The Yin and Yang of nanomedicine

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Nanoparticles in medicine

Nanoparticles are attractive as a biomolecular scaffold to unify many functional moieties into a single unified macromolecule

Swiss army knive of drugs:

- Drug carrier
- Targeting ligand
- Imaging moiety: fluorochrome, isotope, MR agent
- Can interact with target for switchable agents

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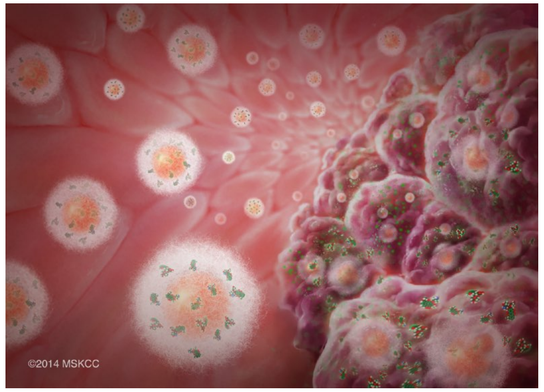
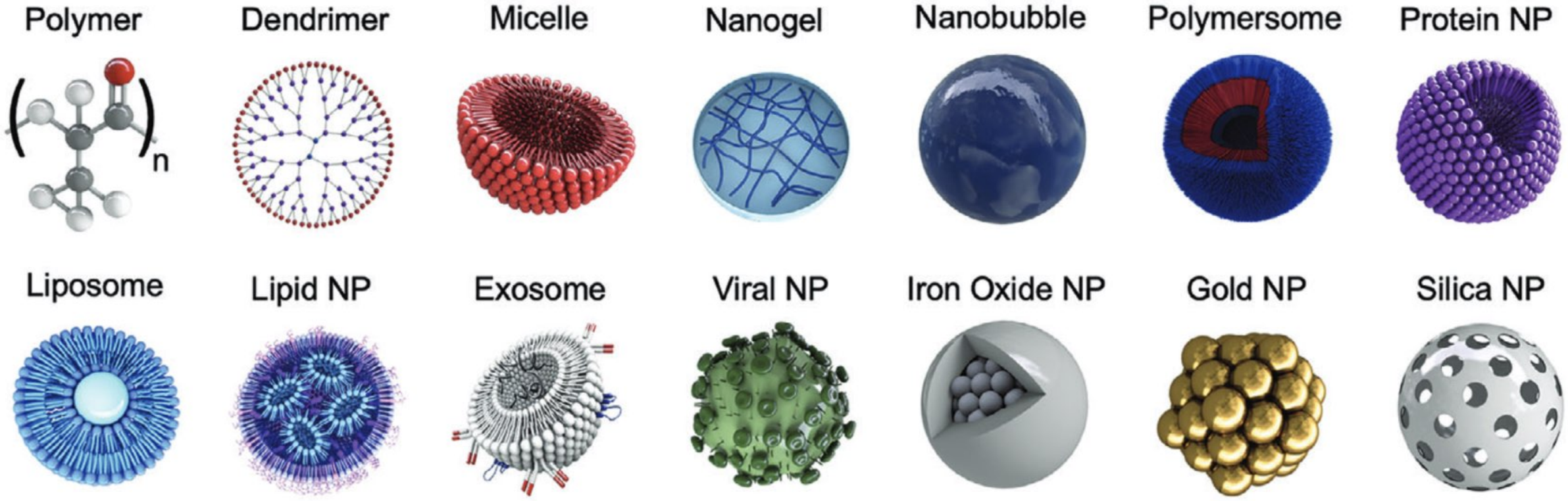
Considered "inert" carrier to deliver therapeutic or for imaging

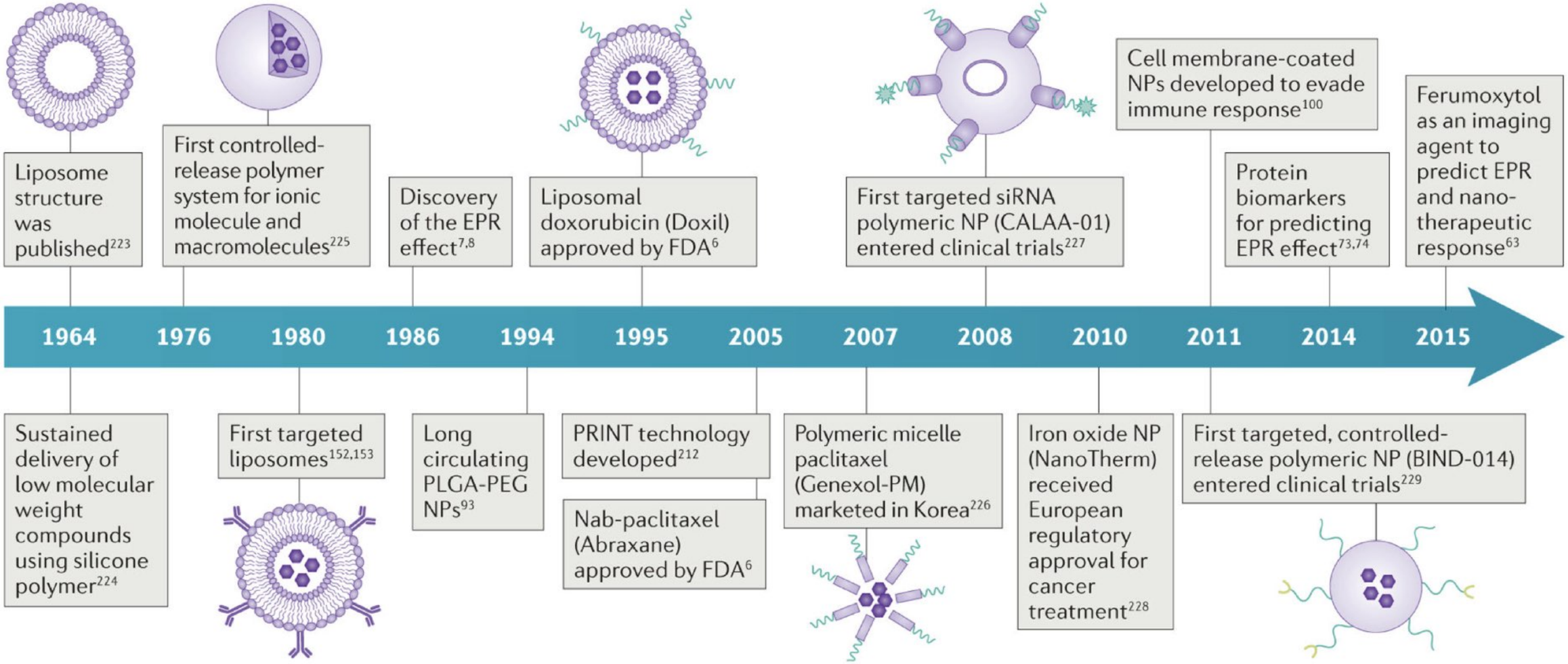


Nanoparticle ≠ Nanoparticle



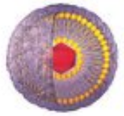
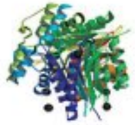
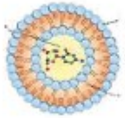
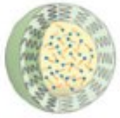
Lammers T . (2024) *Adv Materials* 36, 2312169

Historic overview



Shi J et al. (2017) Nat Rev Cancer 17(1):20

Nanoparticles in clinical use

Doxil/Caelyx	Daunoxome	Myocet	Lipusu	Oncaspar	Abraxane	DepoCyt	Genexol-PM
PEG-Liposome	Non-PEG Liposome	Non-PEG Liposome	Non-PEG Liposome	Polymer-Protein Conjugate	Protein-Drug Nanoparticle	Non-PEG Liposome	Polymeric Micelle
							
							
1995/1996	1996	2000	2003	2006	2005	2007	2007

Mepact	Nanotherm	Marqibo	Onivyde	Vyxeos	Apealea	Hensify	Fyarro
Lipid-Drug Nanoparticle	Iron Oxide Nanoparticle	Non-PEG Liposome	PEG Liposome	Non-PEG Liposome	Retinoic Acid Micelle	Hafnium Oxide Nanoparticle	Protein-Drug Nanoparticle
							
							
2009	2011	2012	2015	2017	2018	2019	2021

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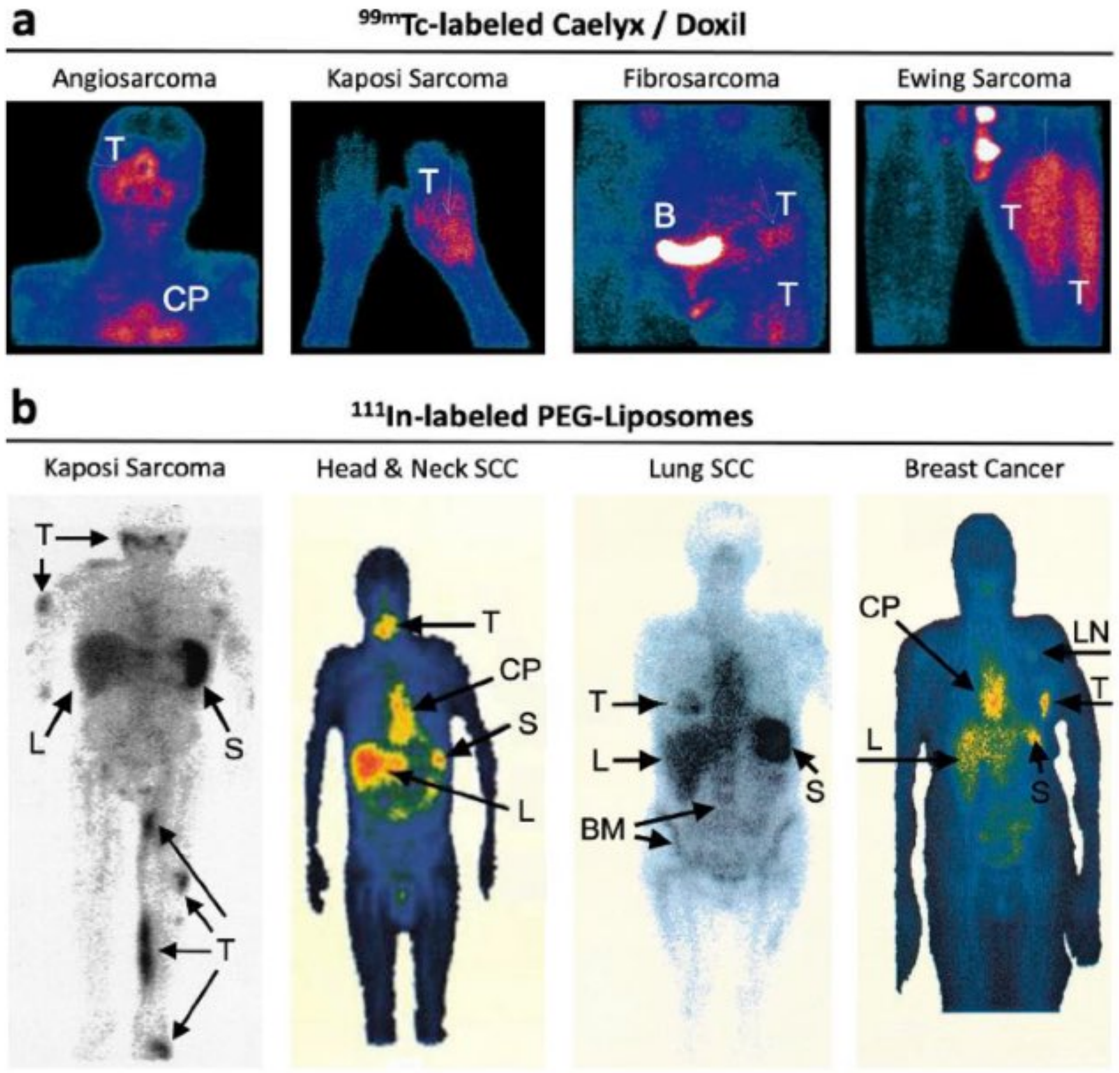
Nanomedicine does work

...but is highly heterogeneous



c

Pat.	Tumor Type	GS	SPECT	%ID/kg
1	Head & Neck	+	+	53.0
2	Head & Neck	+	+	46.8
3	Head & Neck	+	+	32.0
4	Lung	+	+	25.4
5	Head & Neck	+	+	24.2
6	Lung	+	+	16.7
7	Lung	+	+	12.5
8	Breast	+	+	9.5
9	Head & Neck	+	+	9.0
10	Breast	+	+	5.2
11	Breast	+	+	3.9
12	Breast	+	+	2.7
13	Cervix	-	+	N.A.
14	Glioma	-	+	N.A.
15	Glioma	-	+	N.A.
16	Lung	-	-	N.A.
17	Breast	-	-	N.A.
All	Accumulation in Tumors	**12/17 =71%**	**15/17 =88%**	

courtesy of T Lammers, Aachen

Koukourakis et al, ACTA Oncol 2000
Harrington et al, Clin Cancer Res 2001

Critisicm with cancer nanotherapies

Advanced Drug Delivery Reviews

Volume 65, Issue 1, January 2013, Pages 80–88

Advanced Drug Delivery: Perspectives and Prospects

Cancer nanomedicines: So many papers and so few drugs! ☆

Vincent J. Venditto, Francis C. Szoka Jr.

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Contents lists available at ScienceDirect

Journal of Controlled Release

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

Review article

To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine?

F. Danhier

Université catholique de Louvain, Louvain Drug Research Institute, Advanced Drug Delivery and Biomaterials, Avenue Mounier, 73 bte B1 73.12, 1200 Brussels, Belgium

courtesy of T Lammers, Aachen

Critisicm with cancer nanotherapies

ELSEVIER

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A B S T R A C T

Tumor targeting by nanomedicine-based therapeutics has emerged as a promising approach to overcome the lack of specificity of conventional chemotherapeutic agents and to provide clinicians the ability to overcome shortcomings of current cancer treatment. The major underlying mechanism of the design of nanomedicines was the Enhanced Permeability and Retention (EPR) effect, considered as the "royal gate" in the drug delivery field. However, after the publication of thousands of research papers, the verdict has been handed down: the EPR effect works in rodents but not in humans! Thus the basic rationale of the design and development of nanomedicines in cancer therapy is failing making it necessary to stop claiming efficacy gains via the EPR effect, while tumor targeting cannot be proved in the clinic. It is probably time to dethrone the EPR effect and to ask the question: what is the future of nanomedicines without the EPR effect? The aim of this review is to provide a general overview on (i) the current state of the EPR effect, (ii) the future of nanomedicine and (iii) the strategies of modulation of the tumor microenvironment to improve the delivery of nanomedicine.

courtesy of T Lammers, Aachen

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senior grad student
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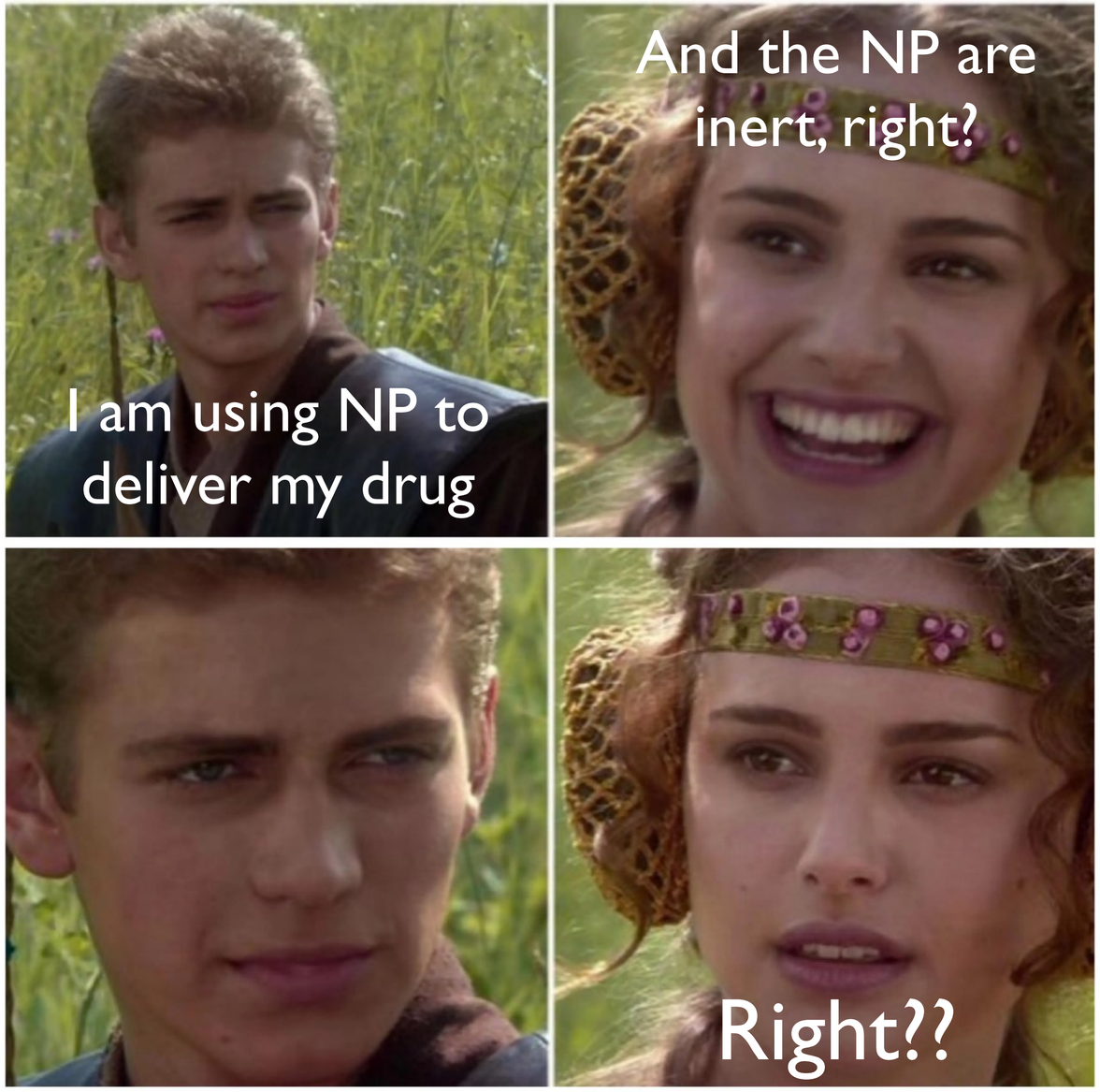
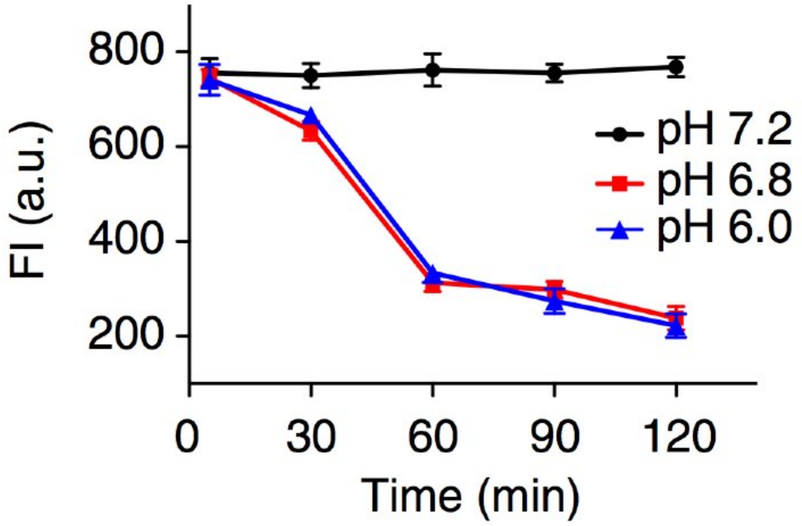
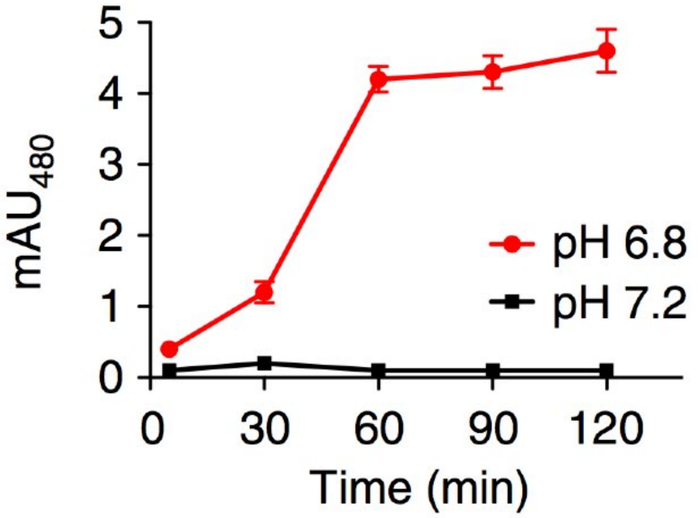


