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ONLINE WORKSHOP | FEBRUARY 26, 2021

SINGLE CELL METABOLOMICS WORKSHOP

ORGANIZED BY:
 Rima Kaddurah-Daouk, *Duke University*
 Jennifer Kirwan, *Berlin Institute of Health*
 Andrew N. Lane, *University of Kentucky*
 Mioara Larion, *National Cancer Institute*

PROGRAM

10:00 Welcome and Introduction Rima Kaddurah-Daouk, *Duke University*

Session I Chair: Mioara Larion, *National Cancer Institute*

10:05 "Single cell metabolomics for biomedical and drug research"
 Thomas Hankemeier & Ahmed Ali, *University of Leiden*

10:35 "High throughput metabolomics of individual cells in the brain"
 Jonathan Sweedler, *University of Illinois Urbana-Champaign*

11:05 "Optical methodologies to characterize the metabolic underpinnings of breast cancer"
 Nimmi Ramanujam, *Duke University*

11:35 Break


Session II Chair: Jennifer Kirwan, *Berlin Institute of Health*


11:55 "Towards super-resolution metabolic imaging using mass spectrometry imaging"
 Ian Gilmore, *National Physical Laboratory, London*


12:25 "Integrative approaches to study cancer and immune cell metabolism"
 Shawn Davidson, *Princeton University*

General Discussion Chair: Jonathan Sweedler, *University of Illinois Urbana-Champaign*

12:55 Discussants: S. Davidson, I. Gilmore, T. Hankemeier, I. Lanekoff, L-I. McCall, N. Ramanujam, J. Sweedler

Sponsored by:


Metabolomics Association of North America




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Nimmi Ramanujam
 Duke University of Leiden

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Optical methodologies to characterize the metabolic underpinnings of breast cancer

Nimmi Ramanujam, Ph.D.

Director, Global Women's Health Technologies

Robert W. Carr Professor of Biomedical Engineering

Duke University, Durham, NC

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Disclosures



Talking: Nimmi Ramanujam
ZENOLUX
BIOMEDICAL

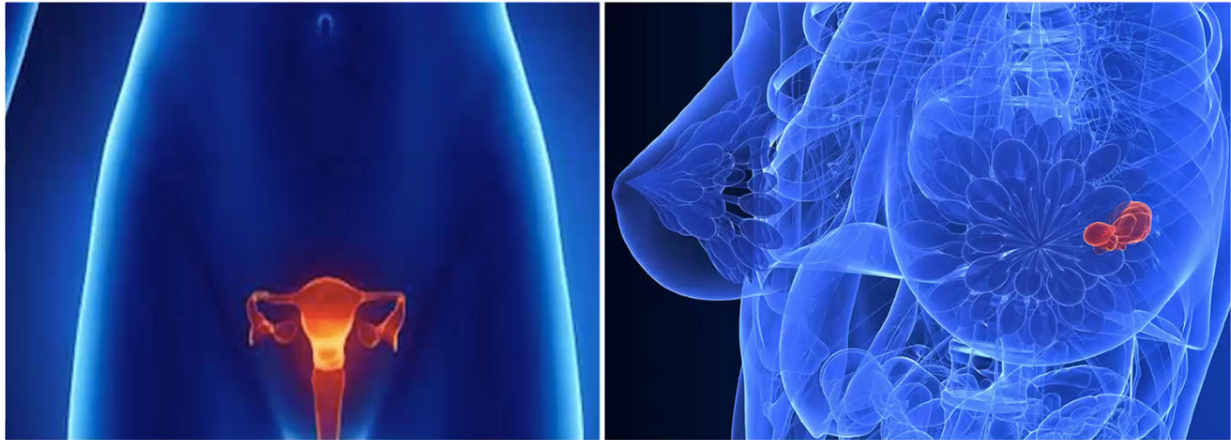
I am a named inventor on a patents and patent applications that is licensed to Calla Health, Inc. and Zenalux Inc., two companies I founded, developing products related to the research reported. I, along with Duke University, have equity ownership in Calla Health and Zenalux.



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Talking: Nimmi Ramanujam

A Focus on Women's Cancers

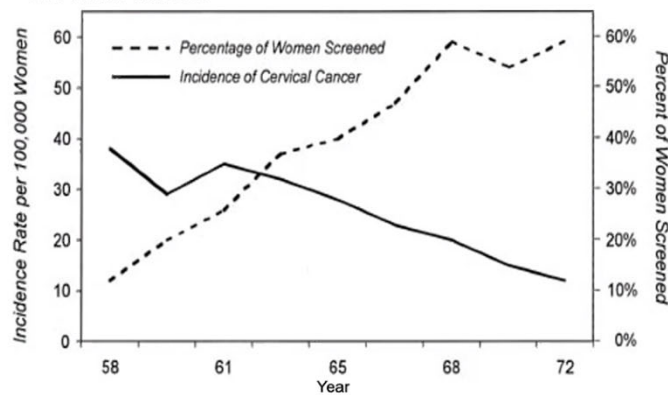


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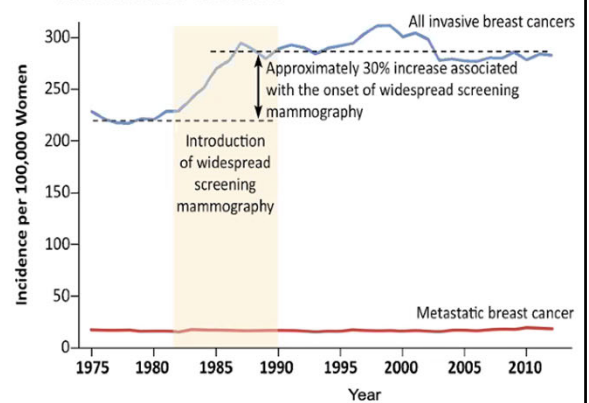
RE: Single cell metabolomics symposium
Cunningham, Stephen
I am here as well. I will try to stay through the end

Two women's cancers: two solutions

Increase screening decreases incidence of cervical cancer



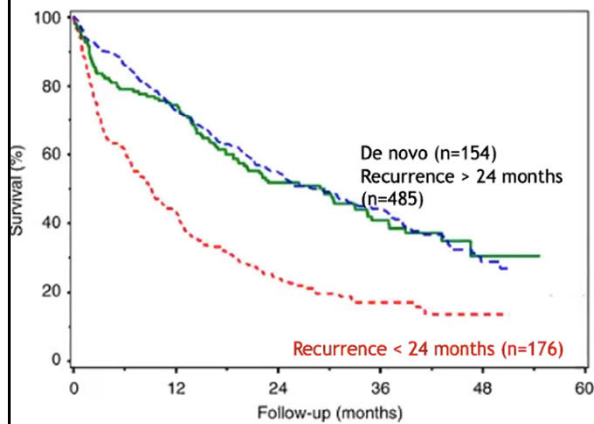
Increase screening does not decrease metastatic disease



