

# Illuminating Biology: Revealing Metabolic Fingerprints with Spatial Multi-Omics

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Cancer Research UK  
**Scotland Institute**  
(Formerly Beatson Institute)



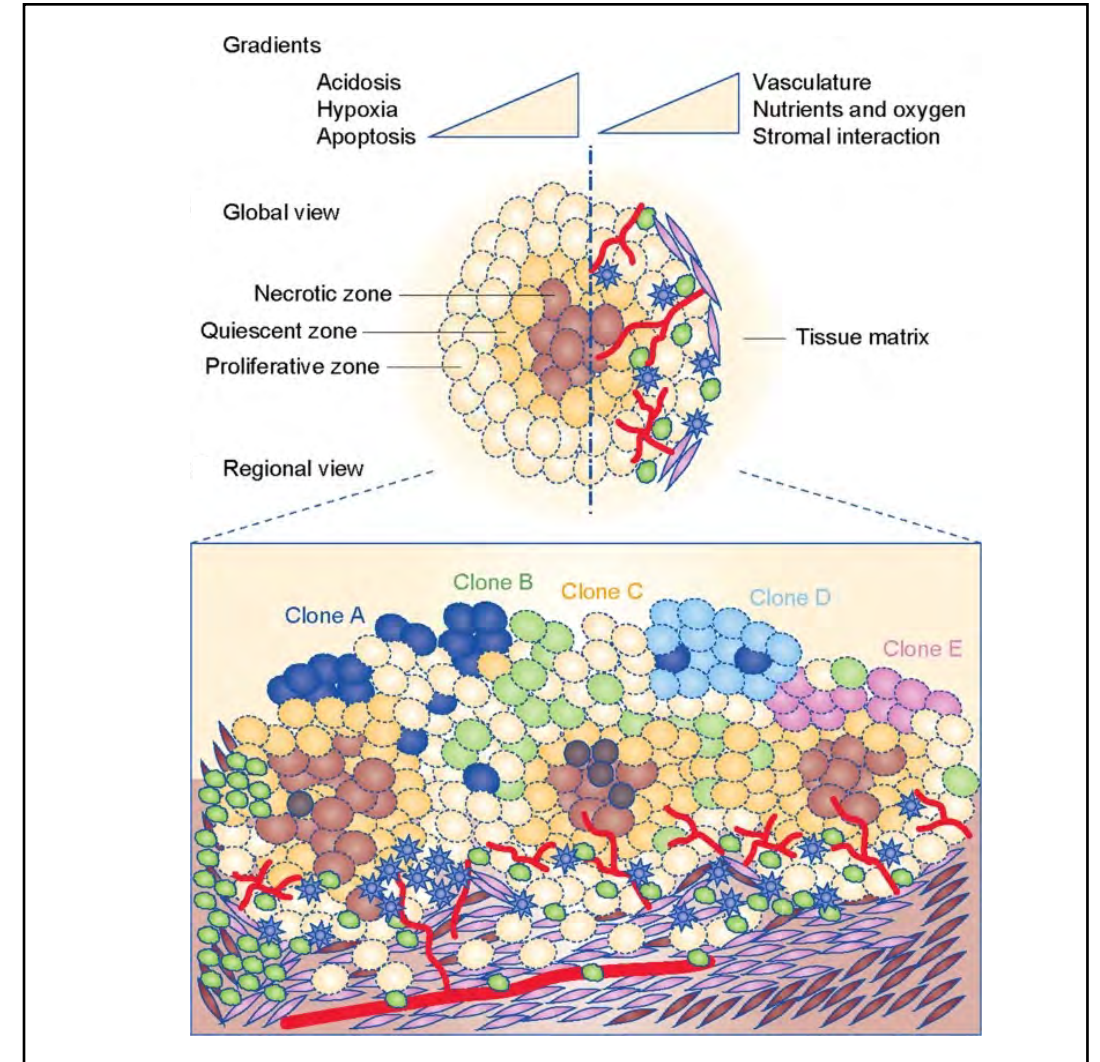
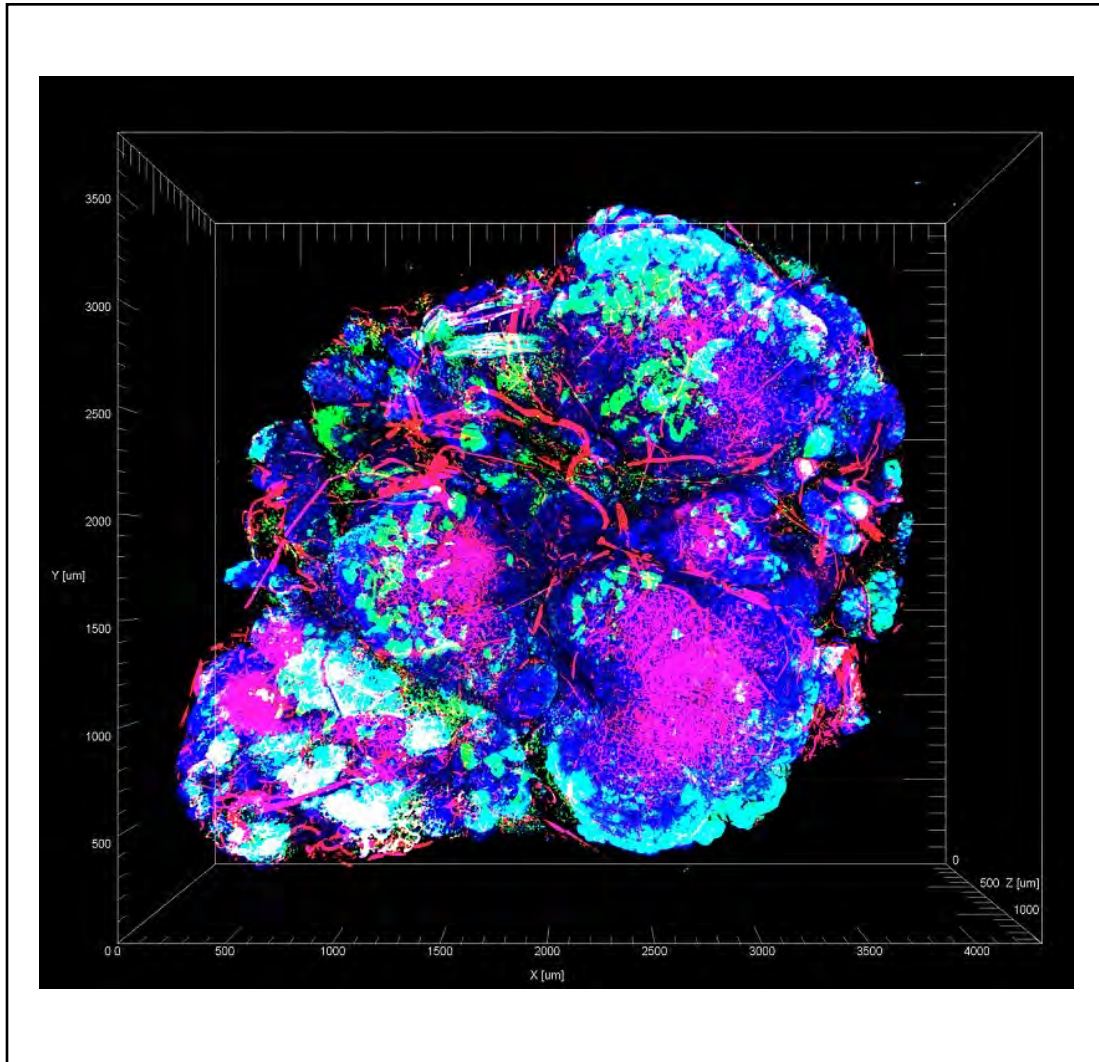
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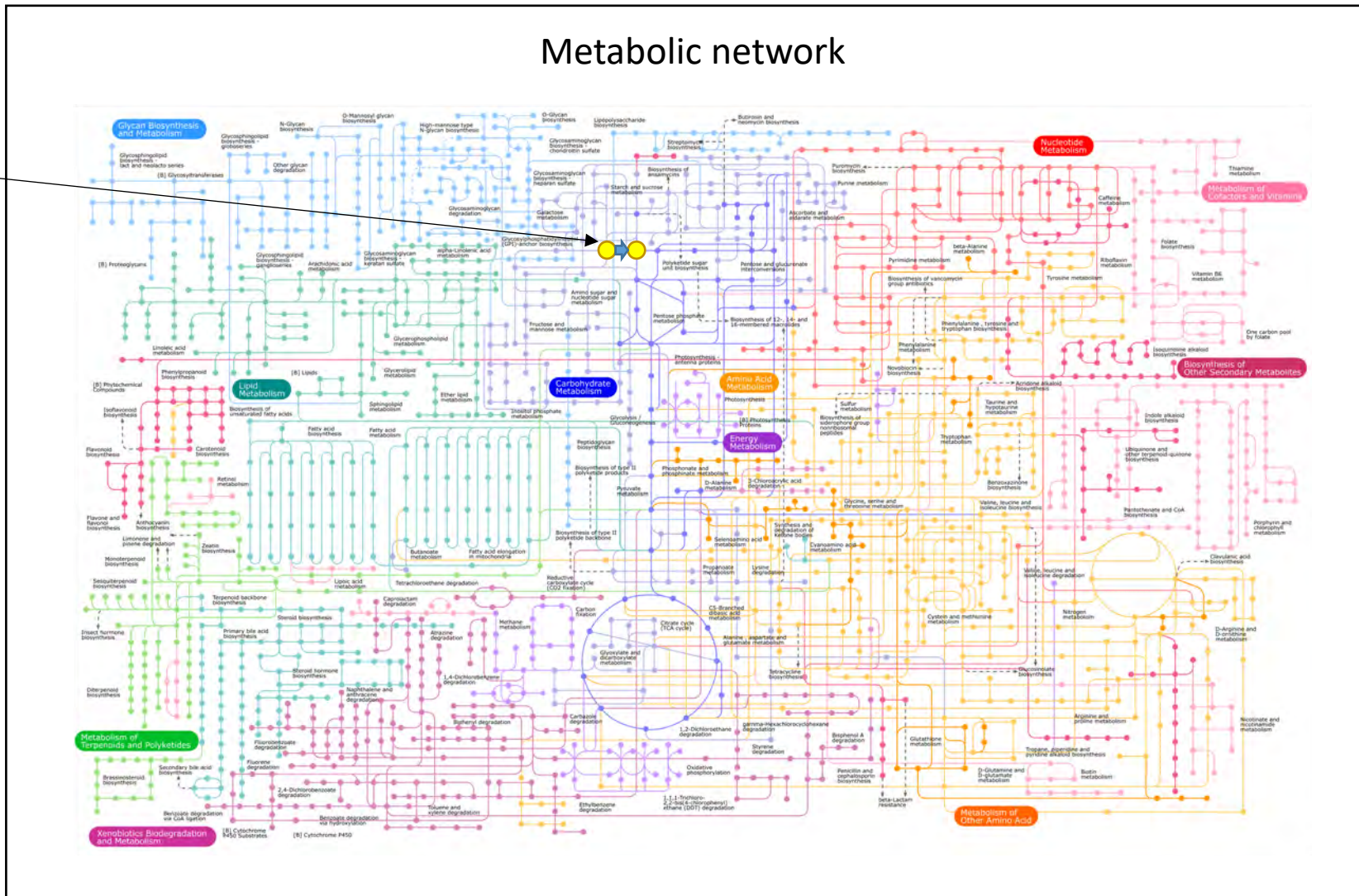
# Illuminating cancer heterogeneity



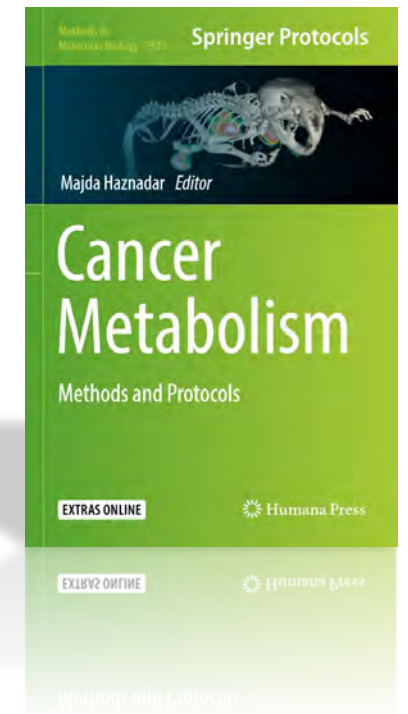
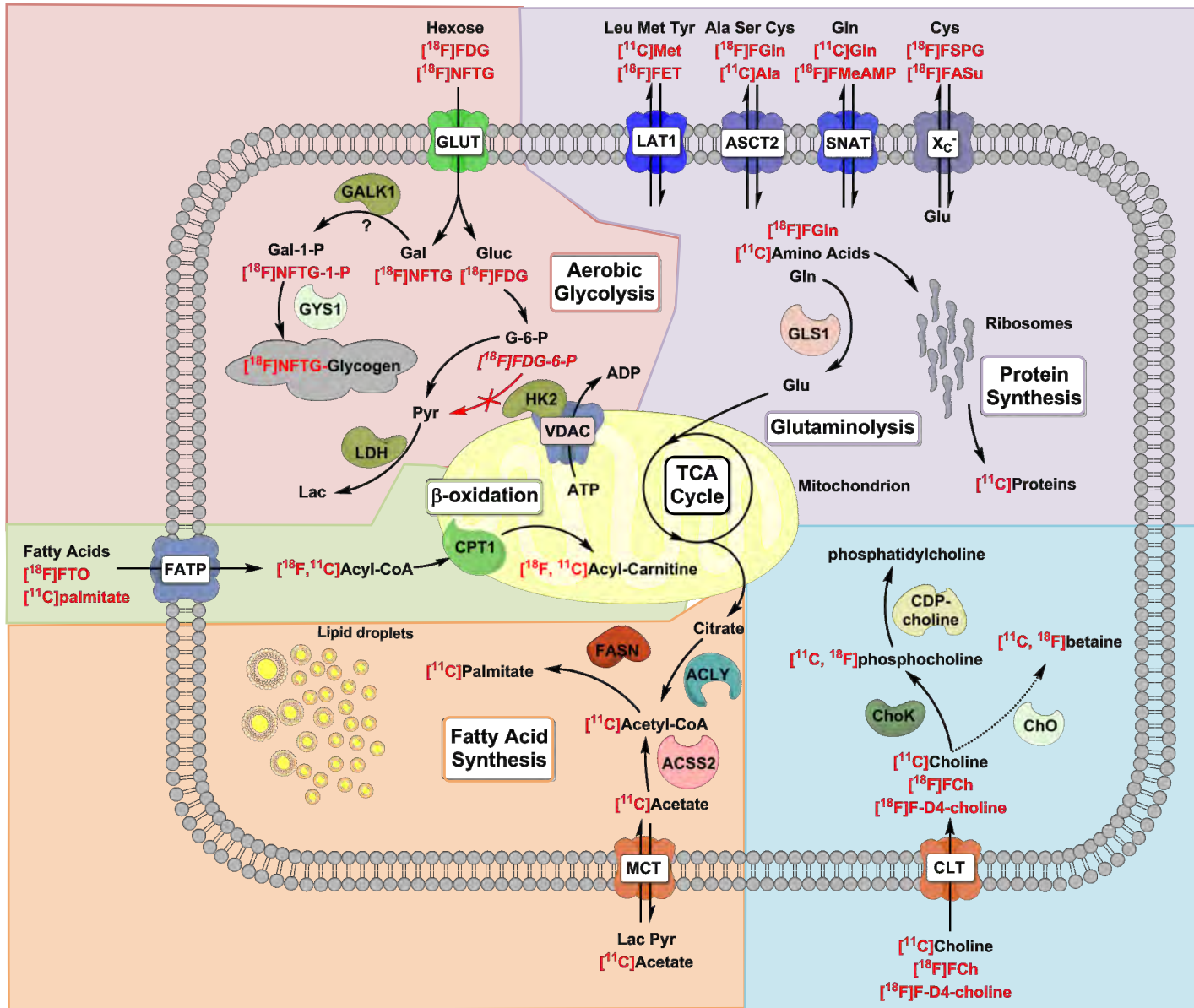
# Imaging key nodes in cancer

