Biomaterials for MX

MSE – 471

Prof. Maartje M.C. Bastings

Course 5: Targeting and Drug Delivery

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Course Content & Time Table

BLOCK 1: Introduction and materials overview

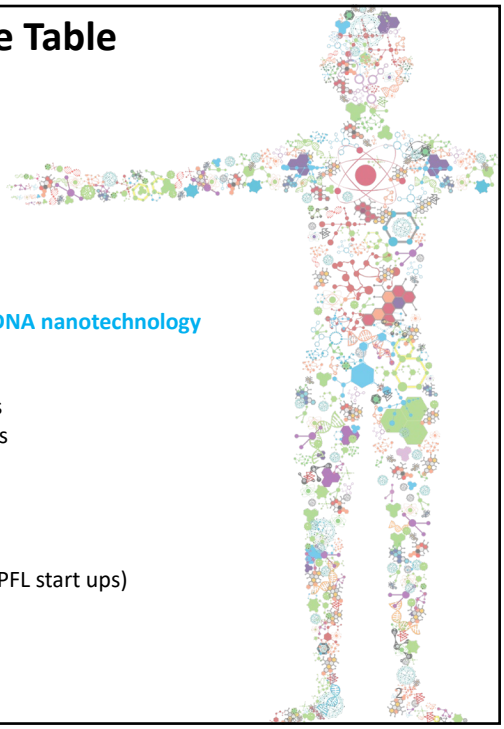
11-9	Lecture 1.	Intro to biomaterials and biology
18-9	Lecture 2.	Naturally derived biomaterials
25-9	Lecture 3.	Implants and metals
2-10	Lecture 4.	Polymers, Particles, and Surfaces

BLOCK 2: Interactions and specific applications

9-10	**Lecture 5.**	**Materials for drug delivery and targeting: DNA nanotechnology**
16-10	Lecture 6.	Materials for cell adhesion: scaffolds
---	*Break*	
30-10	Lecture 7.	Materials for immune engineering: vaccines
6-11	Lecture 8.	Materials for tissue engineering: heartvalves

BLOCK 3: Measurements, regulation and translation

13-11	Lecture 9.	Characterization and performance
20-11	Lecture 10.	Sensors and diagnostic devices
27-11	Lecture 11.	Translation to industry, patents, spin-offs (EPFL start ups)
4-12	Lecture 12.	Regulatory aspects and trials (EPFL TTO)
11-12	Lecture 13.	Revision and conclusion
18-12	Open discussion and hand in of lab papers	



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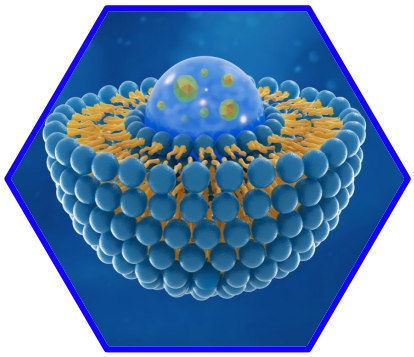
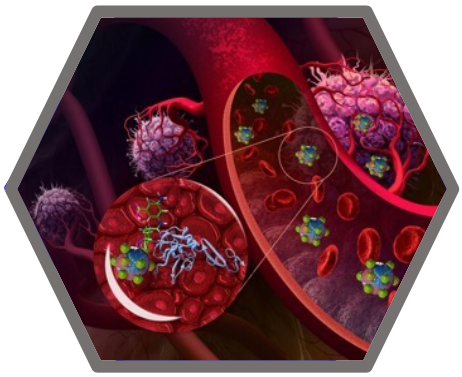
Today's focus

Targeting



Drug Delivery



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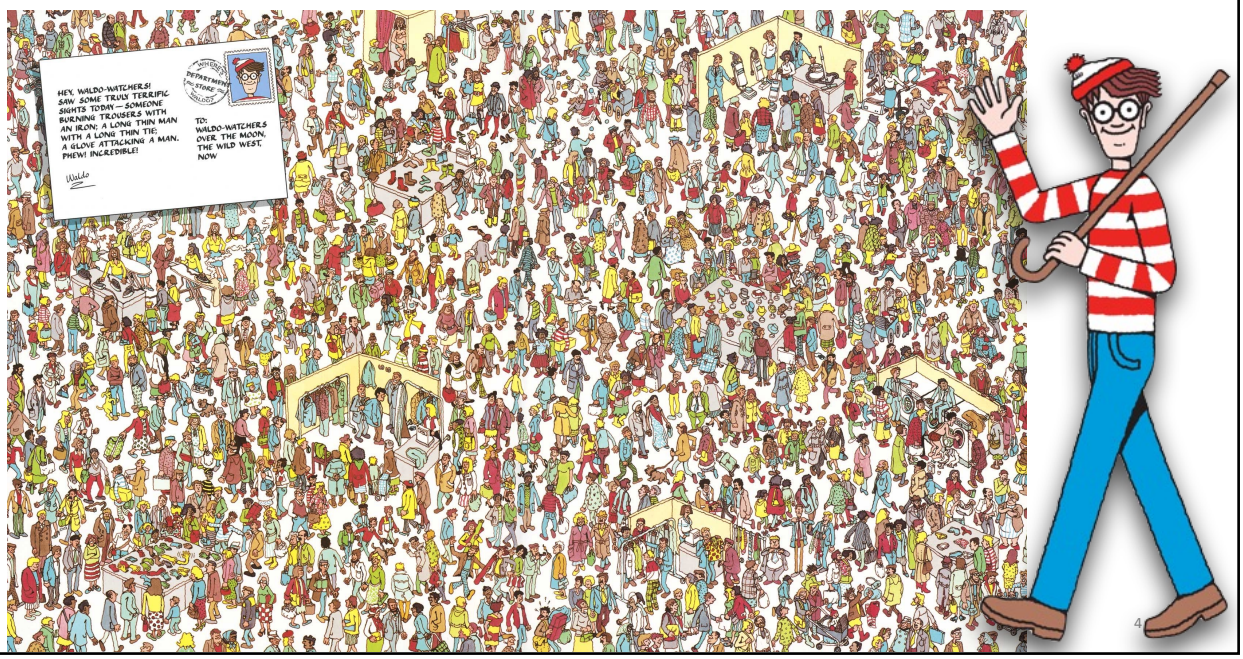
How to find a diseased cell in the body?



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Targeting

This is what turns a biomaterial into a therapeutic

What we want

find the diseased cell
only bind to it
deposit drugs
only kill the sick cell
leave without side effects

What generally happens

find a full tissue (or more than 1)
90+% get cleared before binding
partial drug deposition
kill much more than just diseased cells
side effect, toxicities, immunities

HOW TO IMPROVE NANOPARTICLE THERAPEUTICS?

SOLUTION: SPECIFIC AND SELECTIVE TARGETING

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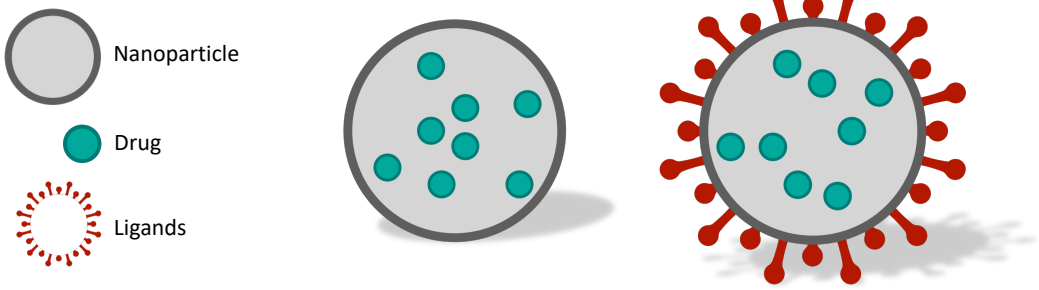
The TARGETING Paradigm



THE MATERIAL
[1] Uniform = (more) predictabe
[2] Shape alters interactions

THE LIGANDS
[1] Do we need so many?
[2] Do they need to be flexible?

