Vectorisation de nanoparticules par anticorps monoclonaux

Functionalization of nanoparticles with monoclonal antibodies

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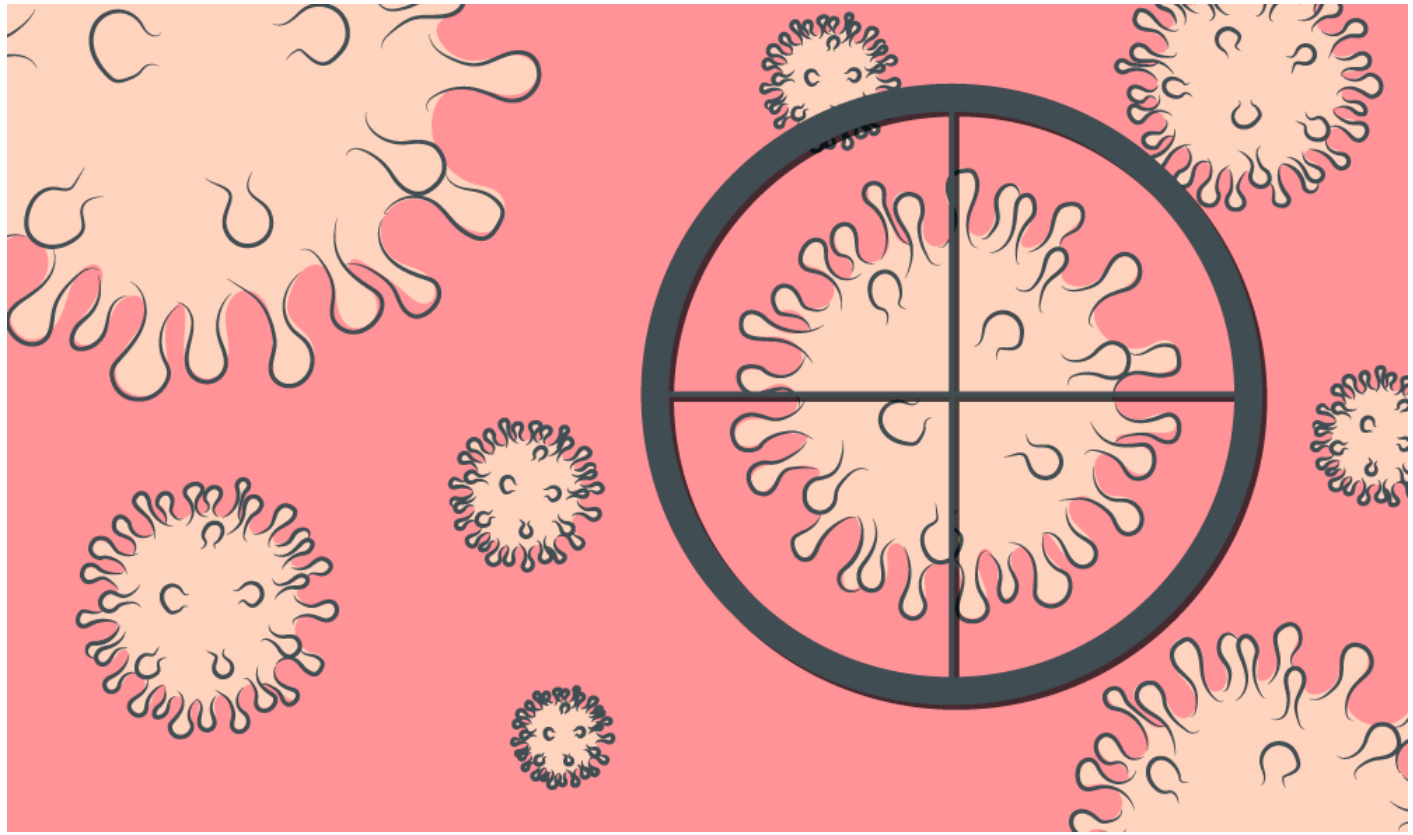
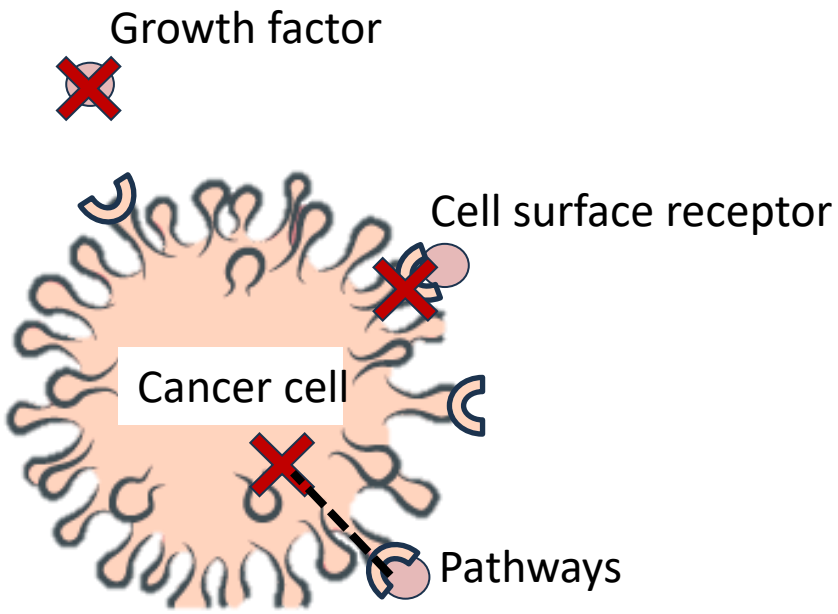
Disclosure

- Co-founder: Recobia Therapeutics; TherO2; TMAD; NH Theraguix
- Scientific Board Member: Syndivia; Biper Therapeutics; PearlBiosystem
- Consulting: Nano-H; General Inception; Leaf Pharmaceuticals; Nickl Therapeutics; Seraphym; Dice; Ceptur Therapeutics; Poly-Dtech

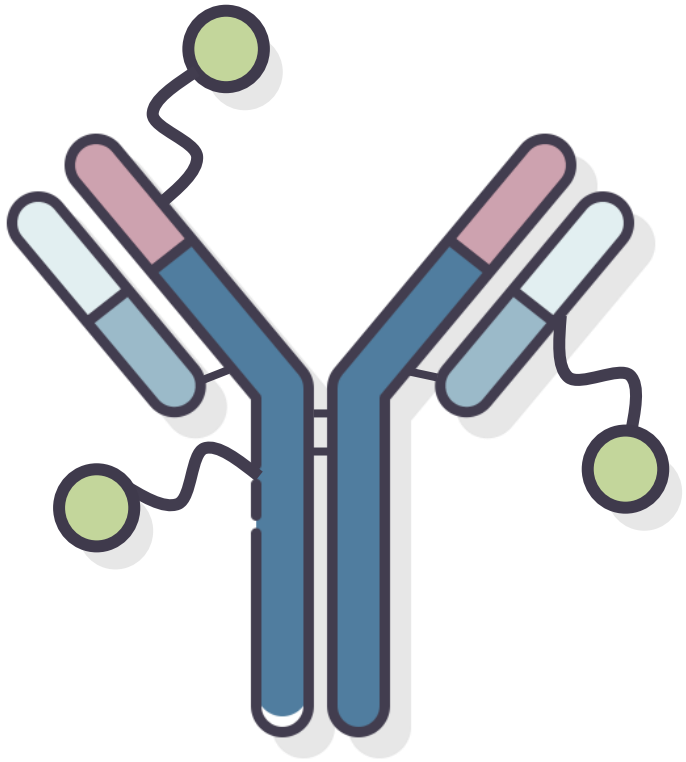
What is a targeted therapy?





Biomarker	Molecule	IndicationMutati
Mutation KRAS	Cetuximab/ Panitumumab	Colorecatal
Mutation EGFR	Gefitinib/Erlotinib	Lung
Fusion EML4-ALK	Crizotinib	Lung
Fusion cKIT	Imatinib	GIST
Amplification HER2	Trastuzumab/ Lapatinib	Breast

Antibody drug conjugates (ADCs)



Antibody backbones

- IgG isotypes
- Possibility to be conjugated
- FcγRn-binding

Type of linkers

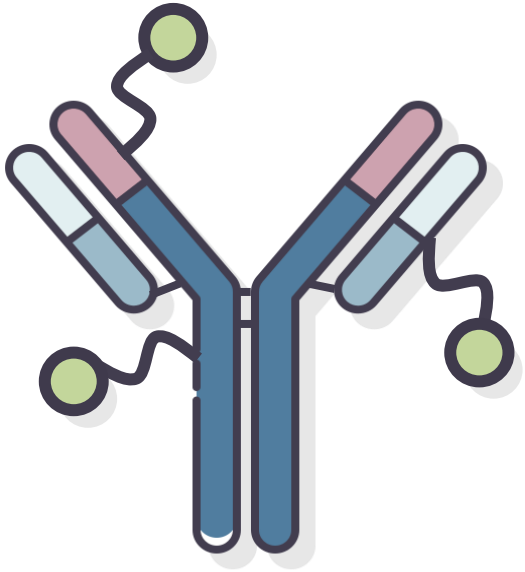
- Cleavable (acid sensitive, esterase sensitive, peptide-based)
- Non-cleavable

Payload

- Auristatins (Brentuximab vedotin)
- Chalicheamicin (Gemtuzumab ozogamicin)
- Emtasine (Trastuzumab emtasine)
- Topoisomerase I inhibitors (Trastuzumab deruxtecan)
- *etc.*

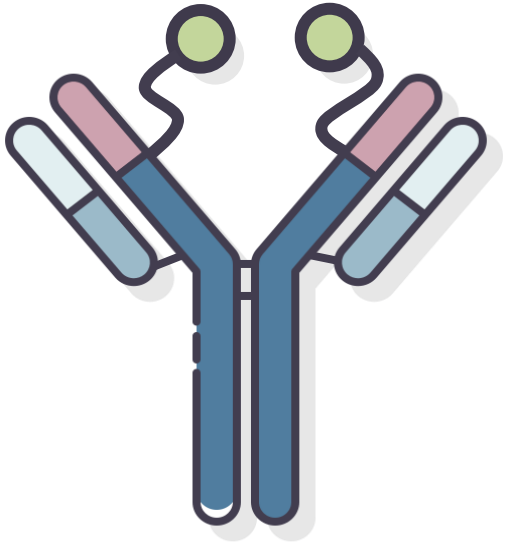
Adapted from Beck et al. Nat Rev Drug Discov 2017

Various strategies can be employed to generate ADCs



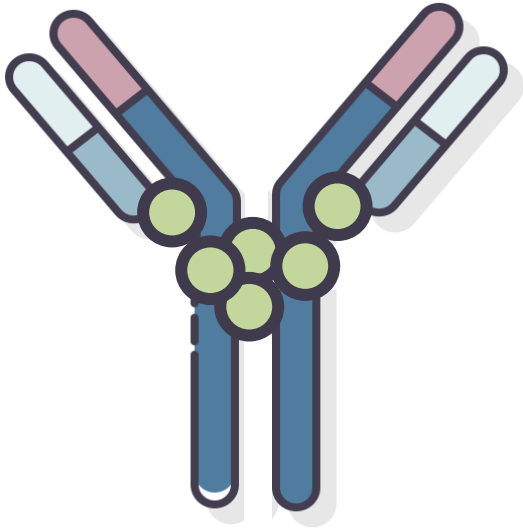
Lysines

+ Covalent
+ Easy to produce
- Non-specific conjugation
- Batch to batch variations



