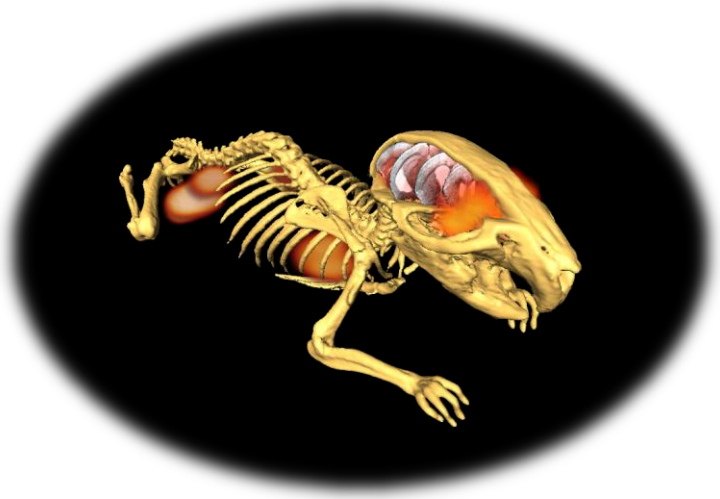


UNIVERSITY OF EASTERN FINLAND

PET basics - and imaging at Kuopio-Biomedical Imaging Unit (Kuopio-BIU)

FIN3R symposium 6.11.2023

Kimmo Jokivarsi

Staff Scientist

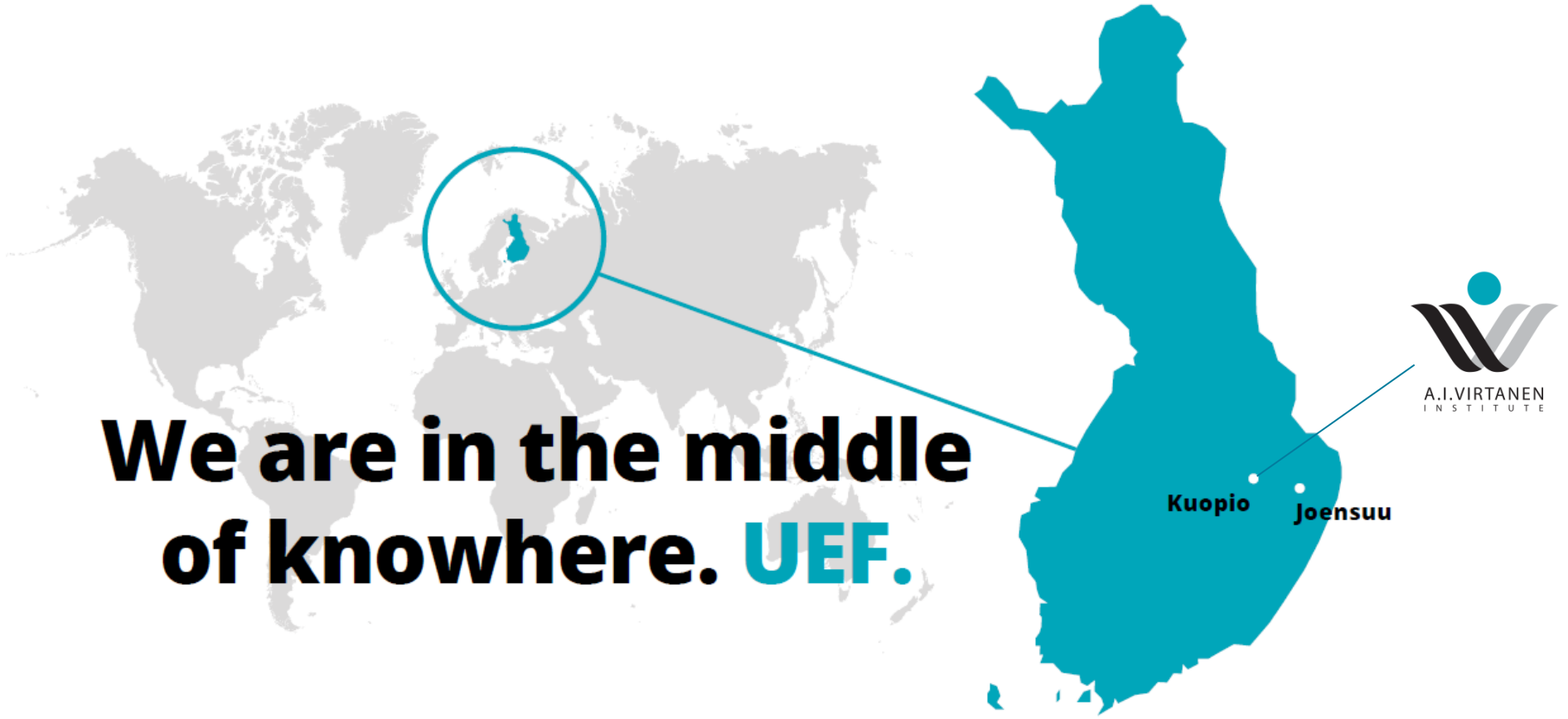
Kuopio-BIU, A.I.Virtanen institute

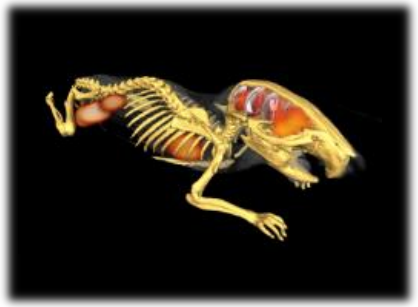
UEF, Kuopio campus

A.I.VIRTANEN INSTITUTE

FINNISH BIOMEDICAL IMAGING

EURO BIOIMAGING


We are in the middle
of knowhere. UEF.
A.I.VIRTANEN
INSTITUTE
Kuopio
Joensuu



Kuopio Biomedical Imaging Unit (BIU)

National pre-clinical MRI center
Part of Finnish Biomedical Imaging-node in EuroBioImaging

} Access to academic and commercial researchers

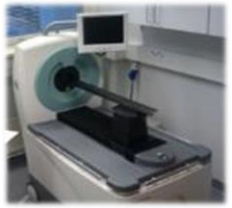
Ex Vivo

0.7 T (29.8 MHz) 3 T 7 T 9.4 T 11.7 T (500MHz)

In Vivo

Simultaneous PET/MRI

Nuclear Imaging (BIU+KUH)



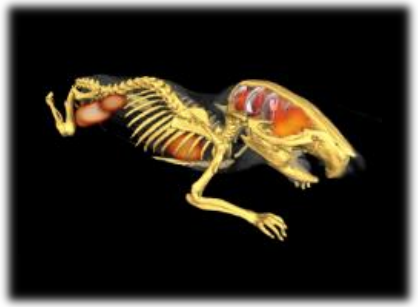
PET

PET tracers

uCT

MRI community of ~35 researchers

Faculty of Health	Prof. Olli Gröhn	Functional MRI
	Prof. Jussi Tohka	Advanced data-analysis
	Res.Dir. Alejandra Sierra Lopez	Microstructural MRI
	Res.Dir. Mikko Kettunen	Metabolic MRI
	Res. Elias Ylä-Herttuala (KUH)	Cardiac MRI
Faculty of Natural Sciences	Res.Dir. Mikko Nissi	Cartilage MRI
	Prof. Ville Kolehmainen	Advanced data-analysis



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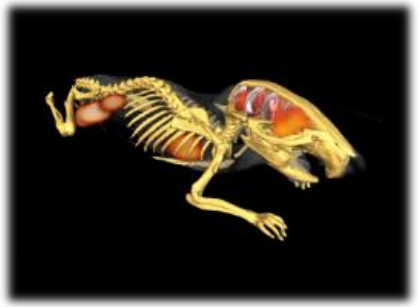
MRI
Resol : 50 µm (ex vivo) – 100 µm (in vivo)
Temp. resol : <secs – mins - hours
Imaging time : mins - hours
Sensitivity : µM - mM
No ionizing radiation

Non-invasive (3D) pre-clinical imaging

PET
Resol : 1 mm (in vivo)
Temp. Resol : secs – mins
Imaging time : mins - hour
Sensitivity : pM - nM
Ionizing radiation

CT
Resol : 5 µm (ex vivo) - 30 µm (in vivo)
Temp. Resol : secs
Imaging time : secs - mins
Sensitivity : mM
Ionizing radiation

➡ Structure – Function – Metabolism – Clinical translation



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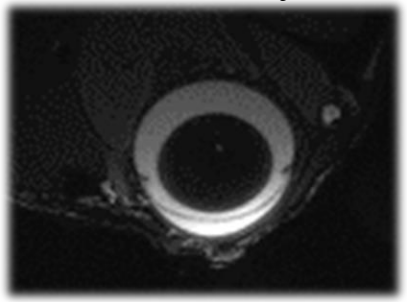
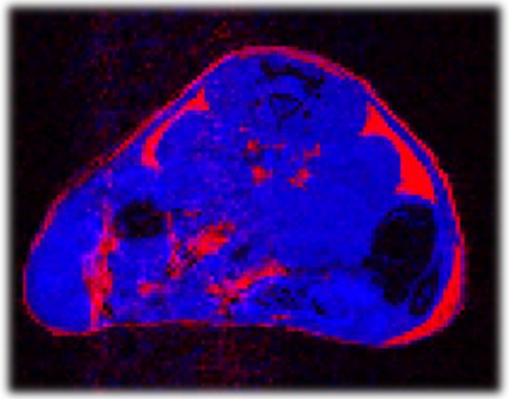
} Access to academic and commercial researchers

