

Hot Topic Discussion

# A framework for designing delivery systems

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October 19, 2020



# Why is this a hot topic?

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

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

2017

## PERSPECTIVES

### Analysis of nanoparticle delivery to tumours

Stefan Wilhelm, Anthony J. Tavares, Qin Dai, Seichi Ohta, Julie Auslet, 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 efficiency. 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 (monocytic 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 monocytic 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 filtration system excretes nanoparticles smaller than 5.5 nm in hydrodynamic diameter<sup>1,2</sup>. 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<sup>3</sup>. To determine the current delivery efficiency to solid tumours, we used Scopus and Google Scholar databases and the search term 'nanoparticle delivery' and identified 224 manuscripts (Fig. 1A). 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. This, we conclude from these data represent the current state of development. From

### Effect of removing Kupffer cells on nanoparticle tumor delivery

Anthony J. Tavares<sup>1,2</sup>, Wilson Poon<sup>1,2,3,4</sup>, Yi-Nan Zhang<sup>1,2,3,4</sup>, Qin Dai<sup>1,2</sup>, Rinkinder Beal<sup>1</sup>, Ding Ding<sup>1,2,3,4</sup>, Ben Ouyang<sup>1,2,3,4</sup>, Angela Li<sup>1,2</sup>, Juan Chen<sup>1</sup>, Gang Zheng<sup>1</sup>, Clinton Robinson<sup>1</sup>, and Warren C. W. Chan<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>

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**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 meta-analysis shows that 0.7% of nanoparticles are delivered to solid tumours. This low delivery efficiency has major implications in the translation of cancer nanomedicine, as most of the nanomedicine are sequestered by non-tumour 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 tumours. Here, we hypothesize that the removal of the liver macrophage 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 tumours. 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 tumours either through the engineering of multifunctional nanoparticles or through manipulation of biological barriers.

**Significance**  
Nanomaterials are developed for treating and diagnosing

## ARTICLES

<https://doi.org/10.1038/nmat463-019-0566-2>

nature materials

### The entry of nanoparticles into solid tumours

Shrey Sindhwani<sup>1,2</sup>, Abdulah Muhammad Syed<sup>1,2,3</sup>, Jessica Ngai<sup>1,2,3,4</sup>, Benjamin R. Kingston<sup>1,2,3</sup>, Laura Maiorino<sup>1,2,3,4,5</sup>, Jeremy Rothschild<sup>1</sup>, Presley MacMillan<sup>1,2</sup>, Yuwei Zhang<sup>1</sup>, Netra Unni Rajesh<sup>1</sup>, Tran Hoang<sup>1</sup>, Jamie L. Y. Wu<sup>1</sup>, Stefan Wilhelm<sup>1</sup>, Anton Zilman<sup>1</sup>, Suresh Gadde<sup>1,2</sup>, Andrew Sulaiman<sup>1</sup>, Ben Ouyang<sup>1,2</sup>, Zachary Lin<sup>1</sup>, Lisheng Wang<sup>1</sup>, Mikala Egeblad<sup>1</sup> and Warren C. W. Chan<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>

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/nmat463-020-0759-1>

### The dose threshold for nanoparticle tumour delivery

Ben Ouyang<sup>1,2,3</sup>, Wilson Poon<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Yi-Nan Zhang<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Zachary P. Lin<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Benjamin R. Kingston<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Anthony J. Tavares<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Michael S. Valic<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Presley MacMillan<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Julien Couture-Senécal<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Gang Zheng<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup> and Warren C. W. Chan<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>

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.

2016

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

2020

nature nanotechnology

## REVIEW ARTICLE

<https://doi.org/10.1038/nmat463-020-0759-1>

Check for updates

## A framework for designing delivery systems

Wilson Poon<sup>1,2,7</sup>, Benjamin R. Kingston<sup>1,2,7</sup>, Ben Ouyang<sup>1,2,3</sup>, Wayne Ngo<sup>1,2</sup> and Warren C. W. Chan<sup>1,2,4,5,6</sup>

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.

Wilhelm, S. *Nature*. **1**, 16014 (2016).

Tavares, A.J. et al. *PNAS*. **114**, 10871–10880 (2017).

