



Biochemical Profiling of Lipids: Applications to Drug Development and Toxicology

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Scientific Approach

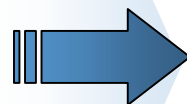


- Building technology for understanding lipid metabolism in global and molecular detail.
 - Lipid metabolism in disease
 - Effects of foods and drugs on lipid metabolism
 - Lipids as central components of individual health status

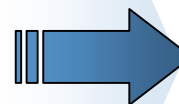
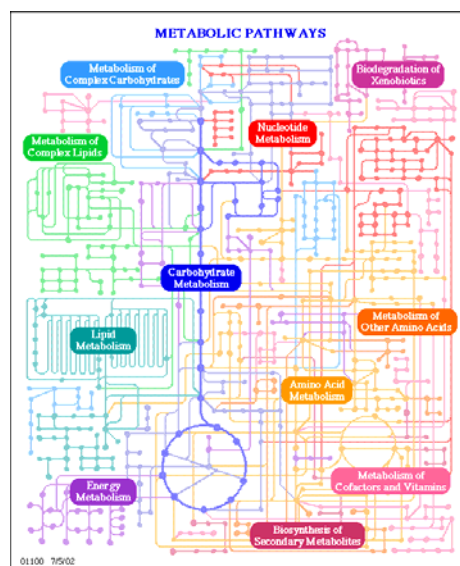
Metabolomics Integrates



Drugs
Nutrition
Exercise
Environment
Genes



Metabolism



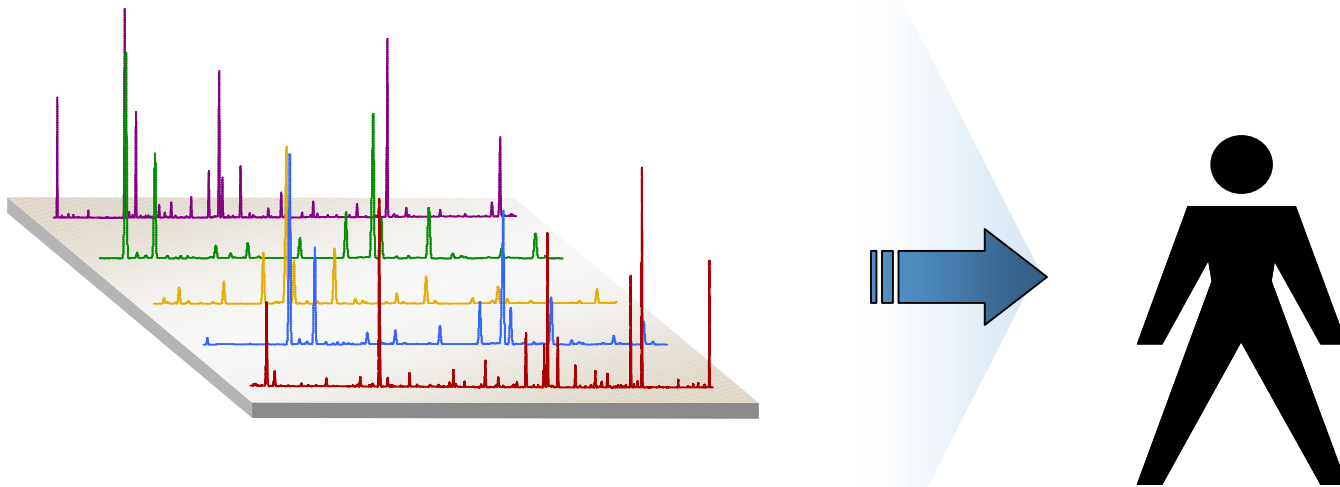
Health

Disease

Metabolic Assessment



- High-content analyses provide *individual* context
- Context allows interpretation



