Where science meets inspired minds.

PBPK Modeling of Radiopharmaceuticals:
From Imaging Data to Clinical Insights

Dr. Hinke Huisman-Siebinga

OSP Community Conference

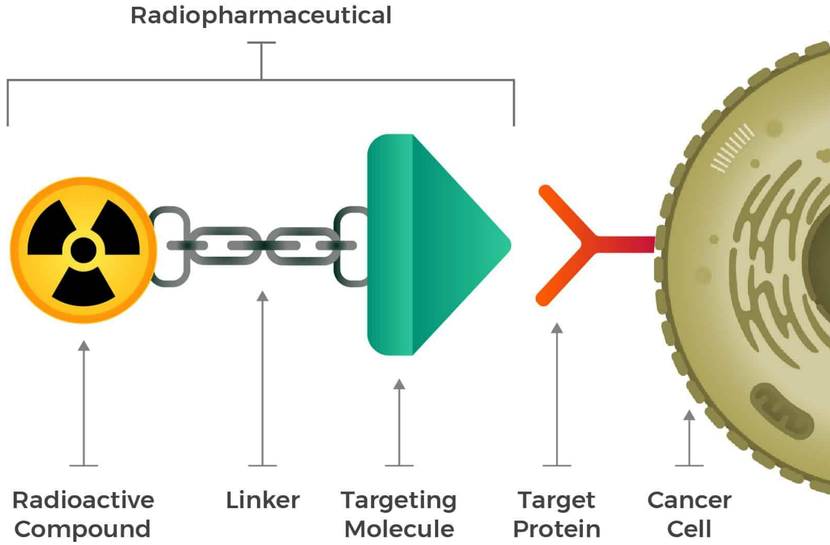
September 25th, 2026

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Radionuclide therapies

Systemic targeted treatment using radiopharmaceuticals

Targeting molecular alternations expressed or upregulated in malignant tumors



Growing availability for cancer treatment:

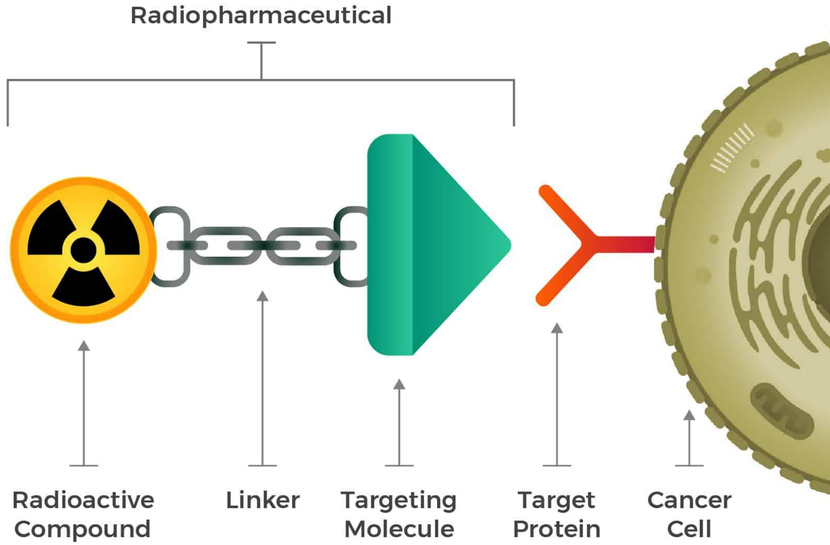
- Neuroendocrine tumors
- Prostate cancer

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Theranostic approach

Therapeutic + diag**nostic**

Similar linker & targeting molecule, different radioactive compound



	Diagnostic radionuclide	Therapeutic radionuclide
Goal	Diagnosis and patient selection	Treatment
Radionuclide	e.g. Gallium-68	e.g. Lutetium-177
Emission	β^+	β^- and γ
Scan	PET/CT	SPECT/CT
Administered activity	~100 MBq	~7.4 GBq

