Hot Topic Discussion

State of the evolution of drug delivery systems

Luke Rhym (Anderson Lab)

June 21, 2021

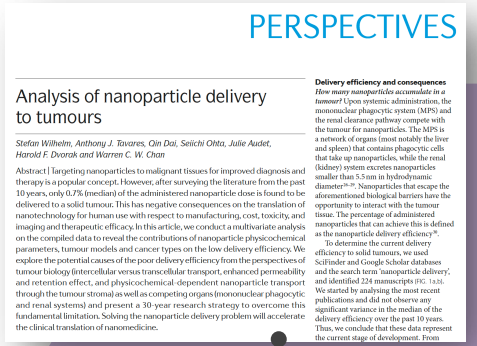
MARBLE CENTER FOR CANCER NANOMEDICINE

Small technologies, BIG impact

KOCH INSTITUTE for Integrative Cancer Research at MIT

Why is this a hot topic?

Median delivery efficiency **0.7%** of an injected dose of NPs in tumor


PERSPECTIVES

Analysis of nanoparticle delivery to tumours

Stefan Wilhelm, Anthony J. Tavares, Qin Dai, Seiichi Ohta, Julie Audet, Harold F. Dvorak and Warren C. W. Chan

Abstract | Targeting nanoparticles to malignant tissues for improved diagnosis and therapy is a popular concept. However, after surveying the literature from the past 10 years, only 0.7% (median) of the administered nanoparticle dose is found to be delivered to a solid tumour. This has negative consequences on the translation of nanotechnology for human use with respect to manufacturing, cost, toxicity, and imaging and therapeutic efficacy. In this article, we conduct a multivariate analysis on the compiled data to reveal the contributions of nanoparticle physicochemical parameters, tumour models and cancer types on the low delivery efficiency. We explore the potential causes of the poor delivery efficiency from the perspectives of tumour biology (intercellular versus transcellular transport, enhanced permeability and retention effect, and physicochemical-dependent nanoparticle transport through the tumour stroma) as well as competing organs (mononuclear phagocytic and renal systems) and present a 30-year research strategy to overcome this fundamental limitation. Solving the nanoparticle delivery problem will accelerate the clinical translation of nanomedicine.

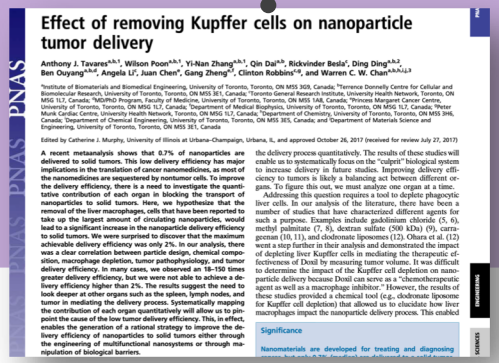
Delivery efficiency and consequences

How many nanoparticles accumulate in a tumour? Upon systemic administration, the mononuclear phagocytic system (MPS) and the renal clearance pathway compete with the tumour for nanoparticles. The MPS is a network of organs (most notably the liver and spleen) that contains phagocytic cells that take up nanoparticles, while the renal (kidney) system excretes nanoparticles smaller than 5.5 nm in hydrodynamic diameter[96–99]. Nanoparticles that escape the aforementioned biological barriers have the opportunity to interact with the tumour tissue. The percentage of administered nanoparticles that can achieve this is defined as the nanoparticle delivery efficiency[30].

To determine the current delivery efficiency to solid tumours, we used SciFinder and Google Scholar databases and the search term 'nanoparticle delivery', and identified 224 manuscripts (FIG. 1a,b). We started by analysing the most recent publications and did not observe any significant variance in the median of the delivery efficiency over the past 10 years. Thus, we conclude that these data represent the current stage of development. From

2016

2017


PNAS

Effect of removing Kupffer cells on nanoparticle tumor delivery

Anthony J. Tavares[a,b,1], Wilson Poon[a,b,1], Yi-Nan Zhang[a,b,1], Qin Dai[a,b], Rickvinder Besla[c], Ding Ding[a,b,2], Ben Ouyang[a,b,d], Angela Li[c], Juan Chen[e], Gang Zheng[d,f], Clinton Robbins[c,g], and Warren C. W. Chan[a,b,h,i,2,3]

Edited by Catherine J. Murphy, University of Illinois at Urbana–Champaign, Urbana, IL, and approved October 26, 2017 (received for review July 27, 2017)

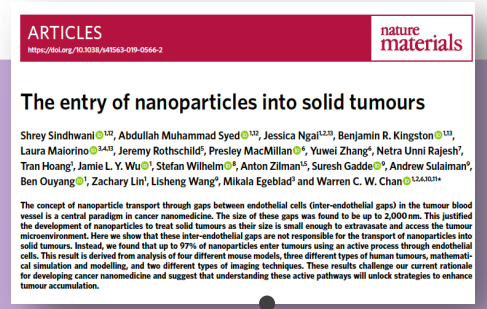
A recent metaanalysis shows that 0.7% of nanoparticles are delivered to solid tumors. This low delivery efficiency has major implications in the translation of cancer nanomedicines, as most of the nanomedicines are sequestered by nontumor cells. To improve the delivery efficiency, there is a need to investigate the quantitative contribution of each organ in blocking the transport of nanoparticles to solid tumors. Here, we hypothesize that the removal of the liver macrophages, cells that have been reported to take up the largest amount of circulating nanoparticles, would lead to a significant increase in the nanoparticle delivery efficiency to solid tumors. We were surprised to discover that the maximum achievable delivery efficiency was only 2%. In our analysis, there was a clear correlation between particle design, chemical composition, macrophage depletion, tumor pathophysiology, and tumor delivery efficiency. In many cases, we observed an 18–150 times greater delivery efficiency, but we were not able to achieve a delivery efficiency higher than 2%. The results suggest the need to look deeper at other organs such as the spleen, lymph nodes, and tumor in mediating the delivery process. Systematically mapping the contribution of each organ quantitatively will allow us to pinpoint the cause of the low tumor delivery efficiency. This, in effect, enables the generation of a rational strategy to improve the delivery efficiency of nanoparticles to solid tumors either through the engineering of multifunctional nanosystems or through manipulation of biological barriers.

