Deutsche Gesellschaft für Nuklearmedizin e.V.

SUMMER SCHOOL 2018

Development of Tracers and Theranostics: Nanoparticles

August 30 – September 1, 2018

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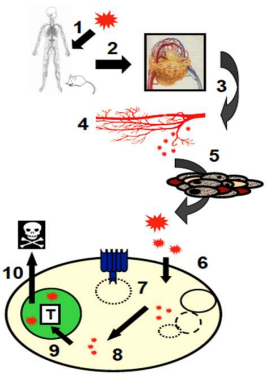
SUMMER SCHOOL 2018

Drug Delivery to Tumors

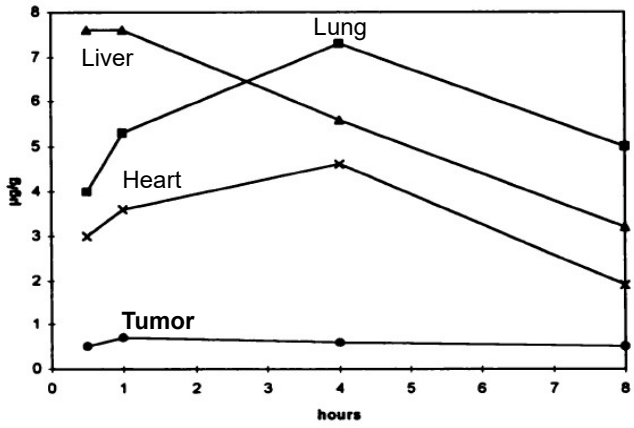
In order to be effective, a chemotherapeutic agent has to…

- 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

Doxorubicin distribution upon i.v. injection in mice



Bosslet et al, Cancer Res (1998)

Drug Delivery to Tumors -Barriers

Barriers to drug delivery to tumors

Chemical barriers	Biological barriers	Physical barriers	Clinical barriers
Low solubility	Renal filtration	Vascular endothelium	Low efficacy
Low stability	Hepatic degradation	Perivascular space	High toxicity
Low molecular weight	High tumor cell density	Cellular membrane	Need for hospitalization
Large volume of distribution	High interstitial fluid pressure	Nuclear membrane	Frequent administration
Charge interactions	Drug efflux pumps	Blood brain barrier	Low cost-effectiveness