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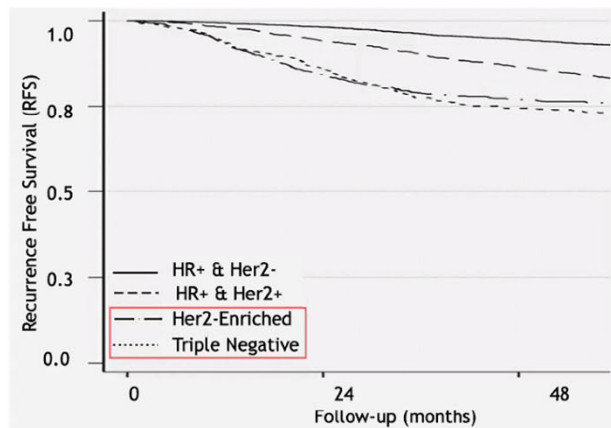
In spite of early detection recurrence affects overall survival

Decreased survival from early recurrence



Adapted from Lobbezoo, *BJC*, 2015

Risk of recurrence by breast cancer subtypes

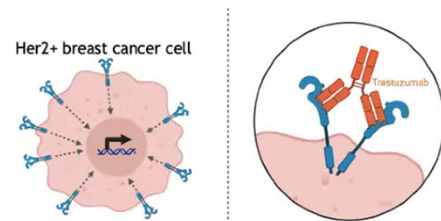


Adapted from C van Maaren, *Int J Can*, 2019

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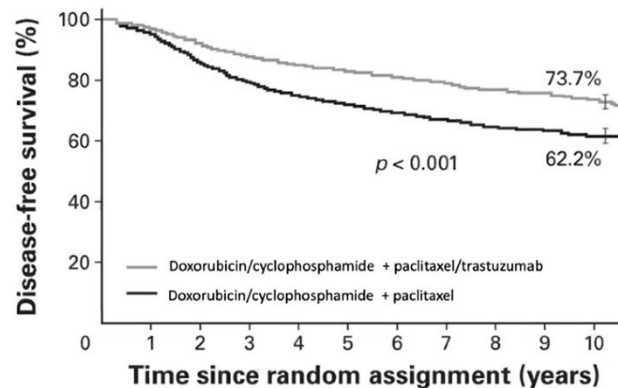
Targeted therapy has improved outcomes, but recurrence persists

Trastuzumab targets Her2



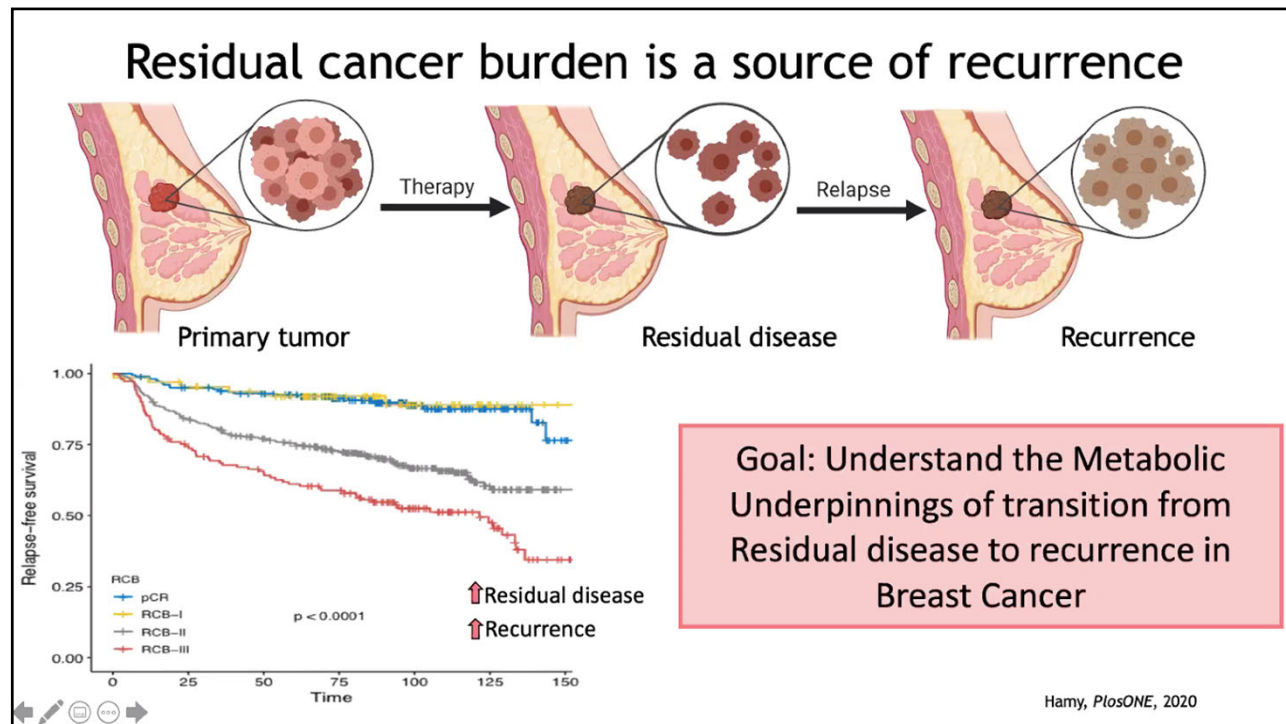
Adapted from Herceptin.com via BioRender

