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Radionuclide therapy

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Radionuclide therapy

Preclinical side
Development

Clinical side
Application

Chemists

Biochemists

Biologists

Biotechnologists

Pharmacists

Physicists (imaging)

Radiochemists

Medical doctors

J. Nucl. Med. 2006, 57, 1941

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Outline

- Radionuclides in cancer treatment
- Types of radiation
- Interaction of radiation with matter
- Targeted cancer therapy: examples
- Factors influencing selection of a radionuclide

Standard treatment options of cancer

- About 80% of patients with localized tumors are cured by a combination of surgery, radiotherapy and chemotherapy
- Patients with distant metastasis and multifocal disease need new options, such as targeted therapy

http://puhuahospital.com/images/ckeditor/images/breast-cancer-standard-treatment-plan.jpg

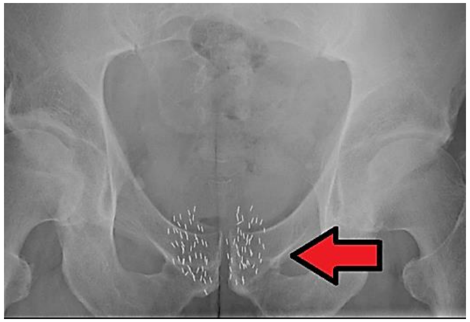
Targeted radionuclide therapy, Speer, 2012

Ionizing radiation for therapy

1. External-beam radiation therapy (EBRT)

- The most common form of RT
- X-ray beam delivers a radiation dose to the tumor
- Damages not only tumors, but healthy tissues

2. Sealed source radiation therapy (Brachytherapy)



3. Systemic RT

Radiopharma-ceuticals

https://readanddigest.com; https://wikipedia.org; https://openPR.com

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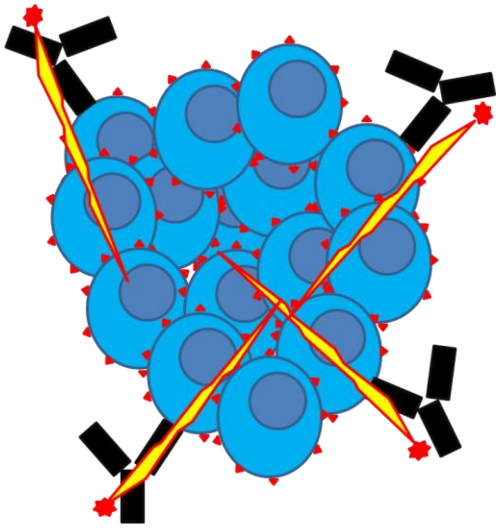
Radionuclides

- Development of resistance by cancer is slow (to alpha emitters with high LET)
- High efficiency of cell killing due to cross-fire irradiation (no need to target each cancer cell)
- Possible to combine with immuno- and chemotherapy
- Different toxicity profile than for drugs (radiosensitive bone marrow and kidneys)



Radioactive decay

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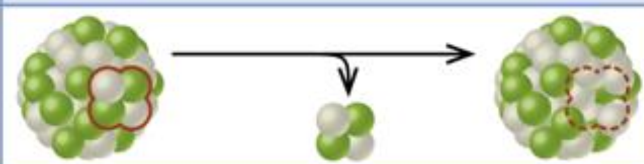
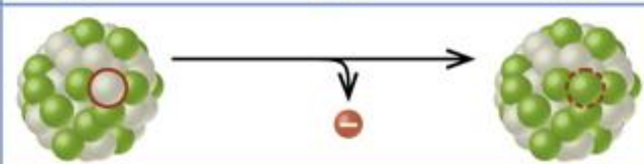
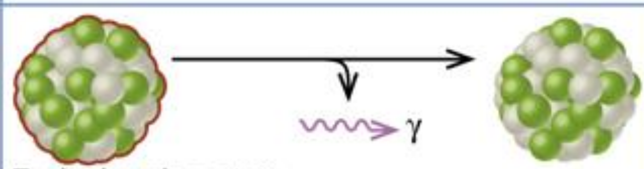
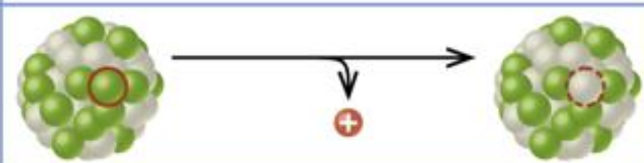
spontaneous breakdown of a nucleus
resulting in the release of energy

Type	Nuclear equation	Representation	Change in mass/atomic numbers	
Alpha decay	$^{A}_{Z}X \quad {}^{4}_{2}He + {}^{A-4}_{Z-2}Y$		A: decrease by 4 Z: decrease by 2	Therapy
Beta decay	$^{A}_{Z}X \quad {}^{0}_{-1}e + {}^{A}_{Z+1}Y$		A: unchanged Z: increase by 1	Therapy
Gamma decay	$^{A}_{Z}X \quad {}^{0}_{0}\gamma + {}^{A}_{Z}Y$	 Excited nuclear state	A: unchanged Z: unchanged	Imaging SPECT
Positron emission	$^{A}_{Z}X \quad {}^{0}_{+1}e + {}^{A}_{Y-1}Y$		A: unchanged Z: decrease by 1	Imaging PET

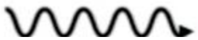
<u>Note:</u> One radionuclide can have several types of emission at the same time

https://chem.libretexts.org/

Radiation emitted by nuclides can be in the form of...

α-particles ($^{4}He^{2+}$) 

β-particles (can be β^{-} and β^{+}) 

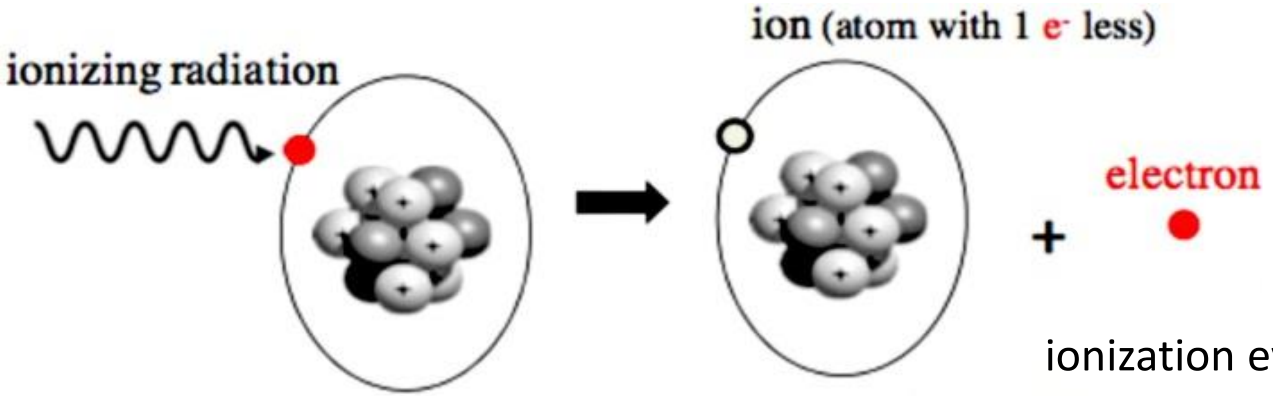
γ-rays (high energy quanta) 

Energy released by the decay of an atom

$1\ eV = 1.6 \times 10^{-19}\ J$

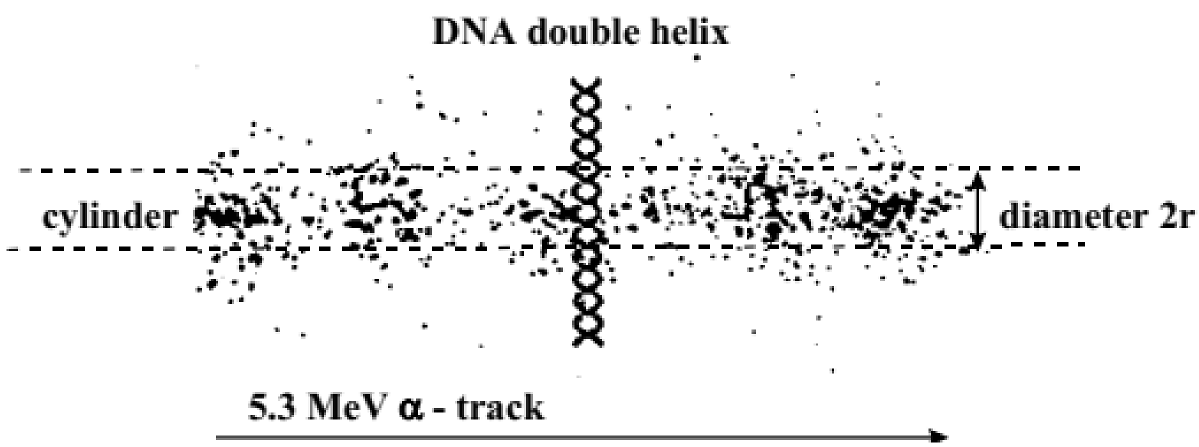
Interaction of radiation with matter

- particles
- high energy photons
- neutrons

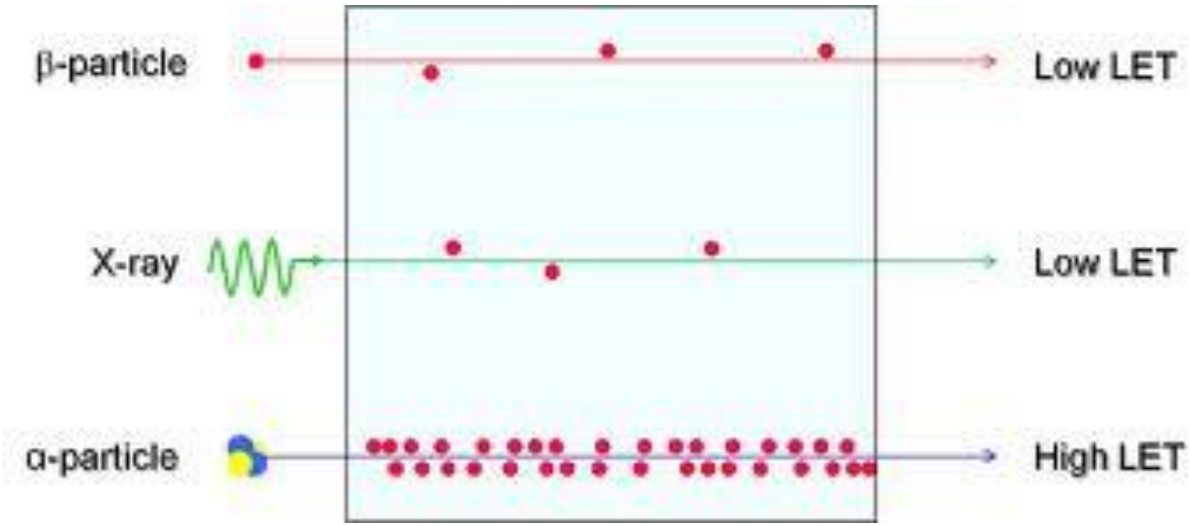


ionization event

Linear Energy Transfer (LET) - amount of energy the particle emits per unit track length and is deposited near it



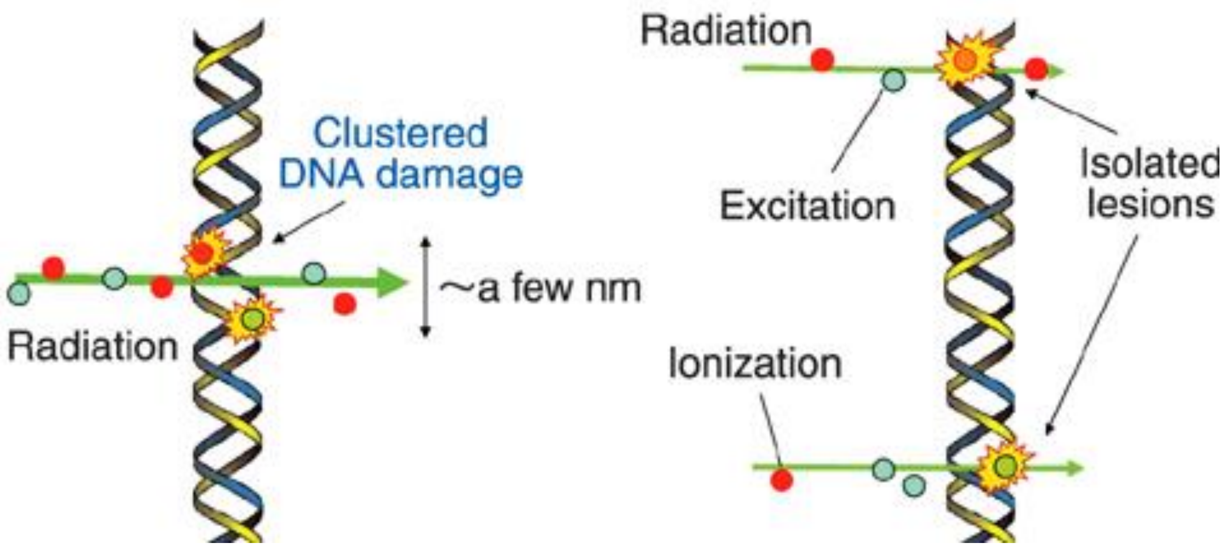
Linear Energy Transfer



ca. 0.2 keV/µm

50-230 keV/µm

High LET



Low LET

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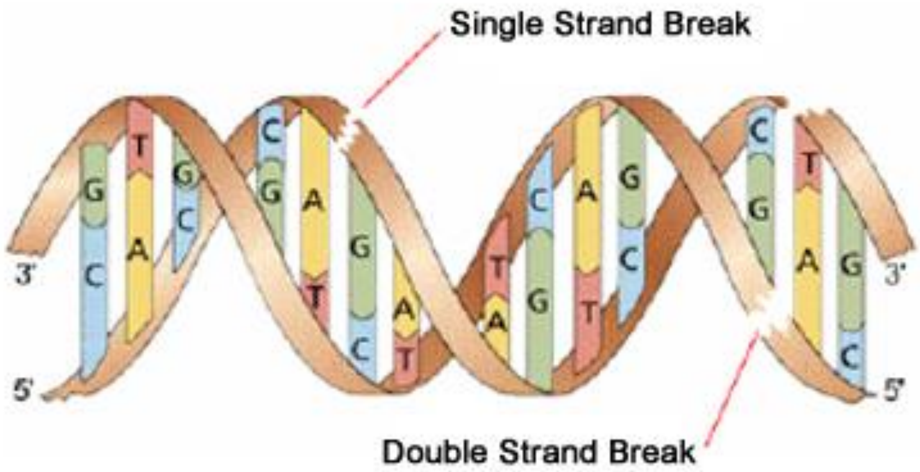
Mechanism of action

