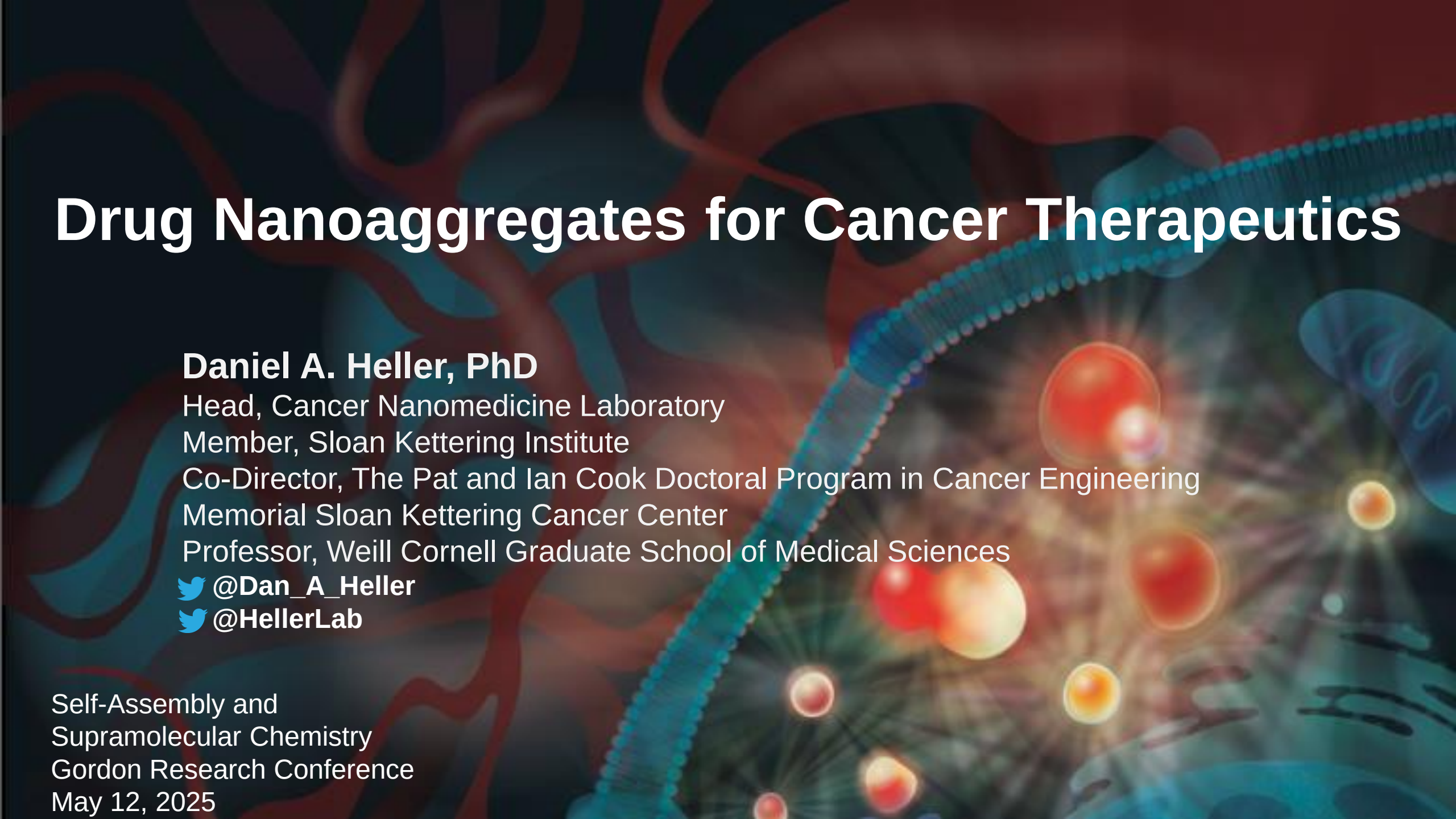
Drug Nanoaggregates for Cancer Therapeutics



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Self-Assembly and
Supramolecular Chemistry
Gordon Research Conference
May 12, 2025

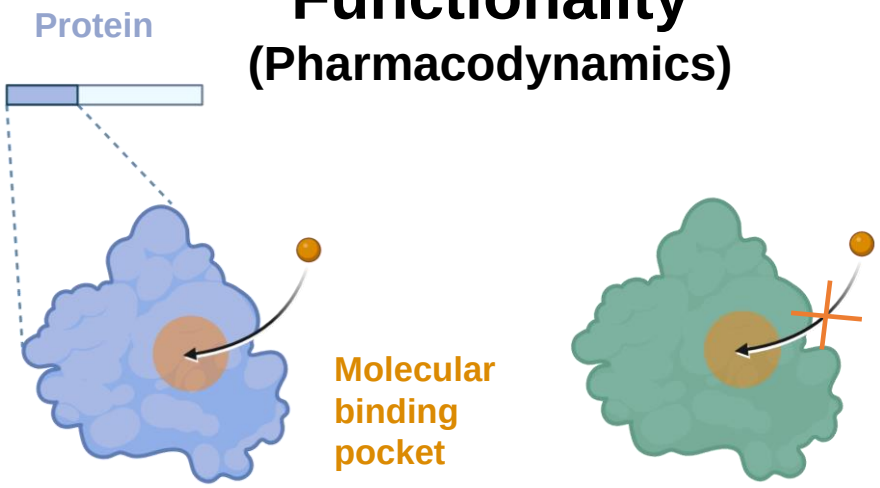
COI Disclosure Information

I have the following financial relationships to disclose:

- Co-founder/Scientific Advisor: Selectin Therapeutics, Inc., Lime Therapeutics, Inc., Nine Diagnostics, Inc.
- Scientific Advisor: Concarlo Therapeutics, Inc., Nanorobotics, Inc., Mediphage Bioceuticals, Inc., Celine Therapeutics, Inc.
- Inventor of “Fucoidan nanogels and methods of their use and manufacture” US patent #9,737,614 and others.

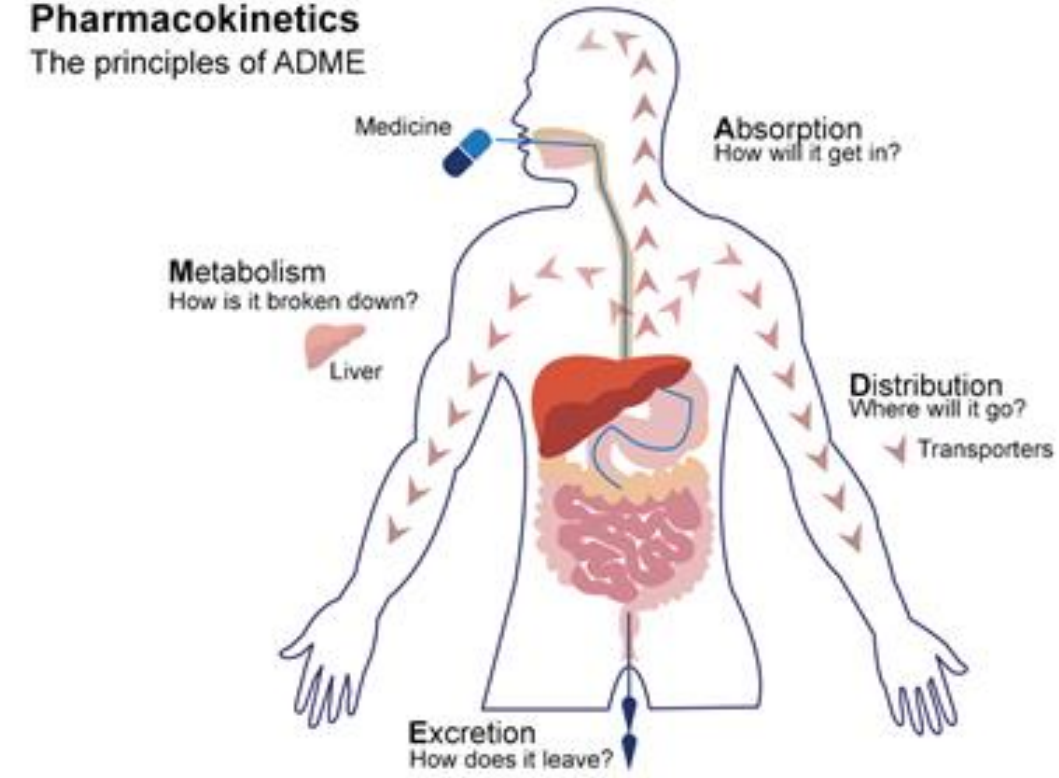
Why Can Some Molecules Be “Drugs” and Others Not?

Functionality
(Pharmacodynamics)

