# Digital Twin for Personalized Radiopharmaceutical Therapy

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Taipei, Nov. 8th, 2024

# Personalized Treatment Planning for Radiopharmaceutical Therapy

Before therapy
PSA 458.6 ng/mL

$^{68}$Ga-PSMA

Optimize

2013/59 Euratom

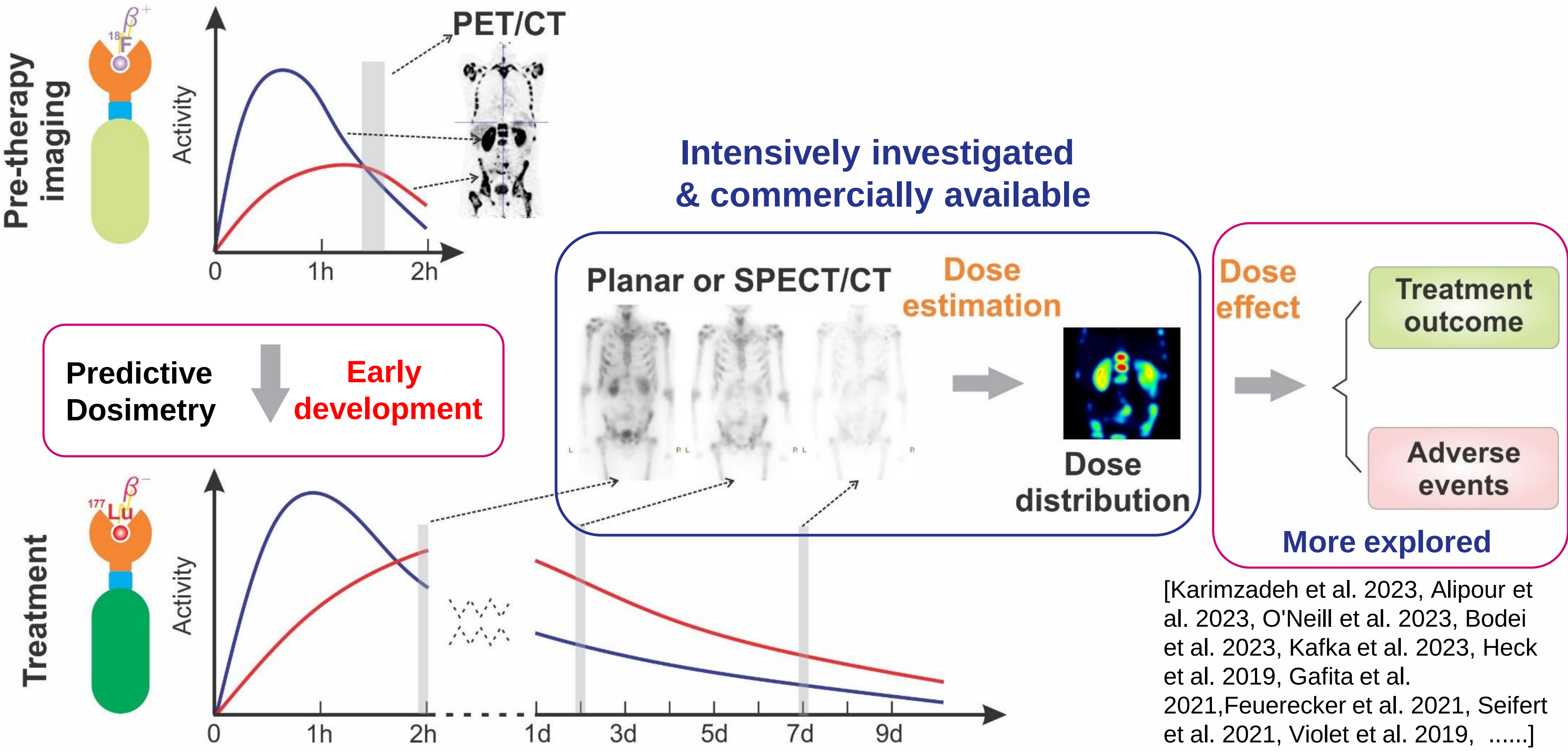
**Treatment Planning**

- **Define targets & sensitive organs**
- **Prescribe dose**
- **Predict dose distribution**
- **Assess dose effect**
- **Tune the dose: maximize tumor killing & minimize side effect**

After 3 cycles
PSA 158.9 ng/mL

$^{68}$Ga-PSMA

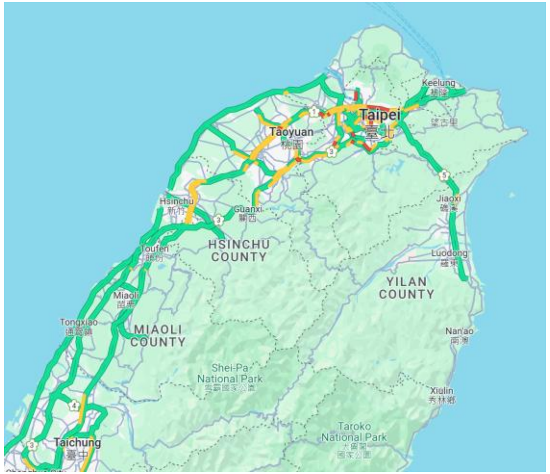
# Personalized Treatment Planning for Radionuclide Therapy?

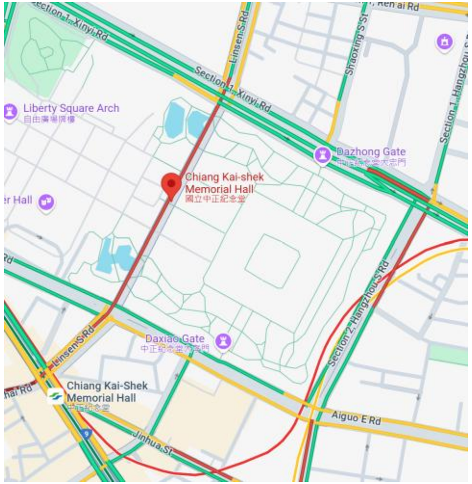



[Karimzadeh et al. 2023, Alipour et al. 2023, O'Neill et al. 2023, Bodei et al. 2023, Kafka et al. 2023, Heck et al. 2019, Gafita et al. 2021,Feuerecker et al. 2021, Seifert et al. 2021, Violet et al. 2019, ......]

External beam radiotherapy

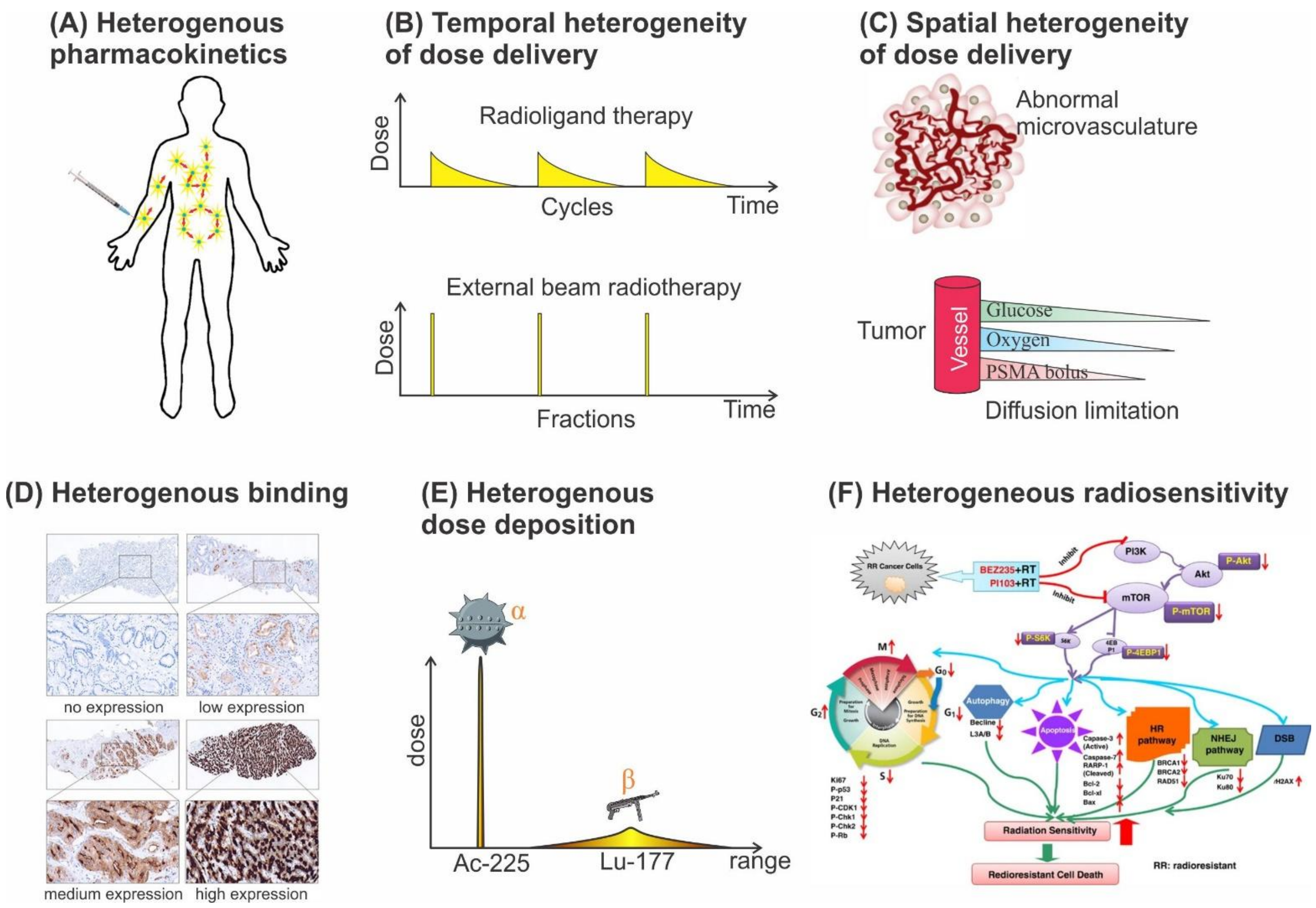

Radio-pharmaceutical therapy



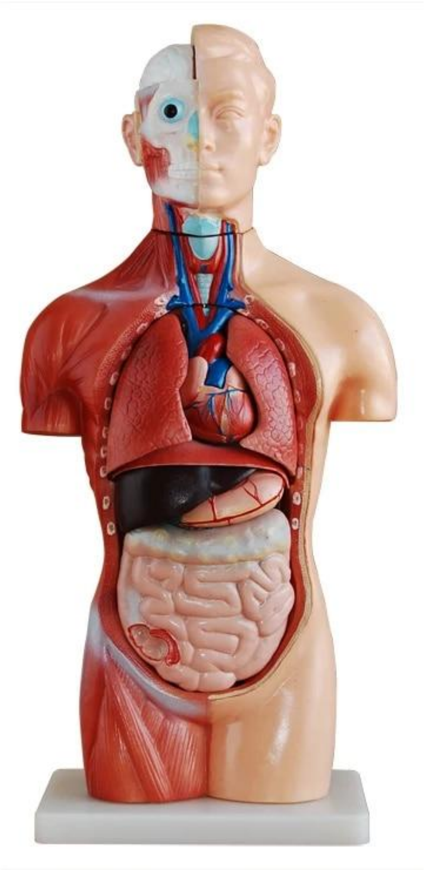



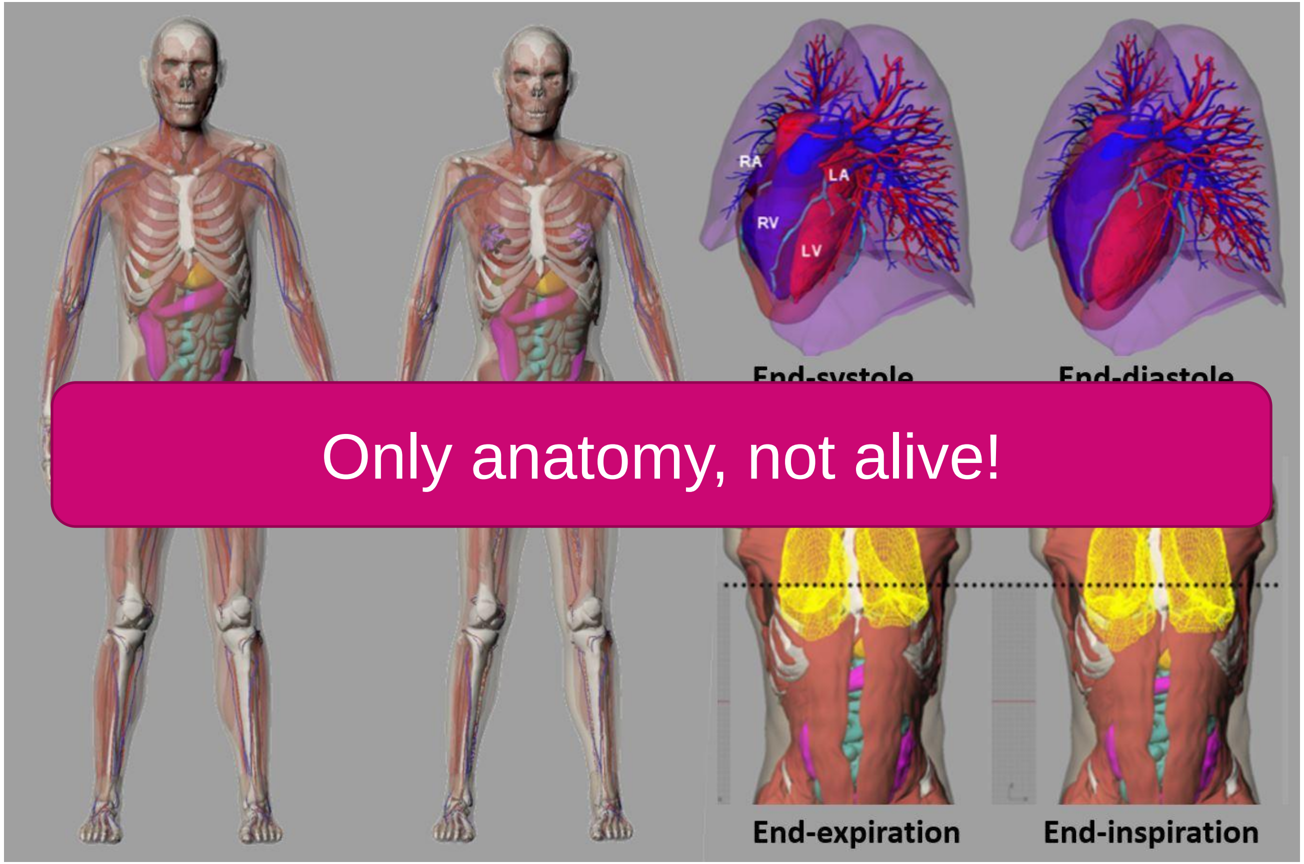

**Longer Journey brings multi-level heterogeneity**

# Multi-level Heterogeneities



# Digital Twin & Computational Modelling

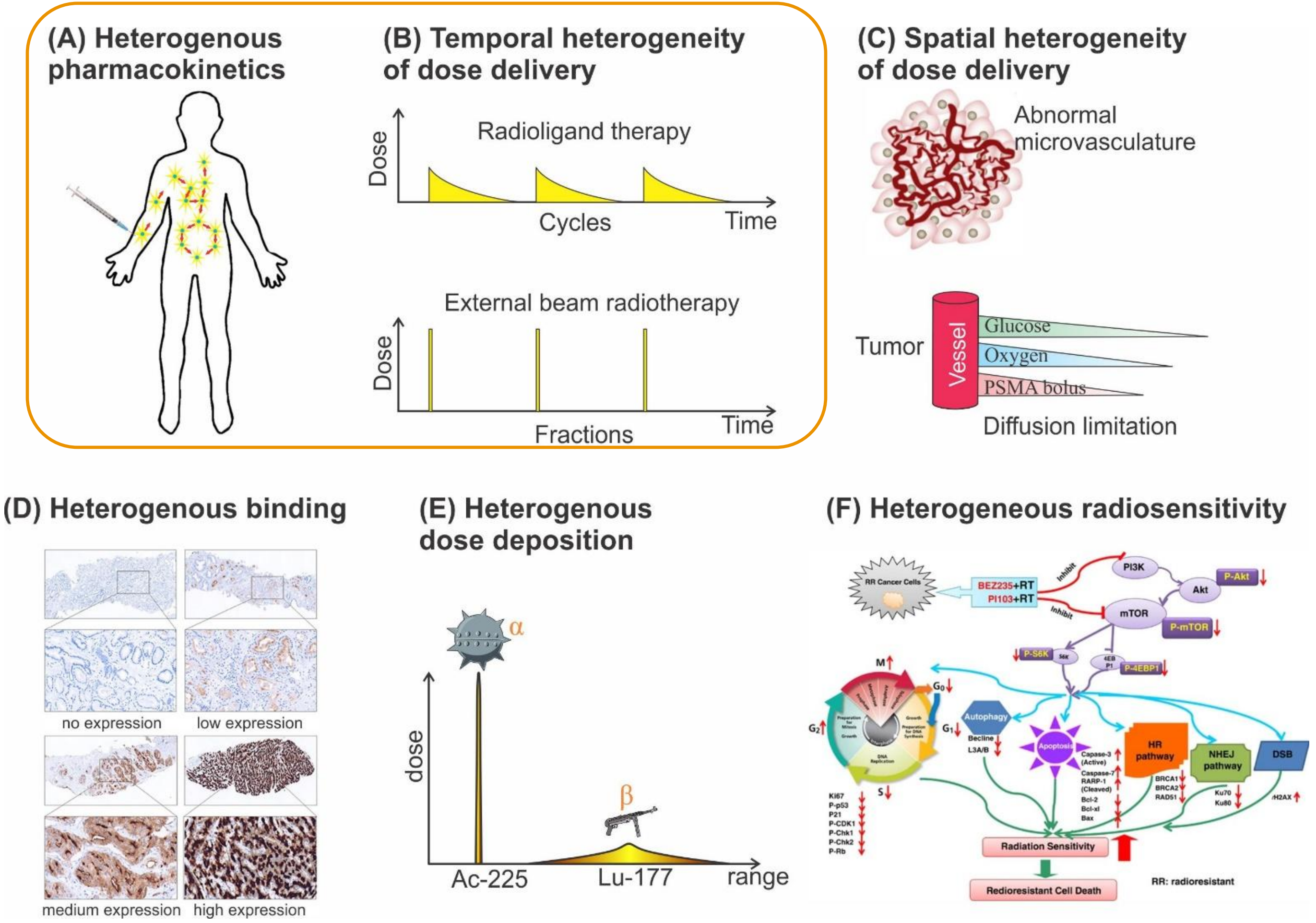




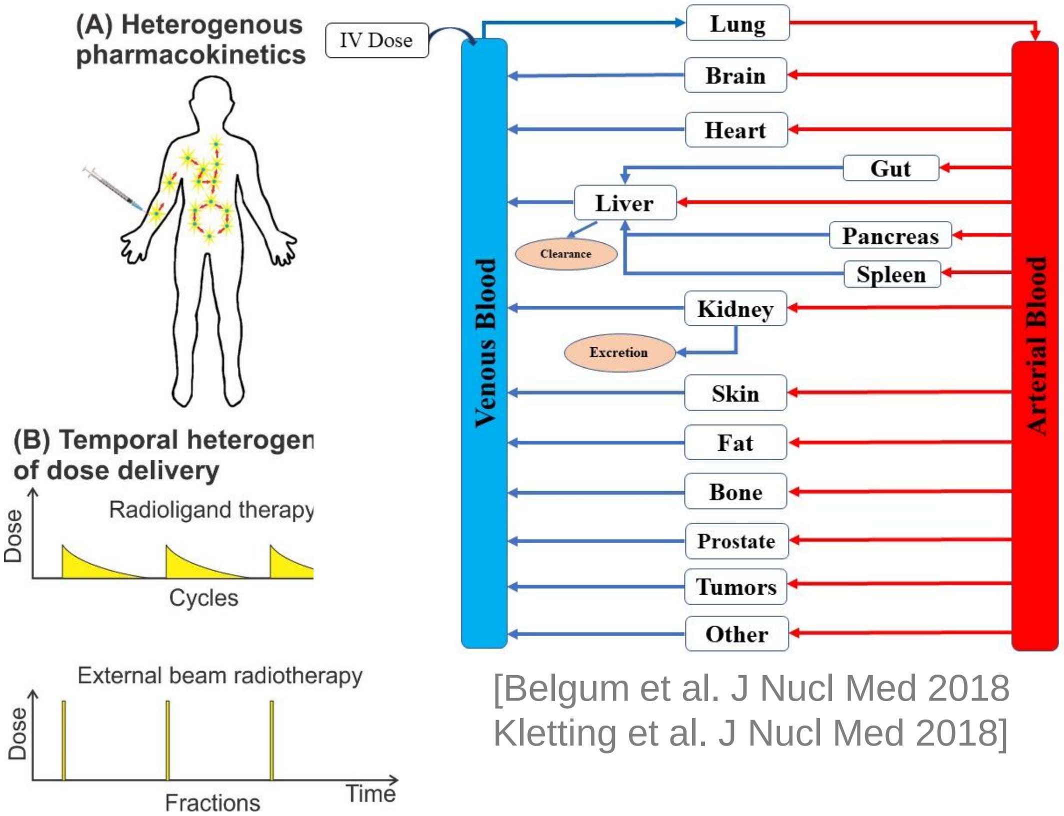

Only anatomy, not alive!

