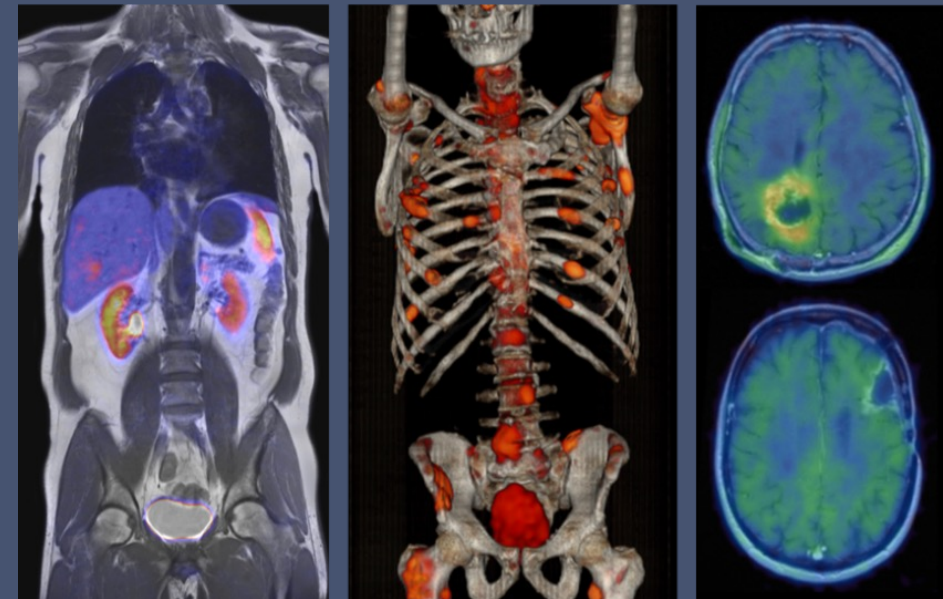


Novel translational applications in immunology and oncology using total body PET

Christian Ia Fougere, M.D.

Department of Nuclear Medicine and Clinical Molecular Imaging



Clinically established & next-generation PET tracers

Tr

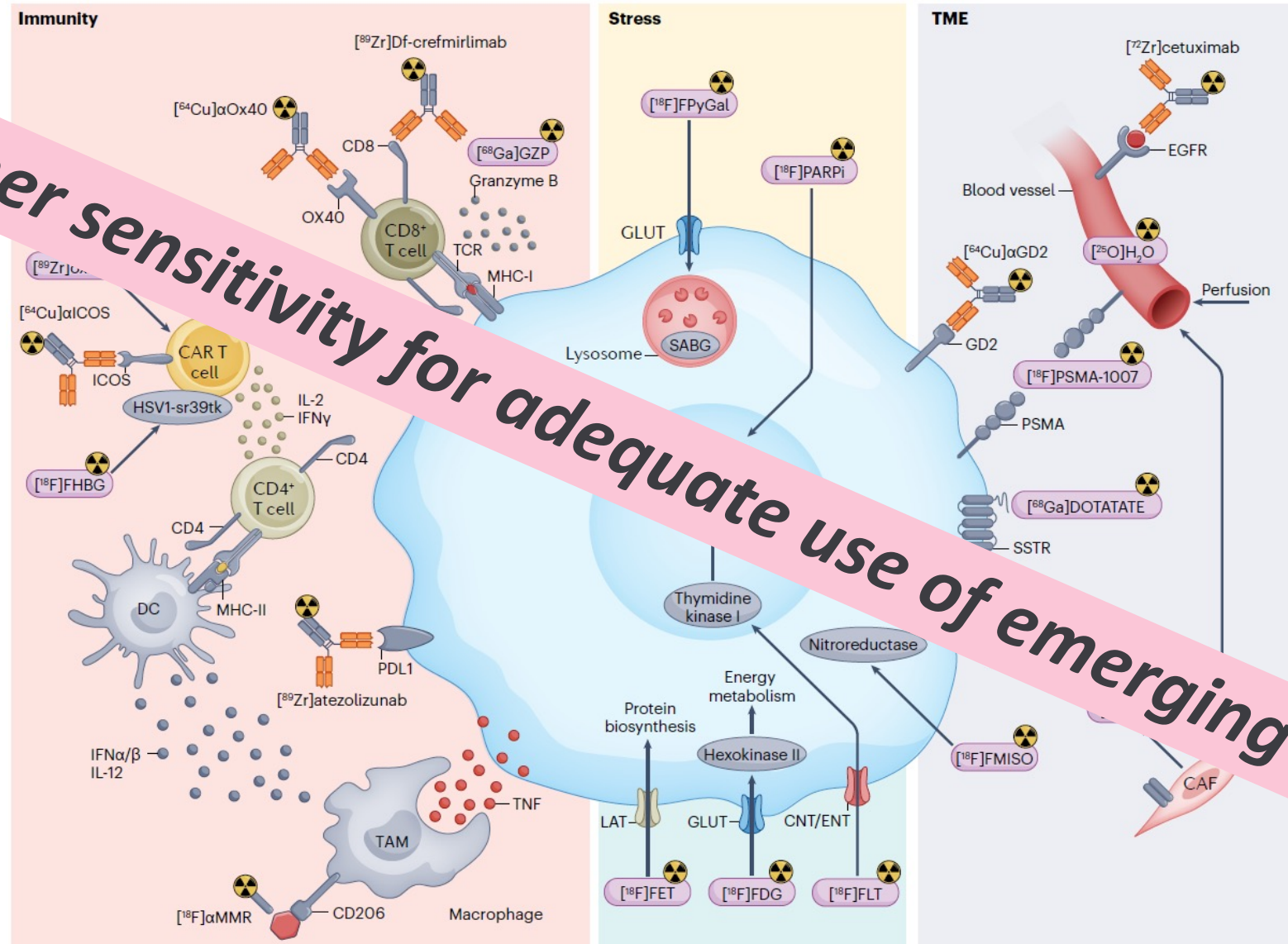
- Sm...
- biological...
- nanobodies
- full size antibodies

Size-effect:

- slow kinetics
- biological half-life
- tissue penetration

Radioisotopes:

- ^{68}Ga (68 min)
- ^{18}F (109 min)
- ^{64}Cu (12.7 h)
- ^{89}Zr (3.3 d)



Need for higher sensitivity for adequate use of emerging probes



Advantage of Long vs. Short Axial Field of View PET/CT

PET-scans:

- 30 min each
- SAFOV: continuous bed motion
- LAFOV: one bed position



Image Quality:

- LAFOV >> SAFOV

COV:

- SAFOV 30min ≈ LAFOV 5min



Quantification in LAFOV

Higher SUV because of noise levels

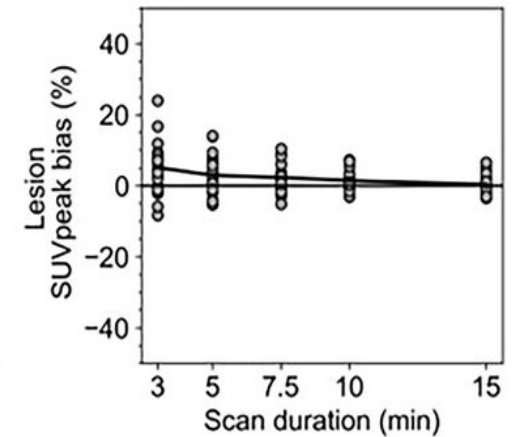
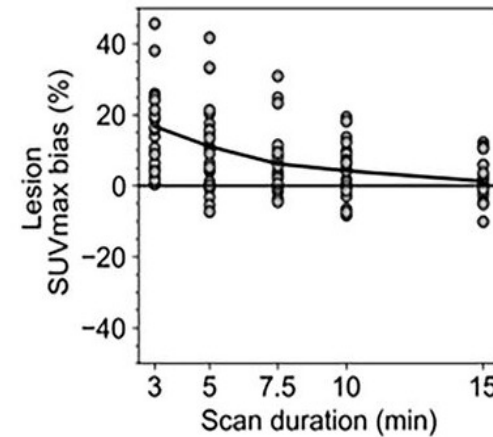
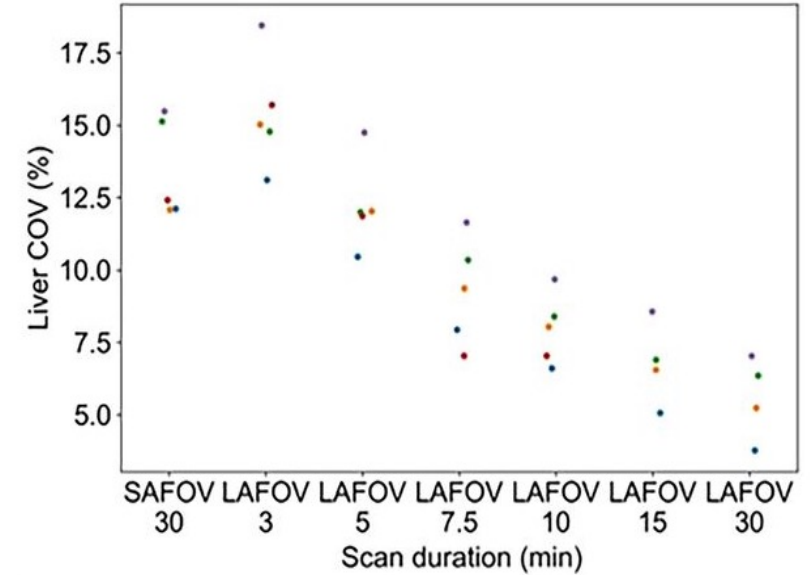
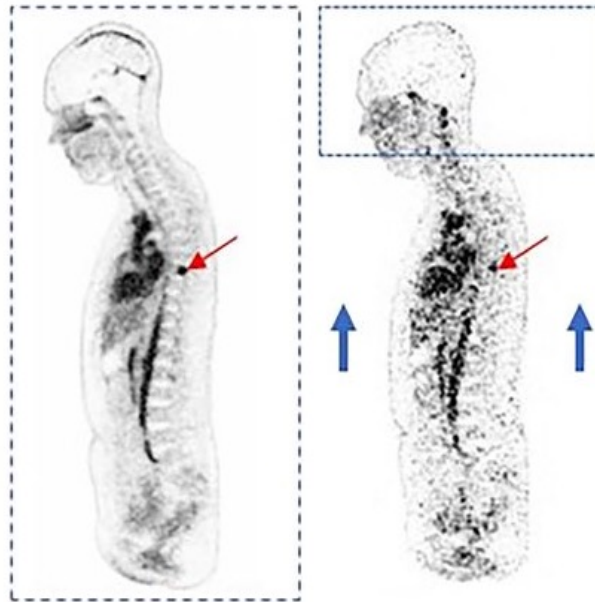
- SUV_{max}: 10 min
- SUV_{peak}: 5 min