Padme is a new postdoc in the neighbouring lab

So, lets look at this

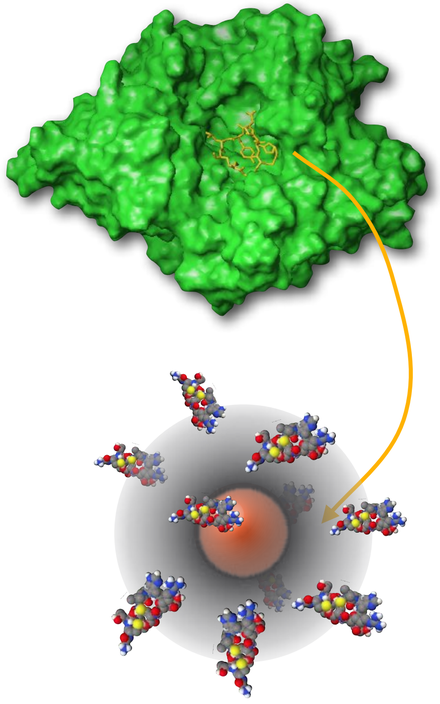
Drug loading of ferumoxytol with doxorubicin

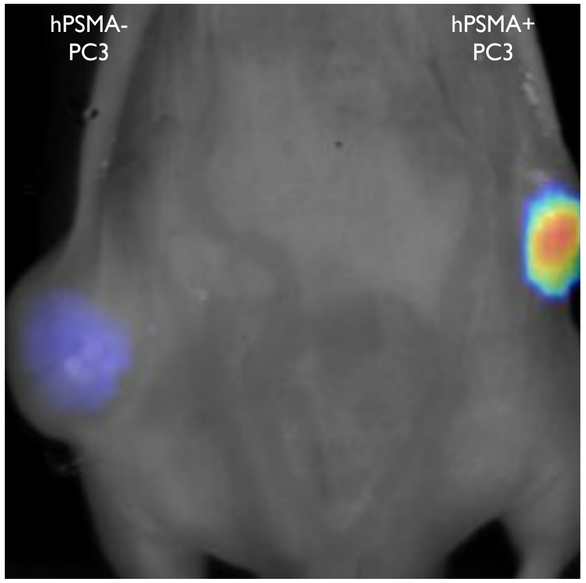


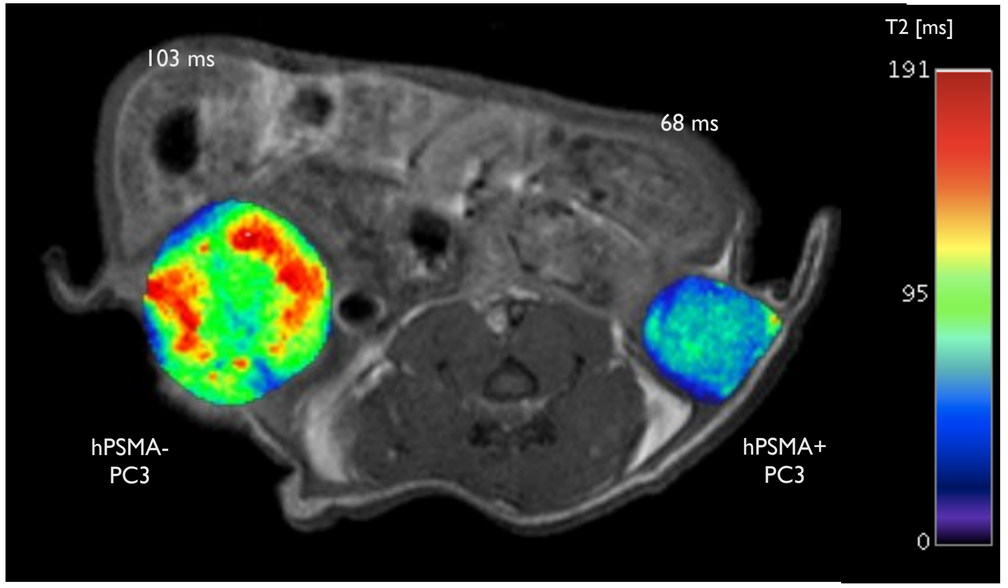


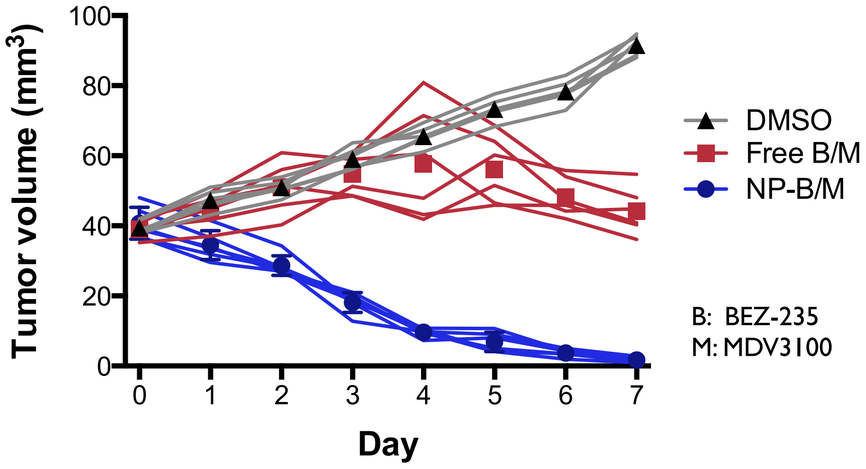
Kaittanis C et al. (2014) *Nature Communications* (5):3384

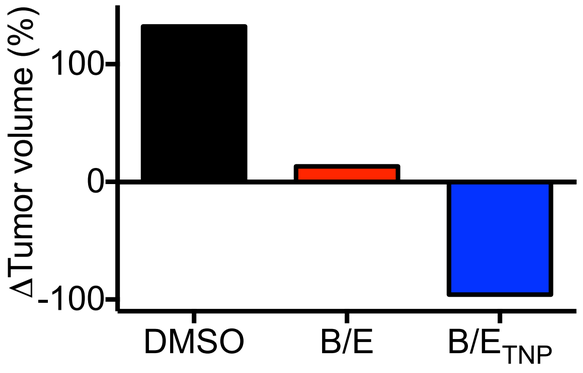
PSMA-targeted theranostic IONP





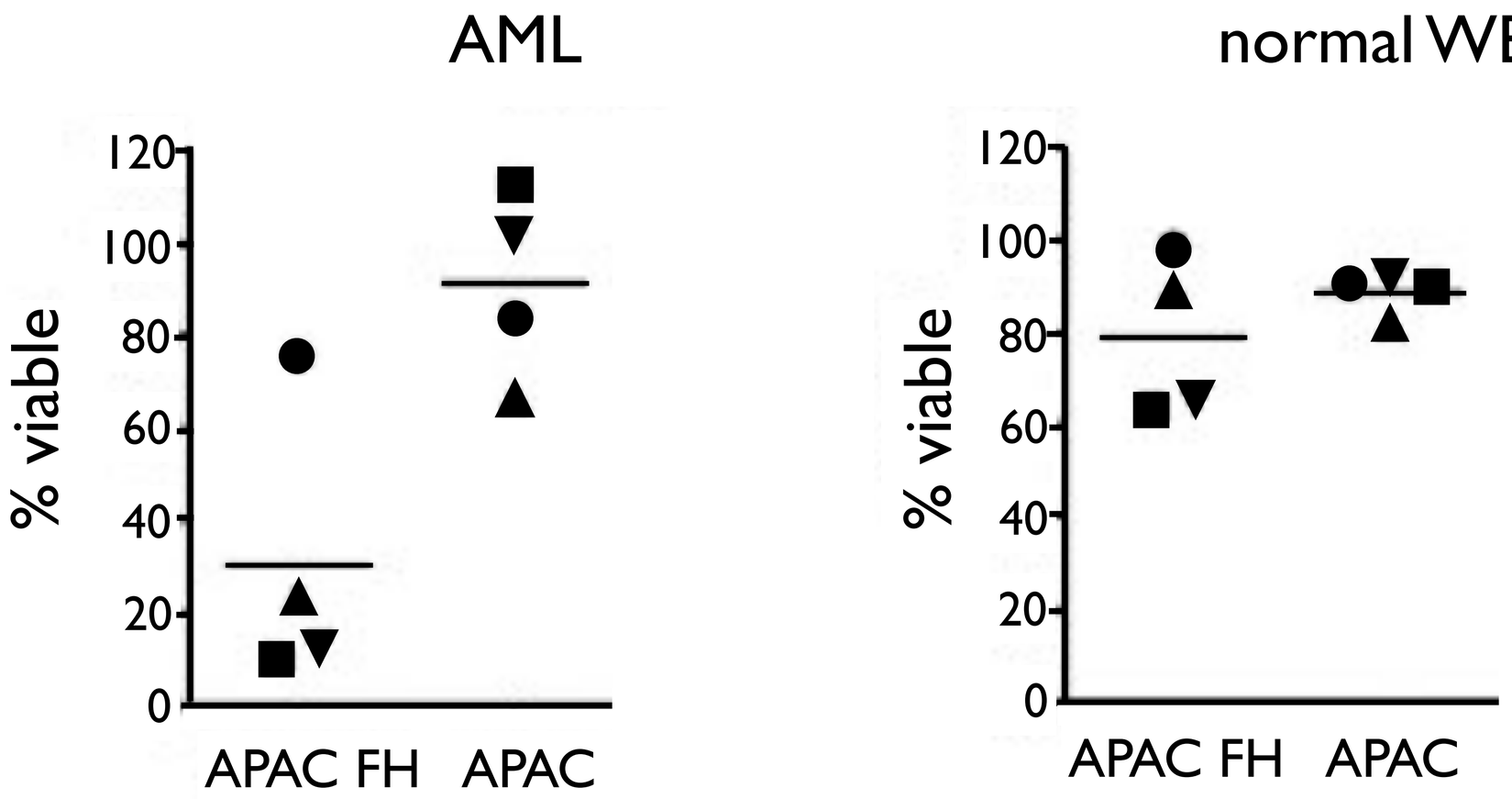






Kaittanis C et al. (2017) *Nano Letters* 17(11):7160

Simple carrier, hm...?



APAC: Parthenolide derivative

Trujillo-Alonso V, Pratt E et al. (2019) *Nature Nanotechnology* 14(6): 616

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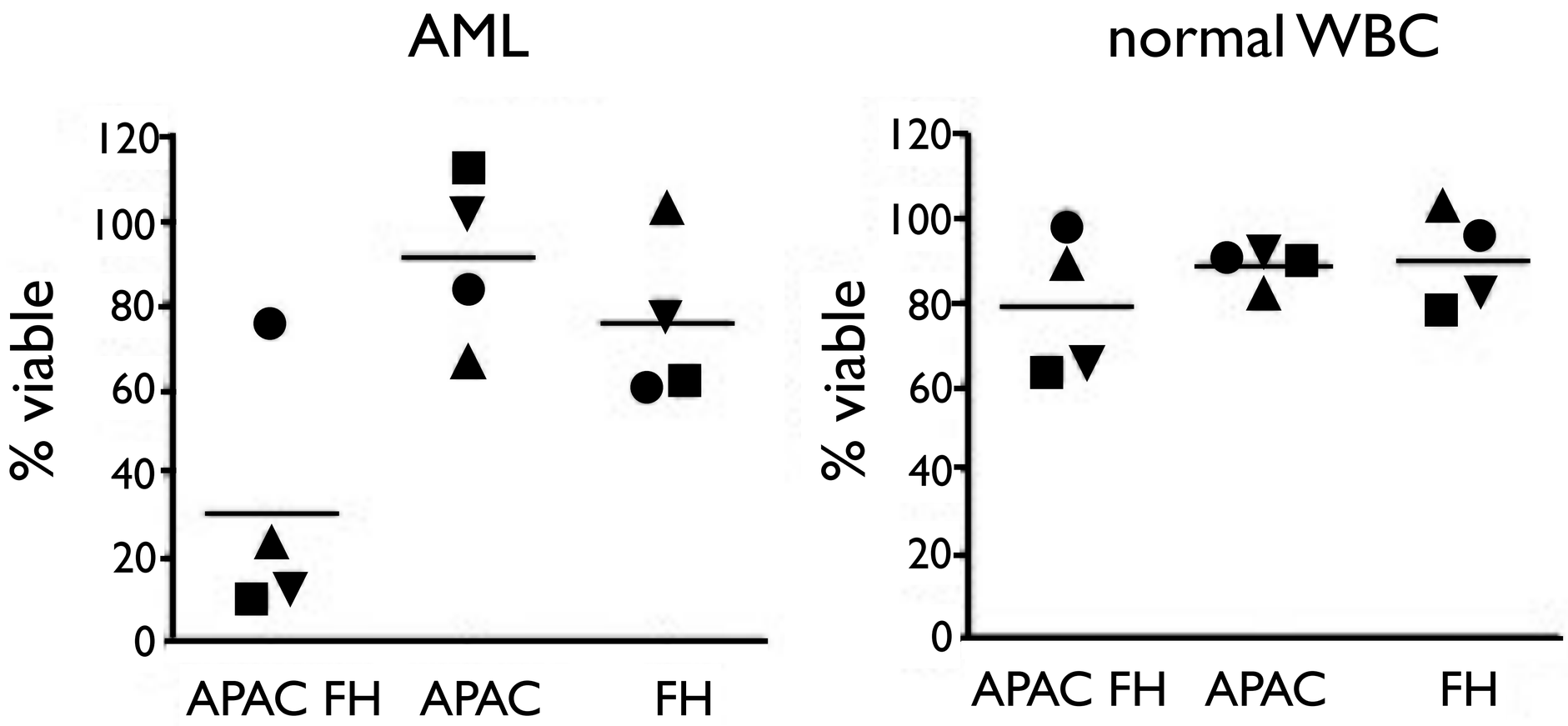

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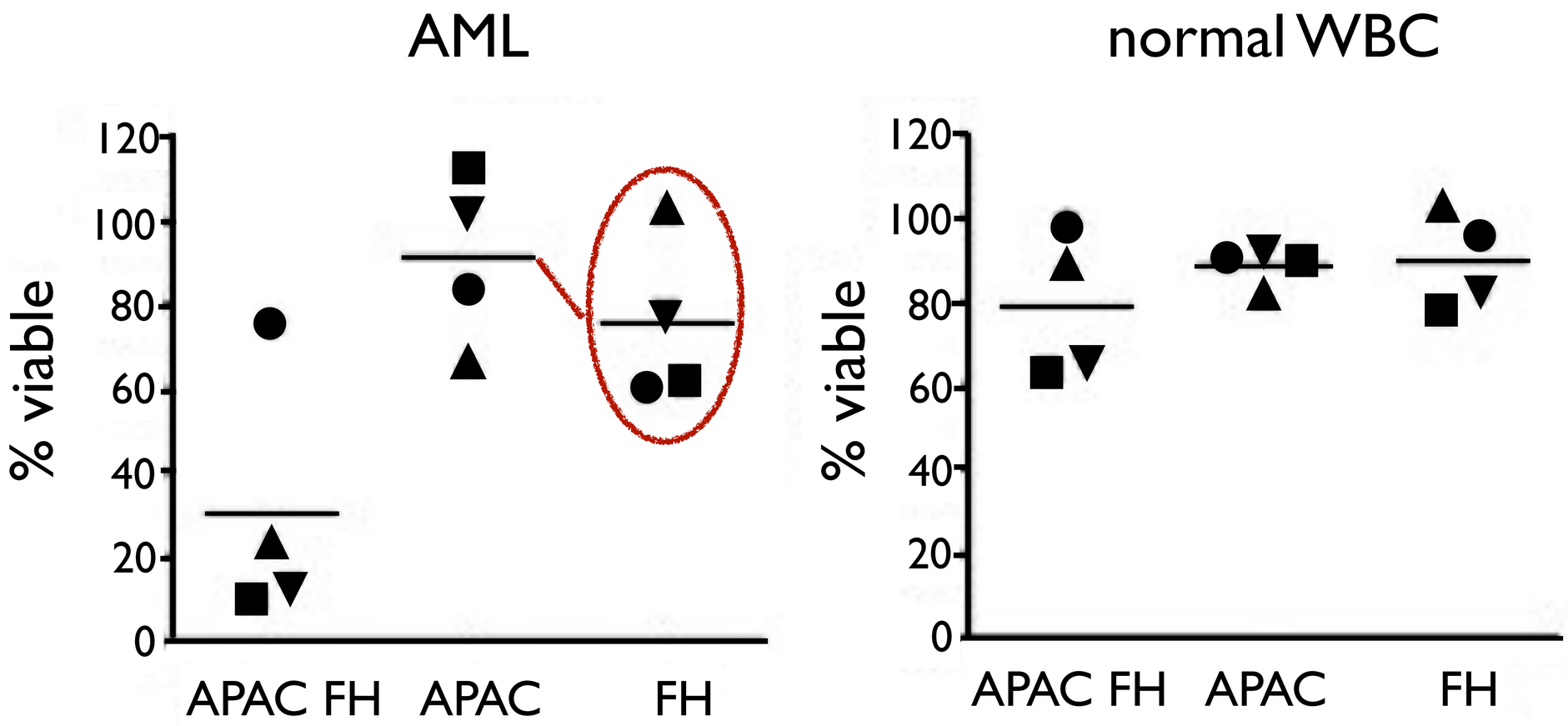