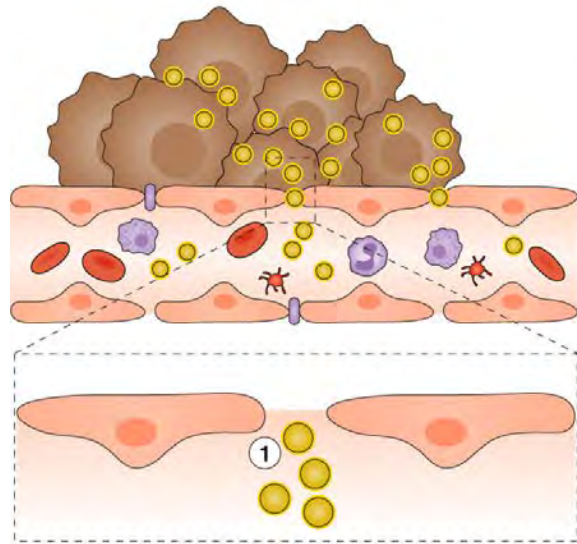
Sindhwani, S. et al. *Nature Materials*. **19**, 566–575 (2020).

Ouyang, B. et al. *Nature Materials* (2020).

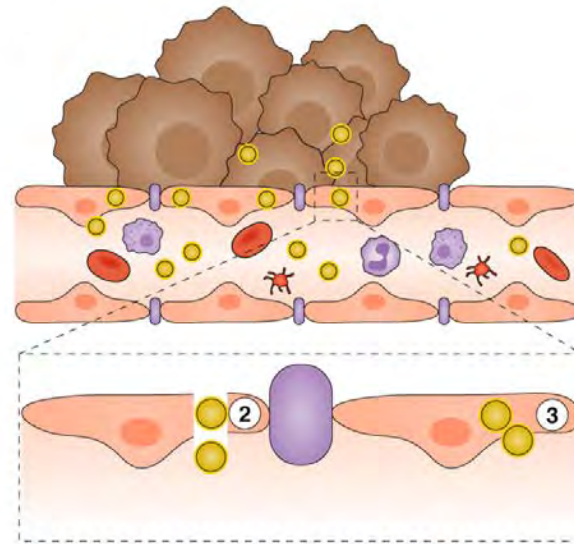
Poon, W. et al. *Nature Nanotechnology* **15**, 819–829 (2020).