Clinical data

Diagnostic imaging

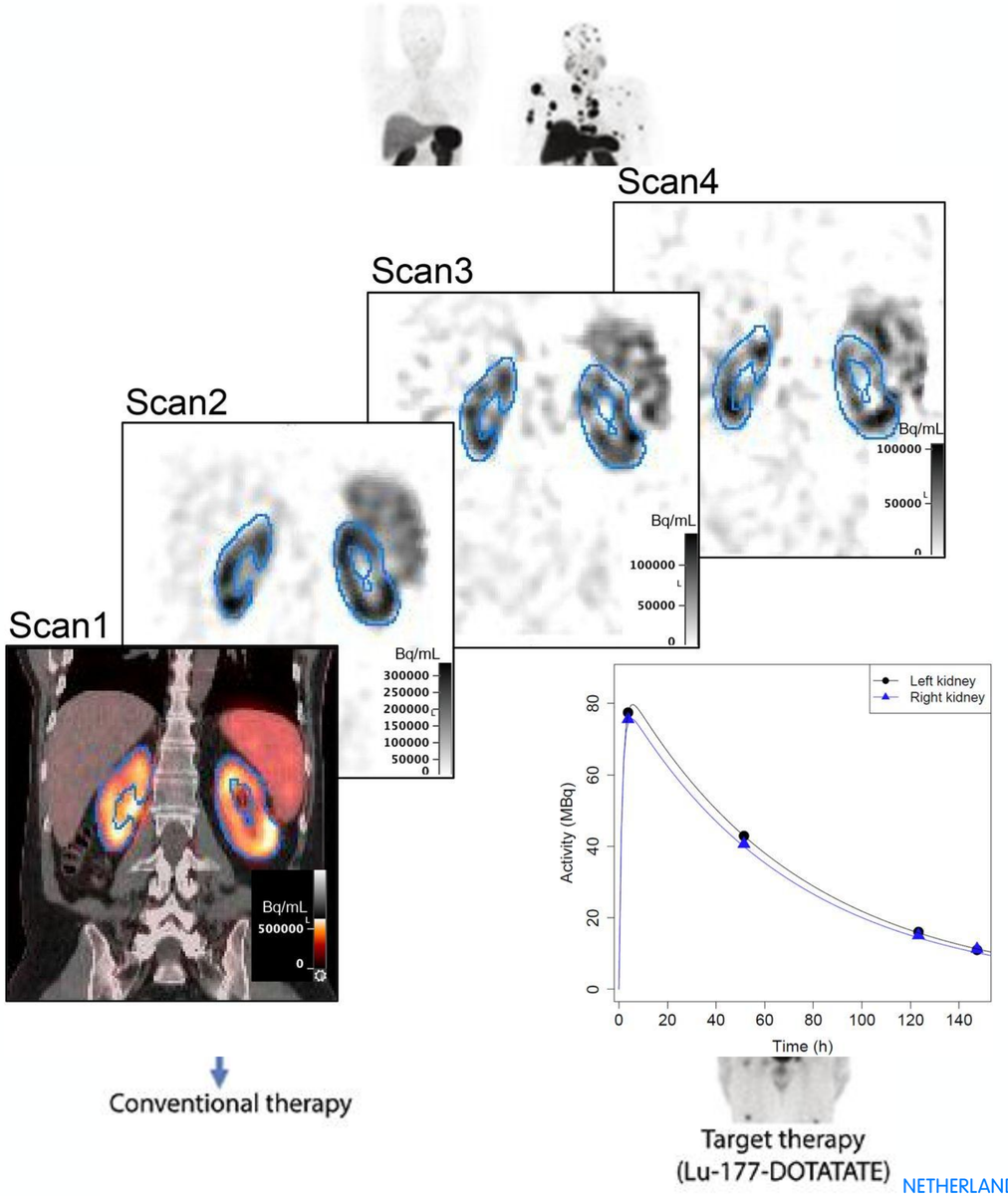
PET/CT scans

We treat what we see

Post-therapeutic imaging

SPECT/CT scans

We see what we treat



Devasia et al. J Nucl Med. 2021; 62: 1118-1125.
Sathekge et al. CME. 2013;8:289-294.

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High variability

~20-30% of patients show no response

Unmet need: early **prediction of individual treatment outcomes** and/or better patient selection

High **inter- and intrapatient variability** in organ and tumor exposure

Likely causes differences in efficacy and toxicity outcomes



Organ uptake



Tumor uptake

Improve understanding

Quantify and account for variability

Leverage available clinical data to their full potential

Enable more optimized and personalized treatment strategies

PBPK modeling to identify and understand **physicochemical, physiological, and pharmacodynamic factors** that impact the biodistribution most

PBPK modelling projects

1. **[^{68}Ga]Ga-HA-DOTATATE** – the impact of **tumor volume** on whole body distribution
2. **[^{68}Ga]Ga-PSMA** – the impact of **folate intake** on whole body distribution

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Introduction

Neuroendocrine tumors

Relatively rare tumors (0.5% of all cancers)

Mostly in gastroenteropancreatic (GEP) tract (62-67%) and lungs (22-27%)

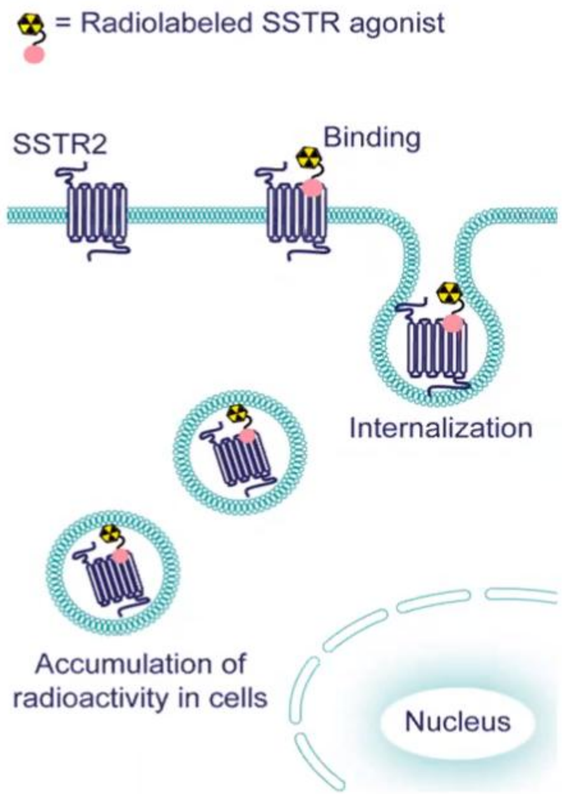
Overexpression somatostatin receptors (SSTRs)

Peptide receptor radionuclide therapy

Treatment of unresectable or metastatic, progressive, well differentiated, SSTR positive GEP NETs in adults

Diagnosis: [^{68}Ga]Ga-DOTATATE

Therapy: [^{177}Lu]Lu-DOTATATE



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Knowledge gaps

Tumor uptake

High interindividual variability in tumor uptake

Unkown which parameters impact tumor uptake most

Tumor sink effect

Increasing tumor volume might lead to lower uptake in healthy organs

Healthy organ uptake is dose-limiting (due to toxicity)

Potential added value in increasing injected activity for patients with lower organ uptake

Information and quantitative evidence is lacking

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Patient data

Retrospective inclusion of patients (n=98)

Intravenous bolus injection of ~100 MBq ^{68}Ga labeled to DOTATATE or HA-DOTATATE

PET/CT scan at 45 minutes post injection

Radioactivity concentrations (MBq/L) were quantified for aorta, spleen, thyroid, liver and tumor lesions

