PET IMAGING
PRACTICAL CONSIDERATIONS

2010 AAPM

Philadelphia, PA

Why PET

- Imaging non-pharmacological tracer doses of radiopharmaceuticals
- Quantitative

- FDG PET: high sensitivity
- Visualization of tumor extent
- Imaging microenvirionment

How sensitive is PET?

The typical activities of ^{18}FDG observed in tumor diagnosis by PET are **0.5 picomole**

The normal / safe level for glucose in the blood is between 3.5 and 7.8 mmol/L

tracer principle in action

Tracers

Is there such a thing as:

- MRI tracer?
- Ultrasound tracer?
- Optical imaging tracer?

Technical issues

Image reconstruction: OSEM vs FBP

- FBP generally results in poor visual image quality, exhibiting high noise, disturbing streak artifacts and low contrast
- FBP is linear, robust, and yields reliable quantitative results

- OSEM results in a more eye-pleasing image
- The positivity constraint in MLEM-based algorithms leads to overestimations of the activity in regions with low activity concentration

Reilhac *et al*. *Simulation-based evaluation of OSEM iterative reconstruction methods in dynamic brain PET studies.* Neuroimage. 2008 Jan 1;39(1):359-68.

Image reconstruction: OSEM vs FBP

- Studying effect of a therapy on a tracer uptake by comparing ROI uptake before and after the treatment

- FBP reconstruction should always be considered

Local tracer uptake

- What can we say about the relationship between tracer uptake as seen on the PET images and the biological state of tissue?
- Can we use directly the in-vitro data for tracer uptake?
- Can we use published K-curve for F-Miso to relate Fmiso SUV to pO2?

No

Local tracer uptake

- Why not?
  - Image resolution
  - Drug delivery issues are going to affect tracer uptake
  - Other microenvironmental factors
- Therapy can affect vasculature => tracer delivery => tracer uptake

What is SUV_{max} ?

- Frequently uptake of a tracer in a lesion is characterized by SUV_{Max}

$$SUV_{max} = \frac{\text{(Max voxel activity (decay corrected) / Volume of voxel)}}{(Activity_{Injected} / Mass_{Body})}$$

- Maximum activity concentration as detected by PET depends on many irrelevant factors:
- voxel size
- patient motion
- device (PET scanner) characteristics
- image reconstruction technique
- number of iterations (for iterative algorithms)
- etc.

- SUV_{Max} is not a real physical quantity

VCU MASSEY CANCER CENTER
Virginia Commonwealth University

Partial Volume Correction

- Allows for recovery of true SUV in an object of a known size even when the object is smaller than the resolution of the PET scanner
- Perfectly suitable for spheres (uniform activity) in a phantom (uniform activity)

- Not applicable to clinical PET tracer distributions characterized by inhomogeneous tracer uptake and undefined shape and volume

PET image deconvolution

- Allows one to “sharpen” the image beyond the physical resolution of the scanner
- Can allow for better detection of small lesions or produce lesion-like artifacts
- The data that is not in the image cannot be recovered unless there is additional information available on the shape, activity distribution etc

An algorithm for automated delineation of functional PET volumes

- Multiple automated segmentation/clustering algorithms have been proposed
- Can be tuned to provide correct delineation of spheres in phantoms (uniform activity concentrations)

- No reference to the tracer
- No reference to the nature of the functional volume

An algorithm for automated delineation of functional PET volumes

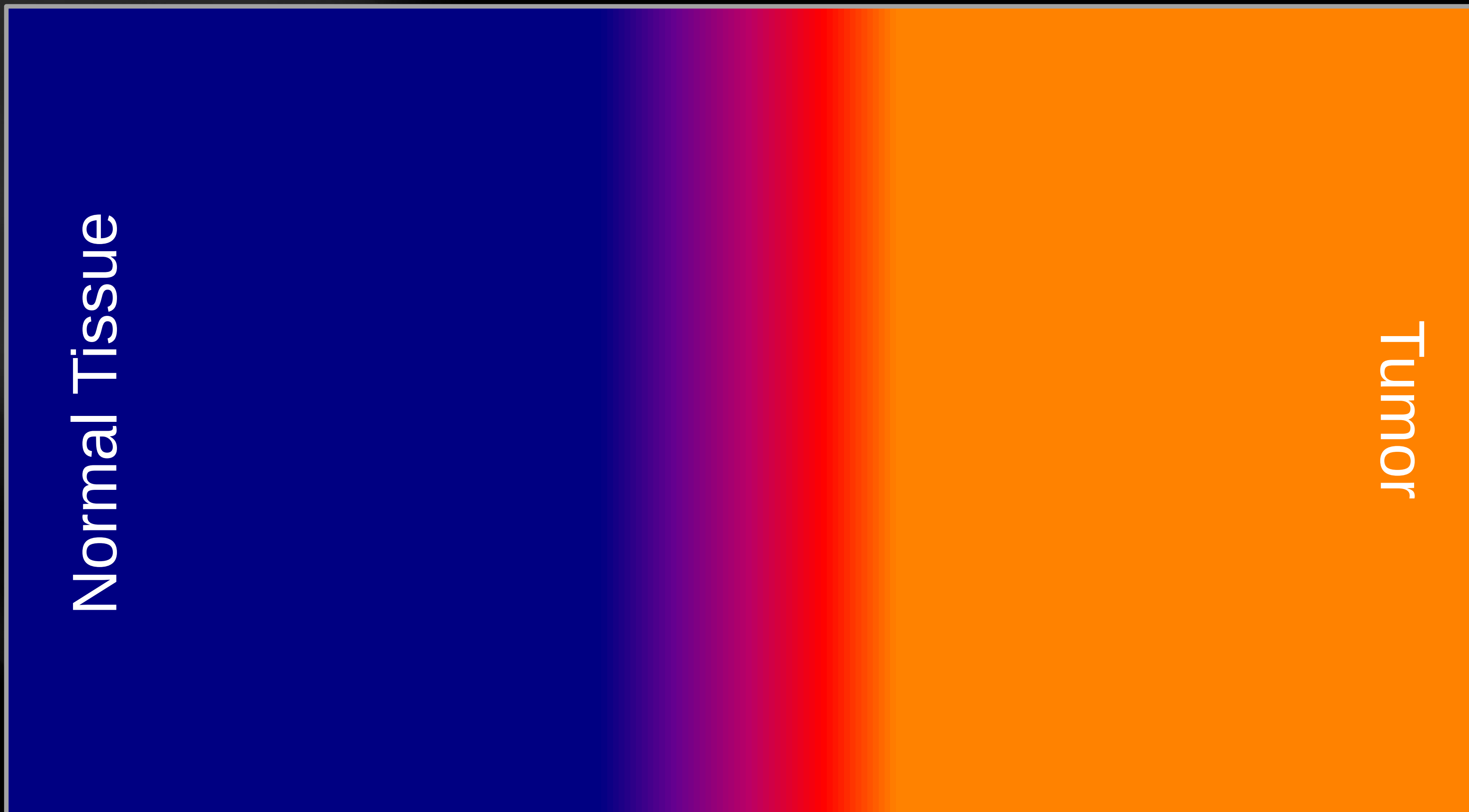
- What is "functional volume"?
- Can the same algorithm be used for delineation of hypoxic regions based on FMiso, FAZA, Cu-ATSM?

- Philosophical: can you obtain biologically-relevant knowledge without providing any biological input?

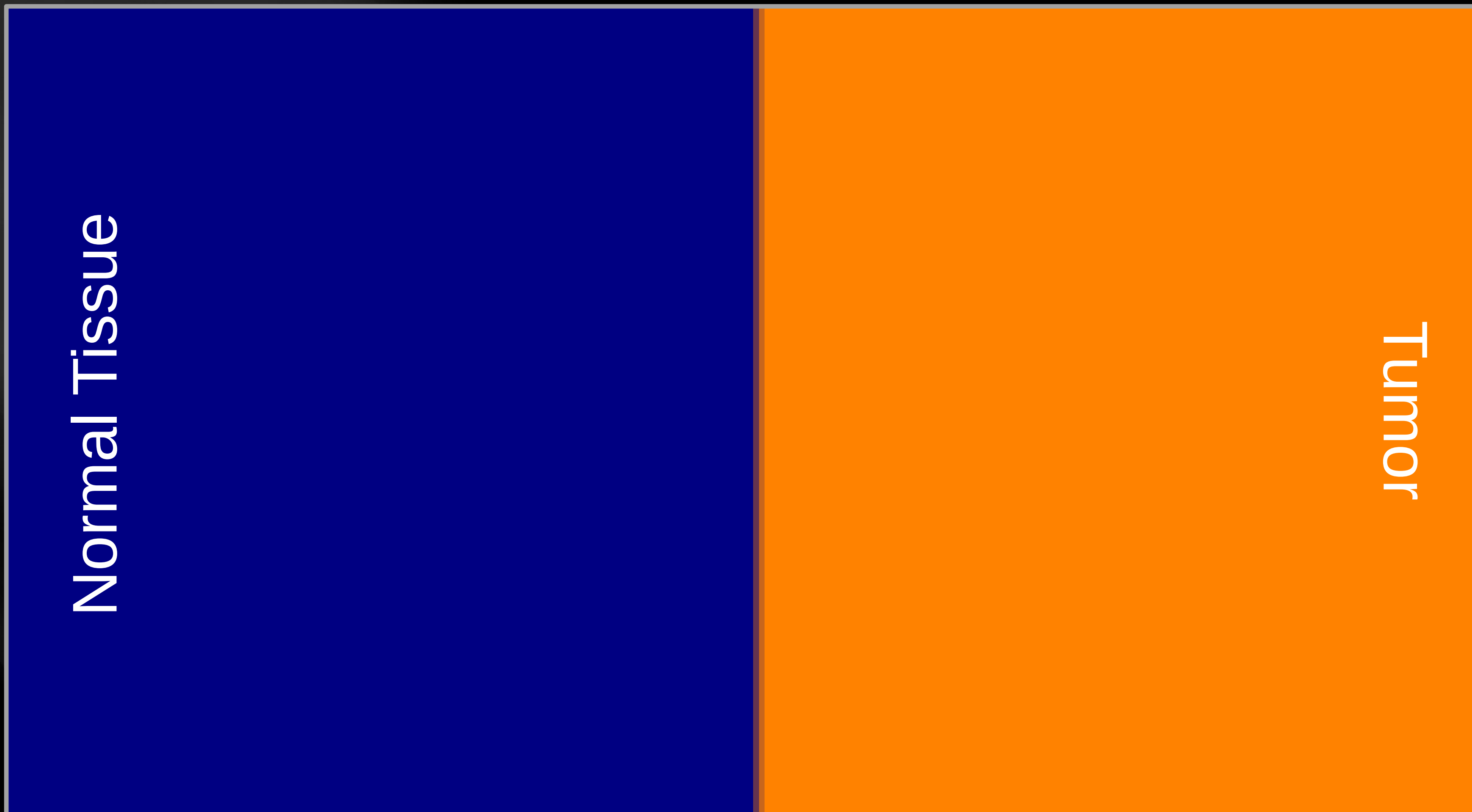
PET segmentation reproducibility

VCU MASSEY CANCER CENTER
Virginia Commonwealth University

PET segmentation reproducibility



PET segmentation reproducibility



Why PET segmentation

- PET image provides quantitative information on the distribution of the tracer
- Resolution 5mm ~ effective resolution of IMRT treatment
- Why do we need to convert PET image into binary (segmented) format?

