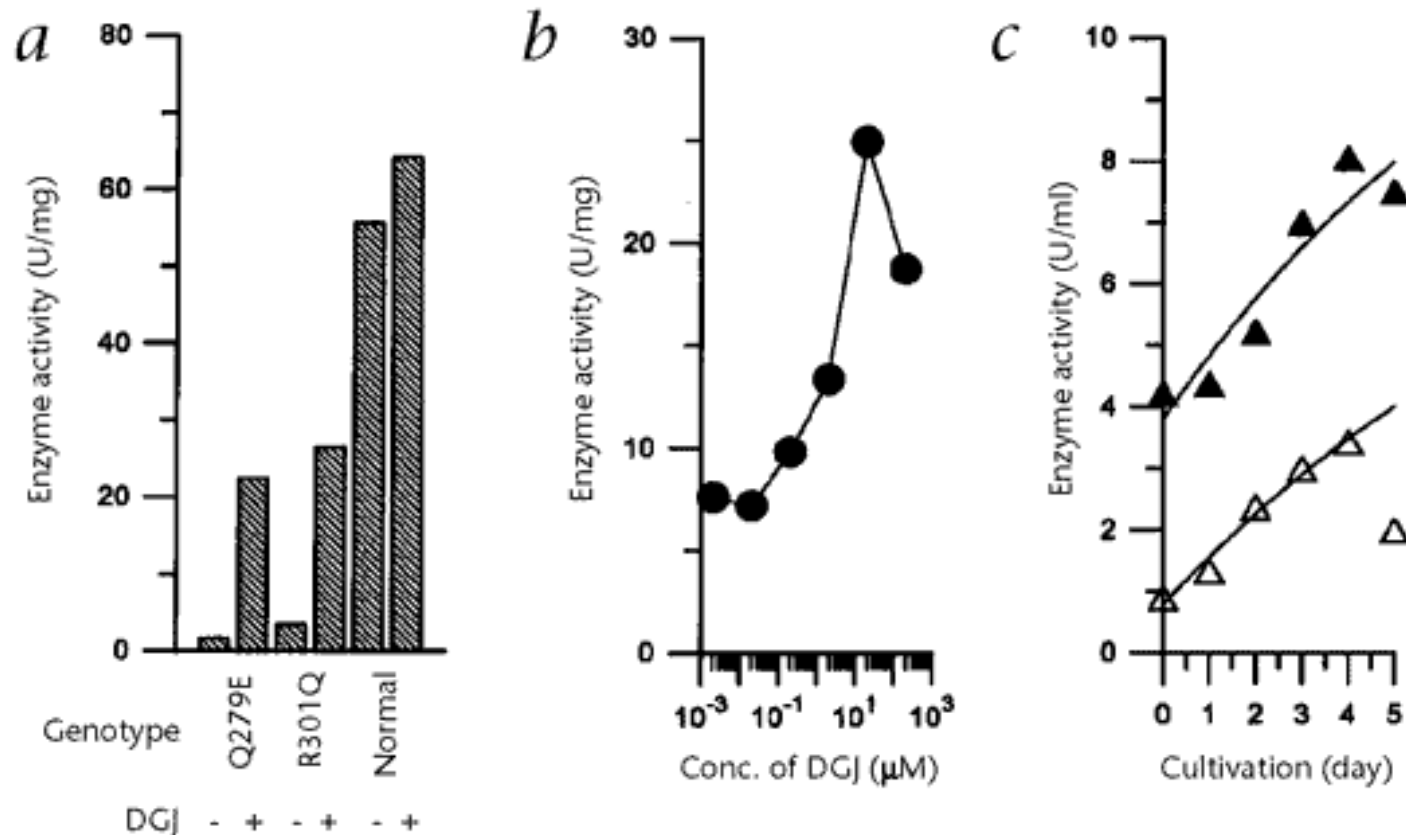
Lysosomal Storage Diseases

- Rare inherited metabolic disorders that result from defects in lysosomal function
- Usually caused by the deficiency of a single enzyme involved in the metabolism of a lipid, glycoprotein or mucopolysaccharide, resulting in the excess accumulation of its substrate in the lysosomes
- Examples – Fabry disease, Gaucher disease, Pompe disease

