The power of sugar and amino acid to deliver therapeutic drugs

Never Stand Still

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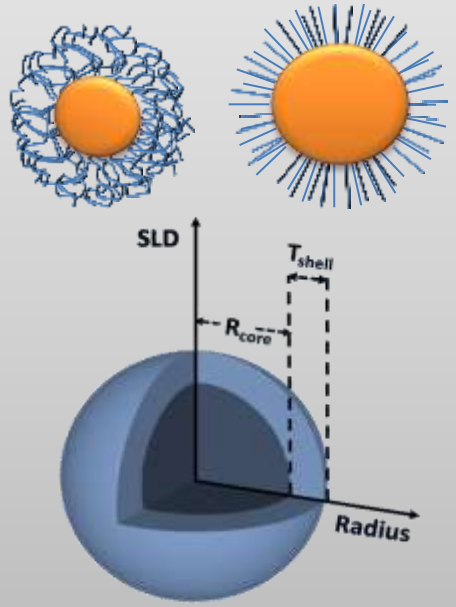
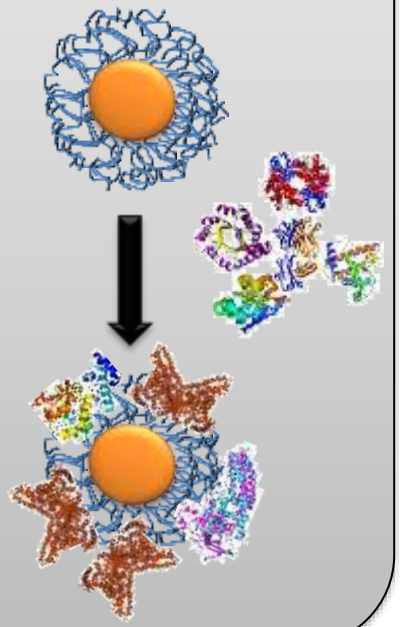
Considerations in nanoparticle design

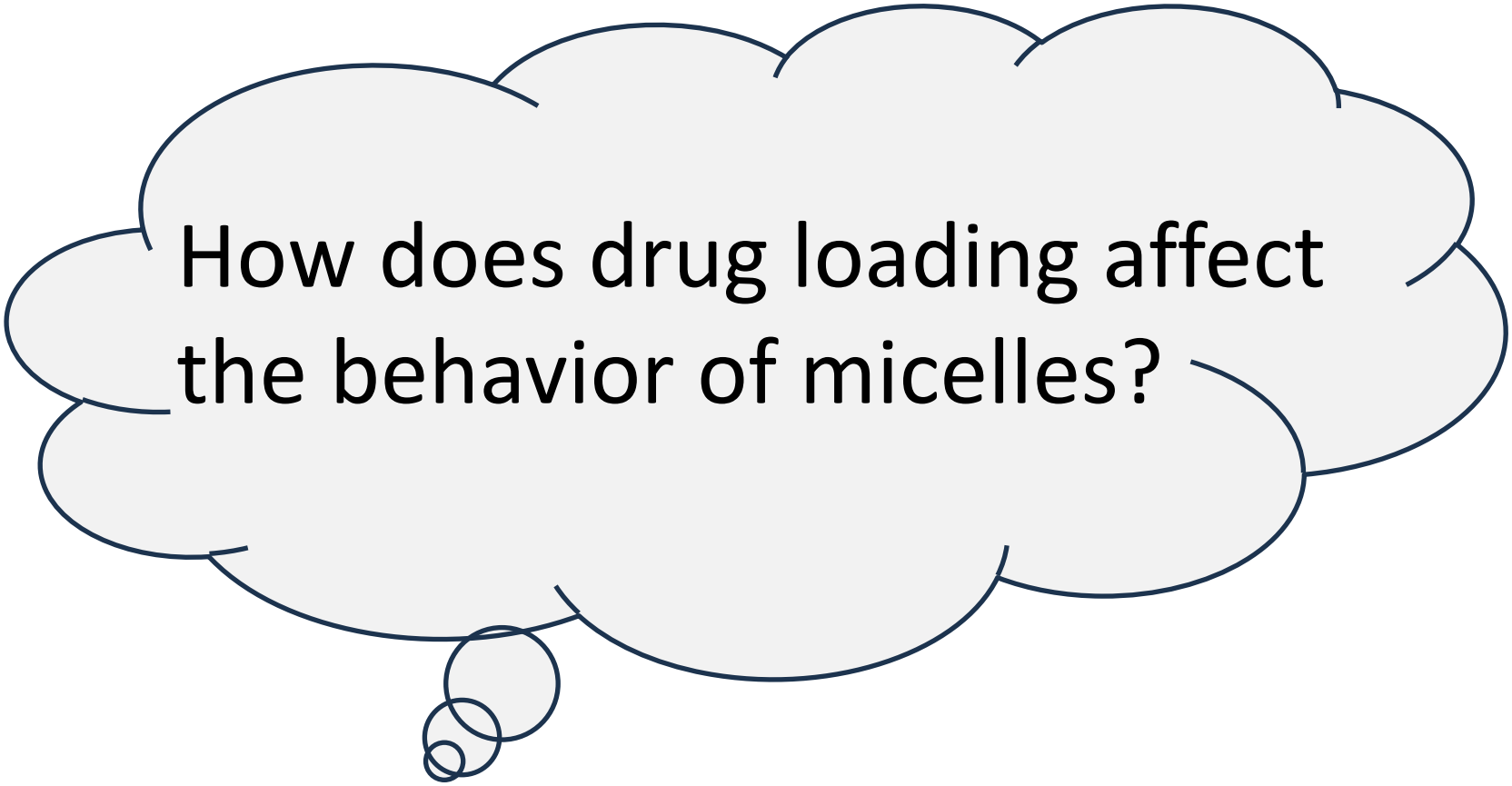
Understanding nanoparticle assembly



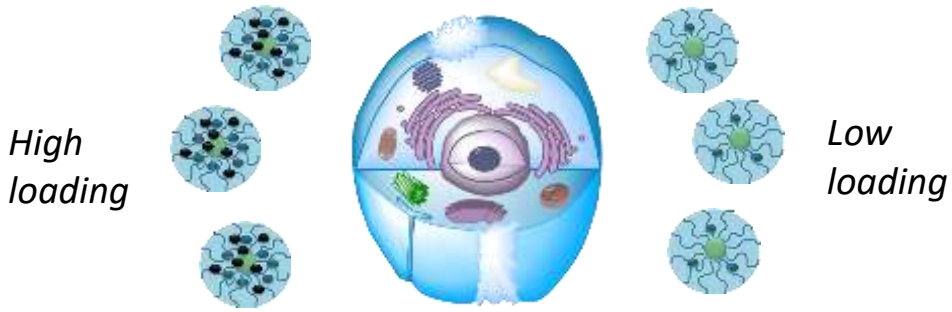
Analyzing the chemistry-biology interface



The relationship between drug and glycopolymer


How does drug loading affect the behavior of micelles?

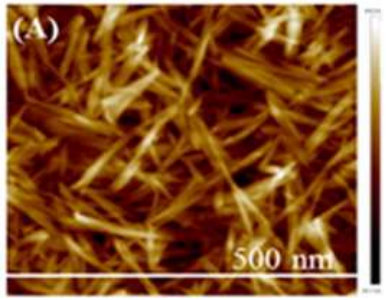
Is it more efficient to have many drug molecules per nanoparticle?



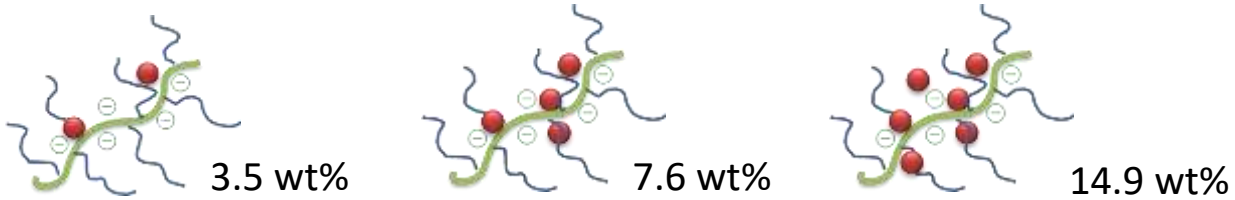
✓The cell cannot distinguish between high and low loading nanoparticles -> more drugs are delivered in high loading nanoparticles

Hypothesis: More drugs per nanoparticles should be better!

Higher loading, better activity! An example

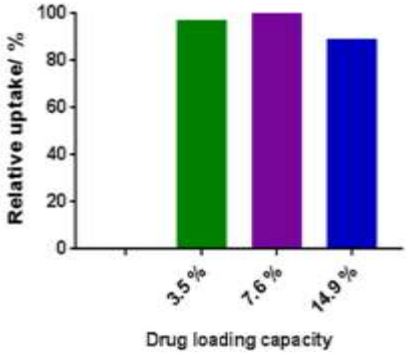


PHEA coated nanocellulose



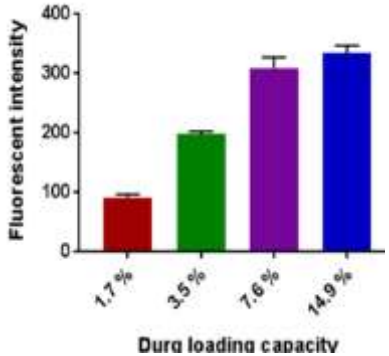
incubated with MCF-7 cell lines at a constant nanoparticle concentration

Nanoparticle uptake



Uptake is independent from loading

Doxorubicin uptake

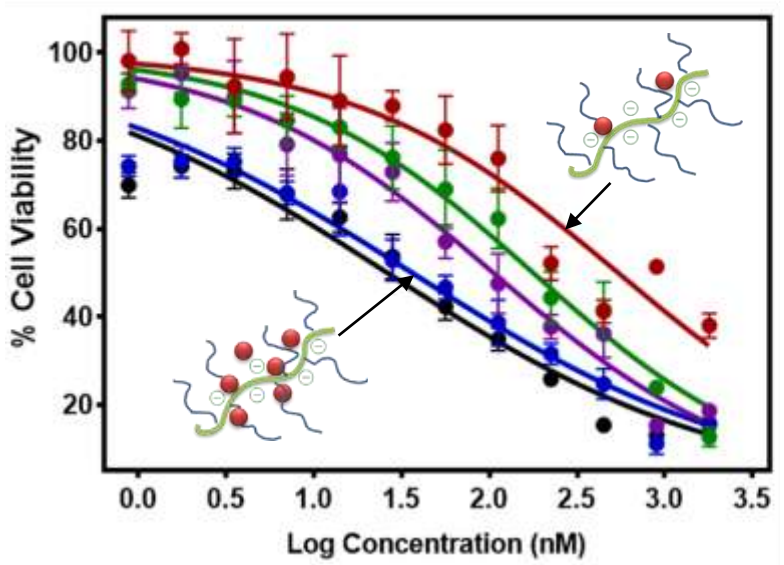


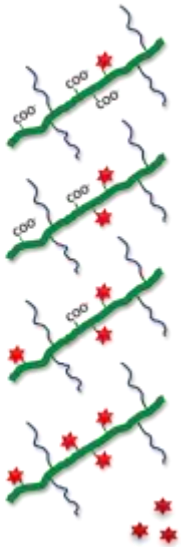
More drug is delivered into the cells

YeeYee Khine

UNSW SYDNEY

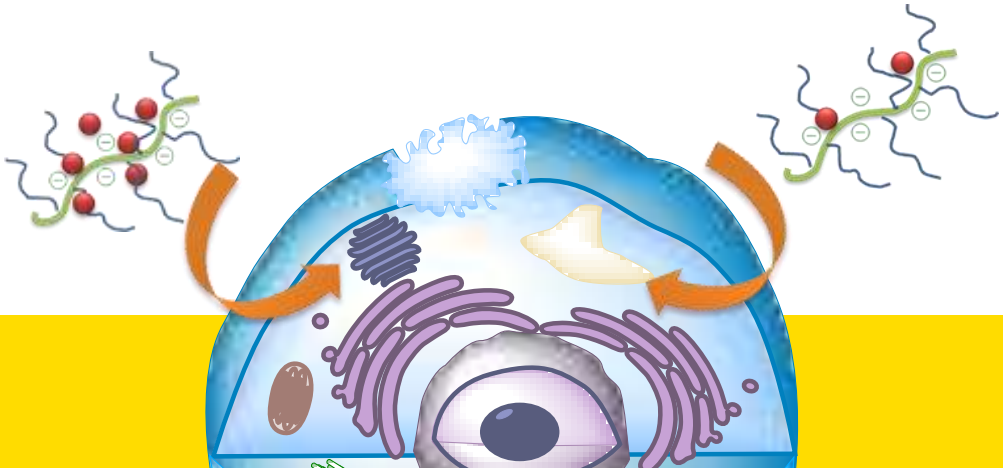
Increased drug loading leads to increased toxicity





Drug loading capacity (%)	IC_{50} (nM)
1.7	541.9
3.5	177.7
7.6	105.3
14.9	36.1
DOX.HCl	26.1

Cytotoxicity

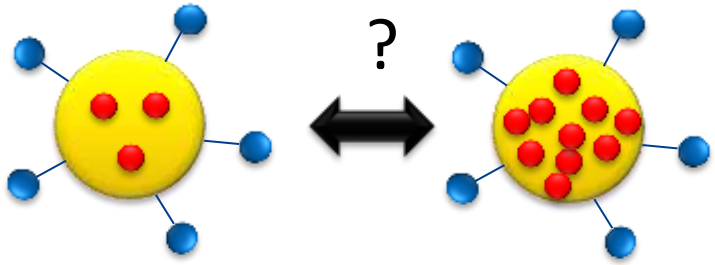


Same rate of uptake, but more drug is delivered in the high loading nanocarrier -> higher toxicity

UNSW SYDNEY

The effect of drug loading on cellular uptake

The more, the better?

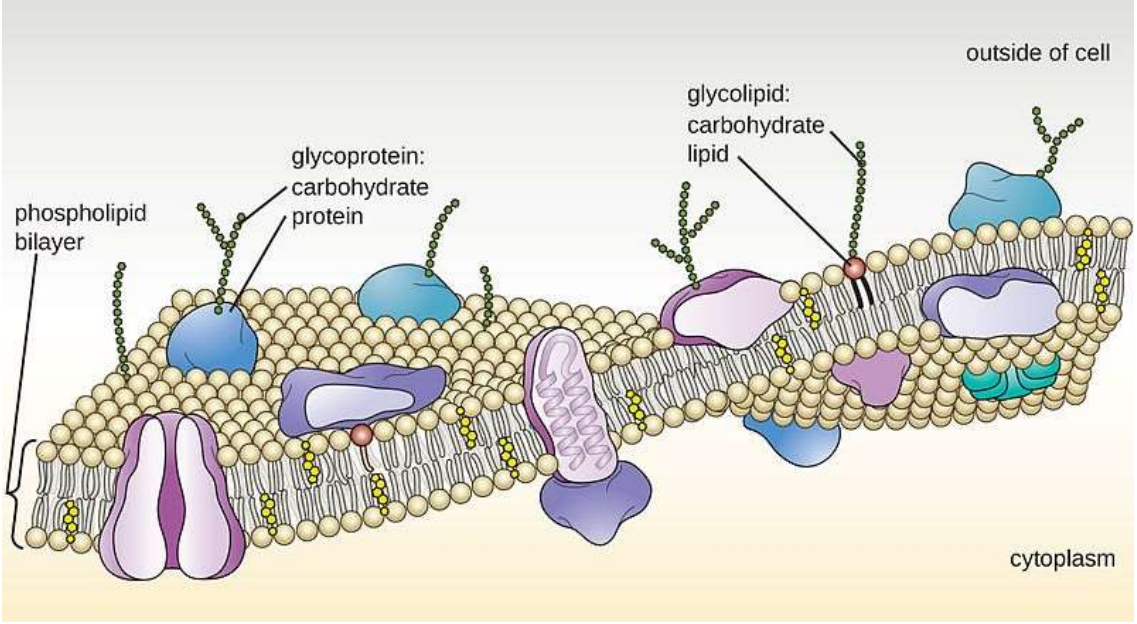


- ✓ More drug loading of Doxorubicin led to higher toxicity
- ✓ The cell cannot distinguish between different drug loading capacity and internalize all nanoparticles at the same rate
- ✓

Does this concept that applies across all systems? Even to glycopolymers?