ImmunoPET/CT

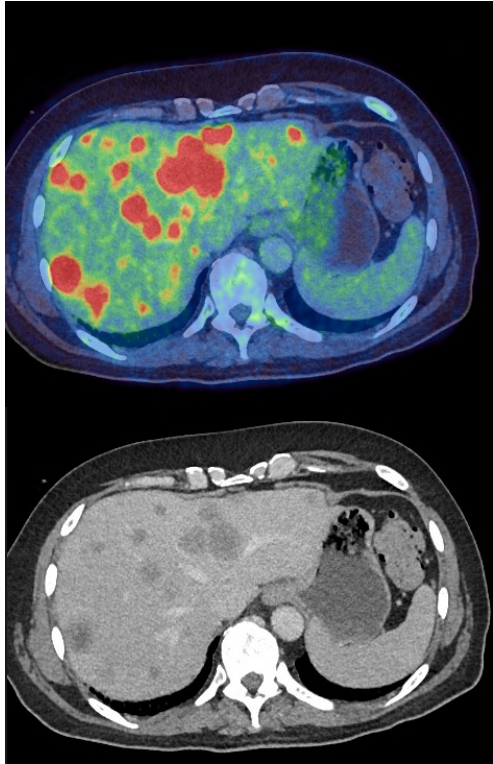


37 MBq ⁸⁹Zr-trastuzumab
PET Imaging 4 days after injection

LAFOV-PET vs. SAFOV-PET



Reveiling heterogeneity and biology with multiple tracer approaches



[¹⁸F]FDG – 1st scan

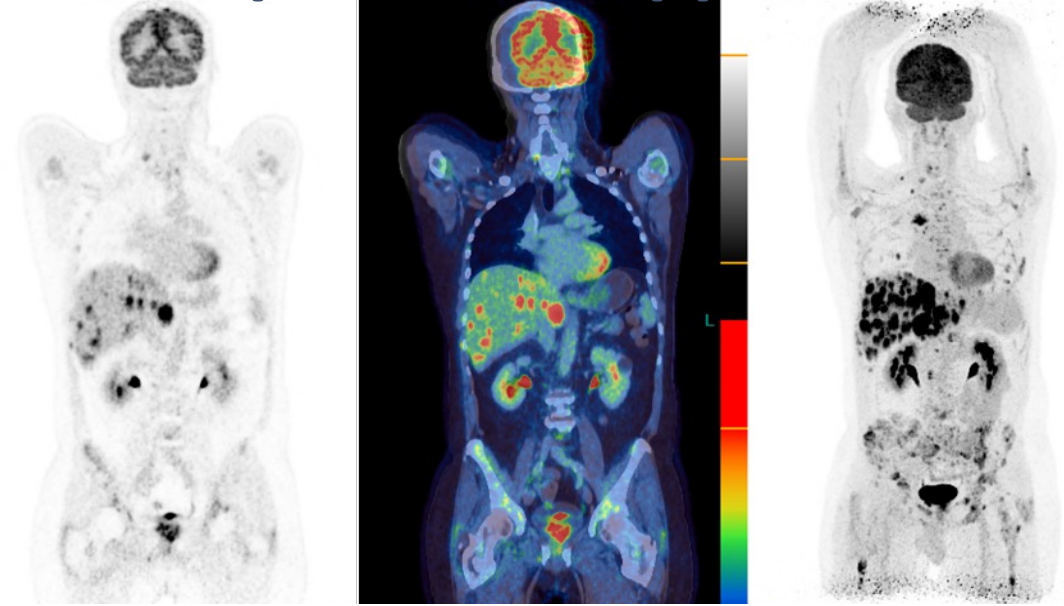
- 0.5 MBq/kg/BW
- 10 min; 60 min p.i.
- ultra LD CT aprox 1 mSV

Delay 6 h



[¹⁸F]PSMA-1007 2nd scan

- 3 MBq/kg/BW
- 5 min; 90 min p.i.
- Diagnostic ce-CT

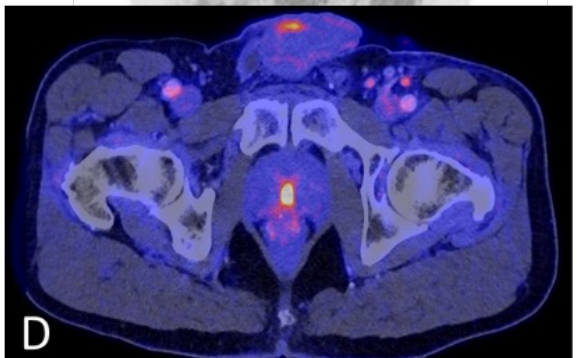
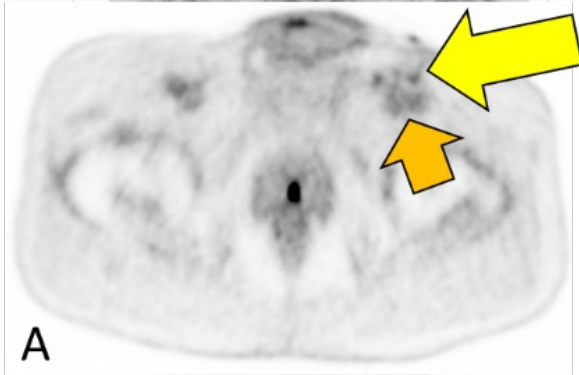
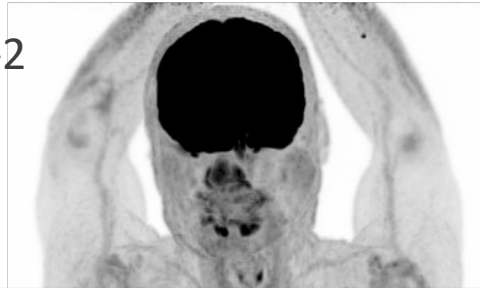


Reveiling metabolic behaviour with late imaging

60 min. p.i.

Foll. Lymphoma grade 1-2
Initial diagnosis
3 MBq/kg/BW

60 min = 5 min scan

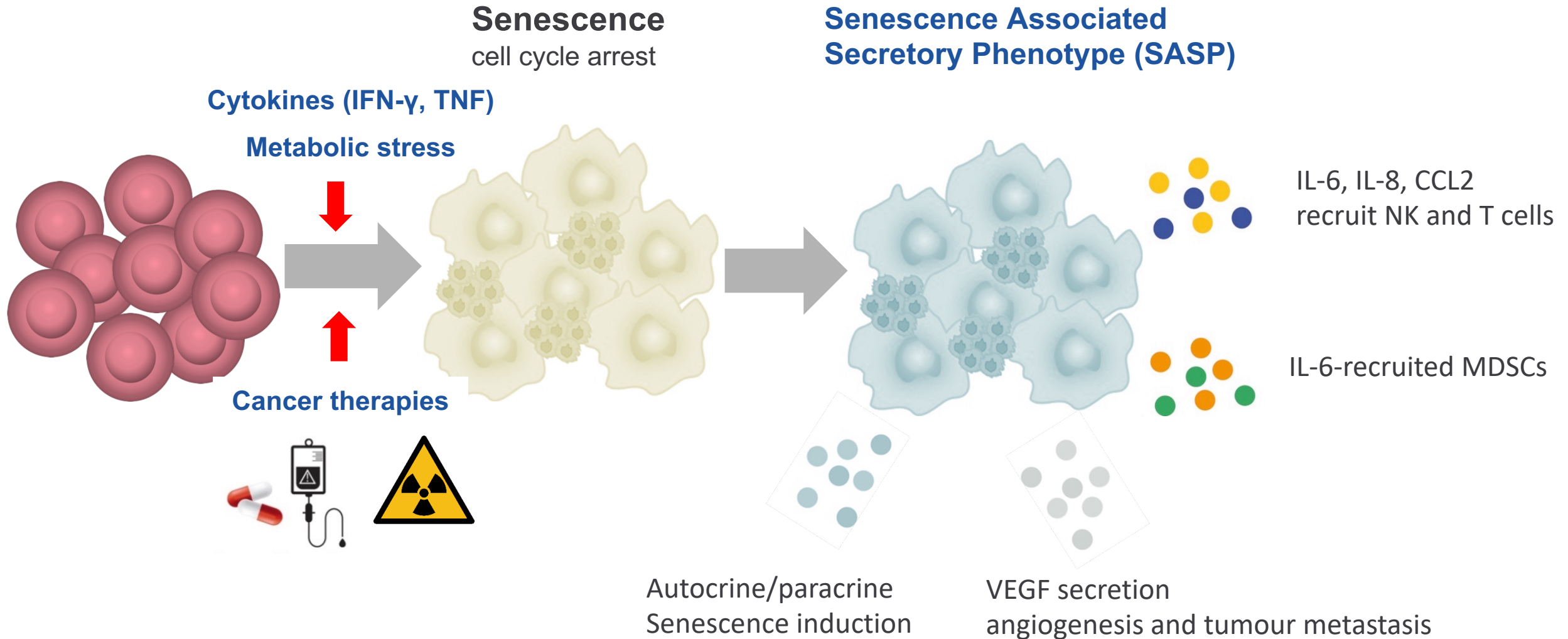


Translational use in oncology

e.g. Imaging of Senescence

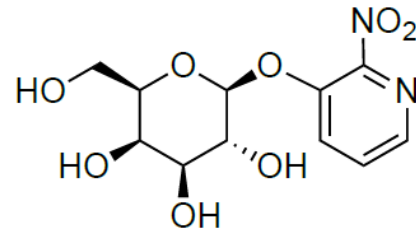


Senescence Associated Secretory Phenotype (SASP)