## Metabolic network

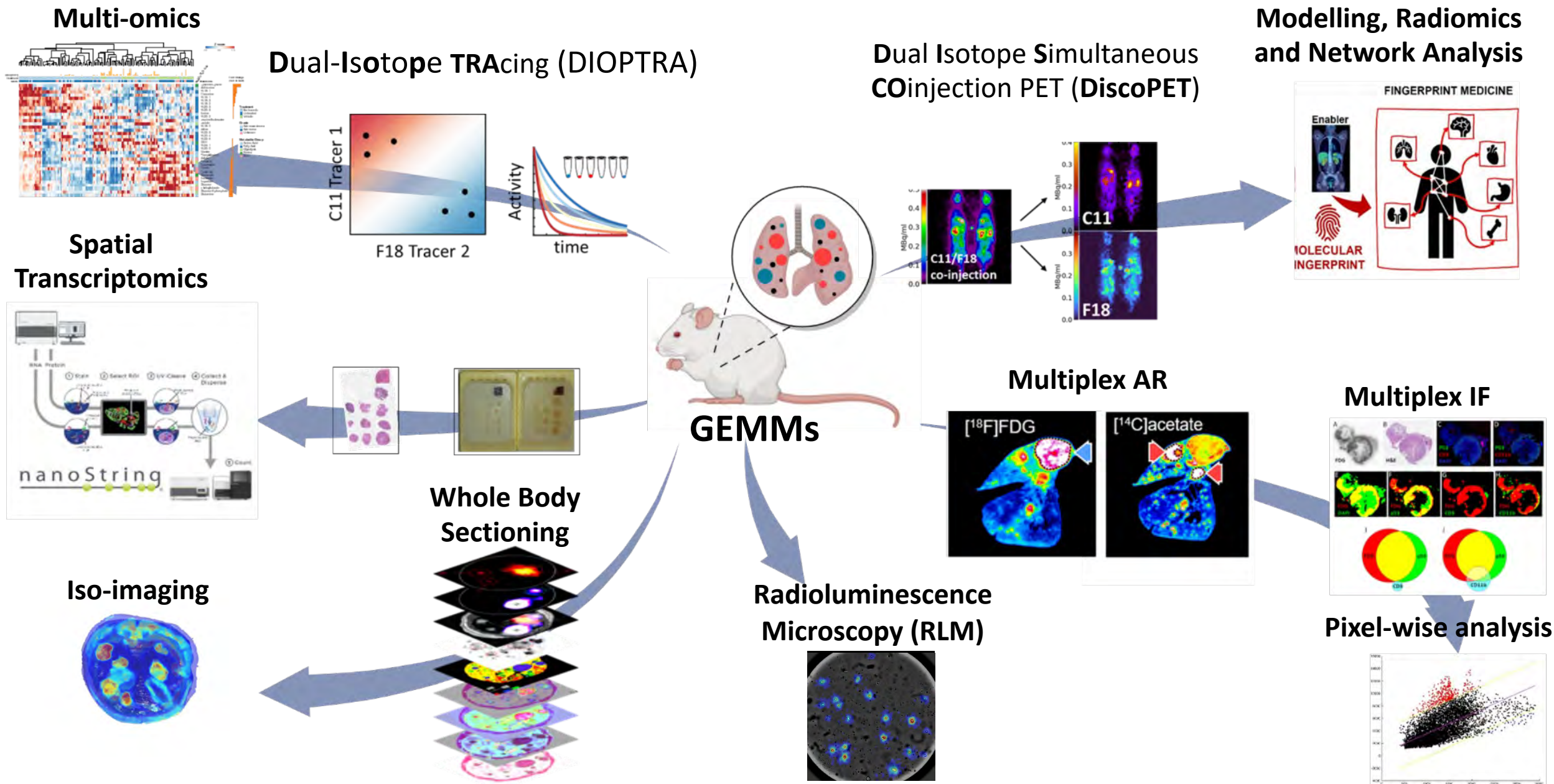
[<sup>18</sup>F]FDG PET



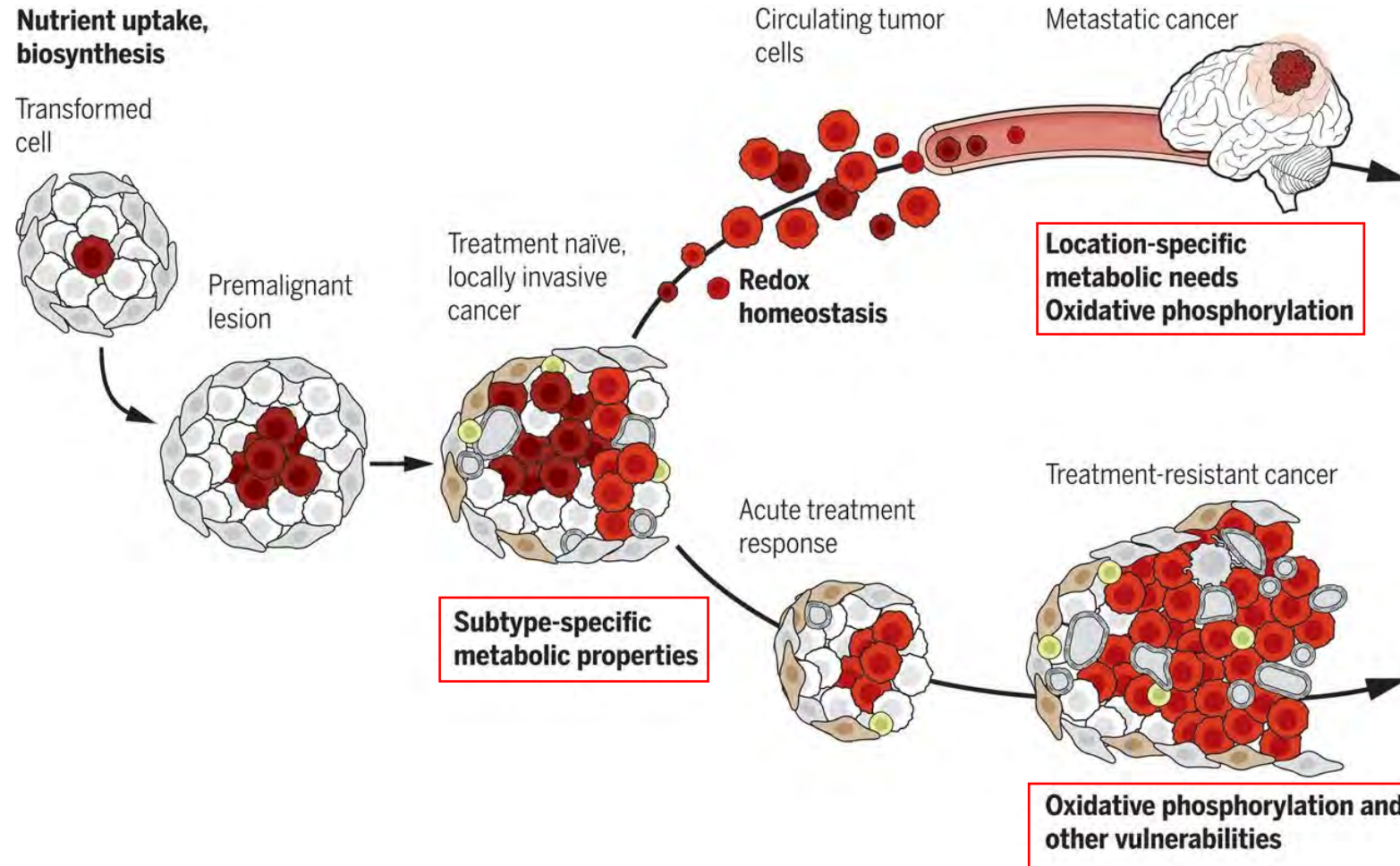
# “Picking winners” from metabolic PET tracers



# Technologies for deep radiotracer validation in the whole-body

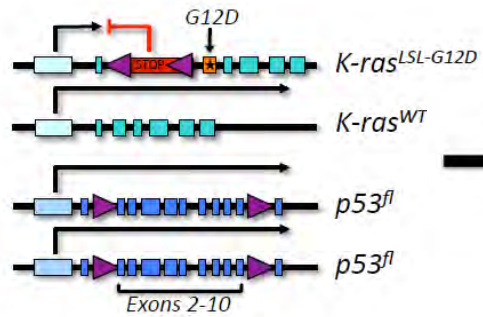
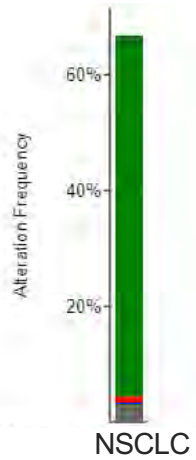


# Illuminating cancer metabolic heterogeneity

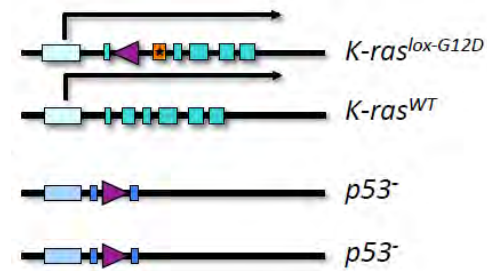


# High fidelity mouse models of lung cancer

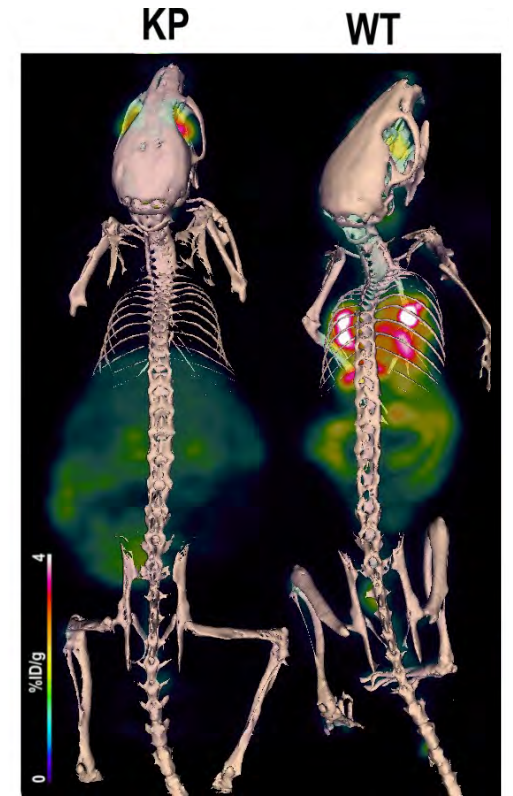
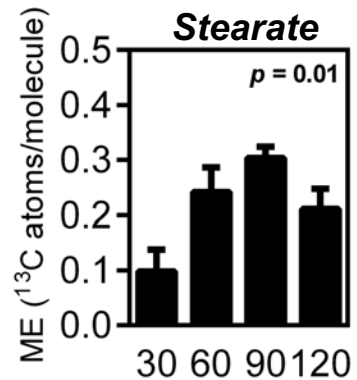
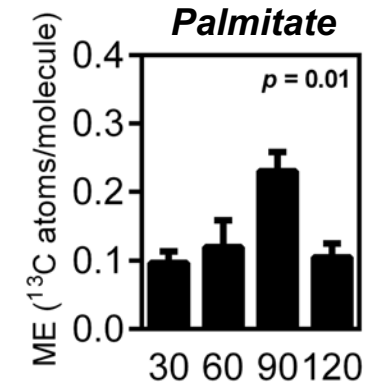
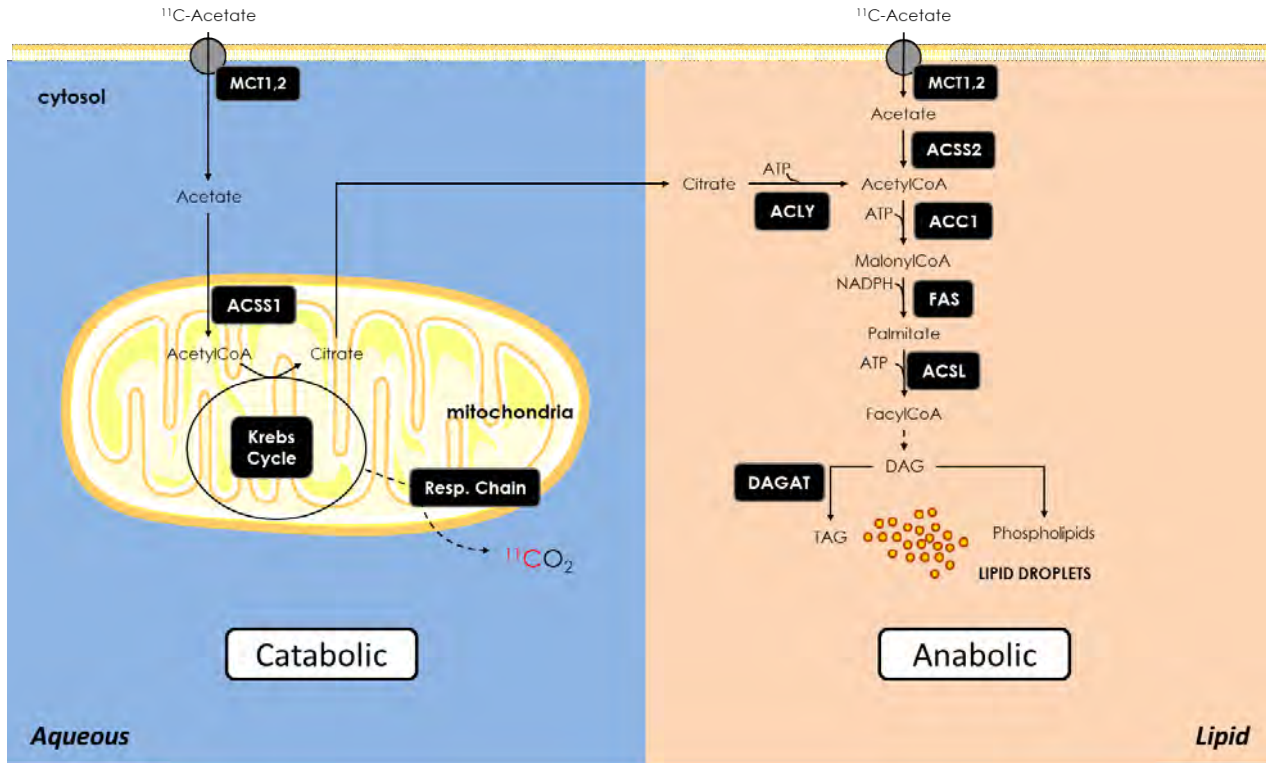
## Non-small cell lung cancer mouse model