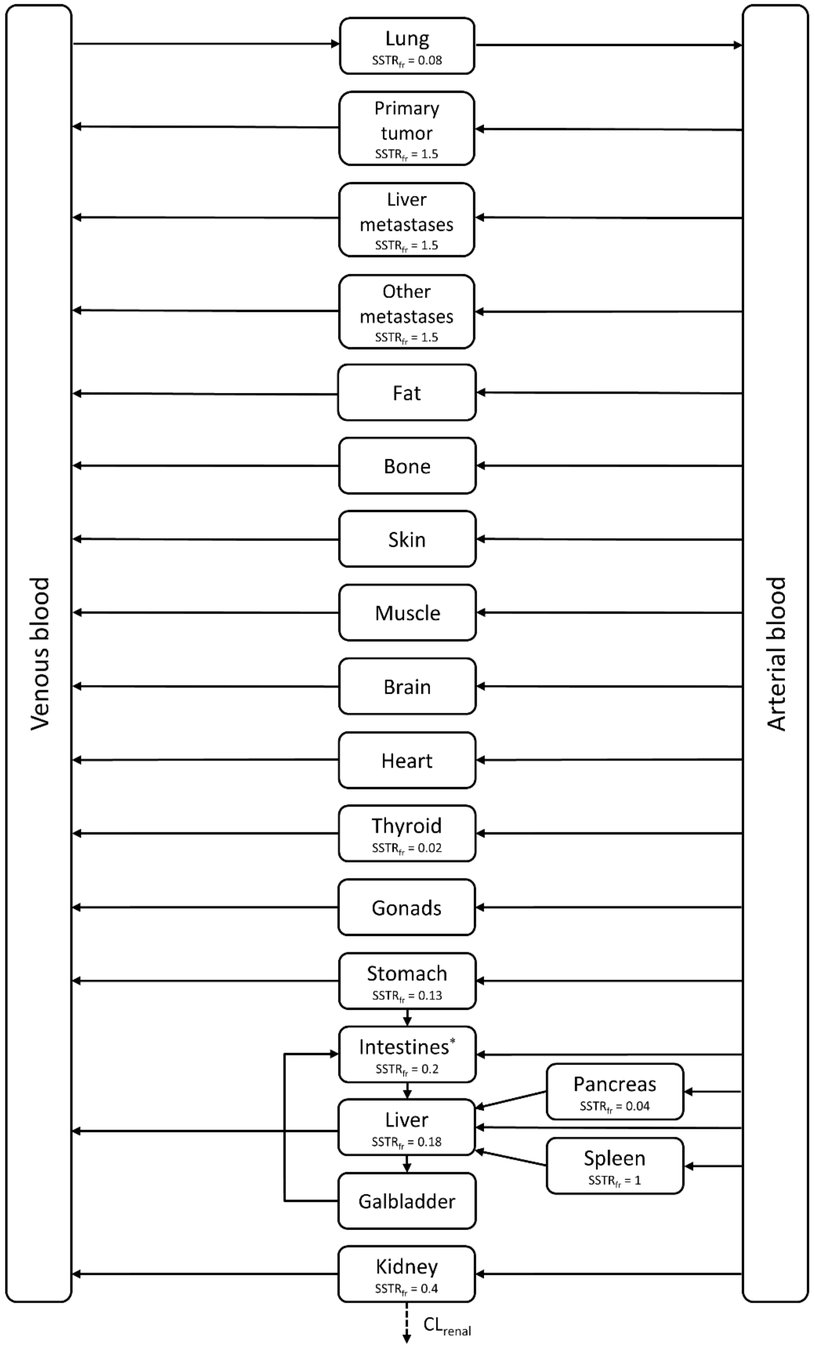
Decay corrected peptide concentrations (µg/L) based on observed radioactivity and administered specific activity (MBq/µg)

Model development

Whole body model structure (v9.0), compartments added:

- Primary tumor
- Liver metastases
- Other metastases

	Primary tumors	Liver metastases	Other metastases
Fraction vascular	0.21	0.17	0.075
Fraction interstitial	0.3	0.3	0.3
Blood flow	152 mL/min/100 g	203 mL/min/100 g	152 mL/min/100 g



Model development

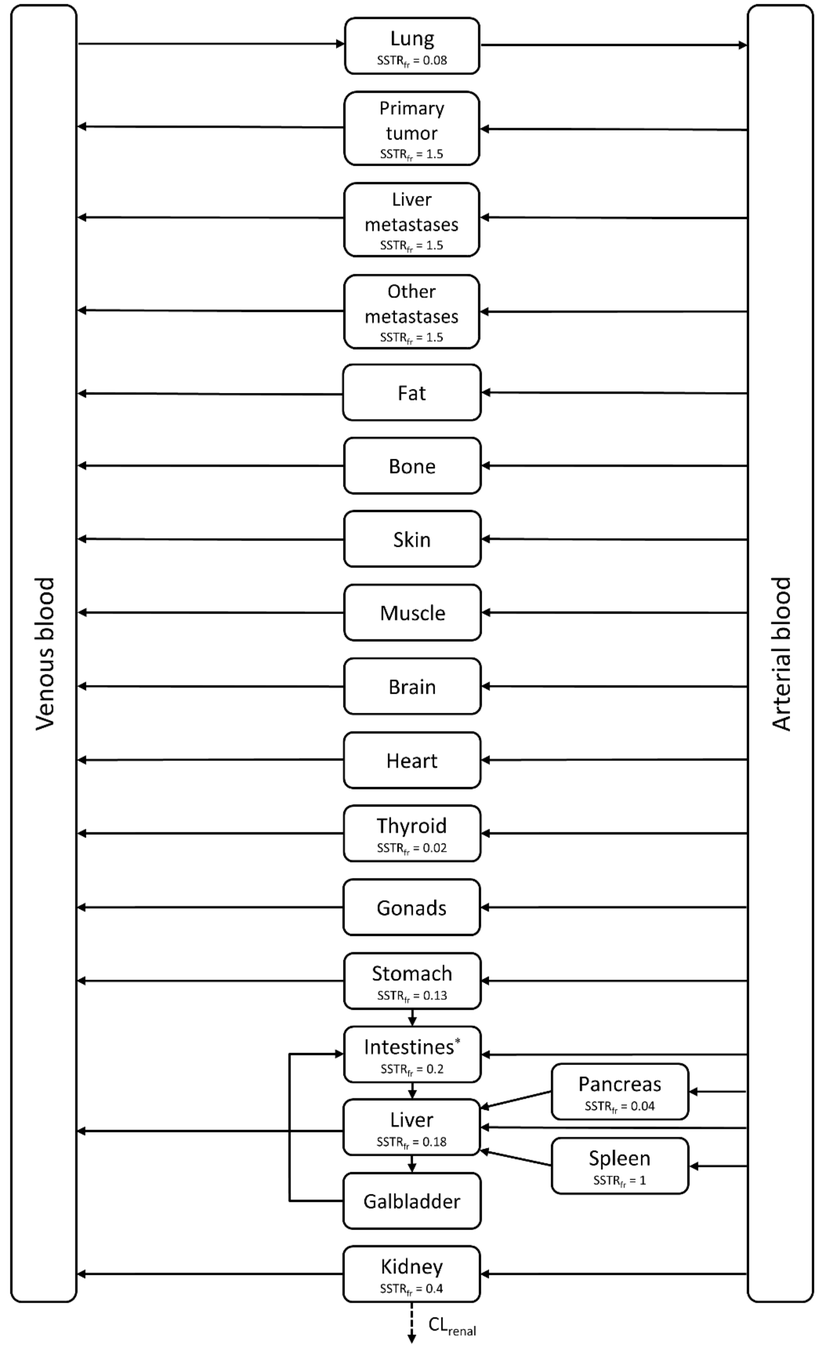
SSTR2 expression fractions relative to spleen