Carbohydrate and polysaccharides in the body

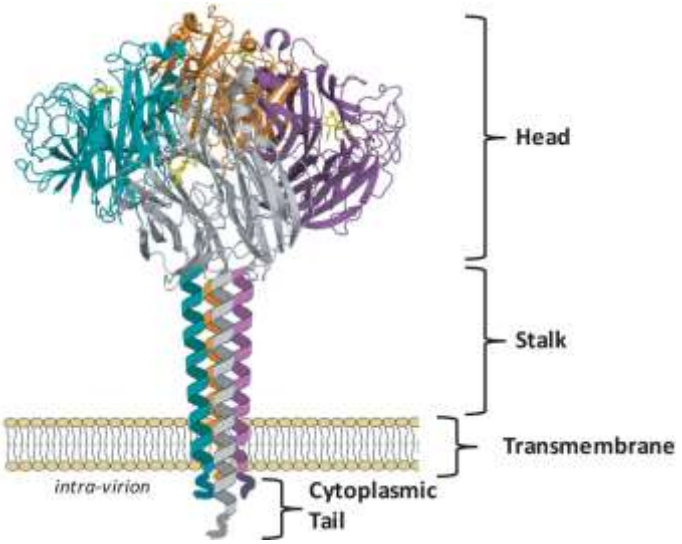
Energy source
Regulate cell processes
Assists in communication between cells and cell and invaders (bacteria)



Lectins: Sugar-binding proteins

bind with carbohydrates reversibly but with high specificity
Latin: legere (to select)

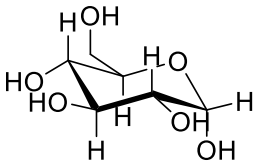
Simple lectins:
Mostly plant lectins



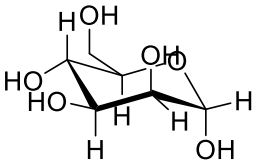
Mosaic Lectins: very diverse in structure
Influenza Virus Hemagglutinin
Asialoglycoprotein (specific for galactose)

Macromolecular Assembly Lectins:
Common in bacteria such as bacterial adhesion lectins

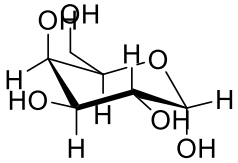
Glycopolymers: Synthetic polymers with pendant carbohydrate (sugar)



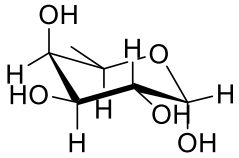
Glucose



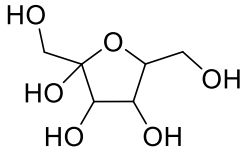
Mannose



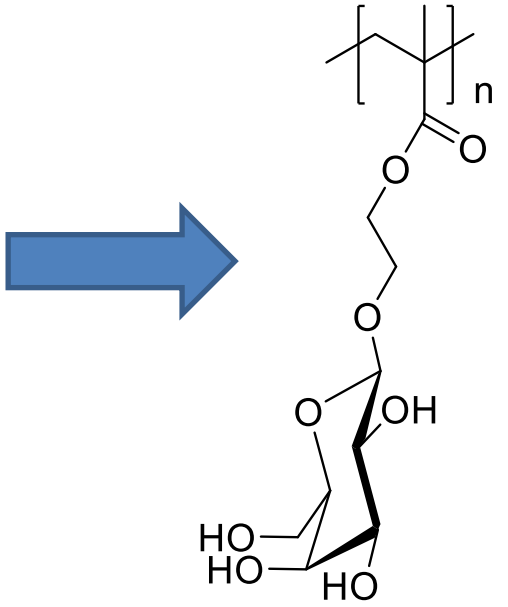
Galactose



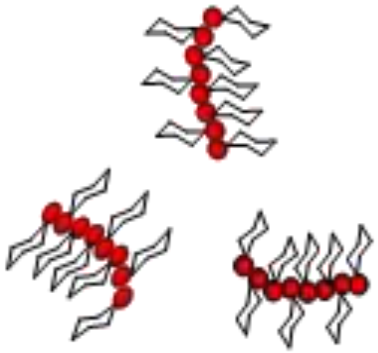
Fucose



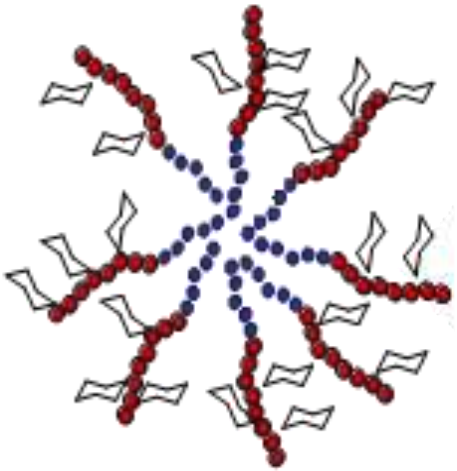
Fructose



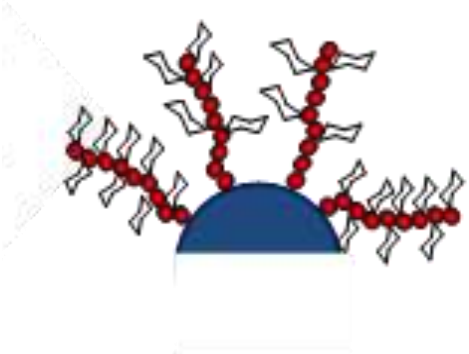
Glycopolymers as multivalent ligand



Linear Glycopolymers

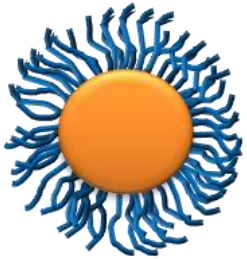


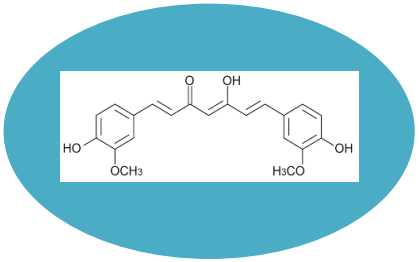
Block copolymers, self-assembled into micelles



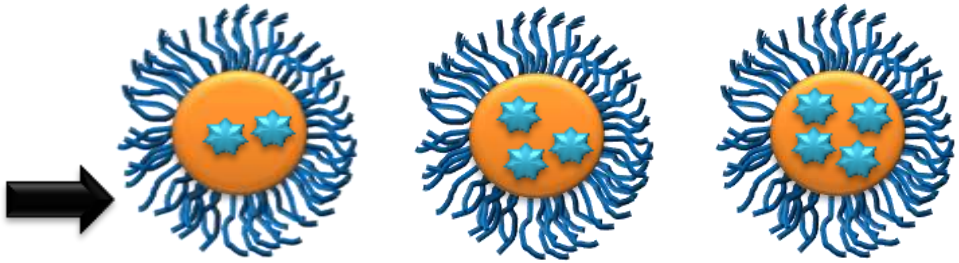
Glycopolymers, grafted onto nanoparticles (e.g. Au)

Effect of drug loading on performance of micelles

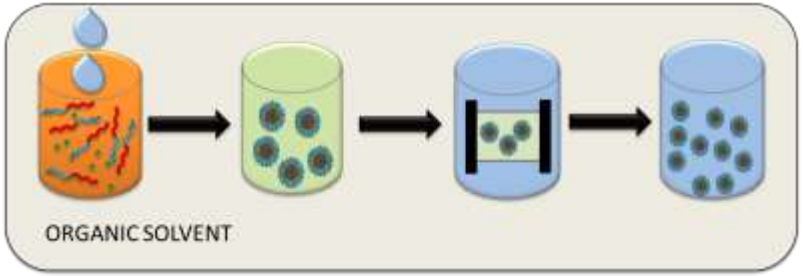




Curcumin



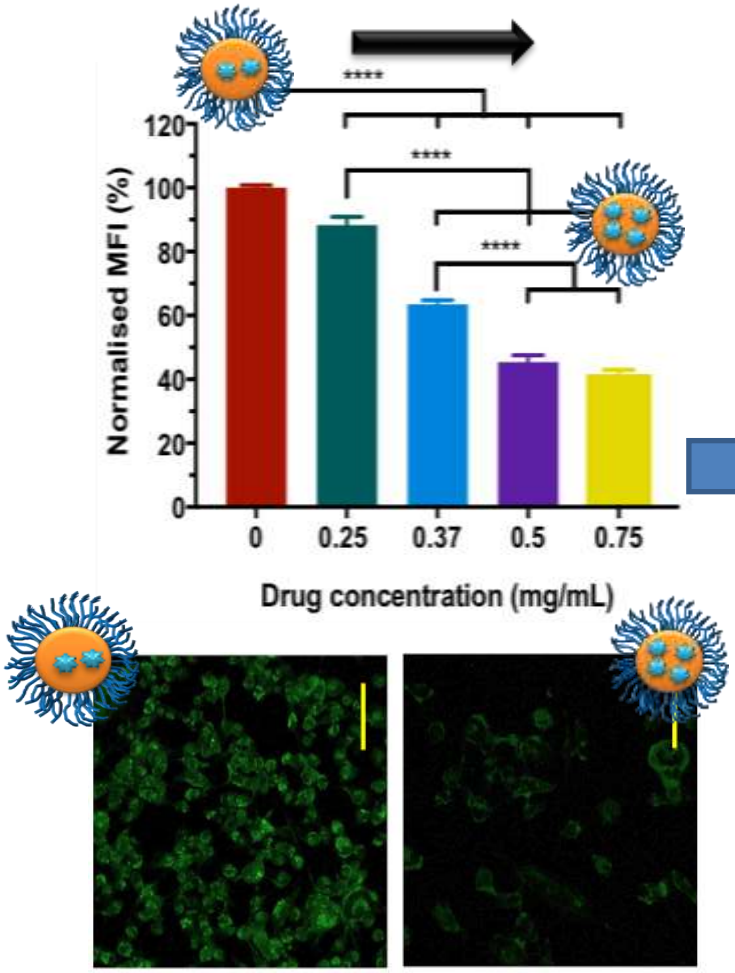
Increasing amount of drugs!

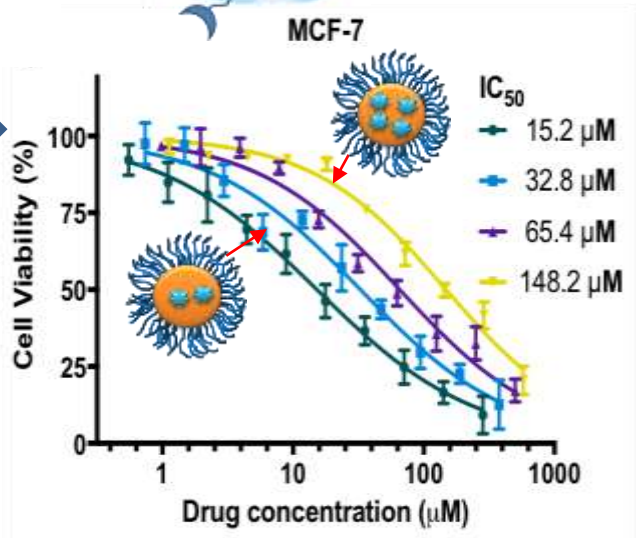


Is it better to have more drugs per nanoparticles?

Cheng Cao

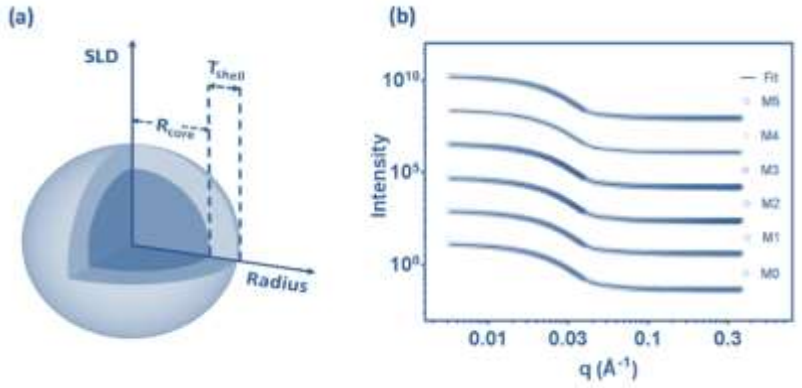
More drugs -> the cancer cells reject the particle

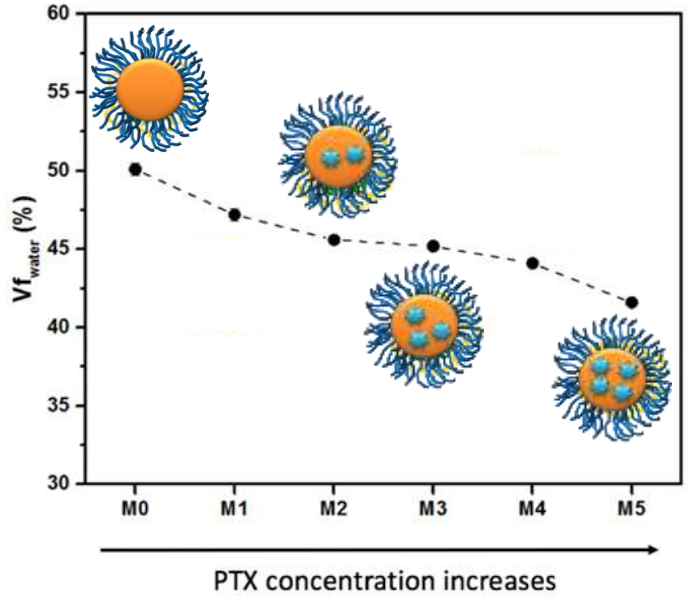




Less uptake-less toxicity

SANS Analysis to understand this unusual activity



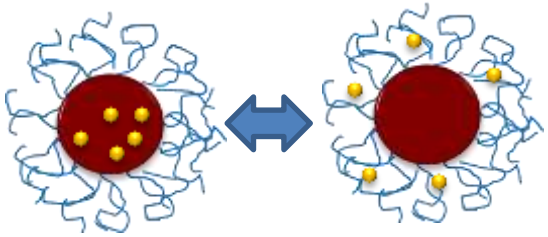


Shell is less hydrated

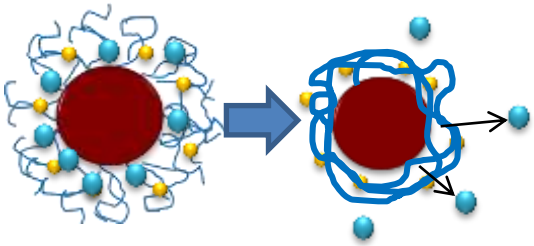
Small angle scattering as an important tool to identify detailed structure