CRE

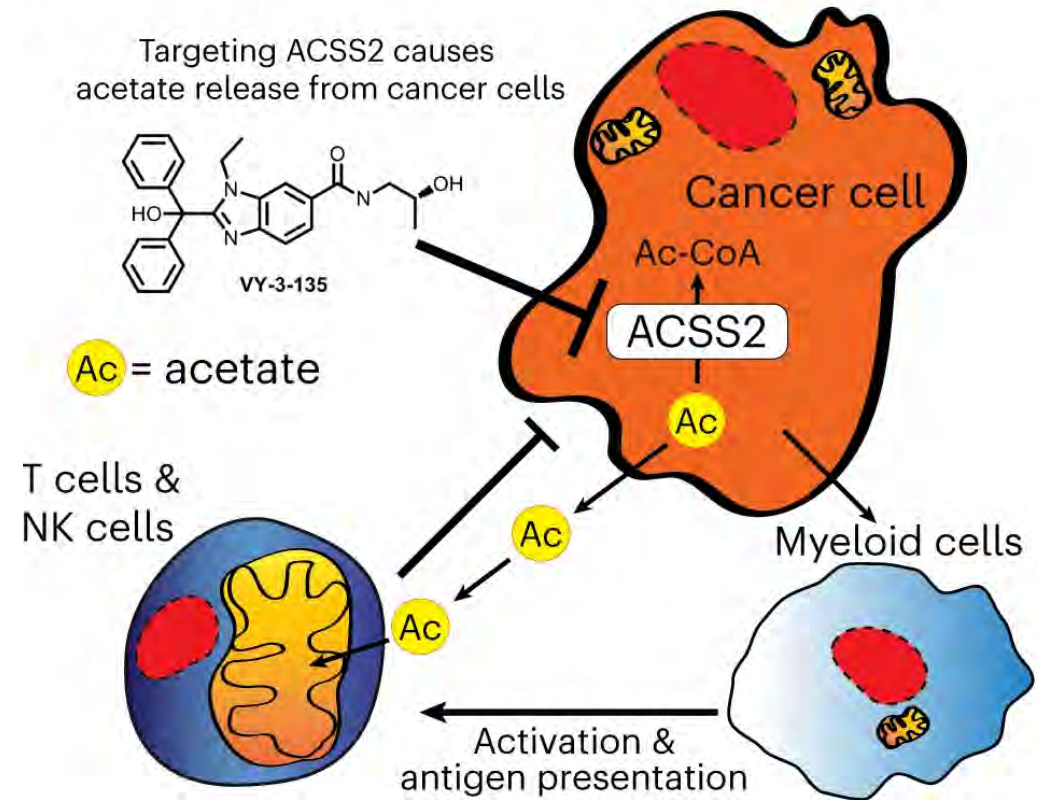
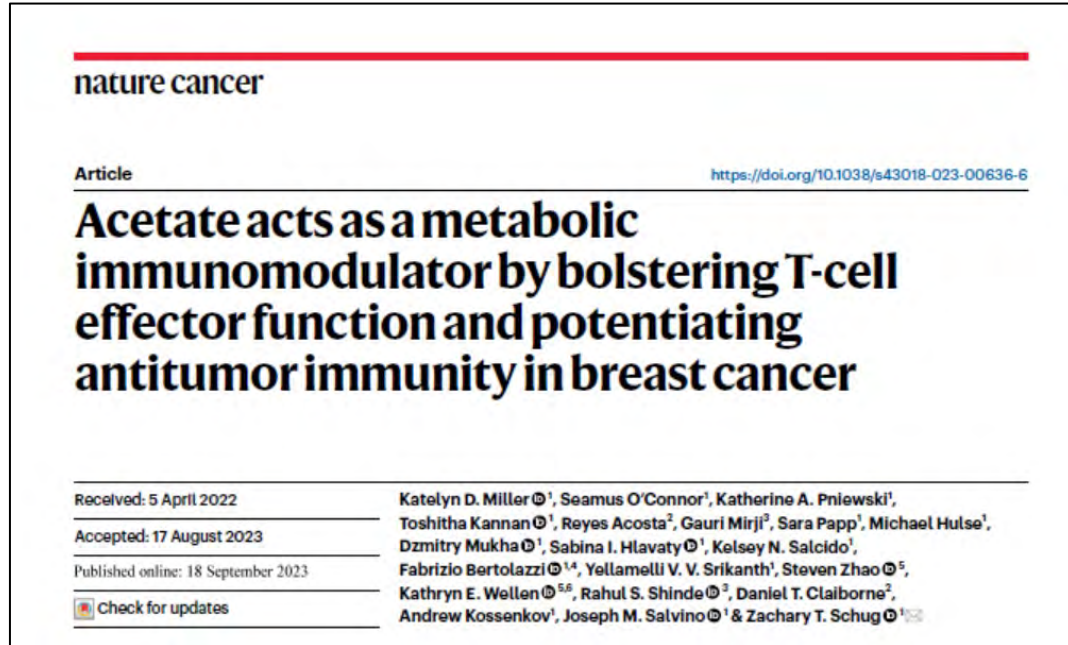


# Late imaging with $^{11}\text{C}$ -acetate improves specificity for fatty acid synthesis





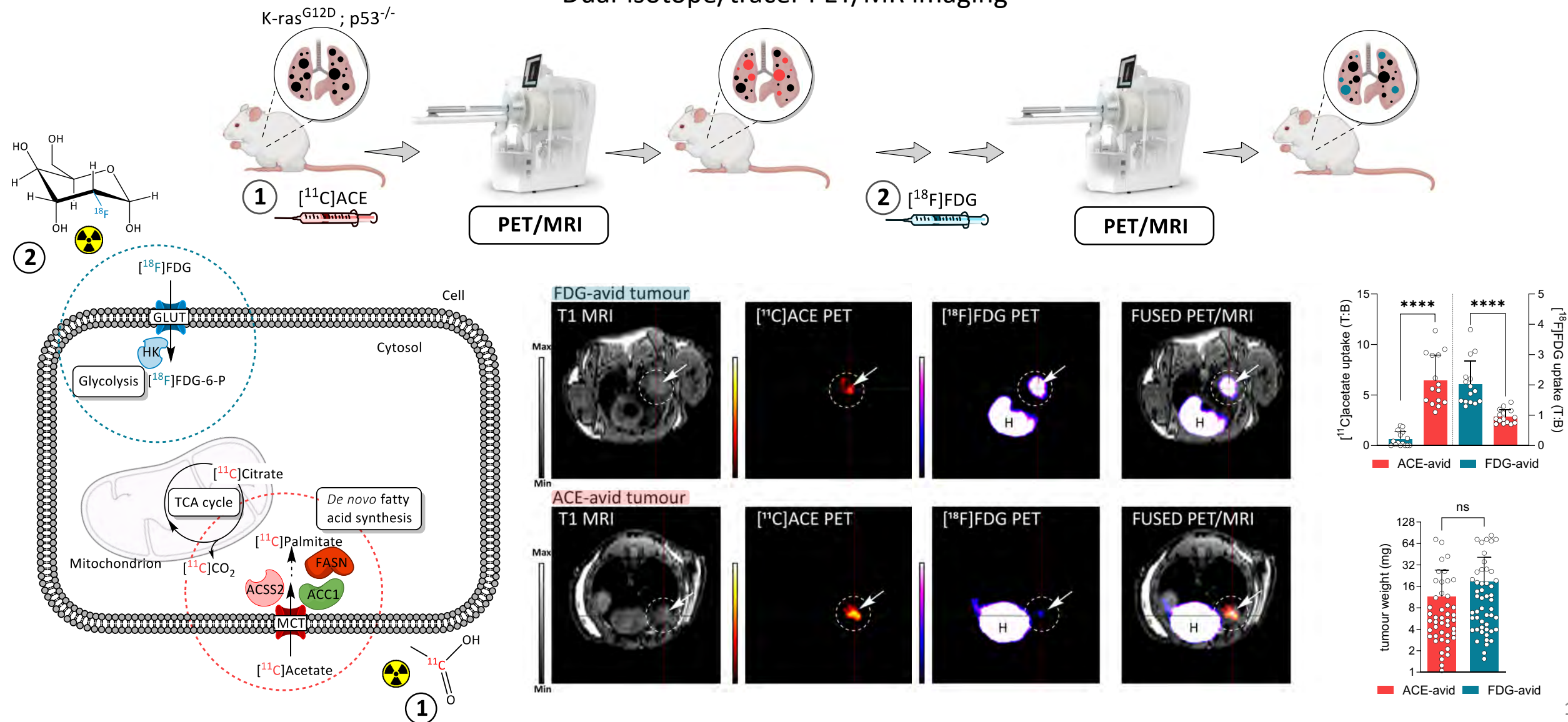
# Immunomodulatory role for acetate in triple negative breast cancer



Miller, K.D., O'Connor, S., Pniewski, K.A. *et al.* Acetate acts as a metabolic immunomodulator by bolstering T-cell effector function and potentiating antitumor immunity in breast cancer. *Nat Cancer* (2023).

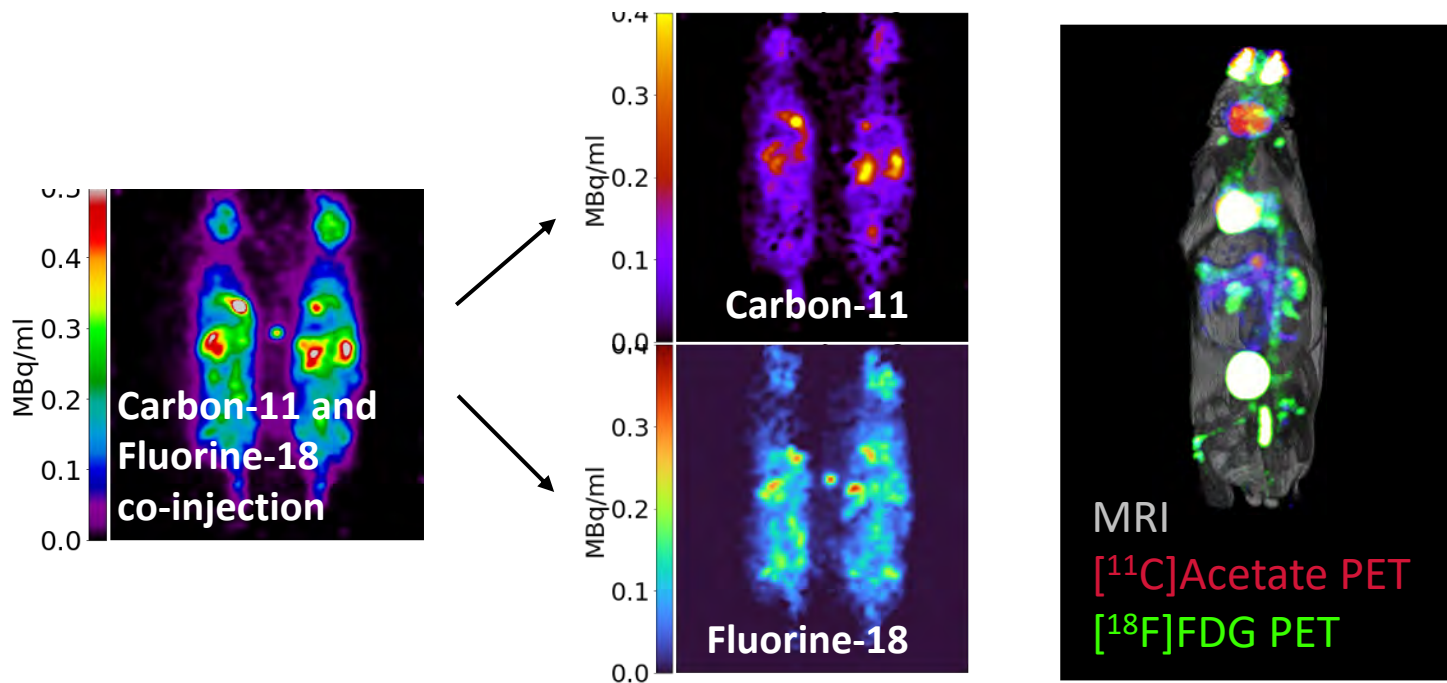
# Dual PET imaging reveals two heterogeneous metabolotypes in lung cancer

## Dual-isotope/tracer PET/MR imaging

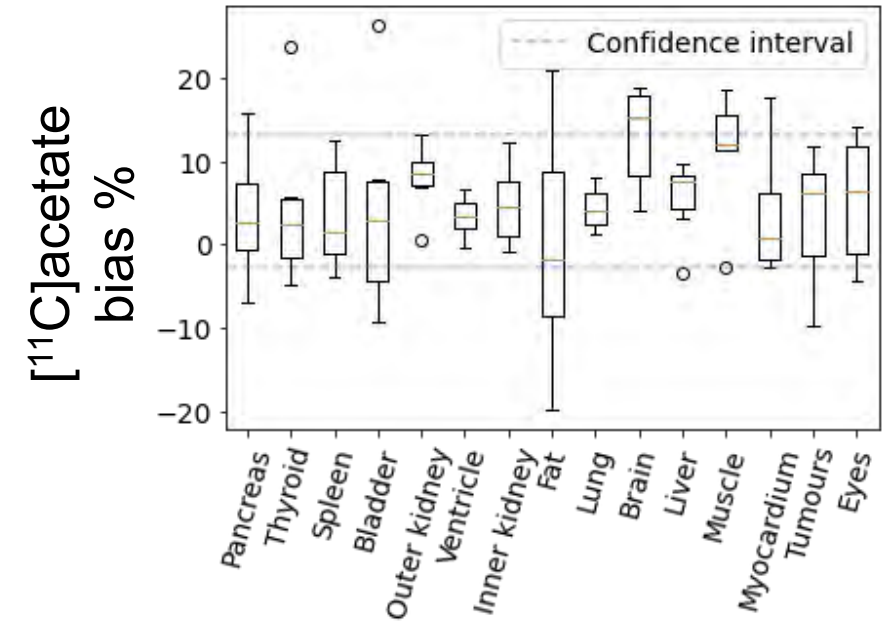


# Dual Isotope Simultaneous COinjection PET (DISCOPET)

## Tracer Multiplexing



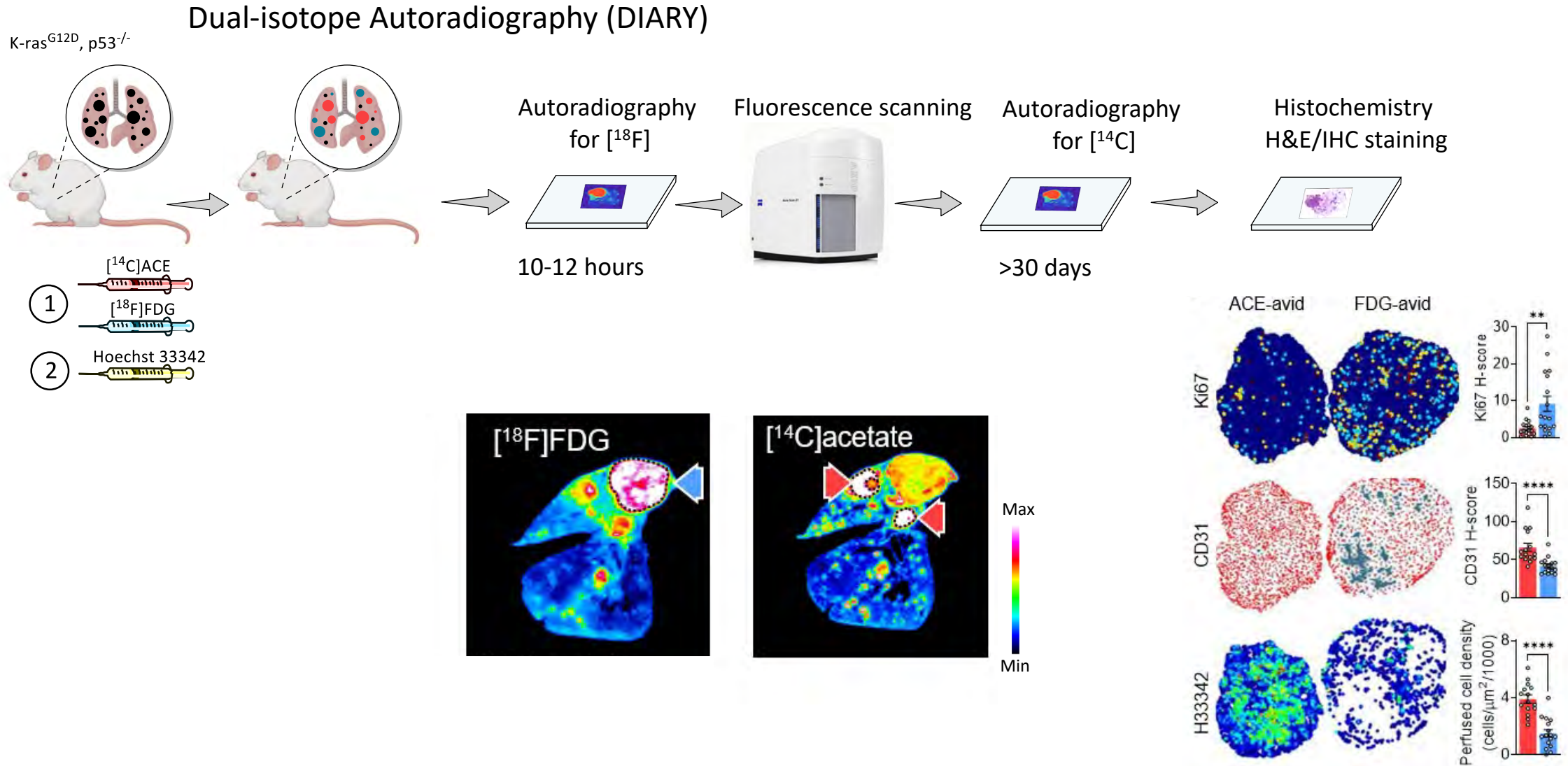
## Separation accuracy for different organs



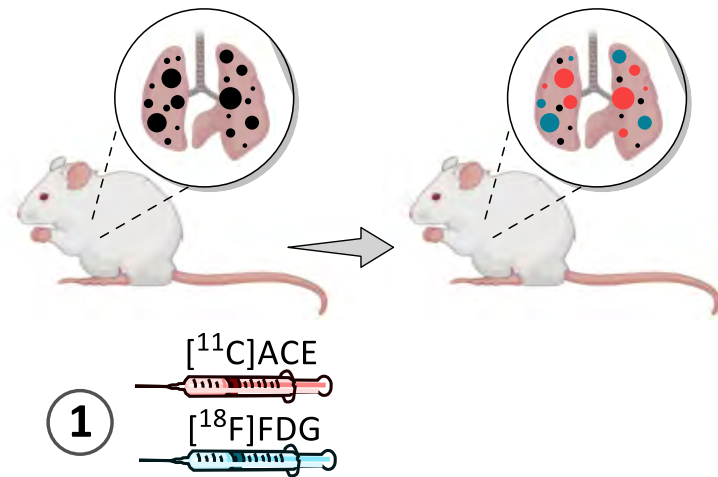
positive bias of 5.2 +/- 8.0%

More reliable in organs such as the thyroid, liver, and lungs, and is least reliable in fat.