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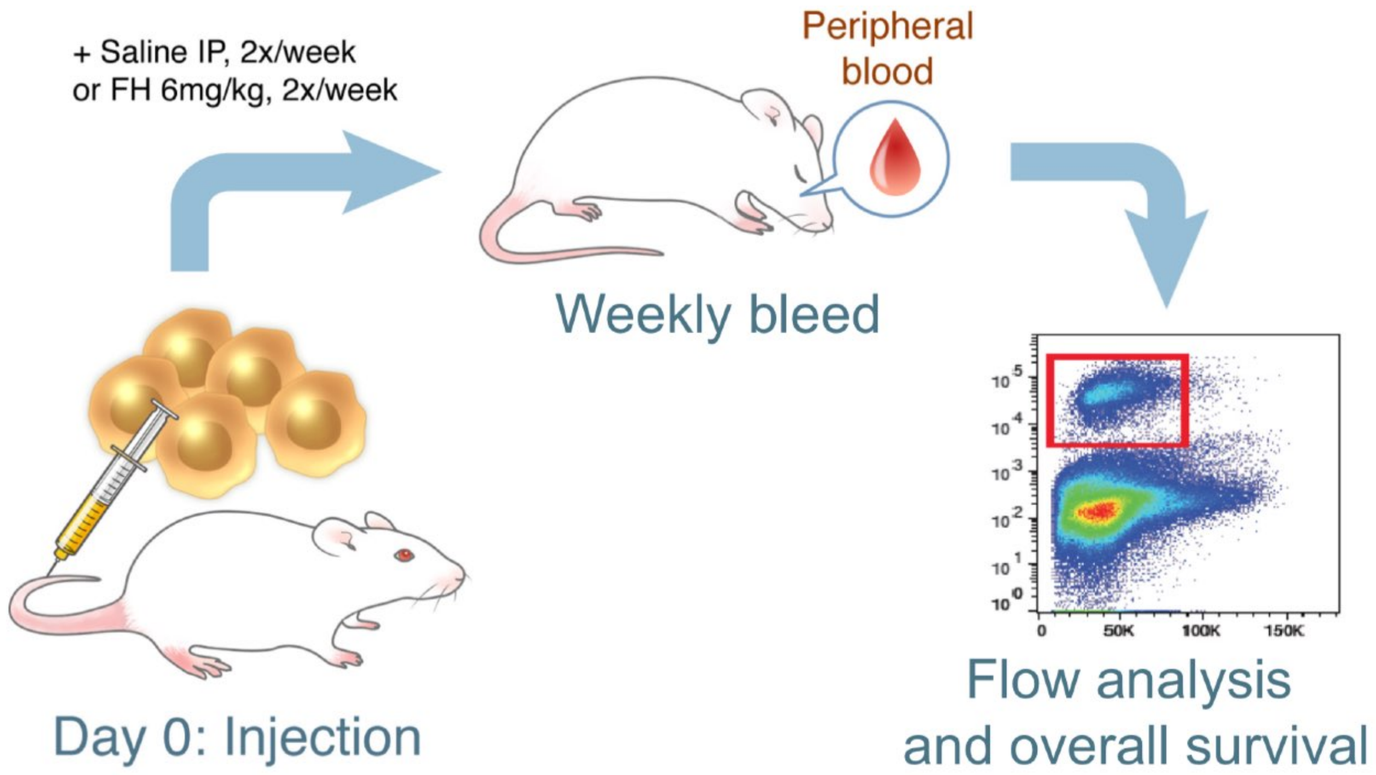
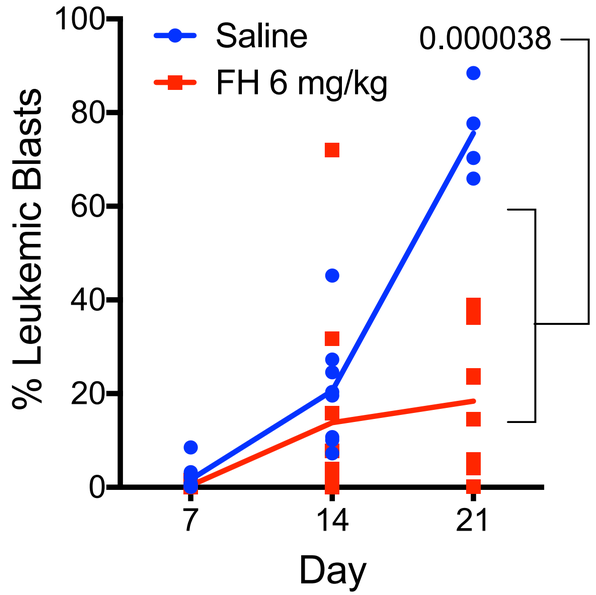
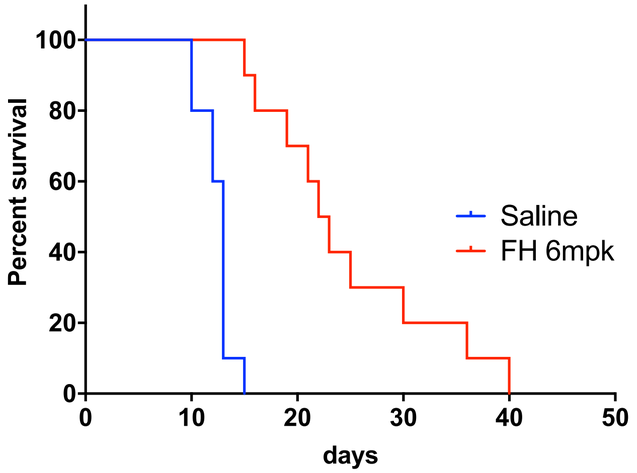
AML therapy with FH







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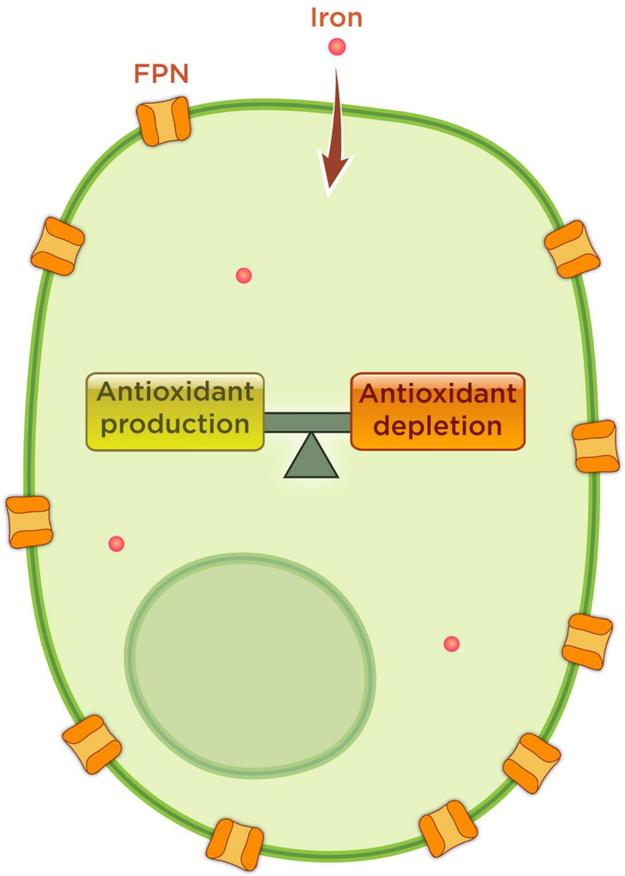
Oxidative Ferrotherapy

normal cell

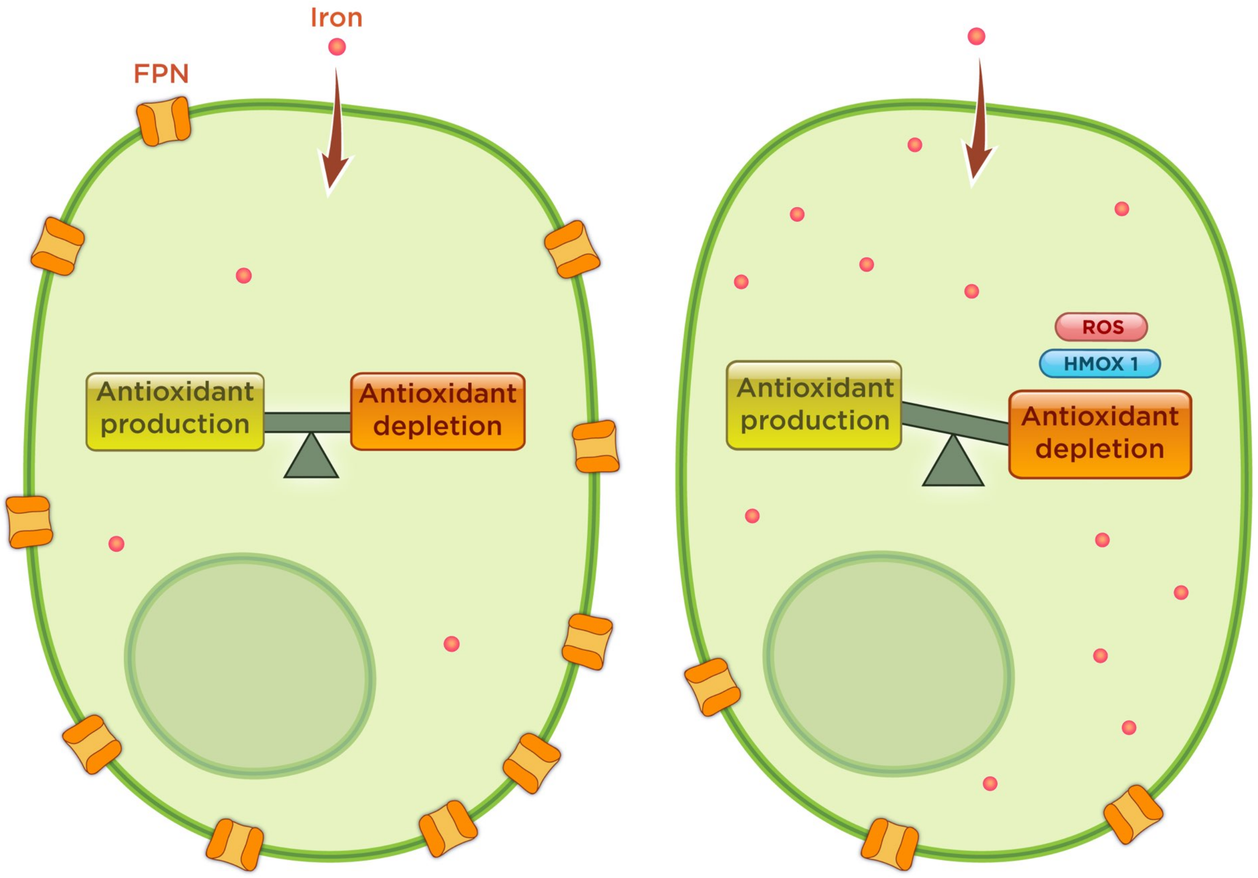


Trujillo-Alonso V, et al. (2019) Nature Nanotechnology 14(6): 616

Oxidative Ferrotherapy

normal cell

cancer cell



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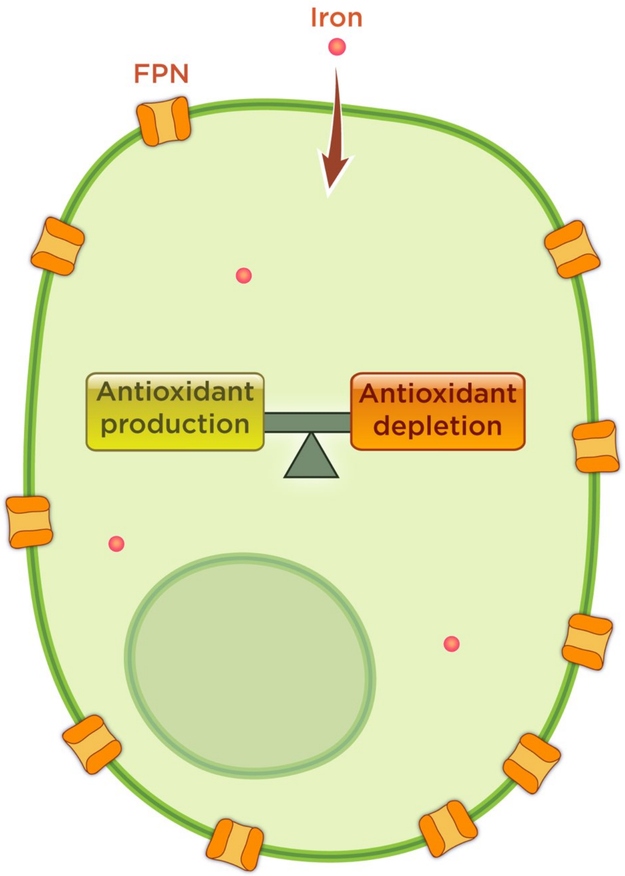

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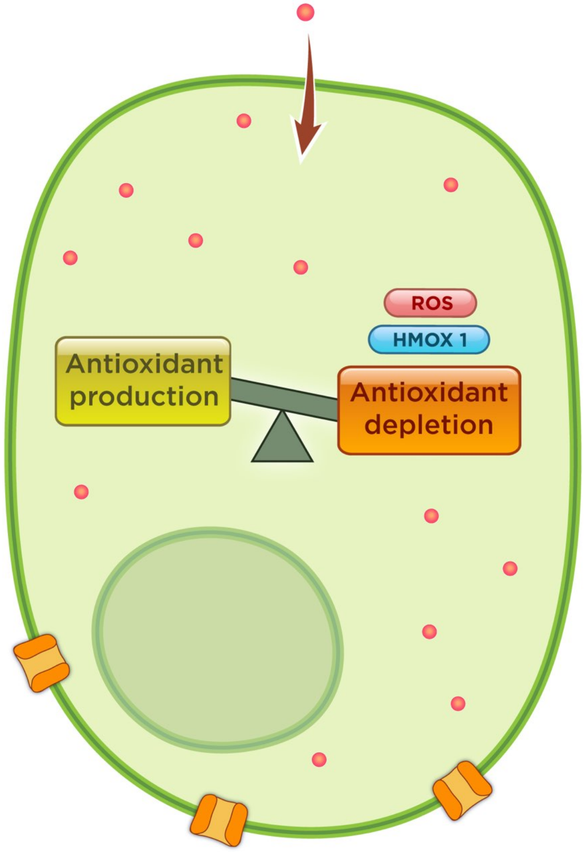
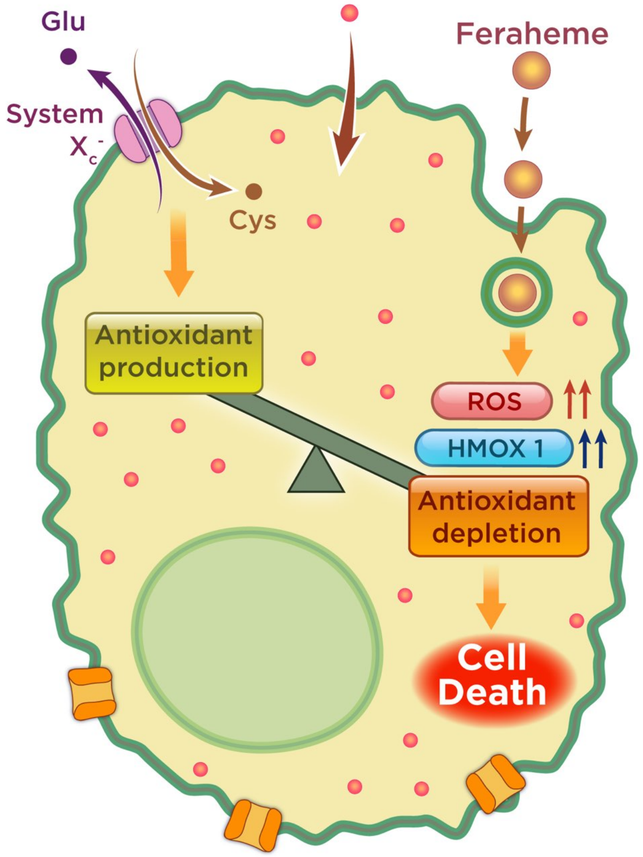


cancer cell & FH



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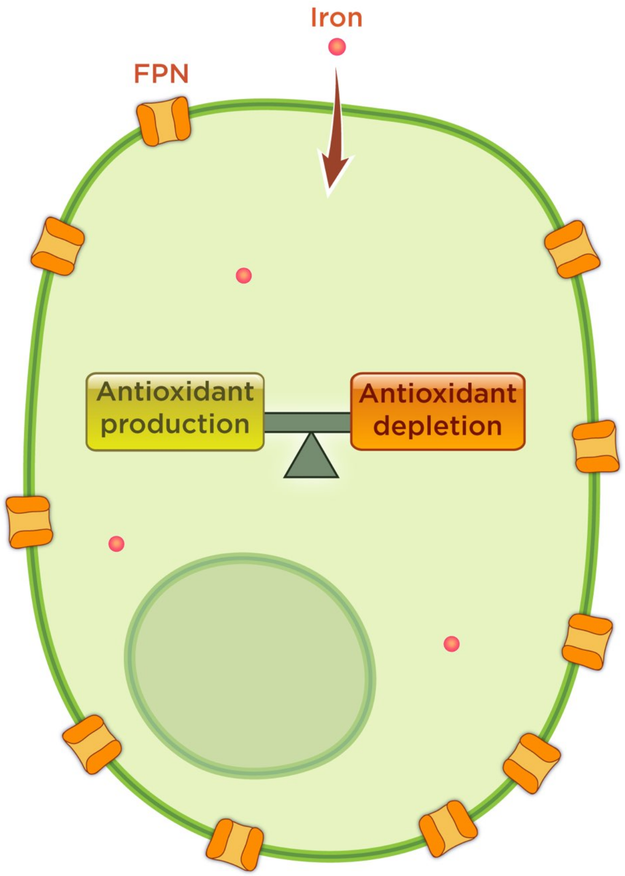

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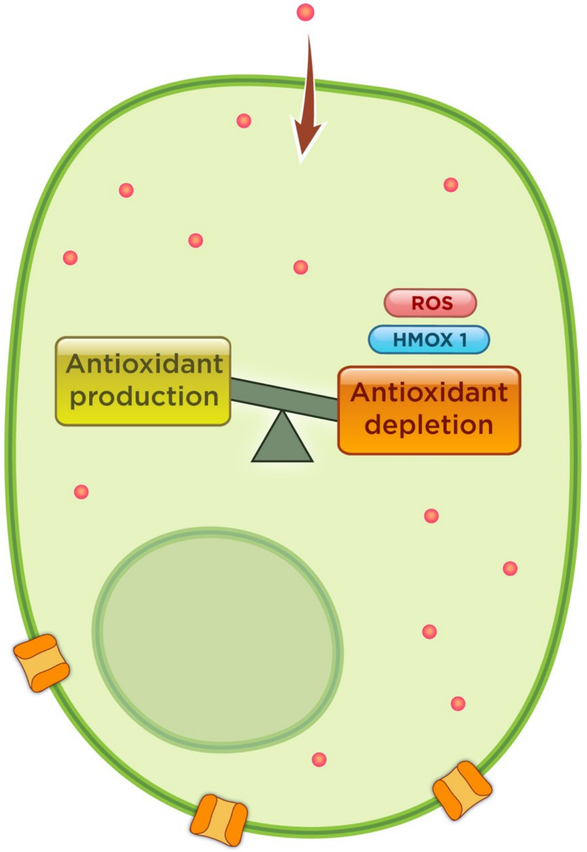

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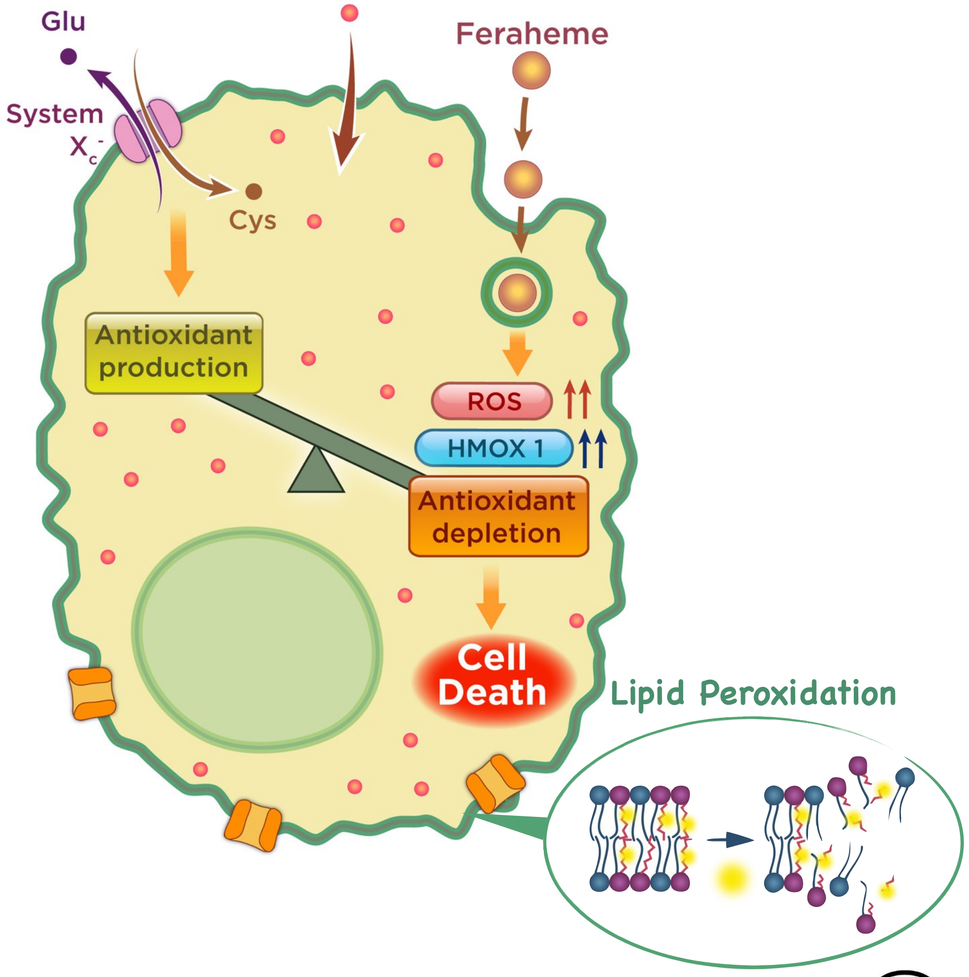

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The nanoparticle knowledge gap