Recent projects

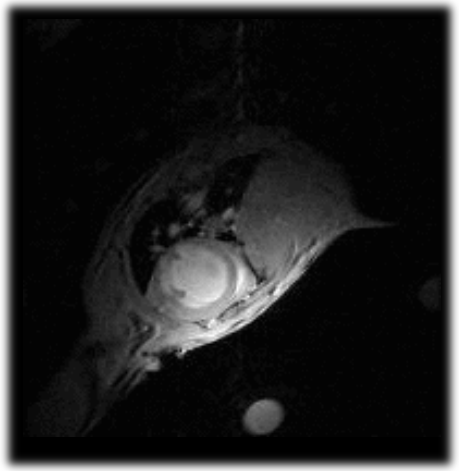
MRI of rat eye



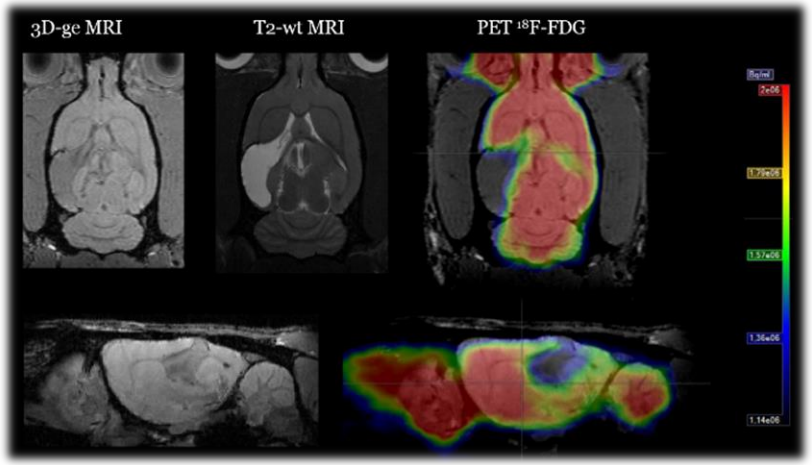
Body fat distribution



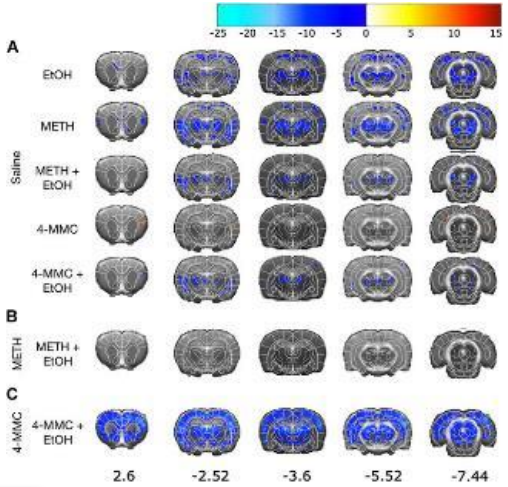
Mouse cardiac MRI



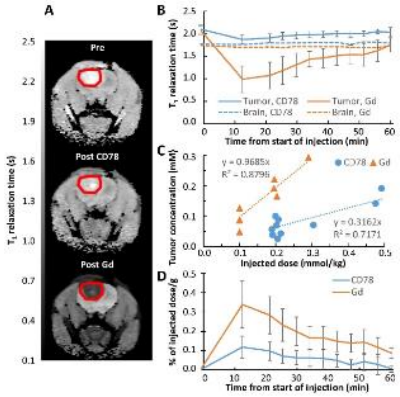
Brain metabolism in trauma



Mn enhanced MRI

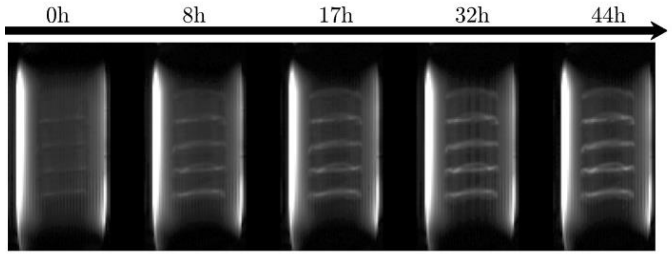


Novel MR contrast agents

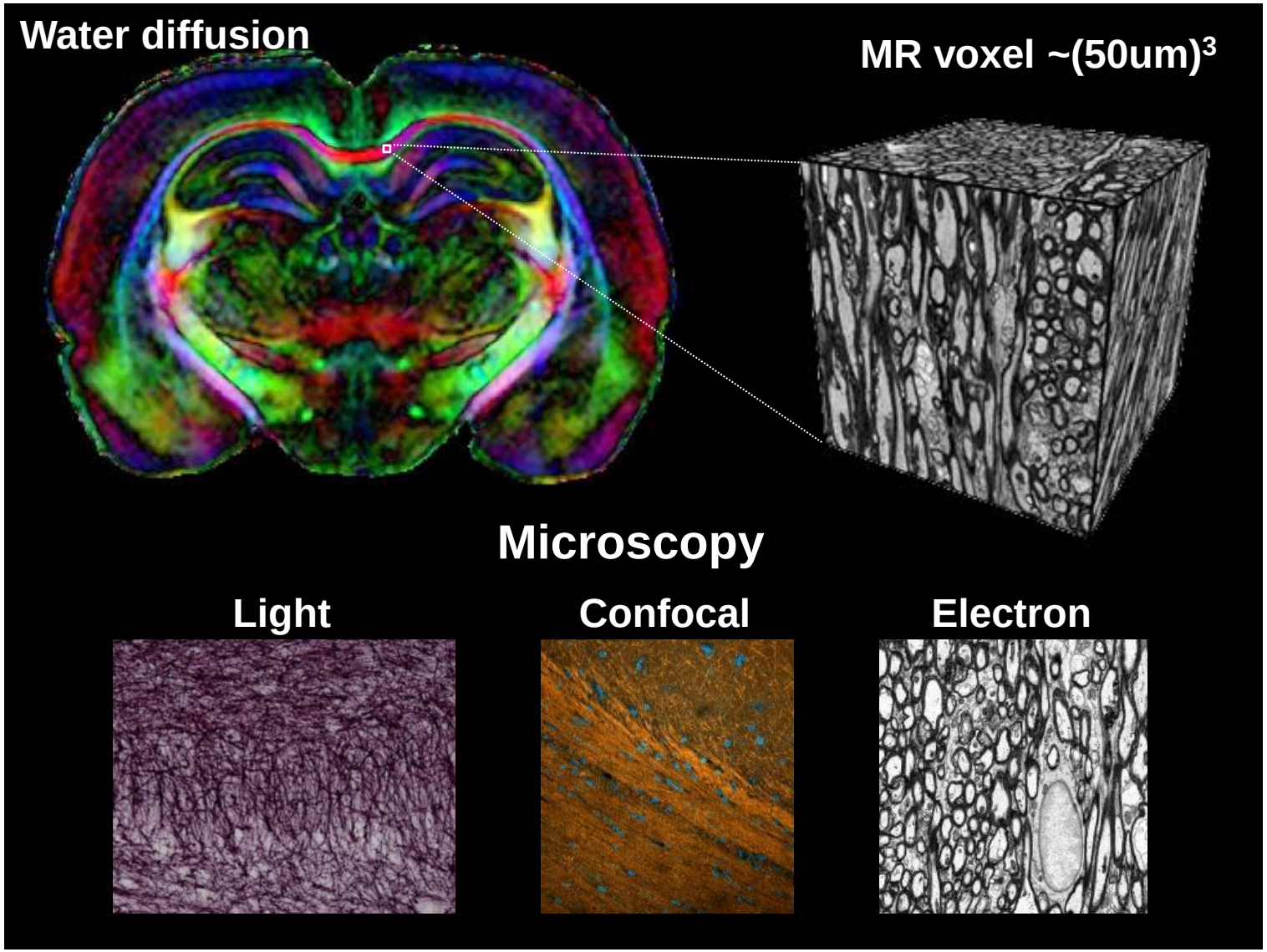


MRI of pine seed

MRI of paper



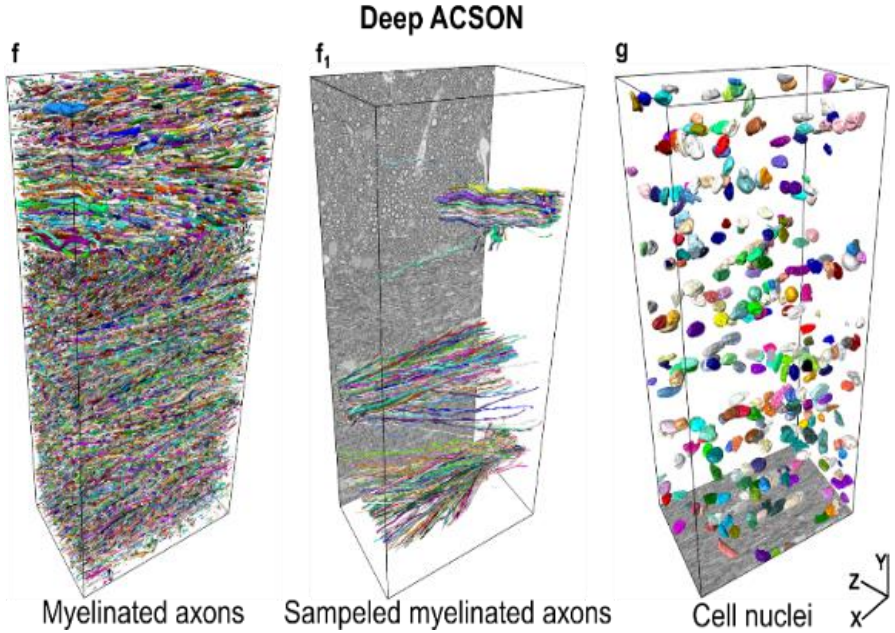
Microstructural MRI (Sierra, Multiscale Imaging Group)