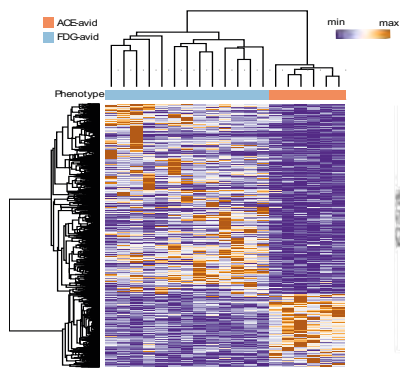
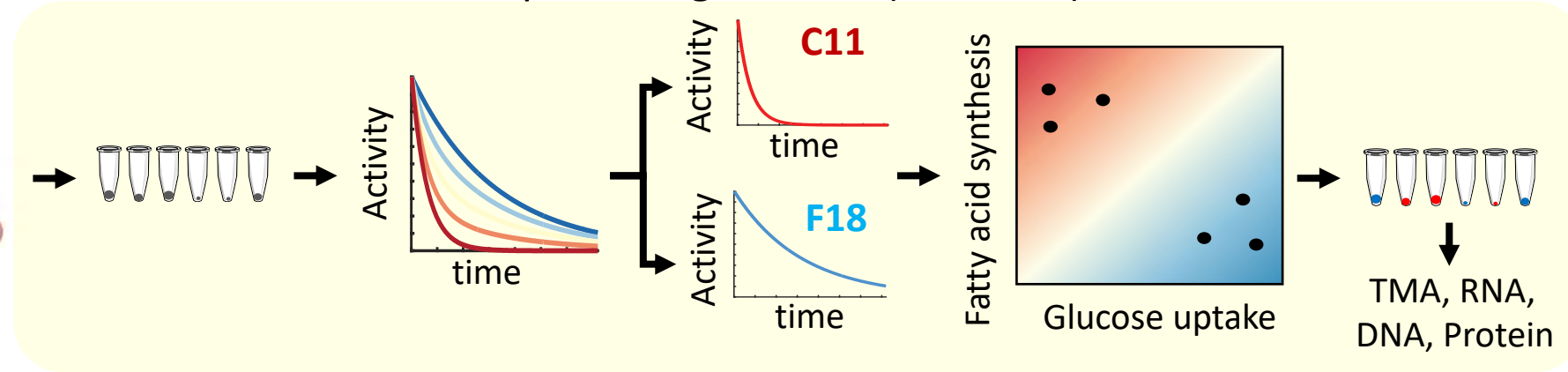
# Metabolotype is associated with tumour proliferation and perfusion



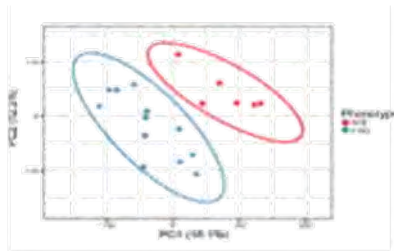
# FDG-avid tumours have high cell cycle activity, ACE-avid tumours have higher fatty acid and oxidative metabolism



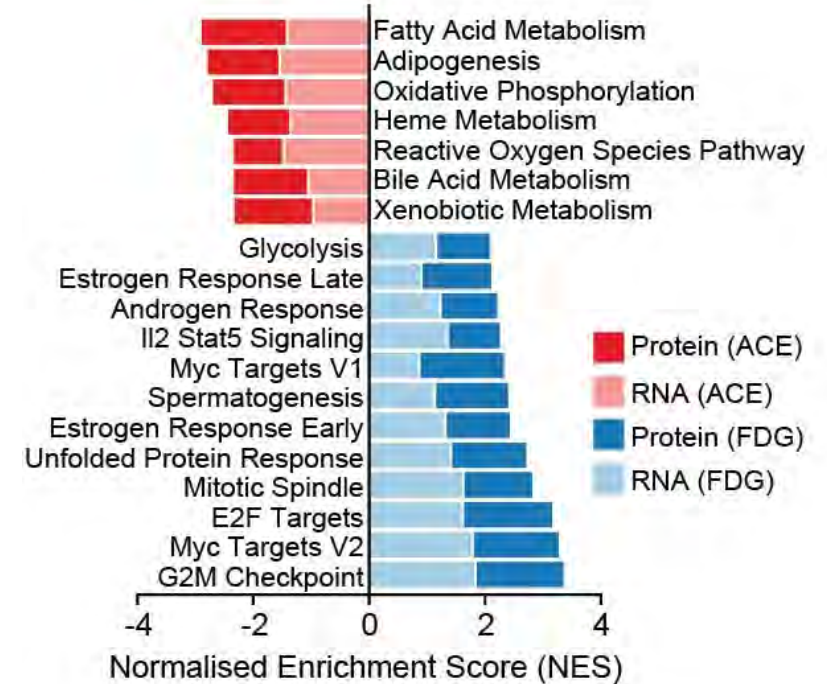
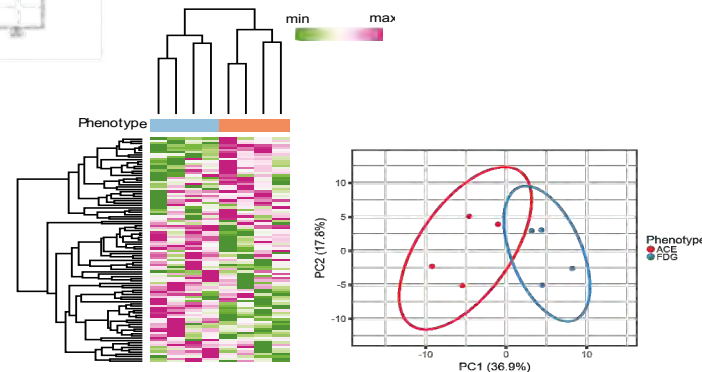
## Dual-isotope tracing method (DIOPTRA)



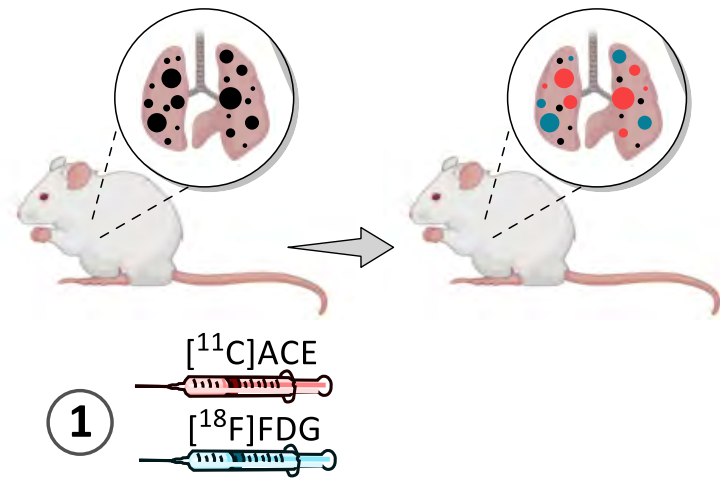
### Transcriptomics



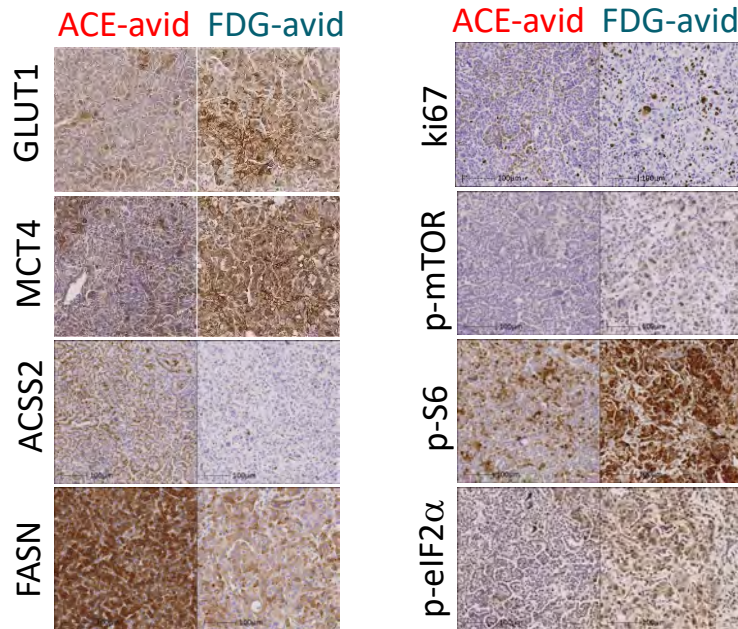
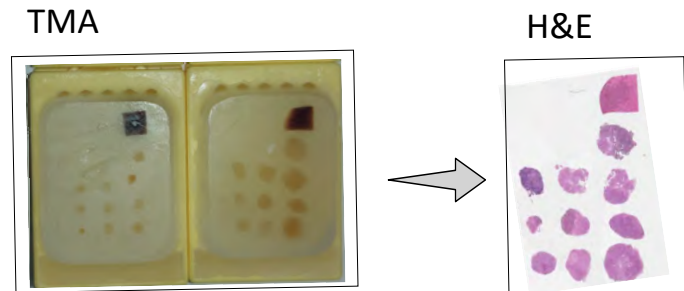
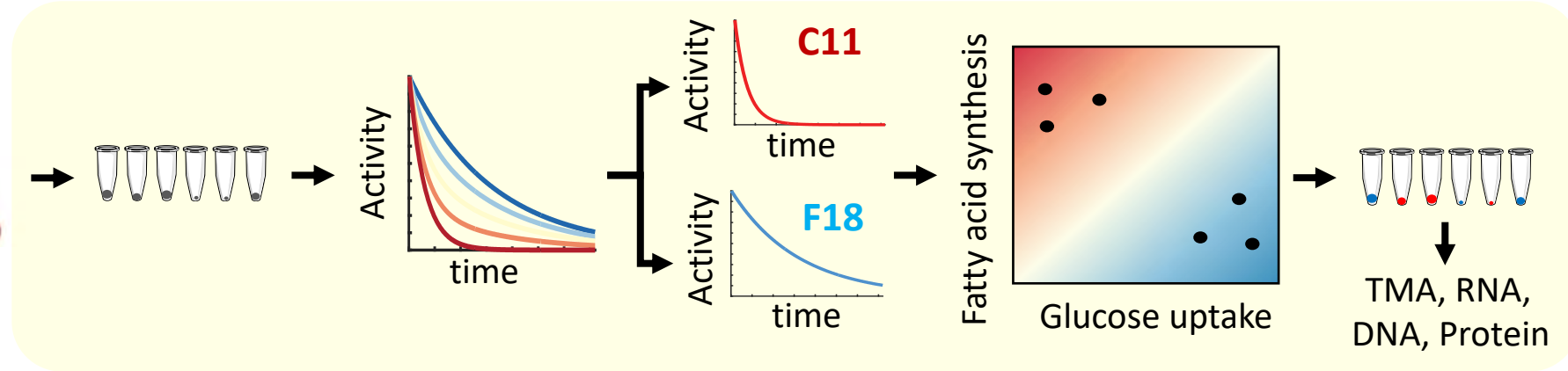
### Proteomics



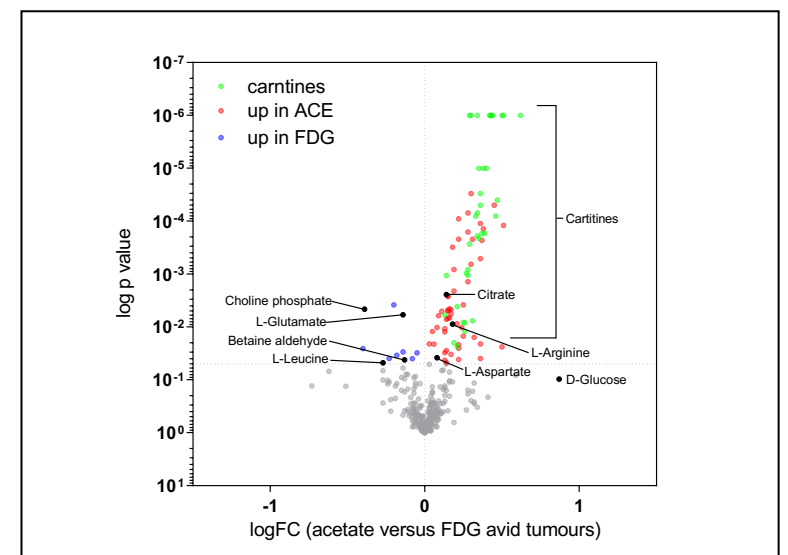
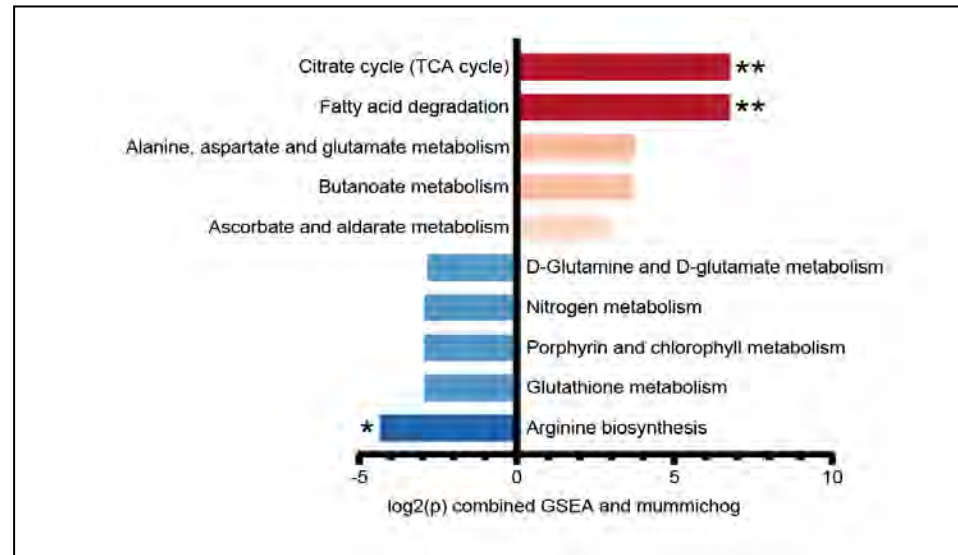
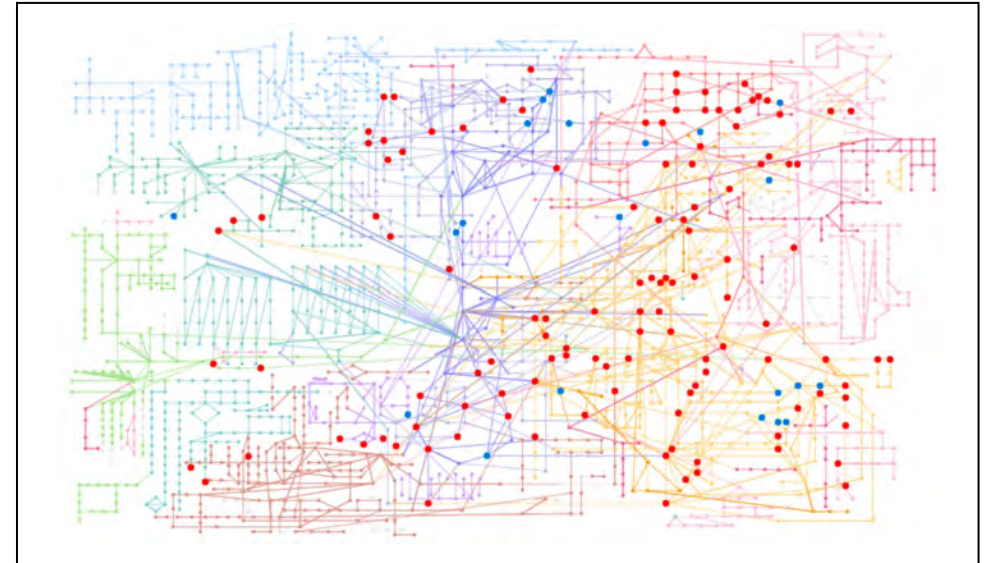
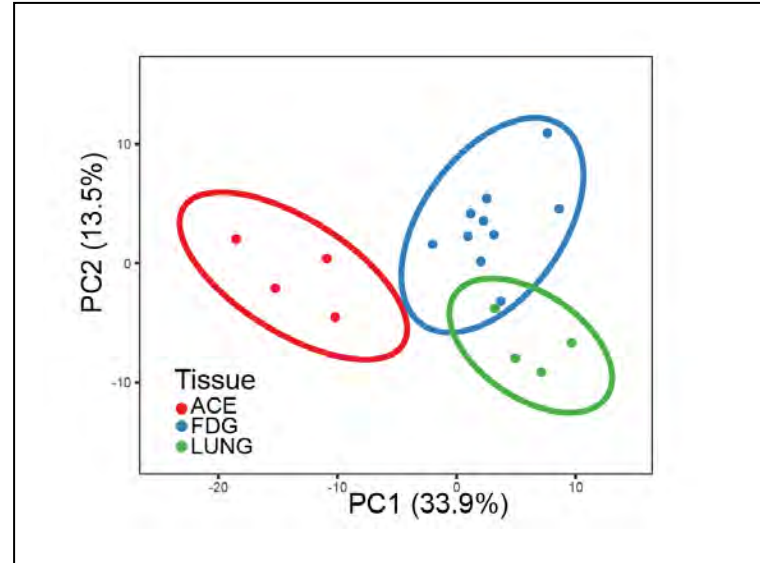
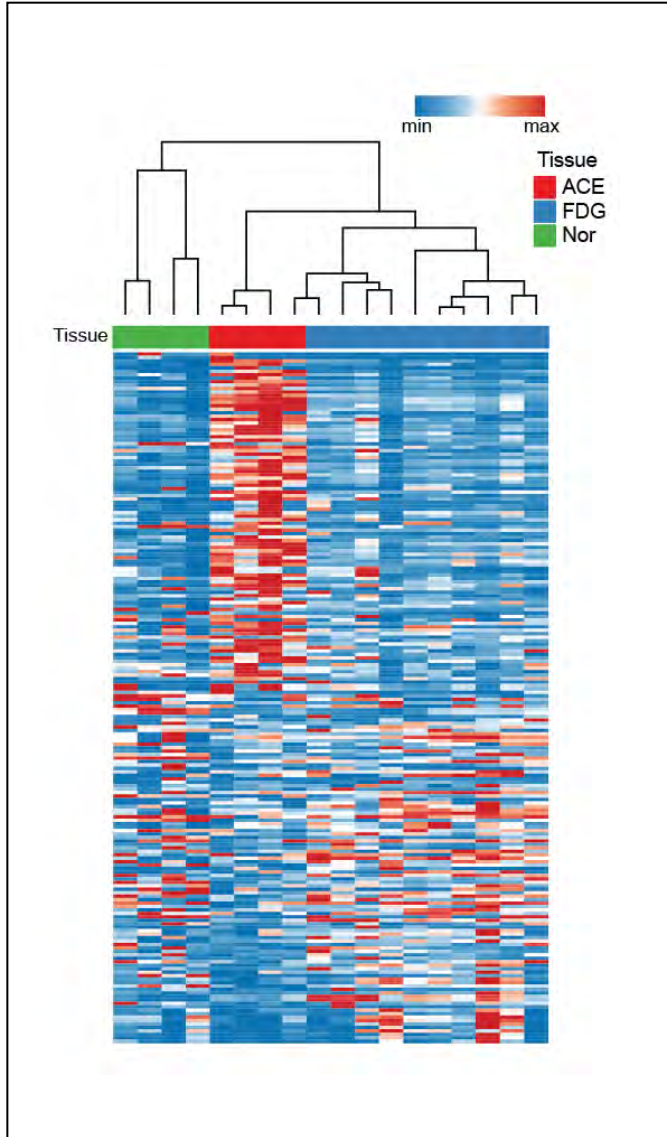
# FDG-avid tumours are glycolytic, more proliferative and associated with a higher integrated stress response