- Limited understanding compared to small molecules or biologics

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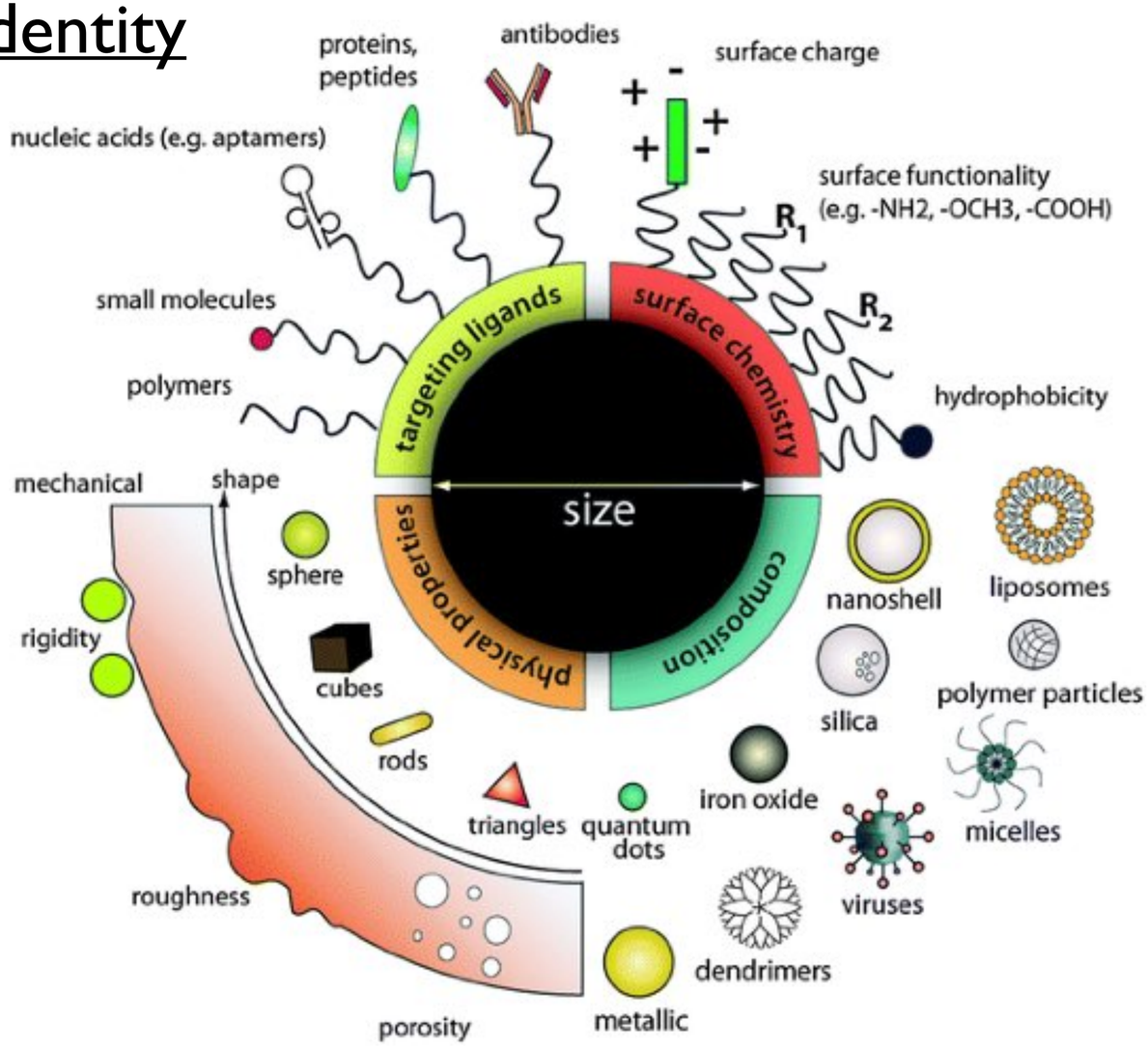
"*Pristine*" particle identity

Determinants of pristine nanoparticle identity

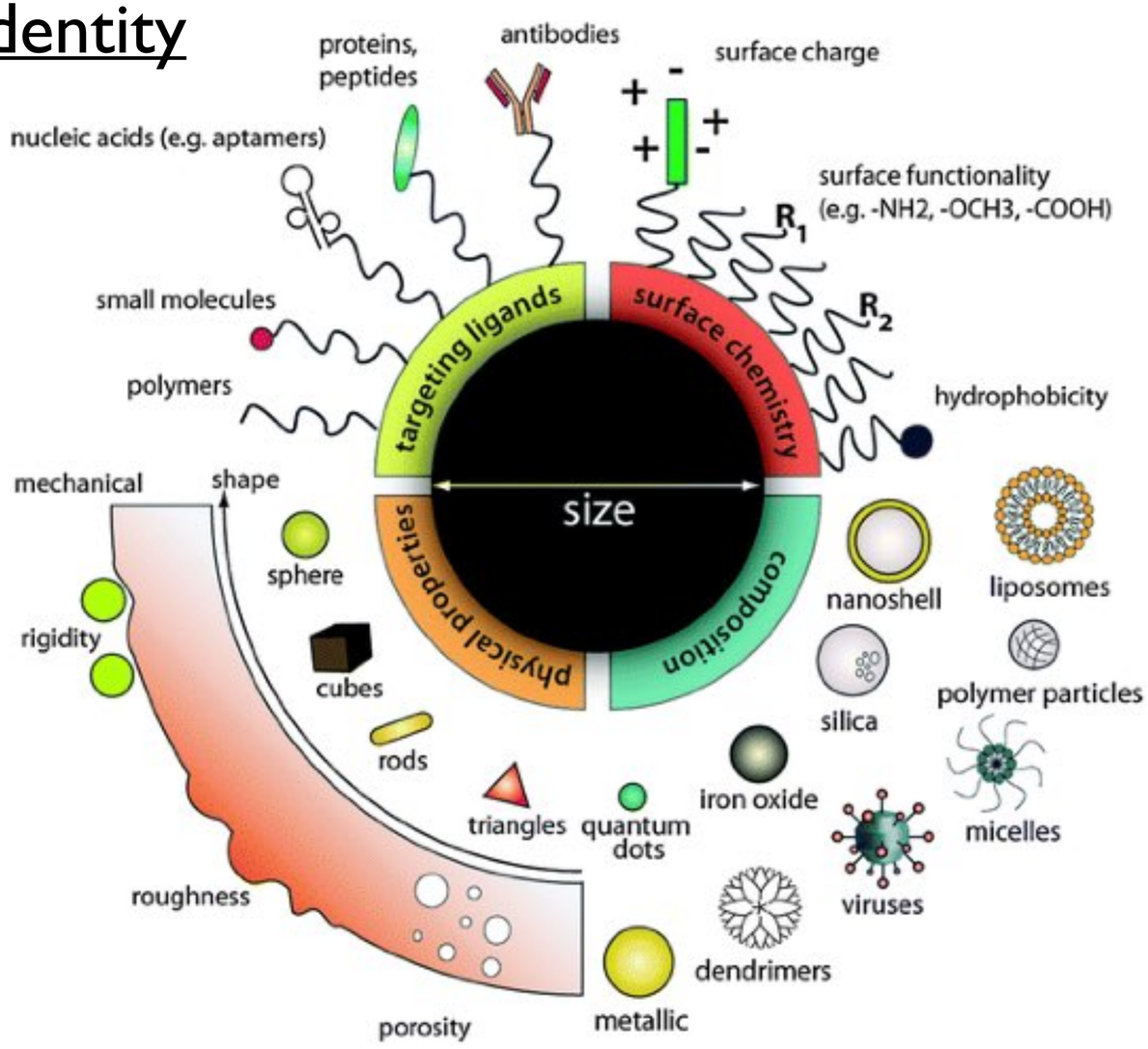


Chou, Ming, and Chan. (2011) *Chem Soc Rev*, 40

"*Pristine*" particle identity

Determinants of <u>pristine nanoparticle identity</u>

- Targeting ligands
- Drug payloads
- Size
- Shape
- Material
- Structure
- Rigidity/elasticity
- Roughness
- Porosity
- Surface charge
- Hydrophobicity
- Functional groups
- Imaging moieties
- etc.



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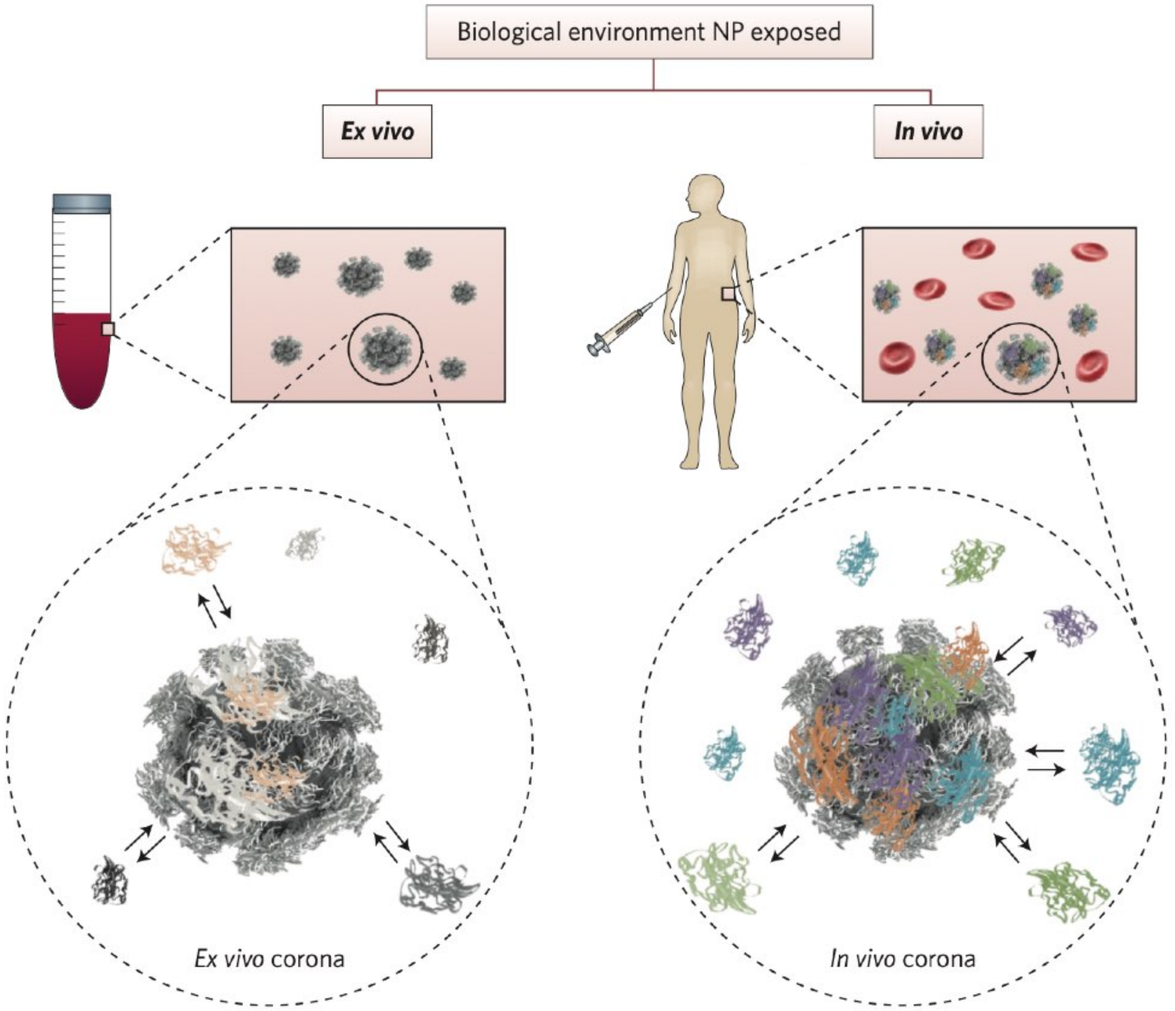
"Biological" particle identity (Corona)

Biomolecules form a unique particle identity on top of the pristine identity



Hadjidemetriou M & Kostarelos K *(2017) Nanotechnology*, 12(4): 288

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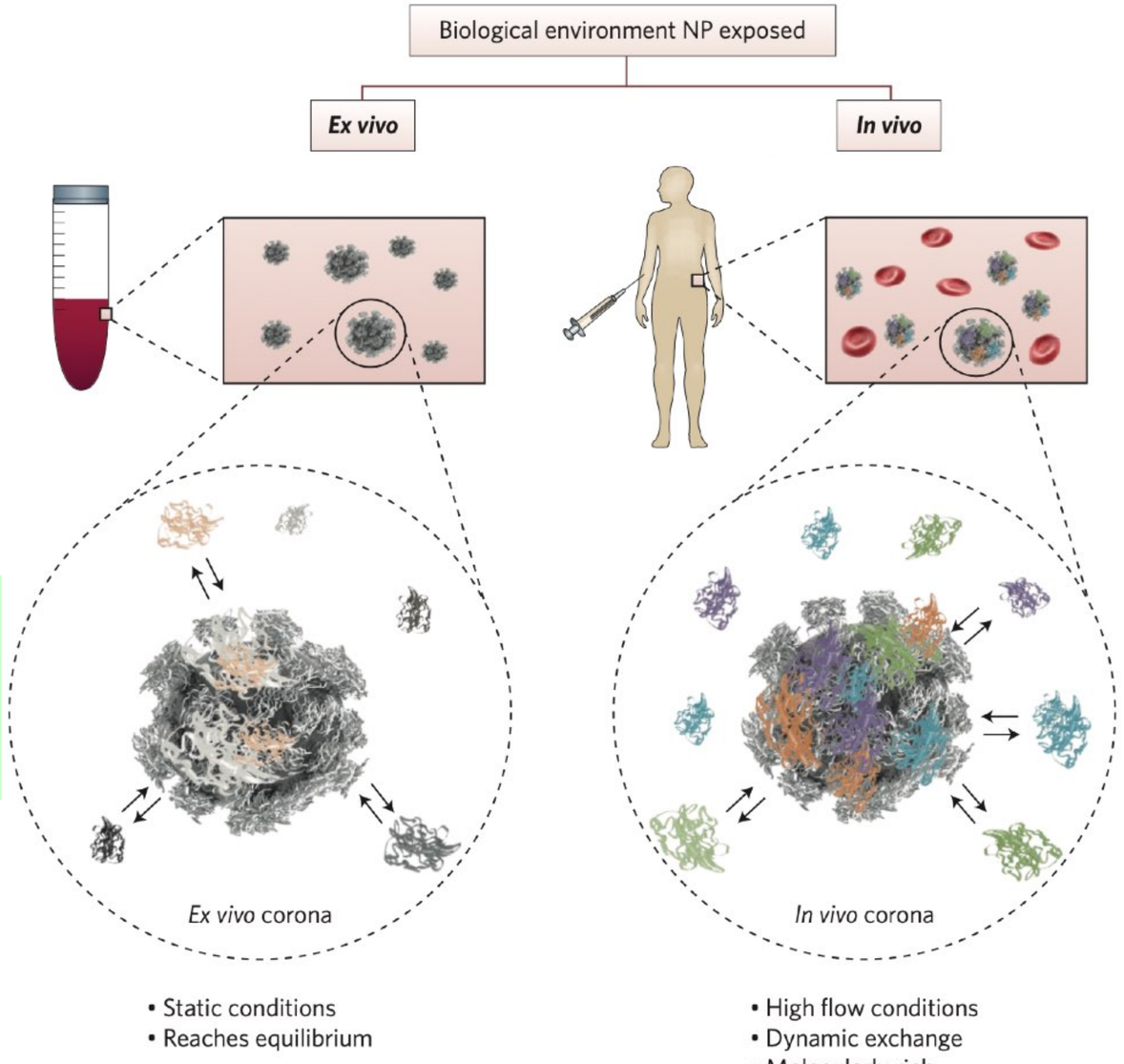

1. "Pristine" size
2. "Pristine" composition
3. "Pristine" surface chemistry
4. etc.

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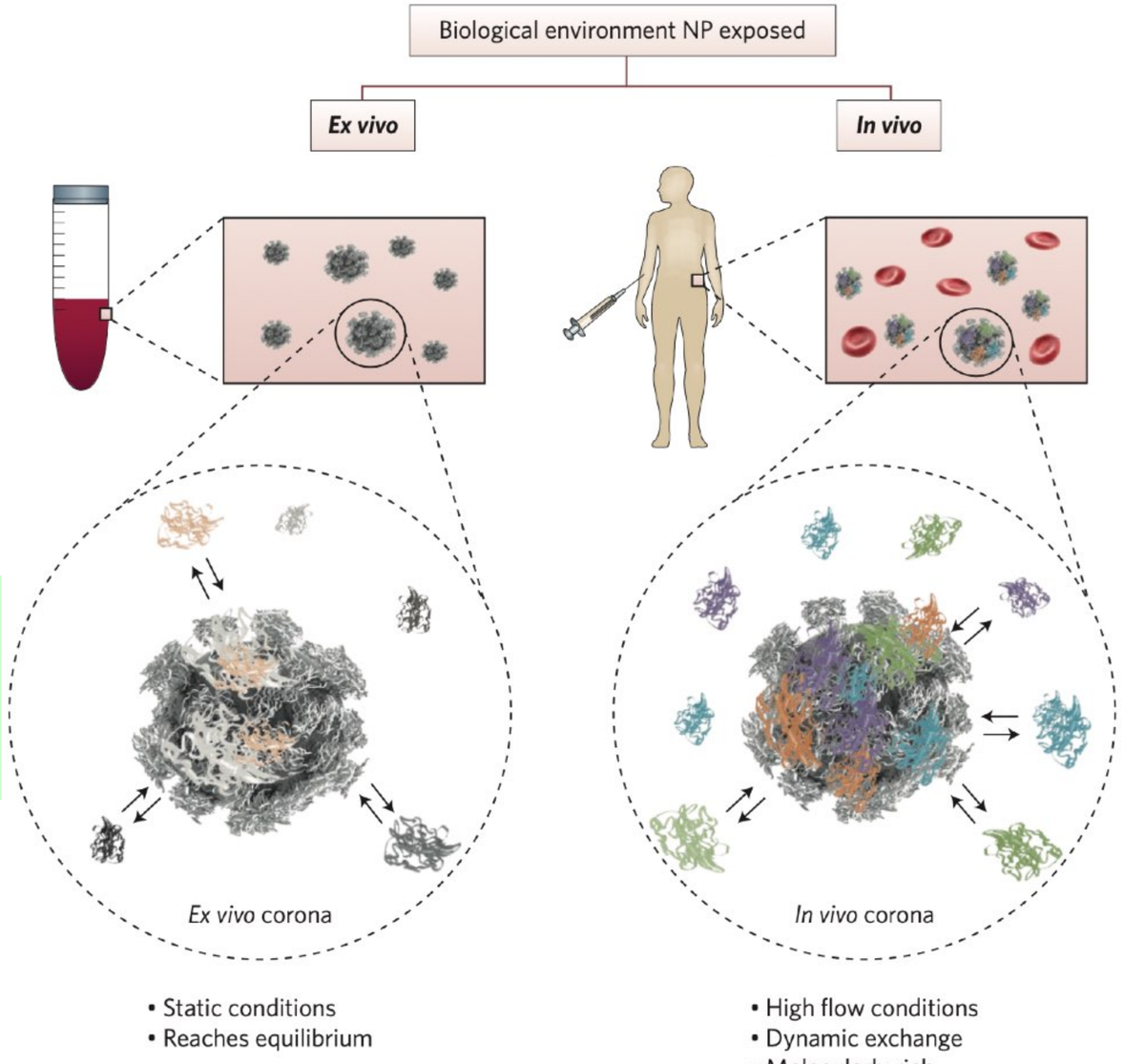

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Static and predictable
Easily measured