Fabry Disease

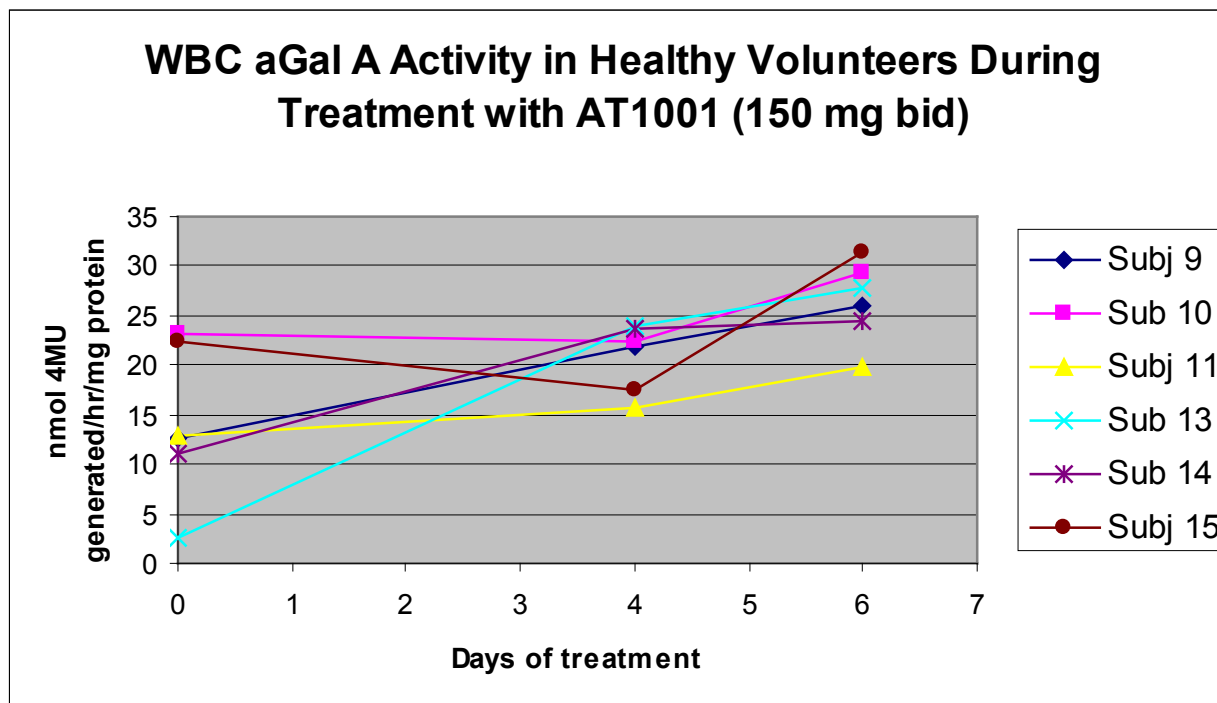
- X-Linked inborn error of metabolism
- Subnormal or absent activity of lysosomal hydrolase, α -galactosidase A (α Gal A)
- Progressive globotriaosylceramide (GL-3) accumulation in tissues leading to end-organ impairment
- Most morbidity and mortality attributable to renal, neurologic and cardiac disease
- Therapies for Fabry Disease
 - Enzyme Replacement Therapy
 - *Chaperone Therapy?*

In Vitro Studies During Discovery Demonstrated α Gal A as a Mechanism of Action Biomarker



Enhancement of α Gal A in lymphoblasts from patients with Fabry disease

PD Biomarker Incorporated into Phase I Clinical Development Program



Biomarker Results Helped Raise New Funds

AMICUS THERAPEUTICS RAISES \$55 MILLION SERIES C FINANCING

September 8, 2005

“ Amicus today announced positive results from its Phase I clinical studies of Amigal and the start of patient enrollment in its Phase II clinical program for the treatment of Fabry disease. In addition to meeting all of its safety endpoints, **the Phase I studies demonstrated proof of concept for Amicus’ pharmacological chaperone technology, showing that Amigal has the ability to increase target enzyme activity levels, even in healthy individuals.**”

