

Erasmus MC

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Radiochemical limitations encountered during the preparation of injections for PET and SPECT studies of receptor-mediated processes

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Introduction

- | | | |
|--------------------------------|------------------|---|
| 1. SPECT and PET | ⇒ minimal on MBq | A |
| 2. Receptor-mediated processes | ⇒ max ligand | B |
| 3. Small animal studies | ⇒ max volume | C |

1. SPECT and PET \Rightarrow minimal on MBq A
2. Receptor-mediated processes \Rightarrow max ligand B
3. Small animal studies \Rightarrow max volume C

Ad A. U-SPECT with sensitivities of 36 cps per MBq ^{123}I , Jongen *et al.*,
EJNMMI 2008

Balance (resolution & sensitivity) vs. MBq

PET ^{68}Ga , ^{124}I (resolution vs. physics) \Rightarrow MBq \uparrow ??

Future ?

- | | | |
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Ad B. Analogues of octreotide, inhibitor of secretion

0.3 nmol per 250 g rat, and <0.1 nmol per 25 g mouse

Analogues of BN, SP, etc, agonist stimulates secretion

Amounts of receptors?

< 0.1 nmol per 250 g rat, and <<0.1 nmol per 25 g mouse

Future: Antagonists?

- | | | |
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Ad C. 0.2 mL per 25 g mouse, 1 mL per 250 g rat ⇒ physiology, PK, PD

HPLC purifications ⇒ HTS? Radiation safety? Data?

Organic solvent, e.g. acetone, ethanol. Data?

SPECT and PET

⇒ minimal on MBq

A

2. Receptor-mediated processes

⇒ max ligand

B

3. Small animal studies

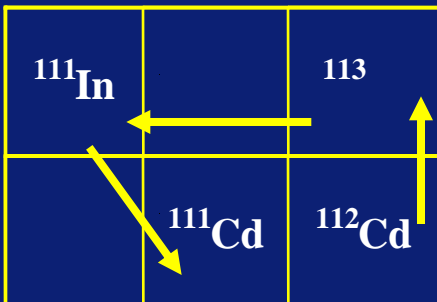
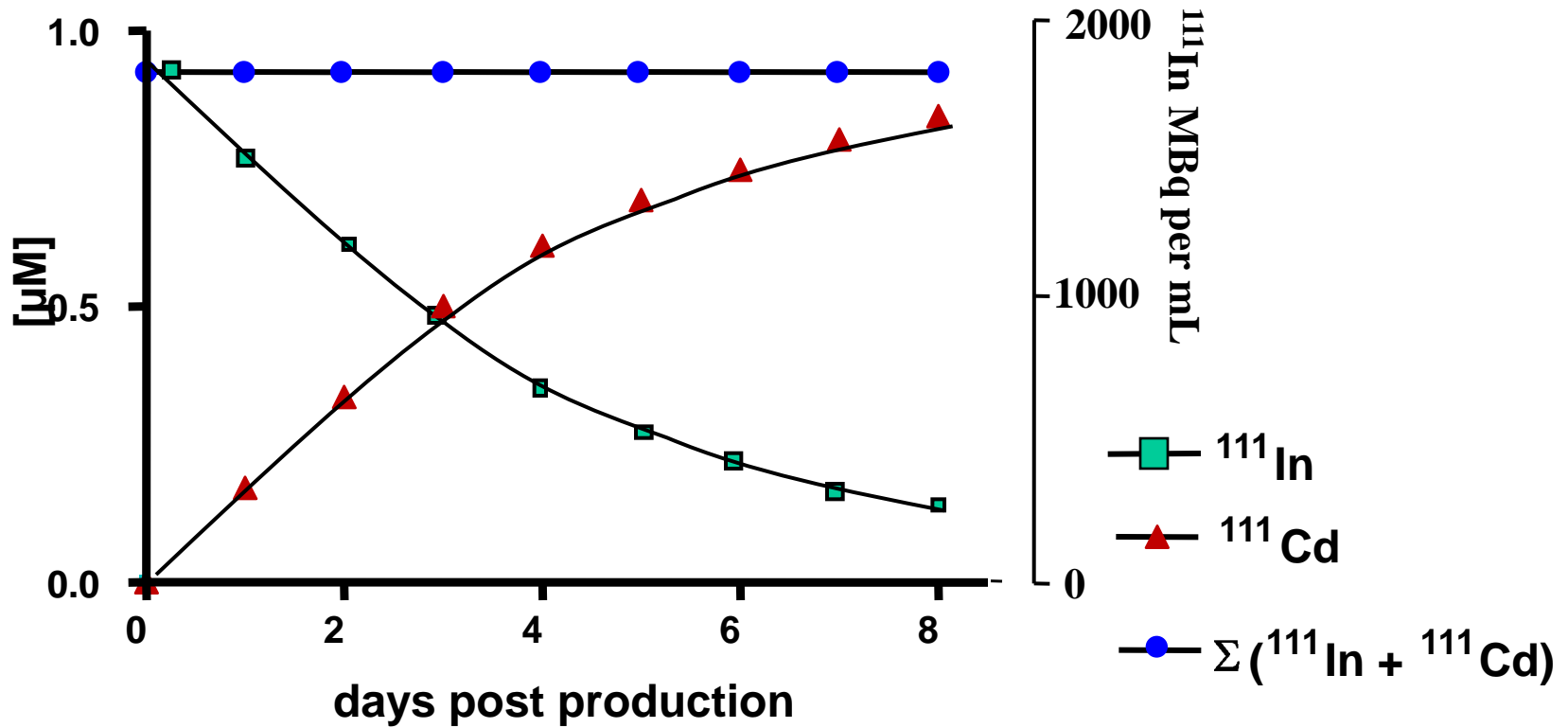
⇒ max volume

C

Ratio (A / B)