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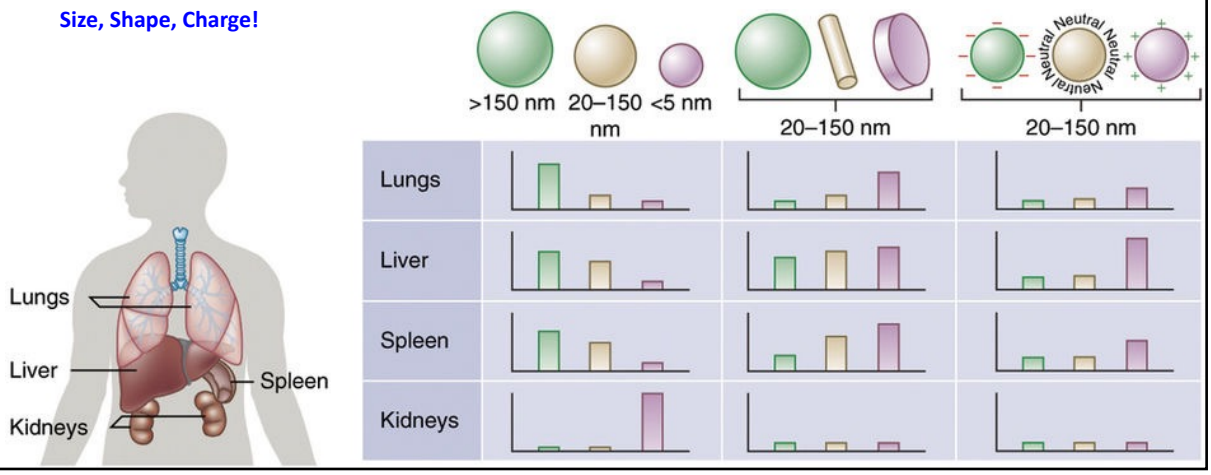
Passive Targeting

Large rigid particles (>2,000 nm) accumulate in the spleen and liver, as well as in the capillaries of the lungs.
> 150 nm, entrapped within the liver and spleen.
Small-sized nanoparticles (<5 nm) are filtered out by the kidneys

2019, Int J of Nanomedicine 14:6631-6644

Size, Shape, Charge!



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Receptors are Everywhere!

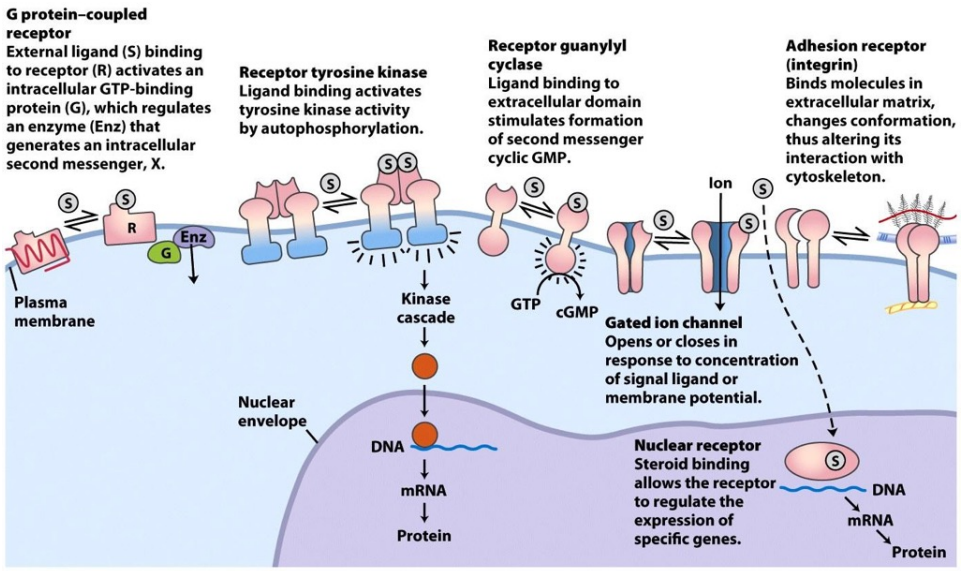

Figure 12-2
Lehninger Principles of Biochemistry, Fifth Edition
© 2008 W. H. Freeman and Company

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Receptor and Ligand = Lock and Key

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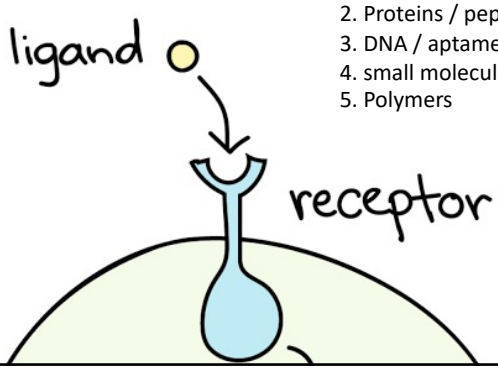
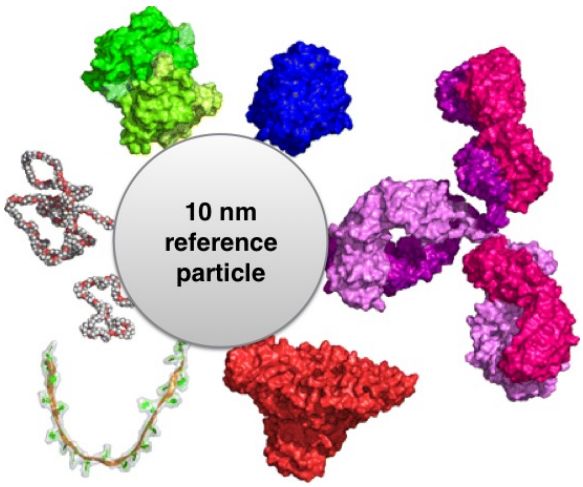
Ligands

A molecule that binds to a receptor is called a ligand.

When a ligand binds to a corresponding receptor, it **activates or inhibits** the receptor's associated biochemical pathway.

Many types of ligands:
1. Antibodies
2. Proteins / peptides
3. DNA / aptamer
4. small molecules
5. Polymers





PEG of 2000 and 5000 g mol−1 (light grey),
streptavidin (green),
transferrin (blue),
antibody (IgG, purple),
albumin (red), single-stranded DNA (20mer)

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List of Targeted Therapy Drugs Approved for Specific Types of Cancer

The FDA has approved targeted therapy drugs for the treatment of some people with the following types of cancer. Some targeted therapy drugs are listed more than once because they have been approved to treat more than one type of cancer. The generic drug name is listed first, with a brand name in parentheses.

ON THIS PAGE

https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/approved-drug-list

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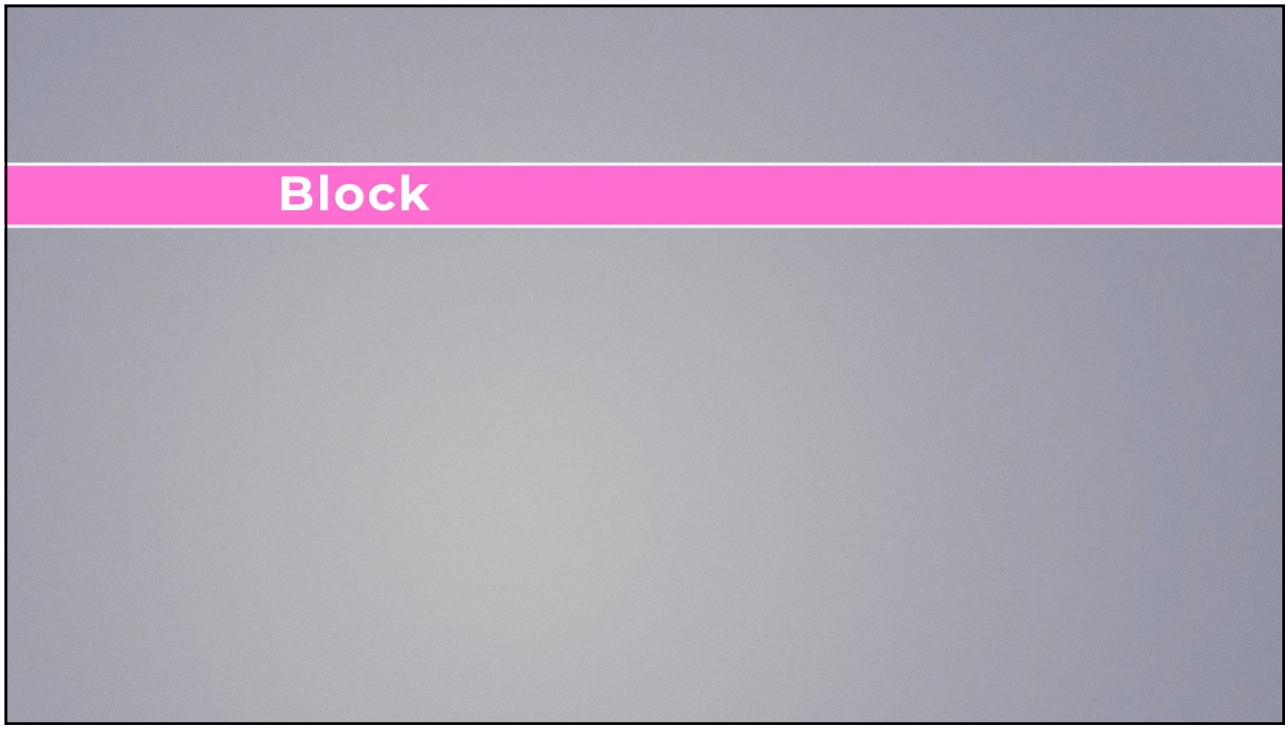