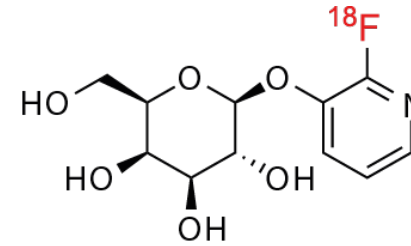


Senescence-Tracer: [¹⁸F]-FPyGAL

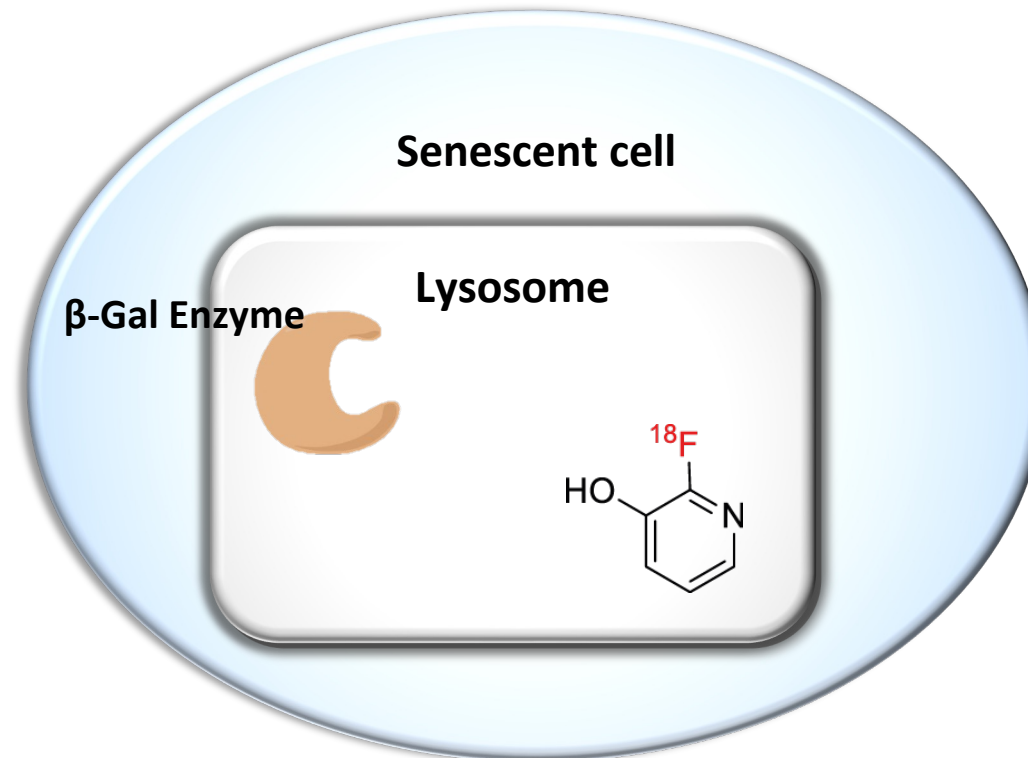
β-Gal Substrate



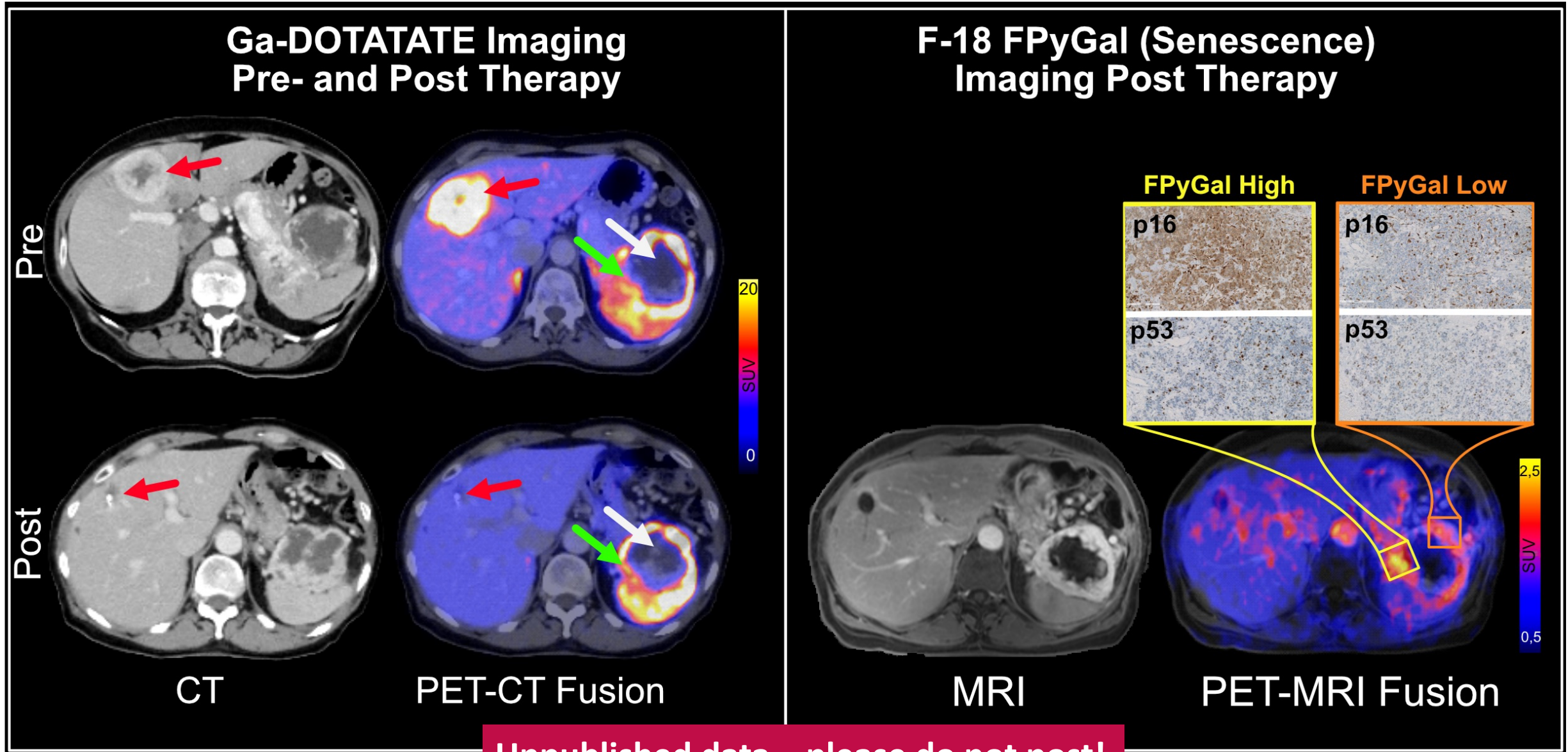
[¹⁸F]-FPyGAL



J. Cotton

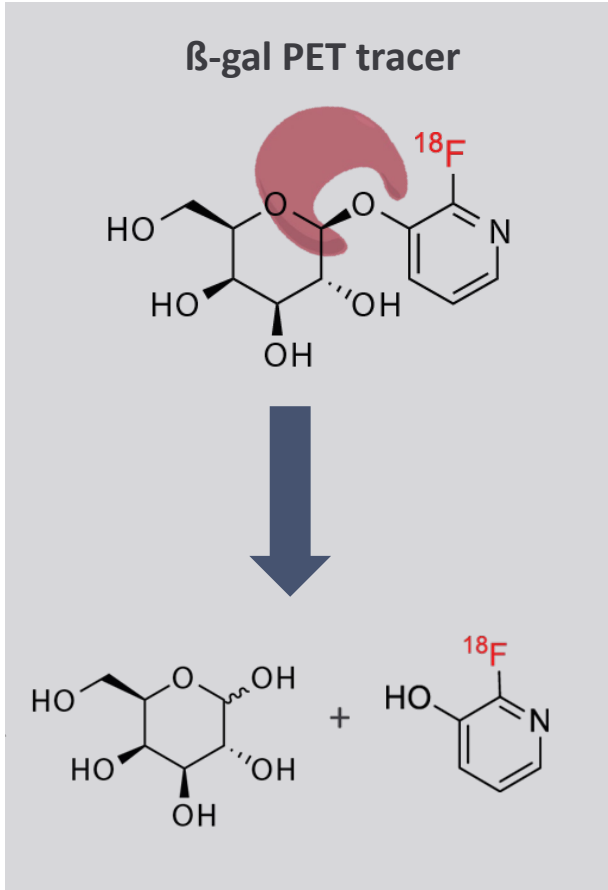


Senescence in Pancreas NET: status post 4 cycles PRRT



Unpublished data – please do not post!

Treatment stratification according to in vivo imaging



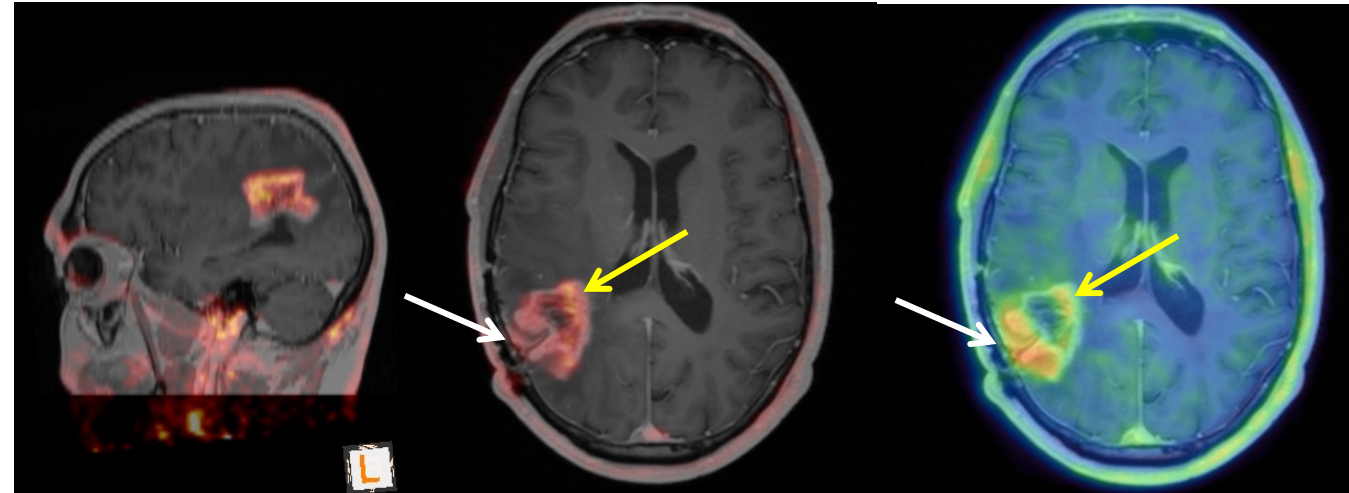
Baseline after RCTx

Combined molecular
& senolytic therapy

3 months follow up

[¹⁸F]PyGAL PET/MRI

[¹⁸F]FET PET/MRI



Translational use in immunooncology



[⁶⁴Cu]Cu-NOTA-ch14.18/CHO – a novel theranostic approach for targeting of GD2 expression

- Disialoganglioside GD2: Tumor associated antigen
 - > overexpressed on cell surfaces of **neuroblastoma, sarcoma**
 - > restricted expression in physiological tissues: promising target for immunotherapies
 - > Dinutûximab beta: chimeric antibody against GD2: **ch14.18/CHO**
 - > **GD2 targeting CAR T-cells**
- Immunohistochemical assessment is challenging in disseminated disease:
 - > intra- and intertumoral heterogeneity
 - > unclear tissue penetration of antibodies
- [⁶⁴Cu]Cu-NOTA-**ch14.18/CHO** developed for non-invasive GD2 assessment