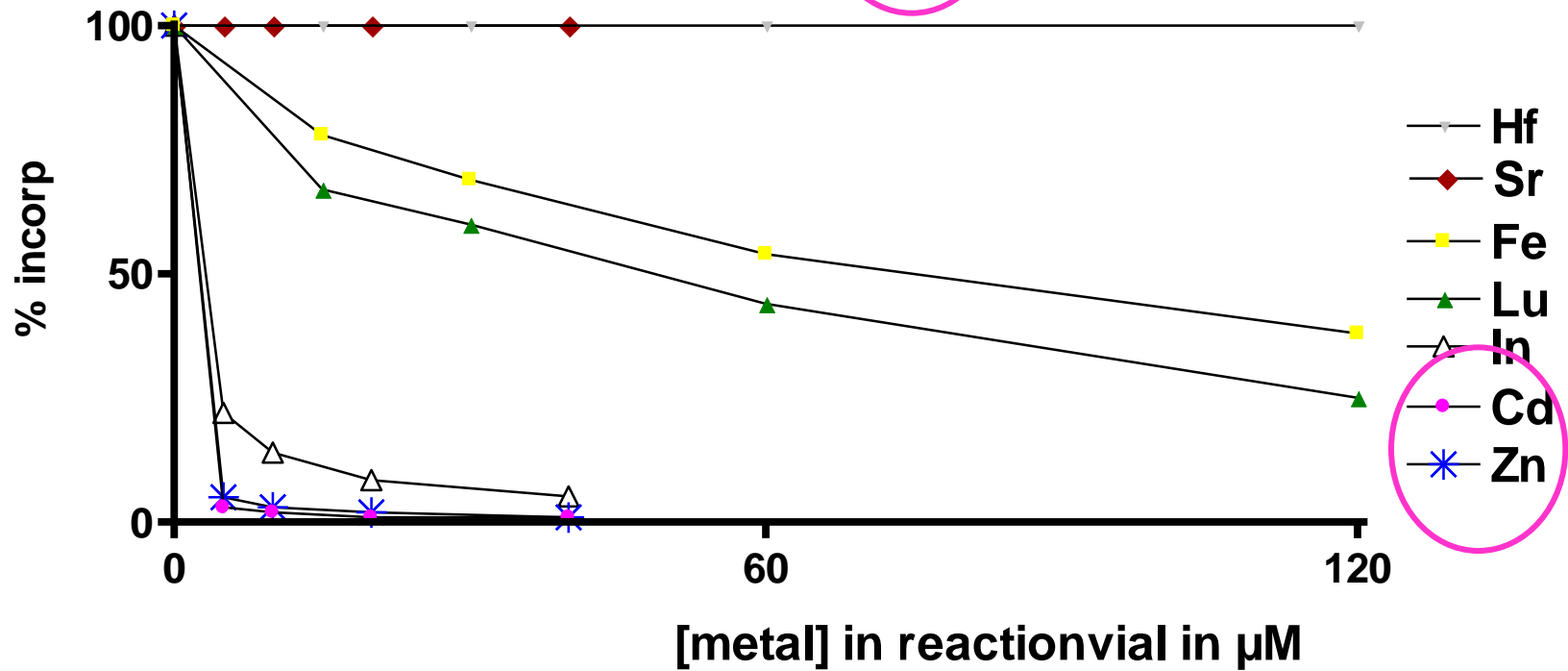
⇒ specific activity [MBq per nmol DOTA-peptide]

Dynamics in the ^{111}In solution



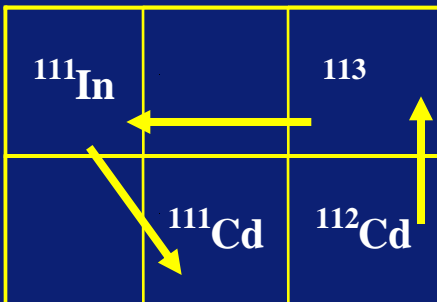
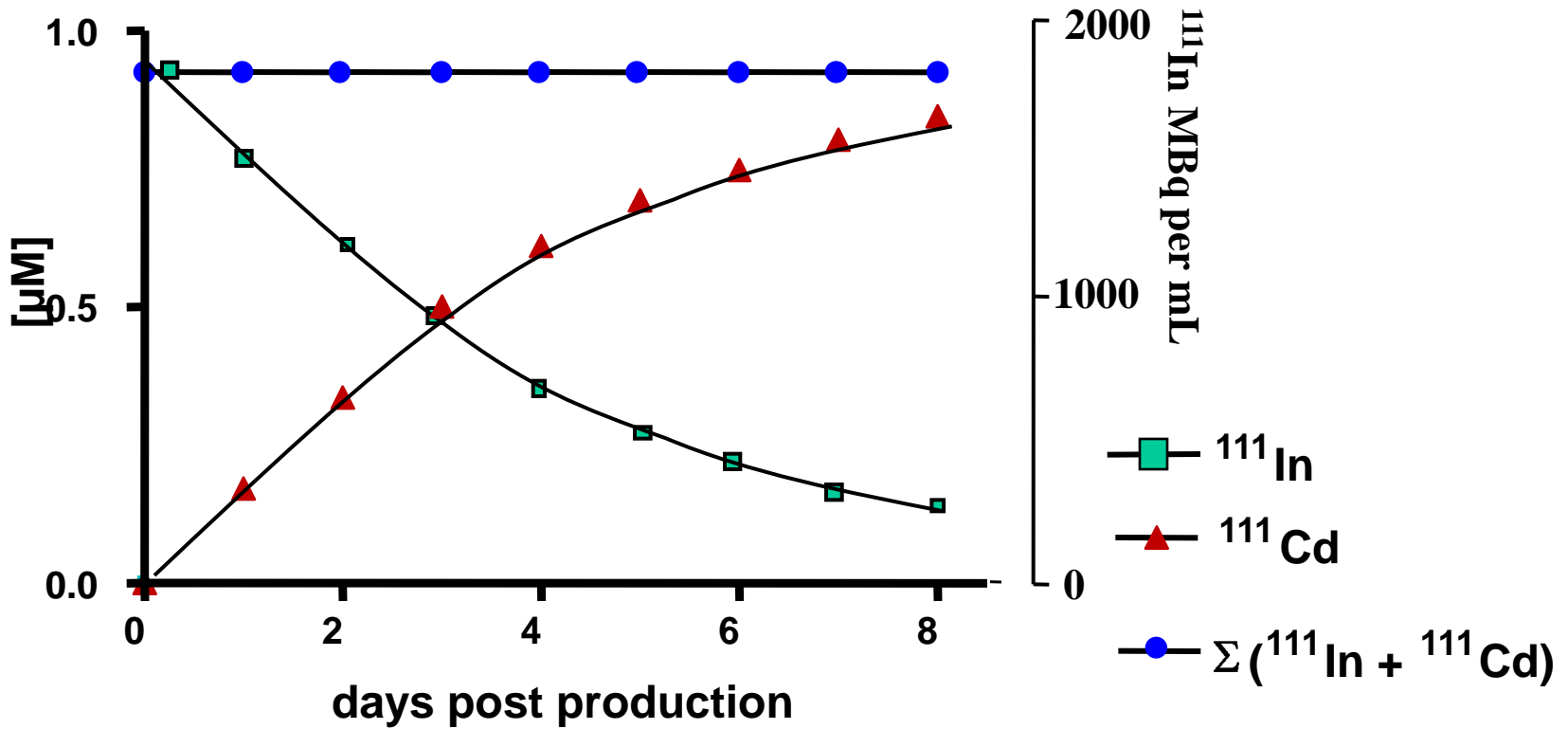
THEORY