- Organ fractions estimated based on data [1]
- Tumor overexpression (fraction = 1.5)

Mechanisms included: receptor binding, internalization, intracellular degradation, receptor recycling, and renal excretion

$$\frac{d}{dt}Complex_i = \frac{k_{off}}{K_D} * R_i * P_i * K_{water,i} - k_{off} * Complex_i$$

$$\frac{\mathrm{d}}{\mathrm{d}t}P_{\mathrm{intracellular},i} = k_{\mathrm{int}} * \mathrm{Complex}_i - k_{\mathrm{deg}} * P_i$$

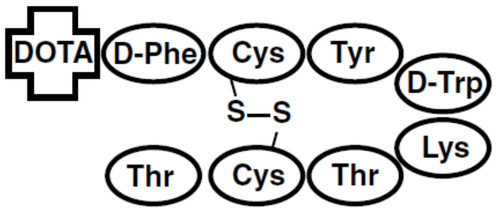


1. Siebinga H, et al. EJNMMI Res. 2023;13(1):8.

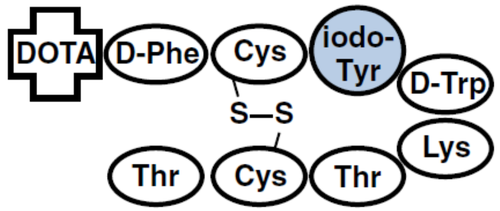
Model development

	DOTATATE	HA-DOTATATE
Molecular weight	1502.3 g/mol	1628.5 g/mol
Lipophilicity	-3.69	-3.12
Fraction unbound	0.69	0.57
K_D (based on IC_{50})	0.20 nmol/L	0.23 nmol/L *
k_{off}	0.012 min^{-1}	0.0071 min^{-1} *
k_{int}	0.161 min^{-1}	0.268 min^{-1}
k_{deg}	0.00012 min^{-1}	0.00012 min^{-1}
Excretion to urine	12% (after 4 hours)	13% (after 4 hours)

* Estimated based on patient data



DOTATATE



HA-DOTATATE

Schottelius et al. EJNMMI Research (2015) 5:22

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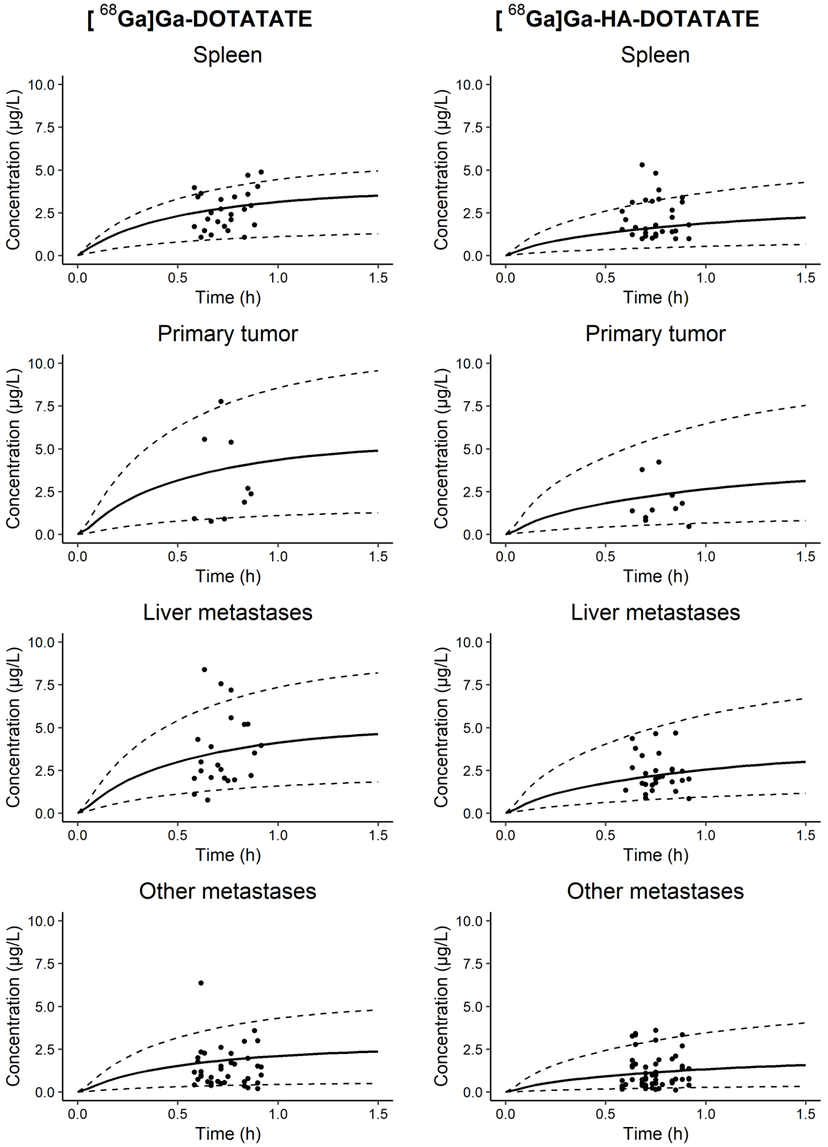
Population predictions