The NEW ENGLAND
JOURNAL of MEDICINE

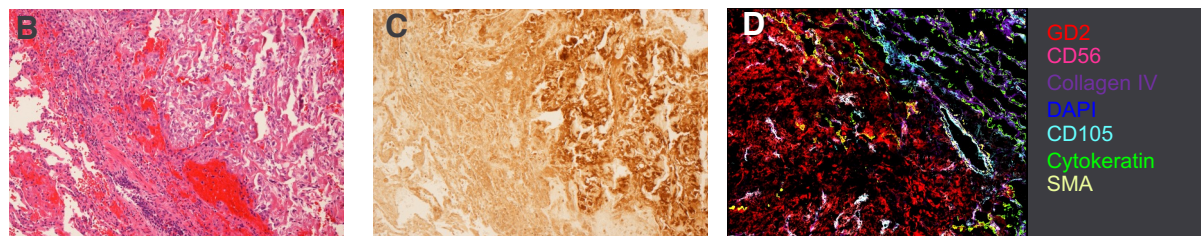
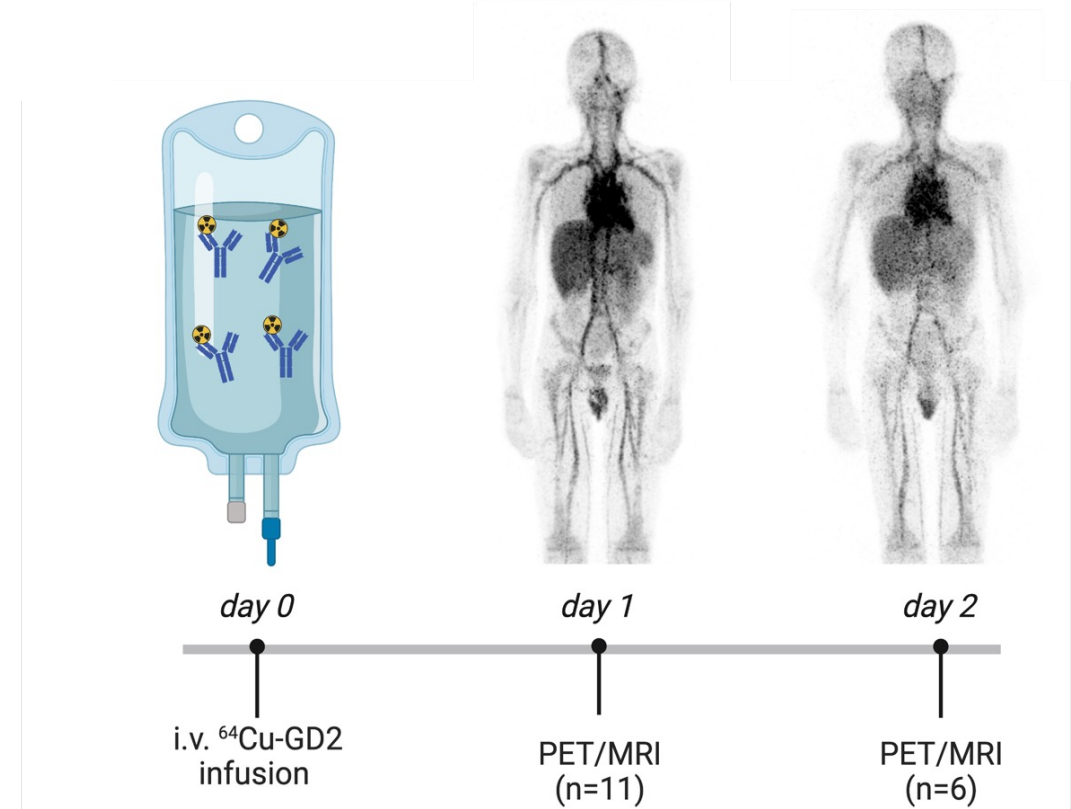
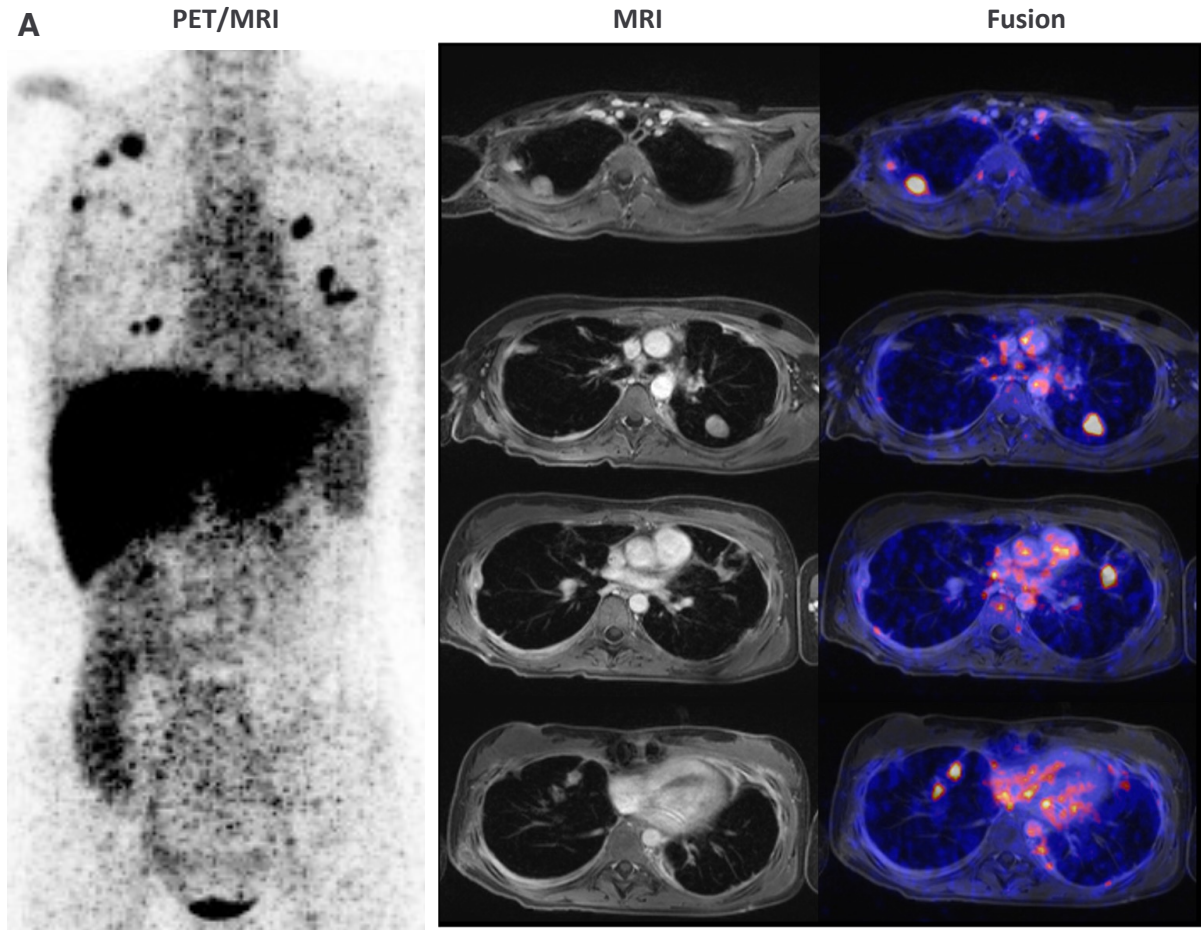
ORIGINAL ARTICLE (FREE PREVIEW)

GD2-CART01 for Relapsed or Refractory High-Risk Neuroblastoma

Francesca Del Bufalo, M.D., Biagio De Angelis, Ph.D., Ignazio Caruana, Ph.D., Giada Del Baldo, M.D., Maria A. De Ioris, M.D., Ph.D., Annalisa Serra, M.D., Angela Mastronuzzi, M.D., Ph.D., Maria G. Cefalo, M.D., Daria Pagliara, M.D., Matteo Amicucci, M.S.N., Giuseppina Li Pira, Ph.D., Giovanna Leone, M.D., *et al.*, for the Precision Medicine Team-IRCCS Ospedale Pediatrico Bambino Gesù*



Heterogeneous expression of GD2 in different cancer entities

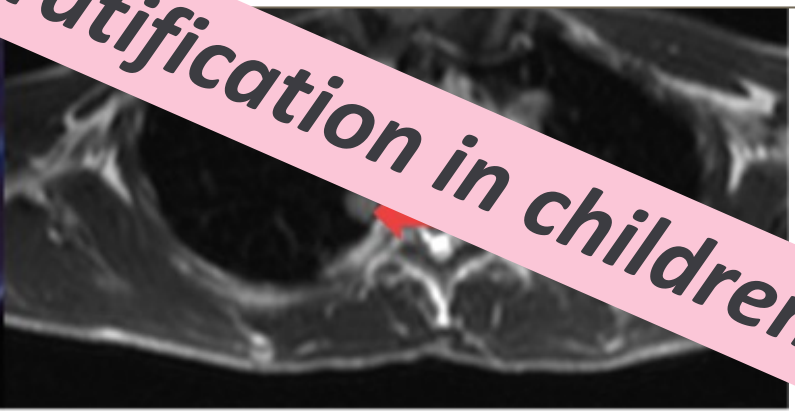
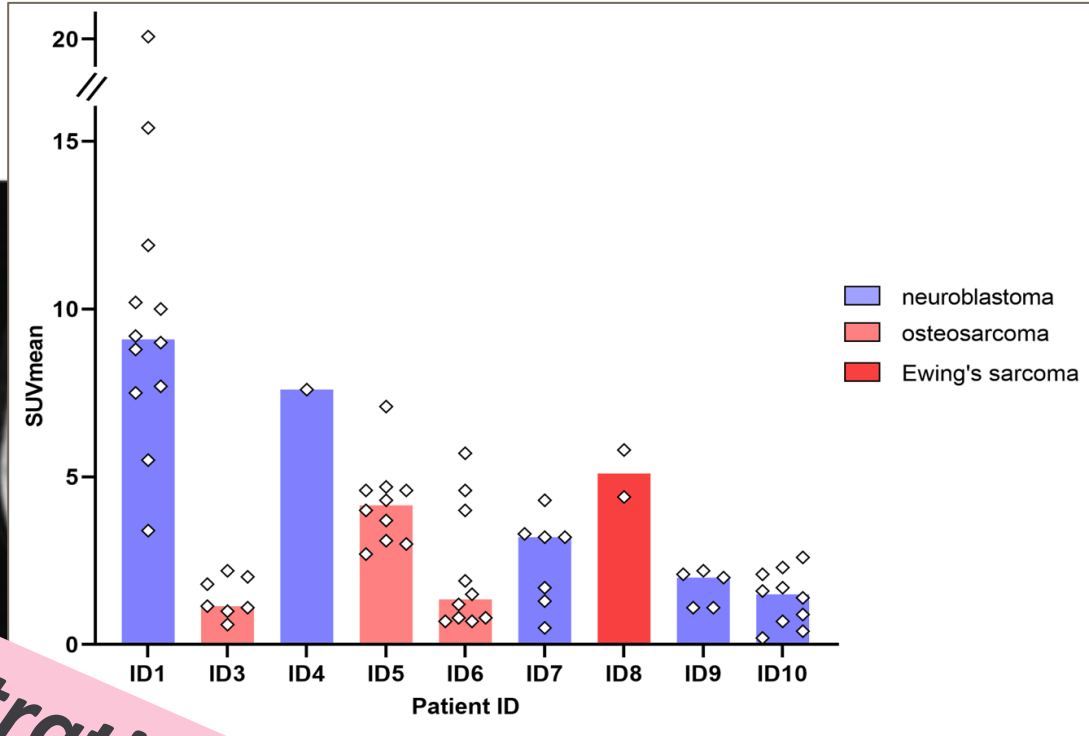
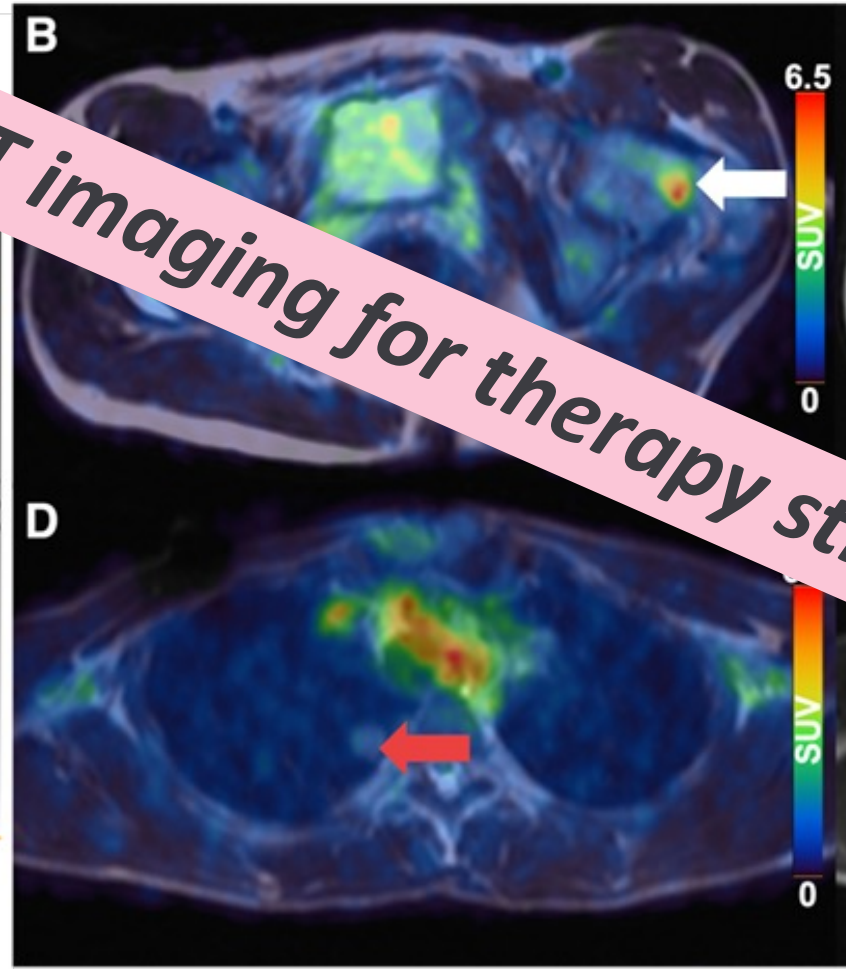


Trautwein et al.,..., la Fougère JNM 2023
 Trautwein et al., ..., la Fougère Nature Communication in review



