nanomedicine and theranostics

- from concepts to clinical translation -

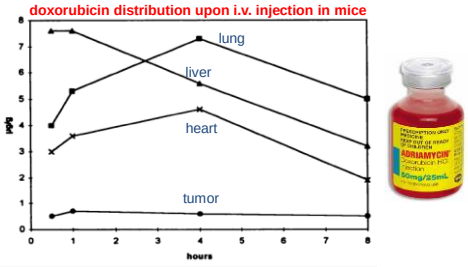
Twan Lammers

Dept. of Nanomedicine and Theranostics, RWTH Aachen
Dept. of Targeted Therapeutics, University of Twente
Dept. of Pharmaceutics, Utrecht University

ExMI

drug targeting to tumors

is difficult

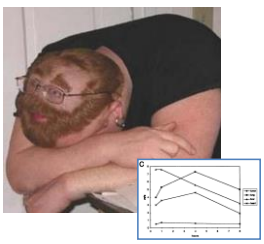


Bosslet et al, Cancer Res (1998)

ExMI

drug delivery systems

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



2 different faces :

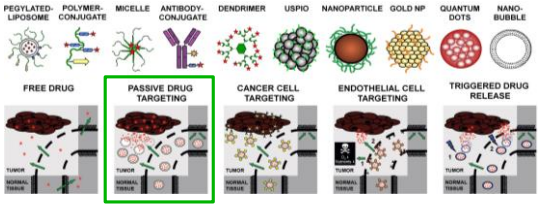
1 : site-specific drug delivery
=> to improve antitumor activity

2 : site-avoidance drug delivery
=> to reduce systemic side effects

ExMI

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



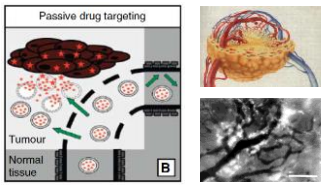
Kunjachan et al, Chem Rev (2015)

passive tumor targeting

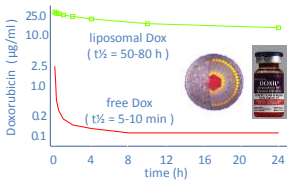
- high blood vessel density +
- high vascular permeability +
- lack of lymphatic drainage →

Enhanced Permeability and Retention (**EPR**) effect

=> efficient accumulation of long-circulating drug delivery systems

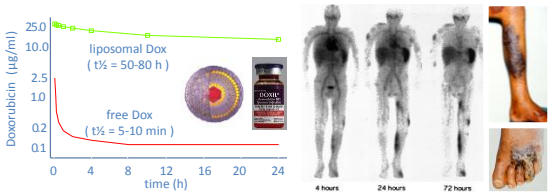


tumor-targeted nanomedicines



Gabizon et al, Cancer Res (1994)

tumor-targeted nanomedicines



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

better tolerability => less cardiomyopathy, nausea, alopecia

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

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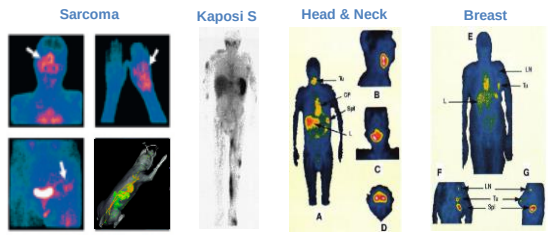
tumor-targeted nanomedicines

EPR is highly variable



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

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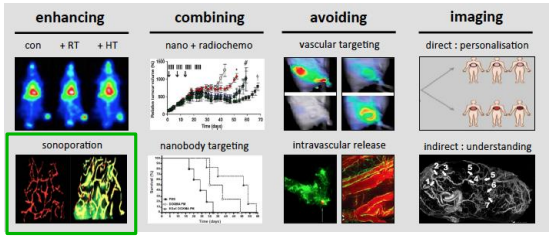
improving tumor-targeted nanomedicine therapies