Engineered cysteines

+ Covalent
+ Site specific
- Difficult to produce

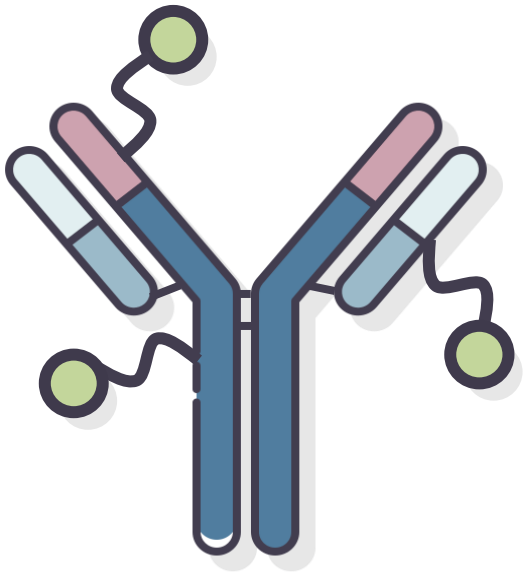


Reduced internal disulfide bonds

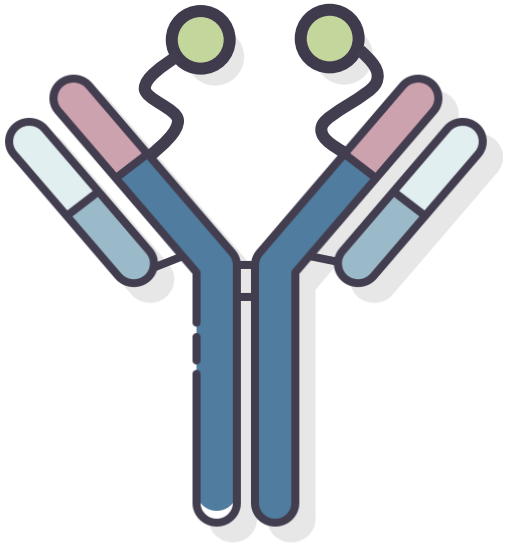
+/- Covalent and non-covalent
+ Site specific
+ Easy-ish to produce

Adapted from Beck et al. Nat Rev Drug Discov 2017

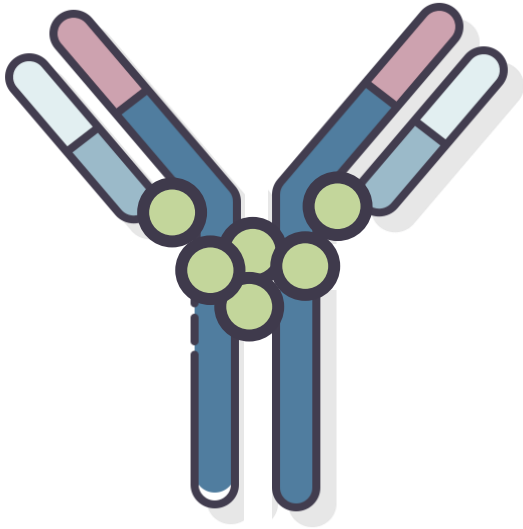
Various strategies can be employed to generate ADCs



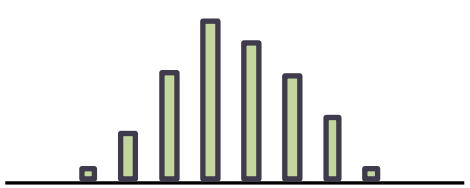
Lysine

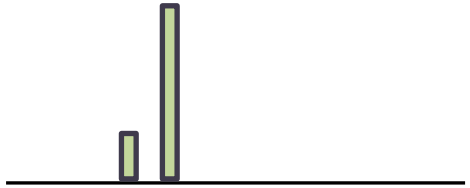


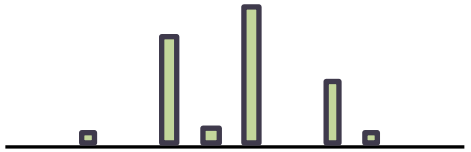
Engineered cysteines



Reduced internal disulfide bonds







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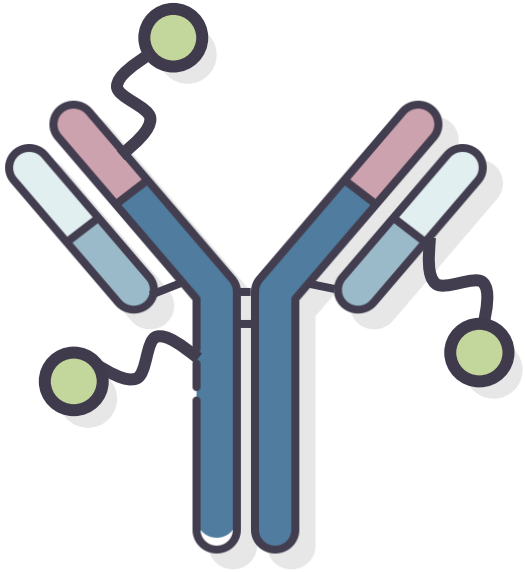

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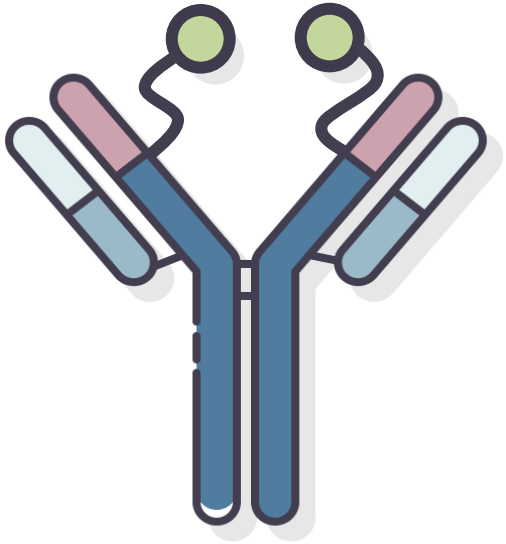
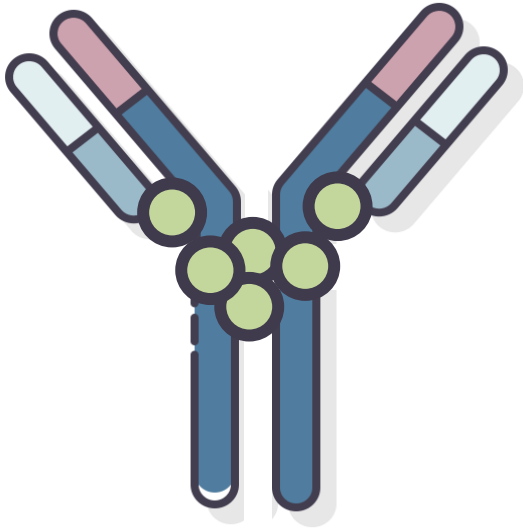


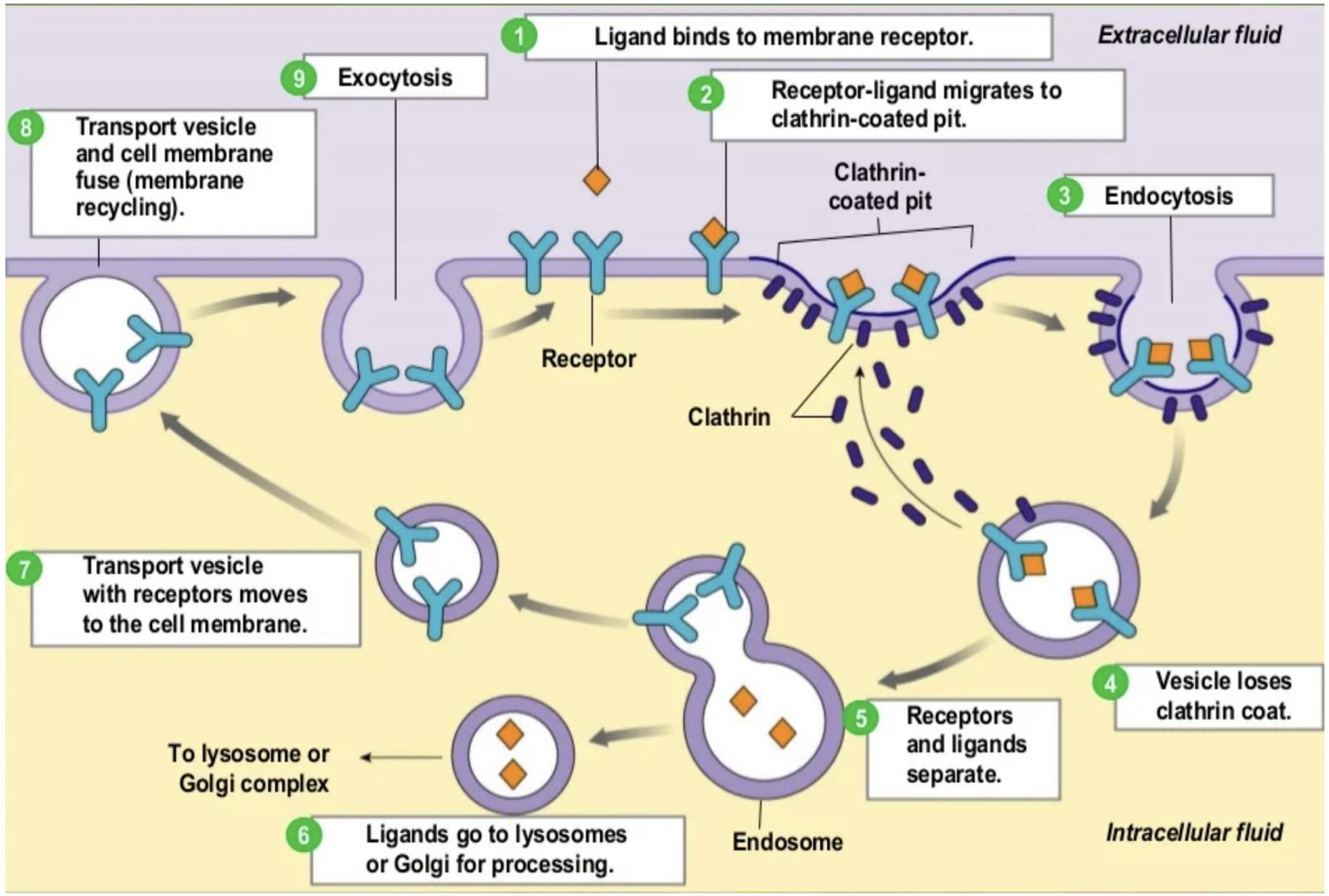
Engineered cysteines



Reduced internal disulfide bonds

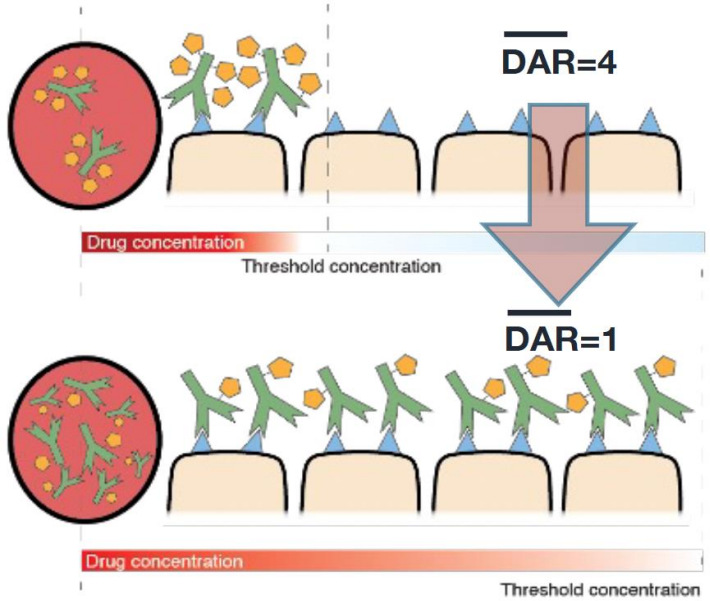
- 12 ADCs have been approved by the FDA
- Multiple multi-billion partnerships established over the last 5 years

Drug release strategy for ADC



Adapted from Salisbury et al. Cold Spring Harb Symp Quant Biol 1982

Could we improved ADC efficiency? Our hypothesis



To Improve therapeutic efficacy

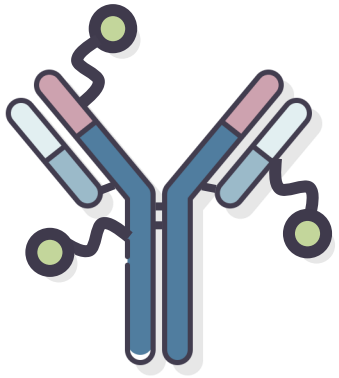
- Reduction of the DAR seems to lead to better tumor penetration due to lower modification of the mAb
- Reduction of the DAR seems to lead to higher amount of mAbs that can be administered to reach the MTD

(Cilliers *et al.* AAPS J 2026, Menezes *et al.* AAPS J 2020, L D Bever *et al.* Bioconjugate Chem 2023)

-- Startups are developing novel linker strategies to generate DAR1 ADCs and are engineering novel linker types for multi-drug DAR1 ADCs (Syndivia, ProfoundBio, Ceptur TX, *etc*.)