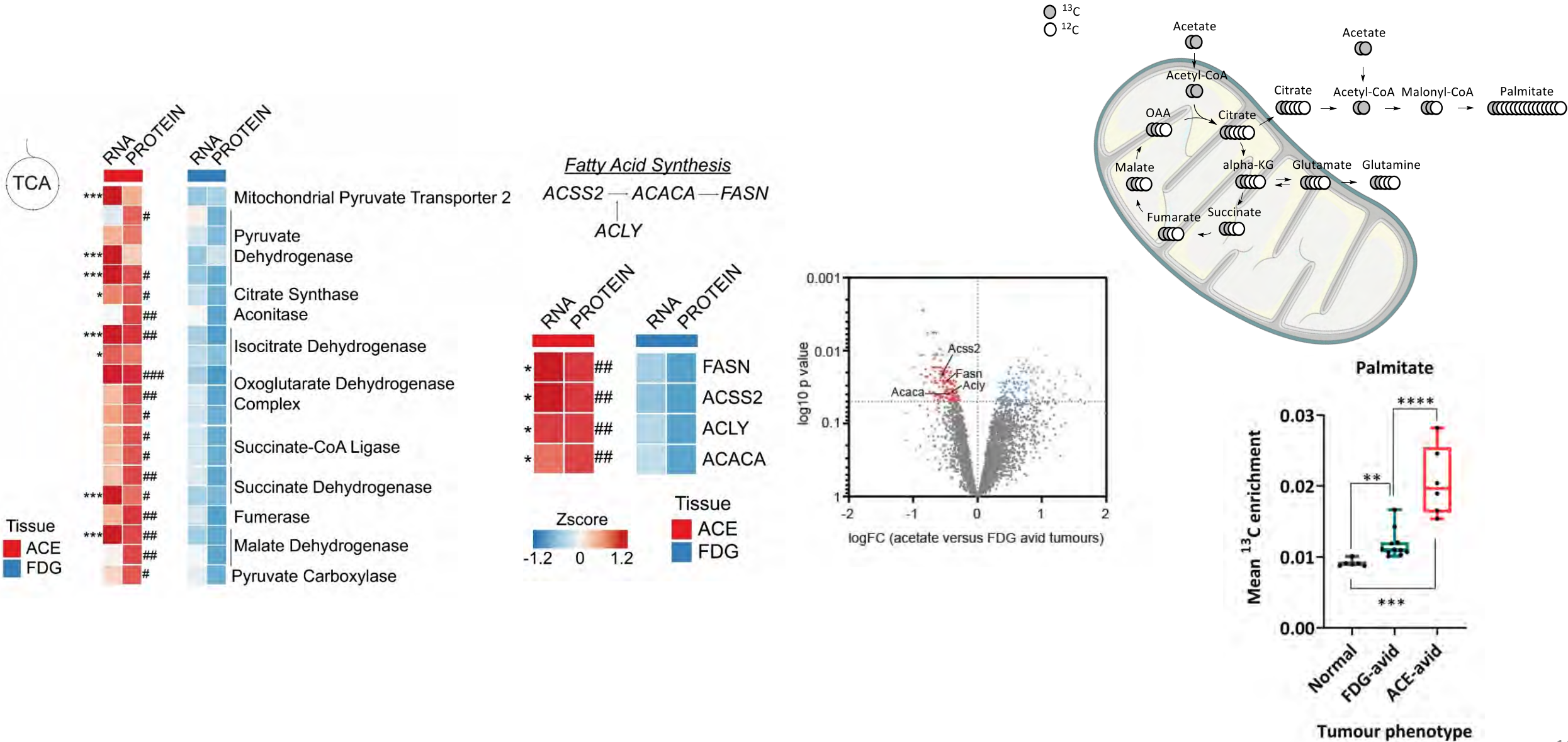
## Dual-isotope tracing method (DIOPTRA)