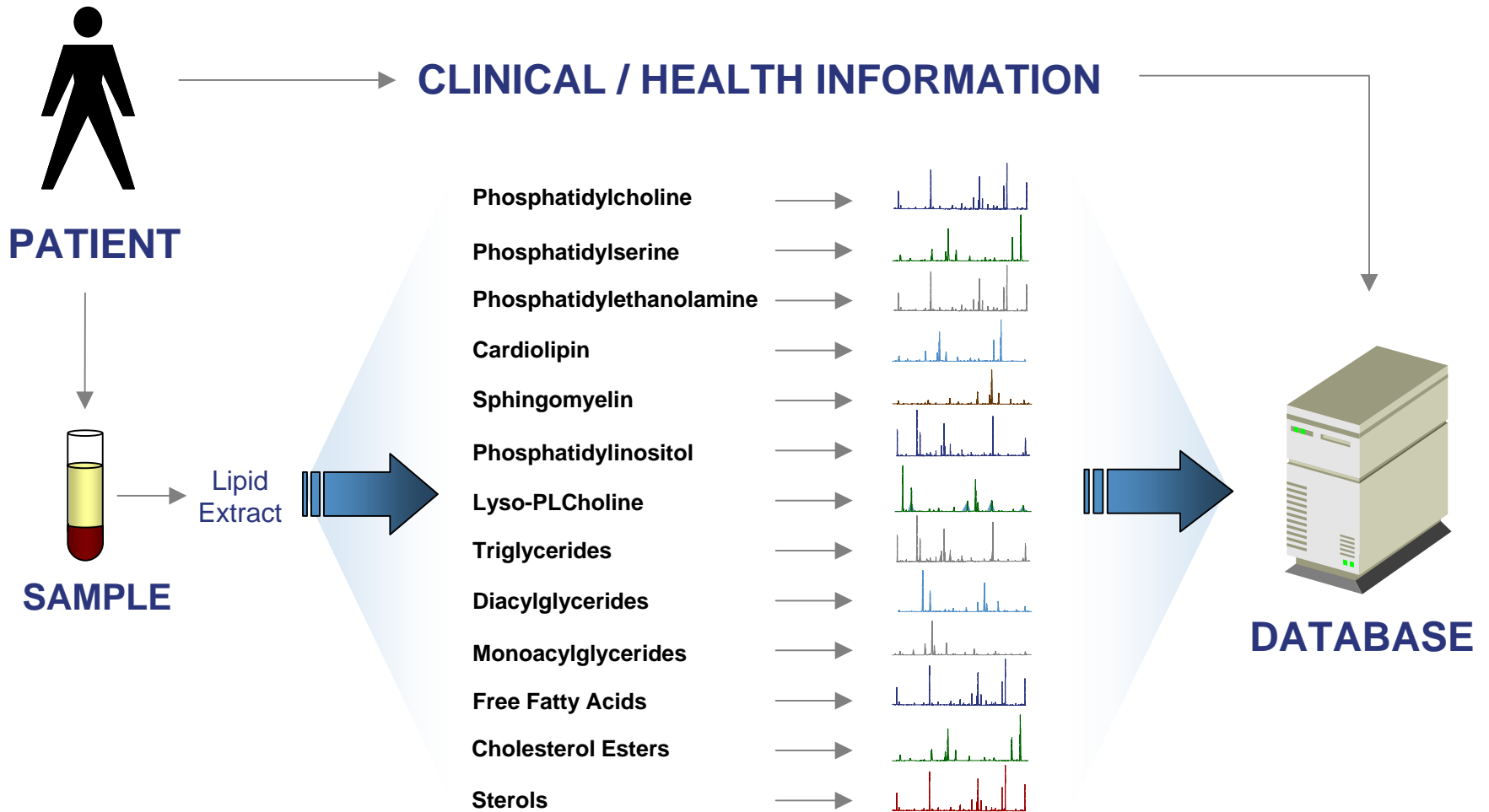
Tools for Enabling Metabolic Assessment



- High-content, quantitative analysis of metabolites
- Analysis of flux through metabolic pathways