PET tracer validation

Interpatient vs Intratumoral tracer uptake variation

Interpatient variation

- Example: Acquiring biopsies from multiple patients and studying correlation between Ki-67 positivity and FLT PET $SUV_{average}$ or SUV_{peak}
- Useful for evaluating predictive power of FLT PET with respect to average Ki-67 positivity of a lesion

Interpatient vs Intratumoral tracer uptake variation

Intratumoral variation

- Example: Acquiring multiple biopsies from every patient and studying correlation between Ki-67 positivity and FLT uptake in a biopsy sample for each patient individually
- Imaging FLT uptake in a tumor sample with autoradiography and comparing it to the spatial pattern of Ki-67 staining in the same/adjacet tissue section

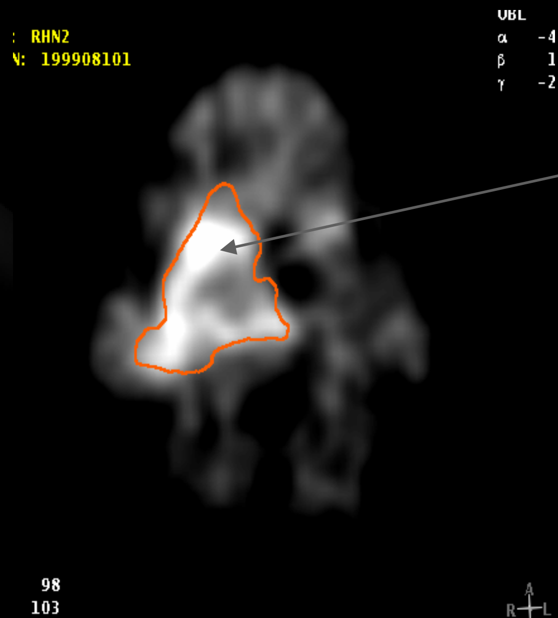
- Useful for evaluating predictive power of FLT PET image with respect to the intratumoral variaions of Ki-67 expression within a lesion

Cu-ATSM-Directed Radiation Therapy

CT

Gross Tumor Volume

^{60}Cu-ATSM-PET



Tumor Hypoxic Map

First suggestion of dose painting to hypoxic sub-volumes

C. Chao et al., IJROBP 2001:49;1171-1182

Washington
WASHINGTON•UNIVERSITY•IN•ST•LOUIS
MIR Mallinckrodt Institute of Radiology

PET tracer validation

- Increased uptake of a tracer in the tumor is not sufficient
- It is necessary to demonstrate spatial concordance between:
  - tracer uptake
  - microenvirionmental feature of interest