Competition of metals on incorporation of radionuclides in DOTA-tate



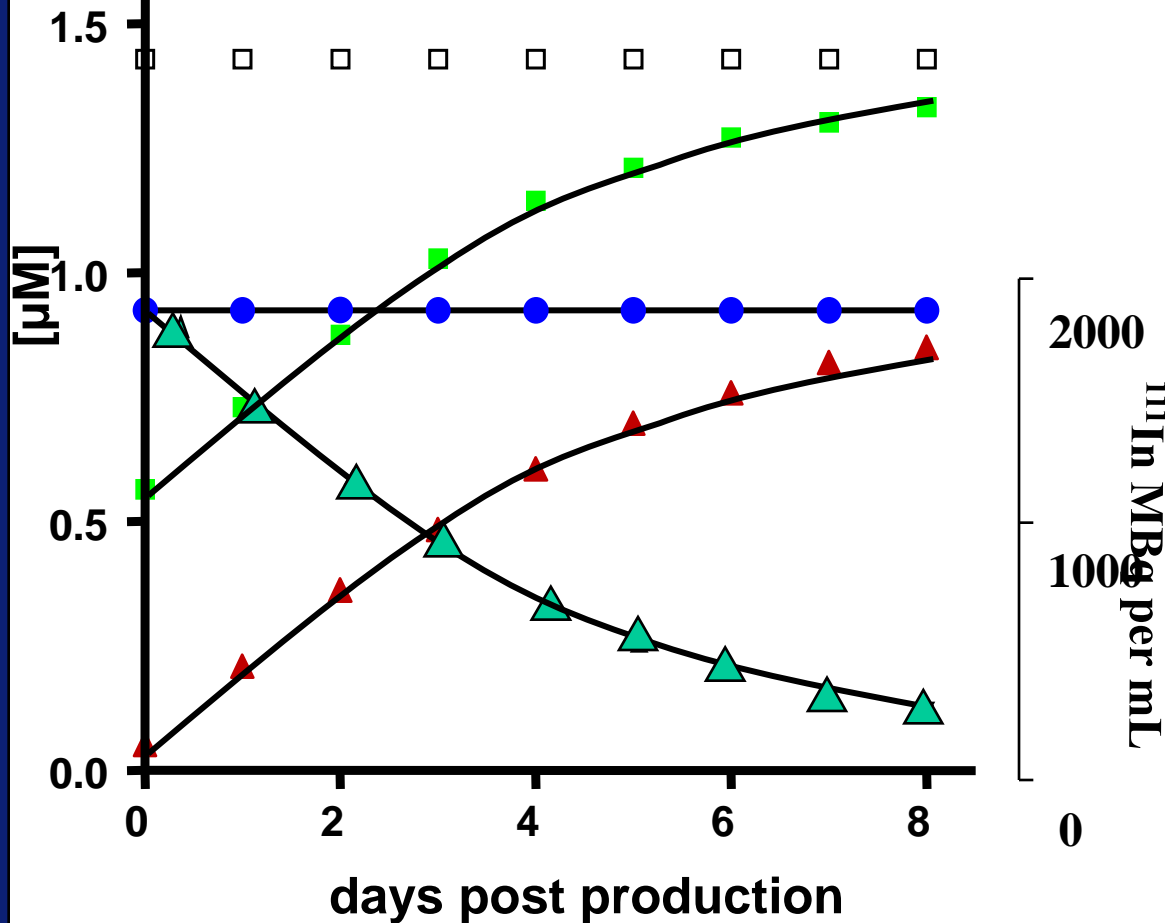
Controlled addition of metals

Dynamics in the ^{111}In solution

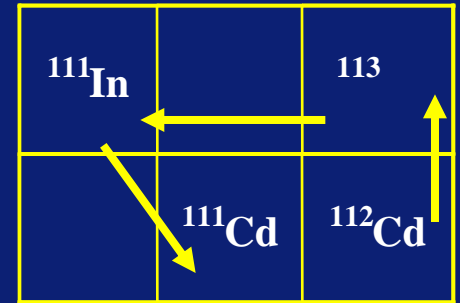


THEORY

Changes in the ^{111}In solution



REALITY



Max achievable SA of ^{111}In -DOTA:

$$\frac{\Sigma ^{111}\text{In}}{\Sigma (^{111}\text{In} + ^{111}\text{Cd} + ^{112}\text{Cd})}$$