Significance

Nanomaterials are developed for treating and diagnosing

Tumor delivery increased up to 150 times, but only achieved **2% median**

Dominant mechanism of extravasation of NPs into solid tumors through **endothelial transcytosis**.


ARTICLES

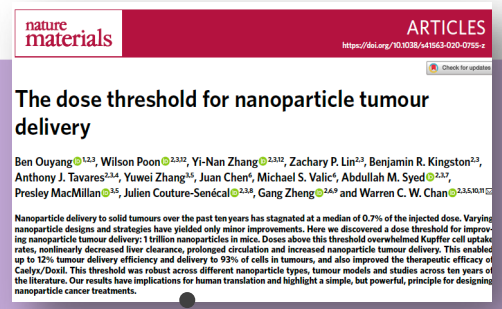
https://doi.org/10.1038/s41563-019-0566-2

nature materials

The entry of nanoparticles into solid tumours

Shrey Sindhwani[1,12], Abdullah Muhammad Syed[1,12], Jessica Ngai[1,2,13], Benjamin R. Kingston[1,13], Laura Maiorino[3,4,13], Jeremy Rothschild[5], Presley MacMillan[6], Yuwei Zhang[6], Netra Unni Rajesh[7], Tran Hoang[1], Jamie L. Y. Wu[1], Stefan Wilhelm[8], Anton Zilman[1,5], Suresh Gadde[9], Andrew Sulaiman[9], Ben Ouyang[1], Zachary Lin[1], Lisheng Wang[6], Mikala Egeblad[3] and Warren C. W. Chan[1,2,4,10,11]*

The concept of nanoparticle transport through gaps between endothelial cells (inter-endothelial gaps) in the tumour blood vessel is a central paradigm in cancer nanomedicine. The size of these gaps was found to be up to 2,000 nm. This justified the development of nanoparticles to treat solid tumours as their size is small enough to extravasate and access the tumour microenvironment. Here we show that these inter-endothelial gaps are not responsible for the transport of nanoparticles into solid tumours. Instead, we found that up to 97% of nanoparticles enter tumours using an active process through endothelial cells. This result is derived from analysis of four different mouse models, three different types of human tumours, mathematical simulation and modelling, and two different types of imaging techniques. These results challenge our current rationale for developing cancer nanomedicine and suggest that understanding these active pathways will unlock strategies to enhance tumour accumulation.


nature materials

ARTICLES

https://doi.org/10.1038/s41563-020-0755-z

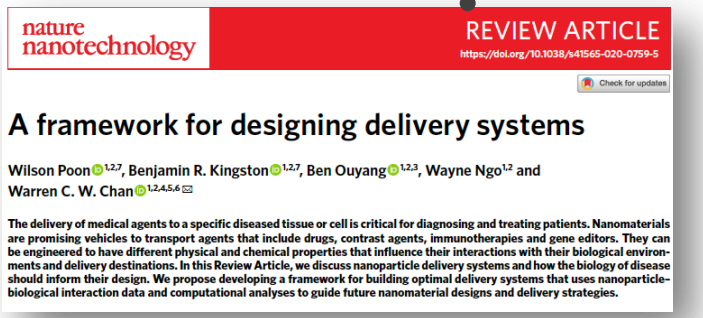
Check for updates

The dose threshold for nanoparticle tumour delivery

Ben Ouyang[1,2,3], Wilson Poon[2,3,12], Yi-Nan Zhang[2,3,12], Zachary P. Lin[2,3], Benjamin R. Kingston[2,3], Anthony J. Tavares[2,3,4], Yuwei Zhang[3,5], Juan Chen[6], Michael S. Valic[6], Abdullah M. Syed[2,3,7], Presley MacMillan[3,5], Julien Couture-Senécal[2,3,8], Gang Zheng[2,4,9] and Warren C. W. Chan[2,3,5,10,11]*

Nanoparticle delivery to solid tumours over the past ten years has stagnated at a median of 0.7% of the injected dose. Varying nanoparticle designs and strategies have yielded only minor improvements. Here we discovered a dose threshold for improving nanoparticle tumour delivery: 1 trillion nanoparticles in mice. Doses above this threshold overwhelmed Kupffer cell uptake rates, nonlinearly decreased liver clearance, prolonged circulation and increased nanoparticle tumour delivery. This enabled up to 12% tumour delivery efficiency and delivery to 93% of cells in tumours, and also improved the therapeutic efficacy of Caelyx/Doxil. This threshold was robust across different nanoparticle types, tumour models and studies across ten years of the literature. Our results have implications for human translation and highlight a simple, but powerful, principle for designing nanoparticle cancer treatments.

