CATALYZING TRANSLATIONAL RESEARCH BY INCREASING METABOLOMIC RESEARCH CAPACITY

Presented by Philip Smith on behalf of the
Metabolomics Working Group
Council of Councils
June 29, 2011

METABOLOMICS WORKING GROUP

NIEHS	David M. Balshaw, PhD
OD	Ravi Basavappa, PhD
NIDDK	*Arthur L. Castle, PhD*
NCI	Robert Croyle, PhD
NIA	Chhanda Dutta, PhD
NIDDK	Padma Maruvada, PhD
NIAAA	Gary J. Murray, PhD
NIMH	Laurie S. Nadler, PhD
NIGMS	Richard T. Okita, PhD
NEI	Steven R. Oversby, PsyD
NHGRI	Lita M. Proctor, PhD
OD	Geetha Senthil, PhD
NIEHS	Daniel Shaughnessy, PhD
NIDCR	Lillian Shum, PhD
NCI	**Dinah S. Singer, PhD**
NIDDK	**Philip Smith, PhD**
NCI	*Barbara Spalholz, PhD*
NHLBI	Pothur R. Srinivas, PhD, MPH
NINDS	Danilo Tagle, PhD
NINR	Xenia T. Tigno, PhD, MS , MS
NIA	José M. Velázquez, PhD
NCI	Mukesh Verma, PhD
OD	Elizabeth Wilder, PhD
NICHD	Karen K. Winer, MD
NIAAA	Samir Zakhari, PhD