# [1-<sup>11</sup>C]acetate-avid tumours have widespread metabolic reprogramming including increased FAO

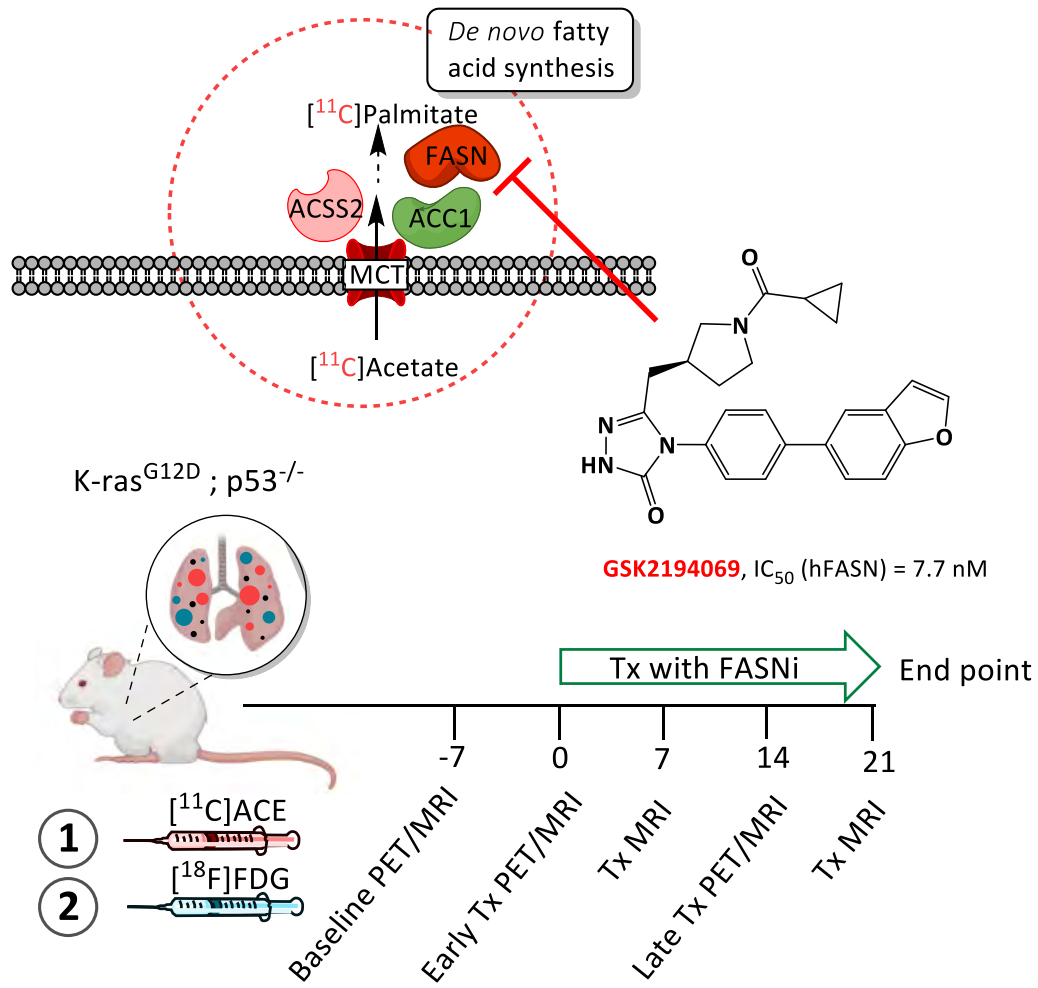


# ACE-avid tumours have increased TCA cycle and *de novo* fatty acid synthesis pathway is highly upregulated

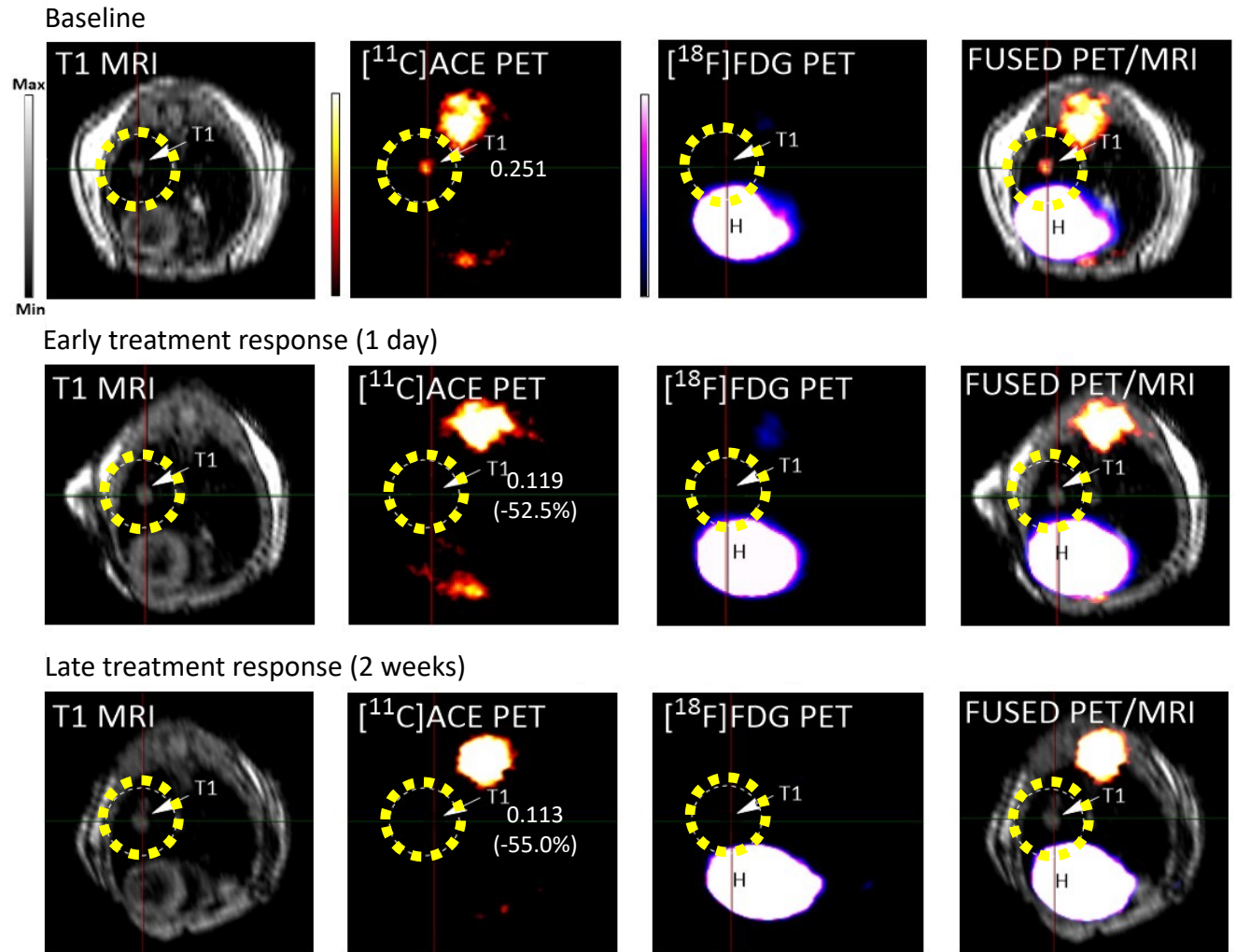




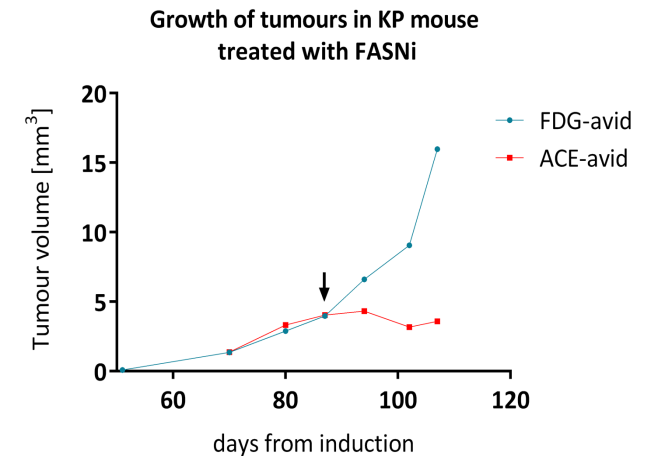
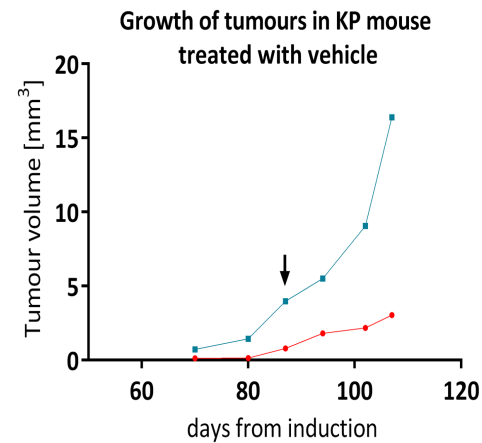
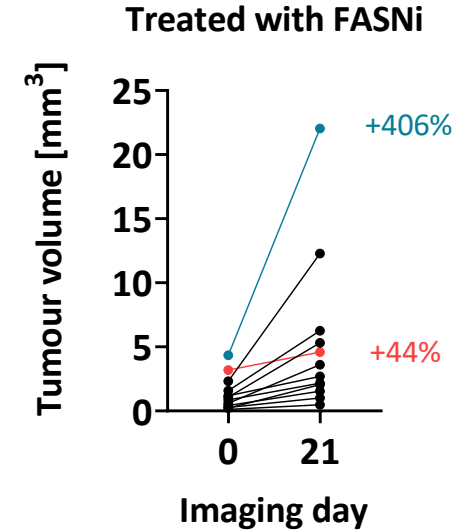
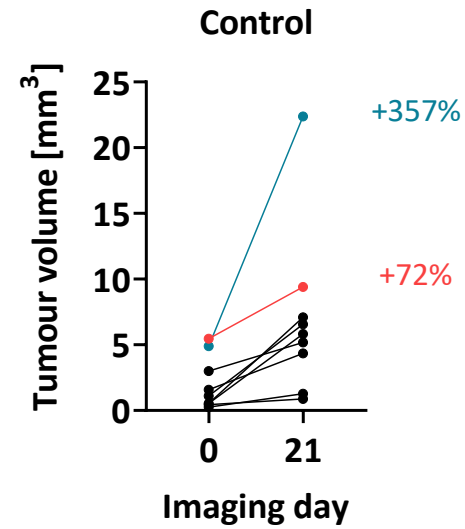
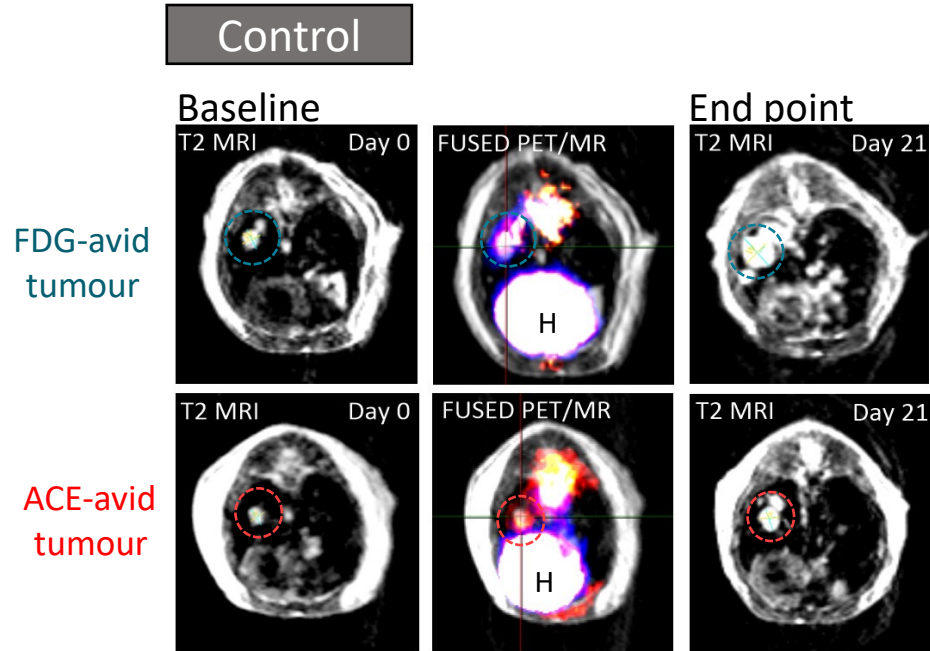
# FASN inhibitor suppressed the uptake of [<sup>11</sup>C]acetate and *de novo* fatty acid synthesis in ACE-avid tumours



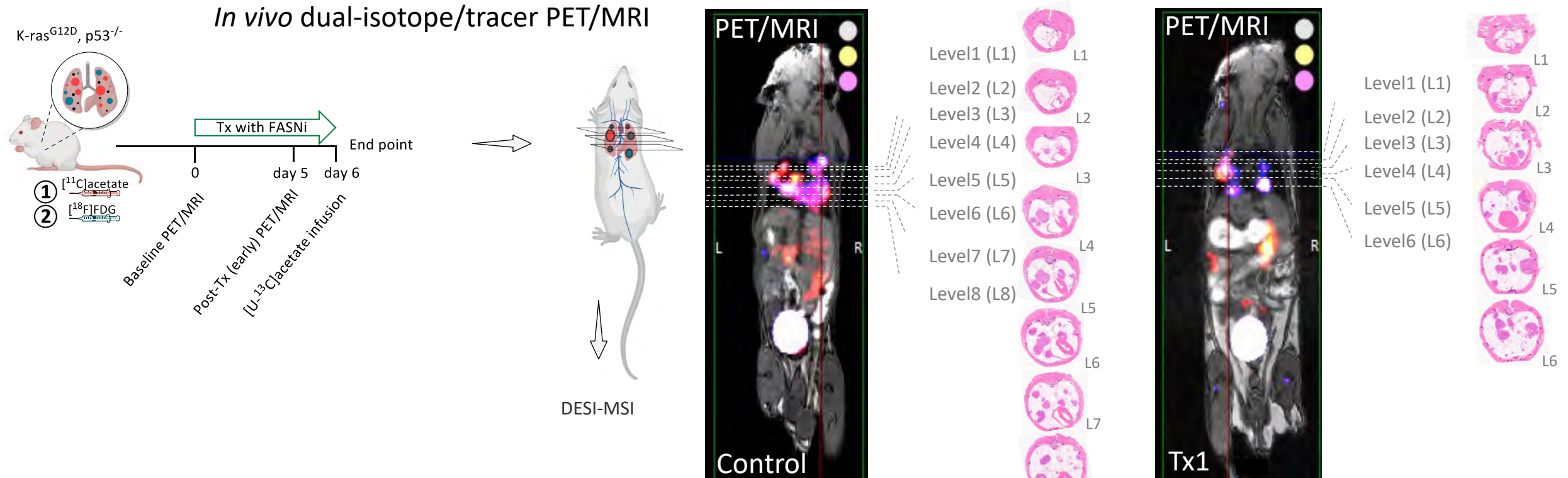
Drug dosage: 30mg/kg (10ml/kg) of GSK2194069 suspended in 5% DMSO, 2% Tween 80, and 0.5% HPMC as an oral gavage given once a day



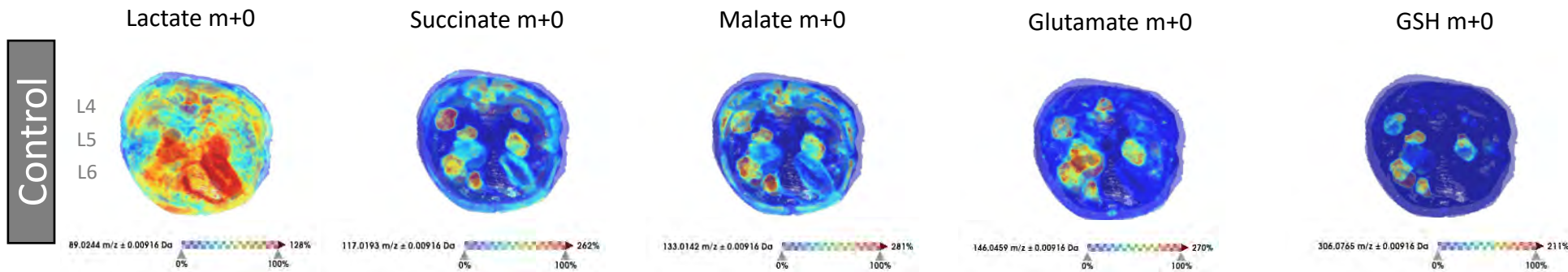
# FDG-avid tumours grow much faster than ACE-avid tumour and only ACE-avid tumours responded to FASNi treatment



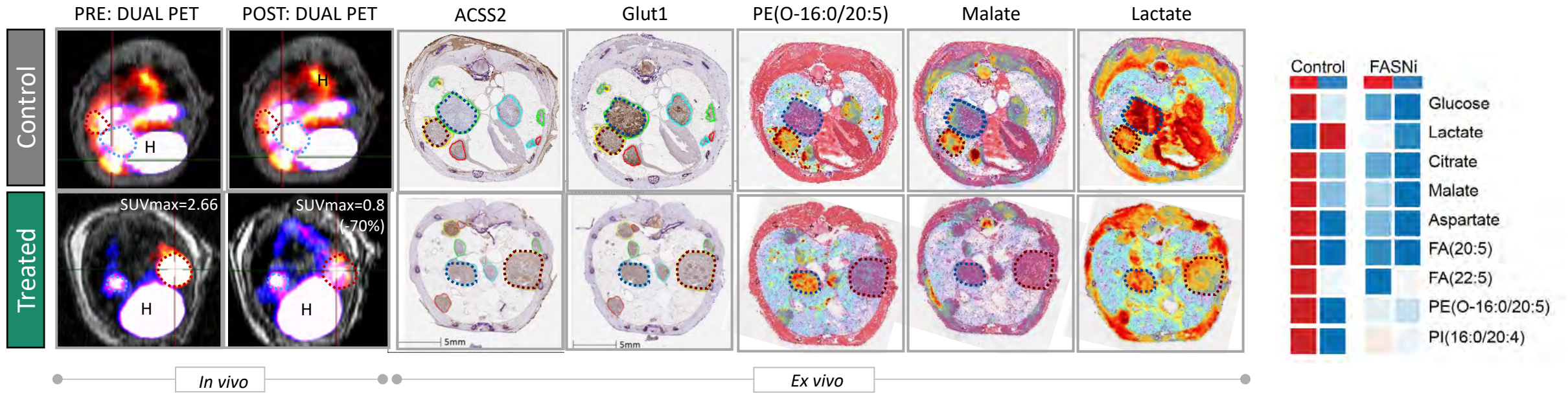
# Early tumour response monitoring showed specific metabolite changes using multimodal PET/MRI and DESI-MSI



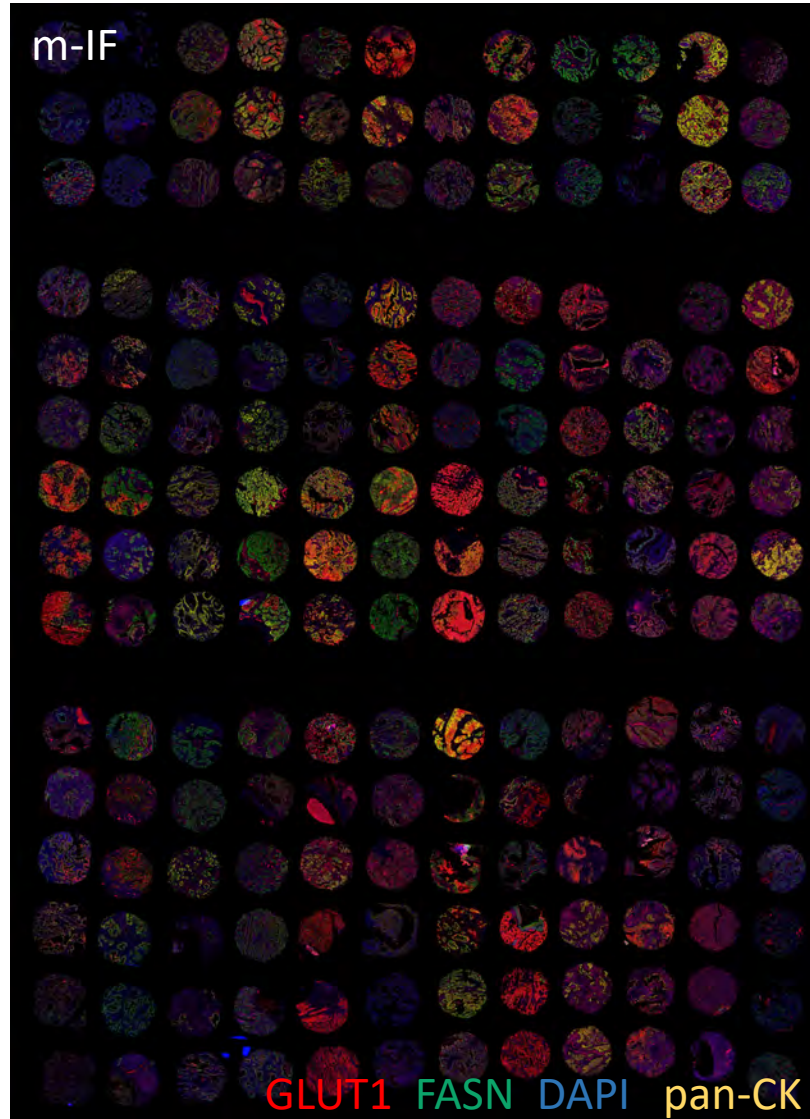
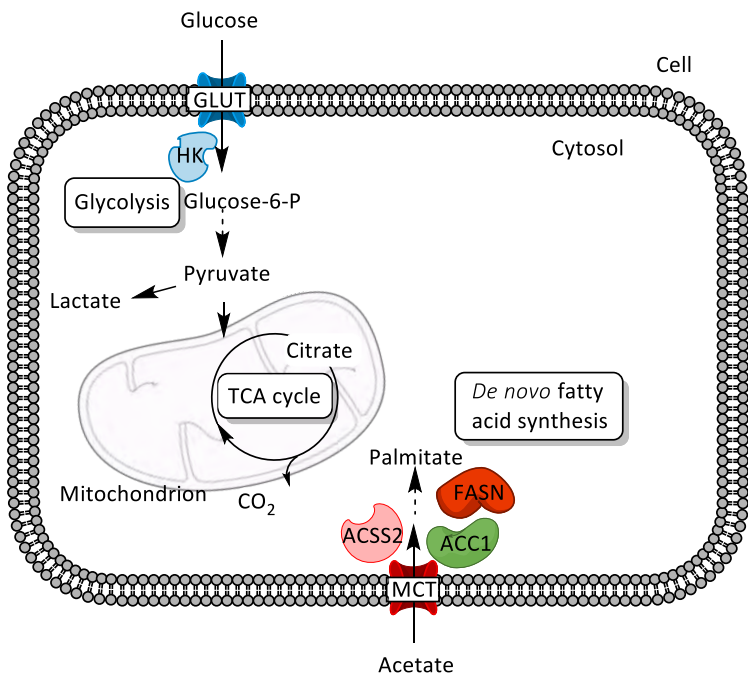
## Ex vivo whole-body DESI-MSI



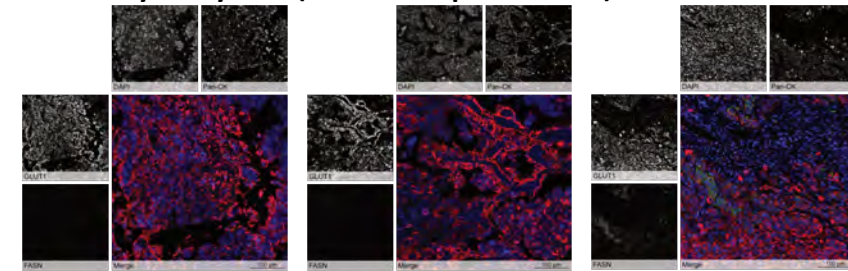
# Early tumour response monitoring showed specific metabolite changes using multimodal PET/MRI and DESI-MSI



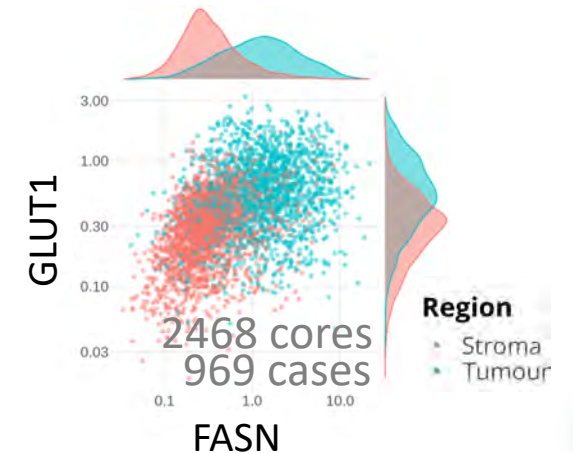
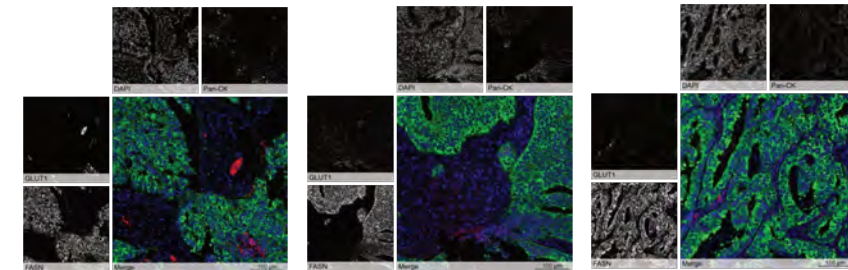
# We observed broad tumour heterogeneity in LUAD patients but need better tools to enable tailored therapy for specific tumour metabolotypes