2020


nature nanotechnology

REVIEW ARTICLE

https://doi.org/10.1038/s41565-020-0759-5

Check for updates

A framework for designing delivery systems

Wilson Poon[1,2,7], Benjamin R. Kingston[1,2,7], Ben Ouyang[1,2,3], Wayne Ngo[1,2] and Warren C. W. Chan[1,2,4,5,6]*

The delivery of medical agents to a specific diseased tissue or cell is critical for diagnosing and treating patients. Nanomaterials are promising vehicles to transport agents that include drugs, contrast agents, immunotherapies and gene editors. They can be engineered to have different physical and chemical properties that influence their interactions with their biological environments and delivery destinations. In this Review Article, we discuss nanoparticle delivery systems and how the biology of disease should inform their design. We propose developing a framework for building optimal delivery systems that uses nanoparticle–biological interaction data and computational analyses to guide future nanomaterial designs and delivery strategies.

Marble Center hot topic Oct 2020

Natalie Boehnke, PhD (Hammond Lab)

Leslie Chan, PhD (Georgia Tech)

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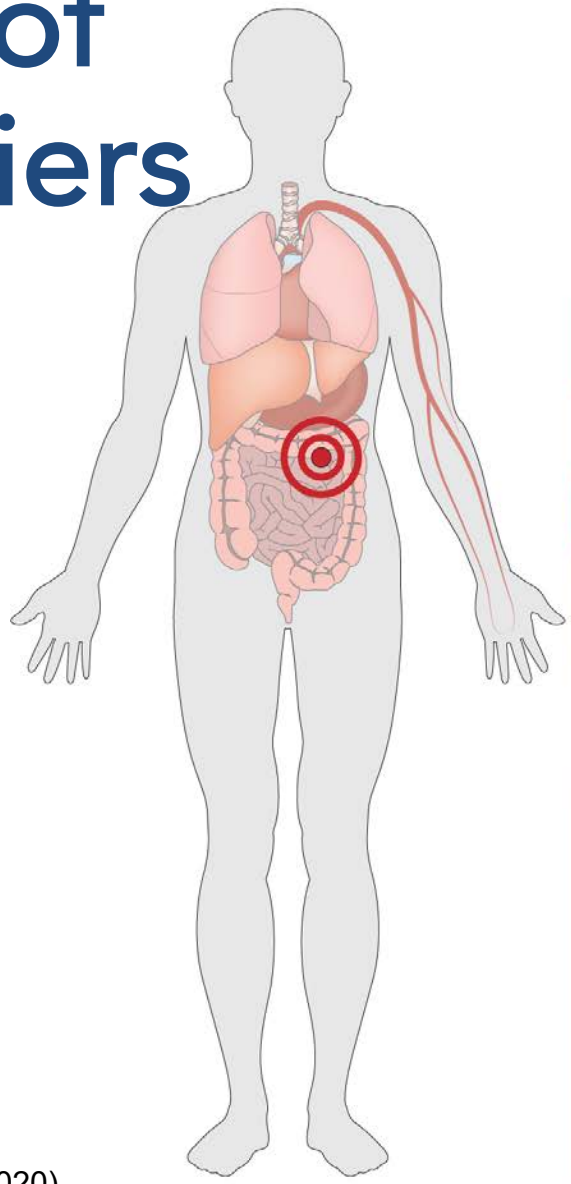
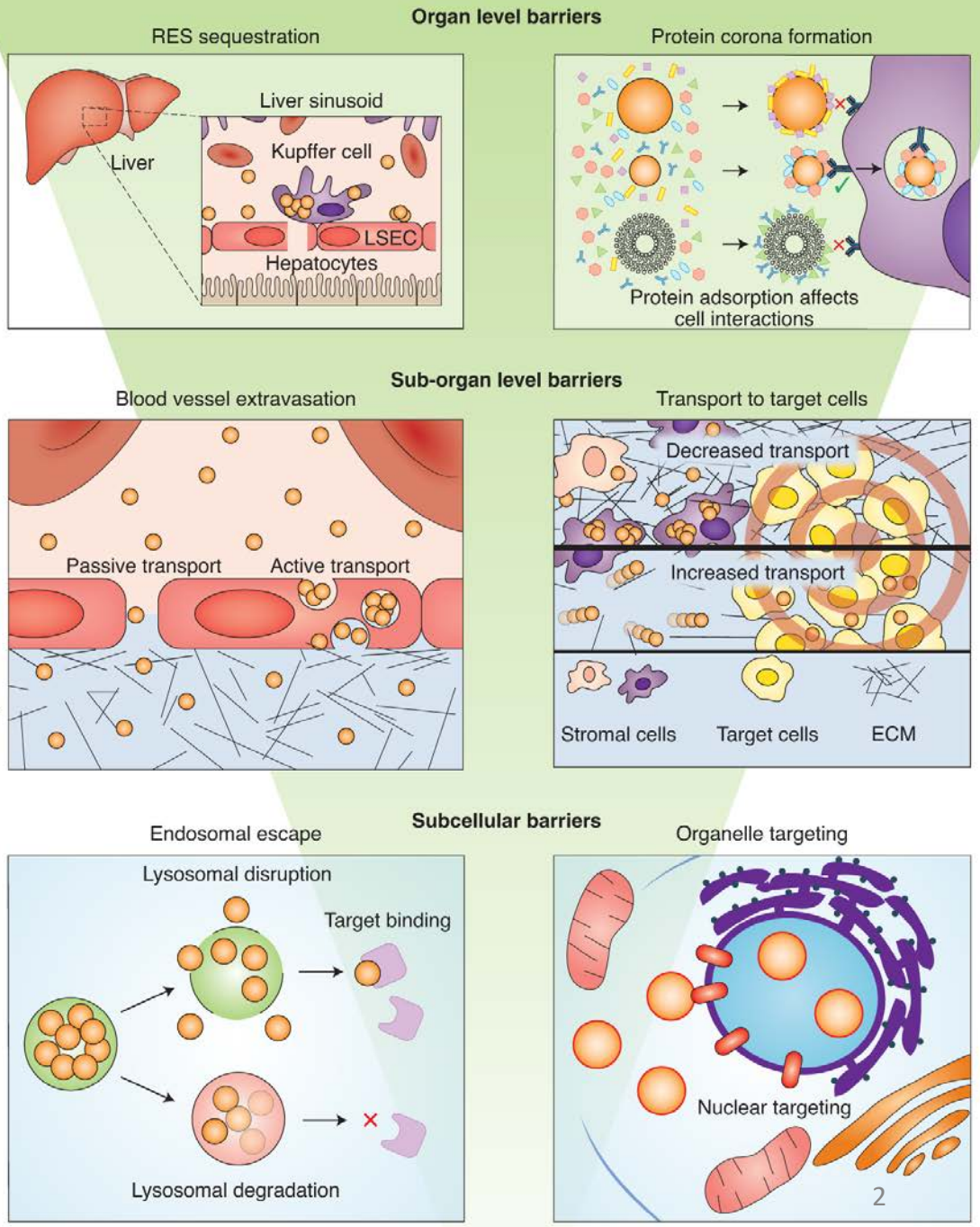
Poon, W. *et al. Nature Nanotechnology* **15**, 819-829 (2020).