Do we have alternatives ?

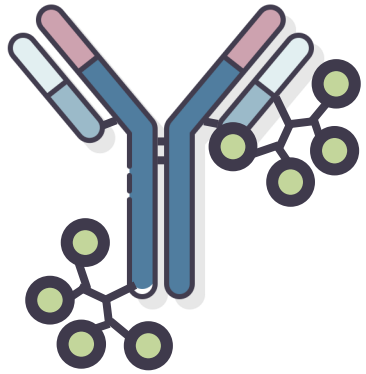
Classical ADCs



\+ Half-life in the body
\+ Controlled release
+/- Site specific
\- Drug loading capacity
\- Batch to batch variation

Clinical routine

Improved linkers for ADCs



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Clinical development
(*Profoundbio; Syndivia; Ceptur Tx, etc.*)

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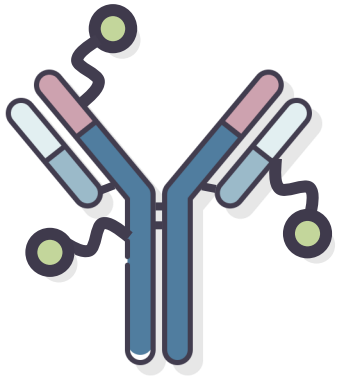
Classical ADCs



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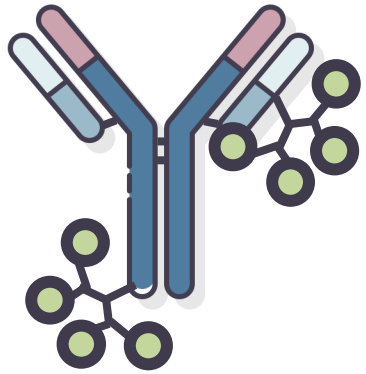

+ Half-life in the body
+ Controlled release
+ Drug loading capacity
+/- Site specific
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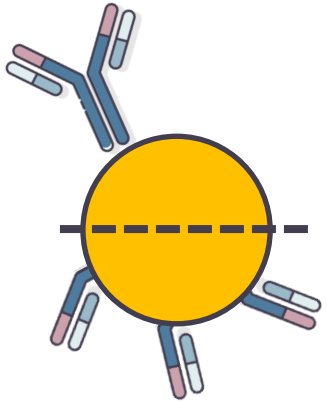
Clinical development
(*Profoundbio; Syndivia; Ceptur Tx, etc.*)

Antibody-conjugated nanoparticles

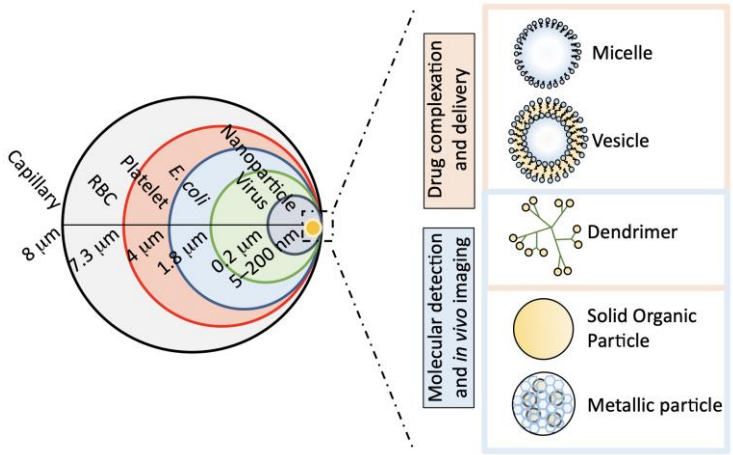


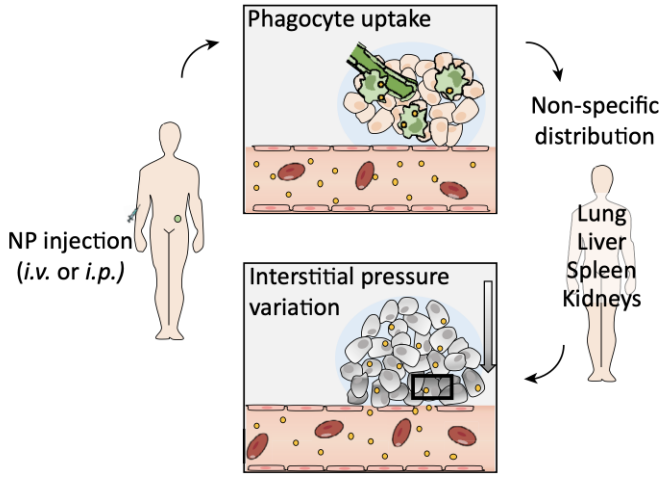
+ No B2B variations with fragments
+ Controlled release
+ Drug loading capacity
+ Site specific with fragment
+/- Half-life in the body dictated by the NPs

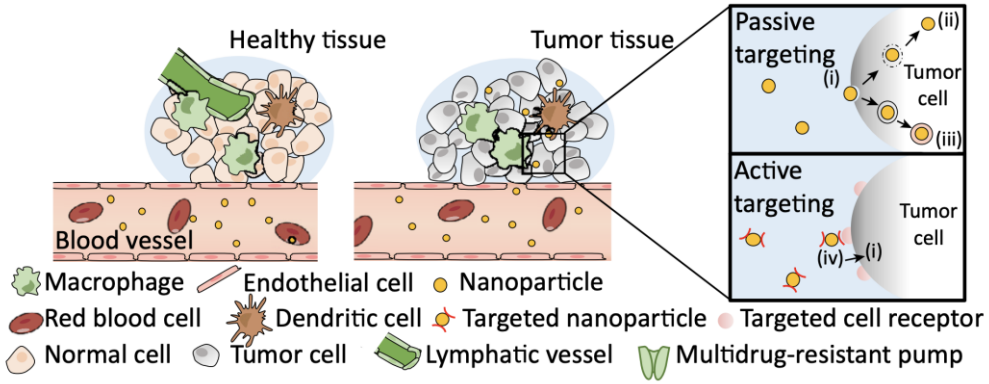
Our lab work

ICANS

Digging into the nanomedicine world







Detappe et al. Trends Mol Med 2018

Some real limitations?

c&en CHEMICAL & ENGINEERING NEWS
LATEST TOPICS MAGAZINE COLLECTIONS PODCASTS CHEMPICS JOBS

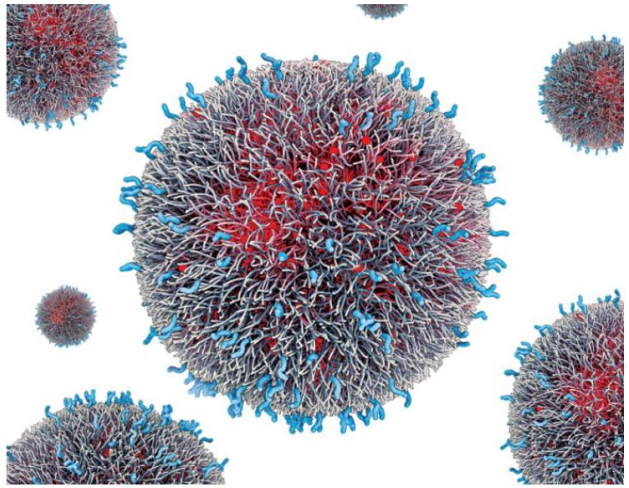
NANOMEDICINES

Does nanomedicine have a delivery problem?

Experts debate controversial paper that suggests delivery efficiencies for cancer nanomedicines are low and not improving

by *Michael Torrice*

June 20, 2016 | A version of this story appeared in **Volume 94, Issue 25**



Credit: Gaël McGill/Digizyme

BIND-014 nanoparticles target tumors actively through small molecules (blue) that can bind to proteins on cancer cells or on the blood vessels feeding tumors. The polymer (gray) particles encapsulate anticancer drugs (red) such as docetaxel.

Cancer drugs don't discriminate. They kill all cells, not just the cancerous ones. So drugmakers often look for ways to minimize how much of a chemotherapy drug ends up in healthy tissue while still delivering sustained high levels to tumors.