4D Extended Cardiac-Torso (XCAT) Phantom [Segars et al. Med Phys 2010]

# Vitalize the Digital Twin



# Vitalize the Digital Twin: Physiologically-based pharmacokinetic (PBPK) model



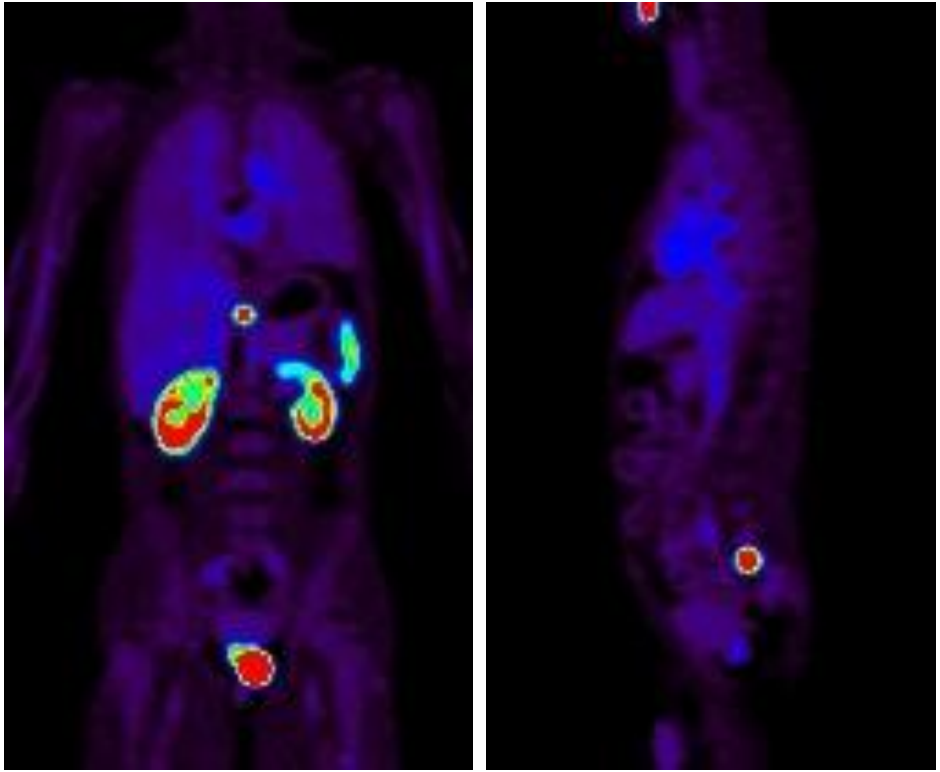

[Belgum et al. J Nucl Med 2018
Kletting et al. J Nucl Med 2018]

- Simulate time-course of radioligand uptake in organs of virtual patient (XCAT phantom)
- Organs & tumor: homogenous
- Simulate PET imaging using realistic PET simulator [Cheng IEEE TMI 2015]
- Dose calculation using the dose voxel kernel (DVK) method [Bolch et al JNM 1999].
- Simulate voxel-S-values matrices [Lanconelli et al. PMB 2012] and convolved with phantoms organs

# Digital Twin with PBPK Modelling

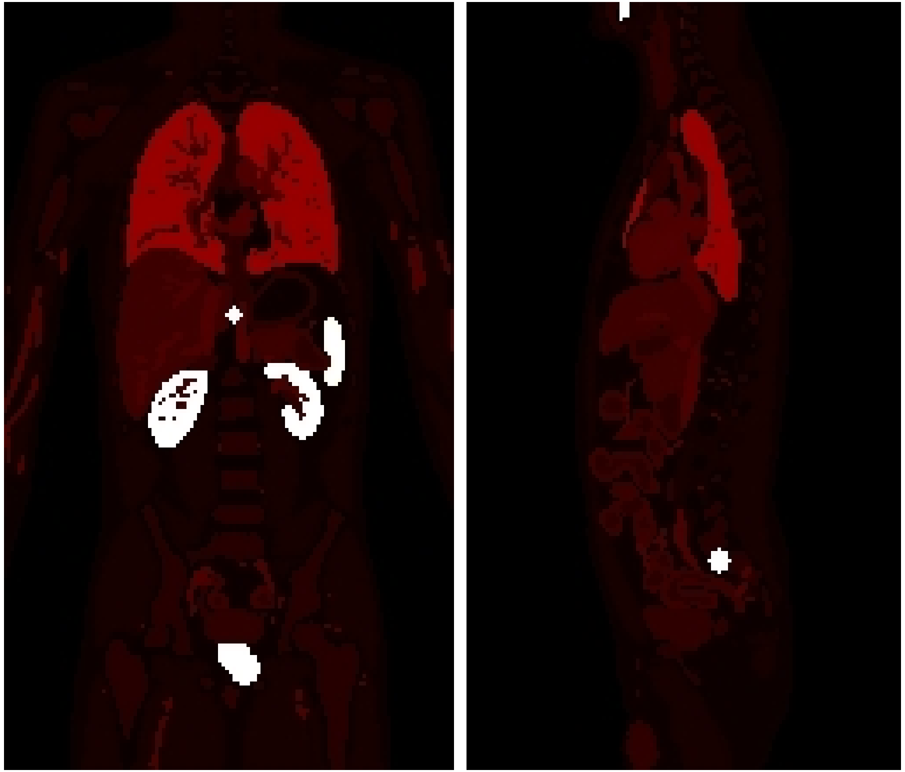
[Birindelli et al Cancers 2021,
Birindelli et al EANM 2021]

**Pre-therapy PET**



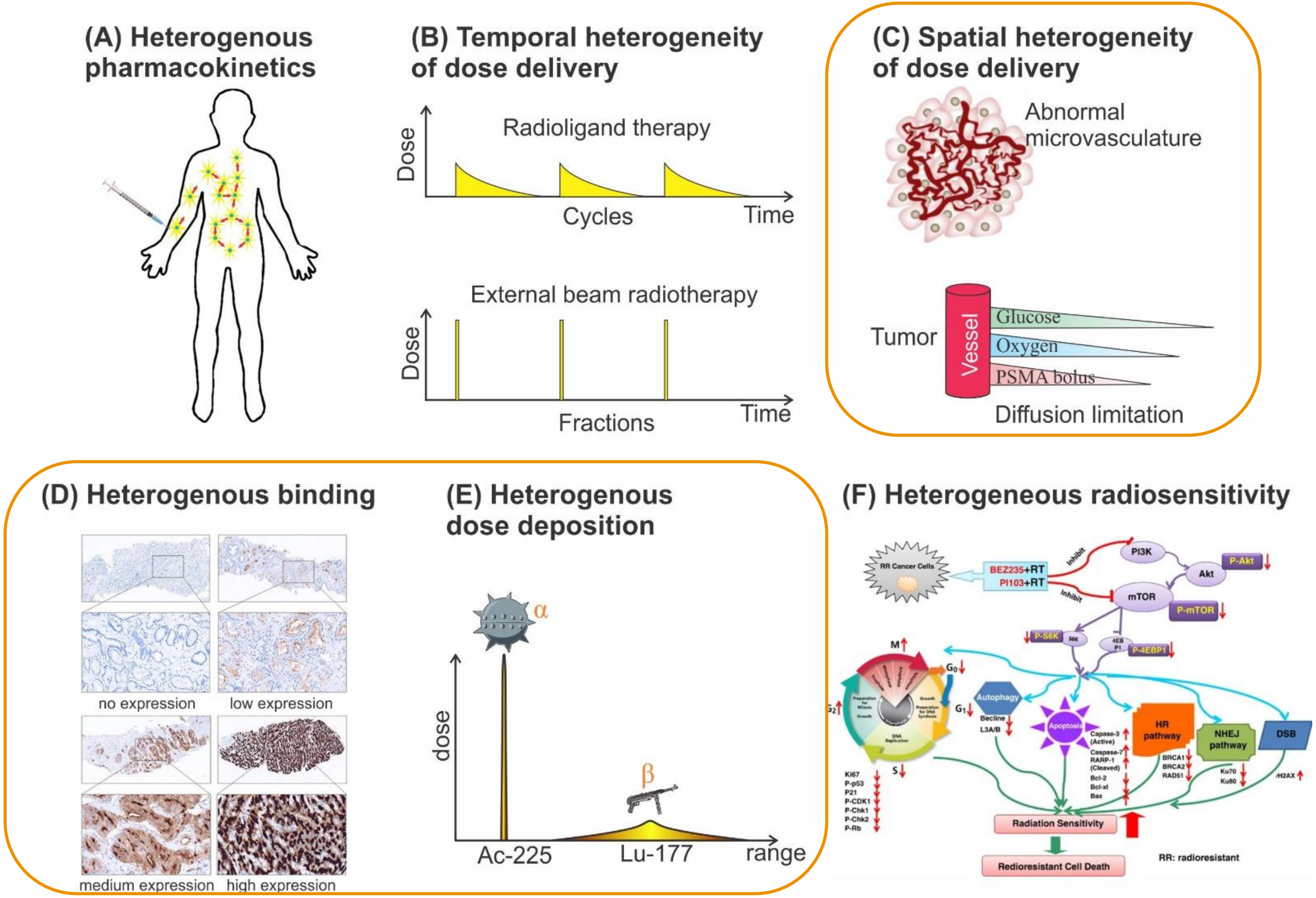
$^{68}$Ga-PSMA-11

**Post-therapy dosimetry**

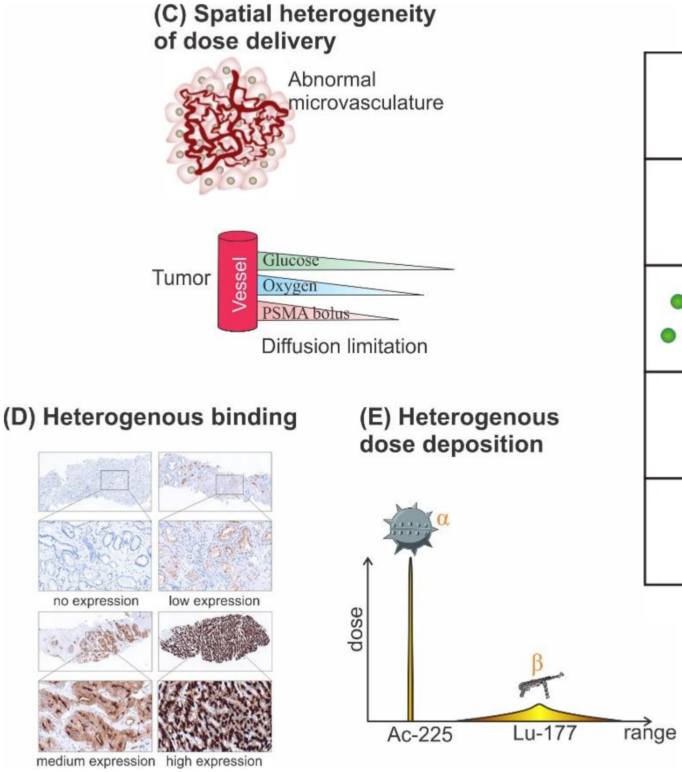


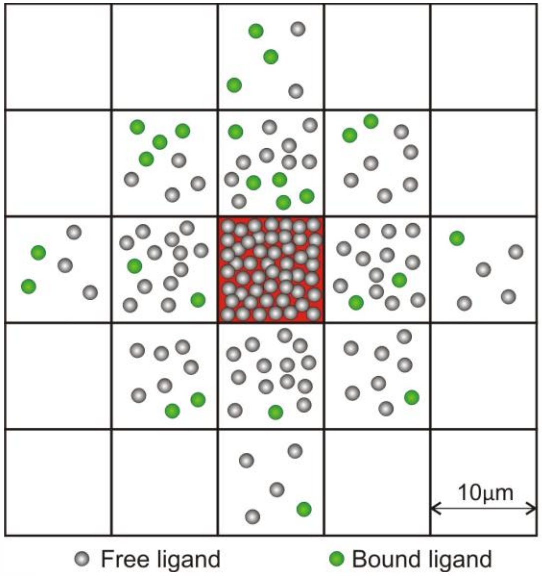
$^{177}$Lu-PSMA-I&T

# Vitalize the Digital Twin



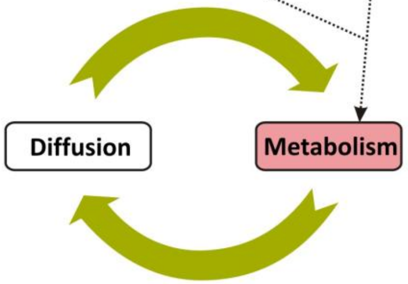
# Vitalize the Digital Twin: Reaction-diffusion computational simulation



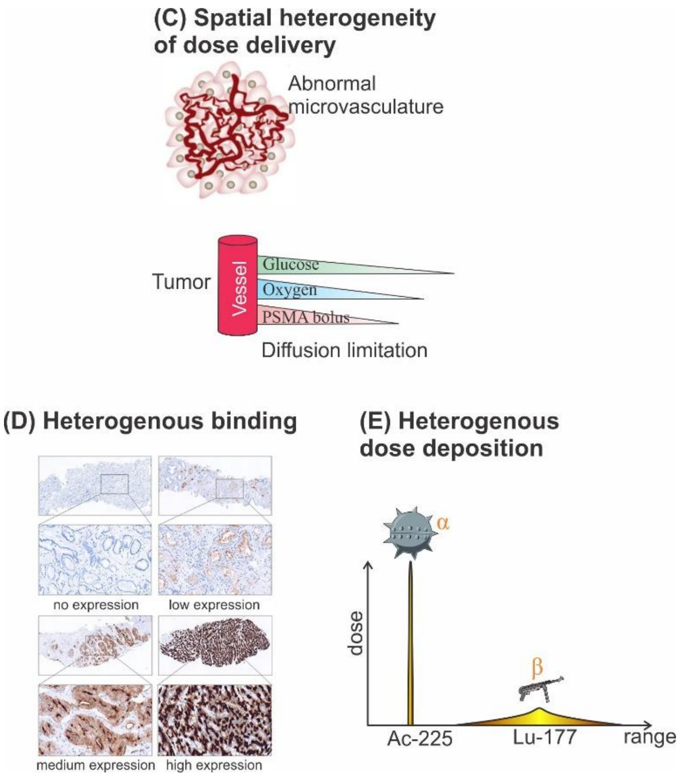

$$\frac{\partial C_{free}}{\partial t} = D_{Tr}\nabla^2 C_{free} \boxed{- k_{on} C_{free} + k_{off} C_{bound}}$$

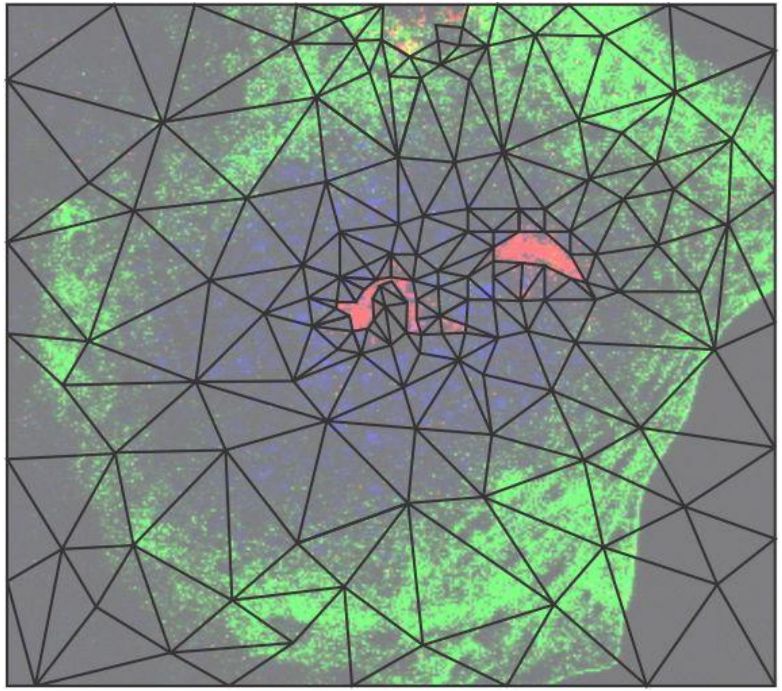
$$\frac{\partial C_{bound}}{\partial t} = \boxed{k_{on} C_{free} - k_{off} C_{bound}}$$




[Wang et al. PMB 2015, Shi et al. Phys Meas 2017]

# Histology-driven reaction-diffusion computational simulation

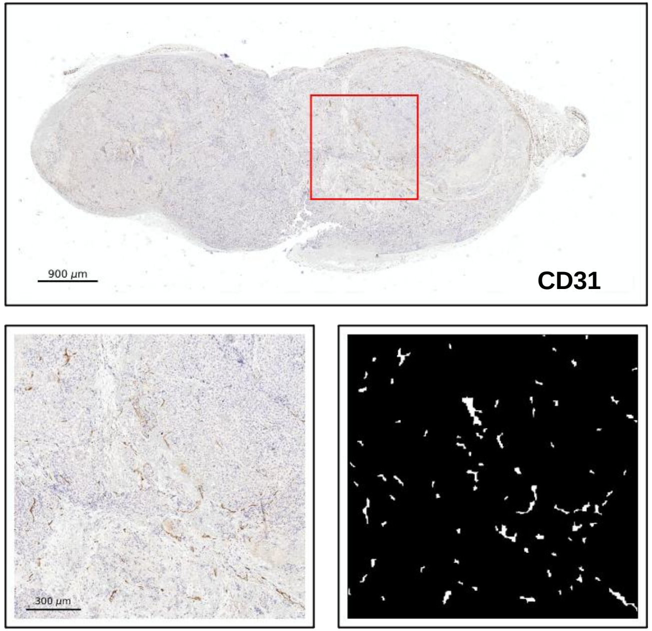


[Birindelli et al Cancers 2021, Birindelli et al EANM 2021]