GD2 heterogeneous expression in PET

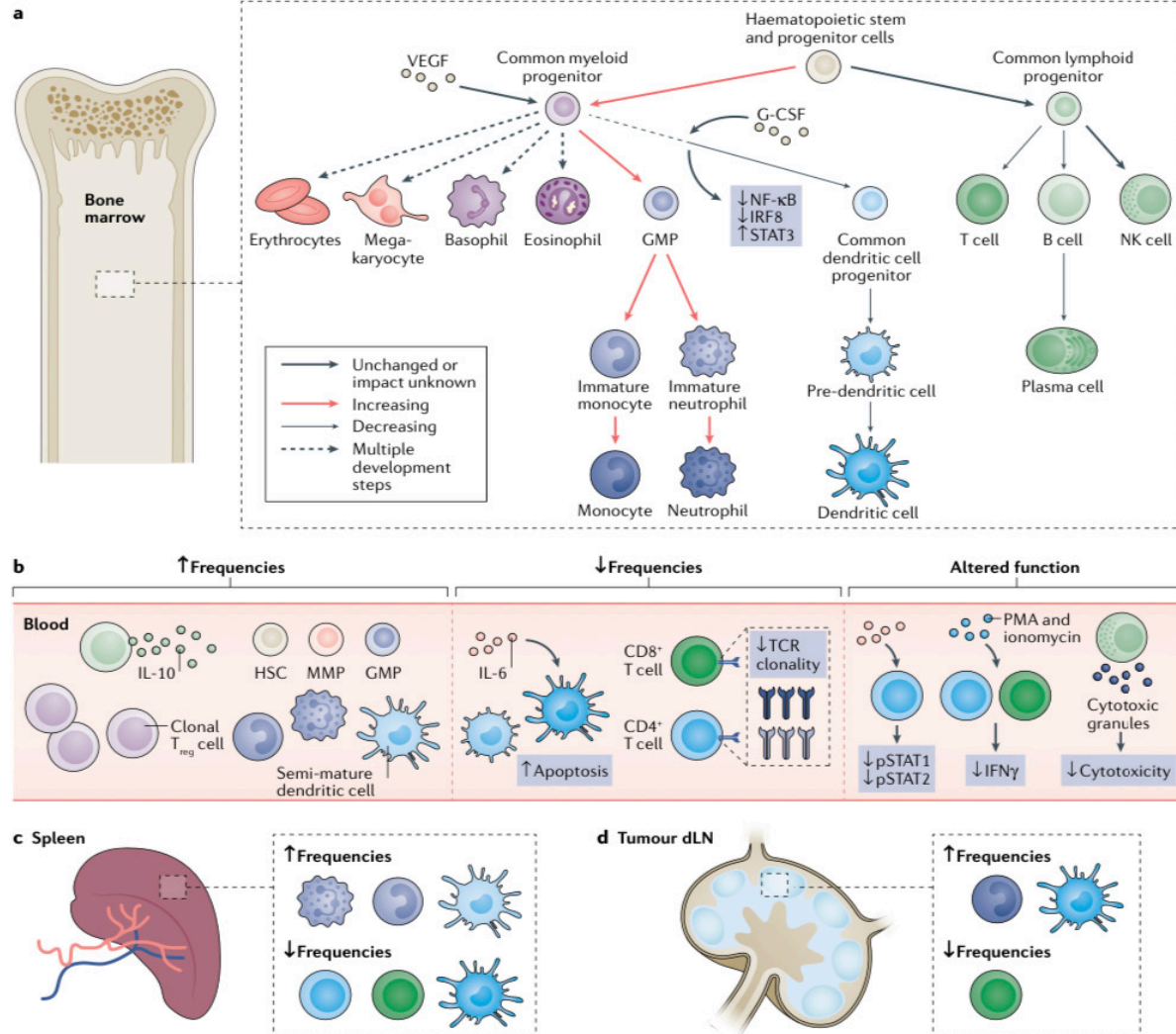
Immuno-PET imaging for therapy stratification in children !



Holistic imaging of immune cells and immune cell activation



Visualization of the temporal dynamics of the involved molecular processes and the immune cell accumulation and homing sites

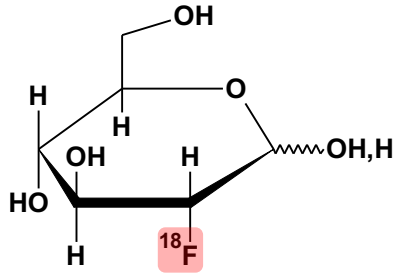


- Cancer induces many functional changes throughout the immune system
- Need to assess the systemic immune landscape beyond the tumor microenvironment
- Peripheral immune system is required to drive an effective natural and therapeutically induced anti-tumor immune response
- Immunotherapy may induce new immune responses rather than reinvigorating pre-existing immune responses



Imaging of Molecular Processes

^{18}F -FDG: [^{18}F]Fluorodeoxyglucose Glucose metabolism (GLUT-1)



Barbara
Schörg



Johannes
Schwenck



Research Paper

Cancer immunotherapy is accompanied by distinct metabolic patterns in primary and secondary lymphoid organs observed by non-invasive *in vivo* ^{18}F -FDG-PET

Johannes Schwenck^{1,2,3*}, Barbara Schörg^{2*}, Francesco Fiz^{1,4}, Dominik Sonanini^{2,5}, Andrea Forschner⁶, Thomas Eigentler⁶, Benjamin Weide⁶, Manuela Martella⁷, Irene Gonzalez-Menendez^{3,7}, Cristina Campi⁸, Gianmario Sambuceti⁹, Ferdinand Seith¹⁰, Leticia Quintanilla-Martinez^{3,7}, Claus Garbe⁶, Christina Pfannenberg¹⁰, Martin Röcken^{3,6,11}, Christian la Fougere^{1,3,11}, Bernd J Pichler^{2,3,11}, Manfred Kneilling^{2,3,6}✉

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3. Cluster of Excellence iFIT (EXC 2180) "Image-Guided and Functionally Instructed Tumor Therapies", Eberhard Karls University, 72076 Tübingen, Germany
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6. Department of Dermatology, Eberhard Karls University, 72076 Tübingen, Germany
7. Institute of Pathology and Neuropathology and Comprehensive Cancer Center Tübingen, Eberhard Karls University, 72076 Tübingen, Germany
8. Department of Mathematics "Tullio Levi-Civita", University of Padua, Italy
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10. Department of Diagnostic and Interventional Radiology, Eberhard Karls University, 72076 Tübingen, Germany
11. German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ) Partner Site Tübingen, 72076 Tübingen, Germany

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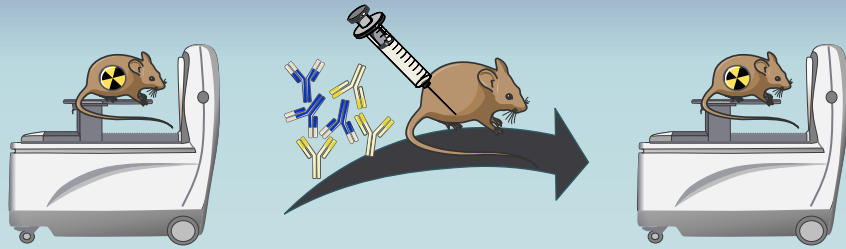
Received: 2019.04.23; Accepted: 2019.09.02; Published: 2020.01.01



Visualization of the systemic immune response

Baseline (^{18}F -FDG-PET)

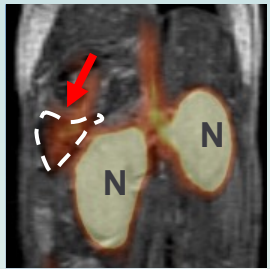
Follow-up (^{18}F -FDG-PET)



Immune-Checkpoint-Inhibitor Treatment

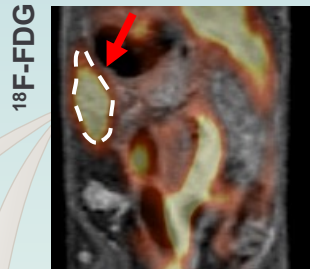
Spleen

^{18}F -FDG



Low Uptake

Responder

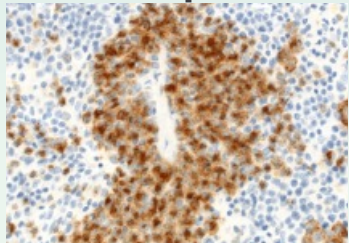


Increased Uptake

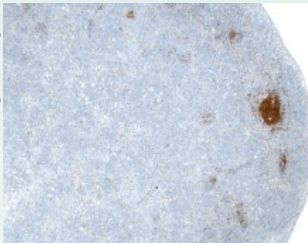
Neutrophils \uparrow

T Cells \downarrow

MPO (400x)



CD3 (25x)

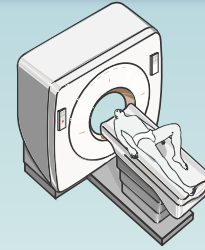


RIP1-Tag2 insular cell carcinoma model

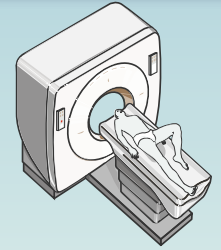
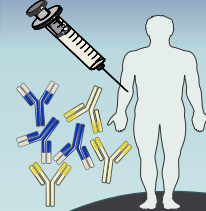
Clinical Translation

Baseline (^{18}F -FDG-PET)

Follow-up (^{18}F -FDG-PET)