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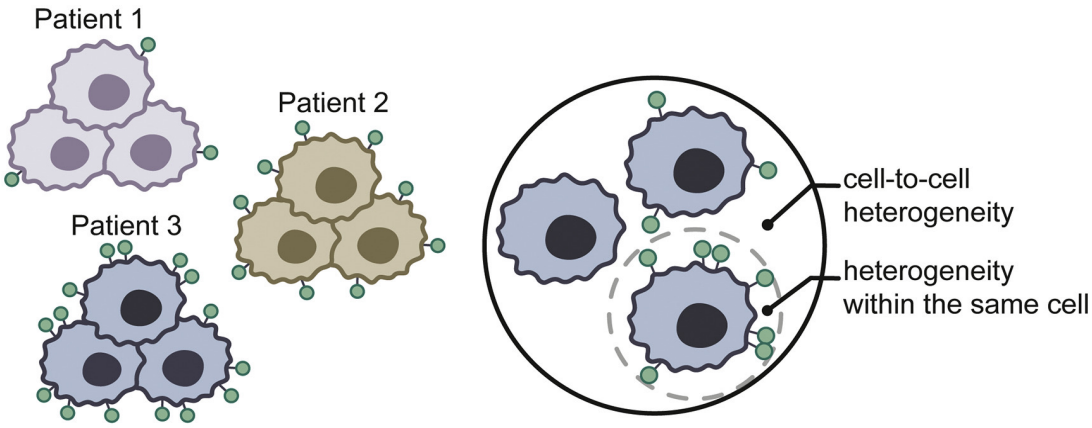
Targeting Challenges: DENSITY

BIOMARKER TESTING



a) Patient heterogeneity

b) Target cell receptor expression

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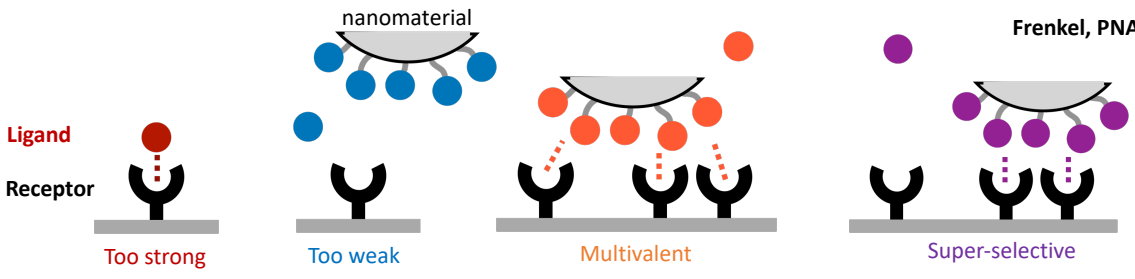
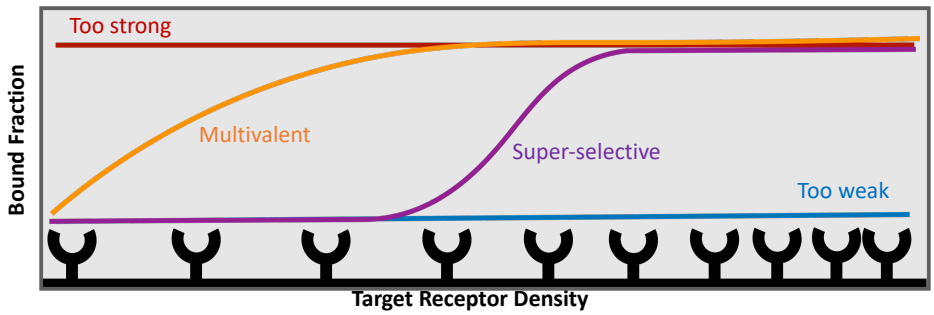
LIGAND-RECEPTOR Interactions



Frenkel, PNAS 2011



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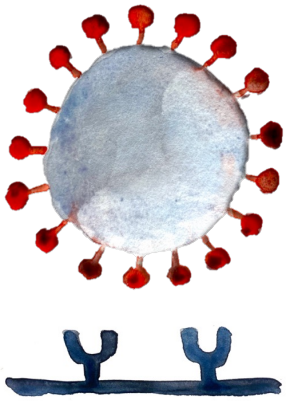
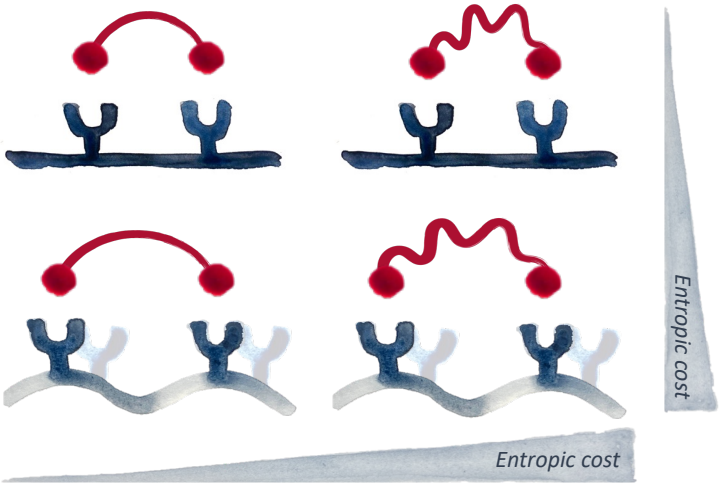
SUPER-SELECTIVE MATERIALS

ENTHALPY driven
High Valency Regime, Flexible



Majority of ligands do NOT interact

ENTROPY driven
Low Valency Regime, Rigid vs Flexible



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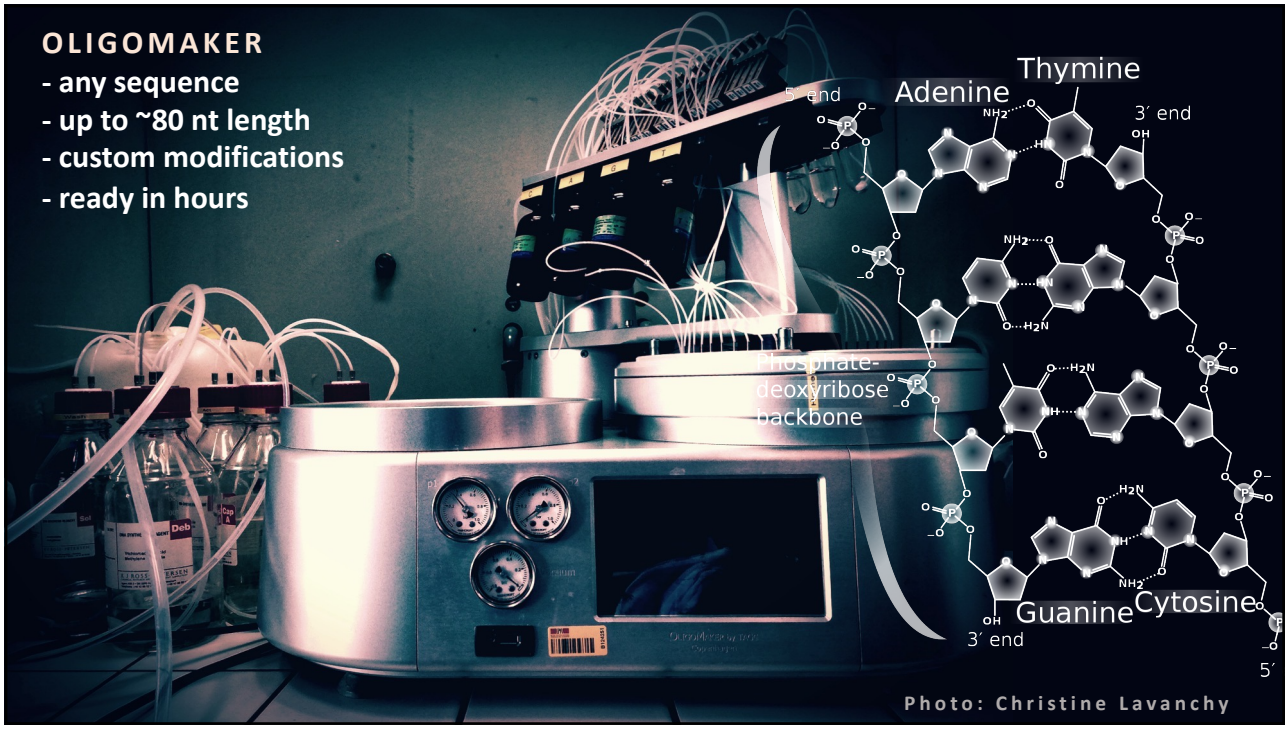