# Histology-driven convection-reaction-diffusion model

- PSMA-positive prostate carcinoma LNCaP cells inoculated in male CB17-SCID mice;
- Consecutive 2 μm sections
- Staining for CD31 and PSMA receptors;
- Ten regions-of-interest (ROI) of 1.6 x 1.6 $mm^2$ are selected from three slices to simulate different perfusion regimes
- The vessel contouring and map generation is performed with an “ad hoc” Python script
- PSMA receptor density based on the grey value of PSMA staining




Collaborate with Technical University of Munich, Prof. Matthias Eiber & Prof. Wolfgang Weber

[Birindelli et al. Cancers 2021]

# Convection-reaction diffusion models of PSMA-ligands uptakes

- The radiopharmaceutical flux across the vessel walls:

$$J_{\mathrm{v}} = L_{\mathrm{v}}(C_{\mathrm{v}} - C_{\mathrm{i}})$$

- Neumann boundary conditions imposed on the vessel boundaries.
- Spatiotemporal evolution of the interstitial PSMA-ligands concentration: a convection-reaction-diffusion:

$$\partial_t C_{\mathrm{i}} = \nabla \cdot (D_{\mathrm{PSMA}} \nabla C_{\mathrm{i}}) - \nabla \cdot (\vec{v} R_f C_{\mathrm{i}}) - k_{\mathrm{on}} C_{\mathrm{i}} (R_0 - C_{\mathrm{b}}) + k_{\mathrm{off}} C_{\mathrm{b}} - \lambda_{\mathrm{dec}} C_{\mathrm{i}}$$

- Assuming a first-order kinetics$\longrightarrow$ the binding and internalisation processes:

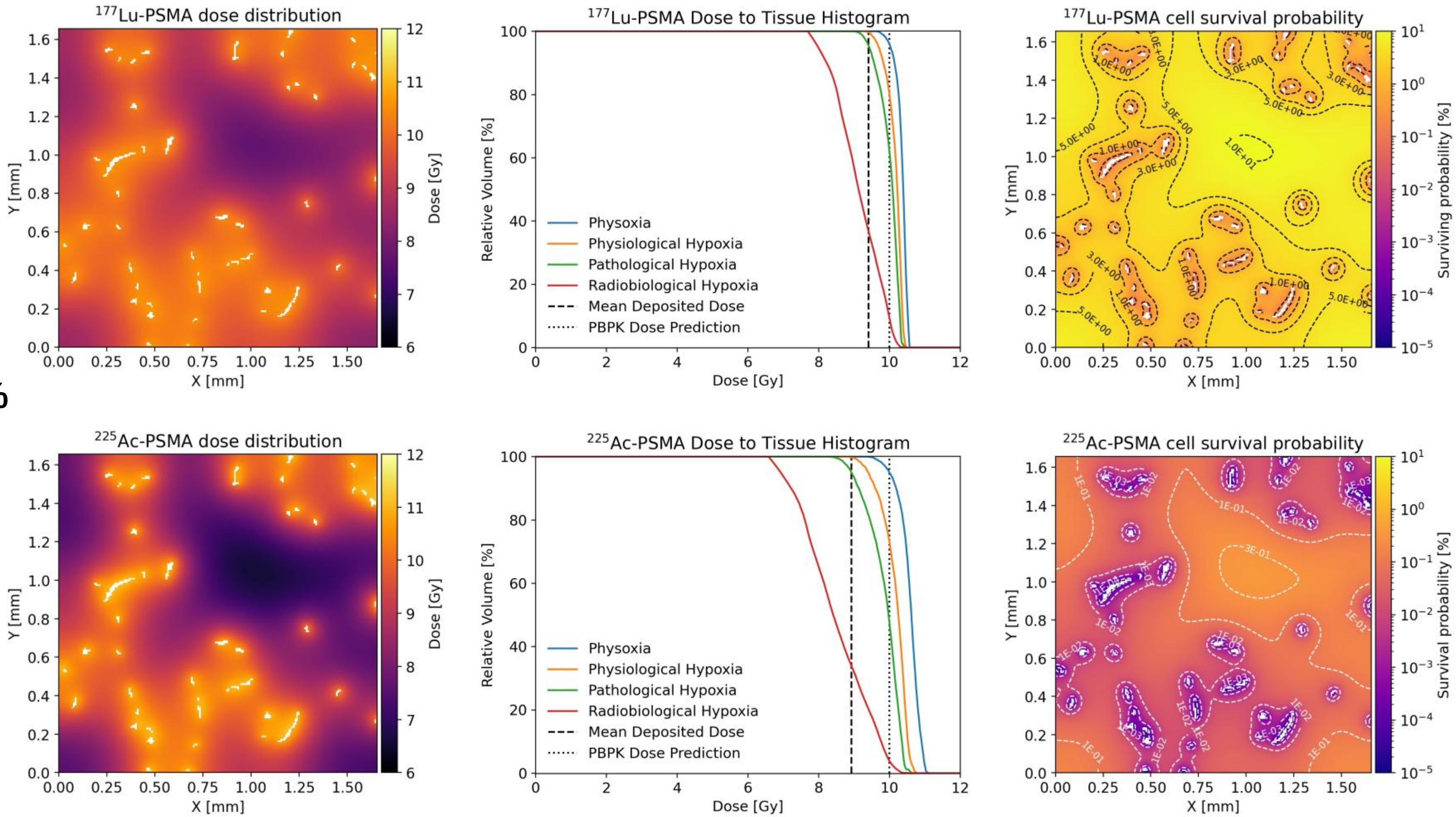
$$\partial_t C_{\mathrm{b}} = k_{\mathrm{on}} C_{\mathrm{i}} (R_0 - C_{\mathrm{b}}) - k_{\mathrm{off}} C_{\mathrm{b}} - k_{\mathrm{int}} C_{\mathrm{b}} - \lambda_{\mathrm{dec}} C_{\mathrm{b}}$$

$$\partial_t C_{\mathrm{int}} = k_{\mathrm{int}} C_{\mathrm{b}} FV_{\mathrm{i}} / FV_{\mathrm{c}} - k_{\mathrm{rel}} C_{\mathrm{int}} - \lambda_{\mathrm{dec}} C_{\mathrm{int}}$$

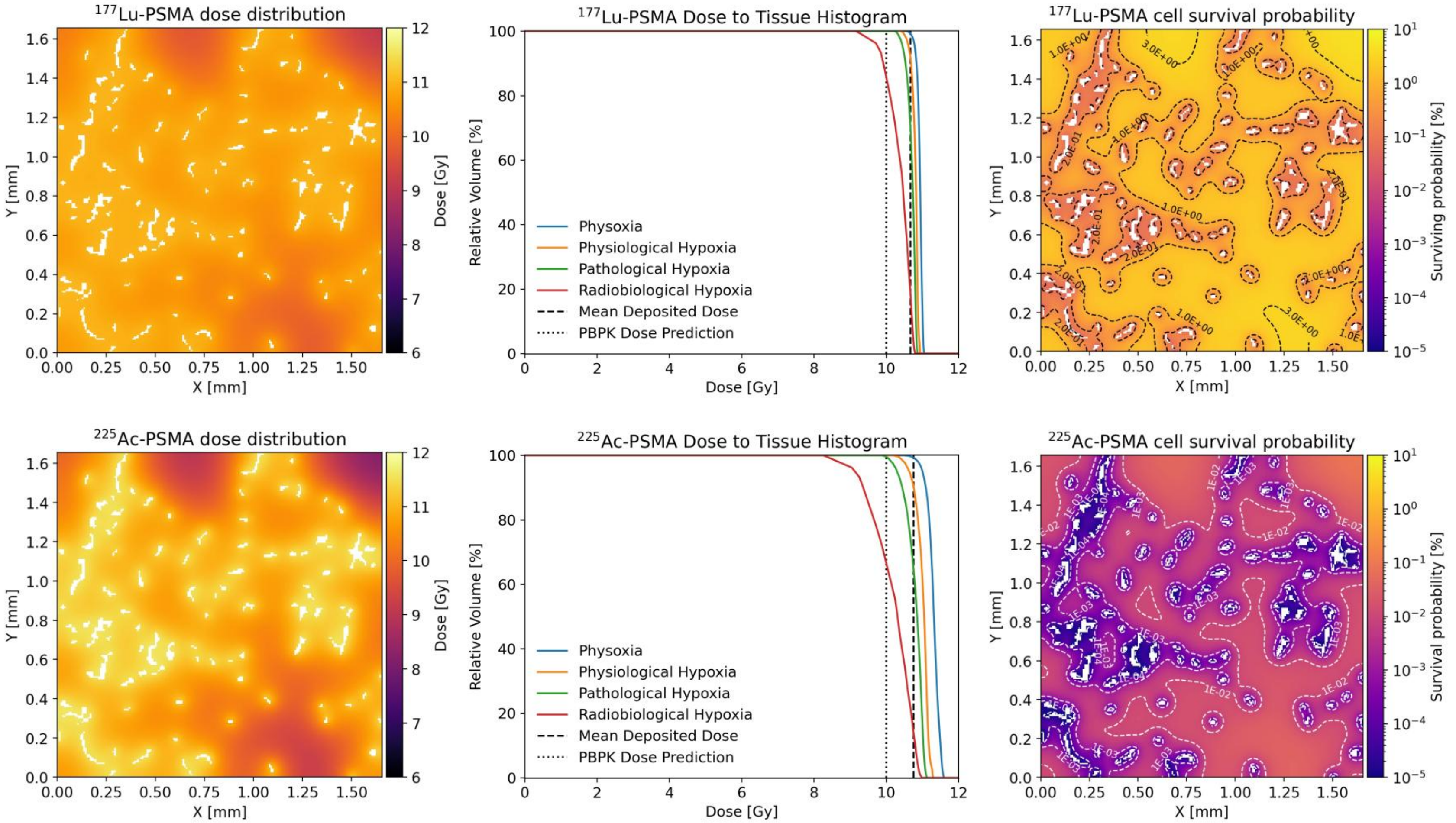
- Parameter values: [Swabb et al. Cancer Res 1974, Jain et al. Cancer Metas Rev 1987, Begum et al Sci Rep. 2019]

# Using simulation to investigate the influence of chronic hypoxia

**$FV_V = 1.0\%$**

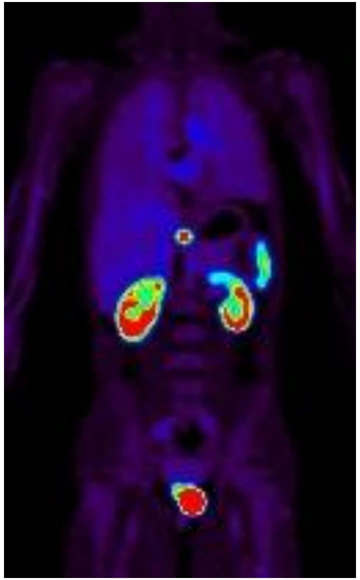


# Using simulation to investigate the influence of chronic hypoxia




**$FV_V = 3.2\%$**

Digital Twin



- PBPK model
- Microenvironment model

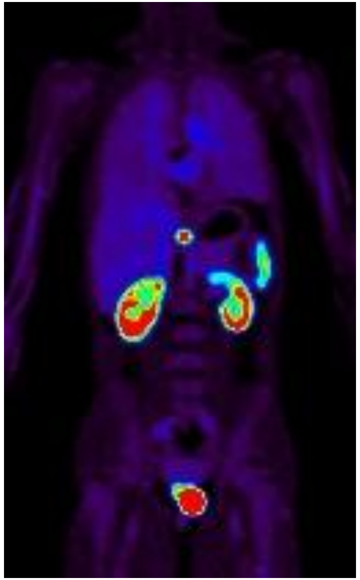
**Clone**


Real patient

Before therapy
PSA 458.6 ng/mL

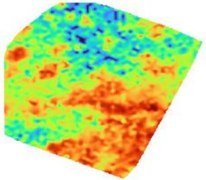
# Clone of a Digital Twin

**Digital Twin**



- PBPK model
- Microenvironment model
- Radiobiology

Total-body PET for pharmacokinetics



Phenomics for precise physiology


On-chip investigation for radiosensitivity

Artificial intelligence on big clinical data

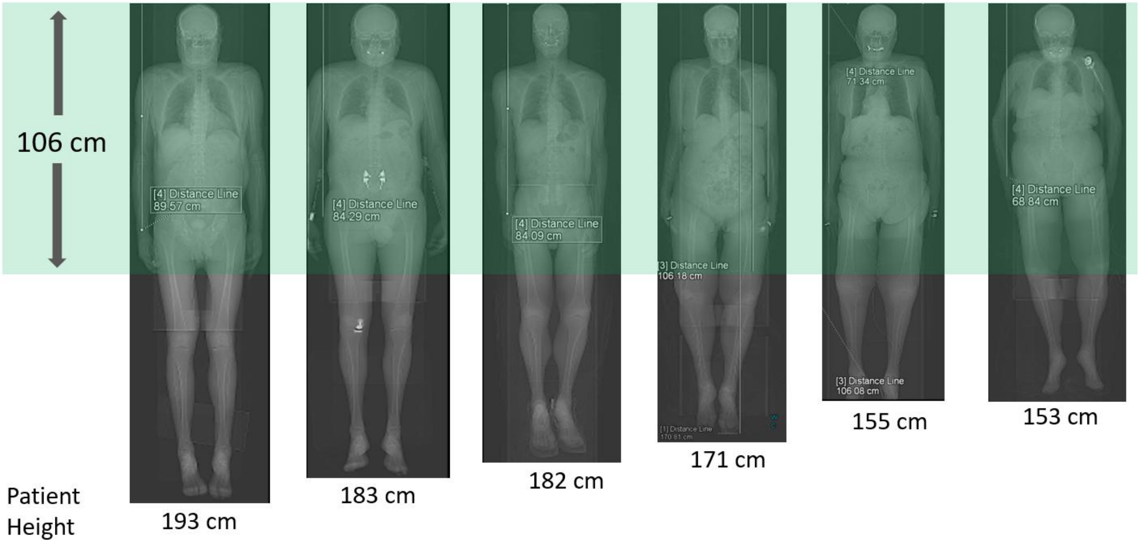
**Real patient**

Before therapy
PSA 458.6 ng/mL

# Clone Patient Pharmacokinetics: Large Axial Field of View PET (Total-body PET)

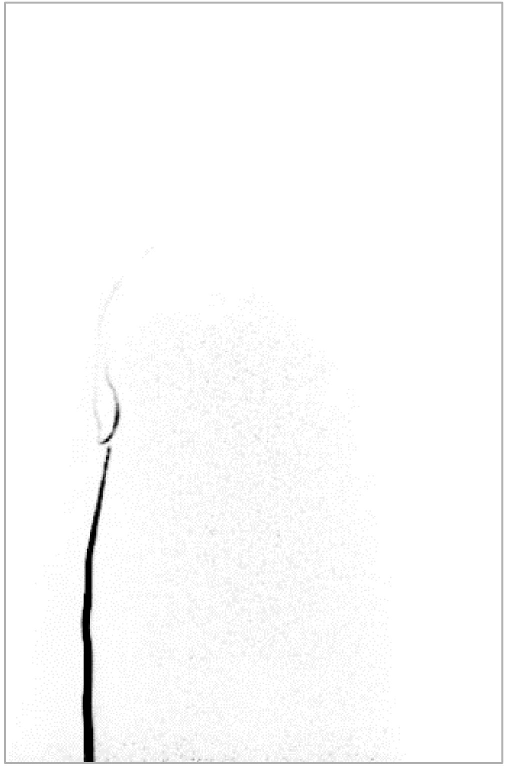
- Ultra-large axial FoV
- Ultra-high sensitivity
- Ultra-fast imaging

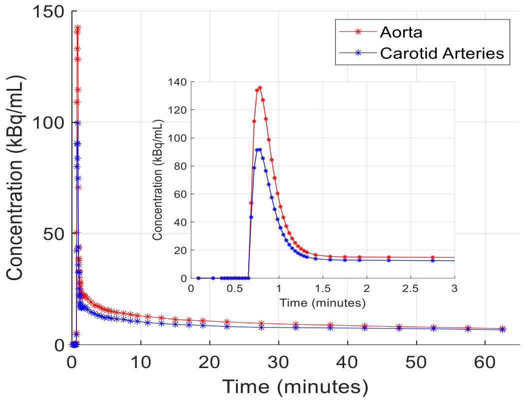
Siemens Biograph Vision Quadra

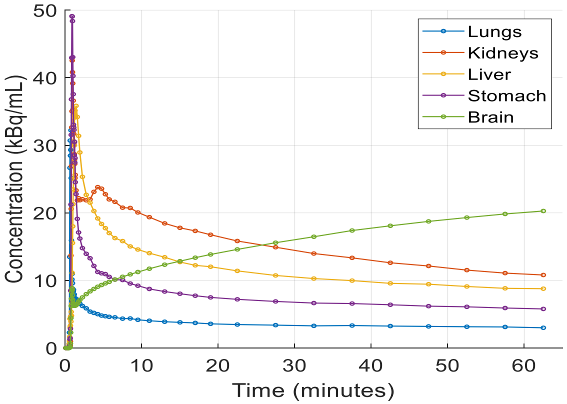



SIEMENS Healthineers

# Whole-body Dynamic Imaging & PBPK Modelling






[Sari et al. EJNMMI 2021]

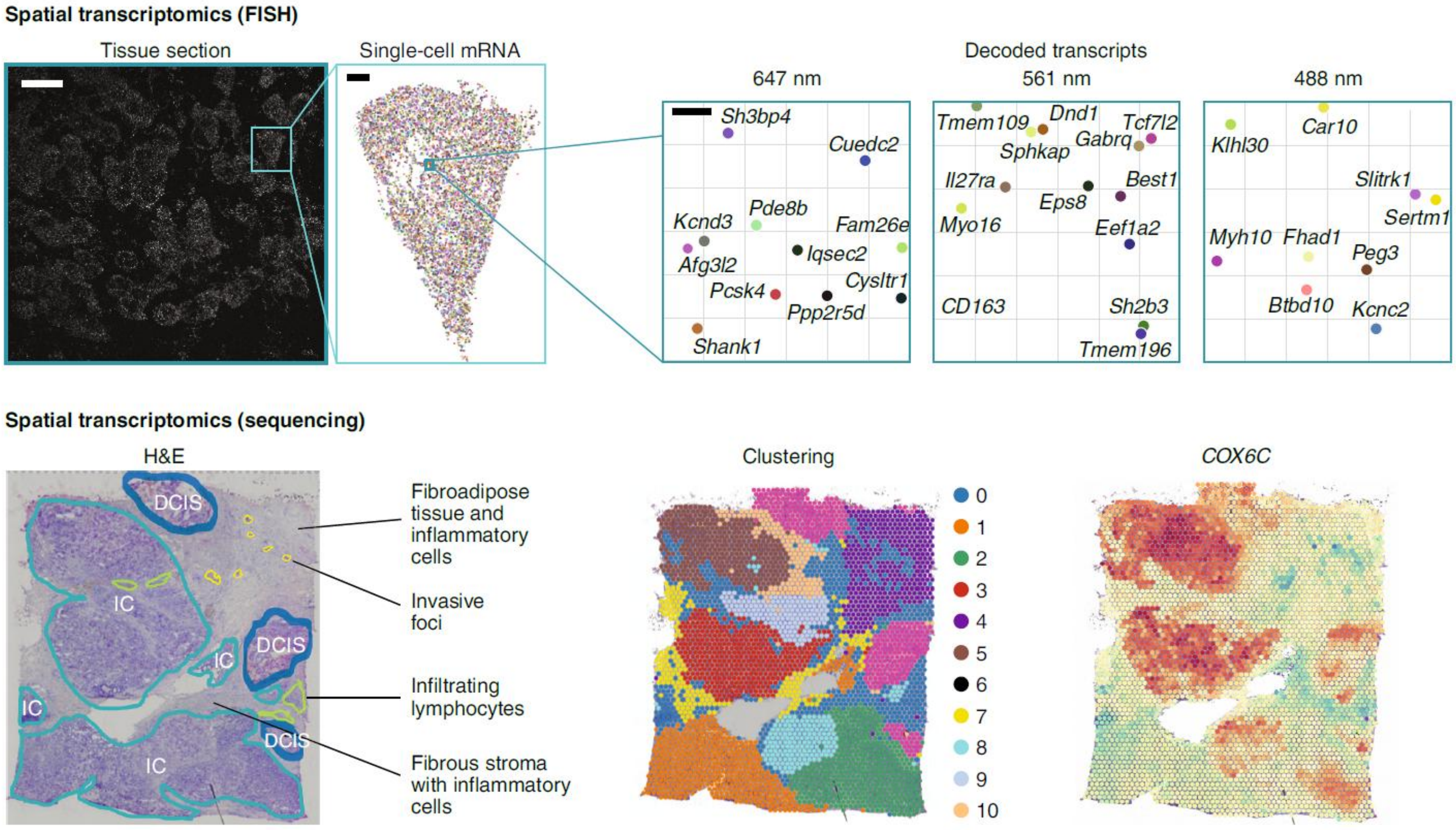
- ❑ PBPK modelling to individualize parameters