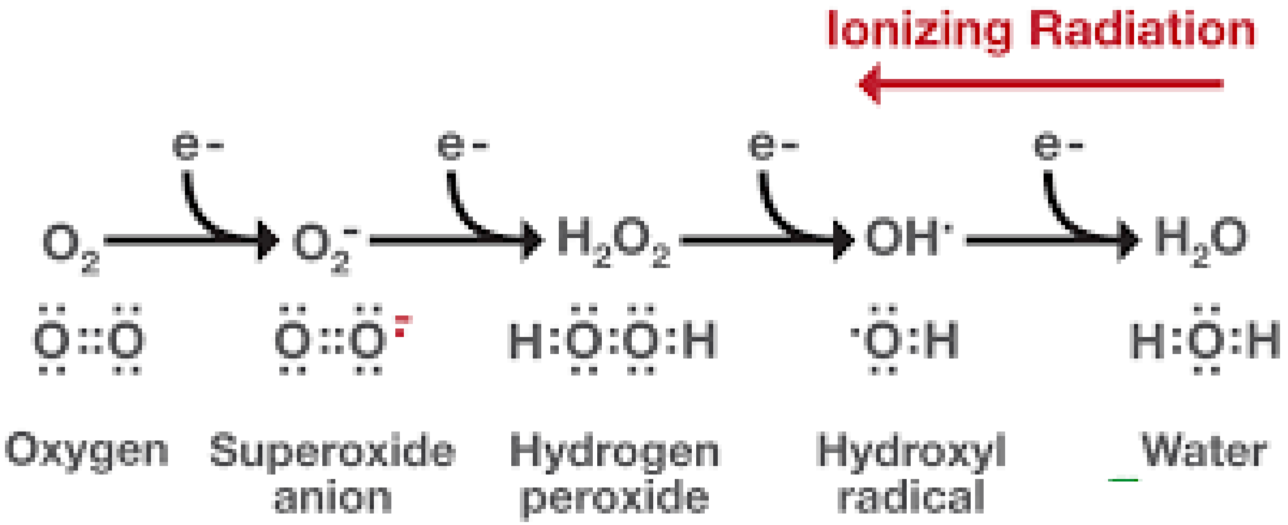


Double strand DNA breaks

- **Mitotic catastrophy**
- **Apoptosis**

+ base damage;
+ DNA-protein cross-linking

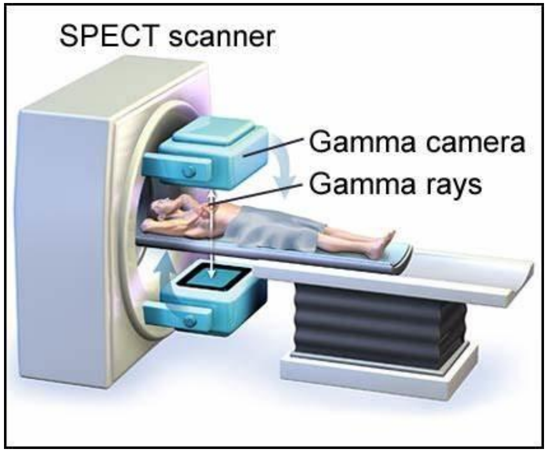
LET- linear energy transfer
Dose- energy deposition per mass unit
Dose rate- dose per time unit



Secondary mechanism of damage is through formation of ROS: Reactive Oxygen Species

Gamma radiation

- **Easily penetrates living bodies**
- **Can be detected by external devices and used for reconstruction of distribution of radioactivity *in vivo***



- **Low local dose**
- **Irradiation of distant normal tissues**
- **NOT USEFUL FOR RADIONUCLIDE THERAPY**

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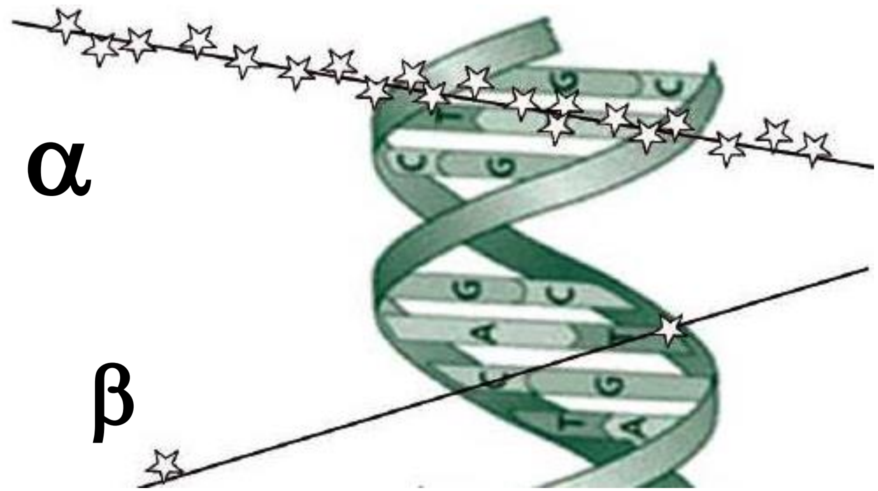
α particles

- **High probability of DSB independent of dose rate**



- **Range up to ~10 cell diameters ⇨ suitable for treatment of single cells and micrometastases**
- **No Oxygen Enhancement Effect ⇨ destroys even hypoxic tumors**

Poor availability of nuclides (^{211}At, ^{223}Ra, ^{225}Ac, ^{227}Th)

Nuclide	Half-life	Daughters	Production
^{212}Bi	60.6 min	^{212}Po, ^{208}Th	Generator
^{213}Bi	45.6 min	^{213}Po, ^{209}Tl, ^{209}Pb	Generator
^{211}At	7.2 h	^{211}Po, ^{209}Bi	Cyclotron
^{225}Ac	10 d	^{211}Fr; ^{217}At, ^{213}Bi, ^{213}Po, ^{209}Tl, ^{209}Pb	Generator
^{227}Th	18.7 d	^{223}Ra,^{219}Ra, ^{215}Po, ^{211}Pb, ^{211}Bi	Generator

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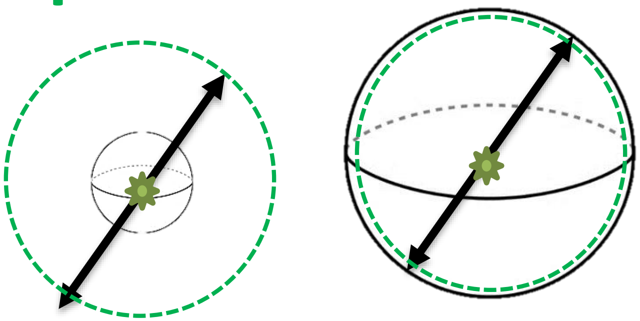
β^- particles

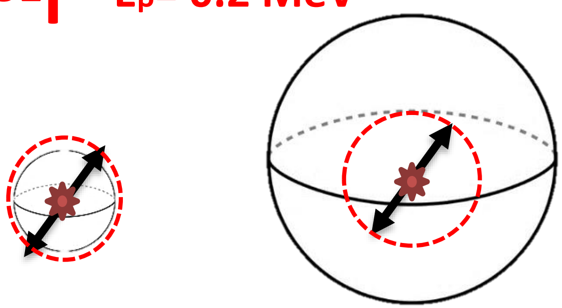
^{90}Y E_β= 0.9 MeV



d= 3 mm
E= 11 mm

d= 11 mm
E= 11 mm

^{131}I E_β= 0.2 MeV



d= 3 mm
E= 3 mm

d= 11 mm
E= 3 mm

Sphere Mass (g)	Absorbed fraction ^{131}I	Absorbed fraction ^{90}Y
0.01	0.77	0.23
0.1	0.89	0.44
1	0.97	0.7
10	0.99	0.86

β⁻ particles

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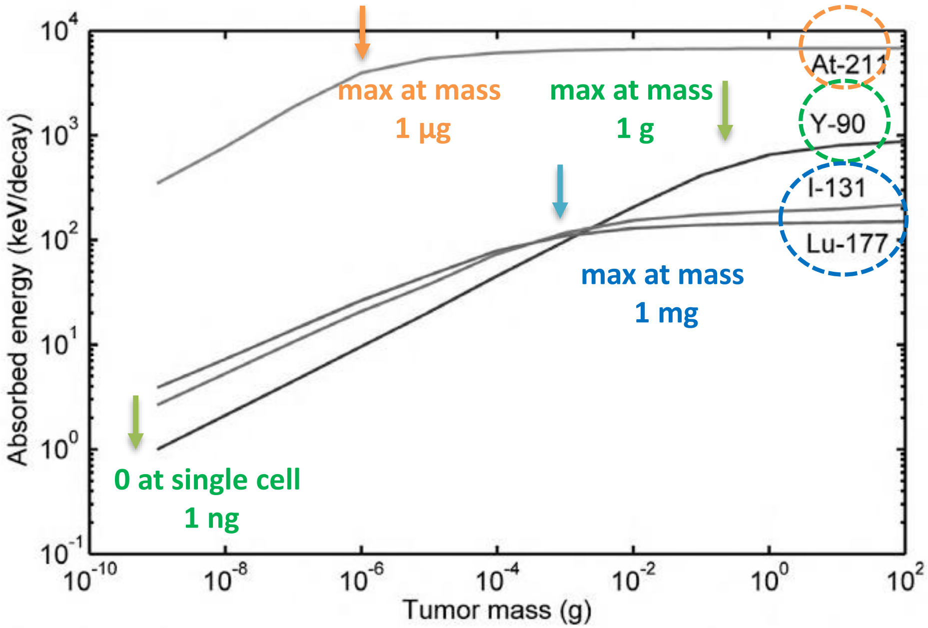

FIGURE 20.1 The absorbed energy per decay versus tumor mass with uniform activity distribution of At-211, Lu-177, I-131, and Y-90.

- Different nuclides are optimal for different tumor sizes
- Low LET, dose rate-dependent effect
- Effect depends on hypoxia/oxygenation of tumours
- Dose is more localized than for gamma

Tod W. Speer "Targeted Radionuclide Therapy"

Commercially available therapeutic radionuclides

Nuclide	Decay mode	Half-life (days)	Average β energy (MeV)	Average range in tissue (mm)	Photon radiation, (keV)
^{188}Re	β^-	0.71	0.764	3.5	155 (15%)
^{90}Y	β^-	2.7	0.935	3.9	-
^{177}Lu	β^-	6.7	0.133	0.67	208 (11%)
^{131}I	β^-	8.0	0.181	0.91	364 (82%)

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Targeted cancer therapy

Passive targeting

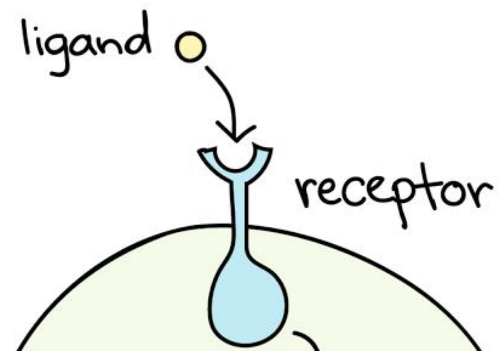
Uses native chemical properties of a nuclide and its participation in biochemical processes in vivo

^{131}I — Na/I symporter

^{223}Ra — Calcium ”analogue”
Same group

Active targeting

Molecular recognition of targets on the surface of tumor cells



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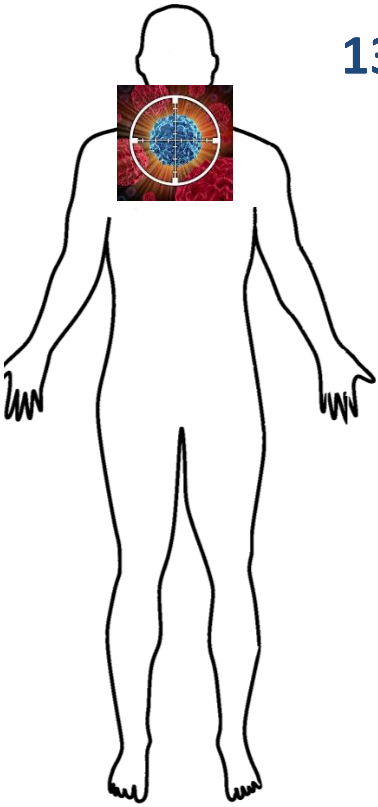
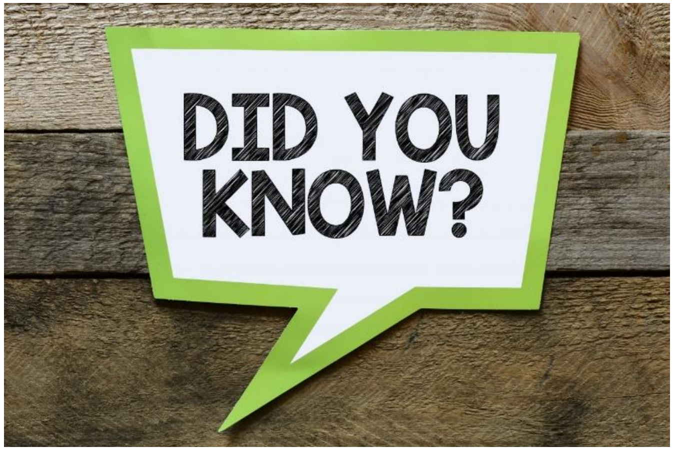
Targeted cancer therapy

Passive targeting -> Metabolism-> Accumulation



^{131}I

- Iodide **->** thyroid (Na/I symporter)
- Therapy of thyroid disorders and thyroid cancer
- Used over 60 years
- Unfavourable radiation profile (high energy gamma), limited use nowadays



After Chernobyl's disaster people were given Lugol's solution containig 10% KI and 5% I.

Do you know why?

fromchernobyltofukushima.com; blogspot.com

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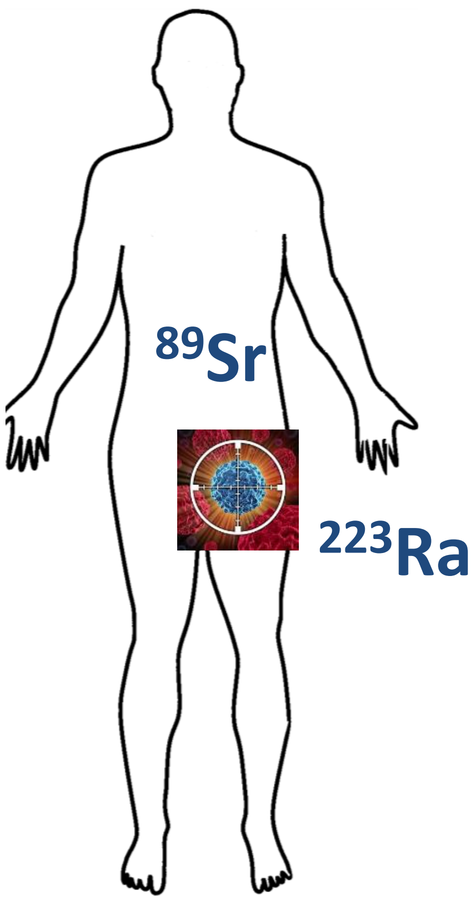
Targeted cancer therapy

Passive targeting -> Metabolism-> Accumulation



- ^{89}Sr, ^{223}Ra, ^{153}Sm **-> Ca analogues** accumulate in bones
- ^{89}Sr high E beta emitter (0.58 MeV) Metastron- for bone metastasis (FDA)
- ^{223}Ra alpha-emitter, high LET. Alpharadin- skeletal bone metastasis and castration-resistant prostate cancer (*very effective, FDA fast track*)

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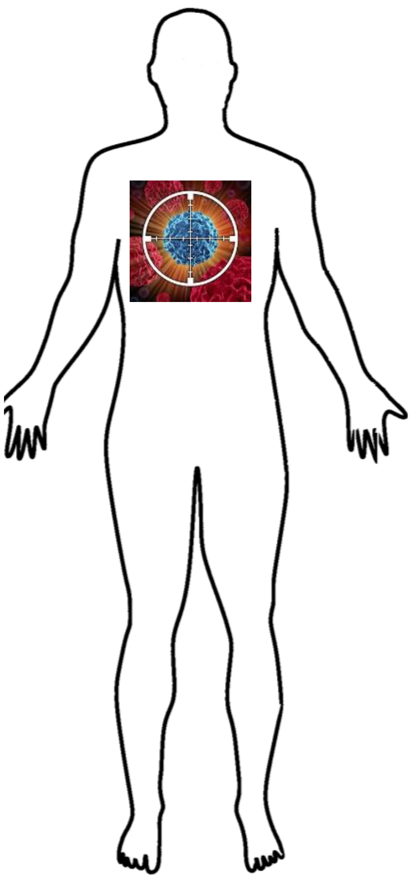
Targeted cancer therapy