Drug Delivery to Tumors –Drug Delivery System

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

2 Different Faces :

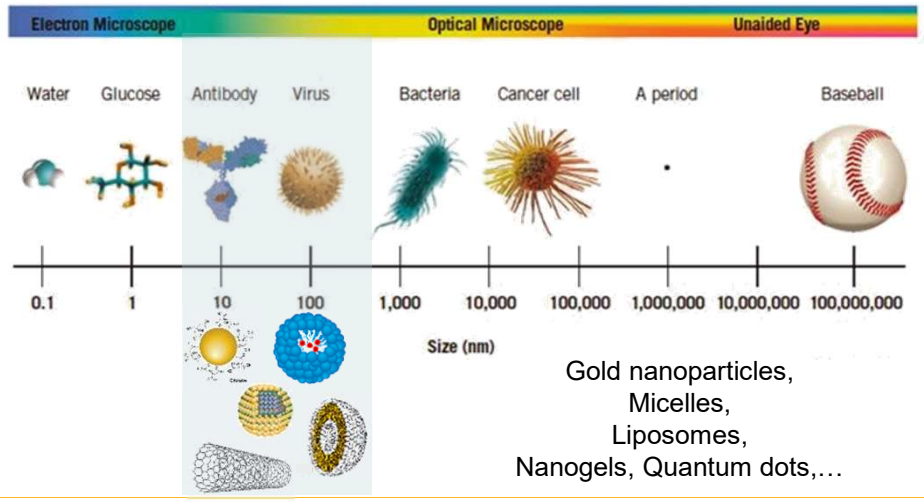
1 : Site-specific drug delivery

→ Improve antitumor activity

2 : Site-avoidance drug delivery

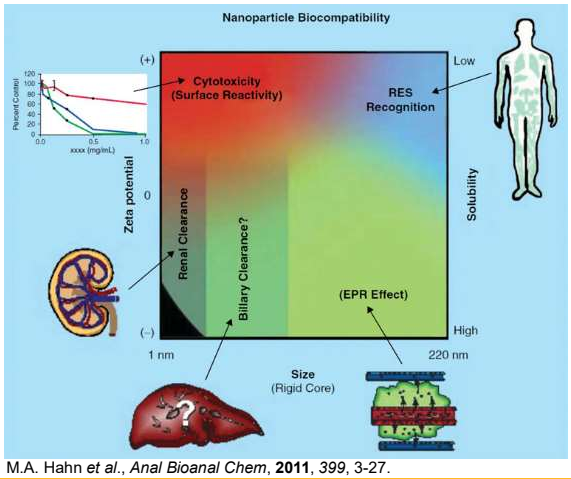
→ Reduce systemic side effects

Drug Delivery to Tumors –"Nano"-Drug Delivery System

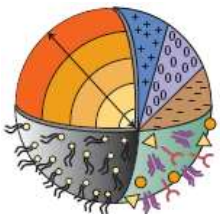


Gold nanoparticles,
Micelles,
Liposomes,
Nanogels, Quantum dots,…

Drug Delivery to Tumors –"Nano"-Drug Delivery System



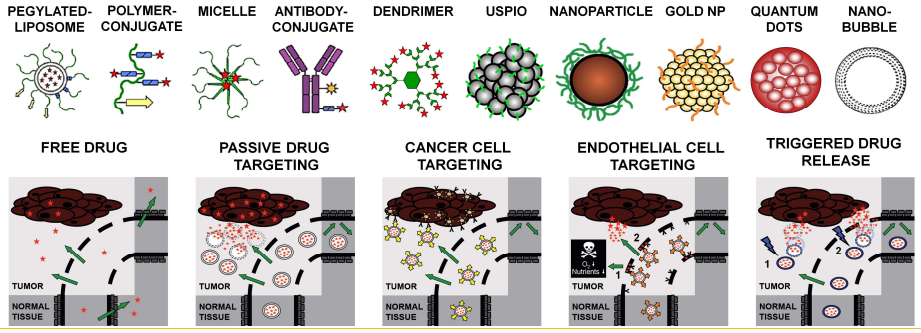
M.A. Hahn *et al.*, *Anal Bioanal Chem*, **2011**, *399*, 3-27.



- Size: 10-100(0) nm
- Hydrophilicity
- **Charge:** neutral, anionic, cationic
- Modification for radiolabeling
- Targeting by Bioligands

Drug Delivery to Tumors –Nanomedicine

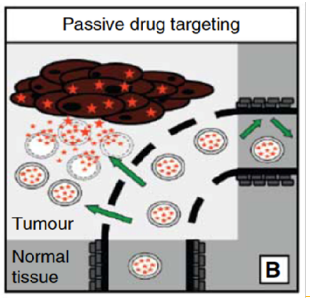
- 1-100(0) nm-sized carrier materials
- **Protects drug from body ⟺ protects body from drug**
- Improve efficacy and reduce toxicity

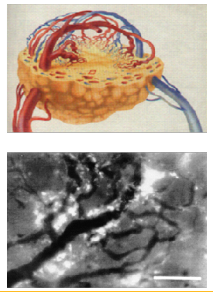


Drug Delivery to Tumors –Nanomedicine

- High blood vessel density +
- High vascular permeability +
- Lack of lymphatic drainage

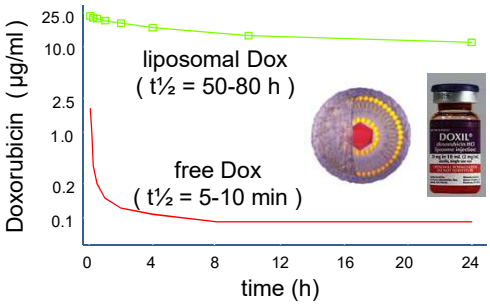
→ Enhanced Permeability and Retention (**EPR**) Effect





Efficient accumulation of **long-circulating** drug delivery systems

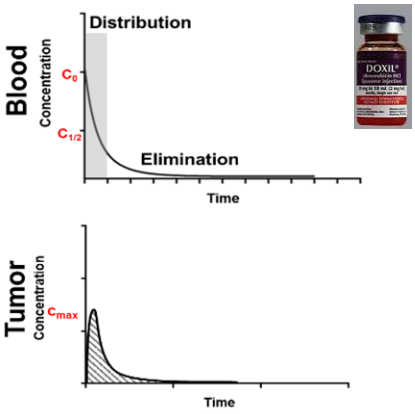
Drug Delivery to Tumors –Passive Targeting



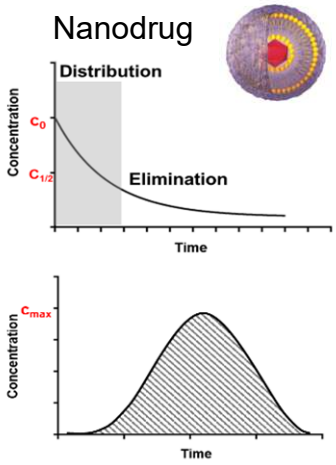
Gabizon et al, Cancer Res (1994)

Drug Delivery to Tumors –Passive Targeting

Low molecular weight drug



Nanodrug



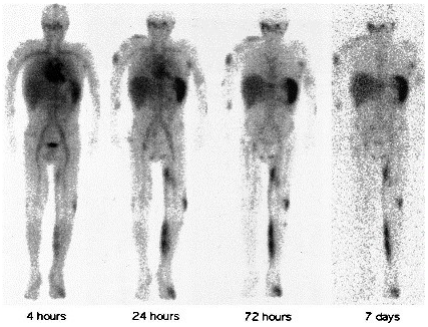
Golombek et al, Adv Drug Deliv Rev. 2018

Drug Delivery to Tumors –Passive Targeting

Kaposi sarcoma :
Improved efficacy vs. ABV

→ 1 CR + 60/133 PR vs. 31/125 PR

Better tolerability
→ **Less cardiomyopathy, nausea, alopecia**

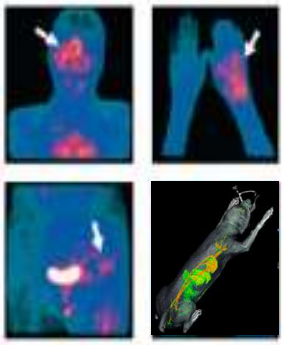


Harrington et al, Clin Cancer Res (2001)
Gabizon et al, Cancer Res (1994)