MOST POPULAR IN PHARMACEUTICALS

mRNA-loaded lipid nanoparticles reprogram cells and edit genes

Ativan may be linked to worse survival outcomes in pancreatic cancer

Without these lipid shells, there would be no mRNA vaccines for COVID-19

How Pfizer scientists transformed an old drug lead into a COVID-19 antiviral

New weight-loss drugs could shift the scales

news & views

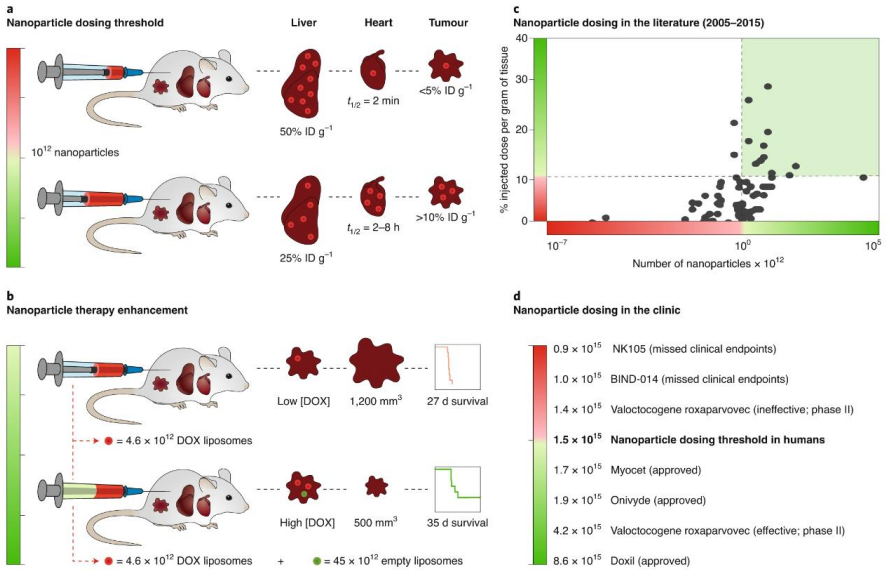
Check for updates

CANCER NANOMEDICINE

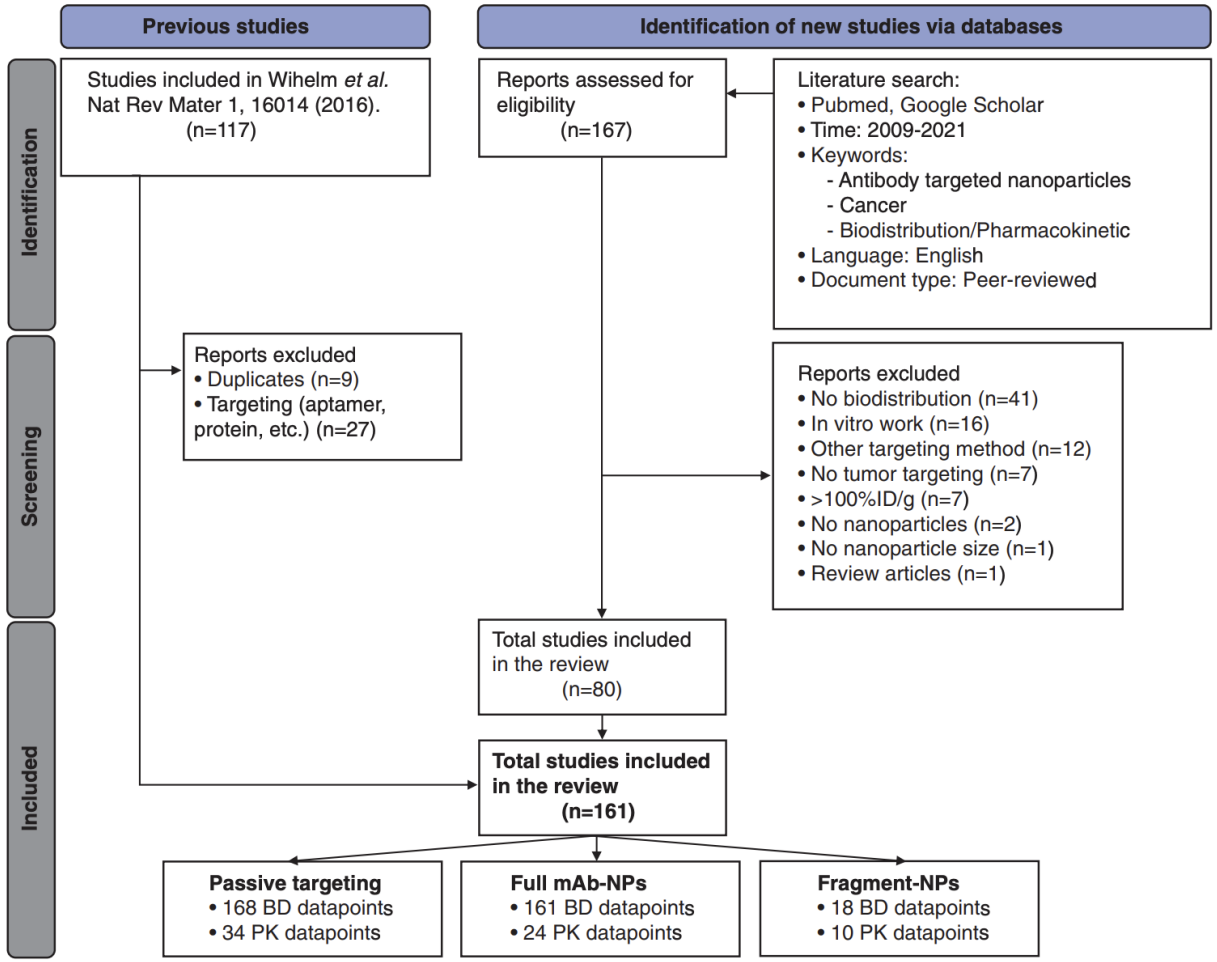
Just dose it

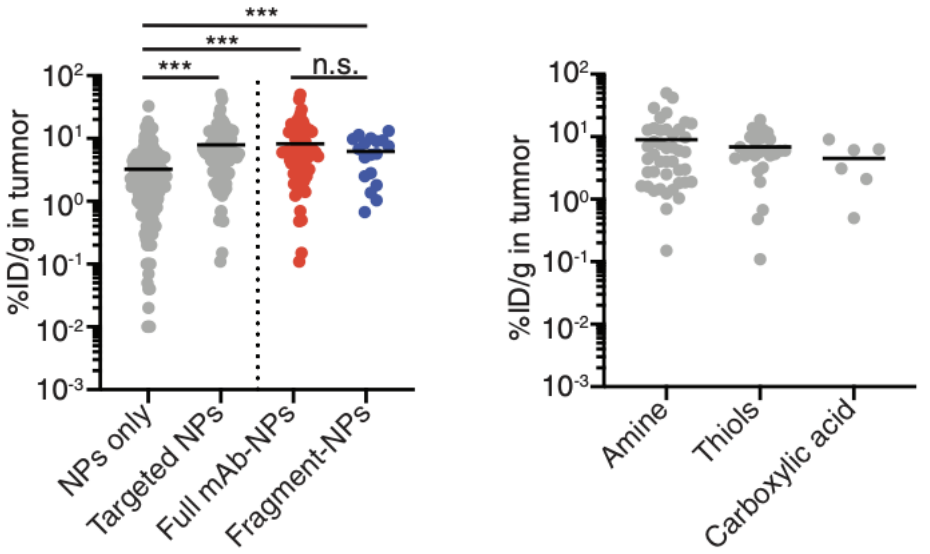
A dose threshold of one trillion nanoparticles in mice has been discovered and is shown to be crucial for overwhelming the nanoparticle uptake kinetics of liver Kupffer cells and for ensuring efficient nanoparticle delivery into solid tumours upon intravenous administration.

Twan Lammers



Toward antibody-nanoparticle conjugates?

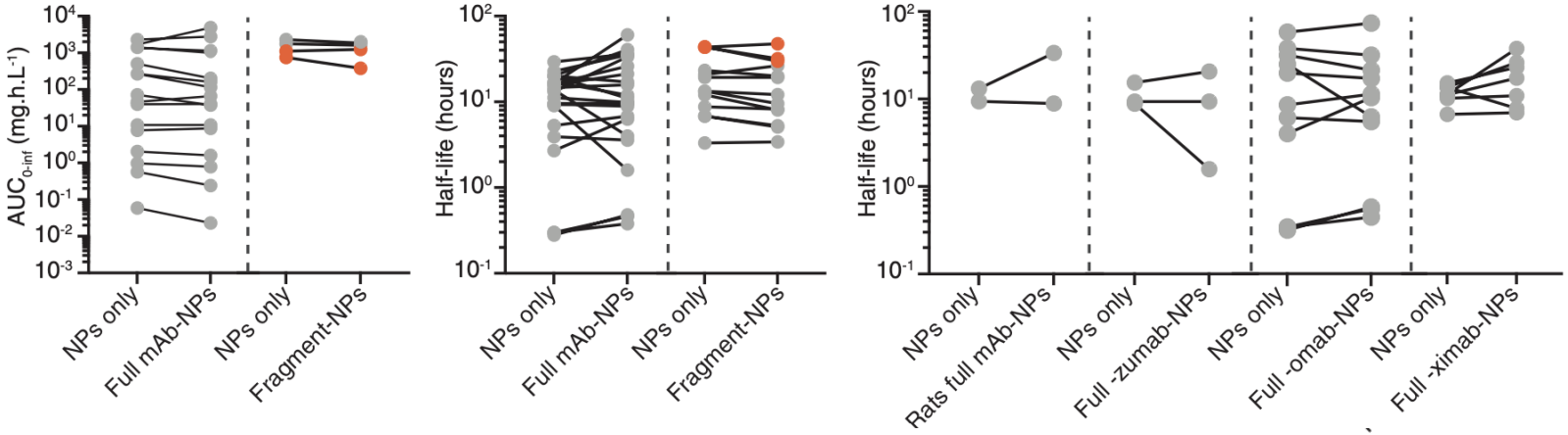


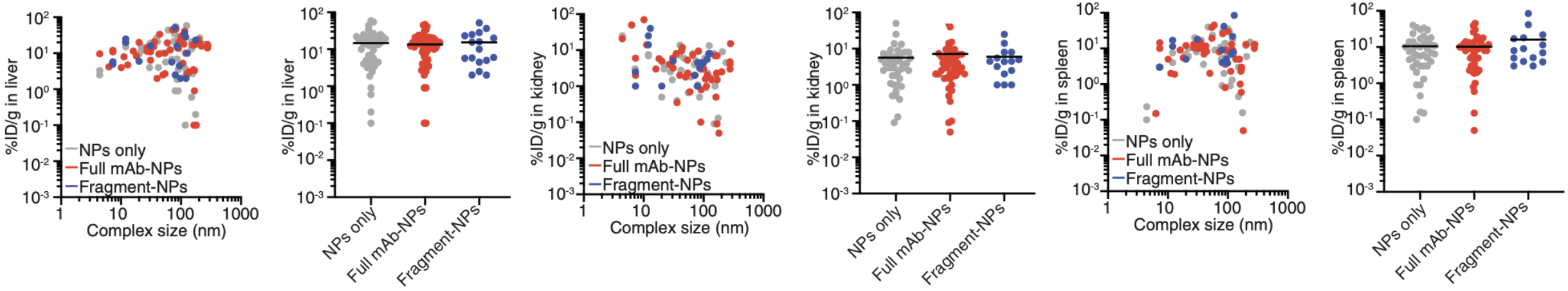


Spoiler alert: Yes, but…

Mittelheisser et al. Adv Mat 2022

The NP drives the pharmacokinetic and biodistribution profile of the conjugate





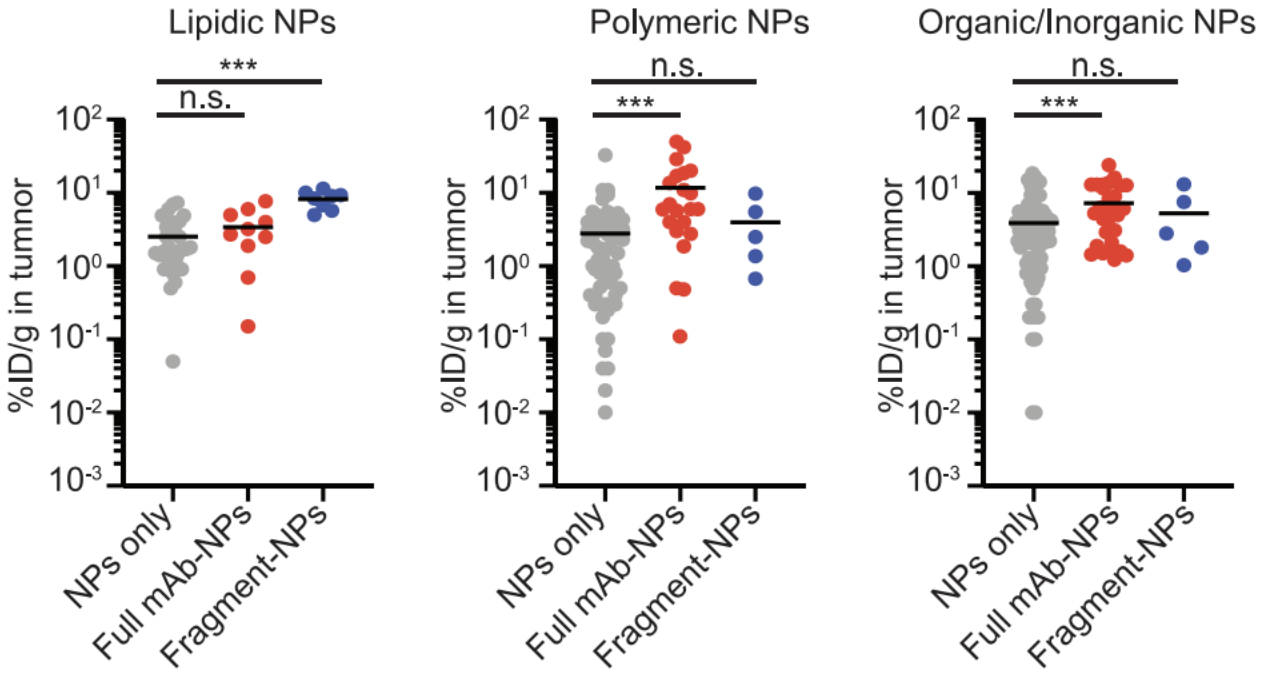
Key messages:

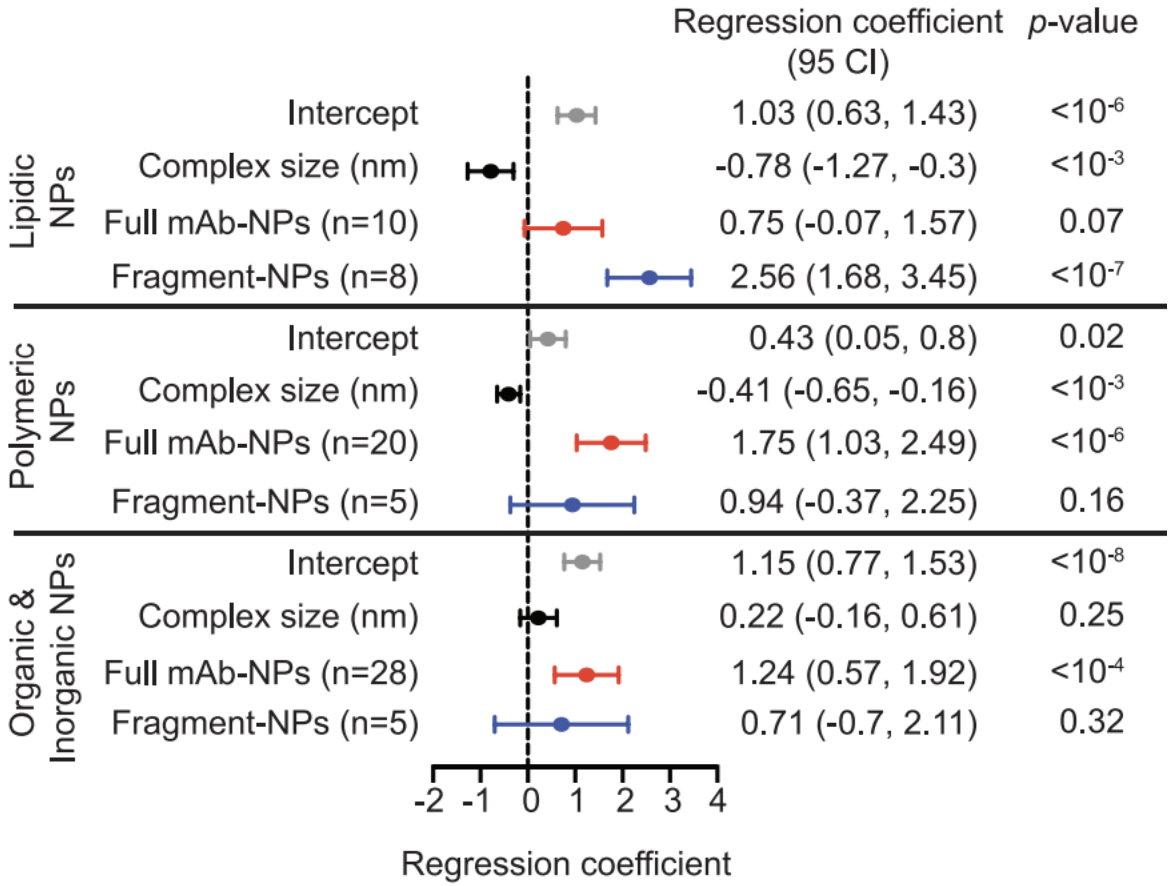
No differences in PK profile based on the size of the moiety

No differences in major organ uptake based on the targeting moiety or the size of the NP

Mittelheisser et al. Adv Mat 2022

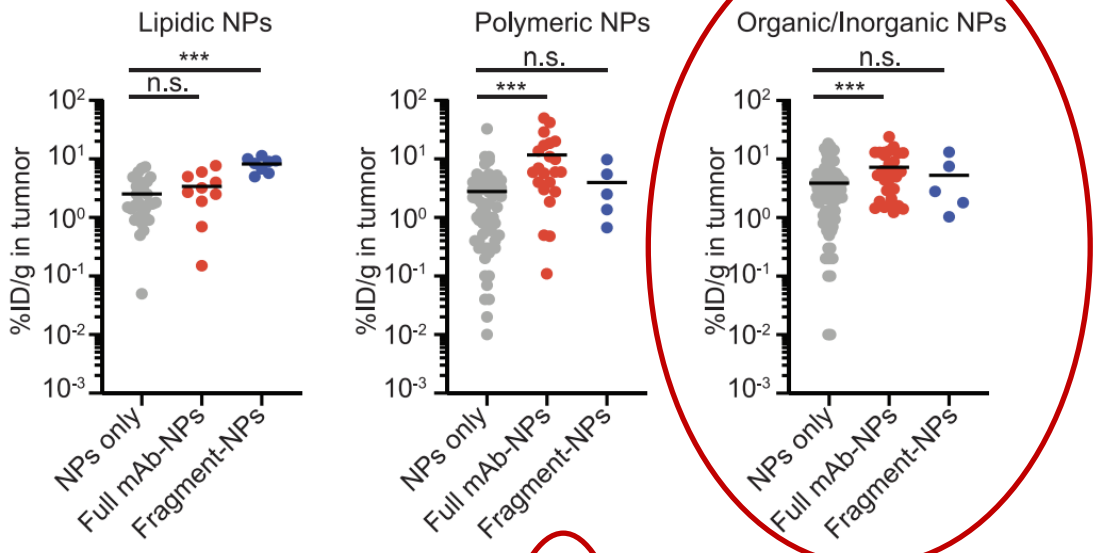
The NP material impacts the tumor uptake post-biofunctionalization

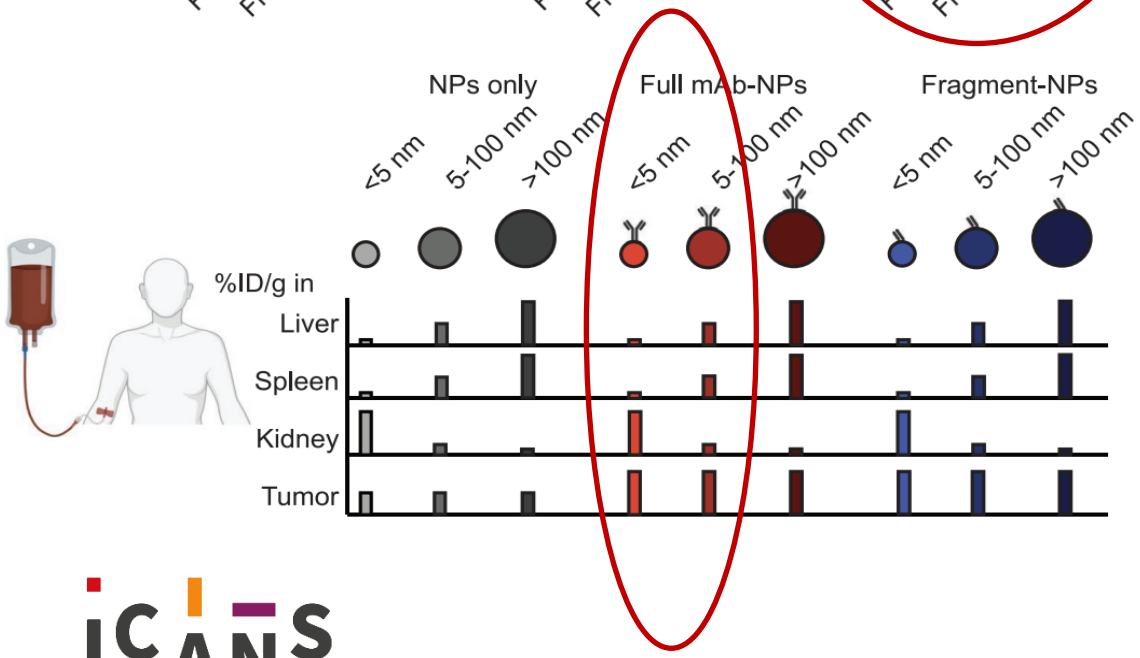


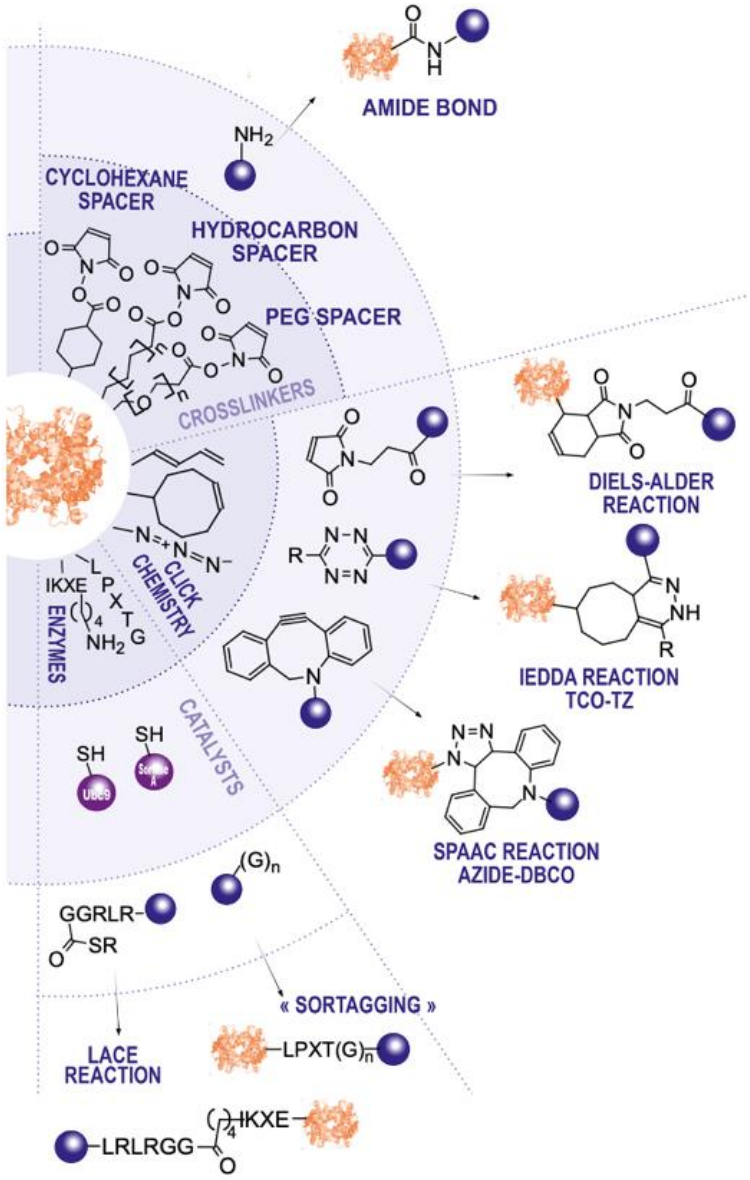


Mittelheisser et al. Adv Mat 2022

Functionalization strategy







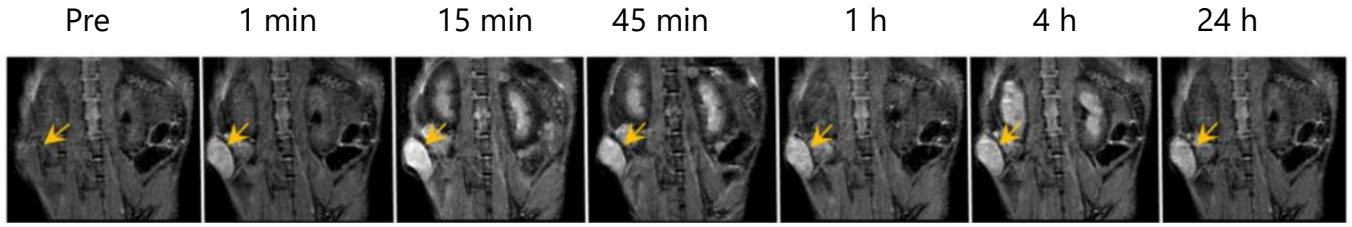
Mittelheisser et al. Adv Mat 2022; Carmes et al. Adv Therapeutics 2023