Immun-Checkpoint-Inhibitor Therapy



Spleen

^{18}F -FDG



Low Uptake

Responder

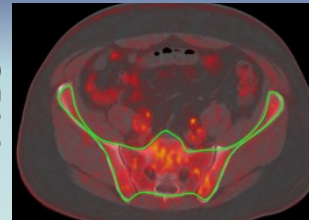
^{18}F -FDG



Increased Uptake

Bone Marrow

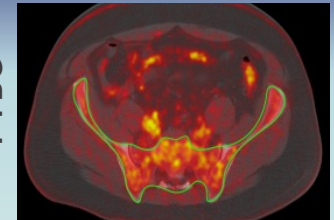
^{18}F -FDG



Low Uptake

Responder

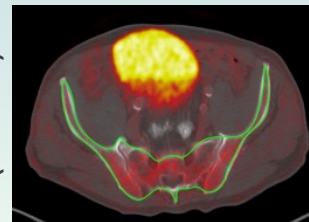
^{18}F -FDG



Increased Uptake

Bone Marrow

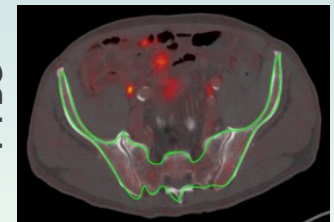
^{18}F -FDG



Low Uptake

Non-Responder

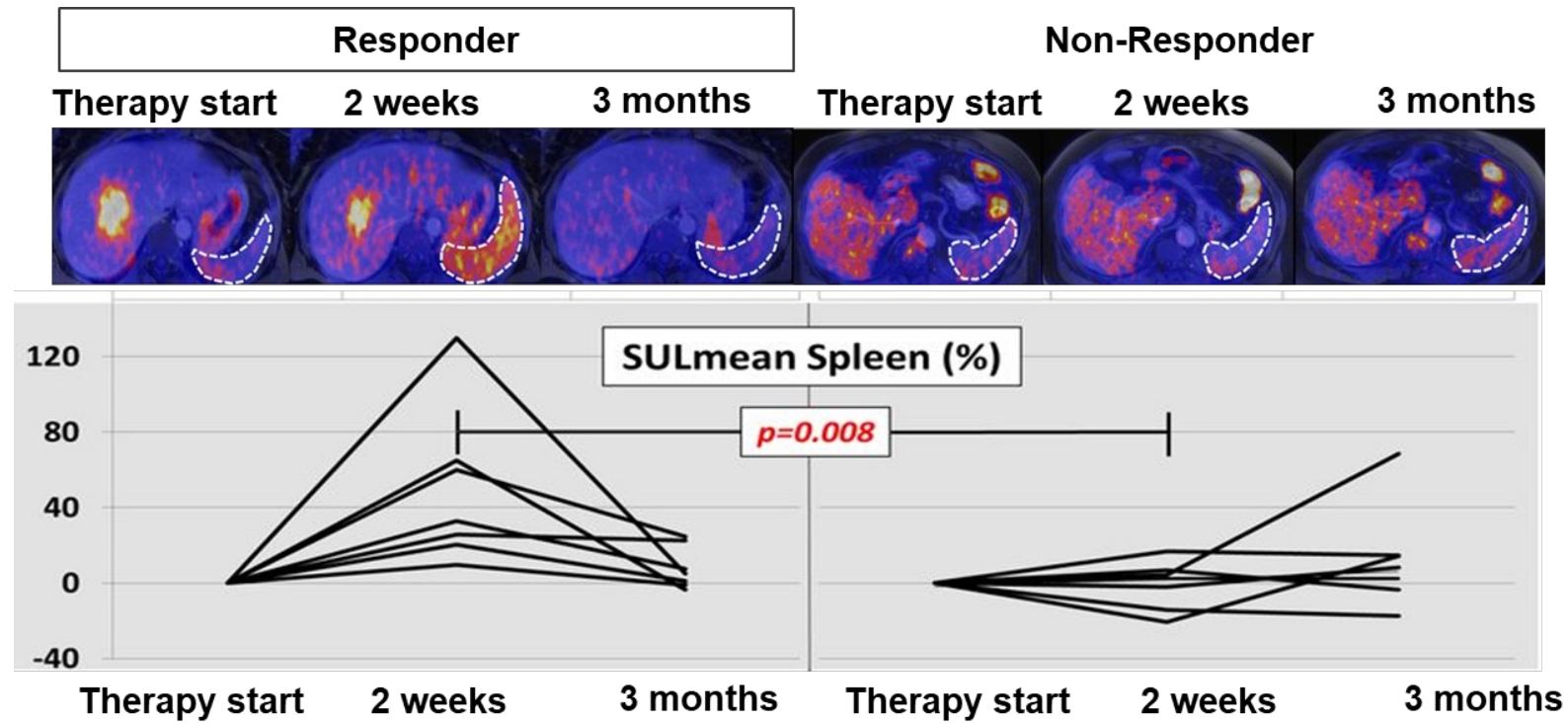
^{18}F -FDG



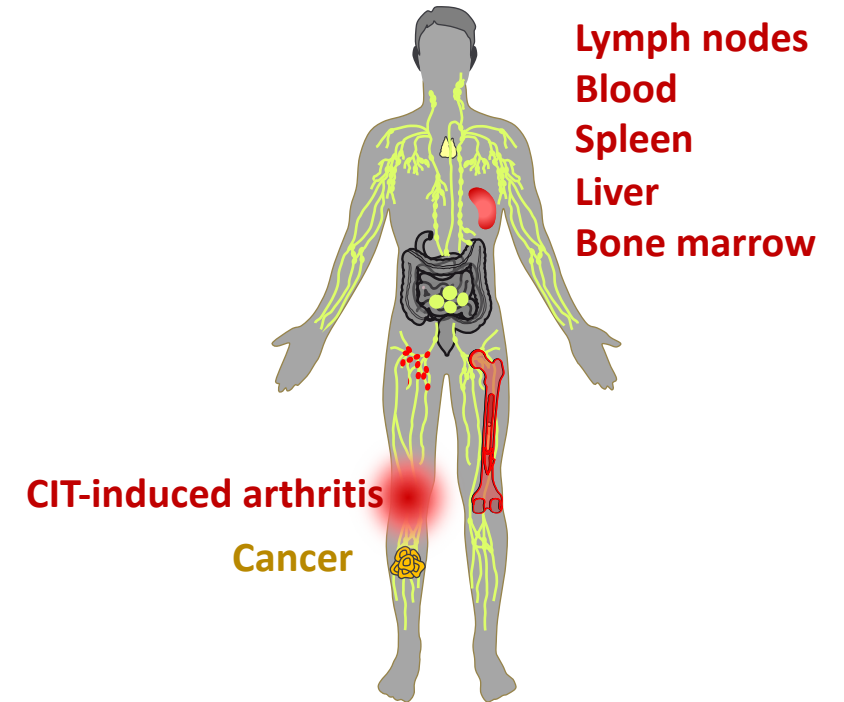
Low Uptake



Glucose metabolism of the spleen – importance of the temporal dynamics

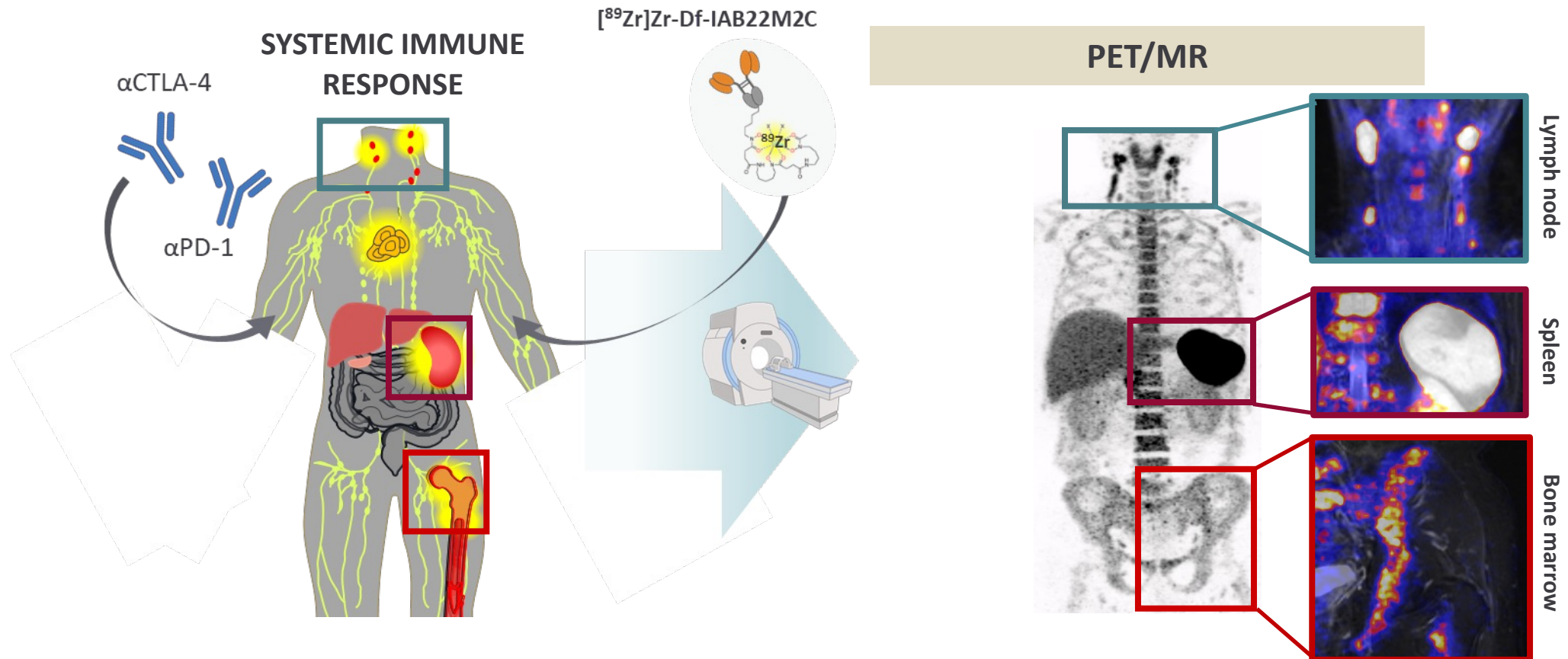


local & systemic



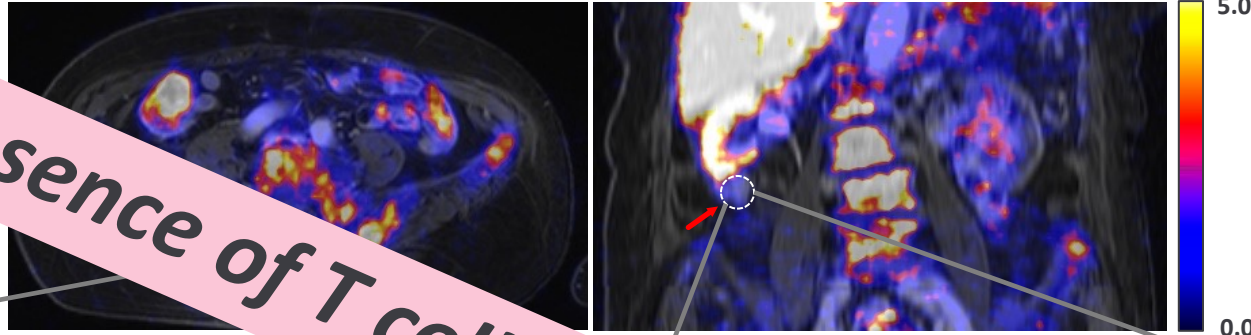
Seith F. et al. JITC 2020

Imaging of the CD8⁺ T cell infiltrate: [⁸⁹Zr]Zr-Df-IAB22M2C



Imaging of the CD8 T cell distribution

[⁸⁹Zr]Zr-Df-IAB22M2C-PET/MRI

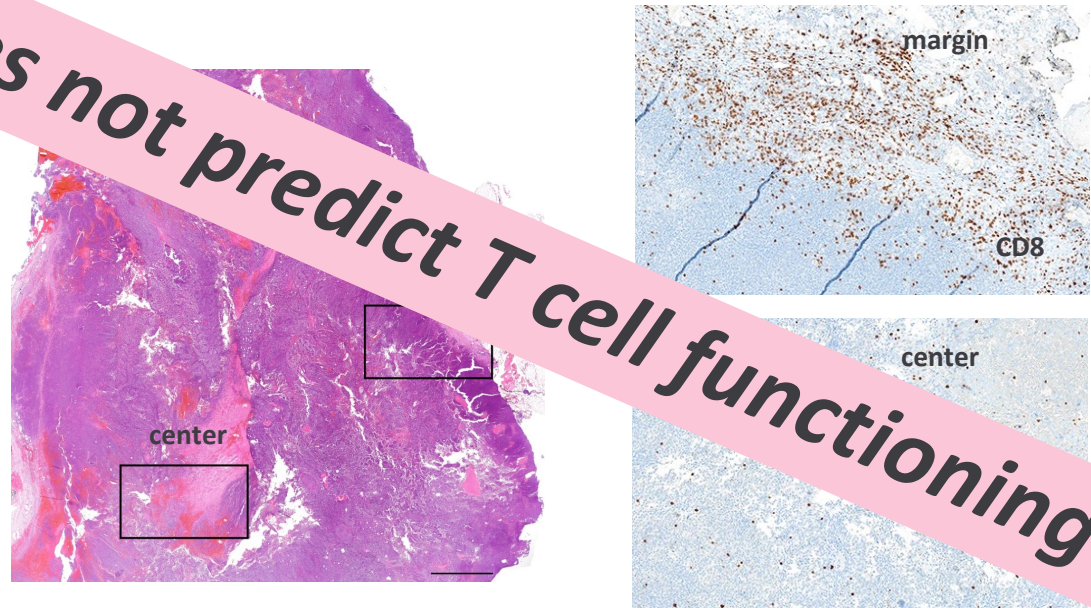


CD8 Minibody
[⁸⁹Zr]Zr-Df-IAB22M2C

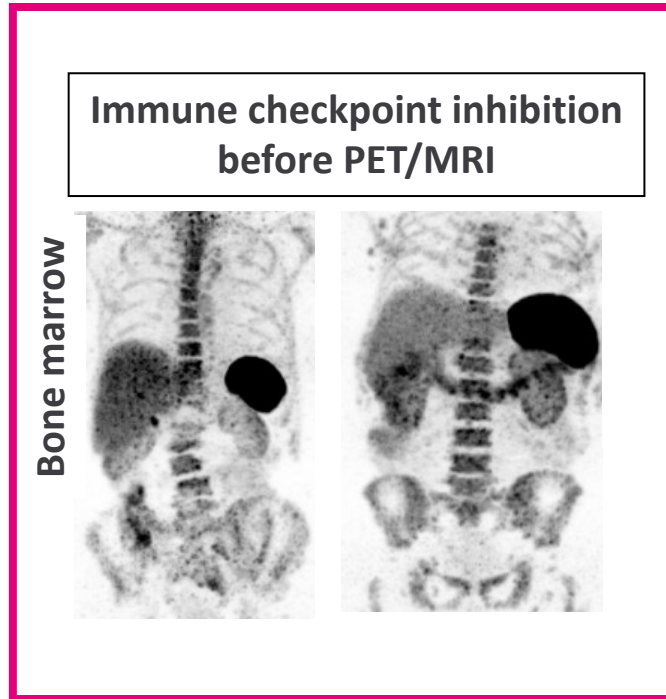
The presence of T cells does not predict T cell functioning



