Targeted Radionuclide Therapy - What are the issues?

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QuickTime™ and a
H.264 decompressor
are needed to see this picture.

Targeted Radionuclide Therapy

The principle aim is to increase the radiation dose to the target (tumour) relative to non-target tissues

Targeted radiotherapy - considerations

- Choice of radionuclide
- Target selection
- Vector Design
- Delivery system
- Radiobiology
- Clinical applications

Choice of Radionuclide

- Physical decay characteristics
  - Mode of decay, half life
- Availability
  - Reliability, scale, cost
- Radiolabelling chemistry
  - Simplicity, stability, pharmacokinetics

Radiolabelling Chemistry

Three main categories

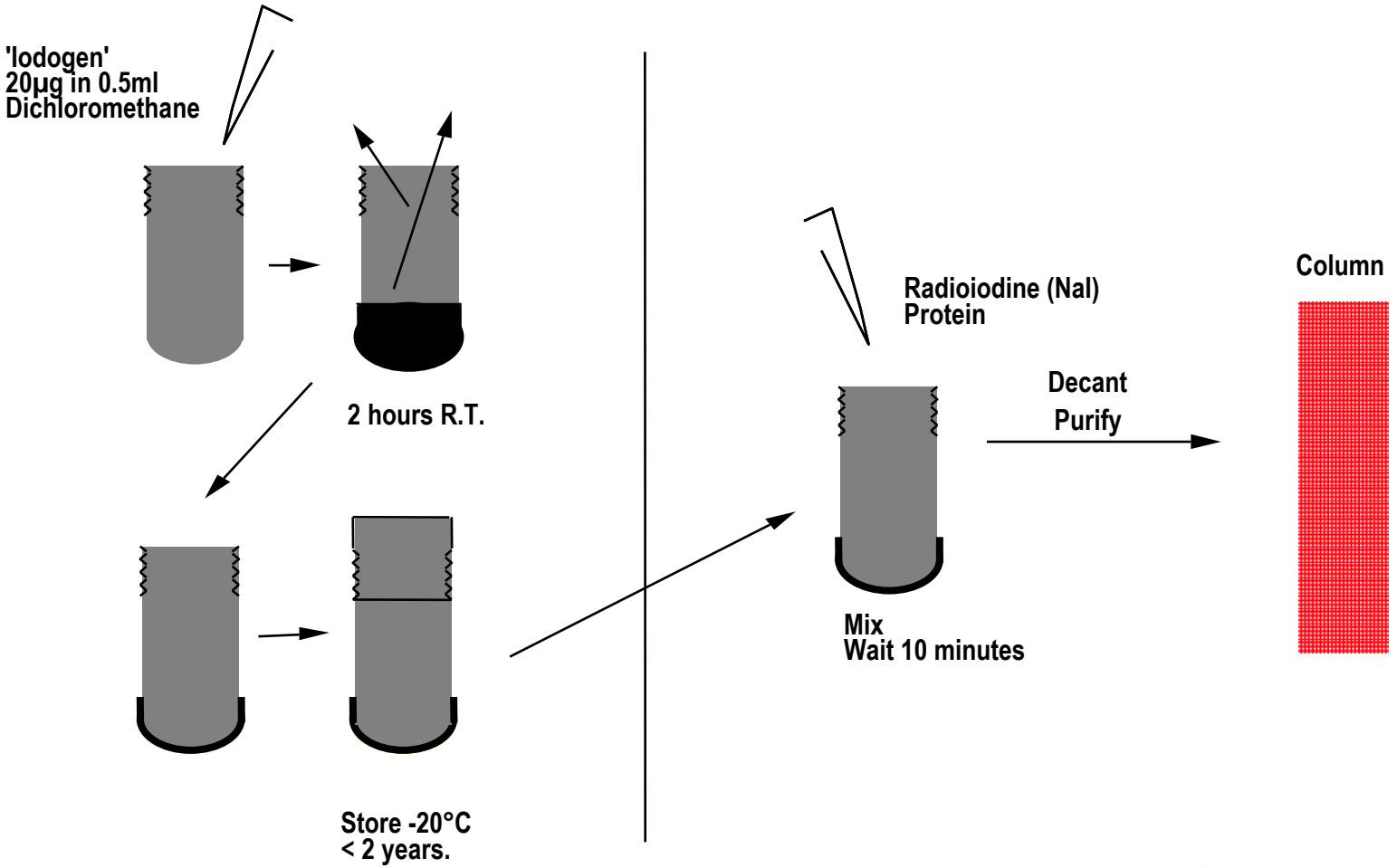
- Halogens -
  Iodine, Astatine
- Group VII elements -
  Technetium/Rhenium
- Trivalent metals -
  Indium, Yttrium, Bismuth

RADIONUCLIDES - THERAPY

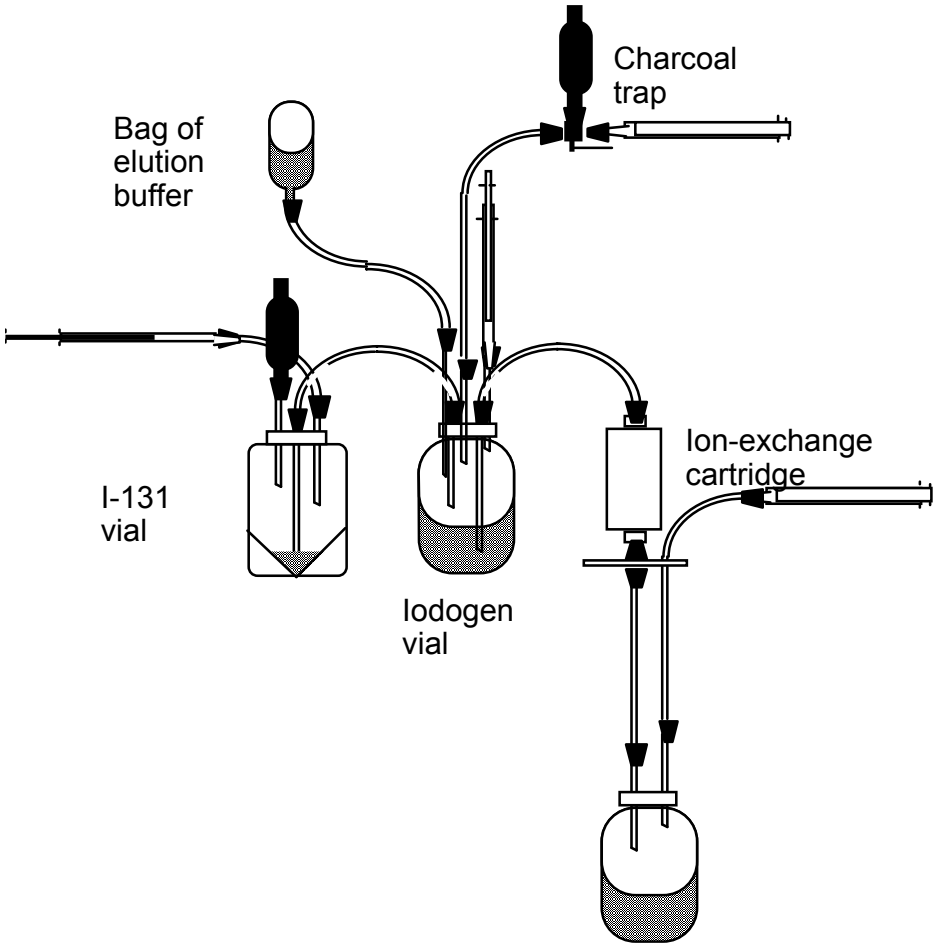
Radionuclide	Type of decay	Energy (MeV) Eβmax	Eγ	Half-life
^{177}Lu	β^- γ	0.2-0.5	113(6)% 208(11%)	6.7 days
^{47}Sc	β^- γ	0.4-0.6	159(68)	82 hours
^{67}Cu	β^- γ	0.4-0.6	185(49)	62 hours
131_1	β^- γ	0.61(86%) 0.33(13%)	0.364(80%) 0.284(6%)	8.04 days
^{186}Re*	β^- γ	1.08	137(9)	89 hours
^{153}Sm*	β^- γ	0.6-0.8	100(28%)	1.9 days
^{32}P	β^-	1.71		14.3 days
^{90}Y	β^-	2.27		64 hours
^{188}Re	β^- γ	2.1	155(15)	17 hours
^{211}At	α	5.8 α)		7.2 hours
^{213}Bi	β^- γ	0.2-0.4 6-8 α)	440(25)	45 mins

* Not carrier free

Iodogen-diagnostic



Iodogen - therapeutic



Target selection

- Location of target - cell surface
- Density of expression - high
- Tissue Distribution - specific to disease
- Internalisation
  - Yes (?)
  - Nuclear trafficking