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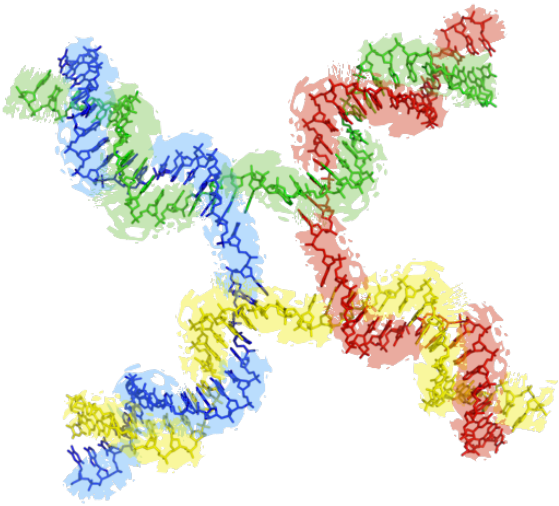
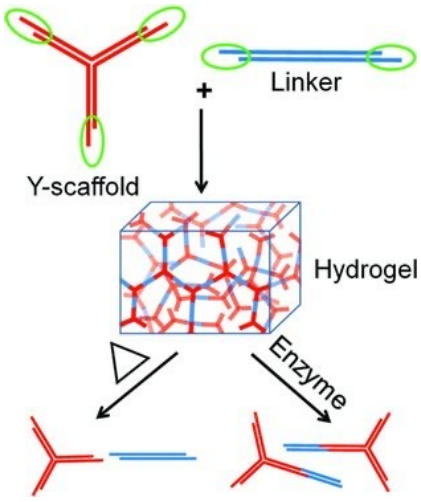
Reprogramming DNA interactions

Short synthetic DNA strands can make new architectures!





Seeman, N (1982). "Nucleic acid junctions and lattices". *J. of Theor. Biol*. **99** (2): 237–47

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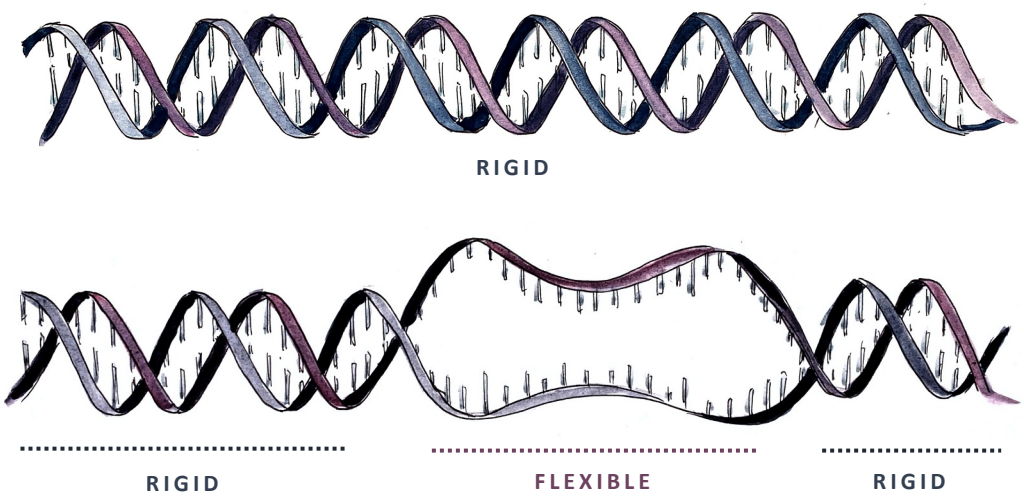
RIGID vs FLEXIBLE



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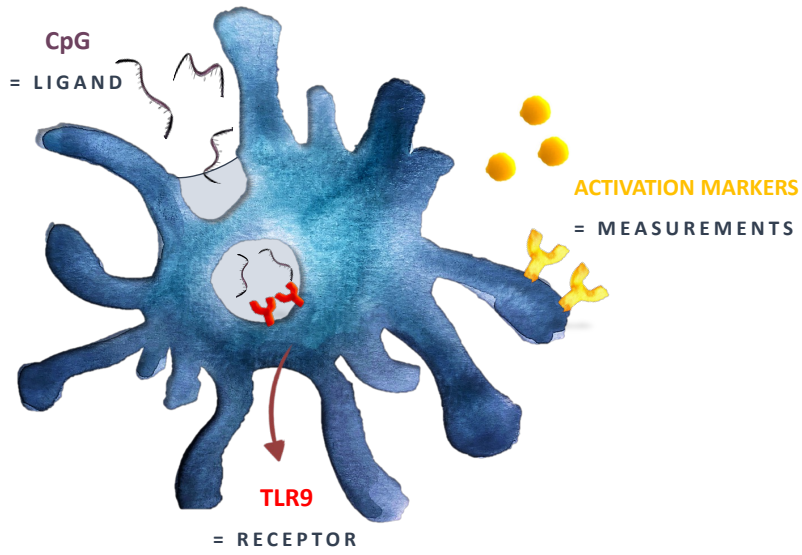
RIGIDITY allows for SELECTIVITY



Comberlato et al., ***Nano Letters***, 2022

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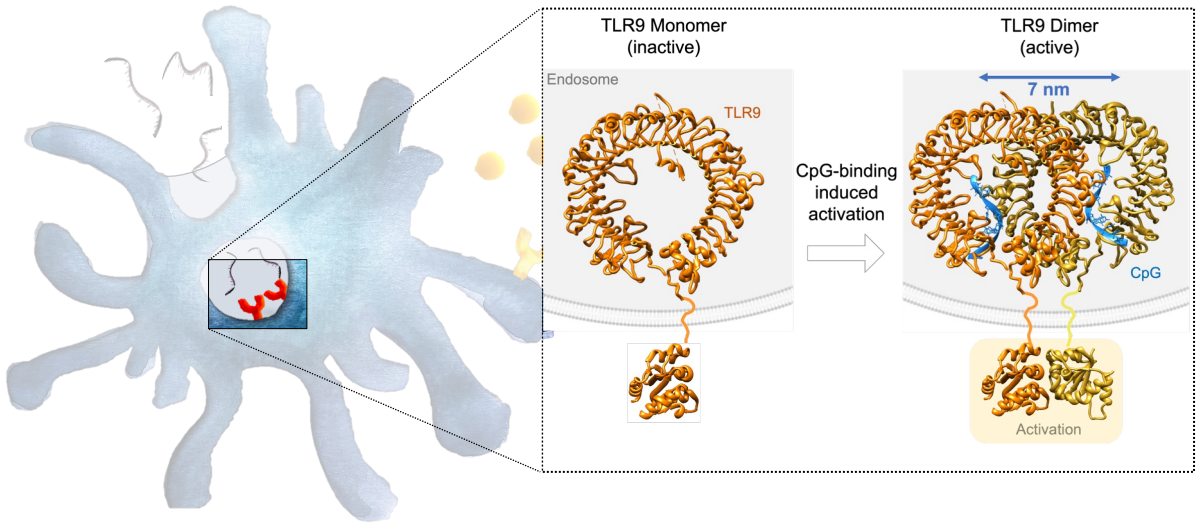
RIGIDITY allows for SELECTIVITY



Comberlato et al., ***Nano Letters***, 2022

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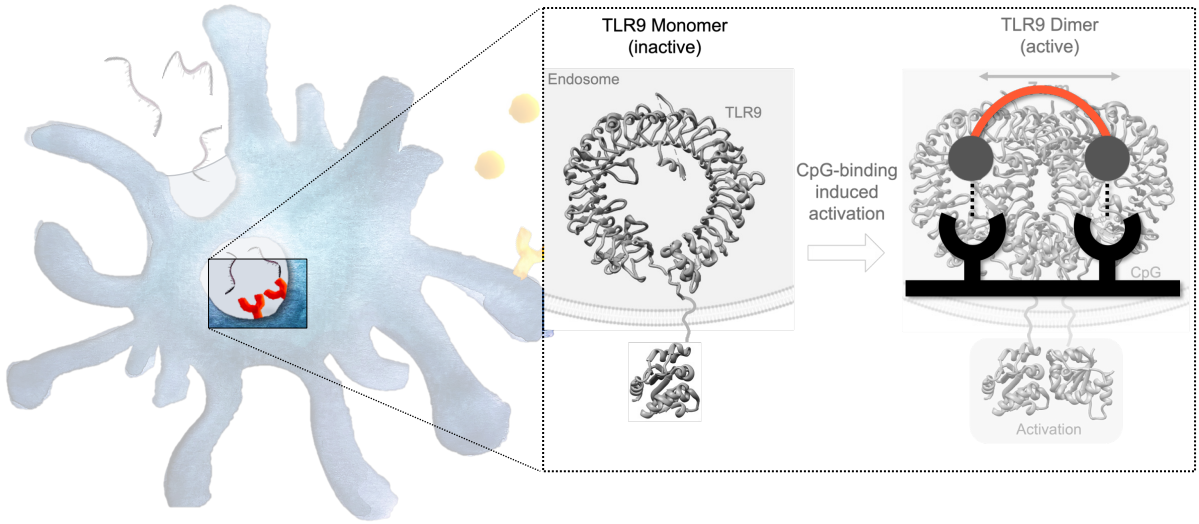
RIGIDITY allows for SELECTIVITY



