The NIH Roadmap to Understanding Biological Pathways and Networks with Metabolomics

Arthur Castle
NIDDK/NIH
Roadmap/OPASI

- Initiated by the Director, Elias A. Zerhouni, M.D. (2004)

- Input from more than 300 nationally recognized leaders in academia, industry, government, and the public

- Identify major opportunities and gaps in biomedical research that no single institute at NIH could tackle alone but that the agency as a whole must address

- The Office of Portfolio Analysis and Strategic Initiatives (OPASI)
  - 2006 NIH Reform Act
  - Common fund (Roadmap) started in 2004

Source: http://nihroadmap.nih.gov/
Major Opportunities

- **New pathways to discovery**
  - Building Blocks, Biological Pathways, and Networks
  - Molecular Libraries and Imaging
  - Structural Biology
  - Bioinformatics and Computational Biology
  - Nanomedicine

- **Research teams of the future**

- **Re-engineering the clinical research enterprise**
Building Blocks, Biological Pathways, and Networks

- **Development** of new technologies to accelerate discovery and facilitate comprehensive study of biological pathways and networks

- **Measure** amounts, locations and interactions of large numbers of individual proteins within a single cell

- **Understand** the metabolic components and networks within the cell, which are commonly referred to as the "metabolome."
Metabolomics Technology Development Initiative (2004)

- **RFA-RM-04-002 R21/R33**
  - The general **aim** of metabolomics is to identify, measure and interpret the complex time-related concentration, activity and flux of endogenous metabolites in cells, tissues, and other biosamples such as blood, urine, and saliva.

- **Metabolites include** small molecules that are the products and intermediates of metabolism, but also carbohydrates, peptides, and lipids

- Ideally, new technologies should yield **quantitative, comprehensive data** and be applicable to achieving anatomical **resolution at the cellular and subcellular level.**
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<th>Awarded Projects</th>
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<tr>
<td>Wayne R Matson</td>
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<td>&quot;Integrating LCEC/LCMS in a Single Metabolomics Platform&quot;</td>
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<td>Herbert Hill</td>
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<td>&quot;The Potential of Ion Mobility Mass Spectrometry for Metabolic Profiling&quot;</td>
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<td>Julian Griffin</td>
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<td>&quot;Metabolomics and Metabolic Compartmentation in the Brain&quot;</td>
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<td>Truman R Brown</td>
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<td>&quot;Metabolic Patterns in 1H NMR Spectra of Biofluids&quot;</td>
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<td>Jonathan V Sweedler</td>
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<td>&quot;Technologies for Cellular Neurometabolomics&quot;</td>
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<td>Michael R Sussman</td>
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<td>&quot;Isotope-Assisted Differential Metabolomics&quot;</td>
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<td>Fred E Regnier</td>
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<td>&quot;Tools for Comparative Metabolomics&quot;</td>
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<td>Gerhard Wagner</td>
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<td>&quot;An Integrated and Sensitive Metabolomics Platform for Human Disease Prediction, Diagnosis and Treatment&quot;</td>
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<td>Norman J Dovich</td>
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<td>&quot;Glycolipid Metabolism in Single Cells&quot;</td>
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<td>Ronald Breaker</td>
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<td>&quot;Sensing Metabolites with Riboswitches&quot;</td>
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<td>John D York</td>
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<td>&quot;Biological Oscilloscopes: Spatio-Temporal Metabolomics&quot;</td>
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<tr>
<td>Dr. Alan M Kleinfeld</td>
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<td>“Profiling unbound metabolites using fluorescent probes”</td>
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<td>Dr. James C Liao</td>
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<td>&quot;Automated Chip-Based Metabolomics Analysis&quot;</td>
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<td>Dr. Henri Brunengraber</td>
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<td>&quot;Dynamic Metabolomics via Isotopomer Analysis&quot;</td>
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Community Infrastructure Standards Workshop (2005)

http://www.videocast.nih.gov

Metabolomics community has since developed the Metabolomics Standard Initiative MSI http://msi-workgroups.sourceforge.net/
NIST-NIH Plasma Standard