Diffusion MRI is sensitive to tissue microstructure

Correlation with microscopy

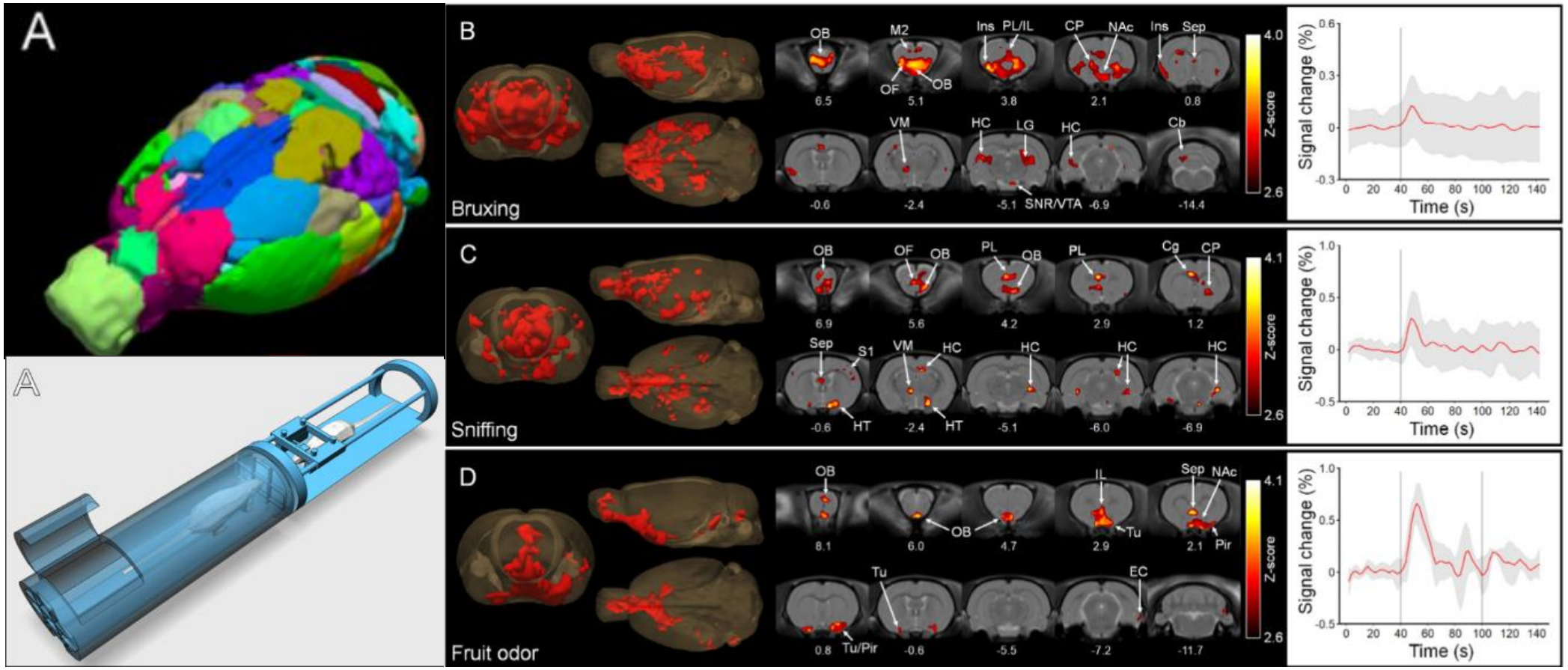
Segmentation and modeling



Abdollahzadeh et al. (2021) *Commun Biol.*

Silent Functional MRI (Gröhn)

Functional networks in **awake** animals



1. Technical development
2. Epilepsy
3. De/Remyelination

Paasonen et al. (2022) *Neuroimage*

Metabolic MRI (Kettunen)

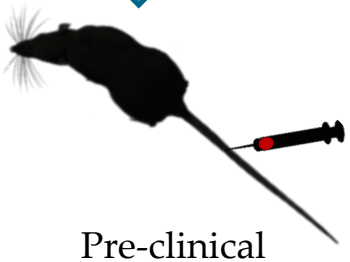
Hyperpolarisation allows **>10,000-fold transient increase of e.g. ^{13}C signal**

⇒ Real-time metabolic spectroscopy and spectroscopic imaging

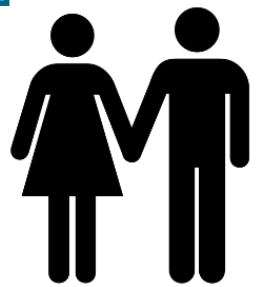
Sample pre-polarised,
MRI can be performed
even at low magnetic field

