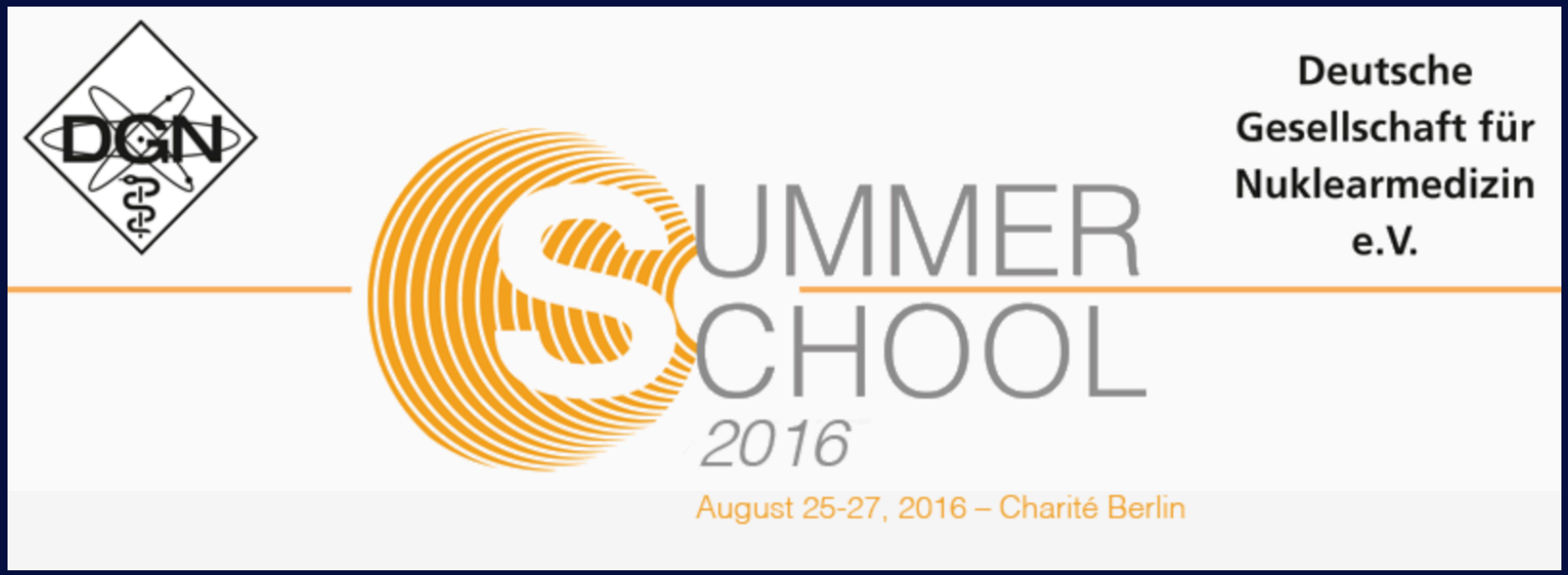
nanoparticles



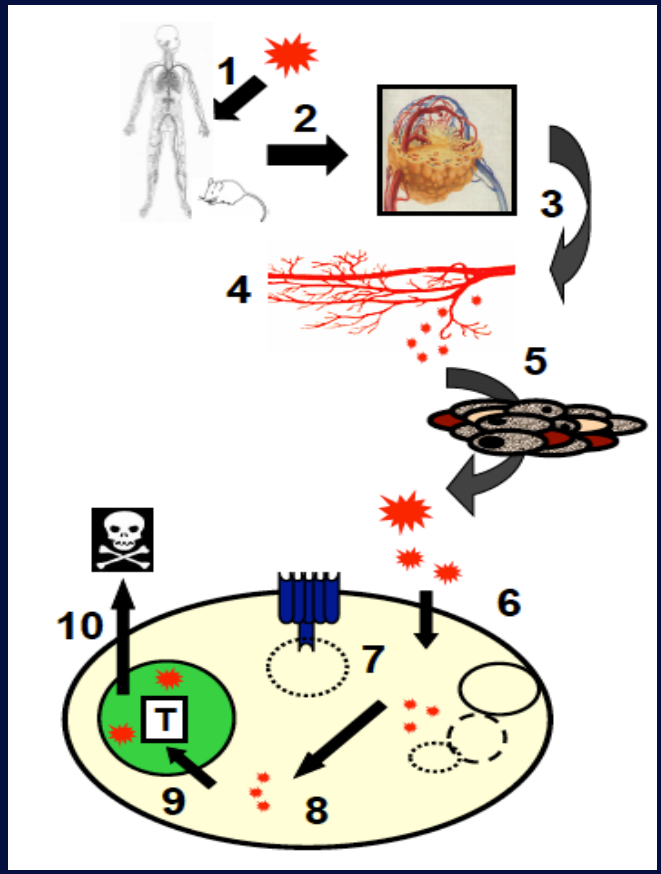
Twan Lammers

drug delivery to tumors

in order to be effective, a chemotherapeutic agent has to

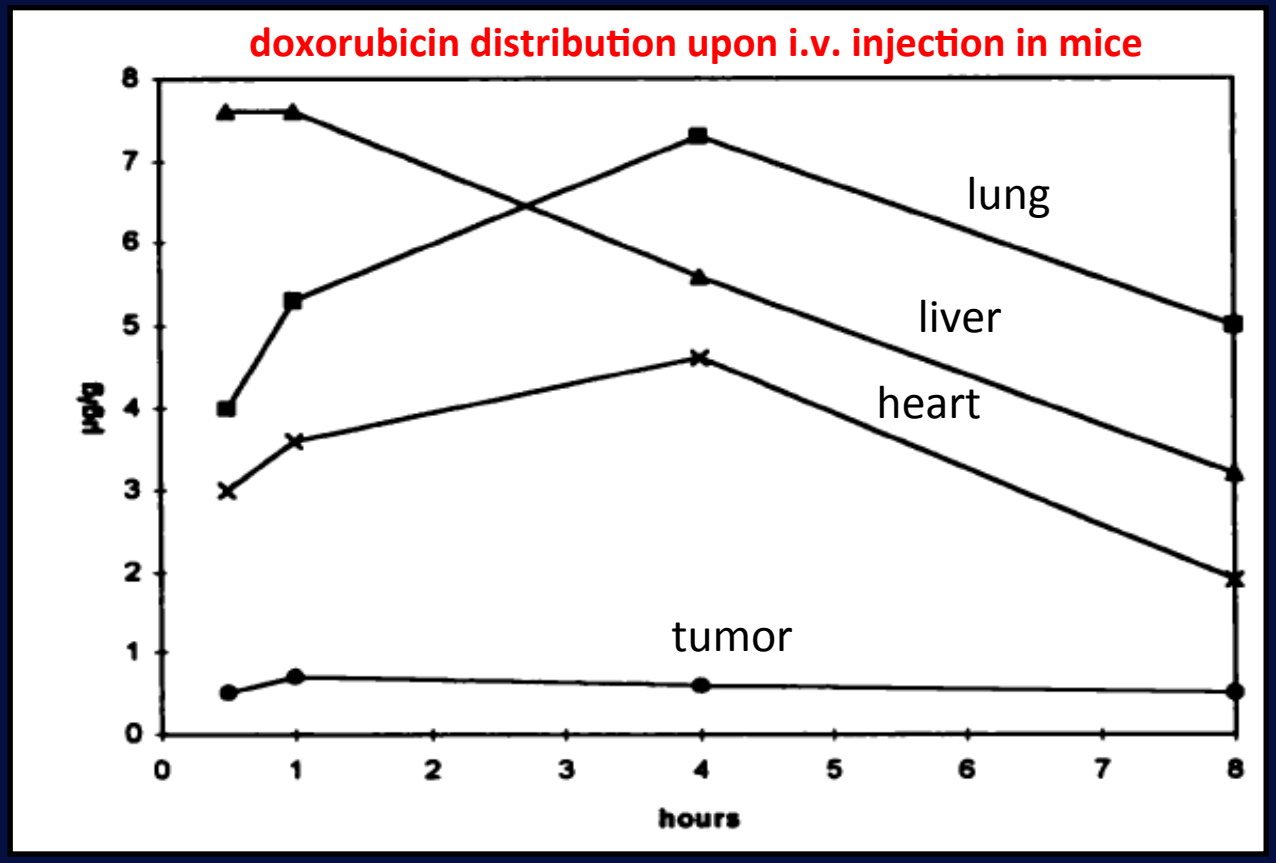
… undertake a long journey …

- be soluble and stable
- be readily available in systemic circulation
- reach the tumor microcirculation
- extravasate into the tumor interstitium
- distribute across the tumor interstitium
- cross the cellular membrane
- localize to the correct cellular compartment
- reach high concentrations at the target site
- remain there for sufficiently long periods of time
- avoid accumulation in healthy off-target tissues



drug delivery to tumors

is difficult



Bosslet et al, Cancer Res (1998)

drug delivery systems

Aim : to increase the efficacy and to reduce the toxicity of a drug by altering its pharmacokinetic and biodistributional parameters

Two different faces :

1 : site-specific drug delivery

=> to improve antitumor activity

2 : site-avoidance drug delivery

=> to reduce systemic side effects

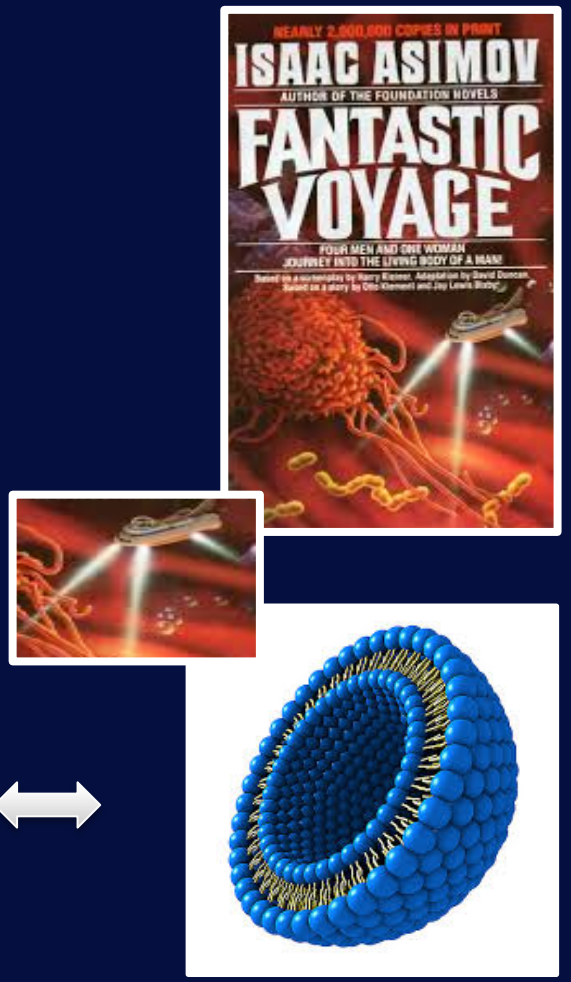
nano

νᾶνος

10^{7} m

12715 km

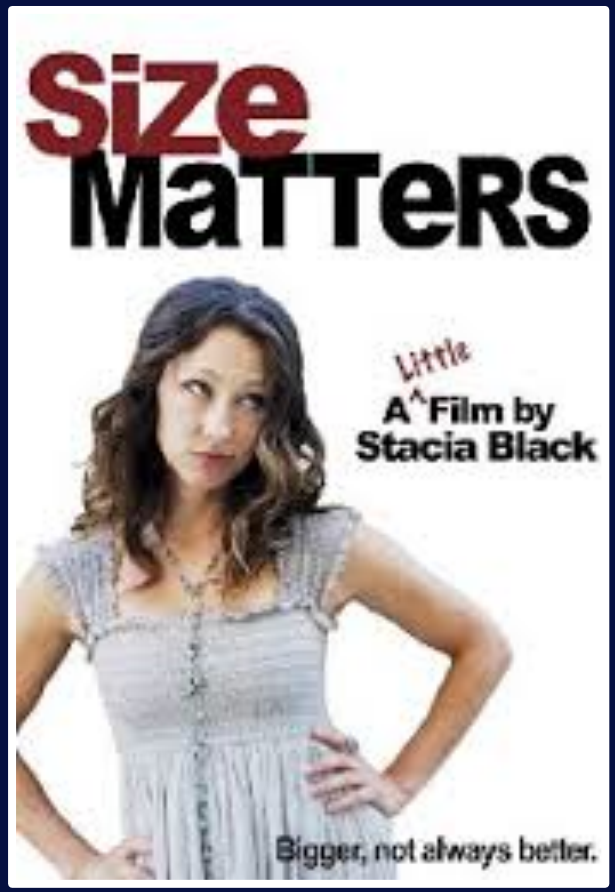
1 m



10^{-7} m

100 nm

size is important

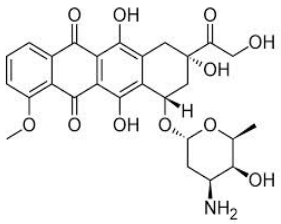


size is important

as it strongly influences : pharmacokinetics, biodistribution, target site accumulation, tissue penetration, cellular uptake, etc