”Magic bullet” by P. Erlich (1900)

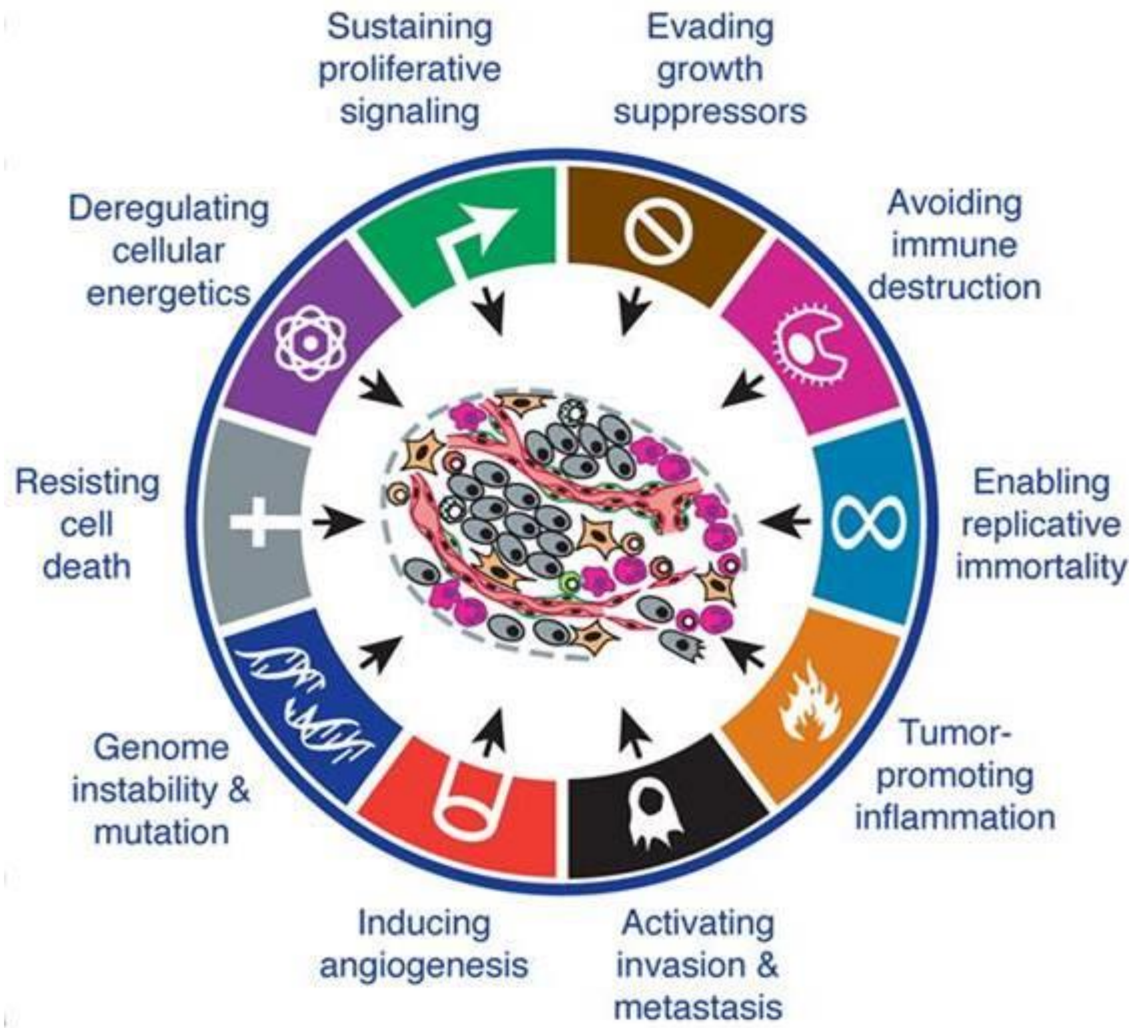
Molecular design of targeted conjugates

Targeting cancer — linker — Therapeutic effect

- Carriers (nanopartiles)
- Proteins (antibodies)

- Drugs
- Toxins
- Radionuclides

Targets for cancer therapy



Hanahan, Weinberg "Hallmarks of cancer" 2000 and 2011

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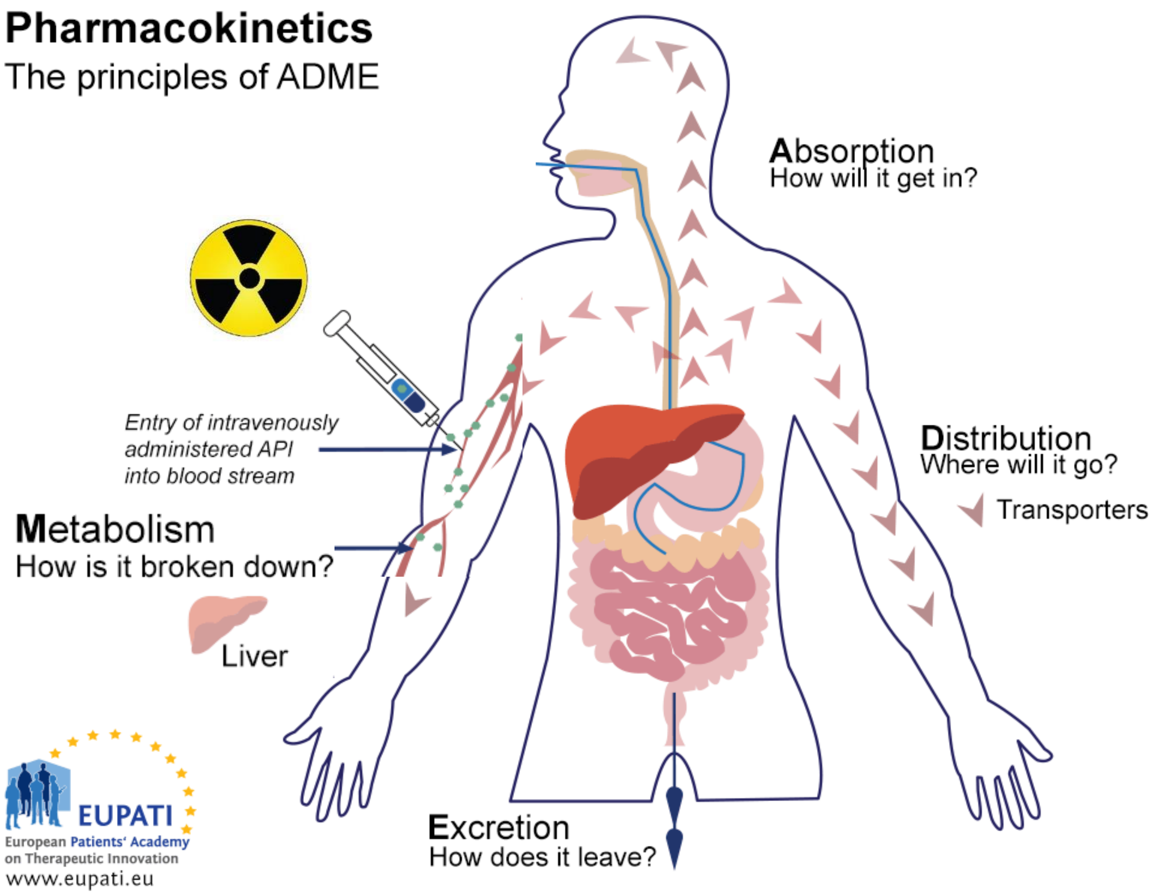
Targets for cancer therapy

Function of target	Target (biomarker)	Targeting molecule	Indication
Immune response of B cells	CD20	Zevalin Bexxar	Lymphoma
Endocrine system, neurotransmission, cell growth	Somatostatin receptors	Somatostatin analogues (e.g. DOTATATE)	NETs
Uptake of folate/unknown	PSMA	ProstaScint	Prostate cancer

Pharmacokinetics: dosimetry

- A Absorption
- D Distribution
- M Metabolism
- E Excretion



Selection of a nuclide makes a difference between success and failure

Factors influencing selection of nuclides (labels):

- **Expected tumor size**
- **Cellular processing of targeting protein by cancer cells**
- **Uptake of protein in excretory organs**
- **Size of targeting protein**

Internalization of radiolabeled proteins

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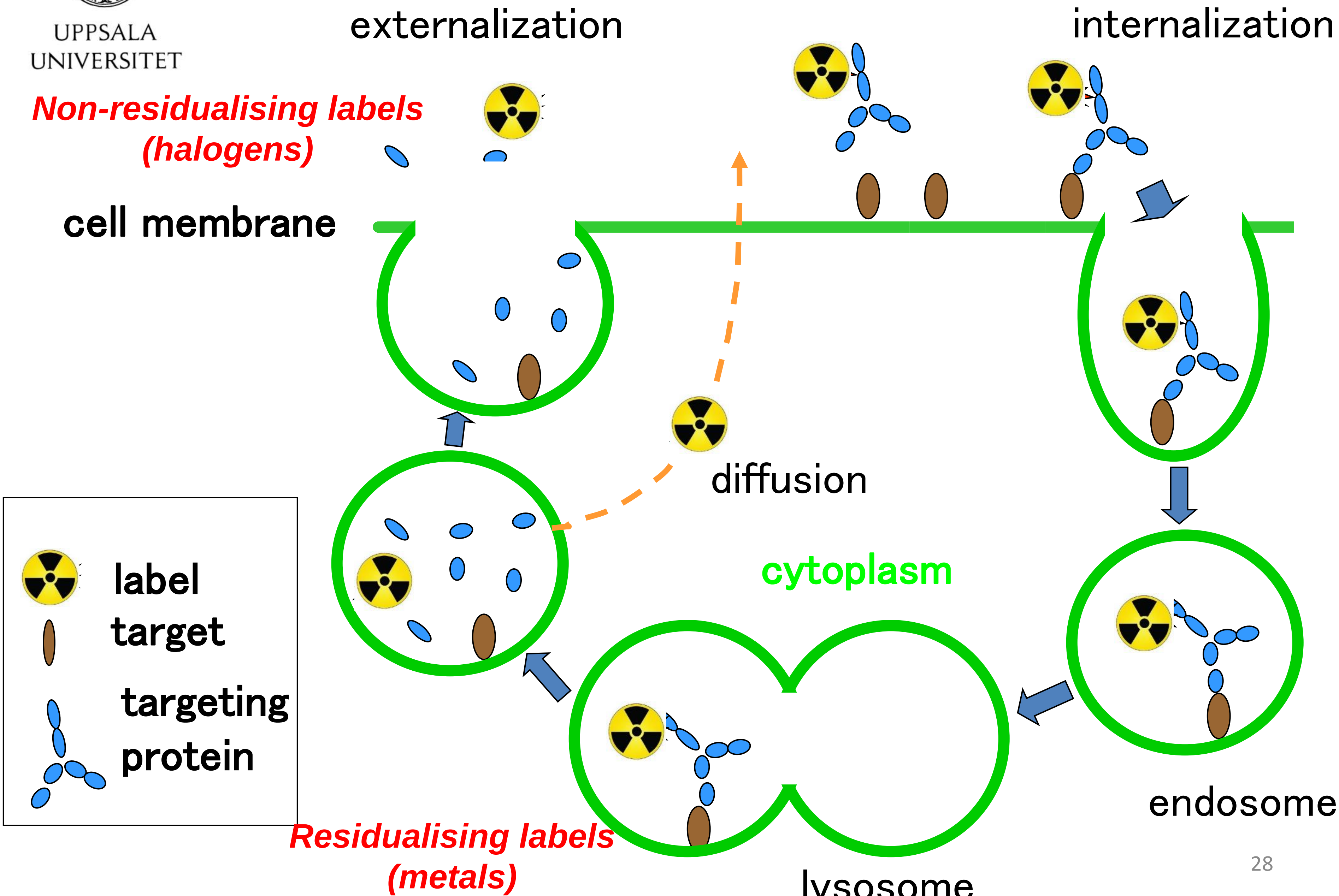
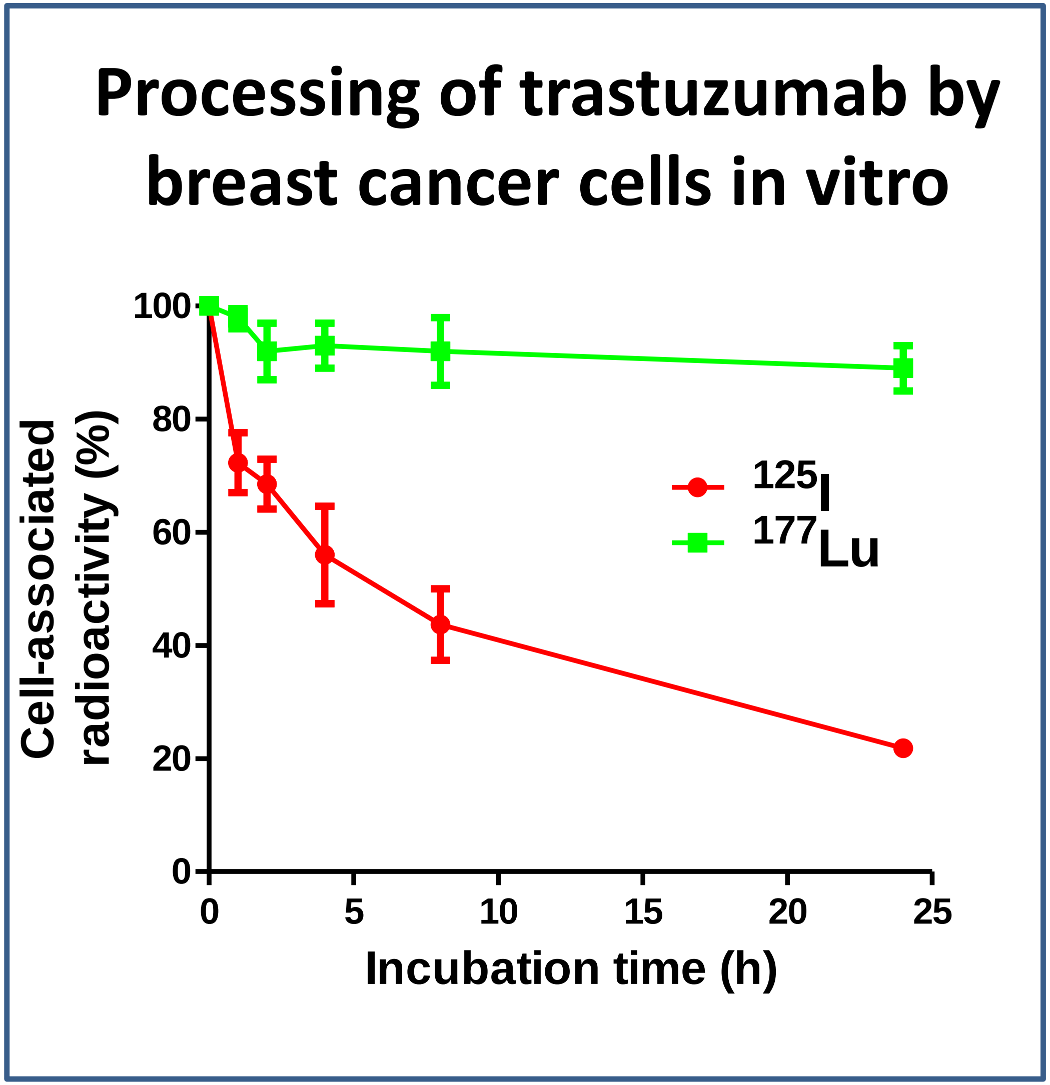
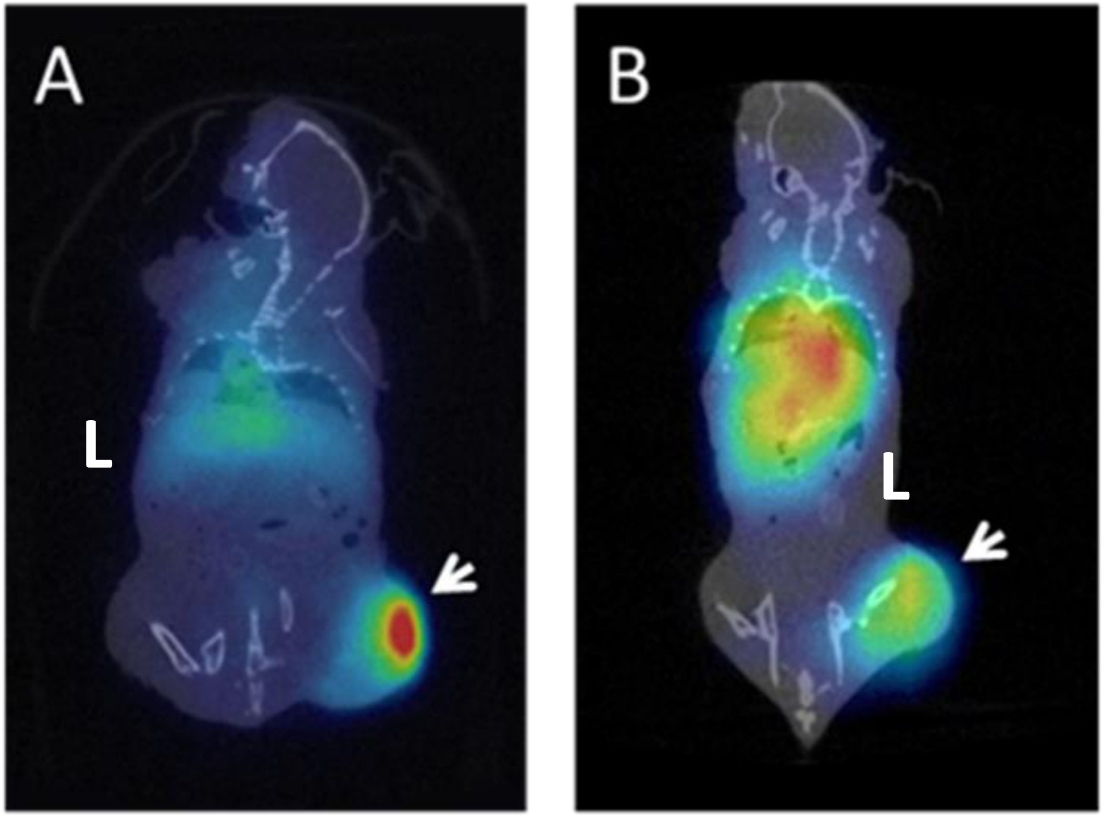