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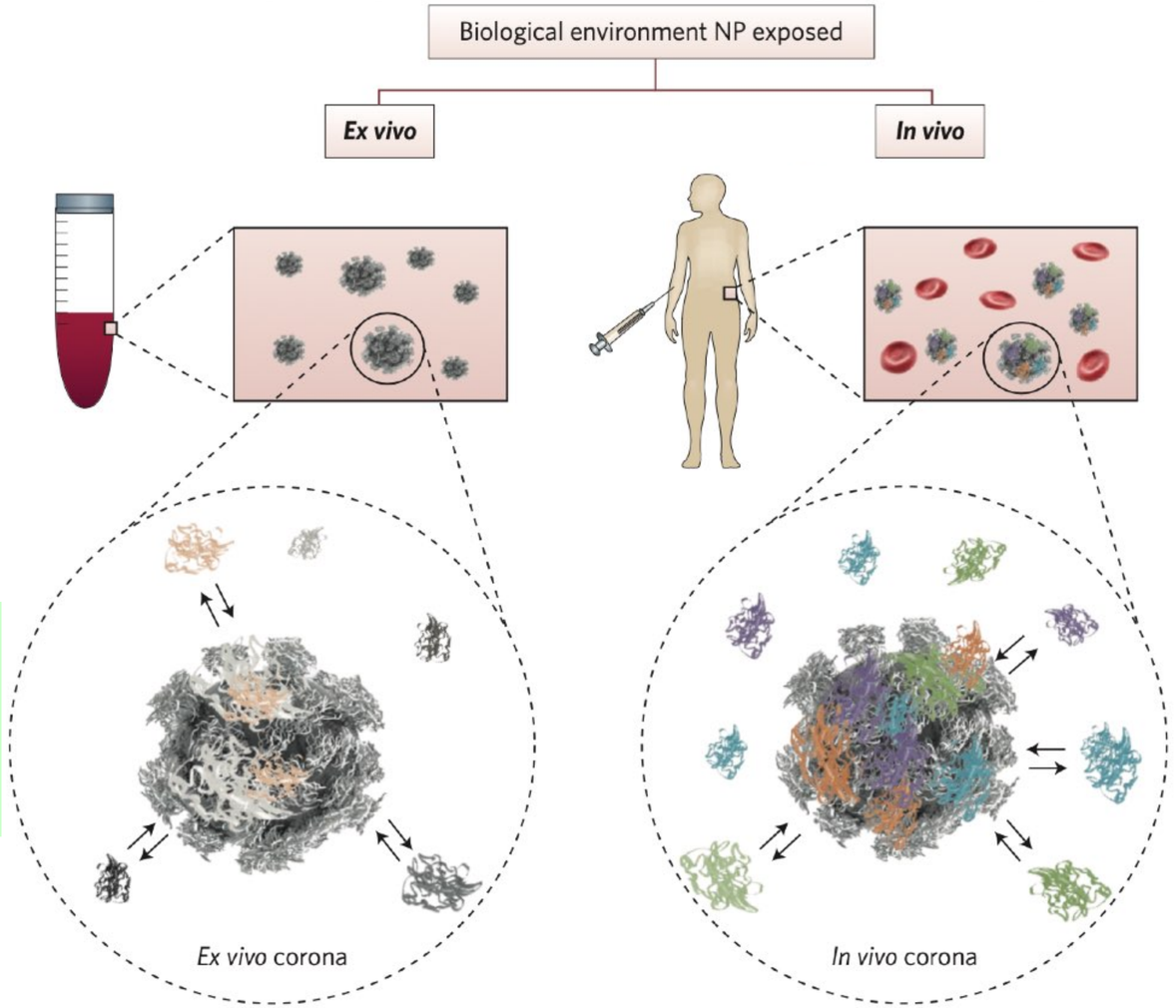

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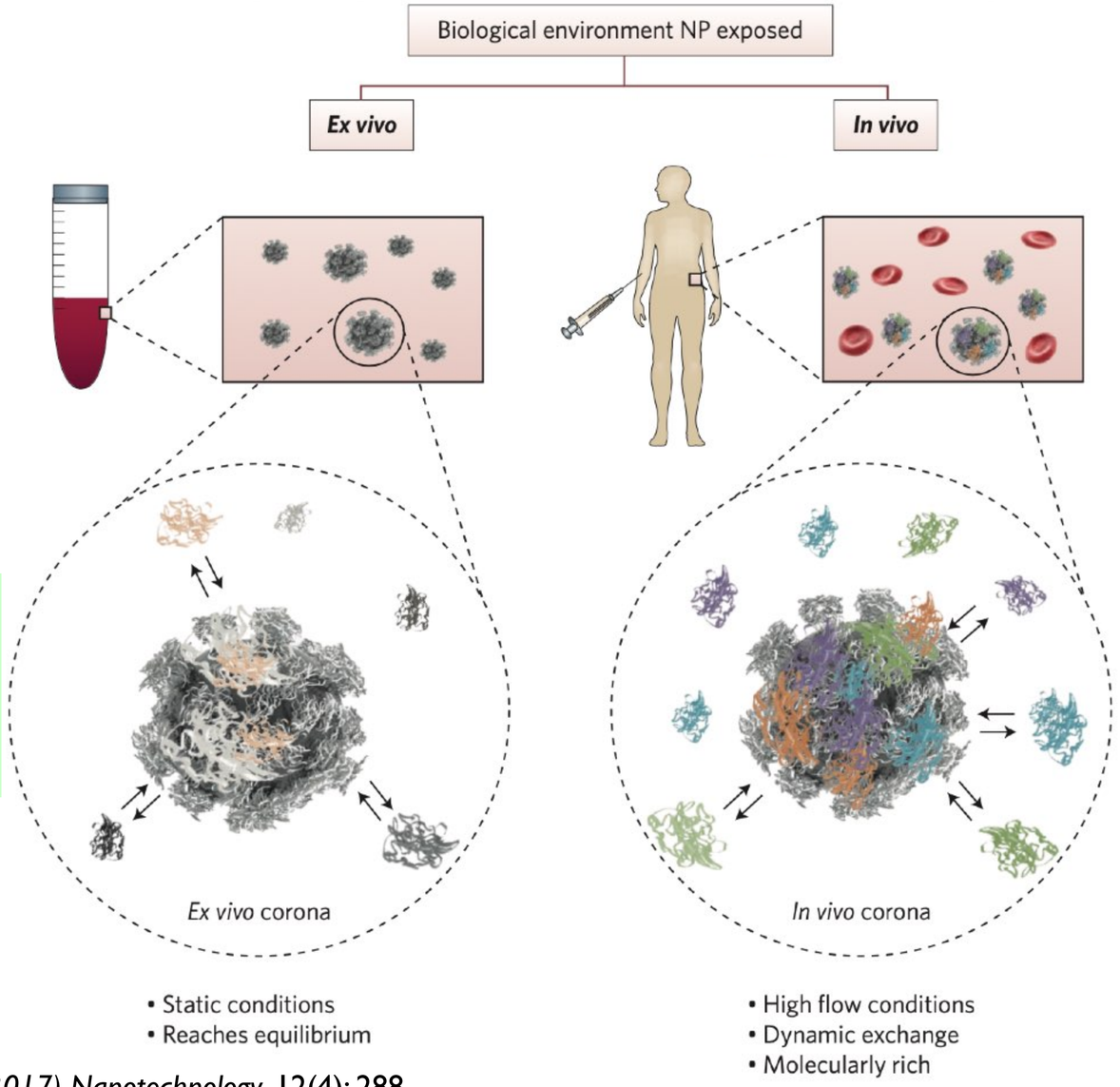

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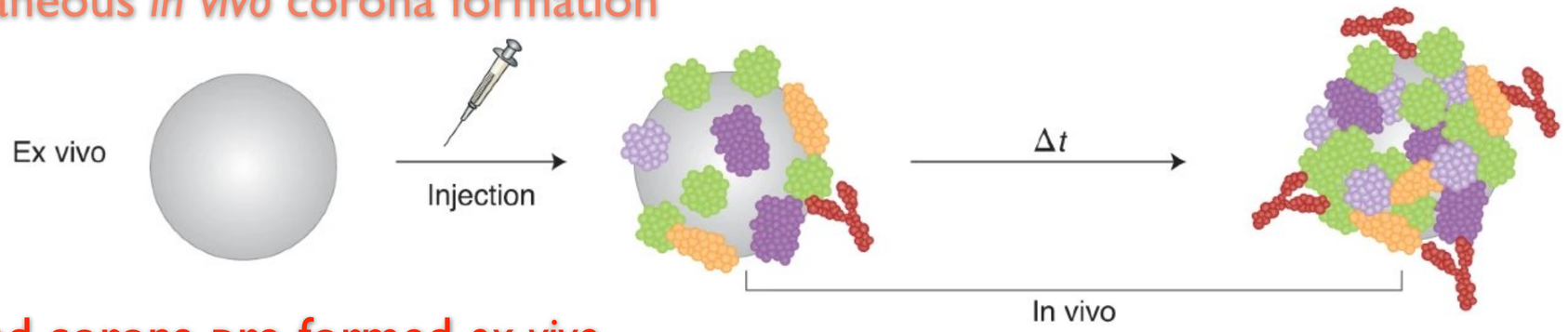
Dynamic and variable
Difficult to monitor

Hadjidemetriou M & Kostarelos K *(2017) Nanotechnology*, 12(4): 288

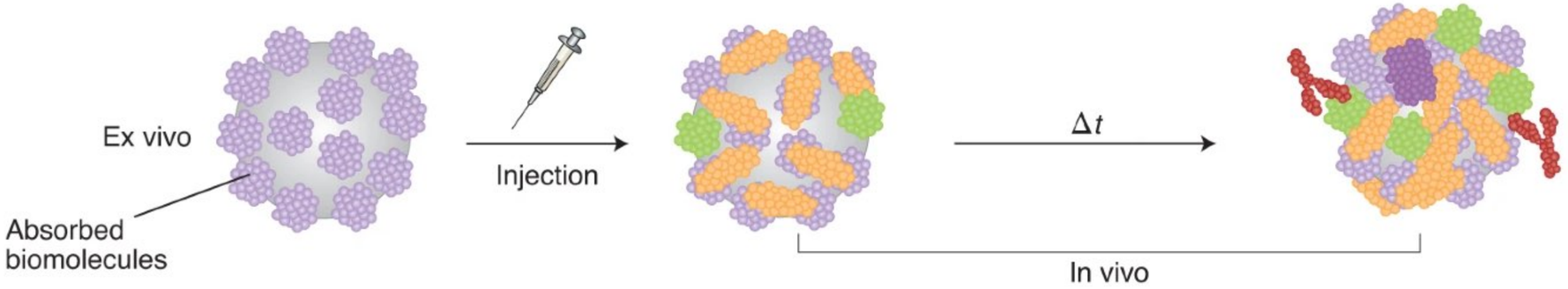
Taking control of nanoparticle identity

Spontaneous *in vivo* corona formation



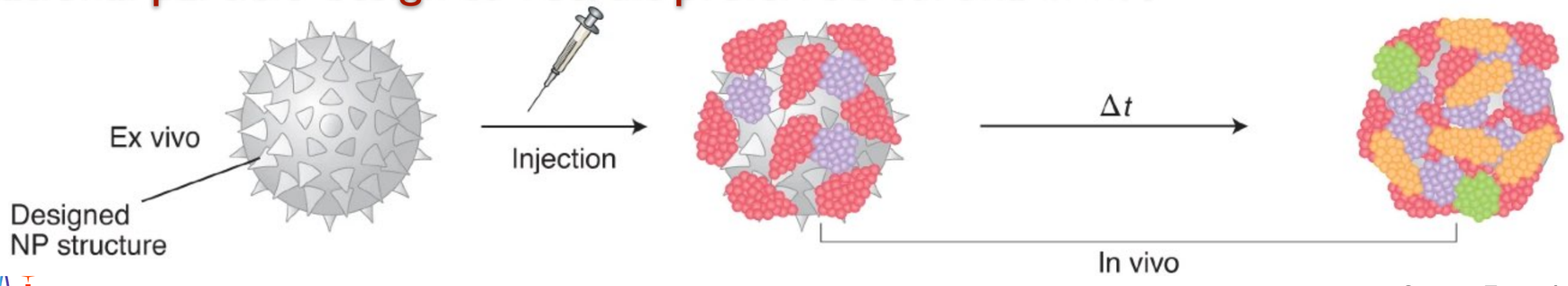
Biological identity of particle may not be compatible with pharmaceutical requirements

Defined corona pre-formed *ex vivo*



Transiently associated biomolecules influence subsequent corona structure

Rational particle design to recruit preferred corona *in vivo*

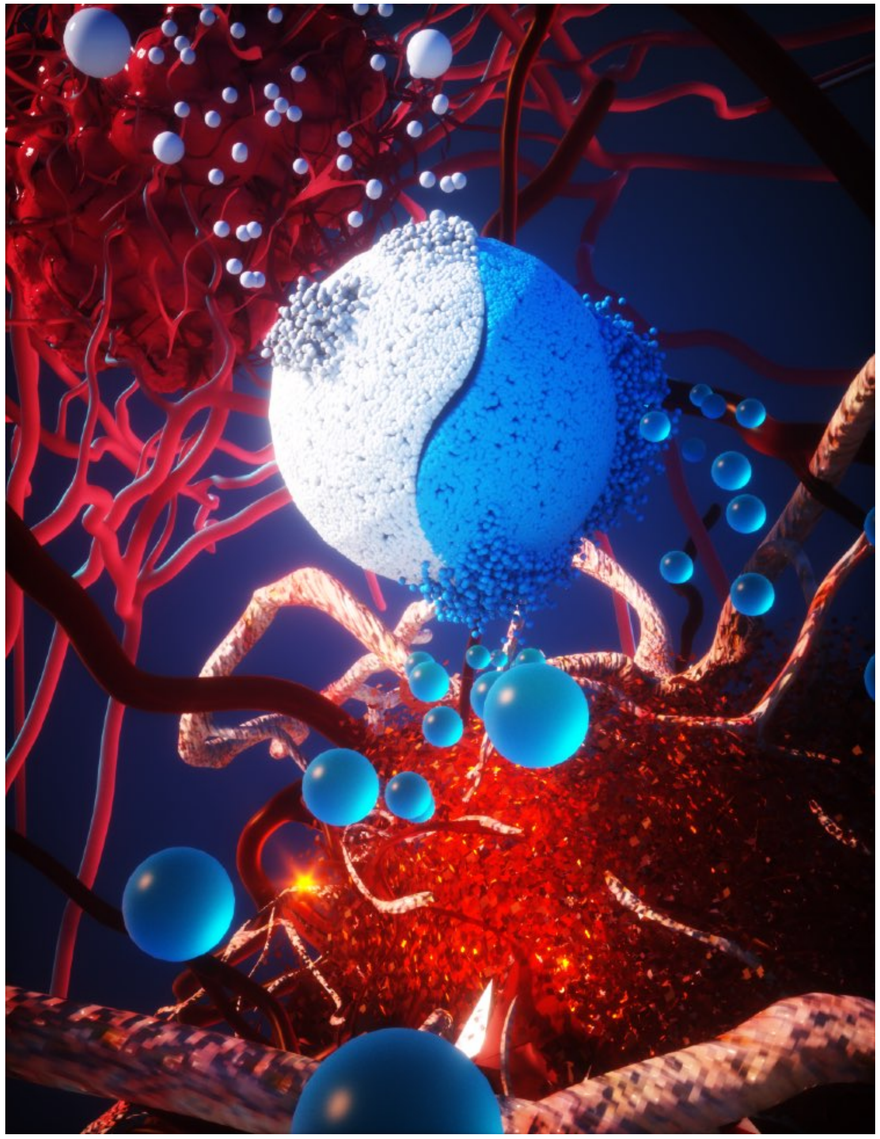


Particle characteristics engineered to facilitate the formation of a specific biological identity

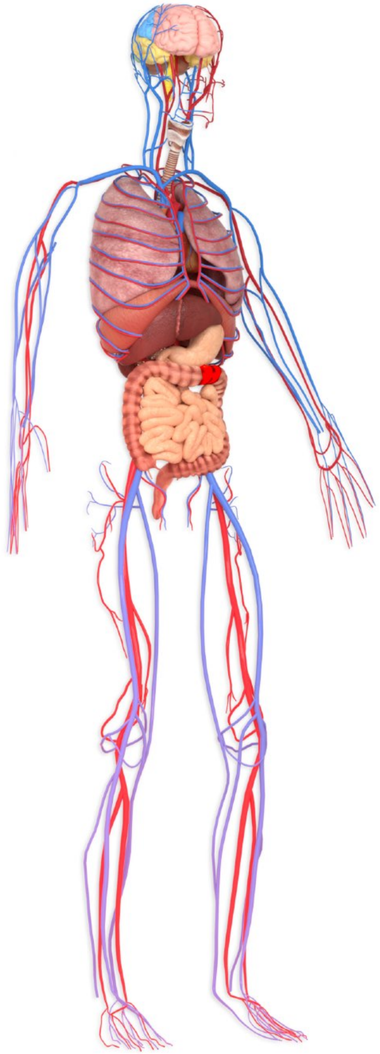
Stater E et al. (2021) *Nature Nanotechnology*, 16(11): 1180

Ancillary effects of NP

- Nanomaterial cannot be assumed to be functionally inert simply because it has low toxicity or high biocompatibility
- **Ancillary effect** = any unanticipated biological effect elicited by nanoparticles and independent of any engineered functionality or drug payload
- Double-edged sword
  - Potentially harmful
  - Could be exploited as therapeutic mechanism



Evidence of NP ancillary effects



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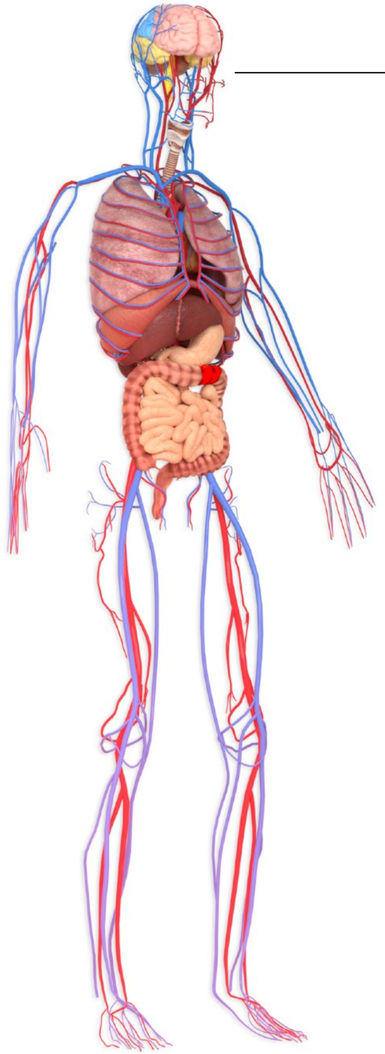

Microvasculature

- Permeabilization of endothelium and BBB
- Modulation of angiogenesis
- Upregulation of endothelial adhesion proteins

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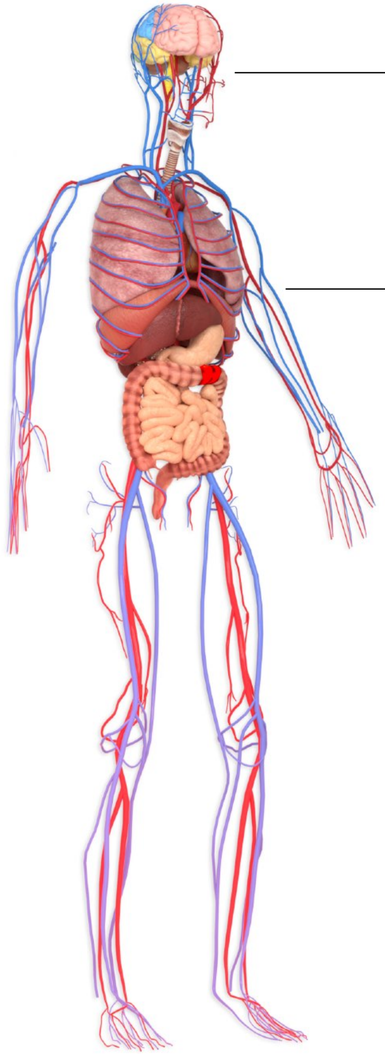

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Evidence of NP ancillary effects