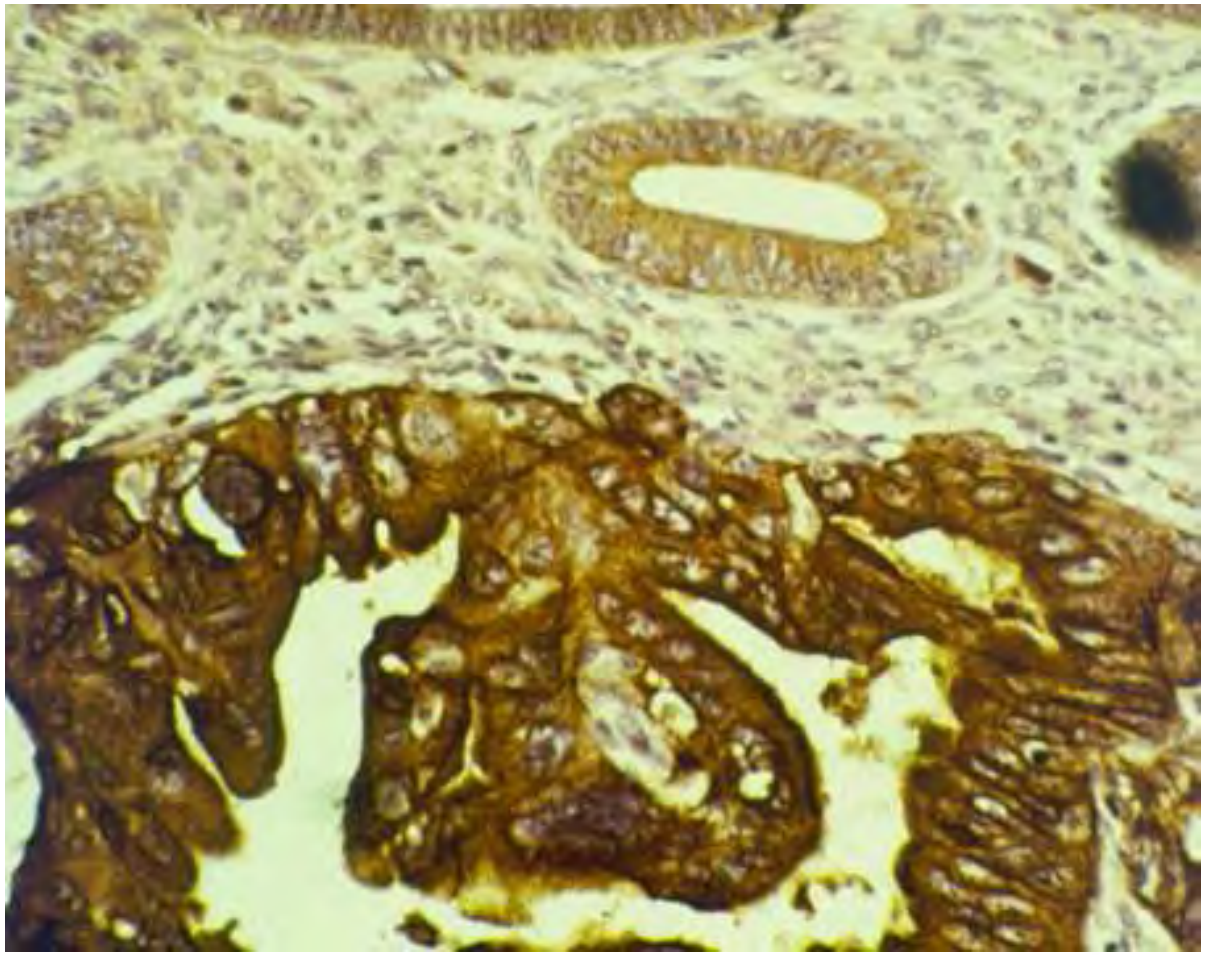
Potential targets

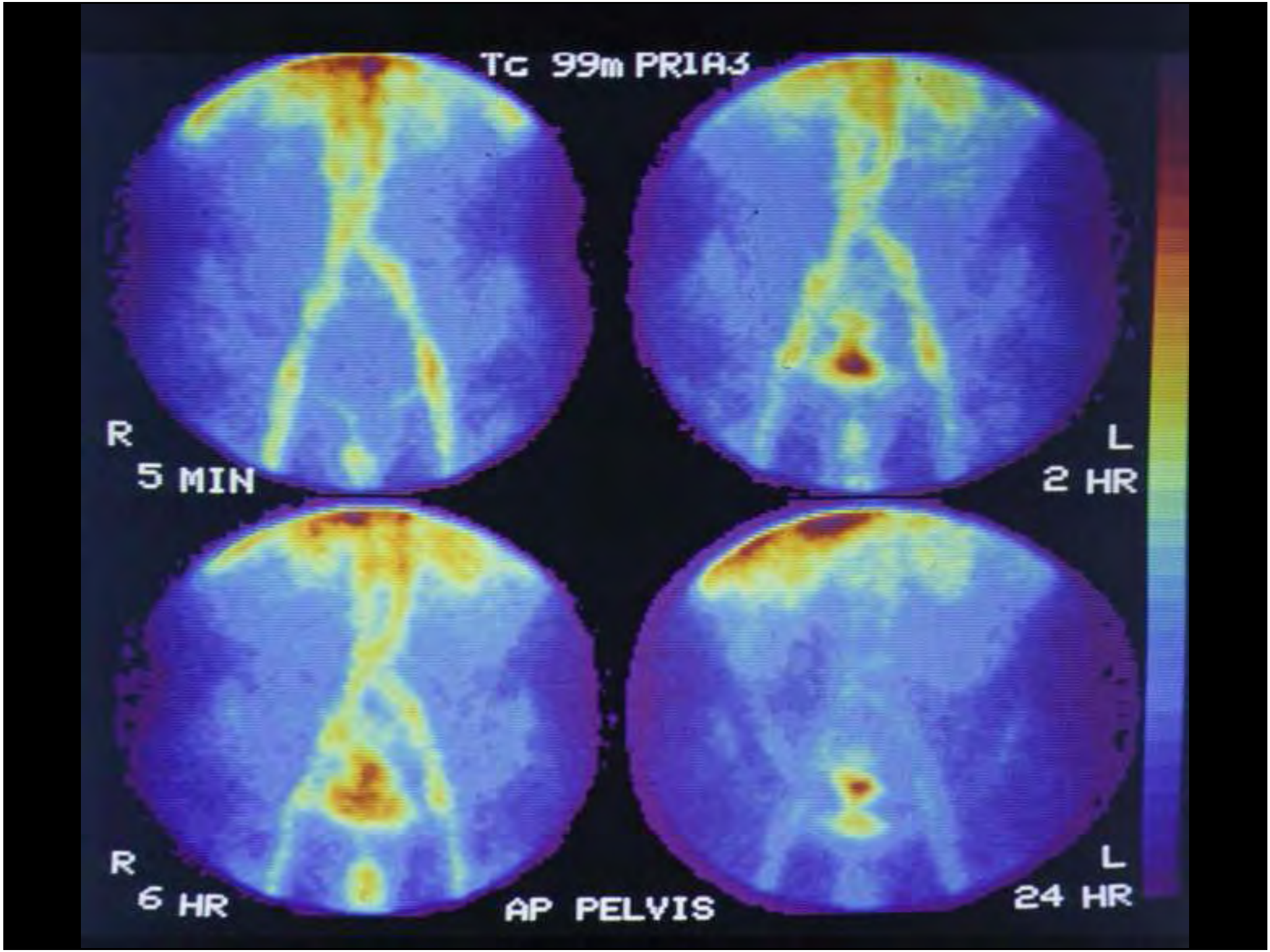
- Growth factor receptors
- Neuropeptide hormone receptors
- Cytokine receptors
- Transporters
- Integrins
- Differentiation markers
- Oncofoetal antigens

Vectors

- Antibodies
- Peptides
- Small molecules (*m*-I(A)BG, chelates)
- *et al.*

HMFG1- Immunohistochemisty




Tc 99m PR1A3
R
5 MIN
L
2 HR
R
6 HR
AP PELVIS
L
24 HR

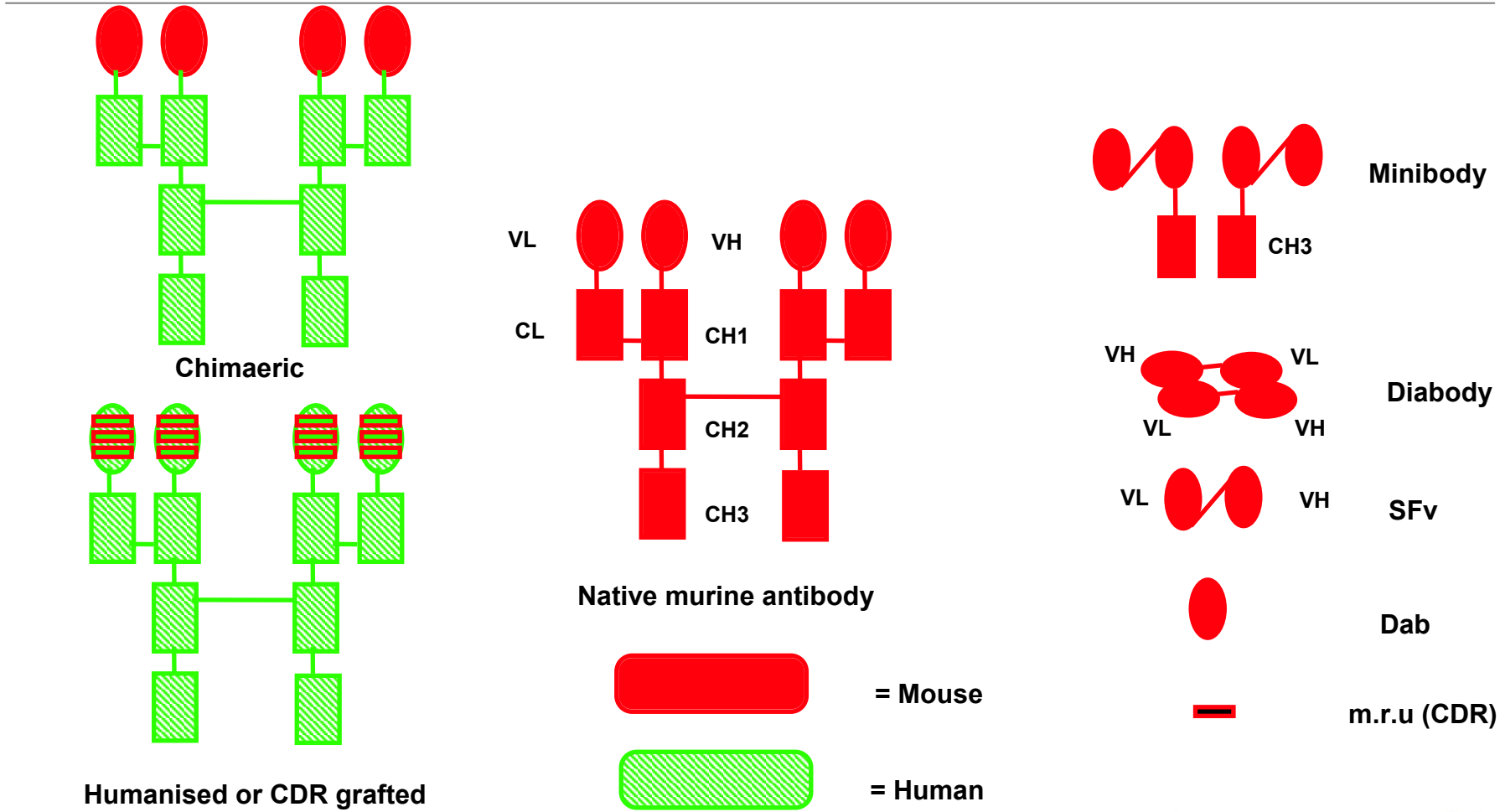
RIT-Problems with direct systemic approach

- Slow blood clearance (1-3 days)
- Low tumour uptake (0.001-0.01% per gram in solid tumours)
- High-non-target uptake (~ 30% liver, kidney)
- Immunogenicity - HAMA

However

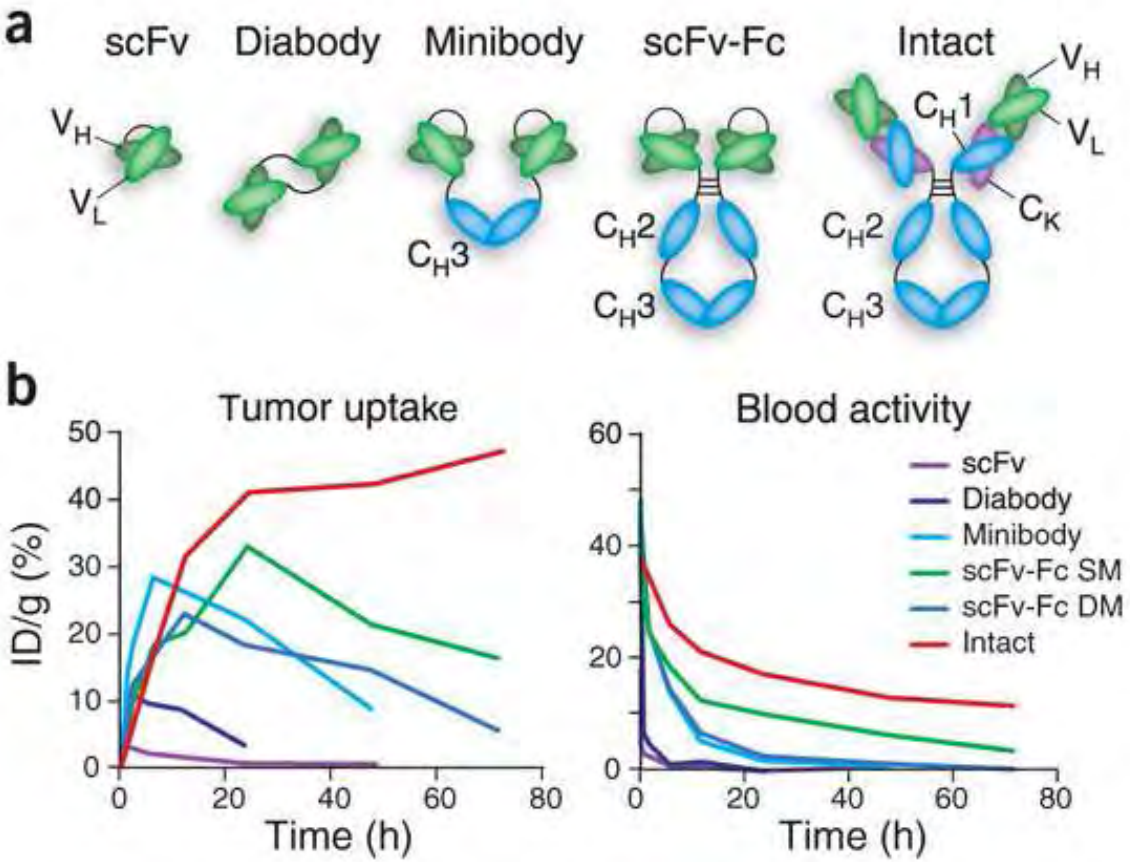
- There are exceptions!