Dinah S. Singer, PhD and Philip Smith, PhD:
Working Group Co-Chair

Arthur L. Castle, PhD, Barbara Spalholz, PhD:
Working Group Co-Coordinator

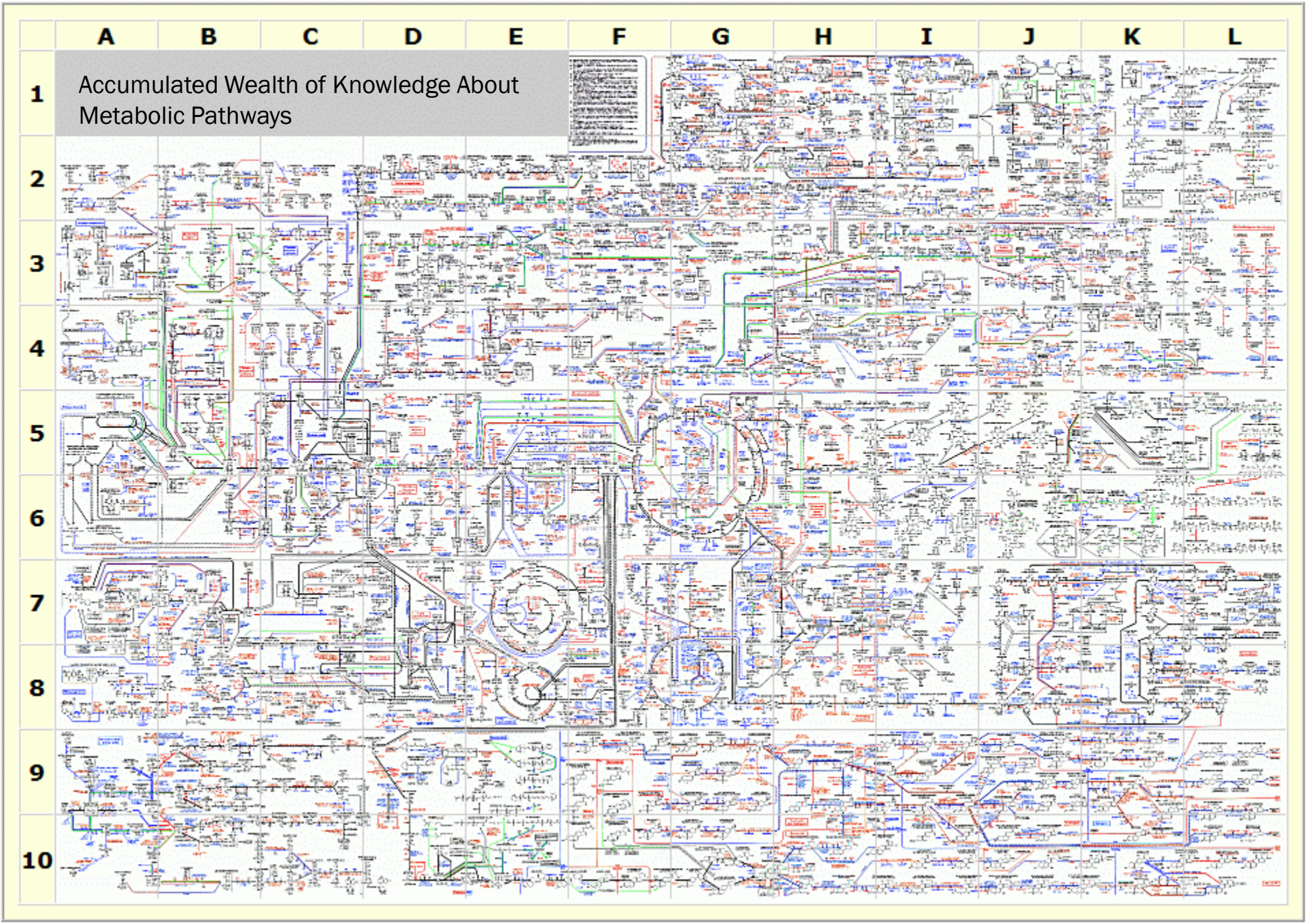
WHAT I PLAN TO COVER TODAY

- Definition and promise of metabolomics
- Portfolio Analysis
- Obstacles to application of metabolomics approaches to biomedical research in the U.S.
- Proposed initiatives to accelerate application of metabolomics to translational research

METABOLOMICS

- Metabolomics is the "systematic study of the unique chemical fingerprints that specific cellular processes leave behind", the study of their small-molecule metabolite profiles. *The Scientist* **19** (8): 25–28.
- Large dimensional metabolic profiling started in the late 1990s with the advent of improved technique in NMR, MS, and dimension reduction and analysis software.
- Early uses were (**un-targeted**) pattern generation /phenotyping for toxicology, and disease categorization without knowing the identity of most metabolites that generated the spectrometry or spectograph patterns.
- Currently, more focus has been placed on measuring many known metabolites (**targeted**) that represent indicators of the metabolic activity of known pathways.

- Oliver SG, Winson MK, Kell DB, Baganz F. Systematicvfunctional analysis of the yeast genome. TIPTECH 1998;16: 373–378.
- Nicholson JK, Lindon JC, Holmes E. Metabonomics: understanding the metabolic responses of livingsystems to Pathophysiological stimuli via multivariatestatistical analysis of biological NMR spectroscopy data.Xenobiotica 1999; 29: 1181–1189.
- Fiehn O. Metabolomics the link between genotypes and phenotypes. Plant Mol. Biol. 2002; 48: 155–171.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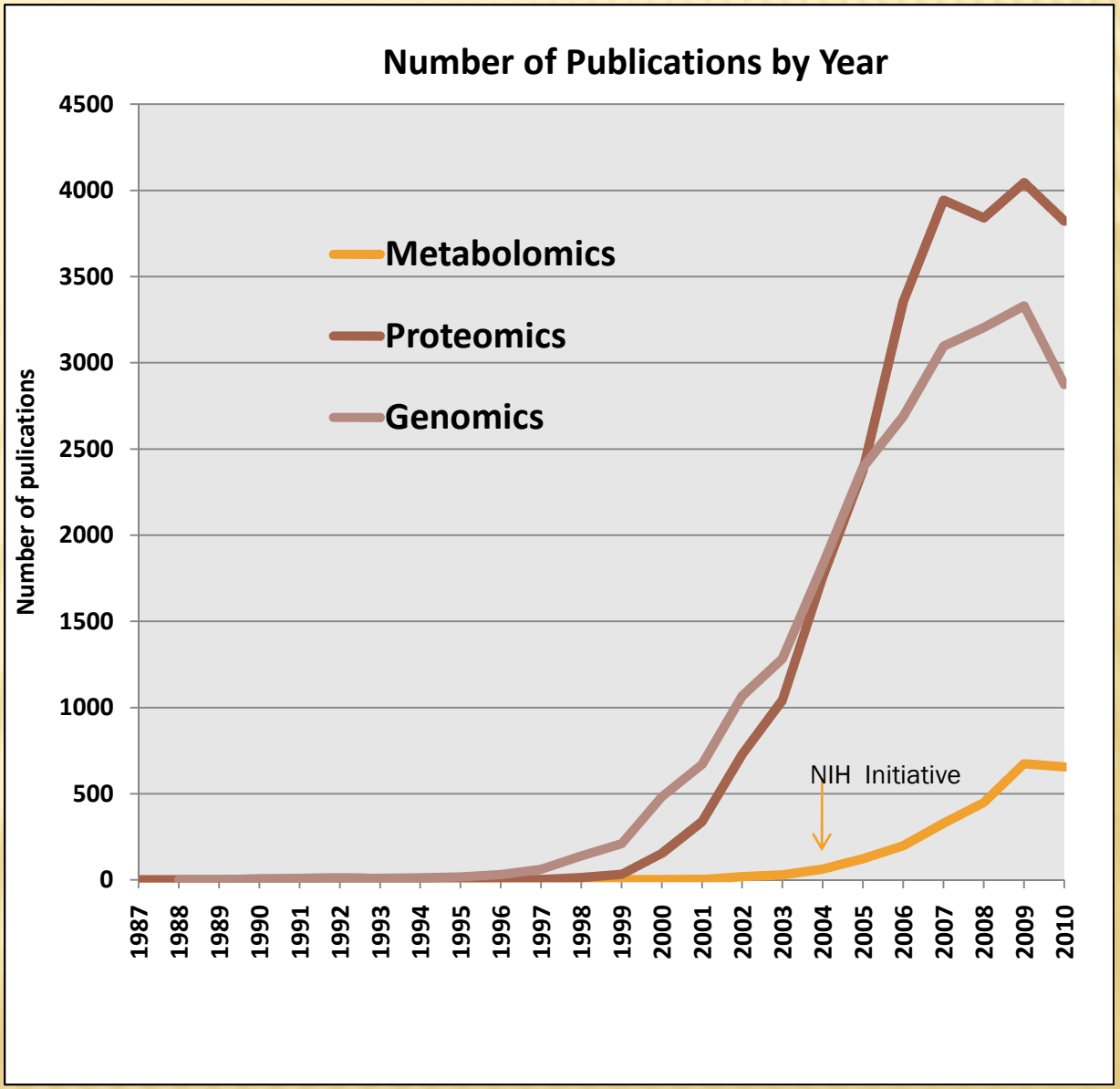
Accumulated Wealth of Knowledge About
Metabolic Pathways