The biology of delivery barriers





Poon, W. *et al. Nature Nanotechnology* **15**, 819-829 (2020).

A generational view of drug delivery

nature biomedical engineering

REVIEW ARTICLE

https://doi.org/10.1038/s41551-021-00698-w

Check for updates

The evolution of commercial drug delivery technologies

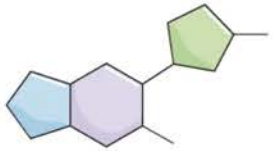
Ava M. Vargason[1], Aaron C. Anselmo[1]✉ and Samir Mitragotri[2,3]✉

Drug delivery technologies have enabled the development of many pharmaceutical products that improve patient health by enhancing the delivery of a therapeutic to its target site, minimizing off-target accumulation and facilitating patient compliance. As therapeutic modalities expanded beyond small molecules to include nucleic acids, peptides, proteins and antibodies, drug delivery technologies were adapted to address the challenges that emerged. In this Review Article, we discuss seminal approaches that led to the development of successful therapeutic products involving small molecules and macromolecules, identify three drug delivery paradigms that form the basis of contemporary drug delivery and discuss how they have aided the initial clinical successes of each class of therapeutic. We also outline how the paradigms will contribute to the delivery of live-cell therapies.

Samir Mitragotri, PhD
(Harvard/Wyss)

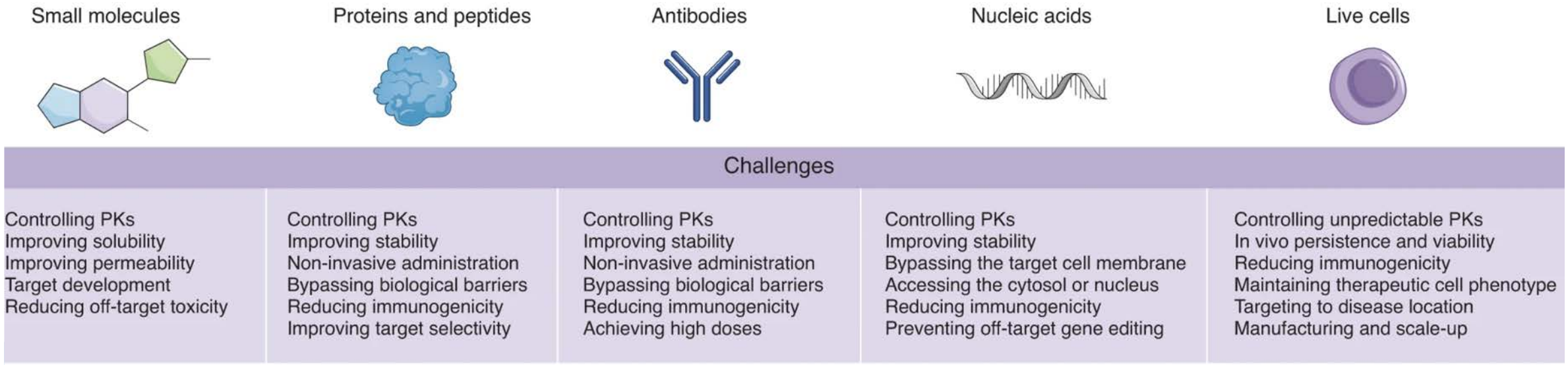
Vargason, A.M., Anselmo, A.C. & Mitragotri, S. The evolution of commercial drug delivery technologies. *Nat Biomed Eng* (2021)