Metabolomics provides both

Quantitative Analysis

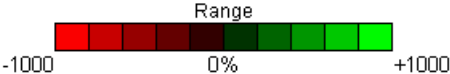


Surveyor[®] Data Visualization



Lipomics Surveyor

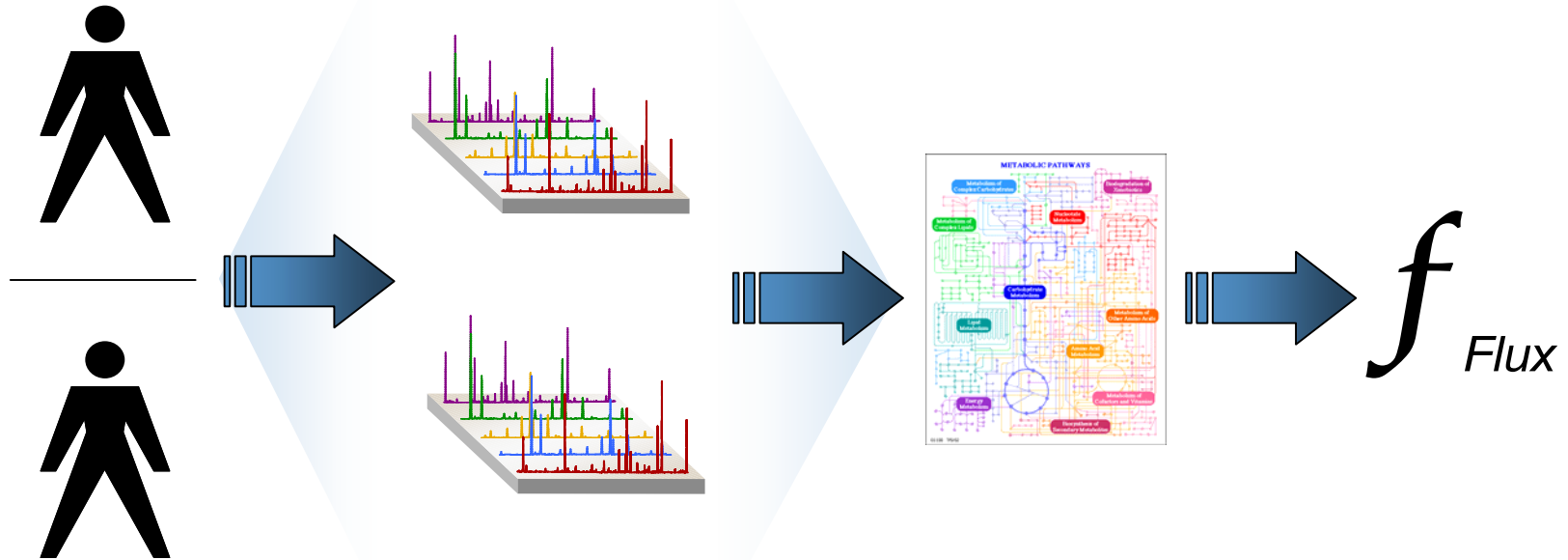
Update >



Tissue	Class	Saturated				n7		n9				n3				n6				Misc			Plasmalogen																	
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Liver	Cardiolipin																																							
Liver	Cholesterol Ester																																							
Liver	Diacylglyceride																																							
Liver	Free Fatty Acid																																							
Liver	Lysophosphatidylcholine																																							
Liver	Phosphatidylcholine																																							
Liver	Phosphatidylethanolamine																																							
Liver	Phosphatidylserine/inositol																																							
Liver	Sphingomyelin																																							
Liver	Total Phospholipid																																							
Liver	Triacylglyceride																																							
Plasma	Cholesterol Ester																																							
Plasma	Diacylglyceride																																							
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Steady-State Flux Analyses



Experimental
Models

Quantitative
Analysis

Map Against
Pathway

Flux
Signature



Building Diagnostics for Metabolic Disease Therapy

Edward Leiter
The Jackson Laboratory

Profiling the Effects of Insulin-Sensitizing Drugs

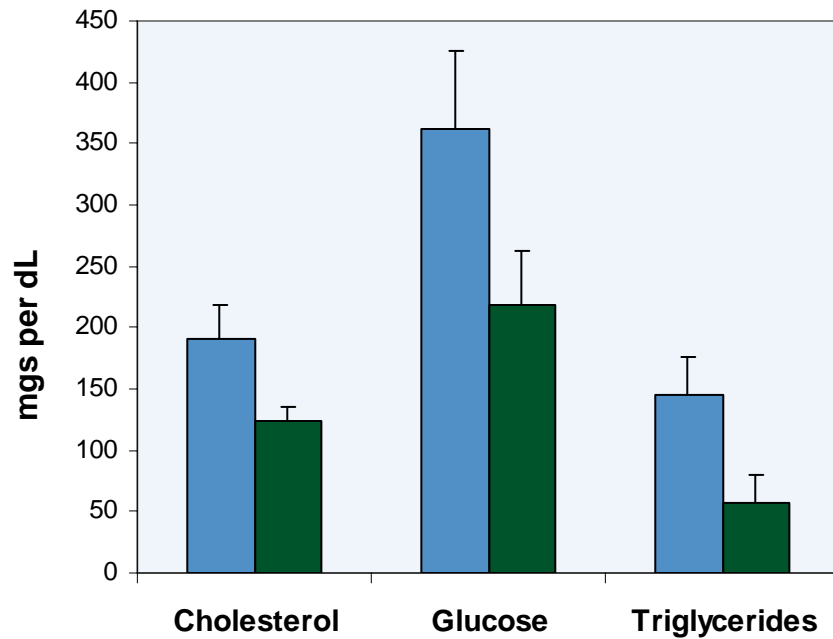


- Investigated the effects of two diabetes drugs on lipid metabolism in a obese-diabetic model
- **PPAR γ agonist:** Rosiglitazone
- **β -3 adrenergic agonist:** CL316,243