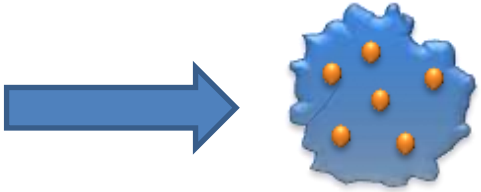
Australian Synchrotron

The drug is in the shell



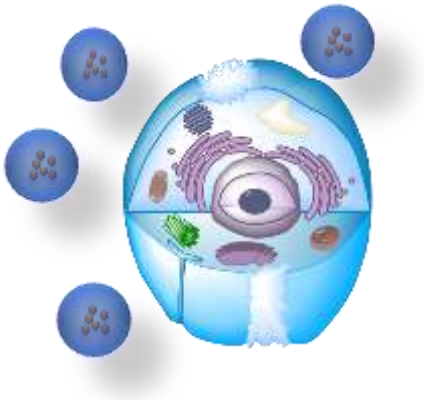
Increasing amount of drug dehydrates shell



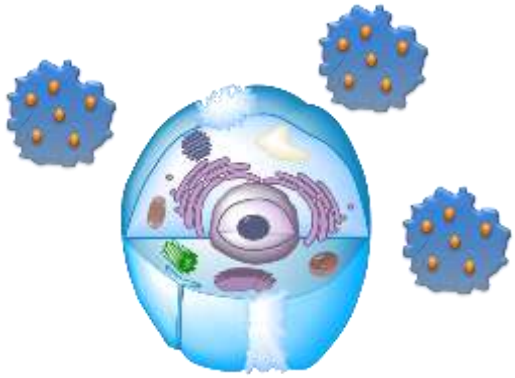


Dehydrated with drugs sitting on the outside

The drug diffused into the shell, which led to dehydration?
The cells rejected the nanoparticles!



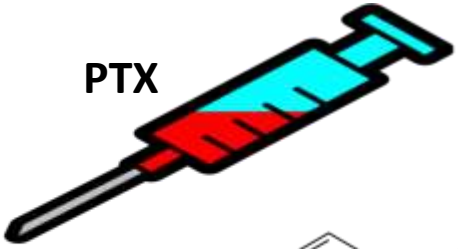
Good uptake



The cell rejects the nanoparticle

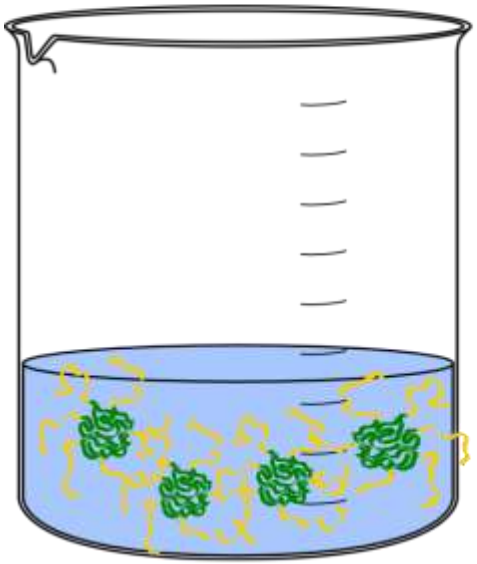
Unique to curcumin?
What about other drugs?

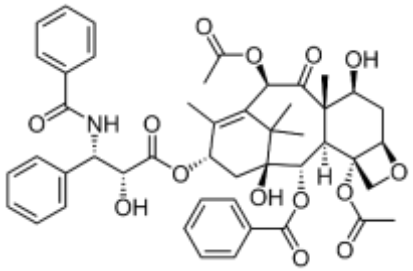
Same polymer, this time paclitaxel



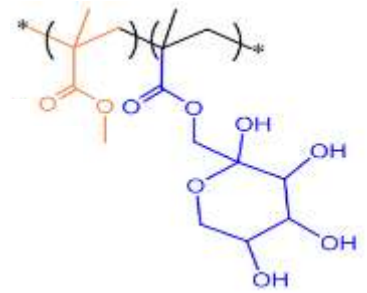
Paclitaxel

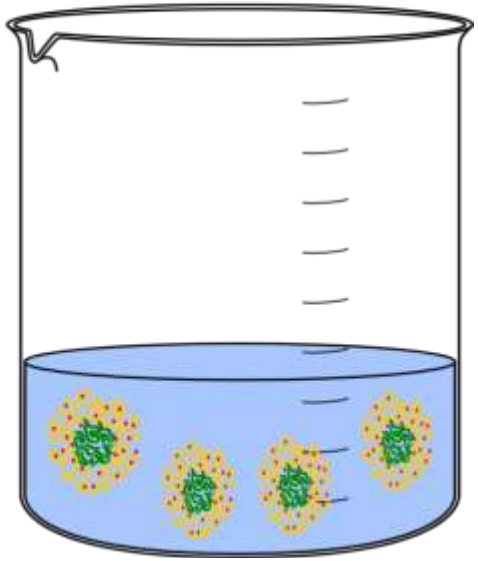
Antineoplastic agent; Works for many cancers, such as breast cancer, pancreatic cancer, cervical cancer, bladder cancer, and head and neck cancer…



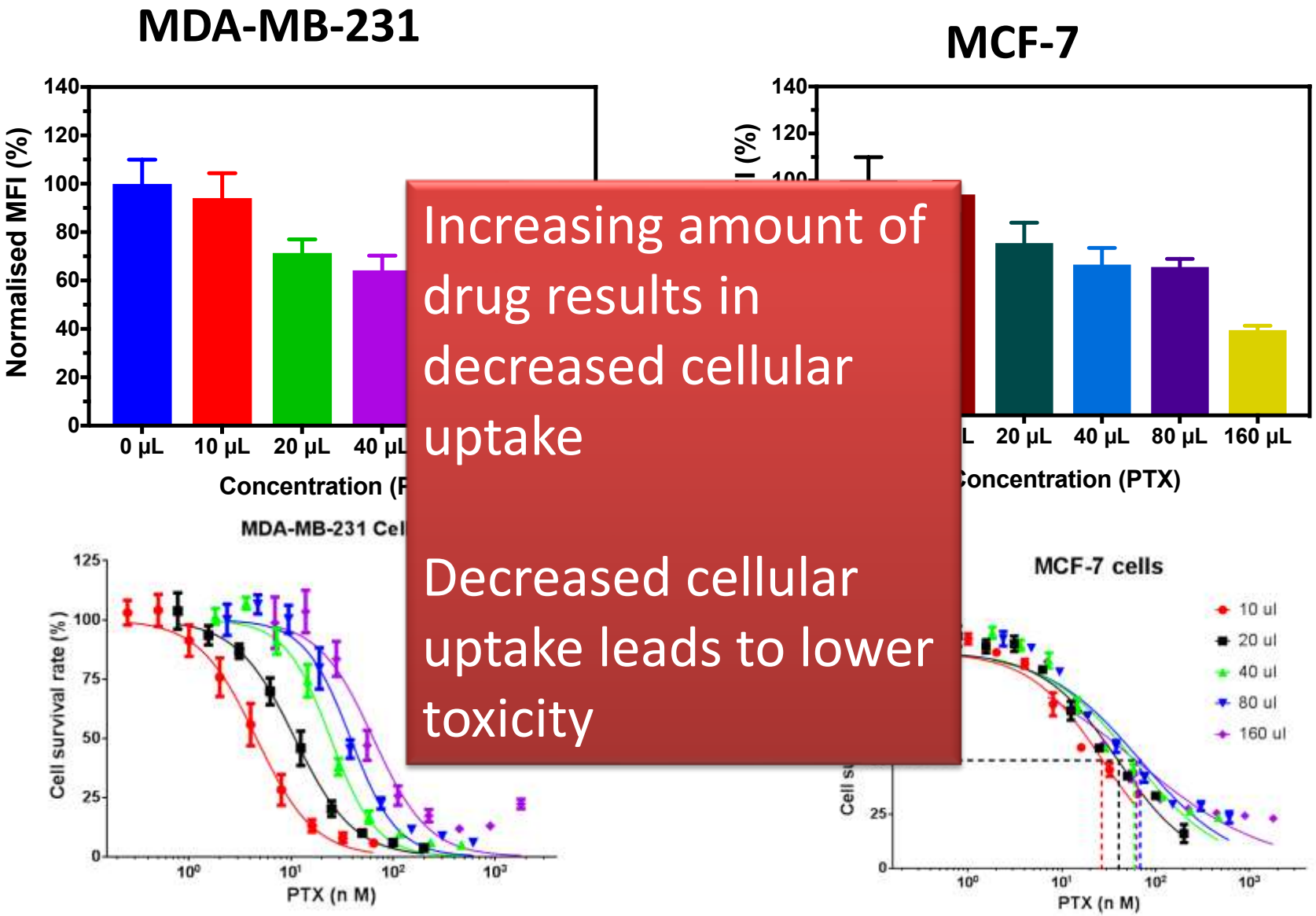


Drug loading



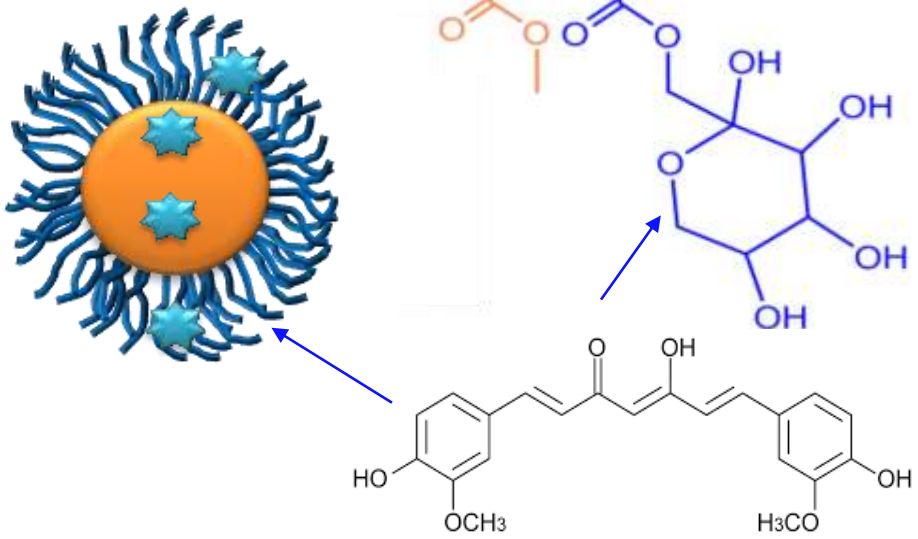


Size ~ 25 nm

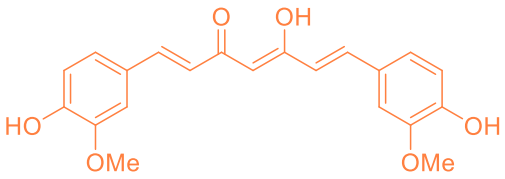

MDA-MB-231
MCF-7
Normalised MFI (%)
140
120
100
80
60
40
20
0
0 µL
10 µL
20 µL
40 µL
20 µL
40 µL
80 µL
160 µL
Concentration (PTX)
Increasing amount of drug results in decreased cellular uptake
Decreased cellular uptake leads to lower toxicity
MDA-MB-231 Cel
Cell survival rate (%)
125
100
75
50
25
0
PTX (n M)
MCF-7 cells
10 ul
20 ul
40 ul
80 ul
160 ul
PTX (n M)

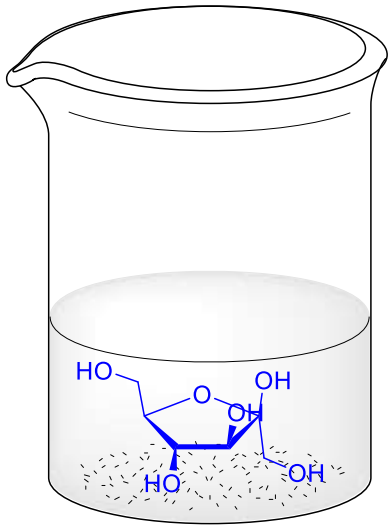
Nanoparticles coated with PEG or similar neutral polymers show better activity with higher drug loading! This is not the same with glycopolymers!

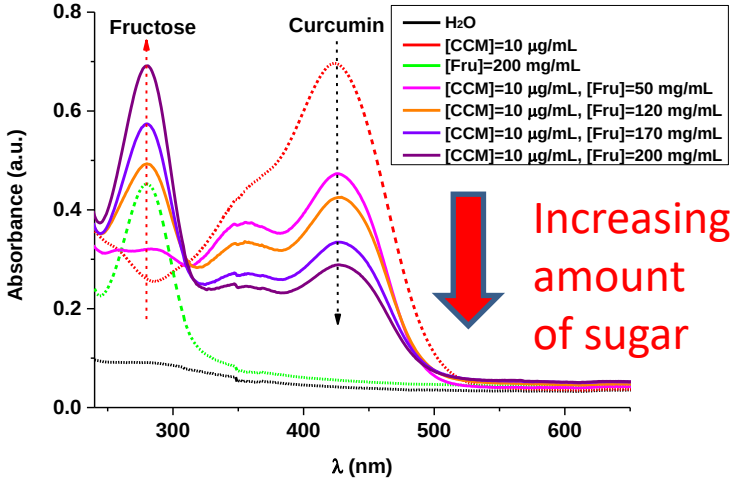
Why is the glycopolymer-drug interaction so complex?