Recombinant antibodies

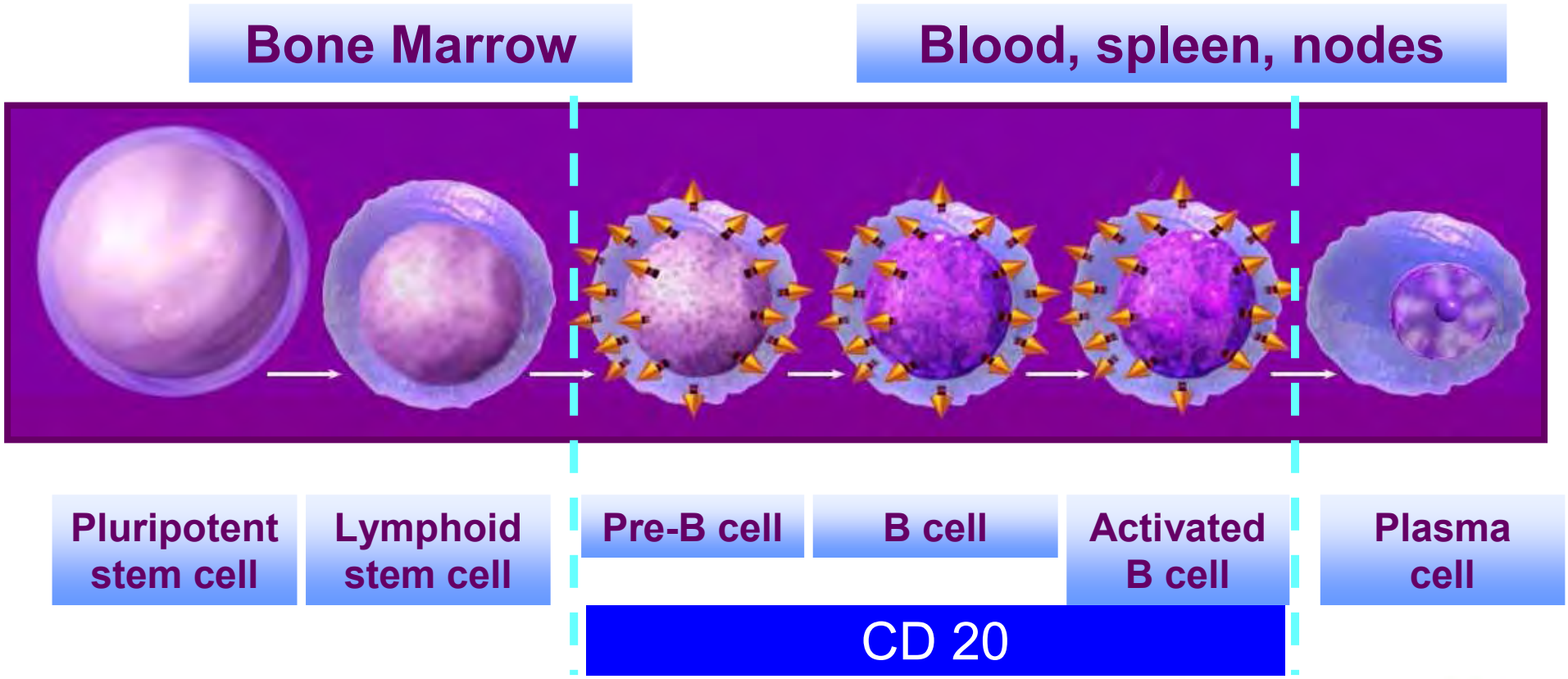


Antibody pharmacokinetics -

Wu AM and Senter PD Nature Biotech 23, 1137 - 1146 (2005)



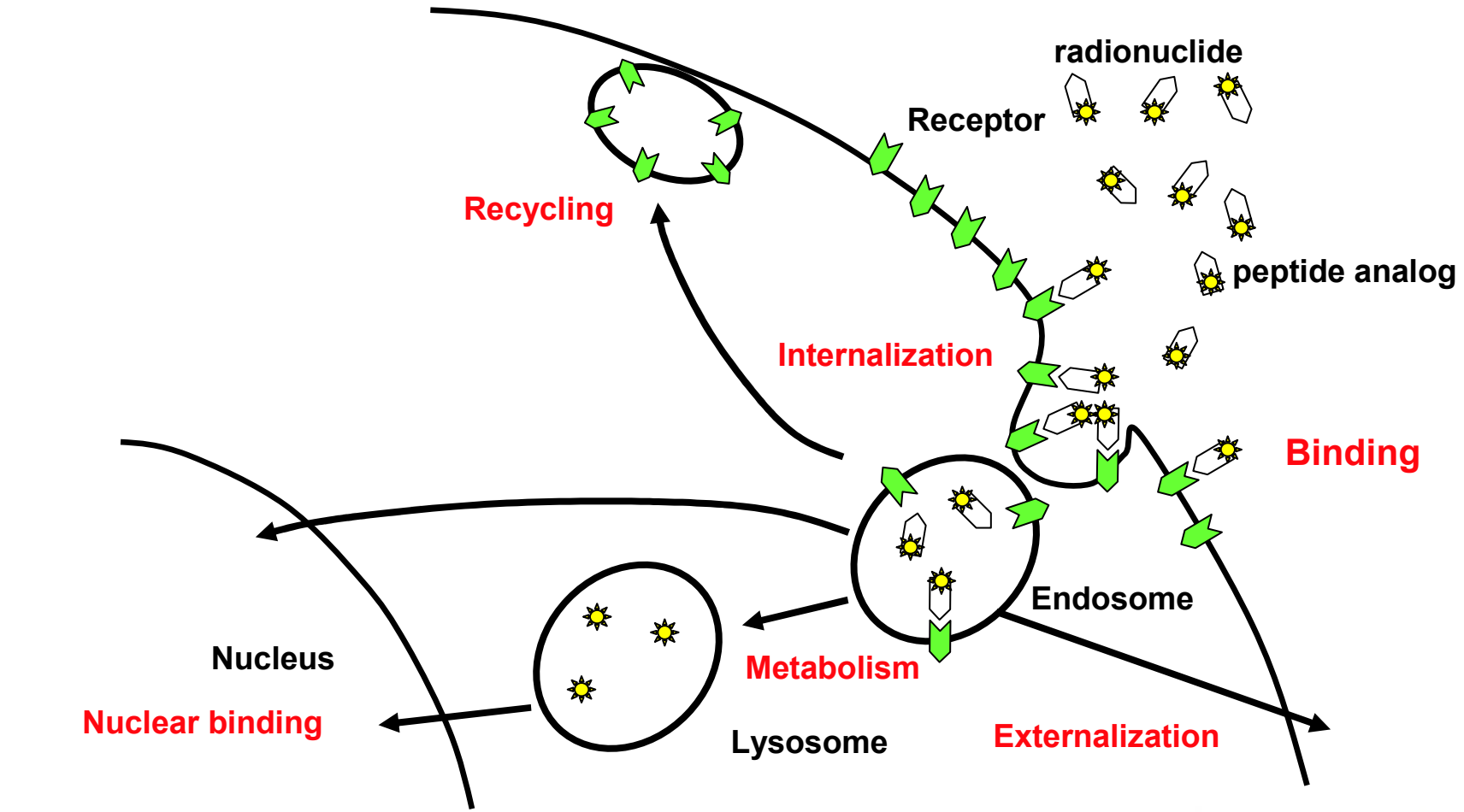
CD20 Expression



Tumour expression of neuropeptides

Peptide	Tumor type
Somatostatin	neuroendocrine tumors, non-Hodkgin lymphoma, melanoma, breast,
a-MSH	melanoma
LHRH	prostate, breast
VIP/PACAP	SCLC, colon, gastric, pancreatic
CCK-2/Gastrin	MTC, SCLC, pancreatic, astrocytoma, stromal ovarian cancer
Opioid	SCLC, neuroblastoma, breast
Neurotensin	SCLC, colon, exocrine pancreatic
Bombesin/GRP	SCLC, breast, colon, glioblastoma, prostate
Substance P	glioblastoma, astrocytoma, MTC, breast, intra- and peritumoral blood vessels

Uptake and cellular processing of peptide analogs



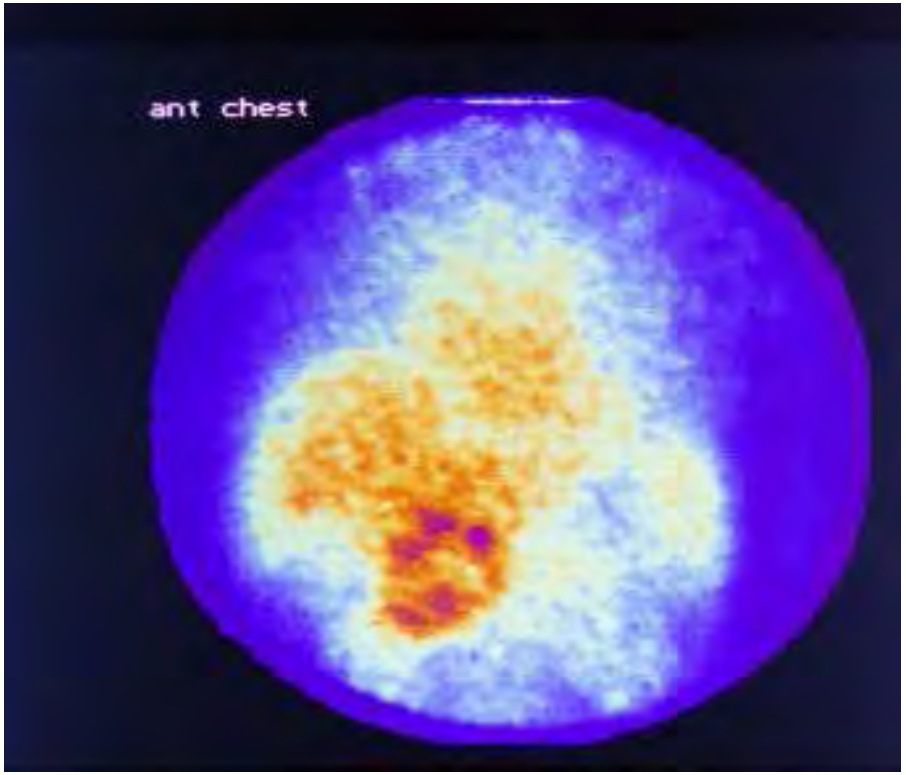
Radiolabelled somatostatin analogues

(D) Phe Thr(ol)

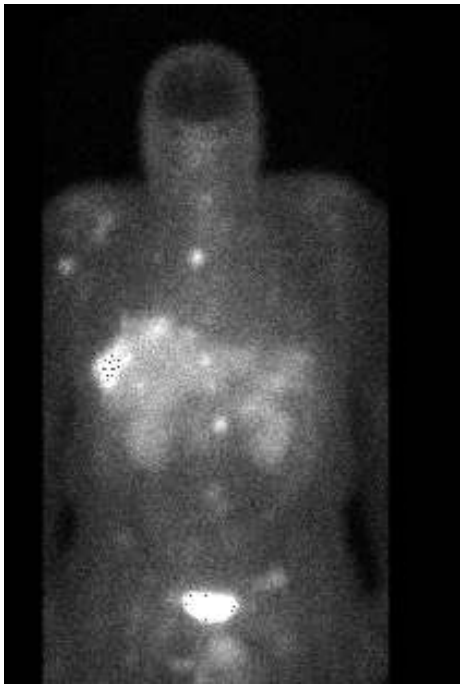
Cys ——— Cys

123-Iodine – Tyr - (D)Trp - Lys -Thr

123-I-Tyr-3 - Octreotide



Octreoscan



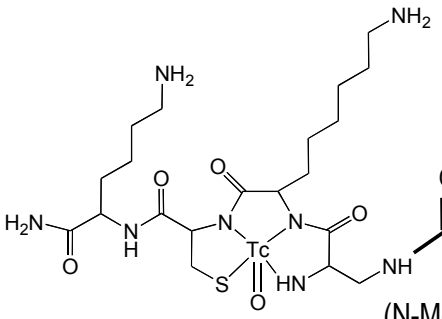
Indium-111- DTPA

(D) Phe — Thr(ol)

Cys — Cys

Phe - (D)Trp - Lys -Thr

Neospect



(N-Me) Phe — Hcy

Tyr - (D)Trp - Lys - Val

Antibodies vs Peptides

ANTIBODIES	PEPTIDES
Large	Small
Immunogenic	Non-immunogenic
‘Biologicals’	Synthetic
Expensive	‘Inexpensive’
Non-toxic	Pharmacological
Stable	‘Unstable’

Delivery systems

- Direct systemic
- Loco-regional
- Indirect (pretargeted)