Comberlato et al., ***Nano Letters***, 2022

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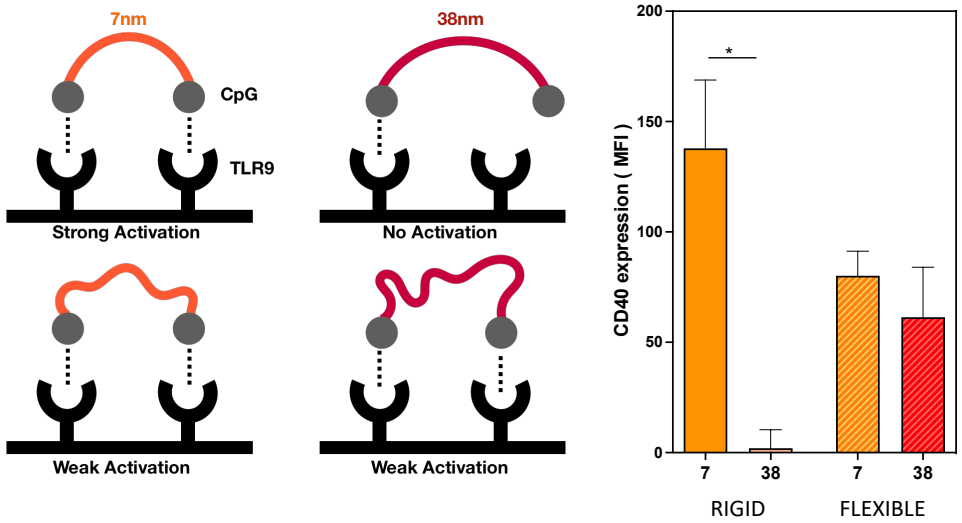
RIGIDITY allows for SELECTIVITY



Comberlato et al., ***Nano Letters***, 2022

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MORE THAN A DOUBLE HELIX

Animation by Shawn Douglas - UCSF

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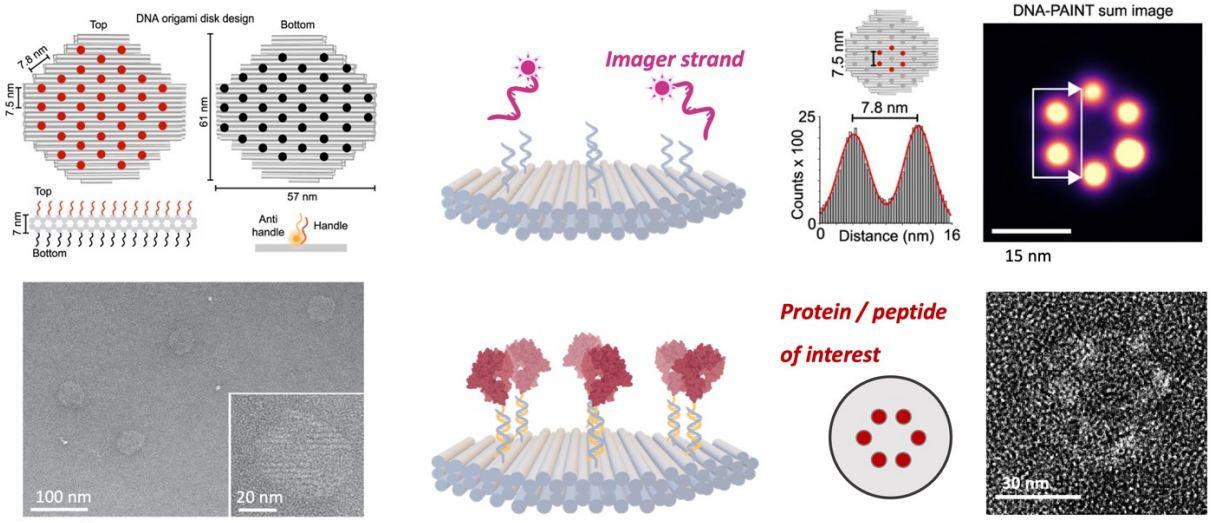
A DNA DISK WITH 36 "PIXELS"



Eklund*, Comberlato*, et al., ***ACS Nano***, 2021

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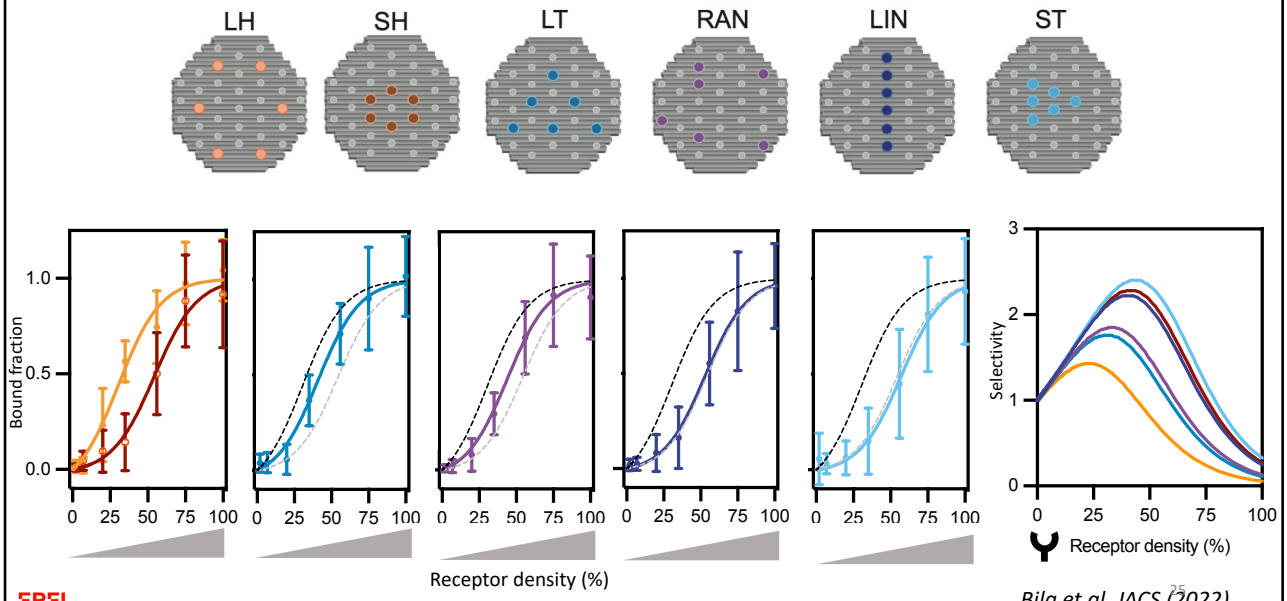
MULTIVALENT PATTERN RECOGNITION



Bila et al. JACS (2022)

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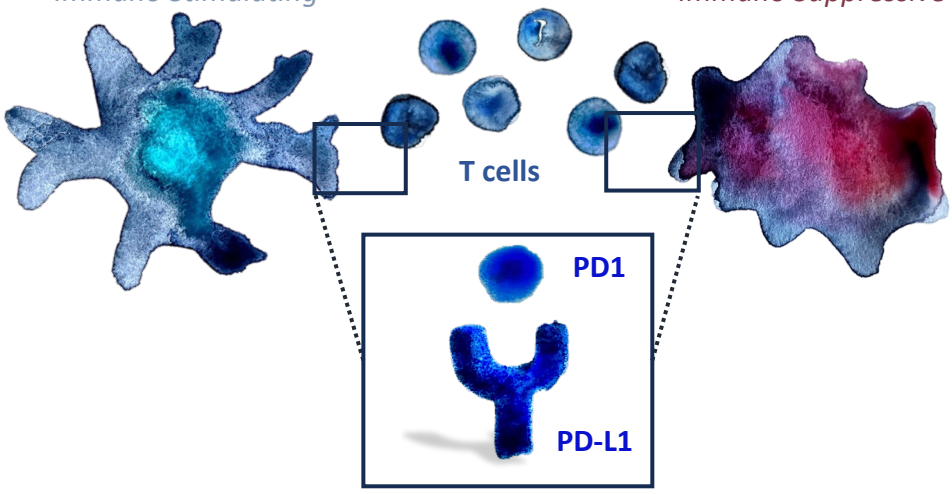
PATTERNS in CHECKPOINT BLOCKADE?