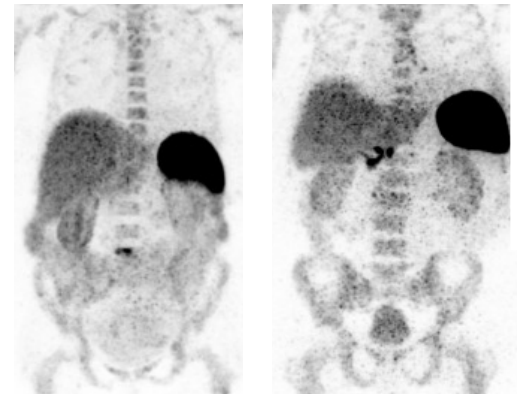
Progress



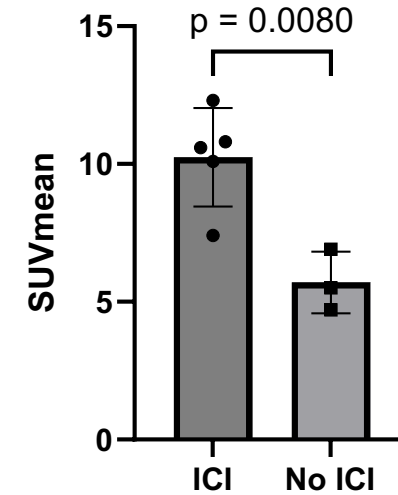
Imaging of the CD8 T cell distribution



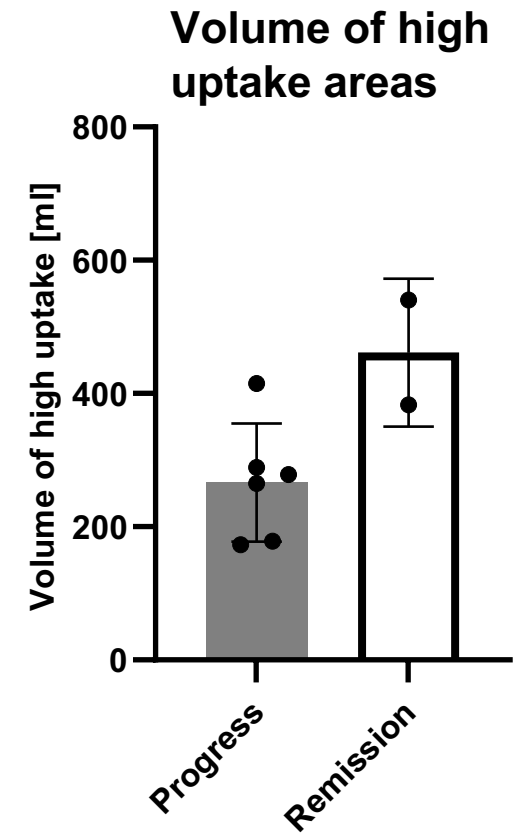
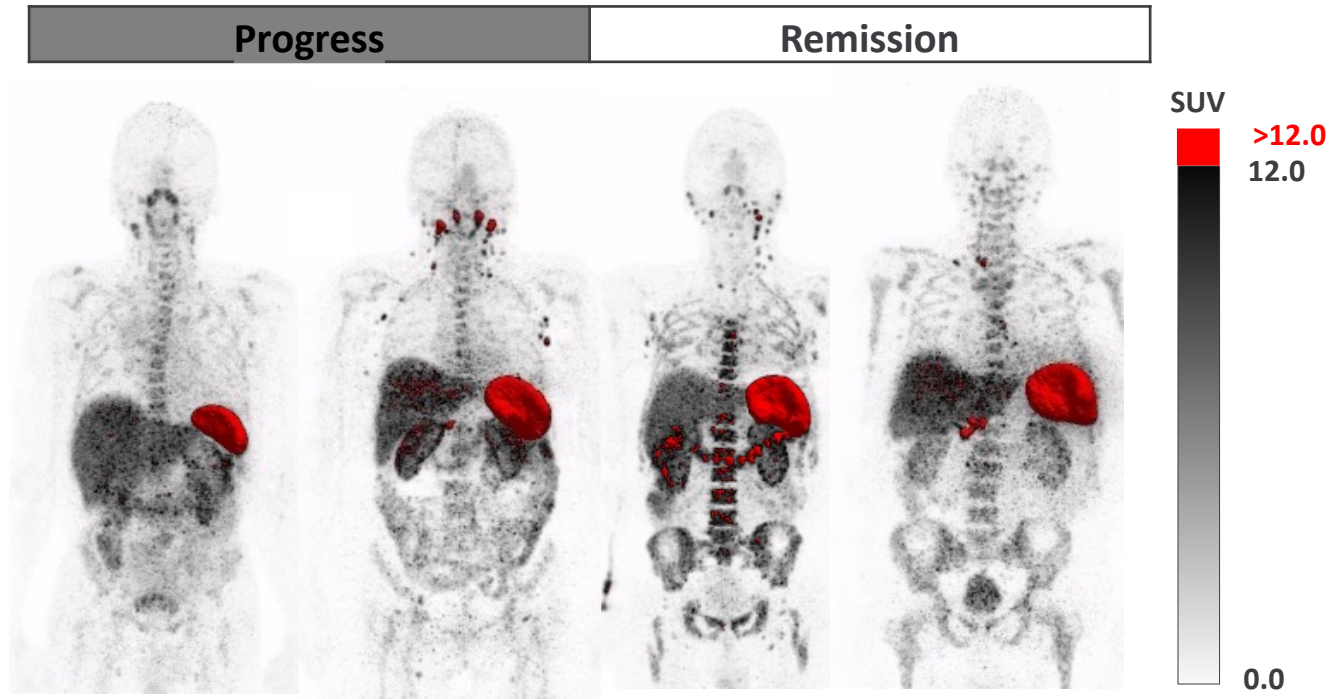
No immune checkpoint inhibition
before PET/MRI



⁸⁹Zr-Df-IAB22M2C-Uptake
Lumbar vertebra

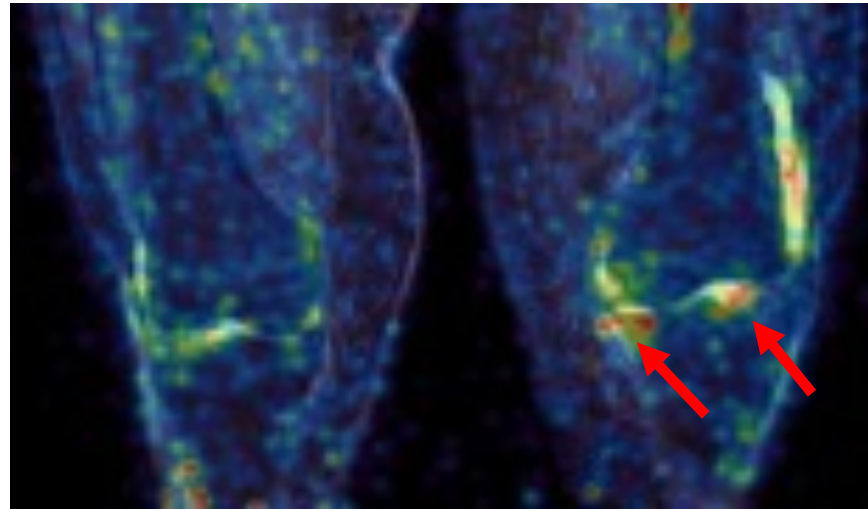


Imaging of the CD8⁺ T cell infiltrate

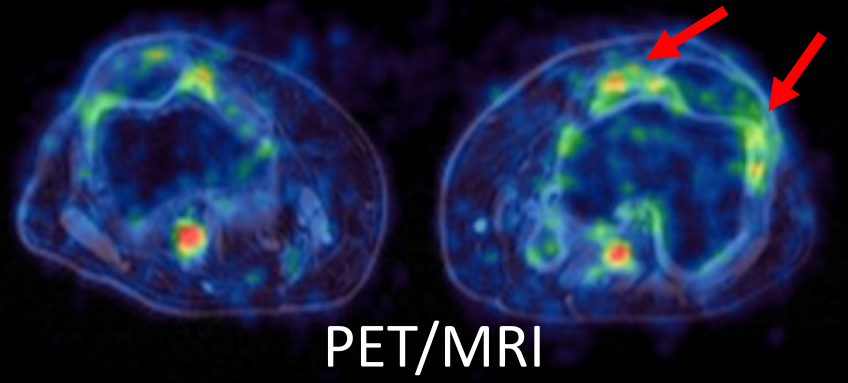


[⁸⁹Zr]-CD8 Minibody PET/MRI – metastatic melanoma - Toxicities

Balance: Tumorimmunity - Autoimmunity



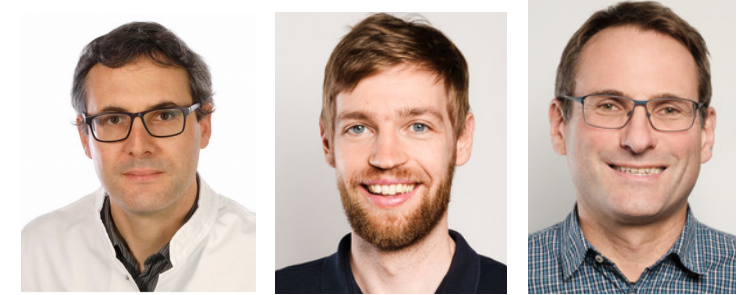
Rheumatoid Arthritis



PET/MRI

In vivo visualization of Toxicities ?