VCU MASSEY CANCER CENTER
Virginia Commonwealth University

Imaging Tracer Distribution

<u>Focus 120 PET</u>

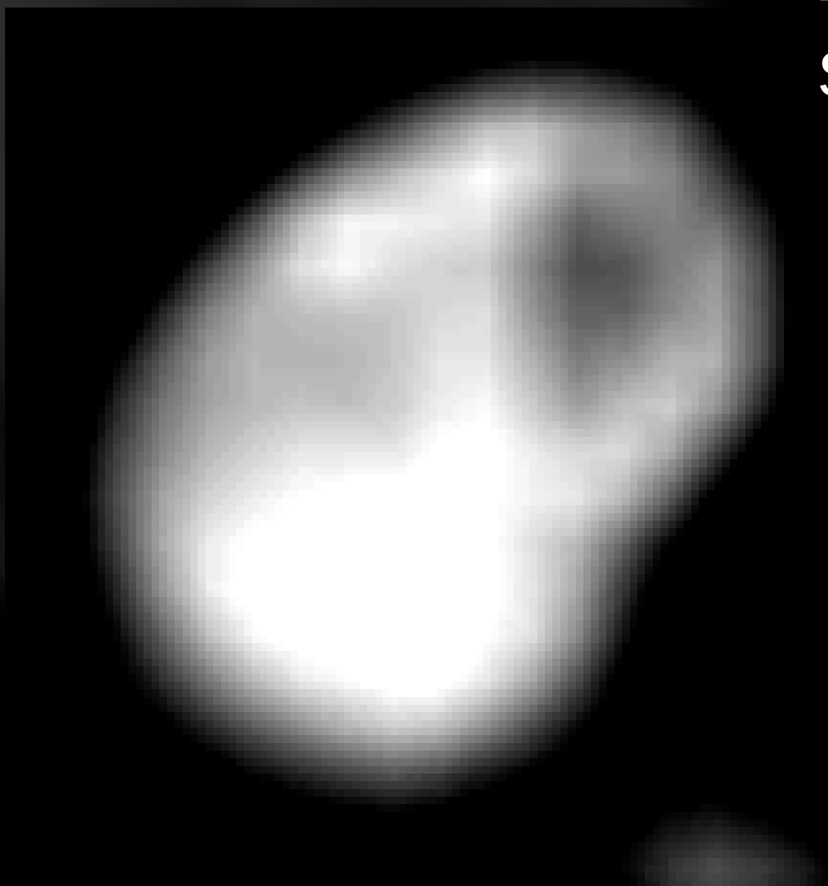
0.87 mm pixel ~2mm resolution

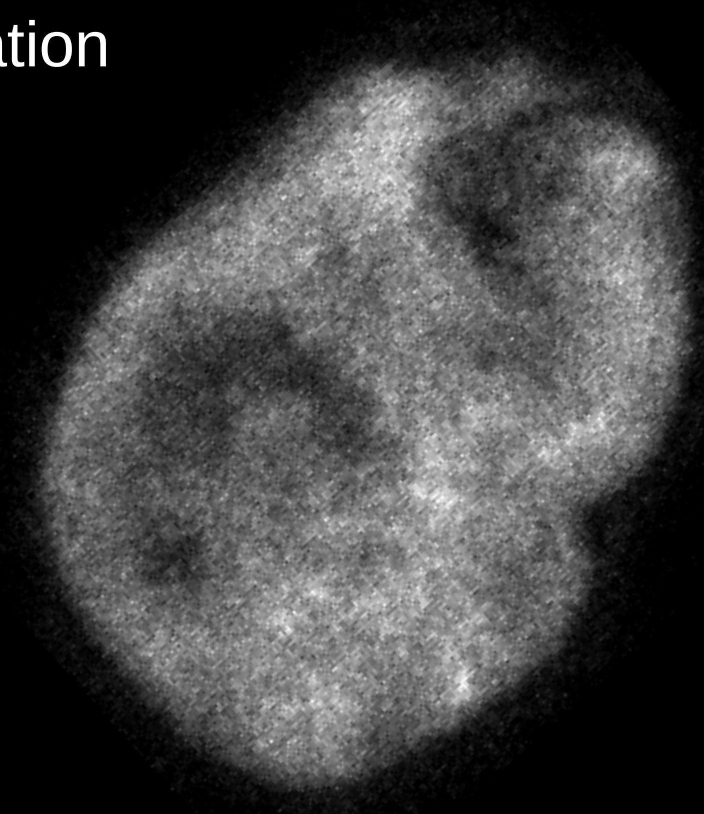
<u>Autoradiography</u>

50 micron pixel ~200 micron resolution

^{18}FDG

Same location





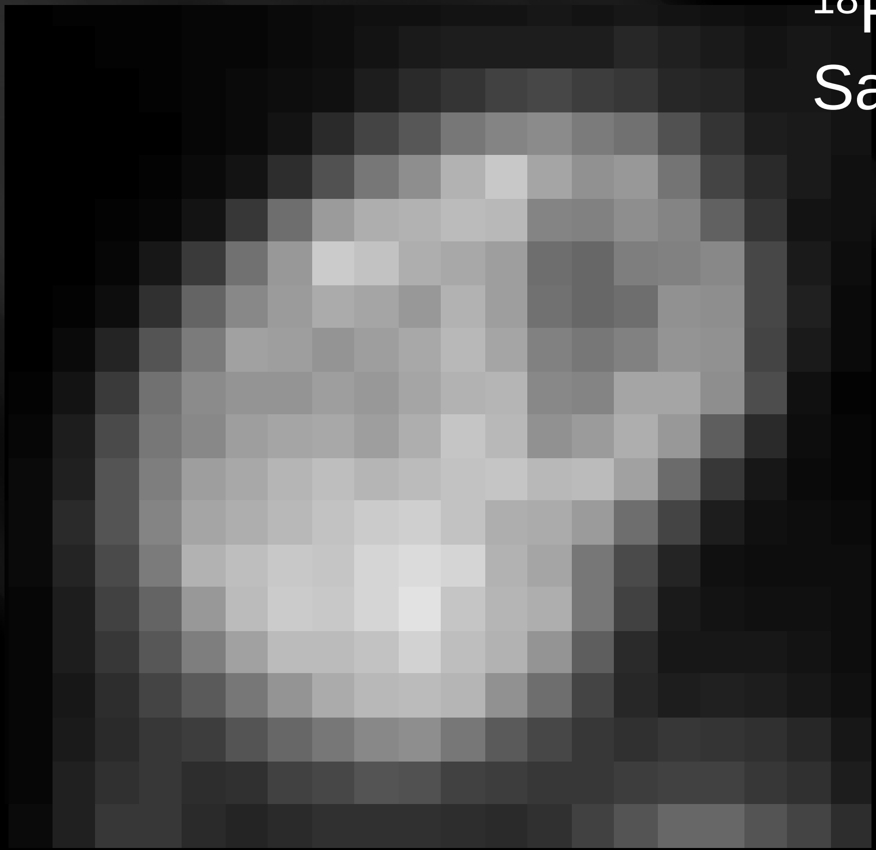
2mm

MASSEY CANCER CENTER
Virginia Commonwealth University

Imaging Tracer Distribution

Focus 120 PET

0.87 mm pixel ~2mm resolution