Targeting the Her2 receptor decreases recurrences

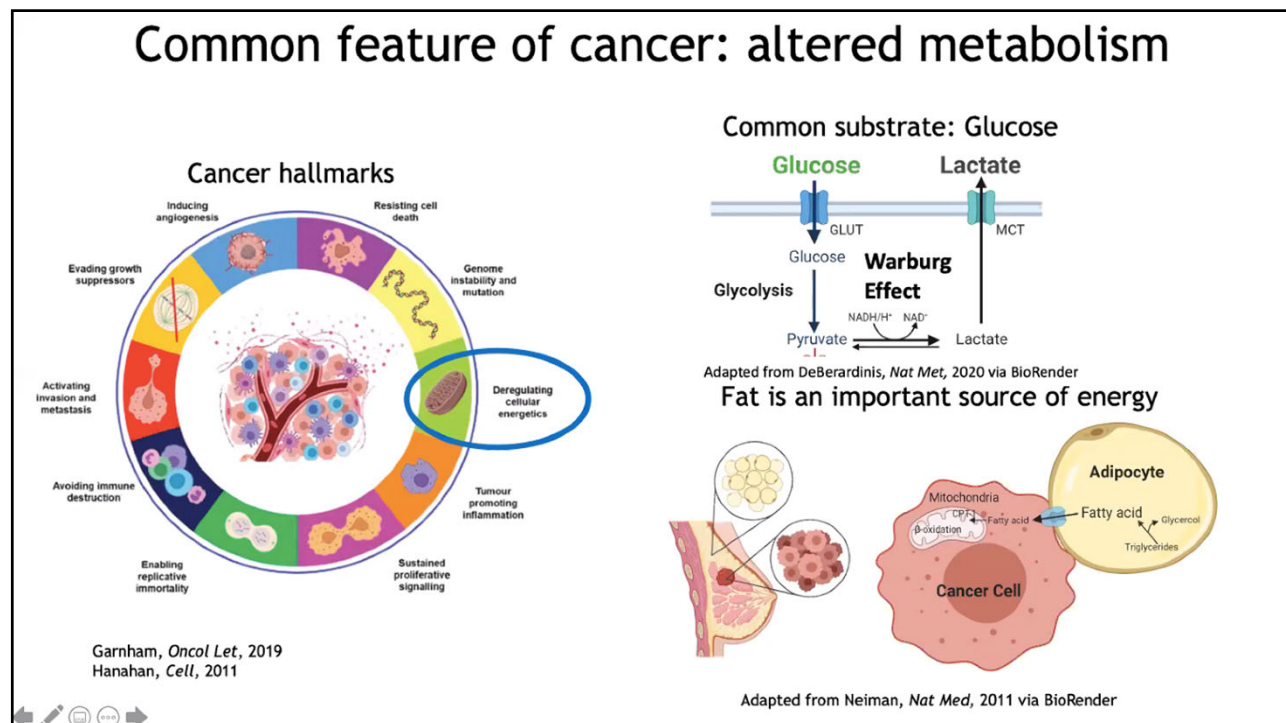


Kristeleit, *Targ Oncol*, 2016 Cameron, *Lancet*, 2017

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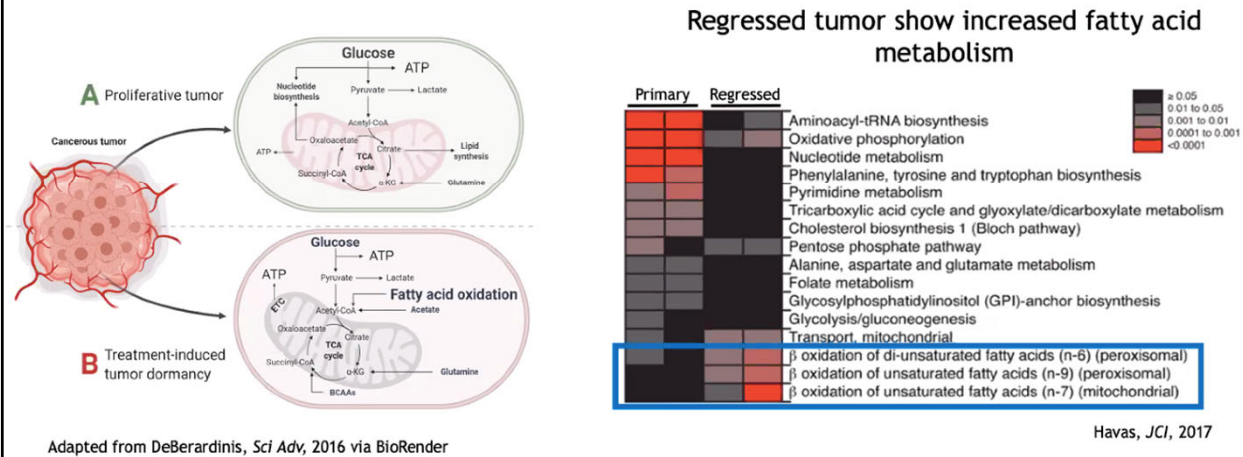


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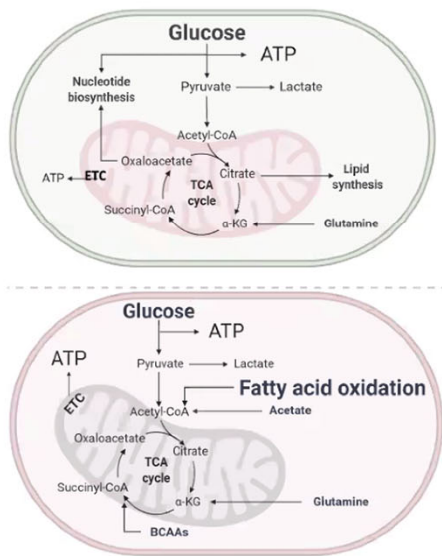
Shift from anaerobic to aerobic metabolism in residual disease



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Pinpointing metabolic changes could allow existing therapies to target metabolic reprogramming

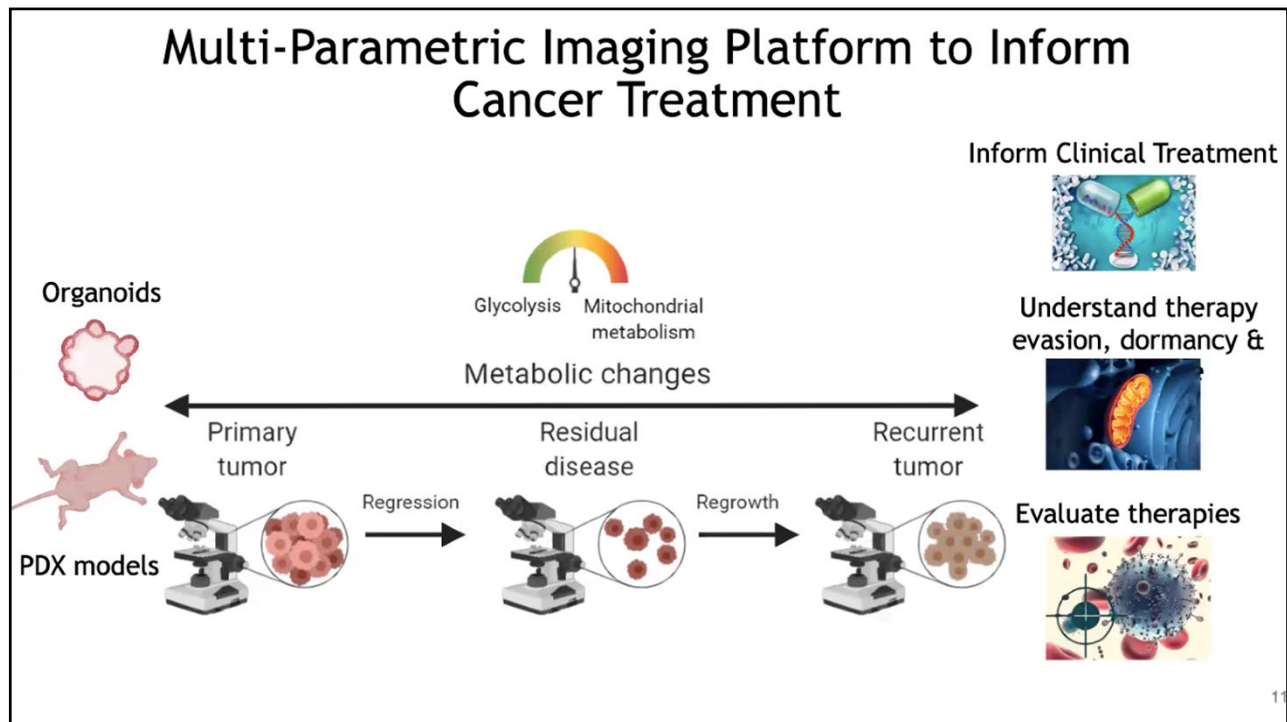
Strategies to target pathways for treatment