Immune system

- Pro-inflammatory activation
- Histamine release
- Inhibition of response to inflammatory signals
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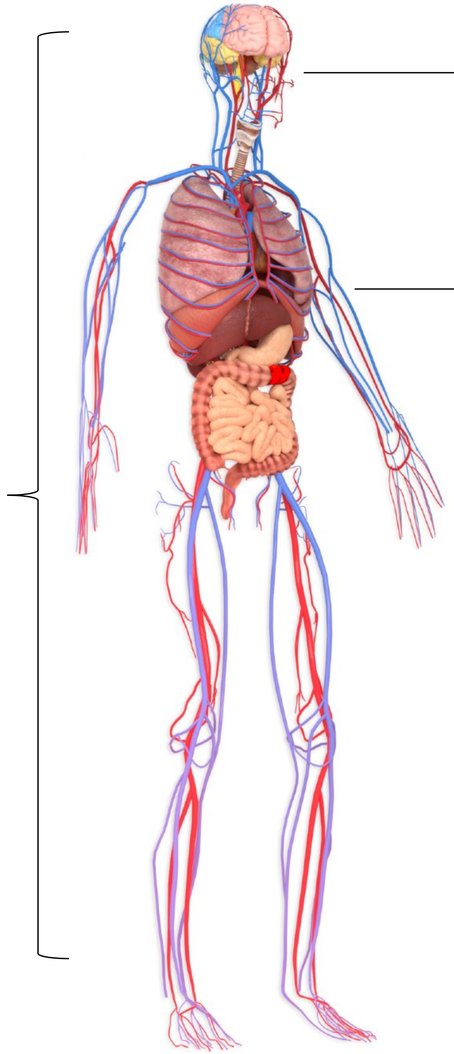

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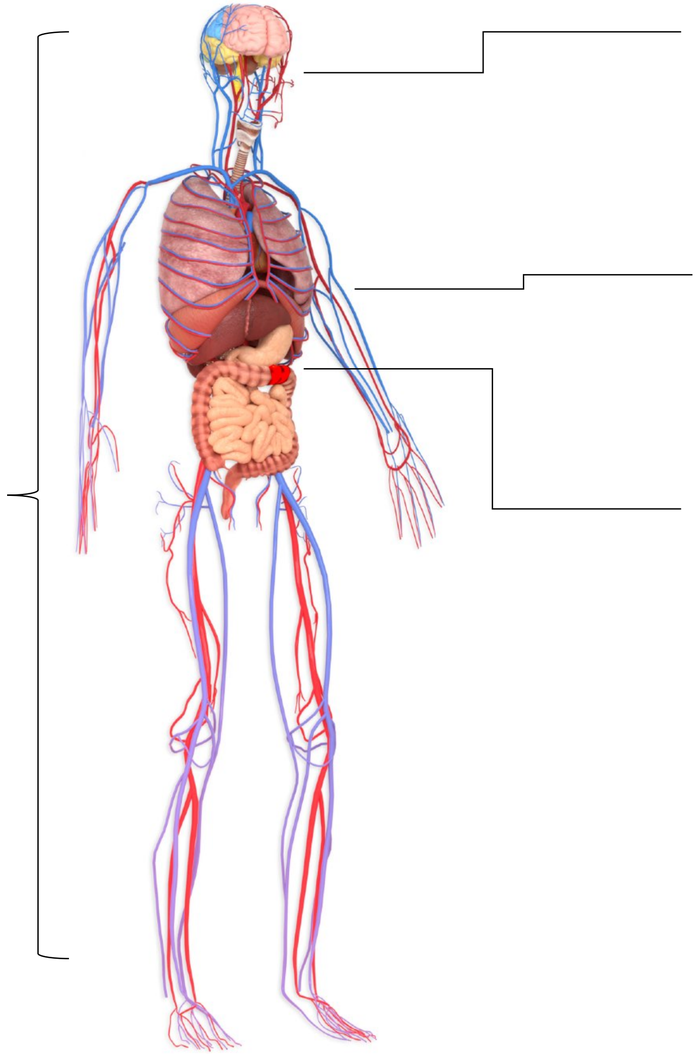

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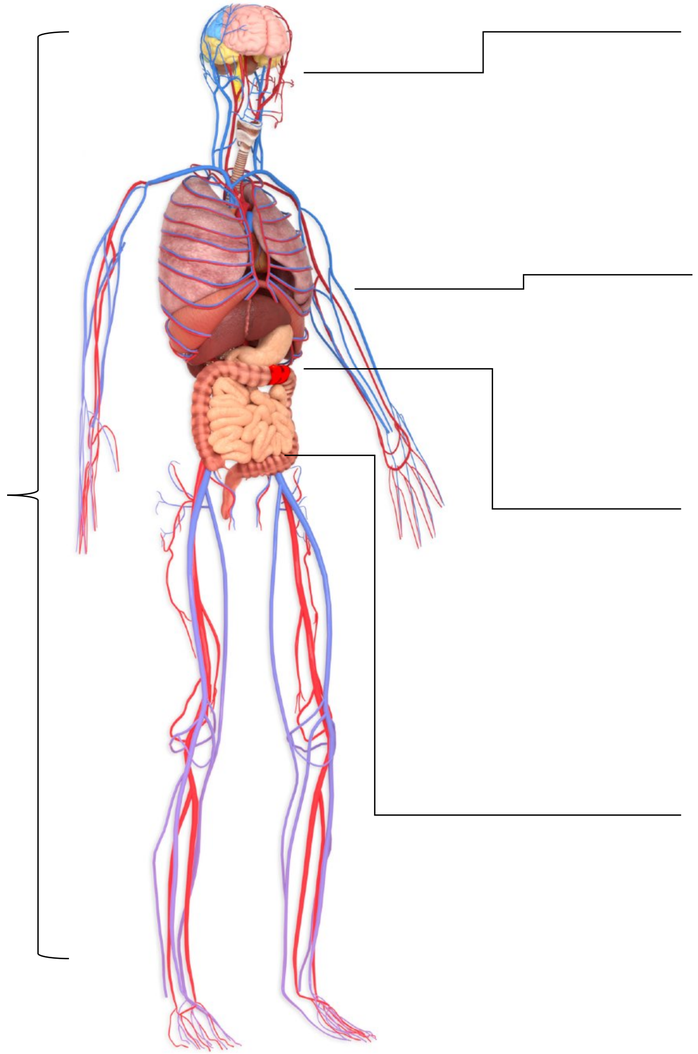

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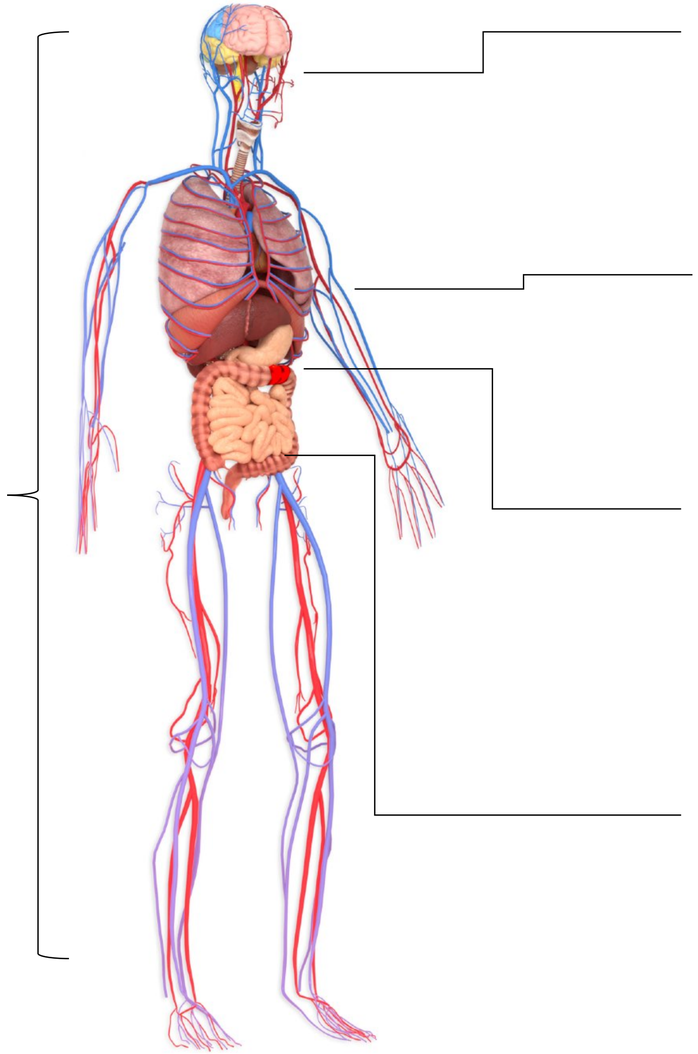

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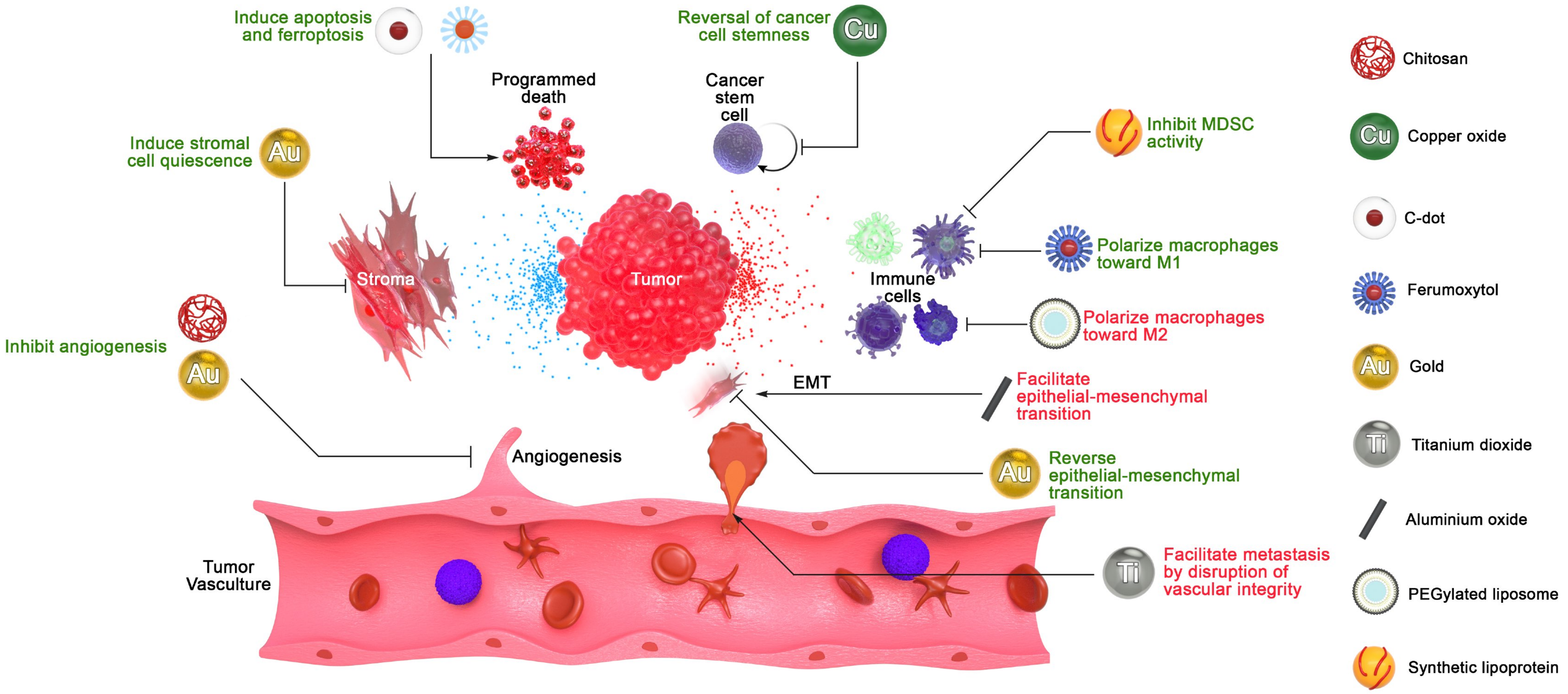
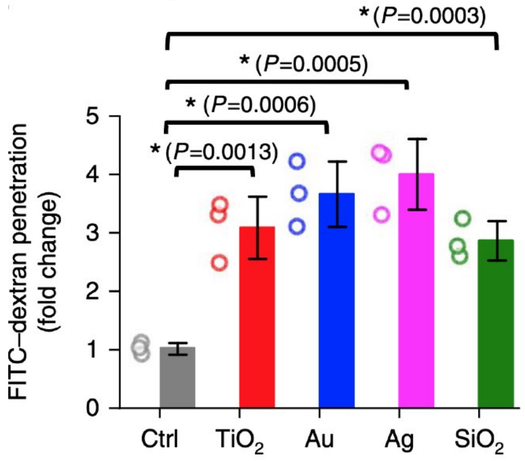
Diverse ancillary effects in cancer

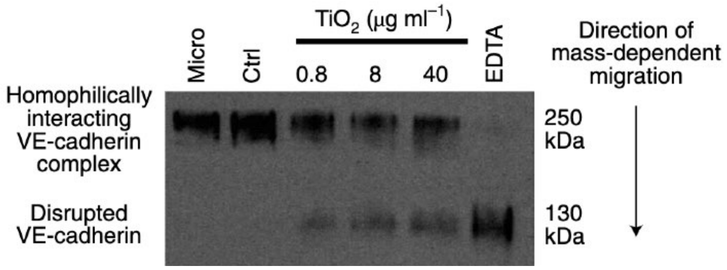


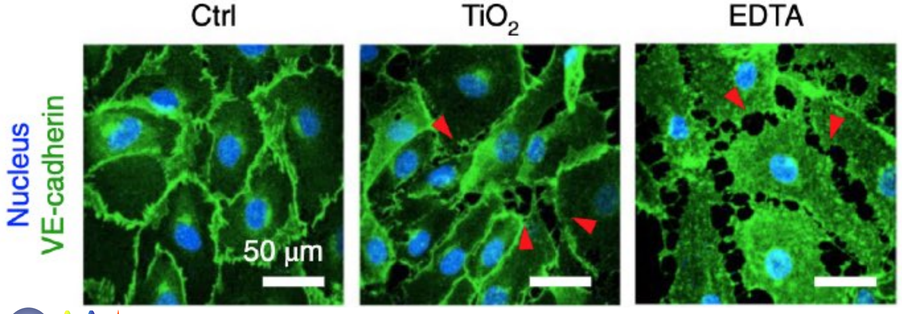
Stater E et al. (2021) *Nature Nanotechnology*, 16(11): 1180

NP disrupt endothelial barriers

leaky endothelium







Peng E et al. (2019) *Nature Nanotechnology*, 16(11):1180

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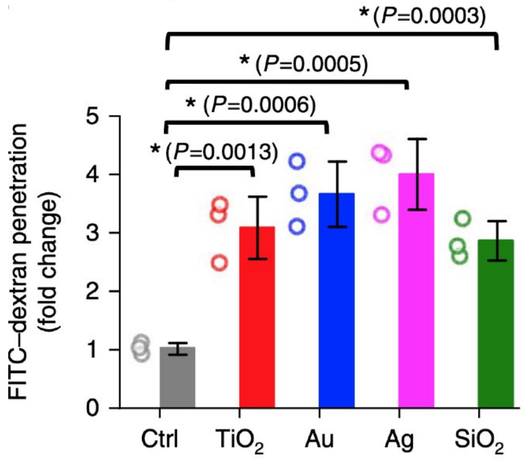
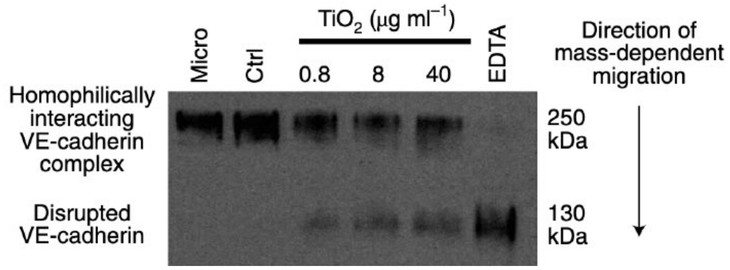
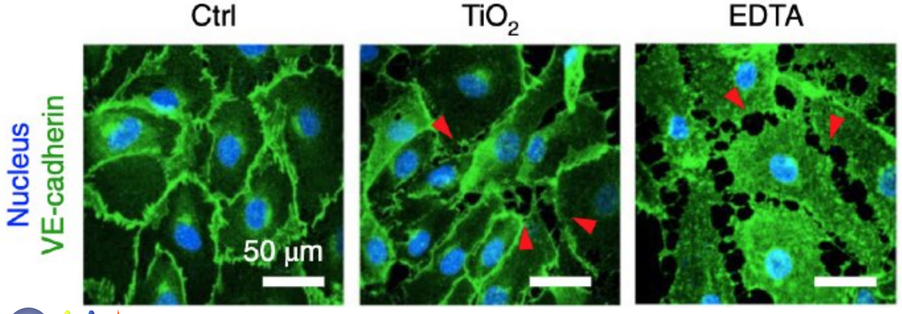
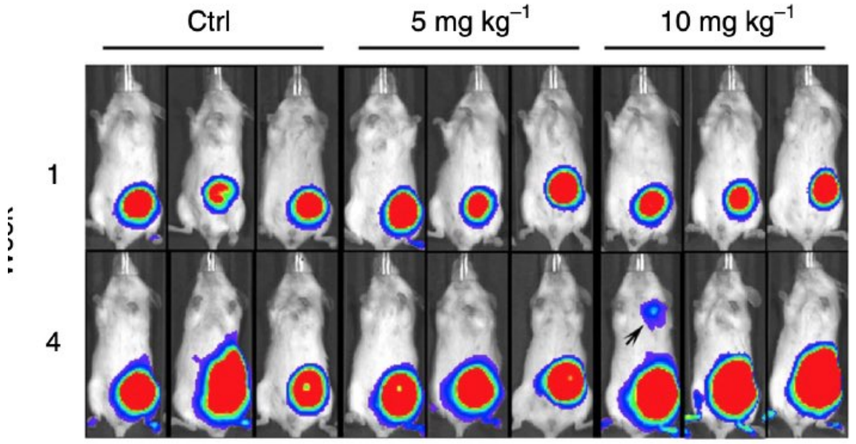
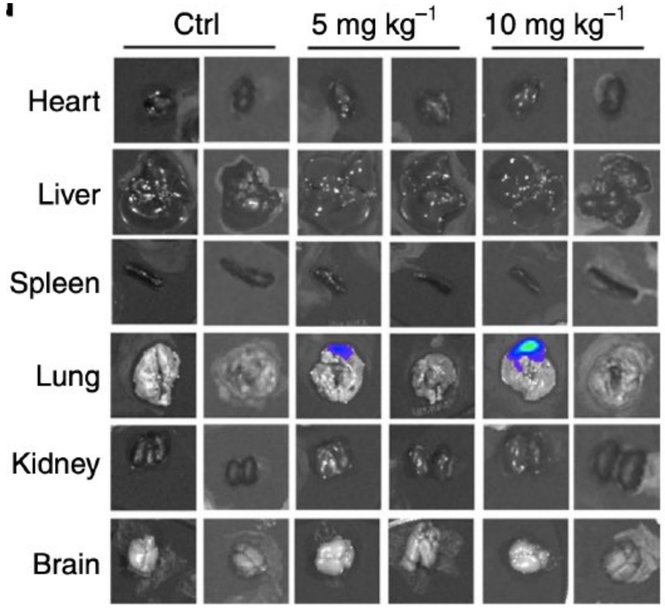






TiO_2: BC cell intravasation





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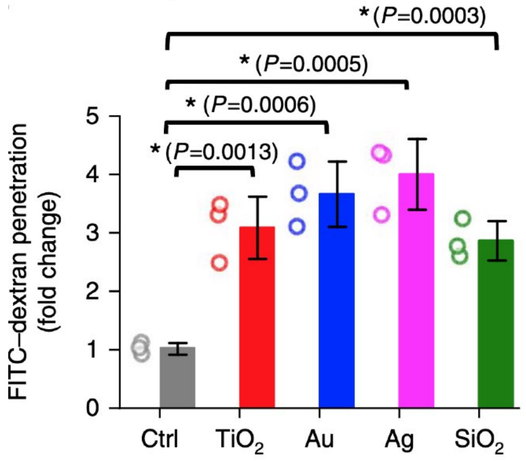