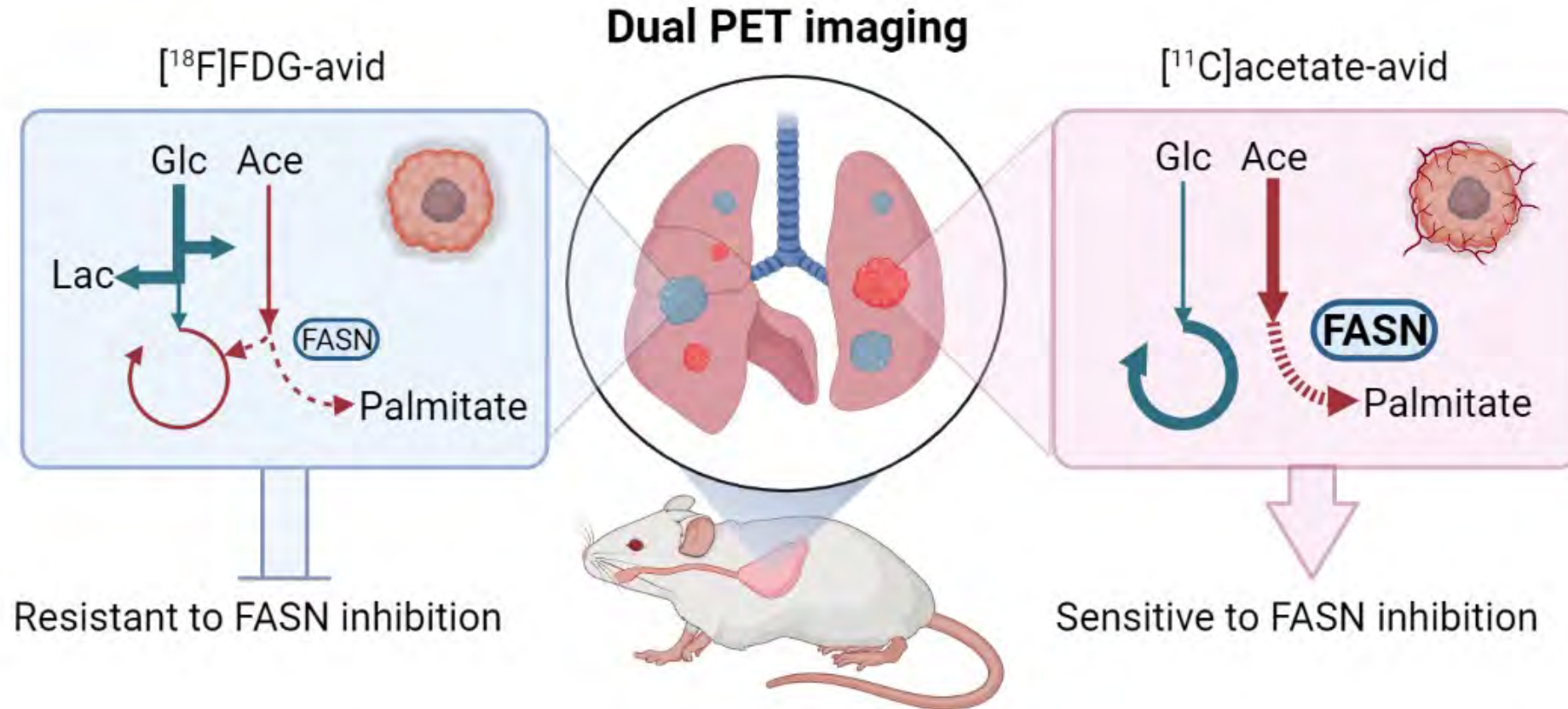
## Glycolytic (GLUT1-positive) tumours



## Lipogenic (FASN-positive) tumours

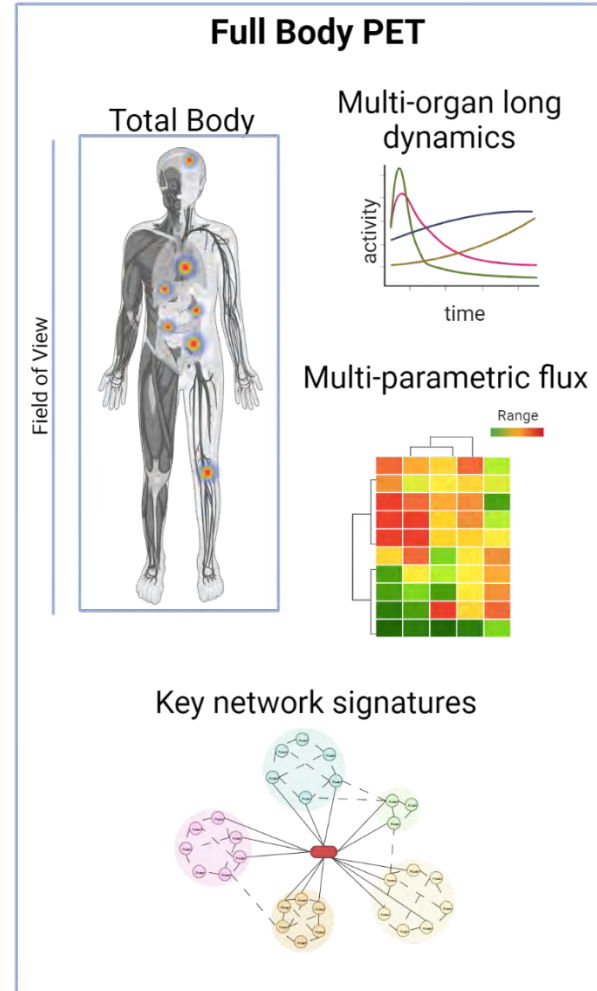
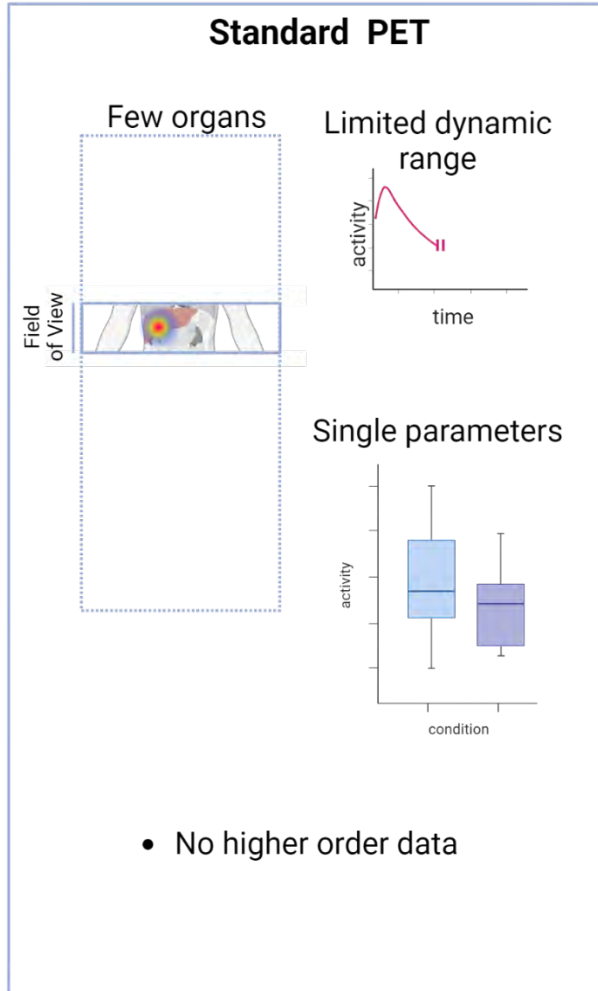


# Dual PET imaging can identify two metabolotypes in lung cancer with different vulnerabilities to treatment

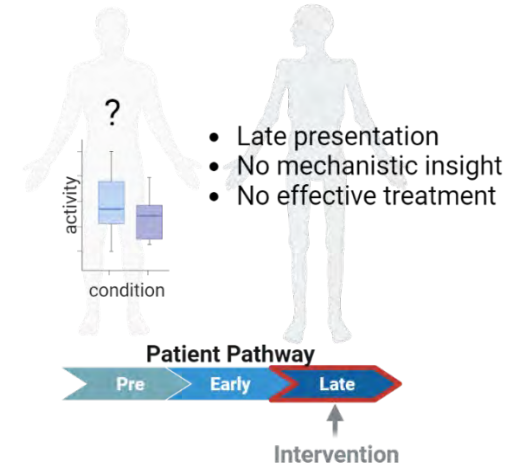


# Transformative Potential of Total-Body PET

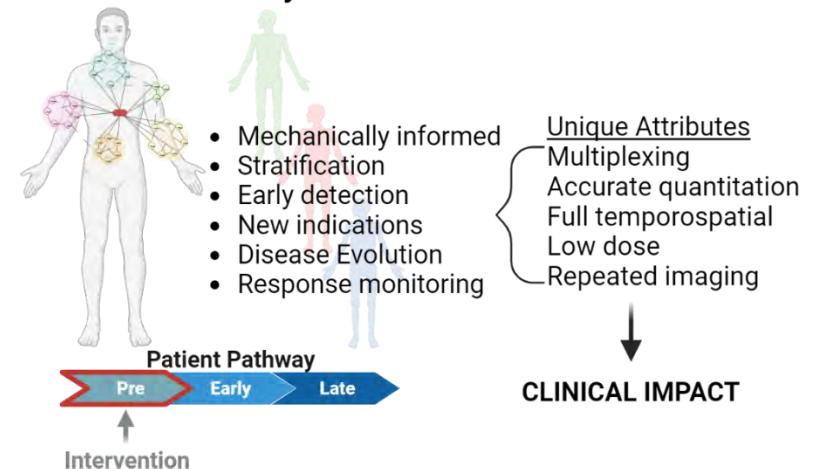
## Transforming the diagnostic pathway



### Standard PET

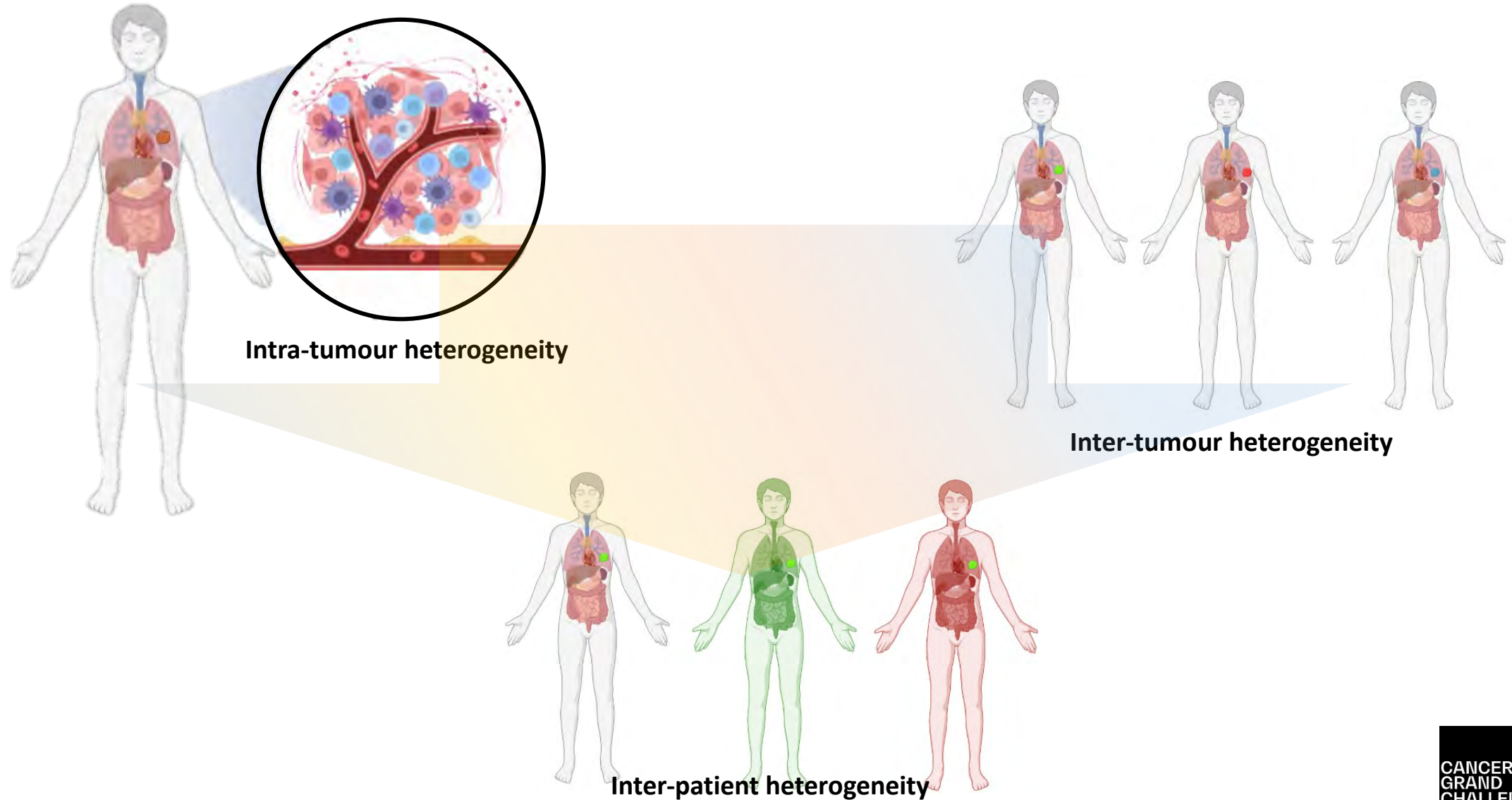


### Full Body PET



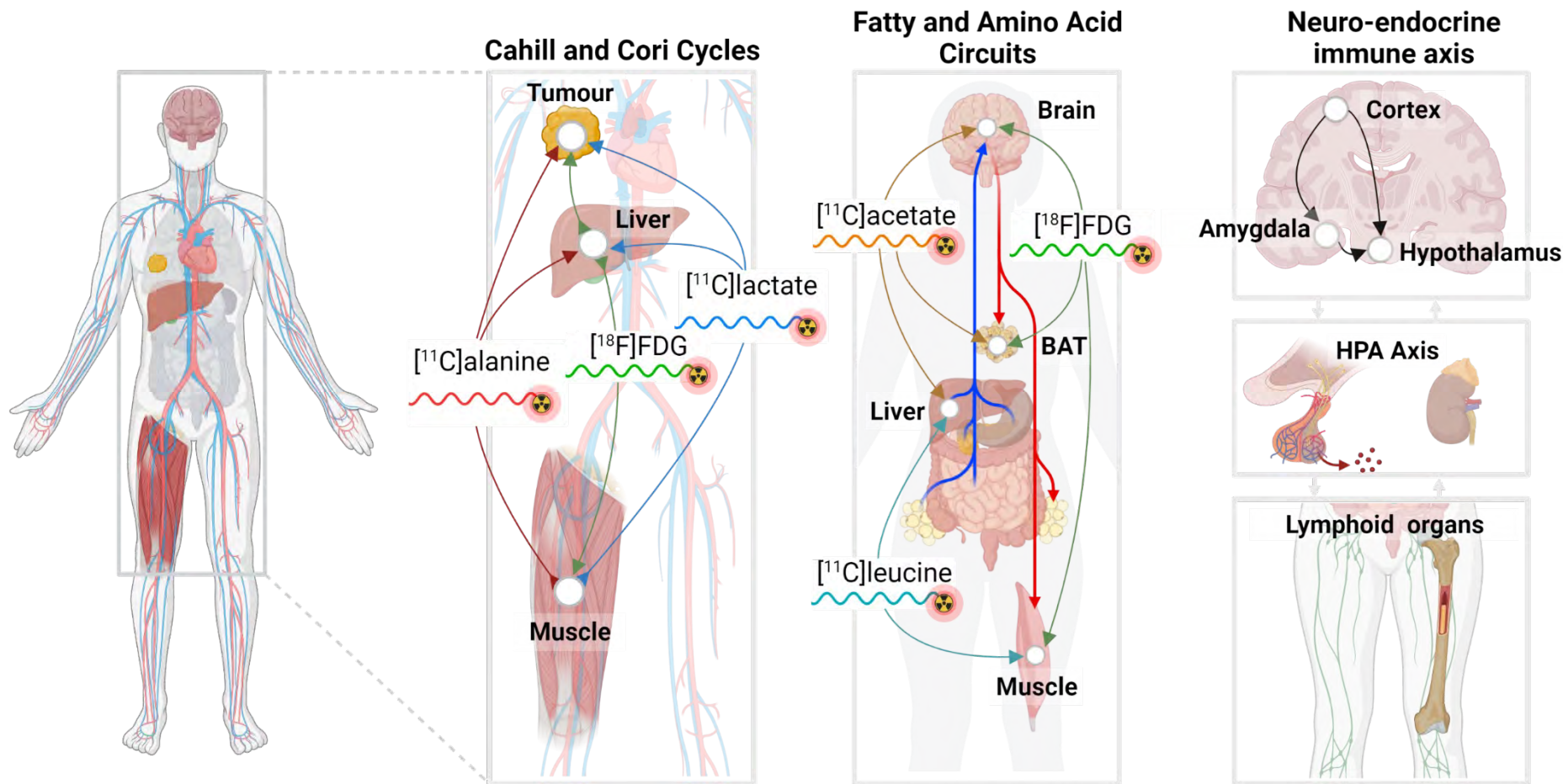
# “Staging the Host” with Total-Body PET Imaging

