Metabolomics Shared Resource

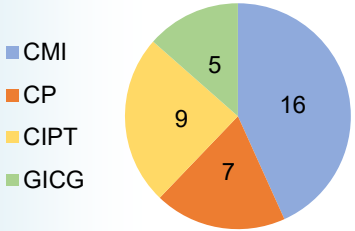
RUTGERS Cancer Institute of New Jersey
RUTGERS HEALTH

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Aims

- The mission of the MSR is to support services that enable CINJ's pre-eminence at the leading edge of cancer metabolism and immunology research
- The MSR offers MALDI-imaging mass spectrometry provided by a Bruker SOLARIX instrument, capable of distinguishing tumor regions (e.g., hypoxic core versus proliferative perimeter) but not single cells
- We lead methodological development, develop peer-reviewed educational content and resources as well as metabolomics assays to our members

Research Program Support (2018–2022)



44 Members
(1 non-aligned)

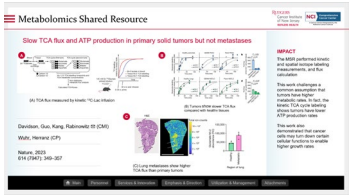
Publications

Total	240
Co-Authored	119
IF>10	79

Peer-Reviewed Grants

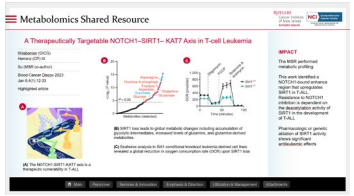
All	38 (1T)
NCI	17 (1T)

CMI, CP



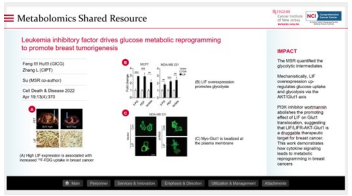
Nature, 2023

CP, GICG



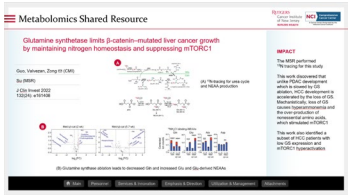
Blood Cancer Discov, 2023

GICG, CIPT, CMI



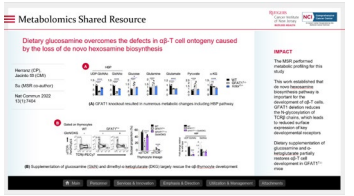
Cell Death & Dis, 2022

CMI



J Clin Invest, 2022

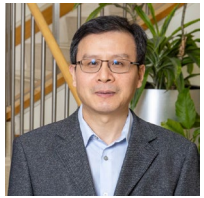
CMI, CP



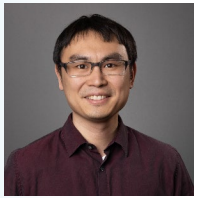
Nat Commun, 2022

Leading Personnel & Roles

Joshua Rabinowitz, MD, PhD
Director



Wenyuan Lu, PhD
Princeton Site Manager



Xiaoyang Su, PhD
Co-Director

Elena Diaz Rubio, PhD
New Brunswick Site Manager

Services & Innovation

New

Spatial metabolomics (30 µm spatial resolution) capable of distinguishing tumor regions (e.g., hypoxic core versus proliferative perimeter) but not single cells

Software development integrates prior literature knowledge and “global optimization” machine learning to determine with high fidelity the molecular formulas and nearest molecular neighbors of unknown metabolites

Nat Methods. 2021;18(11):1377-85

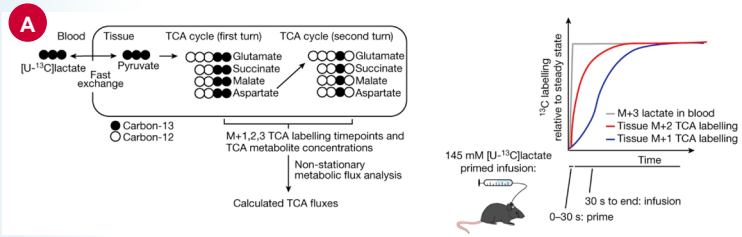
Accurately assess the incorporation of stable isotopes, we developed R package Accucor2