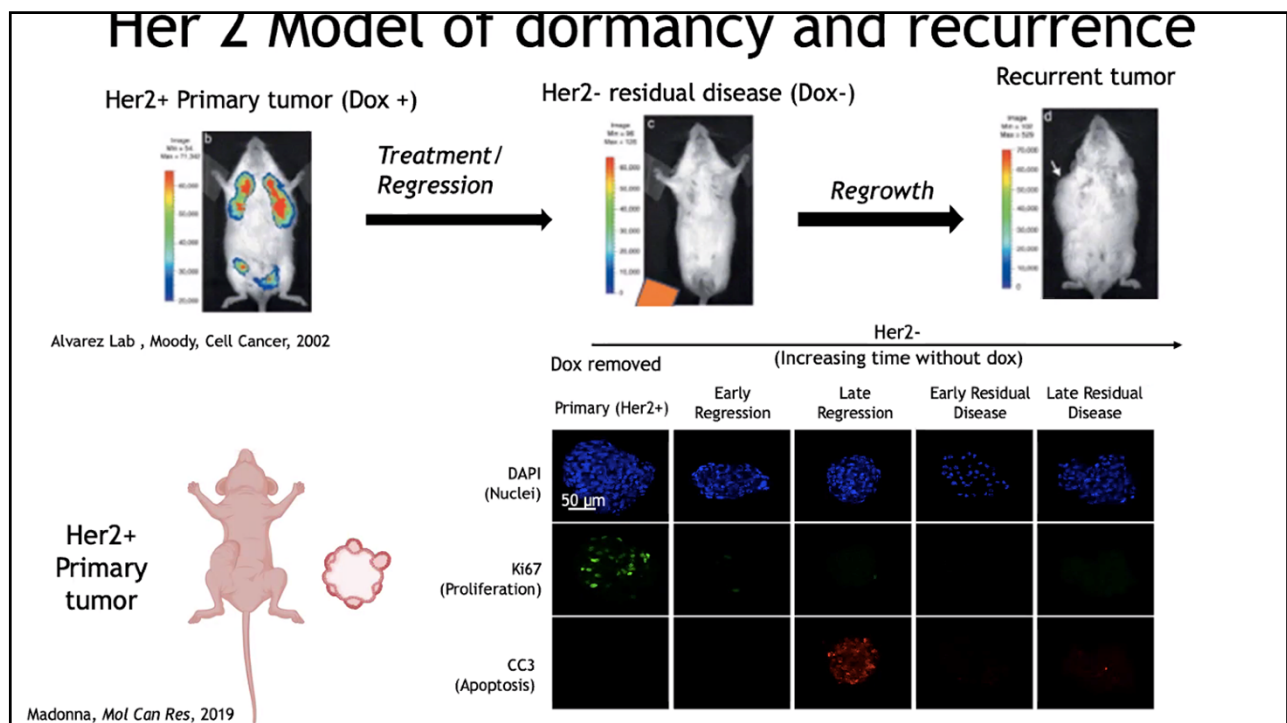
Target pathway and protein	Agent	Development stage
Glycolysis		
GLUT1	WZB117, silibinin, and RNAi	Preclinical studies
Hexokinases	2-deoxyglucose, lonidamine, 3-bromopyruvic acid, and methyl jasmonate	Preclinical and clinical studies
Lactate dehydrogenase A (LDHA)	GNE-140, FX11, galloflavin, and RNAi	Preclinical studies
Oxidative phosphorylation		
Mitochondrial membrane potential	MKT-077	Clinical studies
Mitochondrial complex I	Metformin, phenformin	Metformin is approved for the treatment of type 2 diabetes
Mitochondrial complex III	Arsenic trioxide	Preclinical and clinical studies

Adapted from DeBerardinis, *Sci Adv*, 2016 via BioRenderAdapted from Martinez-Outschoorn, *Nat Rev*, 2017

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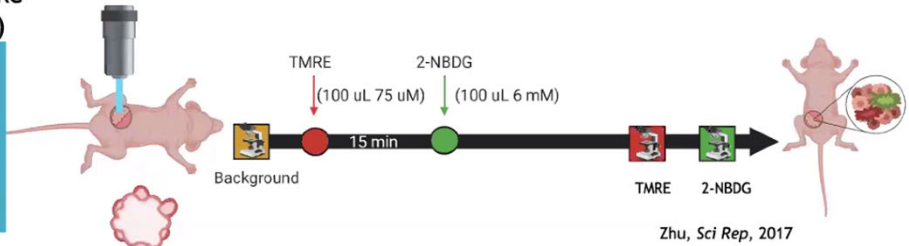
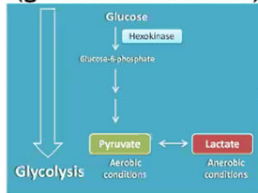
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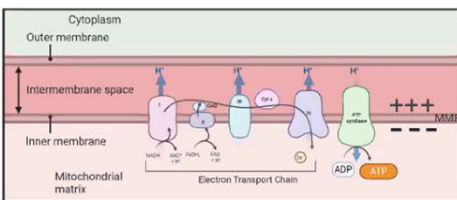
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Sequential imaging allows for *in vivo* multi-parametric imaging

2-NBDG: Glucose uptake (green fluorescence)

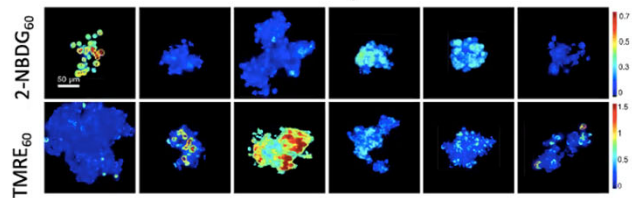


TMRE: MMP (red fluorescence)



ThermoFisher

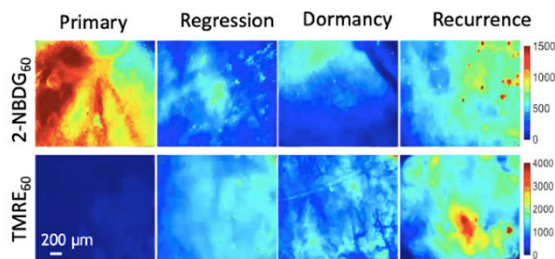
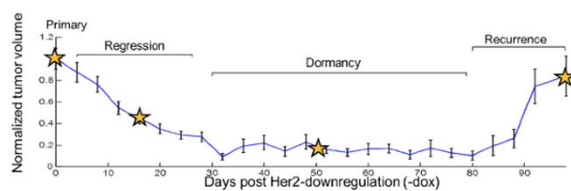
Longitudinal Imaging of TMRE +2-NBDG in mammospheres



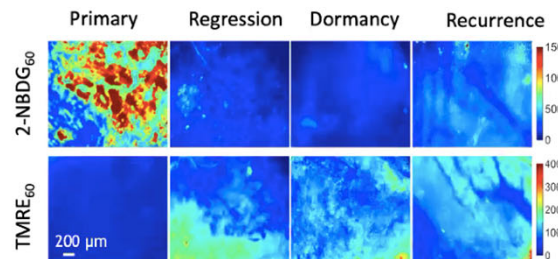
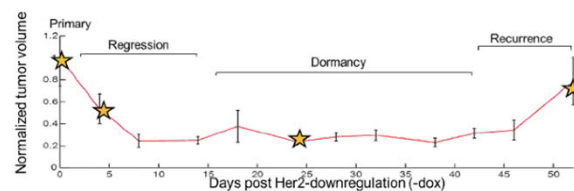
Madonna, Mol Can Res, 2019

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Imaging captures metabolic reprogramming following treatment of primary tumor