# How tumor biology impacts NP delivery

## EPR effect

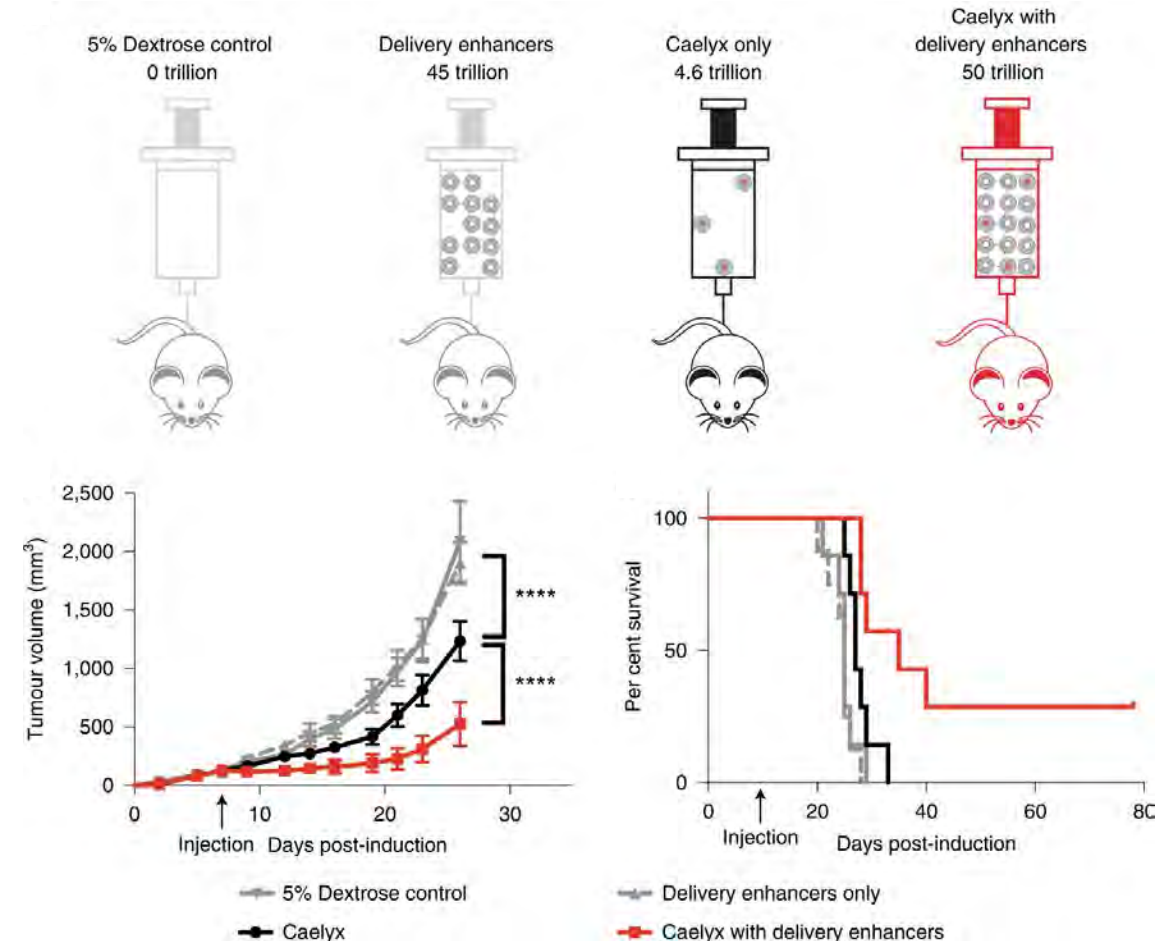


## Transcytosis



● AuNP   
 ▬ Tight junction   
 ▭ Endothelial cell   
 ▭ Tumour cell

## Dose threshold for improving NP tumor delivery

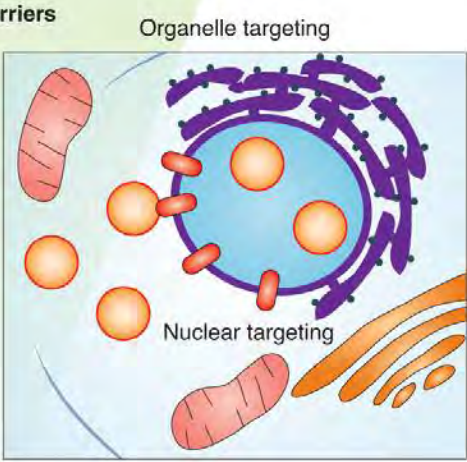