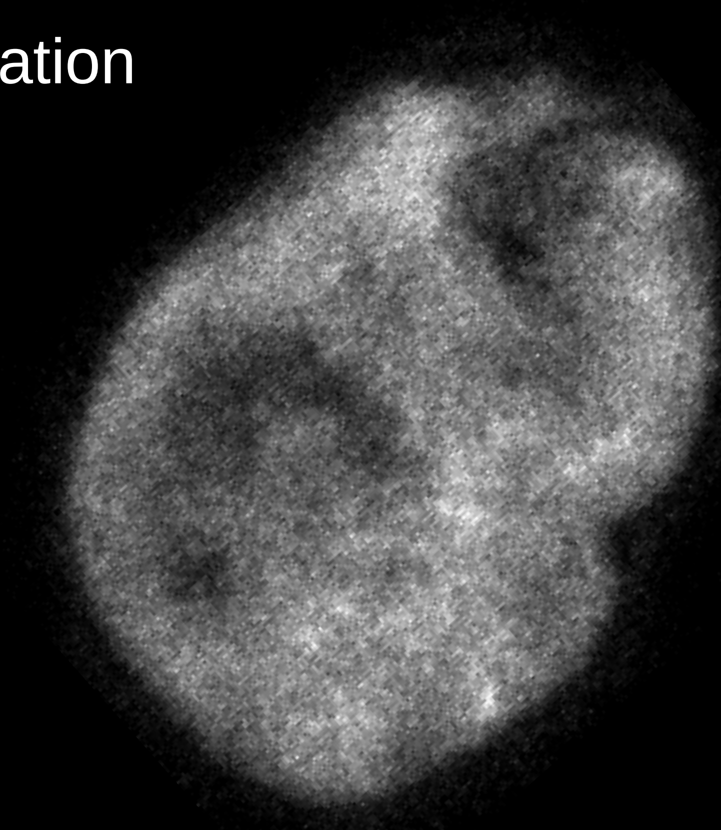
ORIGINAL DATA

^{18}FDG

Same location

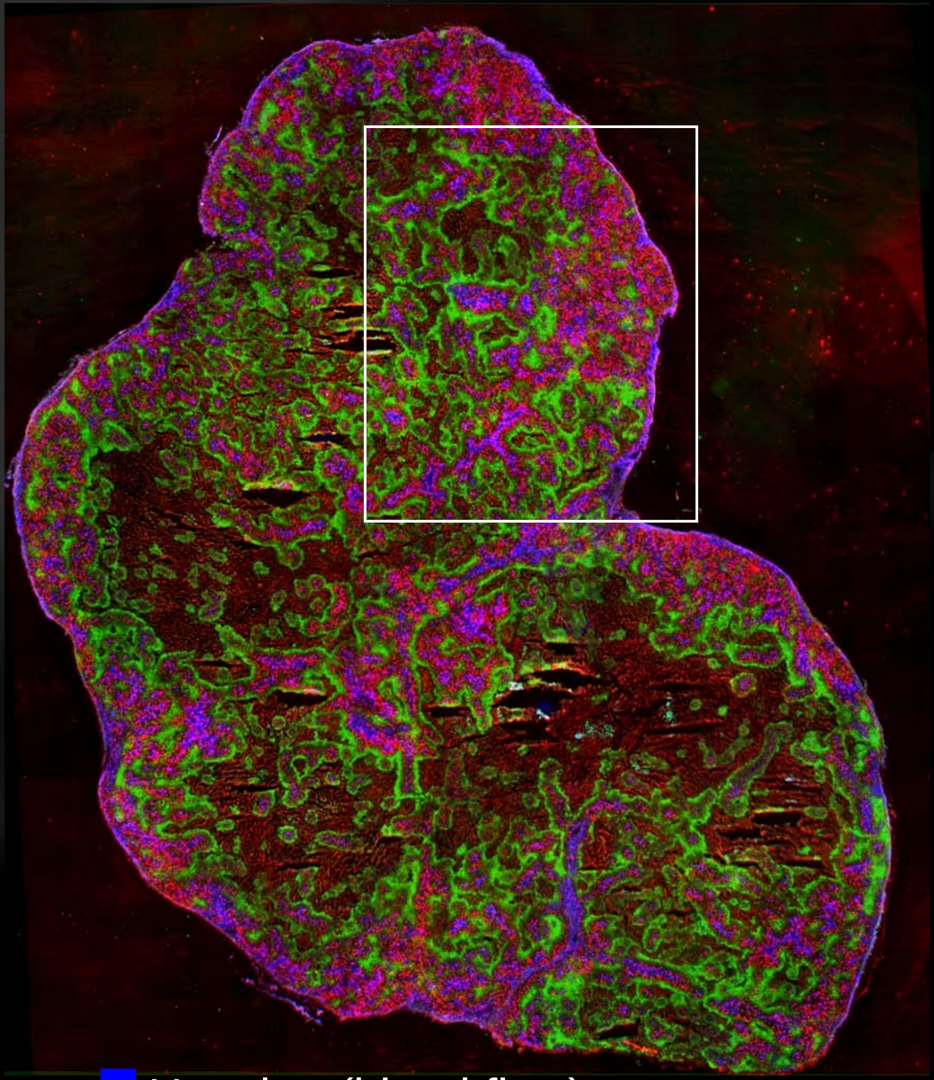
Autoradiography

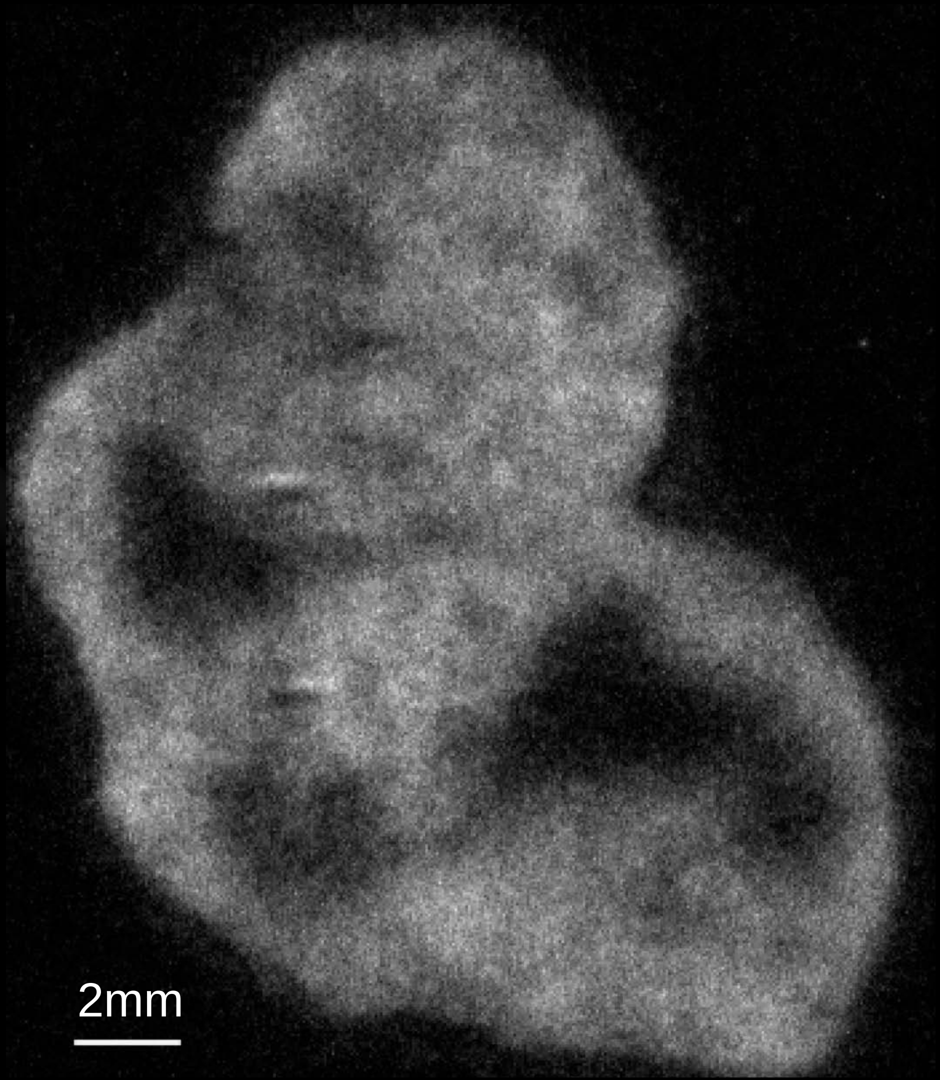
50 micron pixel ~150 micron resolution



MASSEY CANCER CENTER
Virginia Commonwealth University

HT29 xenograft

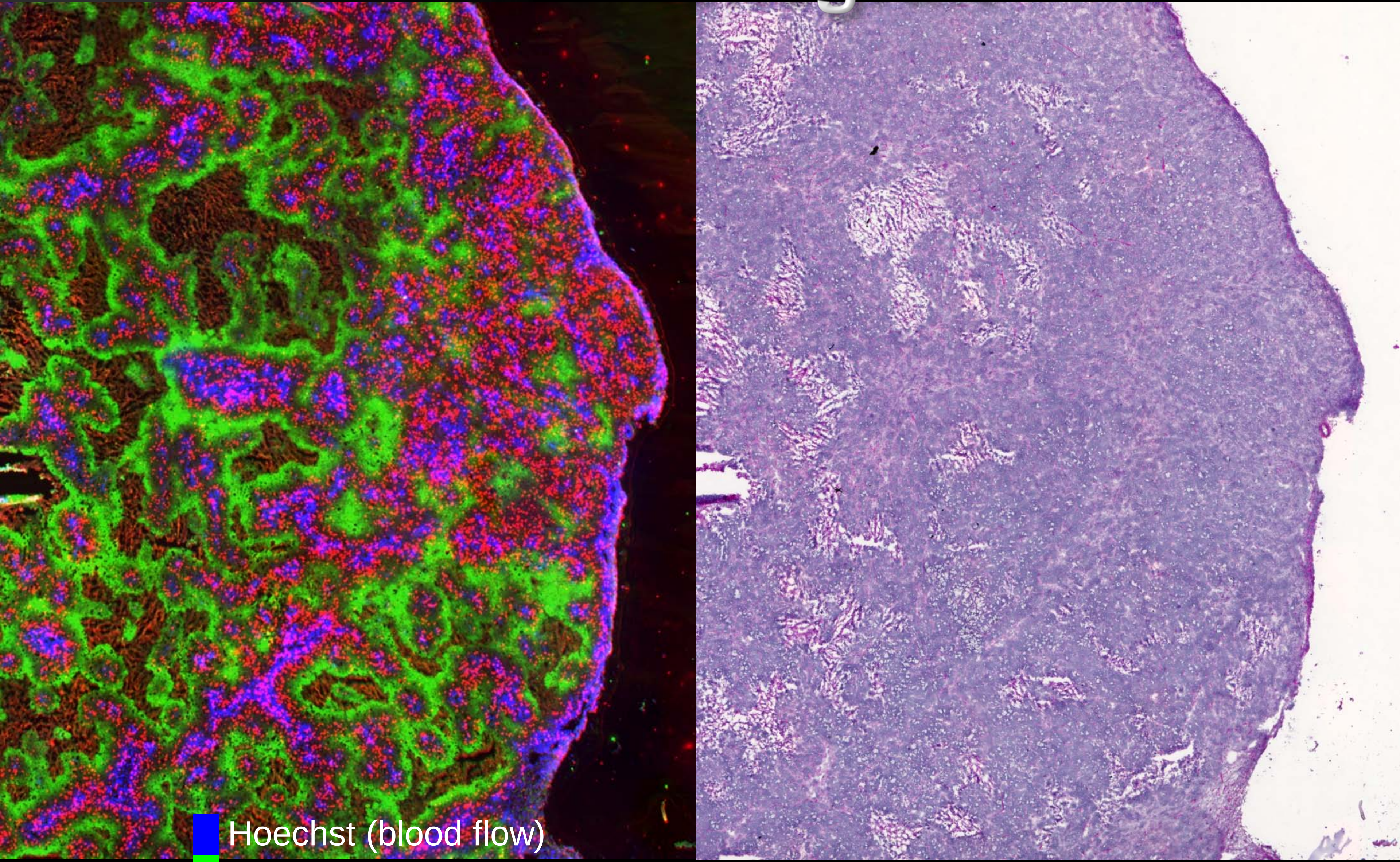




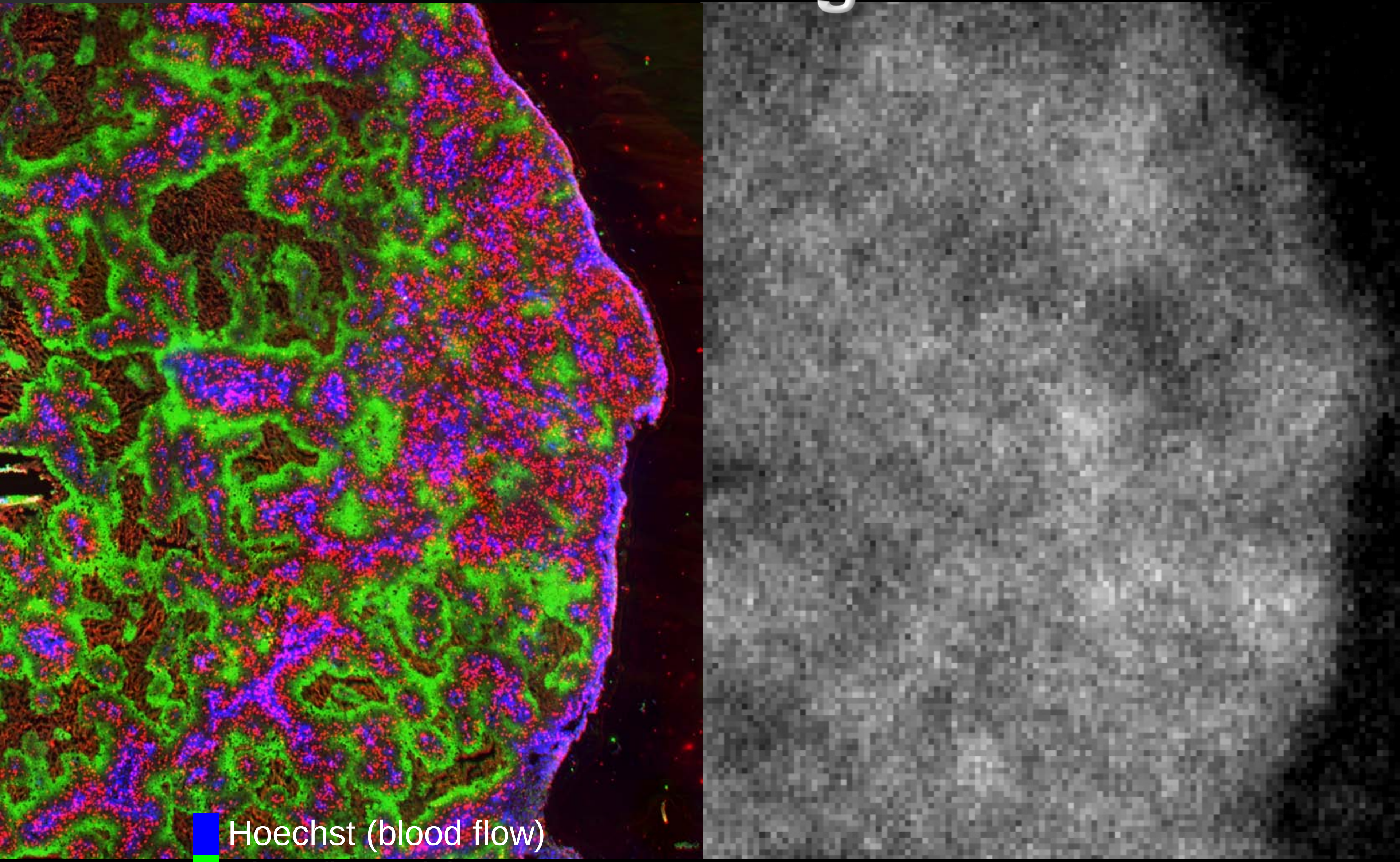
^{18}FDG

VCU MASSEY CANCER CENTER
Virginia Commonwealth University

HT29 xenograft