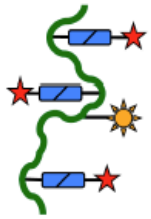
drug

1 nm



polymer

1 - 10 nm



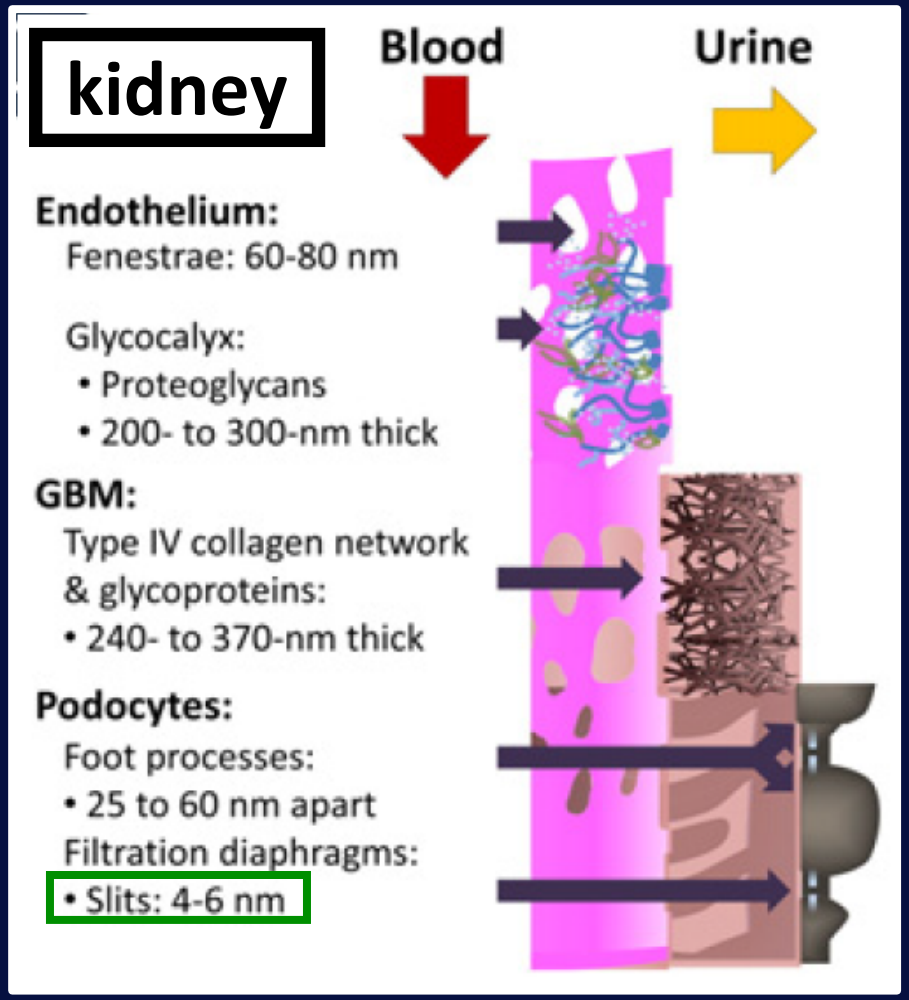
liposome

100 nm

microbubble

1000 nm

nanoparticles

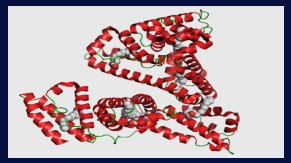


albumin : 67 kDa / ~7 nm

Bertrand et al, J Control Release (2012)

nanoparticles

albumin : 7 nm

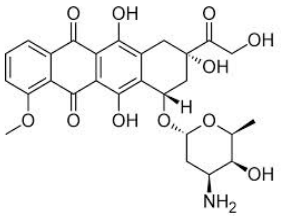


=> useful as carriers for drug delivery

rapid elimination ← → slow elimination

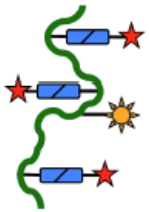
Drug

1 nm



Polymer

10 nm



Liposome

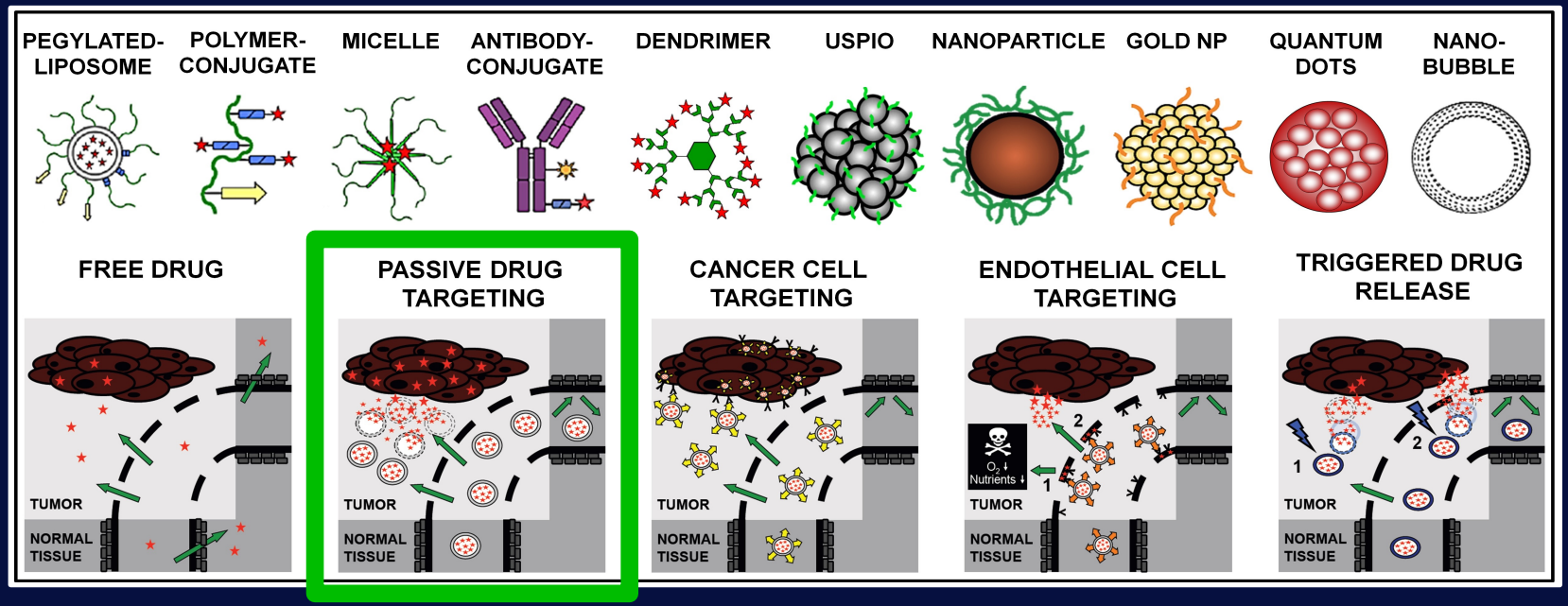
100 nm

Microbubble

1000 nm

nanomedicine

- 1-100(0) nm-sized carrier materials
- **protect the drug from the body**
- **protect the body from the drug**
- improve efficacy and reduce toxicity



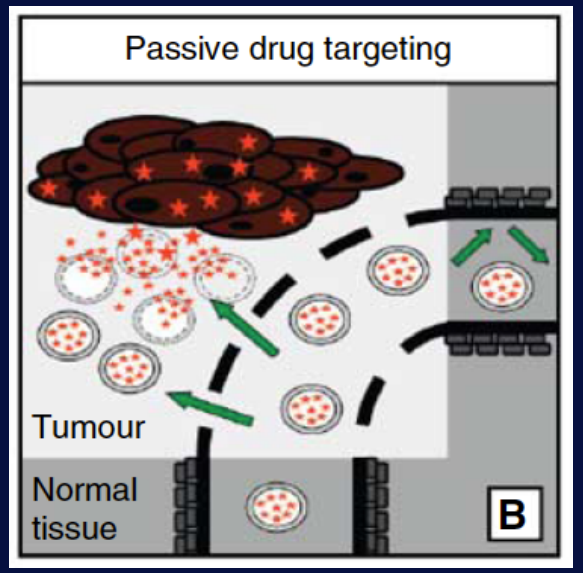
Kunjachan et al, Chem Rev (2015)

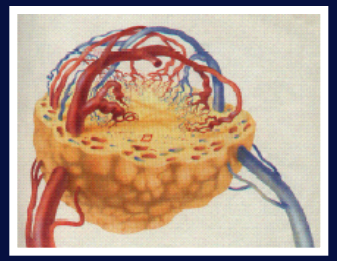
tumor targeting via EPR

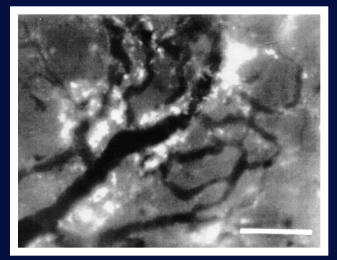
- high blood vessel density +
- high vascular permeability +
- lack of lymphatic drainage →

Enhanced Permeability and Retention (EPR) effect

=> efficient accumulation of long-circulating drug delivery systems

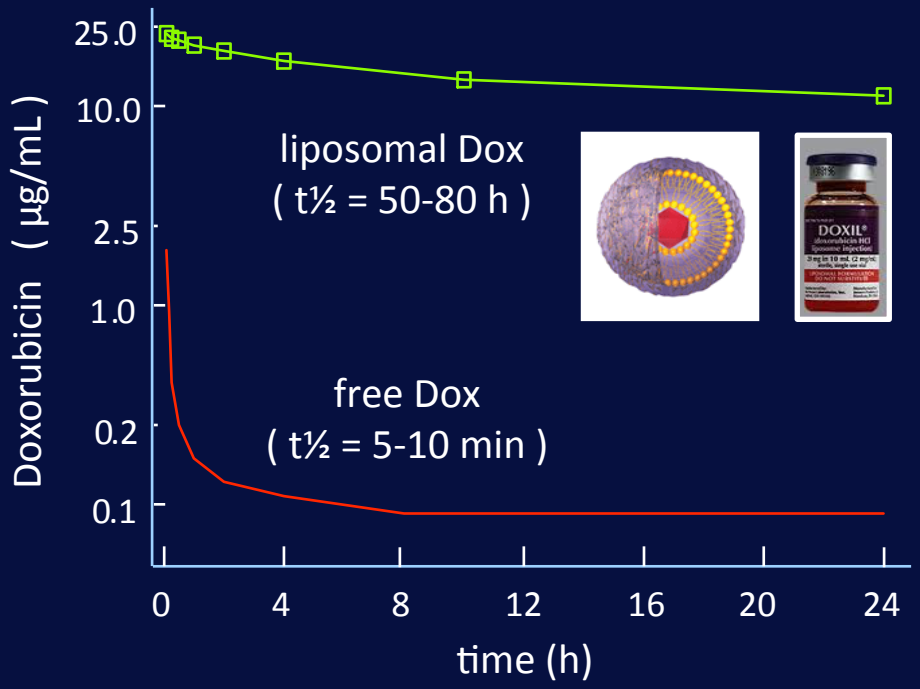






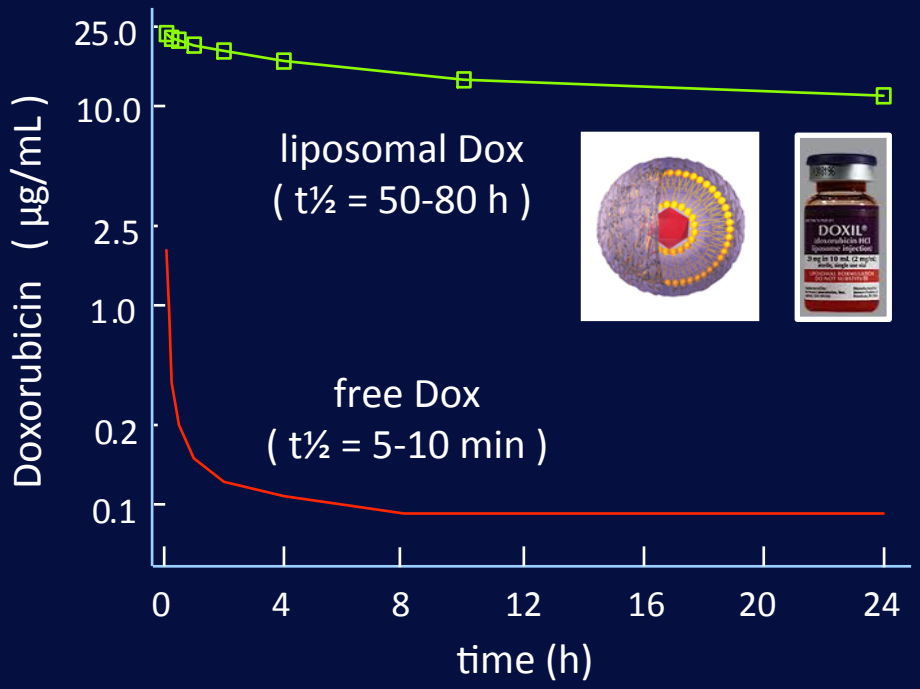
Maeda, Jain et al

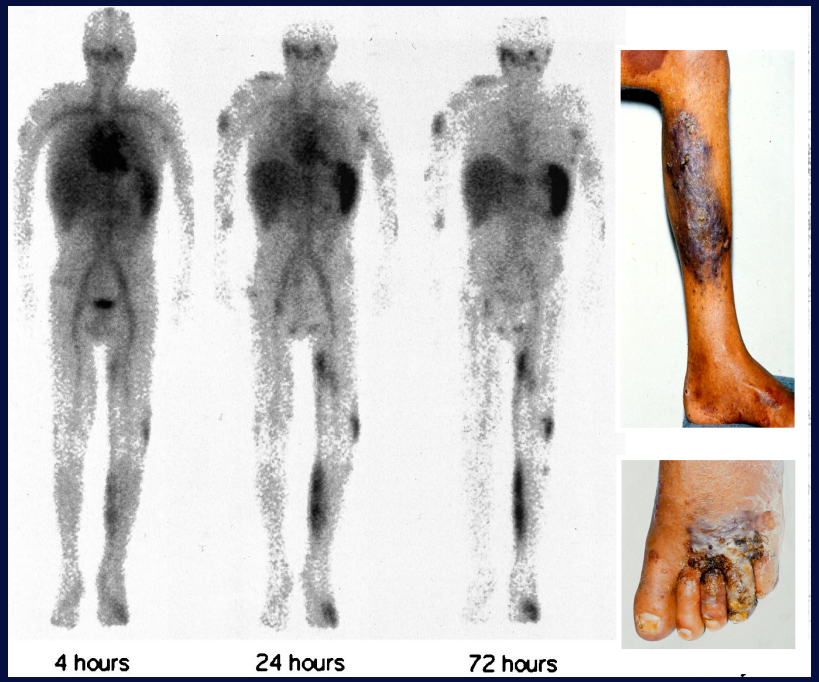
tumor targeting via EPR



Gabizon, Barenholz et al, Cancer Res (1994)

tumor targeting via EPR





in Kaposi sarcoma : improved efficacy vs. ABV => 1 CR + 60/133 PR vs. 31/125 PR

better tolerability => less cardiomyopathy, nausea, alopecia

Gabizon, Barenholz et al, Cancer Res (1994)

Harrington et al, Clin Cancer Res (2001)