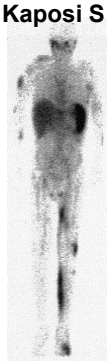
Drug Targeting to Tumors

EPR is highly variable

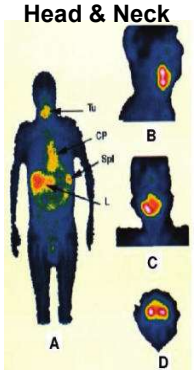
Sarcoma



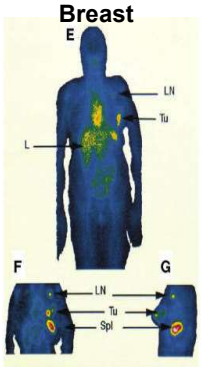
Kaposi S



Head & Neck



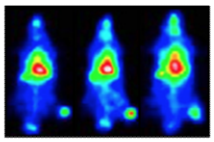
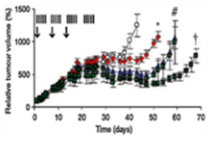
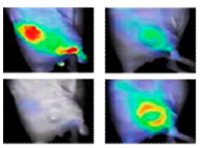
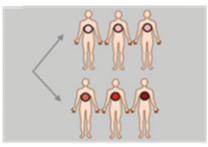
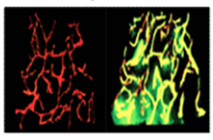
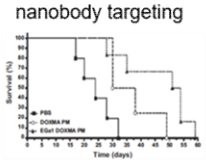
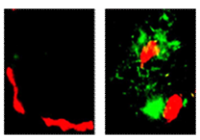
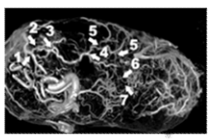
Breast



Koukourakis et al, Acta Oncol (2000) *Harrington et al, Clin Cancer Res (2001)* *Hansen et al, ACS Nano (2015)*

How to Overcome Heterogeneity in EPR-mediated Tumor Targeting

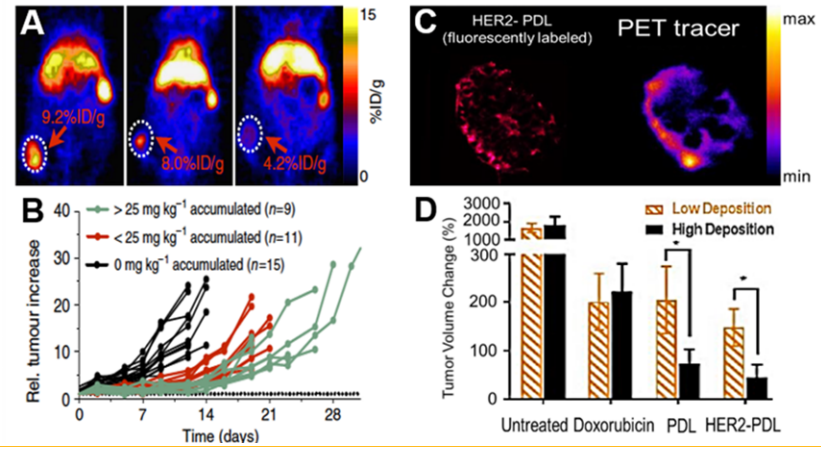
EPR

enhancing	combining	bypassing	imaging
con + RT + HT	nano + radiochemo	vascular targeting	direct : personalisation
			
sonoporation	nanobody targeting	intravascular release	indirect : understanding
			

Golombek et al, Adv Drug Deliv Rev. (2018)

How to Overcome Heterogeneity in EPR-mediated Tumor Targeting

Imaging EPR

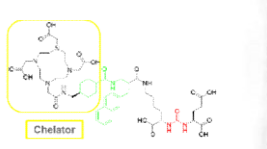


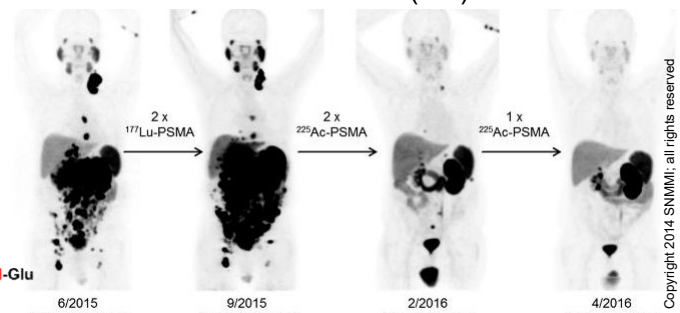
Golombek et al, Adv Drug Deliv Rev. (2018)

Theranostics

Theranostic pairs in Nuclear Medicine: ^{68}Ga/ (^{90}Y) ^{177}Lu/ ^{225}Ac

PSMA-617





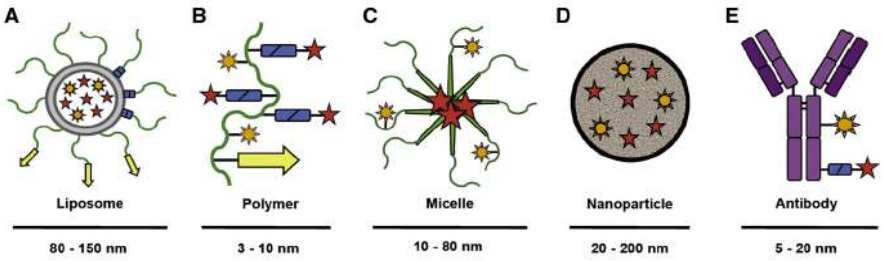
Clemens Kratochwil et al. J Nucl Med 2016;57:1941-1944