Sensitivity analysis identified factors that impact distribution most:

- SSTR2 density for organs
- Administered peptide amount
- Tumor blood flow
- Tumor fraction vascular

Prediction interval: ranges based on previous model[1] or quartiles (literature)

Adequate model fit for population



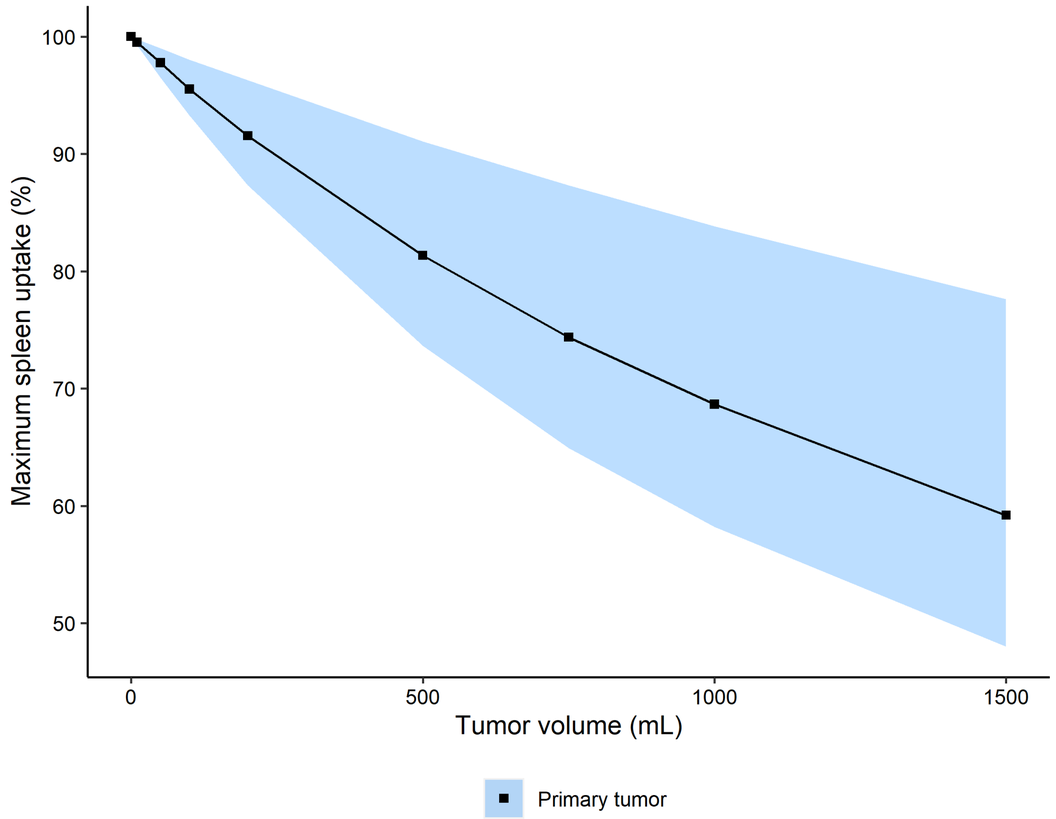
1. Siebinga H, et al. EJNMMI Res. 2023;13(1):8.

Tumor sink effect simulation

Tumor sink effect: decrease in spleen uptake with increasing tumor volume

Little effect for typical patient (<200 mL tumor volume)

However, clinically relevant effect for tumor volumes >550 mL



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Conclusions

Variability in tumor blood flow and tumor blood volume appeared most important for tumor uptake

A tumor sink effect was not predicted for the majority of patients

Clinical relevance

For patients with higher total tumor volumes, **injected activity might be increased** to increase radiation delivery to tumor sites while not exceeding maximum organ doses

PBPK modelling projects

1. **[^{68}Ga]Ga-HA-DOTATATE** – the impact of **tumor volume** on whole body distribution
2. **[^{68}Ga]Ga-PSMA** – the impact of **folate intake** on whole body distribution

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Introduction

Prostate cancer

Second leading cause of cancer dead in men worldwide

Accounts for ~15% of all cancers in men

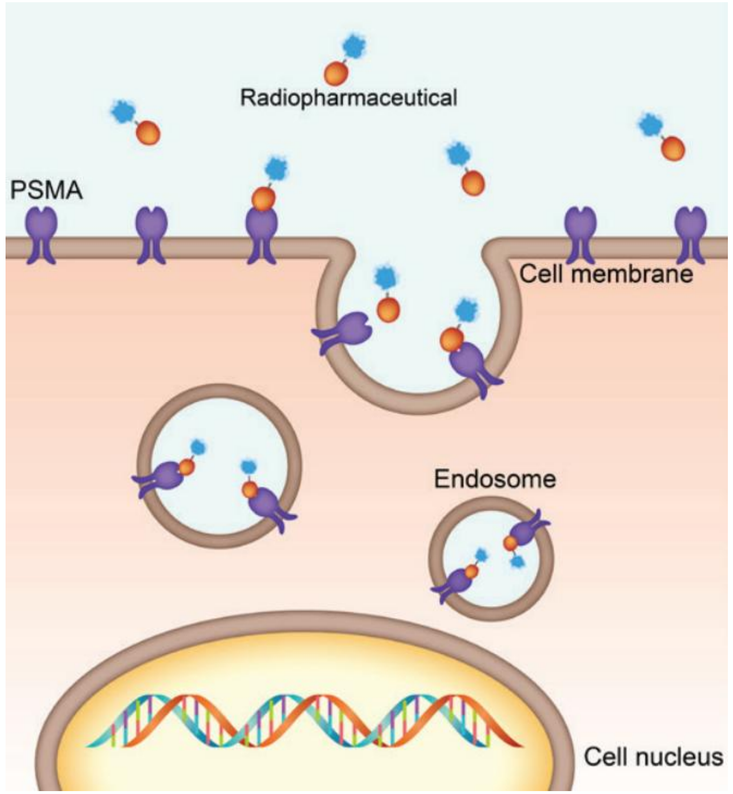
Overexpression prostate-specific membrane antigen (PSMA)