Development of ultrasmall gadolinium NPs

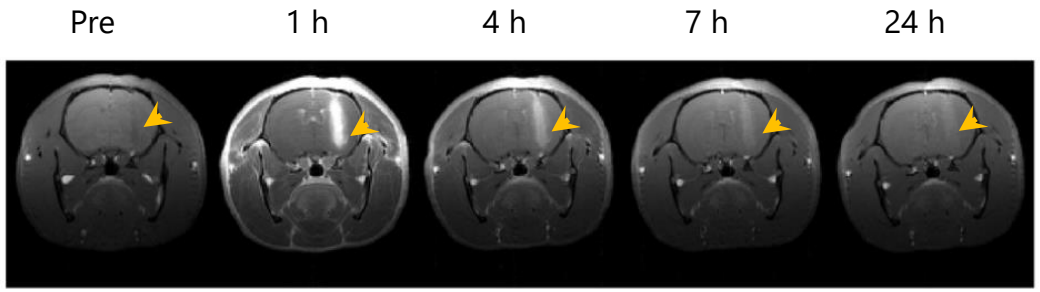
Detappe et al. J Contorl Release 2016

Development of ultrasmall gadolinium NPs

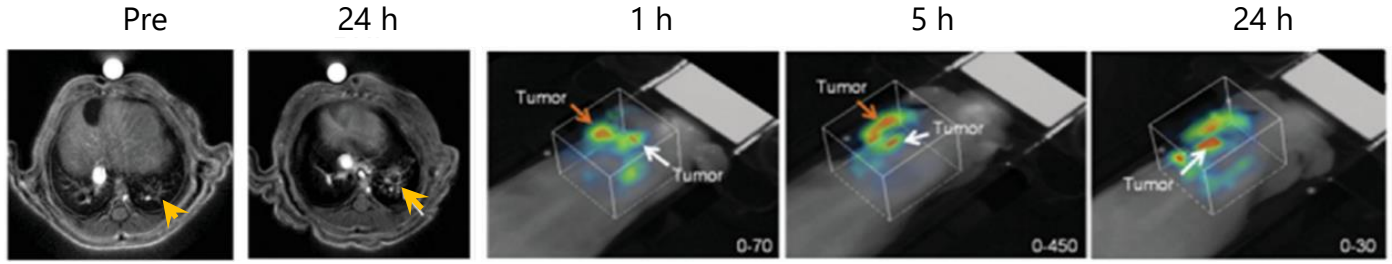
Subcutaneous PDAC



Orthotopic GBM

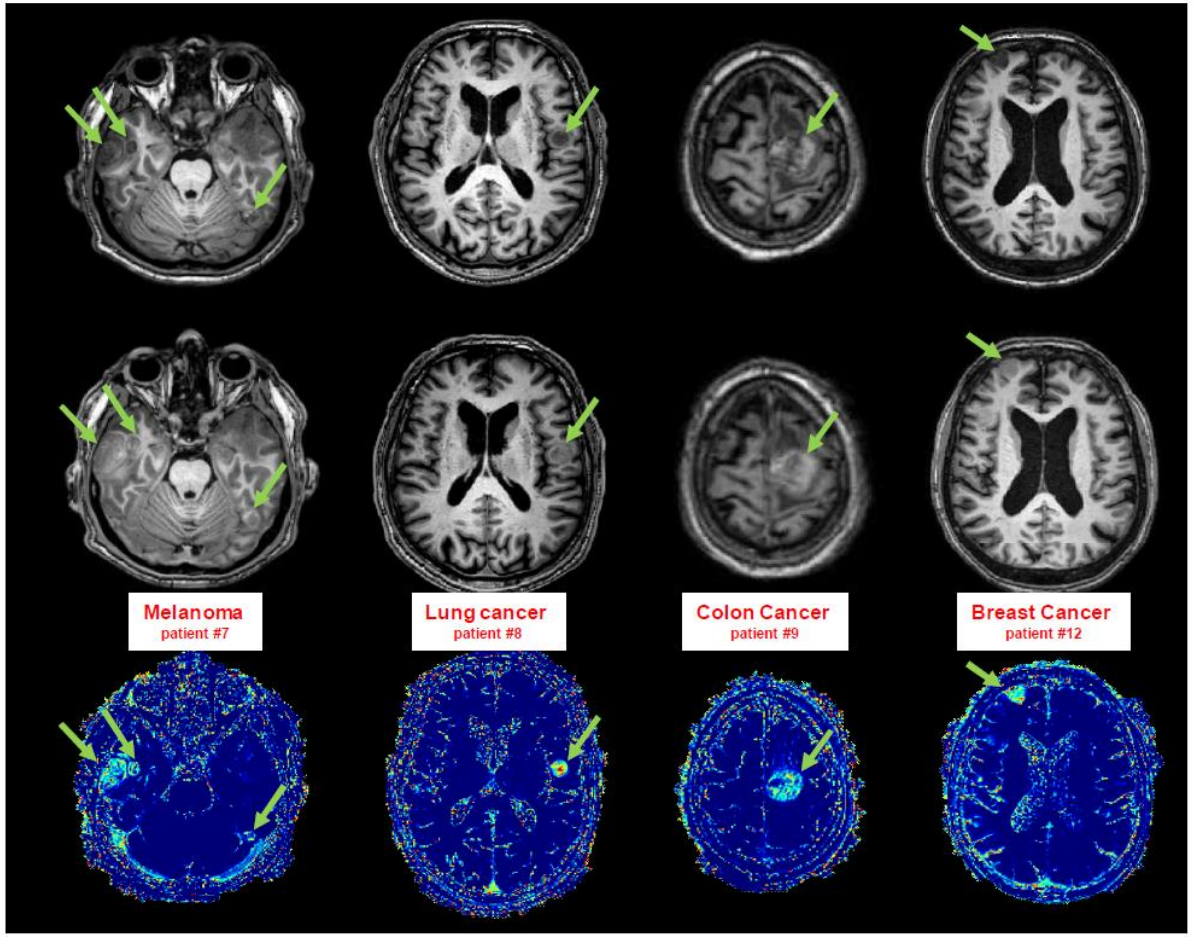


Orthotopic NSCLC



Kotb et al. Theranostics 2016
Bianchi et al. PNAS 2014

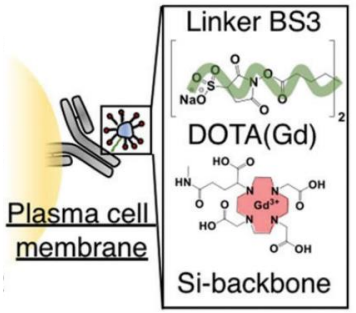
Clinical translation of gadolinium-based NPs

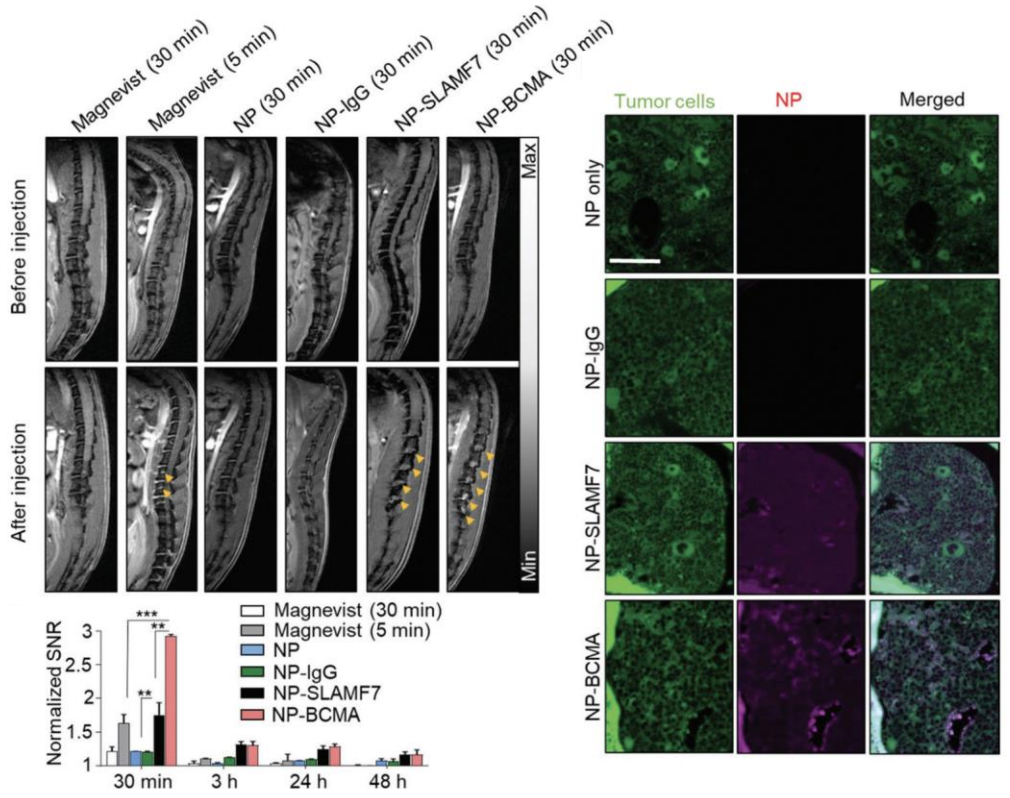


+++ Tumor uptake due to passive internalisation (EPR-effect)
- Short tumor retention

Very et al. Sci Adv 2020

Example of full-mAb NP functionalization through homobifunctional linker functionalization

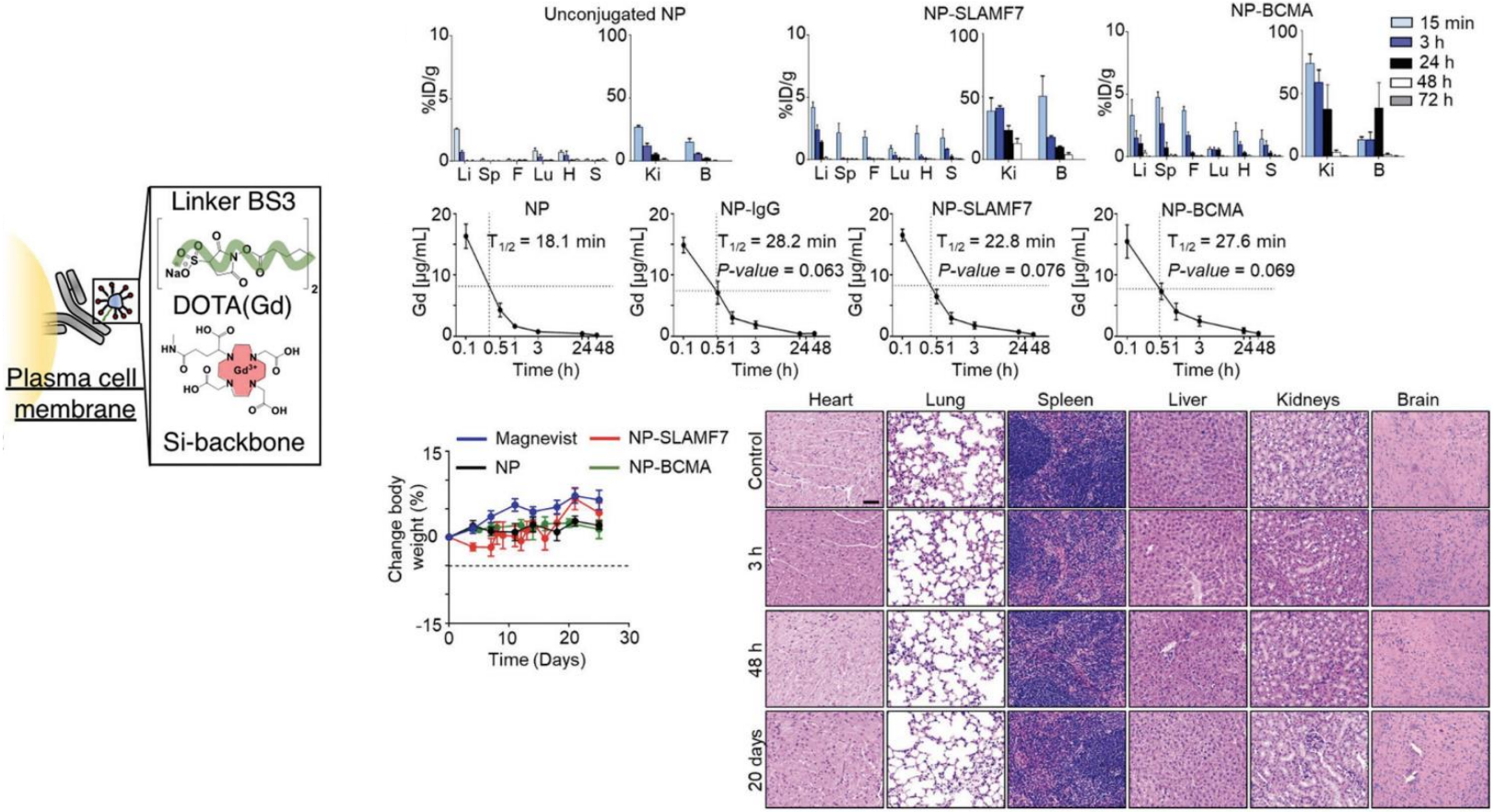




- Improved MR sensitivity with NP-BCMA vs. FDA-/EMA-approved MRI contrast agents and non-targeted NPs