~80mM
100-700k ppm
polarisation

Cells,
Organoids

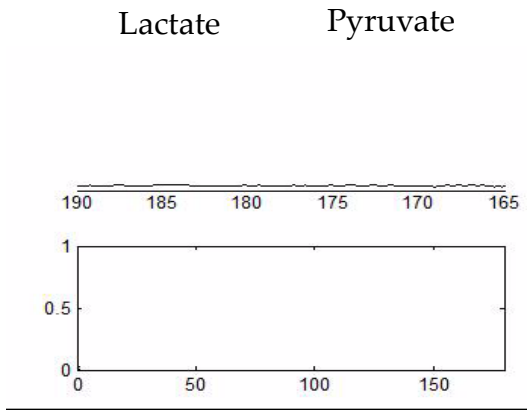


Pre-clinical
imaging



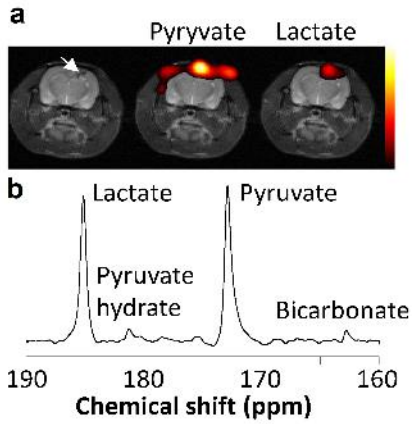
Clinical
translation

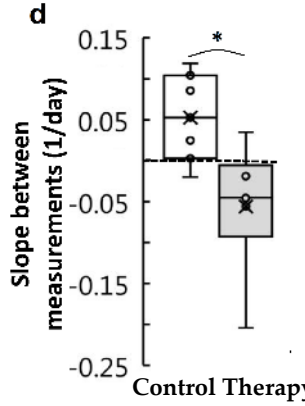
Hyperpolarised signal



Normal Signal

Gene therapy response

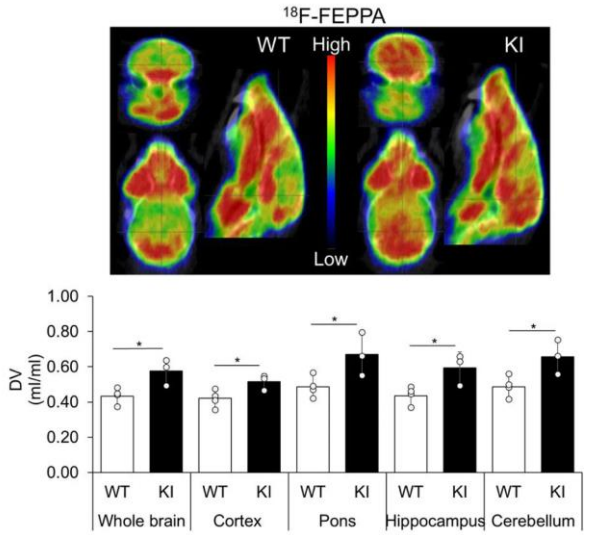




Nivajärvi/Olsson et al. (2020) *NMR Biomed*

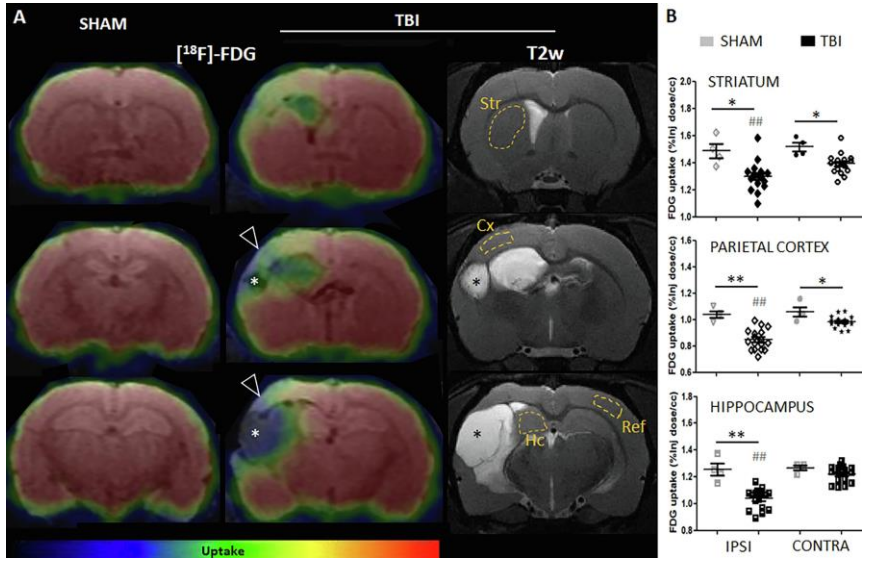
Radionuclide Imaging

Brain inflammation



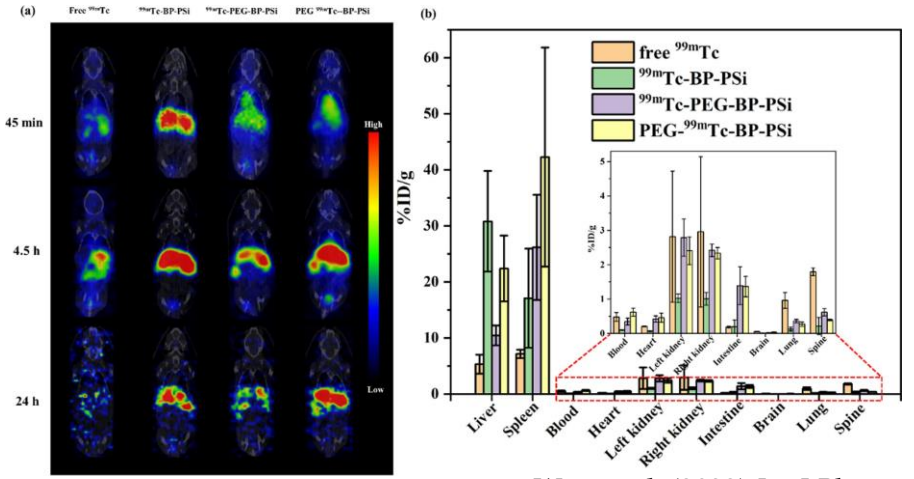
Takalo et al. (2020) *Mol Neurogen*

Hypometabolism in TBI



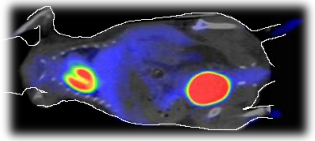
Yasmin et al. (2022) *Brain Res.*

Nanomedicine



Wen et al. (2022) *Int J Pharm.*

Cardiac metabolism

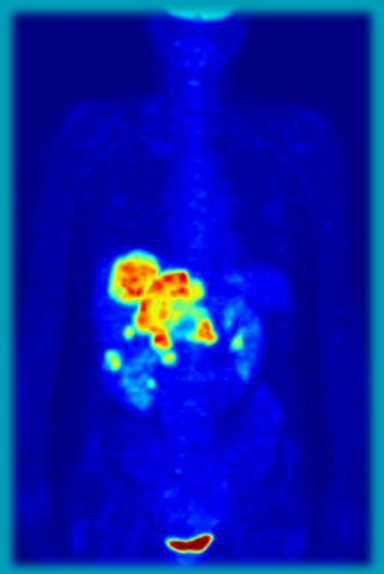


PET tracers (KUH)

^{18}F and ^{11}C-labelled tracers
^{18}F-FDG, ^{18}F-FEPPA, ^{18}F-Fallypride, ^{18}F-PE2i, ^{18}F-FPEB …

^{68}Ga and ^{89}Zr-labelled particles

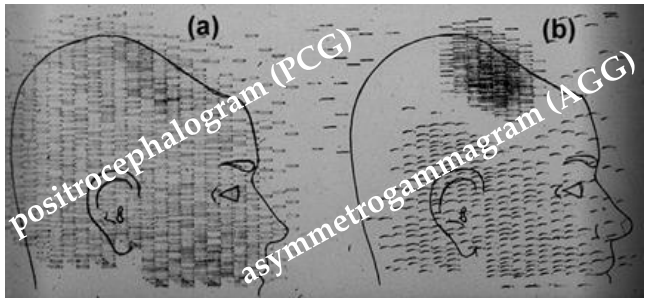
Simultaneous whole-body PET/MRI



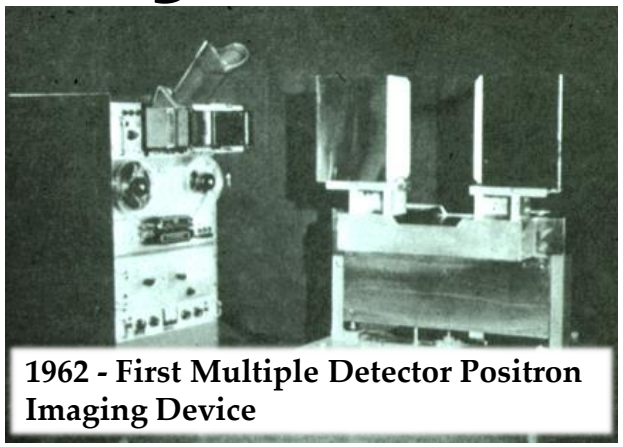
PET

Positron Emission Tomography

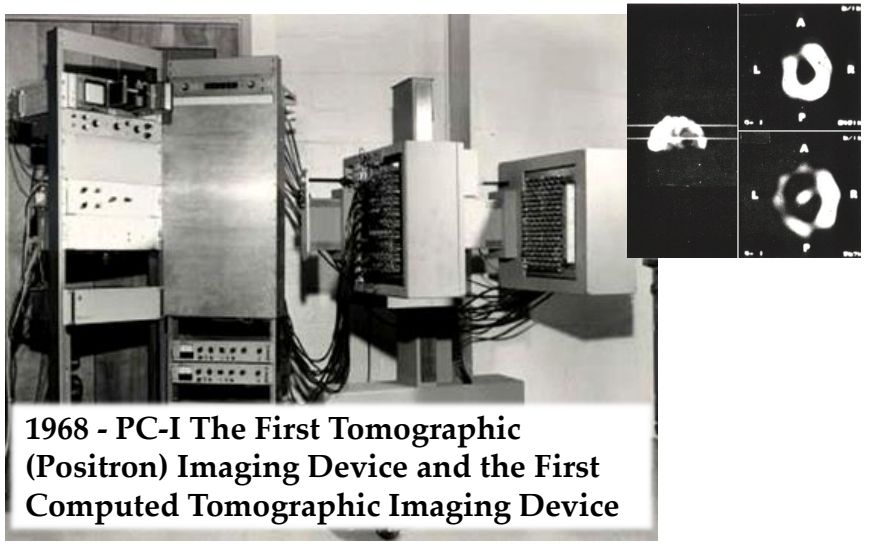
Bits of History of PET…



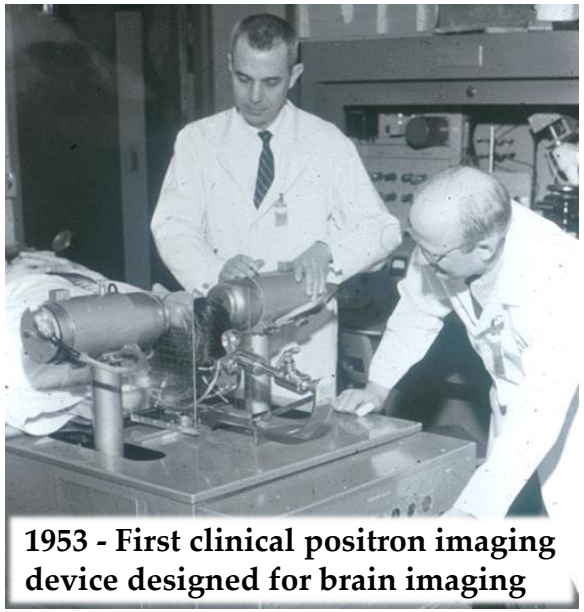
Brownell, G.L., Sweet, W.H. "Localization of brain tumors with positron emitters", Nucleonics 1953, 11:40-45.



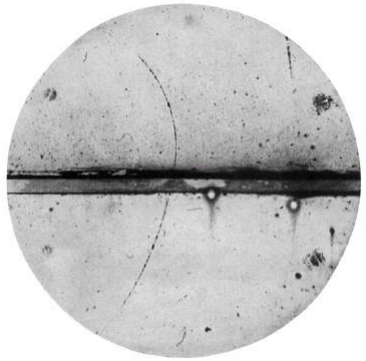
1962 - First Multiple Detector Positron Imaging Device



1968 - PC-I The First Tomographic (Positron) Imaging Device and the First Computed Tomographic Imaging Device



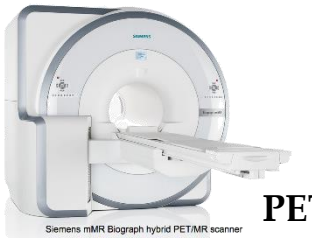
1953 - First clinical positron imaging device designed for brain imaging



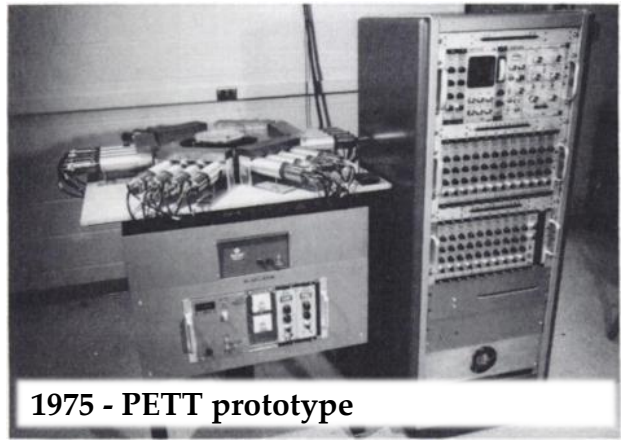
First positron track observed by Carl Anderson (1932)