Locoregional Therapy
of glioblastoma

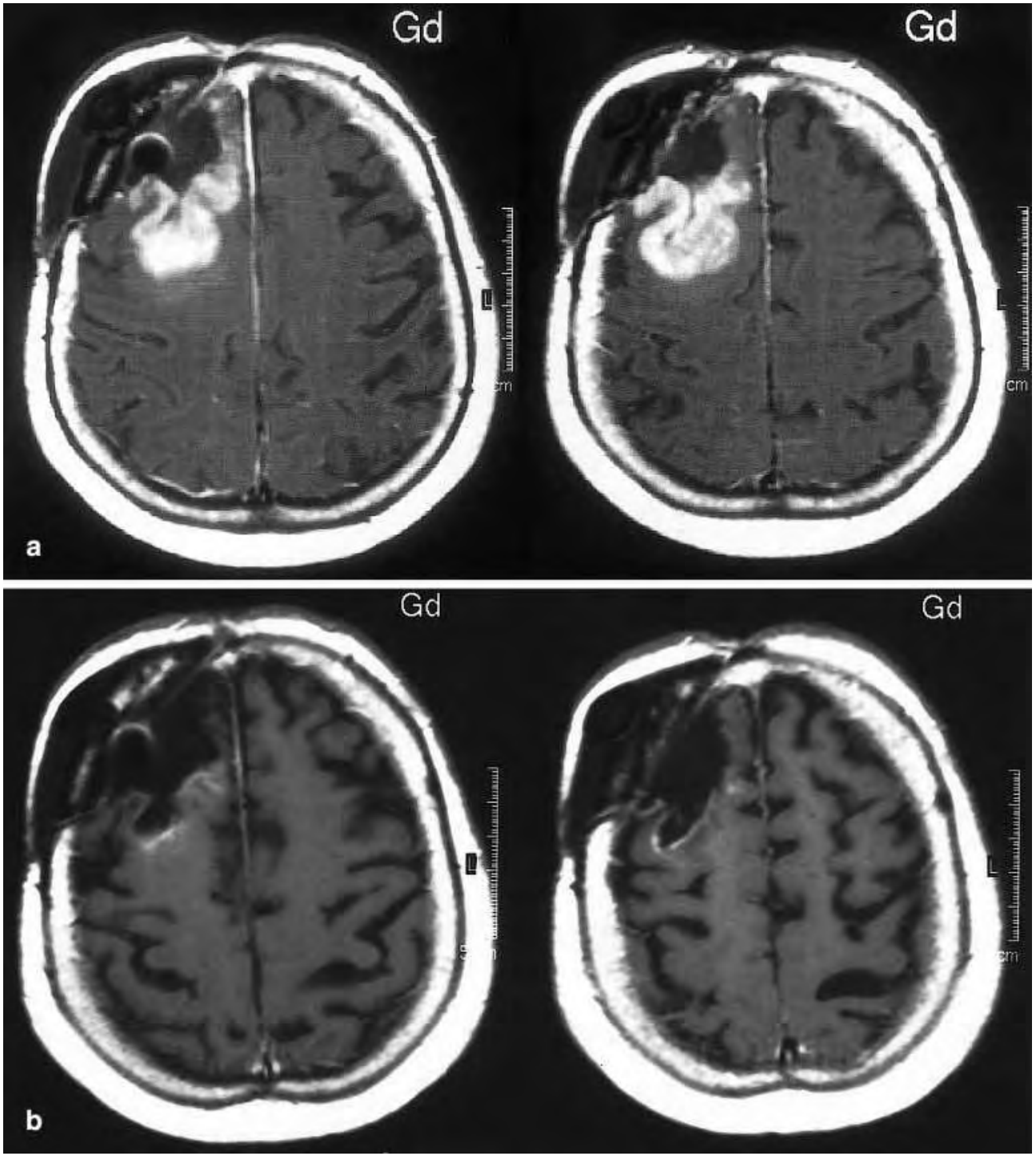
Before

And

After

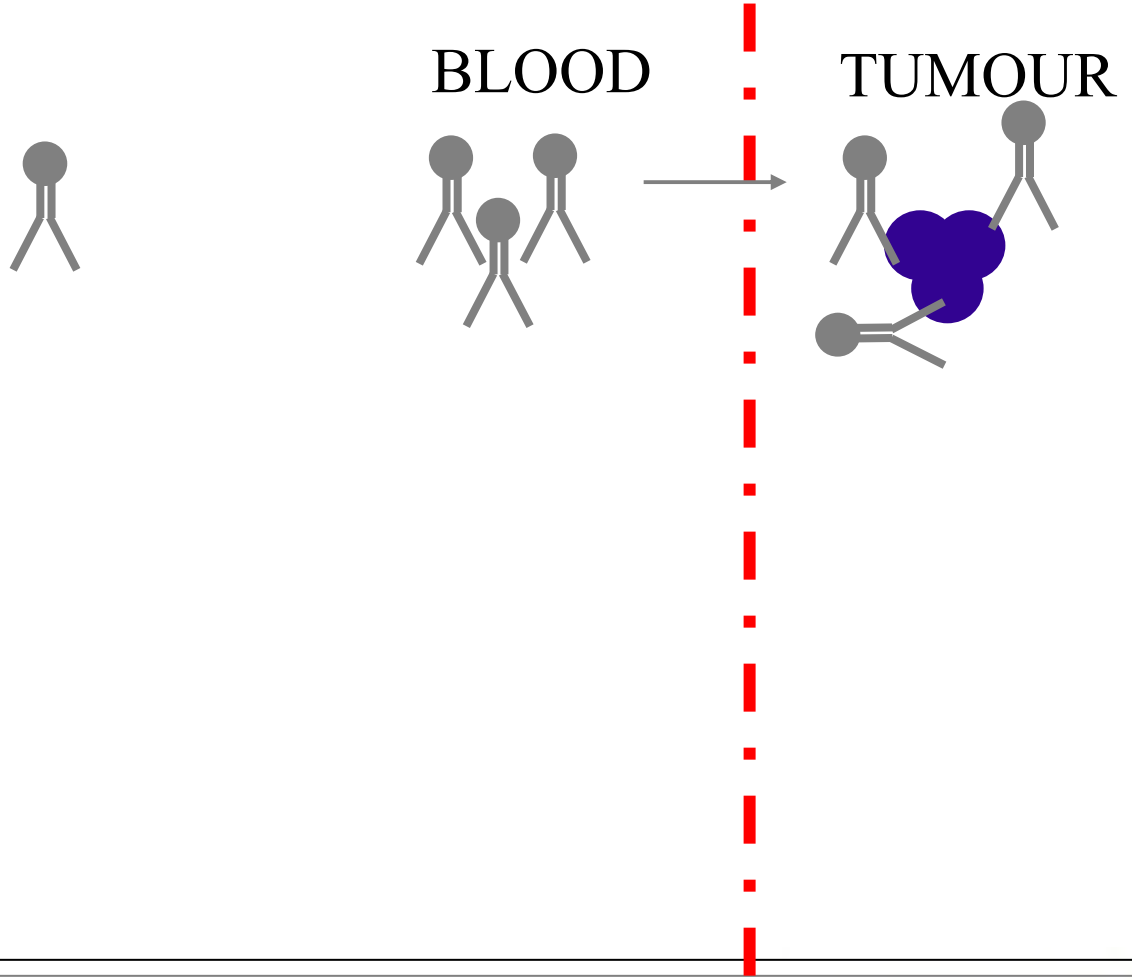
4x 25mCy Y-90
labelled antibody

From Riva et al
EJNM 2000 27:601



Antibody Pre-targeting

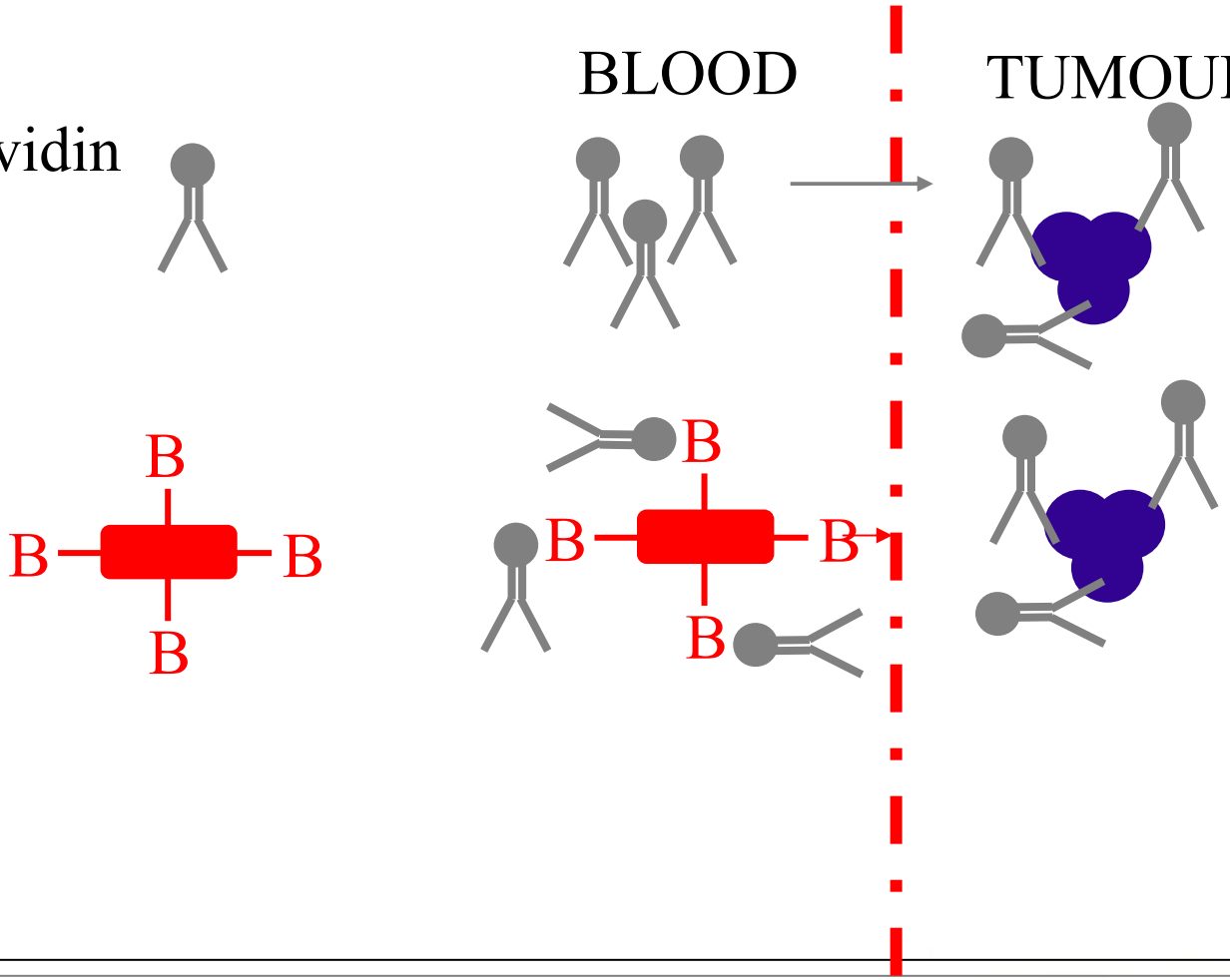
Step 1:
Antibody-streptavidin



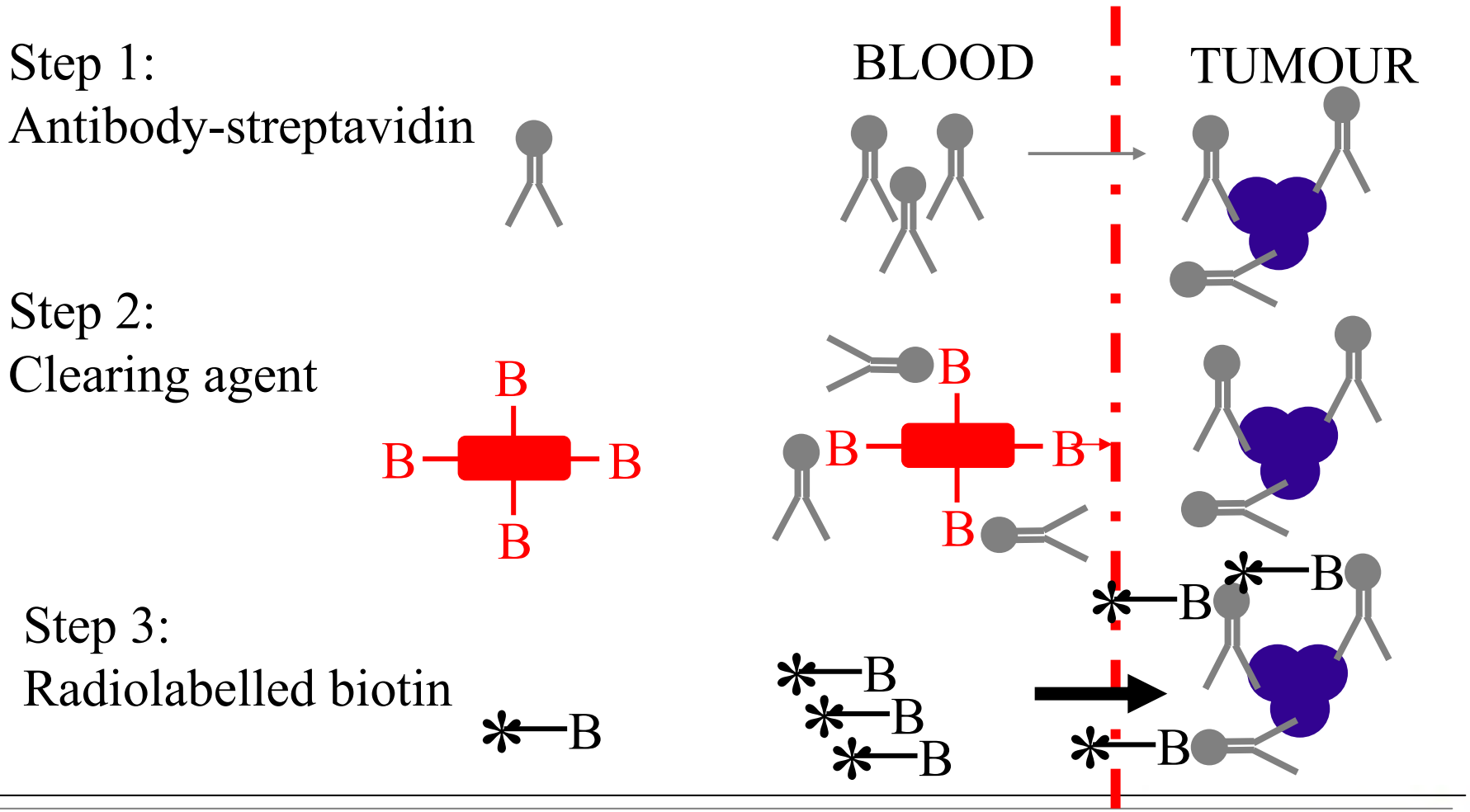