■ $\Sigma (^{111}\text{In} + ^{111}\text{Cd} + ^{112}\text{Cd})$

■ $\Sigma (^{111}\text{Cd} + ^{112}\text{Cd})$

● $\Sigma (^{111}\text{In} + ^{111}\text{Cd})$

▲ $\Sigma ^{111}\text{Cd}$

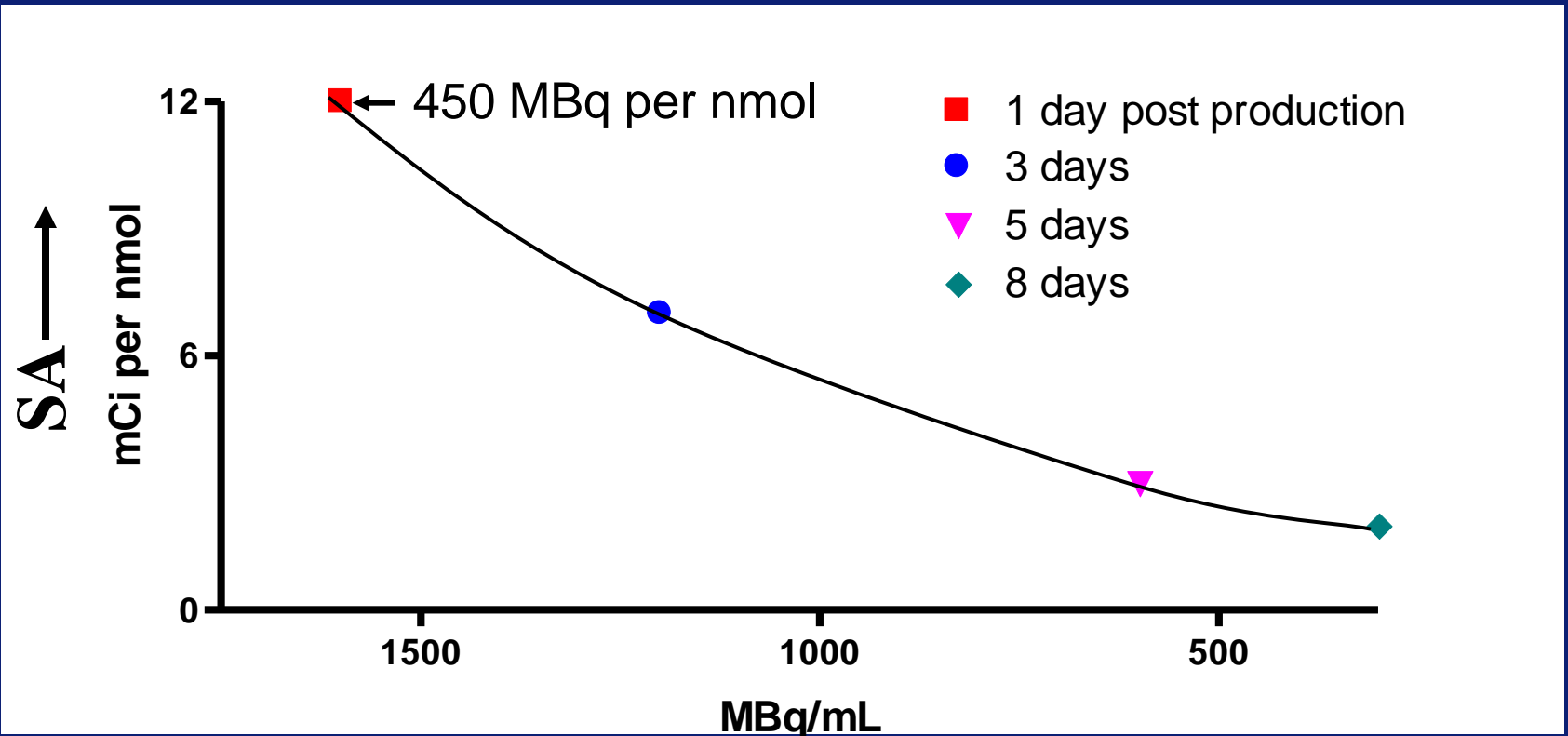
▲ $\Sigma ^{111}\text{In}$

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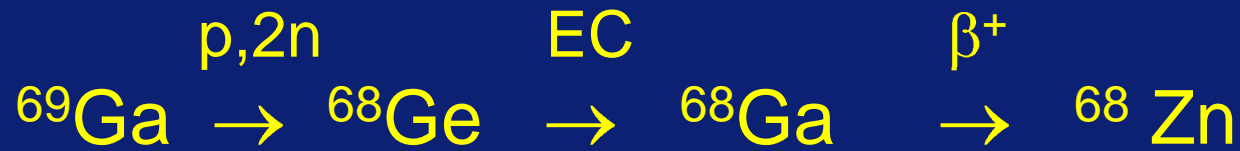
^{111}In MBq per mL
 0 1000 2000

Max SA of the radioligand

SA as f(days after production)