Lab Invest. 2021;101(10):1403-10

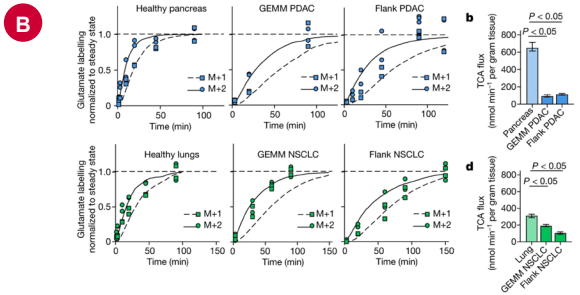
Continuing

- Water-Soluble Metabolite Quantitation
- Lipid Quantitation
- Novel or Unexpected Metabolite Discovery
- Expert Consultation
- Training

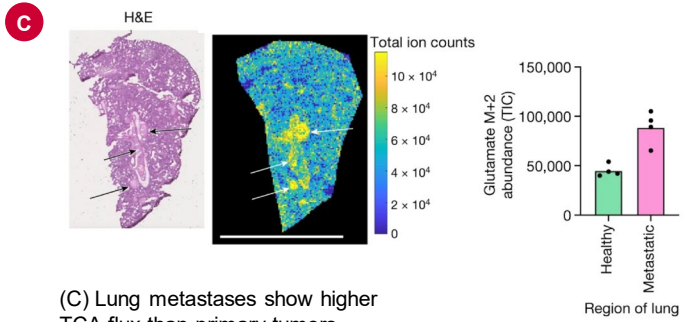
Slow TCA Flux and ATP Production in Primary Solid Tumors but not Metastases



(A) TCA flux measured by kinetic ^{13}C-Lac infusion



(B) Tumors show slower TCA flux compared with healthy tissues



(C) Lung metastases show higher TCA flux than primary tumors

Davidson, Guo, Kang, Rabinowitz ✉ (CMI)

Wuhr, Herranz (CP)

Nature, 2023
614 (7947): 349–357

IMPACT

The MSR performed kinetic and spatial isotope labeling measurements, and flux calculation

This work challenges a common assumption that tumors have higher metabolic rates. In fact, the kinetic TCA cycle labeling shows tumors have lower ATP production rates

This work also demonstrated that cancer cells may turn down certain cellular functions to enable higher growth rates

A Therapeutically Targetable NOTCH1–SIRT1– KAT7 Axis in T-cell Leukemia

Khiabanian (GICG)
Herranz (CP) ✉

Su (MSR co-author)

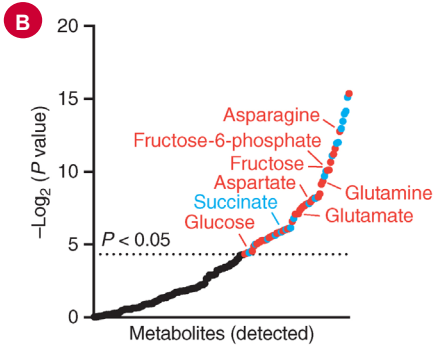
Blood Cancer Discov 2023
Jan 6;4(1):12-33

Highlighted article

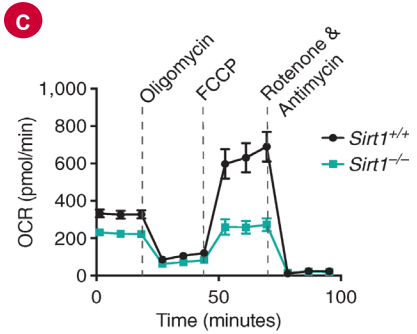
A

(A) The NOTCH1-SIRT1-KAT7 axis is a therapeutic vulnerability in T-ALL

B



C



(B) SIRT1 loss leads to global metabolic changes including accumulation of glycolytic intermediates, increased levels of glutamine, and glutamine-derived metabolites.

(C) Seahorse analysis in Sirt1-conditional knockout leukemia-derived cell lines revealed a global reduction in oxygen consumption rate upon SIRT1 loss

IMPACT

The MSR performed metabolic profiling

This work identified a NOTCH1-bound enhance region that upregulates SIRT1 in T-ALL. Resistance to NOTCH1 inhibition is dependent on the deacetylation activity of SIRT1 in the development of T-ALL

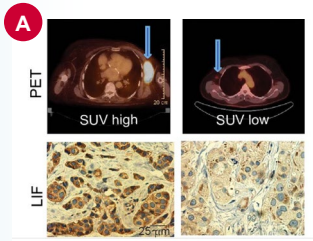
Pharmacologic or genetic ablation of SIRT1 activity shows significant antileukemic effects

Leukemia Inhibitory Factor Drives Glucose Metabolic Reprogramming to Promote Breast Tumorigenesis

