Clinical Metabolomics: An Integral Tool Driving Patient Phenotyping in Precision Medicine.

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Abstract: Precision medicine is experiencing rapid growth and acceptance in the health-care landscape as a driving force for the future of medicine and is defined by the development of treatment strategies that are tailored to groups of patients based on specific biomarkers. Current precision medicine driven clinical trials assign patients to therapies based on the genetic alterations that are thought to be driving their diseases/cancers. BERG has validated the vision of Interrogative Biology® Platform to understand patients by “phenotype” rather than “genotype” by integrating molecular data directly from a patient with clinical and demographic information to develop artificial intelligence driven clinical trials. BERG is applying Bayesian causal inference to deconvolute unstructured clinical and molecular data and integrate this into models with cause and effect relationships that infers the health status of patients and outcome driven trials. At BERG, we have implemented an industrial level high throughput metabolomics platform providing both high quality and depth of information allowing for reliable and broadest capture of the metabolome for the pre-clinical and clinical matrices analyzed. Highlights of the BERG’s in-depth patient stratification approach as well as a route of complementary biomarker discovery will be presented.

Keywords: biomarker; phenotype; omics; clinical; stratification.
Pure genomics is almost blind to the environmental elements. Pharmacogenomics (2015), 16(7), 737–754
Systems-Level Annotation of a Metabolomics Data Set Reduces 25,000 Features to Fewer than 1000 Unique Metabolites
Nathaniel G. Mahieu and Gary J. Patti*
Department of Chemistry, Washington University, St. Louis, Missouri 63130, United States
...It is becoming increasingly evident that many biological studies are underpowered with regard to their ability to come to a robust and statistically significant and justifiable biological conclusion. ...

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Molecular phenotyping of a UK population: defining the human serum metabolome

Warwick B. Dunn · Wanchang Lin · David Broadhurst · Paul Begley · Marie Brown · Eva Zeleva · Andrew A. Vaughan · Antony Halsall · Nadine Hardlin · Joshua D. Knowles · Sue Francis-McIntyre · Andy Tsour ·
Metabolomics
Hydroxyisocaproic acid/nicotinamide ratio in CSF 1 hour after administration

10 mg/kg LY3020371, I.P. 1 hour after administration

Common pathways - GRIA2(mGlu2/3) and ADORA1 – are predicted to be activated in Hippocampus.

10 mg/kg Ketamine, I.P. 1 hour after administration

Comparative Effects of LY3020371, a Potent and Selective mGlu2/3 Receptor Antagonist, and Ketamine, a Non-Competitive NMDA Receptor Antagonist, in Rodents: Evidence Supporting Use for the Treatment of Depression.

Wikipedia

Ketamine has been tested in treatment-resistant bipolar disorder, major depressive disorder, and people in a suicidal crisis in emergency rooms.
BERG has validated the vision of Interrogative Biology® Platform to understand patients by “phenotype” rather than “genotype” by integrating molecular data directly from a patient with clinical and demographic information to learn predictive patterns.

- Use of adaptive multi-omics measurements (proteomics, lipidomics, and metabolomics protocols) in multiple bio-fluids to capture signatures of efficacy and adverse events during clinical trials.

- Development of integrated data analytics to merge clinical phenotypes with OMICs signatures.

- Engaging the structure of clinical trial phases to streamline development of companion diagnostics for multiple aspects of the clinical trial for a unique precision medicine approach.
TECHNOLOGY: INTEGRATED PHENOME ASSESSMENT

IN HOUSE MULTI-OMICS PROTOCOLS:

PROTEOMICS 400+ (BIO FLUIDS)
PTM 4000+ (TISSUE/CELLS)

LIPIDOMICS 110+ OXIDIZED/MEDIATORS
1100+ STRUCTURAL

METABOLOMICS 600+ POLAR ENDOGENOUS METABOLITES

CAPABILITY ~ 6000 SAMPLES PER YEAR
Preclinical: Earlier biomarkers associated with MOA
Phase I: Biomarkers for Adverse Events
Phase II: Biomarkers for Efficacy
Phase III: Assessment of Utility of Biomarker Panel in Broader Population
This is an open label trial evaluating BPM 31510 as a single agent in patients with advanced refractory solid tumors. This is a dose-finding trial currently on-going at the following clinical sites: Weill Cornell Medical College, MD Anderson Cancer Center, and Palo Alto Medical Center.
DECISION SUPPORT TOOLS TO HELP MANAGE PATIENT TREATMENT

Potential Top 10 Molecules In Blood Measured Before Initial Treatment That Potentially Predicts Benefit To BPM 31510 Treatment

CDx markers lower on patients with Clinical-Benefit
CDx markers higher on patients with Overall Clinical-Benefit

Overall Clinical Benefit
No Clinical Benefit

different tumor types

different tumor types
Utilizing the power of the Bayesian Network learner, bAlcis™ (BERG Artificial Intelligence Clinical Information System), multi-omics profiles were aligned to the longitudinal clinical information and subjected to the AI-algorithms that inferred probabilistic cause-and-effect relationships among molecular and clinical variables inferring markers of pancreatic cancer status and defining the interconnectivity of molecular features with clinical phenotype. Network features linking clinical endpoints and key network pressure points will be identified as molecular drivers.
**Healthy Controls**

**The Problem:**
- Metabolic health assessment requires a visit to the clinic to measure ~20 different molecules that currently defines a patient’s metabolic health status
- There needs to be new approaches developed that 1) are cost effective, 2) allow patients to collect several samples at home when they feel sick, 3) are more stable than conventional blood collection, 4) collect **100 times** the information than traditional approaches

**The Solution:**
- Utilizing dried blood spots (DBS) [a technique used in newborn screening] and dried urine strips combined with metabolomics, shotgun lipidomics, and flux metabolomics analysis, we have demonstrated that these combined approaches can provide informative, stable, and economic solutions for population health assessment

**Evidence:**
- These studies have recently been published demonstrating the utility of these approaches for population health assessment
Conclusions

• There are major challenges implementing and streamlining precision medicine in global healthcare and clinical trial development

• However, there are solutions that unravel the paradox of giving the right drug, to the right person, at the right time

• These solutions can be beneficial if engaged early on in clinical trial development using phenomic technologies
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