COMPARING LITERATURE TRENDS IN OTHER "OMICS" FIELDS24

Number of Journal Articles in Metabolomics (Scopus Database: searched in Abstract, Title and Keywords)			
Year	Metabolomics	Proteomics	Genomics
1987	0	0	
1988	0	0	1
1989	0	0	1
1990	0	0	7
1991	0	0	9
1992	0	0	15
1993	0	0	9
1994	0	0	13
1995	0	0	18
1996	0	0	32
1997	0	2	61
1998	0	15	139
1999	0	33	210
2000	3	155	484
2001	2	339	671
2002	19	728	1,068
2003	29	1,044	1,284
2004	63	1,756	1,827
2005	123	2,376	2,394
2006	199	3,354	2,690
2007	330	3,943	3,095
2008	449	3,841	3,203
2009	675	4,046	3,331
2010	656	3,822	2,874
Total	2,548	25,454	23,436



BRANCH CHAIN AA AND DIABETES RISK

WANG ET AL NAT MED. 2011 APR;17(4):448-53. R01DK081572

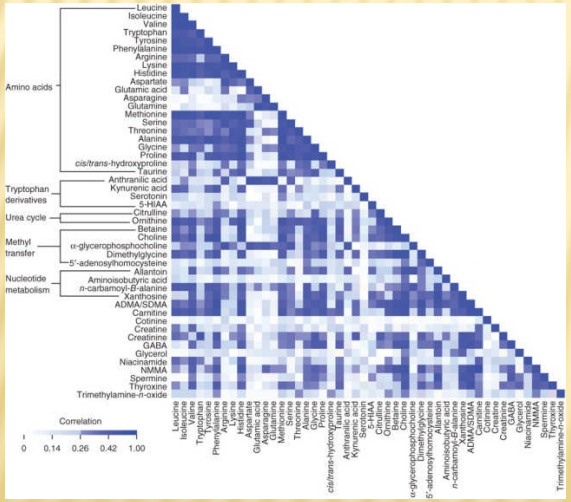
Framingham Offspring Study

- 2,422 normoglycemic individuals followed for 12 years, 201 developed diabetes
- 189 Diabetic 189 matched controls (BMI,FBG,ST, OGTT,HOMA, FI,...) + 400 random controls
- 48 Targeted metabolites selected from several hundred

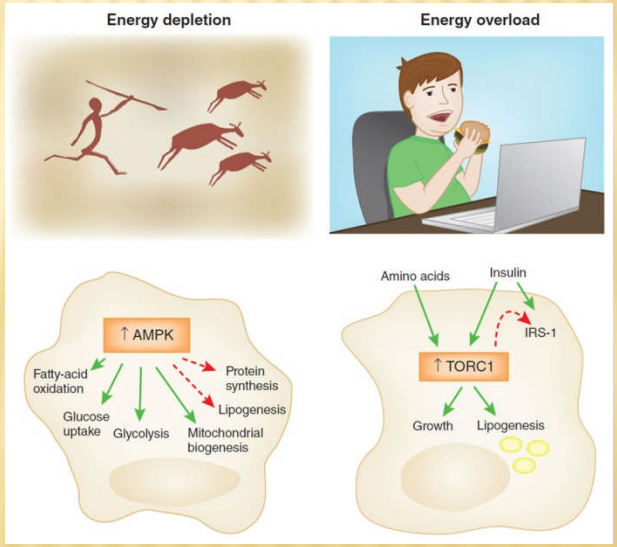
Replication analyses (Malmö Diet and Cancer study) 163 cases 163 controls

isoleucine, leucine, valine, tyrosine and phenylalanine correlated with future diabetes risk

Use of AA improved diabetes predictions 2 fold over insulin measures and up to 5-7 fold over other clinical measures.