Cyclotron-produced positron-emitter ^{68}Ga



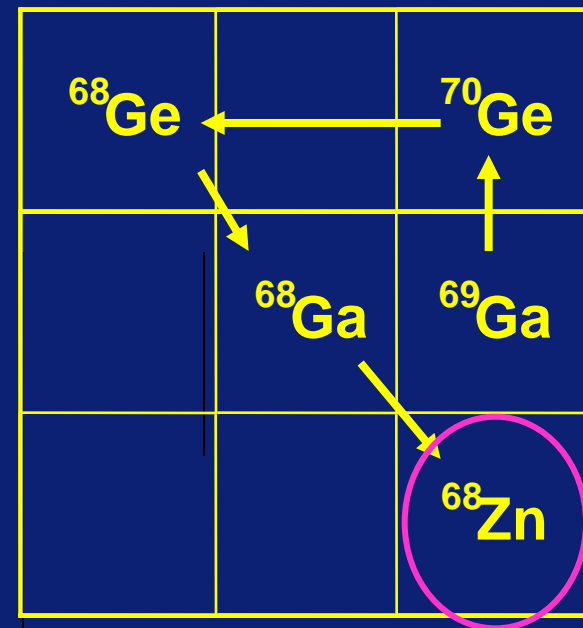
$T_{1/2}$: ^{69}Ga : stabile

$T_{1/2}$: ^{68}Ge : 270 d

$T_{1/2}$: ^{68}Ga : 68 min*

$T_{1/2}$: ^{68}Zn : stabile

* MeV	[%]
0.511	178
1.077	3



Conclusions

- **ingrowth of contaminants = competitors for DOTA in RA-material**

THM: Focus on Cd, Cu, Fe, Zn,..., always present and are competitors for DOTA

⇒ use radionuclide asap

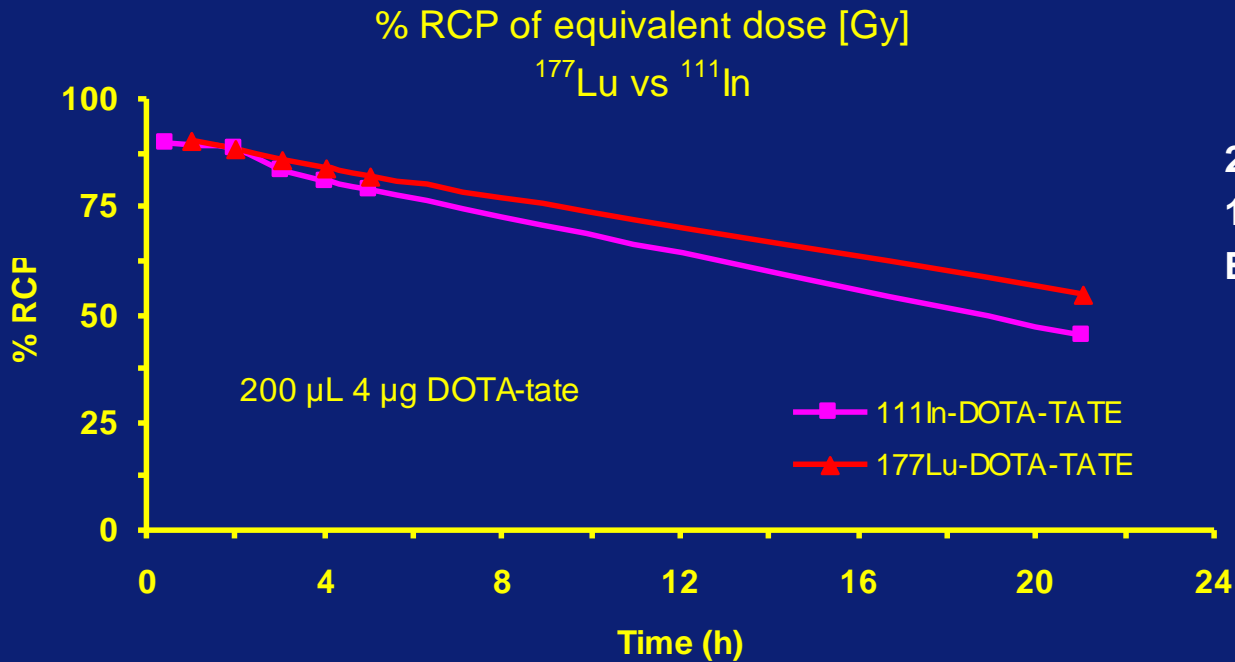
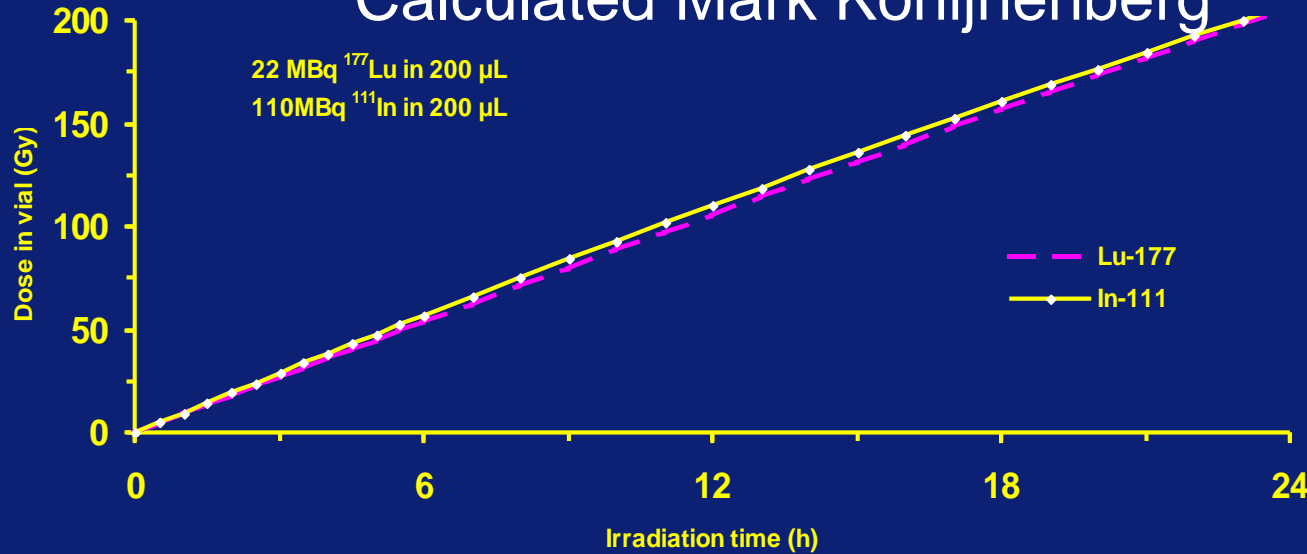
1. SPECT and PET \Rightarrow minimal on MBq **A**
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3. Small animal studies \Rightarrow max volume **C**