Cellular retention of radionuclides



The use of residualizing labels (metals) improves cellular retention of radionuclides delivered by antibodies because antibodies are internalized!

Retention in excretory organs



^{124}I: non-residualizing **^{111}In: residualizing**

Size of a targeting protein

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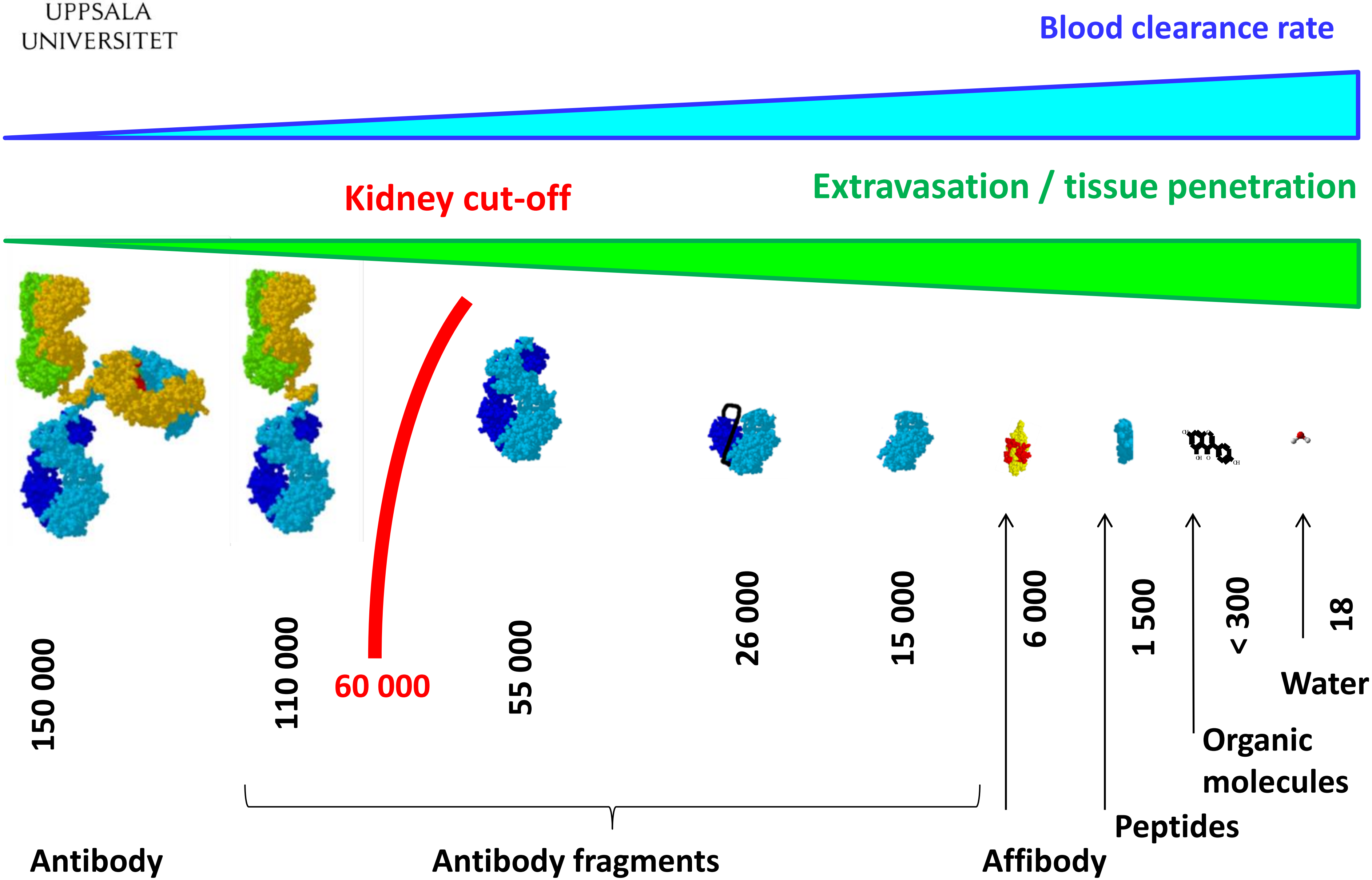

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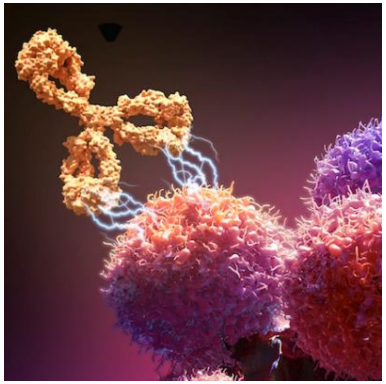
Radioimmunotherapy



using mAbs / their fragments for radionuclide therapy

- ✓ **using therapeutic mAbs already approved for clinical use**
- ✓ **historically, mAbs were the first targeting vectors**
- ✓ **high affinity to targets**

But…

- ❖ **Long-half life in blood -> damaging normal organs**

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Radioimmunotherapy of lymphoma: clinical success

ZEVALIN

(^{90}Y-ibritumomab tiuxetan)

	ZEVALIN (n=64)*	Rituximab (n=66)**
ORR	83%	55%
CR	38%	18%

Witzig. *J Clin Oncol*. 2002;20:2453-2463.

BEXXAR

(^{131}I-tositumomab)

	BEXXAR (n=64)*	Chemo (n=66)**
ORR	65%	28%
CR	20%	3%

Bexxar: Commercial failure, withdrawn from the market in 2014

Kaminski *J Clin Oncol*. 2001;19:3918-28.

Size optimization of proteins

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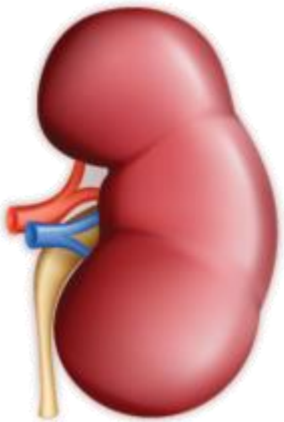
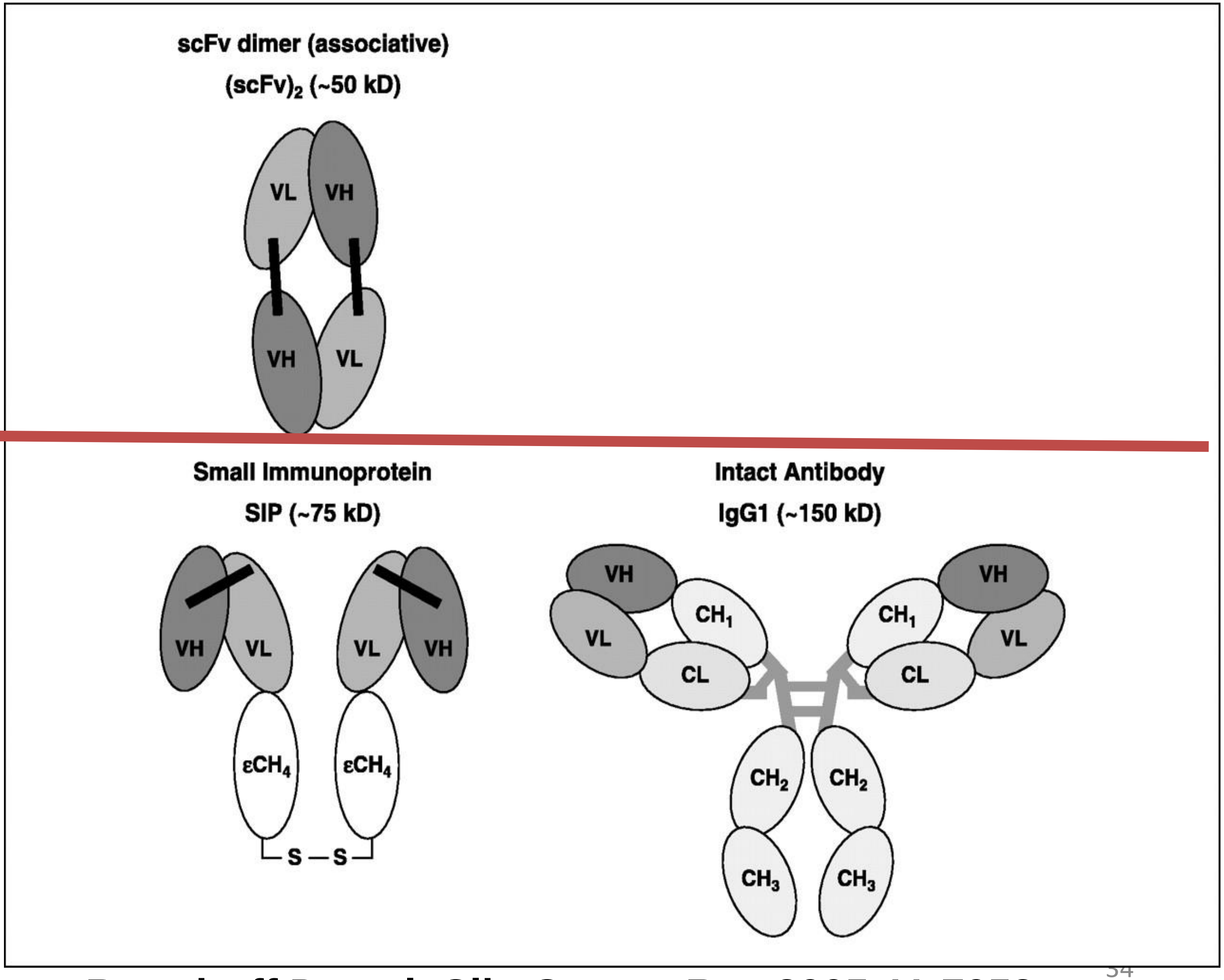
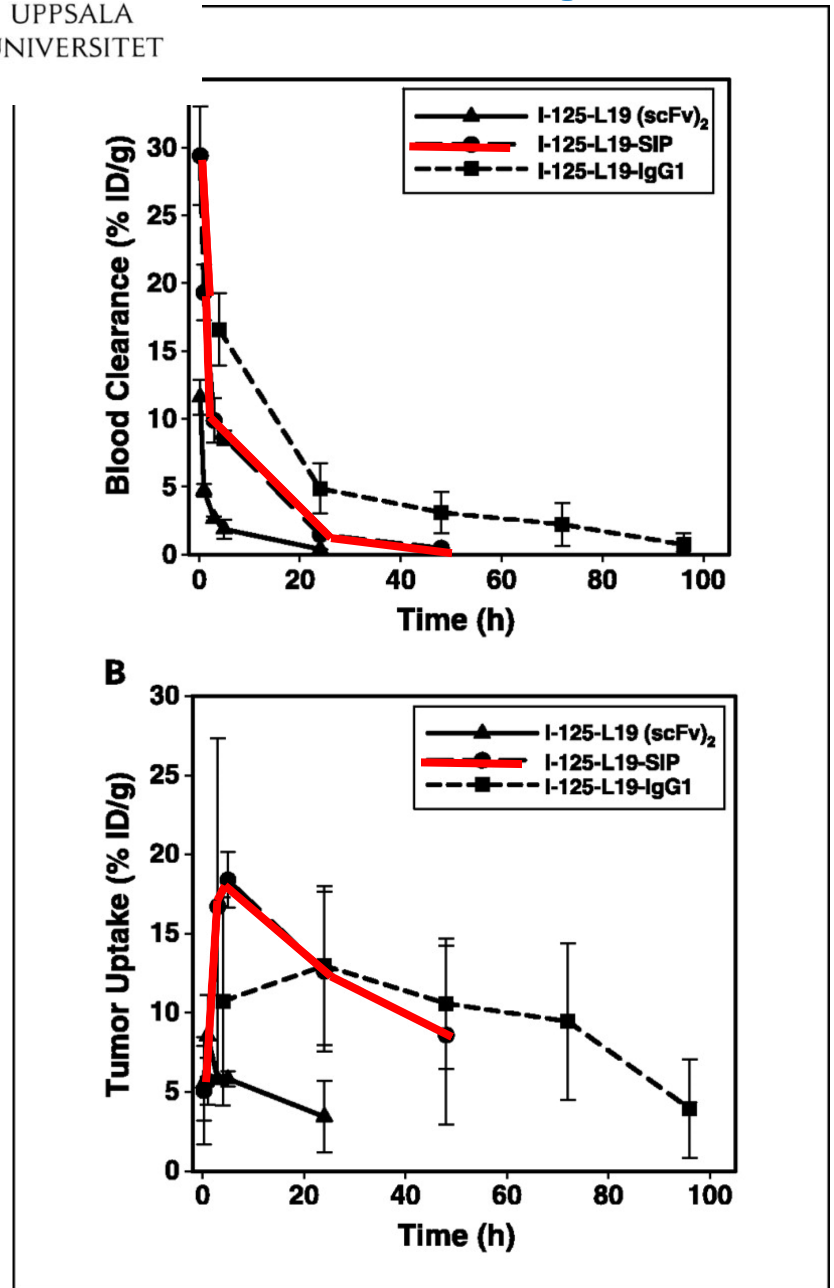
kidney filtration cut-off ~ 60 kDa