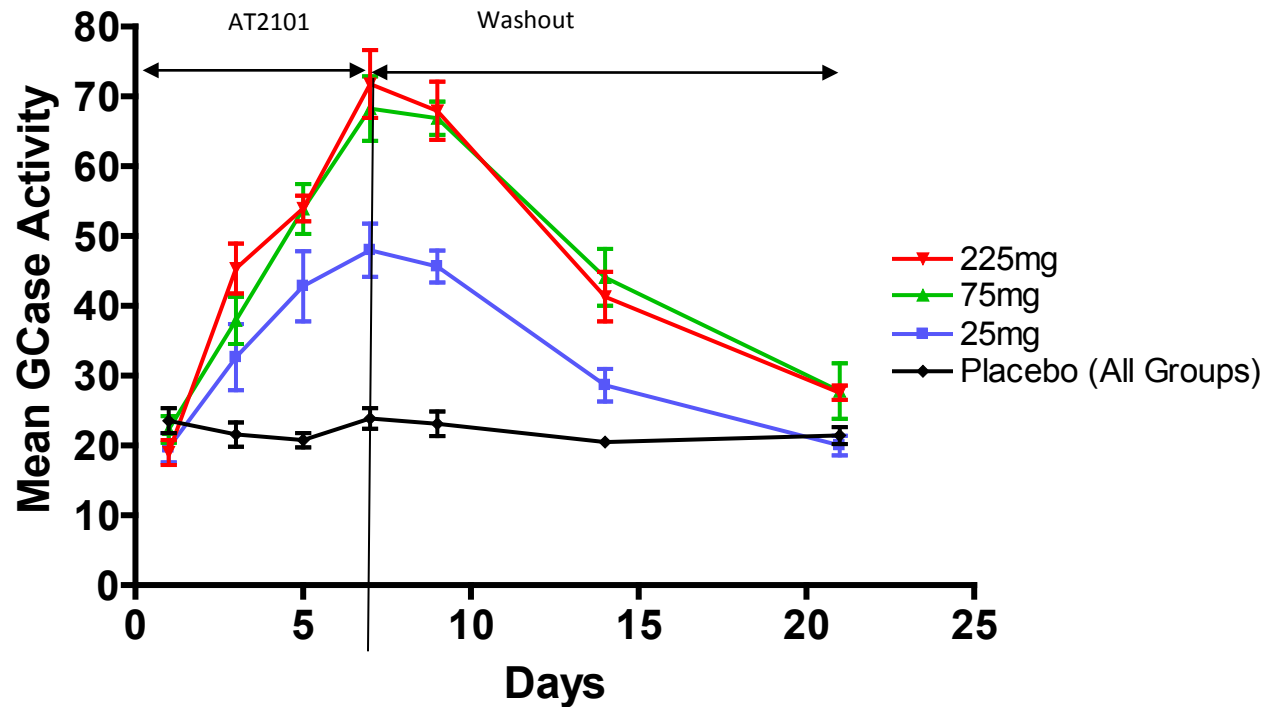


Gaucher Disease

- Most common lysosomal storage disease
- Autosomal recessive inheritance
- Subnormal or absent activity of lysosomal acid β -glucocerebrosidase (GCase)
- Progressive accumulation of substrate glucocerebroside in tissues leading to end-organ impairment
- Most morbidity and mortality attributable to hepatosplenomegaly, bone and neurologic disease
- Therapies for Gaucher Disease
 - Enzyme Replacement Therapy
 - Miglustat (enzyme inhibitor that decreases production of substrate)
 - *Chaperone Therapy?*

GCase as PD Biomarker in Phase I MAD Study

GCase activity in white blood cells during repeated daily oral doses of AT2101 for 7 days followed by a 14-day wash-out period



DJ Palling et al., Am. College Med Genetics, Nashville, Tennessee, March 2007 (poster presentation)

Clinical Relevance of Biomarkers:

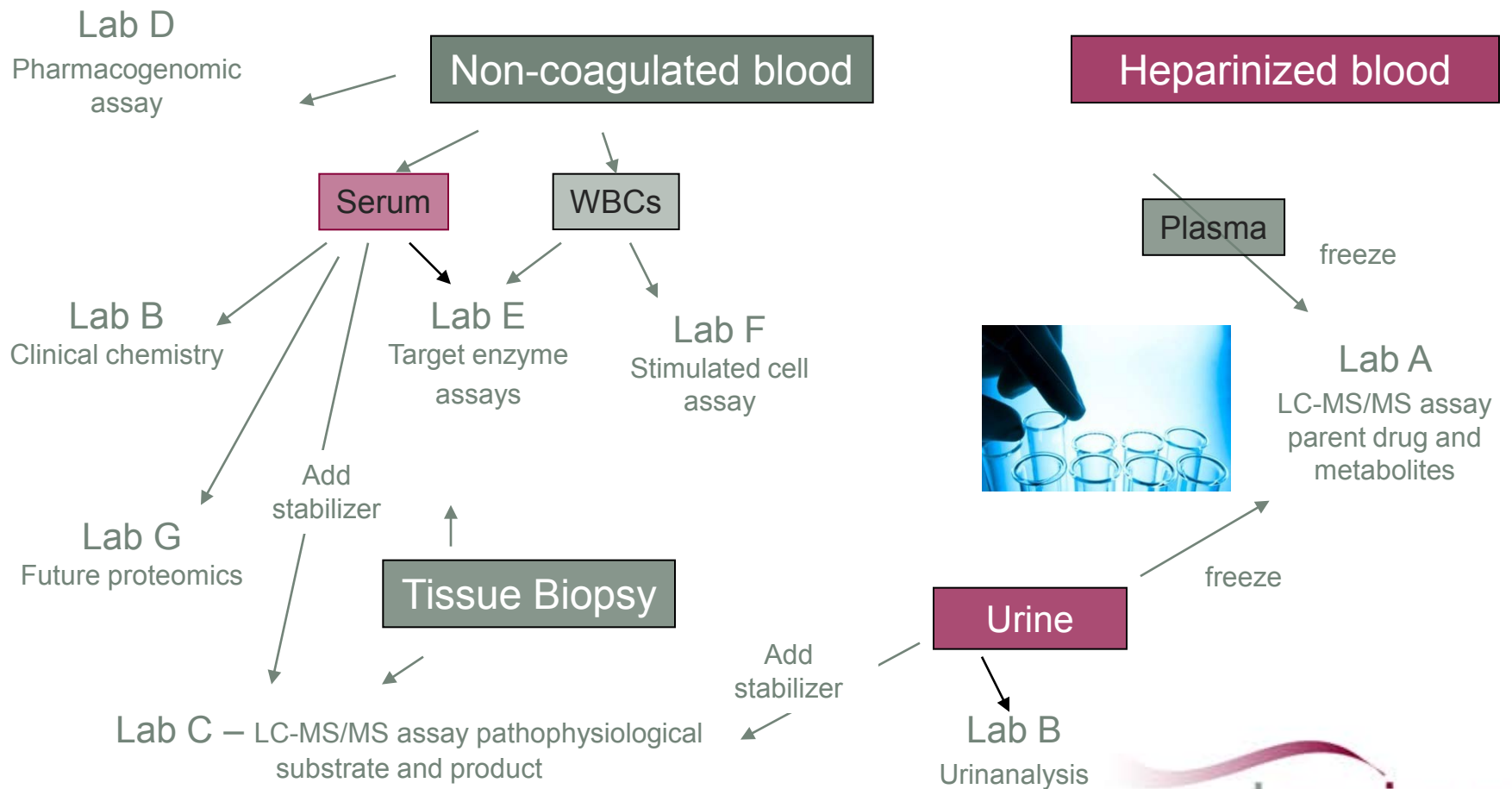
- If a biomarker is to be used to differentiate between healthy individuals and those with a disease, need to determine a priori the descriptive statistical parameters for the two populations
 - Mean, range, variance
 - Is there population overlap?
 - How does the population difference compare to the measurement error?
- May need to first conduct a survey study to collect data
- Determine appropriate sample size (based on statistical power to detect meaningful difference)

Normal Range and Variation of the Biomarker

- *Example: Novel drug for treatment of a rare metabolic disease caused by an enzyme deficiency*
 - Phase II study: Patients were “pretreated” for 2 weeks with the drug to determine if they were “responders”. Only responders were to be enrolled in a 12-week open-label trial
 - Original definition of responder was “If baseline enzyme activity is less than 1% of normal, then Day -15 enzyme activity must be at least 2% of normal”
- *Key Issue: Need to define “normal”*
 - Measured enzyme activity in healthy subjects (N=21)
 - AVG = 22.8 nmol/mg protein
 - SD = 5.7, Range = 11.0 - 33.5
 - Cannot discern an increase from 1% to 2% of normal
 - Changed inclusion criteria based on X-fold increase from baseline for individual patient

Complex Sample Collection and Processing

Example – Phase IIa study – 14 tests, 7 labs



Challenges and Learnings

- Time to develop assay (translate from lab bench to clinic)
 - Assay through-put, sensitivity & specificity, reliability
- Defining normal baselines for novel assays
 - Can be readily done in early phase
- Complex sample collection and processing
 - Role of project management
 - Staff training (mock runs)
 - Barcode system to reduce errors, maintain chain of custody

Challenges and Learnings (continued)

- High demands on data management and data analysis; quantity and speed
 - Integrated IT solutions
- Ethical issues (e.g. tissue banking, privacy, data integrity)
 - Issues must be recognized early and solutions developed early
- Evolving regulatory environment
 - Engage early with regulatory agencies

Summary

- Purpose of biomarkers is to enable better decisions
- Question to be answered should drive the technology used
- Understand biomarker variability and clinical relevance in study populations
- Recognize challenges and plan early



Q & A