A generational view of drug delivery

Small molecules	Proteins and peptides	Antibodies	Nucleic acids	Live cells
				
Challenges				
Controlling PKs Improving solubility Improving permeability Target development Reducing off-target toxicity	Controlling PKs Improving stability Non-invasive administration Bypassing biological barriers Reducing immunogenicity Improving target selectivity	Controlling PKs Improving stability Non-invasive administration Bypassing biological barriers Reducing immunogenicity Achieving high doses	Controlling PKs Improving stability Bypassing the target cell membrane Accessing the cytosol or nucleus Reducing immunogenicity Preventing off-target gene editing	Controlling unpredictable PKs In vivo persistence and viability Reducing immunogenicity Maintaining therapeutic cell phenotype Targeting to disease location Manufacturing and scale-up

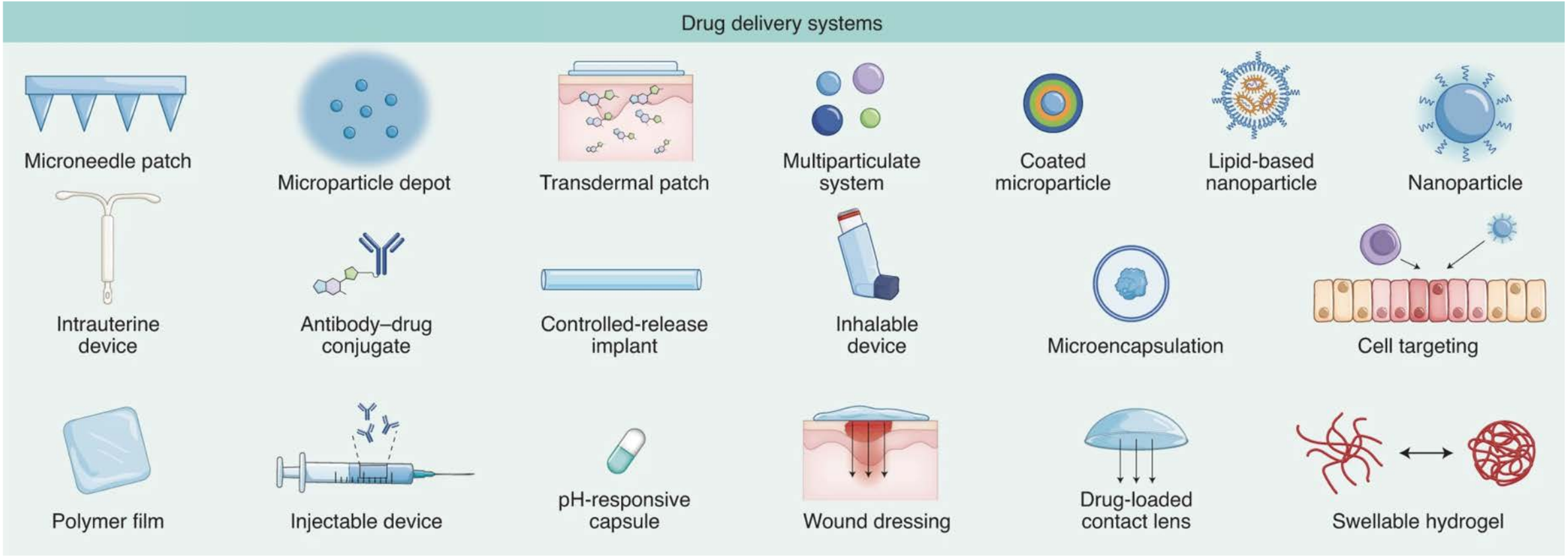
Vargason, A.M., Anselmo, A.C. & Mitragotri, S. The evolution of commercial drug delivery technologies. *Nat Biomed Eng* (2021)

A generational view of drug delivery



Vargason, A.M., Anselmo, A.C. & Mitragotri, S. The evolution of commercial drug delivery technologies. *Nat Biomed Eng* (2021)

A generational view of drug delivery



Vargason, A.M., Anselmo, A.C. & Mitragotri, S. The evolution of commercial drug delivery technologies. *Nat Biomed Eng* (2021)