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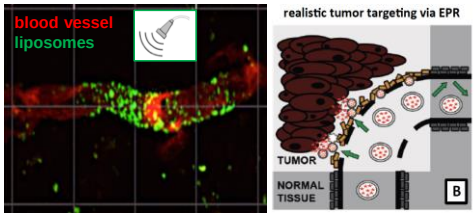
sonoporation

helps to improve extravasation and penetration

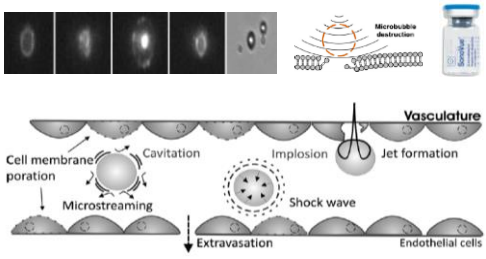
=> penetration is a big problem : for nanomedicines, antibodies and standard drugs



Lammers et al, J Control Release (2012)

sonoporation

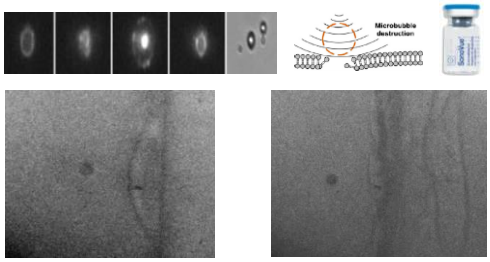
is based on the combination of ultrasound and microbubbles



Lentacker et al, Soft Matter (2009)

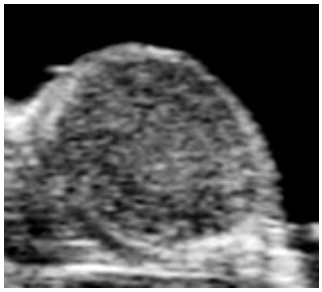
sonoporation

is based on the combination of ultrasound and microbubbles



Prentice et al, Nature Physics (2005)

sonoporation

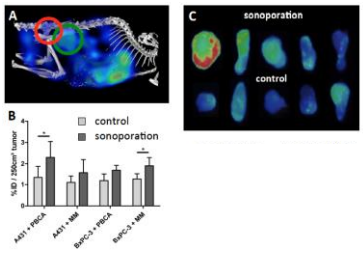


Theek et al

ExMI

sonoporation

improves the tumor accumulation and penetration of liposomes

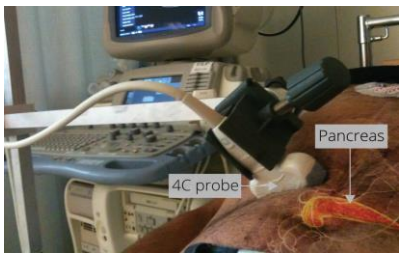


Theek et al, J Control Release (2016)

ExMI

sonoporation

first clinical proof-of-concept : 10 patients with pancreatic cancer



Dimcevski et al, J Control Release (2016)

ExMI

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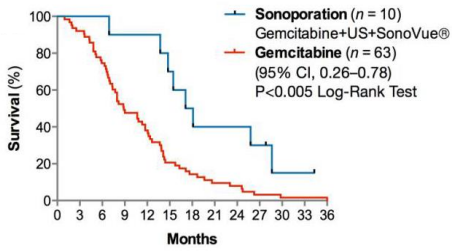
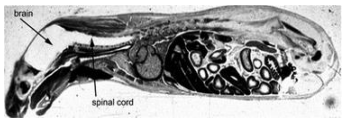


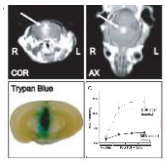
Dimcevski et al, J Control Release (2016)

ExMI

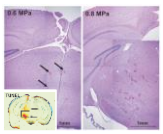
sonoporation for drug delivery to the brain



Pardridge et al, Drug Discov Today (2007)



Dasgupta et al, Drug Discov Today (2016)