Baseline metabolite correlation matrix

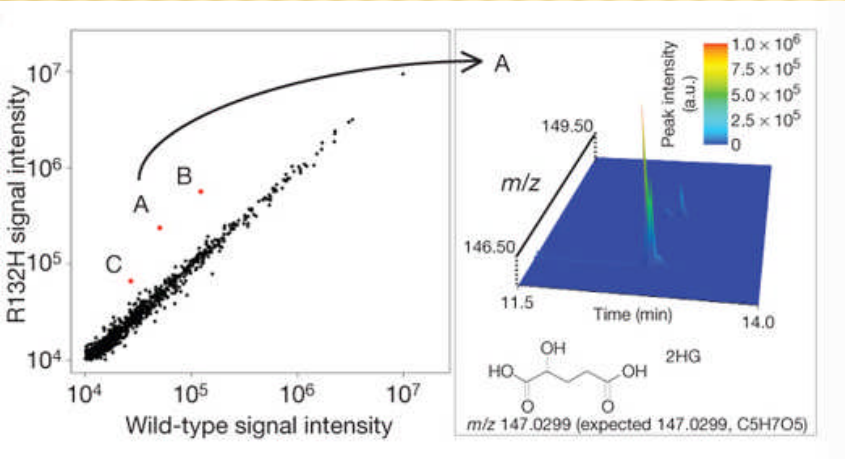


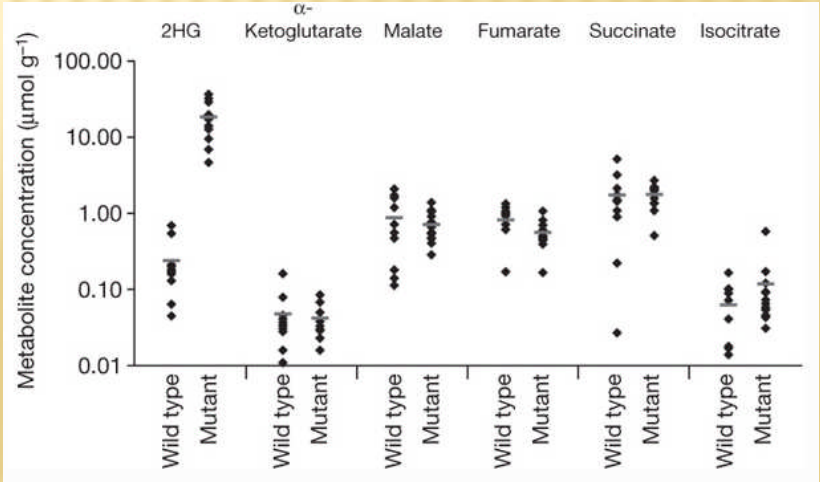
Nat Med. 2011 Apr;17(4):418-20.

CANCER-ASSOCIATED IDH1 MUTATIONS PRODUCE 2-HYDROXYGLUTARATE (2-HG)

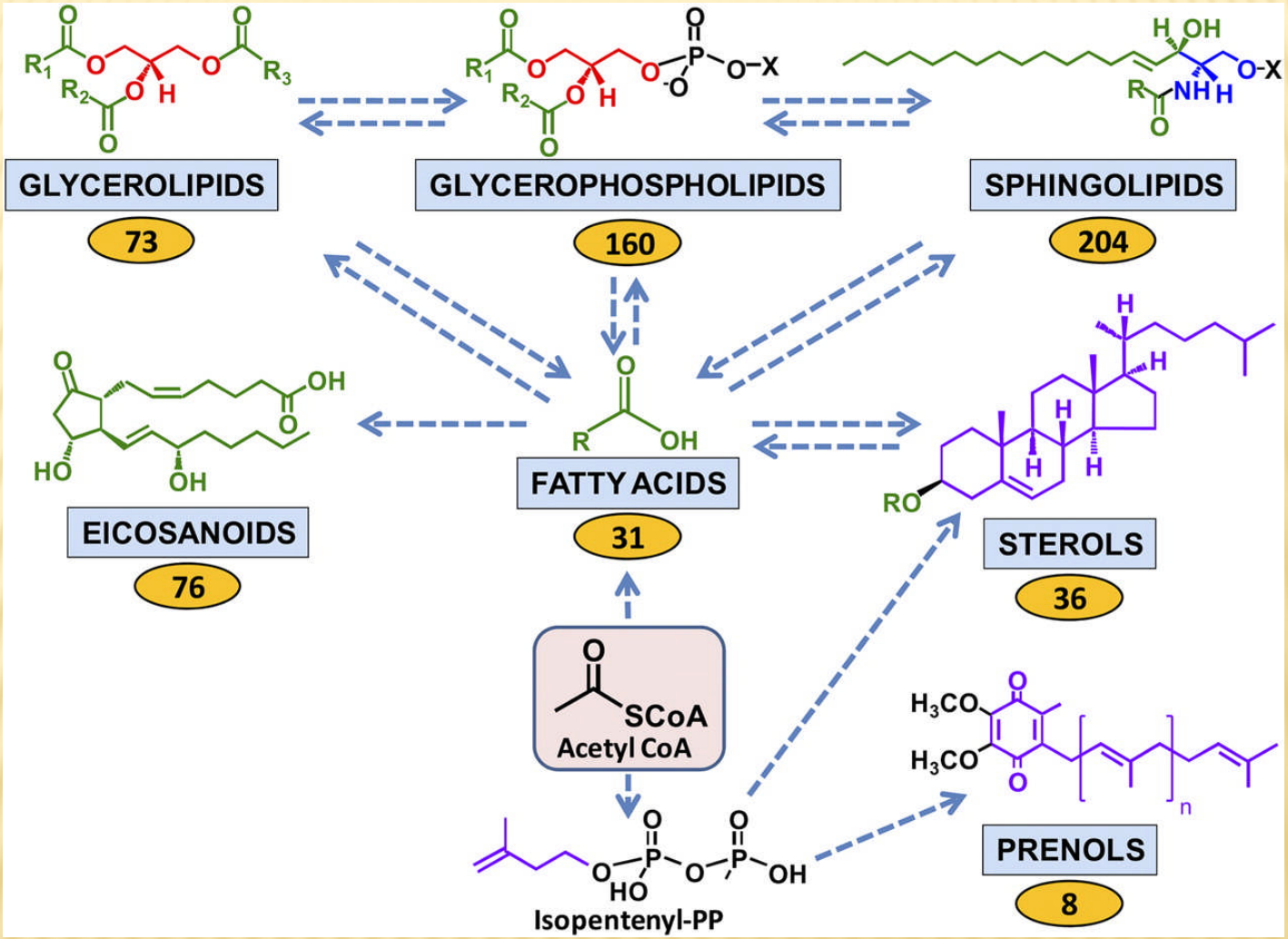
DANG ET AL, NATURE 462:739 (2009)