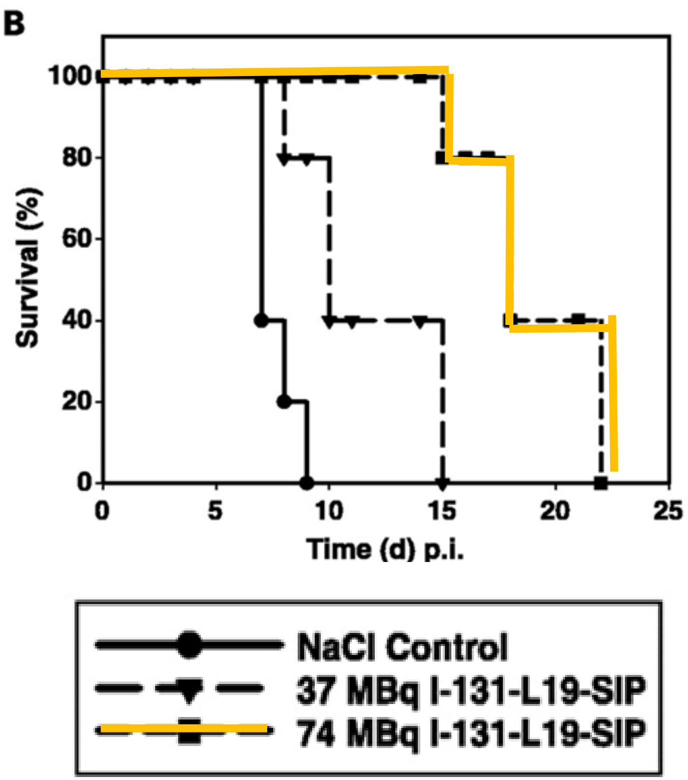




Berndorff D et al. Clin Cancer Res 2005;11:7053s

Size-optimization: ^{131}I-L19-SIP





Berndorff D et al. Clin Cancer Res 2005;11:7053s

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Radioimmunotherapy of solid tumours: no success yet

Issues to be solved:

- **High radioresistance of solid tumours**
- **Low dose rate during radioimmunotherapy**
- **Low doses delivered to tumors**
  - **- Slow extravasation of intact antibodies**
  - **- Slow tissue penetration**
  - **- Slow blood clearance ⇨ high dose to bone marrow**

Possible solutions:

- **treatment of minimal residual disease**
- **(neo) adjuvant settings- combination therapy**
- **<u>Size reduction of targeting protein</u>**

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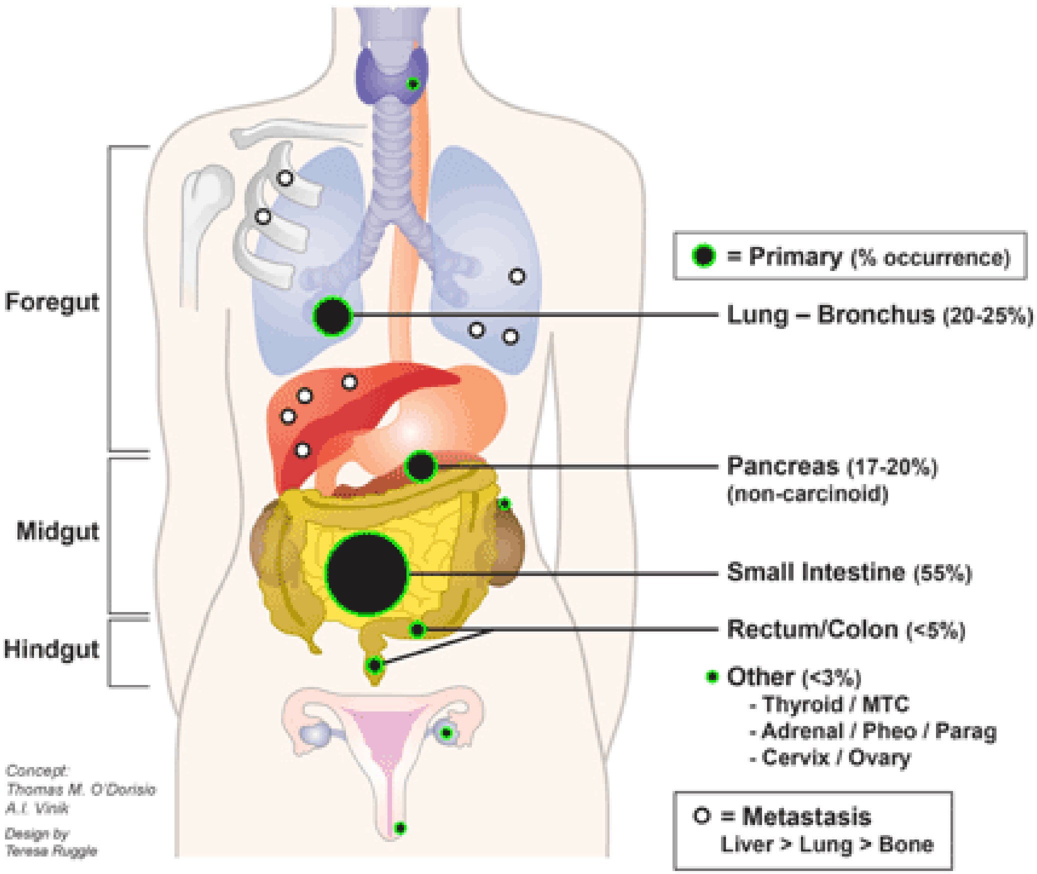
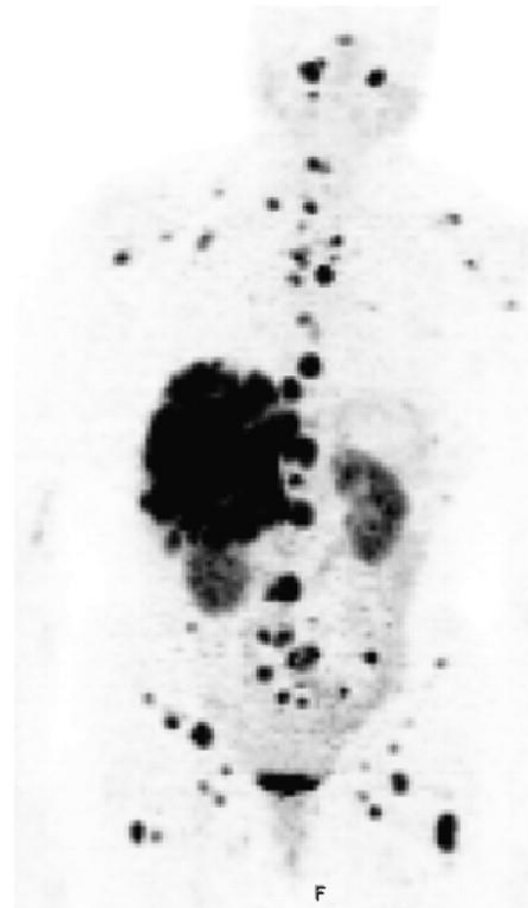
Targeted radionuclide therapy of NETs

Figure 1: Anatomical Distribution of Neuroendocrine Tumors



A PET scan with ^{68}Ga-DOTA-TOC



Metastases of NETs

J Nucl Med ***2007****, 48, 4,* ***508-518***

Targeted radionuclide therapy of NETs

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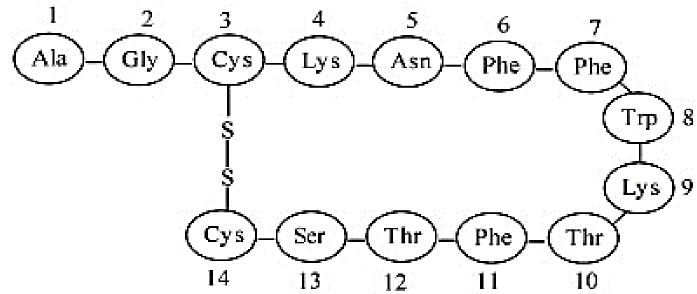
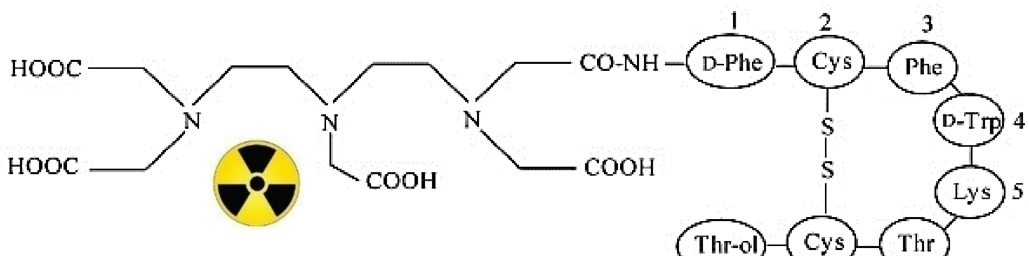


Somatostatin-14

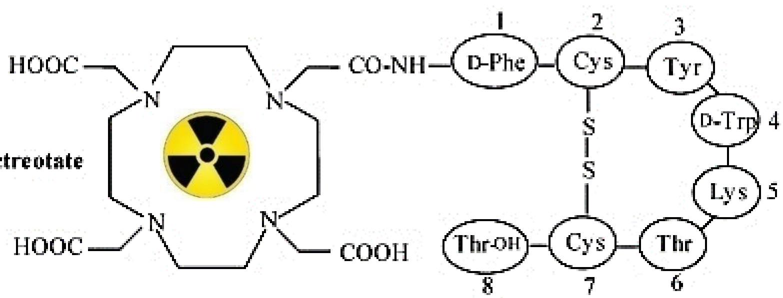
Somatostatin



DTPA^0-D-Phe^1-octreotide (OctreoScan)

Somatostatin analogue DTPA-Octreotide

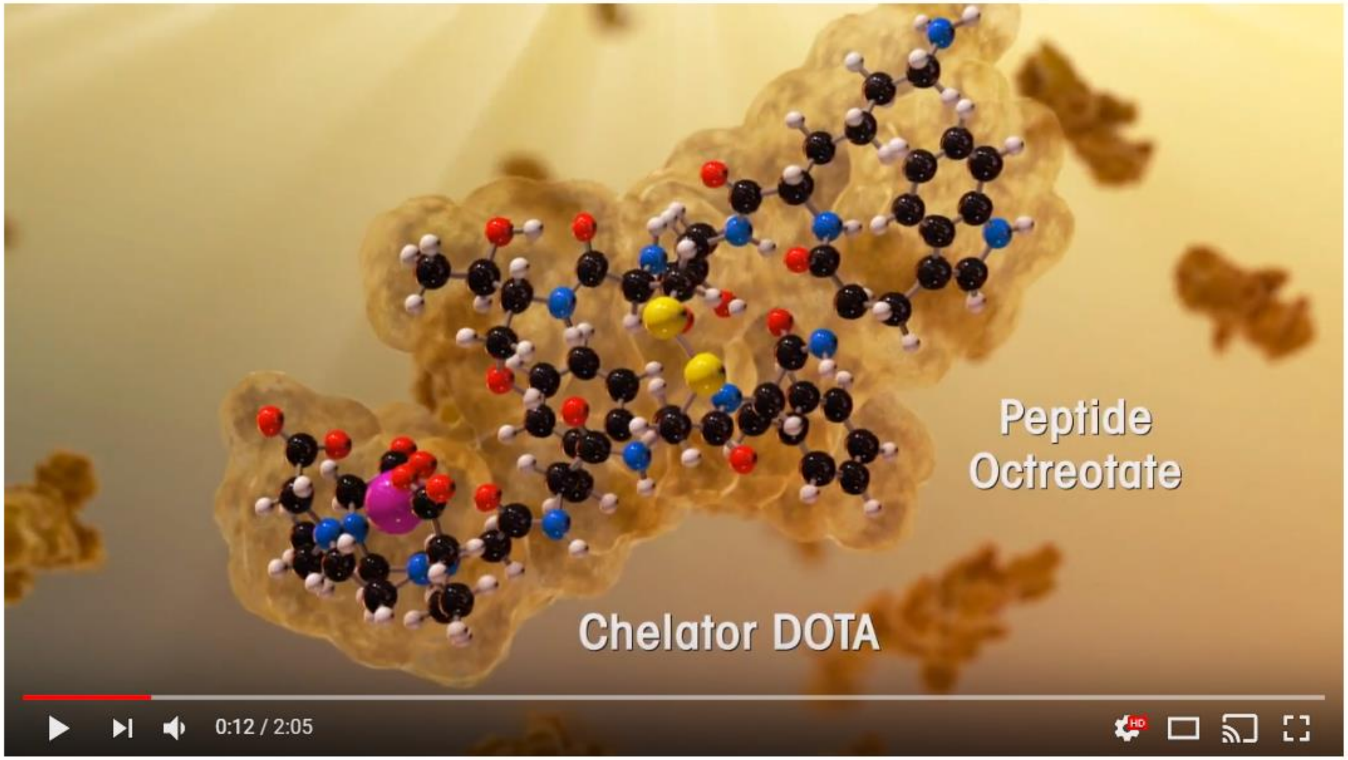
[DOTA^0,D-Phe^1,Tyr^3]octreotate (DOTA-TATE)



Somatostatin analogue DOTA-Octreotate

Theranostics 2012 2(5):481-501

^{177}Lu-DOTA-octreotate for targeted radionuclide therapy of NETs



Targeted Radionuclide Therapy.wmv

177Lu-DOTA-TATE was FDA approved in January 2018 for treatment of NETs

Targeted radionuclide therapy of NETs: (limited) clinical success

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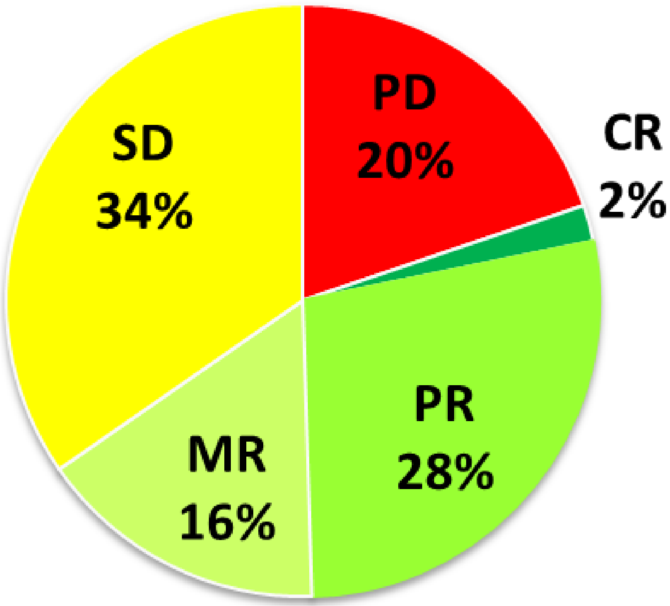

Treatment With the Radiolabeled Somatostatin Analog [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate: Toxicity, Efficacy, and Survival:

Kwekkeboom ***J Clin Oncol 2008: 26:2124-2130***

SD stable disease
CR, PR, or MR - remission
PD progressive disease

Message: size reduction of targeting protein might be the key to success

Targeted radionuclide therapy of prostate cancer

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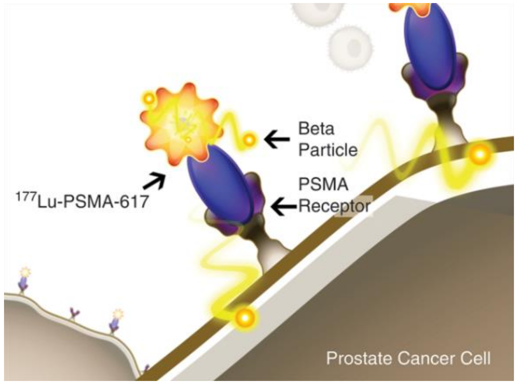
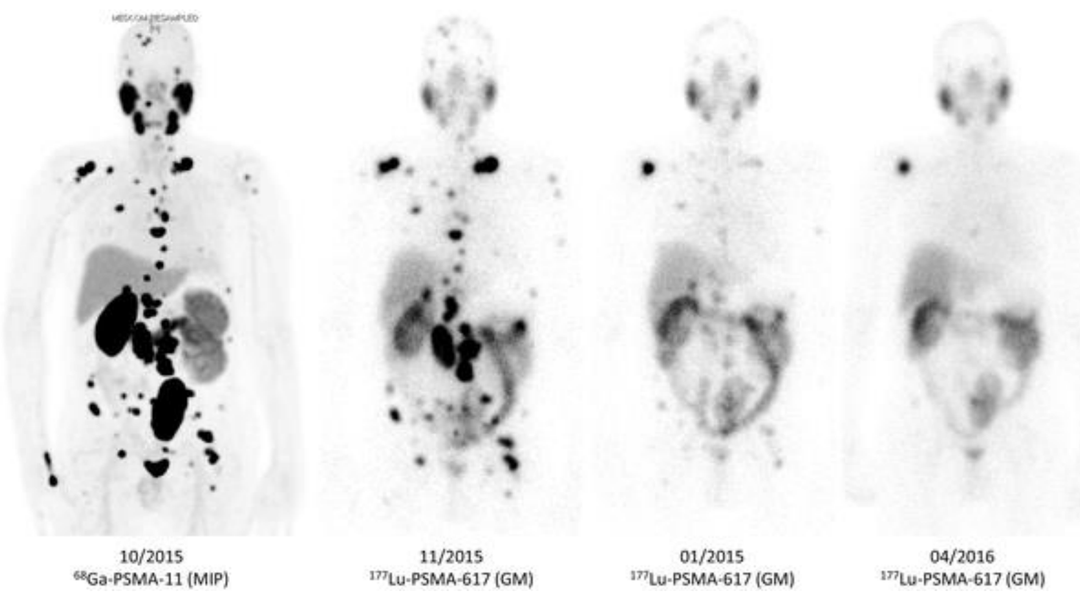


Target: prostate-specific membrane antigen (PSMA) is a biomarker for prostate cancer

Ligands: various small molecules < 5 kDa

PET Imaging with ^{68}Ga



Beta therapy with ^{177}Lu

Clin Transl Imaging **4,** 487–489 (2016)

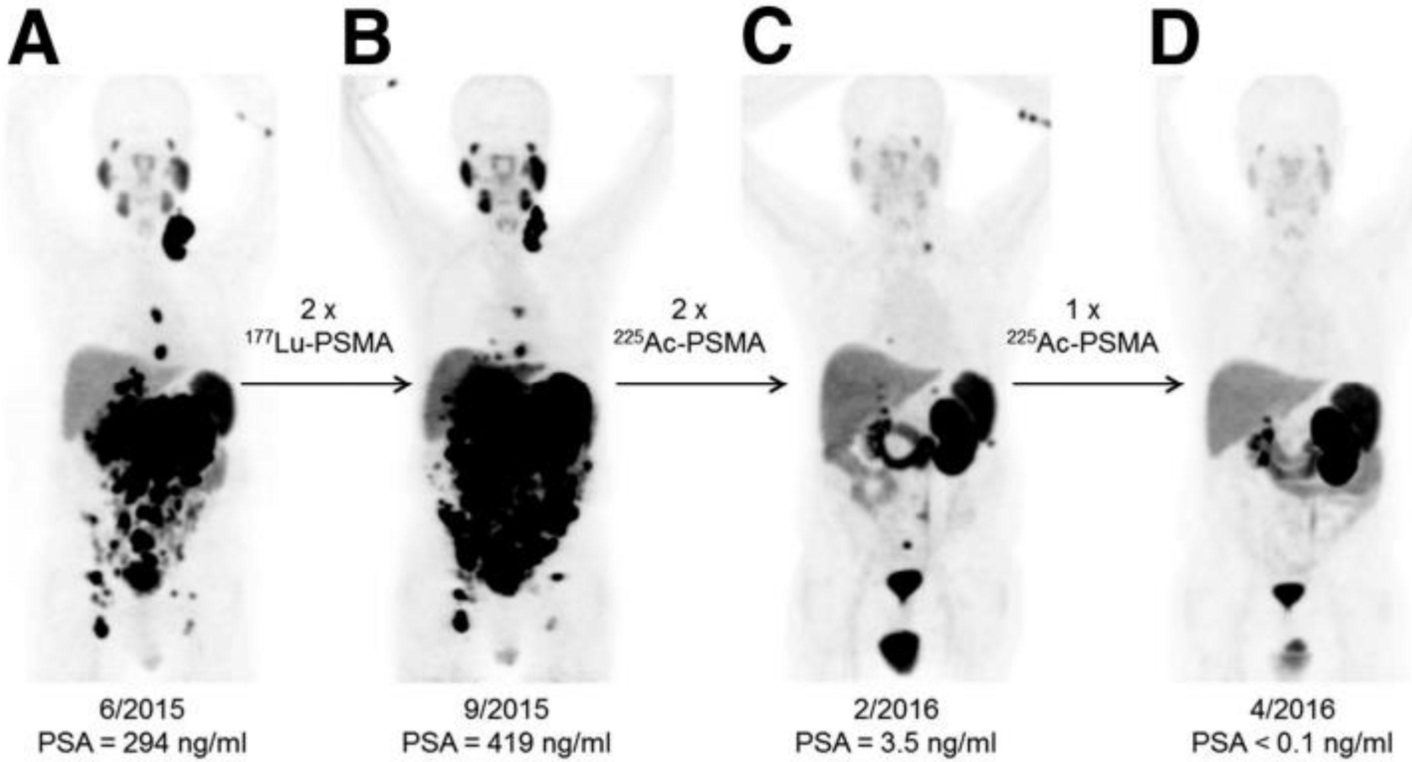


Figure 5. ^{68}Ga-PSMA-11 positron emission tomography (PET)/computed tomography (CT) scans of a patient comparing the initial tumor spread (**A**); restaging after 2 cycles of β^- emitting ^{177}Lu-PSMA-617 reveals progression (**B**). In contrast, restaging after second (**C**) and third (**D**) cycles of α emitting ^{225}Ac-PSMA-617 shows impressive response. This research was originally published in JNM. Kratochwil et al. ^{225}Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer. *J. Nucl. Med.* 2016, *57*(12), 1941–1944. © by the Society of Nuclear Medicine and Molecular Imaging, Inc. [4].

Not approved yet. Hundreds of PSMA clinical trials all over the world!

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Personalized treatment. Current status

"…All patients received a single infusion at a dose level of 40 to 60 mCi/m^2 based on a previous phase I, dose-finding trial…"

Liersch. J Clin Oncol. 2005;23:6763-70

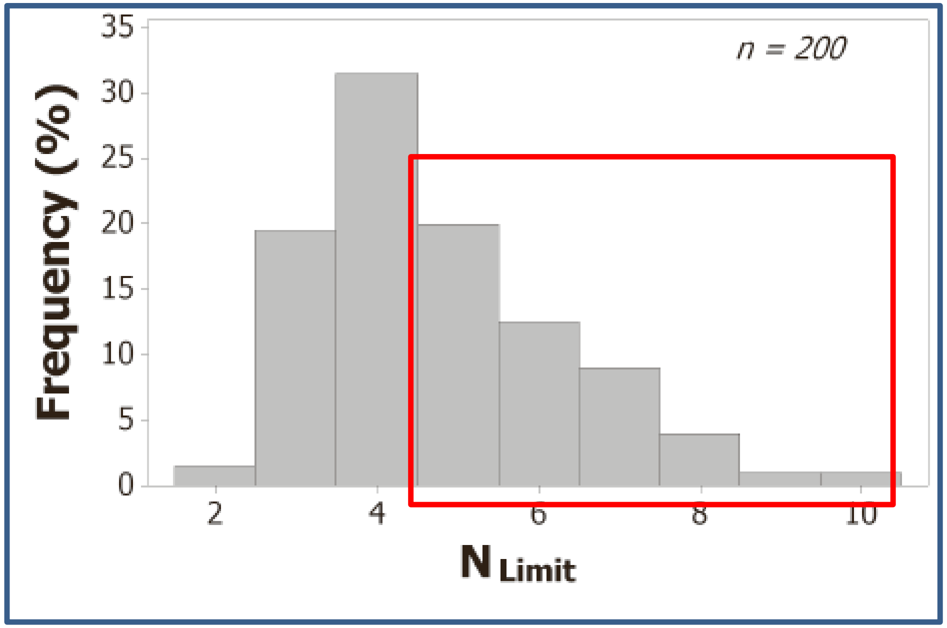
"…a total dose of 75 mCi/m^2 was administered…"

Meredith. Clin Cancer Res. 1996;2:1811-8

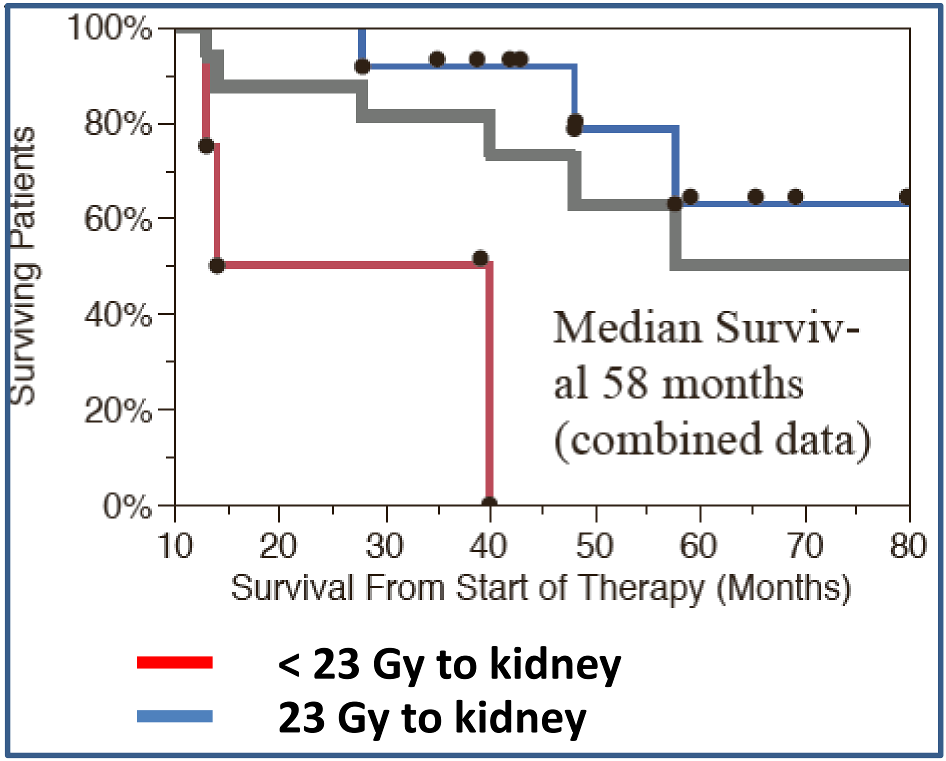
Administration of maximum tolerated activity determined in Phase I/II ⇨ activities determined for the least resistant patients ⇨ undertreatment of many patients

Personalized treatment. Patient-specific dosimety

Dosimetry-guided treatment of NET using ^{177}Lu-DOTA-TATE



Maximum number of cycles with 7.4 GBq of ^{177}Lu-DOTA-octreotate per patient before reaching 2 Gy to the bone marrow or 23 Gy to the kidney

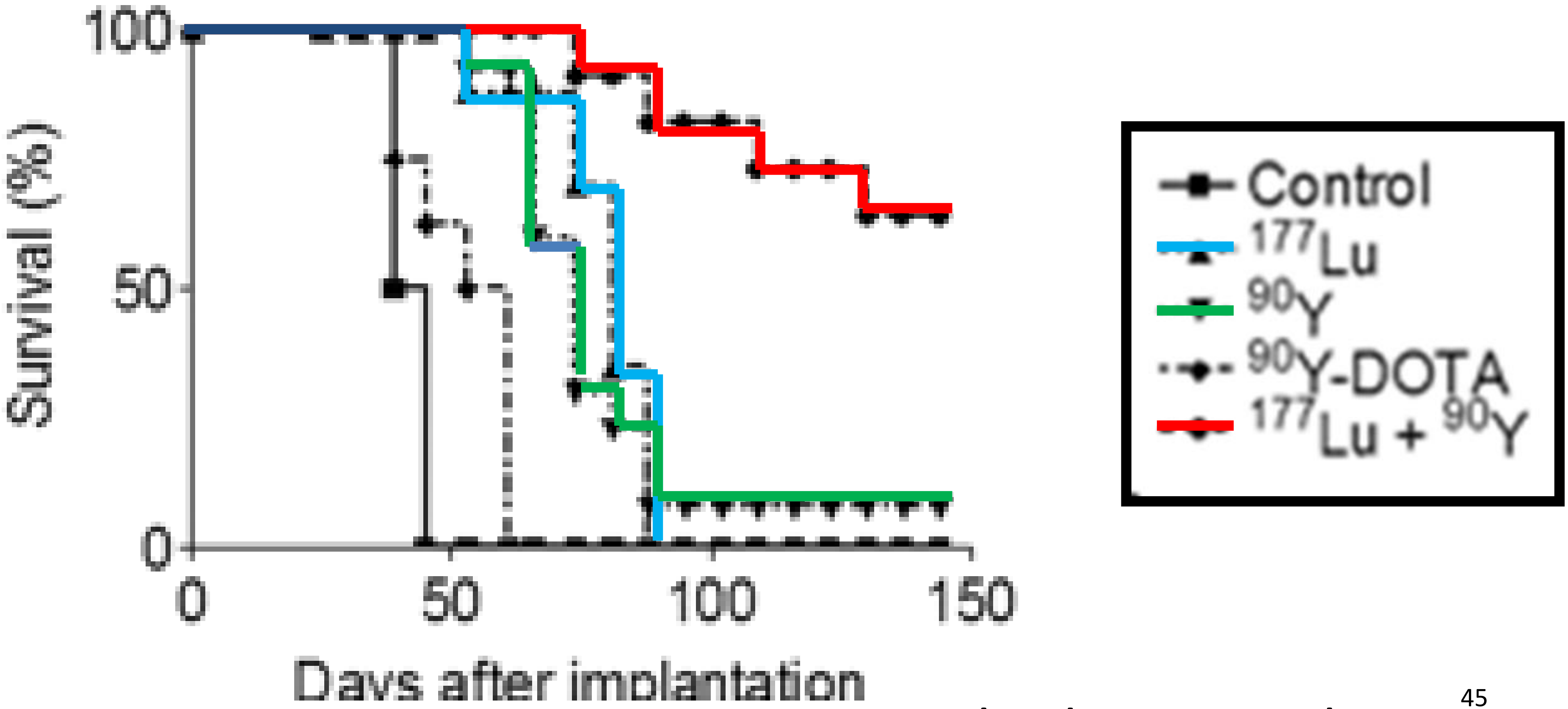


Dosimetry- guided therapy of advanced colorectal NETs with ^{177}Lu-DOTA-TATE

Garske-Roman. PhD thesis. Uppsala

Radionuclide cocktail approach

Treatment of small and large somatostatin receptor-positive tumors using ^{90}Y and ^{177}Lu-labeled somatostatin analogue



De Jong. J Nucl Med. 2005;46 Suppl 1:13S.