HT29 xenograft

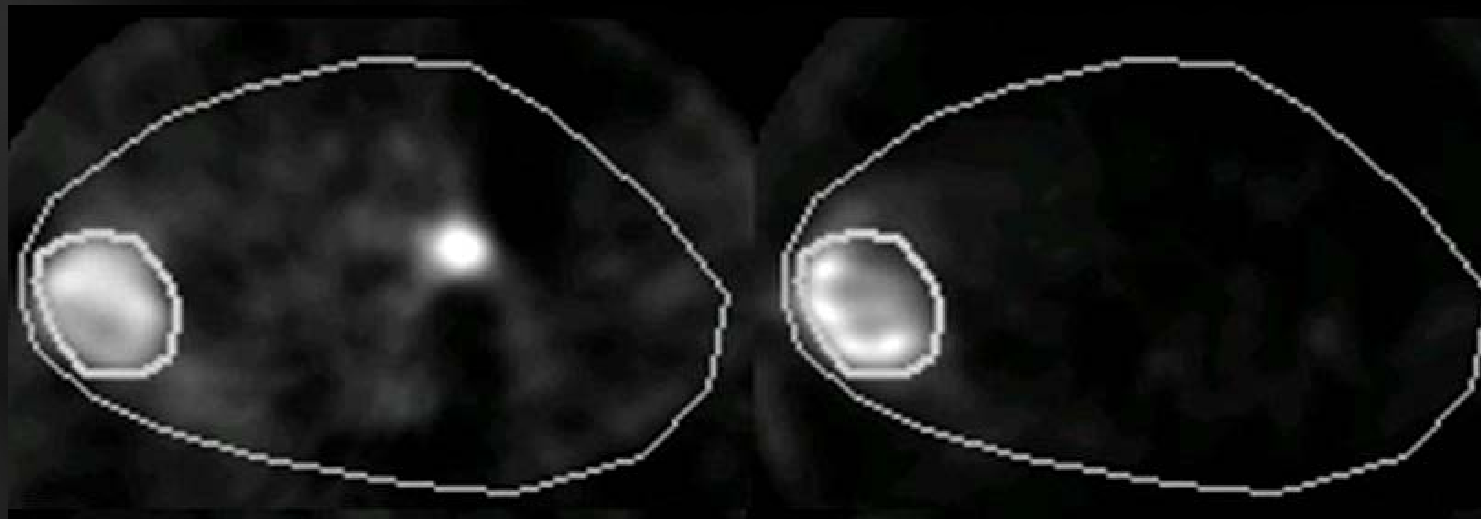


VCU MASSEY CANCER CENTER
Virginia Commonwealth University

Cu-ATSM

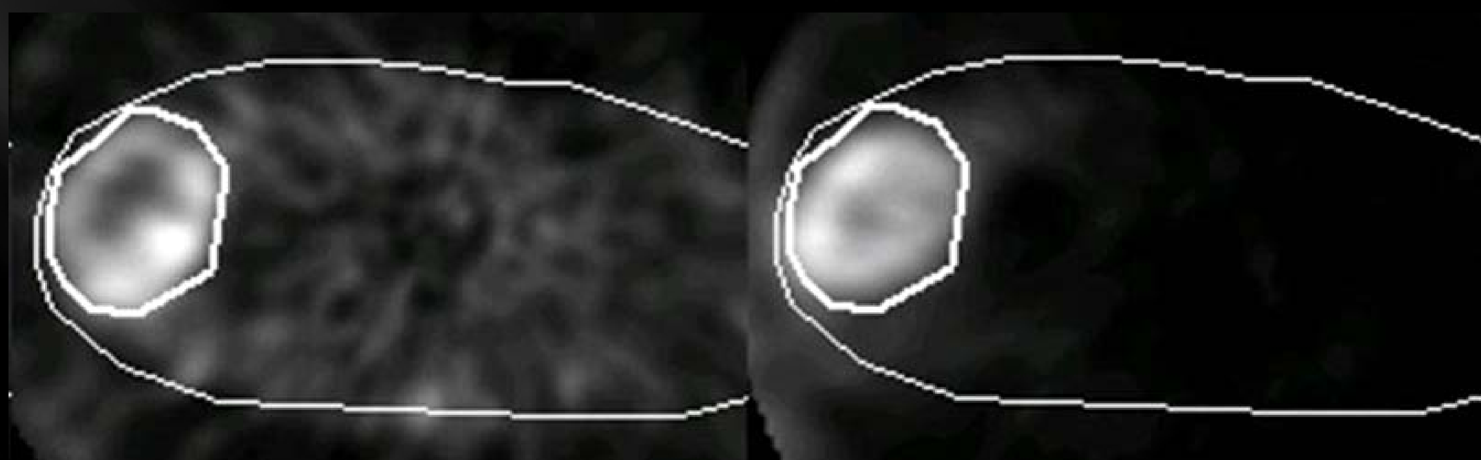
CuATSM in R3327-AT

Rat 1



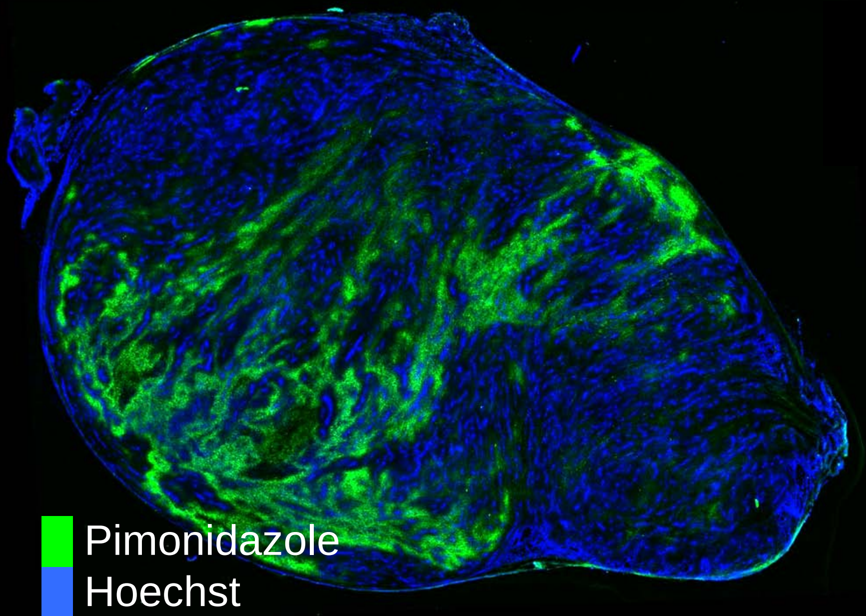
Early (2hr p.i.) Late (16hr p.i.)

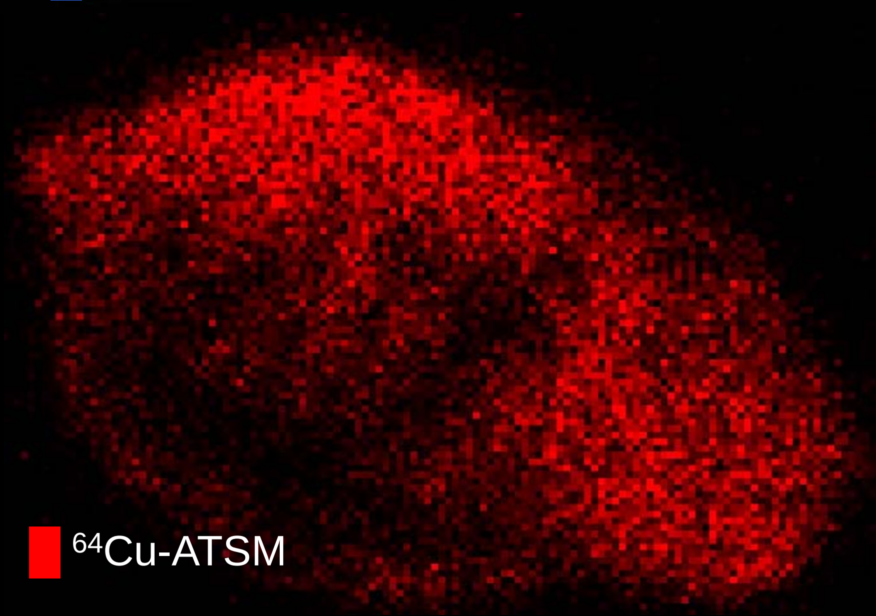
Rat 2

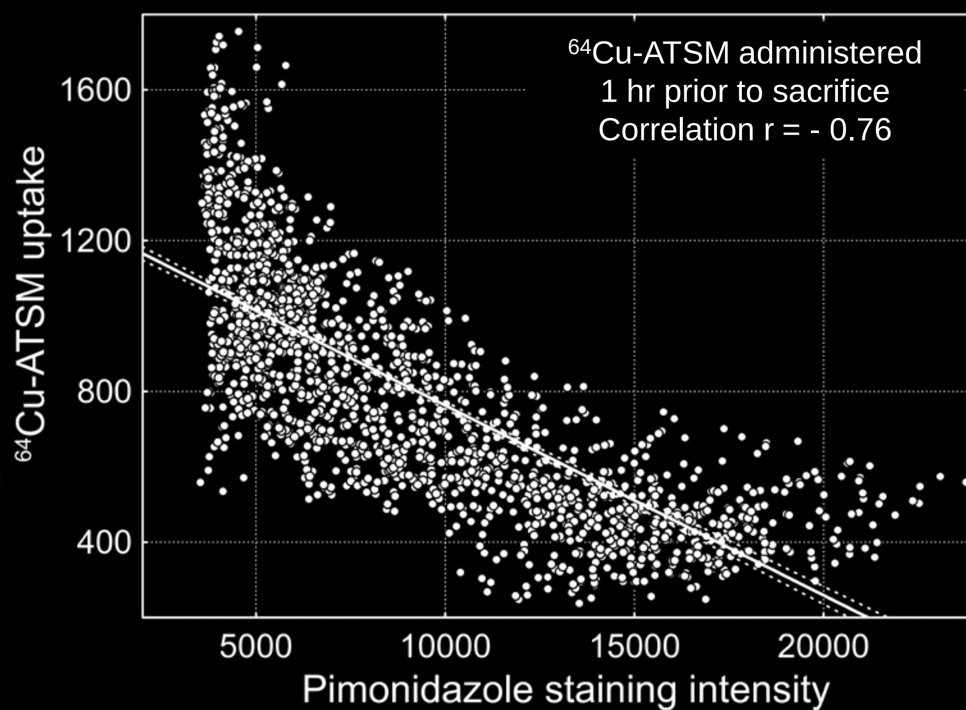


Early (2hr p.i.) Late (16hr p.i.)

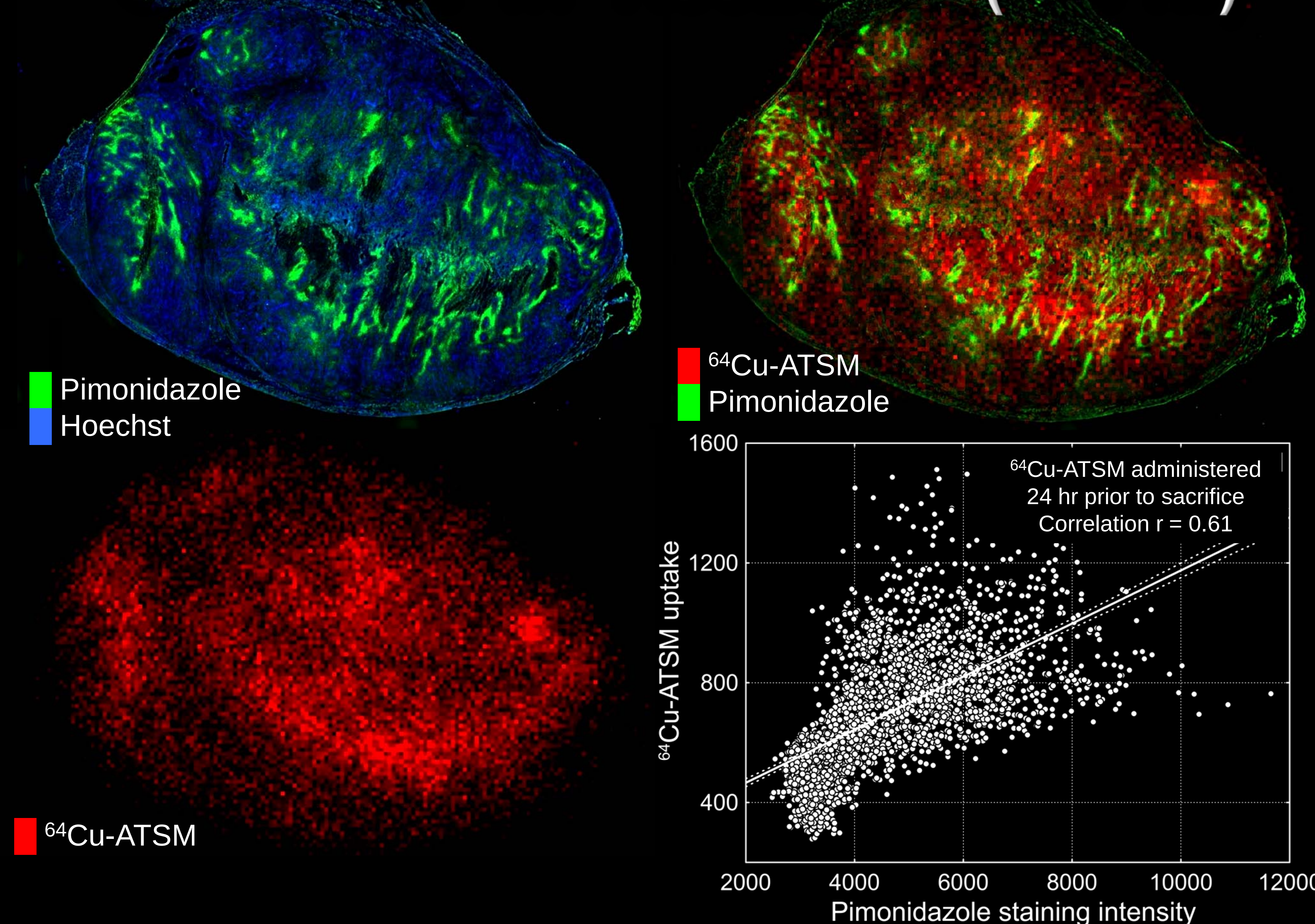
^{64}Cu-ATSM in R3327-AT (-1 hr)