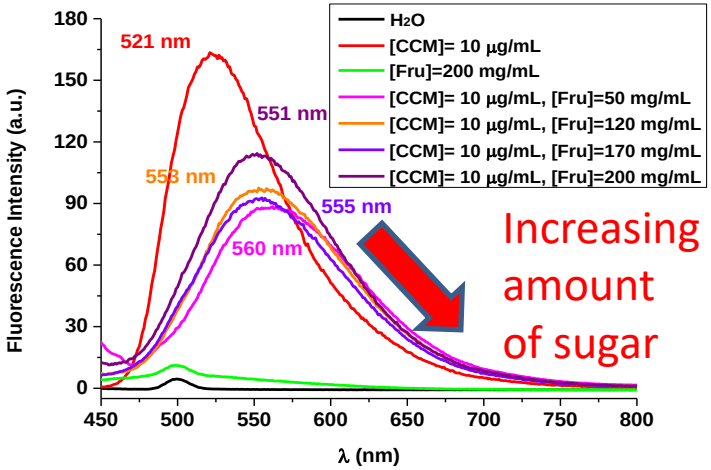


Mixing of sugar and curcumin



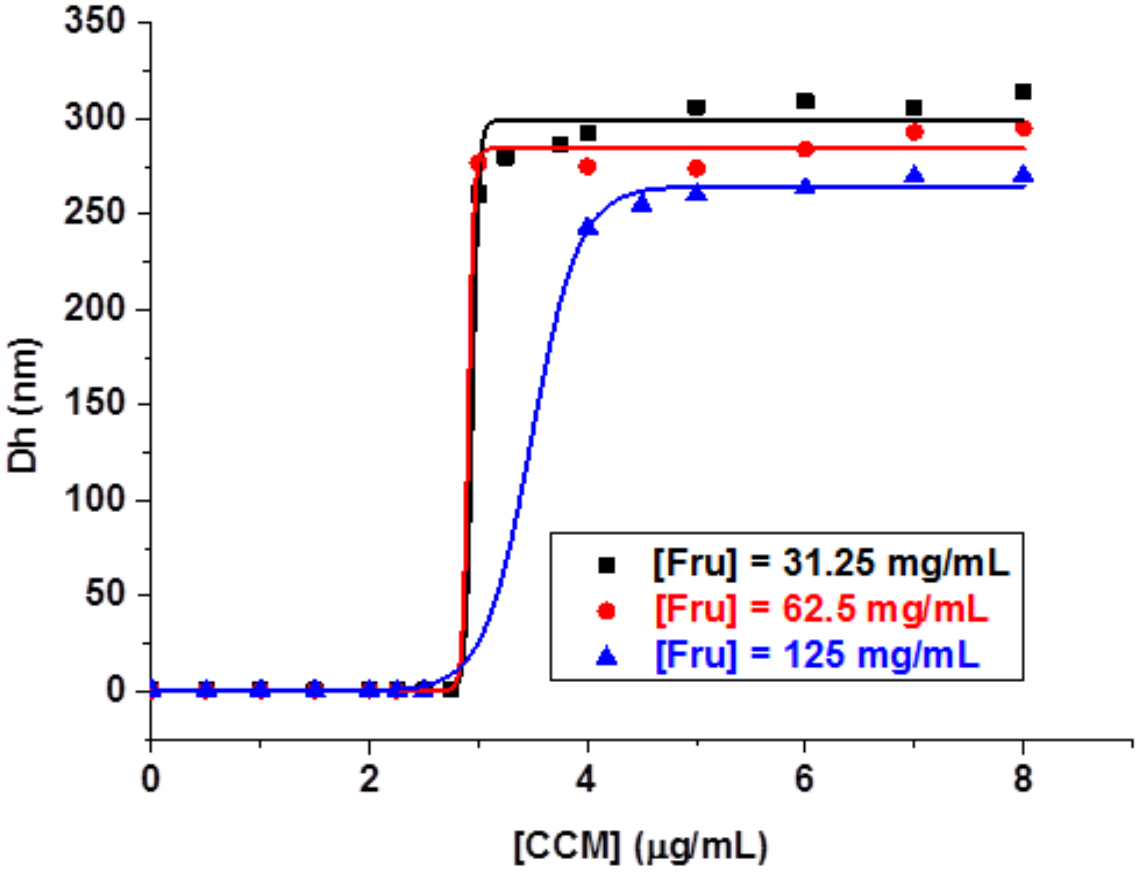


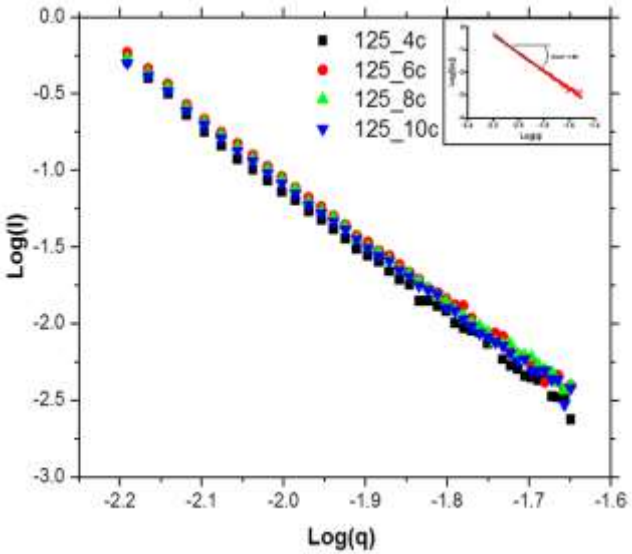




Change of environment with increasing fructose concentration

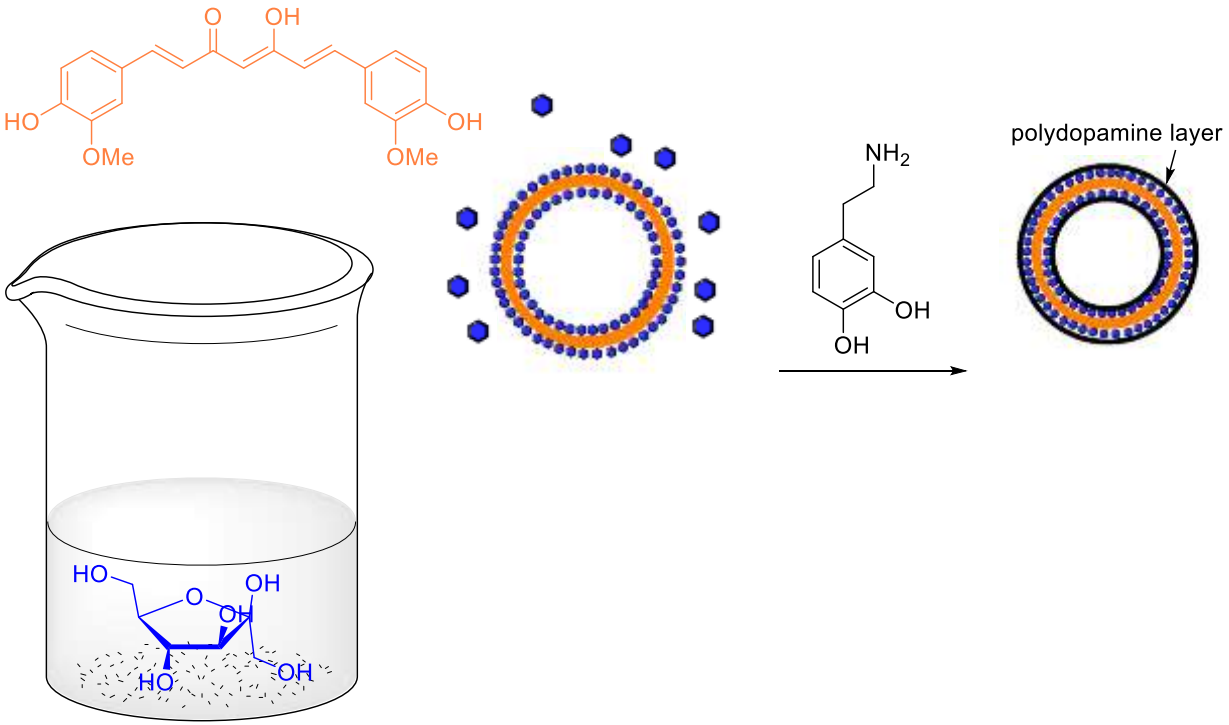
DLS analysis of Water-Curcumin solution





Formation of vesicle-like structures

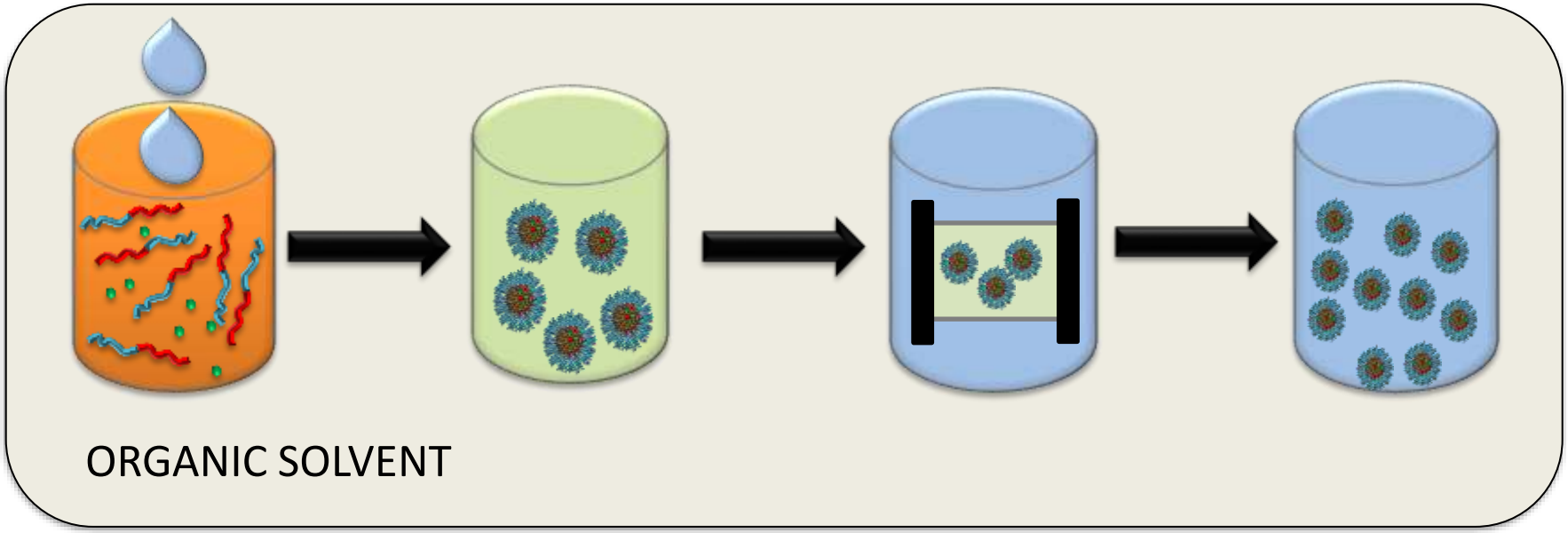
Stabilization of capsules with dopamine for analysis



Mixing sugars with curcumin results in the formation of nanocapsules -> strong H-bonding between water-soluble sugar and hydrophobic curcumin

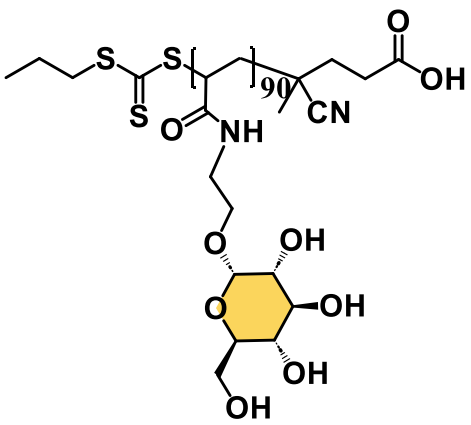
If glycopolymers bind to drugs, can they be used to deliver drugs?

Challenges with drug delivery



Multi-step
Use of organic solvents
Encapsulation determined by drug-polymer interaction-> often low

Wishlist:



Drug

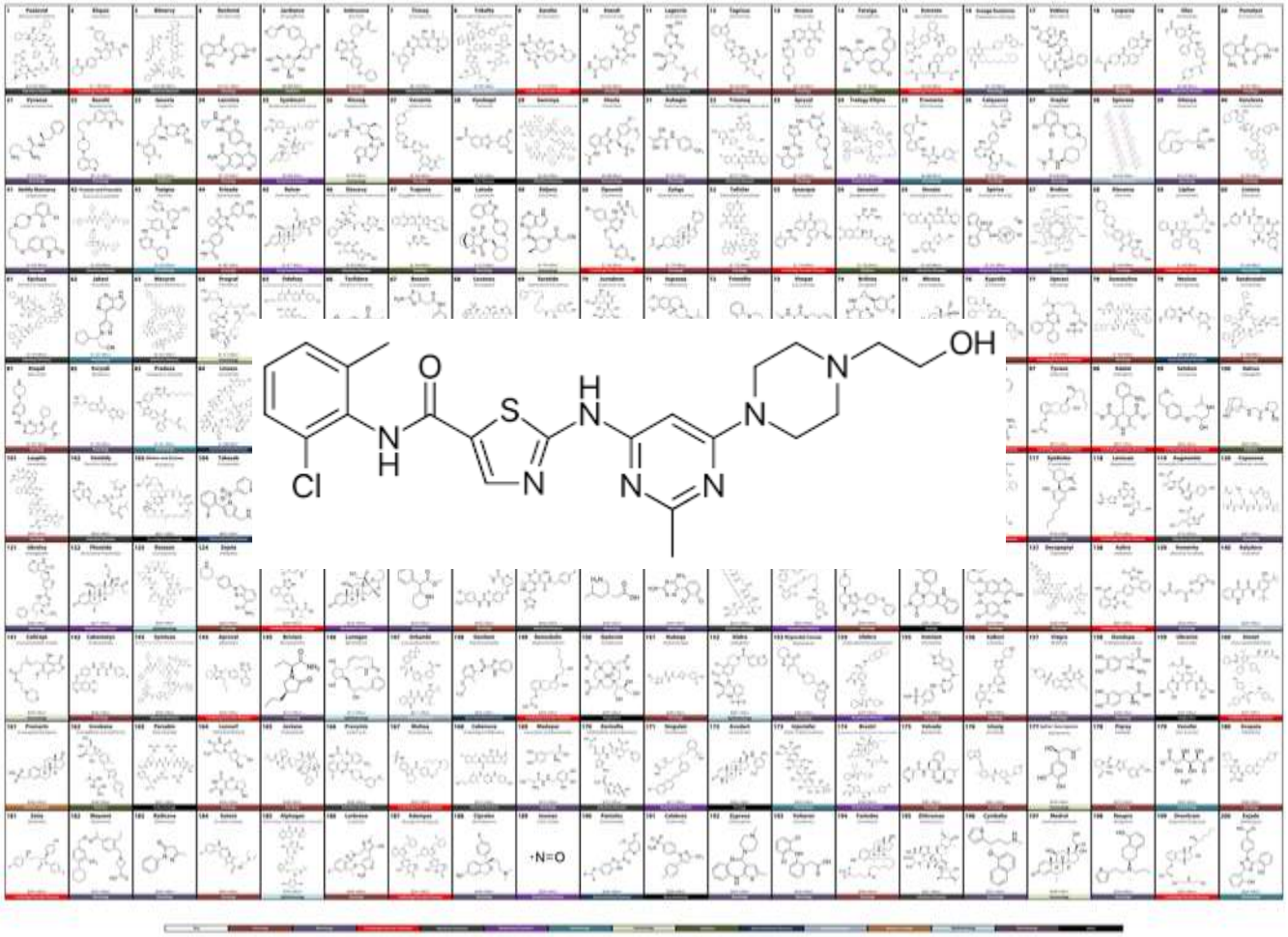
Mixing in water

mixing drug and drug carrier in aqueous solution
No organic solvent
No drug modification required
Solution can be used immediately

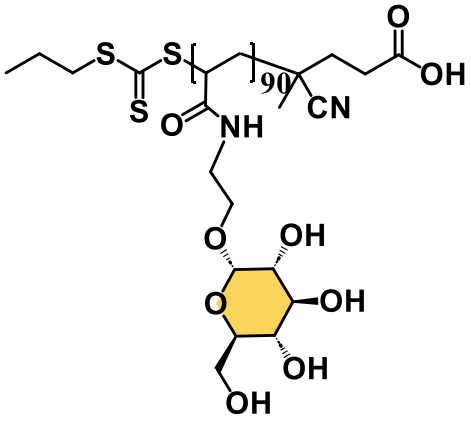
Linqing Tian

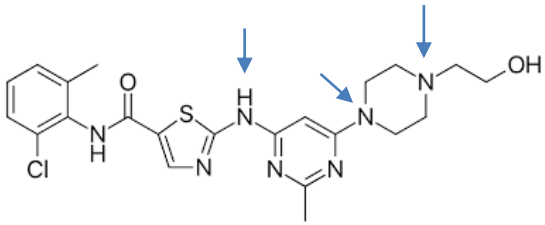
Top 200 Small Molecule Drugs by Retail Sales in 2022

Compiled and Produced by Ryan E. Williams from the Njarðarson Group (The University of Arizona)



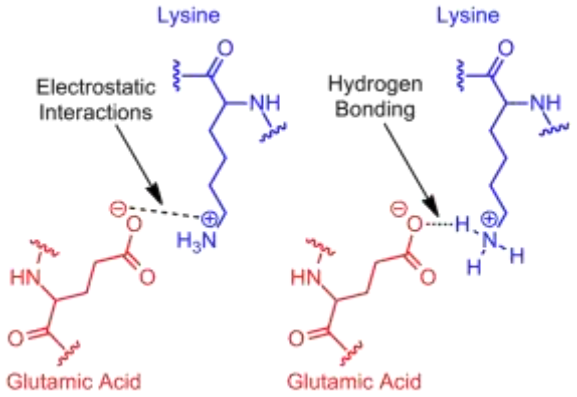
Can glycopolymers enhance the solubility of hydrophobic drugs in water?



