NIH Common Fund Workshop: Metabolomics and Translational Research
Videoconference, Natcher Conference Center, NIH
April 6, 2011
1:00 – 4:00pm (EDT)

The National Institutes of Health Common Fund Working Group on Metabolomics organized a workshop on Metabolomics and Translational Research, April 6, 2011, which included 9 extramural leaders in metabolomics or translational research incorporating metabolomics (see attached participant list). The goal of the workshop was to help NIH identify and prioritize opportunities to further the use of metabolomics in translational research across the interests of the entire NIH. In discussions with the extramural community preceding this workshop, the Working Group identified several critical questions related to this goal:

- What are the best opportunities for the clinical application of metabolomics – today and in the future?
- What are the key roadblocks impeding the application of metabolomics to translational research?
- What would facilitate metabolite peak identification in metabolomic profiling?
- What activities would best support the use of metabolomics in translational research?

These questions, as well as a number of sub-topics relevant to each question, are reflected in the meeting agenda (see attached agenda). A session leader was chosen for each question to facilitate discussion. A summary of the key issues and conclusions under each question is presented below.

<u>Best opportunities for clinical application of metabolomics:</u>
Metabolomic profiling of longitudinal cohorts provides an opportunity to discover biological signatures predictive of disease and response to perturbation (environmental, therapeutic, etc). Such biological signatures can also be used to test hypotheses about disease pathogenesis (reverse translation). There are concerns as to whether or not these studies currently have predictive power and whether they will yield conclusions indicative of the general population, but the potential is uniformly accepted.

A number of participants believed that tools for targeted metabolomics approaches are now ready to go into sets of clinical specimens—case-control studies where some subjects will progress to disease. Limitations in profiling with targeted approaches revolved around the number of sentinels in known pathways, but it was felt that this approach can be used to understand some of the biochemistry that discriminates disease states now.

Simply focusing on targeted analyses, however, misses the opportunity to reveal novel molecules/pathways. But an <u>un</u>targeted approach without standards cannot be validated (or published). A combination of untargeted and targeted approaches, or looking at a small sample set in an unbiased way in order to inform a targeted approach, may offer alternatives to realize the potential of metabolomics now.

There was also discussion of the use of metabolomics for personalized medicine. Careful study design was viewed as essential in this area and is probably a current limitation. It is also possible that different metabolomic technologies might be more appropriate for different disease states. But the potential to link metabolomics with genomics and proteomics and to be able to go back and forth between clinical

and basic (model system) research, or from clinical studies to large human population studies, was viewed to be powerful. In summary, metabolomics was viewed to offer the best opportunity to understand disease physiology and pharmacology.

Key roadblocks impeding application of metabolomics to translational research:
There is a lack of metabolomics capacity, and many researchers who want to use the approach don't have access to it. The few comprehensive metabolomics centers in the US have a huge volume of clients. Their desire to provide service conflicts directly with their interest in furthering technological development and in investigating their own research questions. Frustration also exists in that many "customers" don't understand the intermediary metabolism required to interpret results. There is a significant need to educate clinicians in the disciplines necessary to properly design metabolomics studies to obtain high quality data and interpret the results.

There is also a need to replicate/verify important discoveries between groups/centers, not necessarily using the same platform as the original group. Data sharing of metabolomics results (beyond publications) should be required of NIH funded research, and a specific plan for data sharing that includes data deposition with annotation in a publicly accessible database should be a scoreable criterion in grant application review.

Obtaining clinical samples was identified as a difficult hurdle to conducting translational research in metabolomics. There was a general opinion that NIH should "adjudicate transparency" to help people who want to validate results in large clinical samples by helping them get access to the samples. Access to publicly available clinical samples with sufficient data and metadata on storage conditions would greatly facilitate the use of metabolomics. It was also felt that collaboration between clinicians and metabolomics experts was critical to obtaining the correct samples and to designing appropriate studies. Storage of clinical samples does not generally affect genomics data, but does affect metabolomics measurements, so it is also very important to have metadata on storage conditions for samples in biobanks/repositories.

Finally, the cost of, and time involved in, metabolomics analyses were identified as a major roadblocks. There is continued need to develop metabolomics technologies to reduce the cost and effort involved in analysis. Robust instrument platform development should continue, as well as development of robust computational and statistical abilities and informatics tools to integrate metabolomics with other –omics data. Tools to help with data interpretation that link to physiology in an understandable way are also critical needs.

In summary, it is critical to build metabolomics capacity in order for clinical researchers to have access to this powerful approach. It should be possible to leverage the extensive, but piecemeal, investment that has been made in institutions across the country towards research centers with high throughput capacity for high quality analysis that serve as resources for the scientific community. Additionally, facilitating investigators' access to clinical samples and existing metabolomics data will advance the pace of the field. Common repositories for data and clinical samples would attract others to the field.

What would facilitate peak identification in metabolomic profiling:
Initial discussion centered on the need for a central metabolomics data repository like GenBank or Swissprot - the kind of data that should be in a central data repository and who would manage it. A separate group of extramural scientists met in 2010 to discuss this topic and concluded that the

community would like to be able to compare absolute metabolite concentrations between studies, and so would need access to raw spectra, deconvoluted results, etc, because different labs use different protocols. Curation of the data would be very important and data would need to be consistent with international standards for nomenclature, etc. After much discussion, no consensus was reached on the need for NIH support of a central data repository and many issues in implementation were identified.