Detappe et al. Nanoscale 2019

Example of full-mAb NP functionalization through homobifunctional linker functionalization



- PK of the anti-BCMA/NP is driven by the NP and not the mAbs

Detappe et al. Nanoscale 2019

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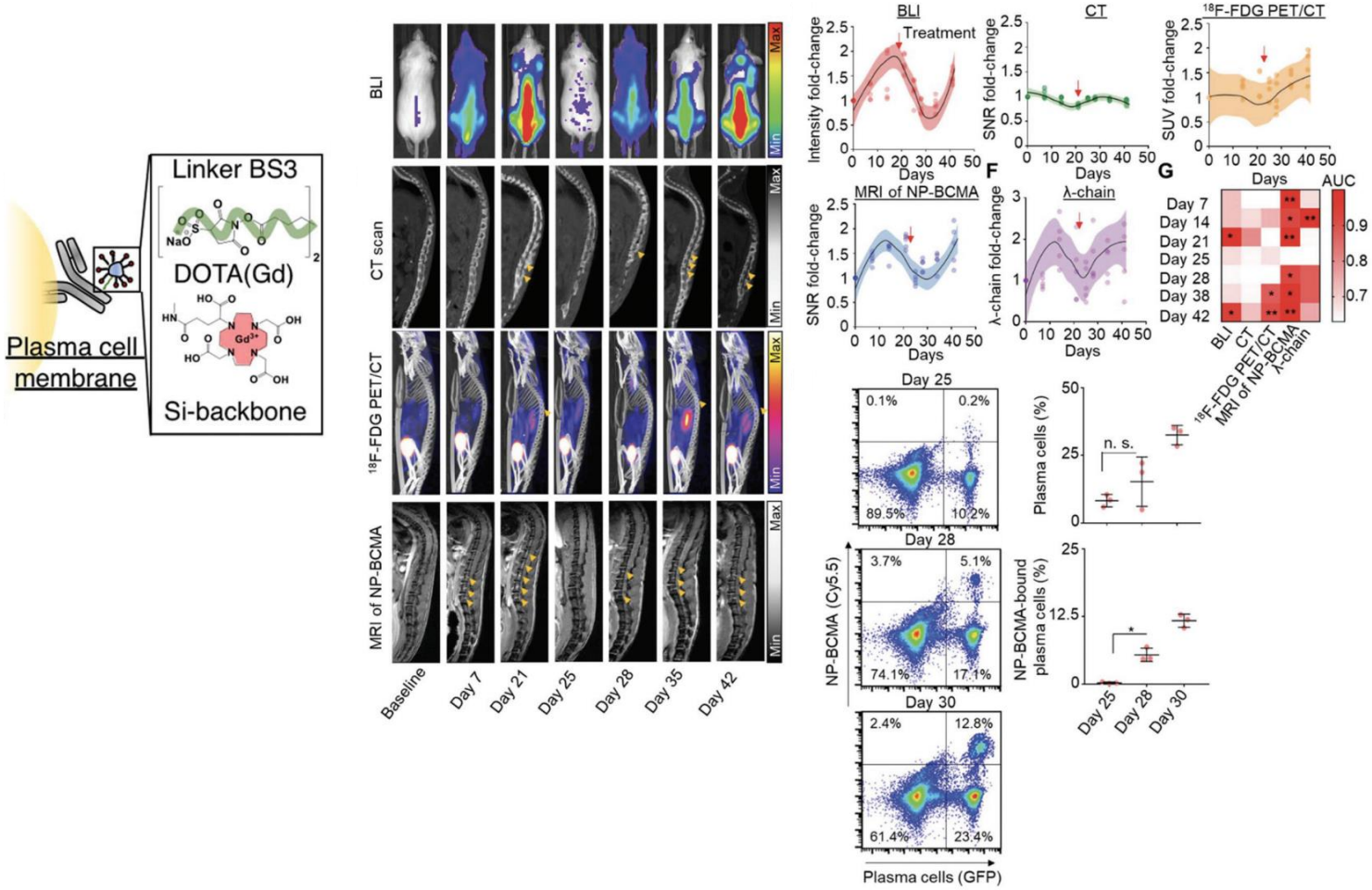
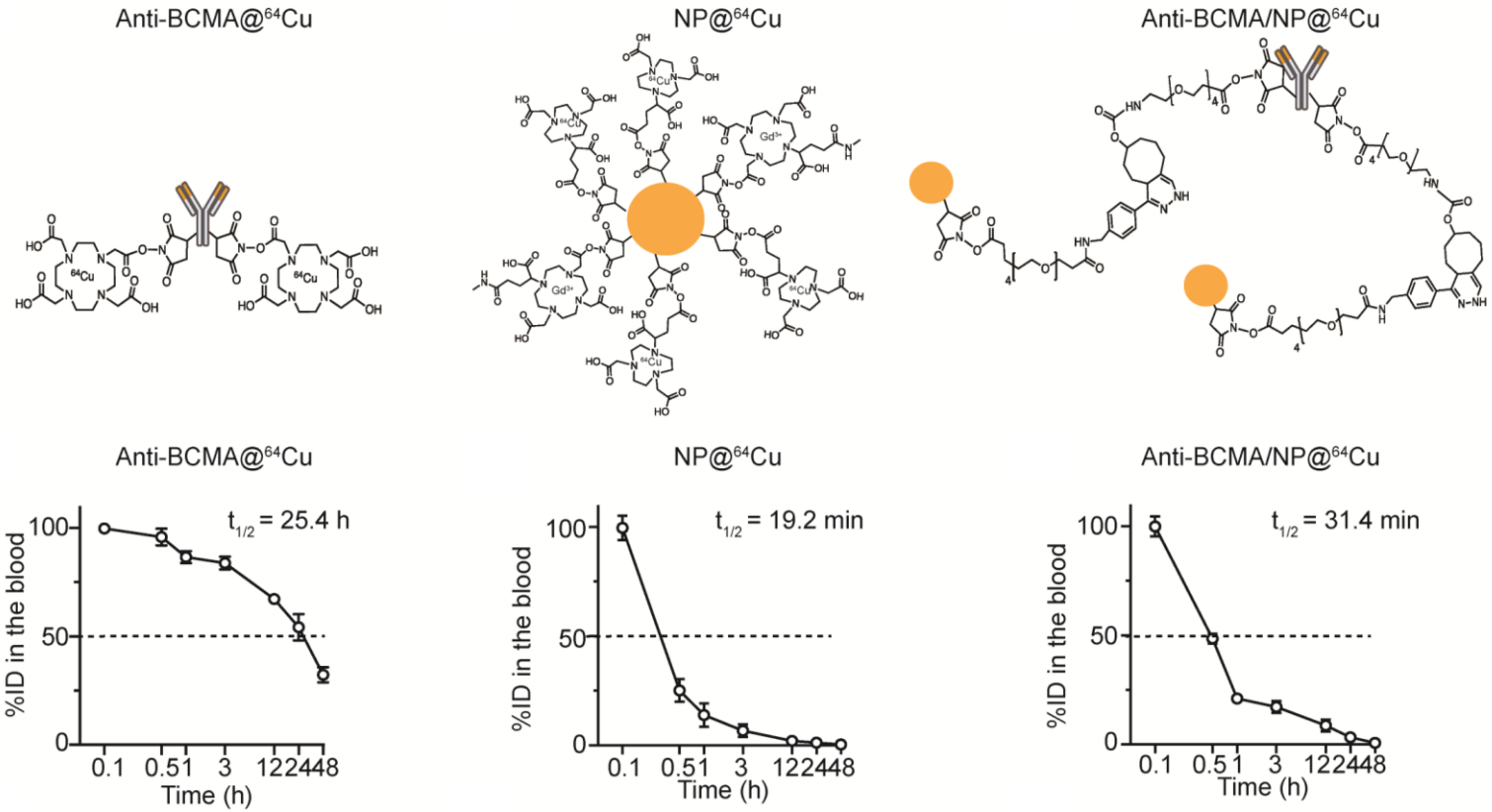


- Improved MR sensitivity with NP-BCMA
- Longitudinal tracking possible due to the lack of long-term retention and degradability of the NP
- 5% of the MM cells labelled with NP is enough for MR signal detection

Detappe et al. Nanoscale 2019

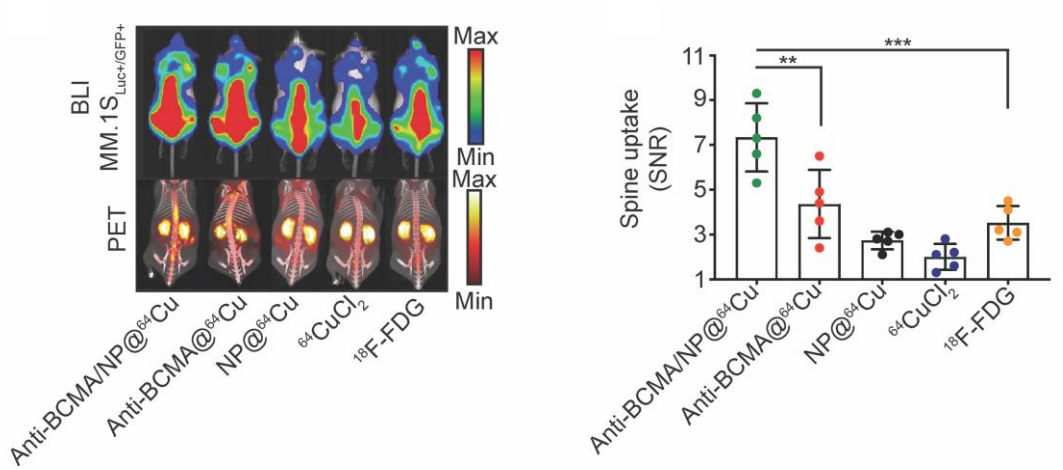
Example of full-mAb NP functionalization through click chemistry approach