- Most gliomas and secondary glioblastomas have a single amino acid mutation in one copy of the gene for the glycolytic enzyme isocitrate dehydrogenase (IDH1) resulting in loss of normal IDH1 activity.
- Metabolomics analysis of wild-type glioma cells compared to those expressing the $IDH1^{mt}$ identified a novel metabolite, 2-HG, resulting from altered IDH1 activity on its substrate, isocitrate.
- Analysis of human tumors verified the presence of 2-HG in those containing the $IDH1^{mt}$.
- Implications for glioma prognosis and for understanding reprogramming of cancer cells.





Human Plasma Lipid diversity



Quehenberger O et al. J. Lipid Res. 2010;51:3299-3305

Keeping an eye on our microbial friends

International Journal of Obesity (2010) 34, 1095–1098

0307-0565/10 $32.00
www.nature.com/ijo

SHORT COMMUNICATION

Gut microbiome-derived metabolites characterize a peculiar obese urinary metabotype

R Calvani[1], A Miccheli[2], G Capuani[2], A Tomassini Miccheli[2], C Puccetti[2], M Delfini[2], A Iaconelli[1], G Nanni[3] and G Mingrone[1]

[1]*Institute of Internal Medicine, Catholic University of Rome,* [2]*Rome, Rome, Italy and* [3]*Department of Surgery, Catholic U*

Obesity is a complex multifactorial disease involving genetic an
pathways. In this regard, metabonomics, that is the study of
systems approach to understand the global metabolic regulatio
study, we have applied a nuclear magnetic resonance (NMR)-b
subjects. Urine samples of 15 morbidly obese insulin-resistant
resistance >3) male patients and 10 age-matched controls
spectroscopy combined with partial least squares-discriminant
surgery (biliopancreatic diversion and gastric bypass, respectivel
urinary metabolic profiles were characterized. NMR-based m
metabolic phenotype (metabotype) that differs from that of
trigonelline, 2-hydroxyisobutyrate and xanthine contributed
discrimination. These preliminary results confirmed that in hum
phenotype. Moreover, the typical obese metabotype is lost aft
International Journal of Obesity (2010) **34**, 1095–1098; doi:10

Journal of proteome research

ARTICLE

pubs.acs.org/jpr

Untargeted Metabolomics Identifies Enterobiome Metabolites and Putative Uremic Toxins as Substrates of Organic Anion Transporter 1 (Oat1)

William R. Wikoff,[†] Megha A. Nagle,[‡] Valentina L. Kouznetsova,[§] Igor F. Tsigelny,[∥,⊥] and Sanjay K. Nigam[*,‡,§,∥,¶]

[†]Genome Center, University of California Davis

[‡]Departments of Pediatrics, [§]Medicine (Division of Nephrology and Hypertension), [∥]Neurosciences, [⊥]San Diego Supercomputer Center, [#]Cellular and Molecular Medicine, and [¶]Bioengineering, University of California San Diego

Supporting Information

ABSTRACT:

NIH Portfolio Analysis in Metabolomics

NIH grants databases were searched for keywords to obtain project lists in Metabolomics

- Two trans-NIH query systems were used: QVR and e-SPA using key words (Metabolomics, Metabonomics, Lipidomics, metabolites profiling) 563 projects were identified.
- Projects were validated by the project team to ensure they had substantial metabolomics components and were further categorized. 273 projects were validated.
- Total costs for each single component projects (R01 etc.) were used regardless of the extent of metabolomics focus. Subcomponent (Core) costs were used for Us Ps etc. Projects could be categorized in multiple categories.