First prospective cell tracking study in Germany

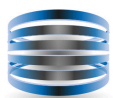
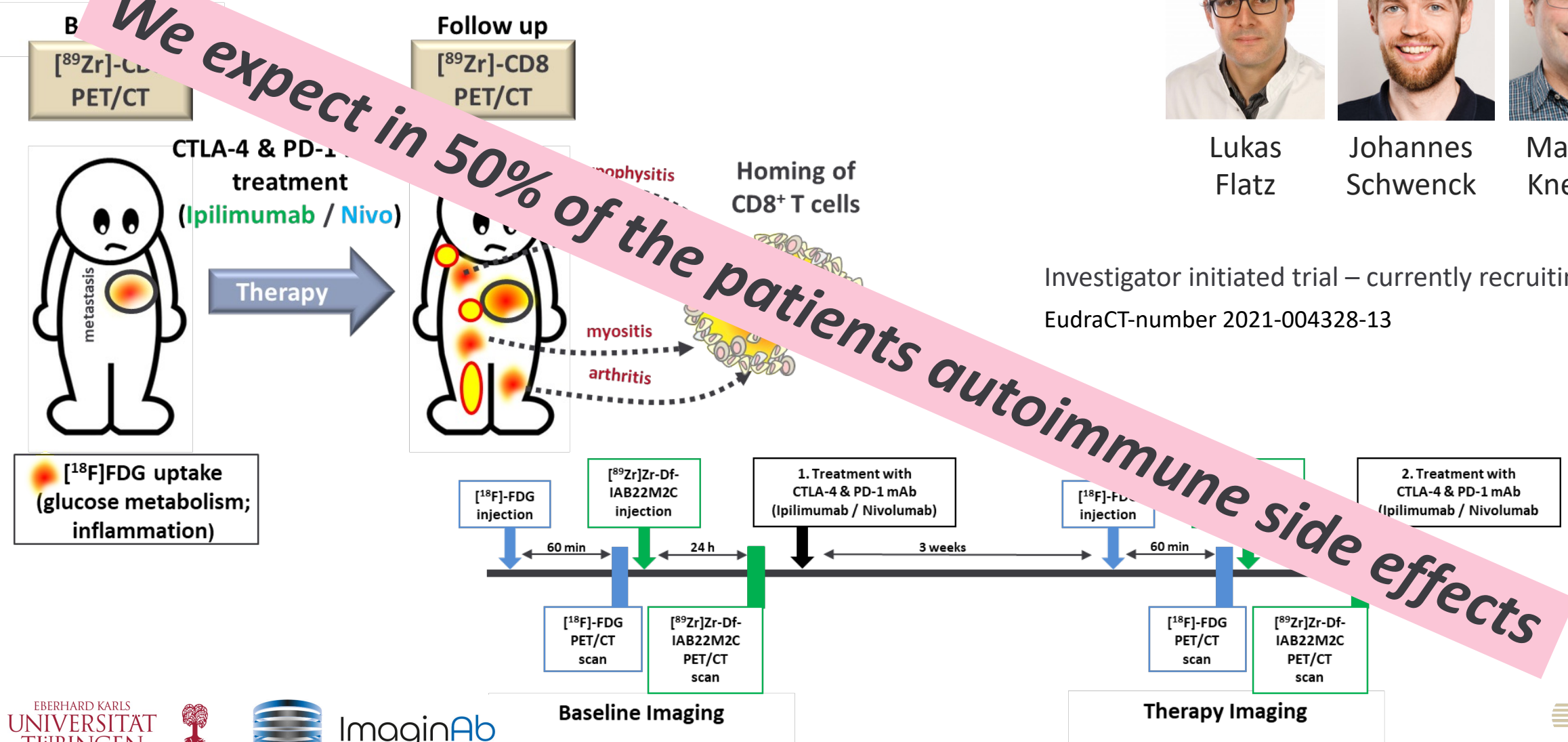


Lukas Flatz

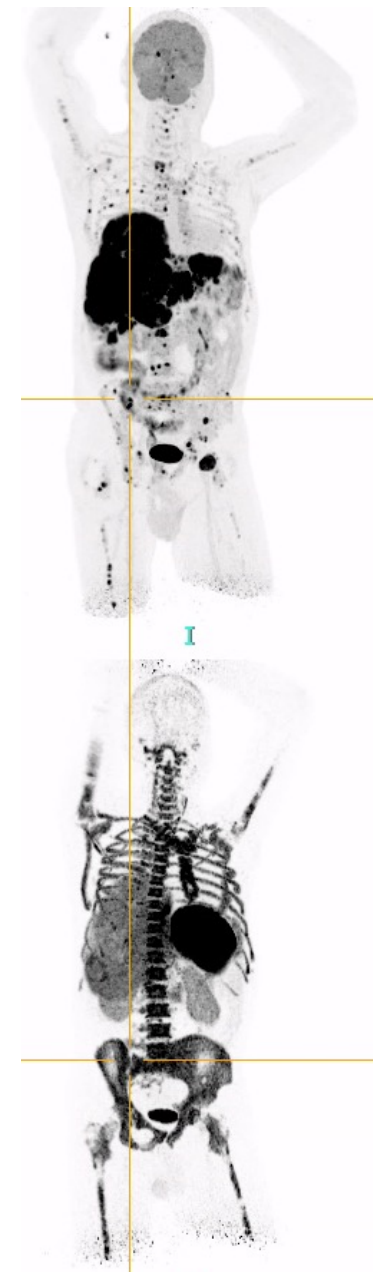
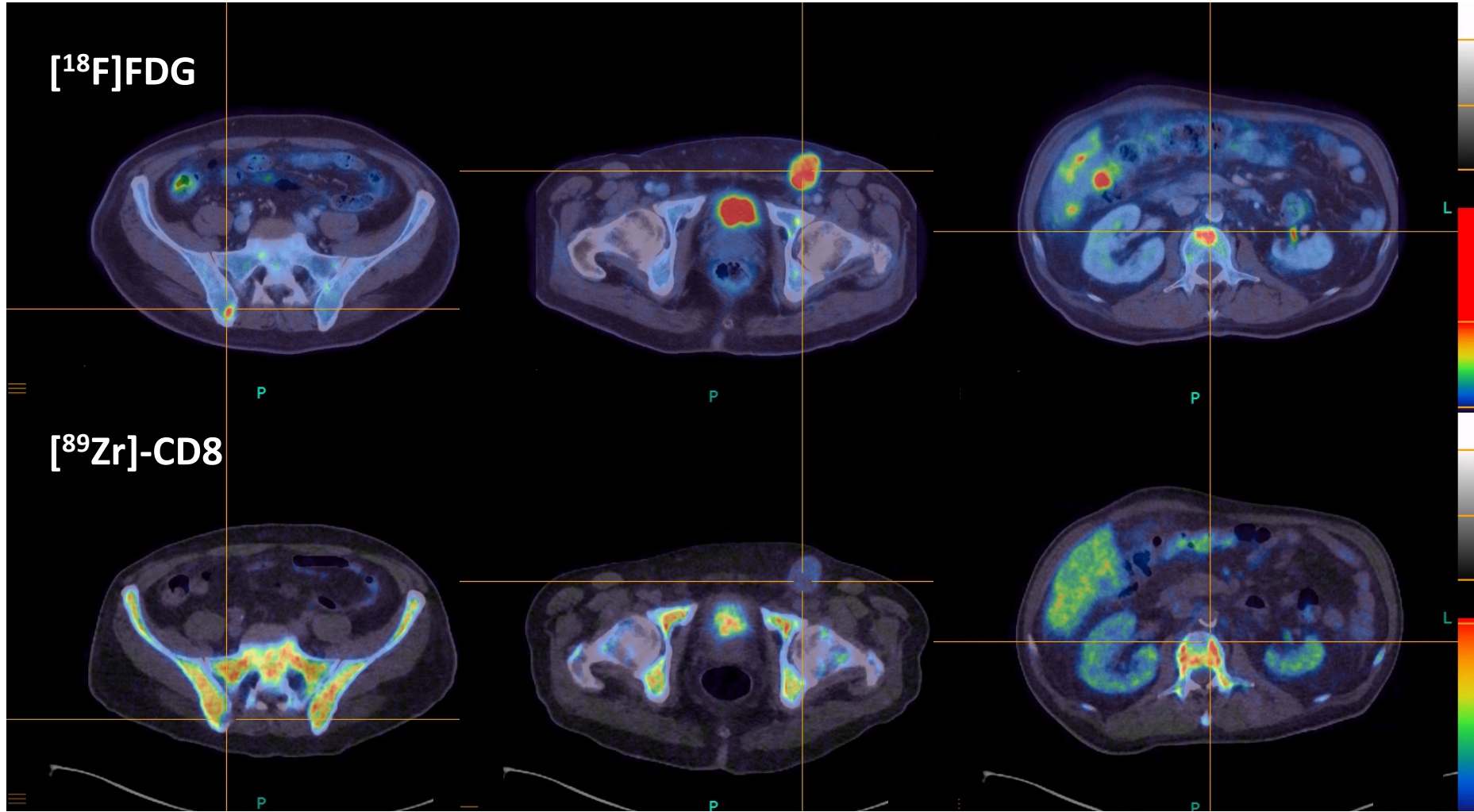
Johannes Schwenck

Manfred Kneilling

Investigator initiated trial – currently recruiting
EudraCT-number 2021-004328-13

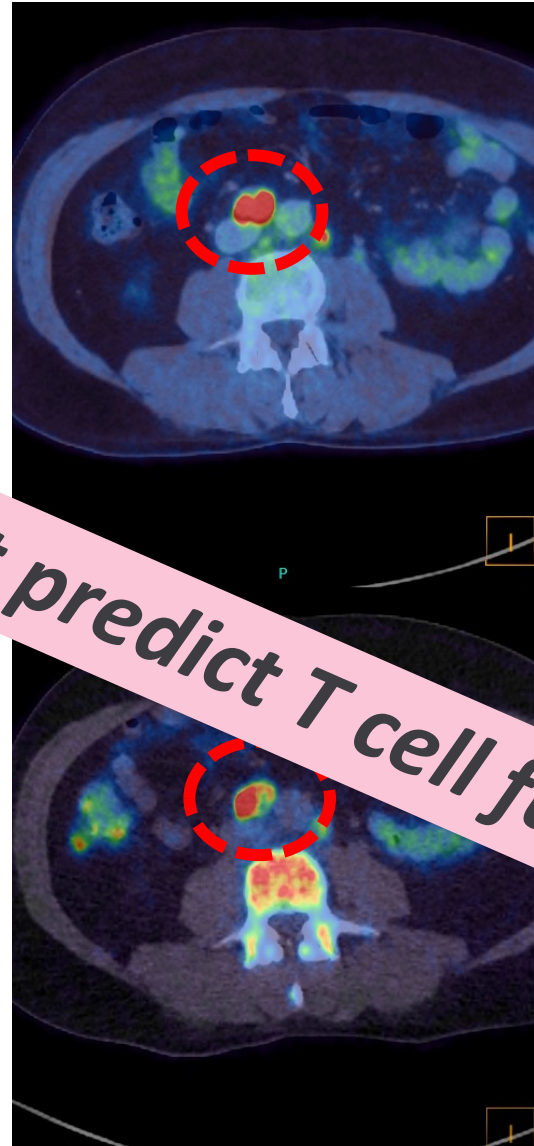


Melanoma prior CIT: mismatch $[^{18}\text{F}]\text{FDG}$ – $[^{89}\text{Zr}]\text{CD8}$: PD



Melanoma prior CIT: mismatch $[^{18}\text{F}]\text{FDG}$ – $[^{89}\text{Zr}]\text{CD8}$: SD

$[^{18}\text{F}]\text{FDG}$



$[^{89}\text{Zr}]\text{-CD8}$



Dual approaches might predict T cell functioning

CD8 Minibody
 $[^{89}\text{Zr}]\text{Zr-Df-IAB22M2C}$

Total Body PET/CT -

the FUTURE for visualization of the systemic immune response

Improved understanding by total body PET/CT and dual approaches



¹⁸F-FDG

Lymph nodes
Blood
Spleen
Liver
Bone marrow

Inflammation
Cancer

[⁸⁹Zr]-CD8 minibody



Dual Tracer Approaches:

¹⁸F t_{1/2} 109 min

Glucose metabolism
Cell proliferation
Hypoxia
Fibroblast activation protein (FAP)
Immune cells (T cells, macrophages ..)
Immune cell activation (CD69, OX40)

Immune cells (T cells, macrophages ..)
Immune cell activation (CD69, OX40)
Angiogenesis
.....



Thank you for your attention

Christian la Fougère, MD
Nuclear Medicine and Clinical Molecular Imaging
christian.lafougere@med.uni-tuebingen.de