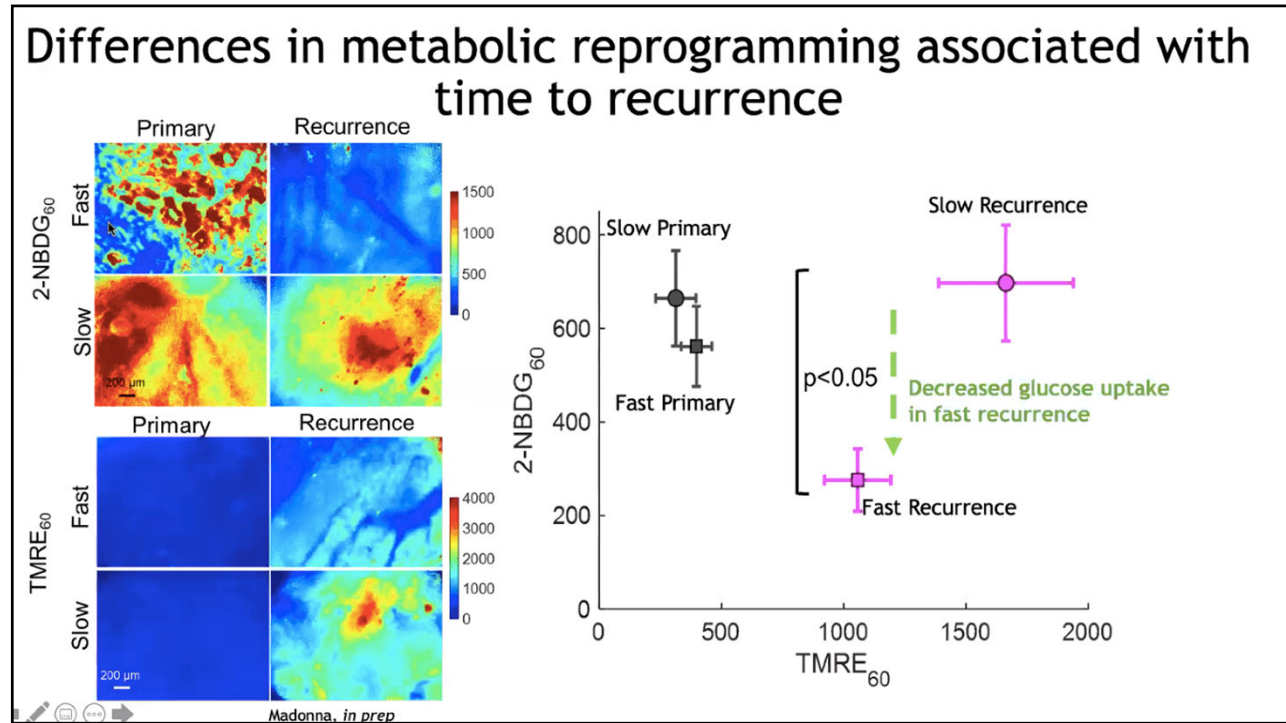
100-day time to recurrence



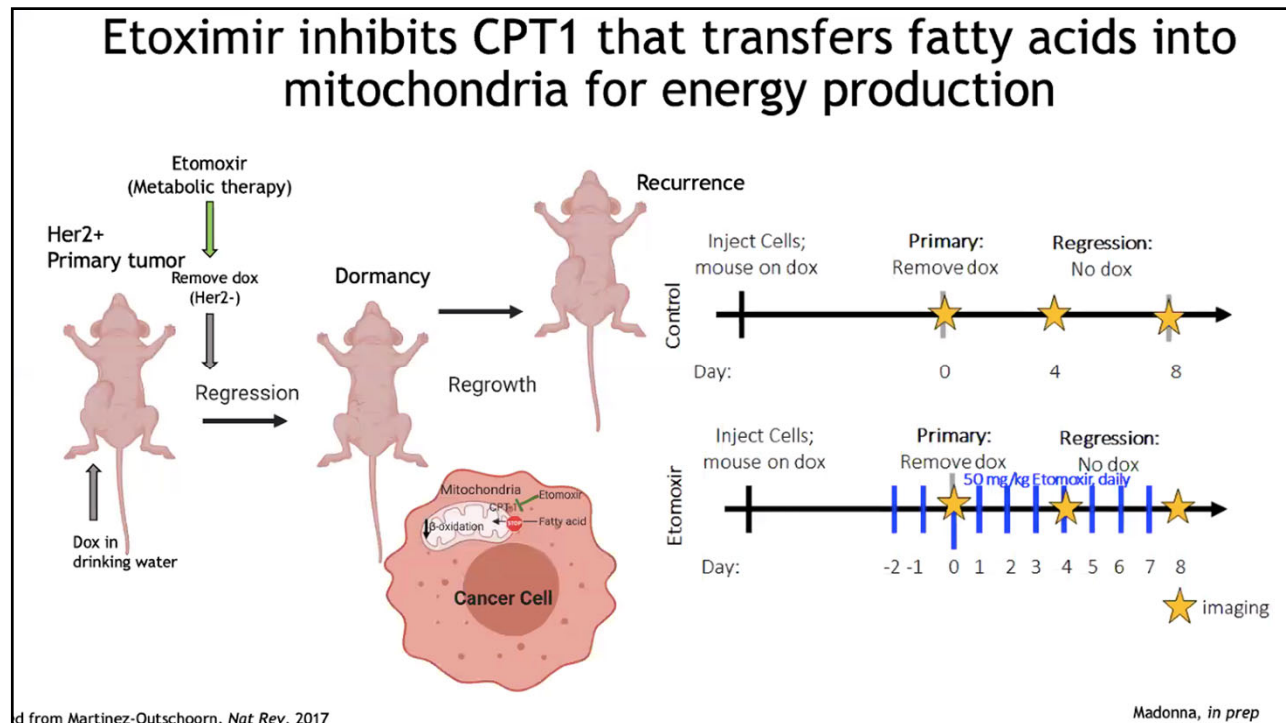
50-day time to recurrence

Madonna, in prep

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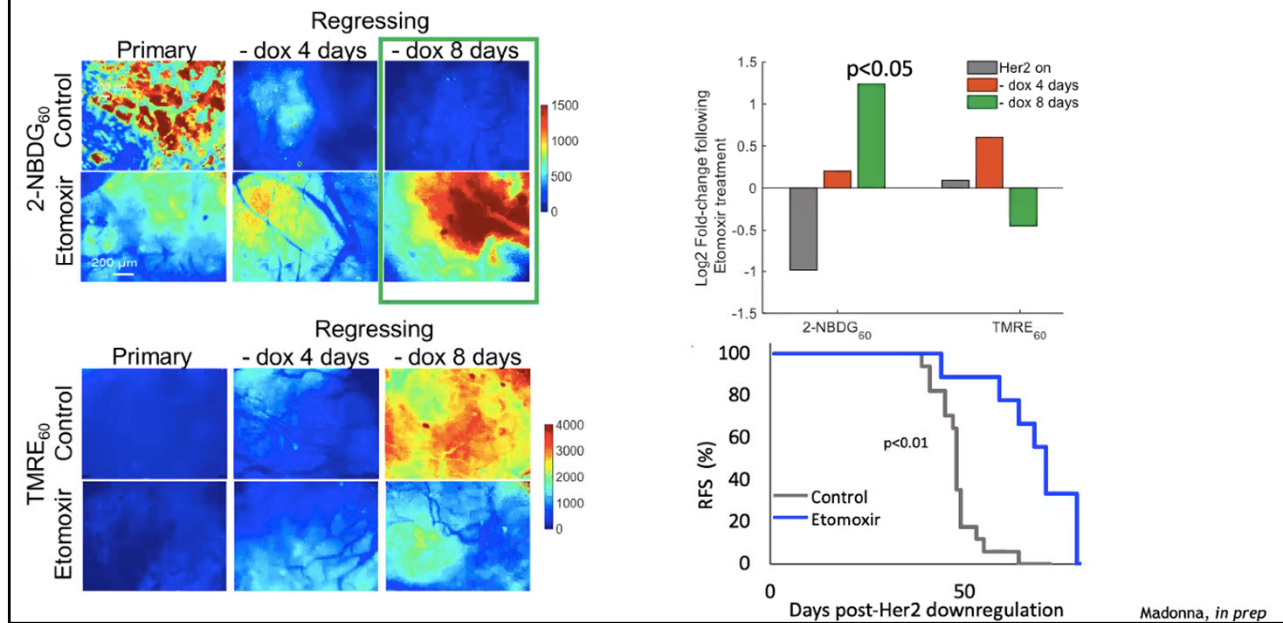
d from Martinez-Otschoorn, Nat Rev, 2017