- Interagency agreement to develop pooled plasma samples with quantitative metabolite measurements
  - > 20 L (20,000 Vials)
  - Measured concentrations for hundreds of metabolites
  - NIH investigators access
  - General access provided by NIST

- Augment individual standards by providing complex standard w/ quantization and methods from multiple laboratories (2008-2009)

- Currently available
Roadmap Transition

- **Common Fund Goals (Roadmap)**
  - Address fundamental knowledge gaps
  - Develop transformative tools and technologies
  - Foster innovative approaches to complex problems

- **Duration of Support**
  - Limited duration of 5–10 years
  - Adopted by the community through IC-funded awards
  - Most ICs support disease specific clinical and basic science
  - Some ICs also support common resources and non disease specific basic science

- **Transition from roadmap to ICs**
  - Co-funding limited number of R01
  - Focus on application of technology to IC mission interests
Using Metabolomics to Investigate Biological Pathways and Networks (2006)

- **RFA-RM-06-010 (RO1)**
  - Establish metabolomics methods and model systems for advancing the understanding of biological pathways and networks; their temporal and spatial resolution; and their regulation in health and disease states.

- Ideally, Projects should form the basis for future studies that may lead to better diagnosis, treatment and prognosis of diseases or better fundamental understanding of pathways and networks.

- Eight projects were funded with six ICs.
Awarded Projects

- Cravatt, Benjamin F: Chemical Probes for Metabolic Pathway Discovery in Human Disease
- Freyer, James P: Differential metabolic network analysis of tumor progression
- Han, Xianlin: Shotgun Lipidomics and Alterations in Sphingolipidomes in Alzheimer's Diseases
- Rabinowitz, Joshua D: Metabolomics of the Virus-host Cell Interaction
- Sweedler, Jonathan*: The Neurometabolome of a Sensory Neuronal Network
- Burant, Charles F: Using Systems Biology to Understand Islet Adaptation and Failure Diabetes
- Frommer, Wolf B*: Sugar signaling networks detected by high content fluxomics
- Dovichi, Norman J*: Glycolipid metabolism in single cells
Applying Metabolomics to ICs
Specific needs

- Program Announcement for Metabolomics led by NCI
- 10 ICs are participating
- Each IC outlined their specific interests in metabolomics
Application of Metabolomics for Translational and Biological Research (R01) (2007)

- **PA-07-301**
  - National Cancer Institute (NCI) (http://www.nci.nih.gov)
  - National Heart, Lung and Blood Institute (NHLBI) (http://www.nhlbi.nih.gov)
  - National Institute on Aging (NIA) (http://www.nia.nih.gov)
  - National Institute of Dental and Craniofacial Research (NIDCR) (http://www.nidcr.nih.gov)
  - National Institute on Drug Abuse (NIDA) (http://www.nida.nih.gov)
  - National Institute of Environmental Health Sciences (NIEHS) (http://www.niehs.nih.gov)
  - National Institute of General Medical Sciences (NIGMS) (http://www.nigms.nih.gov)
  - National Institute of Mental Health (NIMH) (http://www.nimh.nih.gov)
  - National Institute of Neurological Disorders and Stroke (NINDS) (http://www.ninds.nih.gov)

Each ICs area of interest are listed in this announcement
Application of Metabolomics for Translational and Biological Research

- Promote the use of metabolomics technologies in translational research in human health and disease for the purposes of enabling and improving disease detection, diagnosis, risk assessment, prognosis, and prediction of therapeutic responses.

- Specific scopes and objectives of the participating ICs are presented in this PA

- Four projects were funded in 2008

- This PA is open on standard receipt dates until Jan 2010
NIDDK area of interest