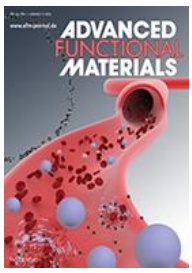


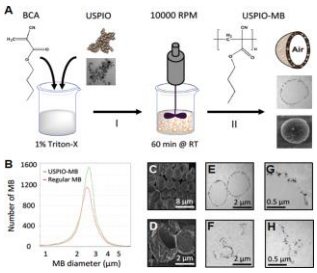
Kinoshita et al, PNAS (2006)

ExMI

sonoporation for drug delivery to the brain

USPIO-loaded microbubbles for mediating and monitoring BBB opening





Lammers, Koczera et al, Adv Funct Mater (2015)

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sonoporation for drug delivery to the brain

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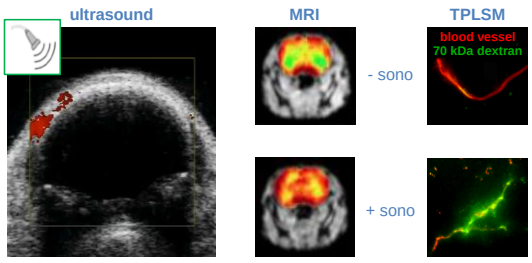
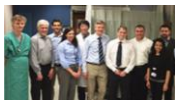
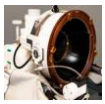


Lammers, Koczera et al, Adv Funct Mater (2015)

ExMI

sonoporation for drug delivery to the brain

November 2015


FOCUSED ULTRASOUND FOUNDATION

Accelerating the Development and Adoption of Focused Ultrasound

Virtual Press Conference

Blood-Brain Barrier Opened Non-Invasively With Focused Ultrasound

The blood-brain barrier has been non-invasively opened in a patient for the first time. A team at Sunnybrook Health Sciences Centre in Toronto used focused ultrasound to enable temporary and targeted **opening of the blood-brain barrier (BBB)**, allowing the more effective delivery of chemotherapy into a patient's malignant brain tumor.

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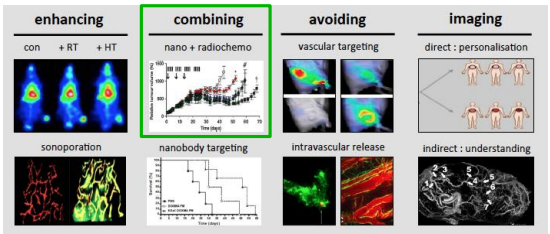
improving tumor-targeted nanomedicine therapies



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nano-radiochemotherapy

Lammers et al, Nano Today (2010)

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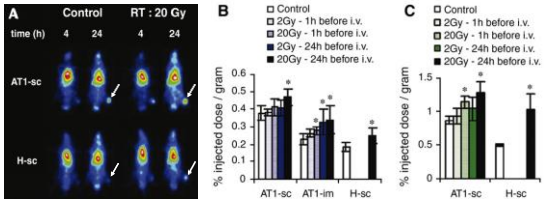
radiotherapy improves tumor targeting

5 nm ^{131}I-pHPMA polymers | 5 nm polymers + RT | 10 nm polymers + RT



Lammers et al, J Control Release (2007)

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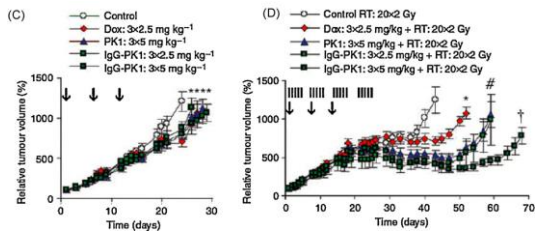
tumor targeting improves Doxorubicin-RCT

- radiotherapy | + radiotherapy



Lammers et al, Brit J Cancer (2008)