^{68}Ga (89% β^+) **$t_{1/2}$ = 68min**	^{177}Lu(β^- / γ) **$t_{1/2}$ = 6.7d**
^{111}In (>99.9 % EC) **$t_{1/2}$ = 67.9 h**	^{90}Y (> 99% β^-) **$t_{1/2}$ = 64h**
	^{225}Ac (α) $t_{1/2}$ = 10d

(Nano)Theranostics

Nanotheranostics

- Important advantage of nanomedicine formulations is that they **enable the combination of drugs and imaging agents** within a single formulation



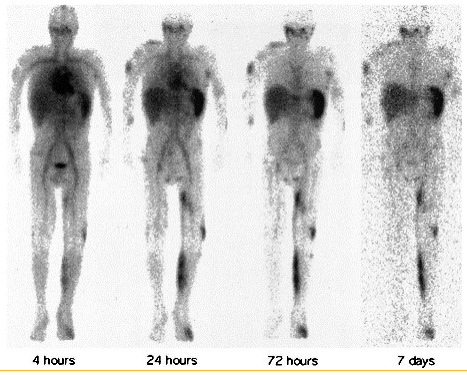
Lammers et al, Acc Chem Res (2011)

Nanotheranostics

- **Monitoring tumor targeting to predict therapeutic outcome**

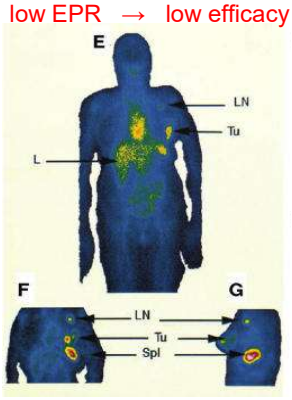
Doxil® in Kaposi Sarcoma

high EPR → high efficacy



Doxil® in Breast Cancer

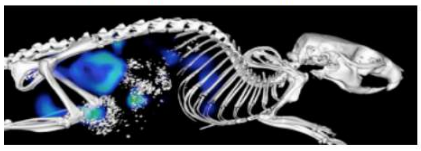
low EPR → low efficacy



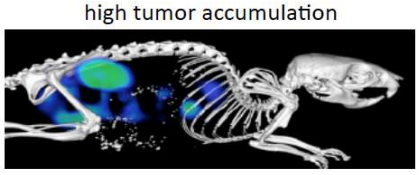
Nanotheranostics : Preclinical Proof-of-concept

Tumor accumulation correlates with antitumor efficacy

low tumor accumulation

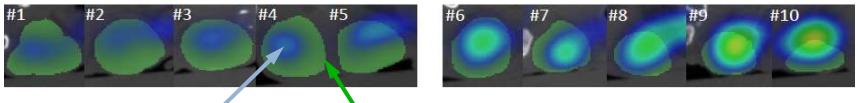


high tumor accumulation



low accumulation => poor efficacy

high accumulation => good efficacy



tumor accumulation

tumor size

Shi et al, ACS Nano (2015)
Theek et al, J Control Release (2016)

Nanotheranostics : Preclinical Proof-of-concept

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

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DOI: 10.1038/ncomms11838 OPEN

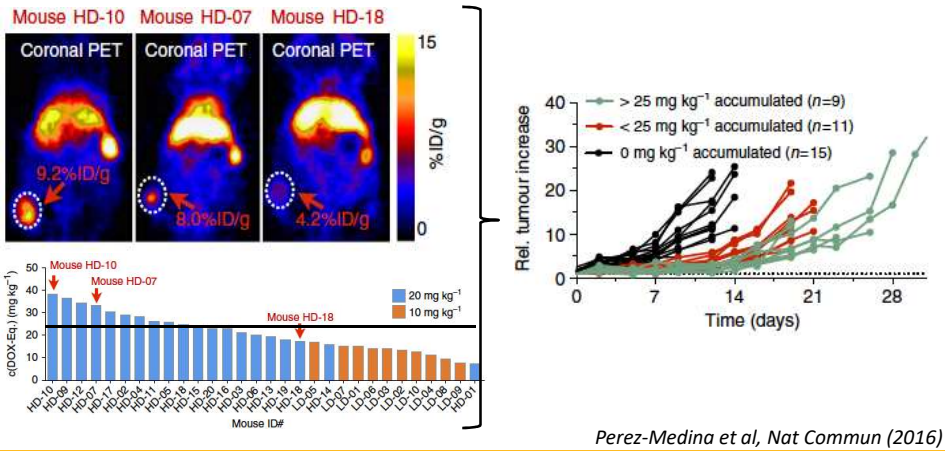
Nanoreporter PET predicts the efficacy of anti-cancer nanotherapy

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, Science Transl Med (2015)
Perez-Medina et al, Nat Commun (2016)

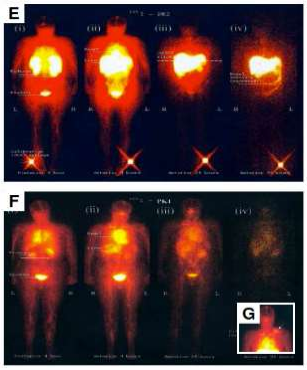
Nanotheranostics : Preclinical Proof-of-concept