Peptide radioligand therapy

Treatment of progressive, PSMA-positive metastatic castration-resistant prostate cancer in adults

Diagnosis: [^{68}Ga]Ga-PSMA

Therapy: [^{177}Lu]Lu-PSMA



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Competing compounds

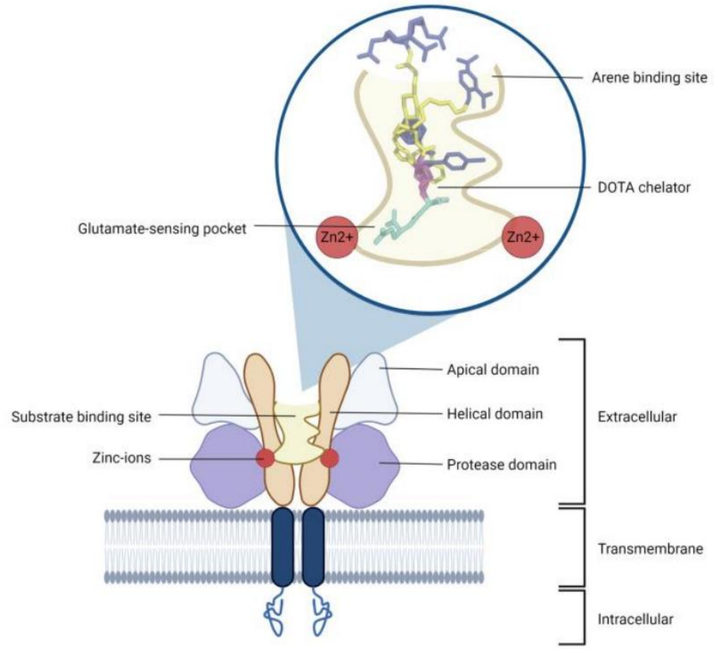
Other compounds may also target binding site of PSMA

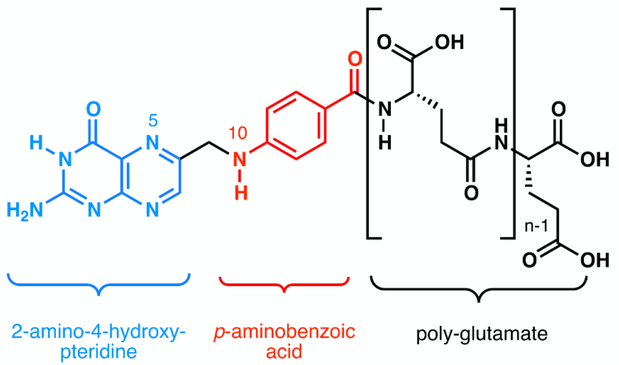
Potential competitor by blocking binding of PSMA-targeting ligand

Folates (folic acid (monoglutamate) and related compounds (poly-glutamates))

Possible undesirable effects (affect decision making or efficacy)

Effect of folate co-administration on [^{68}Ga]Ga-PSMA-11 PET/CT needs to be quantified





van der Gaag, S. et al. Biomedicines 2022, 10, 3020.

Model development

Whole body model structure (v9.0), compartments added:

- Salivary glands
- Primary tumor
- Tumor metastases

	Primary tumors	Tumor metastases
Volume	9.5 mL	100 mL
Fraction vascular	0.05	0.05
Fraction interstitial	0.38	0.38
PSMA expression fraction	1 *	1.4
Blood flow	16.4 ml/min/100g *	16.4 ml/min/100g *

* Estimated based on patient data

Begum NJ, et al. Nucl Med.2018;59:929–33.
Kletting P, et al. PLoS ONE. 2016;11:e0162303.
Queisser A, et al. Mod Pathol. 2015;28:138–45.

Model development

PSMA receptor amounts estimated based on data

Mechanisms included: receptor binding, internalization, intracellular degradation, receptor recycling, and renal excretion

$$\frac{d}{dt}Complex_i = \frac{k_{off}}{K_D} * R_i * P_i * K_{water,i} - k_{off} * Complex_i$$

$$\frac{\mathrm{d}}{\mathrm{d}t}P_{\mathrm{intracellular},i} = k_{\mathrm{int}} * \mathrm{Complex}_i - k_{\mathrm{deg}} * P_i$$

Molecular weight	1011.9 g/mol
Lipophilicity	-3.8
Fraction unbound	0.43
K_D	0.06 nmol/L
k_{off}	0.015 min^{-1}
k_{int} tumor	0.001 min^{-1}
k_{int} other tissue	0.035 min^{-1}
k_{deg} tumor	0.00014 min^{-1}
k_{deg} other tissue	0.00037 min^{-1}