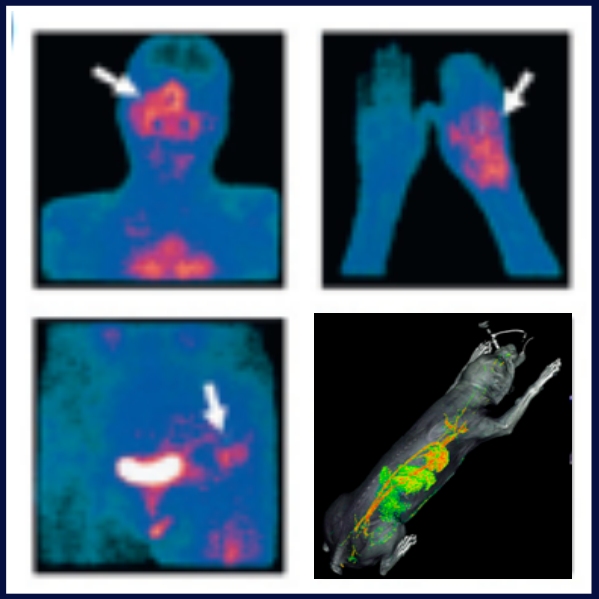
tumor targeting via EPR

is highly variable

=> both in animal models and patients

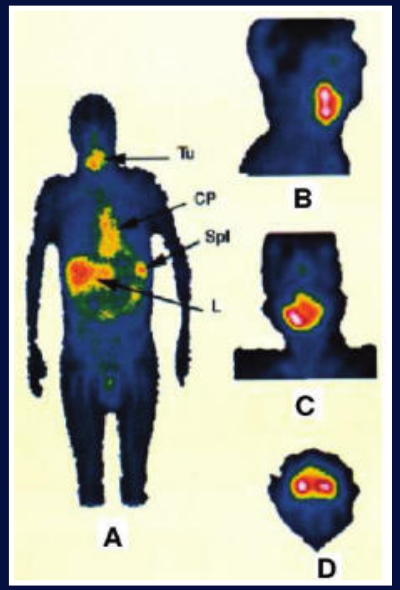
=> even within a single patient and single tumor

Sarcoma

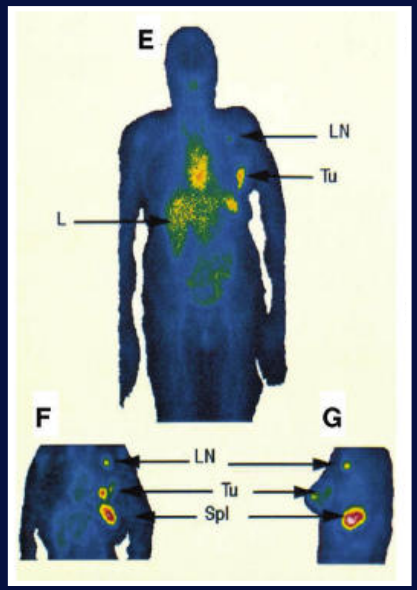


KS

Head & Neck



Breast

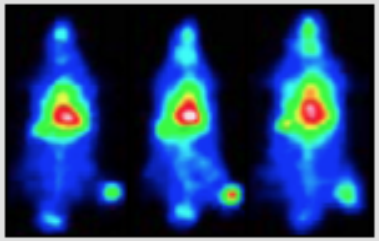


strategies to improve (EPR-based) nanomedicine therapies

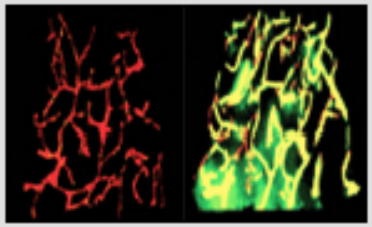
concepts vs. carrier materials

enhancing

con + RT + HT

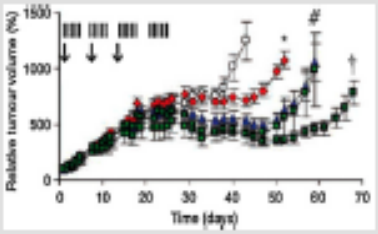


sonoporation

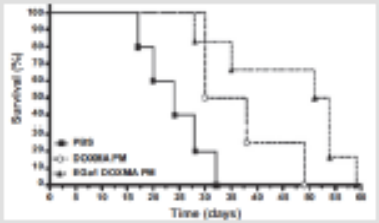


combining

nano + radiochemo

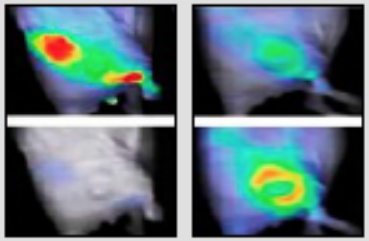


nanobody targeting

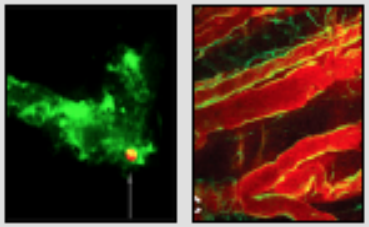


avoiding

vascular targeting

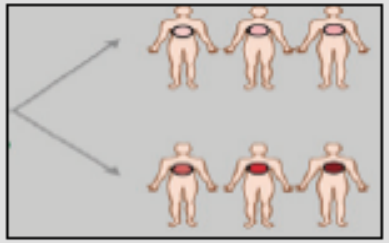


intravascular release

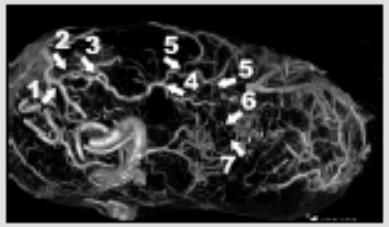


imaging

direct : personalisation



indirect : understanding



imaging drug targeting

=> most straightforward and clinically relevant strategy

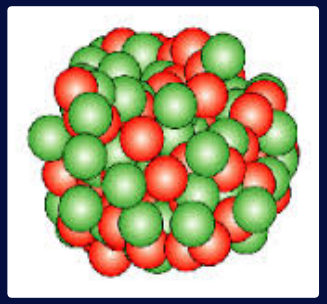
to improve tumor-targeted (nano-) therapies

(nano) theranostics

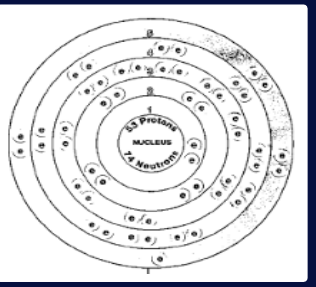
theranostics

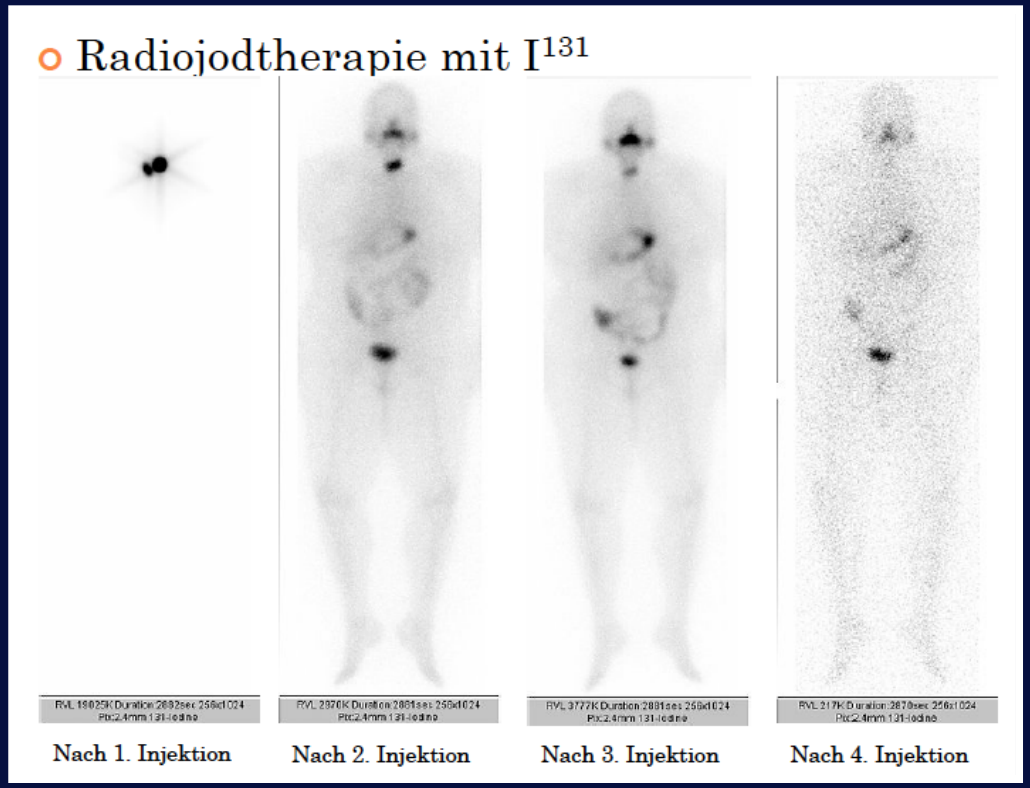
combining diagnosis and therapy to individualize and improve treatments

=> ^{131} iodine-based diagnosis and therapy of thyroid cancer



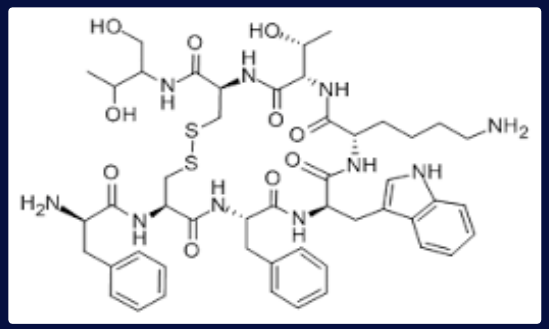
^{131}I = 0.1 nm

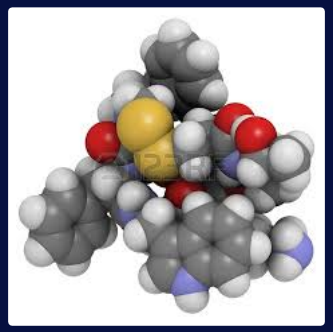


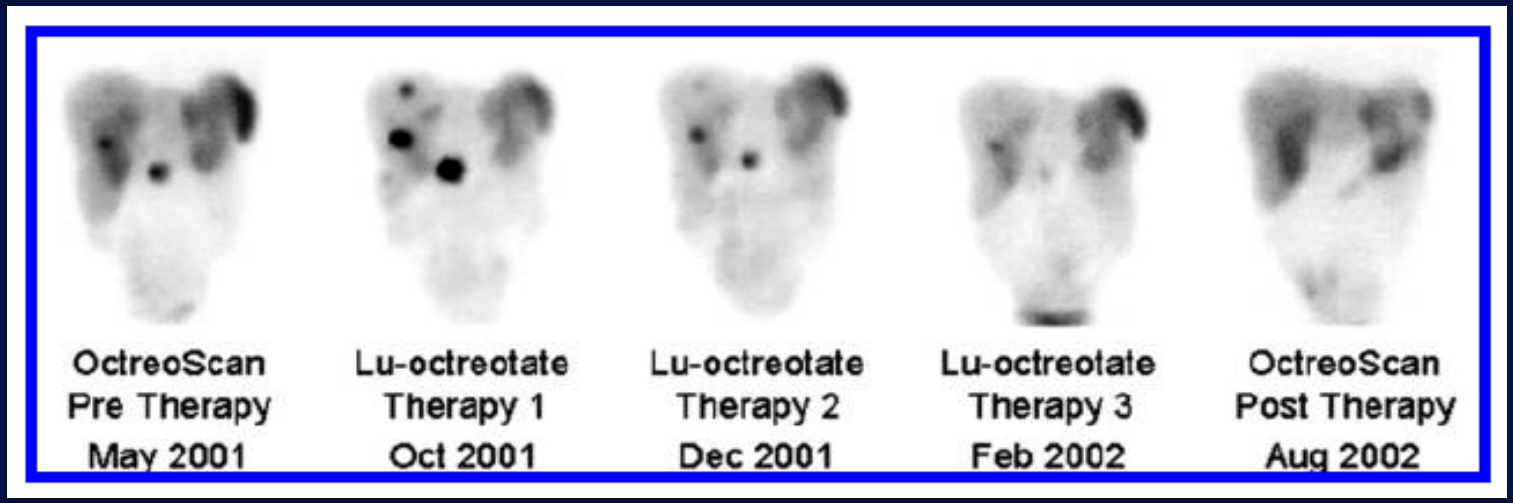


theranostics

theranostic pair => ^{111}In-DOTATOC + ^{177}Lu-DOTATATE in SSTR-positive tumors



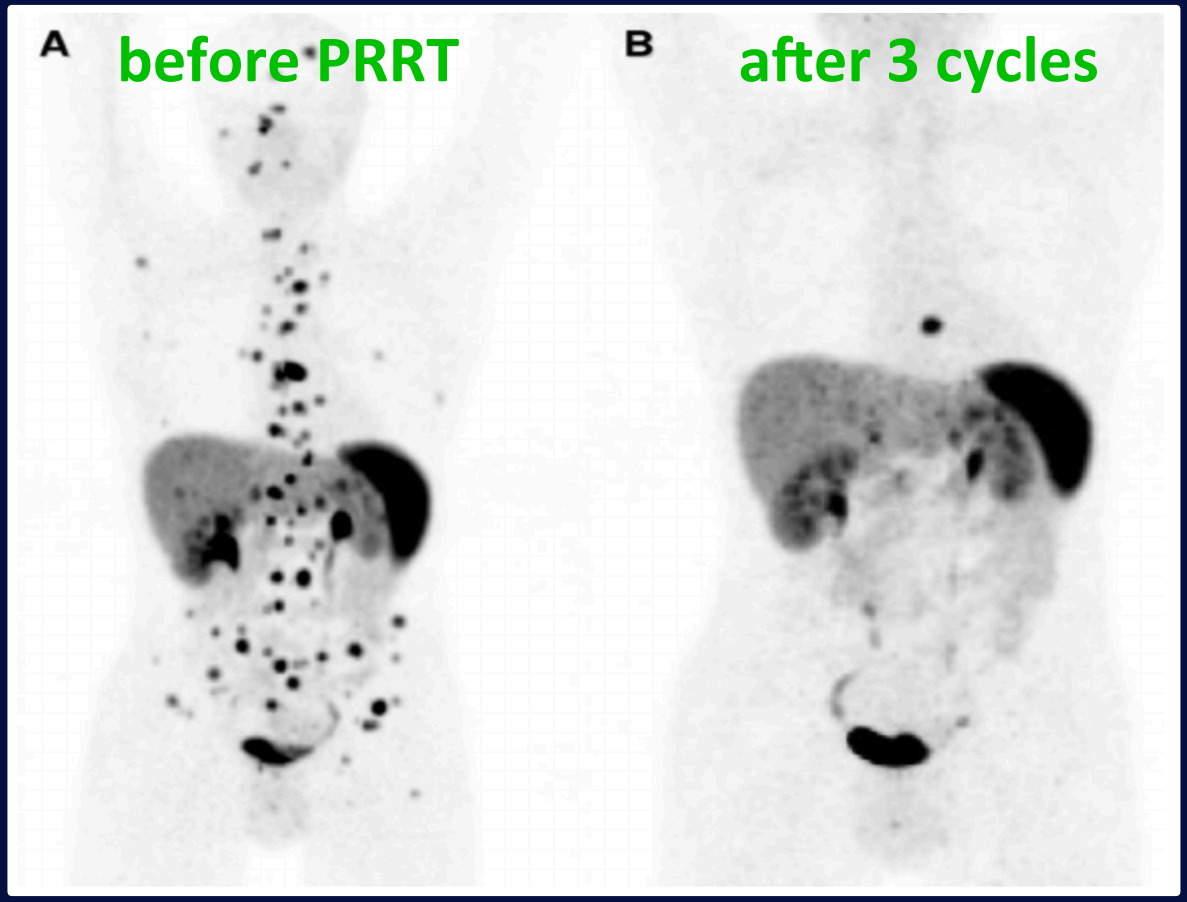




De Jong, Acc Chem Res (2011)