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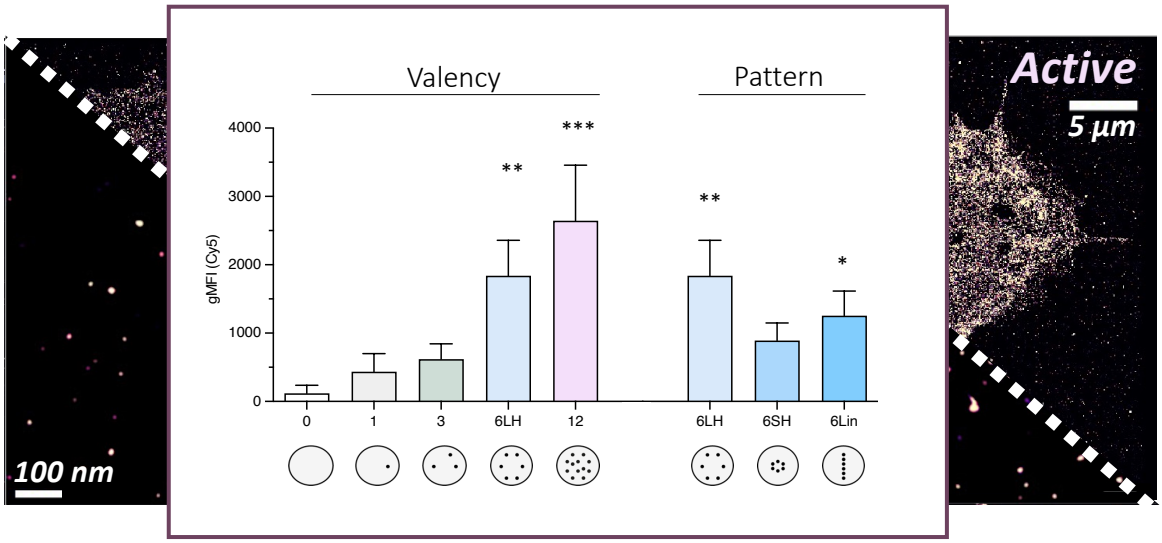
PATTERNS in CHECKPOINT BLOCKADE



*Paloja et al, **ACS Nano,** 2023*

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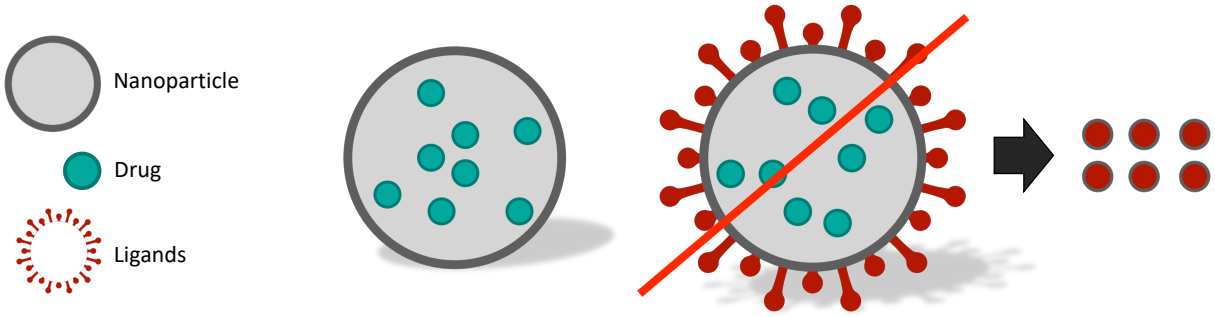
The TARGETING Paradigm

PASSIVE TARGETING NANOPARTICLE

ACTIVE TARGETING NANOPARTICLE



THE MATERIAL
[1] Uniform = (more) predictabe
[2] Shape alters interactions

THE LIGANDS
[1] We need only 6!!
[2] Rigid in geometric pattern!!

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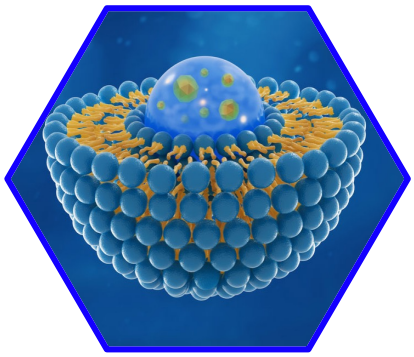
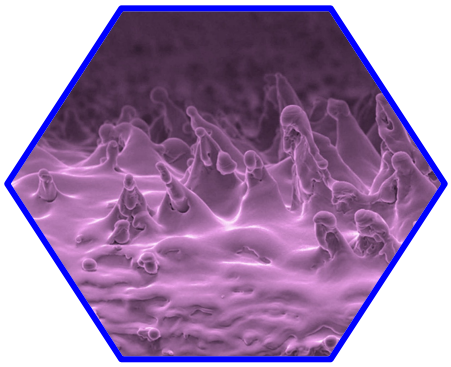
Today's focus

Targeting



Drug Delivery



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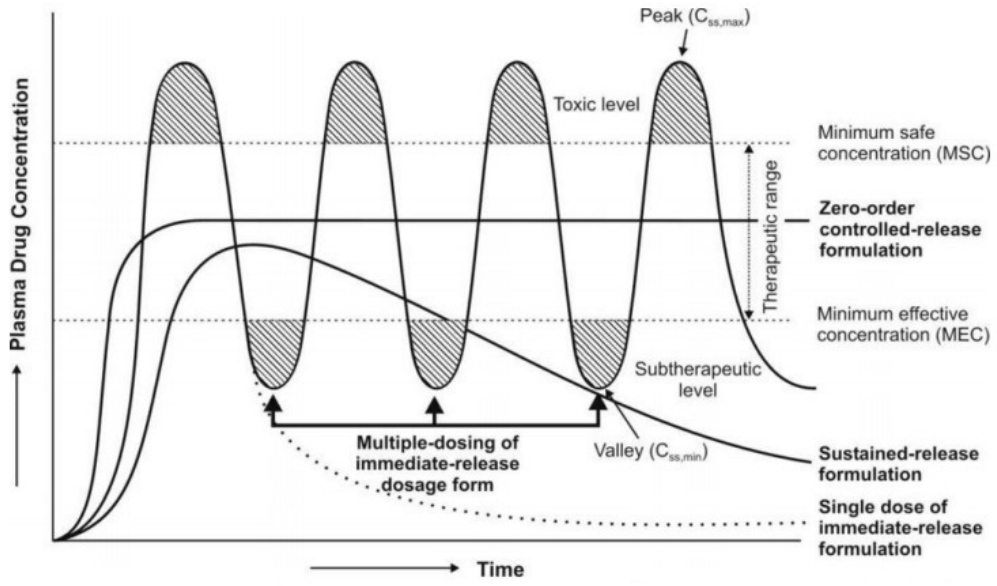
Drug release kinetics



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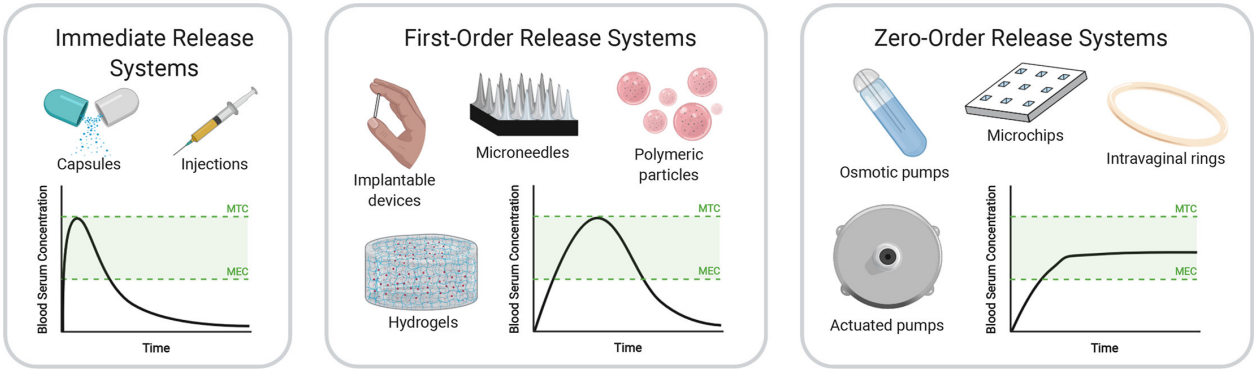
Engineered drug release systems