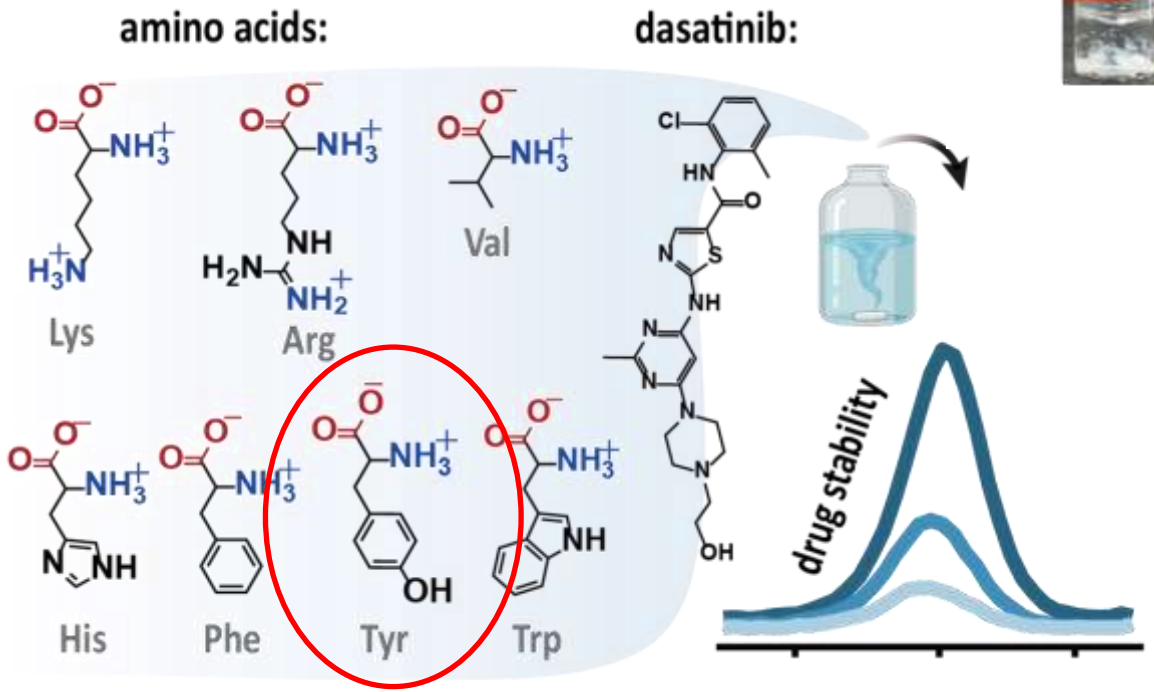


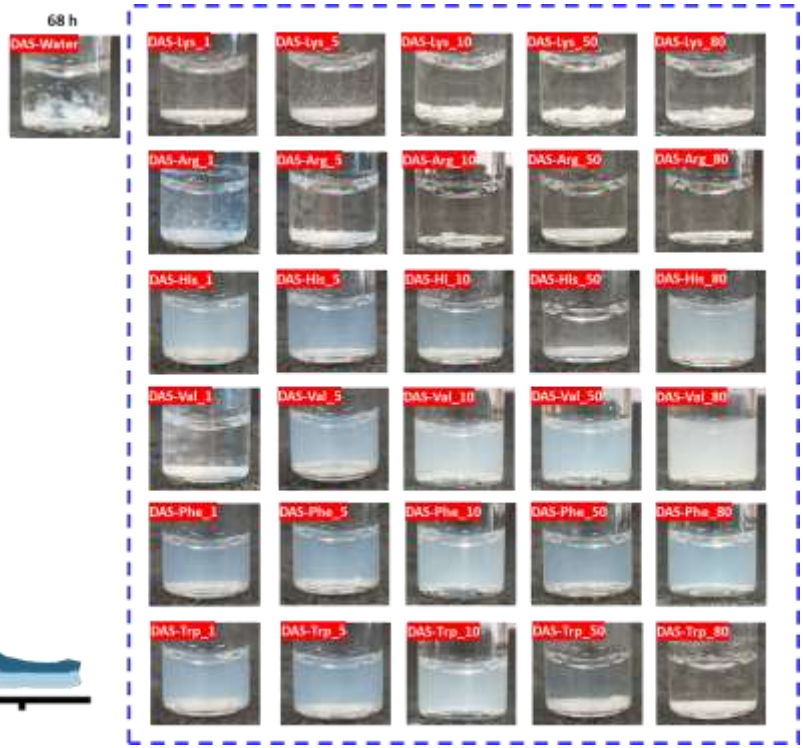
NO!

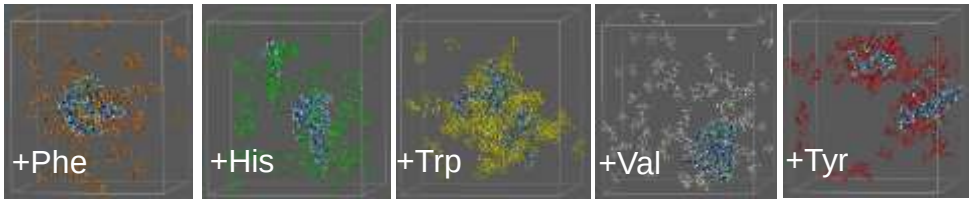
Enhancing interaction with strong H-bonding AND electrostatic interactions

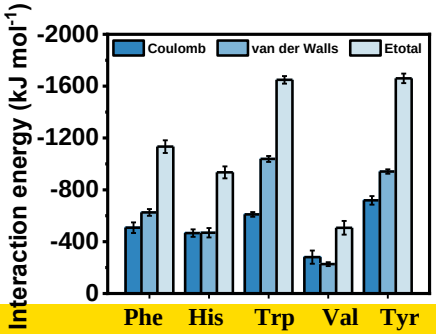


Which amino acid might have the best performance?

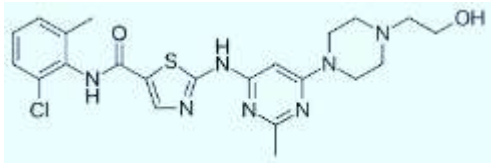


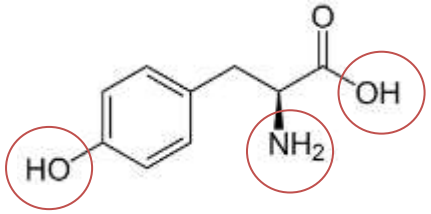




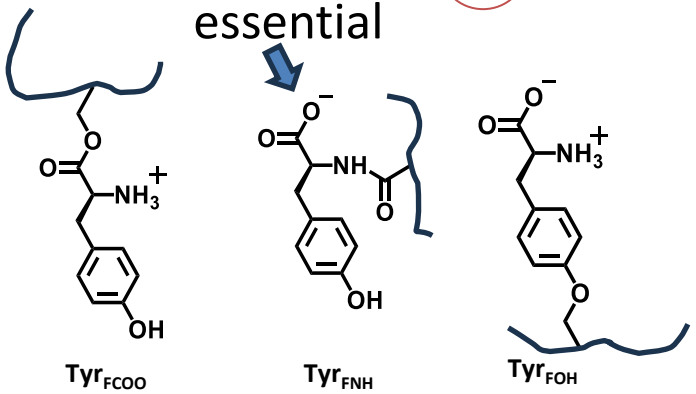


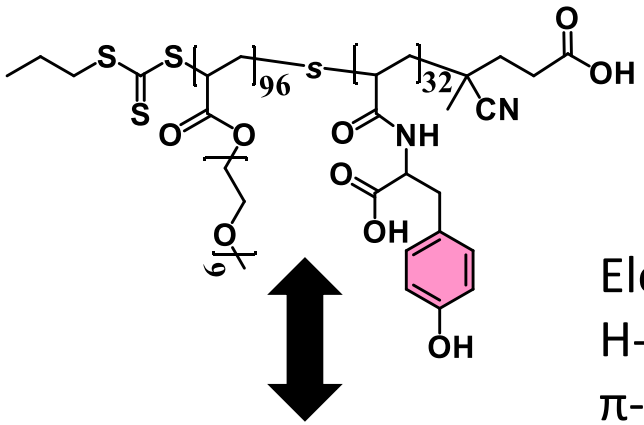
Copolymer with tyrosine to enhance interaction with dasatinib