5) National Institute of Diabetes and Digestive and Kidney Disease: The NIDDK is interested in applying metabolomic technologies to the study of metabolism in diabetes, and diabetes-related complications and other metabolic disorders, insulin resistance, energy balance, kidney and urologic diseases, hematologic diseases, digestive diseases, liver diseases and nutrition. The scope of interest includes the following areas: (1) whole body metabolomics analyses and cellular intermediate metabolism, e.g., the regulation of gluconeogenesis and glucose disposal, protein turnover rate and regulation, cellular and whole body lipid fluxes, interaction between carbohydrate and lipid metabolism, rate of tricarboxylic acid cycle flux and energy production in the cell, and the effect of nutrient co-factors on the regulation of these processes; (2) identification and characterization of metabolic phenotypes of rare metabolic diseases and identifying more common metabolic factors relating to predisposition to obesity and insulin resistance and metabolic alterations in diabetes and its complications that may improve treatment strategies; (3) global metabolomic studies of ion movement and fluid electrolyte dynamics as they relate to kidney function; (4) energy balance and nutrition, including the understanding of normal and abnormal absorption, digestion and excretion of macro- and micro-nutrients, their physiologic function, and mechanism of action/interaction within the body, nutrient influence on gene regulation; endocrine functions relating to feeding behavior; the role of nutrient antioxidants, and the general improvement in assessing complex nutritional status in health and disease.
Awarded Projects

- Raftery Y, Daniel  Advanced Methods in NMR-Based Metabolomics
- Sreekumar, Arun  Integrative Metabolomics of Prostate Cancer Progression
- Burgess, Shawn C  Factors Controlling Metabolic Flux in the Liver by NMR Isotopomer Analysis
- Gerszten, Robert E, Wang, Thomas E  Metabolomic predictors of insulin resistance and diabetes
NIH Funded Research Projects with Metabolomics Components

- Abstracts to funded projects are publicly available through CRISP / RCDC

- Many more funded projects include metabolomics methods than have them as the primary focus of research

- Trend toward more targeted measurements and less discovery especially with RO1s

- Many focus on testing hypothesis with perturbation rather than just discovery of biomarkers
NIH RO1 with Metabolomics

Over 50 R01 Grants with major metabolomics components
NIH projects and co-operative agreements with Metabolomics

Over 25 large projects or cooperative agreements with metabolomics components
NIH metabolomics timeline

- **2004**: Roadmap RFA Tech Dev.
- **2005**: Metabolomics Tsuruoka, 14 Projects funded
- **2006**: Metabolomics Boston
- **2007**: Metabolomics Manchester
- **2008**: Metabolomics Boston
- **2009**:

- **2010/11**: NIST/NIH Std, Roadmap RFA Tech App., 8 projects funded
- **20011/12**: Metabolomics PA, 4 projects funded

- **2015**: R01 Metabolomics related, > 50 projects funded
- **P & U Metabolomics related, > 25 projects funded**
Other Opportunities

New! Transformative R01 Program

The NIH Director recently announced a new program to be conducted through the NIH Roadmap that is designed to stimulate disruption of existing paradigms or creation of paradigms where none exists. The Transformative R01 Program (T-R01s) will allow highly creative, “out-of-the-box” projects to be supported. Special areas of Highlighted Need have been identified for the program. The NIH recognizes that new paradigms are needed in these areas and will particularly encourage research that addresses these needs. The broad topics to be highlighted include:

Understanding and Incenting Behavior Change
3-D Tissue Models
Functional Variation in Mitochondria
Transition from Acute to Chronic Pain
Formulation of novel protein capture reagents
Evidence for Pharmacogenomics clinical studies

The T-R01 Program represents a High Risk/High Reward Demonstration Project in which novel approaches to peer review and program management are to be piloted. A Funding Opportunity Announcement (FOA) is anticipated this summer.
Metabolomics Technology/methodology Needs

- More Identifiable target metabolites
- More quantification (esp. clinical samples)
- Faster identification of unknowns metabolites
Understanding of normally present metabolites and variability for both core metabolism and xenobiotics
- Understanding how normal networks vary

Understanding of aberrant metabolism that can be used in predictive, personalized, preemptive and participatory manner to improve patient health in clinical settings
- Using networks knowledge to diagnosis, treat and monitor disease

Using metabolomics to uncover complex mechanisms of disease that involve more systems understanding of metabolism
- This requires testing network observation through perturbations
Summary

- The use and support of metabolomics have increased substantially over the past four years
  - There is a trend to more application and less technology development
  - Much of this application depends on understanding metabolic networks

- NIH supports metabolomics
  - As individual research grants for technology and applications
  - As major components of research grants
  - As core facilities in large projects and cooperative agreements

- NIH released PA describes many sub-areas of particular interests to individual ICs