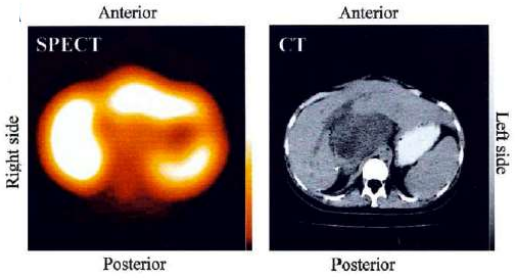
Tumor accumulation correlates with antitumor efficacy



Perez-Medina et al, Nat Commun (2016)

Nanotheranostics : Initial Clinical Efforts





- **Galactosamine-targeted pHPMA-GFLG-doxorubicin** (PK2)
- Efficient liver localization, but not always good tumor accumulation
- Exemplifies how **imaging** can be used **to pre-select patients** in clinical trials

Seymour et al, J Clin Oncol (2001)

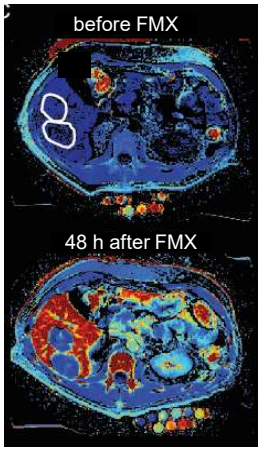
Nanotheranostics : Initial Clinical Efforts

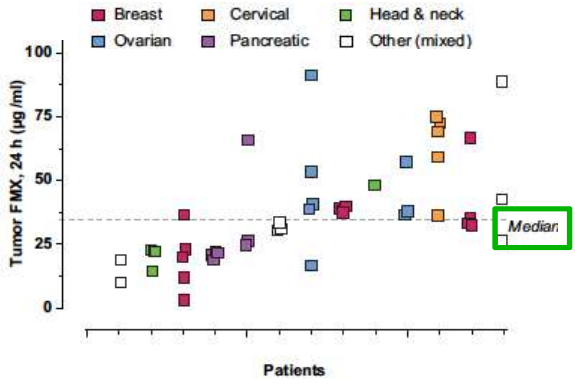
- Lung accumulation/distribution of radiolabeled viral NP in cystic fibrosis (CF) patients
- Patient pre-selection in clinical trials on the basis of non-invasive imaging

Image courtesy: Uta Griesenbach

Nanotheranostics : Clinical Proof-of-concept

Companion diagnostic approach : iron oxide NP (Feraheme®)

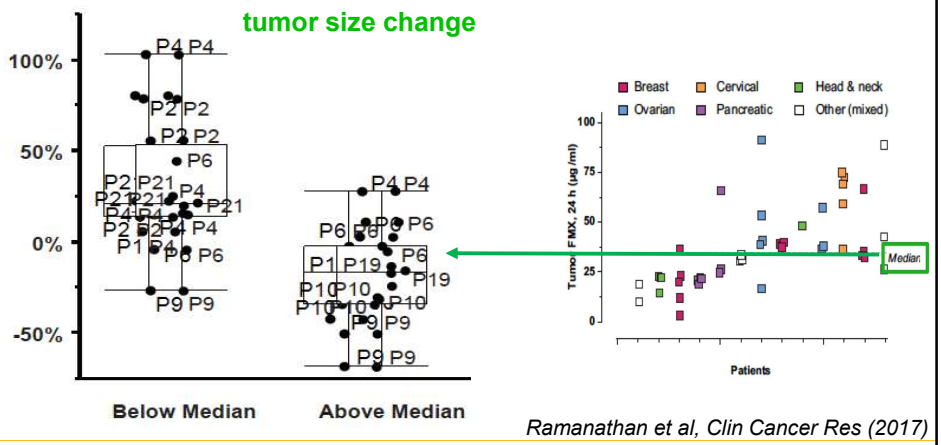




Ramanathan et al, Clin Cancer Res (2017)

Nanotheranostics : Clinical Proof-of-concept

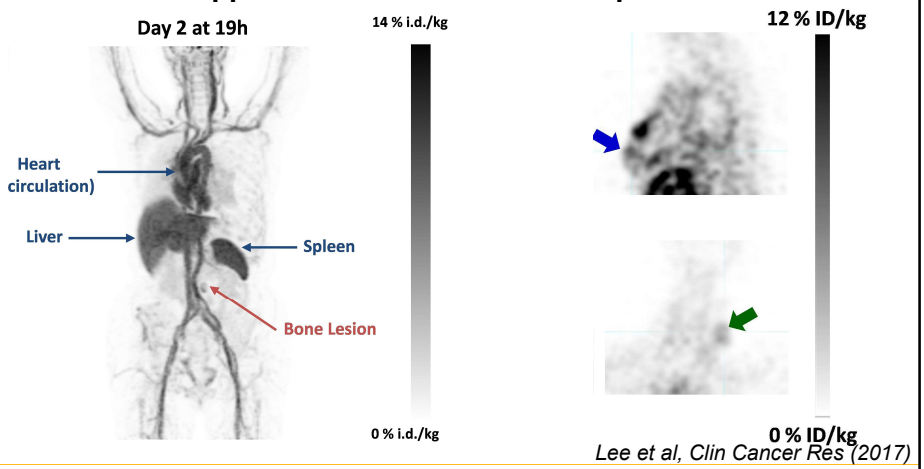
Companion diagnostic approach : iron oxide NP (Feraheme®)