Radionuclide therapy in Sweden

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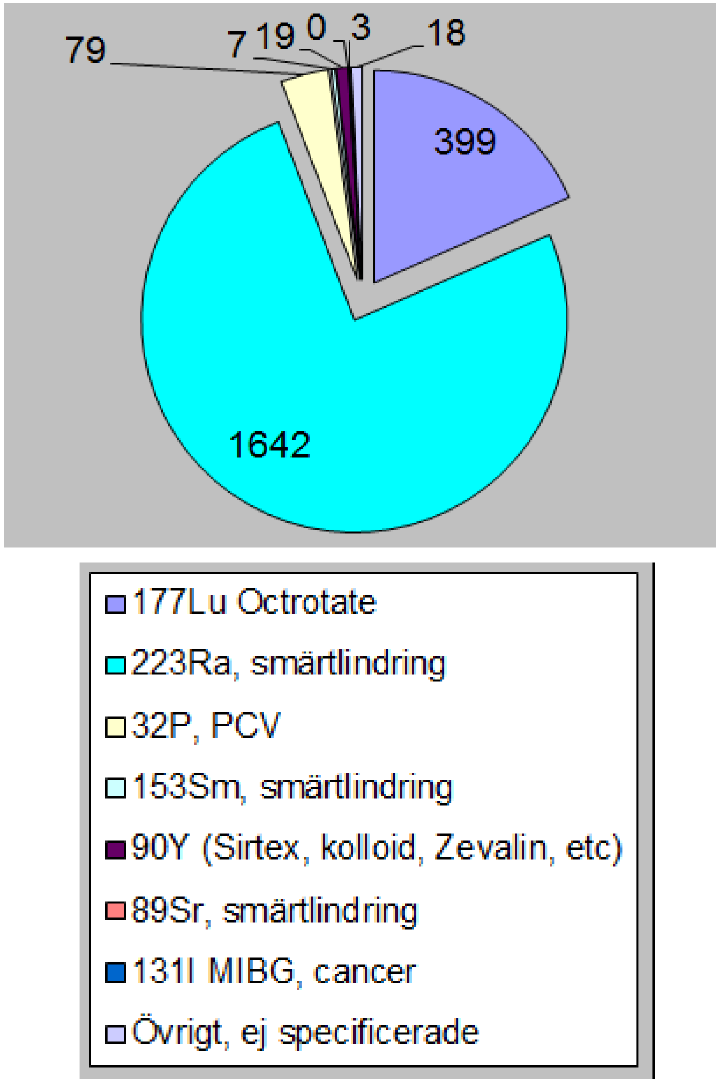
Terapi \ År	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
131I (jodid) hyperthyreos	3142	3131	2804	2652	2760	2818	2590	2376	2294	2324	2402	1992	1898	1865	1938	1846	1765	1802	1871	1735	1668	1666	1663	1634	1501
131I (jodid) cancer	141	171	143	158	165	157	154	171	196	202	245	278	282	259	258	307	377	366	425	450	451	478	420	477	503
89Sr (klorid) cancer	294	290	219	237	269	251	192	168	190	128	104	71	54	52	34	20	24	20	8	3	2	2	0	0	0
32P (fosfat) PCV	288	301	278	317	266	264	291	281	265	251	246	178	208	157	152	150	111	113	97	103	81	83	79	54	40
111In/177Lu (Octreotid/tate) cancer	-	10	11	18	25	19	13	11	21	25	27	21	114	196	222	294	312	356	378	368	341	371	399	486	444
131I (MIBG) cancer	10	15	15	9	20	21	30	10	14	16	10	10	9	8	8	14	13	21	11	4	7	12	3	4	11
153Sm (EDTMP) cancer	-	-	-	-	20	117	148	134	196	254	231	152	133	115	102	100	109	92	72	63	40	43	7	5	56
223Ra (klorid) Smärtlindring	-	-	-	-	-	-	-	-	13	18	54	51	14	9	14	70	124	47	27	432	148	1188	1642	1886	1276
Övrigt	21	64	145	69	78	53	78	44	51	13	30	33	29	28	54	48	39	38	27	31	37	26	37	16	7
TOTALT	3896	3982	3615	3460	3603	3700	3496	3195	3240	3231	3349	2786	2741	2689	2782	2849	2874	2855	2916	3189	2775	3869	4250	4562	3788

http://www.isotopterapi.se/

Radionuclide therapy in Sweden



http://www.isotopterapi.se/

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Take home messages

Advantages of radionuclide targeting:

- **No multidrug resistance**
- **Cross-fire irradiation**
- **No alternative signalling pathways**
- **Different toxicity profile**
- **Independent of immune system of a patient**

Factors influencing selection of labels:

- **Size of tumors**
- **Size of targeting protein (half-life matching)**
- **Cellular processing of targeting protein by cancer cells**
- **Uptake of protein in excretory organs**

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Take home messages

Radioimmunotherapy of lymphoma: clinical success!

Radioimmunotherapy of solid tumors: no success yet…

Possible solutions:

- **Treatment of minimal disease**
- **Reduction of size of radiolabelled proteins to**
  - **reduce bone marrow exposure**
  - **improve extravasation and tissue penetration**
- **Personalized treatment and patient-specific dosimetry**
- **Novel targets / tracers with optimal PK/PD profile**

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Take home messages

Radionuclide therapy at its current state does not completely eradicate the disease but is aiming to:

1) **Extend survival** in combination with other options

2) Provide palliative care by
- Reducing pain (bone metastasis Alpharadin)
- Reducing symptoms (treatment of NET reduces hyperactivity of hormone-secreting glands, hyperinsulinomas etc.)

3) Improve quality of patient's life

Research from the laboratory of Prof. Vladimir Tolmachev

Radionuclide tumour targeting using
engineered scaffold proteins
for imaging and therapy of cancer

Moscow **Stockholm** **Uppsala**

ИБХ

KTH
VETENSKAP
OCH KONST

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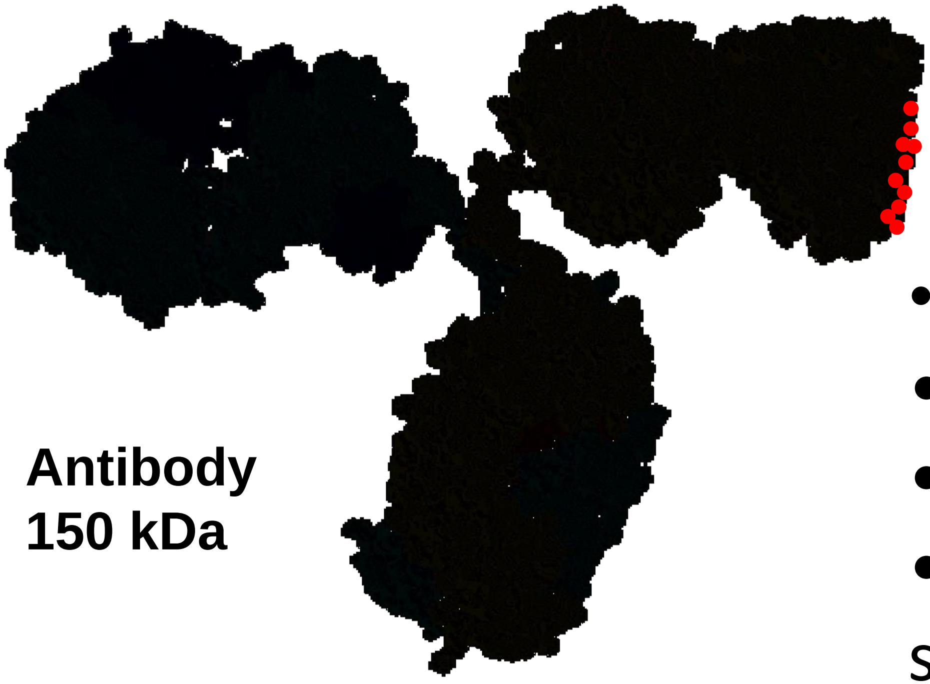
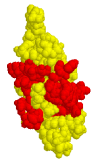
Protein production and analysis

Radiolabeling, *in vitro* & *in vivo* studies

Development of affibody-based radionuclide therapy



Antibody
150 kDa



Affibody Molecule
6-7 kDa

- High (picomolar) affinity
- Small size
- Robustness
- Both recombinant and synthetic production with site specific labelling

Nygren.FEBS J. 2008:2668
Ahlgren. Curr Pharm Biotechnol. 2010:581.

Human Epidermal Growth Factor Receptor (HER2) imaging

HER2 overexpression in:

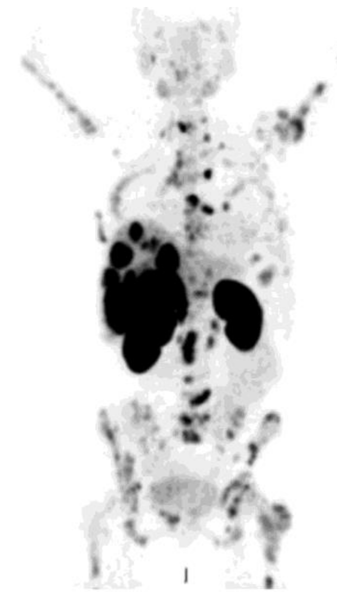
- Breast cancer (20-25%)
- Gastroesophagal cancer (10-20%)
- Ovarian cancer (8-35%)

Targeted therapy Trastuzumab

Imaging:

- Whole-body evaluation of expression
- Selection of patients for therapy
- Monitor response to treatment

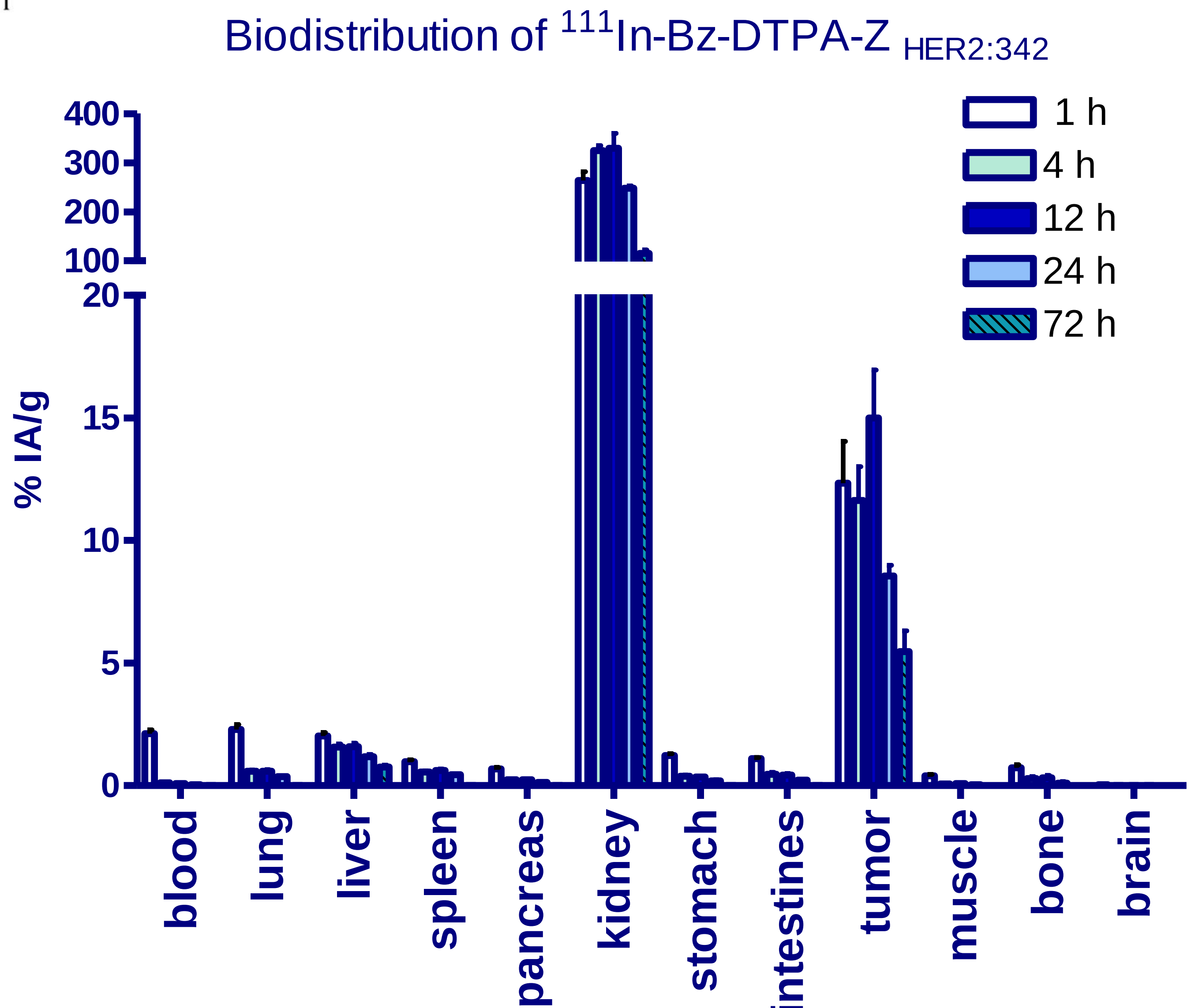
^{89}Zr-trastuzumab (mAb)
5 days after injection



^{68}Ga-anti-HER2 Affibody
2 h after injection

Krasniqi *et al*. *J Nucl Med* 2018;59:885-891

Challenge for therapy: high kidney uptake



1. PK properties of labeled protein: optimizing lipohilicity profile

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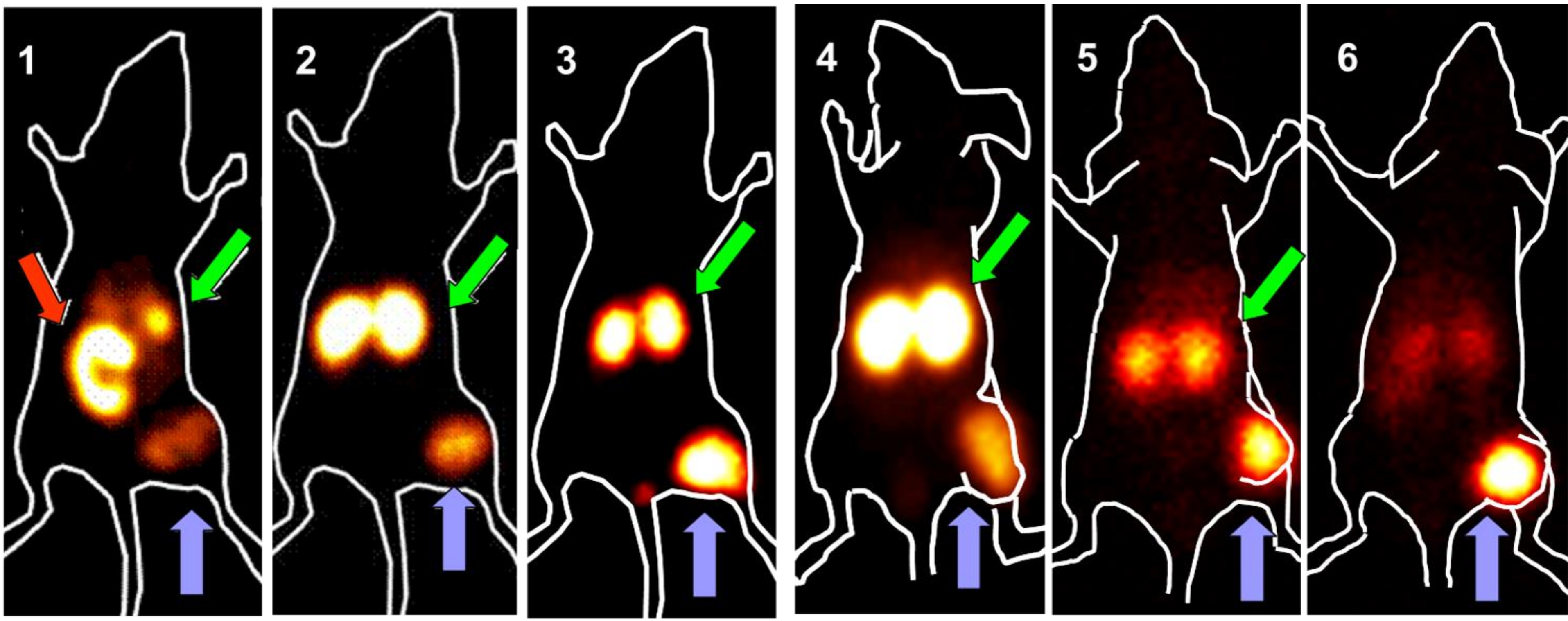

maGGG-Z | maEEE-Z | maESE-Z | Z-KVDC | Z-GSEC | Z-GGGC

tumor

caecum

kidneys

1. Engfeldt et al., Eur J Nucl Med 2007, 34:722;
2. Tran et al., Bioconjugate Chem, 2007, 18:1956;
3. Ekblad et al., Eur J Nucl Med, 2008, 35:2245;
4. Ahlgren et al. J Nucl Med. 2009, 50:781;

5-6. Wållberg et al. J Nucl Med 2011;52:461.