Antibody Pre-targeting

Step 1:
Antibody-streptavidin

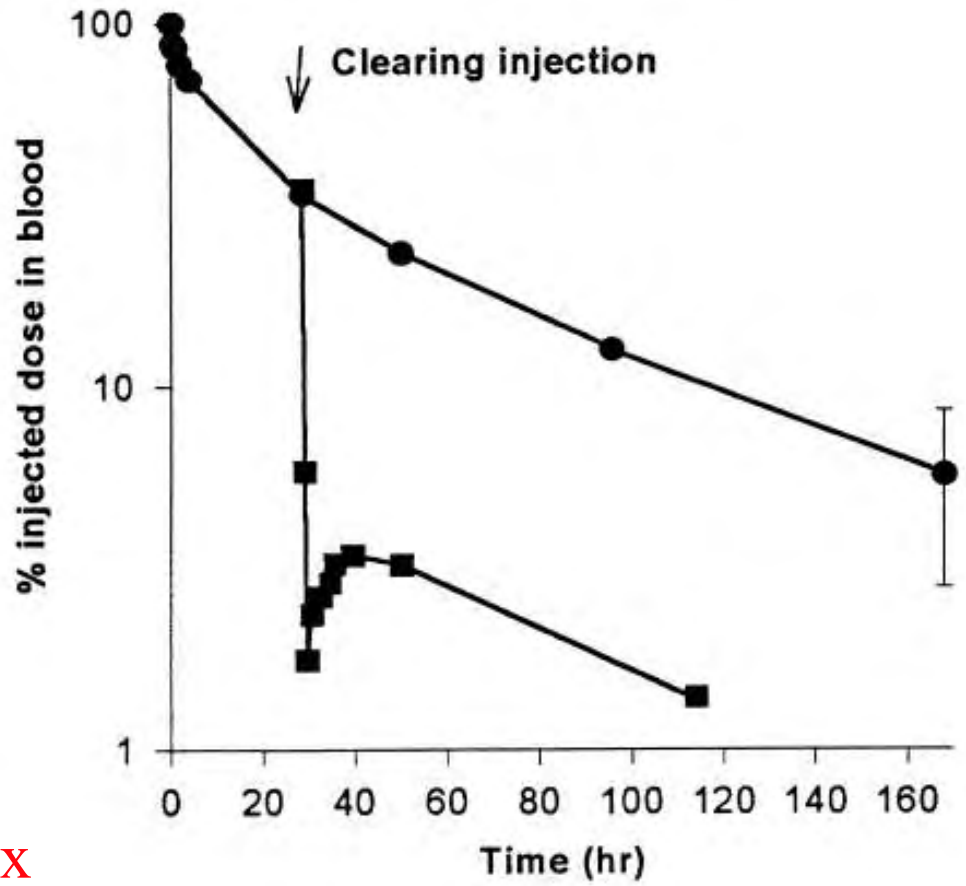
Step 2:
Clearing agent



Antibody Pre-targeting

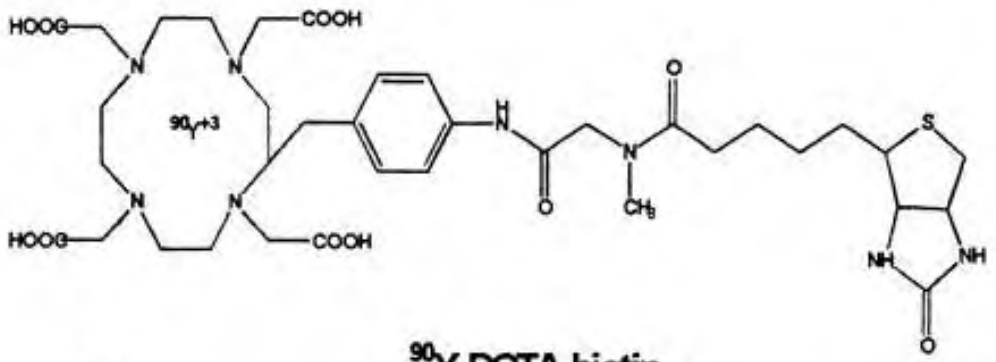


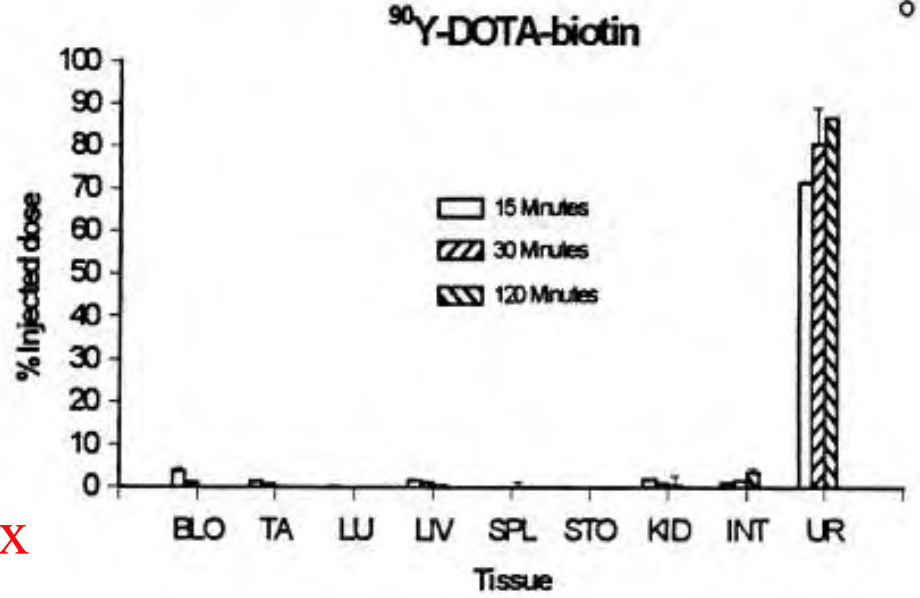
Effect of clearing agent on antibody blood clearance



Courtesy NeoRx

Biodistribution of non-pretargeted DOTA-Biotin.