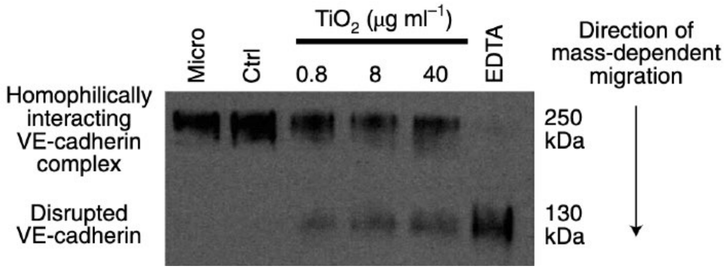

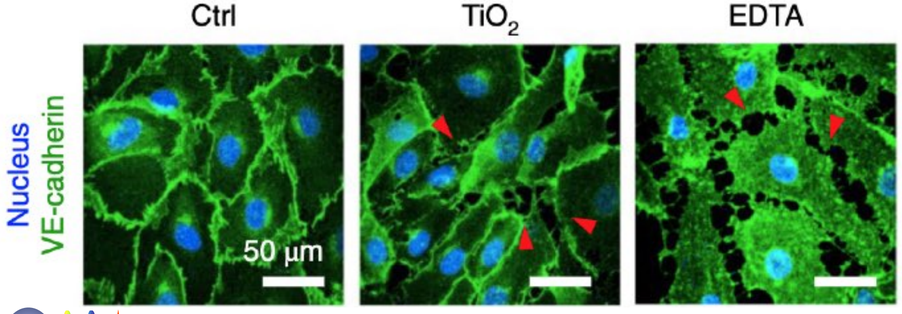

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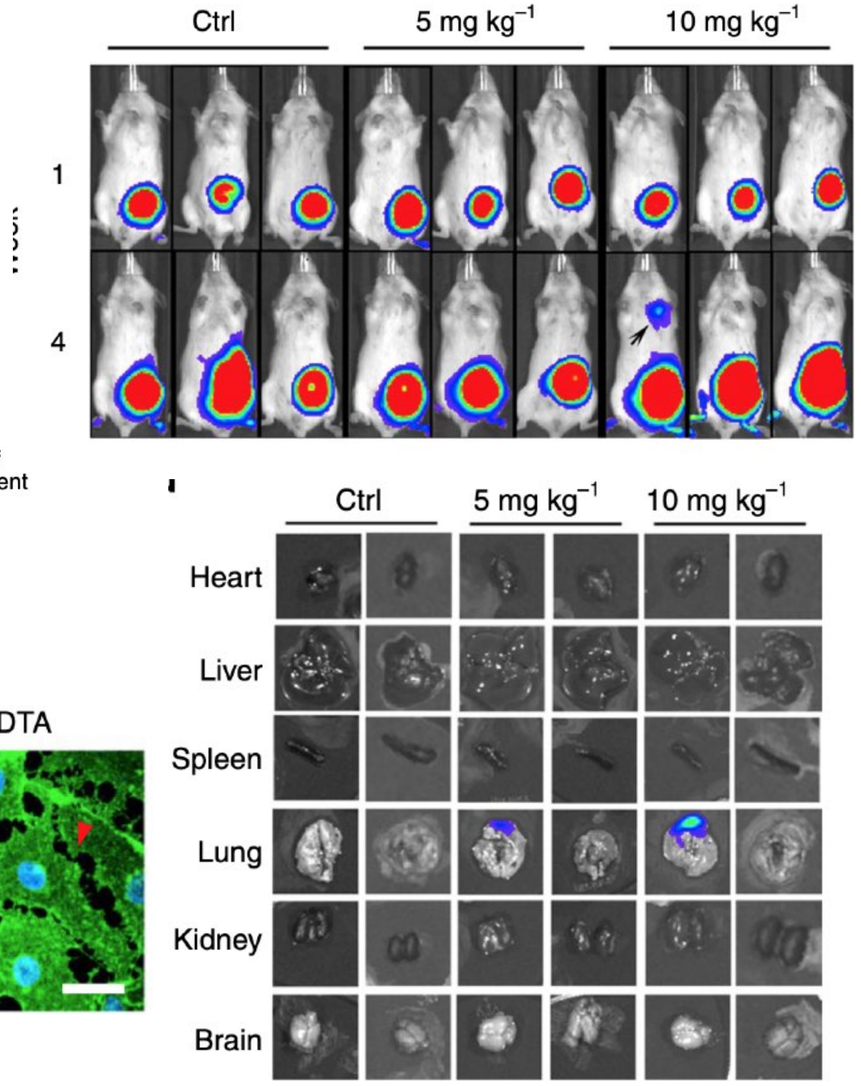

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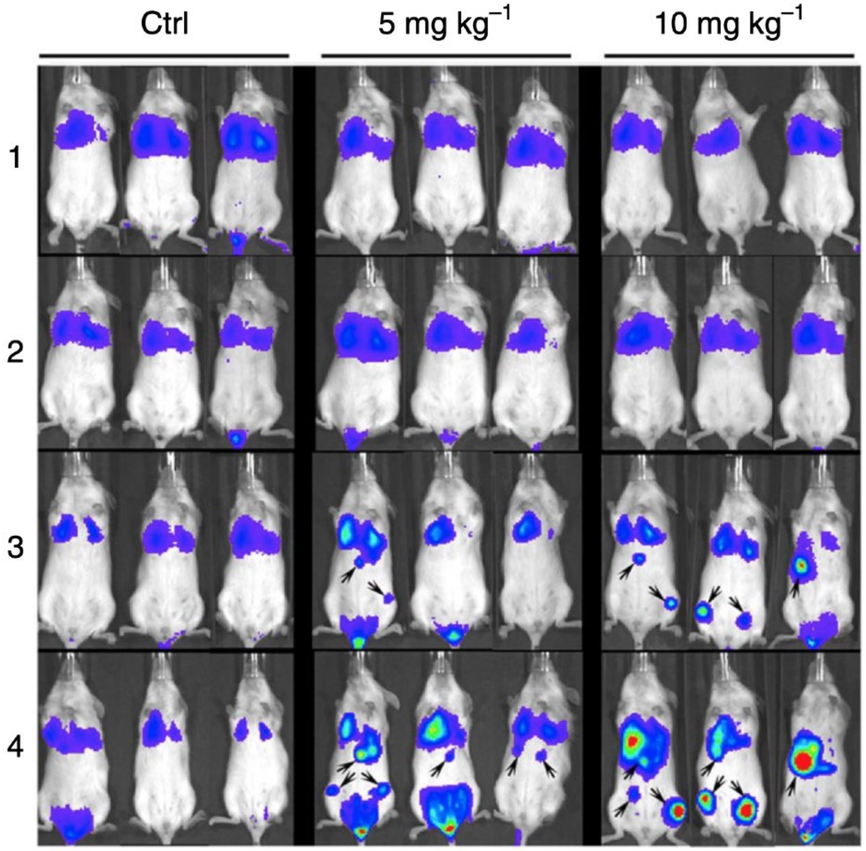
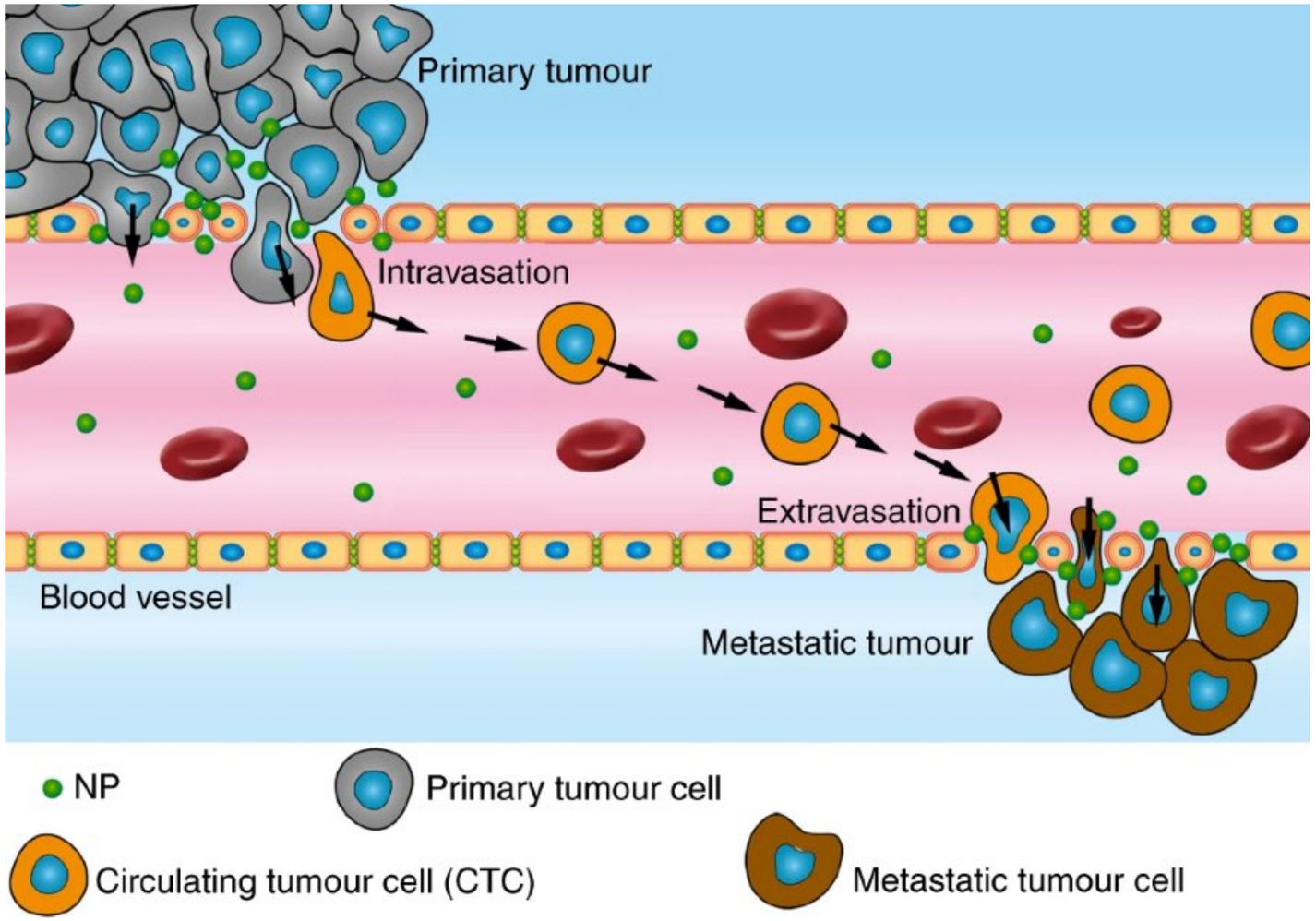


Peng E et al. (2019) *Nature Nanotechnology*, 16(11):1180

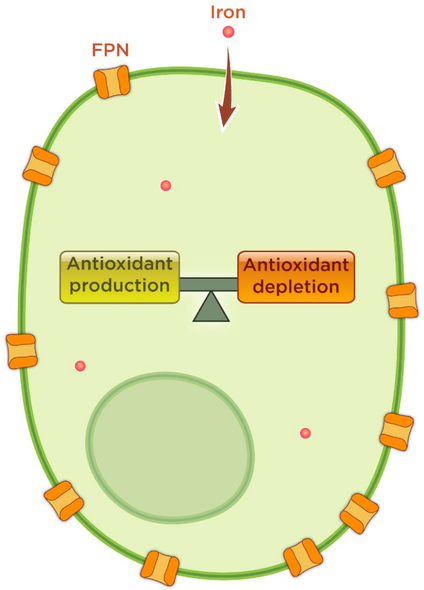
Nanoparticles may facilitate metastasis



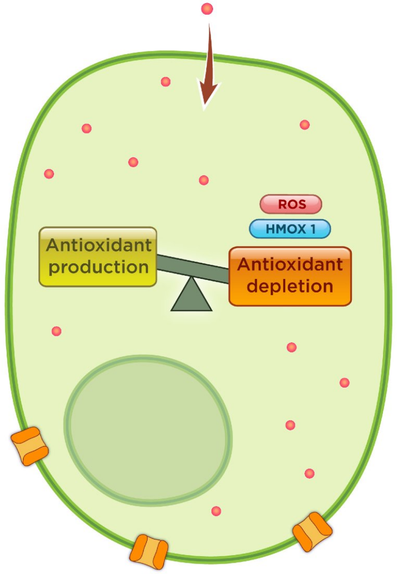
- Microvascular integrity maintained by VE-cadherin homophilic interactions at the adherens junction
- TiO_2 nanoparticles disrupt VE-cadherin binding and junction dissociation
- Particle-induced endothelial cell "leakiness" increased extravasation from primary murine tumors
- Leakiness also facilitated metastatic seeding of distal sites
- Silica and gold NP also showed capacity to disrupt VE-cadherin

Peng E et al. (2019) *Nature Nanotechnology*, 16(11):1180

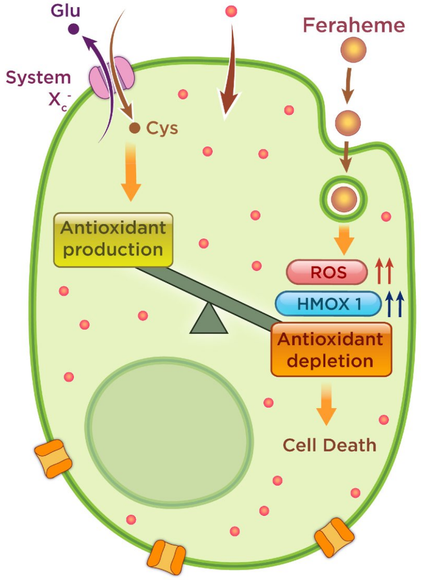
Ferumoxytol kills selectively leukemic cells



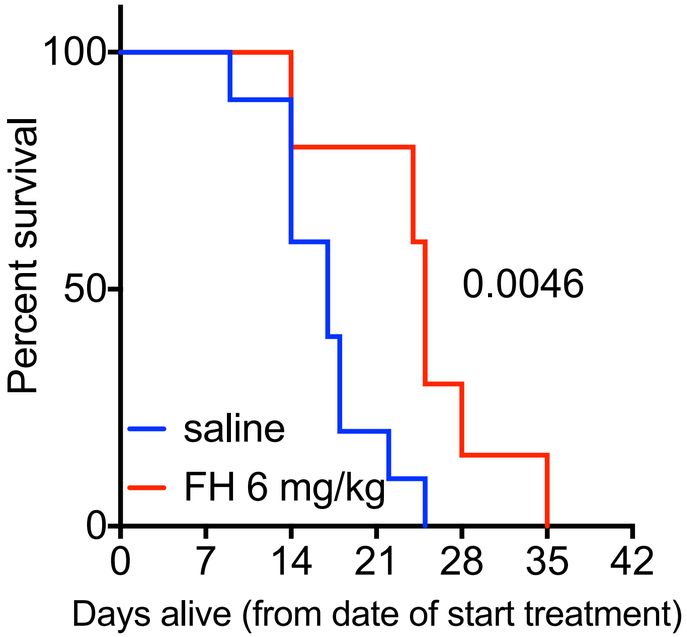
Normal



Leukaemia



FH Treated Leukaemia



Trujillo-Alonso V, Pratt E et al. (2019) *Nature Nanotechnology* 14(6): 616

Evidence of NP ancillary effects

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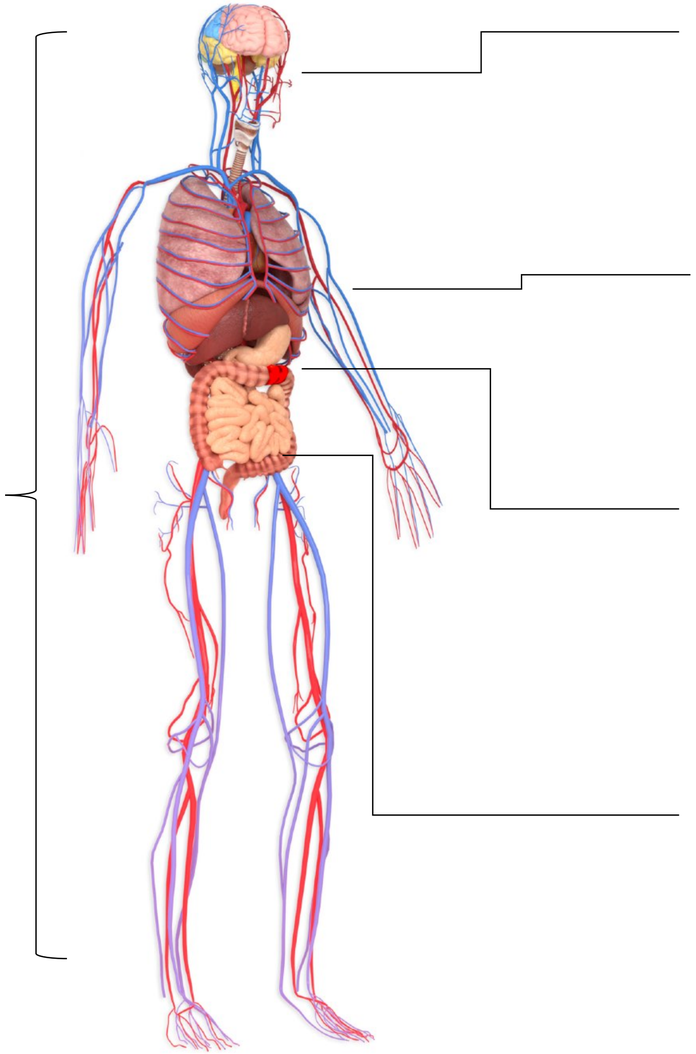

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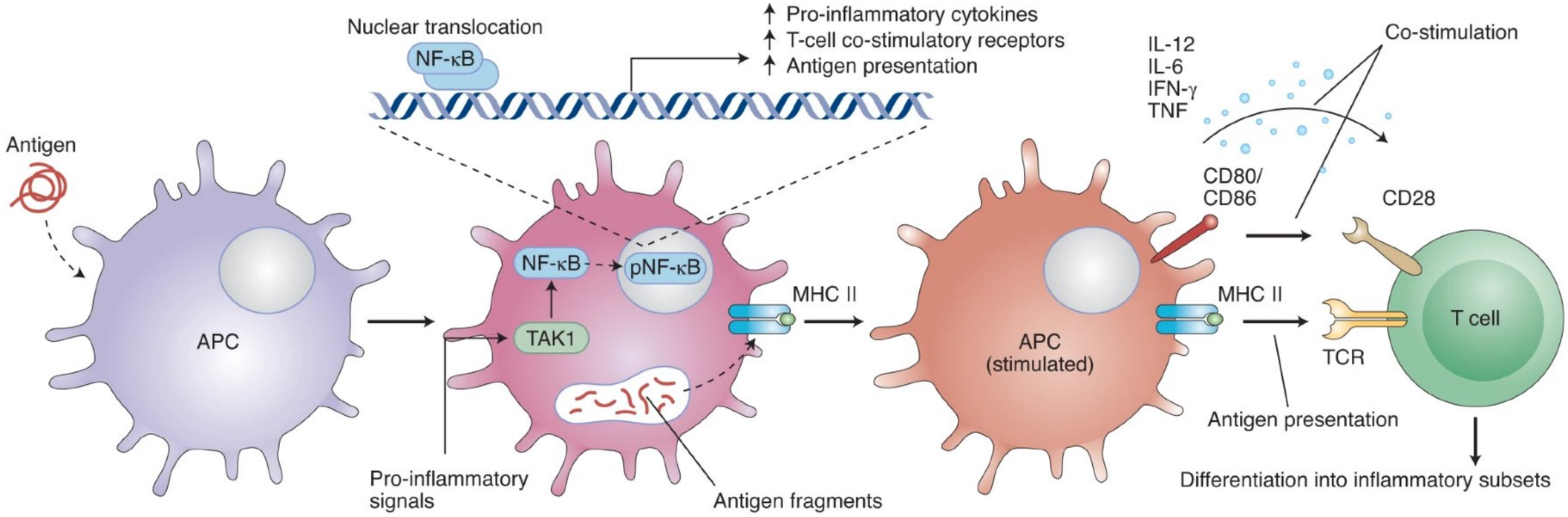
Stater E et al. (2021) *Nature Nanotechnology*, 16(11): 1180