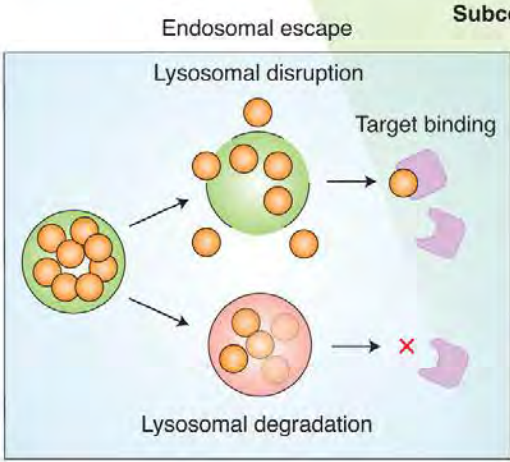
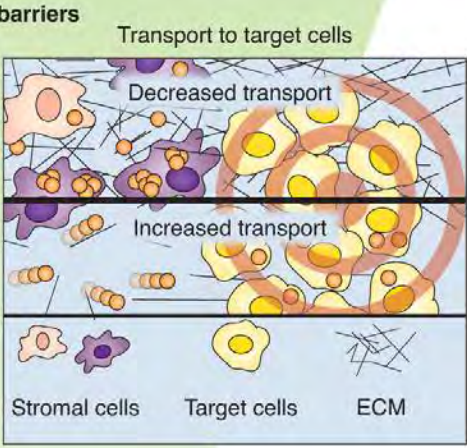
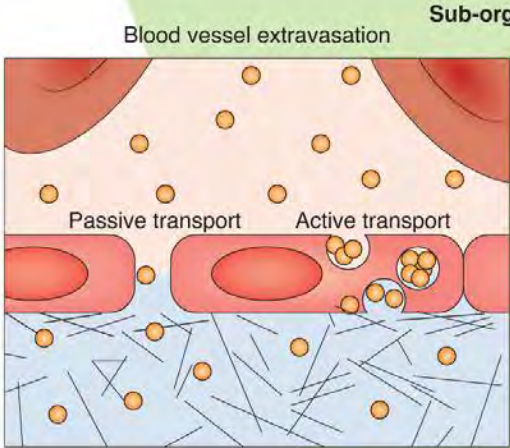
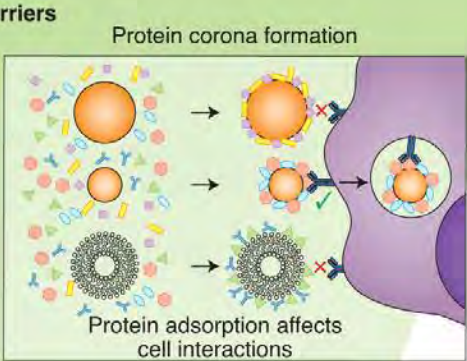
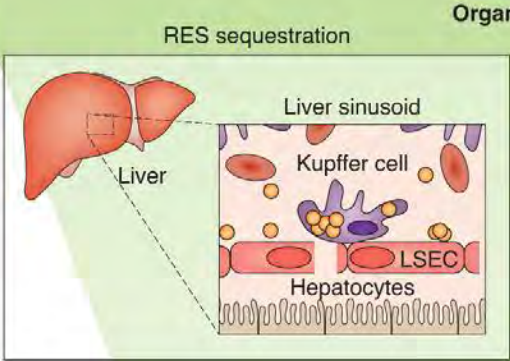
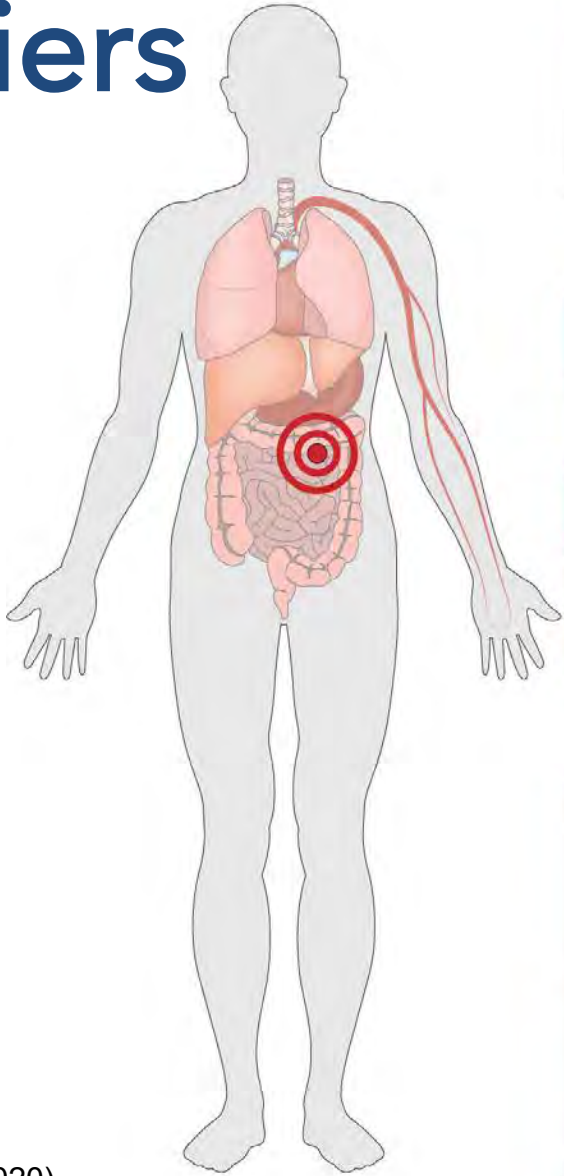


Sindhvani, S. *et al. Nature Materials*. **19**, 566–575 (2020).