^{64}Cu-ATSM in R3327-AT (-24 hr)



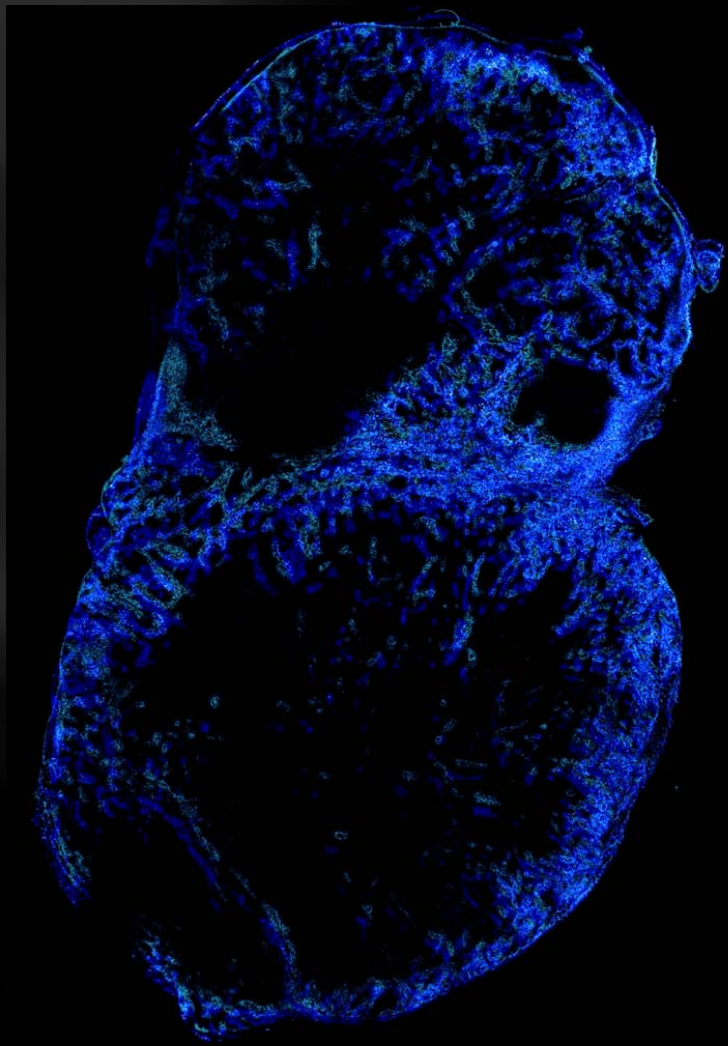
FLT vs FDG

Microscopic tracer distribution

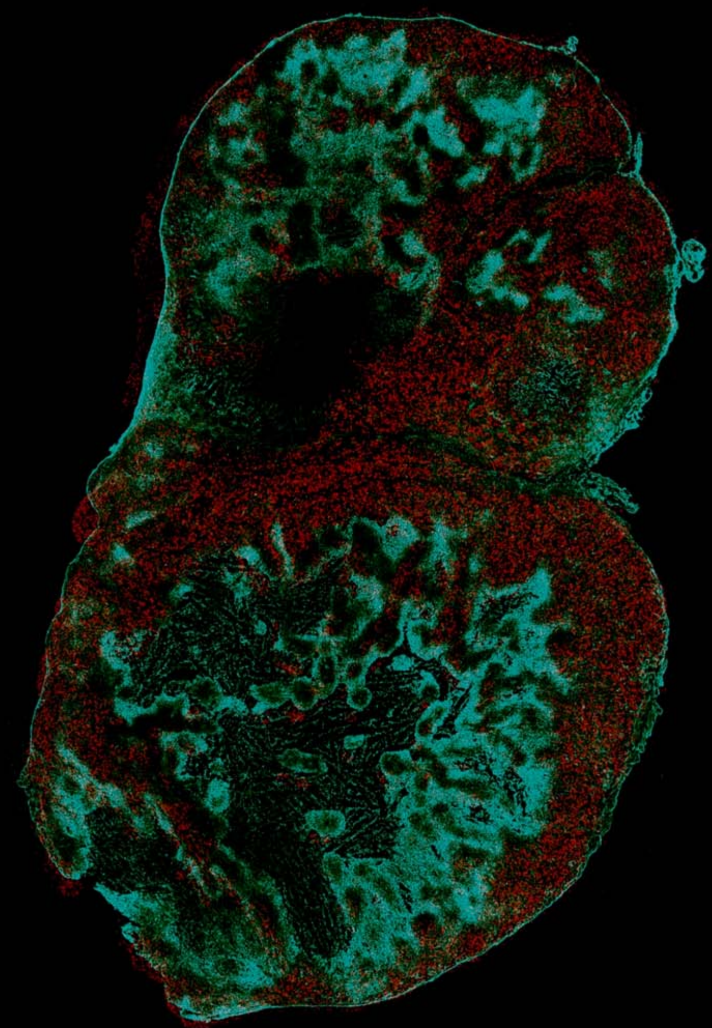
- Co-registration of immunohistochemical images with autoradiograms is performed based on external fluorescent/radioactive markers placed on the slides
- Co-registration of immunofluorescent microscopy images obtained from sequential sections is performed using deformable image co-registration techniques
- Micrometer precision of co-registration

Deformable image registration

Hoechst 1 + Hoechst 2



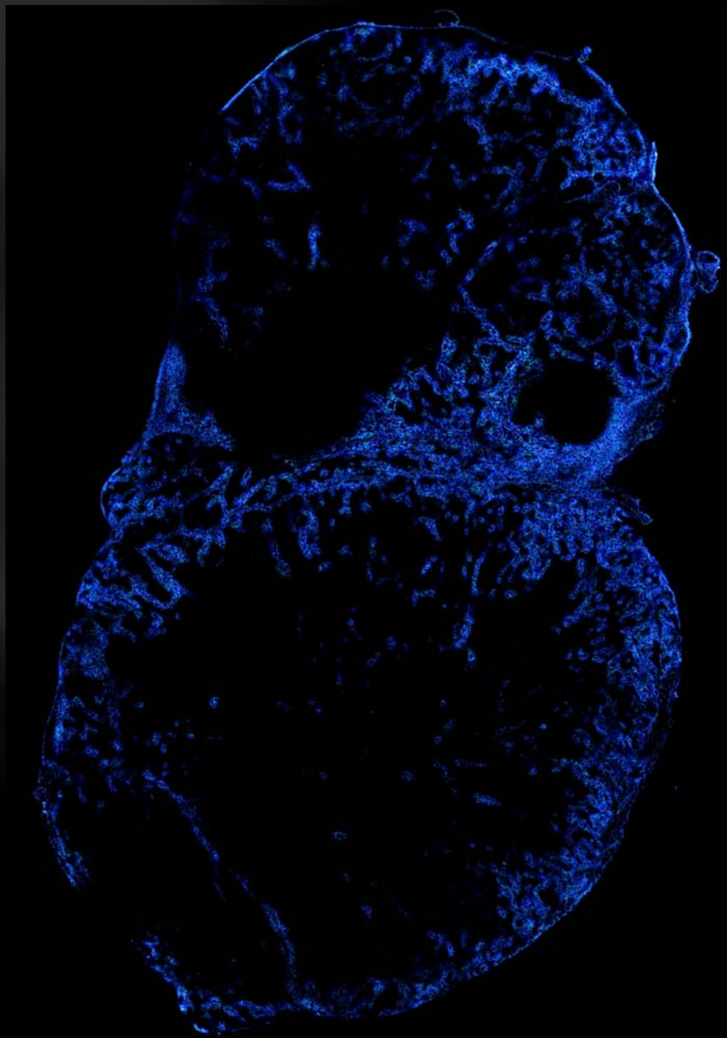
Pimo 1 + BrdU 2



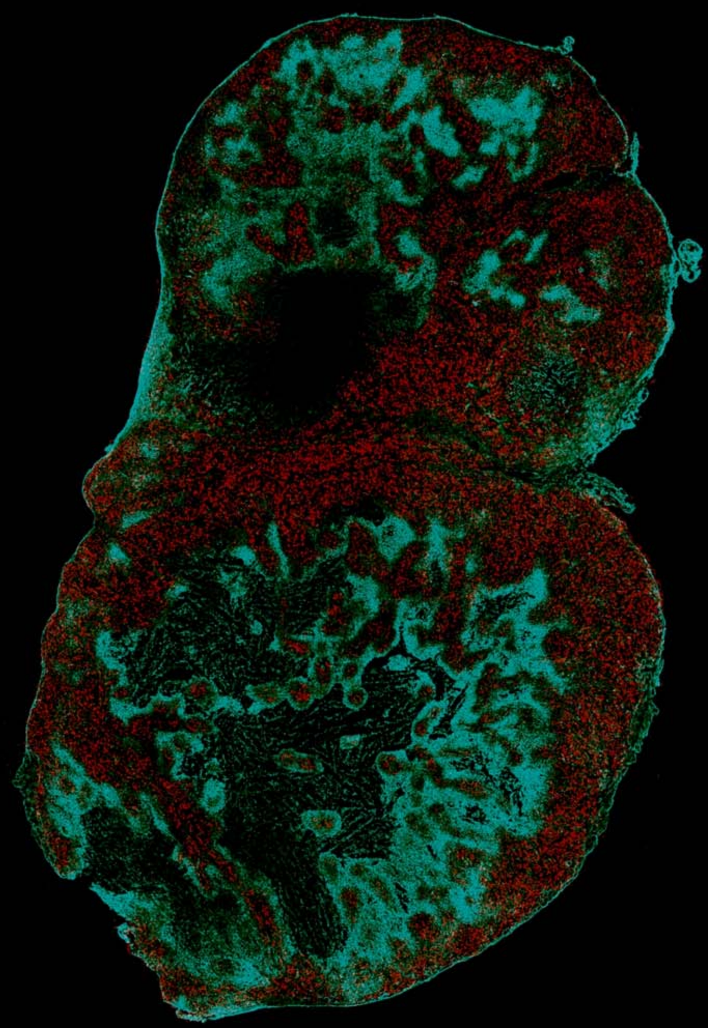
VCU MASSEY
CANCER CENTER
Virginia Commonwealth University