Ratio (A / B) \Rightarrow specific activity [MBq per nmol]

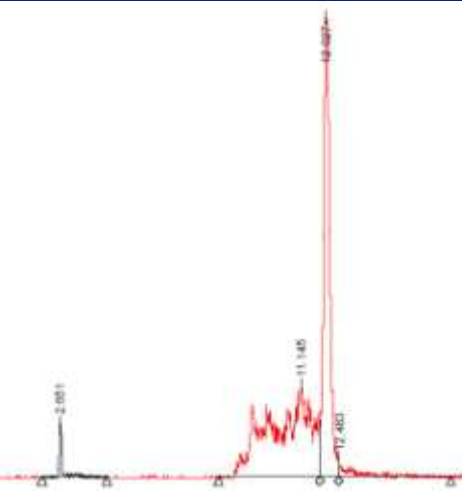
Ratio (A / C) \uparrow \Rightarrow radiolysis \uparrow

A \uparrow + C \downarrow \Rightarrow pH \downarrow and osmolality \uparrow

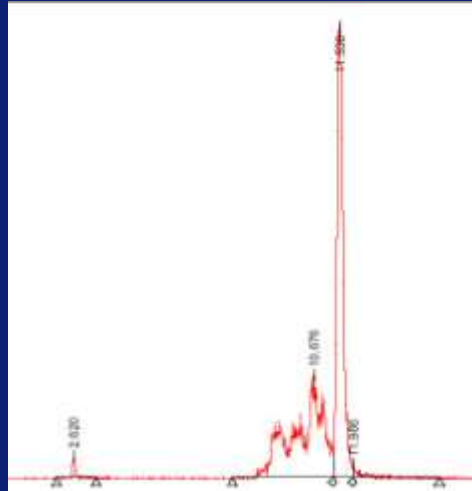
Calculated Mark Konijnenberg



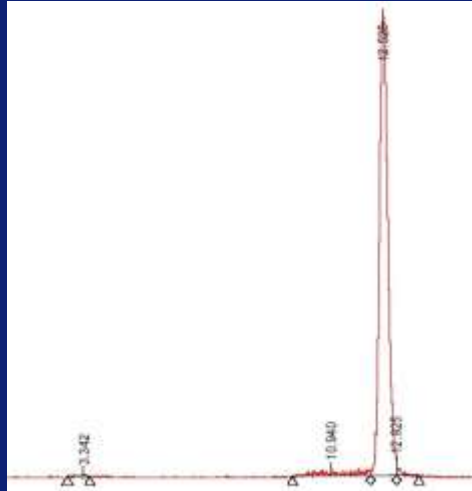
22 MBq ^{177}Lu : 208 Gray (24h)
110 MBq ^{111}In : 206 Gray (24h)
Both in 200 μL



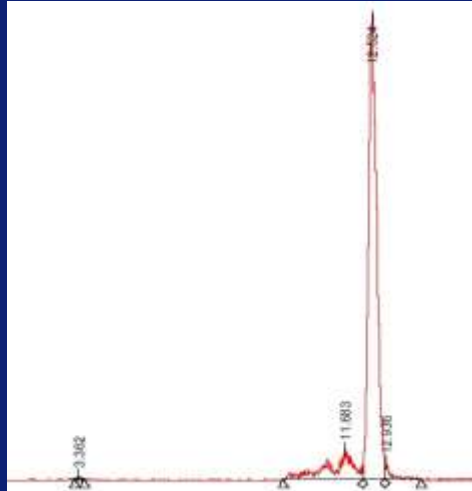
Blanco



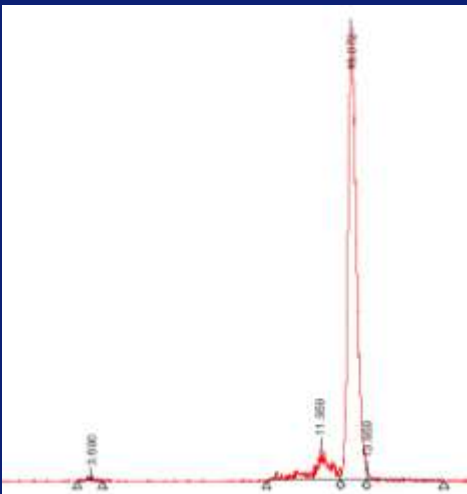
4x diluted



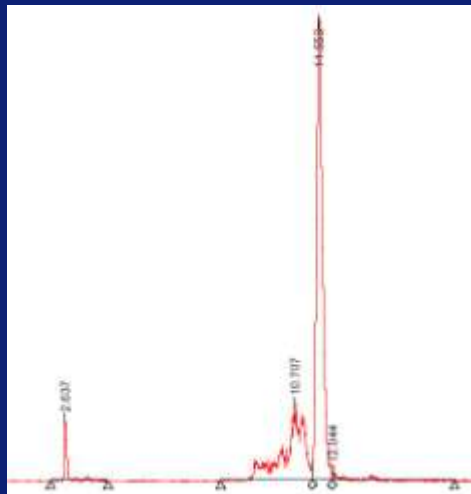
Ascorbic acid



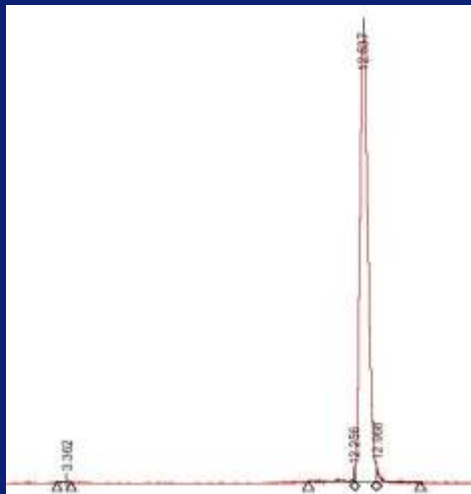
Ethanol



Gentisic acid



Methionin



Ga+Asc+Eth

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Ratio (A / C) \uparrow \Rightarrow radiolysis \uparrow