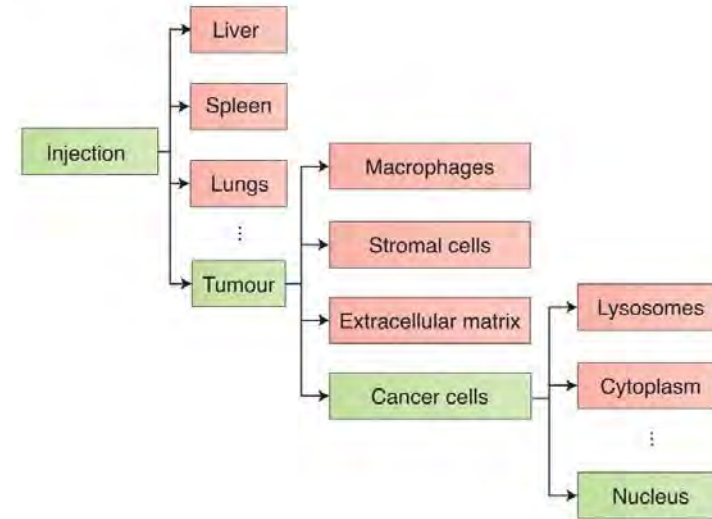
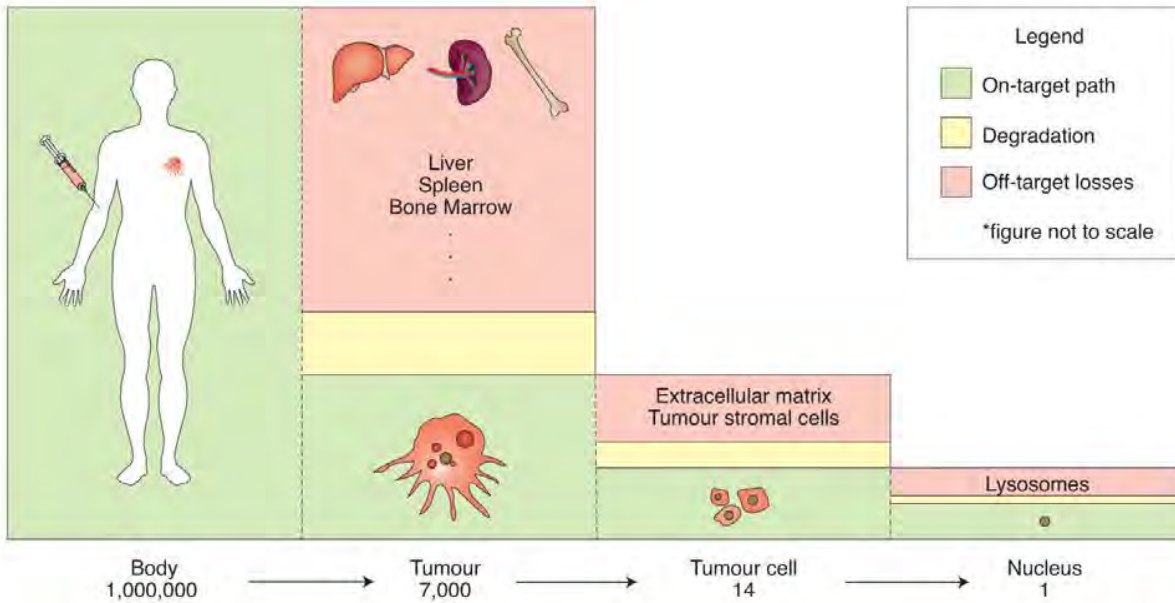
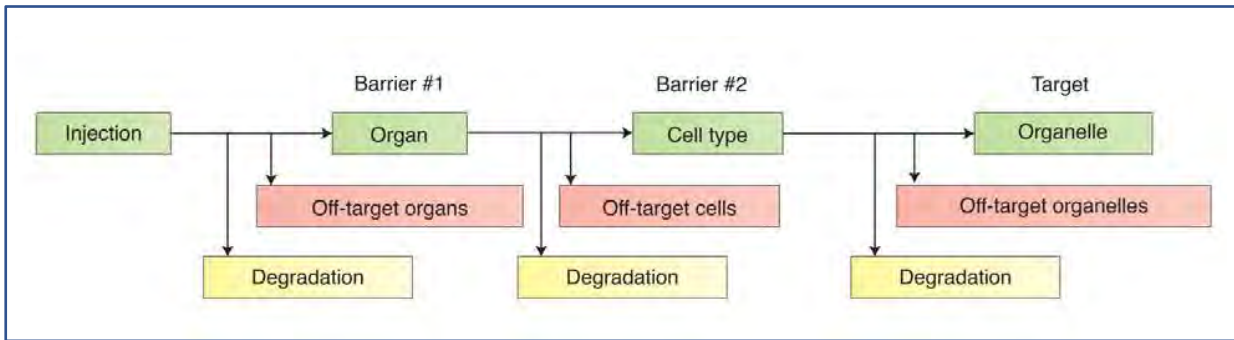
Ouyang, B. *et al. Nature Materials* (2020).