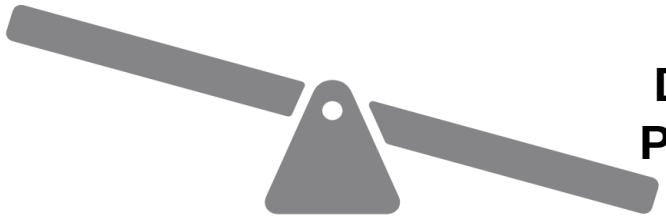


Affinity **Selectivity**

Drug-Like Properties

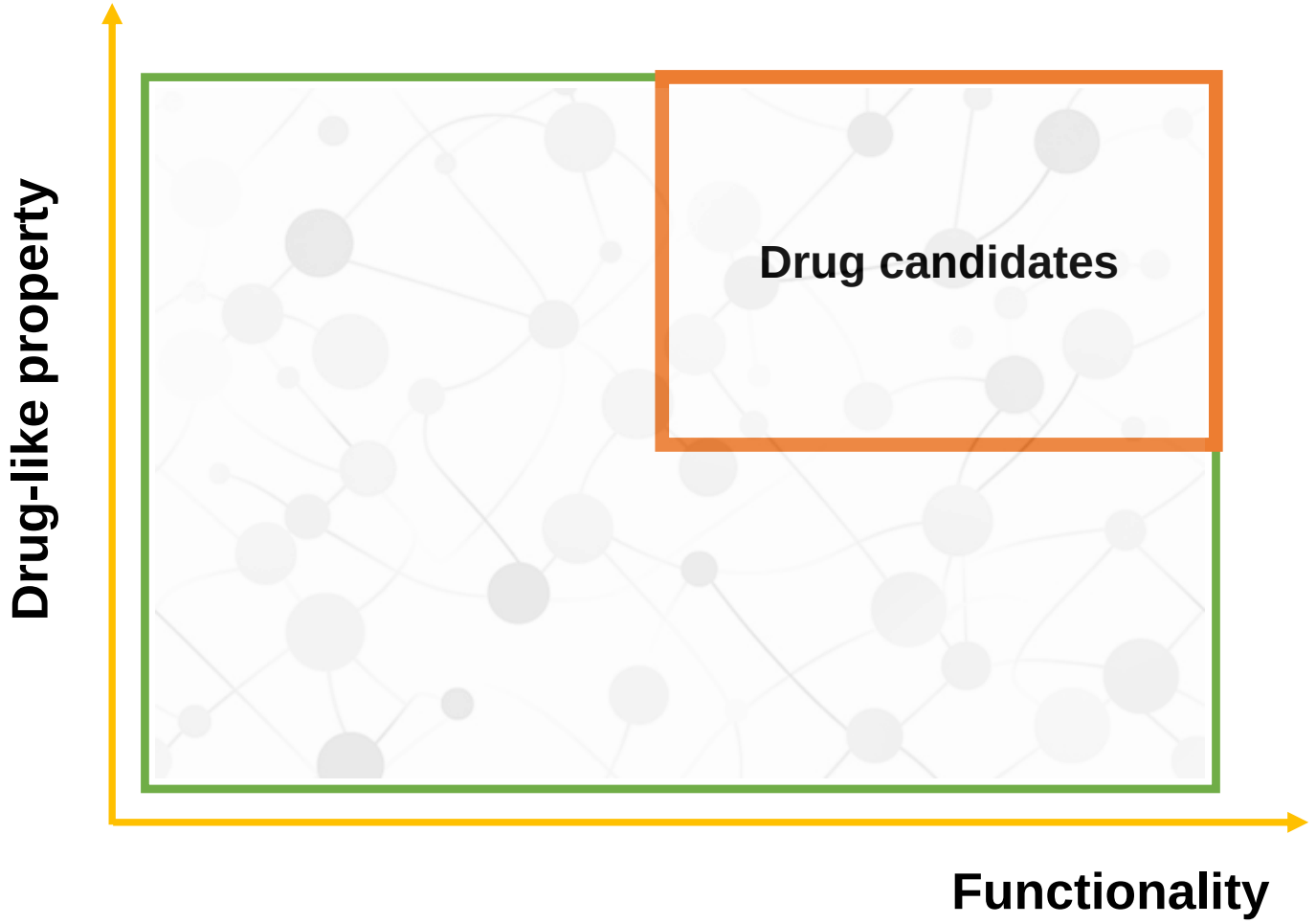


Functionality

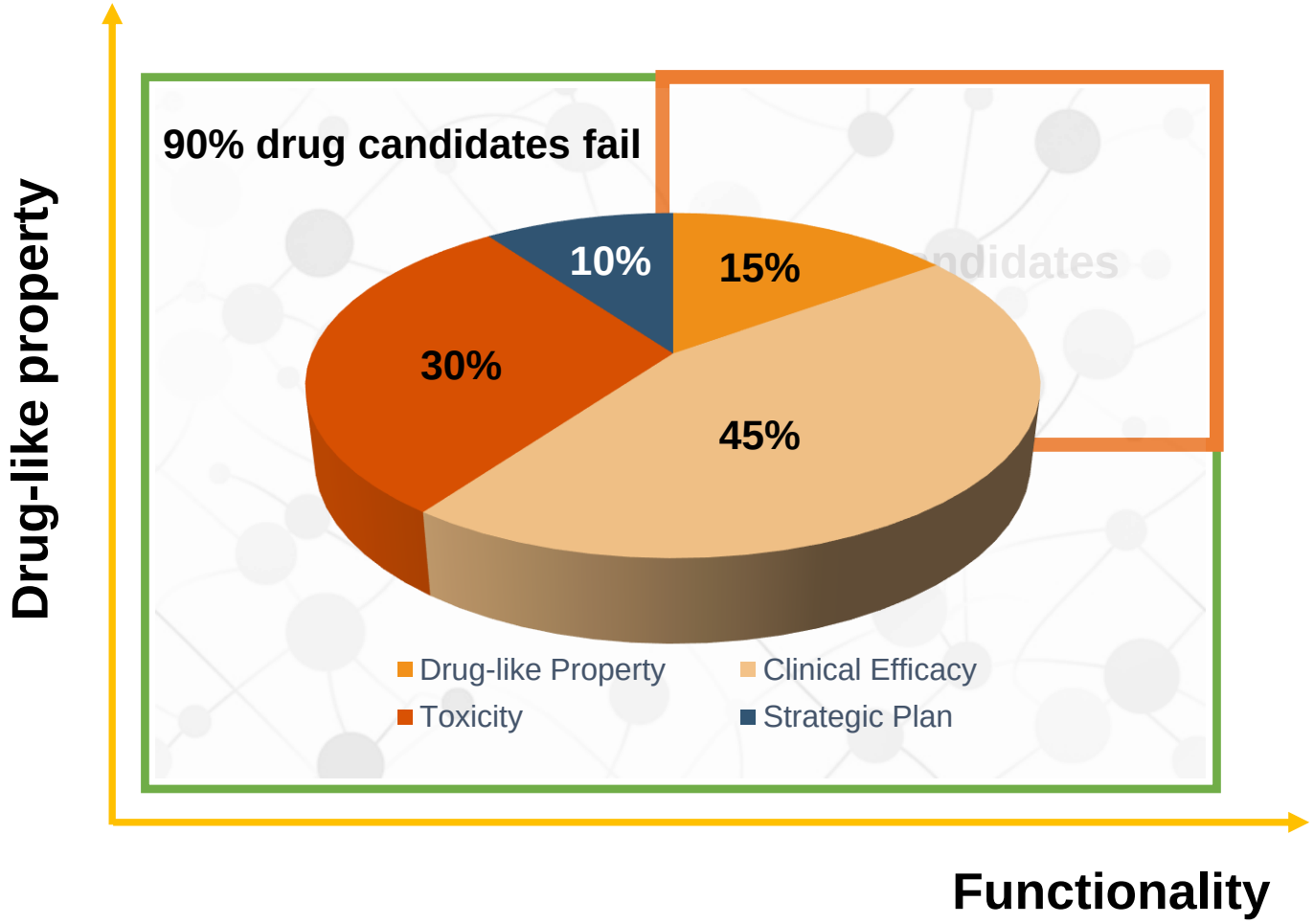


Drug-like Properties

Drug Chemical Space is Limited

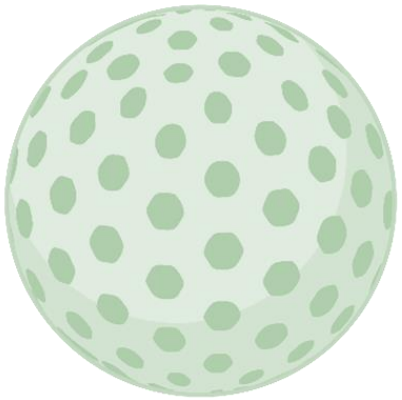


Drug Chemical Space is Limited

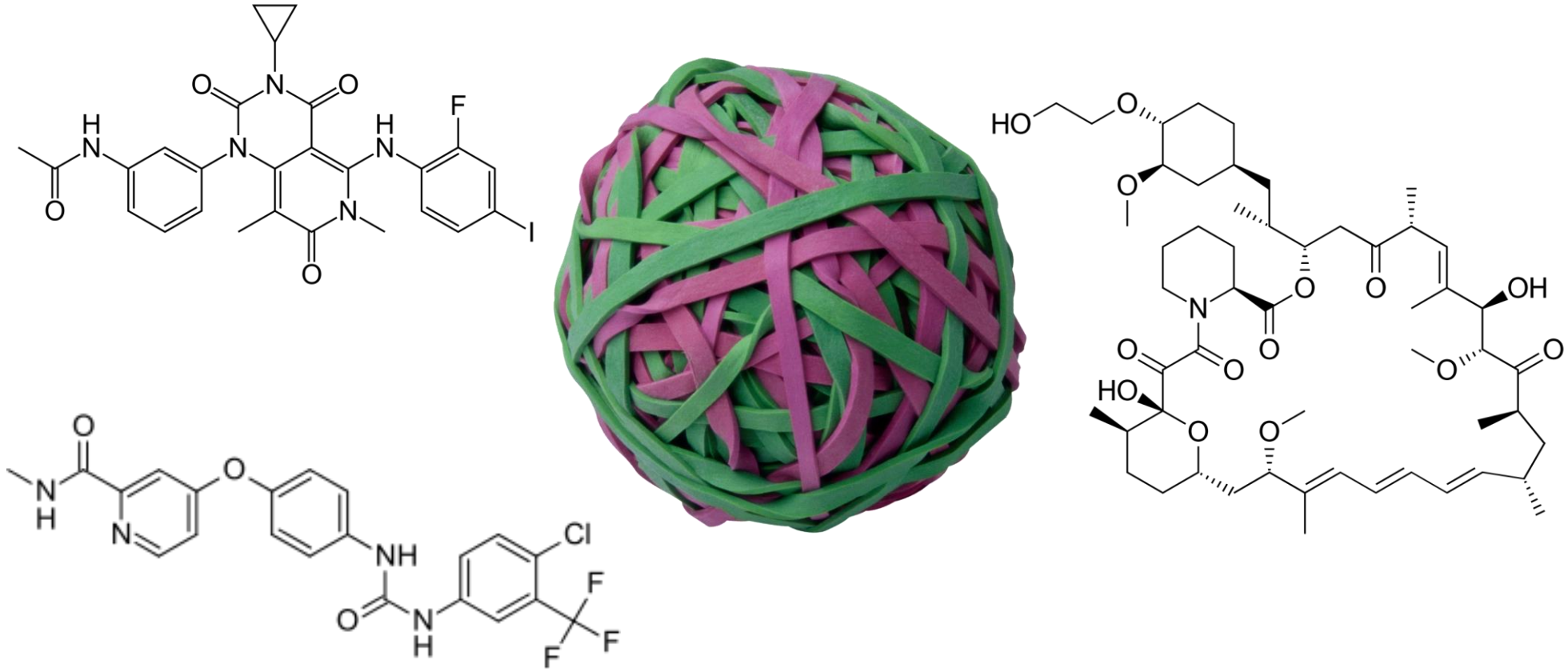


Sun, D., et al. *Acta Pharm Sin B* 2022

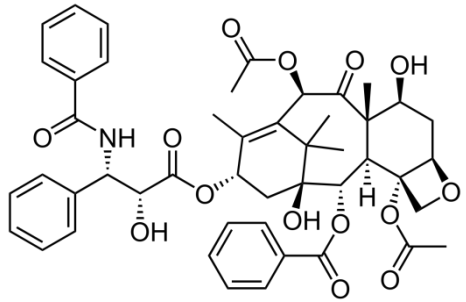
Nanomedicines:
Isolate Pharmacokinetics/ADME from Drug Function/Pharmacodynamics



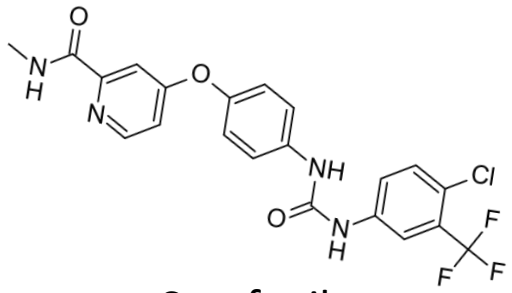
Question: How can we enable, predict, and understand nanoparticle encapsulation of drugs with diverse structures?



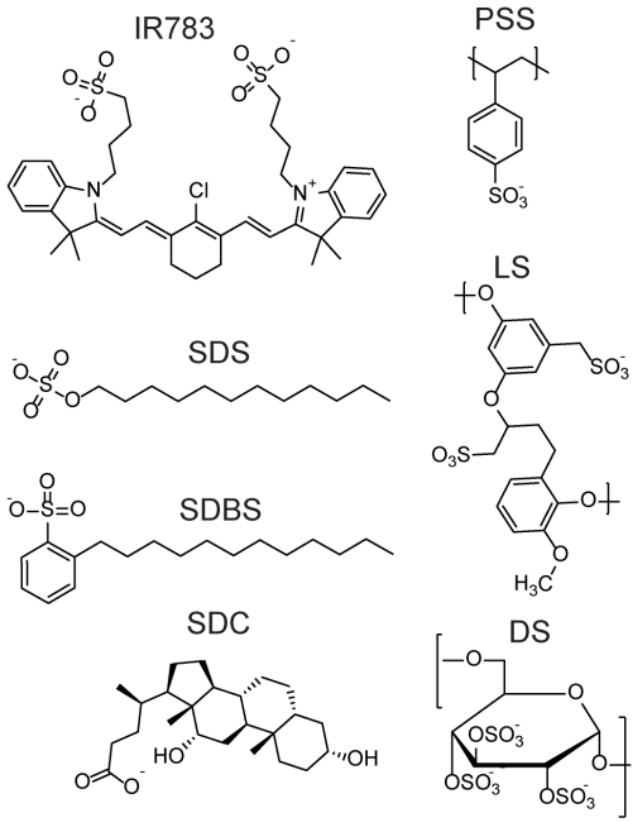
Few Small Molecule Excipients Suspend Hydrophobic Drugs