PET+CT

PET



PET+MRI



1975 - PETT prototype

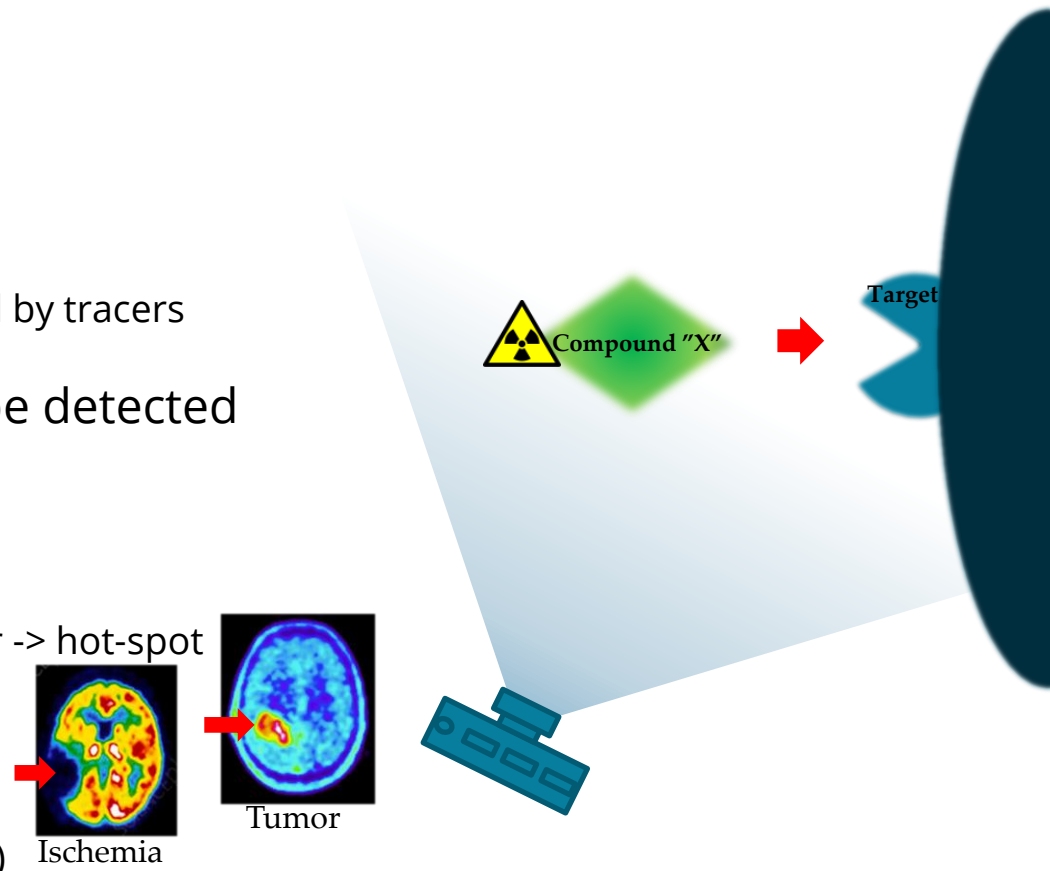
PET

Some bits of the basics...

Nuclear imaging & tracers

- Nuclear imaging uses radioactive tracers (radiopharmaceuticals) to e.g. assess bodily functions and to diagnose disease
- Molecular imaging probe (=tracer)
  - Chemical **compound with specificity** for molecular targets
  - A component that provides **signal** to be detected
  - External detectors capture and form images from **radiation** emitted by tracers
- Tracer applied in trace (i.e. minimal) amounts that can be detected

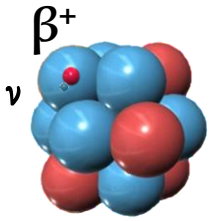
  -> has no pharmacologic effect in vivo
- Functional imaging
  - Increased physiological function -> increased concentration of tracer -> hot-spot
  - Some disease processes result in exclusion of a tracer -> cold-spot
- High sensitivity (10^{-11} – 10^{-12} mol/L)
  - PET 50-100 times more sensitive than SPECT (10^{7} times more vs MRI)



Positron Emission for Tomography…

Fluorine-18 (^{18}F)

- Produced with cyclotron ($[^{18}O]H_2O$)
- The most often used positron emitter
- Small (radioactive) atom (isotope)
  -> when added to a molecule does not deform it "beyond recognition"
- Half-life 109min
  -> i.e. 50% of activity gone in ~2h
  -> long enough for chemistry (labelling) and transportation
- Low radiation burden to patient



Fluorine-18 decay into Oxygen-18

Positron (β^+) emission (and a neutrino)

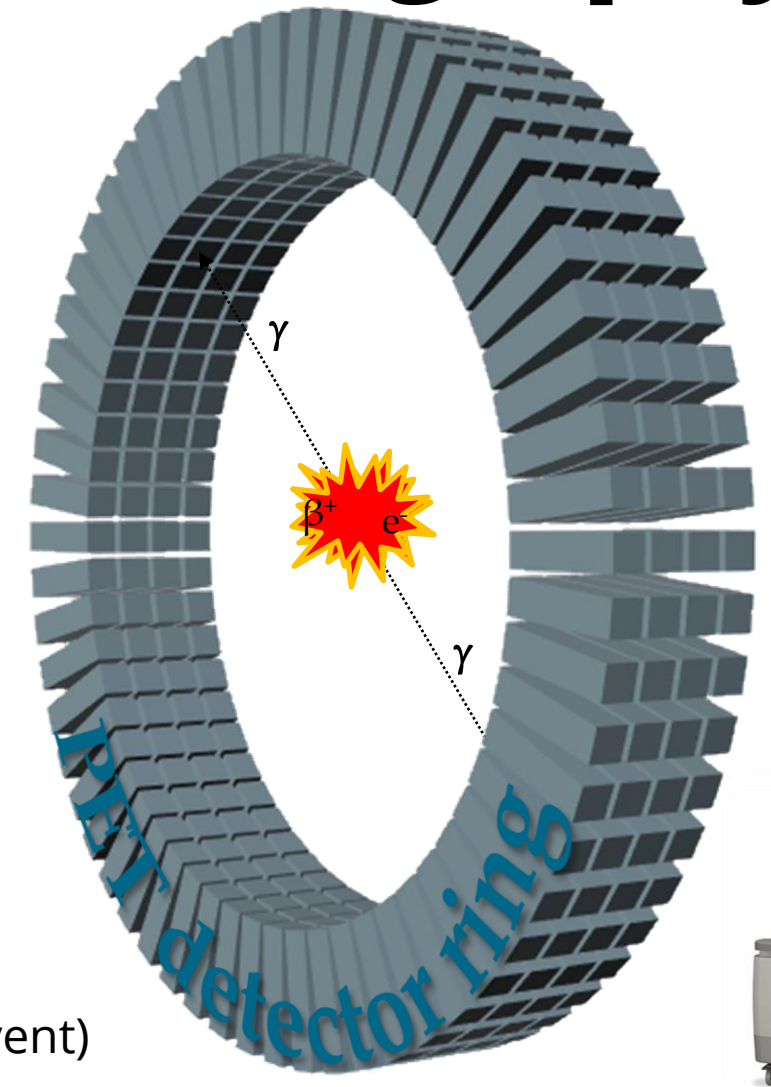
→ Collision with electron (e^-)

→ Annihilation

→ 2 γ's exiting opposite directions

→ 2 "simultaneous" detections (true event)

Collecting data of ~10^9 events

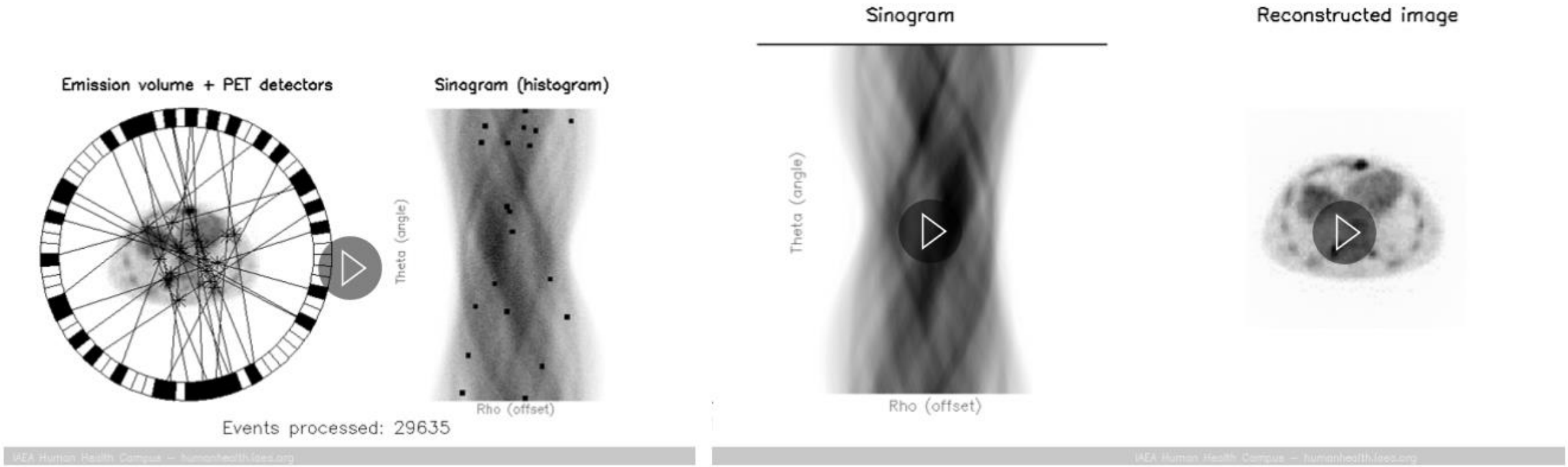


From coincidence to image

PET data collection

Histogramming (cleanup, windowing)