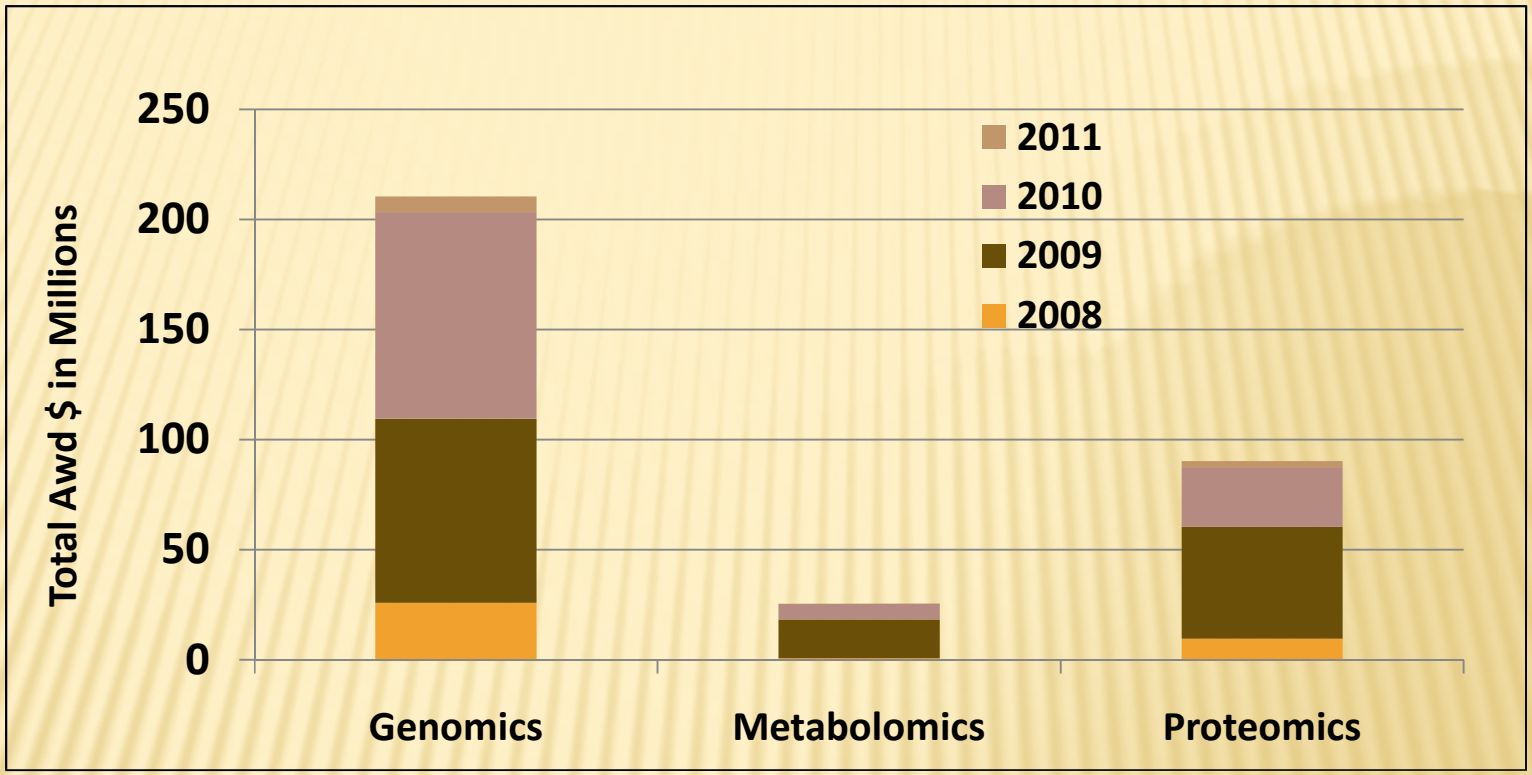
NIH Investment in Metabolomics by Topics

FY 2005 – Present Single Project Mechanisms R, DP, F, K, T

Topic	Total Awarded$	Number of Projects
Technology Development	$ 65,464,257	45
Standards	$ 34,815,891	29
Informatics Algorithms Development	$ 48,303,827	40
tools to measure in situ	$ 17,374,348	12
Metabolites flux	$ 52,587,656	49
Basic research	$ 134,518,374	128
Translational research	$ 69,844,145	68
Training Programs	$ 10,484,773	50

