

Cancer Metabolism

ChemPartner
Dedicated to LifeScience

Target
Validation

Biochemical
Assays

Cell-based
Assays

In Vivo
PK/PD Efficacy

Clinical
Biomarker

Supported by UV-Vis/Fluorescence-based readout, metabolite quantification by LC/MS in various matrices, cellular functional readouts, etc.

Key features in cancer metabolism

- Aerobic glycolysis (Warburg effect)
- Enhanced nutrient uptake
- Re-organization of metabolic pathways to support biosynthesis and balance redox

Target cancer metabolism

- Glucose/glutamine metabolism
- Fatty acid/ lipid synthesis
- Amino acid/nucleotide synthesis
- Metabolic enzyme that are mutated in cancer

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Extensive Experience in Cancer Metabolism



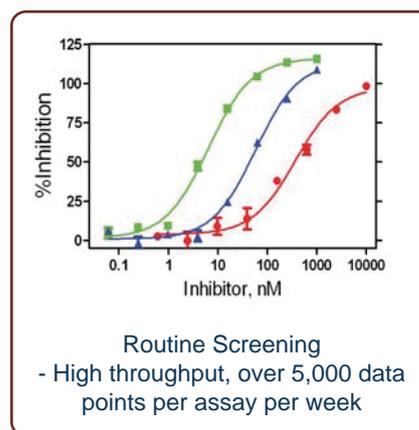
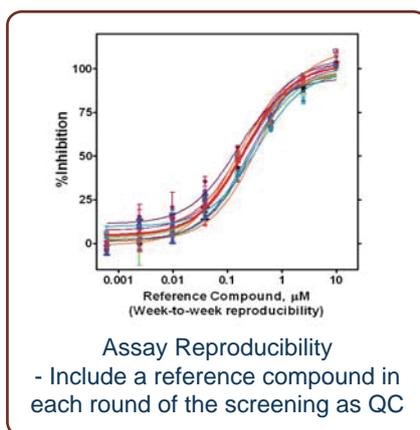
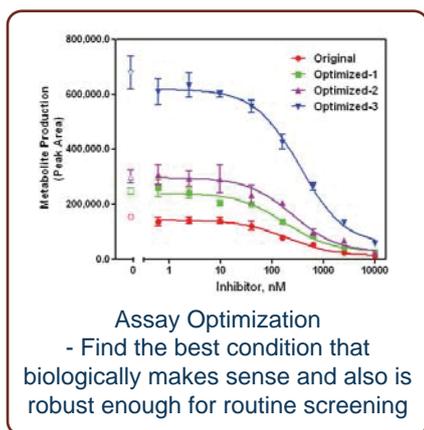
- Chemical synthesis of potent inhibitors targeting various cancer metabolism pathways
- Screening of compounds in biochemical reactions
- Screening of compounds in cell based assays
- Drug sensitivity test using cancer cell panels
- LC-MS based assays for cancer metabolite detection and quantification
- *In vivo* testing in different tumor models of therapeutics targeting cancer metabolism



Compounds

Conditional Medium (secreted metabolites)

Cell Extracts (intracellular metabolites)



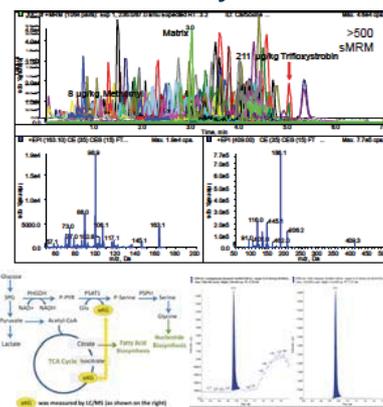
Capability of Using LC-MS for Cancer Metabolite Quantification

Assay development and validation;
More than 200 metabolite monitoring in a single assay;
Application of assay developed for routine compound screening;
Typical metabolite quantitations include:
Products of the Krebs Cycle (acetyl-CoA, lactate, pyruvate, malate, oxaloacetate, etc)
Fatty acids and lipids (Myristoleic acid, Myristic acid, Palmitic acid, Stearic acid, Eicosanoic acid, Acachidic acid etc)
Amino acids (e.g. Serine, Glutamine)
Glucose and its derivatives

Turnaround time:
5 -15 working days depending on the nature of assay specifics

Instrumentation:
ABI5500 and 6500, Waters Q-ToF G2-S, UPLC including Multiplex

Instrumentation allows up to 300 analytes to be quantified simultaneously in each run



ChemPartner made the following contributions to the Nature article:

- Produced 9 mutant proteins, 2 at large quantities to support crystallography.
- Conducted enzymology work to characterize all the mutants Km, Vmax, pH and metal ion effects, forward and reverse kinetics, Ki.

ChemPartner co-authored in an article published in Biochemistry 2011

- Produced 5 glutaminase isoforms and mutants
- Measured Km, kcat, phosphate activation and sensitivity to the allosteric inhibitor

doi:10.1038/nature09807

ARTICLES

Cancer-associated IDH1 mutations produce 2-hydroxyglutarate

Lenmy Dang¹, David W. White¹, Stefan Gross¹, Bryson D. Bertram¹, Mark A. Britten¹, Edward M. Driggers¹, Valeria R. Fantini¹, Myun Gyung Jang¹, Shengfang Jin¹, Maria C. Keenan¹, Kevin M. Marks¹, Robert M. Price¹, Patrick S. Ward¹, Katherine E. Yen¹, Linda M. Lippert¹, Joshua D. Robinson¹, Lewis C. Cantley¹, Craig B. Thompson¹, Matthew G. Vander Heiden¹ & Shantanu M. Su¹

Mutations in the enzyme cytosolic isocitrate dehydrogenase 1 (IDH1) are a common feature of a major subset of primary human brain cancers. These mutations occur at a single amino acid residue of the IDH1 active site, resulting in loss of the enzyme's ability to catalyse conversion of isocitrate to α-ketoglutarate. However, only a single copy of the gene is mutated in tumours, raising the possibility that the mutations do not result in a simple loss of function. Here we show that

BIOCHEMISTRY

Full-Length Human Glutaminase in Complex with an Allosteric Inhibitor

Bryson DeLaRue^{1*}, Stefan Gross¹, Cheng Fang¹, Yi Gao¹, Abhishek Jha¹, Fan Jiang¹, Jianhua Song^{1,2}, Wentao Wei¹ and Jonathan B. Hurw¹

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