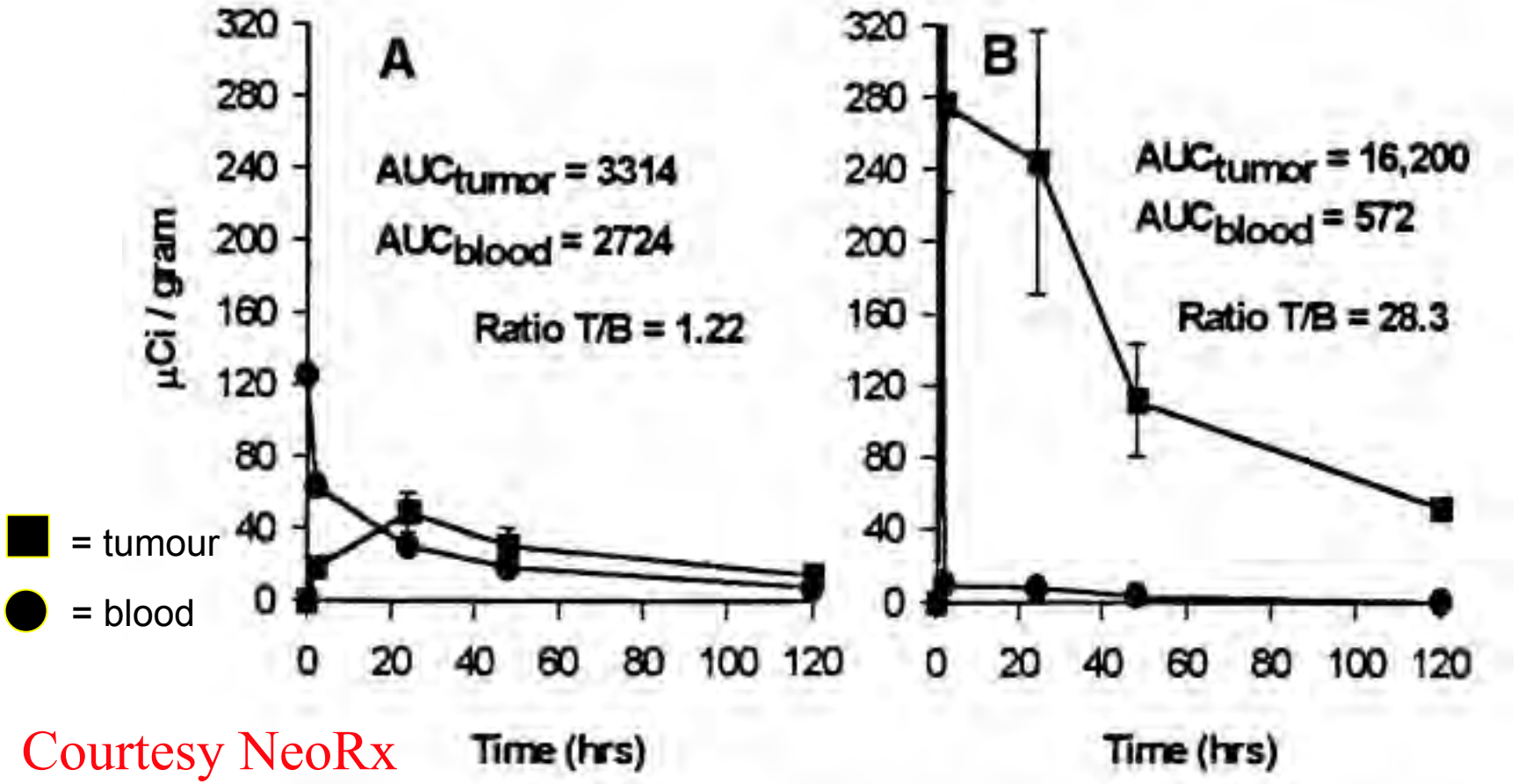




Courtesy NeoRx

200µCi Non-pretargeted 90-Y Labeled antibody

800µCi Pretargeted 90-Y Labeled DOTA-Biotin



Courtesy NeoRx

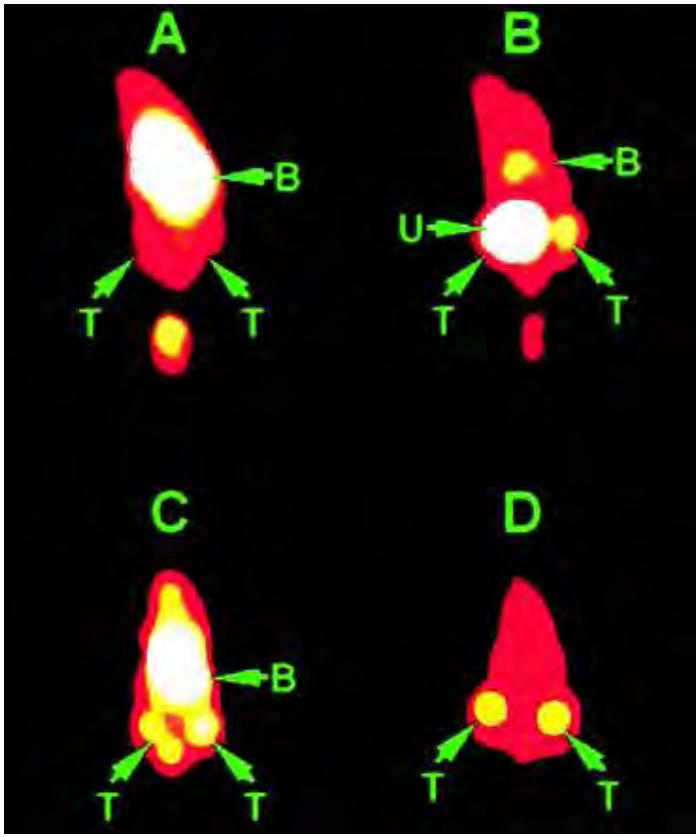
Pre-targeting of anti-CD20 antibodies

A, C = directly labelled antibody

2 hrs

B, D = pre-targeted antibody

24 hrs



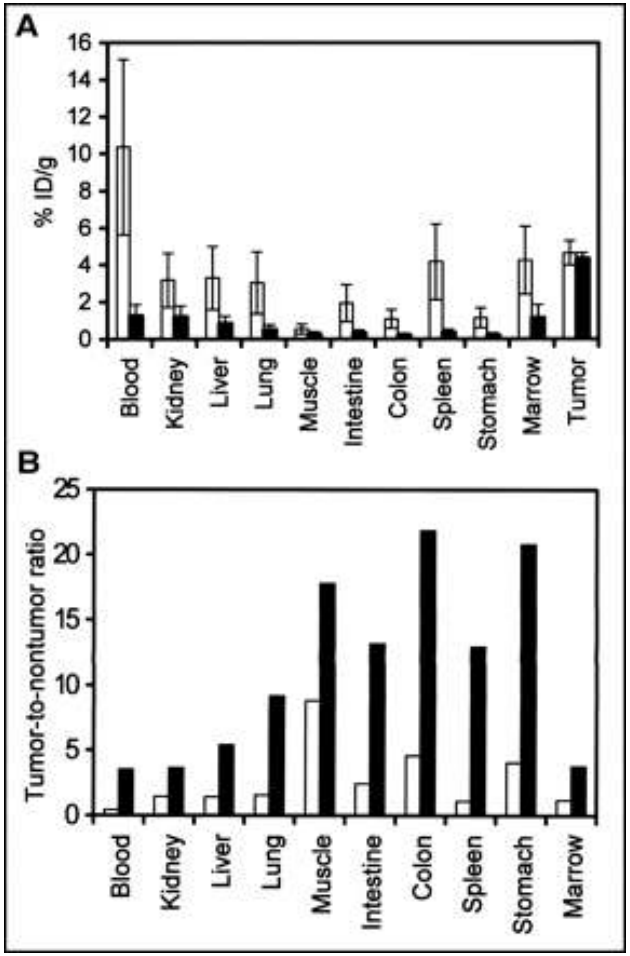
Krishnan Subbiah et al
J Nucl Med (2003) 44: 437-445

Pre-targeting of anti-CD20 antibodies

Directly labelled antibody

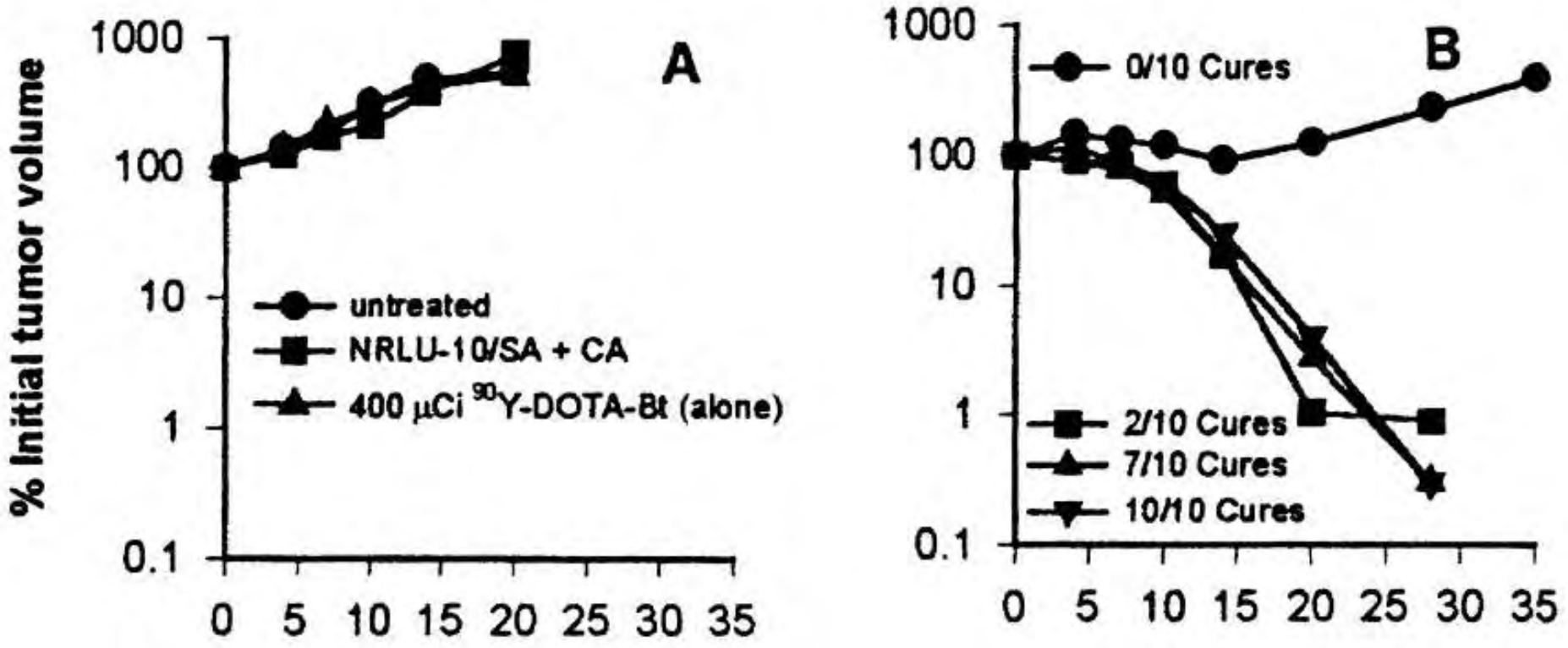
Pre-targeted antibody

Data 24 hours after injection of radioactivity



Krishnan Subbiah et al
J Nucl Med (2003) 44: 437-445

Pre-targeted therapy of SCLC xenografts with ●200µCi 90-Y antibody, ■200, ▲600, ▼800µCi pre-targeted Y-90-DOTA Biotin



D.B.Axworthy PNAS(2000) 97:1802

Radiobiology

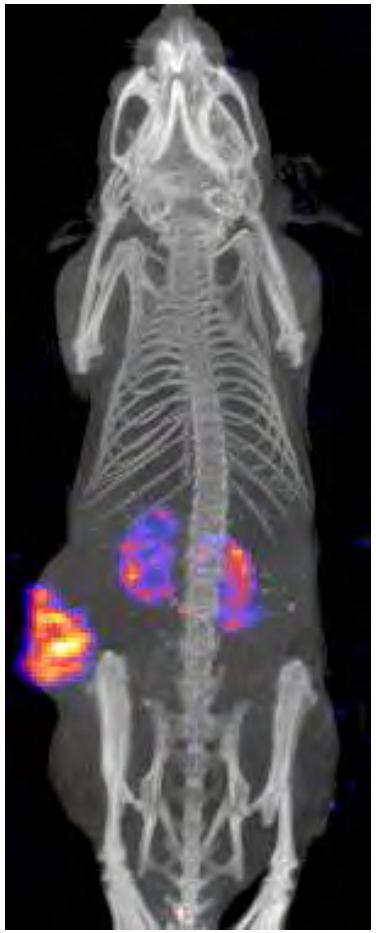
- Complex
- Largely unexplored
- Very important

Radiation doses in TRT

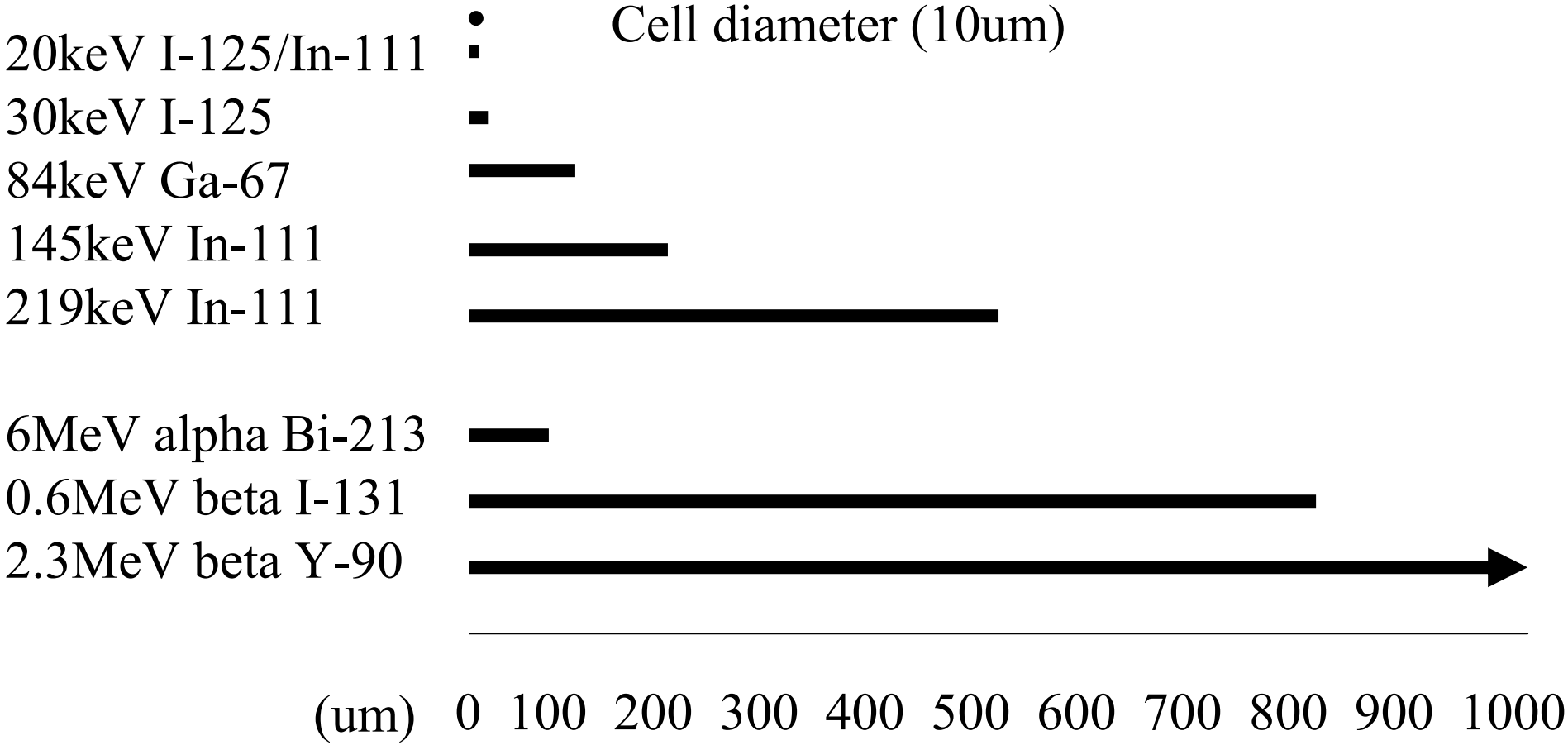
- Radioimmunotherapy ~ 10-20 Gy
- Radiopeptide therapy ~ 50-500 Gy
- Dose rates: Typically 2-20 Gy/day (0.1-1 Gy/hr)
- cf. External beam radiotherapy ~ 10-70 Gy in ~ 2 Gy fractions@100's Gy/hr.