# The biology of delivery barriers



# Modeling NP delivery to tumor cells

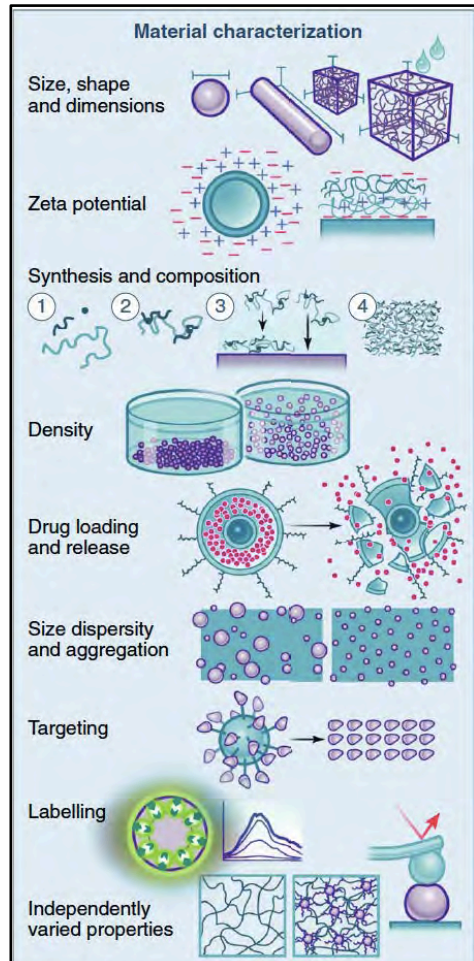


Therapeutic target	Therapeutic example	Barriers needed to be overcome						
		Blood	RES organs	Tumour endothelium	Tumour ECM	Tumour stromal cells	Tumour cell lysosomes	Tumour cell nucleus
Tumour endothelium	P-selectin for anti-metastases	x	x					
Tumour ECM	Hyaluronidase/MMP treatment	x	x	x				
Cancer cell surface	Herceptin/Bi-specific T cell engagers	x	x	x	x	x		
Cancer cell cytoplasm	RNA interference	x	x	x	x	x	x	
Cancer cell DNA	Doxorubicin	x	x	x	x	x	x	x