Some examples

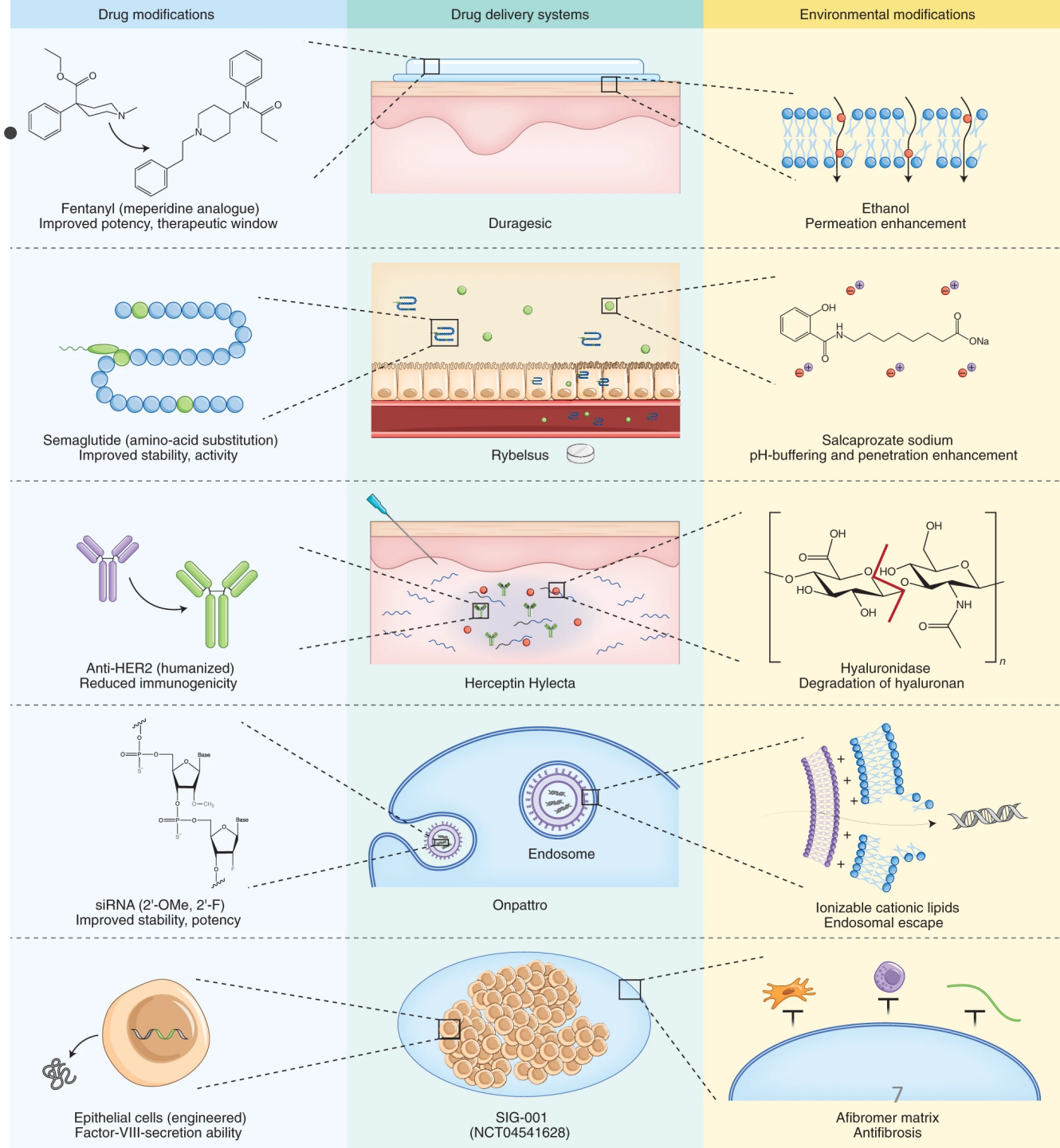
Small molecules

Proteins and peptides

Antibodies

Nucleic acids

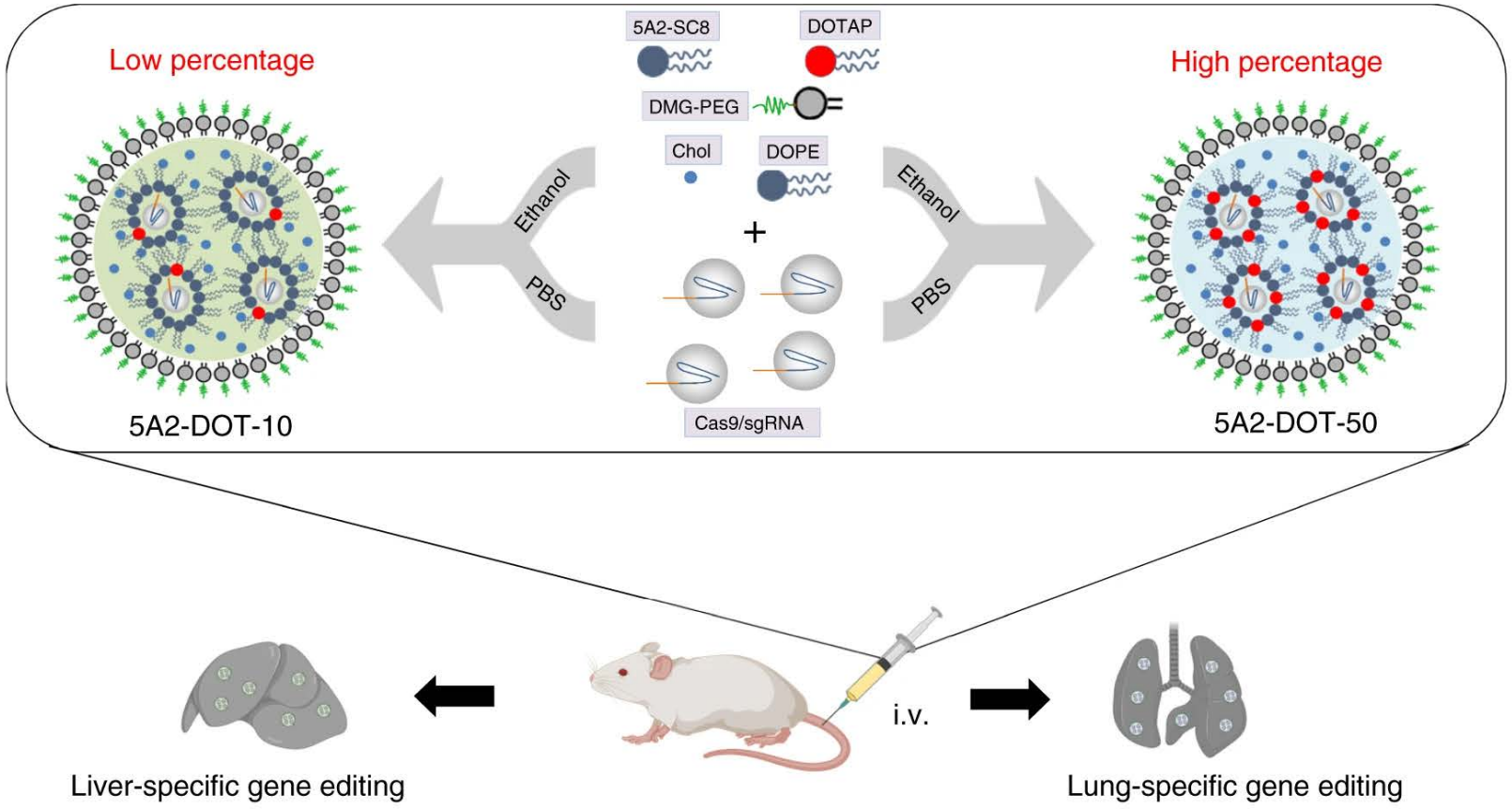
Live cells



Vargason, A.M., Anselmo, A.C. & Mitragotri, S. The evolution of commercial drug delivery technologies. *Nat Biomed Eng* (2021)