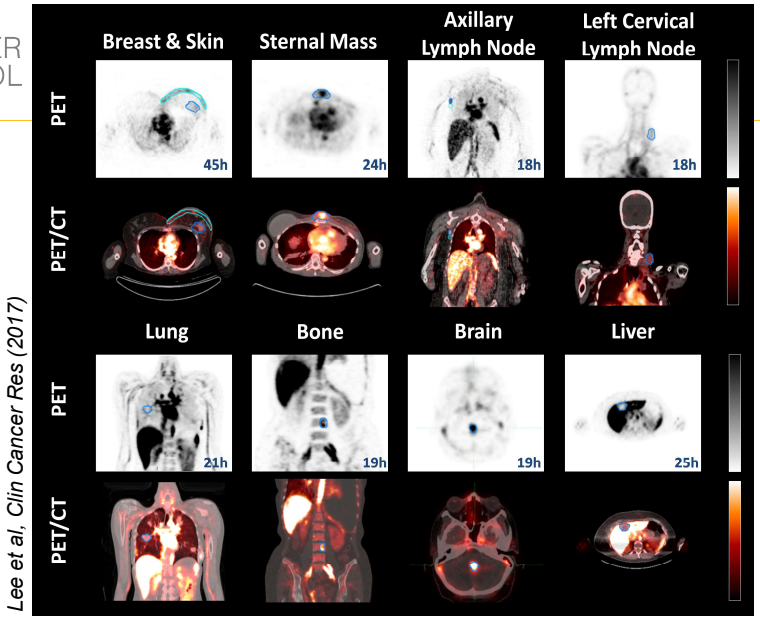
Ramanathan et al, Clin Cancer Res (2017)

Nanotheranostics : Clinical Proof-of-concept

Theranostic approach : ^{64}Cu-labeled Dox-liposomes



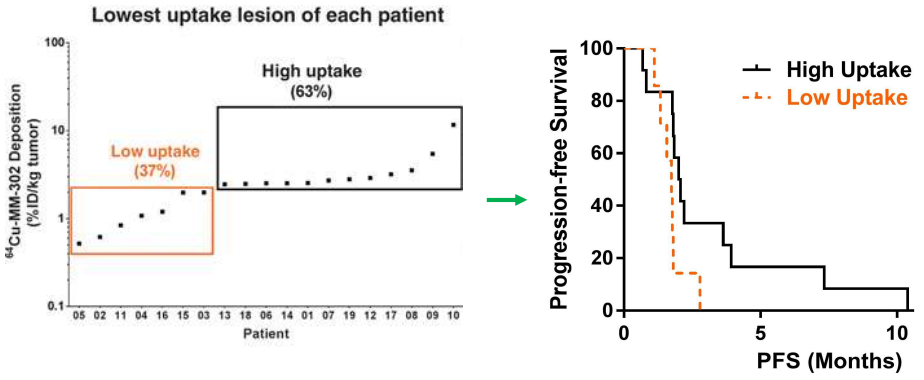
Lee et al, Clin Cancer Res (2017)



Lee et al, Clin Cancer Res (2017)

Nanotheranostics : Clinical Proof-of-concept

Theranostic approach : ^{64}Cu-labeled Dox-liposomes



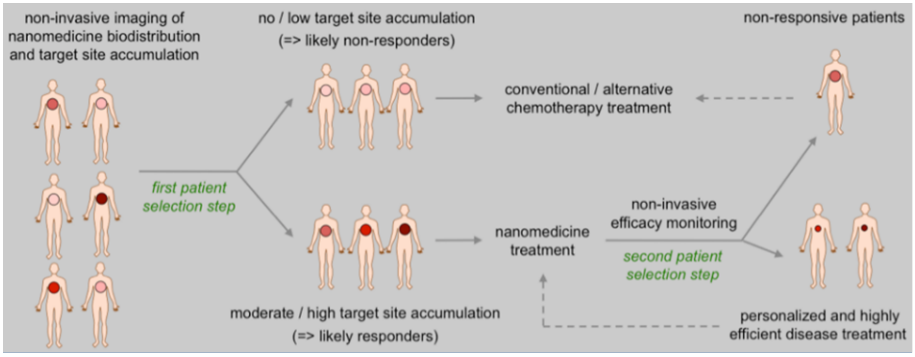
Lee et al, Clin Cancer Res (2017)

Personalized Nanomedicine

Combination of drug targeting + imaging

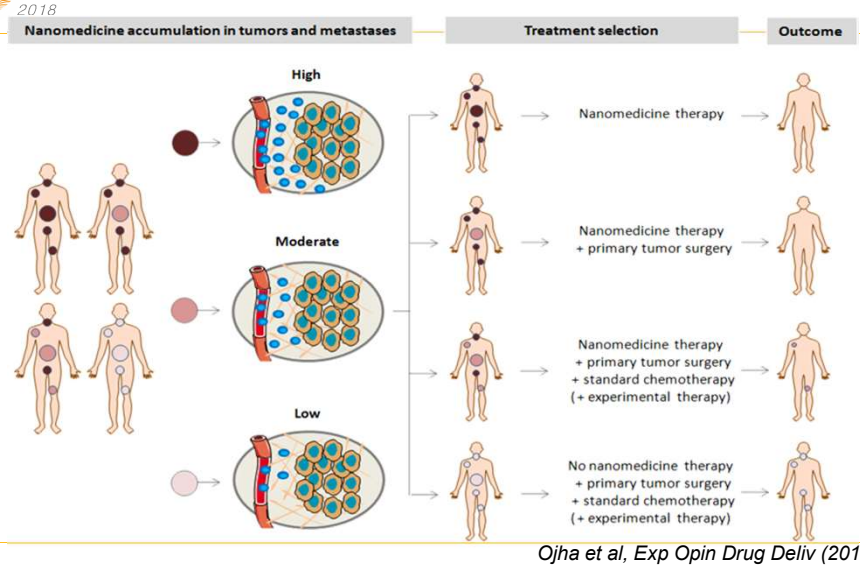
→ Enables patient **pre-selection**

→ Facilitates **clinical translation**



Lammers et al, Clin Cancer Res (2012)