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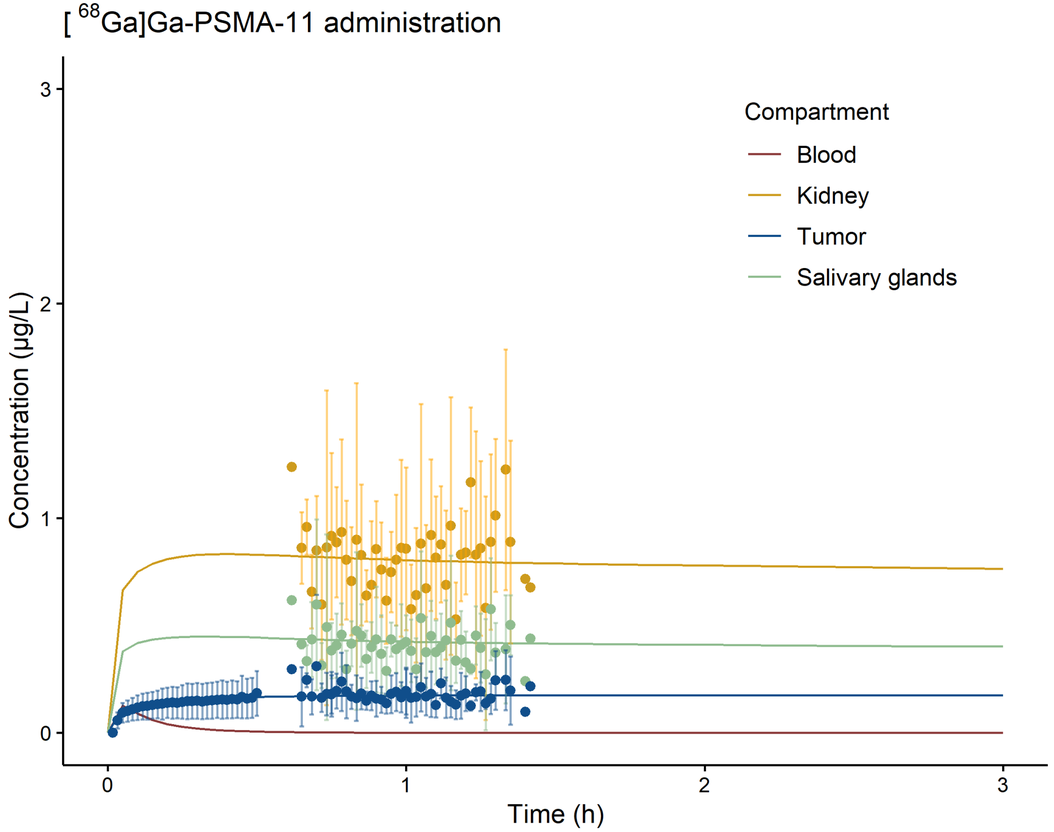
[^{68}Ga]Ga-PSMA predictions

Predictions for typical patient (representing median)

Model evaluation based on retrospective data [1,2]

Adequate model fit

Sensitivity analysis: model not highly reliant on particular input parameters



1. Siebinga H, et al. J Nucl Med. 2023 Jan;64(1):63-68.
2. Olde Heuvel J, et al. PLoS One. 2021 Feb 2;16(2):e0246394.

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Folate model

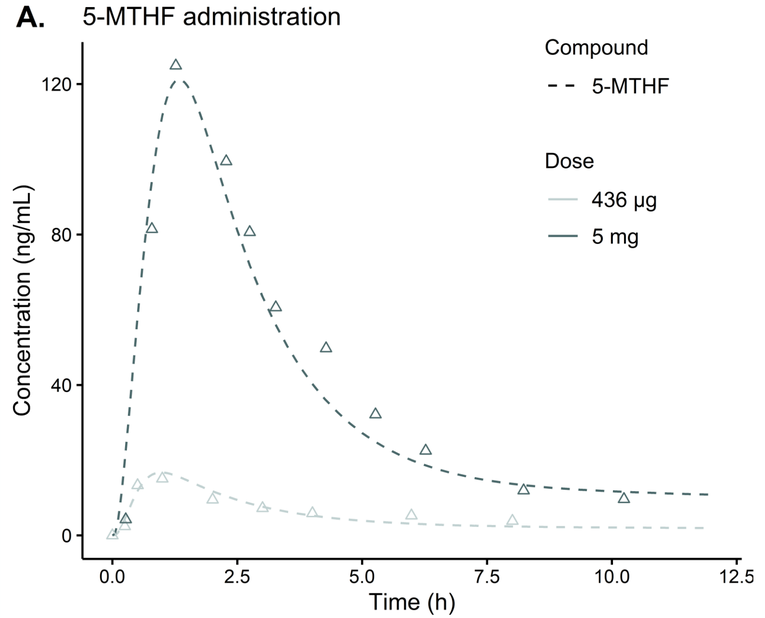
Folic acid and (main metabolite) 5-methylhydrofolate (5-MTHF)

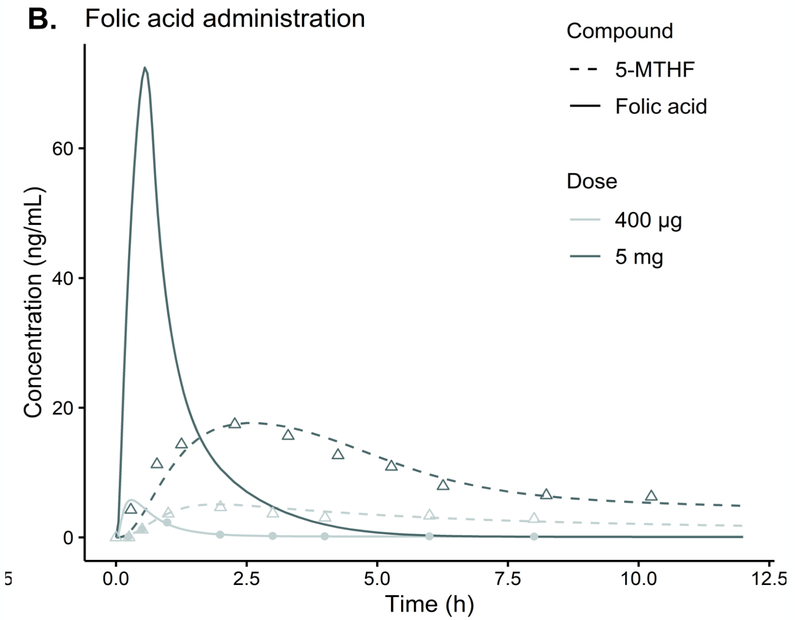
Development and evaluation using literature data [1,2]