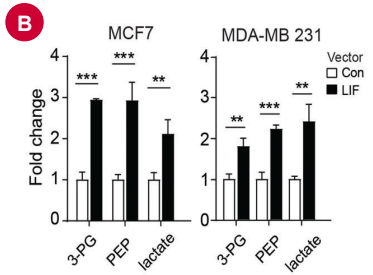
Feng ✉ Hu✉ (GICG)
Zhang L (CIPT) Guo (CMI)

Su (MSR co-author)

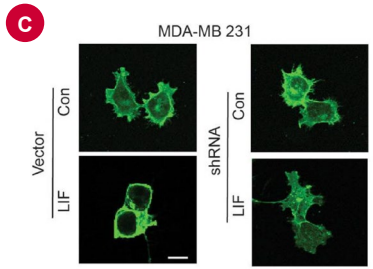
Cell Death & Disease 2022
Apr 19;13(4):370



(A) High LIF expression is associated with increased ^{18}F-FDG uptake in breast cancer



(B) LIF overexpression promotes glycolysis



(C) Myc-Glut1 is localized at the plasma membrane

IMPACT

The MSR quantified the glycolytic intermediates

Mechanistically, LIF overexpression up-regulates glucose uptake and glycolysis via the AKT/Glut1 axis

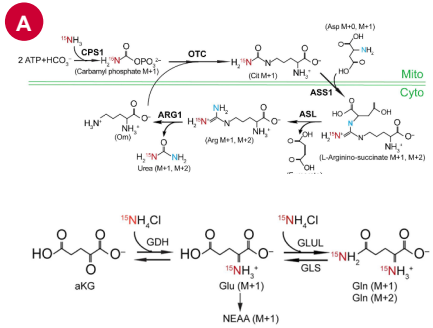
PI3K inhibitor wortmannin abolishes the promoting effect of LIF on Glut1 translocation, suggesting that LIF/LIFR-AKT-Glut1 is a druggable therapeutic target for breast cancer. This work demonstrates how cytokine signaling leads to metabolic reprogramming in breast cancers

Glutamine Synthetase Limits β-catenin–mutated Liver Cancer Growth by Maintaining Nitrogen Homeostasis and Suppressing mTORC1

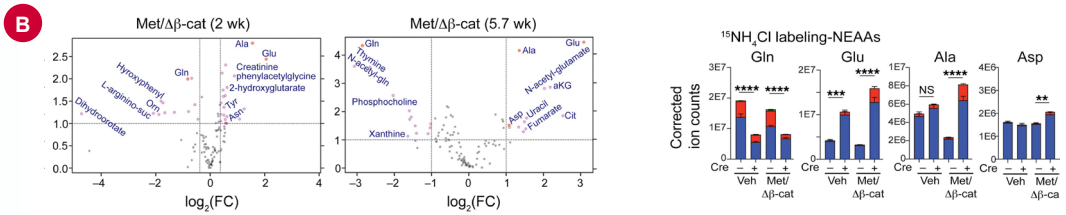
Guo, Valvezan, Zong ✉ (CMI)

Su (MSR)

J Clin Invest 2022
132(24): e161408



(A) ^{15}N-tracing for urea cycle and NEAA production



(B) Glutamine synthase ablation leads to decreased Gln and increased Glu and Glu-derived NEAAs

IMPACT

The MSR performed ^{15}N tracing for this study

This work discovered that unlike PDAC development which is slowed by GS ablation, HCC development is accelerated by the loss of GS. Mechanistically, loss of GS causes hyperammonemia and the over-production of nonessential amino acids, which stimulated mTORC1

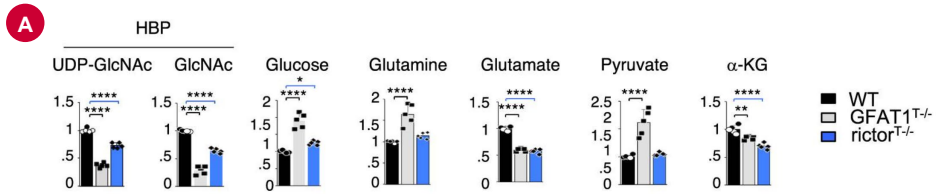
This work also identified a subset of HCC patients with low GS expression and mTORC1 hyperactivation

Dietary Glucosamine Overcomes the Defects in αβ-T cell Ontogeny Caused by the Loss of de novo Hexosamine Biosynthesis