Madonna, in prep

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Targeting fatty acids to changes metabolic repro

Talking: Nimmi Ramanujam

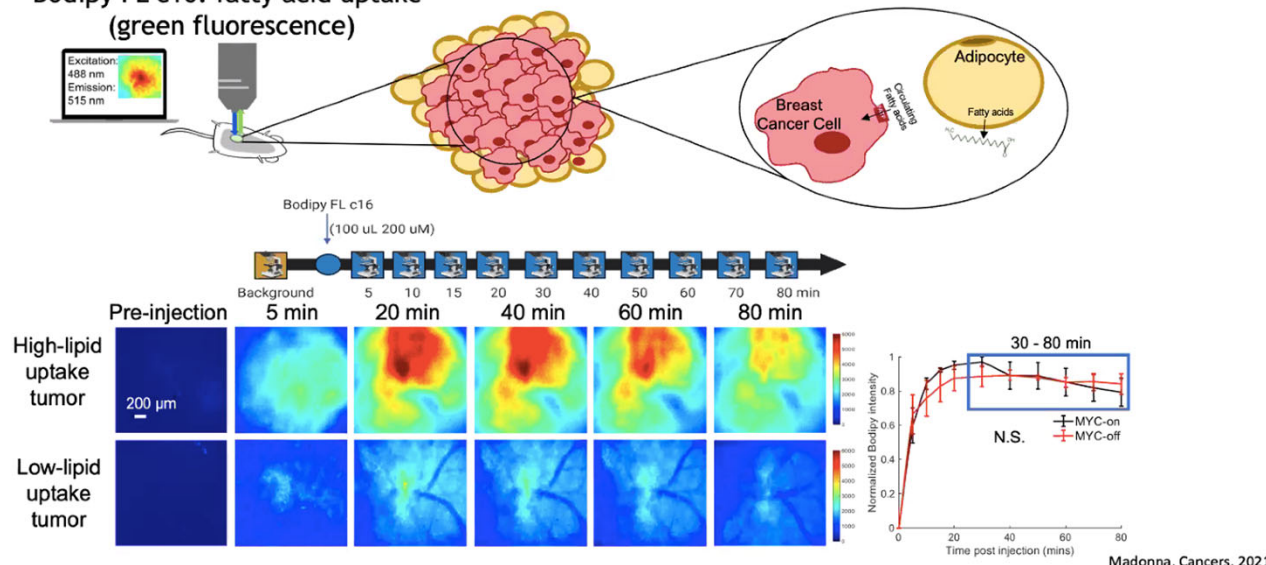


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Next step: imaging fatty acid metabolism Myc regulated GEM models

Talking: Nimmi Ramanujam

Bodipy FL c16: fatty acid uptake
(green fluorescence)

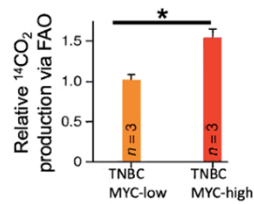
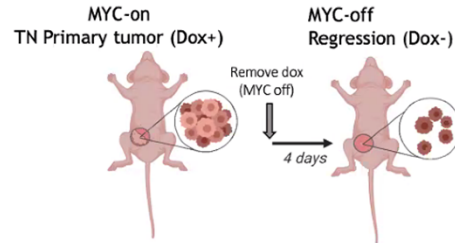


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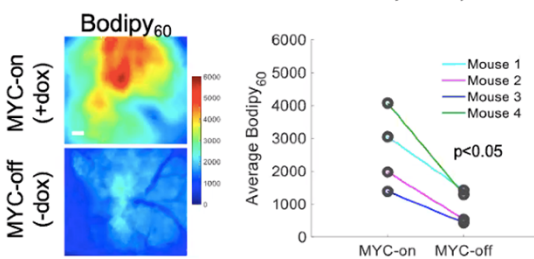
Bodipy₆₀ responds to biological perturbation *in vivo* and is paired with mitochondrial imaging to metabolically phenotype

Talking: Nimmi Ramanujam

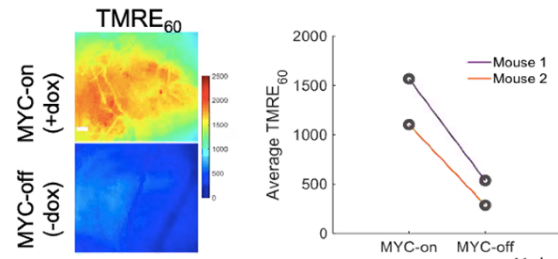
MYC-high cell lines show increased FAO

Camarda, *Nature Med.*, 2016

MYC-on tumors have increased fatty acid uptake



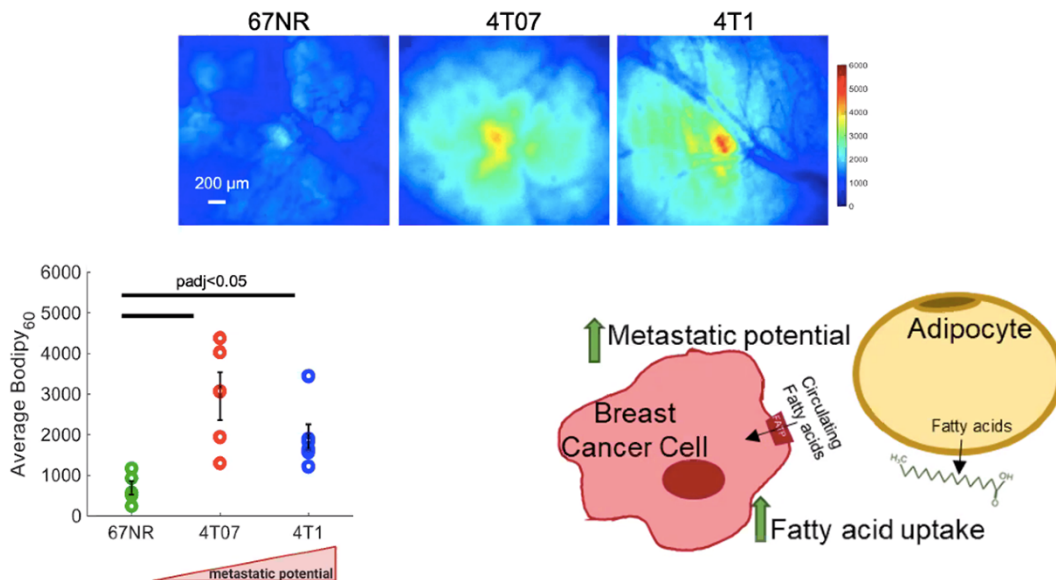
MYC-on tumors have increased mitochondrial metabolism