Assess decrease in [^{68}Ga]Ga-PSMA accumulation in target sites after folate co-administration

Different dosages:

- 150 µg 5-MTHF (i.e. folate containing food)
- 400 µg folic acid (i.e. vitamin supplements)
- 5 and 10 mg folic acid (i.e. folate supplements)





1. Obeid R, et al. Nutrients. 2020;12.
2. Willems FF, et al. Br J Pharmacol. 2004;141:825-30.

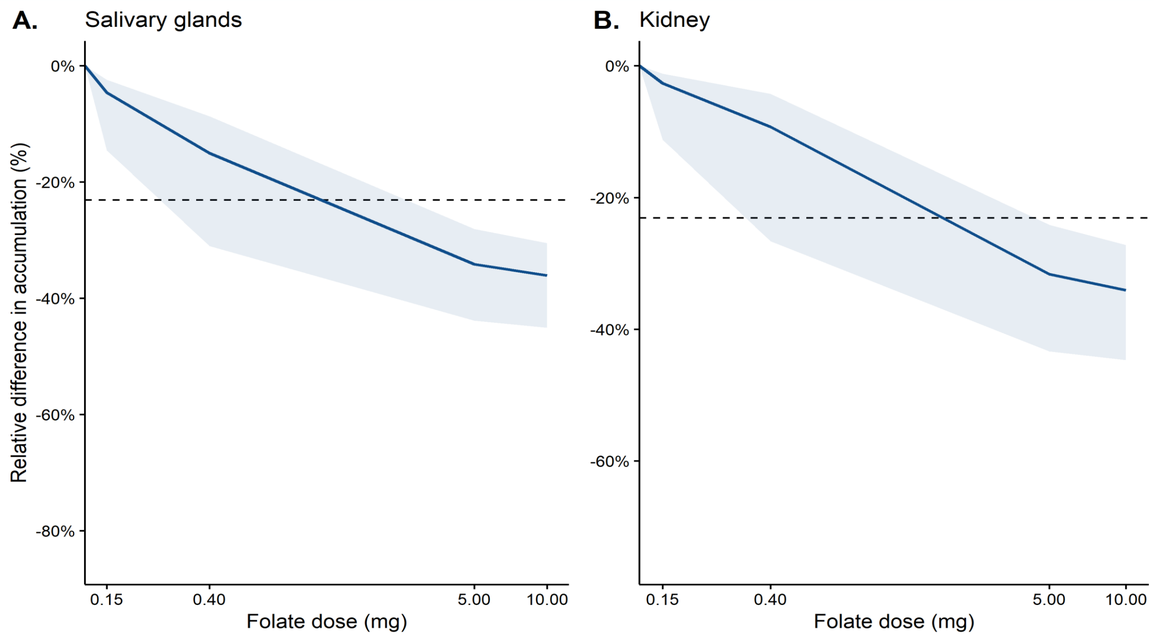
Impact on organ uptake

No clinically relevant effect

- Folate containing food (150 µg)
- Vitamin supplements (400 µg)

High doses of 5 and 10 mg resulted in most profound effect

- Salivary glands: 34% and 36% decrease
- Kidneys: 32% and 34% decrease



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Impact on tumor uptake

No clinically relevant effect

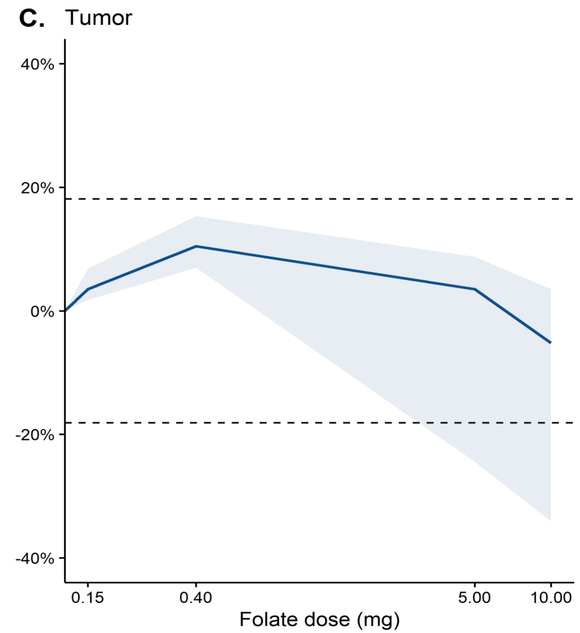
Overexpression of target compared to healthy tissues

No tumor saturation achieved after 10 mg folate dose

Results implied that higher folate doses might reduce tumor uptake

Extrapolation to folate dose of 36.5 g → decrease of 15% (2 – 42%)

However, extrapolation from evaluated folate model



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Conclusions

PBPK predictions showed decreased organ uptake with co-administration of high folate doses (i.e. 5 and 10 mg)

No effects on tumor uptake were predicted, though higher folate doses might reduce tumor uptake as well

Clinical relevance

In silico predictions could help to **inform future studies** (with [^{177}Lu]Lu-PSMA) to find optimal folate doses to **reduce normal organ uptake** without affecting tumor accumulation

Thank you!

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Prof. Dr. Thomas Dorlo
Dr. Linda de Wit – van der Veen
Dr. Jeroen Hendrikx

Example references

Siebinga H, de Wit-van der Veen BJ, Beijnen JH, Dorlo TPC, Huitema ADR, Hendrikx JJMA. A physiologically based pharmacokinetic model for [68Ga]Ga-(HA-)DOTATATE to predict whole body distribution and tumor sink effects in GEP-NET patients. EJNMMI Res. 2023 Feb;13(1):8.

Siebinga H, Hendrikx JJMA, Huitema ADR, de Wit-van der Veen BJ. Predicting the effect of different folate doses on [68Ga]Ga-PSMA-11 organ and tumor uptake using physiologically based pharmacokinetic modelling. EJNMMI Res. 2023 Jun;13(1):60.

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