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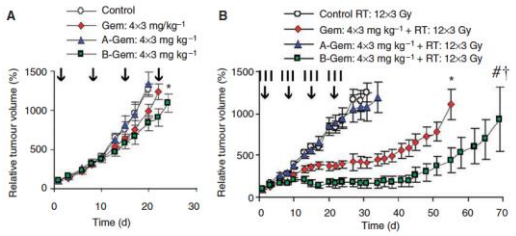
tumor targeting improves Gemcitabine-RCT

- radiotherapy + radiotherapy



Lammers et al, Brit J Cancer (2008)

improving tumor-targeted nanomedicine therapies

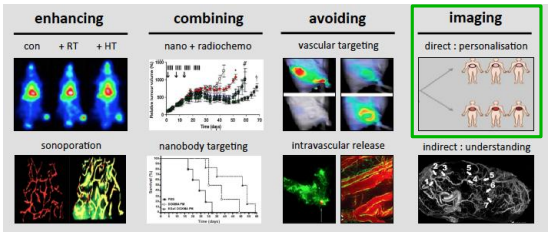
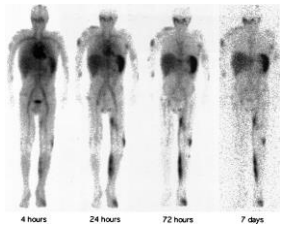


image-guided drug delivery

monitoring tumor targeting to predict therapeutic outcome

Doxil® in Kaposi Sarcoma

high EPR => high efficacy



Doxil® in Breast Cancer

low EPR => low efficacy

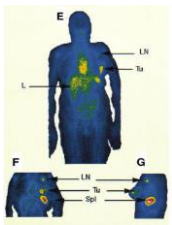
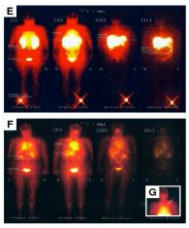
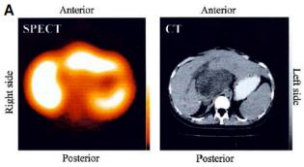


image-guided drug delivery





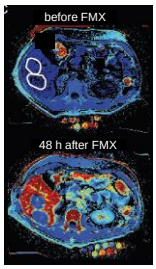
- galactosamine-targeted poly(HPMA)-doxorubicin (PK2)
- good liver localization, but inefficient accumulation in HCC tumors
- exemplifies how imaging can be used to pre-select patients in clinical trials

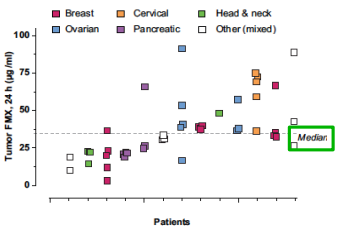
Seymour et al, J Clin Oncol (2001)

ExMI

clinical proof-of-concept

companion diagnostic approach : iron oxide NP (Feraheme®)





Ramanathan et al, Clin Cancer Res (2017)

ExMI

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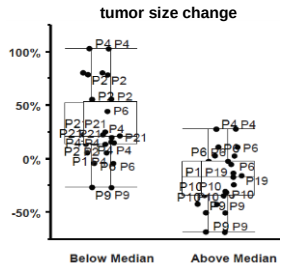
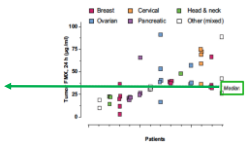


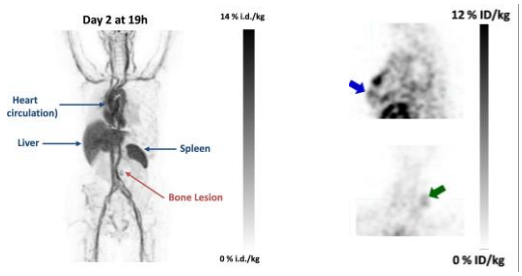


Ramanathan et al, Clin Cancer Res (2017)