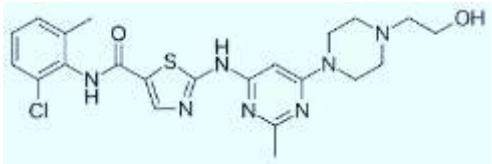




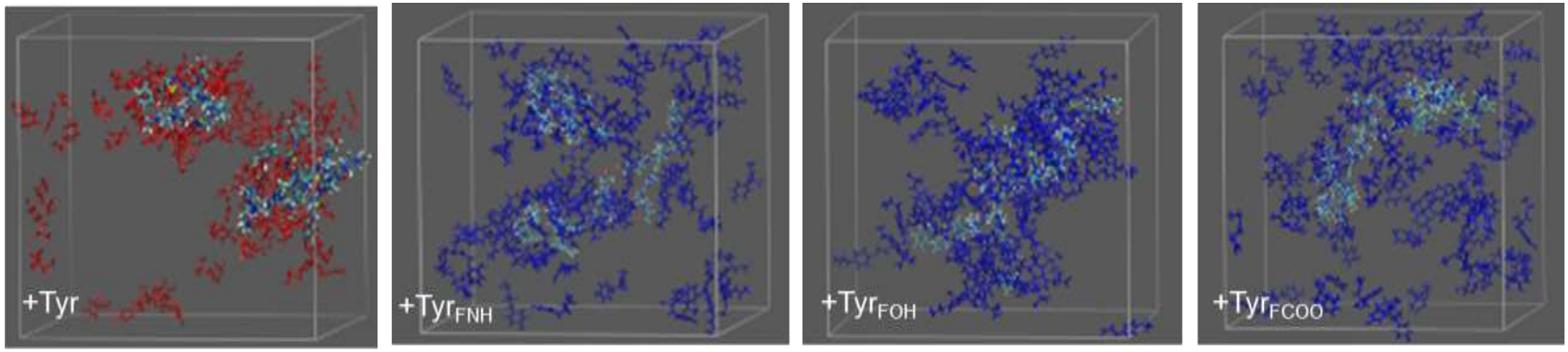
essential



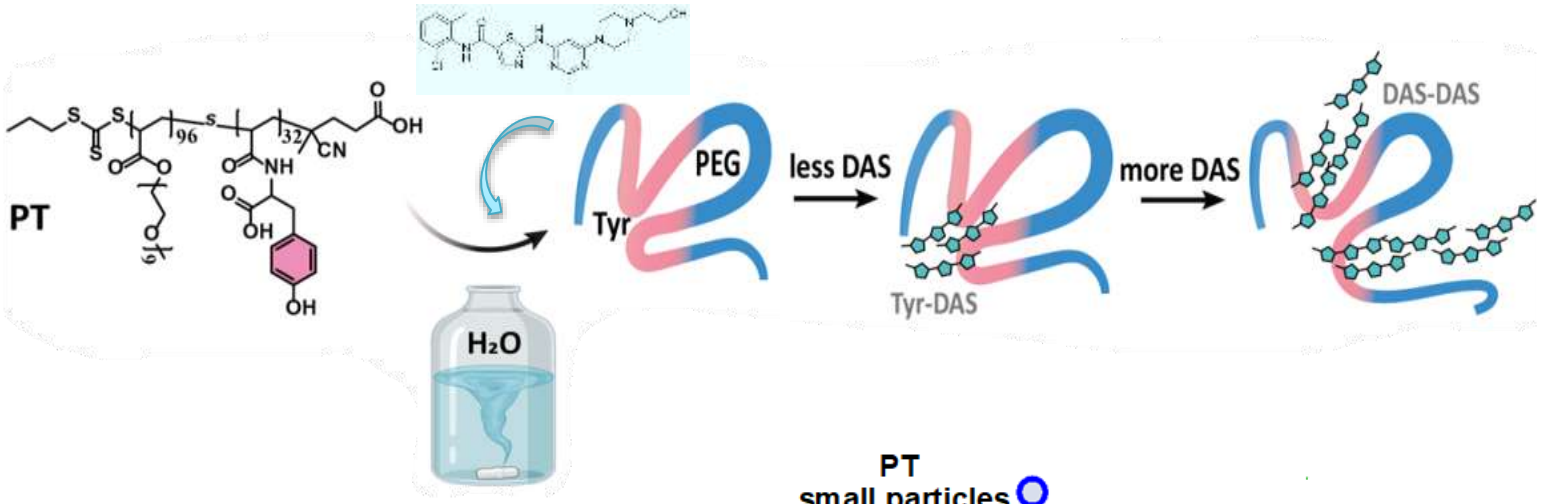




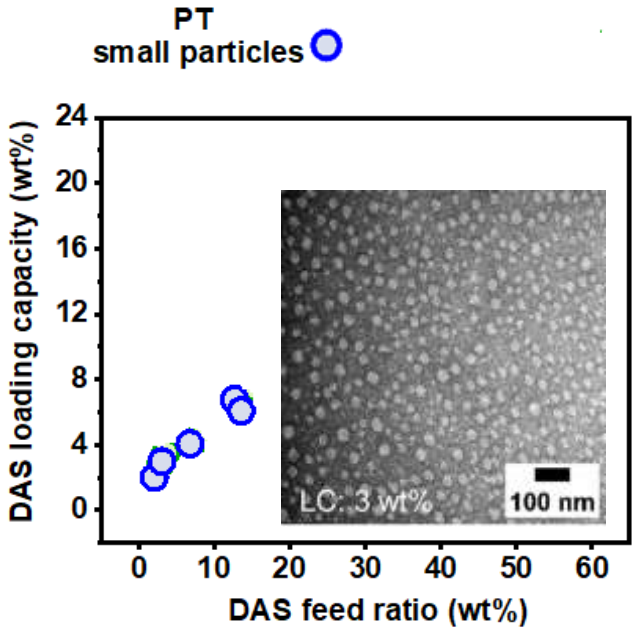
Electrostatic
H-binding
π-π- stacking



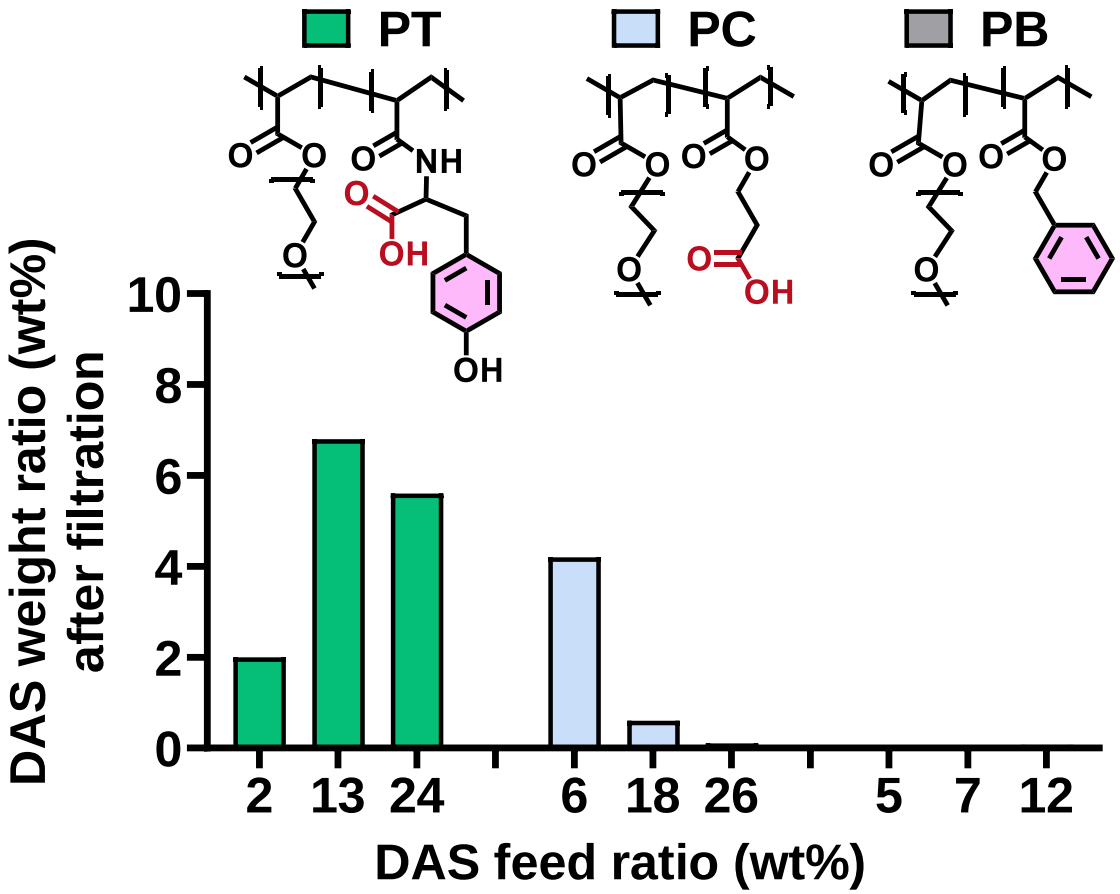
Direct dissolution of hydrophobic drugs



Polymer can help dissolve some DAS, nanoparticles are formed

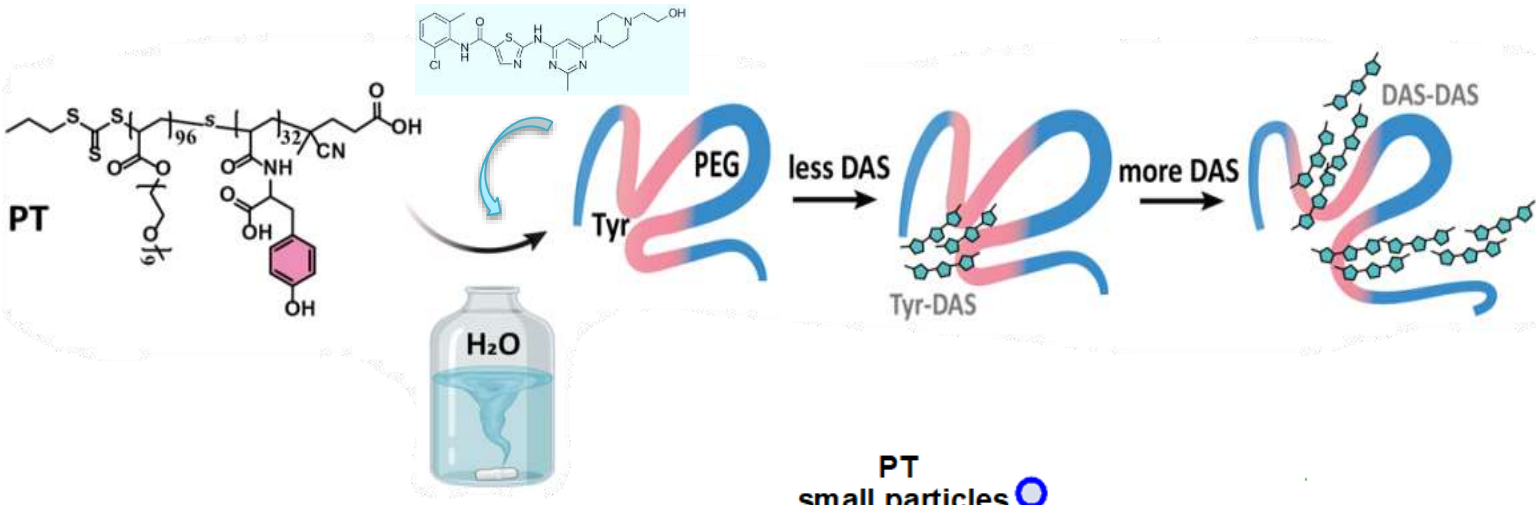


Is amino acid really essential?



No loading with COOH or phenyl groups only!

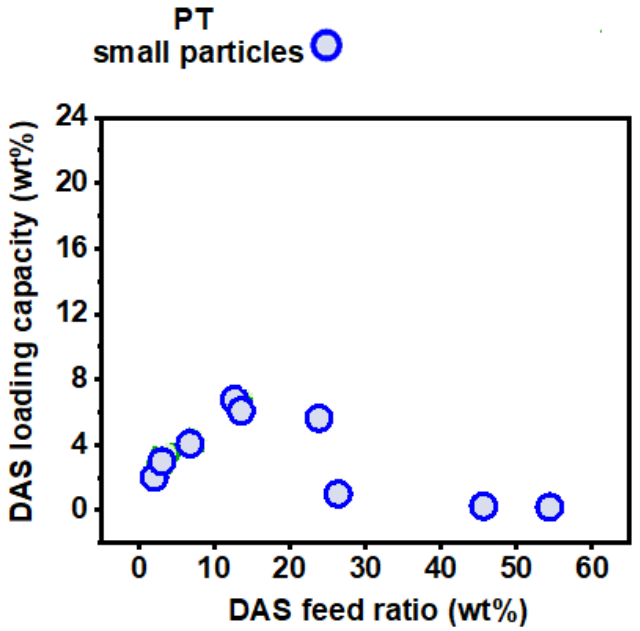
Direct dissolution of hydrophobic drugs



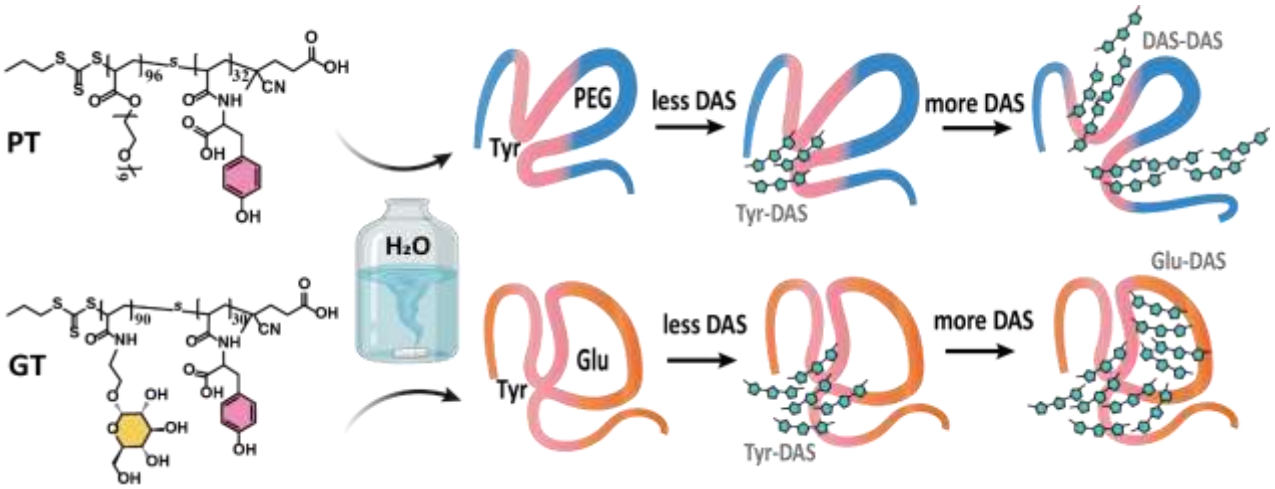
Polymer can help dissolve some DAS, nanoparticles are formed

HOWEVER: system collapses after adding 15wt% drug

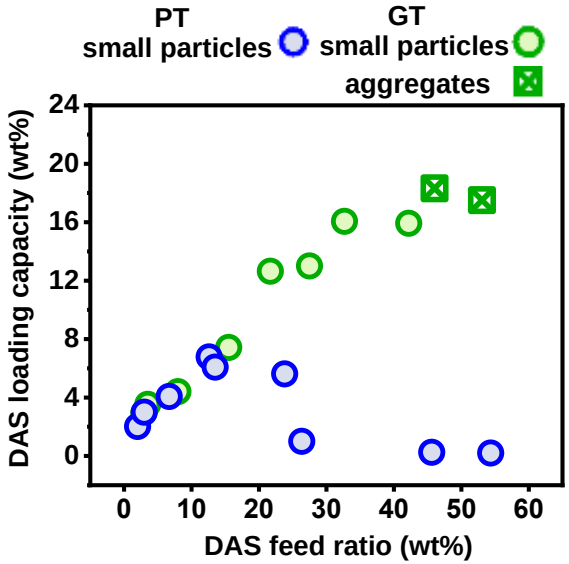
-> Drug precipitates



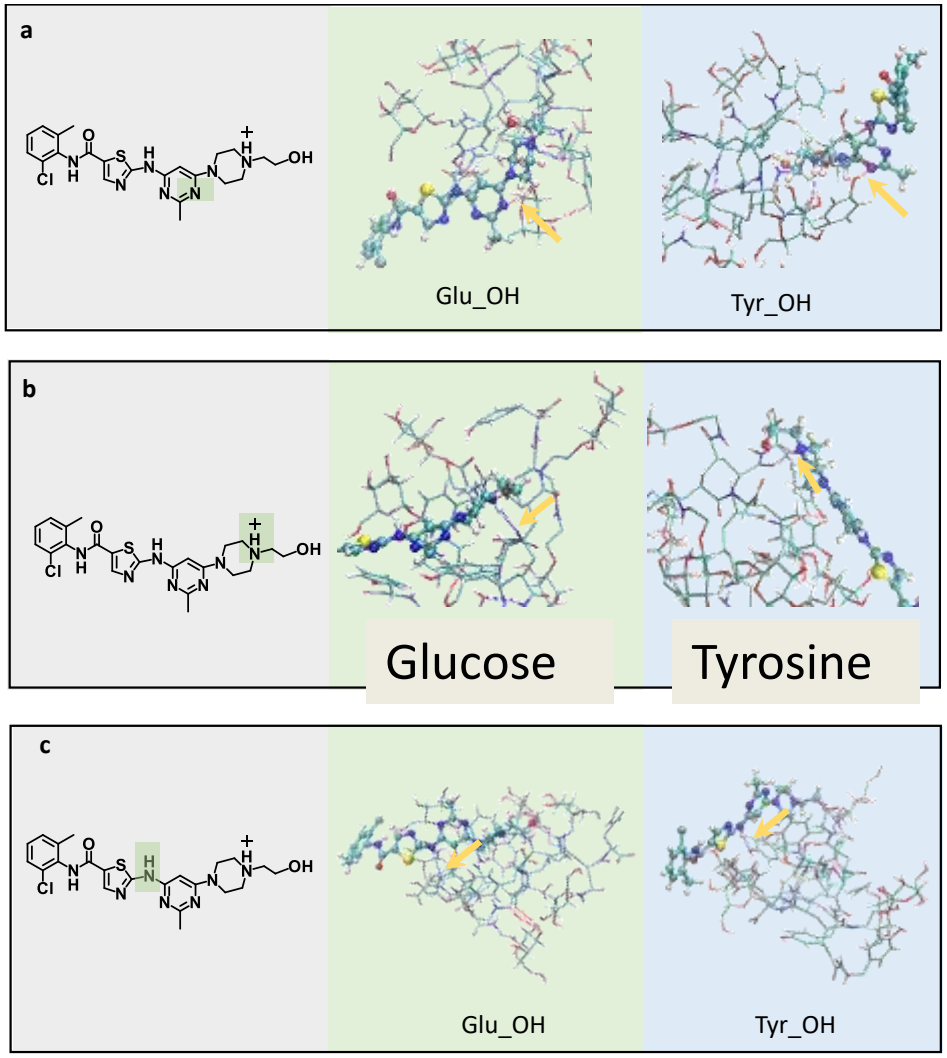
The power of sugar and amino acids



Solubility is enhanced

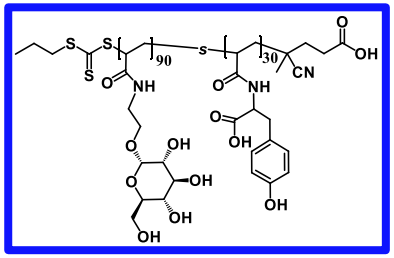


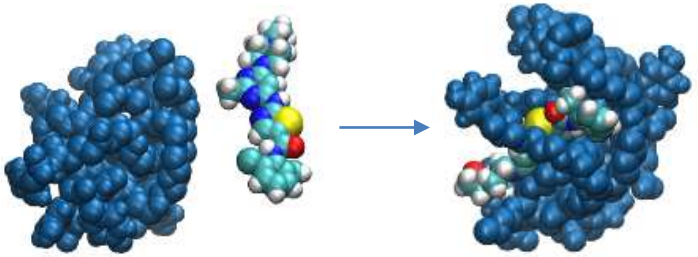
Sugar and amino acid working together

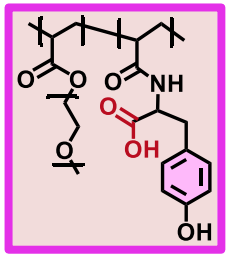


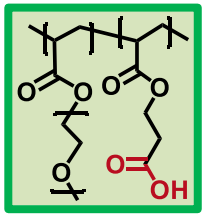
Different parts of the drug can for H-bonding to tyrosine and glucose

