April 2017

HMT Newsletter

Friends and Colleagues,

A couple of milestones for HMT this month. HMT-America has now been fully operating in the US for 4 years achieving a growing clientele and biomarker pipeline. In addition, having had a prosperous year, we are now opening an European office (HMT-E) this summer. More below on this exciting development. This month we also get you in touch with our latest in cancer metabolism research. HMT-A is showcasing our C-SCOPE and F-SCOPE packages at AACR while Dr. Laura Shelton has picked out 10 of our most recent articles on cancer metabolism for you to enjoy.

Sincerely,

Alexander Buko, PhD
Vice President
Human Metabolome Technologies America

HMT Updates

News release

HMT launches EU office

On March 29, Human Metabolome Technologies announced that we will open a branch in Leiden, Netherlands, to improve and expand business opportunities in Europe.
There are multiple reasons to break ground in Leiden. Leiden has a robust biotechnology community of its own with the Leiden Bio Science Park, Leiden University, many pharmaceutical/biotech companies and several Medical research centers making up a great translational research environment in which HMT can contribute. Second, the Netherlands is the center of Europe and it gives an advantage for logistics to receive client samples from Europe, Africa and the Middle East. Additionally, Leiden is just 15 minutes from Schiphol airport. Lastly, Leiden is where Philipp Franz von Siebold settled after leaving Japan. As the first European physician to introduce western medicine to Japan during the *Sakoku* era, a period of national isolation in the 19th century, the Japanese have great admiration for Dr. Siebold.
HMT was founded in 2003 using very unique capillary electrophoresis technology for metabolomics analysis. Ten years later the first overseas office was established in Boston, Massachusetts with nearly 100 projects a year in North America and Europe. We want to build on this success with opening a new office in the Netherlands to better provide our services to the European research community.

Event

AACR Annual Meeting 2017

Thank you for visiting our exhibition booth at AACR2017 this past week!
We were happy to talk with many of the researchers in exciting fields such as synthetic metabolic inhibition, metabolism on immune cells and also cohort metabolomics projects.

See you at the next AACR meeting in Chicago!

Featured articles

Cancer metabolism continues to be an exciting area of research, often giving new insight and direction. We have rounded up *our 10 most recent articles* all utilizing metabolomics resulting in novel findings and new directions.

Dr. Laura Shelton
Manager, Scientific Project Development
Human Metabolome Technologies America

Novel aspects of cancer bioenergetics

PHGDH Expression is Required for Mitochondrial Redox Homeostasis, Breast Cancer Stem Cell Maintenance and Lung Metastasis

Samanta D., *et al., Cancer Research*, **76**, *pp*. 4430-4442.

Tumor hypoxia promotes a number of adaptions, including the promotion of breast cancer stem cell (BCSC) enrichment. As this population is highly invasive and metastatic, it represents an important facet of tumor biology. It was found that BCSC's upregulate a number of enzymes in the serine synthesis and the one carbon cycle pathways. Targeting one enzyme, phosphoglycerate dehydrogenase (PHGDH) resulted in decreased NADPH levels and altered redox homeostasis, leading to apoptosis.

HMT eNews (November 2016) special article by Dr. Samanta:
"Cancer metabolism under Hypoxia"

Decreased Expression of Fructose-1,6-bisphosphatase Associates with Glucose Metabolism and Tumor Progression in Hepatocellular Carcinoma

Hirata H., *et al., Cancer Research*, **76**, *pp*. 3265-3276.

Lower expression of FBP1 is associated with advanced tumor stage and higher tumor recurrence rates in HCC. Together with genetic analysis, the metabolic profile of the in vitro model revealed evidence of gluconeogenesis and enhanced aerobic glycolysis, which suggested its potential as a therapeutic target in HCC patients.

Artelation in the nutritional usage

Differential Glutamate Metabolism in Proliferating and Quiescent Mammary Epithelial Cells

Coloff J.L., *et al., Cell Metabolism*, **23**, *pp*. 867-880.

Using a 3D tissue model it was found that proliferating and quiescent mammary epithelial cells differentially utilize glutamate. While proliferating cells catabolized more glutamine via the transaminases, coupling amino acid synthesis to TCA cycle anaplerosis, quiescent cells upregulated glutamate dehydrogenase and amino acid synthesis was reduced. Similarly, highly proliferating tumor cells couple glutamine consumption to amino acid synthesis and TCA anaplerosis.