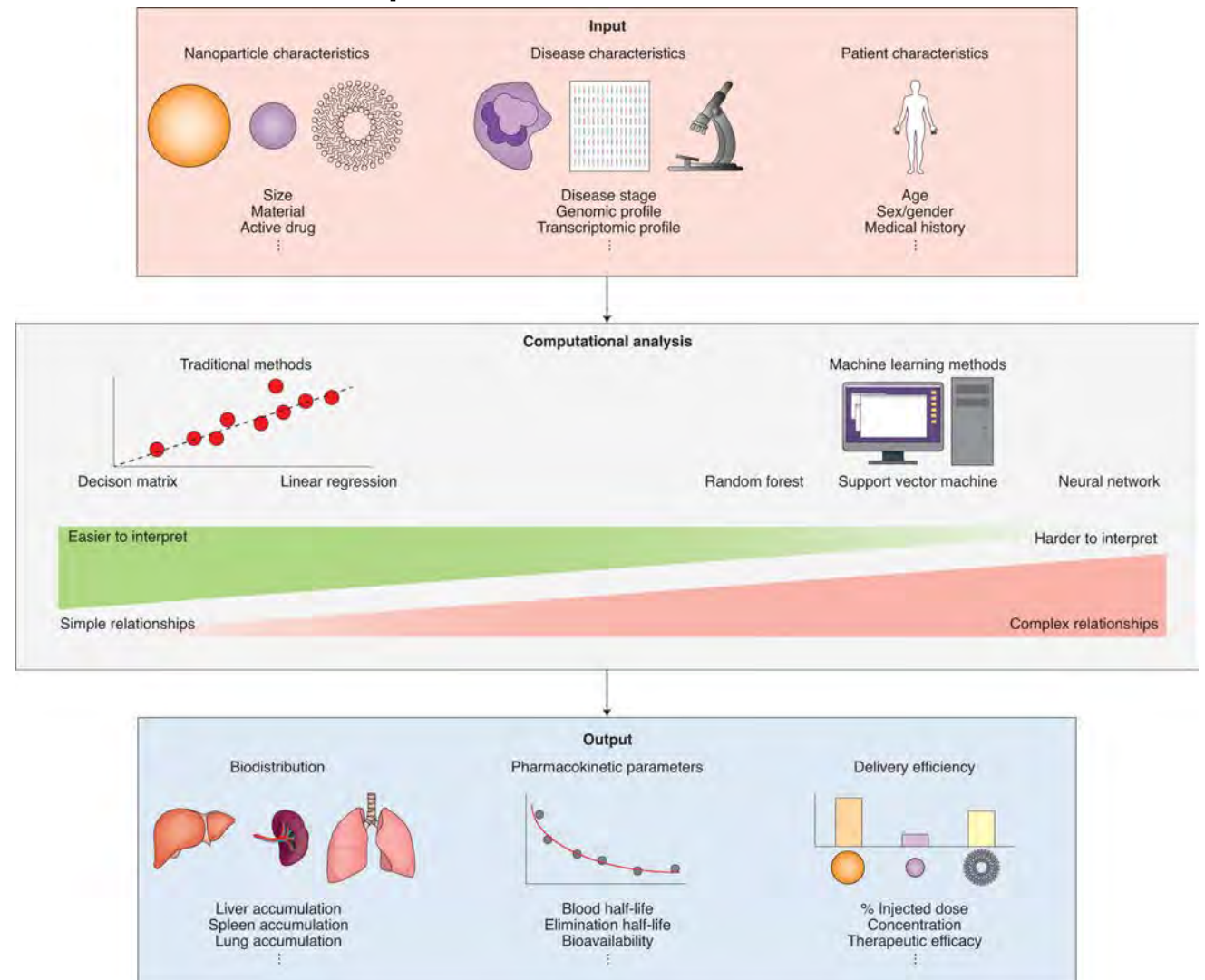
# How do we identify the ideal NP?

## Classically



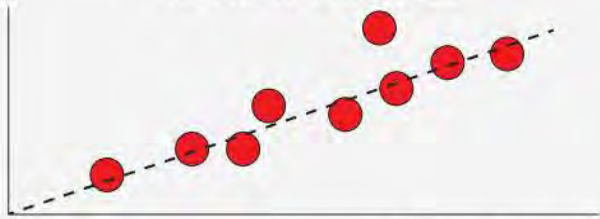
Collect nano-bio interaction data from *in vitro* + *in vivo* studies