Madonna, *Cancers*, 2021

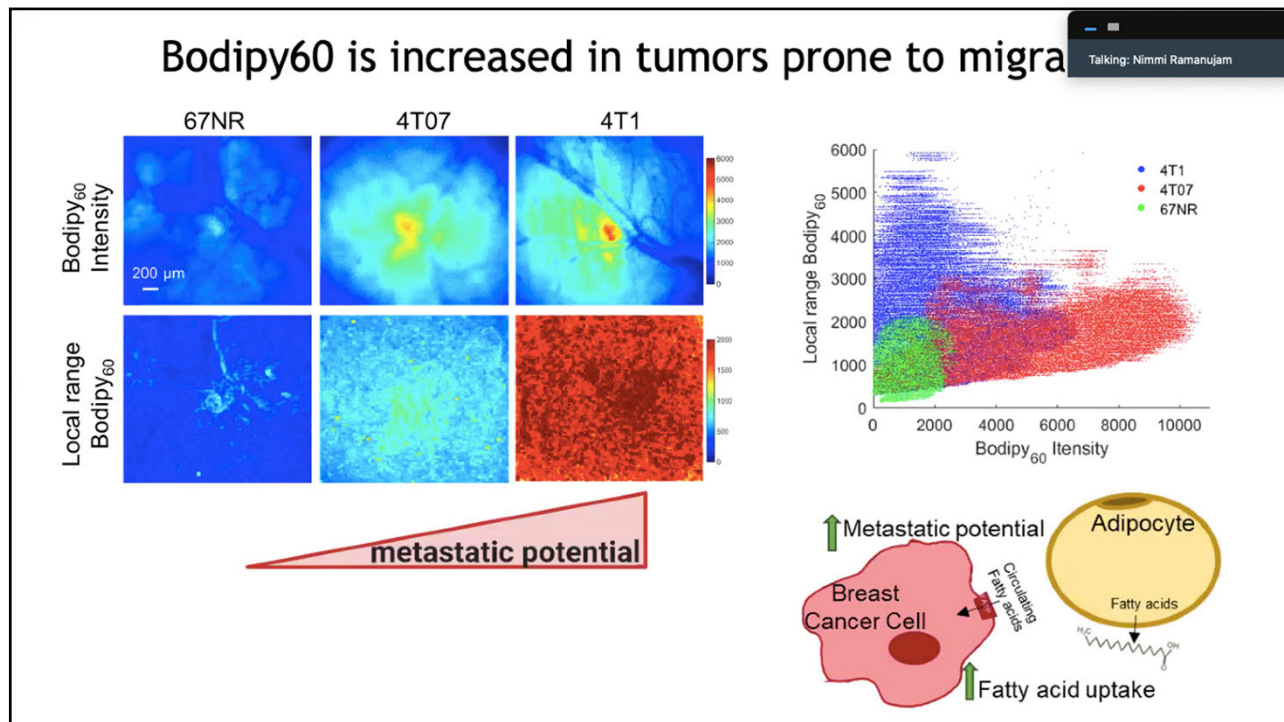
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Bodipy₆₀ is increased in tumors prone to migrate