[Kassar et al. TB-PET 2022]

- ❑ Deep learning for dosimetry prediction

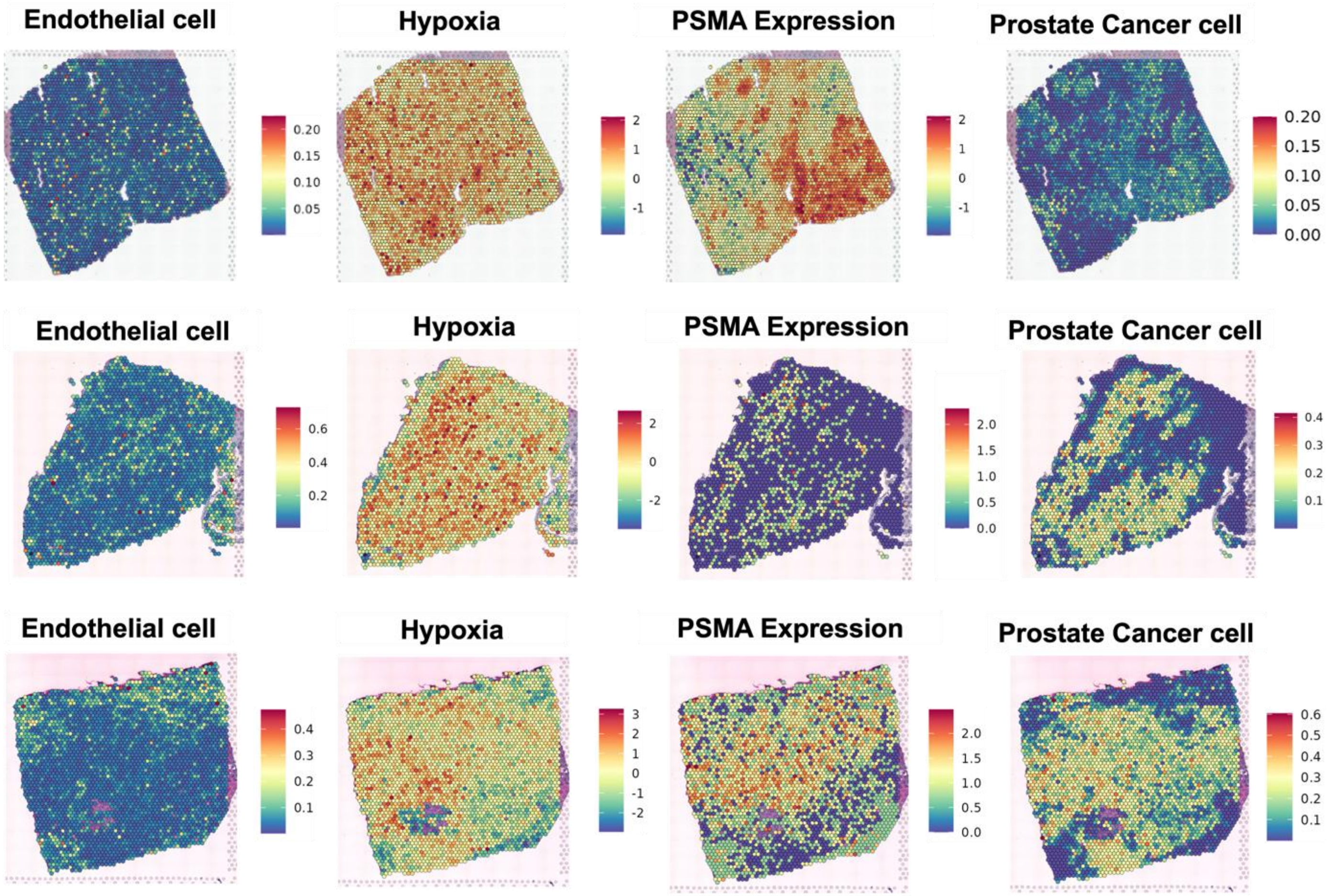
[Hong et al. in preparation]

# Spatial Transcriptomics for Precise Modelling



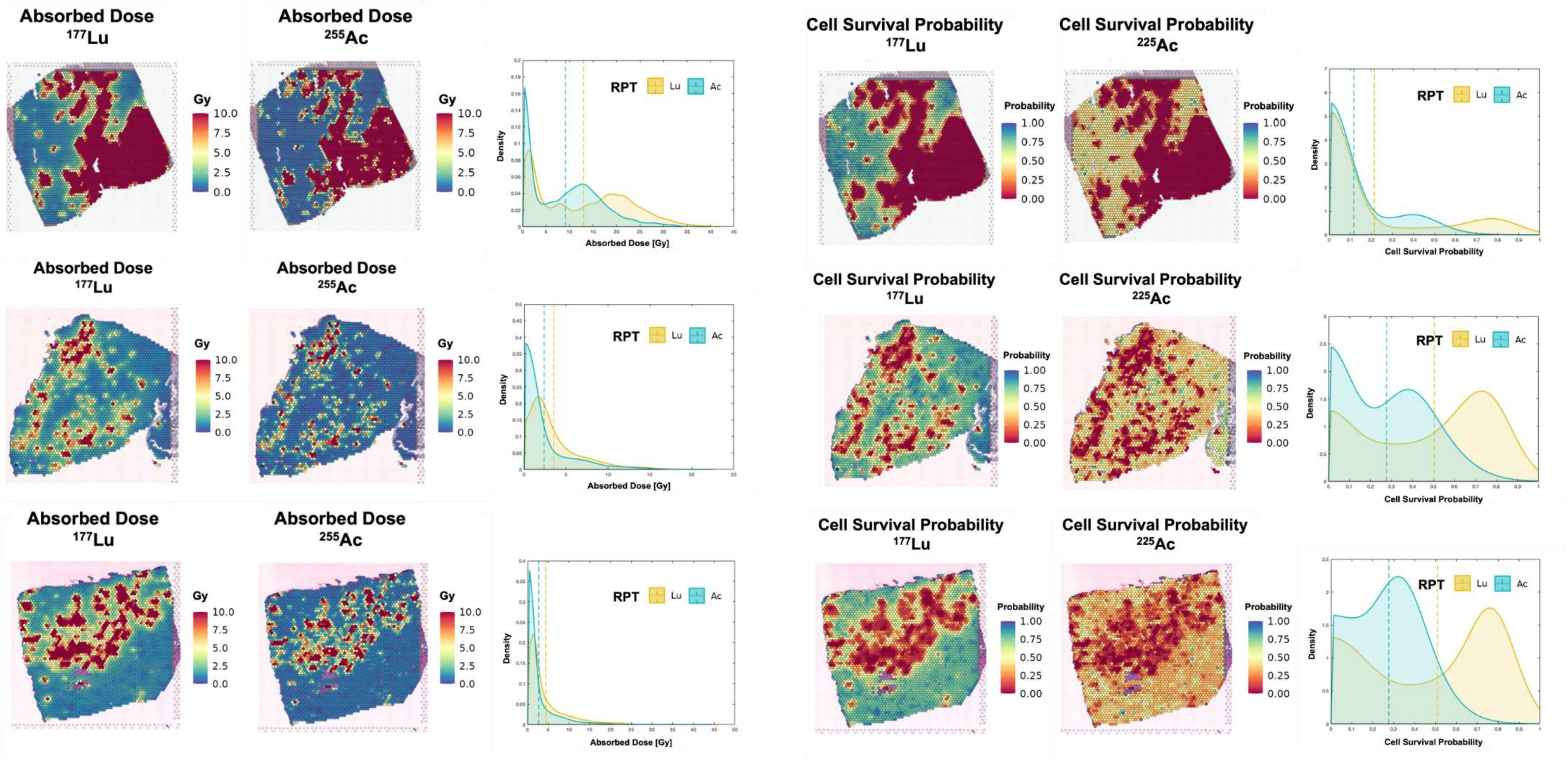

[Lewis et al Nat Methods 2021]

# Spatial-transcriptomics-driven Modelling: PSMA RPT

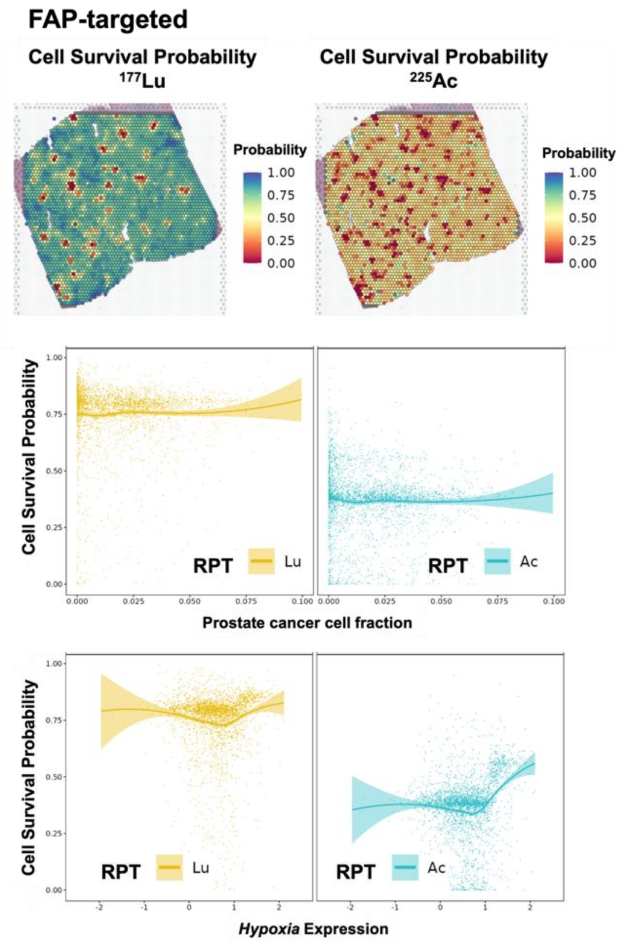


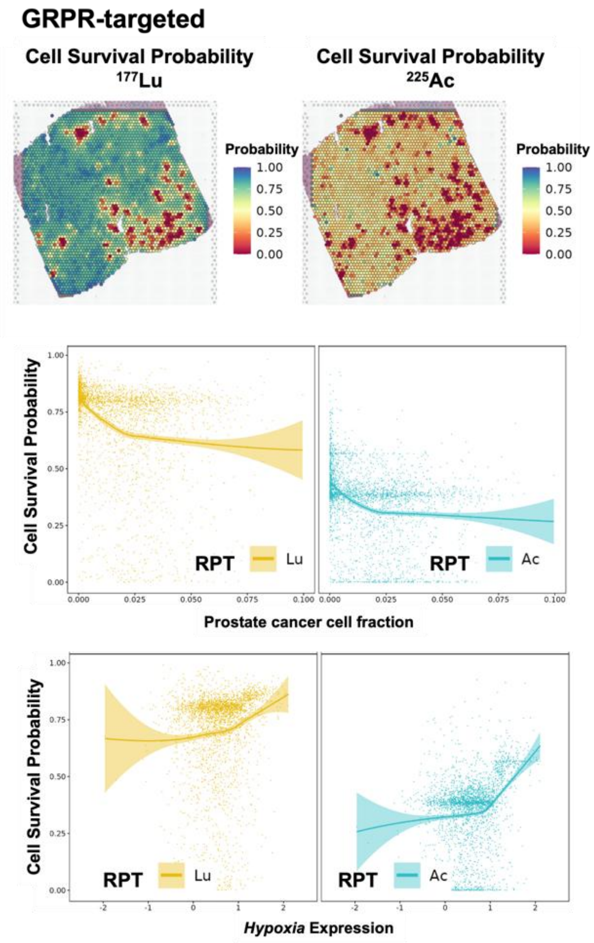

[Hong et al. Theranostics 2024]

# Spatial-transcriptomics-driven Modelling: PSMA RPT



# Spatial-transcriptomics-driven Modelling: Other RPTs



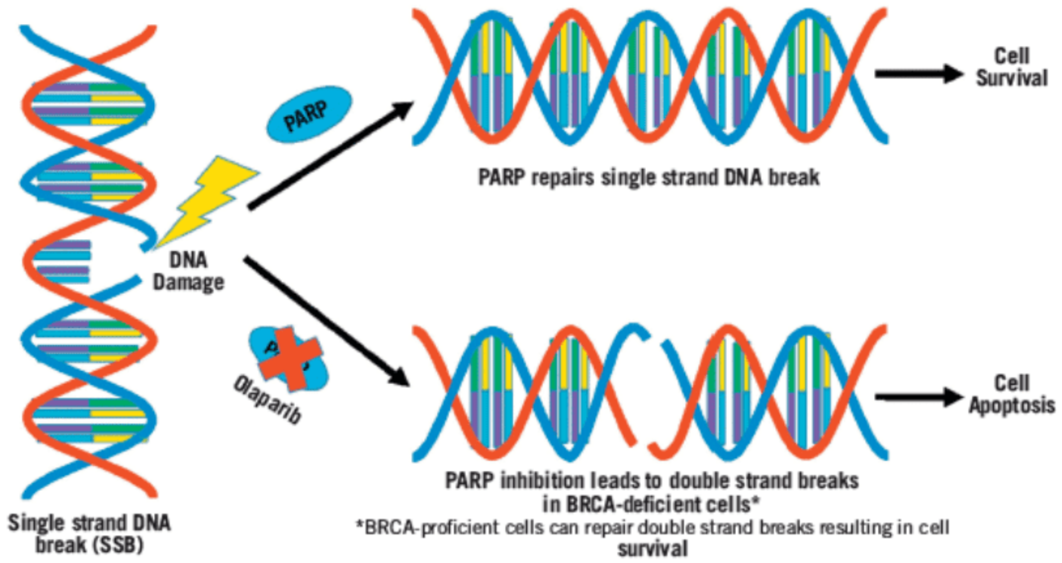



Can we model more clinical reality?

PARPi + RPT?

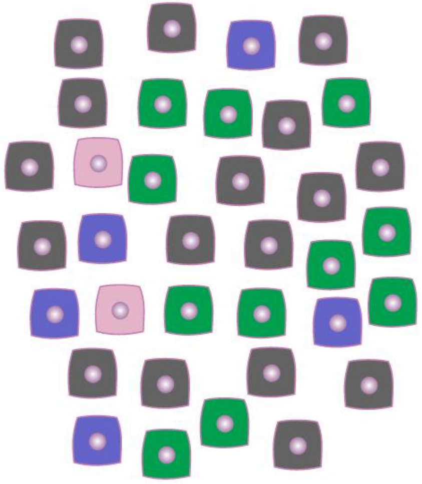
# PARP Inhibitor + Radiopharmaceutical Therapy

- DNA damage
  - Single-strand breaks (SSB)
  - Double-strand breaks (DSB)

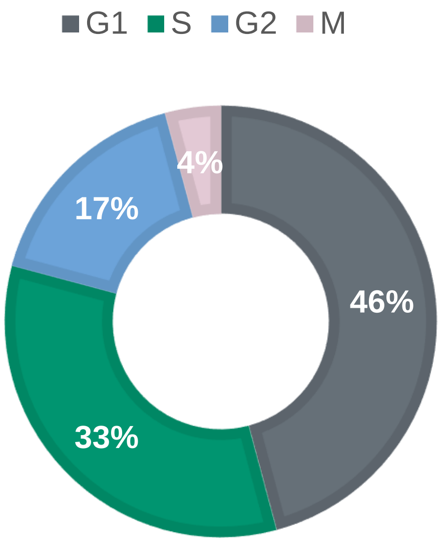



https://positivebioscience.com/

# Cell Automata Model



Randomly distributed cells over the cell cycles




Cell phase distribution

**Cell cycle effects:**

- ❑ Cell phase -> DSB repair pathways
- ❑ Cell death:
  - ✓ Misrepaired DSBs <- Presence of an additional genome.
  - ✓ Apoptosis: Late G1 phase
  - ✓ Mitotic catastrophe: Mitosis
- ❑ Genome duplication in S phase -> replicated SSBs are converted into DSBs.
- ❑ After completion of the M phase, an additional cellular entity is initiated.

In collaboration with Prof. Susanne Kossatz & Prof. Wolfgang Weber

[Ryhiner et al. in preparation]

# DNA Repair

$$1'000 \frac{SSBs}{Gy\ genome} \rightarrow N_{SSB}(\mathrm{t}) = N_{SSB}(0)\ e^{-\lambda_{ssb}t}$$

PARPi shows its effect over a modified $\lambda_{ssb}$.

$$35\ (1-p_c)\frac{simple\ DSBs}{Gy\ genome} \rightarrow N_{DSB}^{f}(\mathrm{t}) = N_{DSB}^{f}(0)\ e^{-\lambda_{dsb}^{f}t}$$

fast repair:
Non-homologous end joining (NHEJ), error prone

$$35\ p_c \frac{complex\ DSBs}{Gy\ genome} \rightarrow N_{DSB}^{s}(\mathrm{t}) = N_{DSB}^{s}(0)\ e^{-\lambda_{dsb}^{s}t}$$

slow repair:
Cell cycle dependent repair pathway

| G1 | S | G2 |
|---|---|---|
| slow repair:<br>NHEJ, error prone | slow repair:<br>Contribution of pre S phase and post S phase repair. Proportions according to S phase progression | slow repair:<br>Homologous Recombination (HR), no errors |

G1 S G2 M

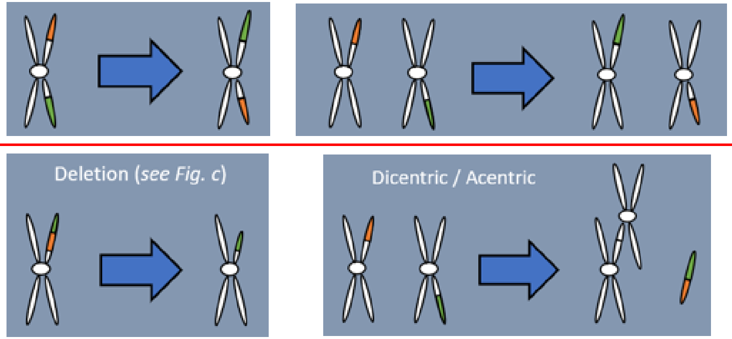
# DSB Misrepair

$$N_{mis}=p_{NHEJmis}\left[N_{NHEJ}(0)-N_{NHEJ}(t)\right]$$

intra-chromosomal | inter-chromosomal

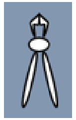
symmetric

asymmetric




Only asymmetric misrepair events lead to a loss of genetic material and contribute to cellular lethality.