A \uparrow + C \downarrow \Rightarrow pH \downarrow and osmolality \uparrow

0.1 mL 40 MBq, pH 3.5-4, 1000 mosmol. LD50 in mice? Empirical

Literature combinations of injection volume, inj rate, components etc ??

New batch $^{111}\text{InCl}_3$, asapap \Rightarrow 22 % more $^{111}\text{In}^{3+}$ per mL per day \Rightarrow less \dagger



Radiochemical limitations encountered during the preparation of injections for PET and SPECT studies of receptor-mediated processes

- 1. Radiochemistry**
- 2. Animal handling, physiology, incl administration**
- 3. Sensitivity cameras**

Interaction 1. and 2.

- | | | |
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organic solvents

Een labeling per week voldoende

200 MBq in gelabeld op vrijdag vs dag x		
^{111}In (MBq/ μg)	dagen	^{111}In (MBq/ μg)
200	vrijdag	200
156	zaterdag	-
122	zondag	-
95	maandag	80
74	dinsdag	50
58	woensdag	35
45	donderdag	20

Conservering geldt alleen nog voor DOTA-TATE

Handling Radioactivity (NanoSpect/LinoView/PET)

Dosis op 0,3 cm: (injecteren van muizen/ratten)					
Nuclide	MBq	mSv/30 sec	Omgevingsdosistempo		Maximaal aantal injecties
¹¹¹ In:	100	8	0,088	$\mu\text{Sv.m}^2.\text{MBq}^{-1}.\text{h}^{-1}$	61
	10	0,8			614
¹⁷⁷ Lu:	100	0,6	0,0063	$\mu\text{Sv.m}^2.\text{MBq}^{-1}.\text{h}^{-1}$	857
	10	0,1			8571
^{99m} Tc:	100	2	0,023	$\mu\text{Sv.m}^2.\text{MBq}^{-1}.\text{h}^{-1}$	235
	10	0,2			2348
⁶⁸ Ga:	100	15	0,16	$\mu\text{Sv.m}^2.\text{MBq}^{-1}.\text{h}^{-1}$	34
	10	1,5			338

Dosis op 1 meter			
Nuclide	MBq	$\mu\text{Sv/h}$	h/jaar
¹¹¹ In:	100	8,8	227
	10	0,9	2273
¹⁷⁷ Lu:	100	0,6	3175
	10	0,1	31746
^{99m} Tc:	100	2,3	870
	10	0,2	8696
⁶⁸ Ga:	100	16,0	125
	10	1,6	1250

Stability after labeling DOTA- and DTPA-peptides

Tested with ^{111}In -DOTA-TATE and ^{111}In -Octreoscan

Up to 24 h stable

Phosphate added before labeling: **No incorporation**

Activiteit ^{111}In :	per 1 mL	per 0,5 mL	per 0,2 mL
Fri	1250	615	234
Sat	976	480	183
Sun	762	375	143
Mon	596	293	112
Tue	465	229	87
Wed	363	178	68
Thurs	284	140	53

^{111}In at day of production

$t=0$ 1800 MBq/mL

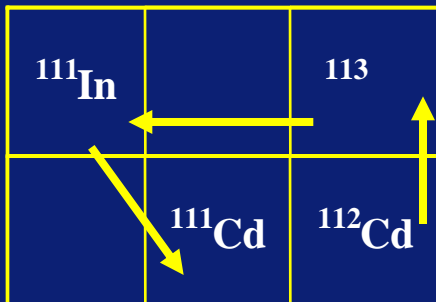
$$37 \text{ MBq} \equiv 2.15 \cdot 10^{-11} \text{ mol}$$