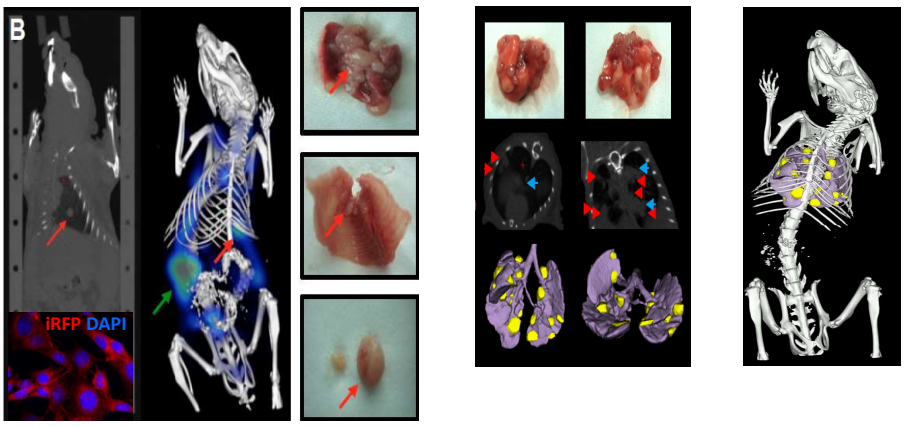
Beyond Solid Tumor Targeting



Ojha et al, Exp Opin Drug Deliv (2015)

Beyond Solid Tumor Targeting -Targeting Metastasis

Hybrid CT-FMT imaging of iRFP-transfected 4T1 tumors and metastases

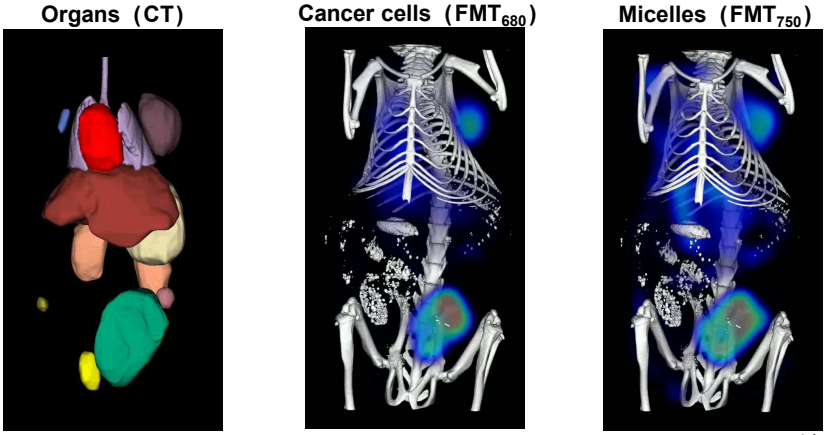


Rizzo et al (in prep)

Beyond Solid Tumor Targeting -Targeting Metastasis

Accumulation of polymeric micelles in tumors and metastases

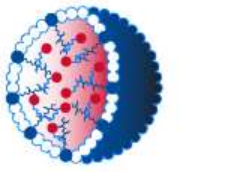
Organs (CT) | **Cancer cells (FMT_{680})** | **Micelles (FMT_{750})**



Rizzo et al (in prep)

Beyond Solid Tumor Targeting -Targeting Metastasis

Efficacy of docetaxel-loaded polymeric micelles (CriPec®) in metastatic TNBC



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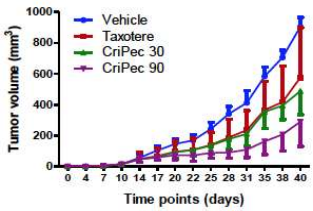
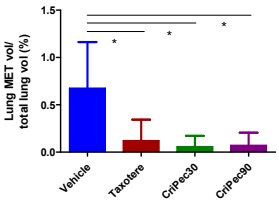
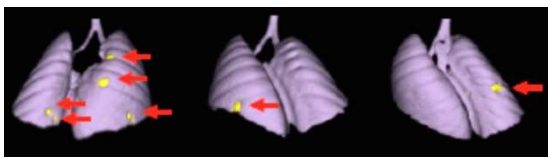
TUMOR



LUNG METASTASES





Biomaterials 2010
Angew Chem 2012
ACS Nano 2014
Nano Today 2015

Rizzo et al (in prep)

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Cristal Therapeutics

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Pipeline

Currently, four programs are in various stages of (non)clinical development as indicated in the pipeline overview.