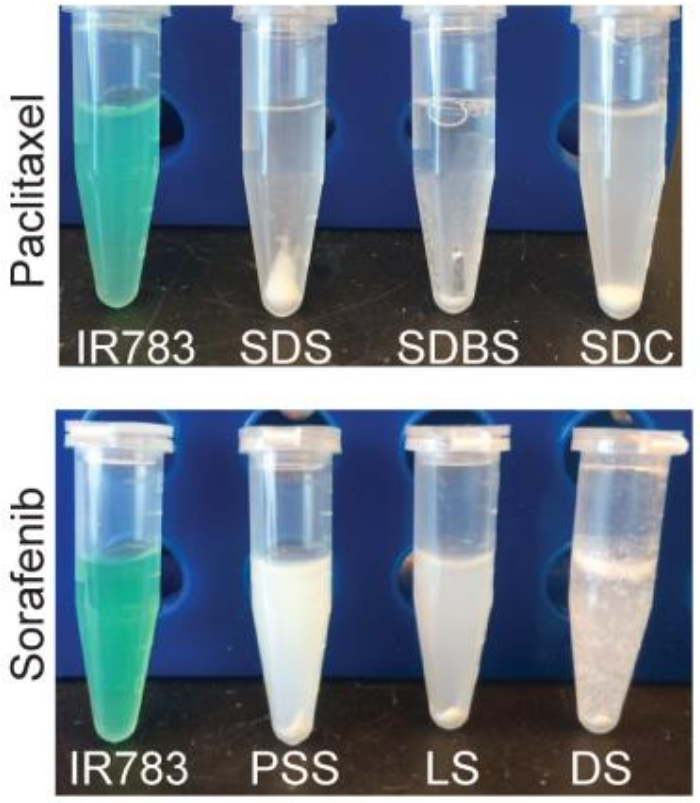


Paclitaxel

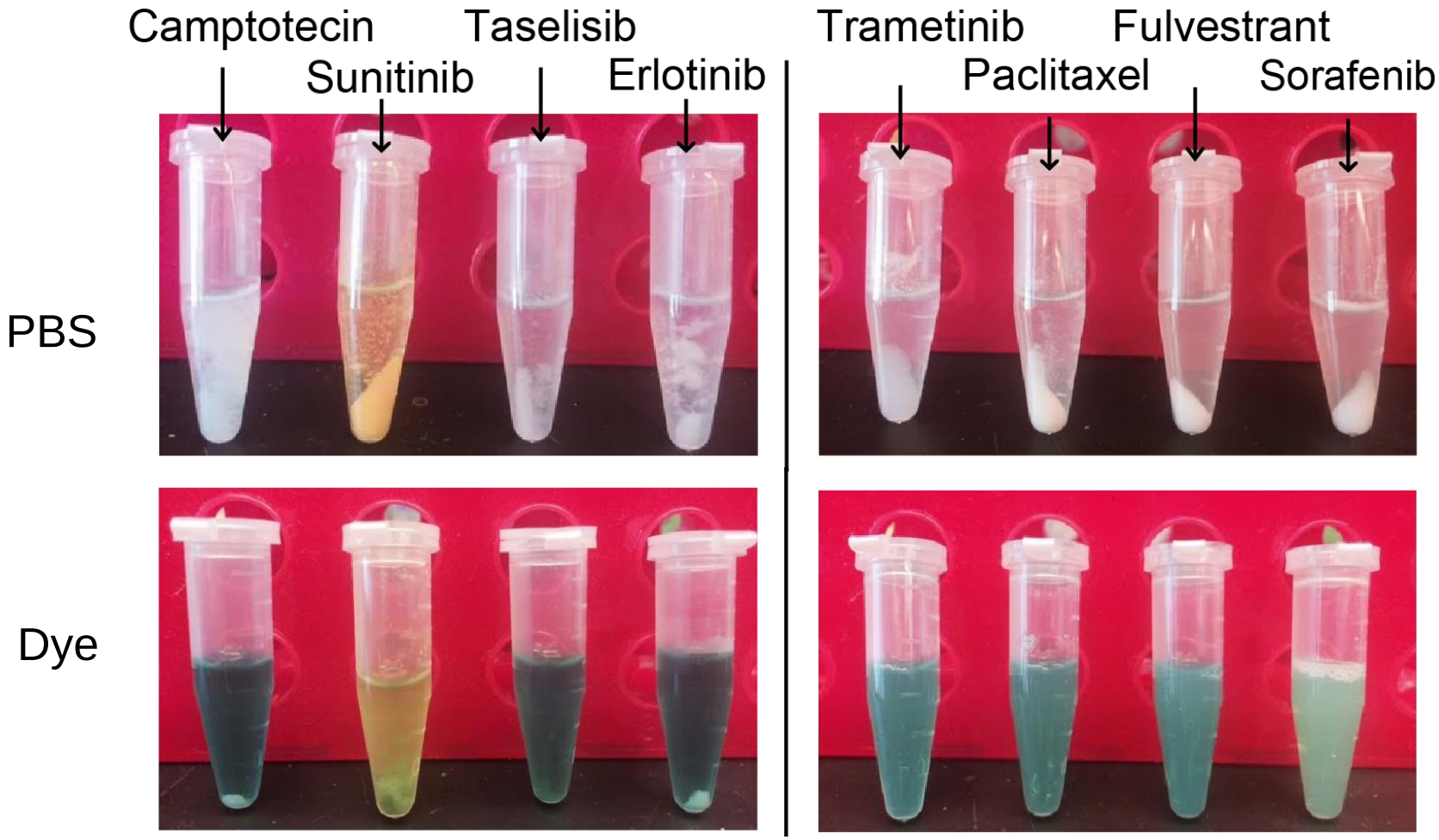


Sorafenib

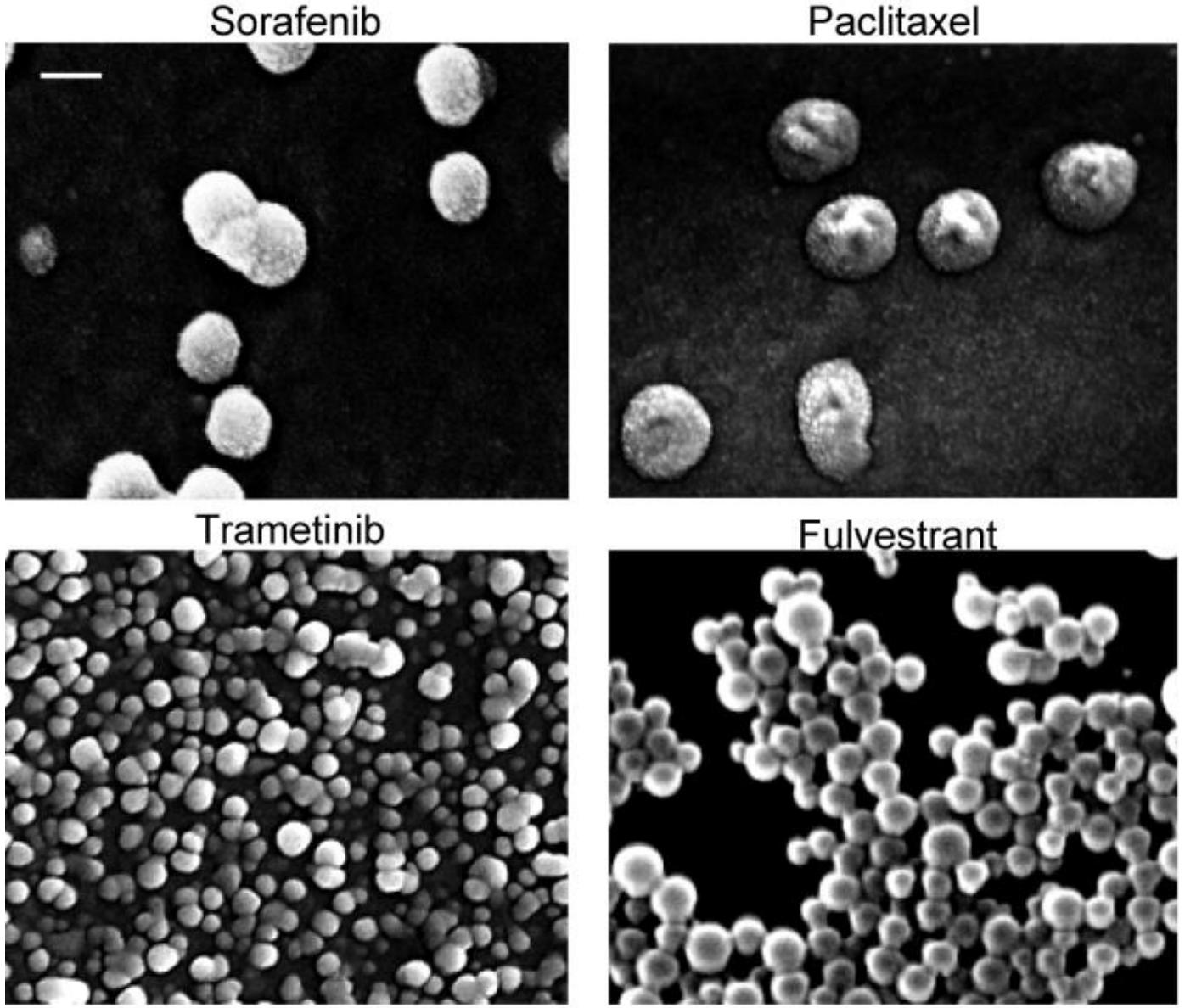




Some Hydrophobic Drugs Self-Assemble with Indocyanines to Form Nanoparticles



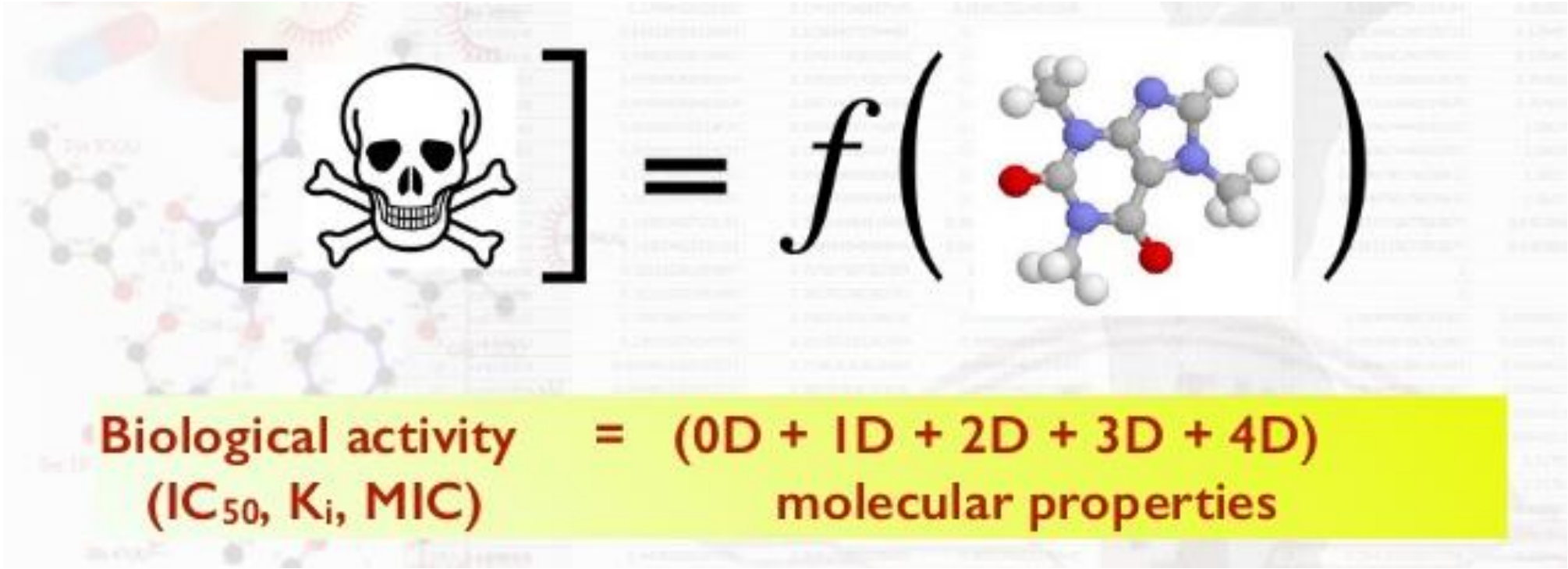
Indocyanine-Drug Suspensions Form Nanoparticles



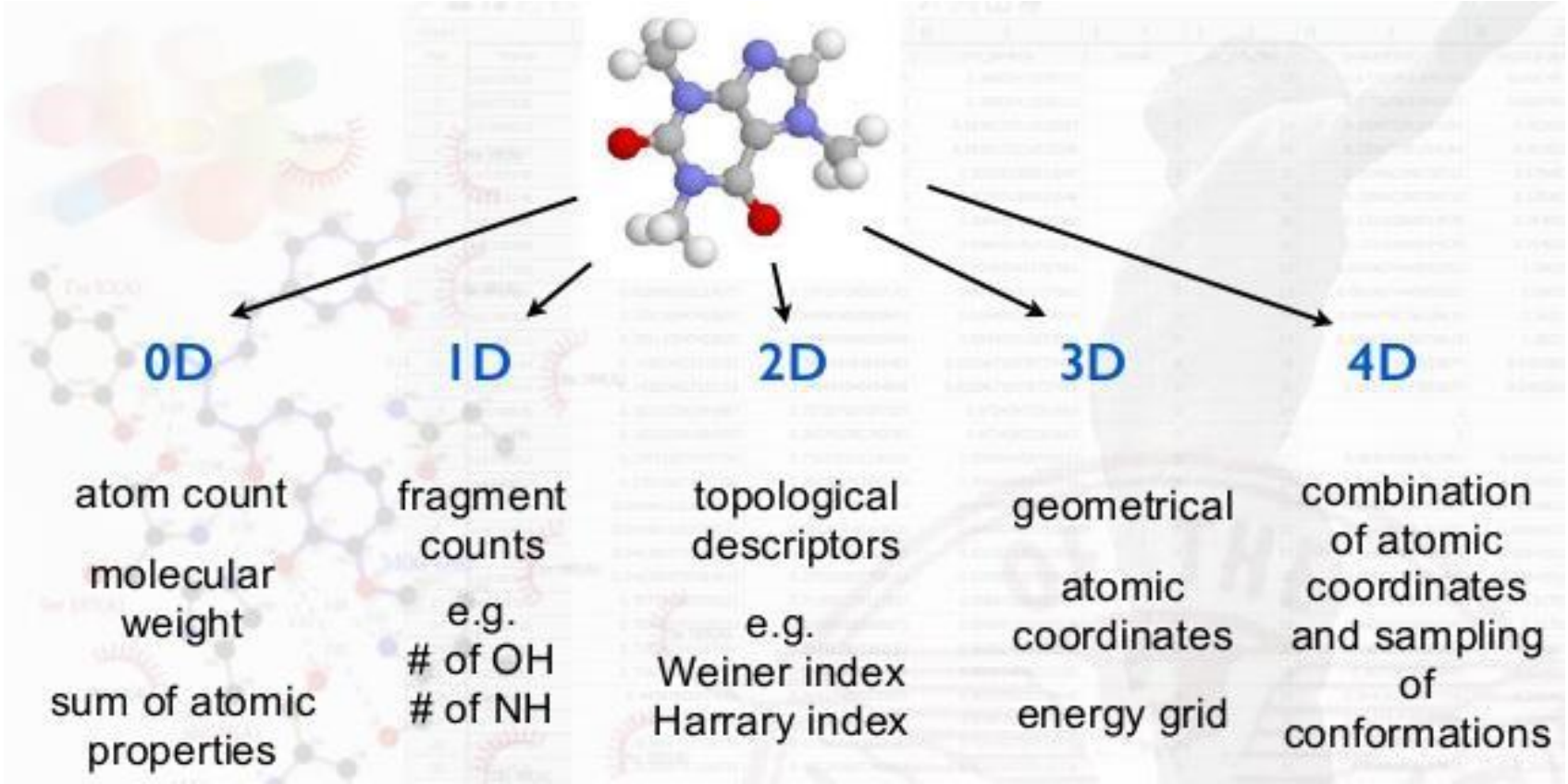
Shamay, et al., *Nat Mater*, 2018

Which molecular structural features facilitate drug self-assembly into nanoparticles?