https://www.pharmaexcipients.com/drug-delivery/zero-order-drug-delivery/

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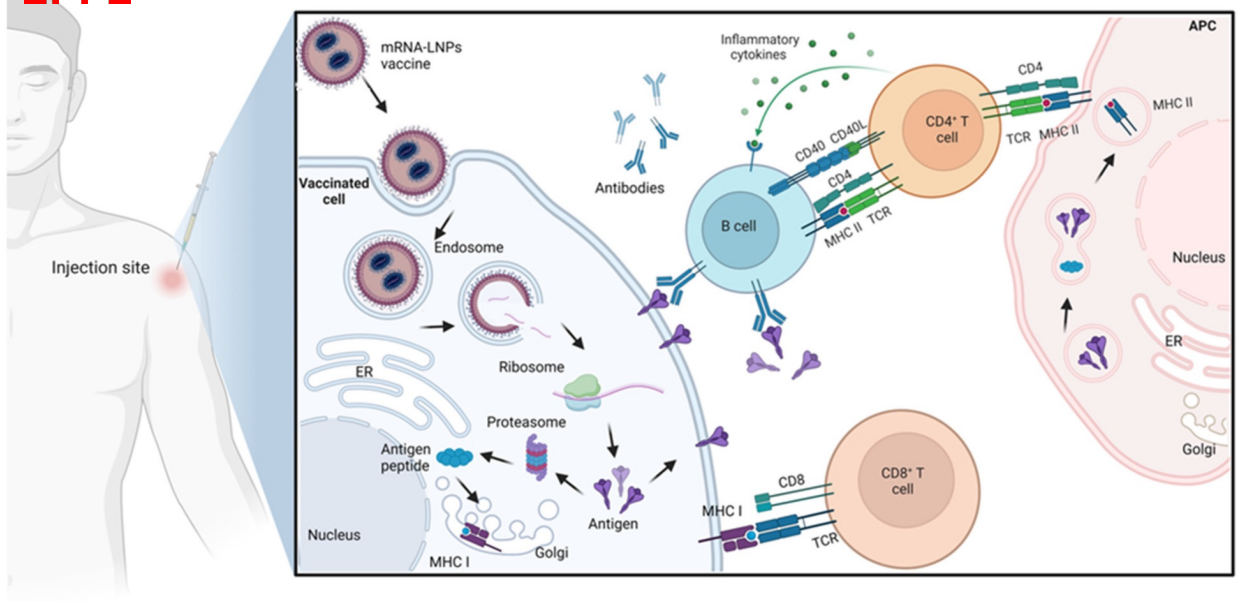
COVID vaccine : various “release” time scales



Pharmaceutics **2023**, *15*(7), 1972;

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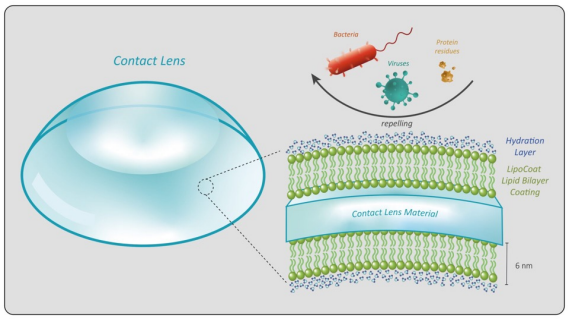
Contact lenses : coating vs bulk



Tear film mimicking lipid-bilayer coating
Breathable layers keep eyes healthy
Soft coating properties offers all-day comfort
Keeps lens moist by hydrophylic modification

TIME!
Day, week, month…

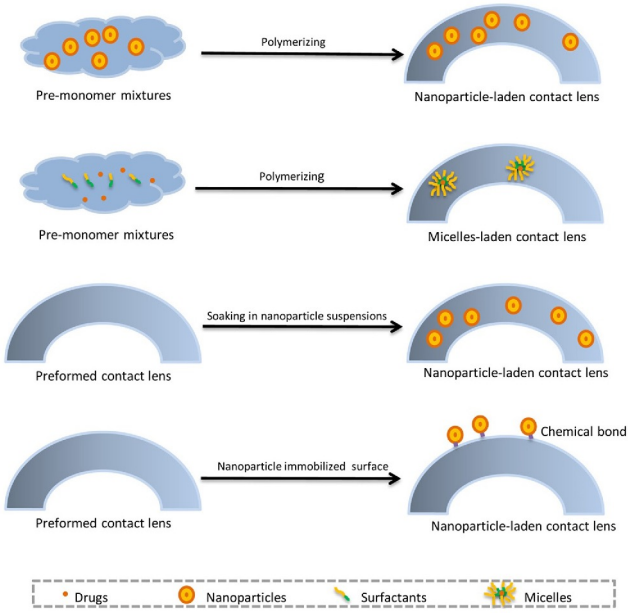


Fig. 13. Different methods for preparing nanoparticles-laden into contact lens.

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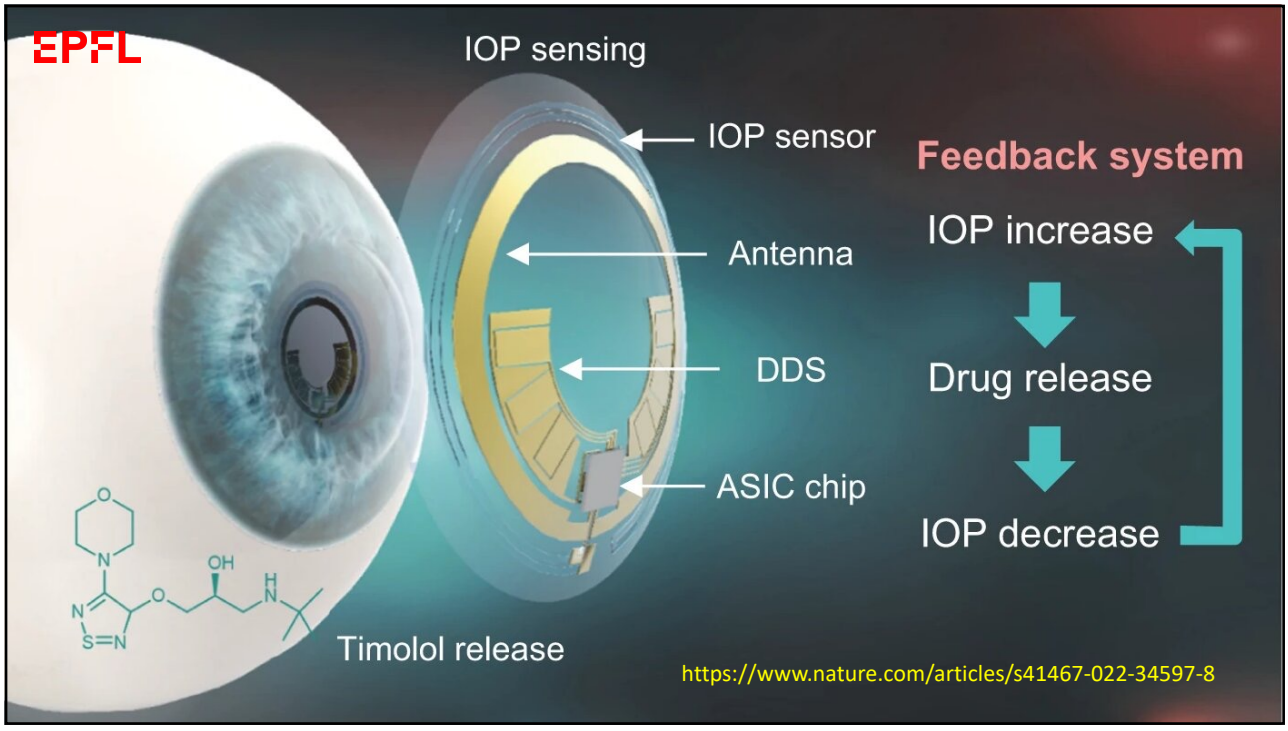

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SPRINGER LINK https://link.springer.com/article/10.1007/s40005-022-00607-6/tables/1 Log in

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Home > Journal of Pharmaceutical Investigation > Article > Table 1

Table 1 Representative list of FDA/EMA-approved and globally-marketed nanomedicine-based formulations

From: **Nanomedicine-based commercial formulations: current developments and future prospects**

Type of formulation	Nanosystem type	Product name	Active ingredient(s)	Company	Approving organization and approval date	Indication(s)	References
Lipid-based nanomedicine	Liposome	Doxil®	Doxorubicin hydrochloride	Johnson and Johnson	FDA (1995) EMA (1996)	Metastatic ovarian cancer, HIV-associated Kaposi's sarcoma, multiple myeloma	James (1995); Barenholz (2012)
	Lipid complex	Abelcet®	Amphotericin B	Liposome Co	FDA (1995)	Aspergillosis in patients refractory to or intolerant of conventional amphotericin B and for invasive fungal infections	Rust and Jameson (1998)
	Liposome	DaunoXome®	Daunorubicin citrate	Galen Ltd	FDA (1996) EMA (1996)	HIV-associated Kaposi's sarcoma	Kaposi's sarcoma: DaunoXome approved (1996)
	PEGylated liposome	Caelyx®	Doxorubicin hydrochloride	Janssen Pharmaceutica NV	EMA (1996)	Metastatic breast cancer, ovarian cancer, AIDS-related Kaposi's sarcoma	Ranson et al. (2001)
	Unilamellar liposome	AmBiosome®	Amphotericin B	NeXstar Pharmaceuticals	FDA (1997) EMA (2006)	Fungal infections in febrile neutropenic patients; Aspergillosis, candidiasis, and cryptococcosis infections refractory to amphotericin B	Boswell et al. (1998)