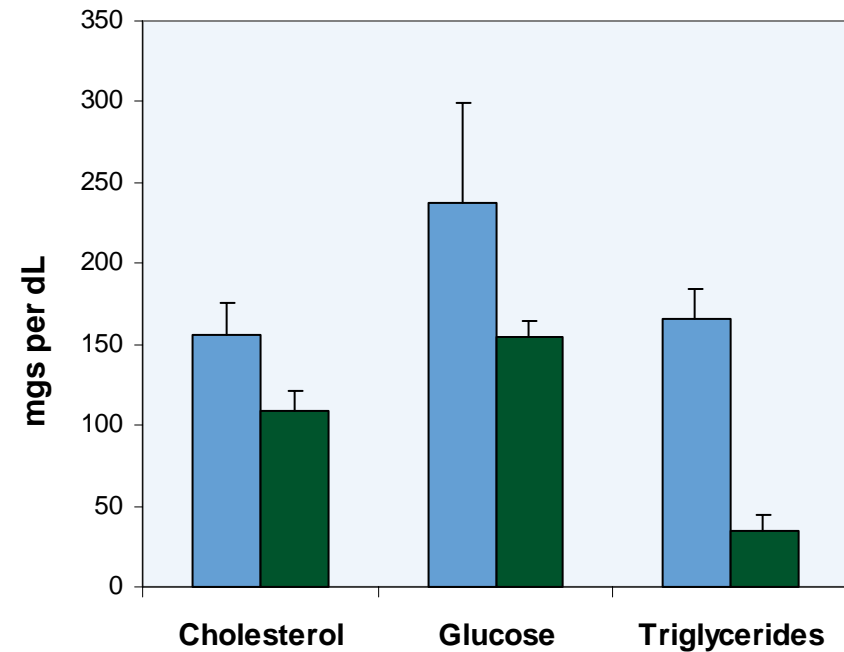
Clinical Biomarkers



PPAR- γ



β 3-Adrenergic



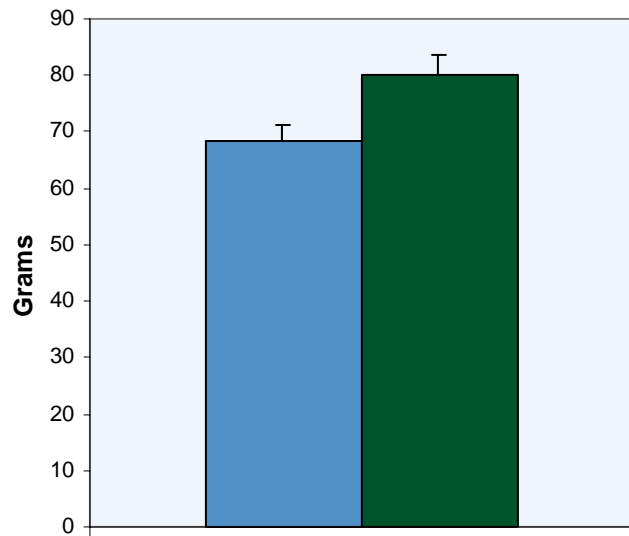
Control

Treatment

Body Weight Following Treatment

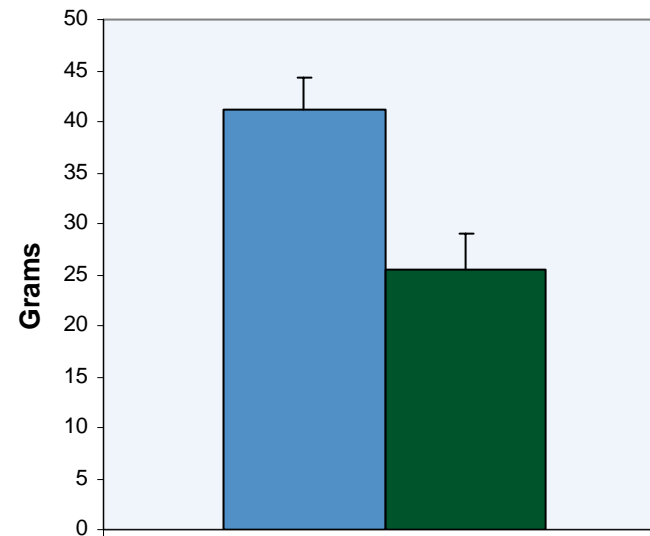