QSAR: Quantitative Structure-Activity Relationship

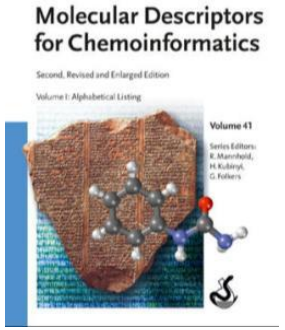


Molecular Descriptors
Convert Drug Structures into Quantities

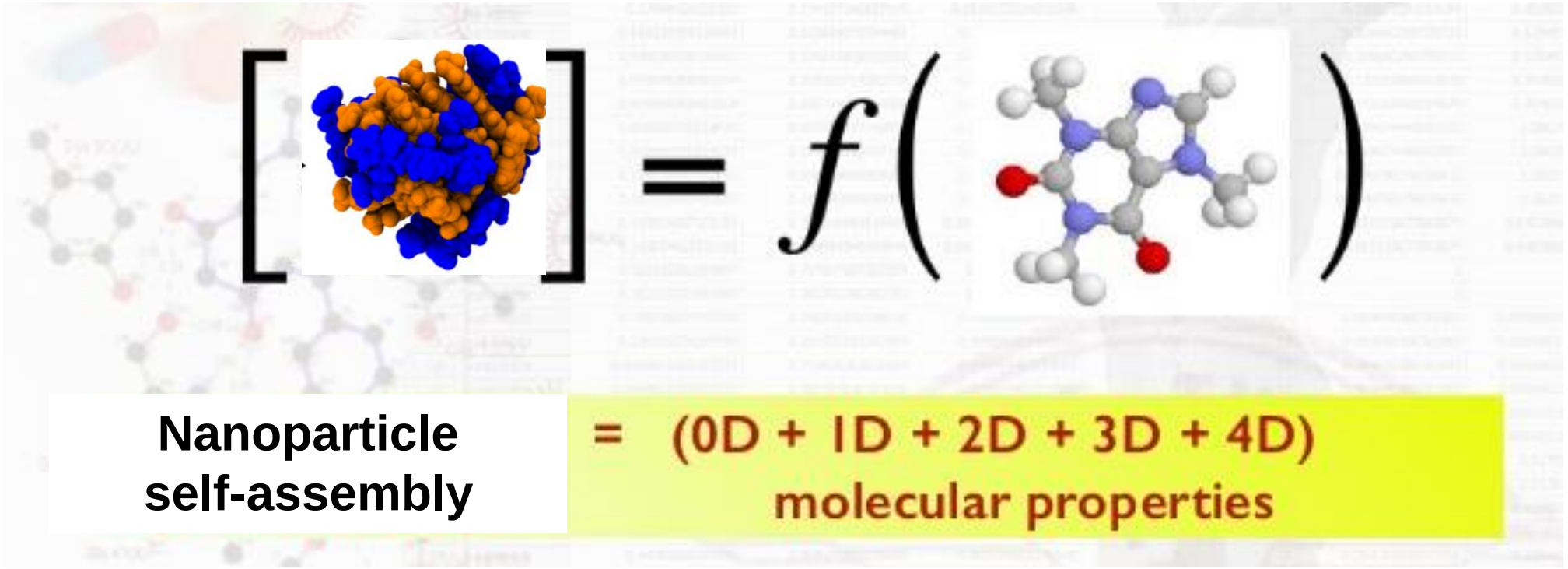


"*The molecular descriptor is the final result of a logic and mathematical procedure which **transforms** chemical information encoded within a symbolic representation of a molecule into a useful number"*

Roberto Todeschini, *Molecular Descriptors for Chemoinformatics*

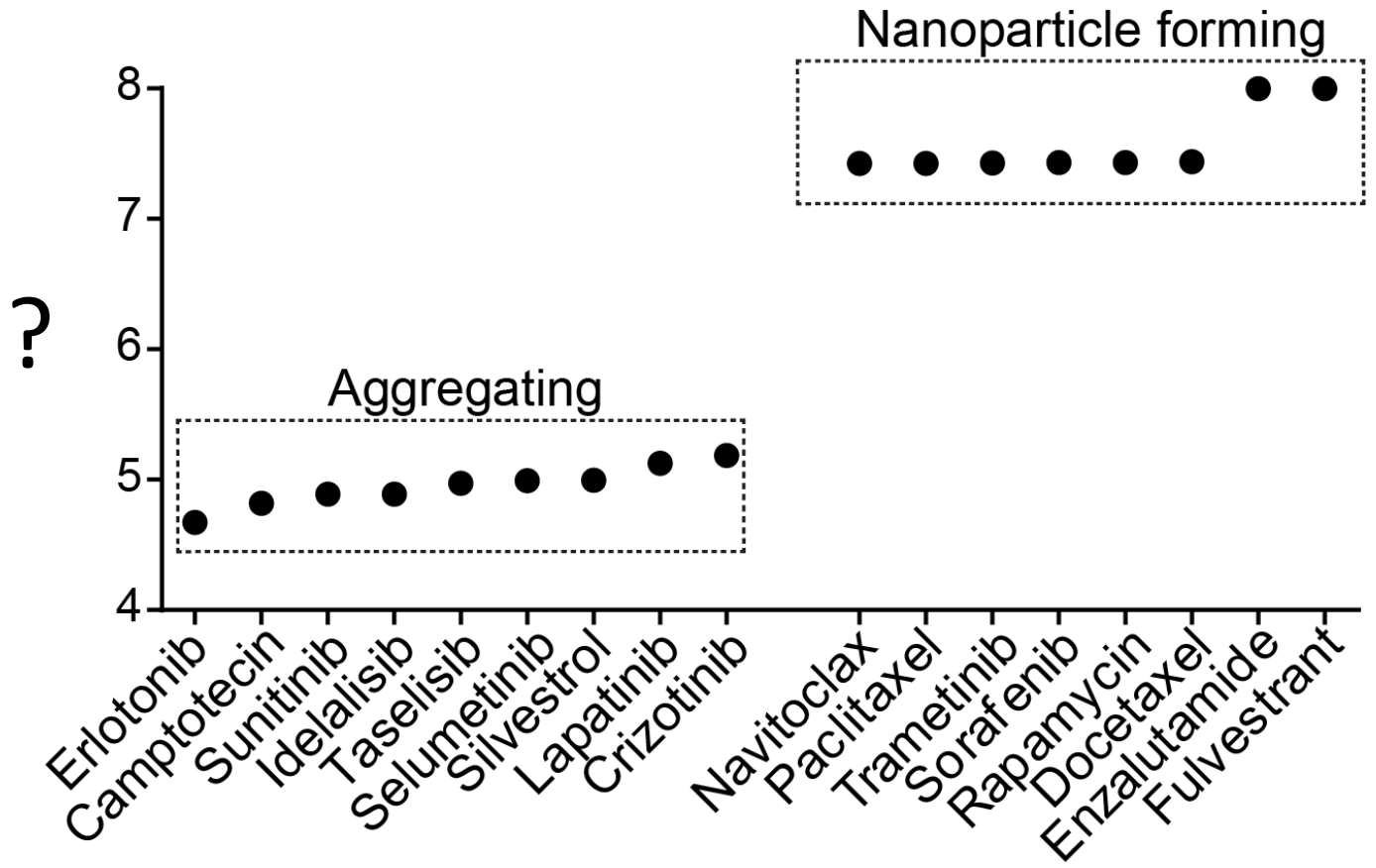


QSNAP: Quantitative Structure-Nanoparticle Assembly Prediction



Yosi Shamay

A Molecular Descriptor Separates Drugs by their Nanoparticle Self-Assembly Property



SpMAX4_Bh(s) Descriptor:

Leading eigenvalue of the Burden matrix *weighted by the intrinsic state*

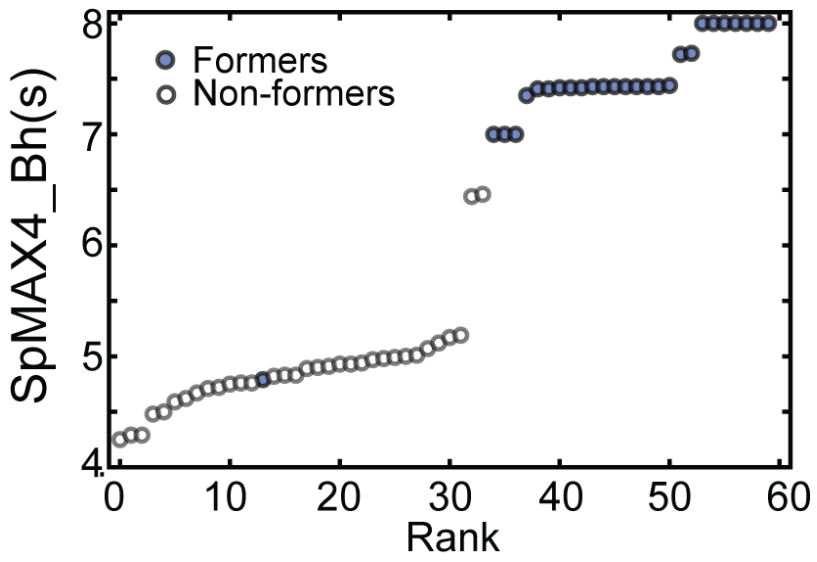
Intrinsic State Reflects the Electronegativity of an Atom or Chemical Group

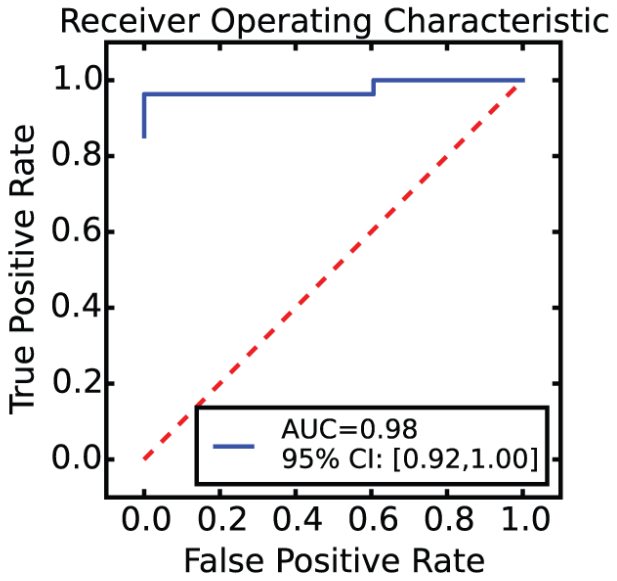
$$I_i = \frac{(2/L_i)^2 \cdot \delta_i^v + 1}{\delta_i}$$

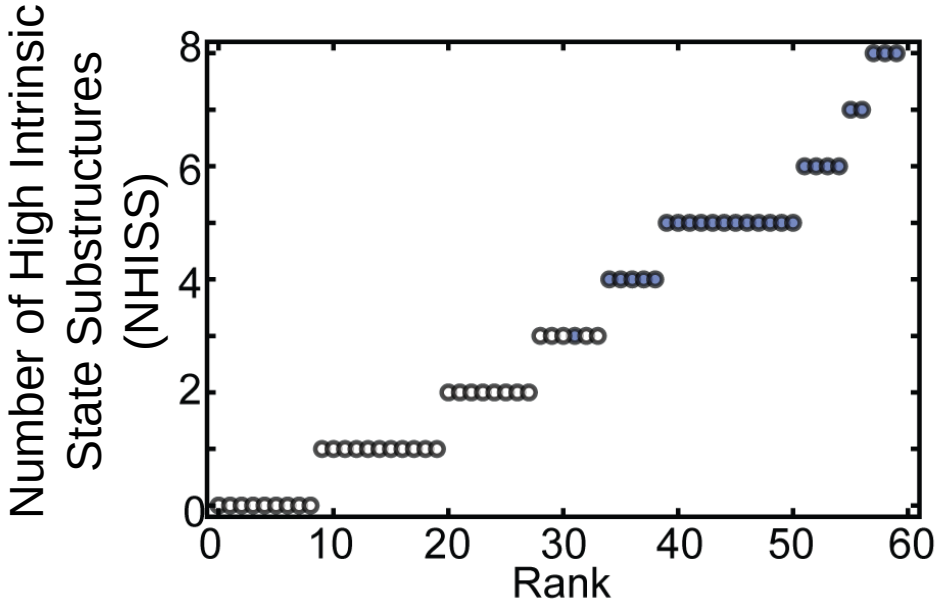
where L is the principal quantum number of the atom, δ^v is the number of valence electrons, and δ is the number of sigma electrons of the atom.