theranostics

theranostic pair => ^{68}Ga-DOTATOC + ^{90}Y-DOTATATE in SSTR-positive tumors

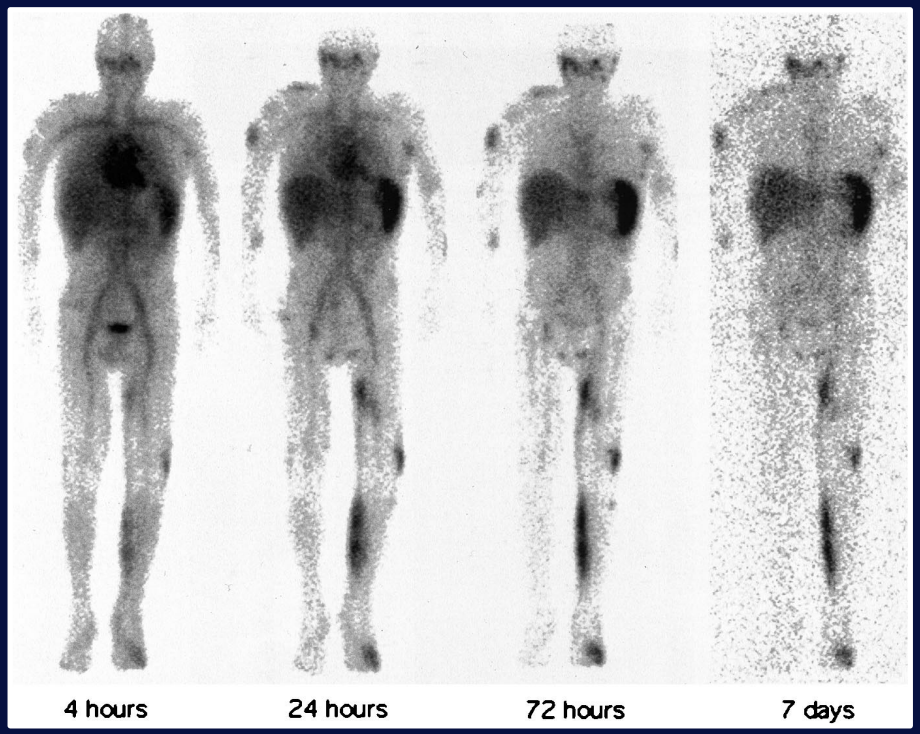


Prasad et al, EJNMMI Res (2015)

nanotheranostics

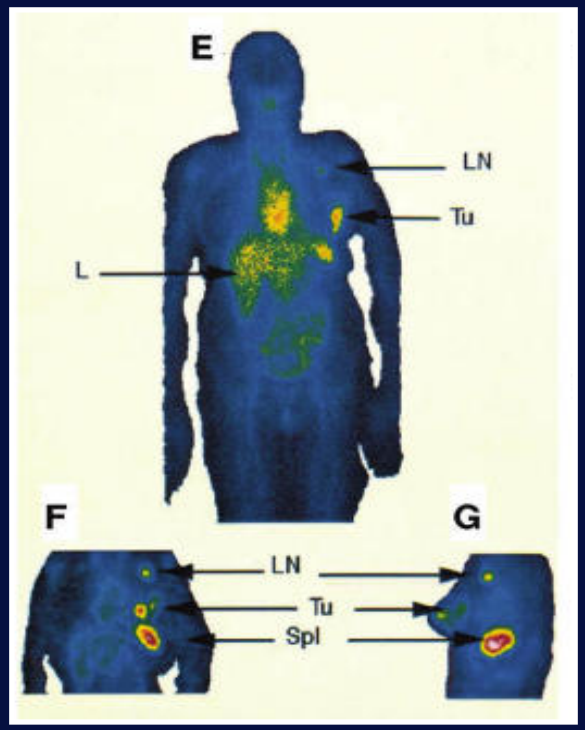
Doxil® in Kaposi Sarcoma

high EPR => high efficacy



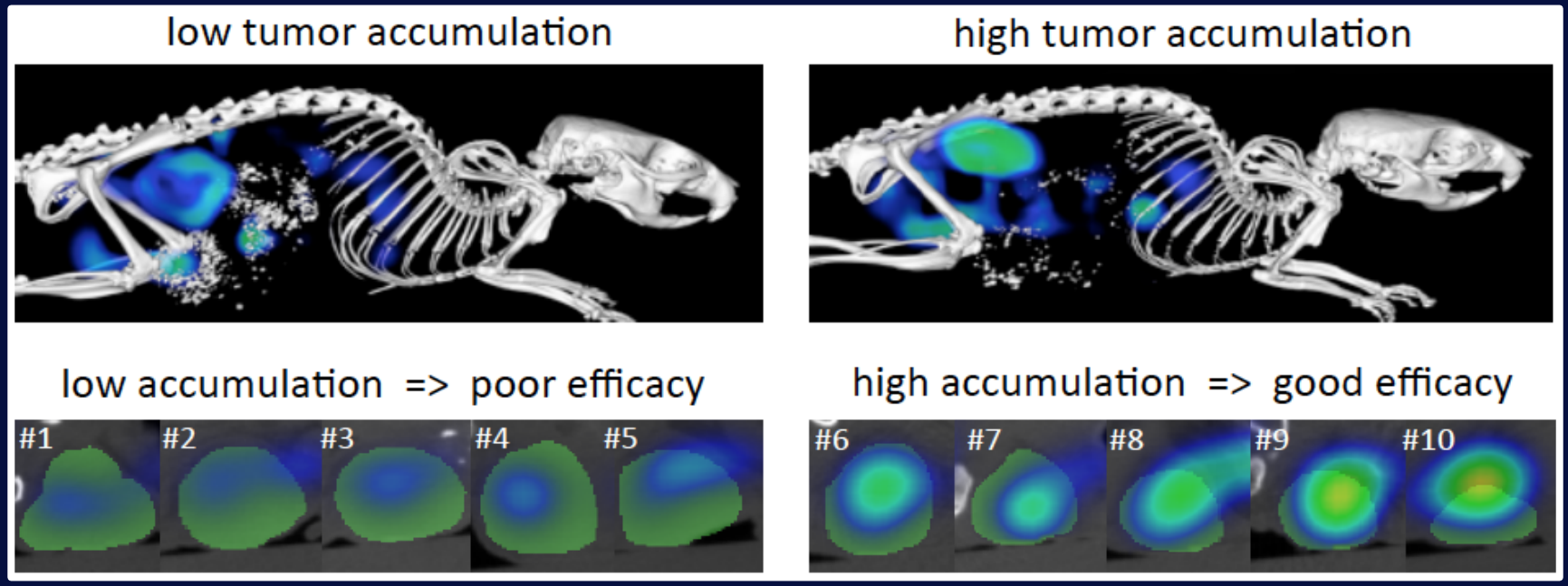
Doxil® in Breast Cancer

low EPR => low efficacy



nanotheranostics

stratifying responders from non-responders on the basis of EPR imaging



Shi et al, ACS Nano (2015)
Theek et al (in prep)

nanotheranostics

=> tumor accumulation correlates with antitumor efficacy

Imaging Nanoprobe for Prediction of Outcome of Nanoparticle Chemotherapy by Using Mammography[1]

Radiology

BIOENGINEERING

Predicting therapeutic nanomedicine efficacy using a companion magnetic resonance imaging nanoparticle

Miles A. Miller,[1,2]* Suresh Gadde,[3]* Christina Pfirschke,[1] Camilla Engblom,[1] Melissa M. Sprachman,[1] Rainer H. Kohler,[1,2] Katherine S. Yang,[1] Ashley M. Laughney,[1] Gregory Wojtkiewicz,[1] Nazila Kamaly,[3] Sushma Bhonagiri,[3] Mikael J. Pittet,[1,2] Omid C. Farokhzad,[3,4†] Ralph Weissleder[1,2,5†]

nature COMMUNICATIONS

ARTICLE

Received 21 Oct 2015 | Accepted 5 May 2016 | Published 20 Jun 2016

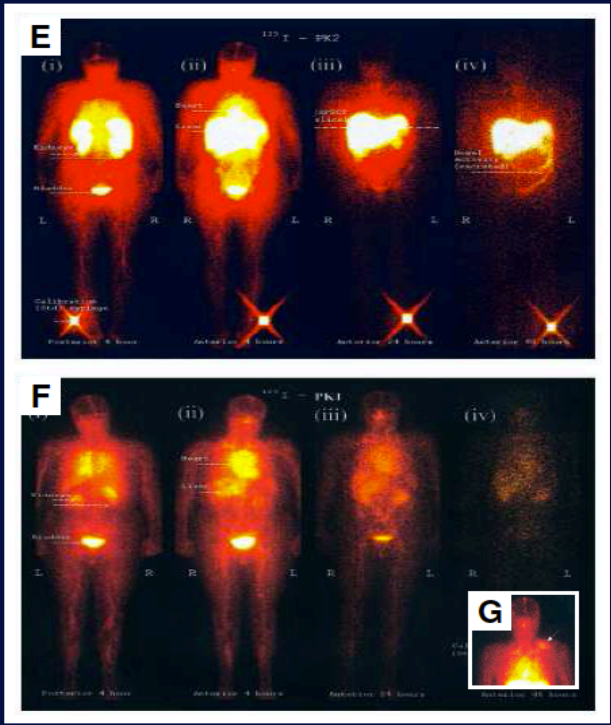
DOI: 10.1038/ncomms11838 OPEN

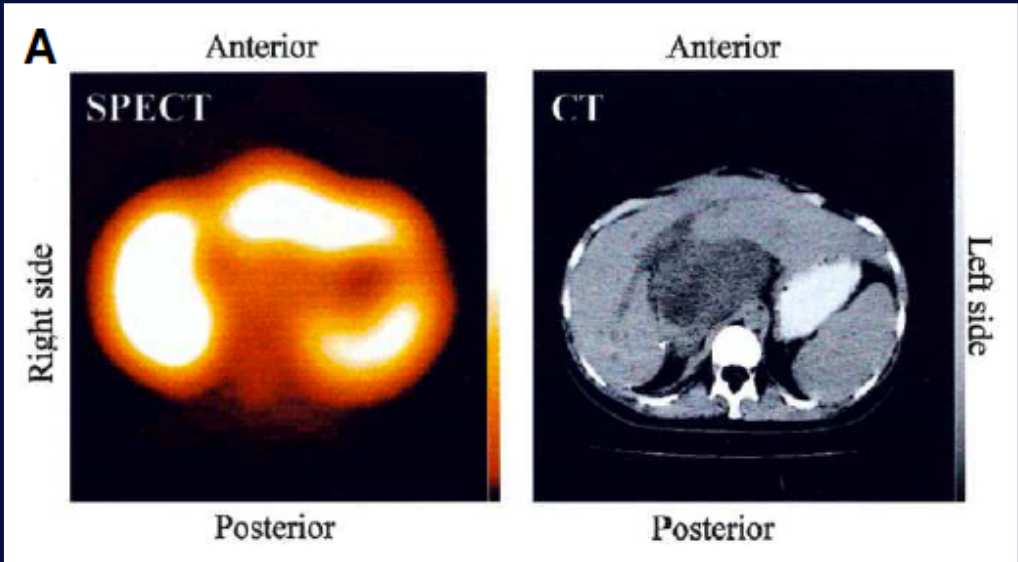
Nanoreporter PET predicts the efficacy of anti-cancer nanotherapy

Carlos Pérez-Medina[1,2,3], Dalya Abdel-Atti[4], Jun Tang[4], Yiming Zhao[1], Zahi A. Fayad[1], Jason S. Lewis[4,5,6], Willem J.M. Mulder[1,7] & Thomas Reiner[4,5]

Karathanasis et al, Radiology (2009)
Miller et al, Sci Transl Med (2015)
Perez-Medina et al, Nat Commun (2016)

nanotheranostics





- Gal-pHPMA-Dox (PK2) : efficient liver localization, but inefficient tumor accumulation
- explains the relatively disappointing response rates (15%)
- exemplifies the need to combine drug targeting and imaging

Seymour et al, J Clin Oncol (2001)

nanotheranostics

- lung accumulation/distribution of radiolabeled viral NP in CF patients
- patient pre-selection on the basis of non-invasive imaging