- **Majority of the portfolio is Basic Research, with over $ 69 million (16%) invested in Translational Research**
- **Percentage calculated based on the total amount of $211M awarded for Single projects (Mechanisms R, DP, F, K, T)**

Comparing the NIH Investment in Other "Omics" Fields in Translational Research (FY 2008-2011)



"Omics" Fields	2008	2009	2010	2011	Grand Total
Genomics	$ 25,913,961	$ 83,529,488	$ 93,877,672	$7,137,180	$ 210,458,301
Metabolomics	$ 760,996	$ 17,620,677	$ 7,125,183	$ 149,982	$ 25,656,838
Proteomics	$ 9,671,349	$ 50,798,279	$ 27,025,316	$2,756,224	$ 90,251,168
Grand Total	$ 36,346,306	$151,948,444	$ 128,028,171	$10,043,386	$ 326,366,307

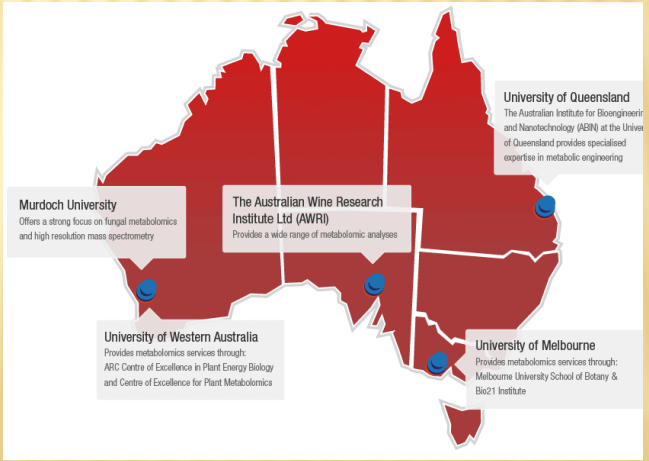
FOREIGN EFFORTS

BBSRC, UK Plant and Microbial Metabolomics: $10.4M

Canadian Human Metabolome Database: $8.1M

Institute for Advanced Biosciences, Keio University, Japan 100M+

Netherlands Metabolomics Center: $67M

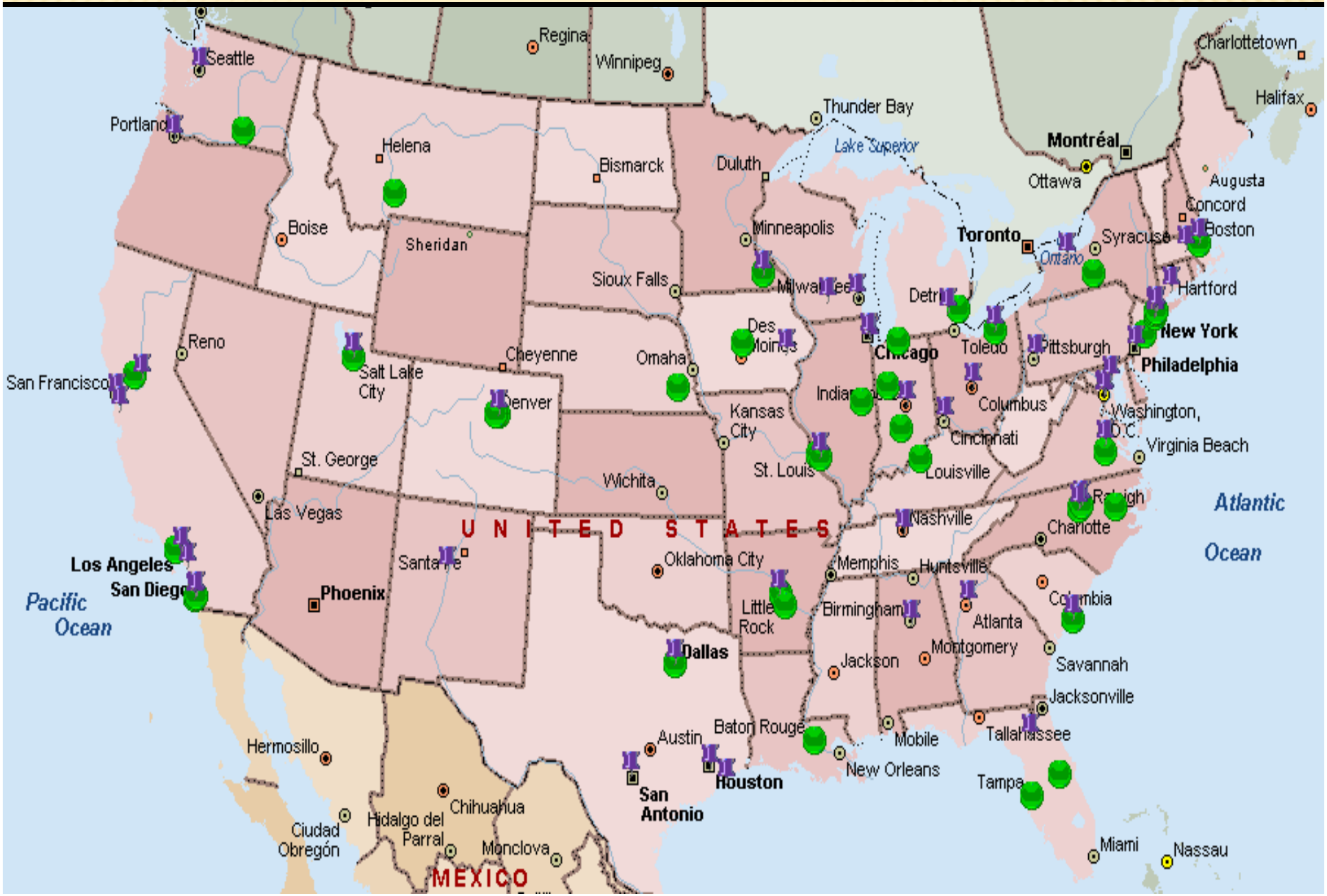


Australia Metabolomics Bioplatforms: $208M

NIH INVESTMENT IN METABOLOMICS

- NIH funded specific metabolomics technology development and implementation projects starting in 2004 as part of the first Roadmap.
  - These project focused on improving NMR, MS, and molecular probes such as FRETs.
  - NIST created a reference standard for distribution to the community
- Metabolomics use mostly as a discovery aim for NIH grants has steadily increased over the past 5 years.
- Lipid Maps consortium represents a comprehensive effort in metabolomics of lipid species in plasma (Glue grant from NIGMS).
- Thirty eight core facilities have been identified as providing metabolomics services with a few having substantial facilities (Duke, Broad, UCSD, UCD).

Clinical and Translational CTSA Centers (purple) and Metabolomics –Ready Sites(green) Overlap 62%



CURRENT LIMITATIONS IN METABOLOMICS

- Metabolomics research has grown substantially in the US over the last five years but has not keep pace with genomics and proteomics research.
- Most of the growth is in basic research; however, metabolomics presents unique opportunities for advances in translational research as the metabolome represents a more current view of physiological/pathological conditions.
- An extramural virtual workshop was conducted with leaders in the field to explore the needs.

METABOLOMICS NEEDS

- Increase national metabolomics capacity in specialized facilities that provide high quality data, analyses, and interpretation, for use by clinical researchers.
  - Improve sample sharing with established longitudinal cohorts and reduce costs to clinical/translational researchers