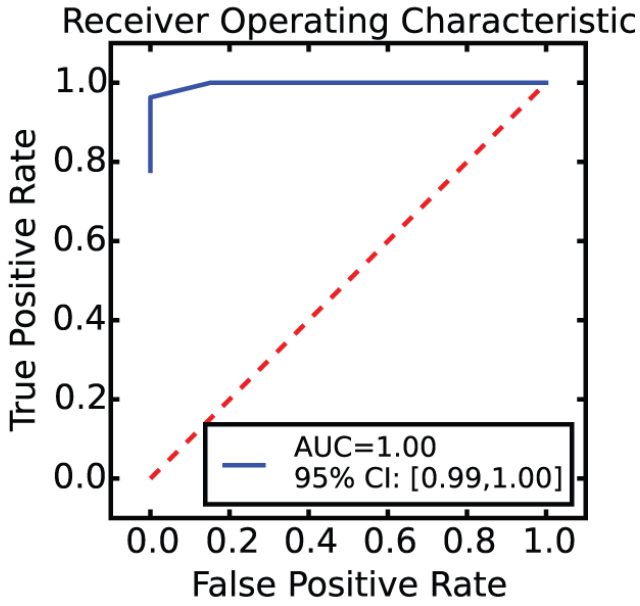
Group	Intrinsic state
-F	8.0
=O	7.0
-OH	6.0
≡N	6.0
=N	5.0
-Cl	4.1
=S	3.7
-O-	3.5
-SH	3.2
=CH2	3.0
=N-	3.0
-Br	2.8
=C=	2.5
-I	2.1
>N-	2.0
-S-	1.8
>C=	1.7
>CH2	1.5
>CH-	1.3
>C<	1.3

Intrinsic State Predictive Value Approaches 100%





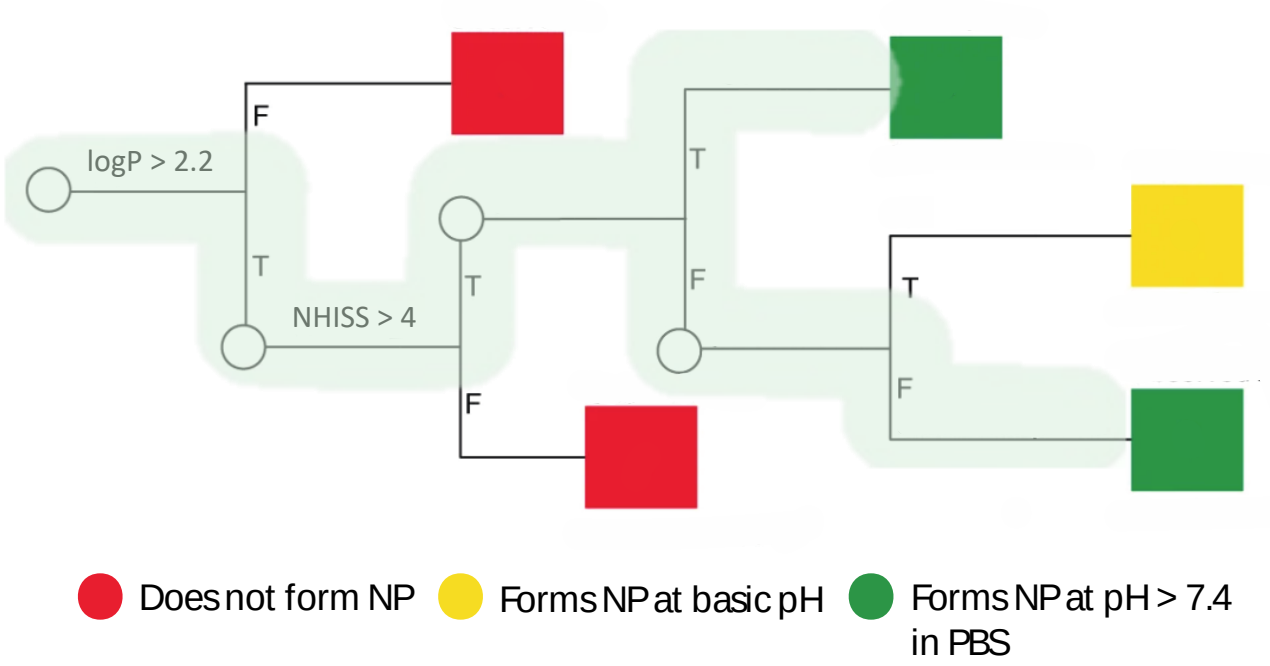




Drug Encapsulation Predicted by logP and NHISS (Number of High Intrinsic State Substructures)

$$\log P = \log [X]_{octanol} / [X]_{water}$$

$$NHISS = n_{fluorine} + n_{carbonyl} + n_{sulfinyl} + 2n_{sulfonyl} + n_{nitroso} + 2n_{nitro}$$



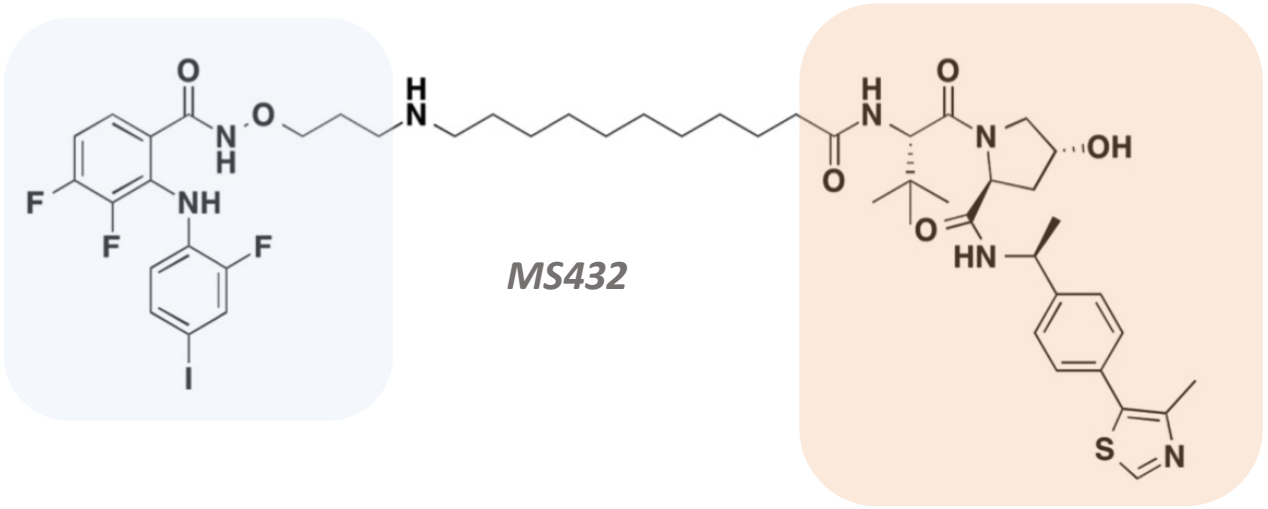
Shamay, et al., *Nat Mater* 2018

How Can We Improve the Properties of Non-Drug-Like Drugs?

Proteolysis Targeting Chimeras (PROTACs) Can Degrade "Un-Druggable" Targets

But are not "Drug-Like" and Often Exhibit Poor Pharmacokinetics/Penetration of Cells or Tumors

MEK 1/2 ligand



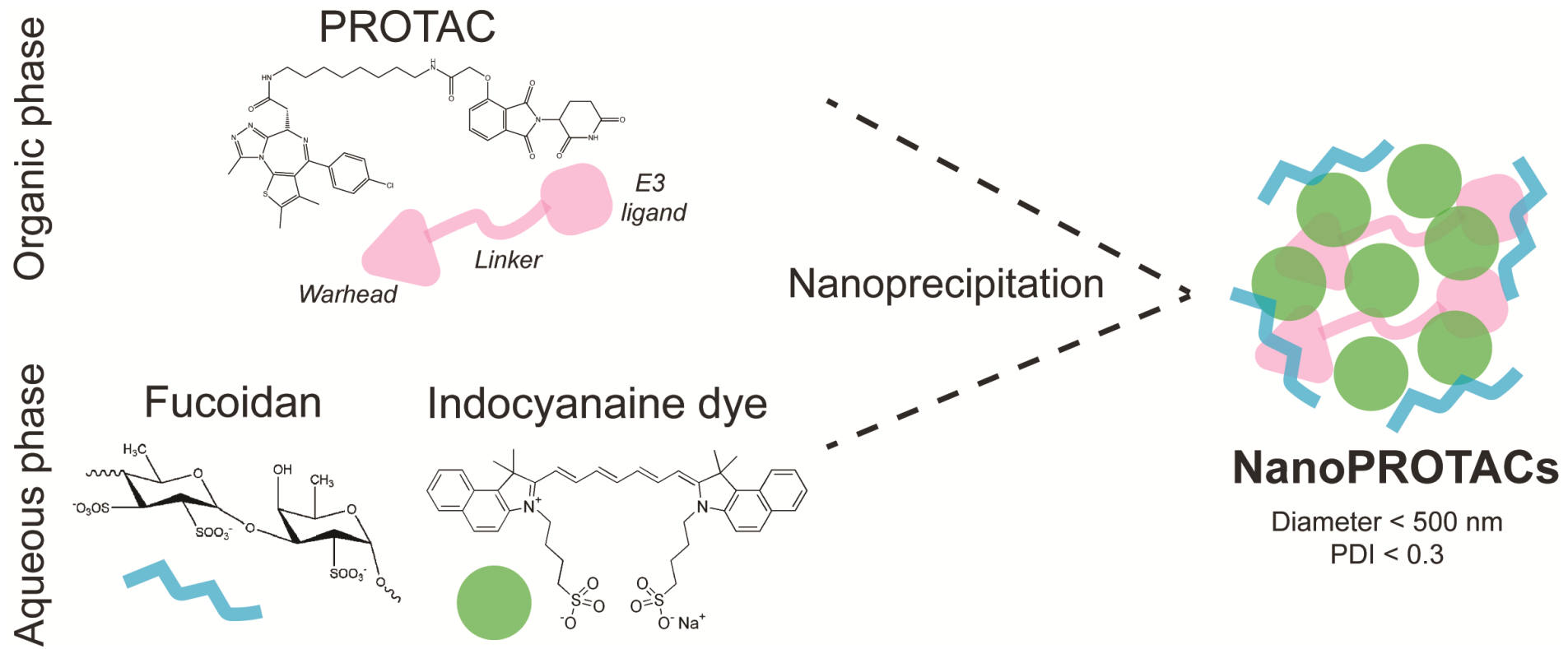
MS432

E3 ligand (VHL)

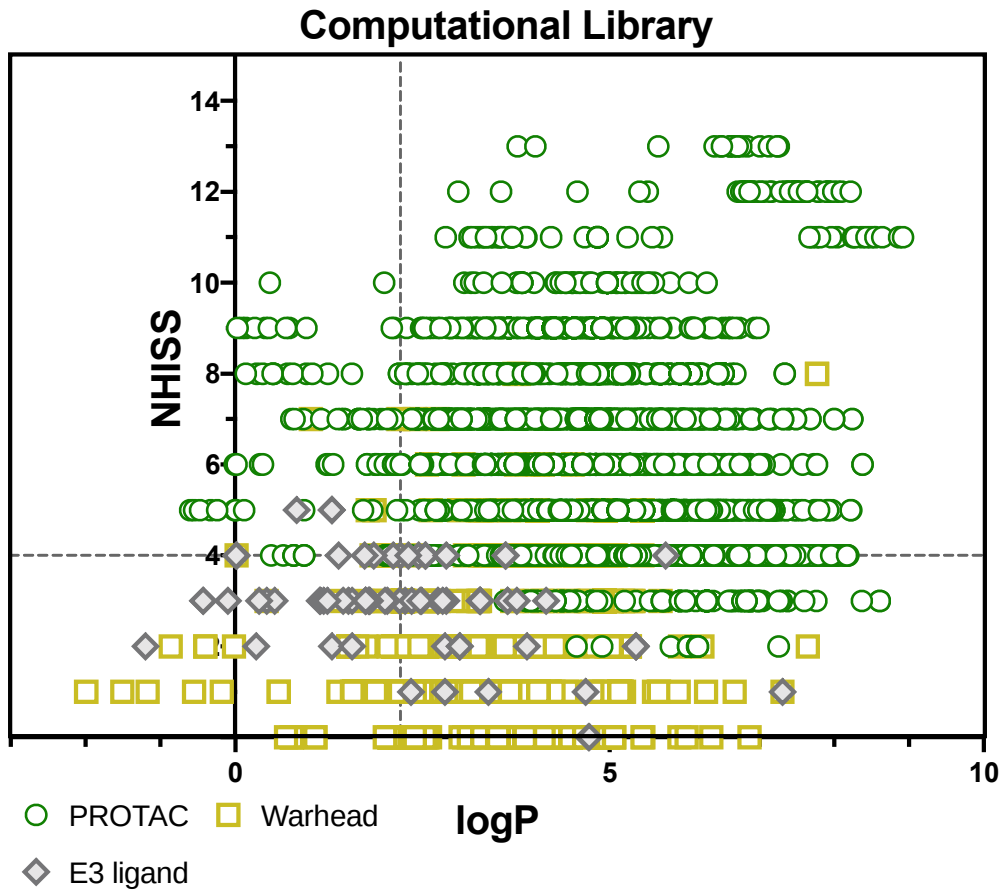
	Lipinski's Rule	MEK Degrader
logP	< 5	> 9
MW (Da)	< 500	~1100
H-bond donors	< 5	6
H-bond acceptors	< 10	9

Wei, J.; Jin, J., J. Med. Chem 2019

Targeted Nanoparticle PROTACs (NanoPROTACs) Developed to Improve Delivery



NanoPROTAC QSNAP: Formation is Predicted by NHISS/logP Descriptors



Vogt, et al., Unpublished

Can We Find Better Descriptors via QSNAP?