Reasonable consensus was reached on the need for additional validated metabolite standards to help move studies from unbiased to targeted approaches. Also, isotopes only exist for a small subset of molecules and these are important for quantification. Frequently, academic researchers get their standards from chemical companies although academic chemistry departments might collaborate in the identification of individual metabolites involving novel structure. Public-private partnerships have been established elsewhere to synthesize such standards. It would be important to identify what kinds of analytes are underrepresented in current libraries in order to direct effort to the greatest need.

While beneficial to the field, a central data repository is not essential at this time because the field is evolving and there are numerous existing smaller databases. Additionally, there are significant implementation hurdles. Additional metabolite standards, however, would help in the definitive identification of metabolites from peaks/spectra.

<u>What activities would best support the use of metabolomics in translational research:</u>
Center/resource core grants for the promotion of unbiased and targeted metabolomics approaches, for both basic and clinical research, are critical to the ability to apply metabolomics to translational research. Often institutional metabolomics cores and the CTSA cores don't collaborate or know each other even when in the same city. Training new metabolomics investigators must go hand-in-hand with infrastructure development because the expertise is essential to a successful resource. Sharing costs/expertise between centers should be explored to spur novel technological development and efficiently use resources. Metabolomics Research Centers could be modeled on the current Diabetes and Obesity research centers. Centers could be focused on a flexible combination of service, clinical application, training, and technology development and promote collaboration between biomedical researchers and metabolomics experts. Consortium arrangements with clinical efforts could facilitate access to clinical samples.

It is essential to broaden the informed user base for doing metabolomics the right way. Everyone agreed that the research community lacks scientists with appropriate interdisciplinary training to conduct metabolomics studies, and most current centers don't have the resources to teach everyone who wants to learn. Expert training requires extensive study in biochemistry, physiology, spectral analysis, and informatics. Training programs for metabolomics, such as research education grants or individual mentored training awards in conjunction with the metabolomics centers, are needed to increase the metabolomics capacity of the US.

There is also a need for additional metabolite standards and a mechanism to make new ones as needed. Support for the identification of needed metabolite standards and production capability would facilitate the transition from unbiased, discovery studies to targeted, quantitative validation approaches and identify new metabolites from peaks/spectra. NIH could contract and/or support small business efforts to direct more resources toward providing needed standards.

NIH should continue to invest in metabolomics technology development, as the cost and time involved in metabolomics analysis is still a major burden to conducting large scale studies.

NIH could also play an important role in mandating the sharing of metabolomics data by requiring that metadata, including all raw data, deconvoluted data with peak IDs, etc., be publicly shared and not just available on a local investigator controlled web site.

AGENDA

AdobeConnect URL: https://webmeeting.nih.gov/metabolomics/

1:00 – 1:15 **Introductions and objectives**

1:15 – 1:45 **What are the best opportunities for the clinical application of metabolomics – today and in the future?**
Session Leader: Robert Gerszten
Possible topics for consideration:

- Mechanistic Understanding – discovering novel interactions/pathways
- Prevention – profiling populations at risk
- Detection/Diagnosis – identifying biomarkers
- Treatment – understanding treatment outcome
- Is it possible to develop biomarkers from metabolic profiles?
- Other

1:45 – 2:15 **What are the key roadblocks impeding the application of metabolomics to translational research?**
Session Leader: Oliver Fiehn
Possible topics for consideration:

- Technology development
- Access to resources and cost
- Availability of standards for peak identification
- Variability between labs/ protocols
- Basic knowledge about common metabolites, e.g. nutrients in the blood, environmental exposures
- Appropriate biological specimens for metabolomics profiling
- How to utilize retrospectively archived specimen sets?
- Other

2:15 – 2:45 **What would facilitate peak identification in metabolomic profiling?**
Session Leader: Christopher B. Newgard
Possible topics for consideration:

- MS data repository
- Additional standards
- Protocol standardization
- More experts in the field
- Informatics tools to mine and integrate data across –omics platforms
- Other

2:45 – 4:00 **What activities would best support the use of Metabolomics in translational research?**
Session Leader: Joshua Rabinowitz
Possible topics for consideration:

- Universal repository for metabolomics data, including curated spectra to facilitate the identification of peaks in individual experiments
- Generation of metabolite (chemical) standards or standard reference material (biological mixture of known metabolites at known concentrations) (How would needs be prioritized?)
- Consensus conference to standardize protocols for metabolite measurement, sample procurement and storage
- Development of in situ measurement tools
- Training programs in metabolomics (long-term effort or short term course)
- Consortia to link metabolomics infrastructure and technology development with biomedical research projects for validation and refinements of technologies and discovery of new biological understanding
- Additional investigator-initiated research:
    - Study designs to measure response to environmental changes and disease using metabolomics
    - Establishment of biological baselines and standards for most common metabolites
    - Impact of pharmaco-nutrient metabolic profiles that play critical roles in health and disease
- Support for multi-platform technology development
- Other

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