PPAR- γ



Body Weight post-treatment

β 3-Adrenergic



Body Weight post-treatment

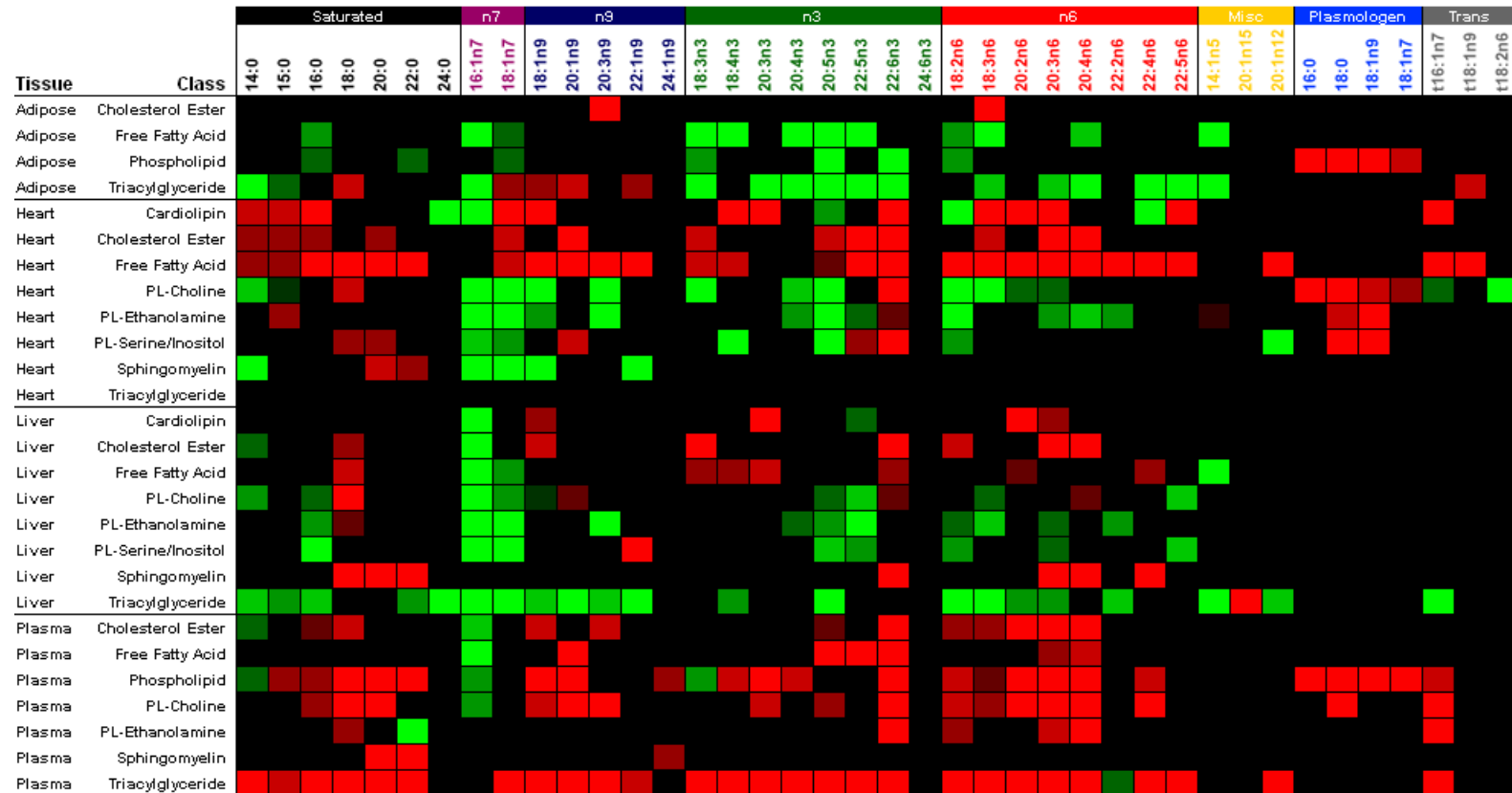
Control



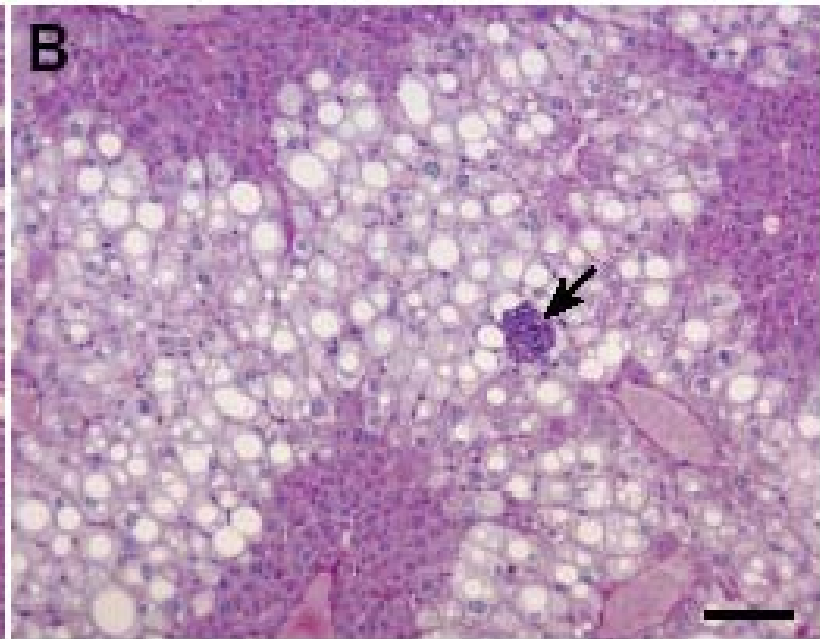
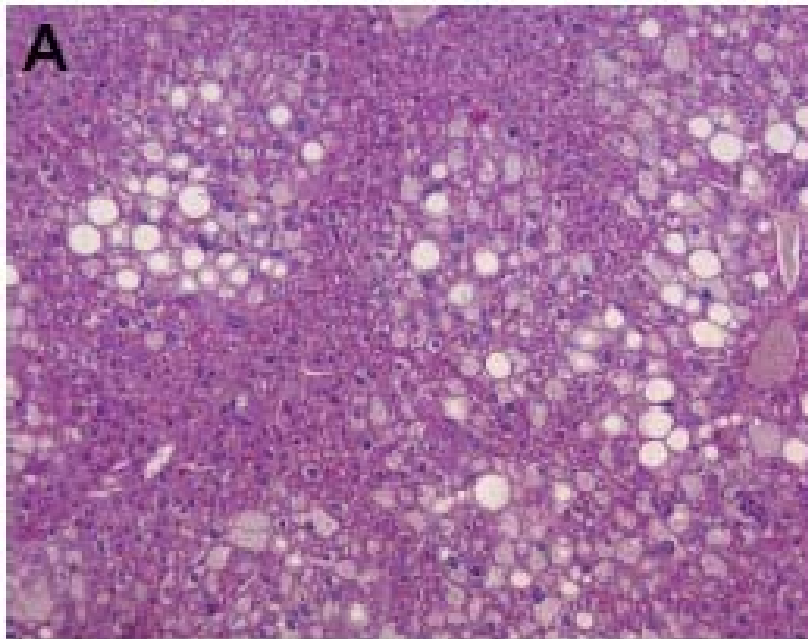
Treatment