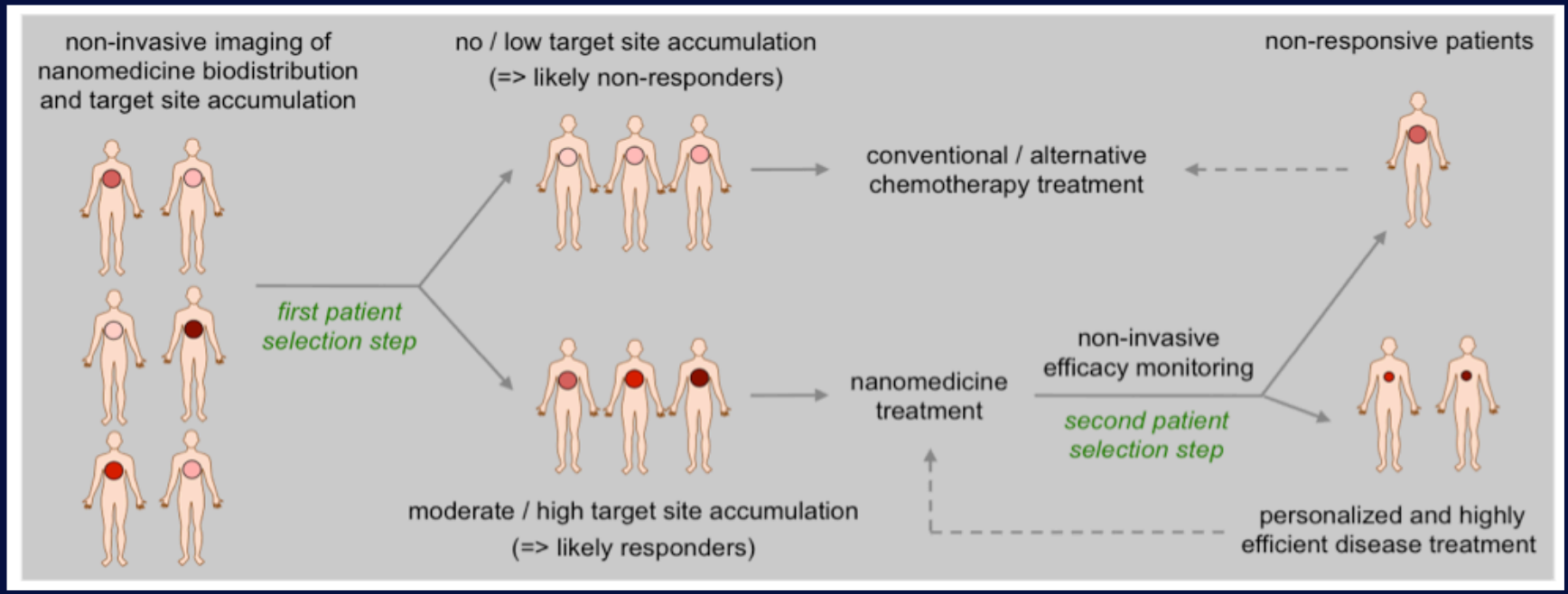
Image courtesy: Uta Griesenbach

personalized nanomedicine

combination of drug targeting + imaging

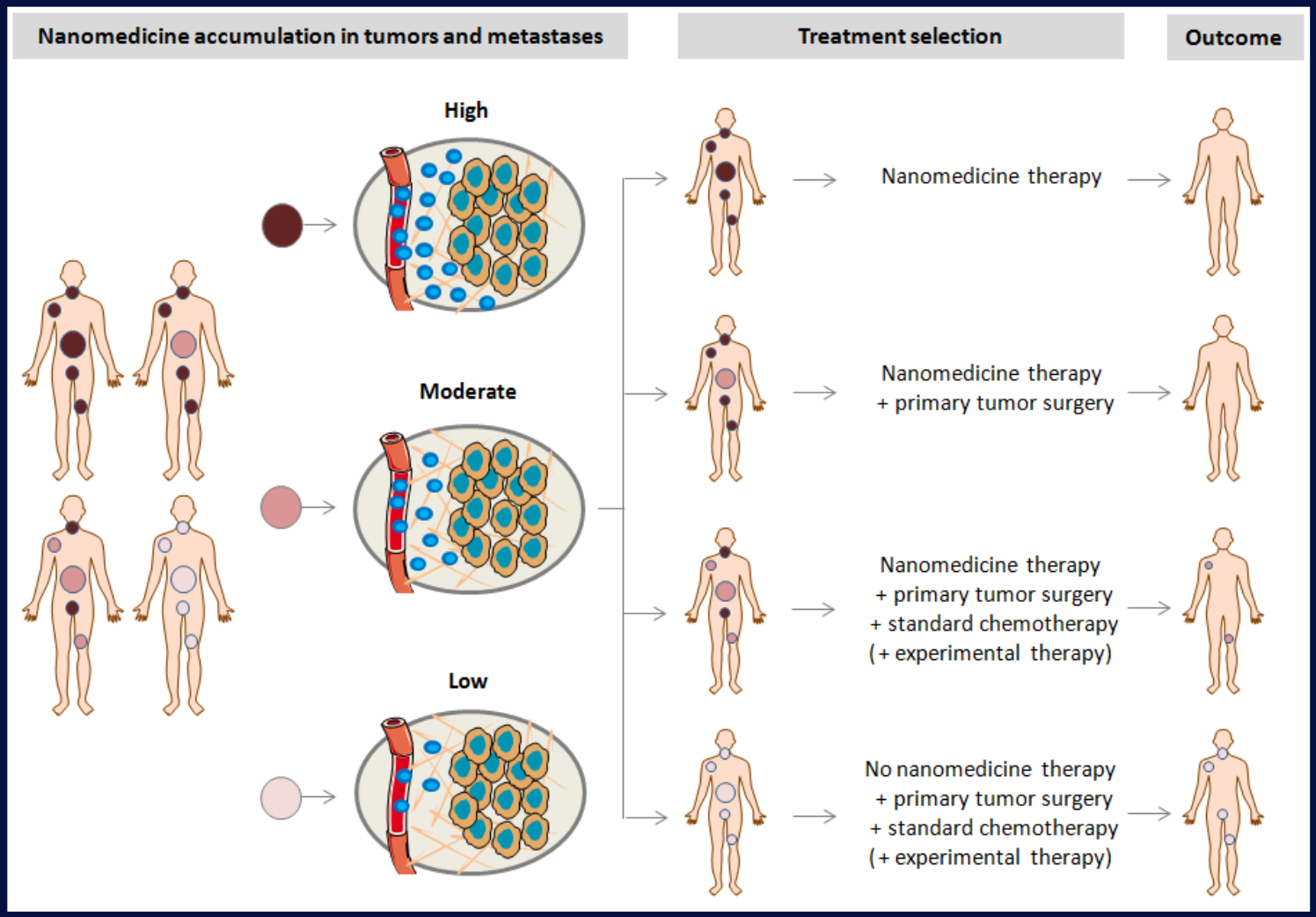
=> to enable patient pre-selection

=> to facilitate clinical translation



Lammers et al, Clin Cancer Res (2012)

beyond solid tumor targeting

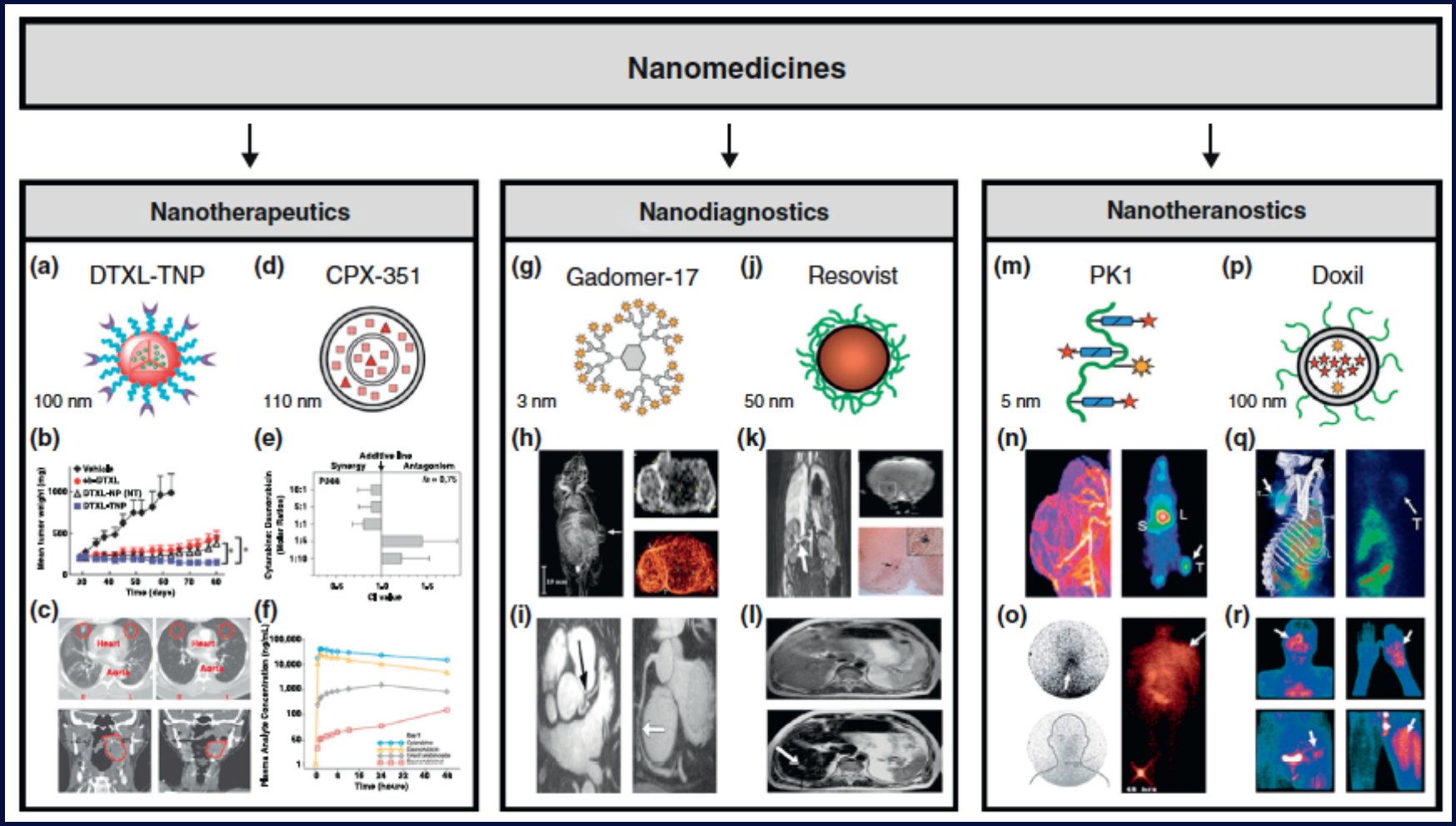


Ojha et al, Exp Opin Drug Deliv (2015)

...

nanodiagnostics

in vivo applications of nanoparticles



Rizzo et al, Curr Opin Biotech (2013)

nanodiagnostics

basic considerations

Typical properties of diagnostics

- short circulation time
- rapid exchange between compartments
- rapid elimination from non-target tissues
- rapid degradation, no retention, no toxicity

Typical properties of nanoparticles

- long circulation
- slow exchange between compartments
- slow elimination from non-target tissues
- slow degradation, prolonged retention (EPR, MPS)

NP useful for diagnostic purposes ??

nanodiagnostics

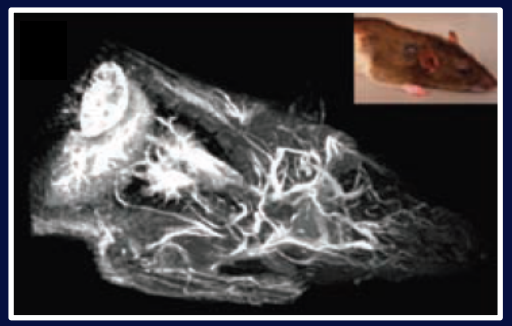
functional vs. molecular imaging

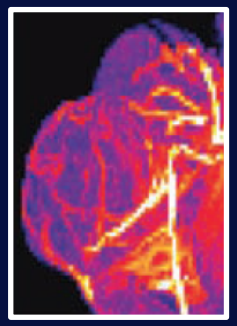
Kiessling et al, Radiology (2014)

nanodiagnostics

for functional imaging

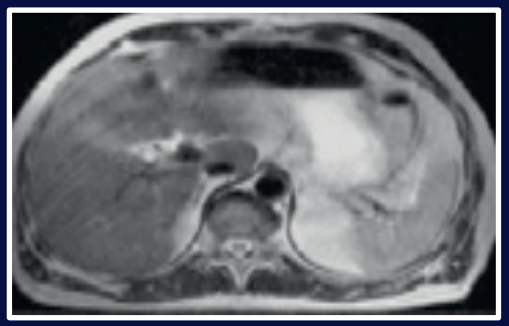
angiography

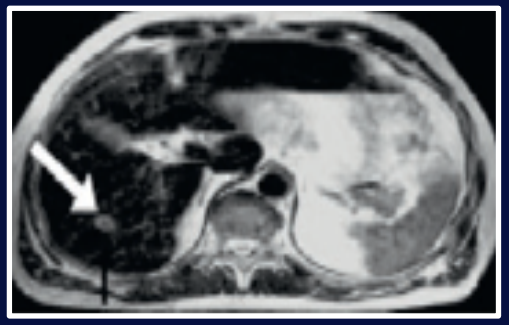




Lammers et al, Br J Cancer (2008)
Chiribiri et al, Am J Card (2008)