Deformable image registration

Hoechst 1 + Hoechst 2



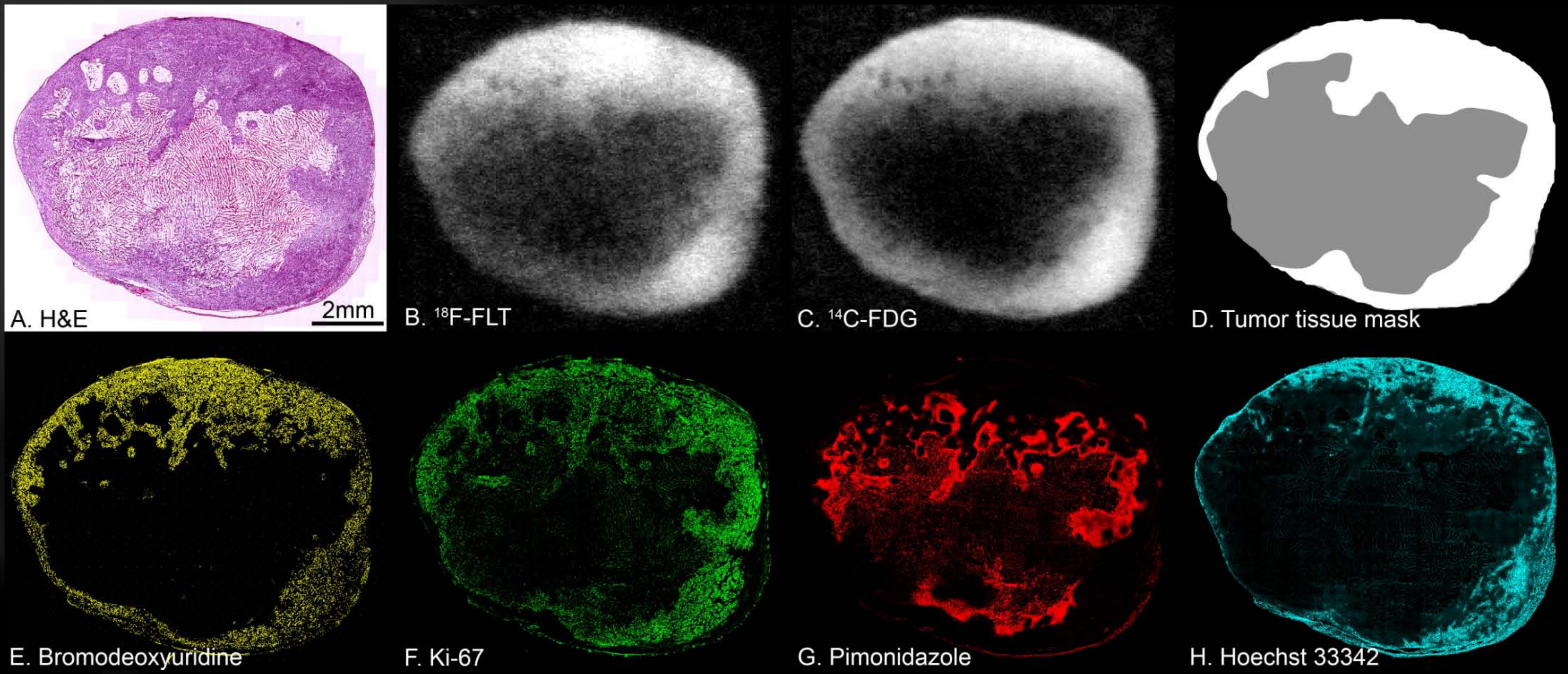
Pimo 1 + BrdU 2



VCU MASSEY CANCER CENTER
Virginia Commonwealth University

Microscopic tracer distribution

- Tumor-bearing mice co-injected with ^{18}F-FLT and ^{14}C-FDG
- Following sacrifice, tumors are frozen embedded and sectioned

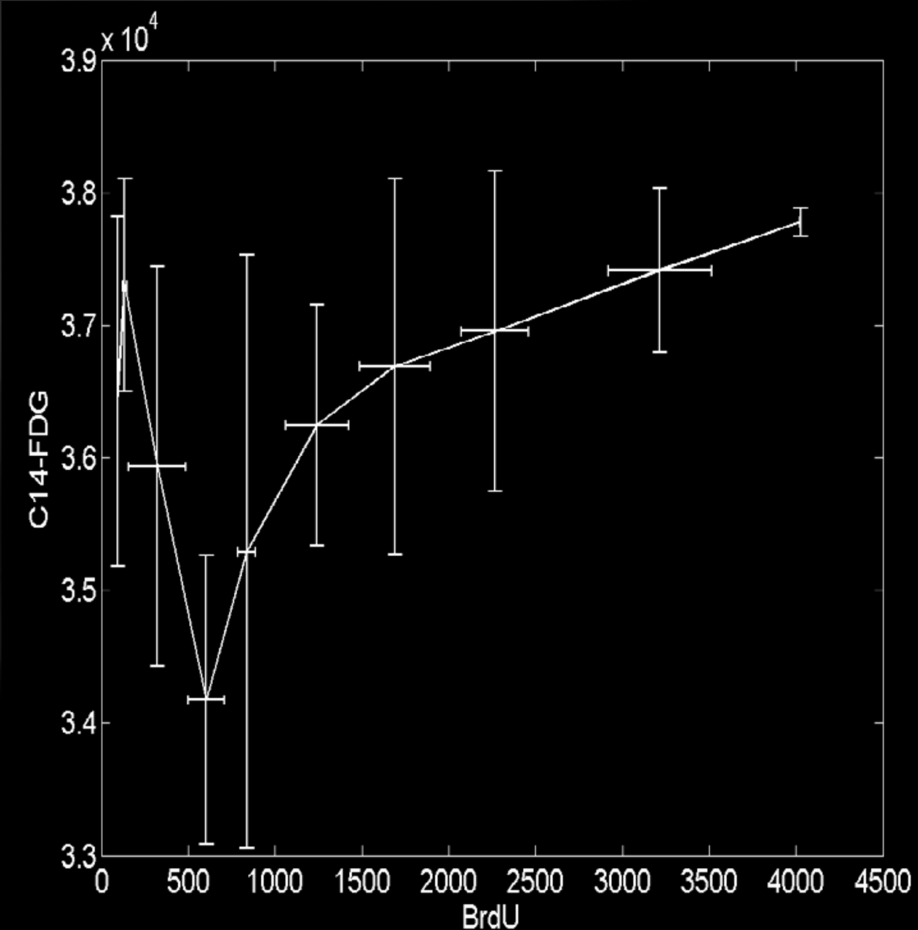


- ^{14}C and ^{18}F autoradiograms of the same tissue section (8micron thick)
- Immunofluorescence from adjacent sections

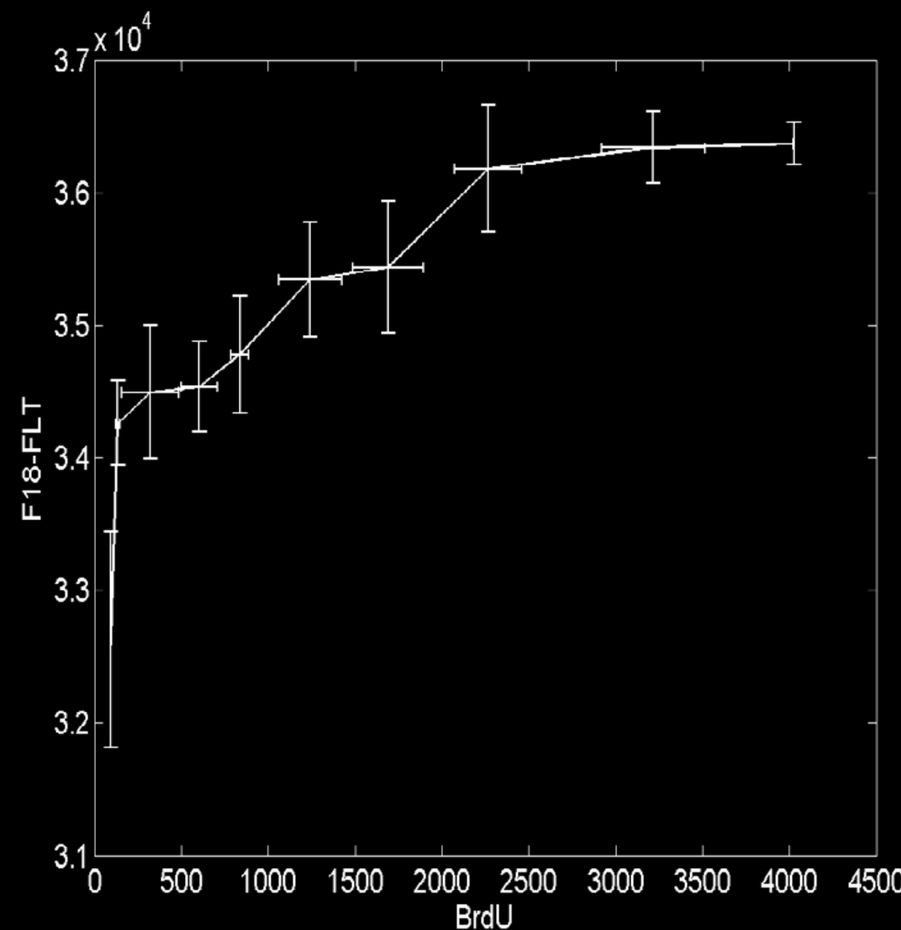
VCU MASSEY CANCER CENTER
Virginia Commonwealth University