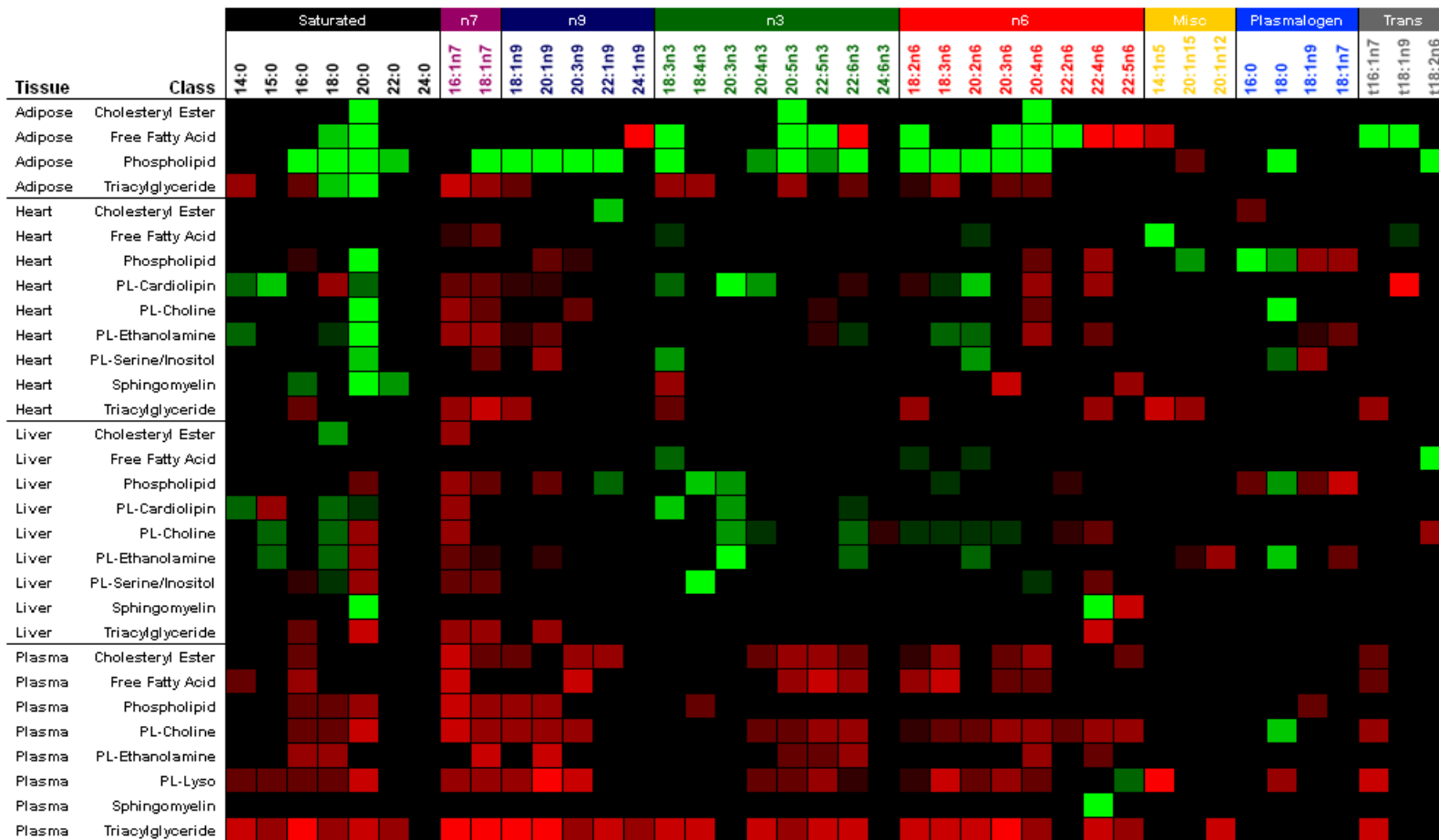
PPAR- γ Treatment



Hepatic Lipid Accumulation



β3-Adrenergic Agonist

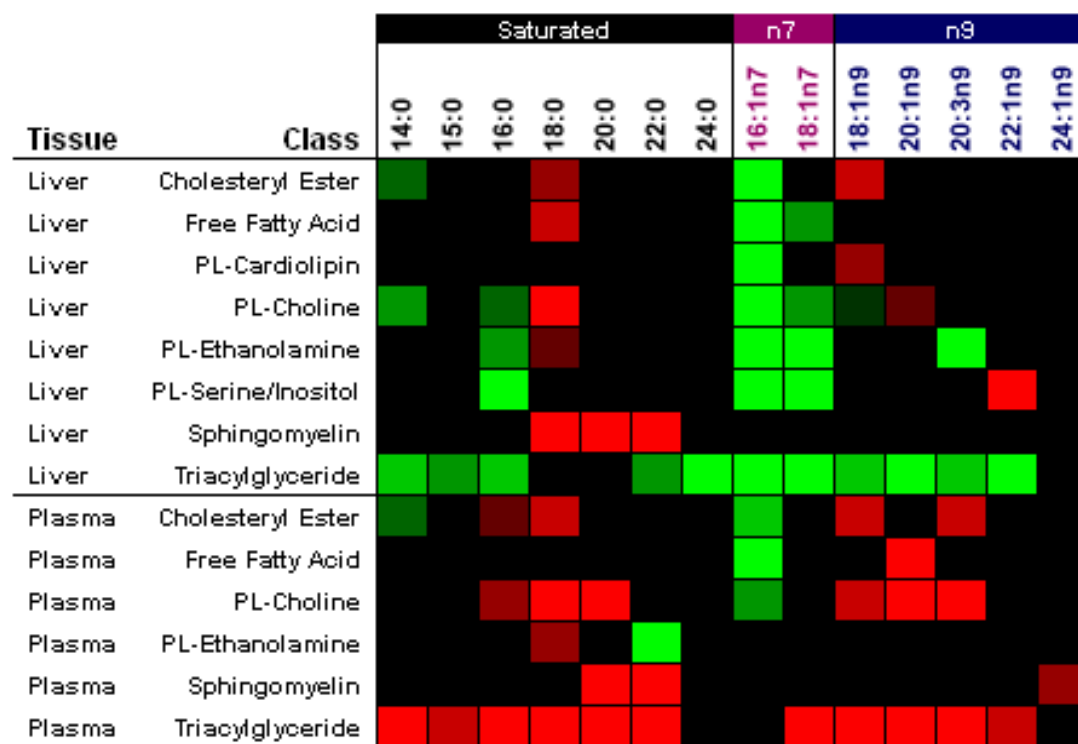


Hepatic Lipid Synthesis



PPAR- γ

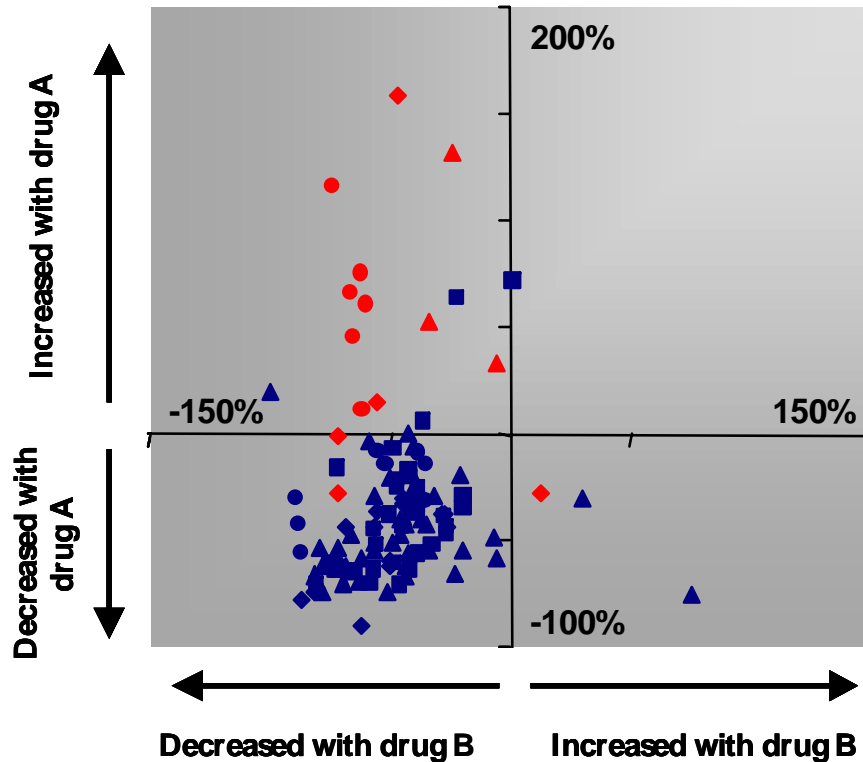
β -3 Agonist



Plasma Metabolome Reveals Mechanism

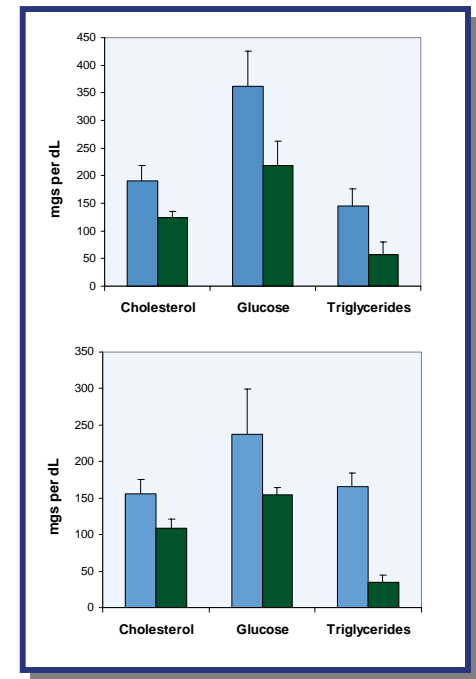


PPAR- γ



■ Signature of lipogenesis

■ All other metabolites



β 3-Adrenergic