What’s next for non-viral drug delivery systems?

Tuning nanoparticle chemistry to achieve tissue-specific delivery



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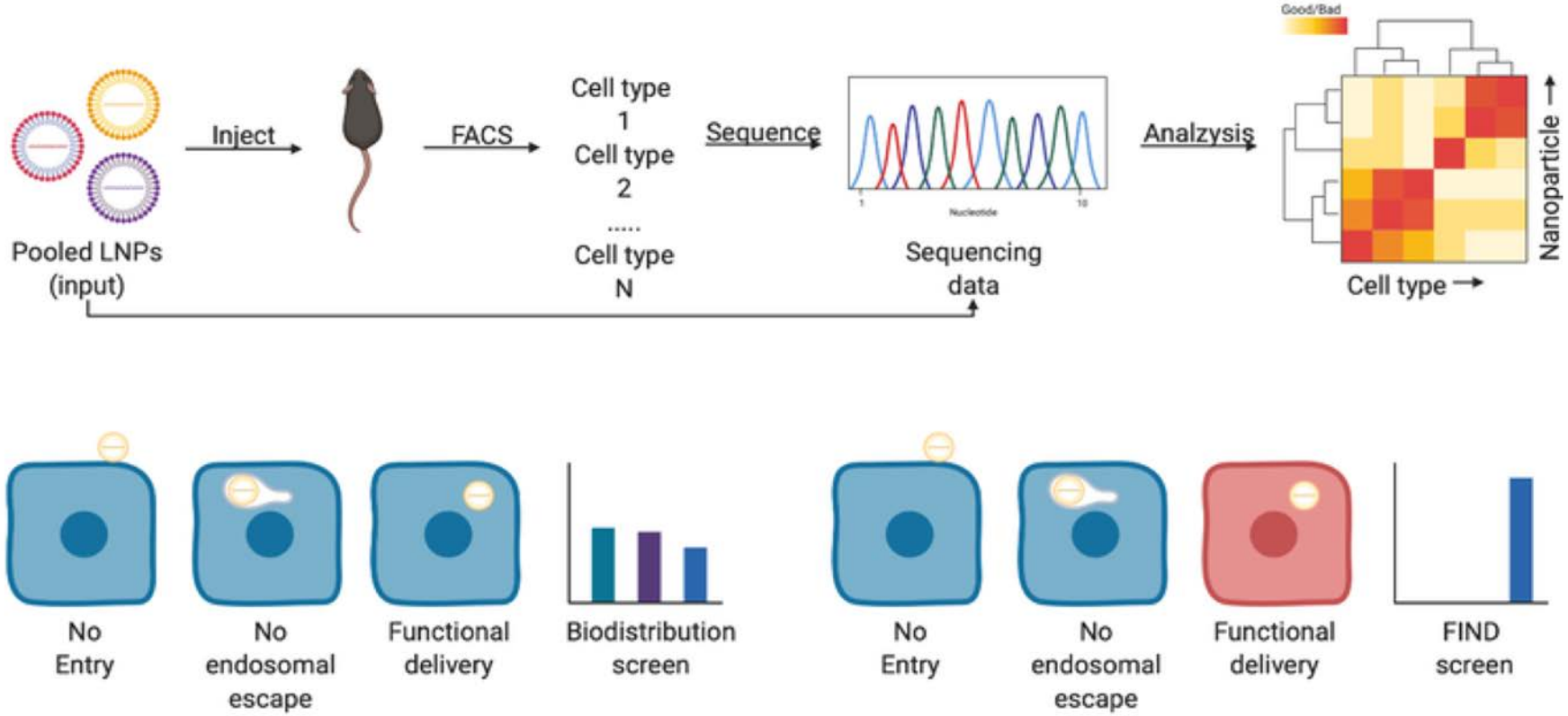
SIEGWART Research Group