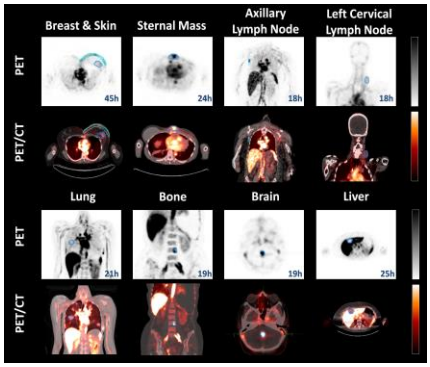
ExMI

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)

clinical proof-of-concept

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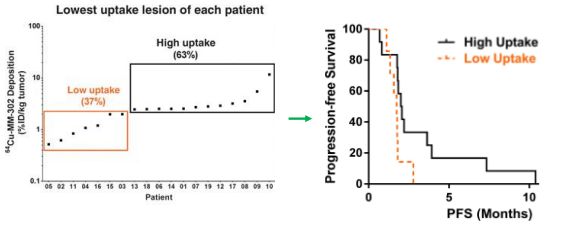

Lee et al, Clin Cancer Res (2017)

Perspective

Clinical Cancer Research

Personalized Nanomedicine

Twan Lammers[1,2,3], Larissa Y. Rizzo[1], Gert Storm[2,3], and Fabian Kiessling[1]

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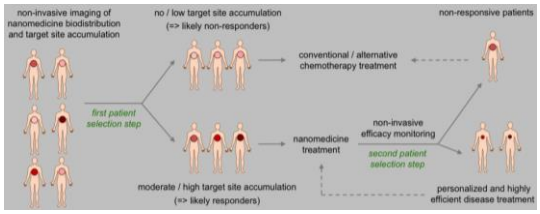
personalized nanomedicine

combination of drug targeting + imaging

=> enables patient pre-selection
=> facilitates clinical translation



Lammers et al, Clin Cancer Res (2012)

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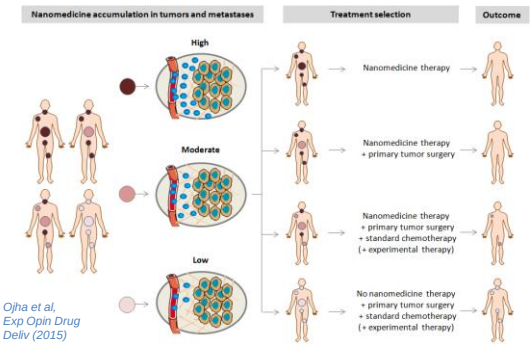
beyond solid tumor targeting



Ojha et al, Exp Opin Drug Deliv (2015)

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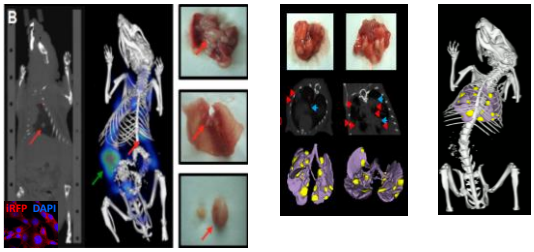
targeting metastasis

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



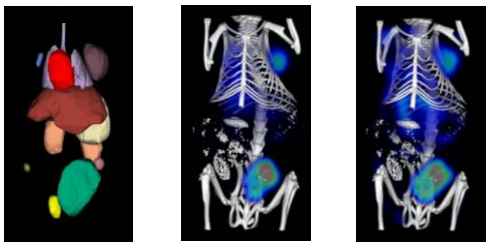
Rizzo et al (in prep)

ExMI

targeting metastasis

accumulation of polymeric micelles in tumors and metastases

organs (CT) | cancer cells (FMT_{680}) | micelles (FMT_{750})

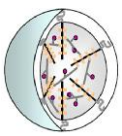


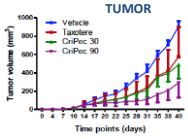
Rizzo et al (in prep)