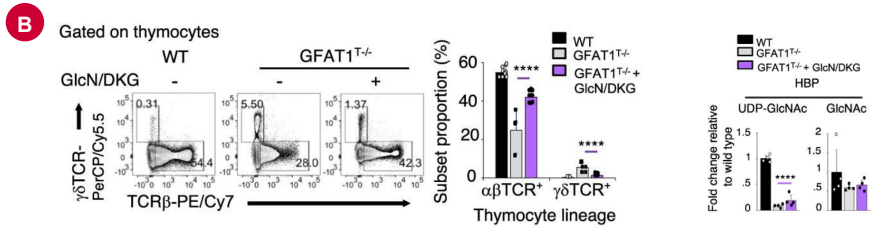
Herranz (CP),
Jacinto ✉ (CMI)

Su (MSR co-author)

Nat Commun 2022
13(1):7404



(A) GFAT1 knockout resulted in numerous metabolic changes including HBP pathway



(B) Supplementation of glucosamine (GlcN) and dimethyl-α-ketoglutarate (DKG) largely rescue the αβ-thymocyte development

IMPACT

The MSR performed metabolic profiling for this study

This work established that de novo hexosamine biosynthesis pathway is important for the development of αβ-T cells. GFAT1 deletion reduces the N-glycosylation of TCRβ chains, which leads to reduced surface expression of key developmental receptors

Dietary supplementation of glucosamine and α-ketoglutarate partially restores αβ-T cell development in GFAT1$^{T-/-}$ mice

Emphasis and Future Directions

Emphasis

- MSR aims to provide CINJ members with easy, cost-effective access to the state-of-the-art metabolite measurement capabilities
- MSR will continue to push the frontiers of tumor metabolism measurement, developing more comprehensive metabolite measurements and novel isotope tracer strategies.

Future Directions

- MSR is seeking funding to purchase an Orbitrap IQ-X mass spectrometer to expand the analytical capabilities offered to members in the fields of untargeted metabolomics and lipid structural identification
- MSR aims to be one of the first SRs in the US to provide users with spatial metabolomics data at cellular resolution as a service

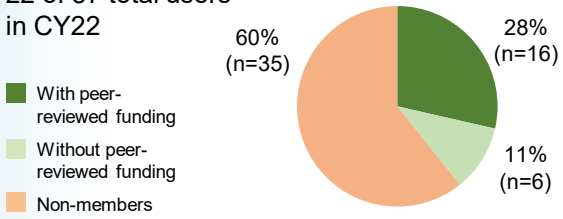
Metabolomics Shared Resource

RUTGERS Cancer Institute of New Jersey
RUTGERS HEALTH

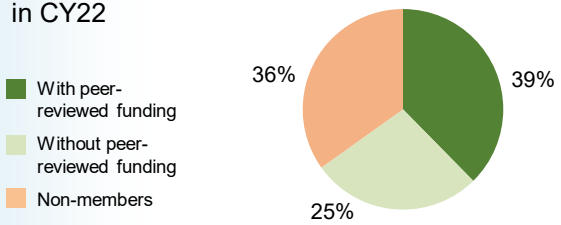
NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Utilization & Management

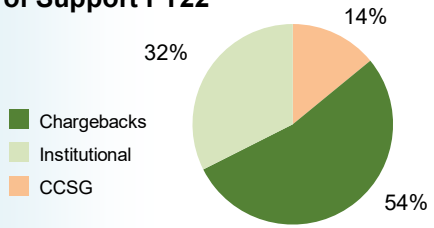
Member Users: 39%
22 of 57 total users in CY22



Member Usage: 64%
6,819 of 10,589 samples in CY22

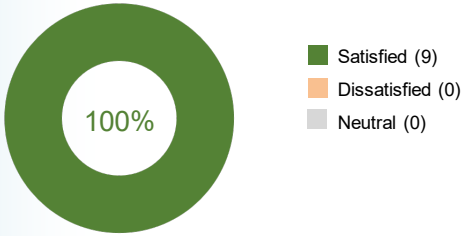


Sources of Support FY22



FY24 Chargeback target: 55%

Satisfaction Survey for CY22 services



Participated: 9 of 22 members (41%)

Organization & Governance

MSR
3.1 FTE

SRACs
- Advisory Committee meets annually
- Discusses operational and scientific progress
- SRM supports organization

SRM
- SR Faculty Directors report to the ADSR
- SRM tracks and supports SRAC recommendations, productivity, service development, outreach

CINJ Director
- RLC
- Finance & Admin
- EAB

Supporting Information

Program Support

- Publications
- Grants
- 5-Year User List

Advisory Committee

- FY23 Presentation
- Action Items
- Notes

Quality Satisfaction

- Annual Survey Action Items

SR Usage

- CY22 Usage

Submitted Information

- Research Strategy
- Aims
- SRM Research Strategy