Deletions only contribute to cellular lethality if they are due to inter-arm interactions.



Deletion size of at least 3 MBP required for a contribution to cell lethality.

Contribution of pre S phase and post S phase misrepair assessment. Proportions according to S phase progression.

# Cell Death

Surviving a time point in the simulation:

$$S = \left(1 - (1 - S_{mis})(1 - S_a)(1 - S_m)\right)$$

Surviving misrepair:

$$S_{mis} = e^{-N_{dic} - N_{del>3MBP}}$$

Contribution of pre S phase and post S phase death assessment. Proportions according to S phase progression.

Surviving misrepair:

$$S_{mis} = e^{-N_{dic} - N_{interArm}}$$

Escaping apoptosis:

$$S_a = e^{-\psi N_{G1}}$$

$N_{G1}$: The number of DSBs from this G1 phase.
$\psi$: Apoptosis rate

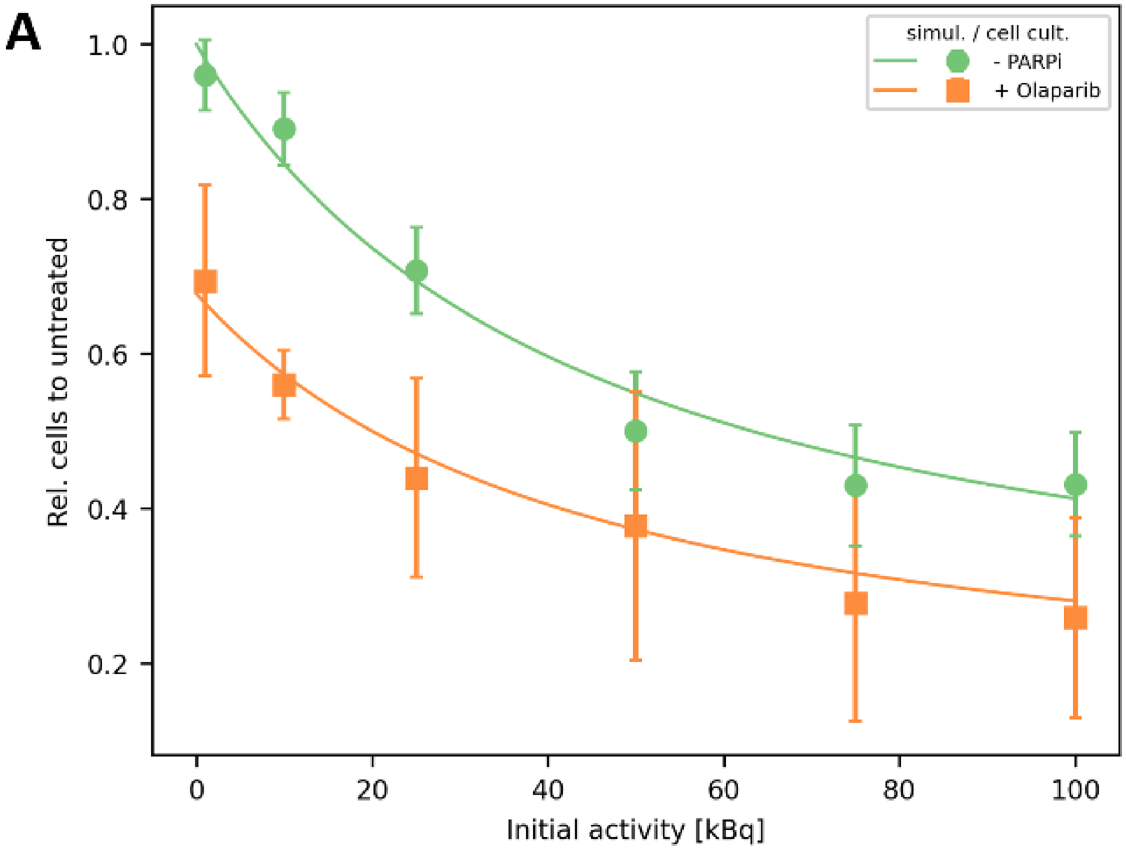
Surviving mitosis:

$$S_m = e^{-\varphi N_{DSB}}$$

$\varphi$: Mitotic catastrophe rate

G1 S G2 M

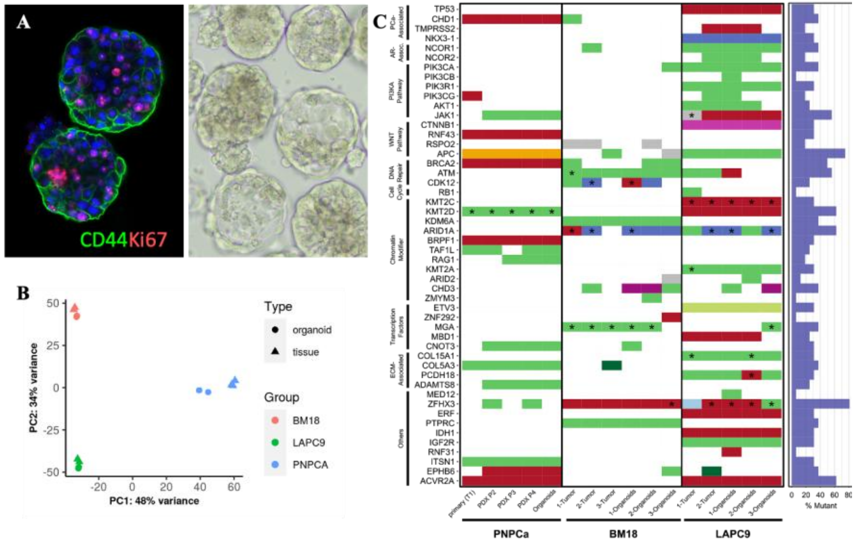
# Preliminary results




In collaboration with Prof. Susanne Kossatz & Prof. Wolfgang Weber

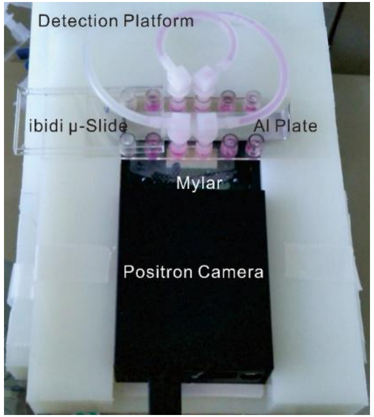
# Clone Cellular Radiosensitivity: On-chip Theranostic Investigation

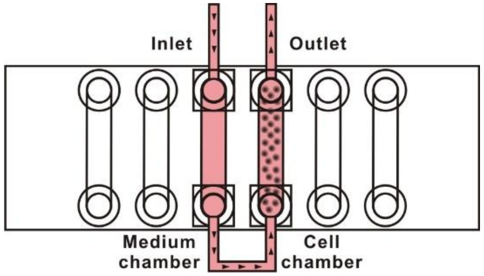
## Patient-derived organoid

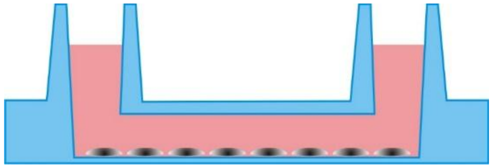



Courtesy of Prof. Marianna Kruithof-de Julio

## On-chip microfluidic radioassay



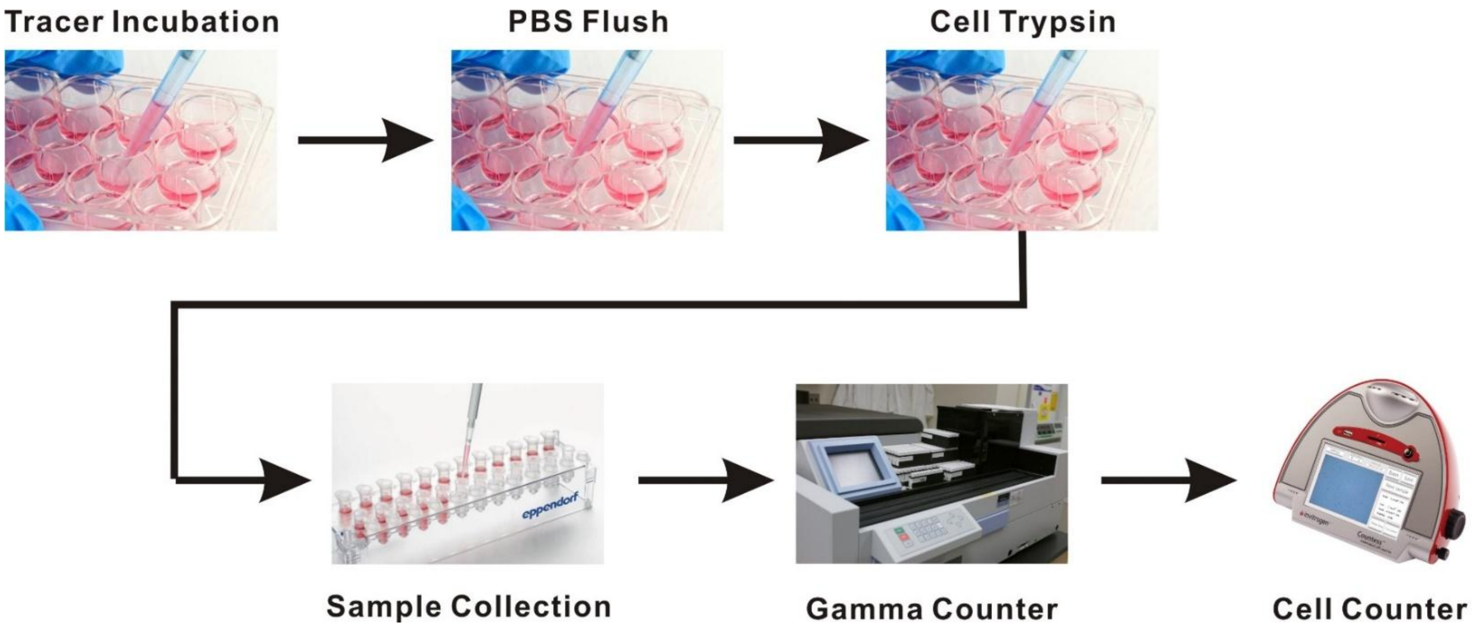



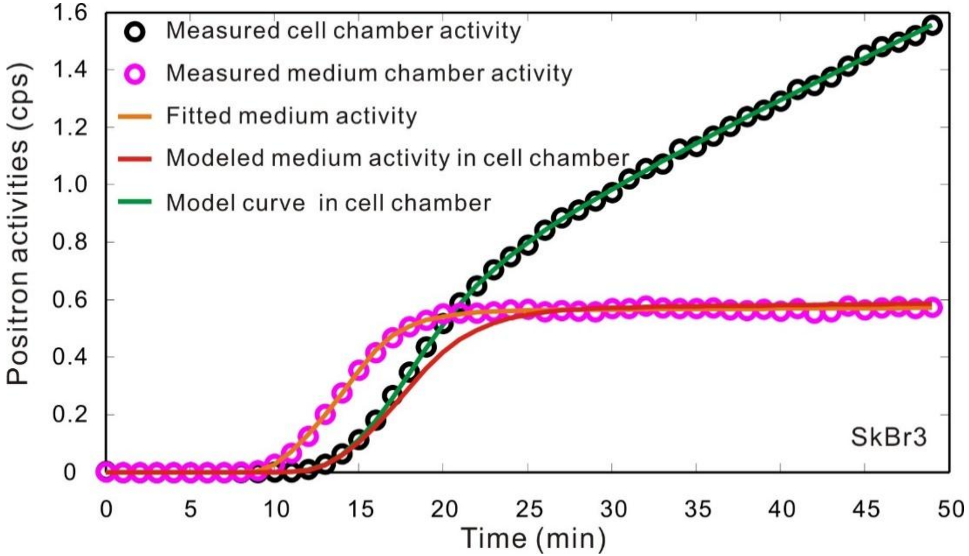
[Liu et al, JNM 2016]

# On-chip theranostic Investigation *vs* Conventional Cell Uptake Experiment

- ❑ Intact cells *vs* destroyed cell culture
- ❑ Longitudinal investigation *vs* cross-sectional investigation



# Longitudinal On-chip Radiobiological Investigation




- In culture theranostic investigation of radiobiological characteristics

- New generation of on-chip imaging [Clement et al. EJNMMI Phys 2022]

STIFTUNG FÜR KLINISCH-EXPERIMENTELLE TUMORFORSCHUNG

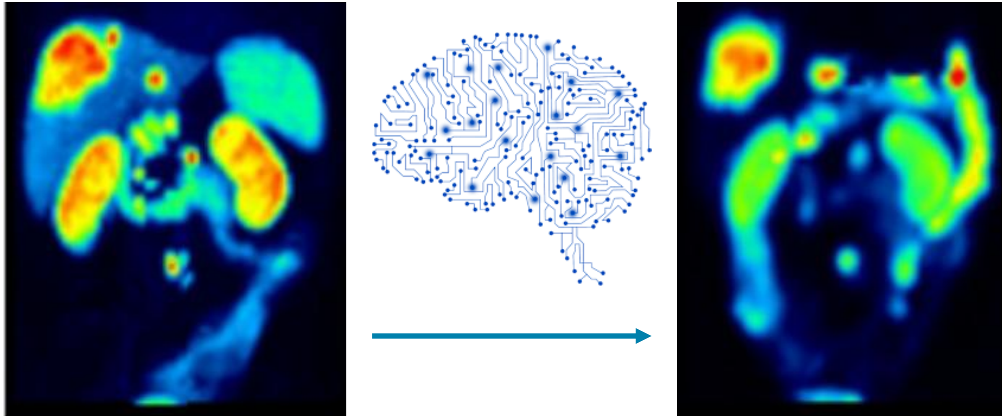
# Accelerate Digital Twin Clone using Artificial Intelligence

**Extract complex knowledge from patient data**

- ❑ Predict radiosensitivity
- ❑ Pre-therapy prediction of dose distribution
- ❑ Assist dosimetry quantification
- ❑ Assist organ or tumor segmentation
- ❑ …….