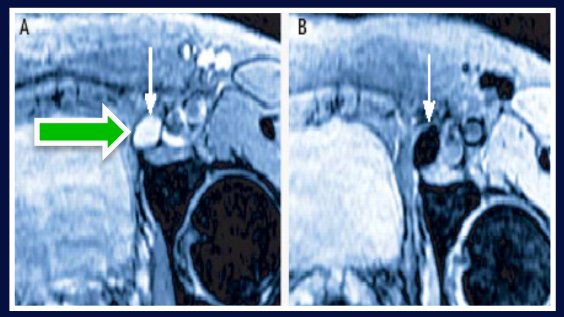
MPS imaging

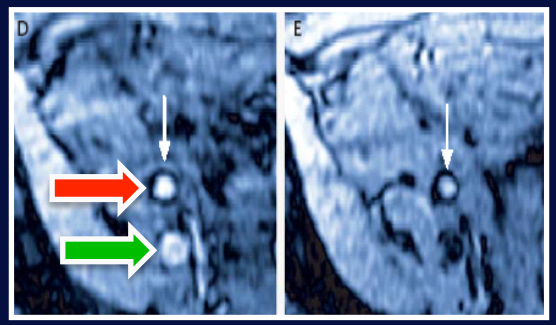




Reimer, Eur Radiol (2003)

lymphography





Harisinghani et al, NEJM (2003)

nanodiagnostics

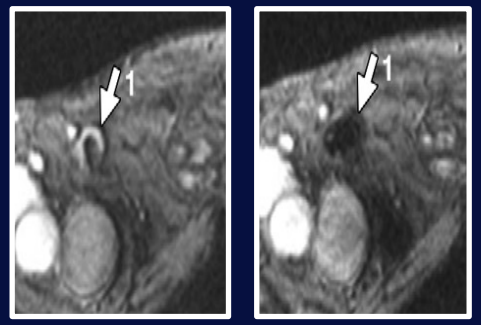
for functional imaging

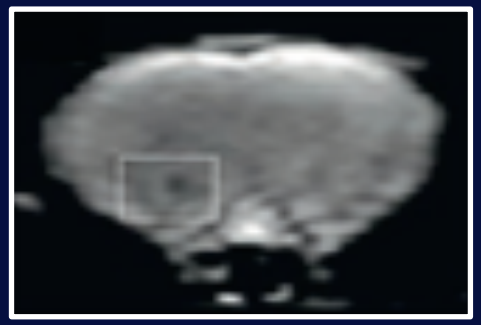
in vivo labeling  ex vivo labeling

nanodiagnostics

for functional imaging

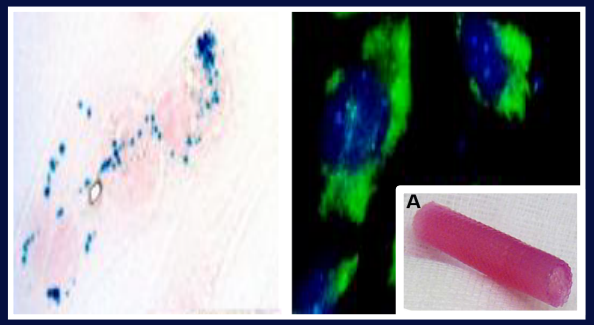
cell tracking

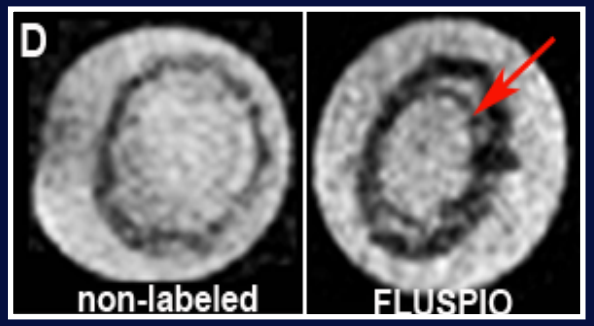




De Vries et al, Nat Biotech (2005)
Politi et al, Stem Cells (2007)

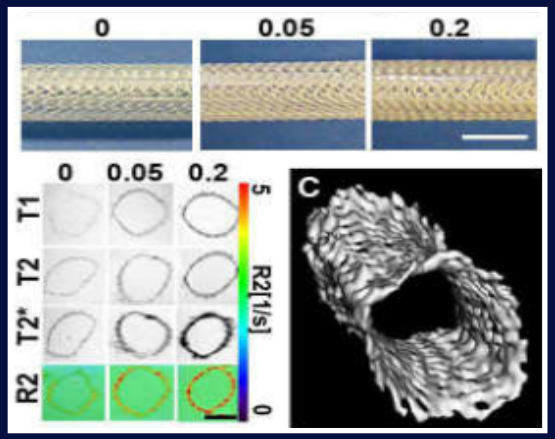
cellular imaging in TE

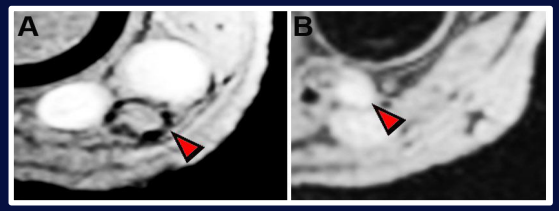




Mertens et al, Theranostics (2014)

scaffold imaging in TE





Mertens et al, Biomaterials (2015)

nanodiagnostics

for molecular imaging

molecular imaging ≠ imaging molecules

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

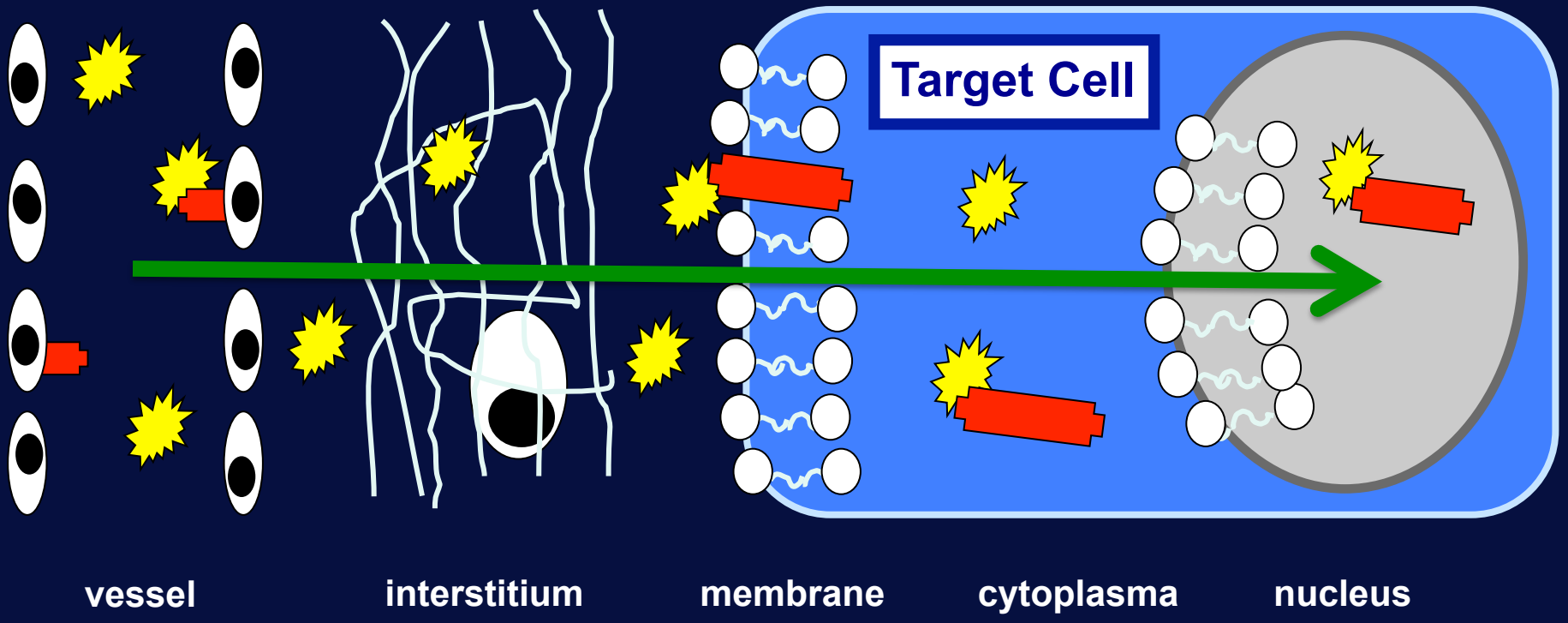
Molecular imaging of HPMA copolymers: Visualizing drug delivery in cell, mouse and man☆

=> imaging of processes taking place at the molecular level

e.g. receptor expression, transporter activity, enzyme activity

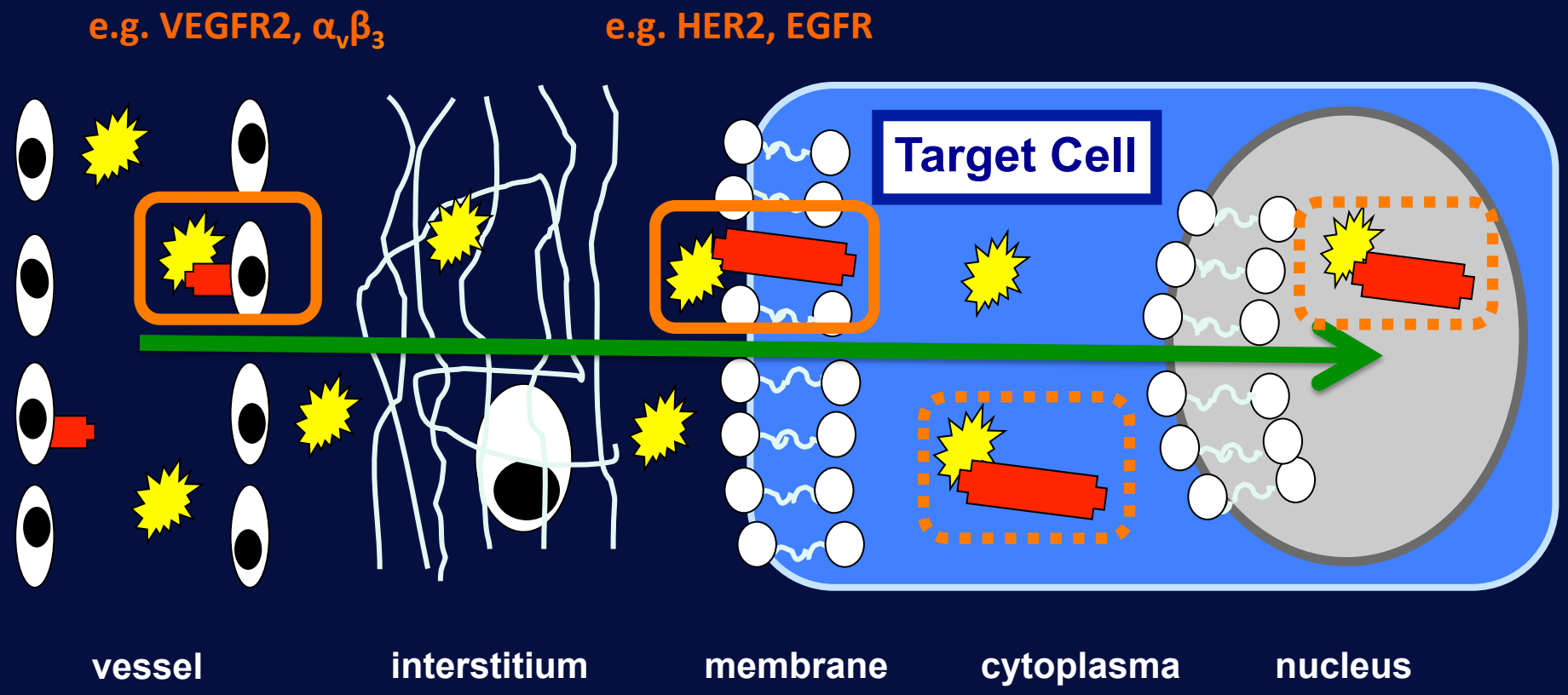
nanodiagnostics

specific molecular imaging using actively targeted NP is difficult



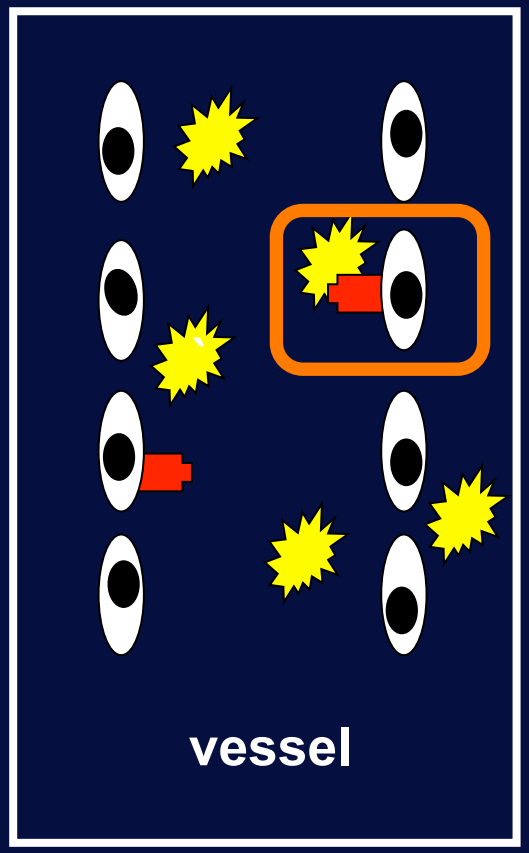
nanodiagnostics

key question : intravascular vs. extravascular targets



nanodiagnostics

intravascular targets



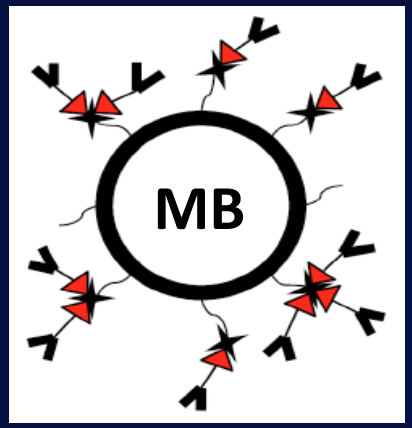
for specific molecular imaging :

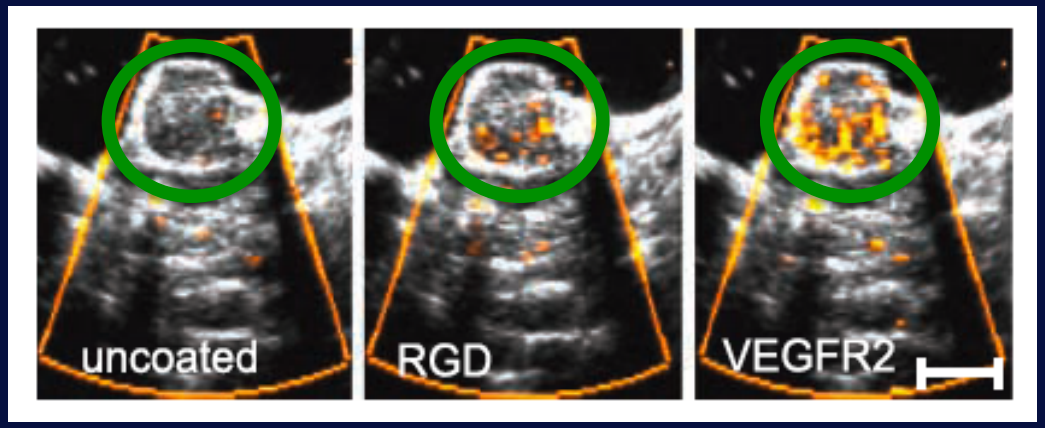
	NP
- high affinity binding	✔
- short circulation time	✖
- no extravasation	✖