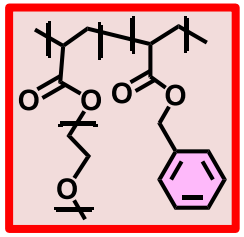
Interactions as seen by NMR

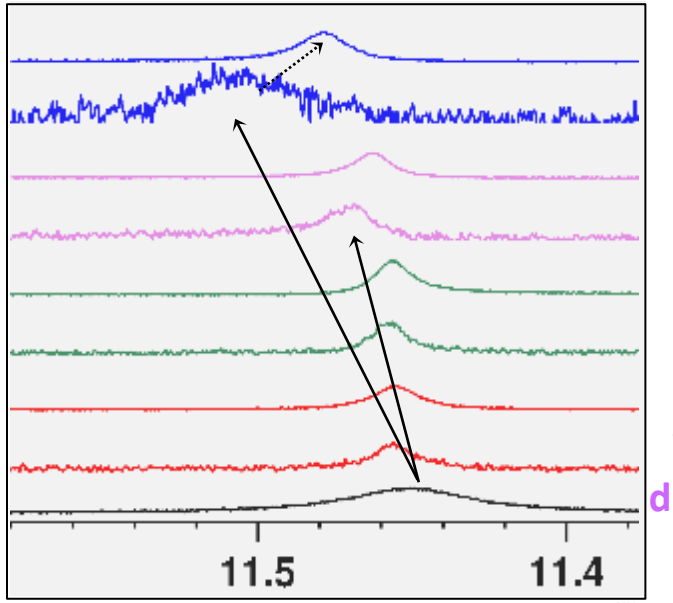


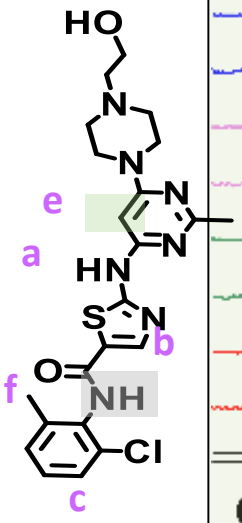


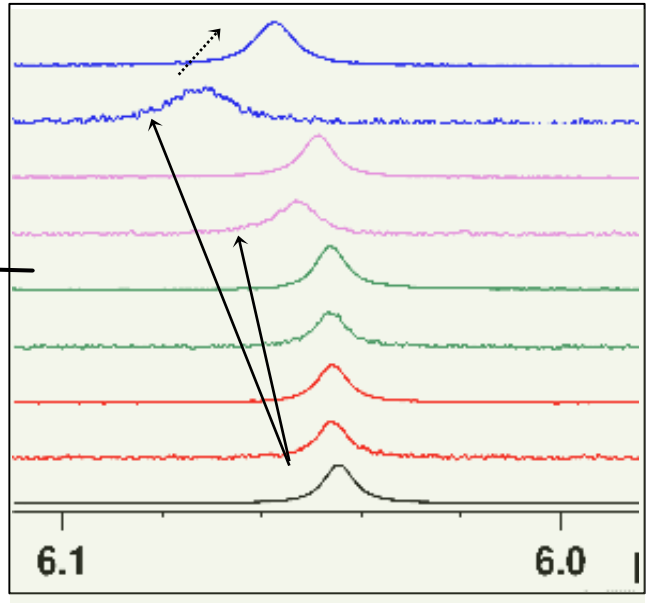




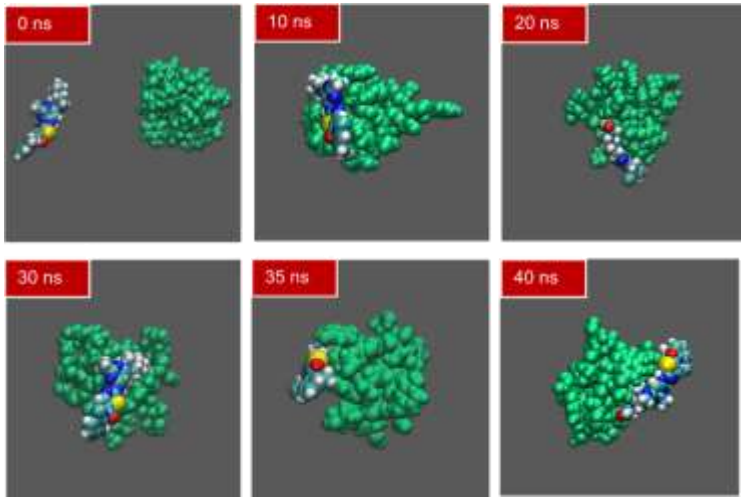


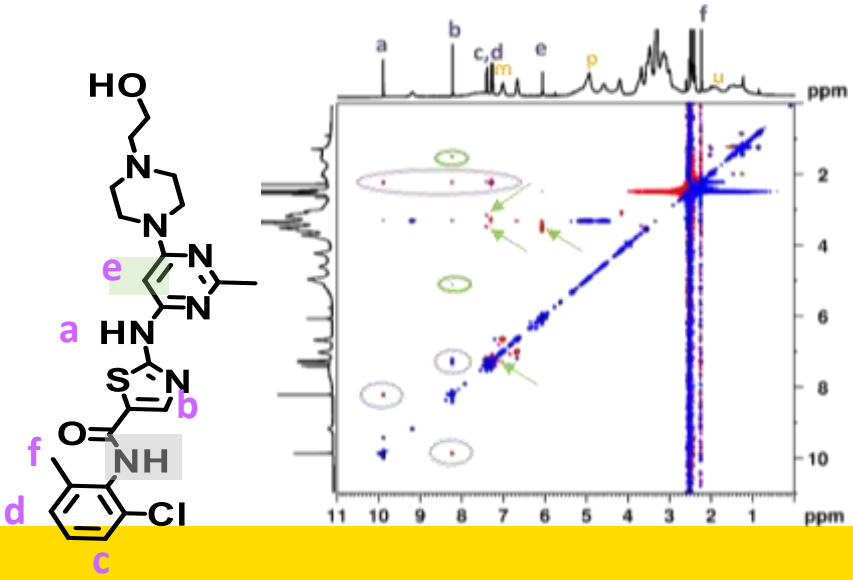


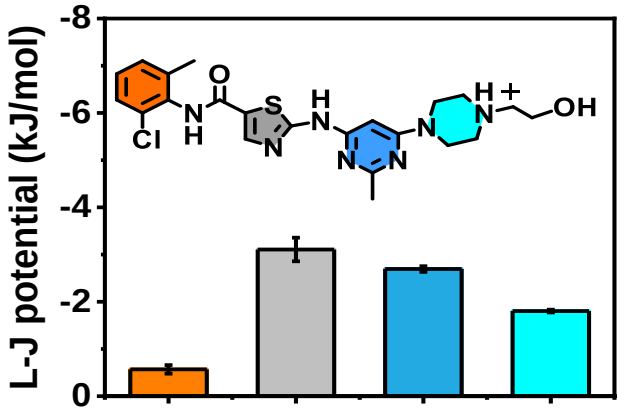




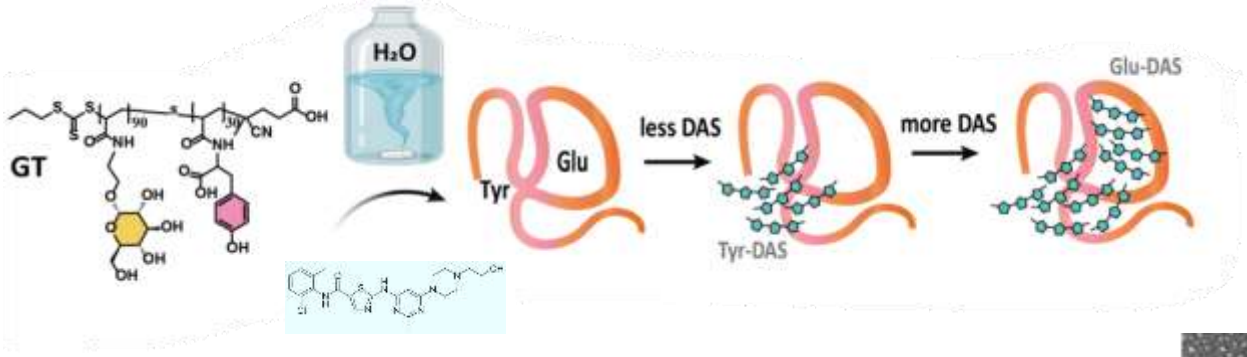
Combining NMR and MD

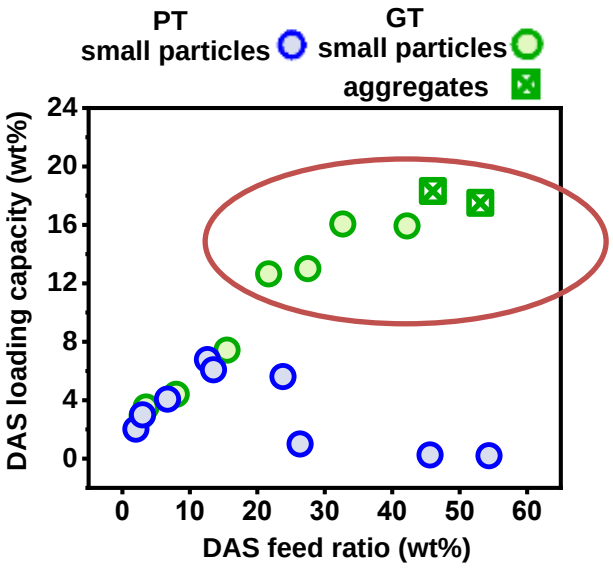


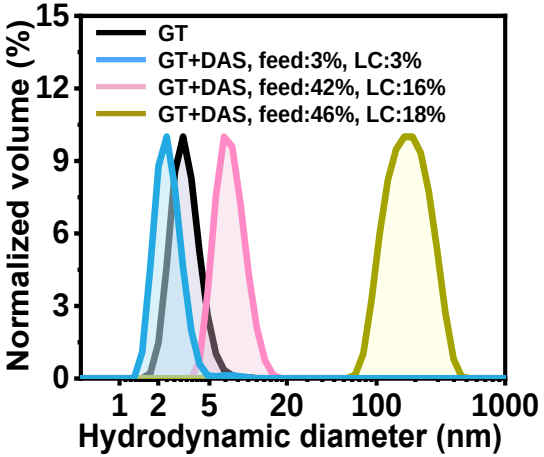


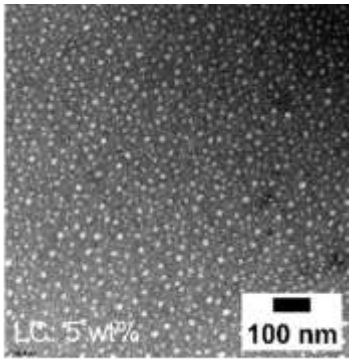


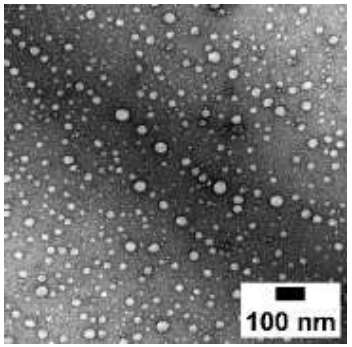
Creation of small nanoparticles in the presence of DAS



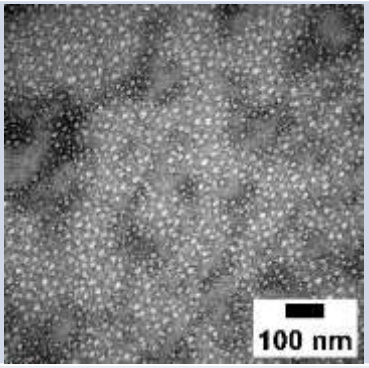
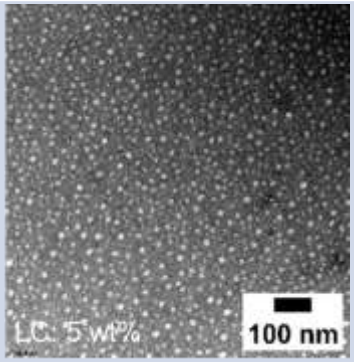
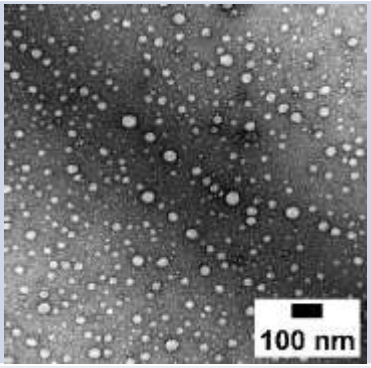
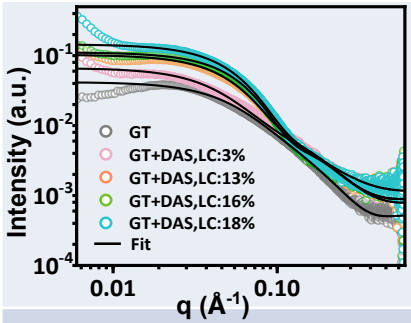


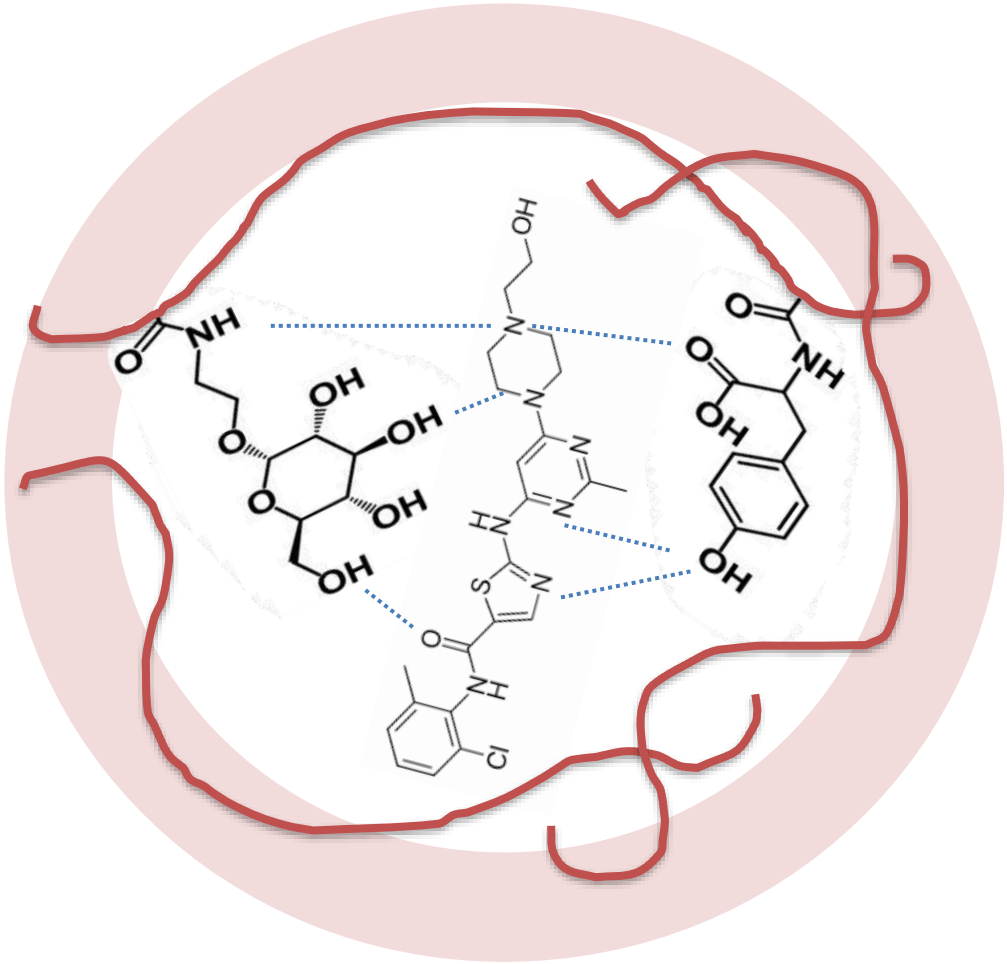






Insight into the structure

Loading content	3 wt%	5 wt %	16 wt %
Hydrodynamic Diameter (DLS)	3 nm	5 nm	10 nm
TEM	10	10	20
			