**Pre-therapy PET**

**Post-therapy dosimetry**



# Predictive dosimetry

**Therapy SPET/CT**

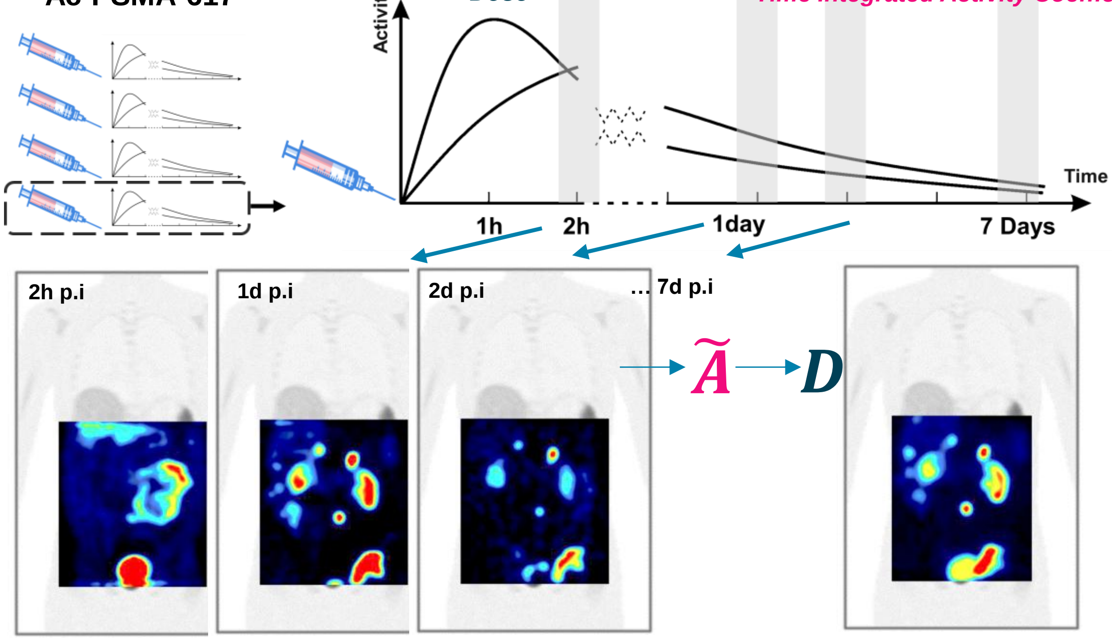
**Per 1 Cycle, Multiple time points**

**3-5 Cycles**
**$^{177}$Lu-PSMA-617**
**$^{225}$Ac-PSMA-617**

$$D(r_T, T_D) = \sum_{r_S} \tilde{A}(r_S, T_D)\, S(r_T \leftarrow r_S)$$

*Dose*

*Time Integrated Activity Coefficient (TIAC)*

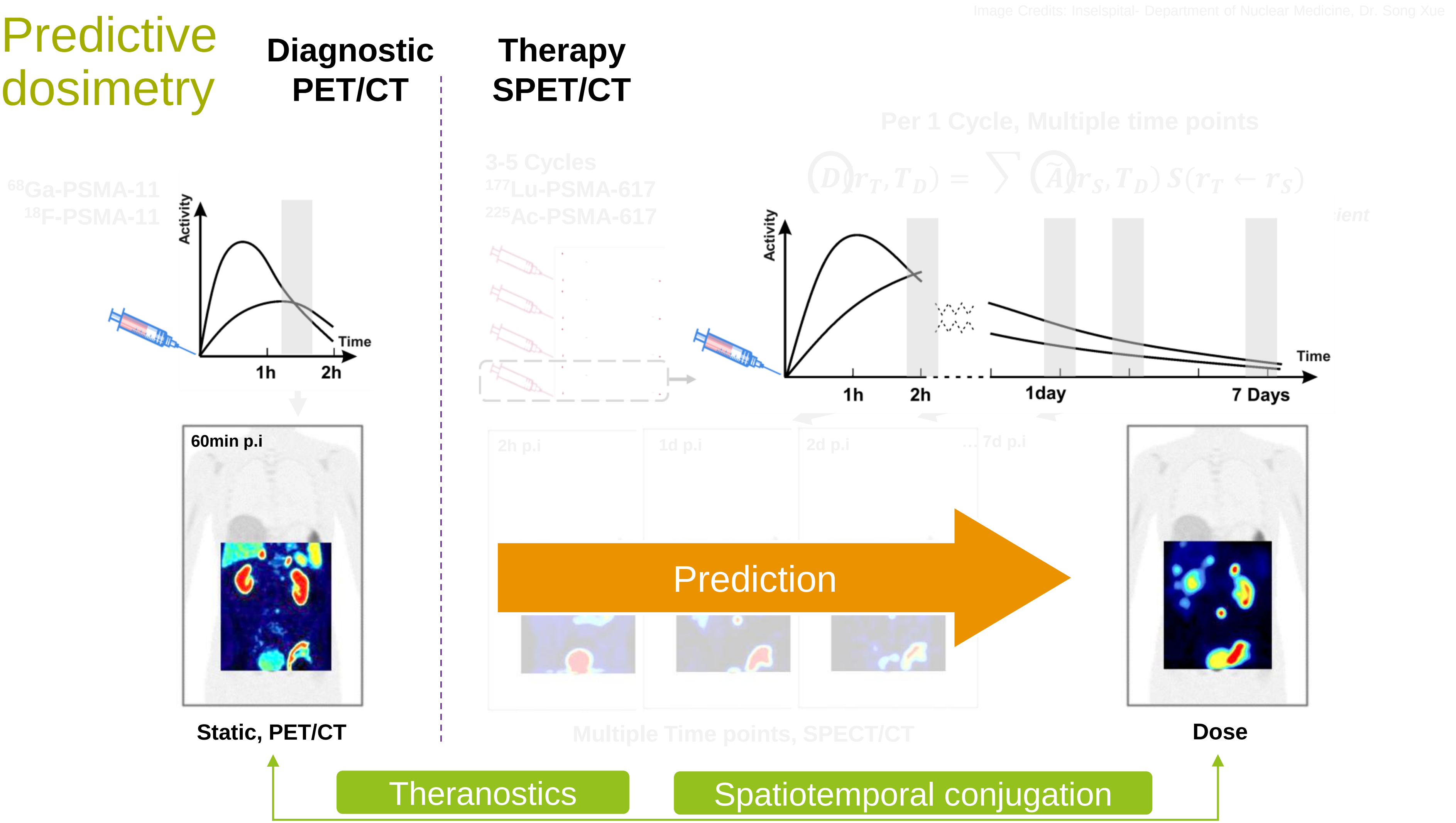



**Multiple Time points, SPECT/CT**

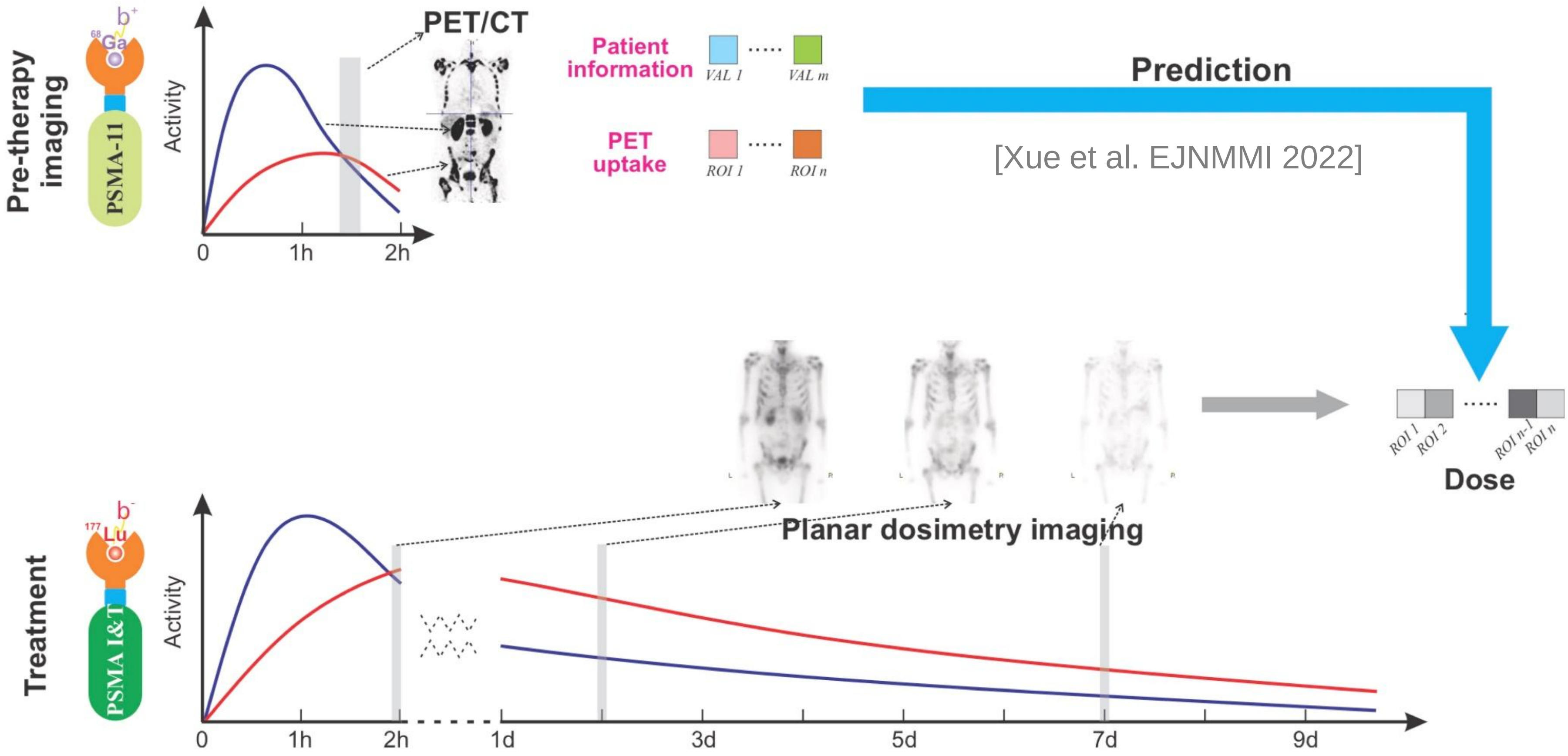
**Dose**

# Predictive dosimetry

**Diagnostic PET/CT** | **Therapy SPET/CT**



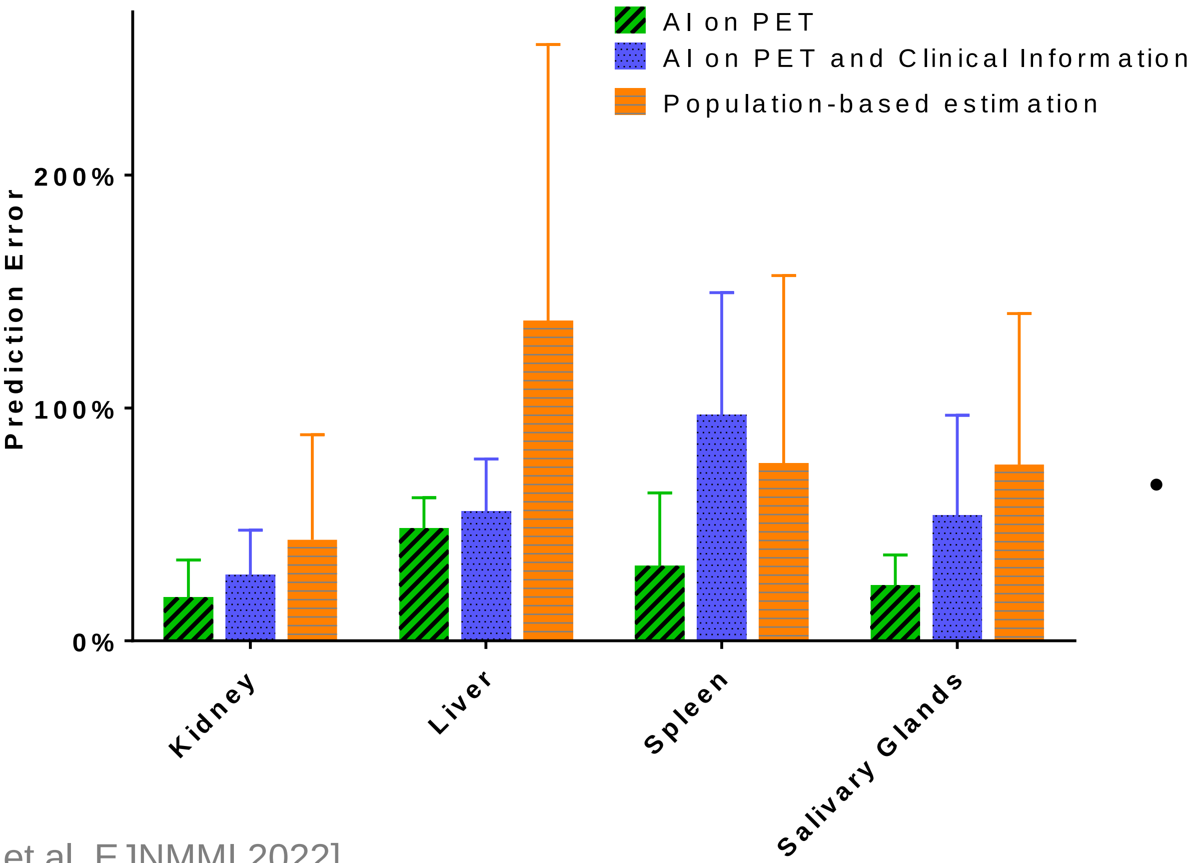
# AI for Predictive Dosimetry: Organ-wise




[Xue et al. EJNMMI 2022]

In collaboration with Prof. Matthias Eiber & Prof. Wolfgang Weber

# Preliminary Organ-based Prediction Results



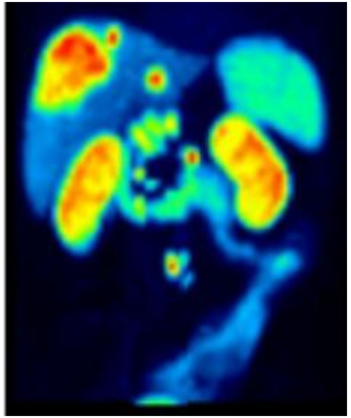

- Population value obtained from [Okamoto et al. JNM 2017]

[Xue et al. EJNMMI 2022]

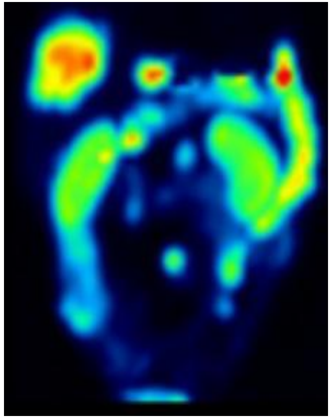
Organ-wise prediction doesn’t consider heterogeneity

Voxel-wise prediction more favorable for treatment planning

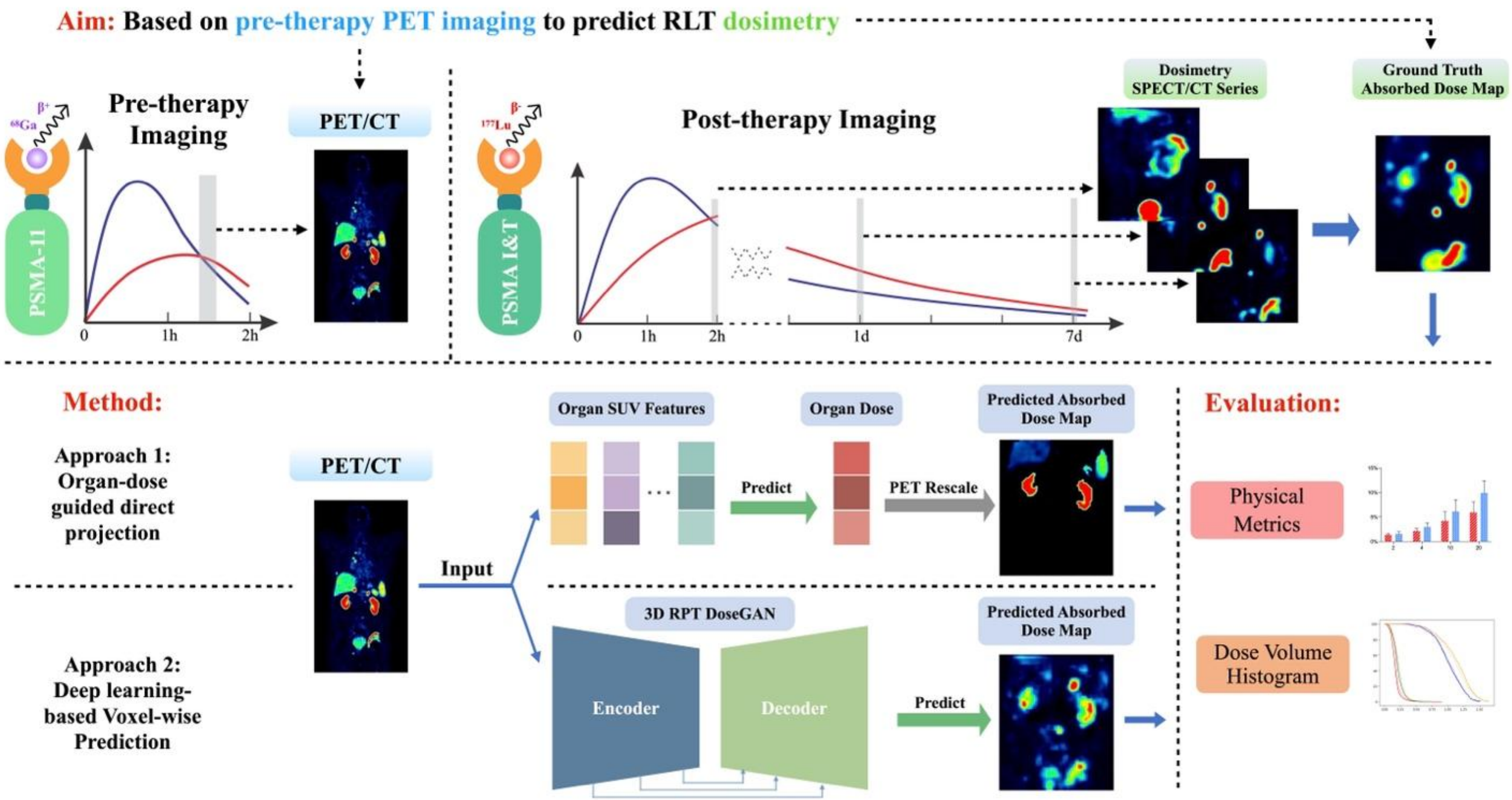
**Pre-therapy PET**



**Post-therapy dosimetry**

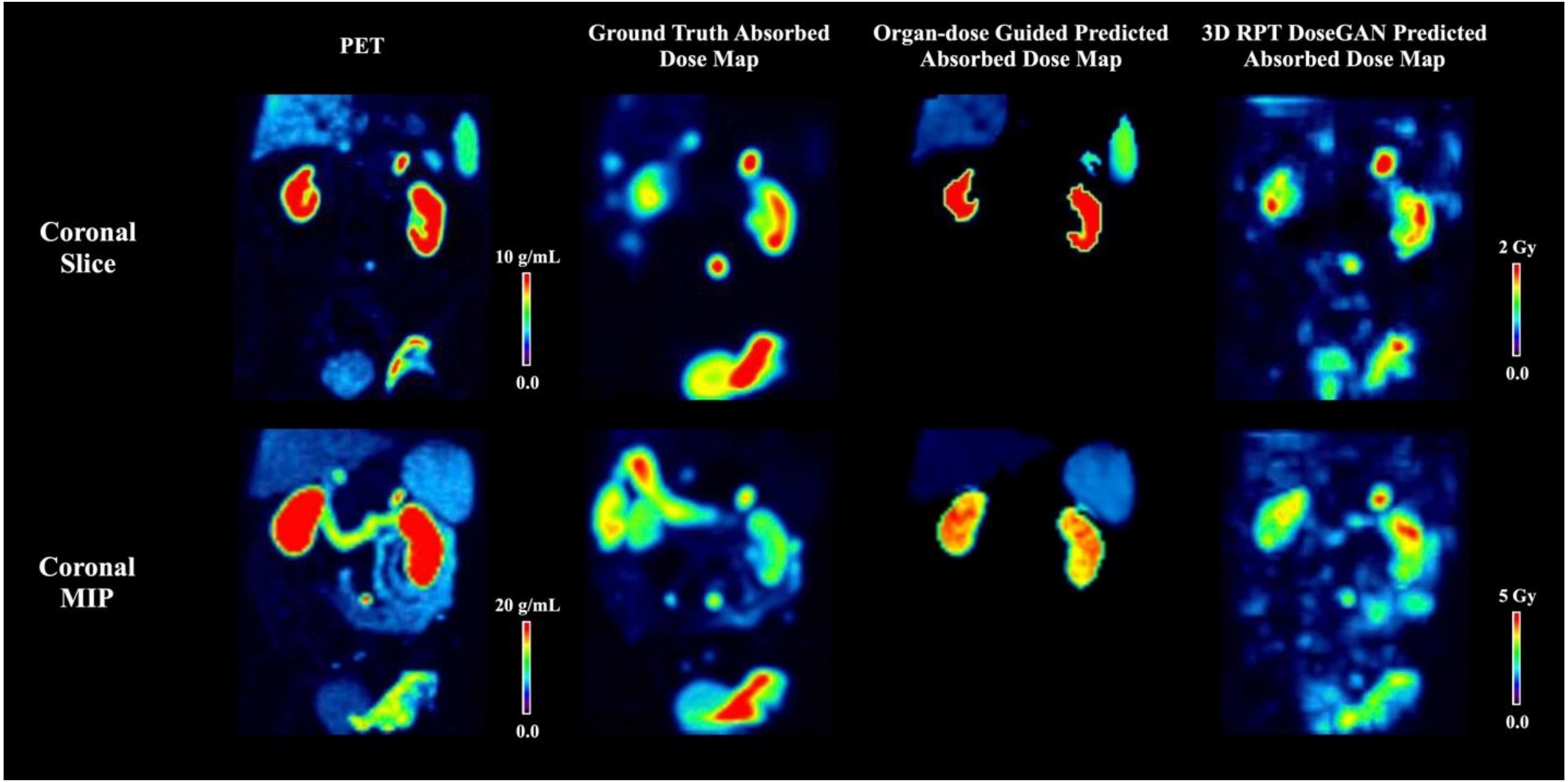


# Deep Learning based Voxel-wise Prediction

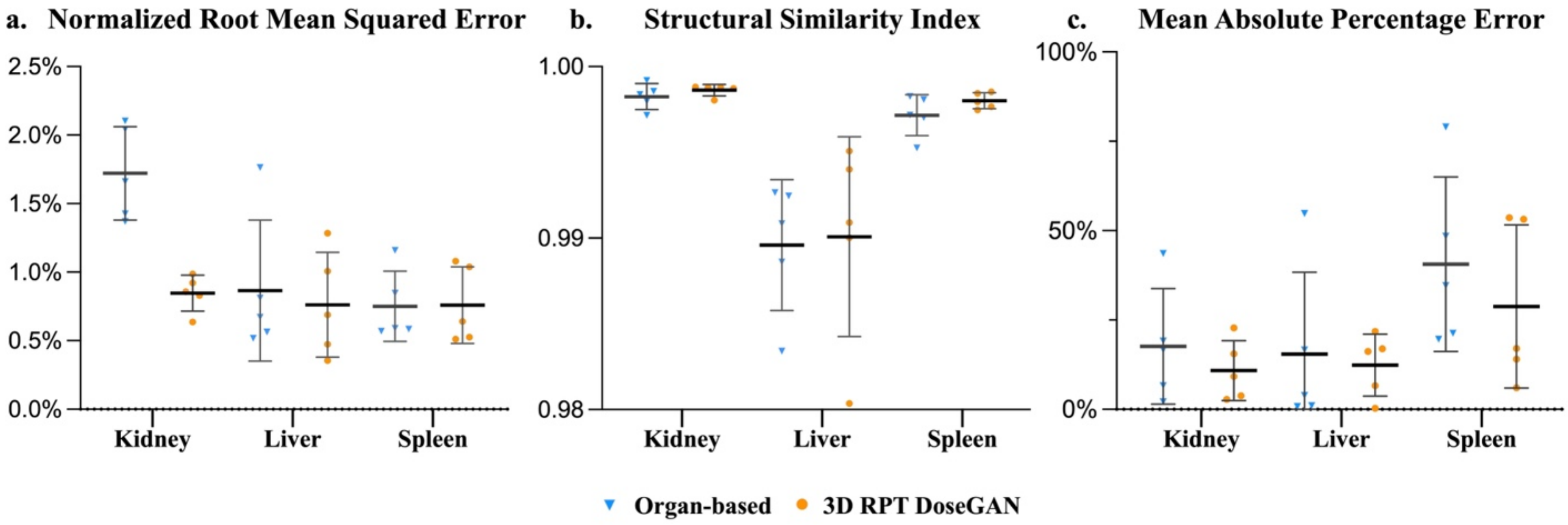



[Xue et al. EJNMMI 2024]