PROPRIETARY PROGRAMS		INDICATION	DISCOVERY	PoC	PRECLINICAL	PHASE I	PHASE IIA
CriPec docetaxel		solid tumours					
CriPec dexamethasone		inflammation					
CriPec ATN		solid tumours					
CriPec oligonucleotides		various					
COLLABORATIVE PROGRAMS							
CriPec peptide	partner	solid tumours					
CriVac antigen		solid tumours					

achieved ongoing

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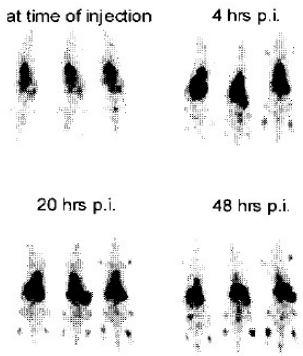
Inflammation

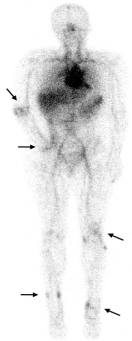
Inflammatory disorders and infections also display “EPR”

^{111}In-PEG-PLP-liposomes in RA



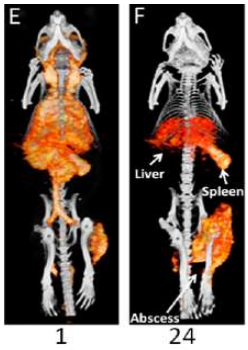
Metselaar et al, Arthr Rheum (2003)

^{111}In-PEG-Lip in RA



Boerman et al (UMCN)

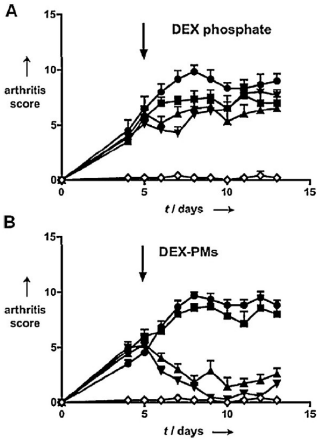
^{111}In-PEG-Lip in SA

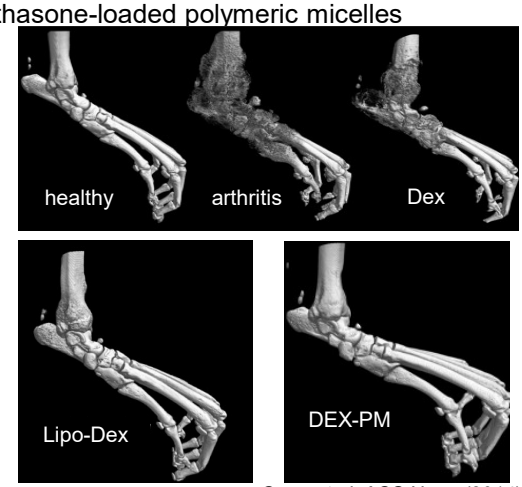


Van der Geest et al, JCR (2015)

Inflammation

Arthritis treatment with dexamethasone-loaded polymeric micelles





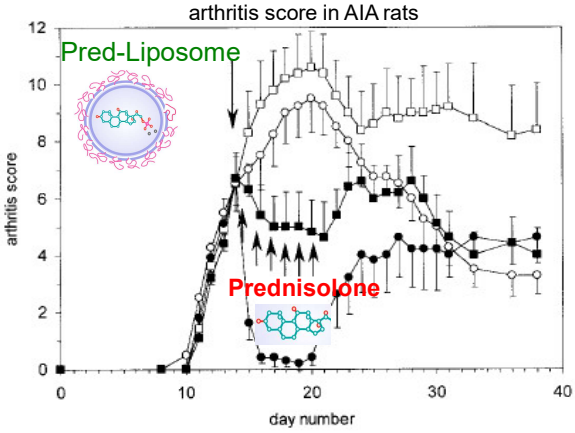
Crielaard et al, Angew Chem Int Ed (2012)

Quan et al, ACS Nano (2014)

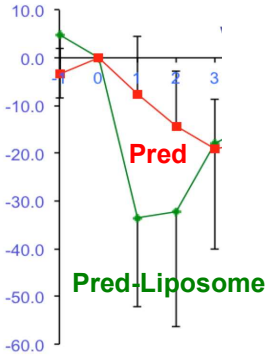
Inflammation

Corticosteroid-loaded liposomes

arthritis score in AIA rats



DAS28 score in RA patients

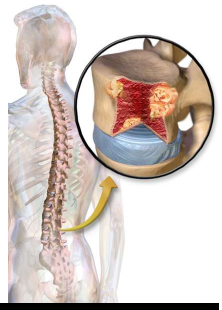


Metselaar et al (Enceladus, RWTH)

Inflammation

Corticosteroid-loaded liposomes

Phase III: **rheumatoid arthritis**
Phase II: **inflammatory bowel disease**
Phase I: **atherosclerosis**
03.2017: **multiple myeloma (at RWTH)**



enceladus

RWTH AACHEN UNIVERSITY
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Center for Translational & Clinical Research (CTC-A)

Summary

- Nanomedicines aim to **improve therapeutic index**
- Nanomedicine rely on **"EPR"**, which is **highly variable**
- Rational concepts are needed to **address heterogeneity**
- **Imaging helps** to individualize and improve nanotherapies

→**Integrate biomarkers** : like biopsies for molecularly targeted therapeutics

	with HER2 testing	without testing
No. of patients	470	2200
Response rate	50%	10%
Years of follow-up	1.6	10

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Thank you

ExMI Experimental Molecular Imaging

HELMHOLTZ-INSTITUT FÜR BIOMEDIZINISCHE TECHNIK

erc STW-KWF DFG SFB TRR57 SFB1056 2014 EFRE.NRW

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