Method

Input Training Data

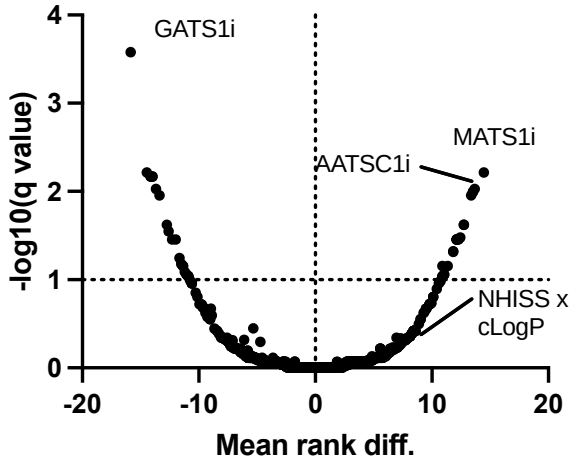
Former = 1
Non-former = 0

Calculation of molecular features using SMILES

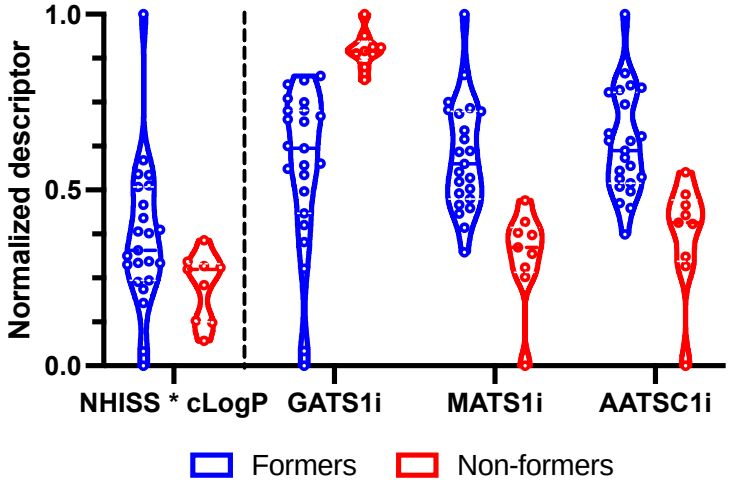
N=1,800 descriptors

Assessment of significant features via FDR (Q=10%)

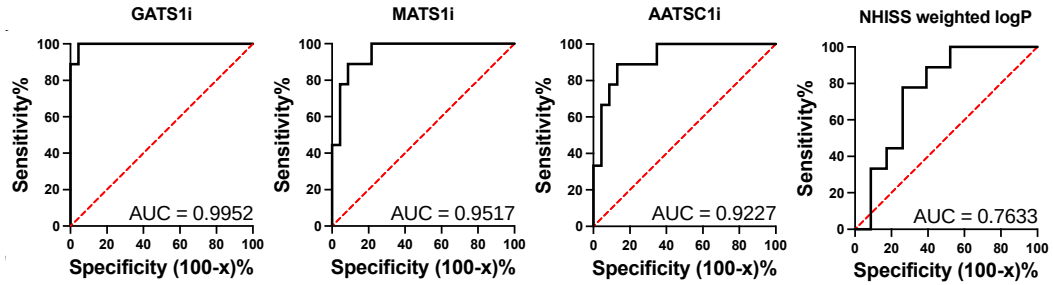
Descriptor Correlation with Self-Assembly



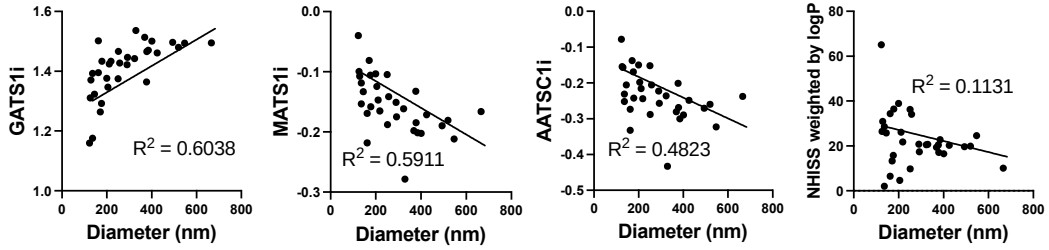
Top Descriptors



Predicting Self-Assembly

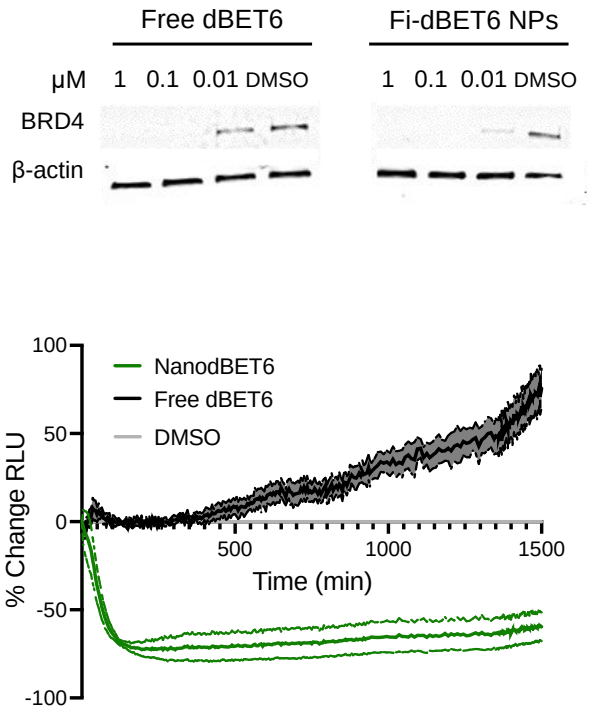


Predicting Nanoparticle Size

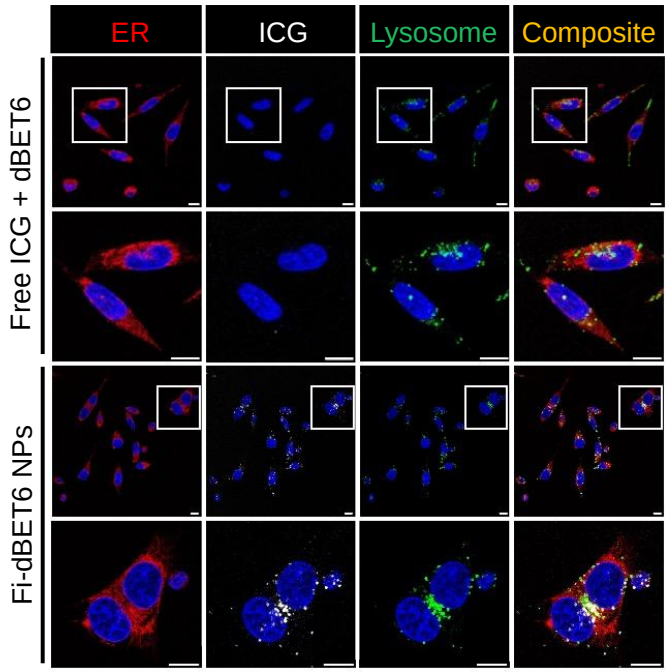


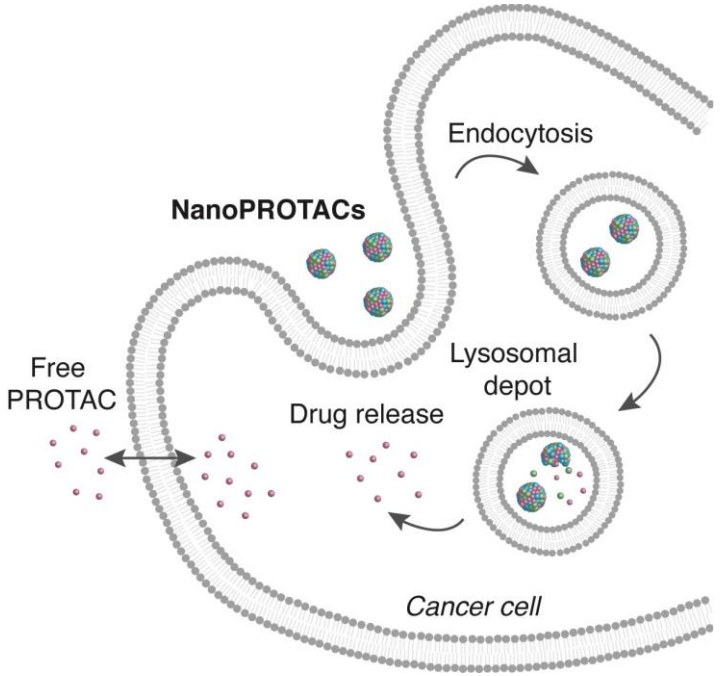
Vogt, et al., Unpublished

Do the Nanoaggregates Improve Drug Delivery/Efficacy?



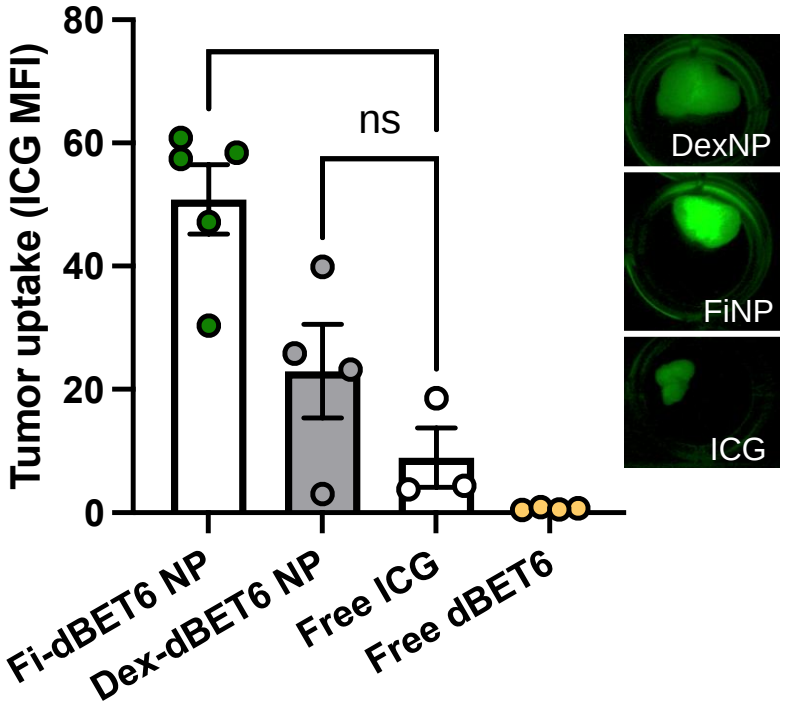
Lysosomal Sequestration



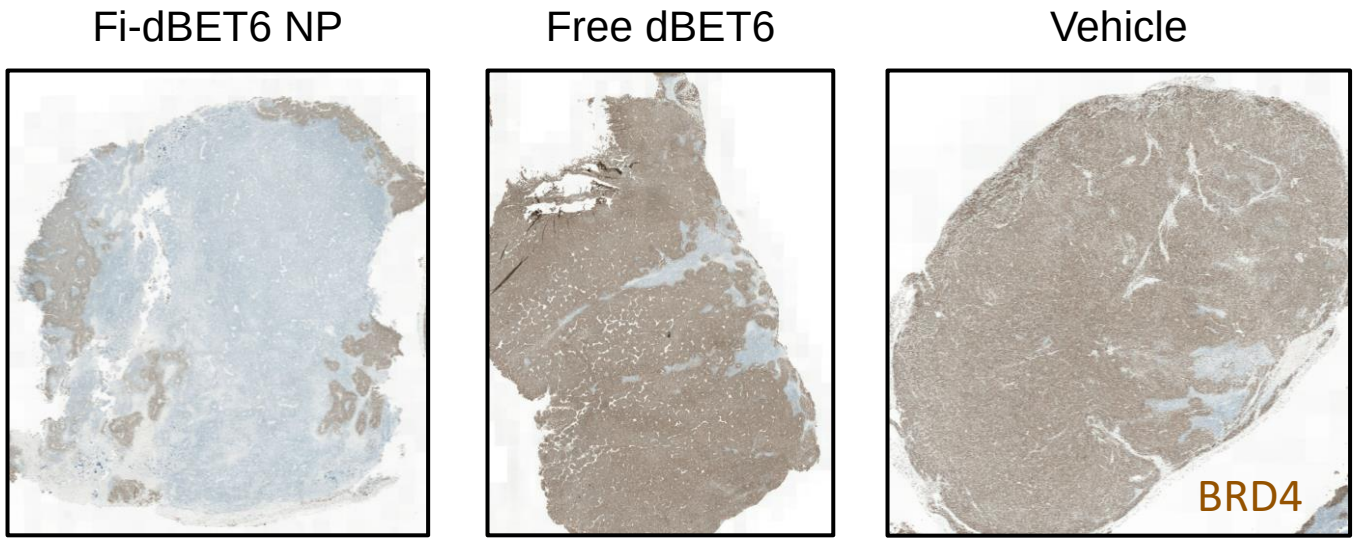


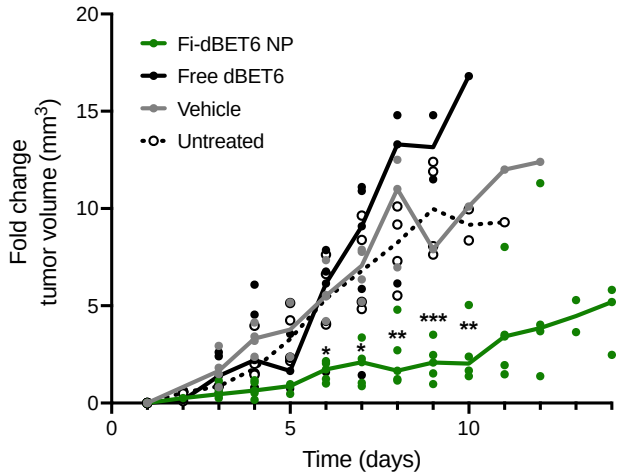
BRD4 Degrader PROTAC NPs Localize to Tumor Xenografts and Efficiently Degrade Target