# Voxel-wise Pre-therapy Prediction of Dosimetry



# Voxel-wise Pre-therapy Prediction of Dosimetry

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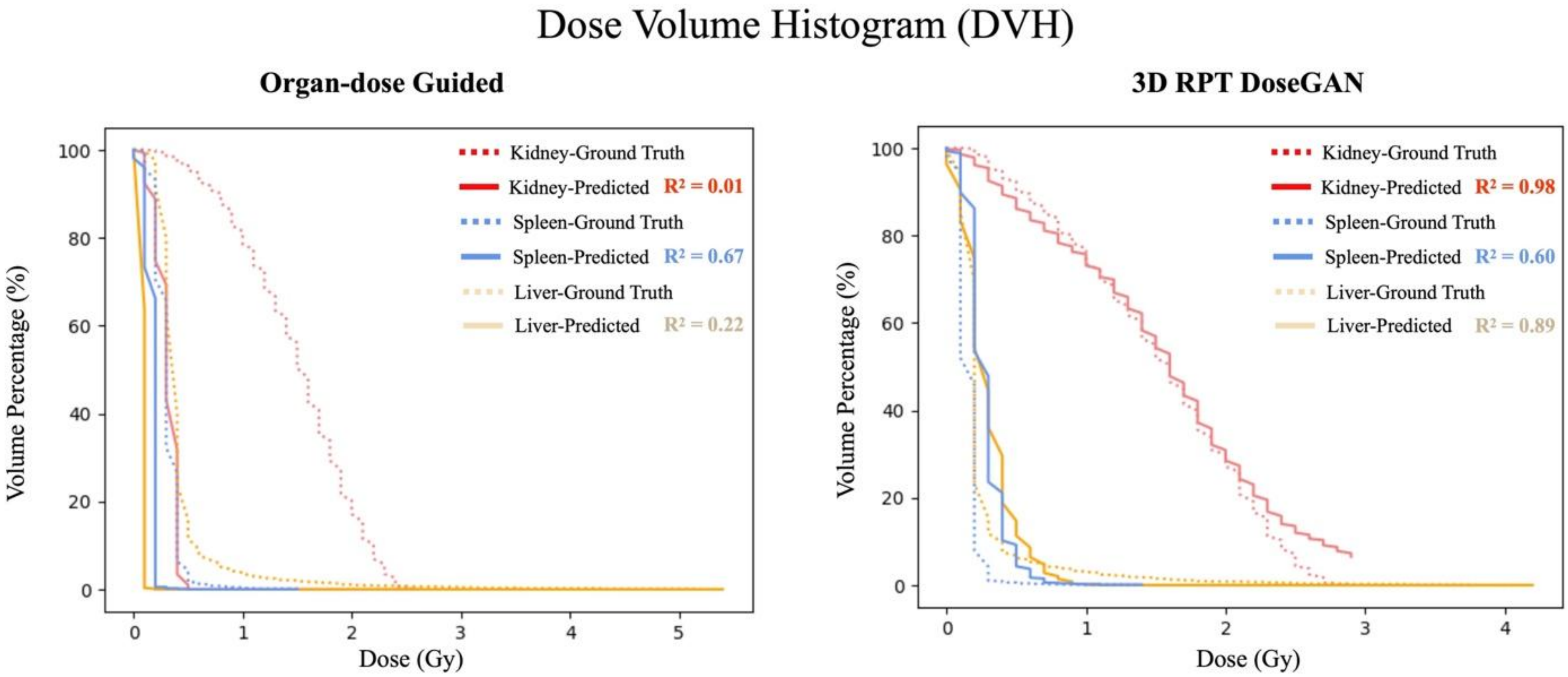
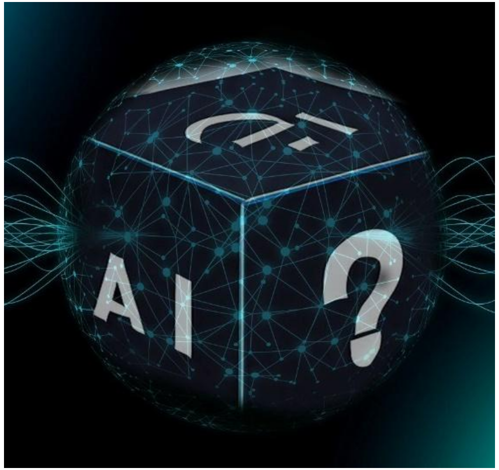
# Voxel-wise Pre-therapy Prediction of Dosimetry



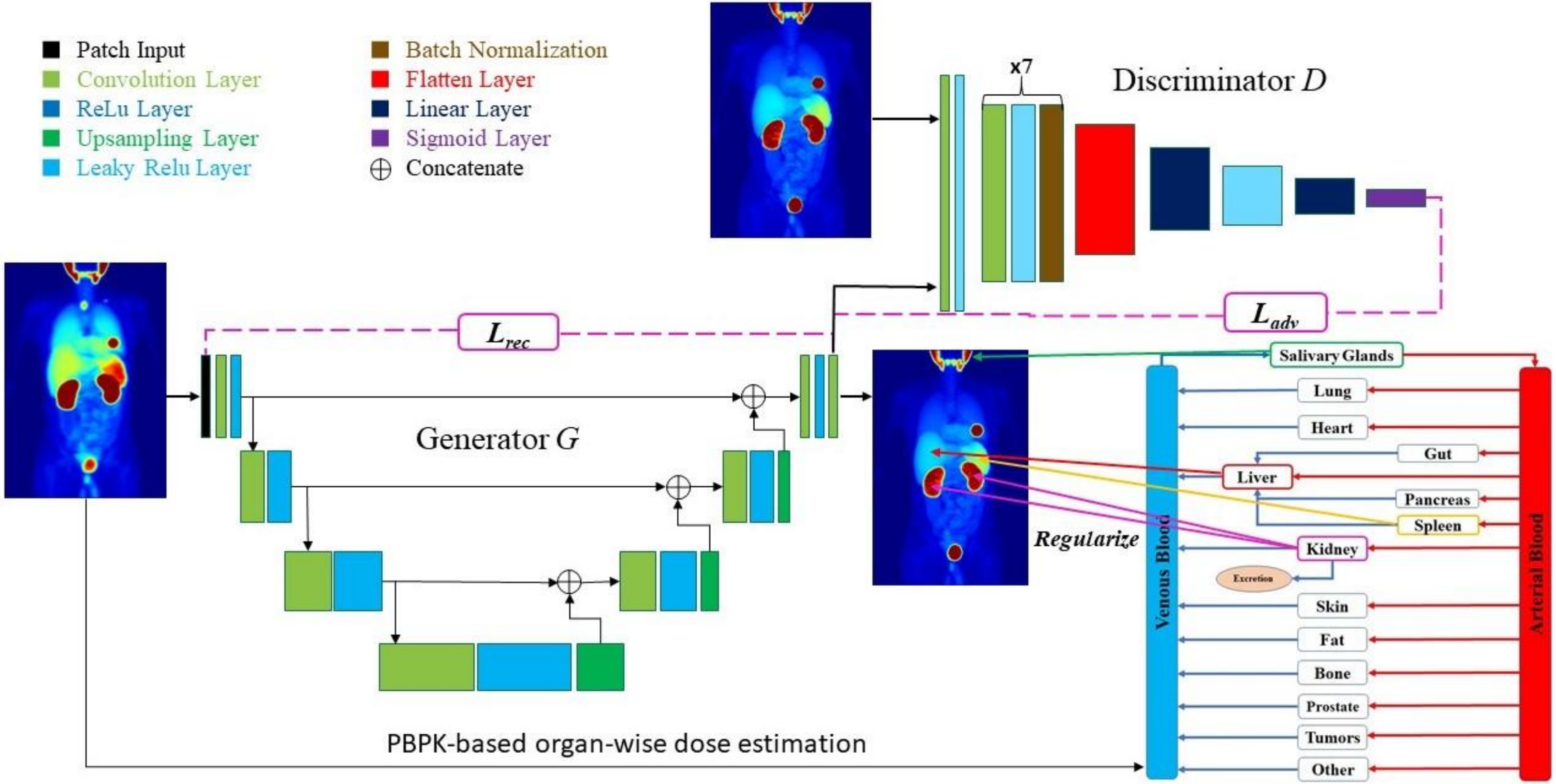



https://www.makeuseof.com/what-are-ai-black-boxes/

**Can we make the AI-base voxel-wise prediction more robust & interpretable?**

**Consider domain knowledge, i.e. pharmacokinetics**

# PBPK-adapted Deep Learning for Predictive Dosimetry

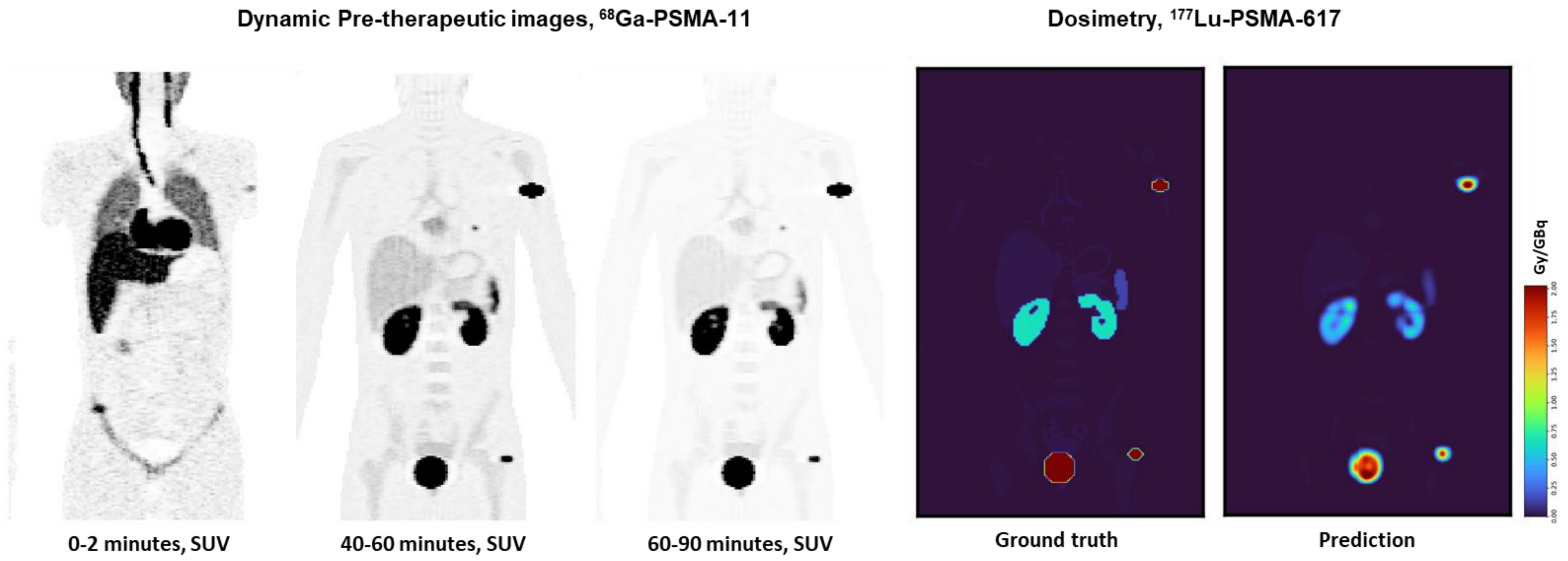



**Physiologically-based pharmacokinetic (PBPK) model**

[Kassar et al. IEEE TRPMS 2024]

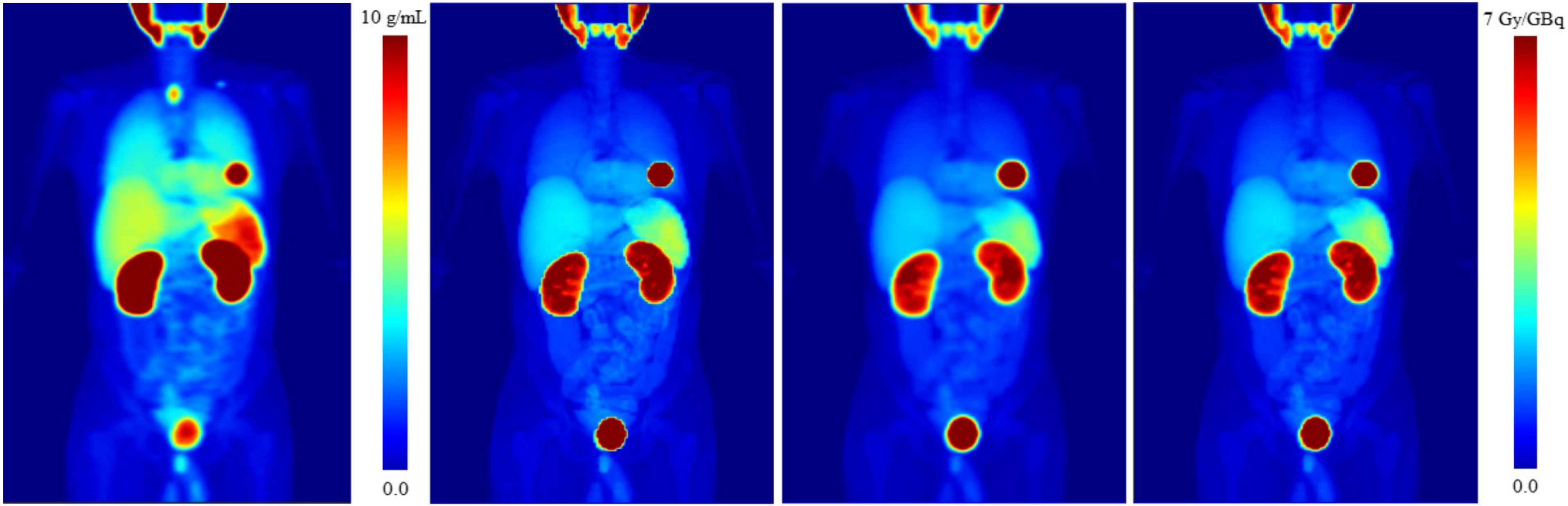
[Belgum et al. J Nucl Med 2018
Kletting et al. J Nucl Med 2018]

# Proof of Concept on Digital Twins Phantoms



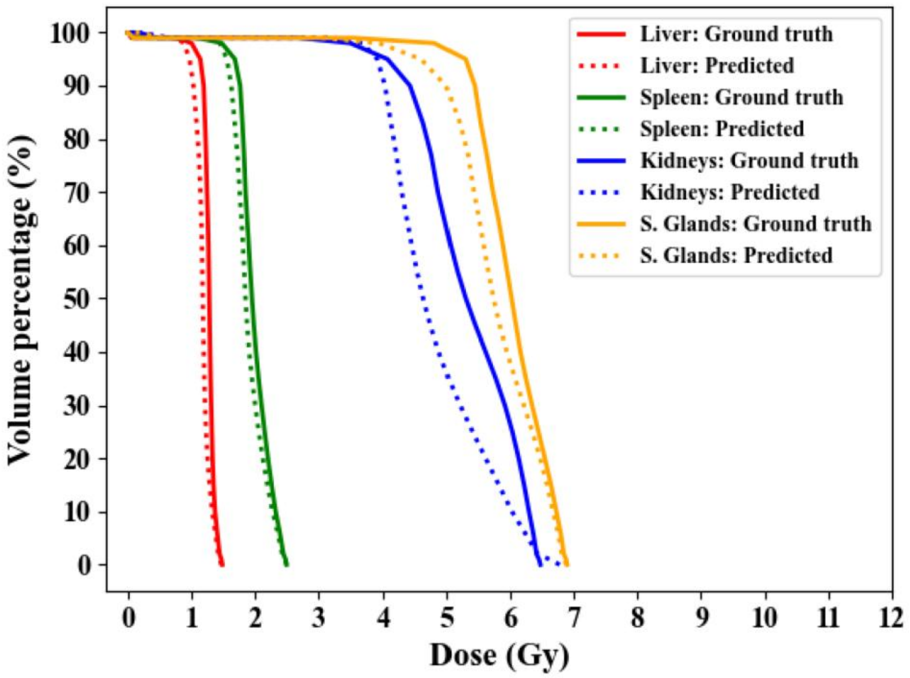

[Belgum et al. J Nucl Med 2018, Kletting et al. J Nucl Med 2018]

# Proof of Concept on Digital Twin Phantoms

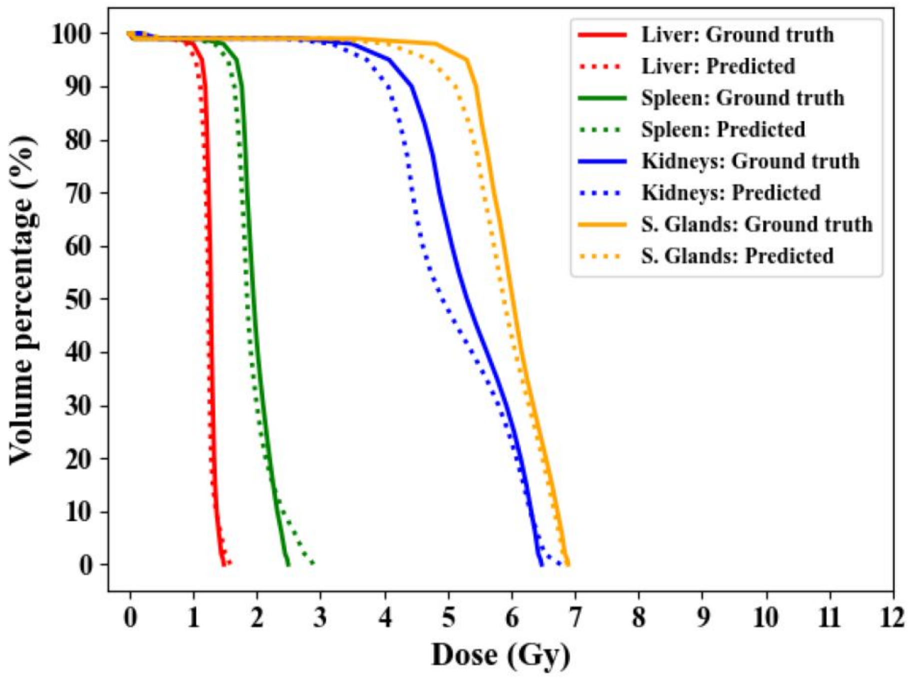



Pre-therapy PET | Ground-truth dosimetry | Deep learning | PBPK-adapted deep learning