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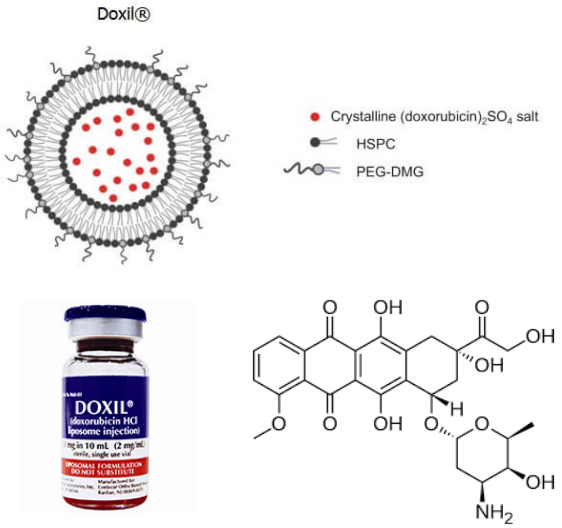
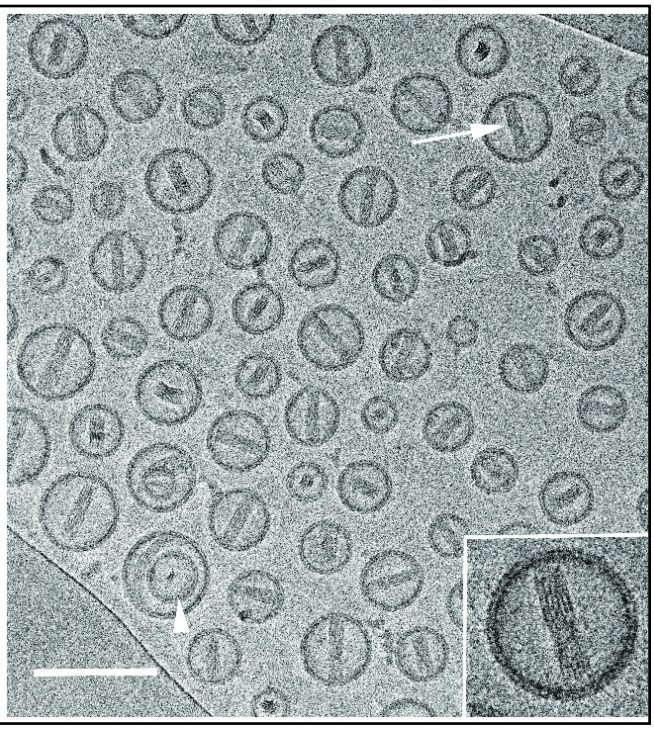
Drug delivery: DOXIL

a commercial Doxil formulation, remote loading produces doxorubicin sulfate $[(DOX\text{-}NH_3)_2SO_4]$ crystals within PEGylated nanoliposomes.





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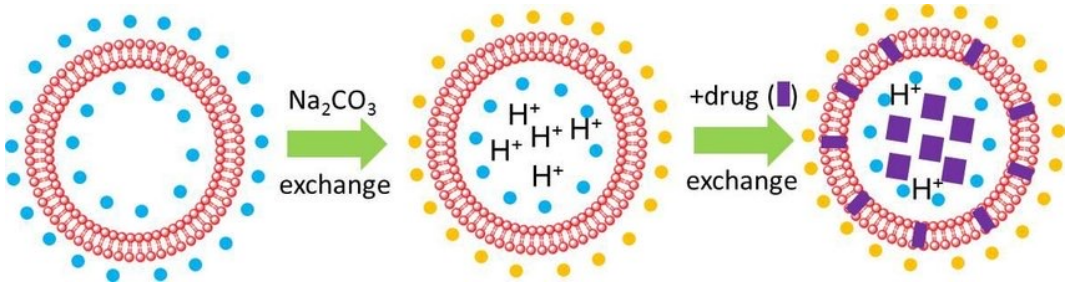
Drug delivery: DOXIL

[1] Make liposomes
[2] Load drugs



Liposomes are prepared by hydrating in citrate buffer

external phase is exchanged with Na2CO3 to create a pH gradient.

The neutral form of the externally added drug can cross the bilayer and is protonated and trapped inside the vesicles.

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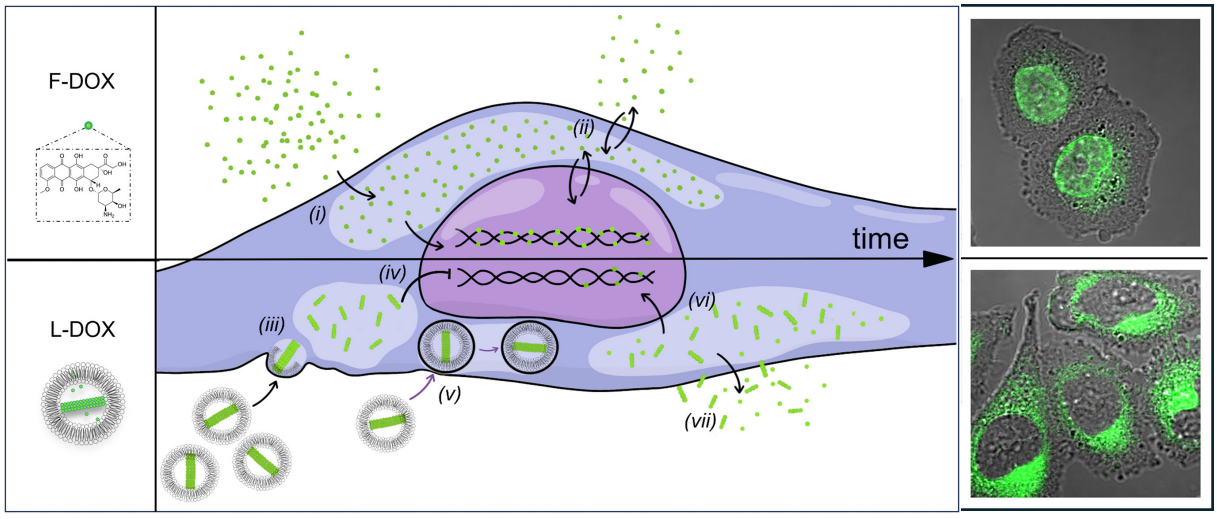
Drug delivery: DOXIL



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Conclusion

Receptors are everywhere and are crucial for the functionality of our cells. Communication happens through ligand-receptor interactions and a plethora of signals can be transmitted.

Ligands are the keys that fit in a specific receptor “lock”. They can be agonistic or antagonistic.

Nature often makes use of multiple ligand/receptor couples to enable the multivalency, strength in numbers, principle. Through multivalency, single interactions can be weak, to prevent random onset of signal pathways. Only when a certain threshold of signals are reached, an interaction is stable enough to start downstream signaling.

Targeting is the concept of placing ligands on materials to guide their directed transport in our body. This will highly reduce drug toxicity and dosing, as ideally all material gets to the right place.

However, targets are often present at many cell types, and one can make use of the density as extra selectivity parameter, and engineer super-selective targeting materials.

Precise control over ligand geometry allows to engineer minimal super-selective materials with only 6 ligands, this is defined as *multivalent pattern recognition*.

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Conclusion

Every drug has its own circulation kinetics and life time, materials can be used to change this.

Devices can ensure controlled continuous release through active dosing or through passive degradation

When materials are used, double (or more) time scales are involved: circulation / uptake of material, degradation / release, molecular interaction of drug / mRNA, biological response, duration of the full cycle

Most of the current drug release systems are lipid nanoparticle formulations for very toxic drugs or for

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Exercises

[1] What is multivalency and why is it used in many natural interactions?

[2] Explain super-selectivity. How would you design a nanoparticle drug delivery system that uses this principle to deliver DOX to cancer cells that have the Her2 receptor?

[3] You have a headache and want to take a dafalgan. The prescription tells you you can maximally take 1g every 6 hours. You have 1 pill of 1gram and 2 of 500mg. Draw the distribution profiles if you

a) Take the 1g
b) Take the 1g and both 500mg at the same time
c) Take a 500mg and 2 hours later another 500mg
d) Take a 500mg and 4 hours later another 500mg
e) Take the 1g and 2 hours later both 500mg together.

What is the best strategy to get rid of your headache the longest?

[4] Free DOX is very toxic to cells. You discovered a small molecule that will keep DOX in its crystalline state. Explain the impact of your discovery in context of cancer medicine.

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