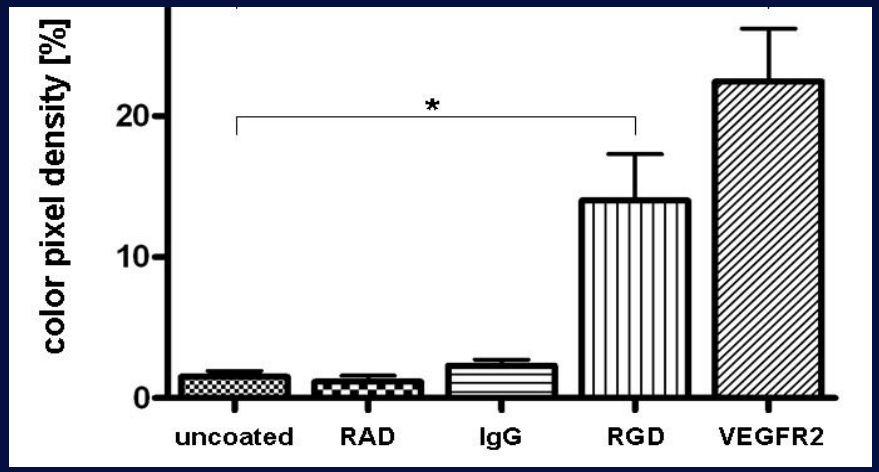
=> “microparticles” instead of nanoparticles

nanodiagnostics

specific imaging of intravascular targets : ligand-modified microbubbles





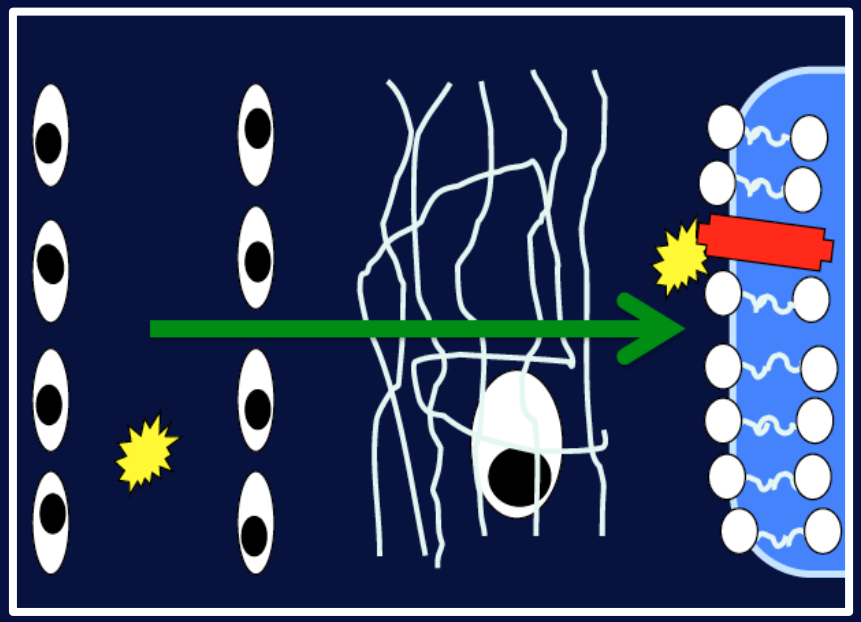


Palmowski et al, Mol Cancer Ther (2008)
Kiessling et al, J Nucl Med (2012)

nanodiagnostics

extravascular targets

how to obtain **highly specific** molecular imaging information ??

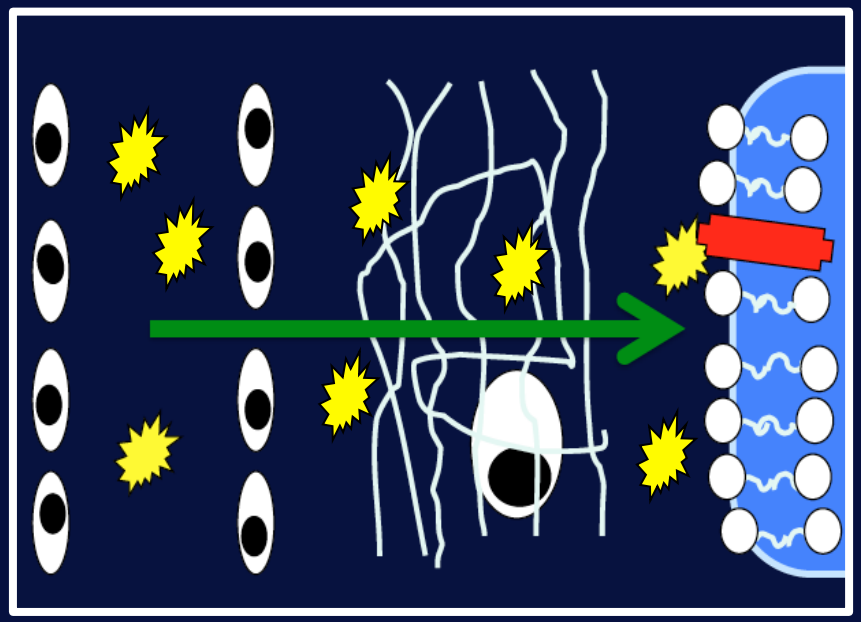


- short circulation time ✔
- significant extravasation ✔
- deep penetration ✔
- no unspecific retention ✔

nanodiagnostics

extravascular targets

how to obtain **highly specific** molecular imaging information ??



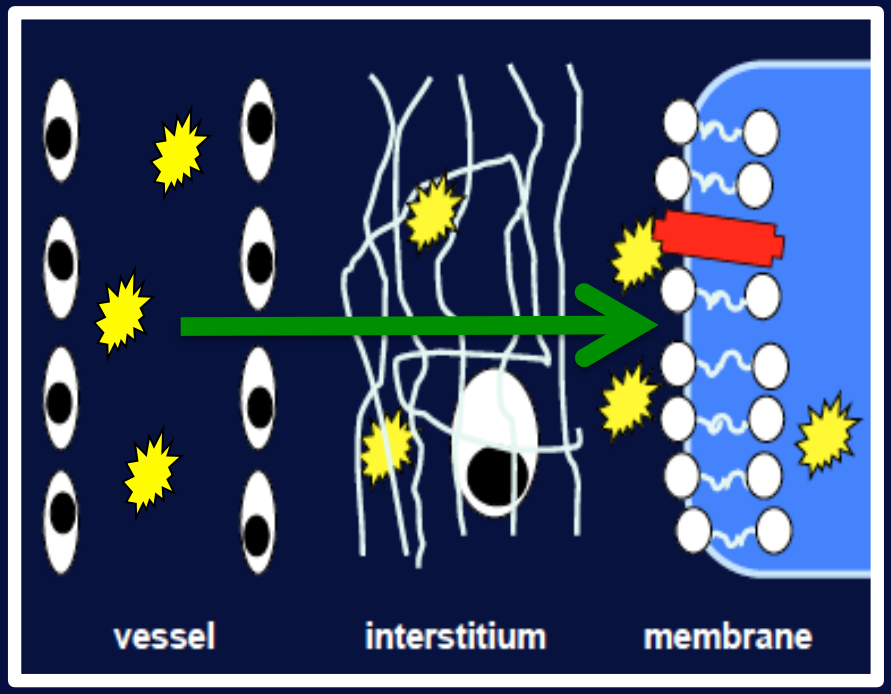
	NP
- short circulation time ✔	✖
- significant extravasation ✔	✔
- deep penetration ✔	✖
- no unspecific retention ✔	✖

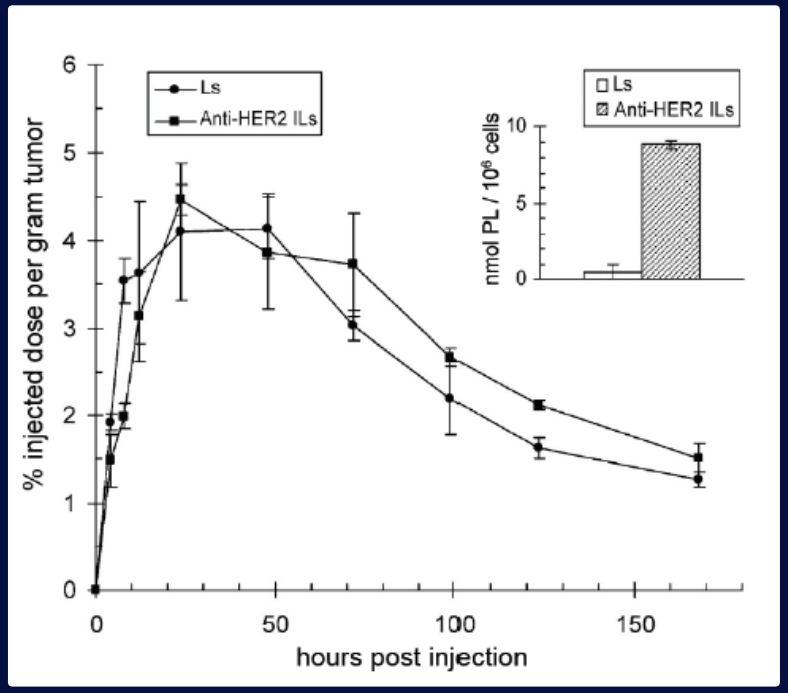
nanodiagnostics

extravascular targets

=> smaller…

=> HER2-targeted vs. non-targeted liposomes (~100 nm)





Kirpotin et al, Cancer Res (2006)

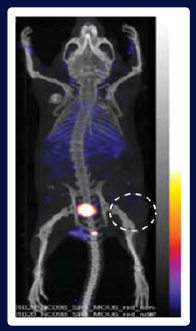
nanodiagnostics

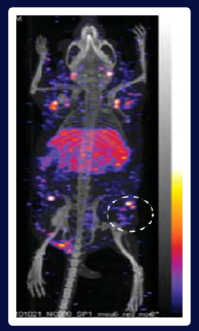
extravascular targets

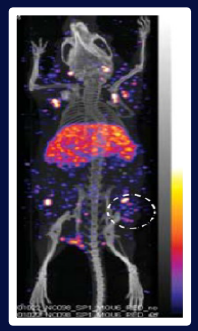
=> smaller…

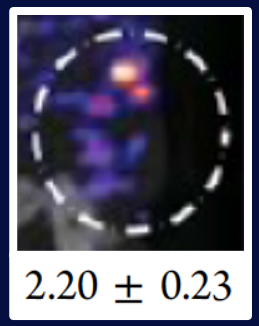
=> HER2-targeted vs. non-targeted gold nanoparticles (~ 30 nm)

AuNP



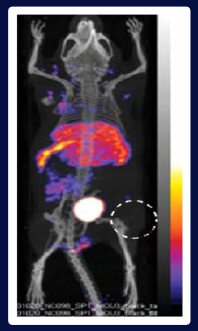


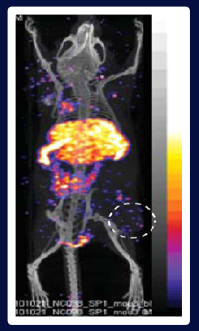


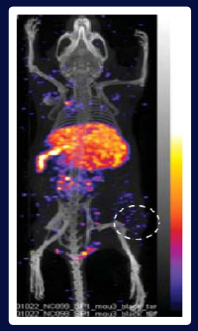


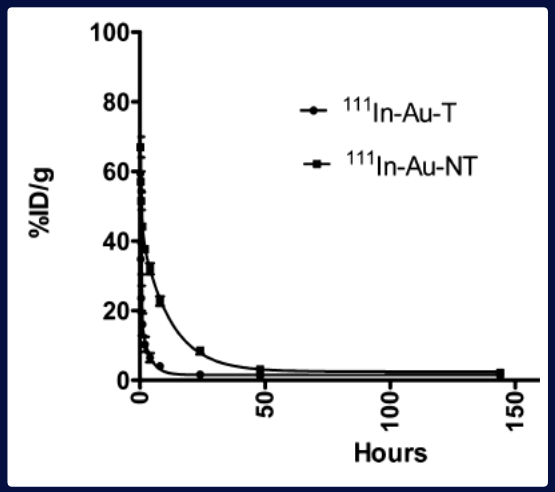
2 h | 24 h | 48 h | tumor @ 24 h

HER2-AuNP









=> *not very useful for molecular imaging…*

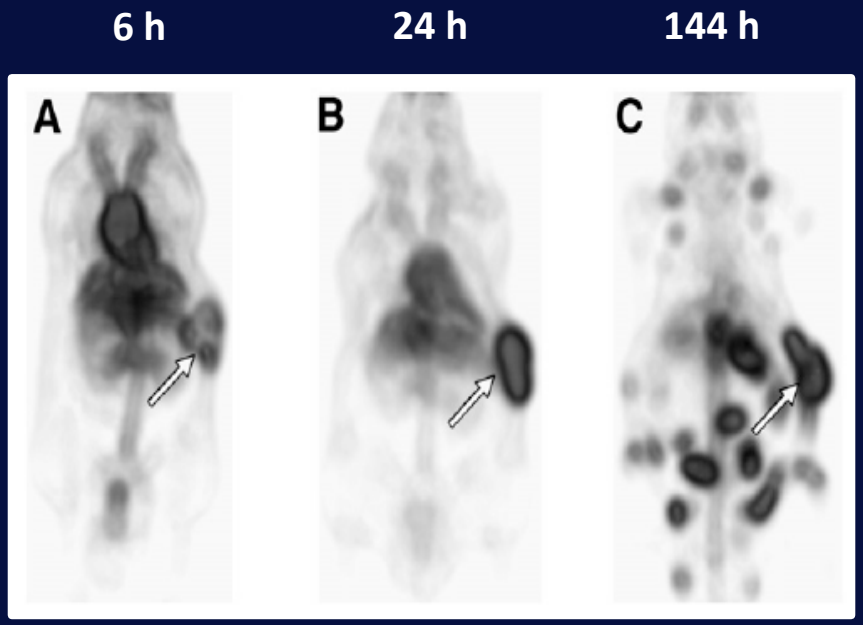
Chattopadhyay et al, Mol Pharmaceut (2012)

nanodiagnostics

extravascular targets

=> even smaller…

=> antibodies : radiolabeled Herceptin (~15 nm)