$$\equiv 10^{-9} \text{ mol/mL}$$

$$\equiv 10^{-6} \text{ M}$$

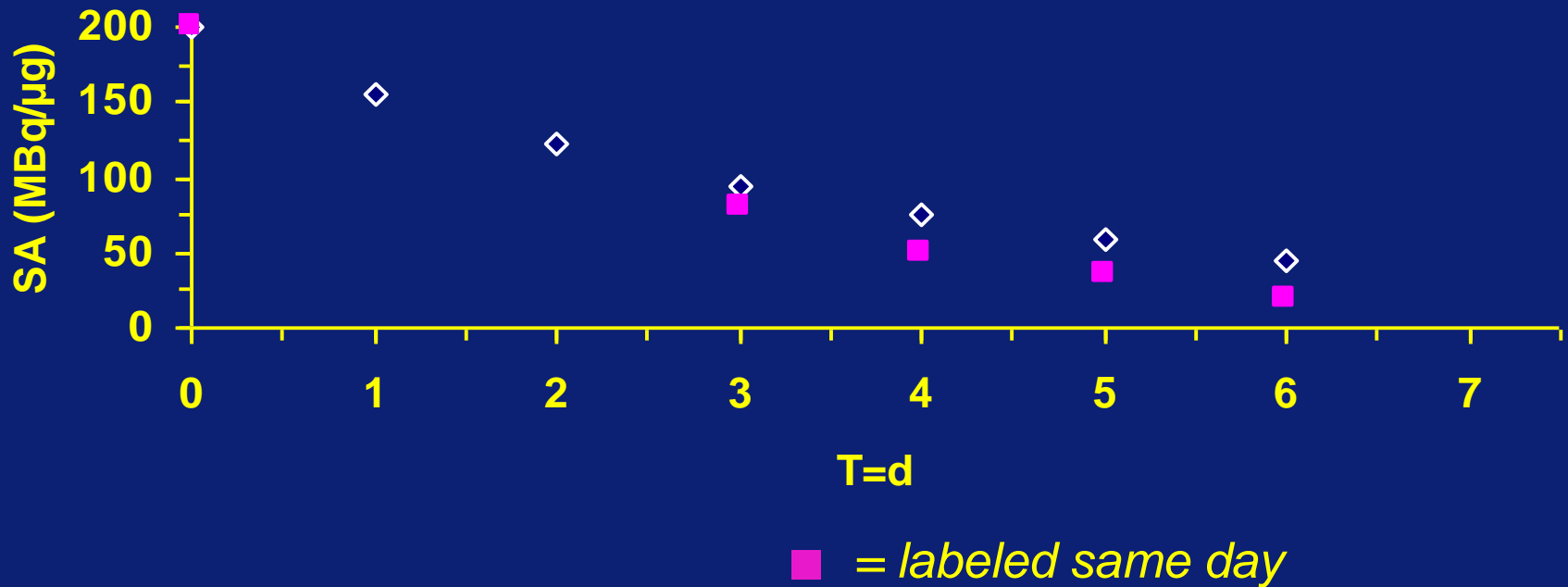
$[\text{In}] + [\text{Cd}]$ is constant

Cd ingrowth confirmed by ICP



Labeling DOTA-peptides

SA ^{111}In in gelabelde DOTA-peptiden gedurende 1 week



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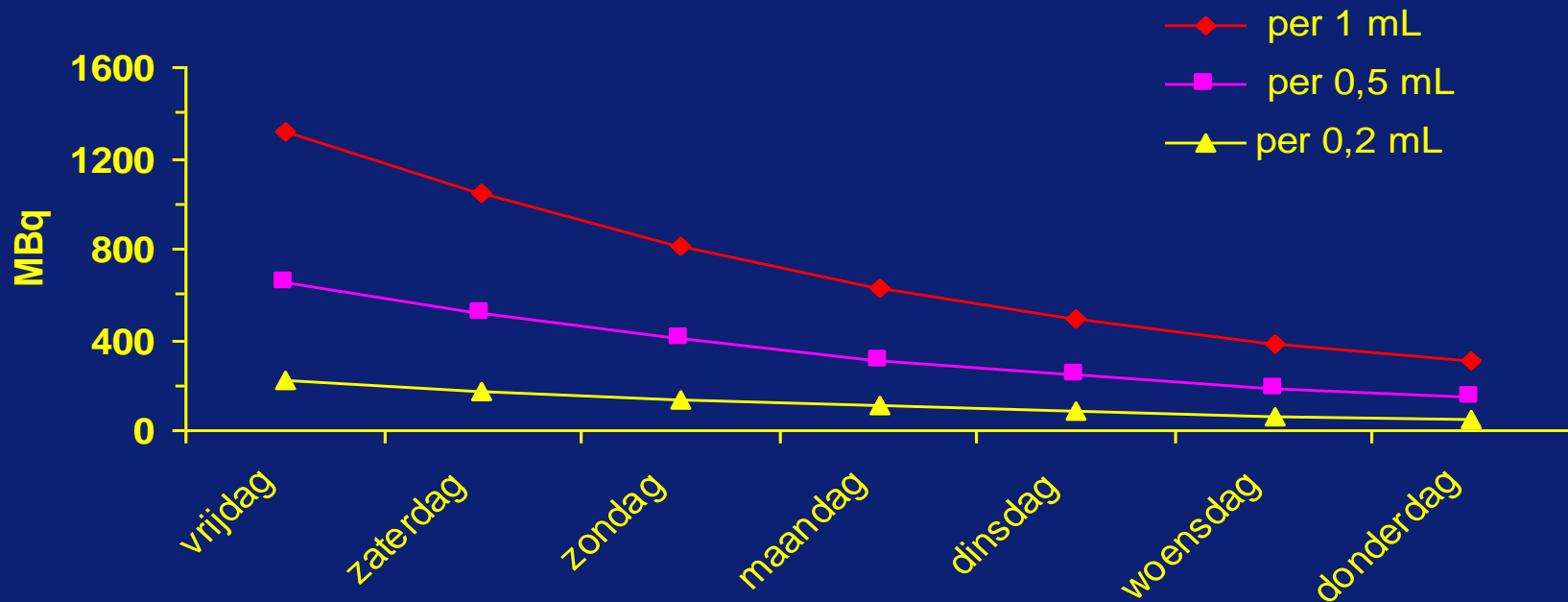
0.1 mL 40 MBq, pH 3.5-4, osmol 1000. LD50 in mice?

New batch InCl_3 , asapap \Rightarrow 22 % more $^{111}\text{In}^{3+}$ per mL per day \Rightarrow no \dagger

Organic solvent, e.g. acetone, ethanol

Activity ^{111}In before administration (pH 7)

Maximale MBq ^{111}In -DTPA/DOXA-peptide per volume



	per 1 mL	per 0,5 mL	per 0,2 mL
vrijdag	1317	648	223
zaterdag	1041	512	176
zondag	813	400	138
maandag	631	311	107
dinsdag	495	243	84
woensdag	387	191	66
donderdag	303	149	51

- | | | |
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Ratio (A / C) ↑ ⇒ pH ↓ and osmolality ↑

0.1 mL 40 MBq, pH 3.5-4, osmol 1000. LD50 in mice? Literature

New batch InCl_3 , asapap ⇒ 22 % more $^{111}\text{In}^{3+}$ per mL per day ⇒ less †