Heterogeneity of dose distribution

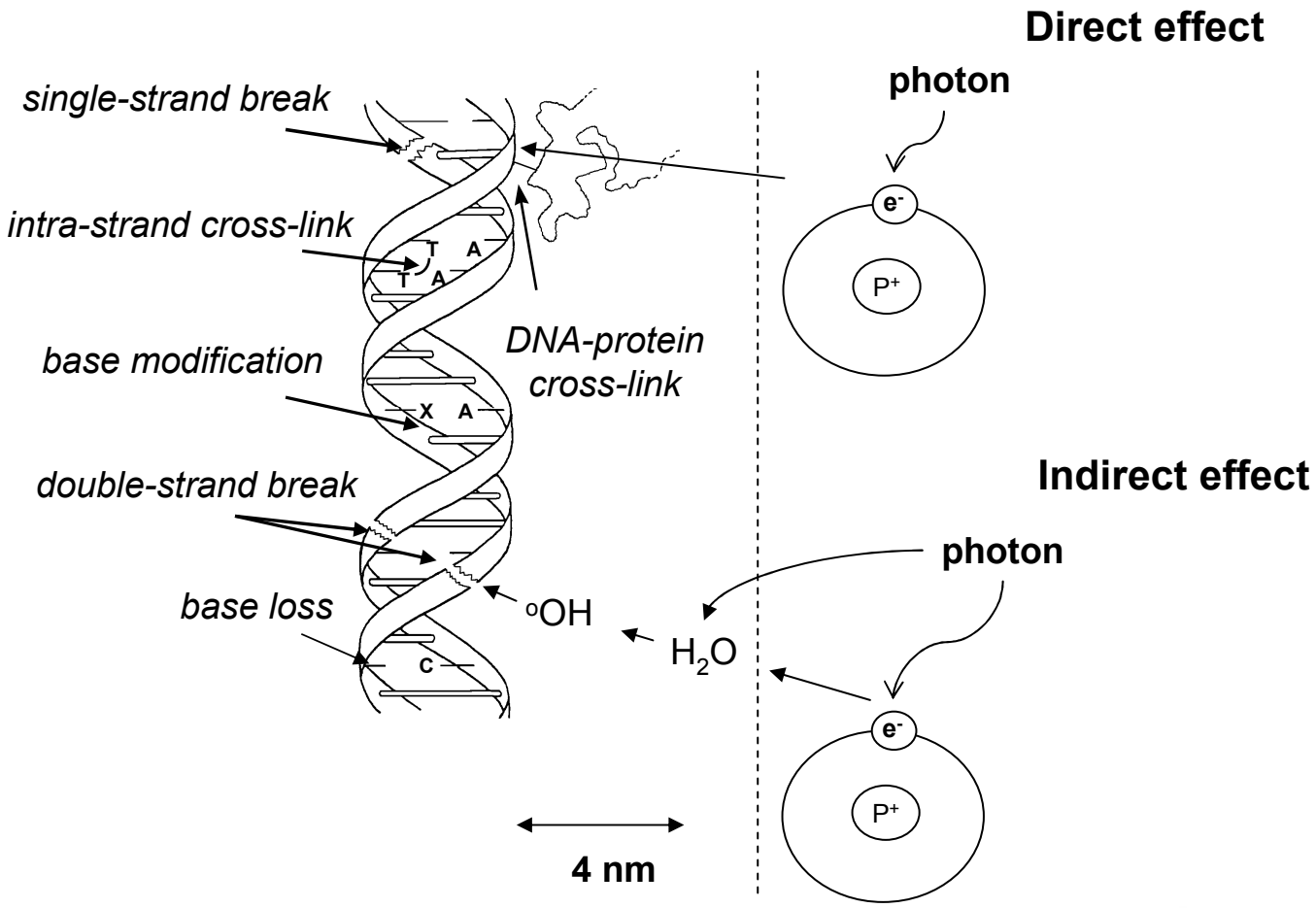
- Macro (tissue) level
- Micro (cellular) level