- PK of the anti-BCMA/NP is driven by th

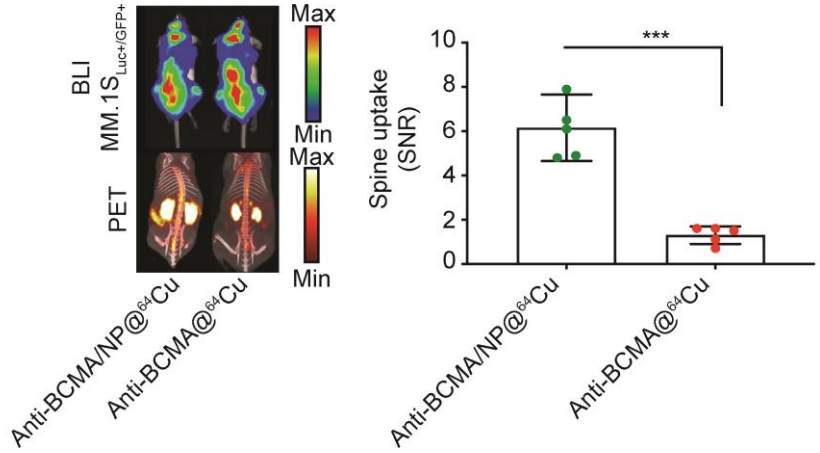
Thomas et al. Adv Health Mat 2021

Full-mAb-NPs vs. ADC



Same amount of radiotracer injected (10 MBq)

- ~4x less mAb required with mAb-NP vs. ADC
- Improvement of the SNR
- Potential diminution of the toxicity in drug delivery
- Nanoparticle to antibody ratio = 1.1

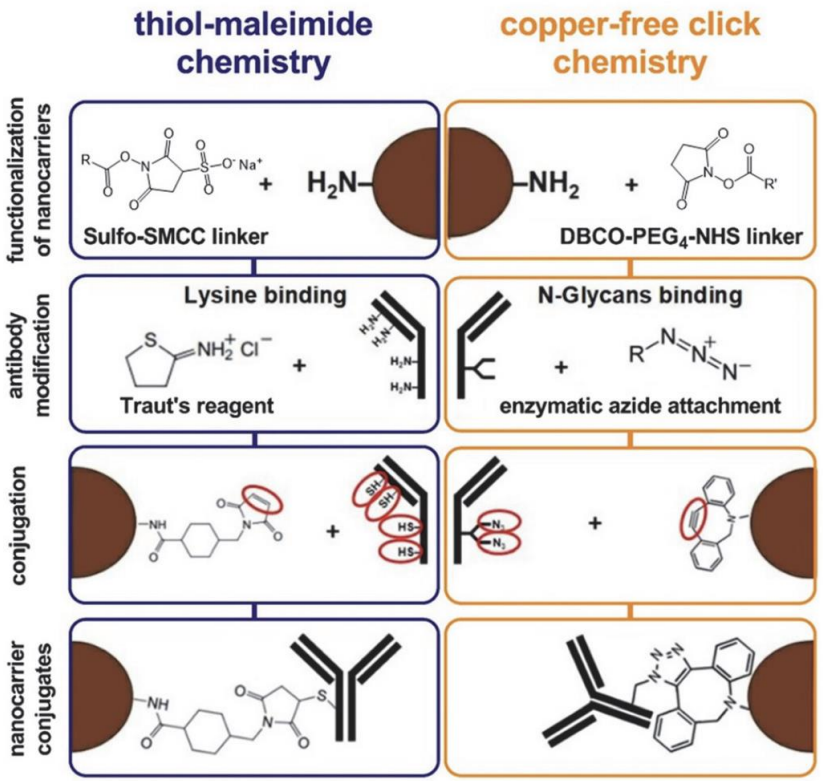


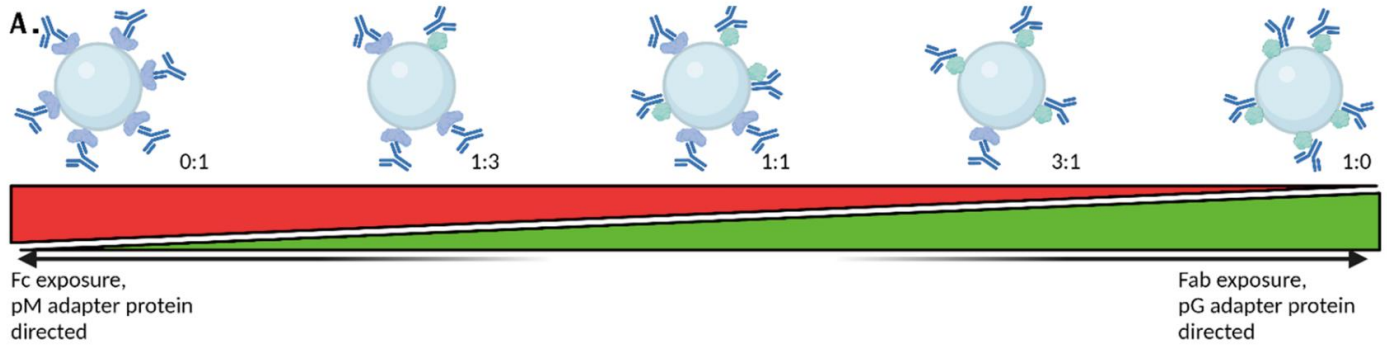
Same amount of mAbs injected (4.2 mg/kg)

- ~4x more radiotracer injected with mAb-NP vs. ADC
- Increase tumor uptake signal (translation for drug delivery)
- Nanoparticle to antibody ratio = 1.1

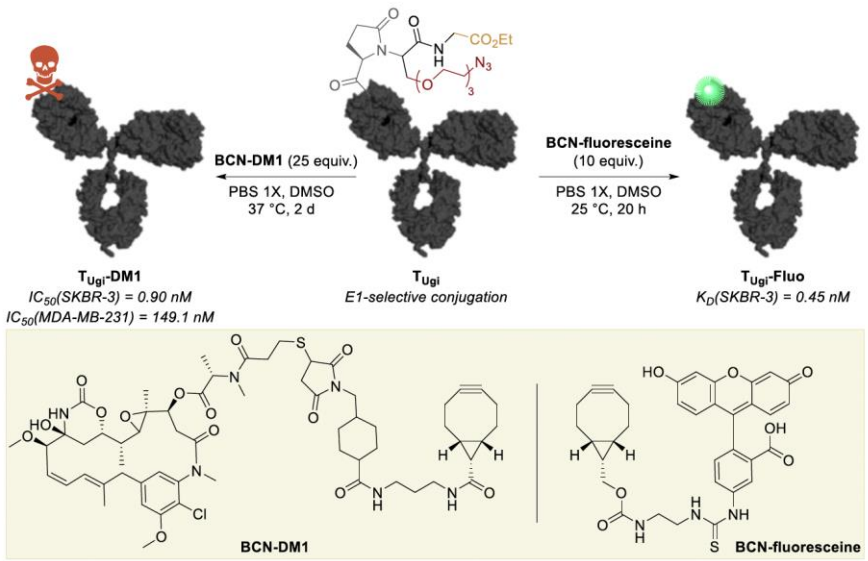
Thomas et al. Adv Health Mat 2021

Limitation of non-specific binding for NP studies and alternative solutions





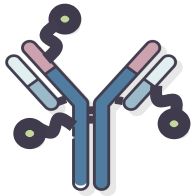
Toward site-specific NP functionalization.
Applications of our E1-selective Ugi-conjugated trastuzumab T_{Ugi}



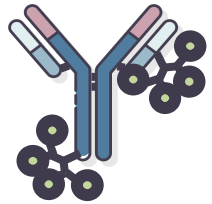
Tholen et al. ACS Nano, 2023, 17, 11665-11678
*Bruckner et al. Nanoscale, **2021**, 13, 9816*

Conclusion

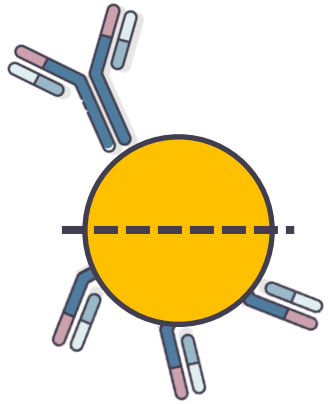
Classical ADCs



Improved linkers for ADCs



Antibody-conjugated NPs



- Require a specific target to be effective, and a rational selection of the therapeutic drug is necessary
- Optimization of the drug linker conjugation and DAR is needed for optimal release and therapeutic efficacy
- Antibody-conjugated NPs could improve ADC efficacy by either reducing toxicity (less amount to be injected for similar efficacy) or increasing efficacy (same amount of mAbs injected)

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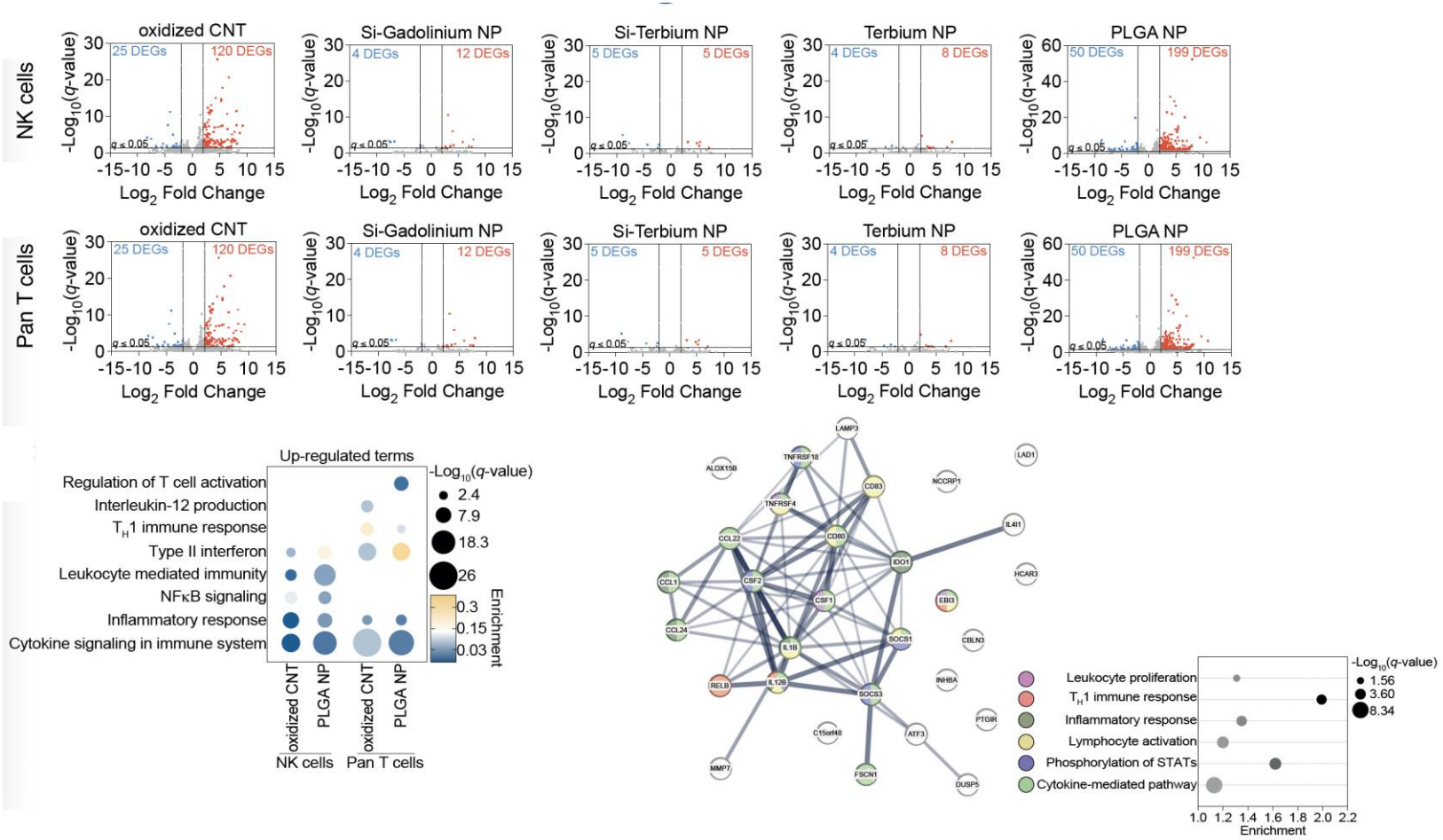
Nanoparticle selection is important, especially for immune-cell targeting applications



Mittelheisser et al. In preparation