Metabolic Assessment



- High-content assays are required to elucidate metabolic basis for phenotype
- Want data on both metabolite concentrations and metabolic flux

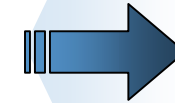
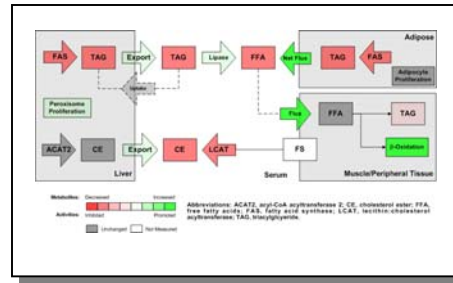
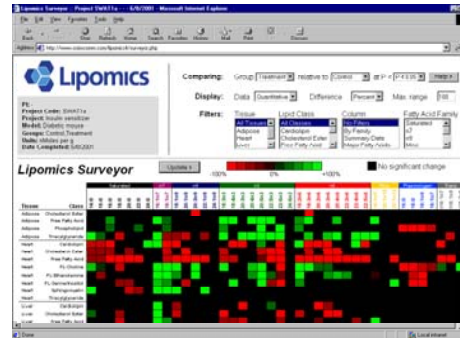
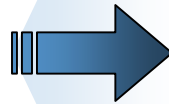
Must know both the identity and quantity of each metabolite

Building Diagnostics



- Single chronic diseases have more than one metabolic (or environmental) cause
- Next generation diagnostics need to provide actionable information.
 - What dysregulation needs treatment?
- Metabolic assessment enables actionable, individual-specific diagnoses.

Delivering Health to the Individual



Nut_x

R_x

Life_x

Individual Dx

Map to Pathway

Action



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