- high affinity binding ✔
- short circulation time ✖
- significant extravasation ✔
- deep penetration ✔
- no prolonged retention ✔/✖

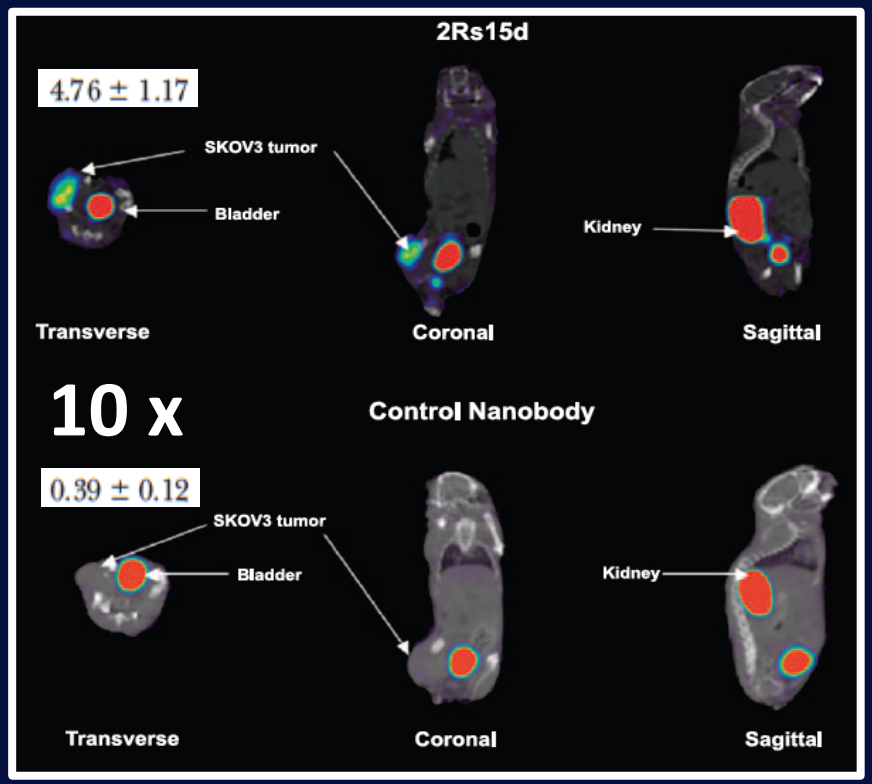
=> *reasonably useful for molecular imaging*

Dijkers et al, J Nucl Med (2009)

nanodiagnostics

nanobodies for **specific** molecular imaging of extravascular targets

highly specific accumulation already at 1 h p.i.



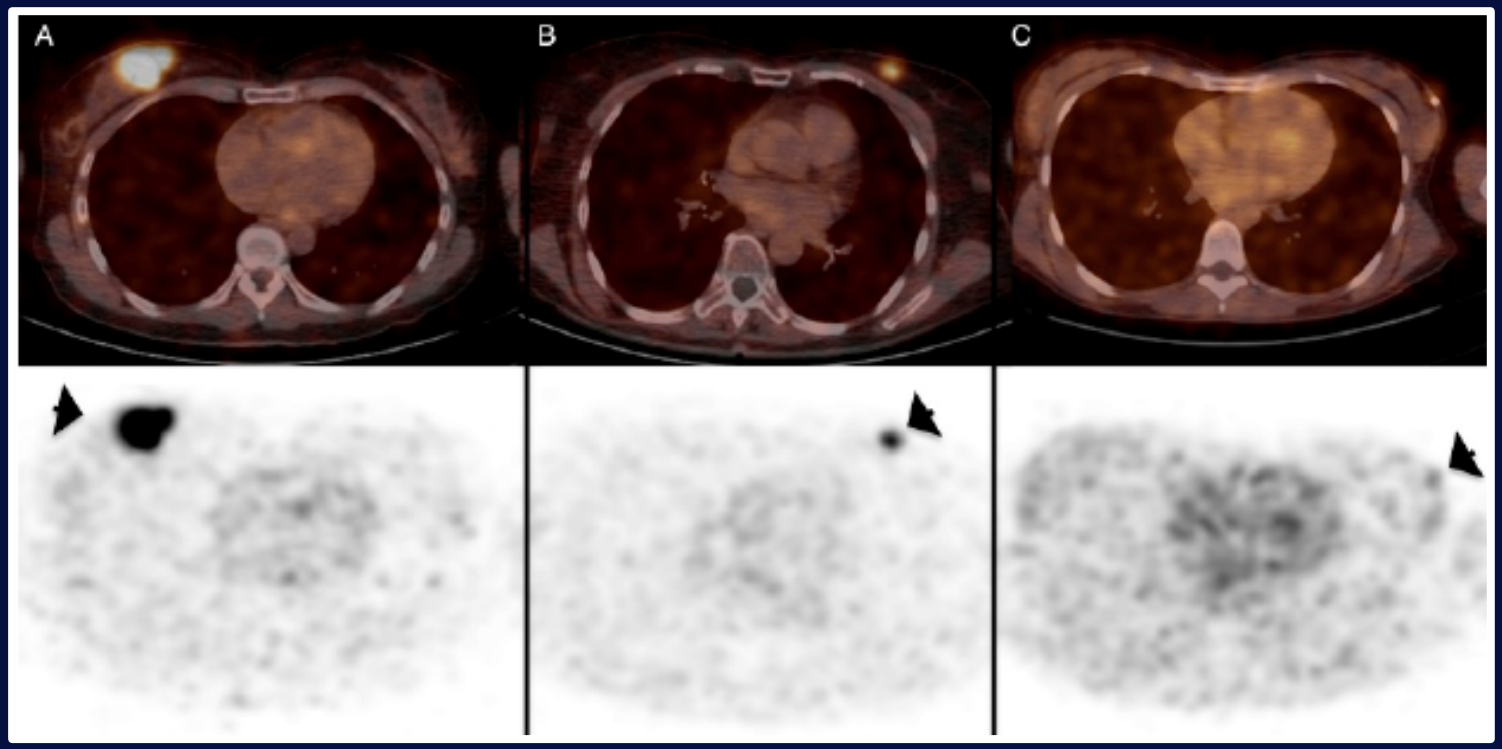
- high affinity binding ✔
- short circulation time ✔
- significant extravasation ✔
- deep penetration ✔
- no prolonged retention ✔

Vaneycken et al, FASEB J (2011)

nanodiagnostics

nanobodies for **specific** molecular imaging of extravascular targets

BC - high HER2 | BC - medium HER2 | BC - low HER2



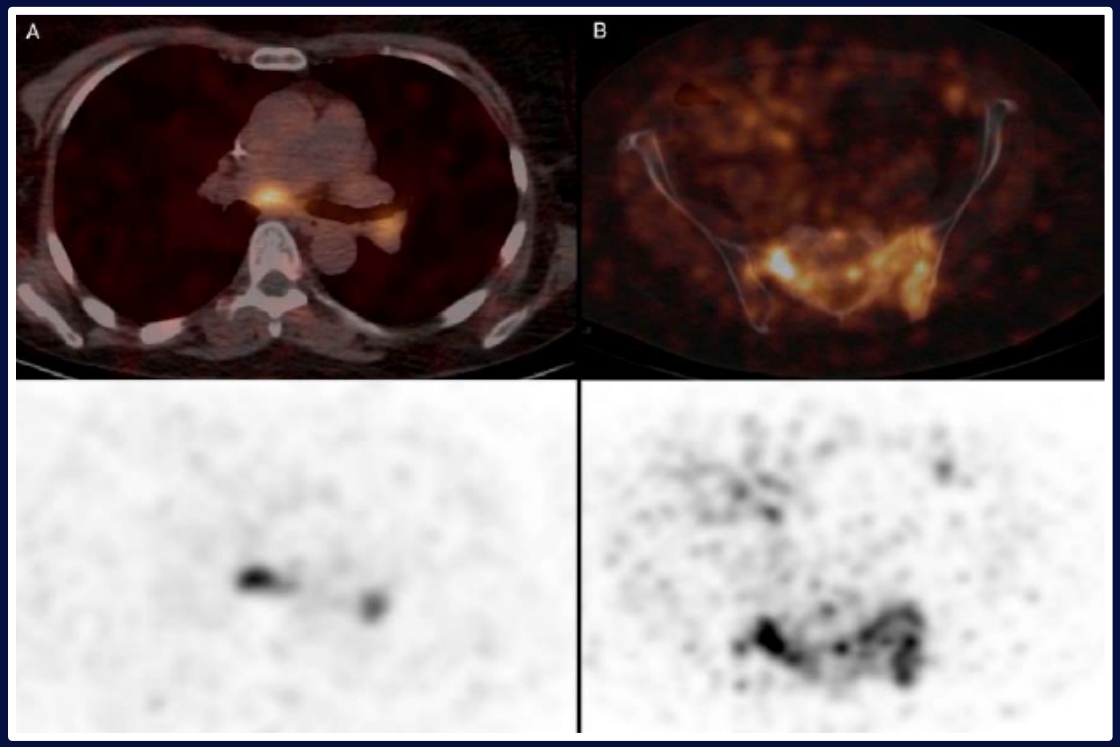
Keyaerts, Xavier et al, J Nucl Med (2016)

nanodiagnostics

nanobodies for **specific** molecular imaging of extravascular targets

HER2 in LN mets

HER2 in bone mets



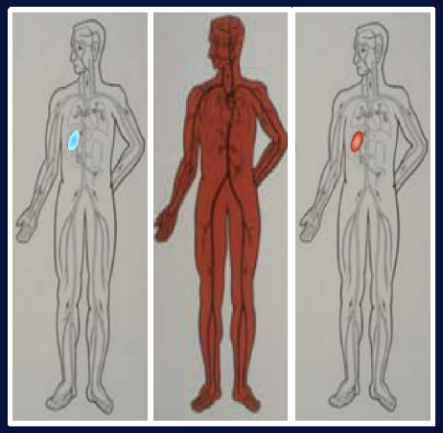
Keyaerts, Xavier et al, J Nucl Med 2016)

nanodiagnostics

for **specific** molecular imaging

of extravascular targets

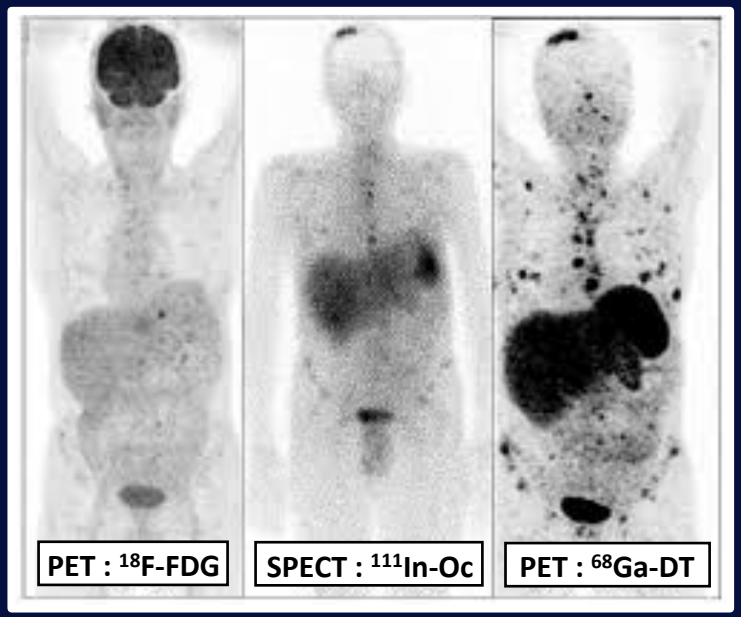
=> the smaller, the better !



FDG (~0.1 nm)

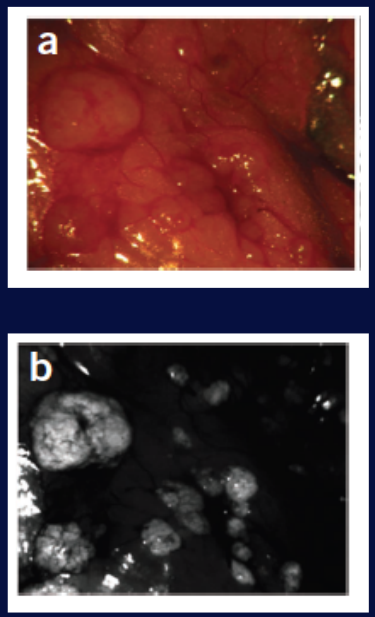
Lee et al

Octreotide / DOTA-TOC (~1 nm)



Bihl et al

Folate-FITC (~1 nm)



Van Dam et al

summary

- Nanoparticles : particular PK properties, useful for drug delivery
- Theranostic NP : useful to individualize and improve NM treatments

- Diagnostic NP : useful for many functional imaging applications
- Diagnostic NP : not very useful for highly specific molecular imaging

- Mol. Imaging : large (μ) for intravascular, small (p) for extravascular
- Mol. Imaging : high specificity required (vs. high concentration in DD)

www.e-smi.eu

imaging life esmi
European Society for Molecular Imaging

Find us on Facebook

TOPIM 2017 | NEUROIMAGING - FROM MOLECULES TO NETWORKS

- ABOUT THE ESMI
- PEOPLE & STRUCTURE
- YOUR MEMBERSHIP
- ESMI MAGAZINE & PUBLICATIONS
- ESMI AWARD
- ESMI JOURNAL

EMIM - EUROPEAN MI MEETING

- EMIM 2017 | Cologne
  - Plenary Speakers
- EMIM 2016 | Utrecht
- EMIM 2015 | Tubingen
- EMIM 2014 | Antwerp
- EMIM 2013 | Torino
- WMIC 2012/EMIM 2012 | Dublin
- EMIM 2011 | Leiden
- EMIM 2010
- EMIM 2009

12th European Molecular Imaging Meeting 5-7 April 2017

Be invited to Cologne, Germany for the EMIM 2017!

12th European Molecular Imaging Meeting
DATE: 5-7 April 2017
VENUE: Hörsaalgebäude University Cologne
Universitätsstr. 33, 50931 Cologne

It is with pleasure to invite you to Cologne for the 12th European Molecular Imaging Meeting: the EMIM 2017. **It's your meeting!** - present and share your research, enlarge your network, and meet friends and collaborators.

We are looking forward to meeting all of you in Cologne!

thank you

tlammers@ukaachen.de

...