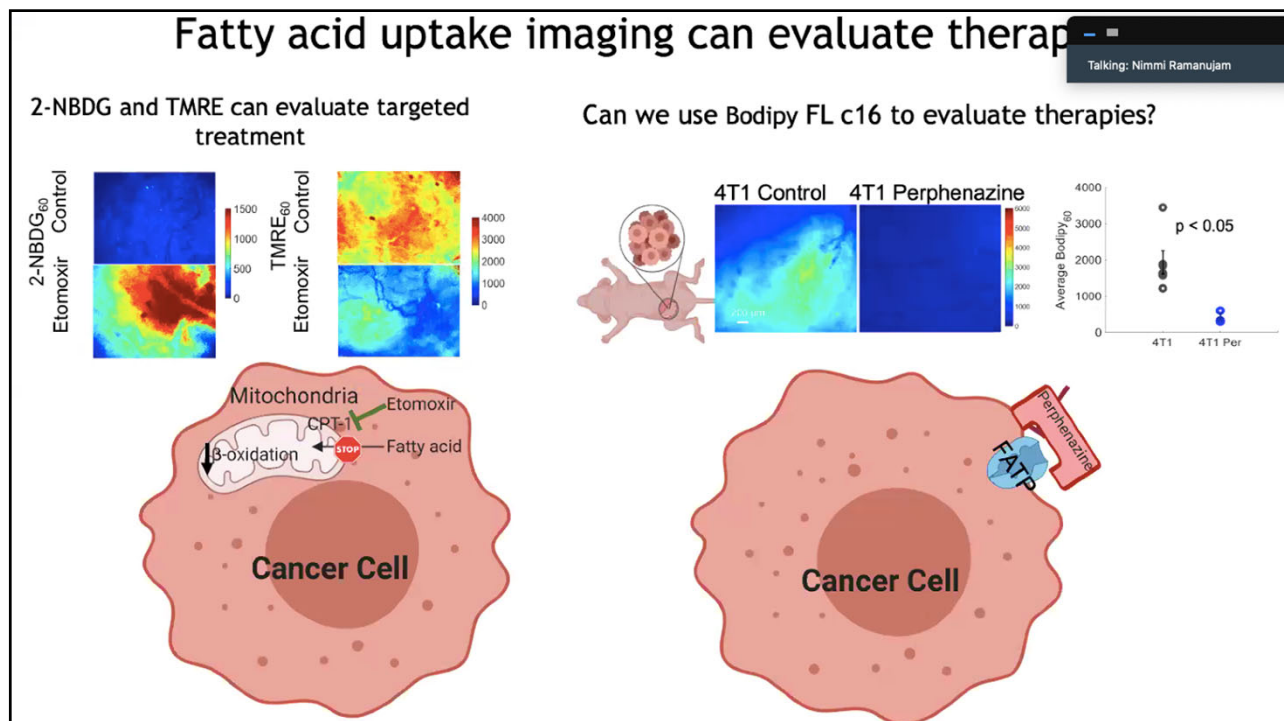
Talking: Nimmi Ramanujam



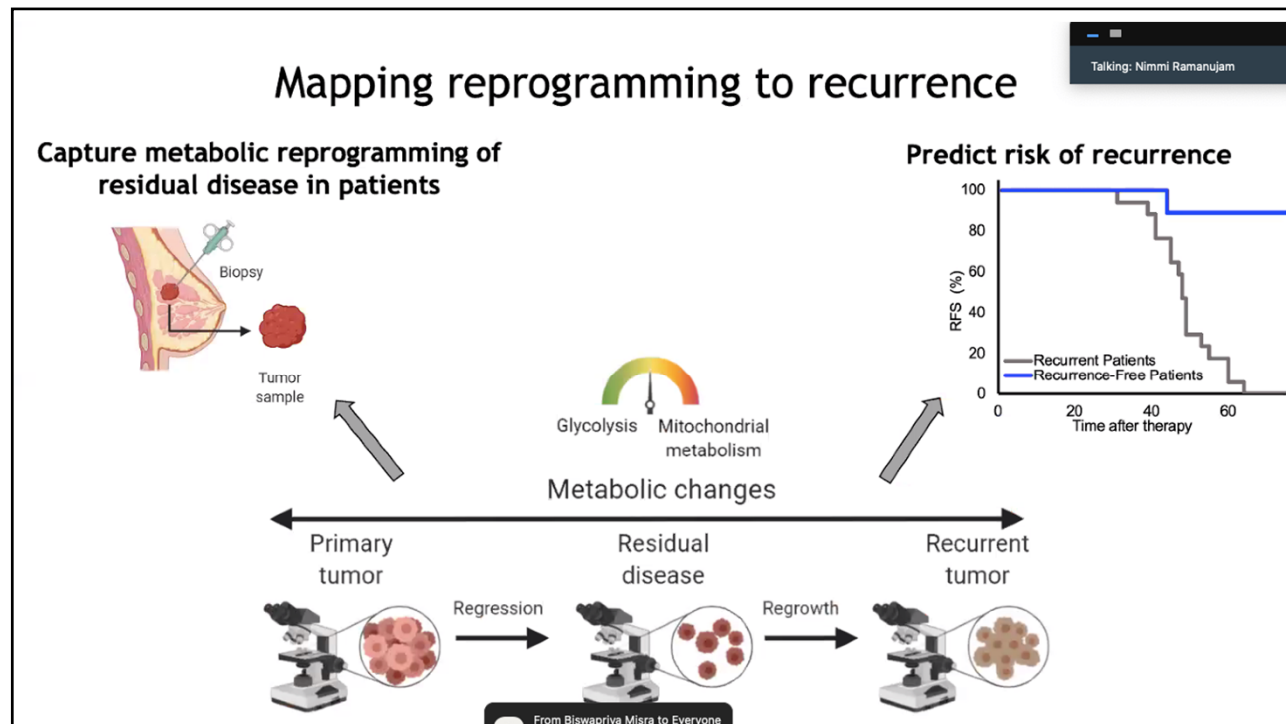
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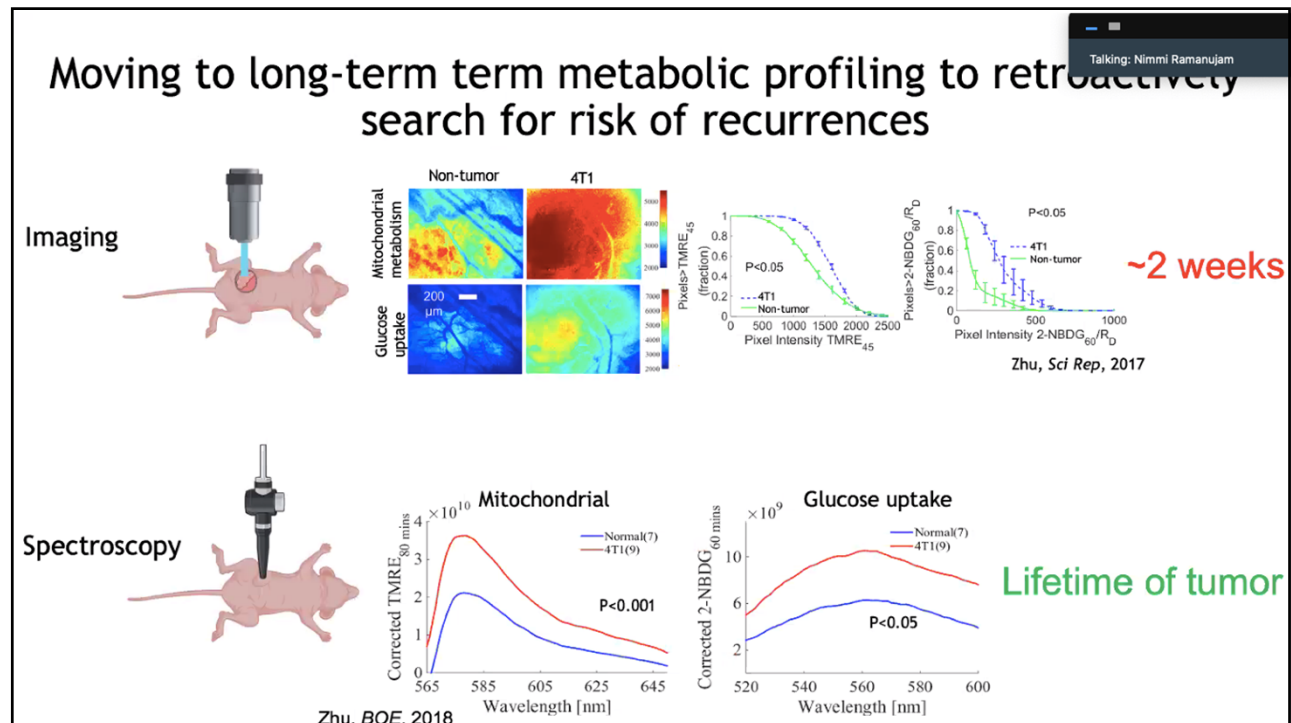
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Conclusions

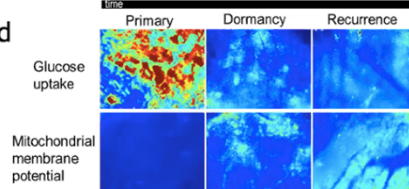
Talking: Nimmi Ramanujam

Our optical techniques of 2-NBDG and TMRE can capture distinct metabolic phenotypes of primary, regressing, dormant and recurrent tumors *in vitro* and *in vivo*.

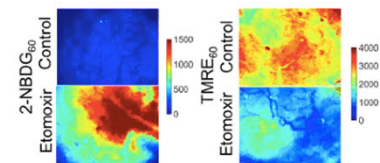
Our imaging platform allows for the longitudinal monitoring of metabolic targeted treatments

Additional Bodipy FL c16 can capture fatty acid uptake *in vivo* across preclinical models to better pinpoint metabolic vulnerabilities

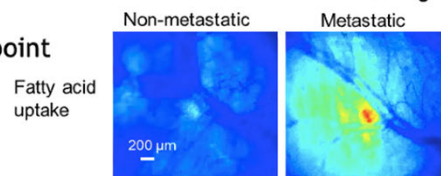
Longitudinal imaging pinpoints key metabolic time points



Monitor metabolic targeted treatment



Alternative fuel sources can be imaged



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Acknowledgements



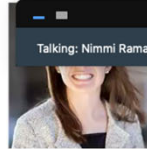
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From Riksanriya Miera to Everyone

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Funding

Talking: Nimmi Ramanujam

- NIH RO1: Culturally Appropriate Screening and Diagnosis of Cervical Cancer in East Africa
- 1R01CA195500-01 (Ramanujam)
- NIH RO1: A Viable Solution for a See and Treat Paradigm for Cervical Pre-cancer in Africa (Ramanujam)
- NCI RO1: Novel see and treat strategies for cervical cancer prevention in low-resource settings (Ramanujam)
- USAID DIV GRANT: See and Treat Model for Cervical Cancer Prevention in Peru (Ramanujam)