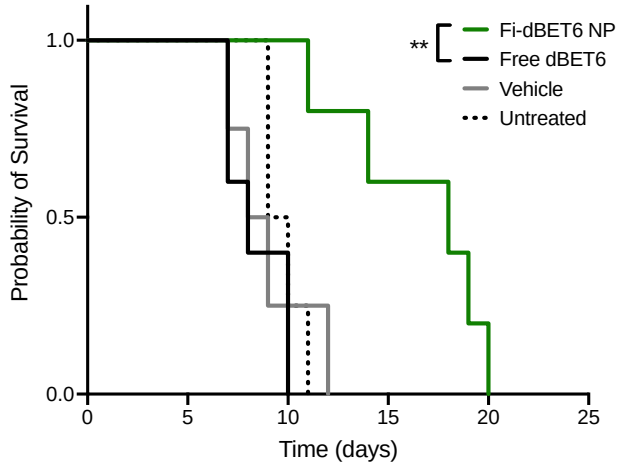
Biodistribution



Target degradation

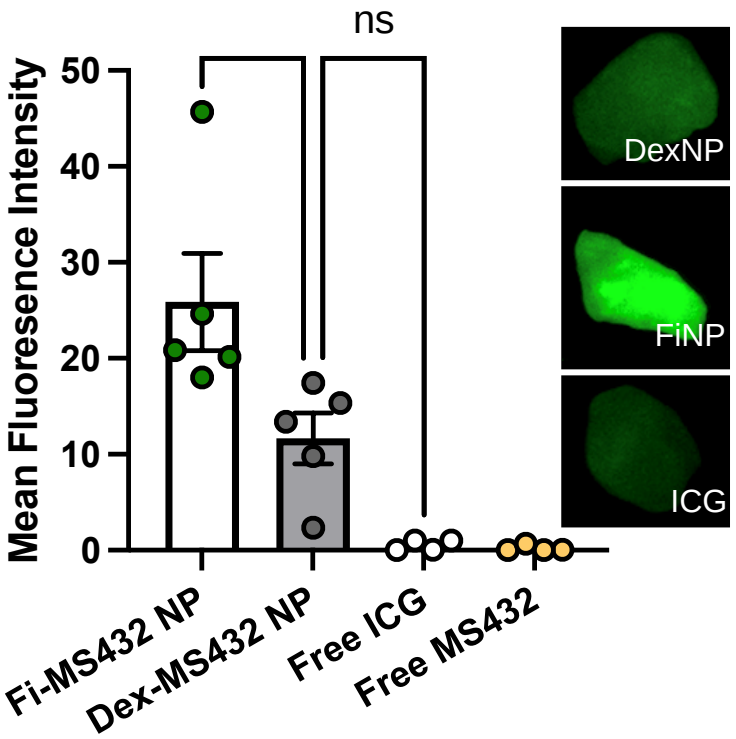




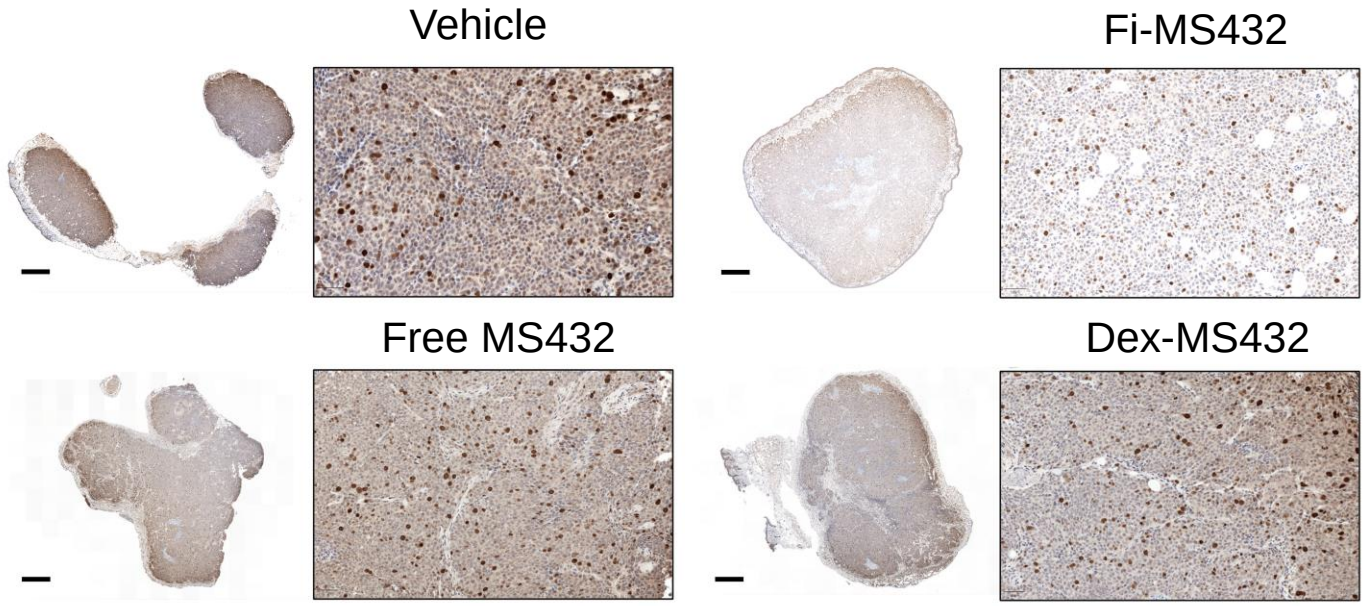


MEK Degrader NPs Localize to P-selectin Positive Xenografts and Efficiently Degrade Target

Biodistribution

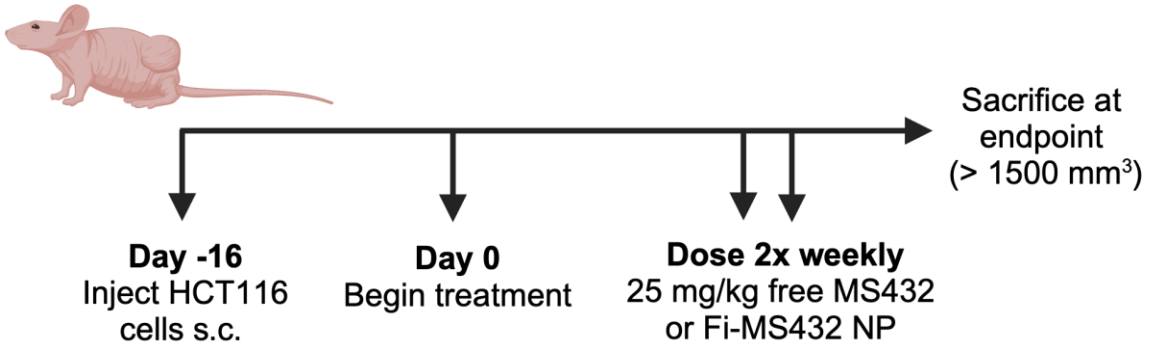


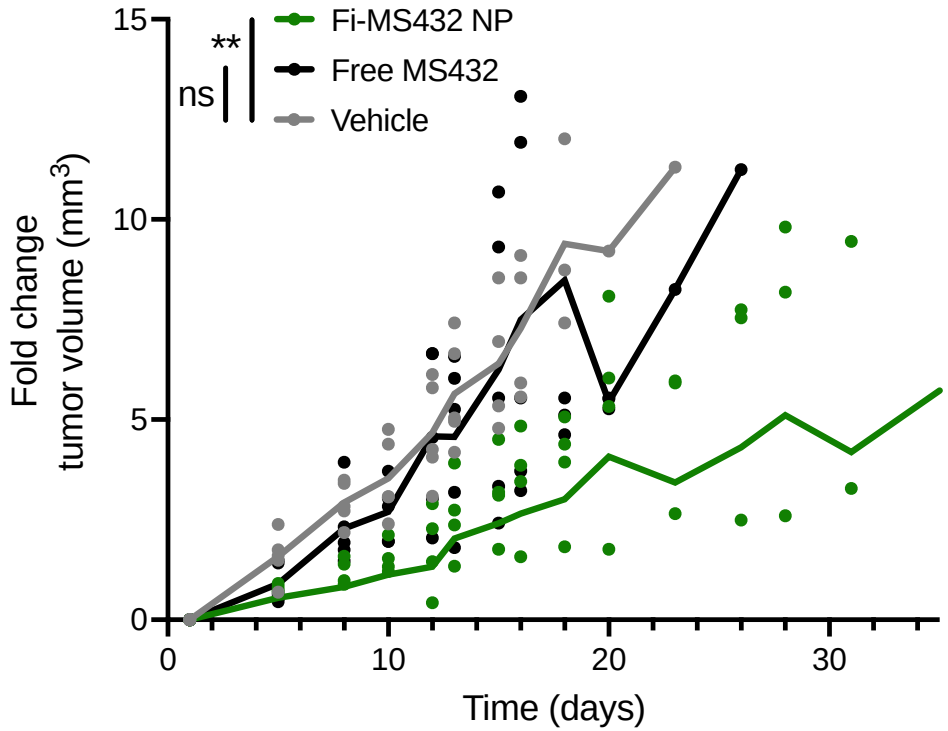
Target degradation

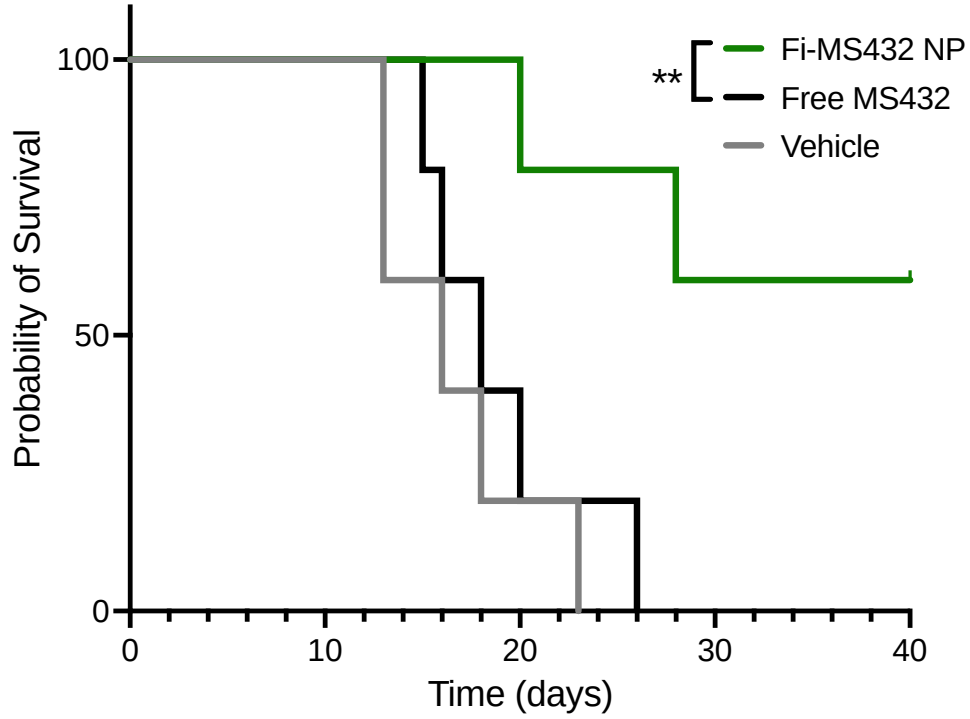


Vogt, et al., Unpublished

Fi-MS432 NPs Improve Anti-tumor Efficacy in Colorectal Cancer Xenografts



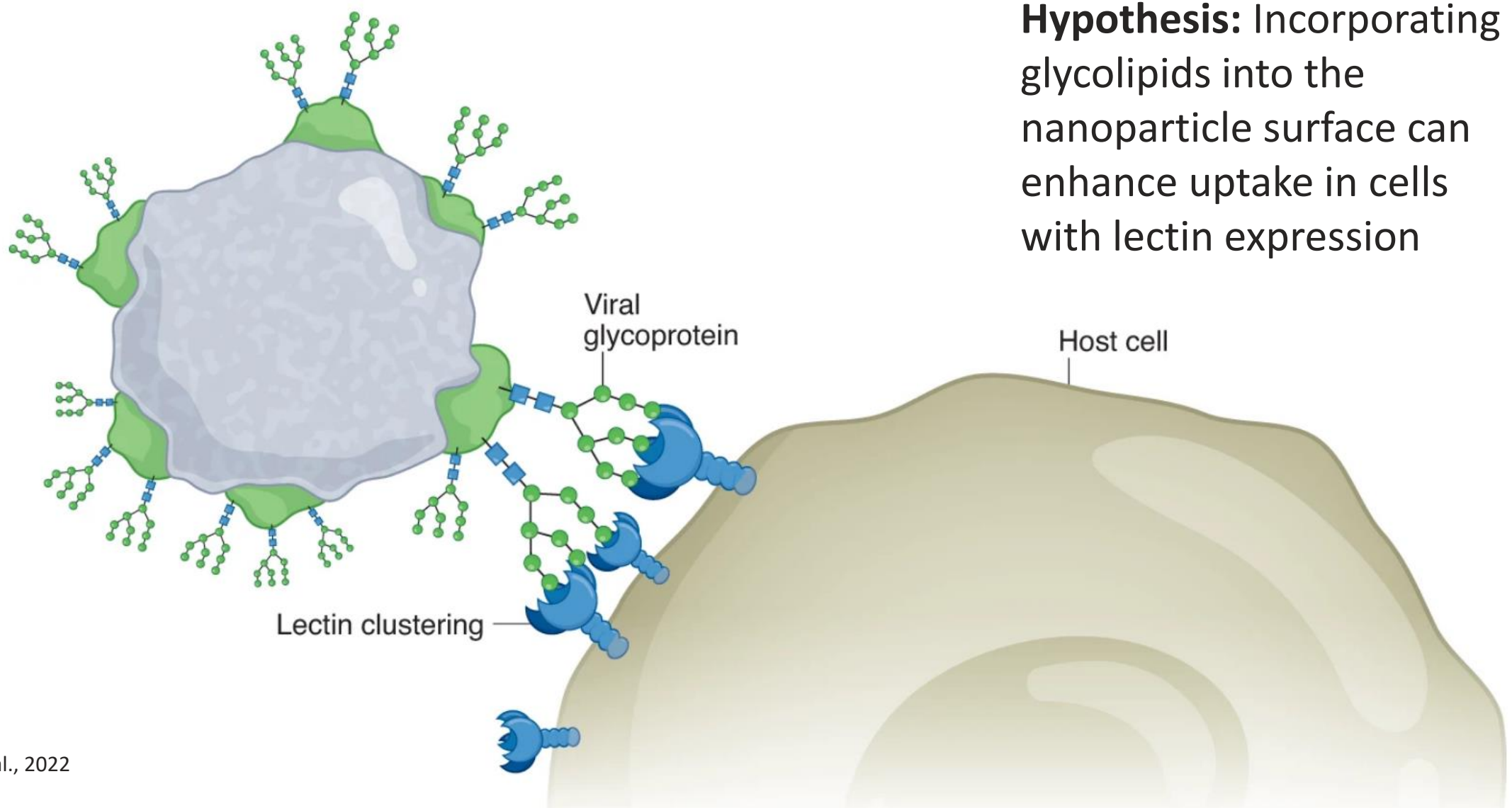




How to Enhance the Targeted Nanoformulation Versatility?