Tissue penetration of electrons/alphas/betas



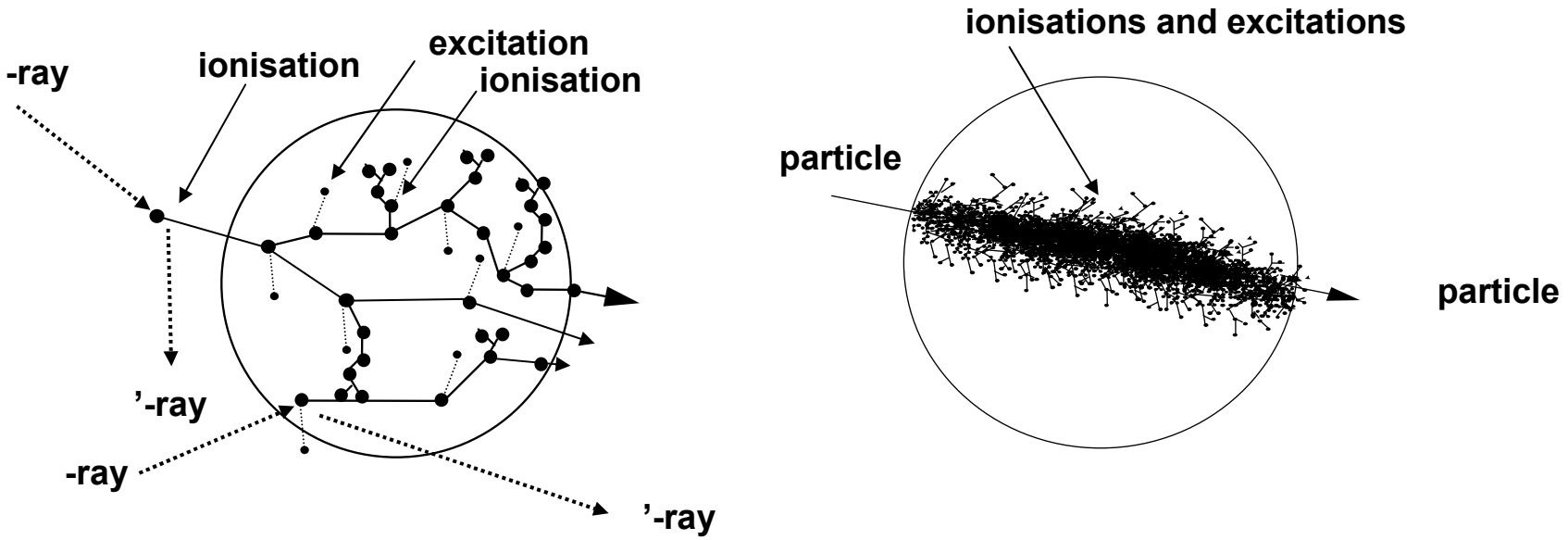
Radiation induced damage



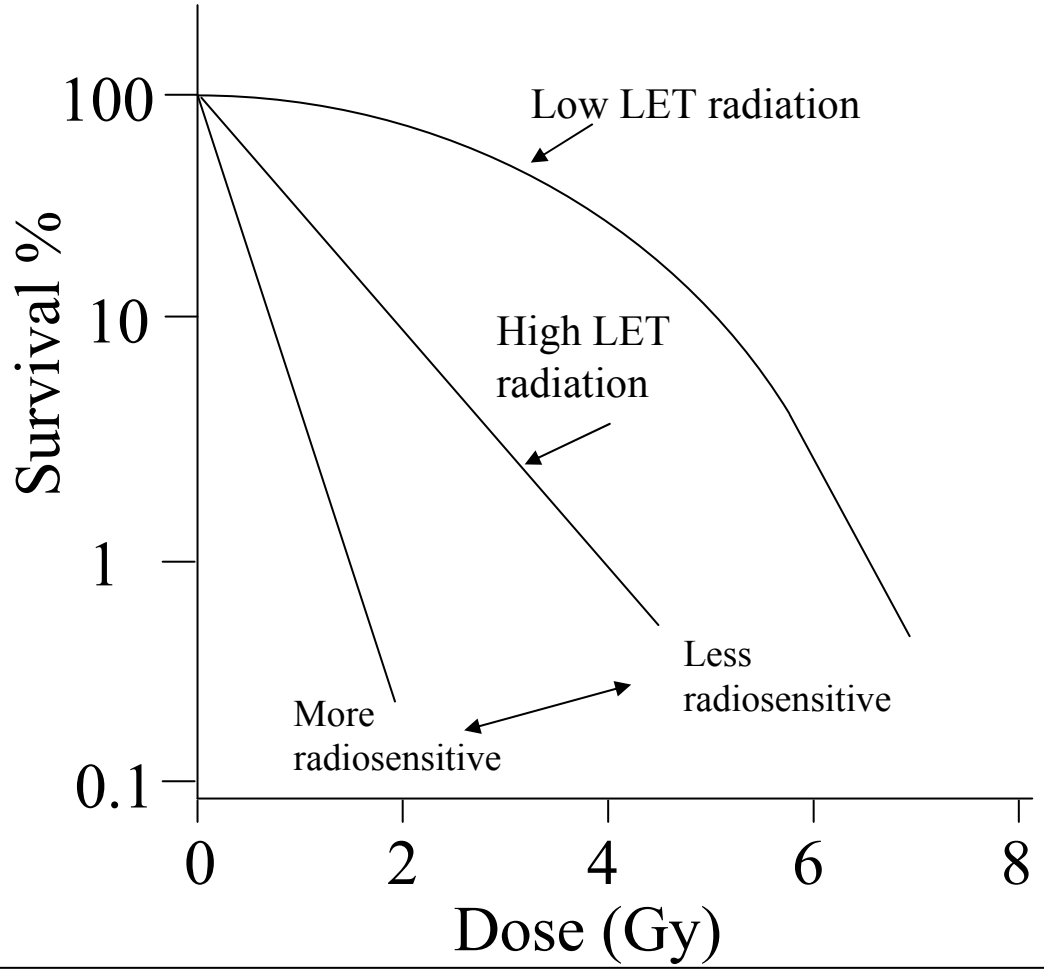
Alphas vs Betas

	Energy	Path-length (μm)	LET(KeV/μm
Y-90	2MeV	3960	0.2
At-211	6MeV	70	97

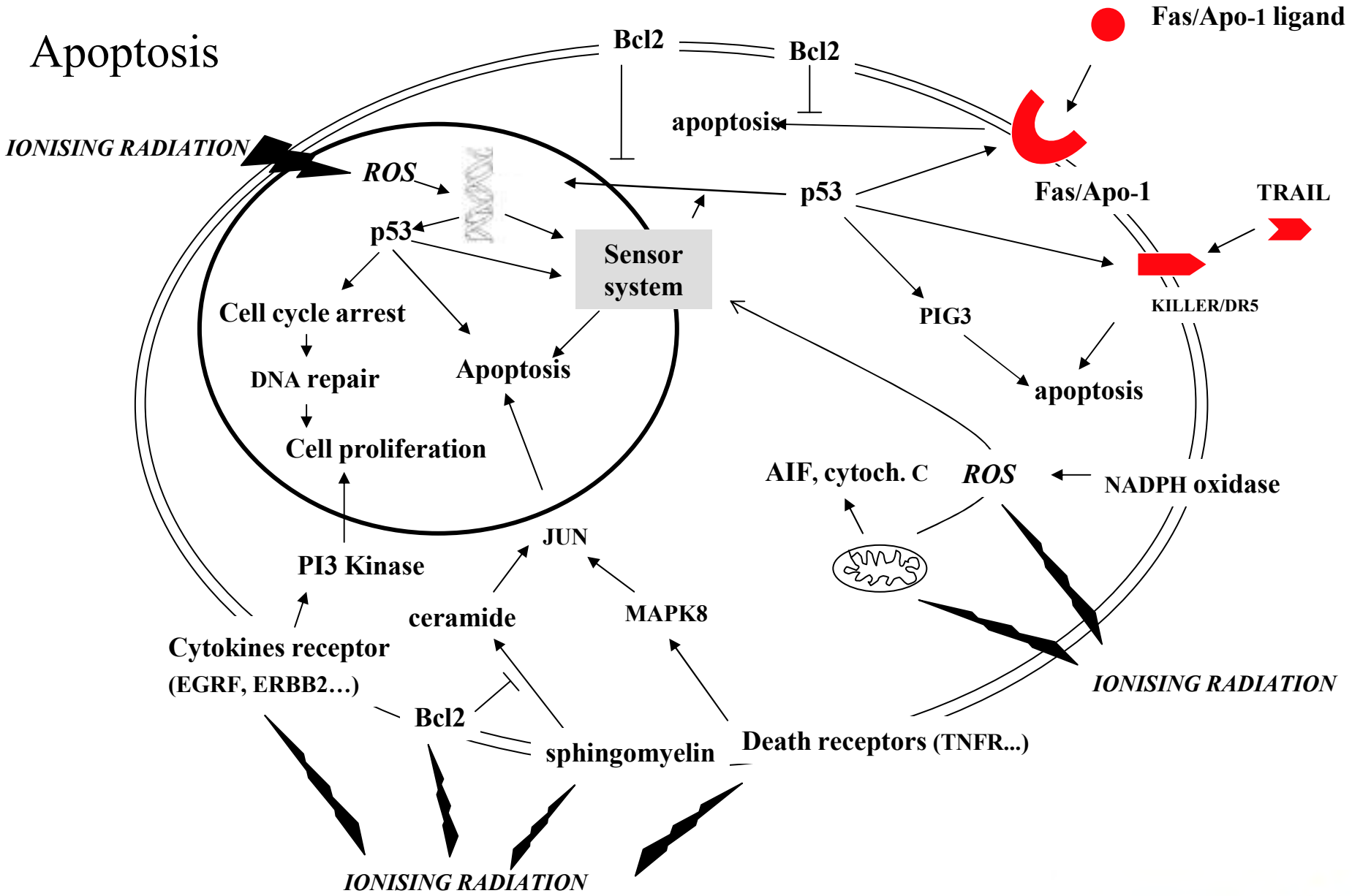
Low vs. High LET



The threshold effect



Apoptosis



Queen Mary University of London

CANCER RESEARCH UK

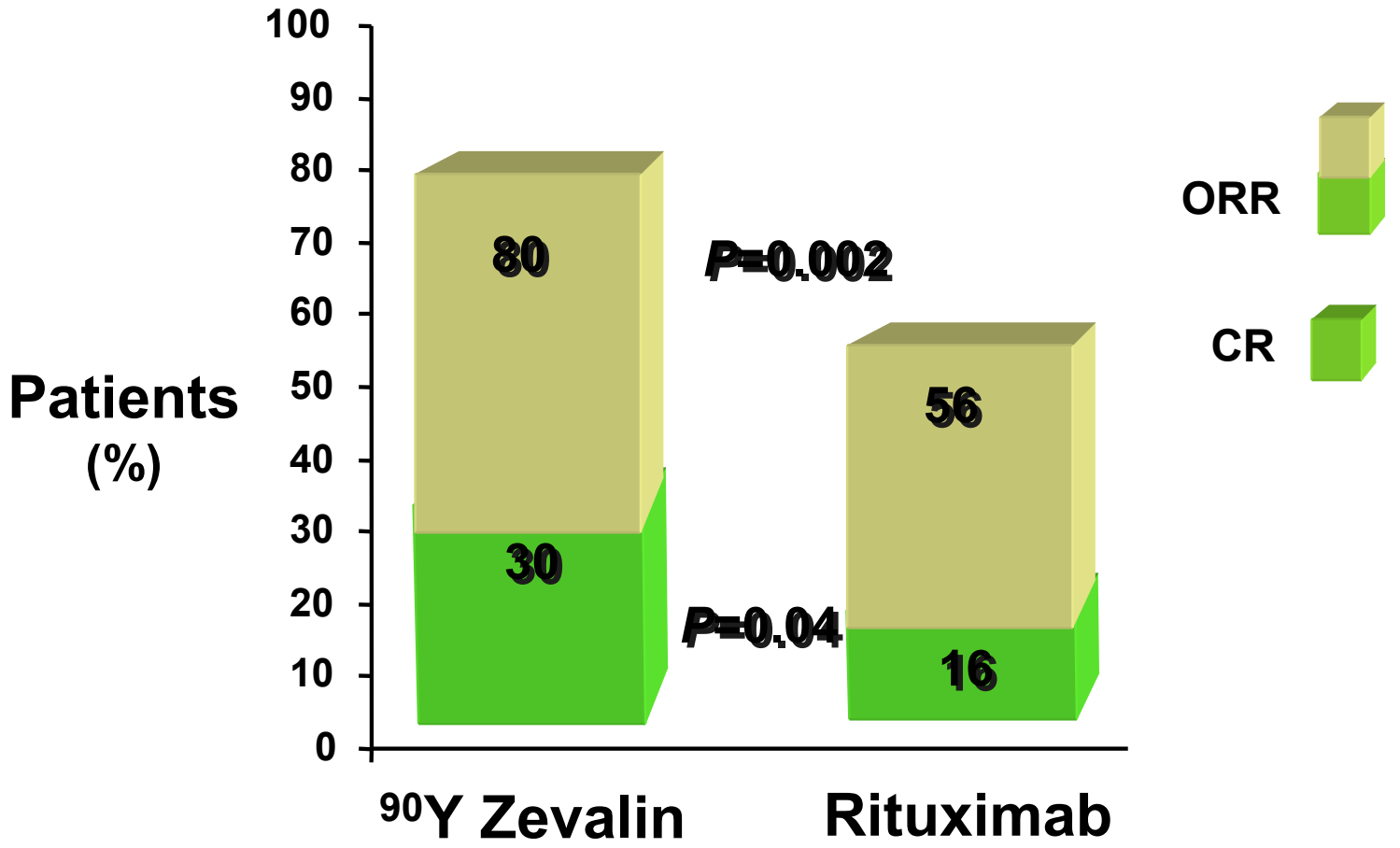
Clinical applications

- Not destined for ‘Universal’ utility.
  - Some ‘niche’ applications
    - Non-Hodgkins Lymphoma
    - Neuroendocrine tumours

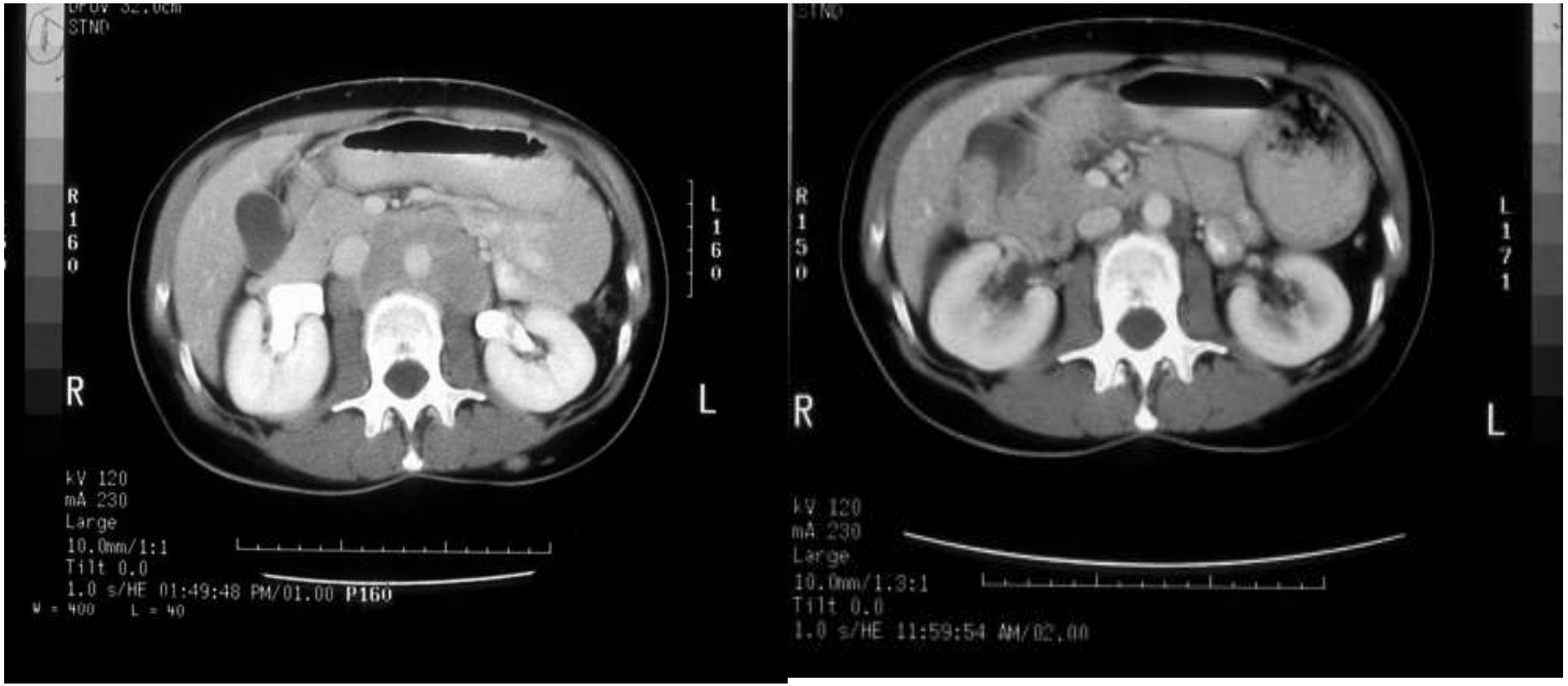
Non-Hodgkins Lymphoma

- Very radiosensitive tissues
- Relatively high antibody uptake
- Non-radiation mediated effects
  - ADCC (antibody-dependent cell cytotoxicity)
  - Receptor (specific) stimulation
  - Apoptosis

^{90}Y Zevalin Versus Rituximab Therapy: Response



Non-Hodgkin's Lymphoma
CT before and after Radioimmunotherapy

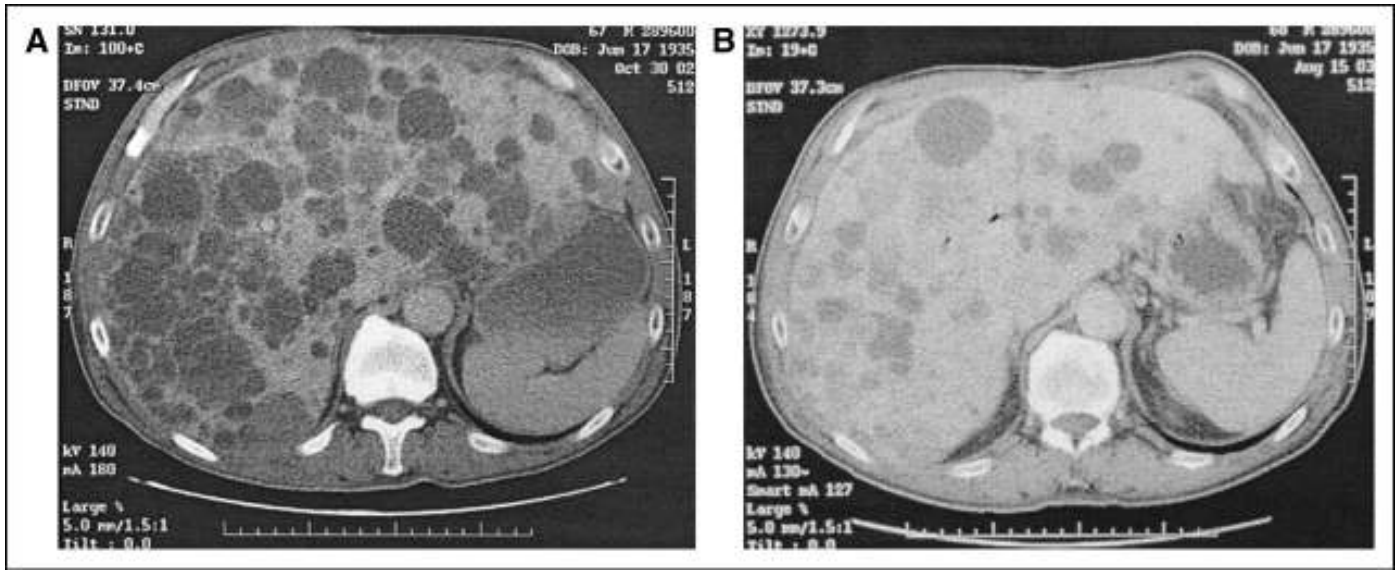


Neuroendocrine tumours

- High target expression
- “High” radiation doses
- Excellent radiopharmaceutical

177Lu-DOTA-TATE

CT of metastasized nonfunctioning endocrine pancreatic tumor before treatment (left) and 3 months after the last treatment (right)



Kwekkeboom, D. J. et al. J Clin Oncol; 23:2754-2762 2005

Thank you