- Train a new generation of scientists in metabolomics with the skills in technology, biochemistry and physiology needed for metabolomics studies.
- Need for more standards and mechanism to make new ones needed. Central resource for metabolite (chemical) standards to facilitate transition from unbiased, discovery studies to targeted, quantitative approaches (validation) and identify metabolites from peaks/spectra
- NIH could assist in developing new technologies and in recommending existing technologies and methods including Enhancing inter-group collaborations across different metabolomics platforms and between studies with human samples and model systems, to discover underlying biological mechanisms

PROPOSED USE OF COMMON FUND TO BUILD METABOLOMICS CAPACITY AND BRIDGE DISCOVERY TO TRANSLATION

- Comprehensive Metabolomics Resource Cores
- Training
- Technology Development
- Reference Standards Development
- Sharing Data and Reagents

1. COMPREHENSIVE METABOLOMICS CORES

- Build on existing resources
- Provide seed funds to bring appropriate expertise together
- Expand on capacity with equipment and other infrastructure
- Include training component
- Funds for pilot studies to expand into new areas
- Assimilate into existing Institutional resource core infrastructure (e.g., CTSAs, SCORs, Centers)

2. TRAINING

- Development of short courses (R25)
- Career awards (K18) to early stage investigators to get hands on training
- Supplements to encourage collaborations between basic and clinical investigators

3. METABOLOMICS TECHNOLOGY DEVELOPMENT

- Define current roadblocks (ongoing)
- Solicit investigator-initiated projects to address major limitations and expand application of metabolomics
- Enhance ability to identify and quantitate molecular entities in key pathways (e.g.,dietary or microbial metabolites)
- Increase sensitivity to decrease sample size

4. REFERENCE STANDARDS SYNTHESIS

- Go from peak discovery to identification and synthesis
- Use RAID like program to take high interest peaks to known molecular entities and produce standards
- Will allow precise identification and quantification across studies
- Expand ability to identify novel pathways and provide comprehensive metabolic phenotype
- Work with international partners to share data on peak identification

5. DATA SHARING AND INTERNATIONAL COORDINATION

- Cloud-based data storage strategy
- Analysis tools on web
- Front-end with protocols and links to collaborative opportunities
- Minimal Data annotation standard developed through International consortium of interested parties
- Link to sources for reagent standards