2. Pretargeting strategy

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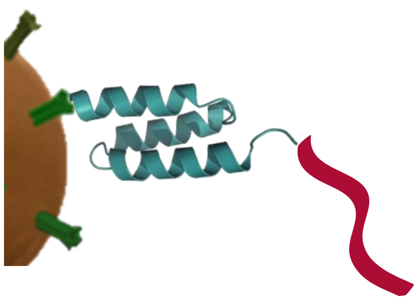
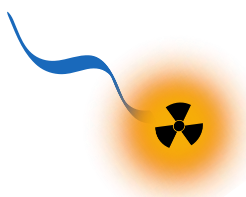
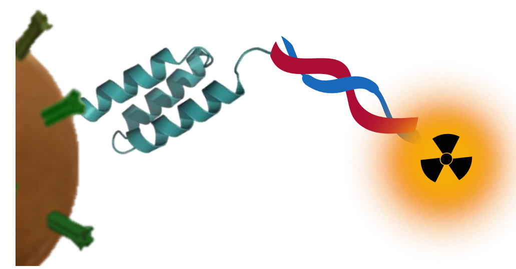


Primary agent
bound to cancer cell



Radiolabeled
secondary agent



Complex formed after
hybridization

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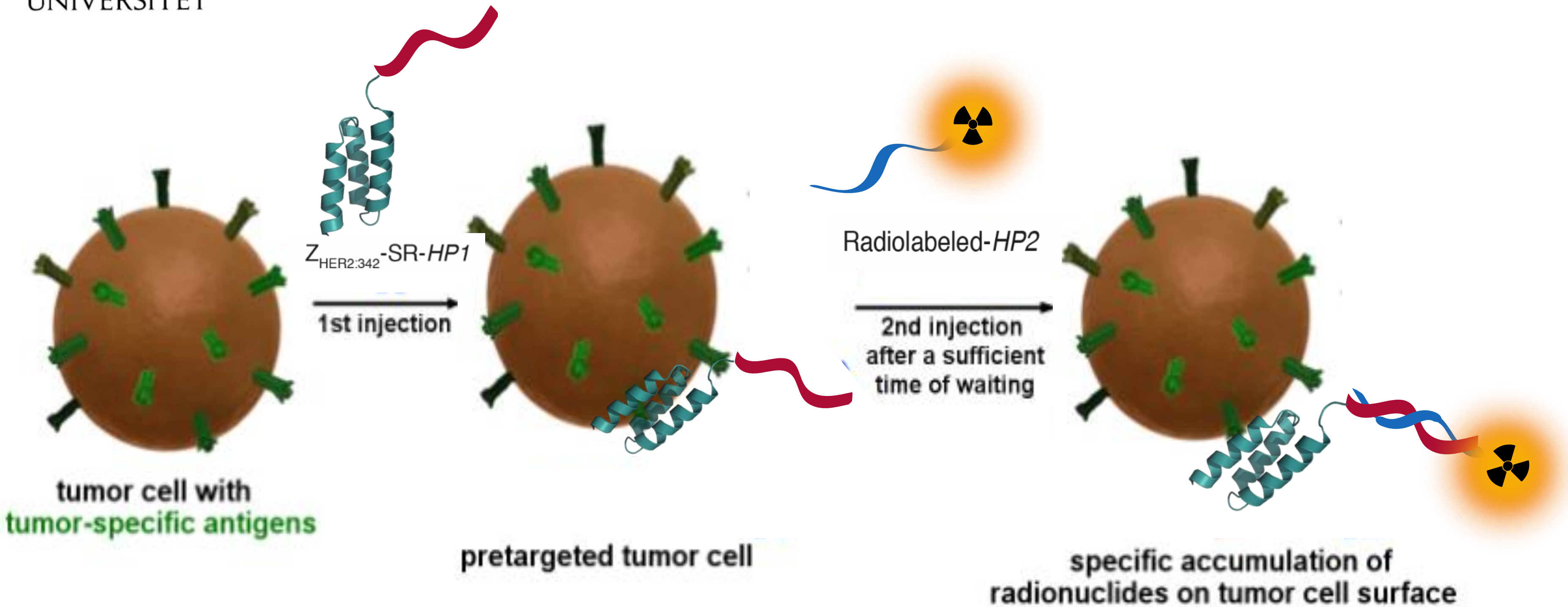
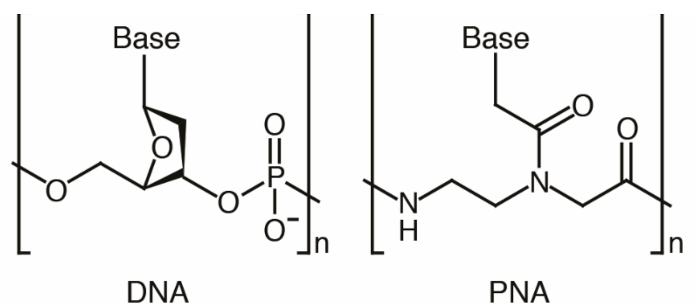
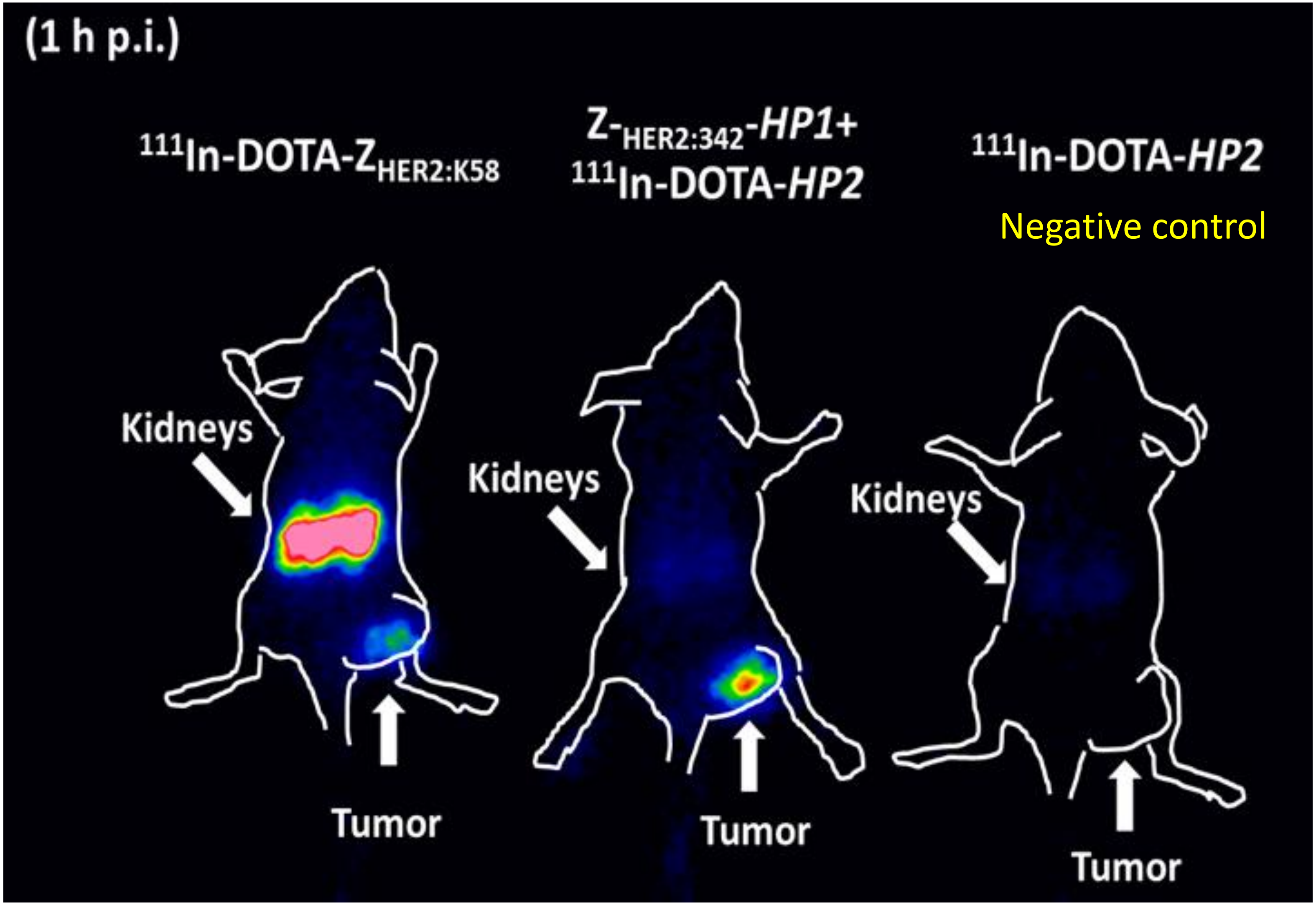
Affibody-based PNA-mediated pretargeting





Westerlund et al. Bioconjug Chem. 2015; Honarvar et al. Theranostics. 2016.

Gamma-camera imaging of mice bearing HER2-expessing SKOV-3 xenografts at 1 h after injection of ^{111}In-labelled agents



Radionuclide Therapy of HER2+ Xenografts Using Affibody-Based PNA Pretargeting

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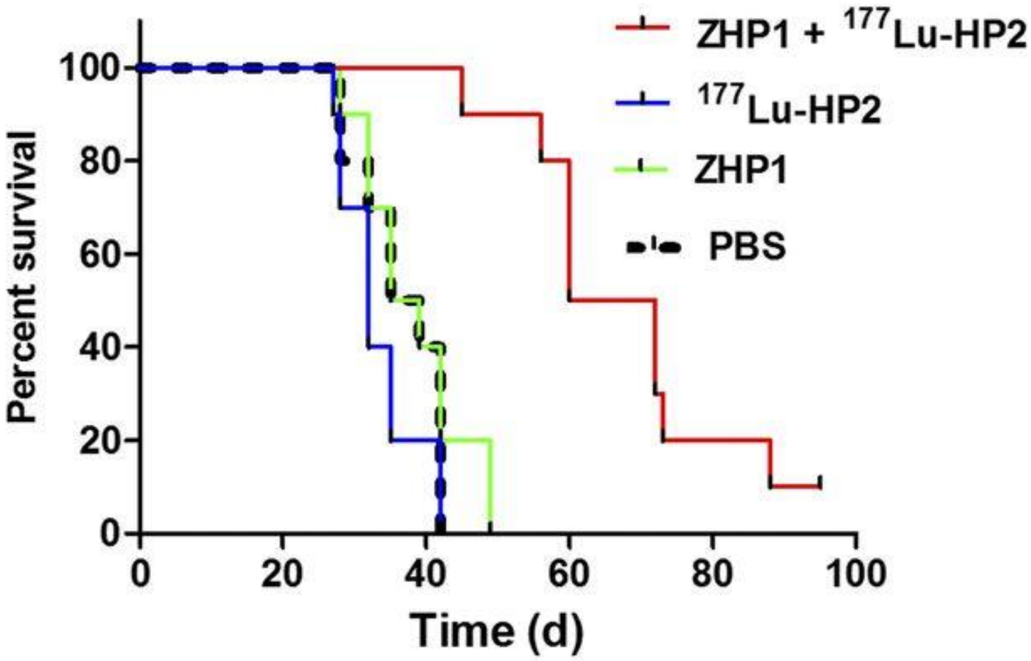

6 cycles of radionuclide therapy with ^{177}Lu-HP2 doubled median survival of mice (66 d. vs 37 d.)

Westerlund, Altai et al. J Nucl Med. 2018 Jul;59(7):1092-1098. doi: 10.2967/jnumed.118.208348.

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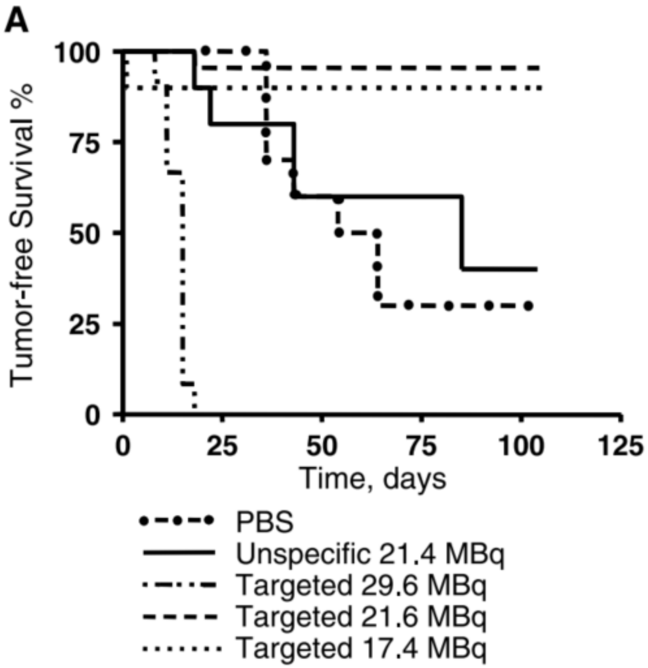
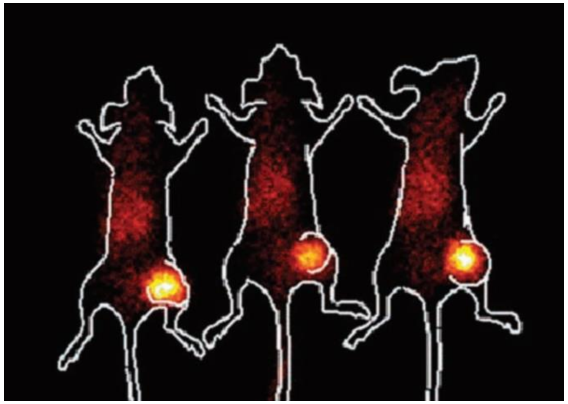
3. Preventing excretion of affibody via kidneys by fusing it with an albumin binder





Radionuclide therapy with ^{177}Lu-affibody-ABD completely prevented the formation of tumors in mice

Tolmachev et al. Cancer Res. 2007; 67(6):2773–82.
Orlova et al. J. Nucl. Med. 2013; 54: 961–968