Process can be accelerated using barcoded nanoparticles



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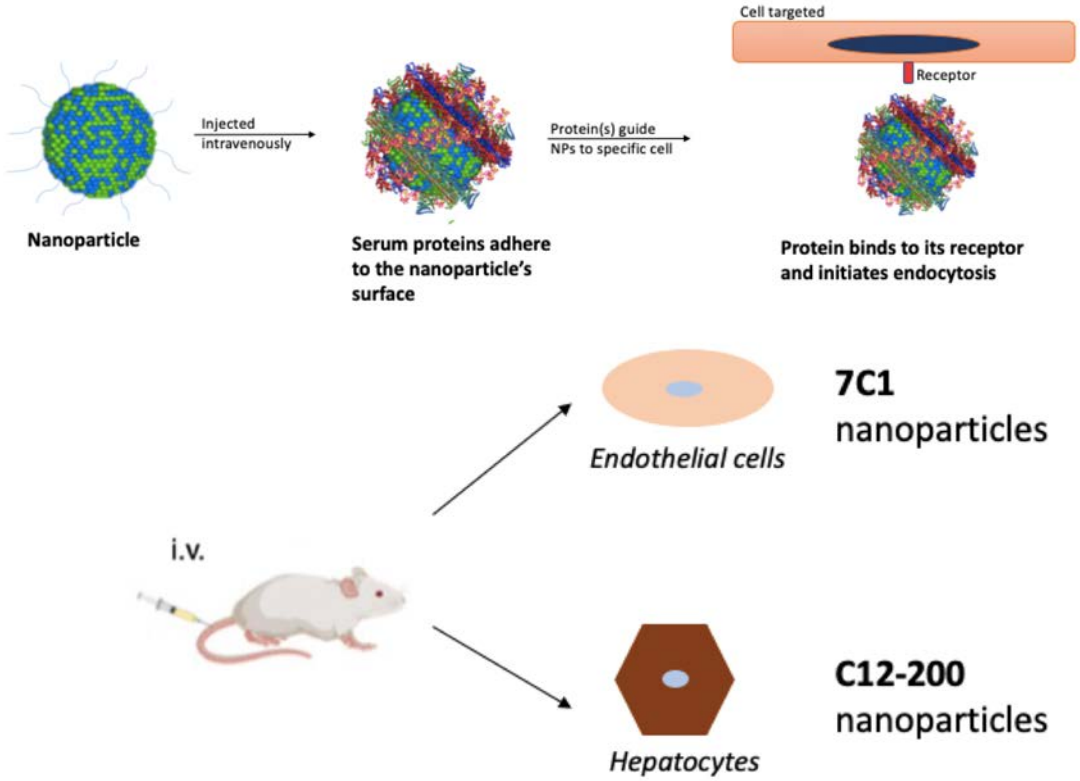
DAHLMAN LAB

Related work in the Anderson lab

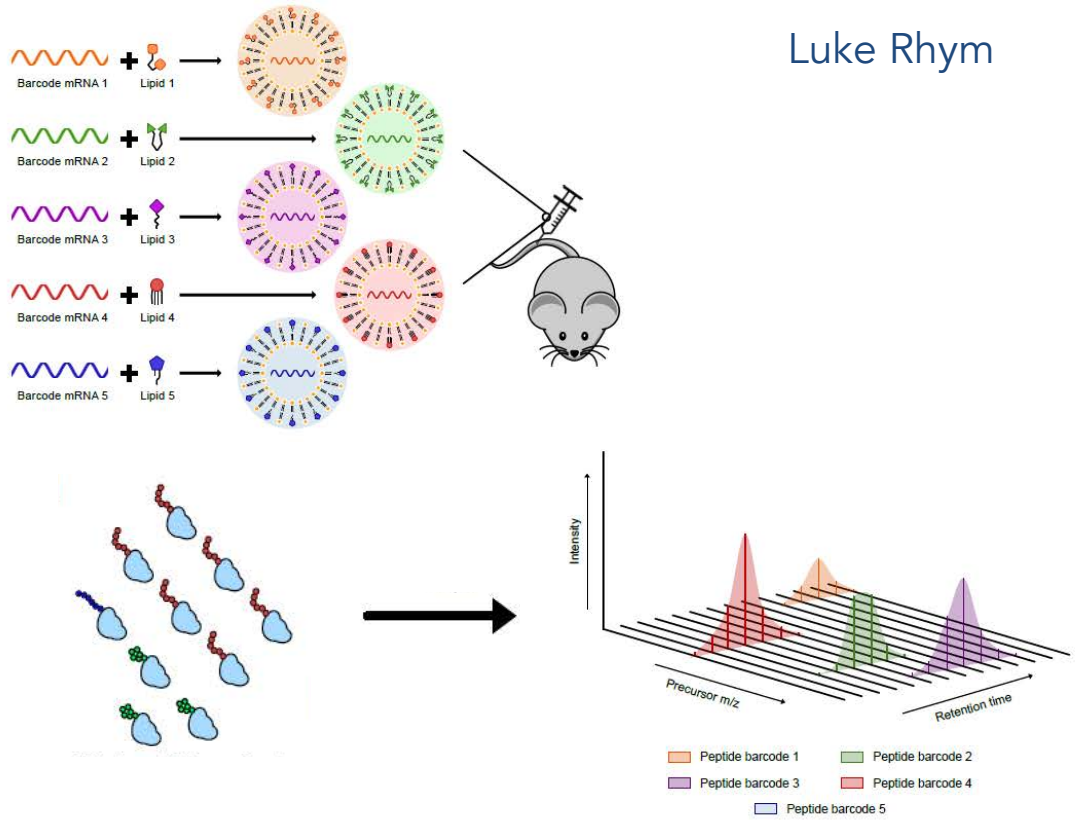
Mechanism behind lung-targeted NPs

Edward Guzman



Improved NP barcoding methods

Luke Rhym



Closing thoughts

- How does this approach compares to more complex, but specific, targeting approaches by introducing mono-clonal antibodies and ligands?

- Material genome atlas for tissue specific drug delivery?