Image reconstruction (e.g. back projection)

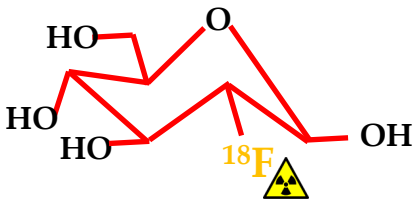


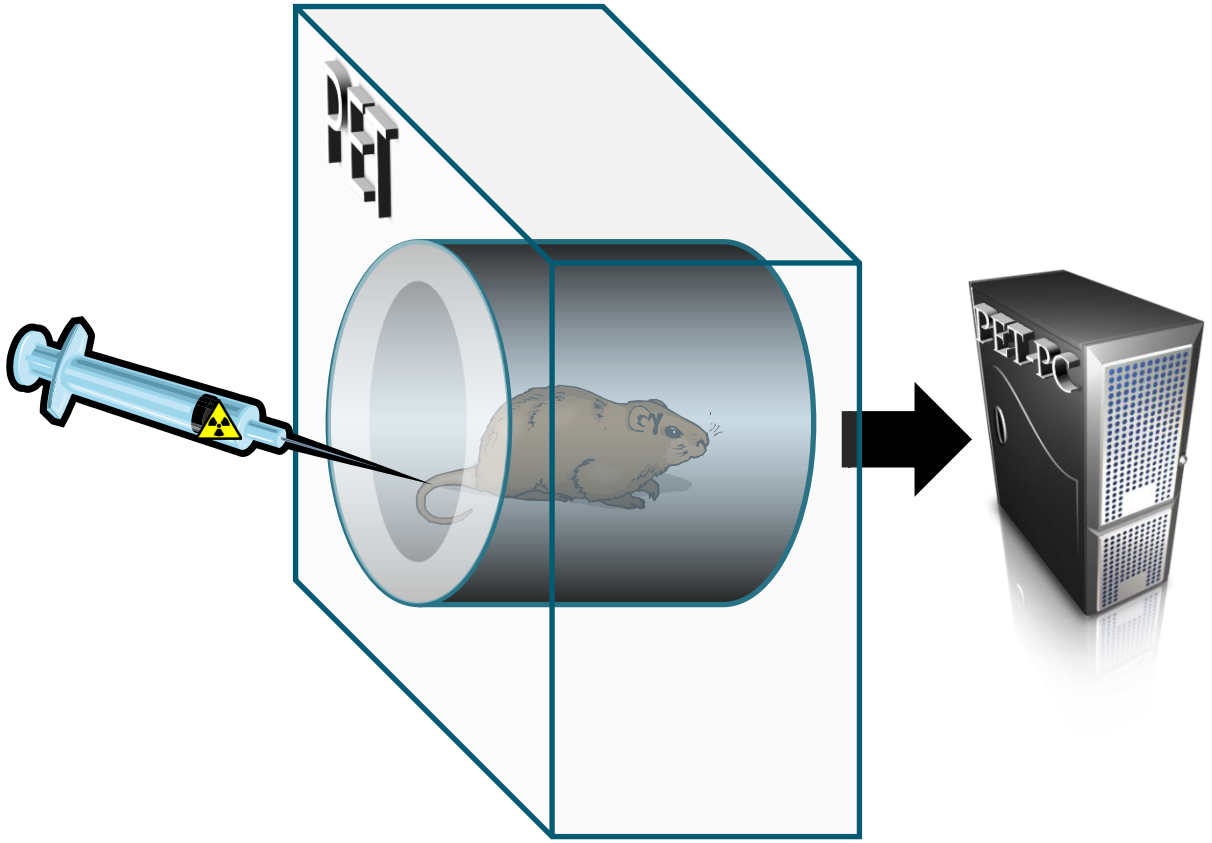
https://humanhealth.iaea.org/HHW/m/MedicalPhysics/NuclearMedicine/ImageAnalysis/3Dimagereconstruction/index.html

Preclinical PET (Glucose metabolism example)

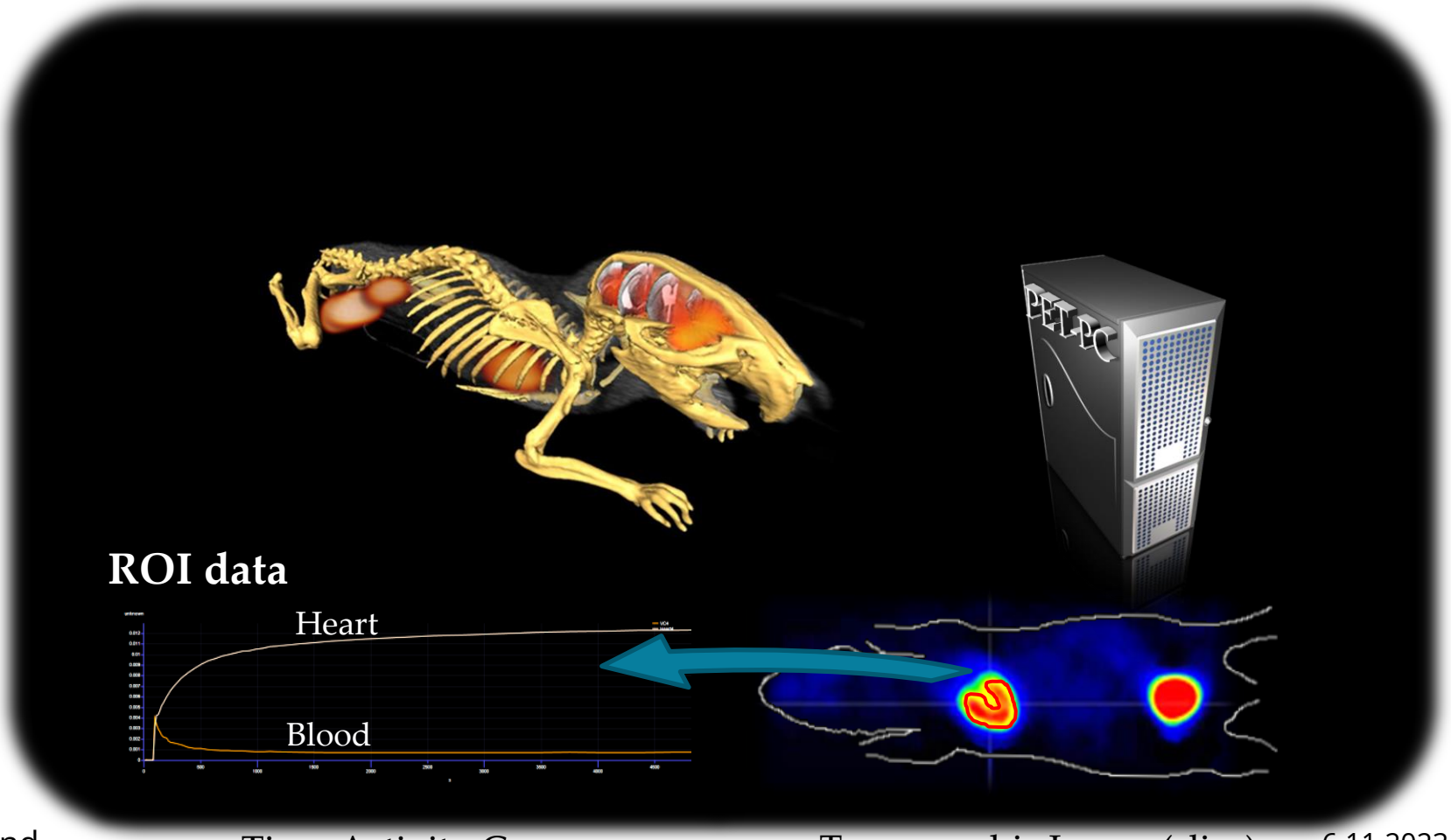
^{18}F-FDG:

Glucose**analogue**





Preclinical PET + CT + MRI



Time-Activity Curve

Tomographic Image (slice)