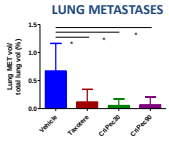
ExMI

targeting metastasis

efficacy of docetaxel-loaded polymeric micelles in metastatic TNBC

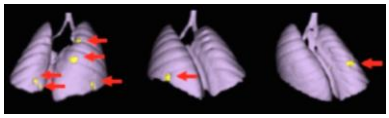






Cristal Therapeutics

Biomaterials 2010
Angew Chem 2012
ACS Nano 2014
Nano Today 2015



Rizzo et al (in prep)

ExMI

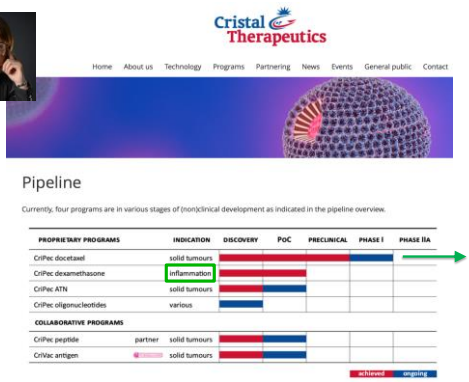
translation

REVIEW

Core-crosslinked polymeric micelles: Principles, preparation, biomedical applications and clinical translation

Marina Talelli[a,b,1], Matthias Barz[c,1], Cristianne J.F. Rijcken[d], Fabian Kiessling[e], Wim E. Hennink[a], Twan Lammers[a,e,f,*]

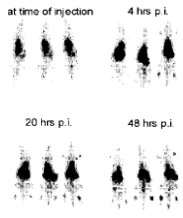
Talelli et al, Nano Today (2015)



inflammation

inflammatory disorders and infections also display "EPR"

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

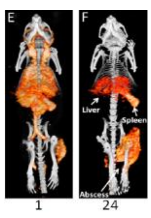


Metselaar et al, Arthr Rheum (2003)

^{111}In-PEG-Lip in RA

Boerman et al (UMCN)

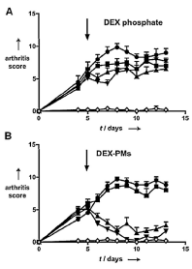
^{111}In-PEG-Lip in SA

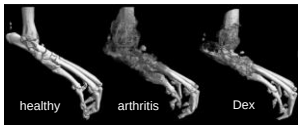


Van der Geest et al, JCR (2015)

inflammation

arthritis treatment with dexamethasone-loaded polymeric micelles





Crielaard et al, Angew Chem Int Ed (2012)

Quan et al, ACS Nano (2014)

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inflammation

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Review

Liposomal corticosteroids for the treatment of inflammatory disorders and cancer

Burcin Ozbakir [a,1], Bart J. Crielaard [a,b,1], Josbert M. Metselaar [d], Gert Storm [a,d,*], Twan Lammers [a,c,d,*]

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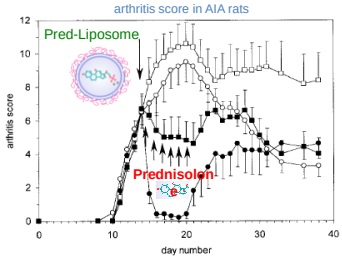
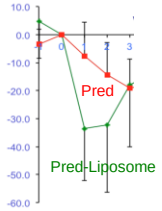
inflammation

corticosteroid-loaded liposomes

arthritis score in AIA rats



DAS28 score in RA patients



Metselaar et al (Enceladus, RWTH)

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translation

corticosteroid-loaded liposomes

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

enceladus

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Center for Translational & Clinical Research (CTC-A)

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summary

- nanomedicines aim to improve therapeutic index
- nanomedicines rely on EPR, which is highly variable
- rational concepts are needed to address heterogeneity
- combinatorial approaches with US and RT boost efficacy
- imaging helps to individualize and improve nanotherapy

=> **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

erc STW-KWF DFG SFB TRR57 SFB1066 2014 EFRE.NRW

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