## Proposed framework



# Computational approaches for understanding nano-bio interactions

Traditional methods



Decision matrix

Linear regression

Machine learning methods



Random forest

Support vector machine

Neural network

Easier to interpret

Harder to interpret

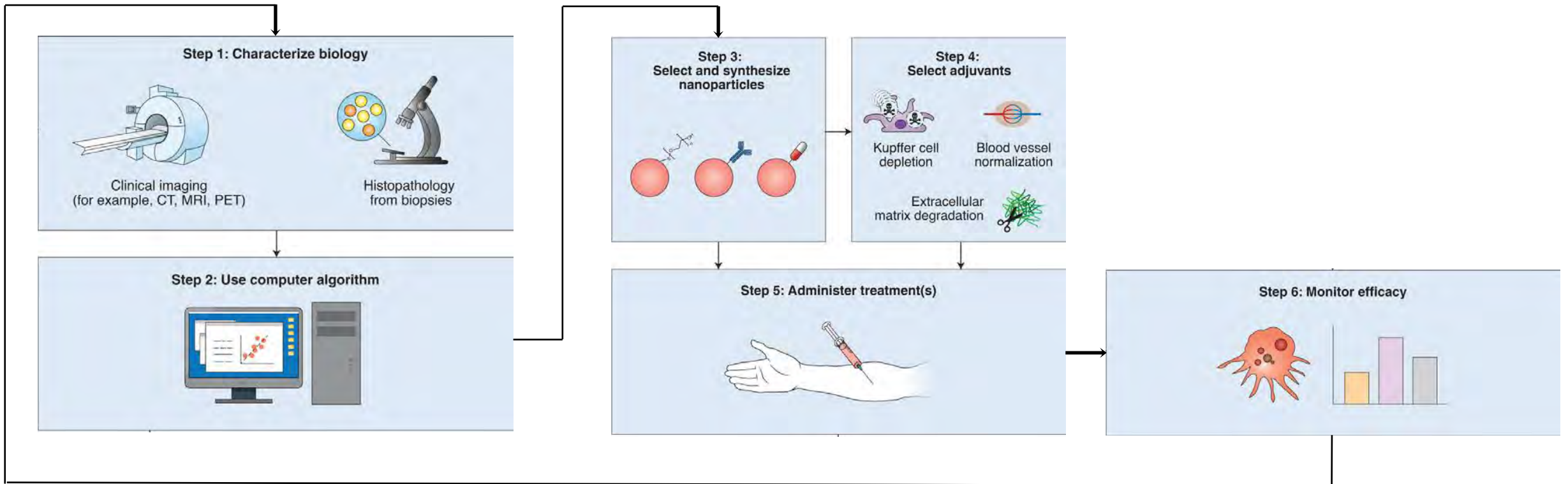
Simple relationships

Complex relationships

## Challenges of using computational approaches:

- Need for large datasets
- Multidisciplinary team of experts including computer science
- Broad algorithms that work across a large variety of nanoparticle formulations or biological applications.

# Workflow for the development of NP for clinical applications





# Proposed questions for designing nanoparticle delivery systems

Question	Rationale for the question
(1) Where is the delivery target?	The specific biological target (organ or tissue, cell type and subcellular location) defines design of the nanoparticle strategy.
(2) What is the cargo or active agent that needs to be delivered to the target location?	This defines the chemistry for incorporating the agents into the nanoparticle for delivery.
(3) Where is the site of administration?	The location of administration and the delivery target location define the delivery pathway.
(4) What are the specific organs, tissues and cells encountered along the delivery pathway?	This defines the barriers that the nanoparticle will encounter.
(5) What are the interactions between the nanoparticle carrier and the body in each of these biological environments along the delivery pathway?	These interactions will determine if the formulation is degraded or sequestered before it can reach its intended target location.
(6) What strategies are available to overcome the barriers at each step in the delivery pathway?	This allows the development of specific strategies to overcome the barriers.
(7) How will any administered components leave the disease site and be excreted from the body?	This helps to define locations of toxicity and elimination routes.

# Where to get started?

Right here!

Marble Center and other KI colleagues

Swanson Biotech Center:

- High throughput sciences
- Genomics and bioinformatics (BioMicro Center)
- Nanotechnology materials

Across the street!



Many KI faculty also have Broad affiliation for easy collaborations

# Discussion Questions

1. What about high-throughput techniques?
2. What other tools or experimental technique would you like to see applied to the advancement of nanomedicine?
3. Are there any examples out there of computing-enabled therapies that have been approved by FDA?