HMT eNews (October 2016)special article by Dr. Coloff:
"A New Dimension of Cancer Metabolism"

Metabolic Adaptation to Nutritional Stress in Human Colorectal Cancer

Miyo M., *et al., Scientific Reports*, **6**: 38415.

Tumor cells often adapt to nutritional stress including periods of low glucose. Colorectal cancer cells were found to survive periods of low glucose by increasing usage of glutamine and TCA cycle activity, allowing for sustained ATP production. GLUD1 and SLC25A13 were found to play pivotal roles in this adaptation, separate from their KRAS mutation status.

SHMT2 drives glioma cell survival in ischaemia but imposes a dependence on glycine clearance

Kim D., *et al., Nature*, **520**, *pp*. 363-367.

Tumor cells metabolically adapt to environments of low oxygen or nutrient availability. It was found that glioma tumor cells in the pseudopalisading zones around necrotic foci highly expressed serine hydroxymethyltransferase (SHMT2) and glycine decarboxylase (GLDC). SHMT2 limited pyruvate kinase activity and reduced oxygen consumption allowing the cells to survive the hypoxic environment. Inhibition of GLDC, and thus glycine clearance, resulted in the build-up of the toxic byproducts aminoacetone and methylglyoxal.

A Metabolic Strategy for Anticancer Drugs

Arginine Deprivation Inhibits the Warburg Effect and Upregulates Glutamine Anaplerosis and Serine Biosynthesis in ASS1-Deficient Cancers

Kremer J. C., *et al., Cell Reports*, **18**, *pp*. 991-1004.

Using global metabolic profiling and C13 isotope tracing it was found that during arginine starvation, ASS1-deficient cancers drive serine synthesis and upregulate glutaminolysis. Targeting these pathways therefore represented a novel metabolic therapy for a wide range of ASS1-deficient tumors.

HMT eNews (March 2017) special article by Mr. Kremer:
"Metabolomics identifies multiple synthetic lethal therapies for ASS1 deficient cancers"

Myc-driven glycolysis is a therapeutic target in glioblastoma

Tateishi K., *et al., Clinical Cancer Research*, **22**, *pp*. 4452-65.

Myc activation in glioblastoma generates a dependency on glycolysis and results in a sensitivity to inhibition of the glycolytic pathway. The inhibition of the NAD+ salvage enzyme Nicotinamine phosphoribosyl-transferase (NAMPT) was found to selectively target the Myc-driven metabolic state and resulted in an attenuation of glioblastoma growth both in vitro and in vivo.

HMT eNews (July 2016) special interview with Dr. Tateishi

Cell-permeable succinate prodrugs bypass mitochondrial complex I deficiency

Johannes K. E., *et al., Nature Communication*, **7**: 12317.

Mitochondrial complex I deficiencies are characterized by low respiration potential and lactate accumulation. Metabolomic analyses and C13 isotope tracer studies revealed that C13 succinate was actively metabolized and resulted in reduced lactate production and increased spare respiratory capacity.

Applications in Immuno-oncology

Novel chemoimmunotherapeutic strategy for hepatocellular carcinoma based on a genome-wide association study

Goto K., *et al., Scientific Reports*, **6**: 38407.

A GWAS study identified an anti-tumor ligand MHC class I polypeptide-related sequence A (MICA) gene as a potential immune target. Histone deacetylase inhibitors (HDACis) were identified as potential candidates resulting in the restoration of MICA expression. Metabolomic analyses revealed alterations in energy supply and stresses as a result of HCACi treatment.

CD44 variant 9 expression as a predictor for gastric cancer recurrence: immunohistochemical and metabolomic analysis of surgically resected tissues

Yamakawa Y., *et al., Biomedical Research (Tokyo)*, **38**, *pp*. 41-52.

CD44 variant 9 was found to be an independent predictor of poorer recurrence-free survival in patients with gastric cancer. Metabolomic analyses revealed a increase in glutathione in CD44 variant tumors suggesting a role for CD44 in the pentose phosphate pathway and maintenance of redox ratios.

HMT is a leading company providing metabolomic profiling based on unique and high performance CE-MS technology. We complete over 400 projects a year and our technology has contributed to the advancement of research in a variety of scientific areas.

Edited by Takushi Oga, PhD

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