Where to use PET? E.g. …

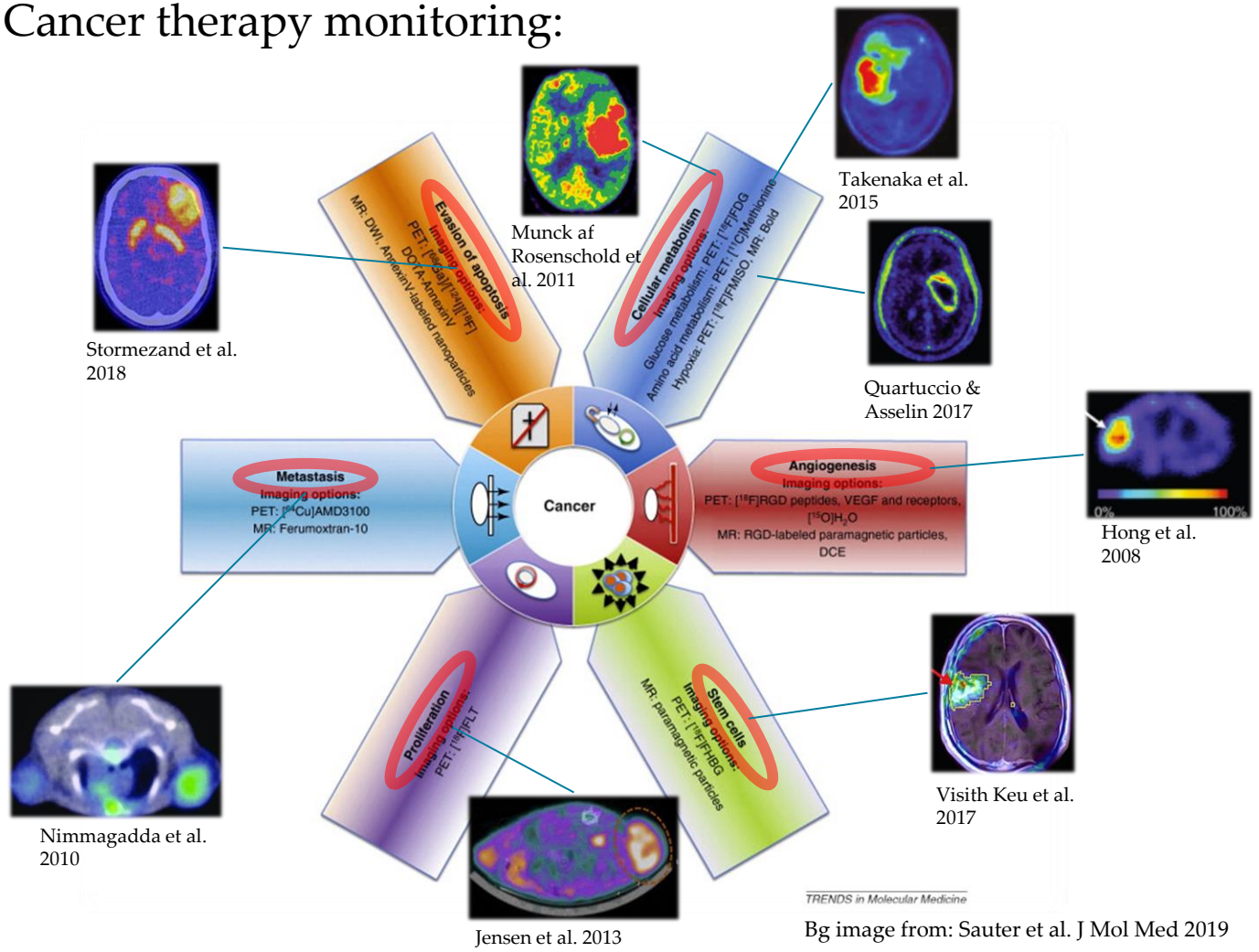
- Molecule biodistribution studies
  - Does the molecule reach target tissue?
  - Does it accumulate in non-target sites (potential toxicity)?
- Dose selection (dose–target occupancy measurements)
- Identify or validate new imaging biomarkers

- Search for surrogate markers of e.g. treatment response
- Compare current medicine vs new compounds

- Earlier detection of disease or associated pathology (before anatomical changes)
- Diagnosis of pre- or minimally symptomatic disease
- Patient grouping (e.g. disease sub-phenotype or early treatment response)

Where to use PET? E.g. …

Cancer therapy monitoring:



Stormezand et al. 2018

Munck af Rosenschold et al. 2011

Takenaka et al. 2015

Quartuccio & Asselin 2017

Hong et al. 2008

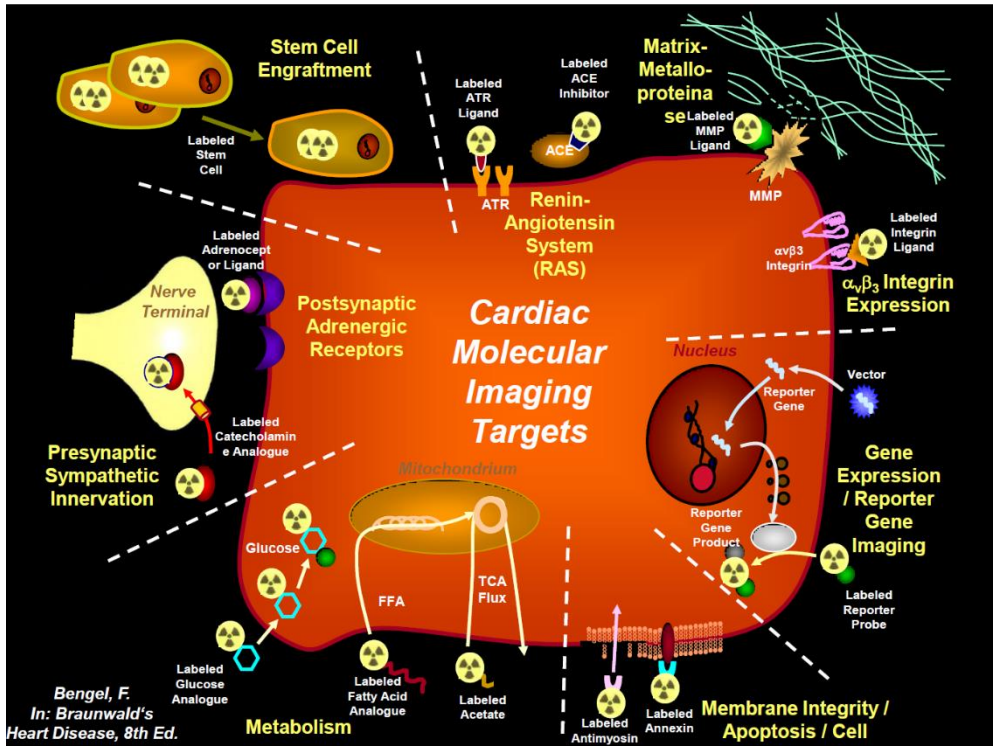
Visith Keu et al. 2017

Nimmagadda et al. 2010

Jensen et al. 2013

Bg image from: Sauter et al. J Mol Med 2019

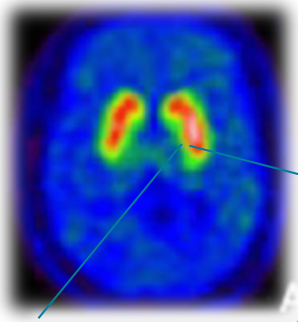
Clinical cardiac imaging:

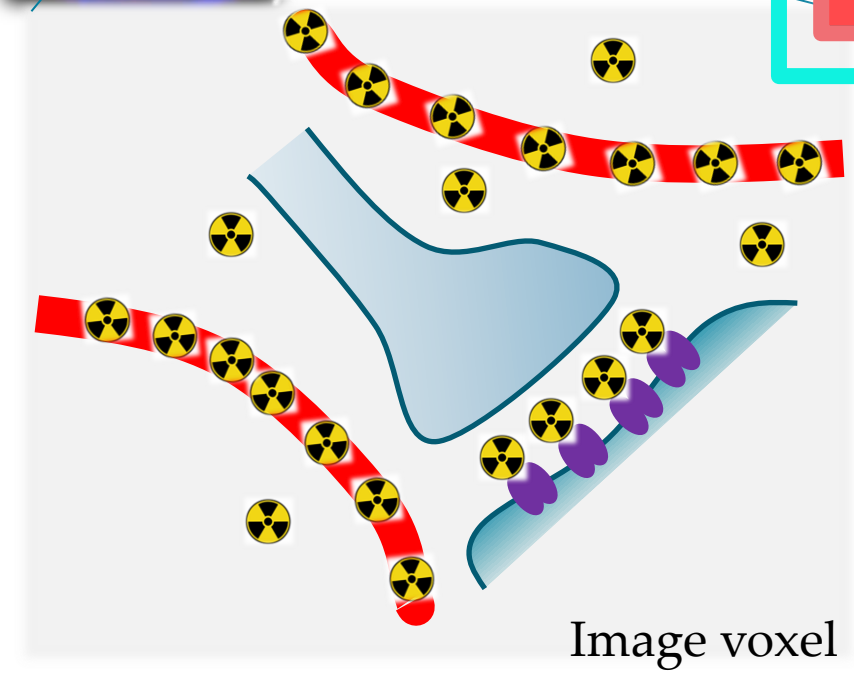


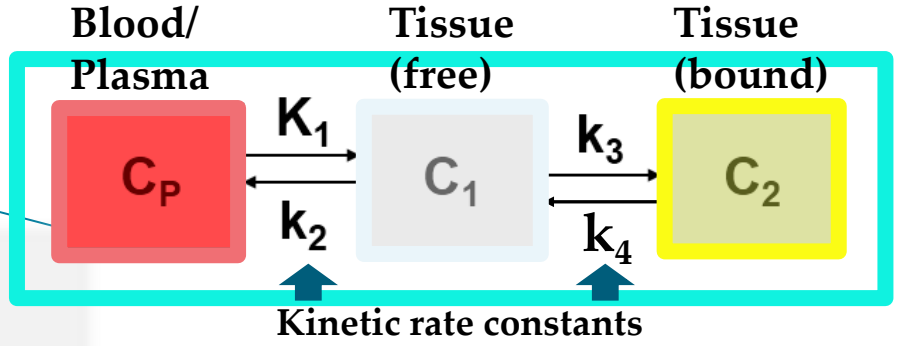
J Knuuti's slides, EHH 2011

-> **Many molecular targets and many (potential) tracers available for imaging**

PET quantification: Compartment model







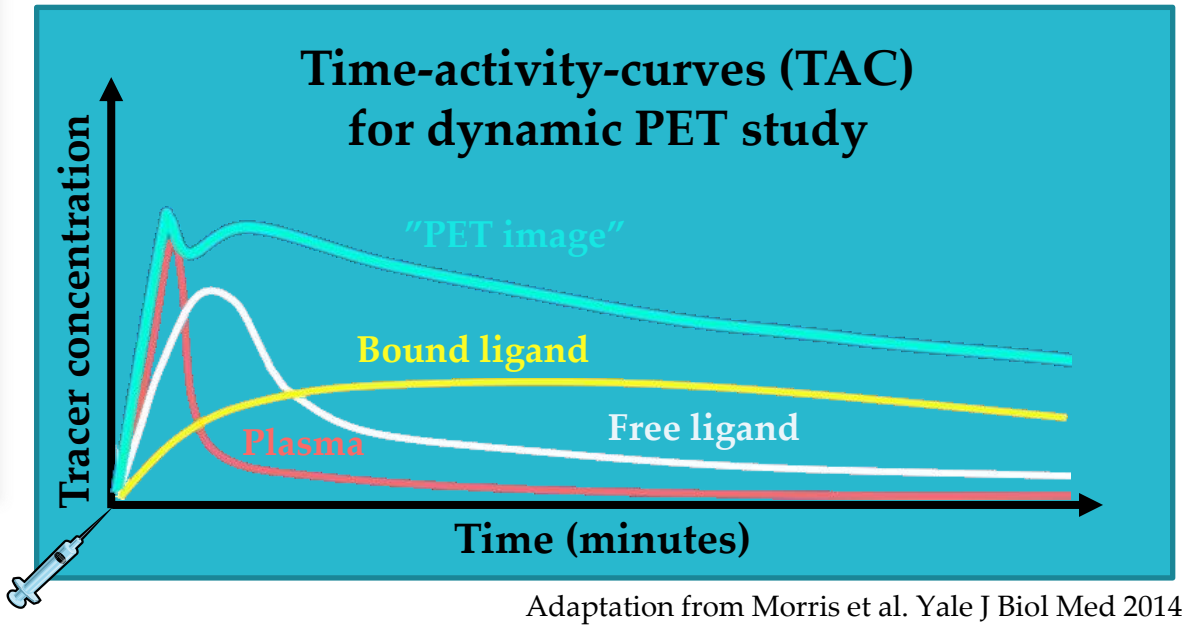
Differential equations:

$$\frac{dC_{free}(t)}{dt} = K_1 C_{plasma}(t) - (k_2 + k_3) C_{free}(t) + k_4 C_{bound}(t)$$

$$\frac{dC_{bound}(t)}{dt} = k_3 C_{free}(t) - k_4 C_{bound}(t)$$

$$PET(t) = C_{free}(t) + C_{bound}(t) + C_{plasma}(t)$$

Microparameters:
K1, k2, k3, k4

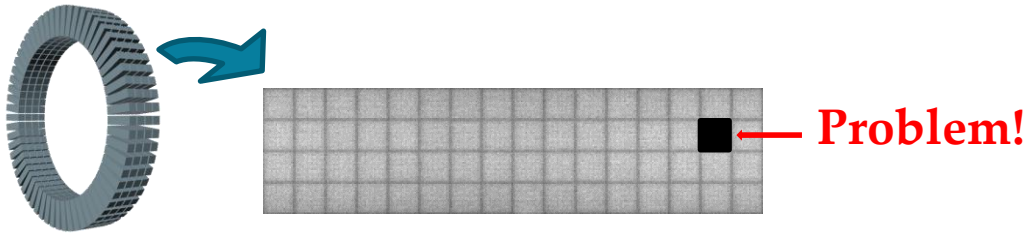


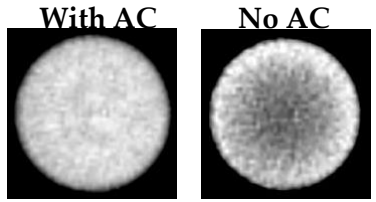
Derived compound parameters:
- Robust
- Biological meaning
  - BP = Binding potential (receptor occupancy)
  - V_d = Volume of distribution (ligand distribution vs C_P)

Adaptation from Morris et al. Yale J Biol Med 2014

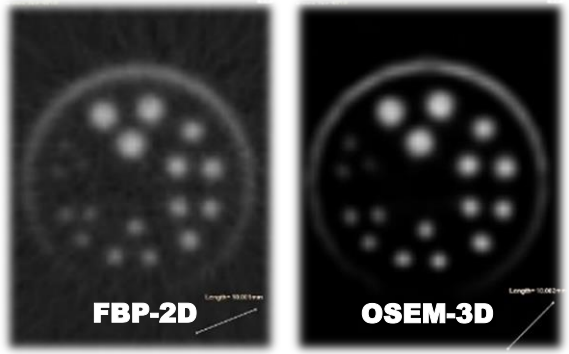
Things affecting quantitative data & results

- Corrections for quantitative 2D- and 3D-data:
  - Detector (normalization)
    - For sensitivity of each detector on the ring
  - Randoms
  - Scatter correction
  - Attenuation correction (AC)
    - Tissue attenuation
  - Dead-time correction





- Isotope
  - ^{18}F, ^{11}C, ^{15}O, ...
  - Half-life, β+-energy (-> β+ range)
- Tracer (molecule)
  - e.g. ^{18}F-FDG (glucose), ^{11}C-raclopride (dopamine), ^{18}F-FEPPA (inflammation)...
- Reconstruction algorithm
  - FBP, MLEM, OSEM, ...
  - A priori info
- Physics (resolution, uncertainty, ...)
  - Non-collinearity of the photons (180±0.25 degrees)
  - Detector (crystal type, dimensions and location)
  - Motion (of the patient; breathing, heart)
  - ...

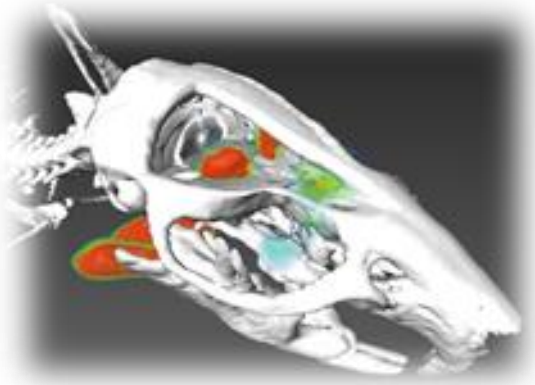


3R principle in practise

- Reduction
  - Longitudinal studies (minimally or non-invasive)
  - By keeping data (e.g. image) quality good
  - Large volume, 4D data; can be reused/revisited for other targets

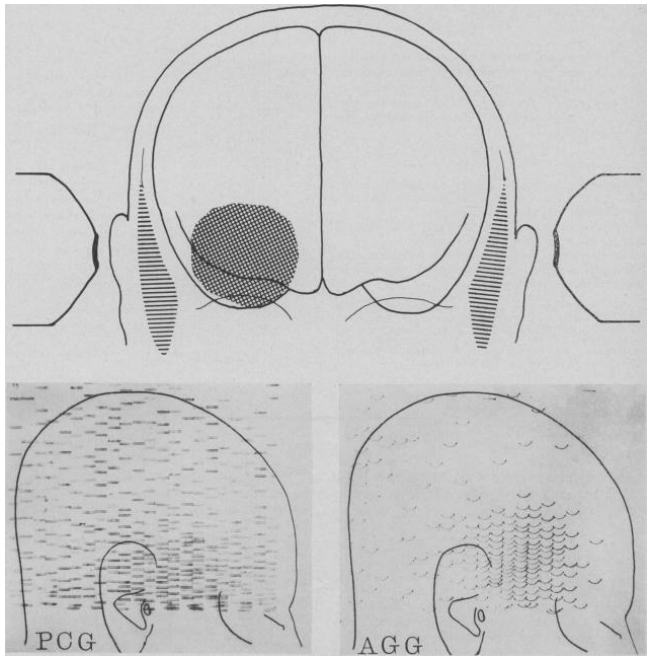
- Replacing
  - Phantom studies as tech check
    - But we do *in vivo* imaging…
- Refining
  - Animal welfare in constant discussion
    - Improved living environment, animal handling, anesthesia and pain medication, aseptic operations, …

Current and future



- Happy to add more collaboration!

Clinical tumor localization with positron imaging
(Botterell EH et al. CMAJ 1961)



~1960's

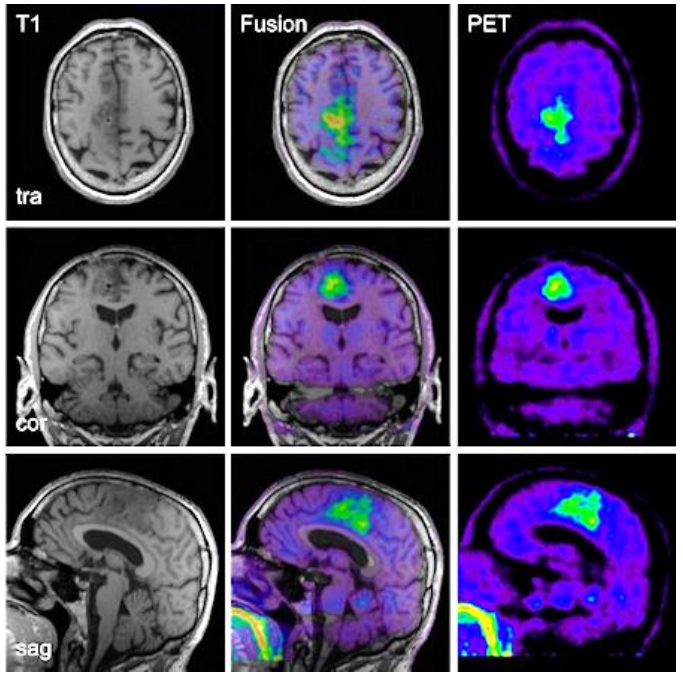
UNIVERSITY OF EASTERN FINLAND

Thank you!

http://www.uef.fi/kuopiobiu/

uef.fi

Astrocytoma with PET-MRI
(Boss et al. J Nucl Med)



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