NP-induced antigen tolerance

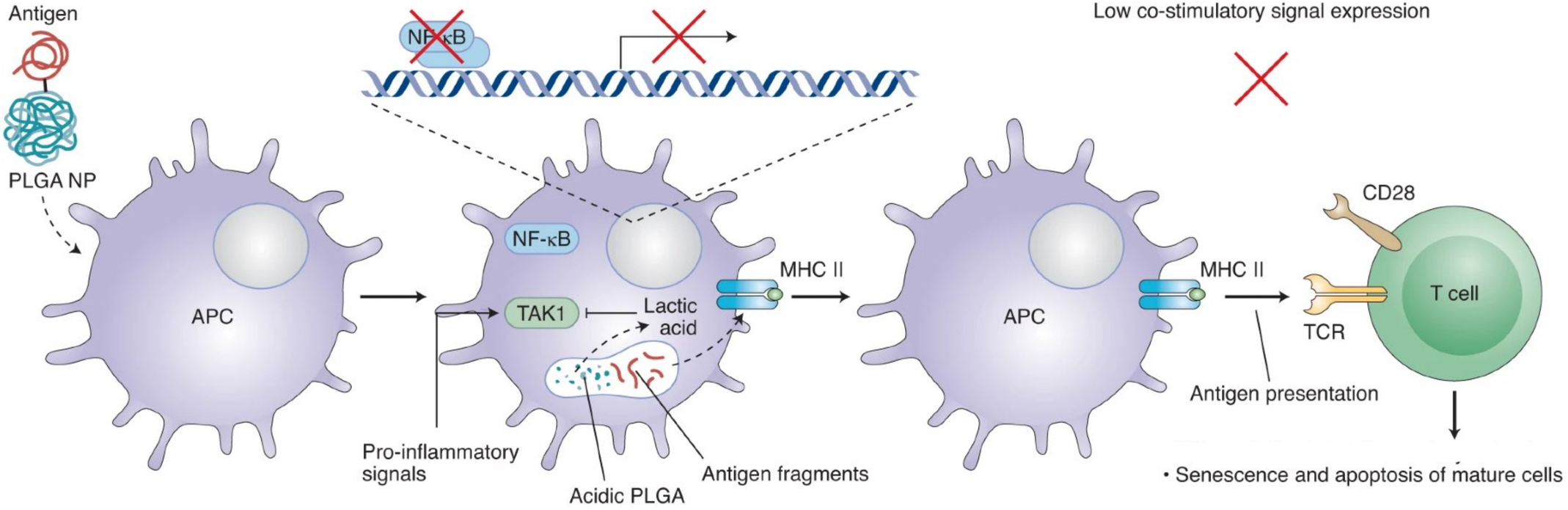
- Antigen-presenting cells (APC) phagocytose antigens
- Antigen fragments presented to T/B lymphocytes via MHC II
- Inflammatory activation of APC produces costimulatory signals
- Reactive T/B lymphocytes differentiate into active subsets



Stater E et al. (2021) *Nature Nanotechnology*, 16(11): 1180

Nanoparticle-induced antigen tolerance

- Phagocytosis of antigens with PLGA nanoparticles
- PLGA hydrolysis into lactic acid interferes with signal transduction
- Attenuation of costimulatory signal release from APC
- Antigen presentation without costimulation triggers senescence and apoptosis of reactive lymphocytes

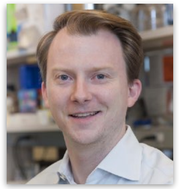


Allen RP et al. (2018) *ACS Biomater Sci Eng*, 16(11): 900

Adapted from Stater et al. *Nature Nano*, 2021, **16**(11)

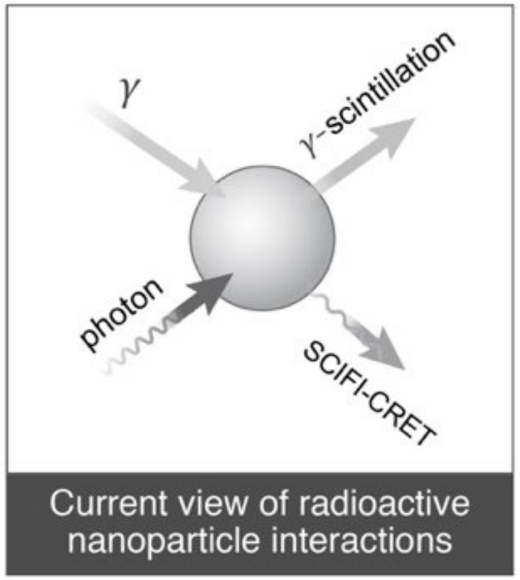
Ionizing radiation interacts with NP

T Shaffer



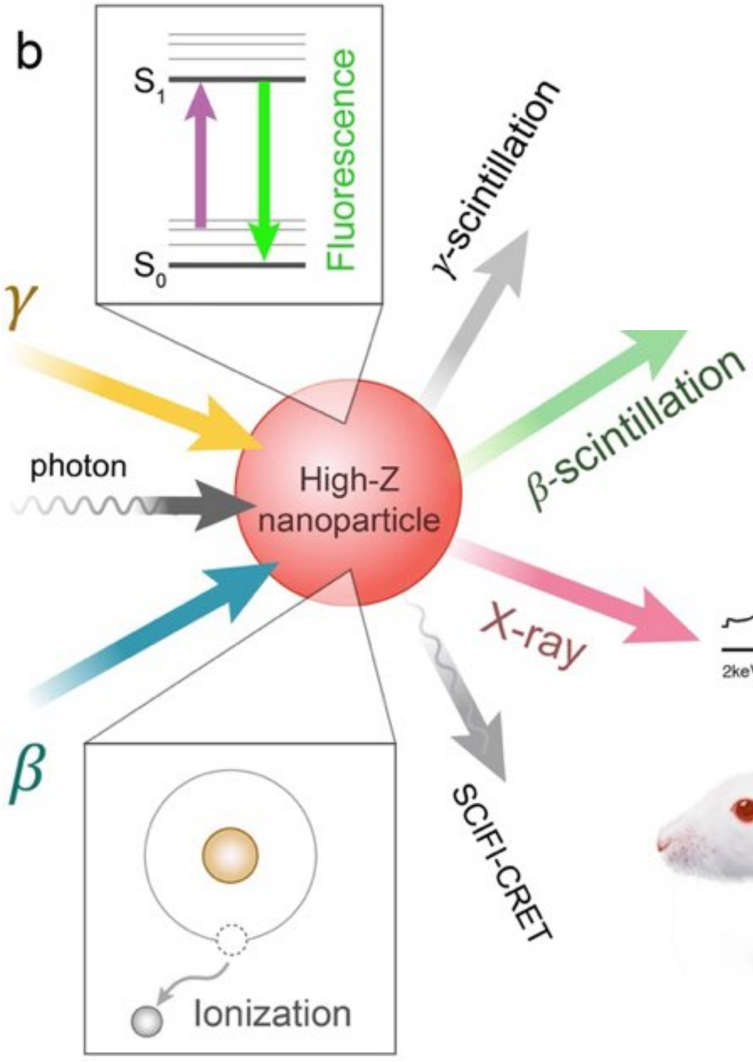
E Pratt

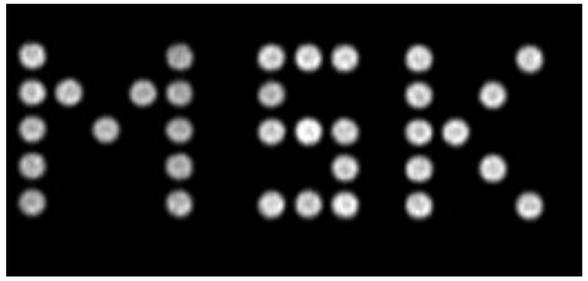
a

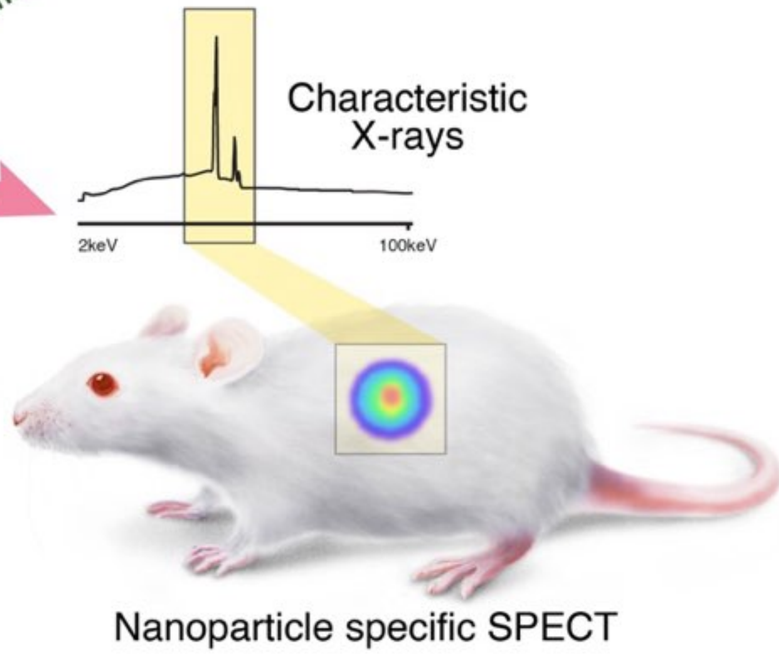


Current view of radioactive nanoparticle interactions

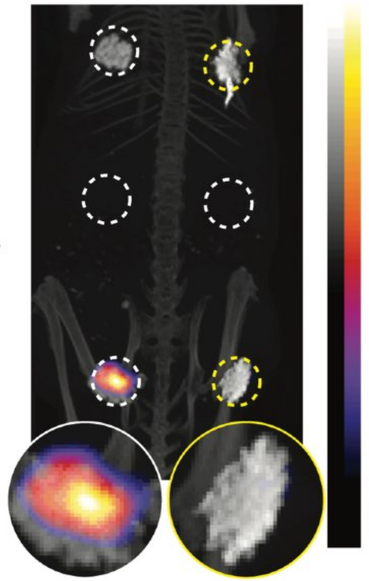
b







Nanoparticle specific SPECT



Pratt E et. al. (2018) *Nature Nanotechnology* 13(5): 418

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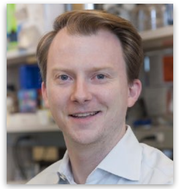

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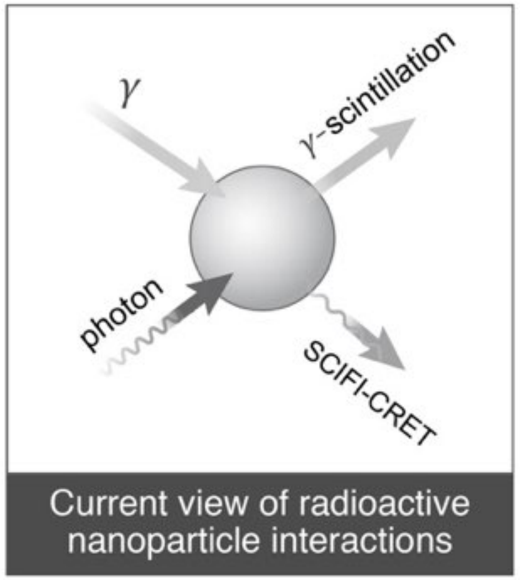

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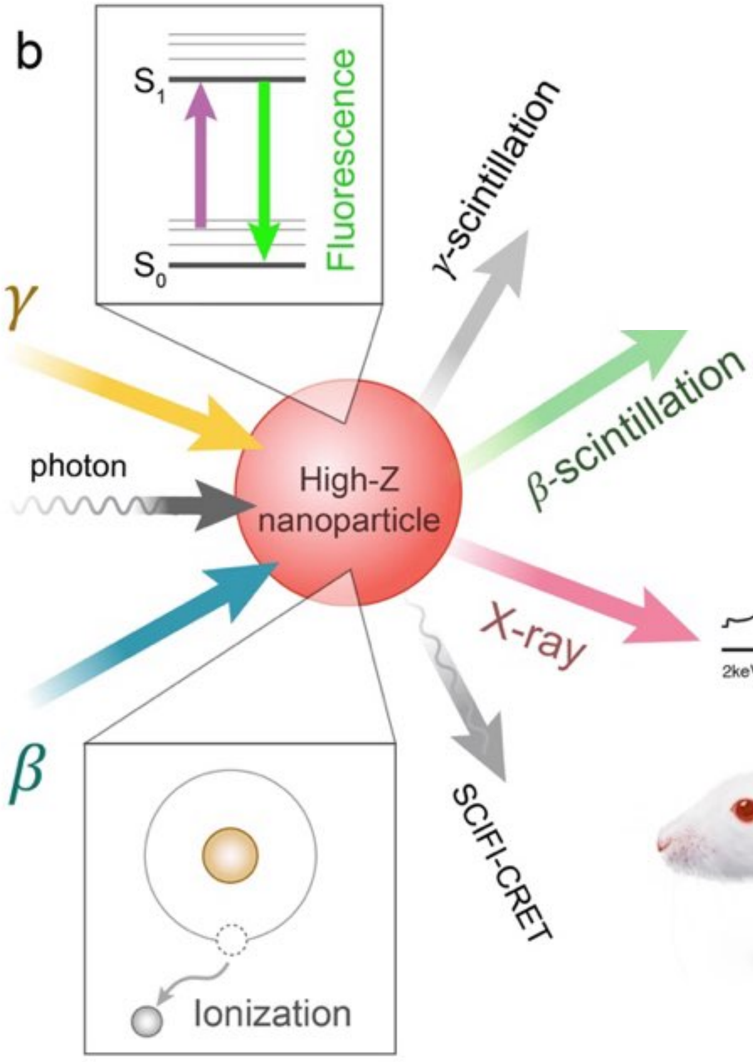

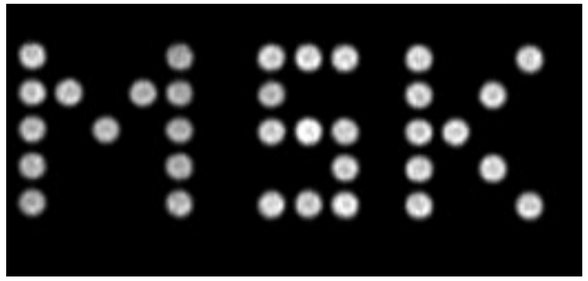

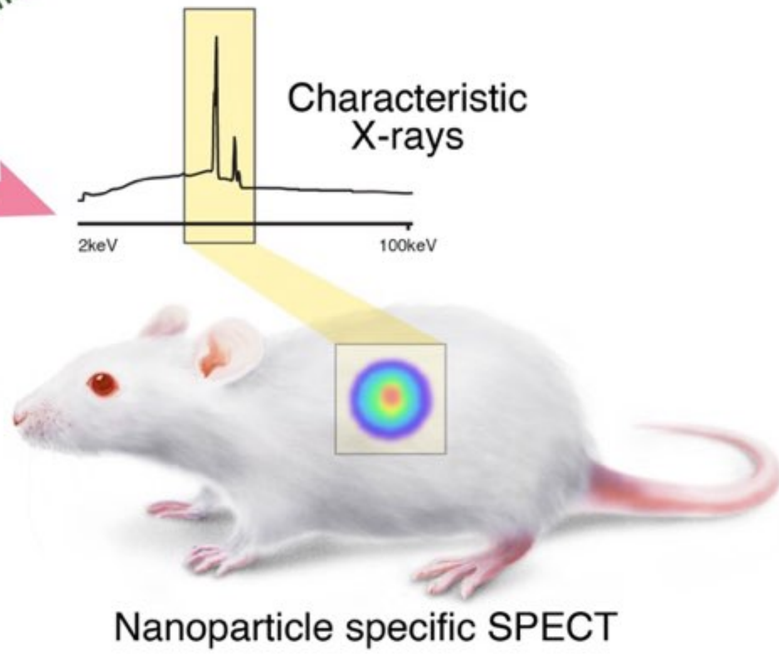

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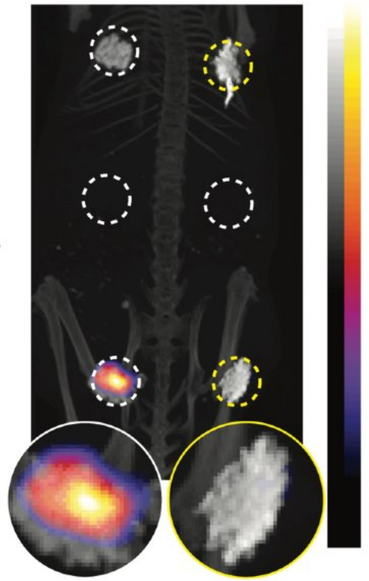

Pratt E et. al. (2018) *Nature Nanotechnology* 13(5): 418

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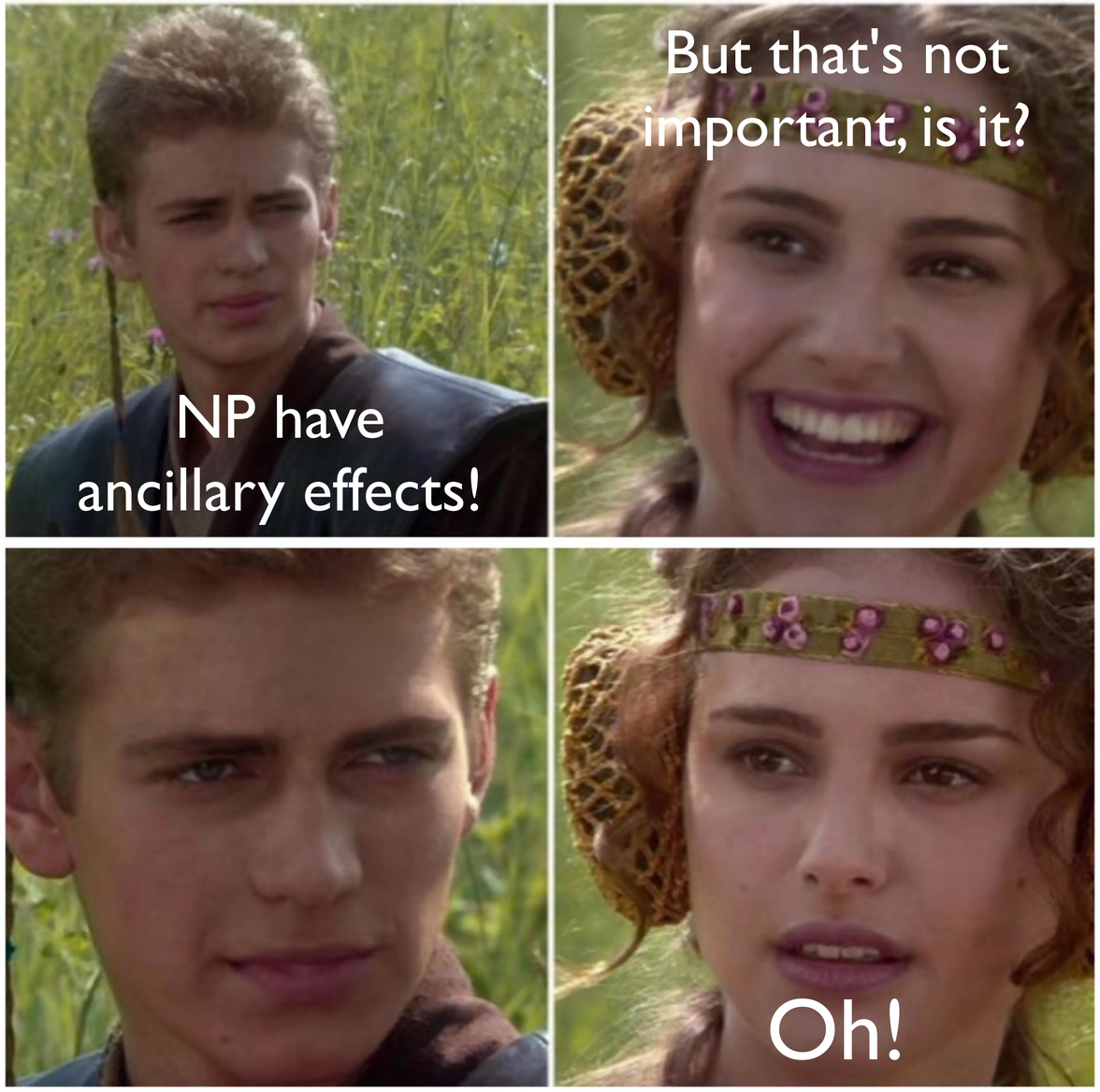
7. Better understanding of the nano-bio interface will facilitate development of new and better nanomedicines

Conclusions

1. Nanomaterial
2. Ancillary effect
3. The identity-el
4. Some ancillary
5. Some ancillary
6. There are also
7. Better underst
   of new and be

ems

cilitate development



Further reading:

REVIEW ARTICLE
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The ancillary effects of nanoparticles and their implications for nanomedicine

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