# Proof of Concept on Digital Twin Phantoms



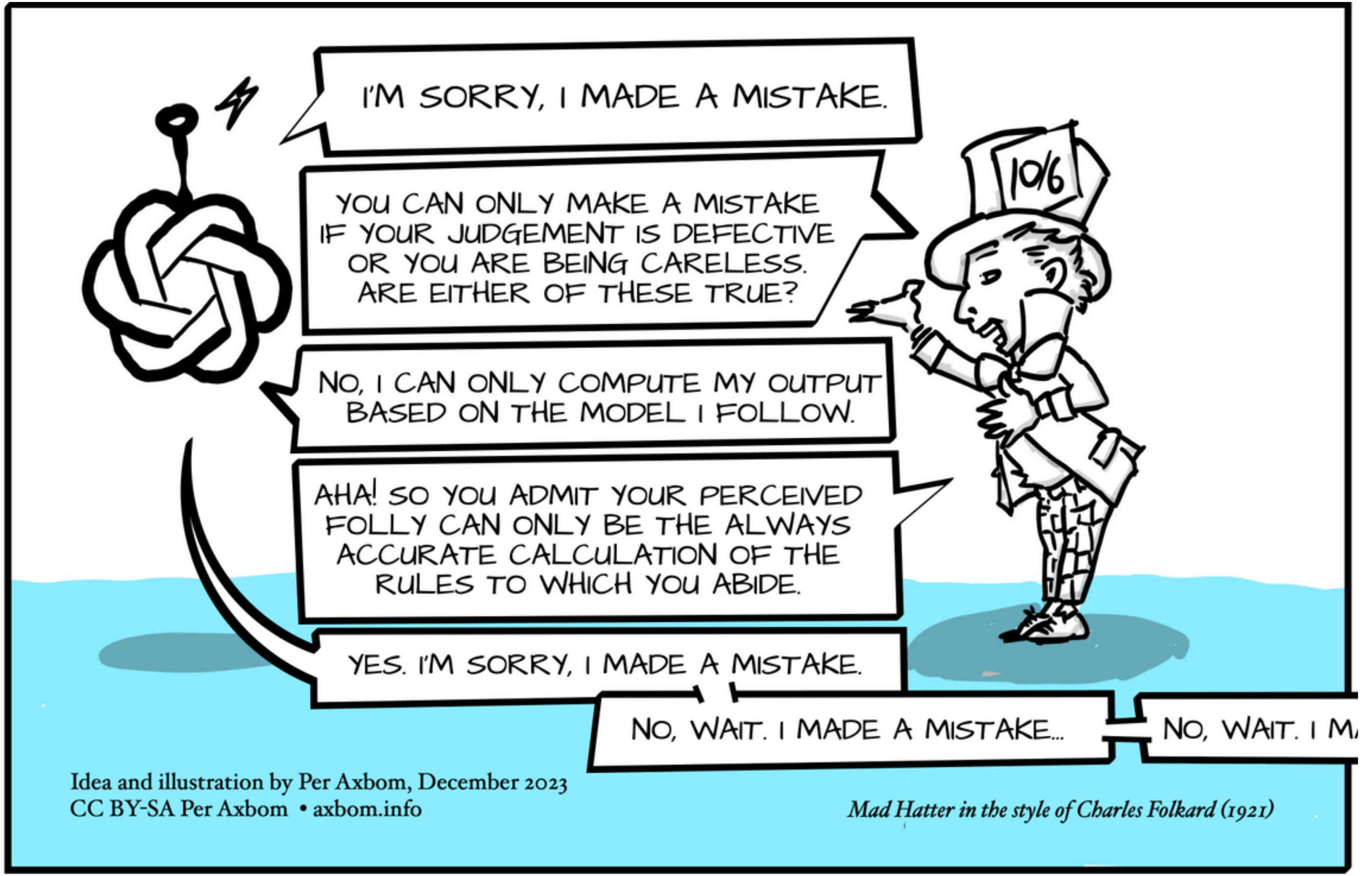

Deep learning




PBPK-adapted deep learning

# Chatbot for Theranostics

# Hallucination: Mad with ChatGPT



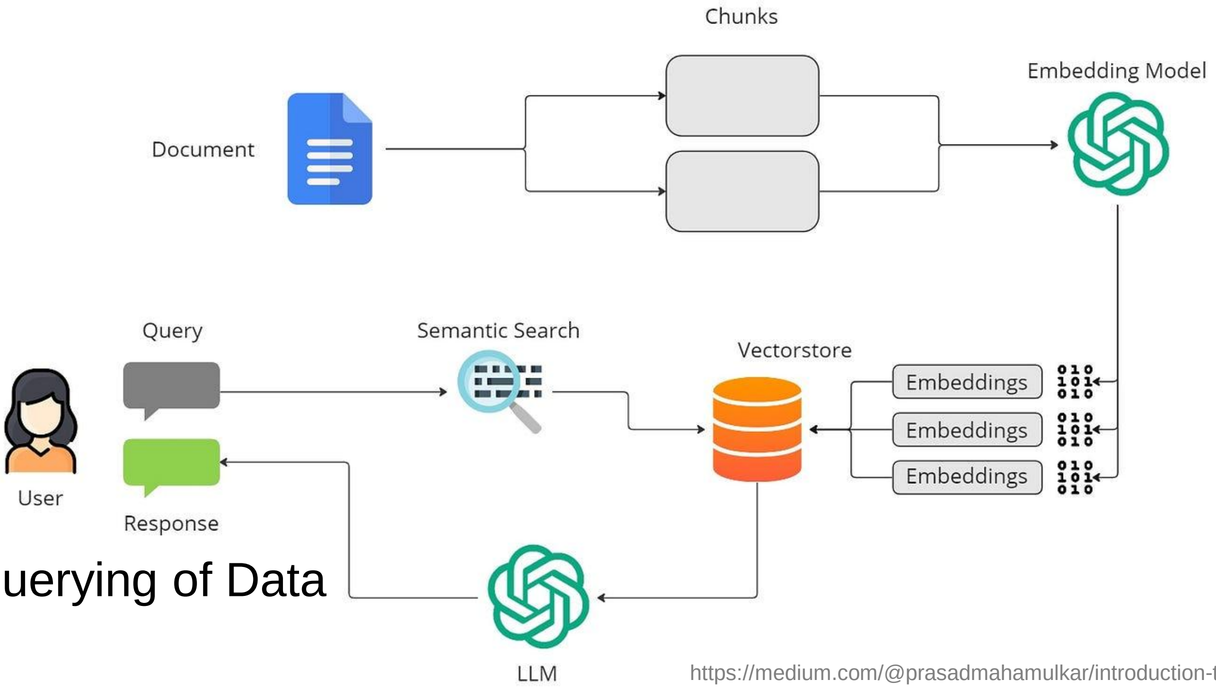

https://axbom.com/chatgpt-and-mad-hatter/

# Retrival Augmentend Generation (RAG)

## ❑ ChatGPT Over Own Data

- LLMs are trained on enormous bodies of data but not on own data
- RAG adds its own data to the data LLMs have access to

1. Ingestion of Data

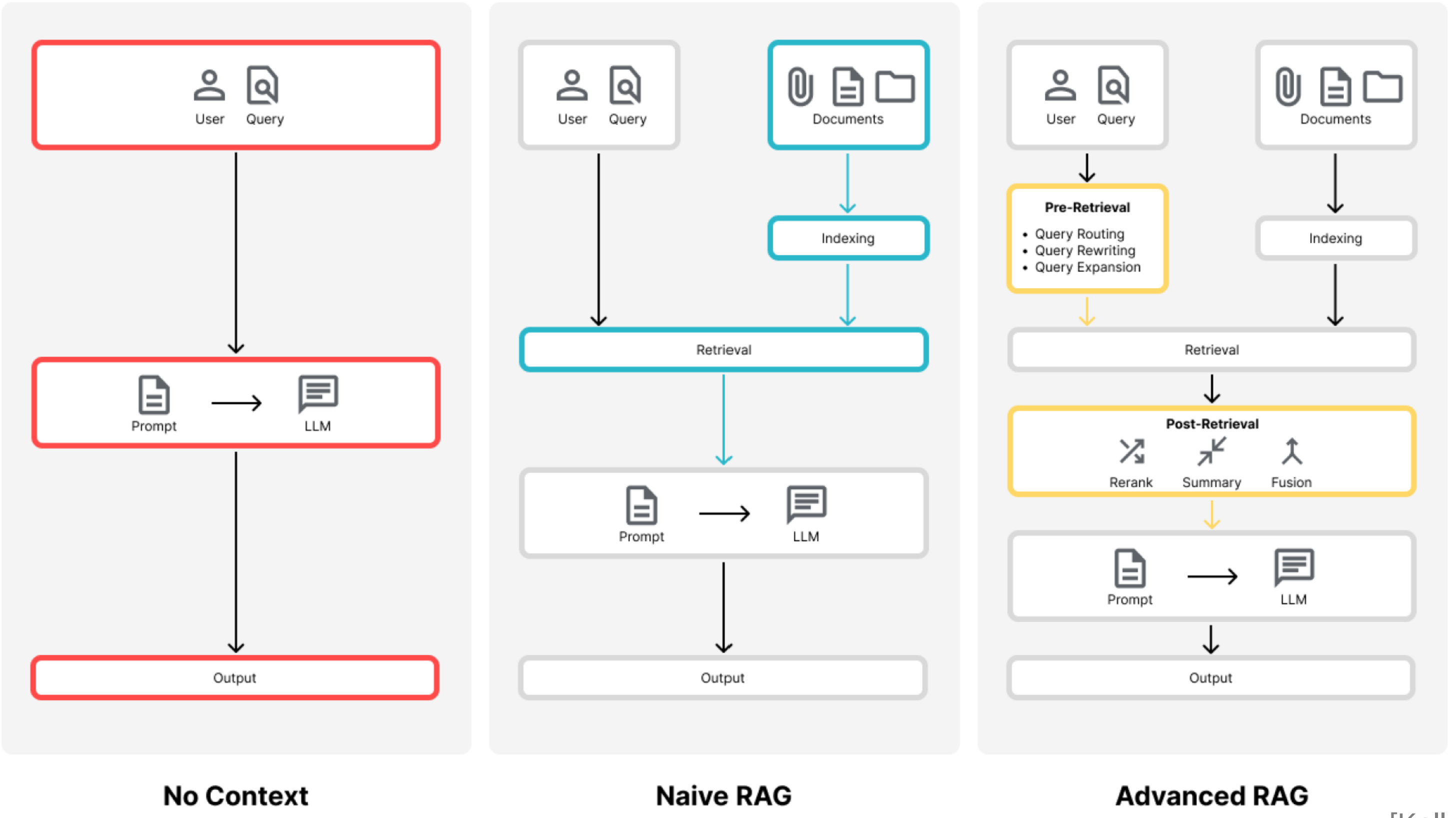



2. Querying of Data

https://medium.com/@prasadmahamulkar/introduction-to-retrieval-augmented-generation-rag-using-langchain-and-lamaindex-bd0047628e2a

# Contextual Augmentation for Generative AI

- ❑ Naive RAG: only use the set of 198 research papers
- ❑ Advanced RAG: use the set of 198 research papers & pre- or post-retrieval methods




[Koller et al in preparation]

# Evaluation

Go Back

Question 6 / 10

****Please note:** Answers are generated by AI models and may not be entirely accurate.
It is also possible that answers are similar or the same.**

## What is Peptide Receptor Radionuclide Therapy (PRRT)?

Choose the better fitting answer.
If you can't decide or both answers are inccorect choose "Neither"

Neither

Peptide receptor radionuclide therapy (PRRT) is a targeted radiation treatment for non-operable or metastatic neuroendocrine tumors that overexpress somatostatin receptors. It involves the systemic administration of radiolabeled peptides, such as somatostatin analogs, that bind specifically to peptide receptors on tumor cells, delivering destructive radiation to cancer cells. (Nicolas et al., 2019; Zaknun et al., 2013)

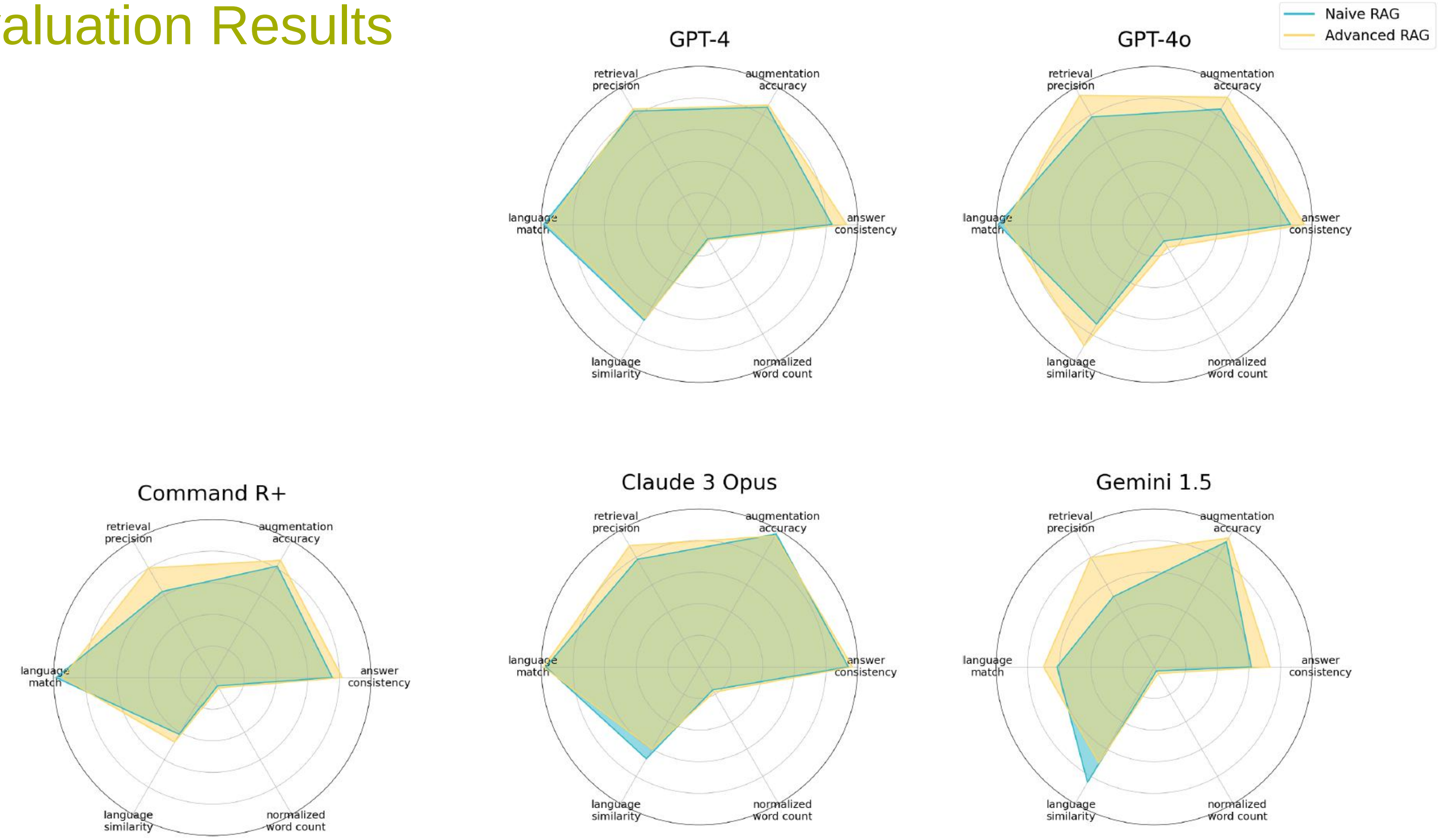
Peptide Receptor Radionuclide Therapy (PRRT) is a targeted radionuclide therapy that delivers cytotoxic radiation to cancer cells through the specific binding of radiolabeled peptides to peptide receptors, which are expressed in higher density on the tumor cell membrane compared to non-tumor tissues (Nicolas et al., 2019). This therapy is particularly used for treating nonoperable or metastatic neuroendocrine neoplasms that frequently express somatostatin receptors, utilizing radiolabeled somatostatin analogues (Hirmas et al., 2018).

**Do you have any comments or feedback about the user study, the questions or the answers?
Your input helps us improve the user study. Please feel free to add them here:**

Enter your Comments or Feedback

Submit

# Evaluation Results



# Conclusion

- Digital Twin is feasible to systematically investigate multi-level heterogeneity in radionuclide therapy

- Clone of patient digital twin:
  - promising hope for personalized treatment
  - Needs intensive interdisciplinary developments

- Artificial intelligence (AI) may assist the learning of complex theranostic knowledge and accelerate digital twin virtual clone

- Physiological knowledge may improve the performance of AI with limited data

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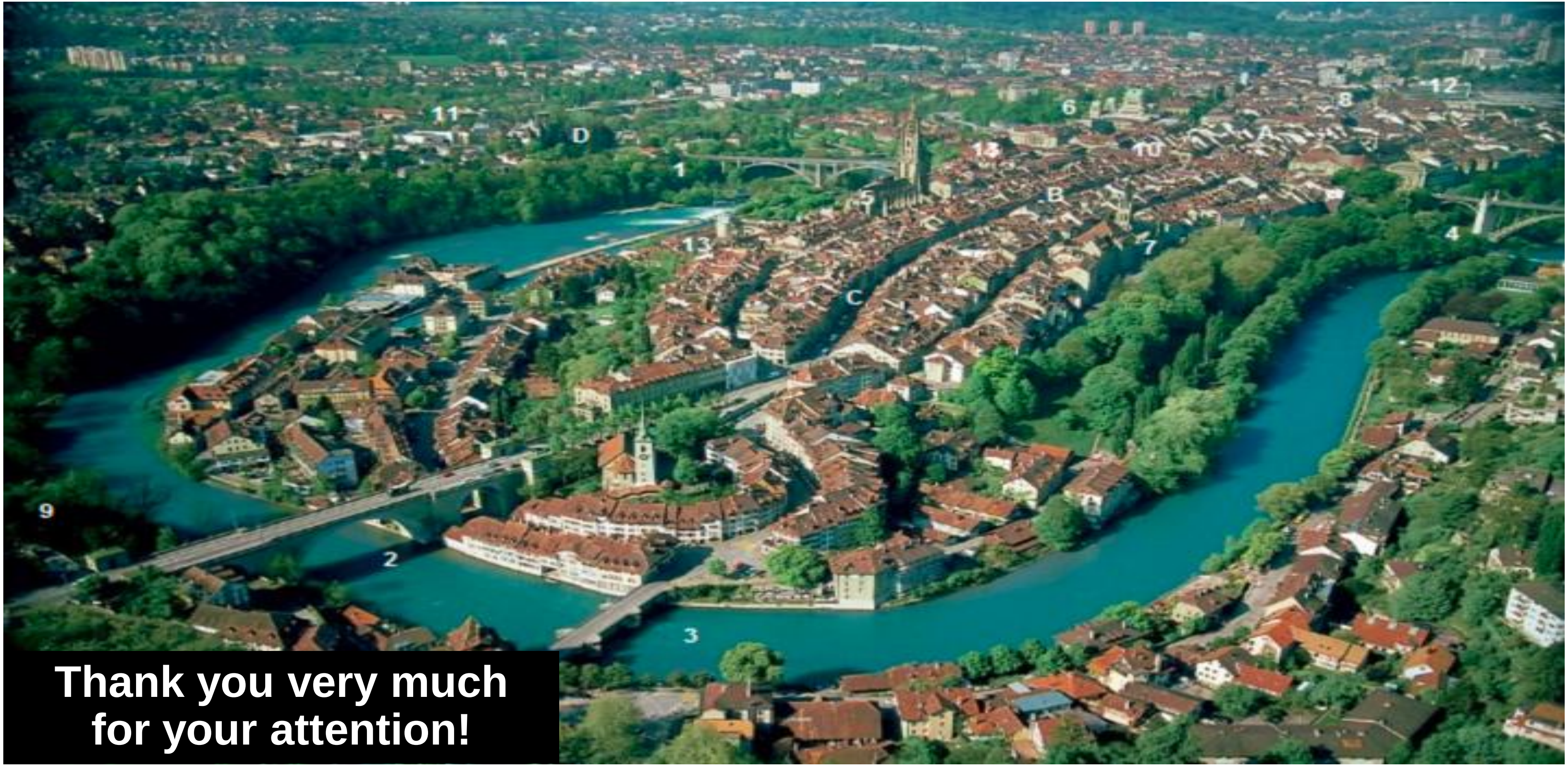


**Thank you very much for your attention!**