	Core-shell nanoparticles of around 5 nm		
N(Agg) MALS	3	4	12



Very small nanoparticles with a core-shell structure

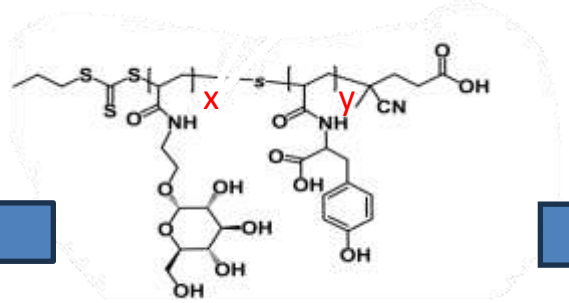
Although the nanoparticles are below 10 nm, they are not single chain nanoparticles

Depending on the amount of drugs, at least 2 polymers (up to 12 polymers) surround the drug core

The role of the polymer size

shorter

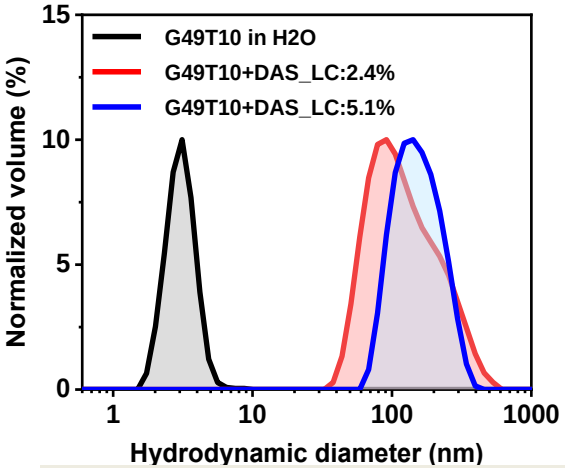
x=49, y= 10

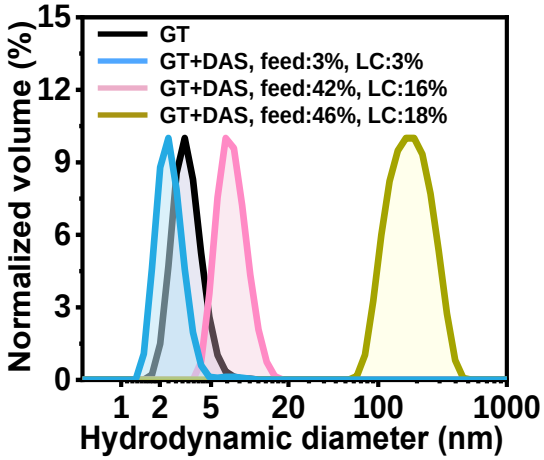


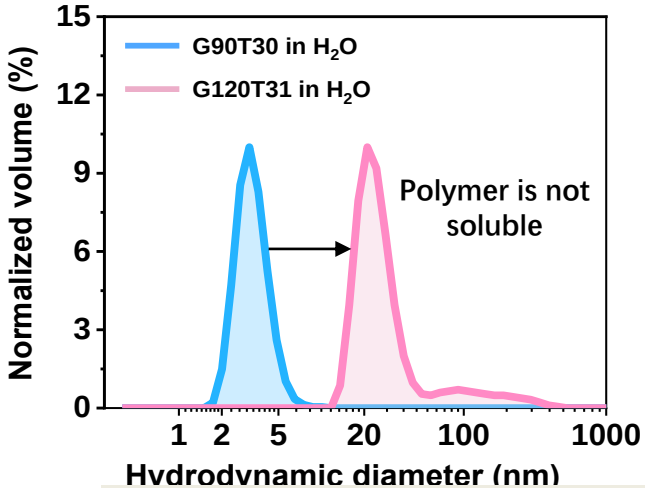
longer

x=120, y= 30

x=90, y= 30



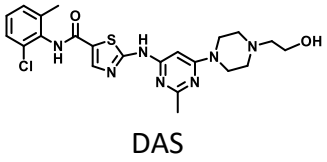


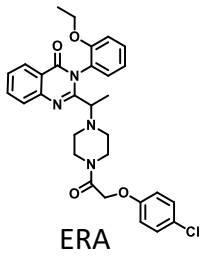


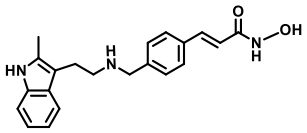
Large particles are formed that aggregate, polymer cannot stabilize drug

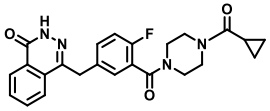
The glycopolymer itself is insoluble, not suitable for the process

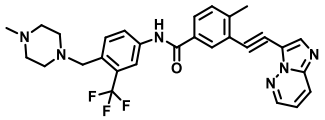
Other drugs? Yes, but….


DAS


ERA


PAN


OLA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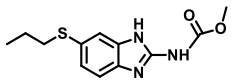
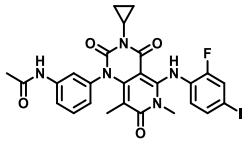
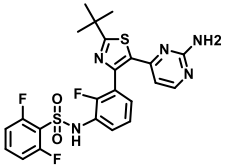
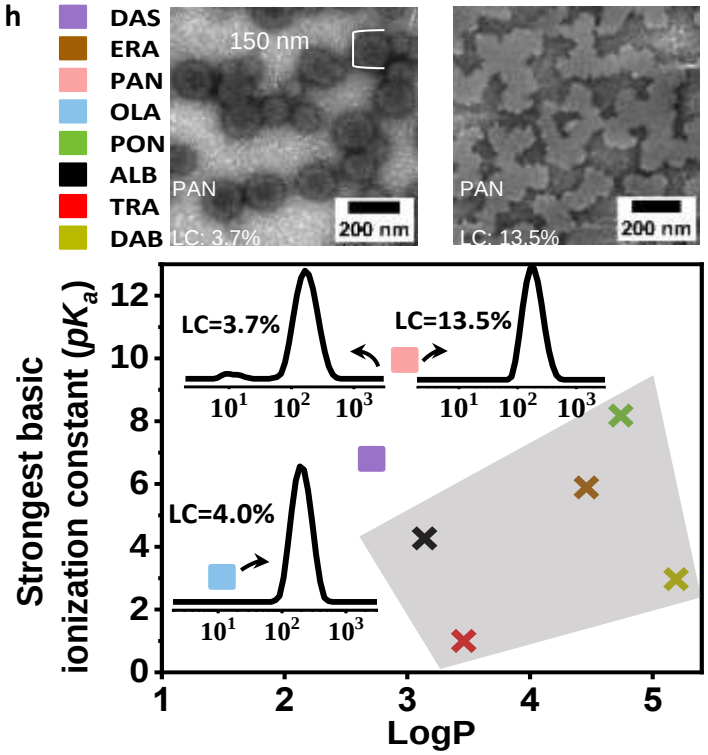
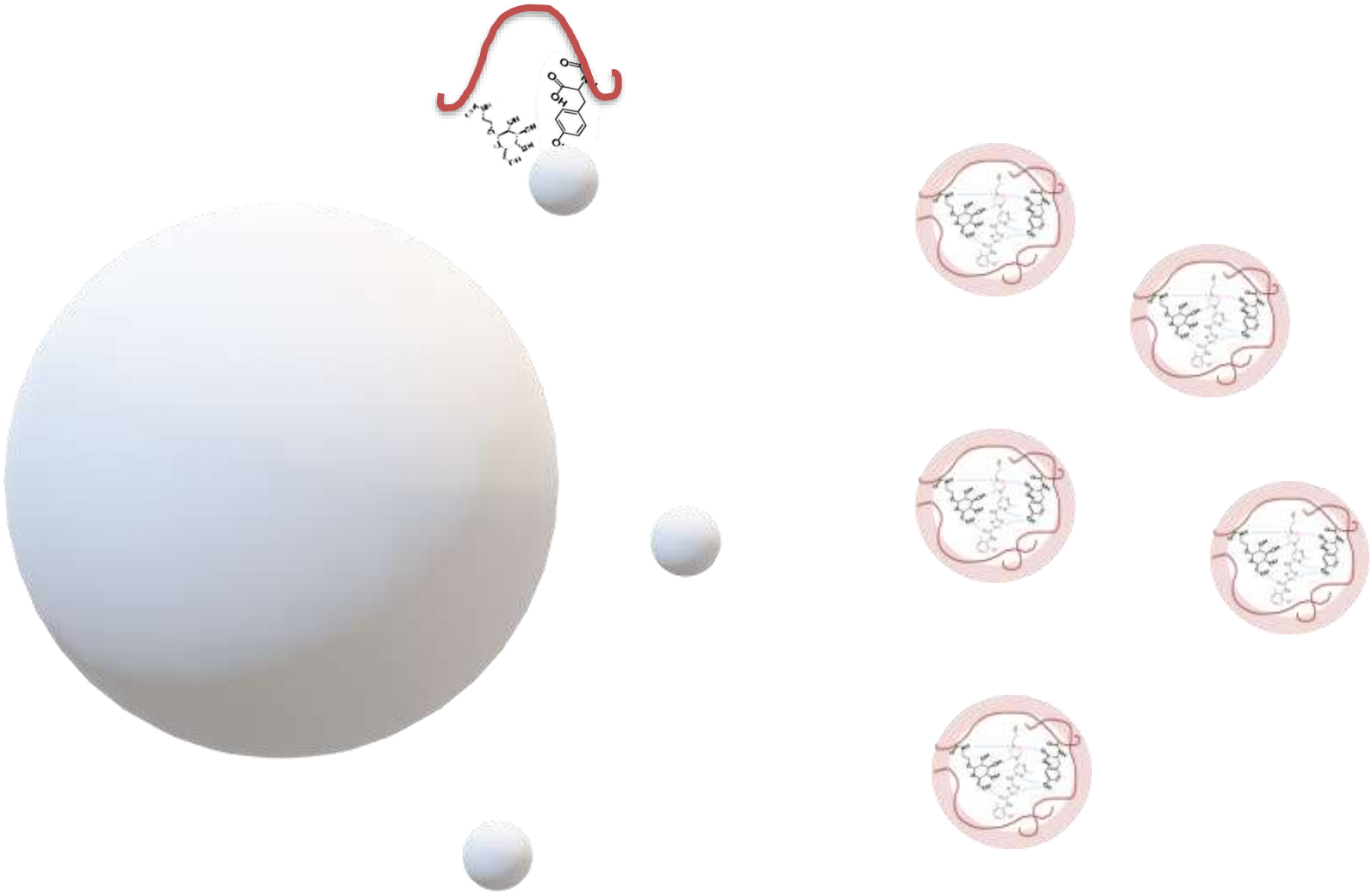

ALB


TRA


DAB

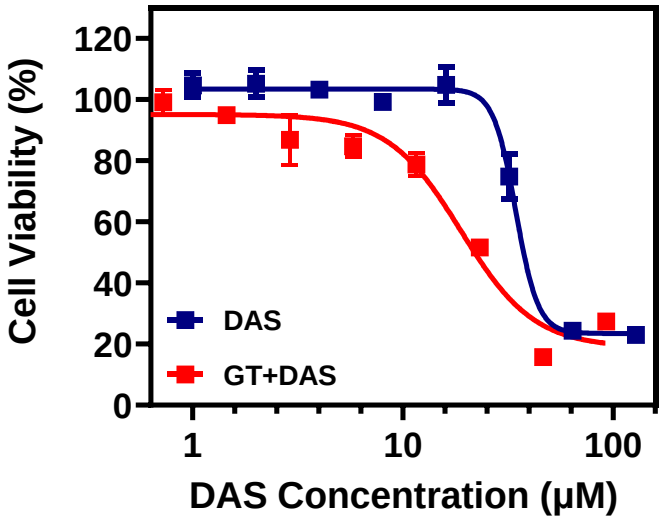


Suitable drugs need to have right hydrophobicity and alkalinity



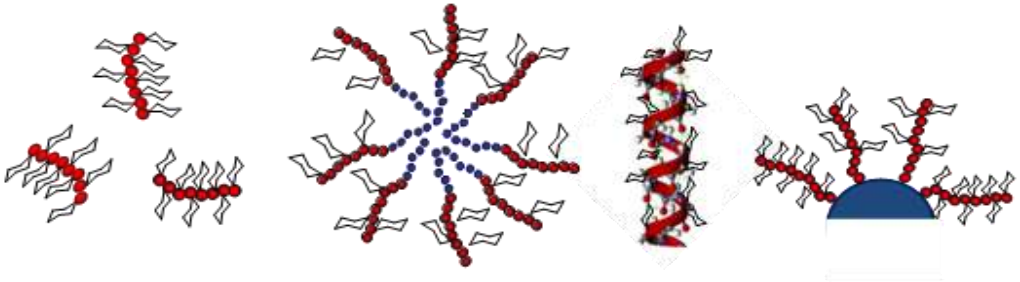
A simple work flow

Stirring of polymer and drug in water



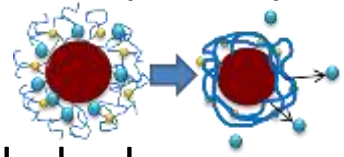
Apply directly to cells

Conclusions:

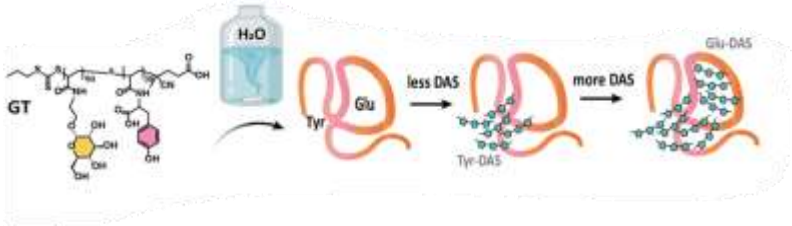


Glycopolymers are bioactive molecules that can enhance cellular uptake

Glycopolymers have a tendency to interact with drugs despite opposite polarity



The strong bond between glycopolymers and drug can be used to help drug delivery



Thank you

Australian Government

Australian Research Council

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