## Causes and Consequences of Tumour Metabolic Heterogeneity

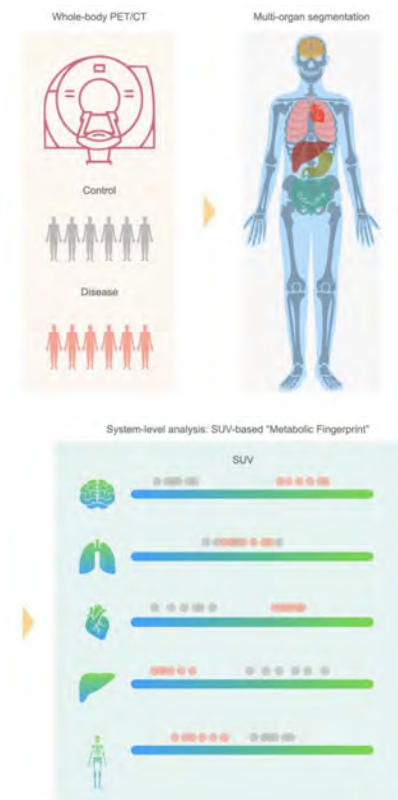




# Total-body PET imaging of inter-organ circuitry in cancer cachexia



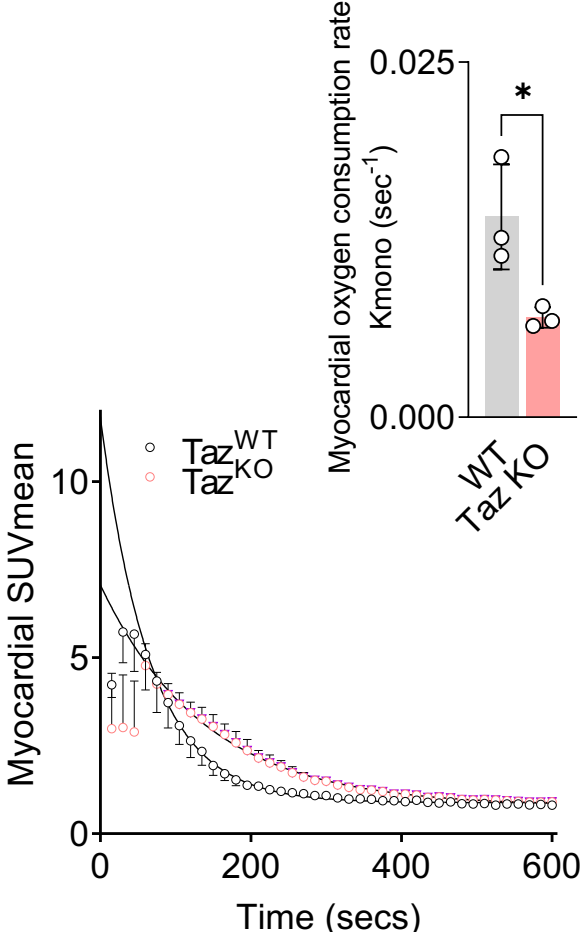
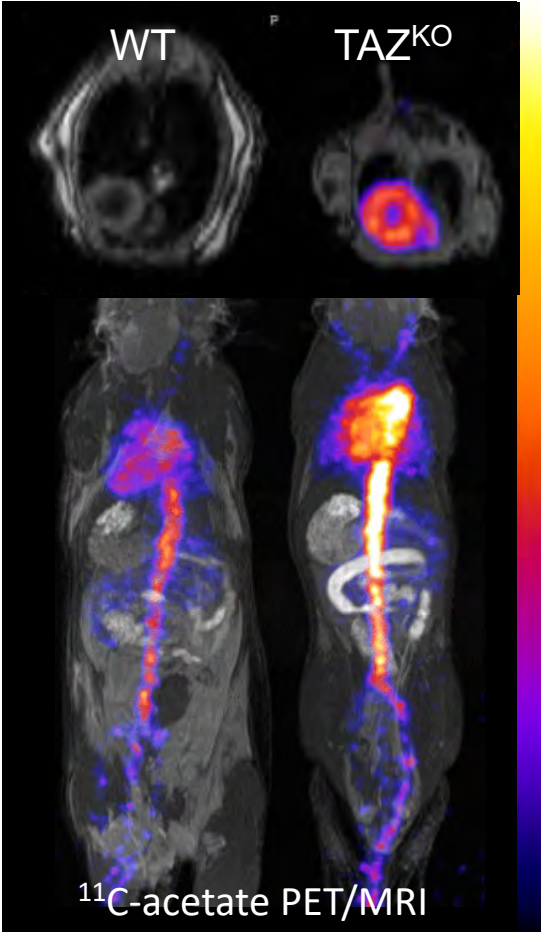
Using explainable AI to develop metabolic fingerprints of cachexia



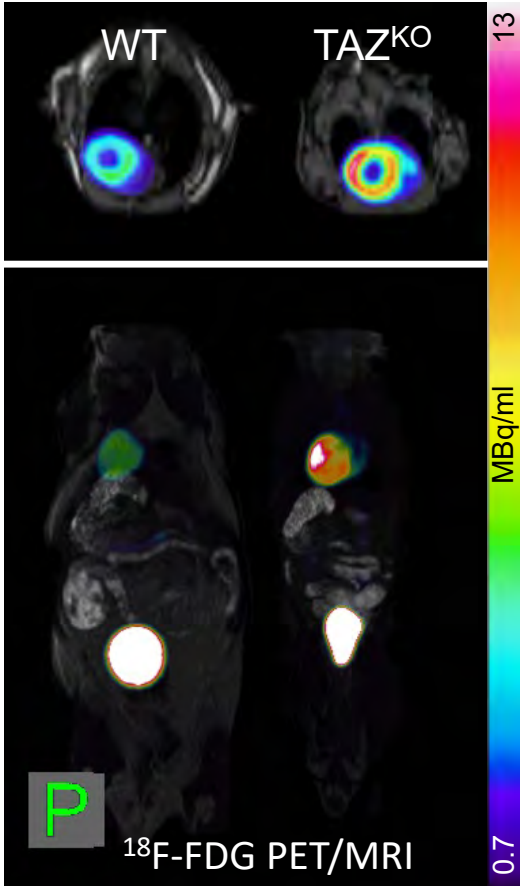
# Cardiac metabolic phenotyping of a mouse model of Barth syndrome



Myocardial oxidation



Myocardial glucose consumption



# Temporal, spatial, tissue-specific determinants of metabolic flux pre and post-cachexia

CANCER  
GRAND  
CHALLENGES



Team:  
CANCAN

## Beatson Genetically Engineered Mouse Models



**Lung Cancer**  
Kras<sup>G12D/+</sup> Trp53<sup>-/-</sup>



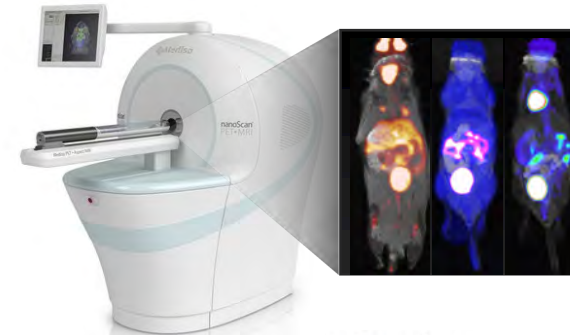
**Pancreatic Cancer**  
Kras<sup>G12D/+</sup> Trp53<sup>R172H/+</sup> Pdx1-Cre



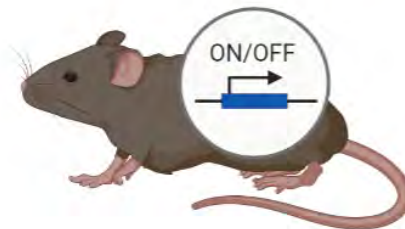
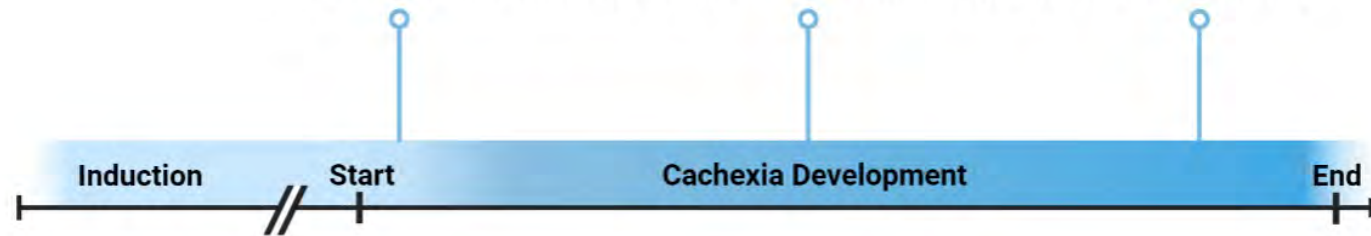
**Colon Cancer**  
Villin-Cre<sup>ERT2</sup> Kras<sup>G12D/+</sup>  
Trp53<sup>-/-</sup> Rosa26<sup>N1-ICD/+</sup>



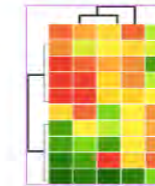
**Implantable**  
C26 Colon Cancer



MS-Metabolomics, (sc)RNAseq, Methylation, NanoString, Metabolic Imaging



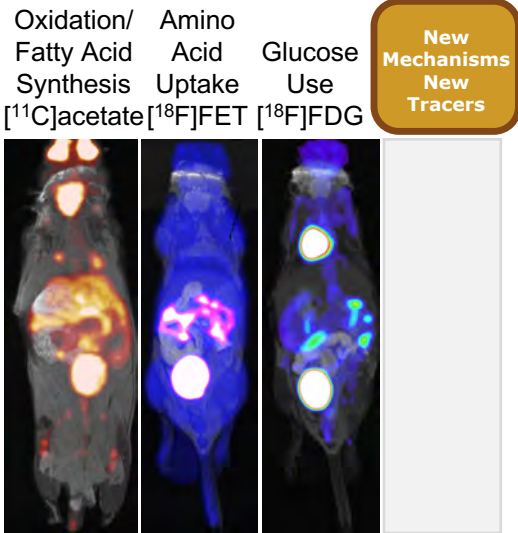
Flux Analysis  
Data Aggregation  
Statistical Review



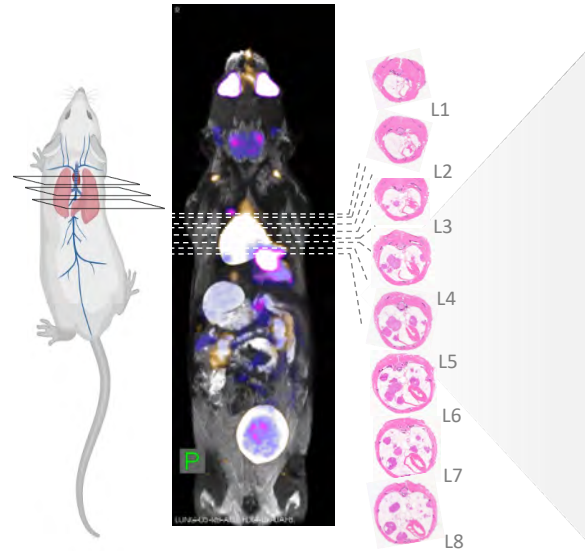
Hypothesis testing  
Independent Validation  
Functional Assessment

# Glasgow CANCAN: Taking a "Google-Earth" view of cancer cachexia

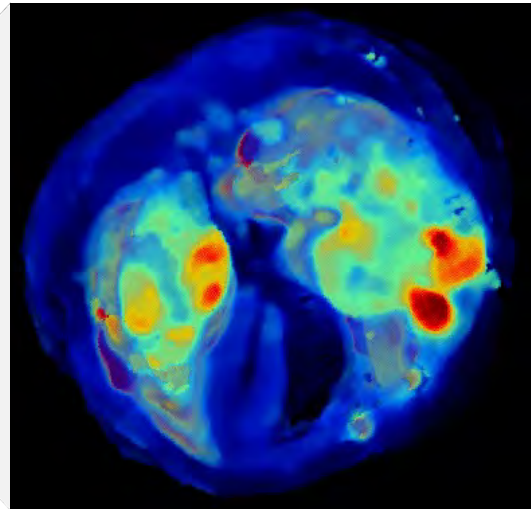
## Metabolic PET imaging of advanced models during cancer cachexia development



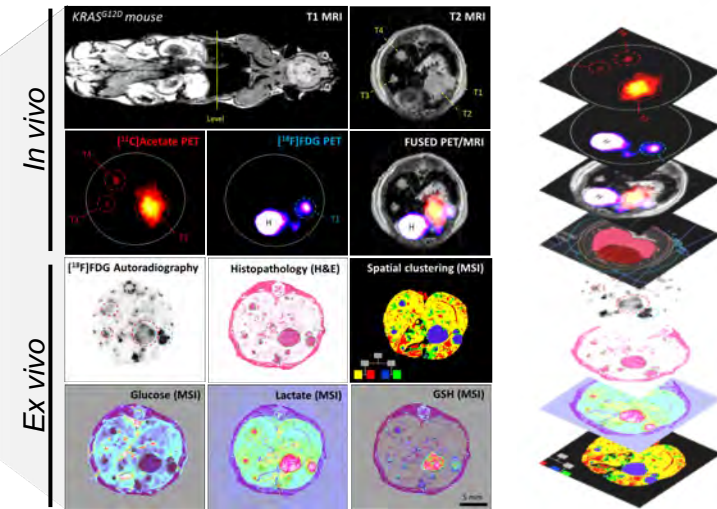
## Integrated molecular imaging of all organs during cancer cachexia development



## Total-body 4D mapping of novel cachexia metabolites in their natural environments



## Zoom from the whole-body to detailed metabolic imaging of different tissues



In collaboration with the Rosetta Grand Challenge...

# Acknowledgments

## CRUK Beatson Institute, Glasgow

### Molecular Imaging Lab

#### **Robert Bielik**

Algernon Bloom

Emma Brown

Gavin Brown

Emer Curley

Lisa Duff

Piotr Dzien

Fraser Edgar

Caroline Findlay

Emma Johnson

Gaurav Malviya

Agata Mrowinska

Irene Caldera Quevedo

**Dmitry Soloviev**

### Leukocyte Dynamics Lab

Leo Carlin

Ximena Raffo Iraolagoitia

Lynn McGarry

### Transgenic Models of Cancer

Karen Blyth

### Transgenic Facility

#### **Douglas Strathdee**

David Stevenson

### Liver Cancer, Disease and

#### Regeneration

Tom Bird

Stephanie May

Miryam Müller

### Histopathology

Colon Nixon

## CRUK Cambridge Institute

Chrysa Kapeni

Maike De La Roche

## King's College London

Gilbert Fruhwirth

## Cold Spring Harbor

Scott Lyons



## Funders...