Pixel-by-pixel analysis
(viable tissue only)

^{14}C-FDG vs BrdU



^{18}F-FLT vs BrdU



VCU MASSEY CANCER CENTER
Virginia Commonwealth University

Tissue processing

- Immunofluorescent staining is done on Ventana Discovery XT autostainer   (36 slides max)
- Image acquisition: Ariol Genetix system equipped with auto slide feeder (40 slides max)

VCU MASSEY
CANCER CENTER
Virginia Commonwealth University

Future directions

- 3D tracer distribution and tumor microenvironment reconstruction
- Orthotopic and carcinogen-induced tumor models
  - Higher clinical relevance
- Tracer validation using surgically excised tumor specimens

Ultimate validation of PET guidance

- Using surgically excised tumor specimens build libraries of 3D tracer distributions and corresponding microenvironmental images (all co-registered)
- Virtual planting of these microscopic 3D tracer distributions into patient's PET/CT
- Use MonteCarlo to obtain simulated PET images (These simulated PET images are still precisely co-registered with the underlying biological 3D data sets)
- Evaluating effect of different PET-based dose painting radiation treatments

Acknowledgements

Jeffrey Williamson
John Humm
Jerry Hirsch
Sean Carlin
Mitchell Anscher
Ross Mikkelsen
Joe O'Donoghue
Jamal Zweit
Sundaresan Gobalakrishnan
Marian Axente
Chris Bass
Jessie He

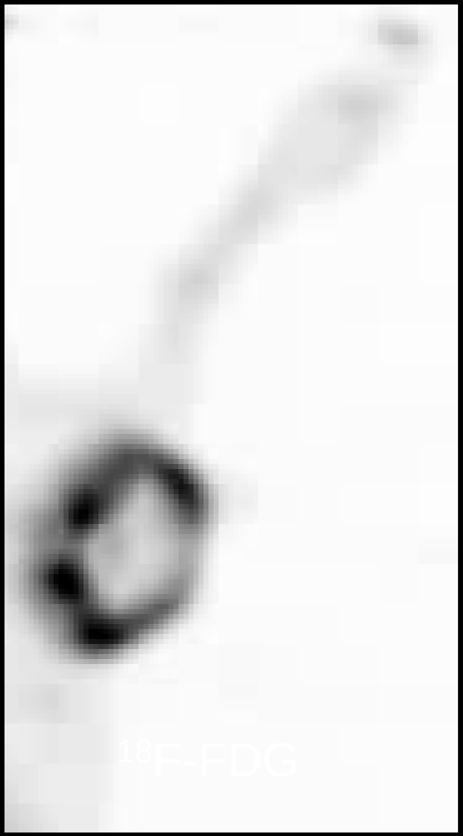
VCU MASSEY CANCER CENTER
Virginia Commonwealth University

What is the best tracer for dose painting?

- Any tracer would do…
- …as long as it is trapped in viable tissue
- Boosting viable tissue beats escalating the dose to the whole lesion

VCU MASSEY CANCER CENTER
Virginia Commonwealth University

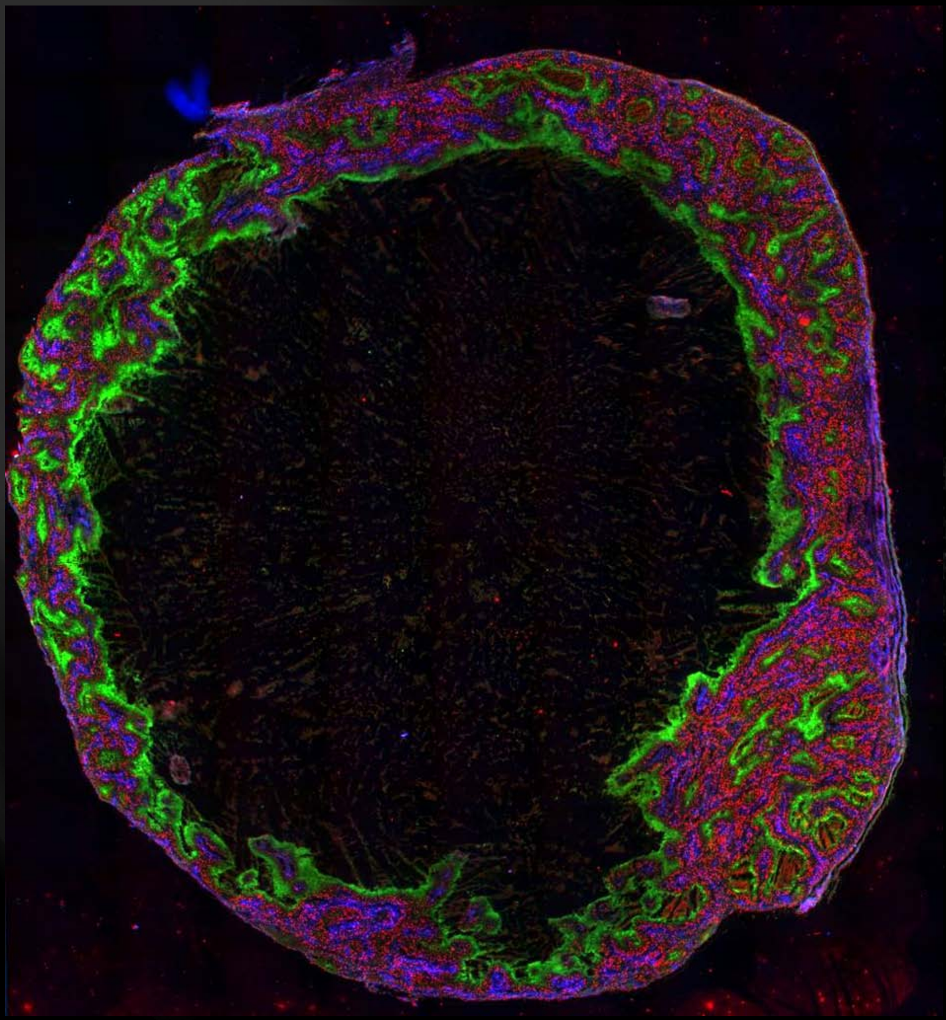
FDG vs F-Miso

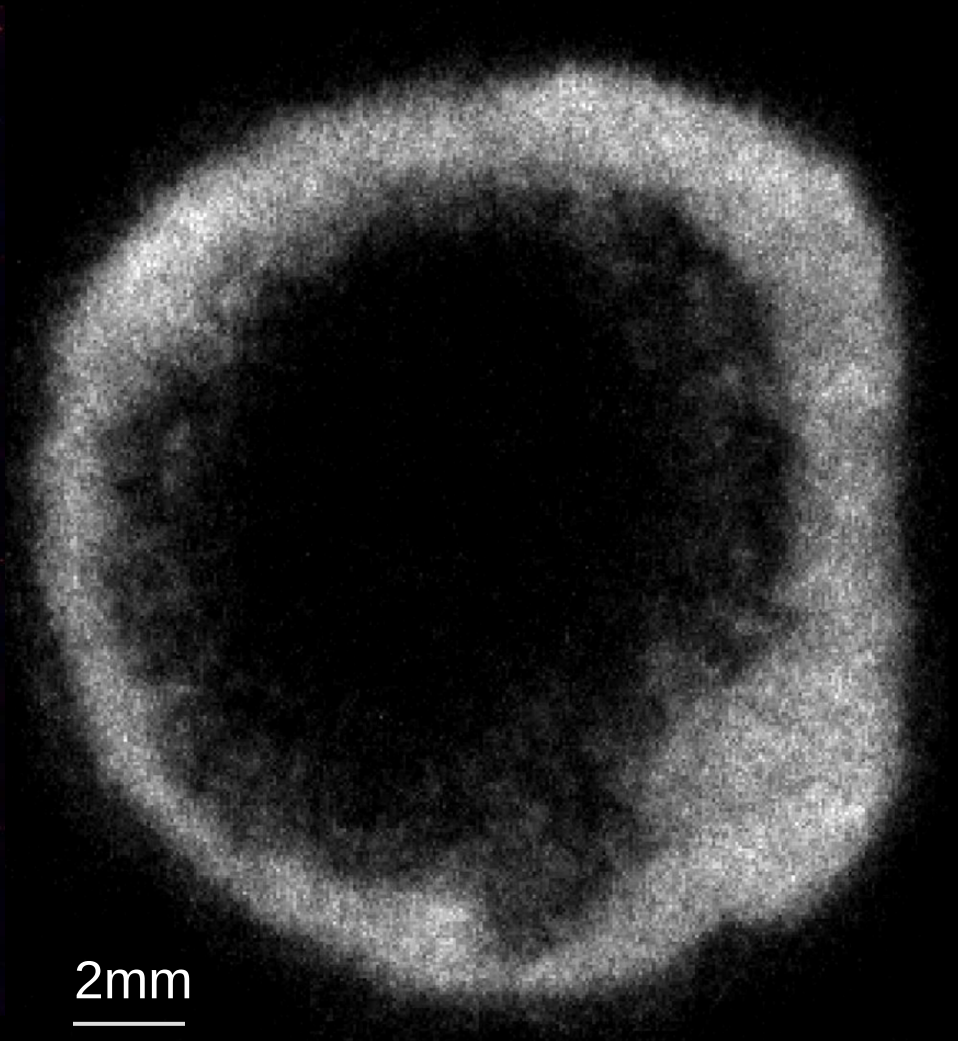


FaDu tumor in a rat imaged twice with microPET using ^{18}F-Miso and ^{18}F-FDG

Courtesy of Joe O'Donoghue and Pat Zanzonico, MSKCC

FDG FaDu


Hoechst (blood flow)
Pimo (hypoxia)
BrdU (dividing cells)


2mm
18FDG