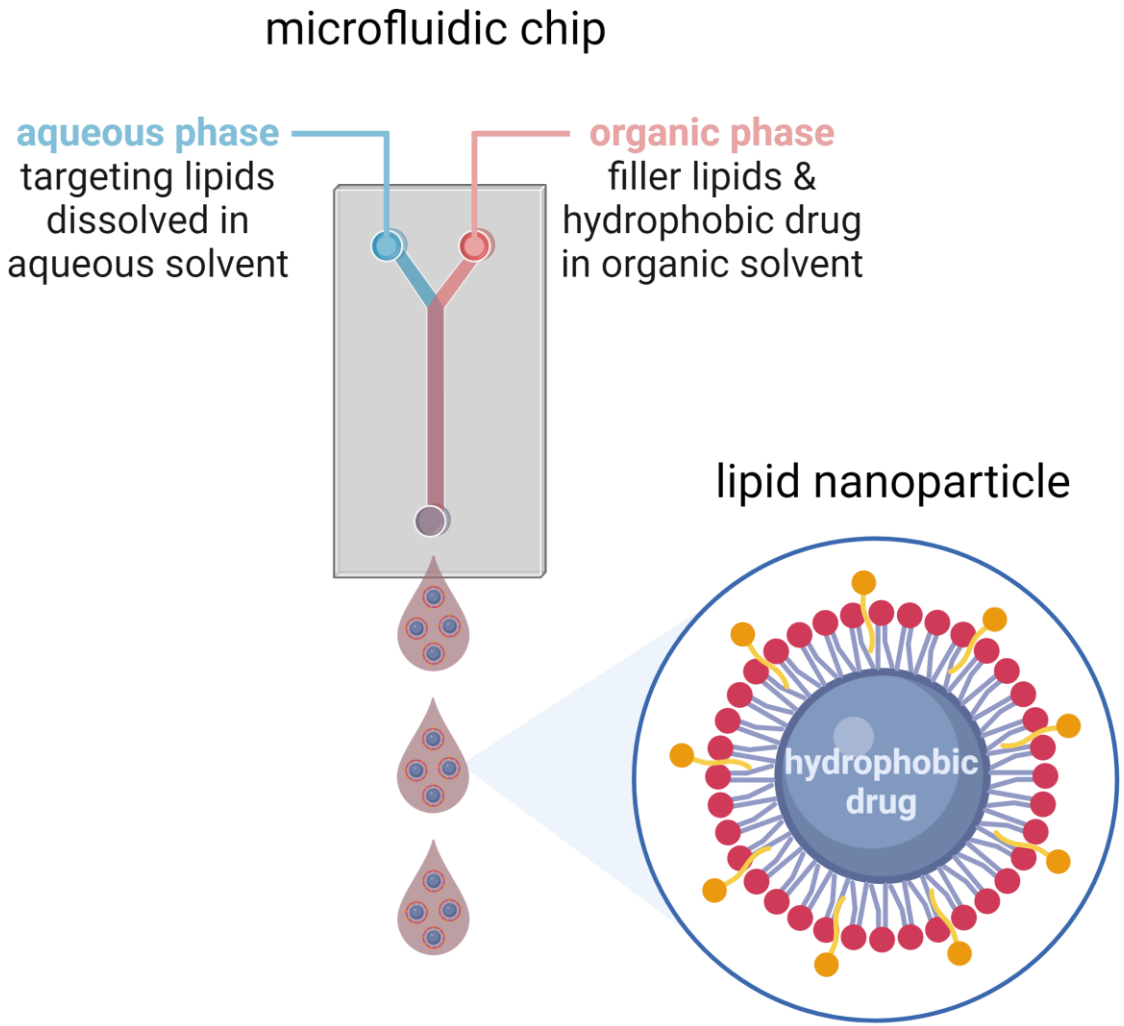
Targeting Lectins via Glycolipids

Hypothesis: Incorporating glycolipids into the nanoparticle surface can enhance uptake in cells with lectin expression



Dugan et al., 2022

Can Lipid/Glycolipid Nanoformulations Enable Versatile Tissue Targeting and Scalability?



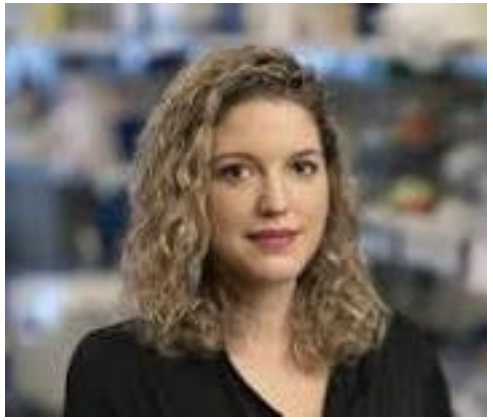
filler lipids

Naturally derived

phospholipids

targeting lipids

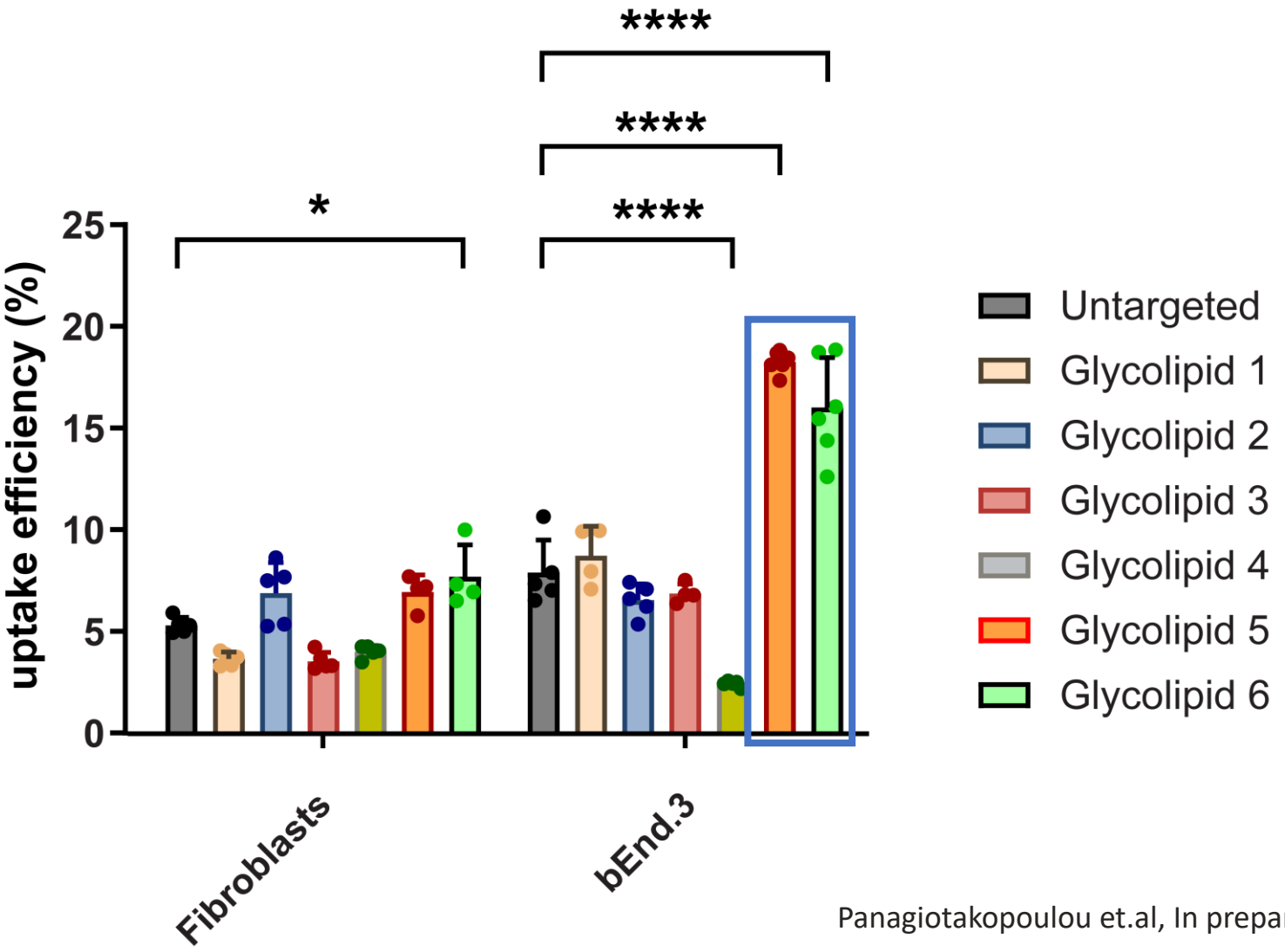
glycolipids



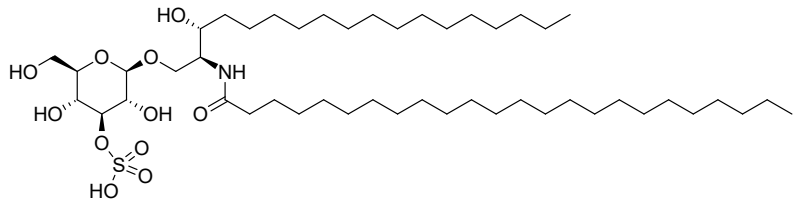
Magdalini Panagiotakopoulou

Emma Grabarnik

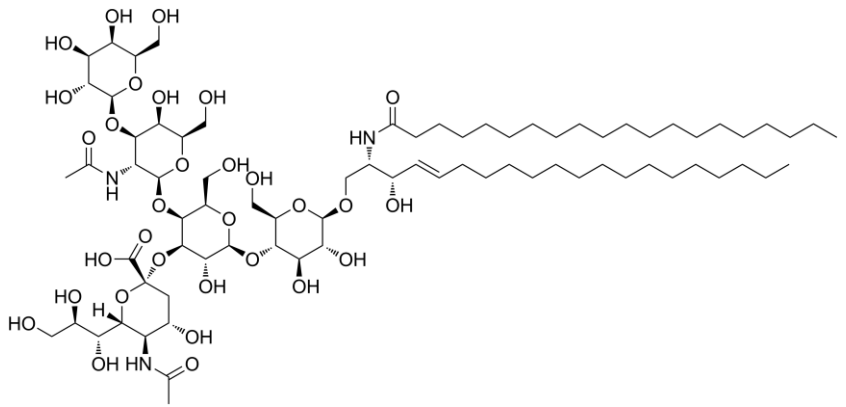
Several Glycolipids Can Target Endothelial Cells



Glycolipid 6 — **Affinity to P-selectin**



Gylcolipid 5 — **Affinity to Galectin-3**



Panagiotakopoulou et.al, In preparation

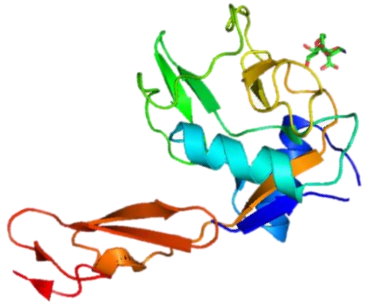
McEver et al., 2015

Corporall et al., 2015

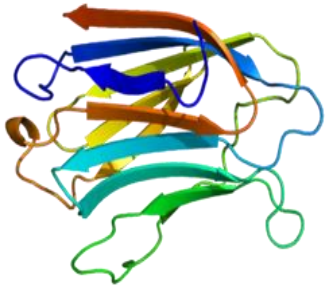
Zanden et al., 2022

Lete et al., 2022

P-selectin and Galectin-3: In Cancer and Inflammation



P-selectin



Galectin-3

- Role in cell adhesion and migration
- Involvement in regulation of immune response

- Upregulation **in cancer, inflammation, fibrosis, cardiovascular diseases**

Barondes et al., J Biol Chem, 1994

Henderson and Sethi, Immunol Rev, 2009

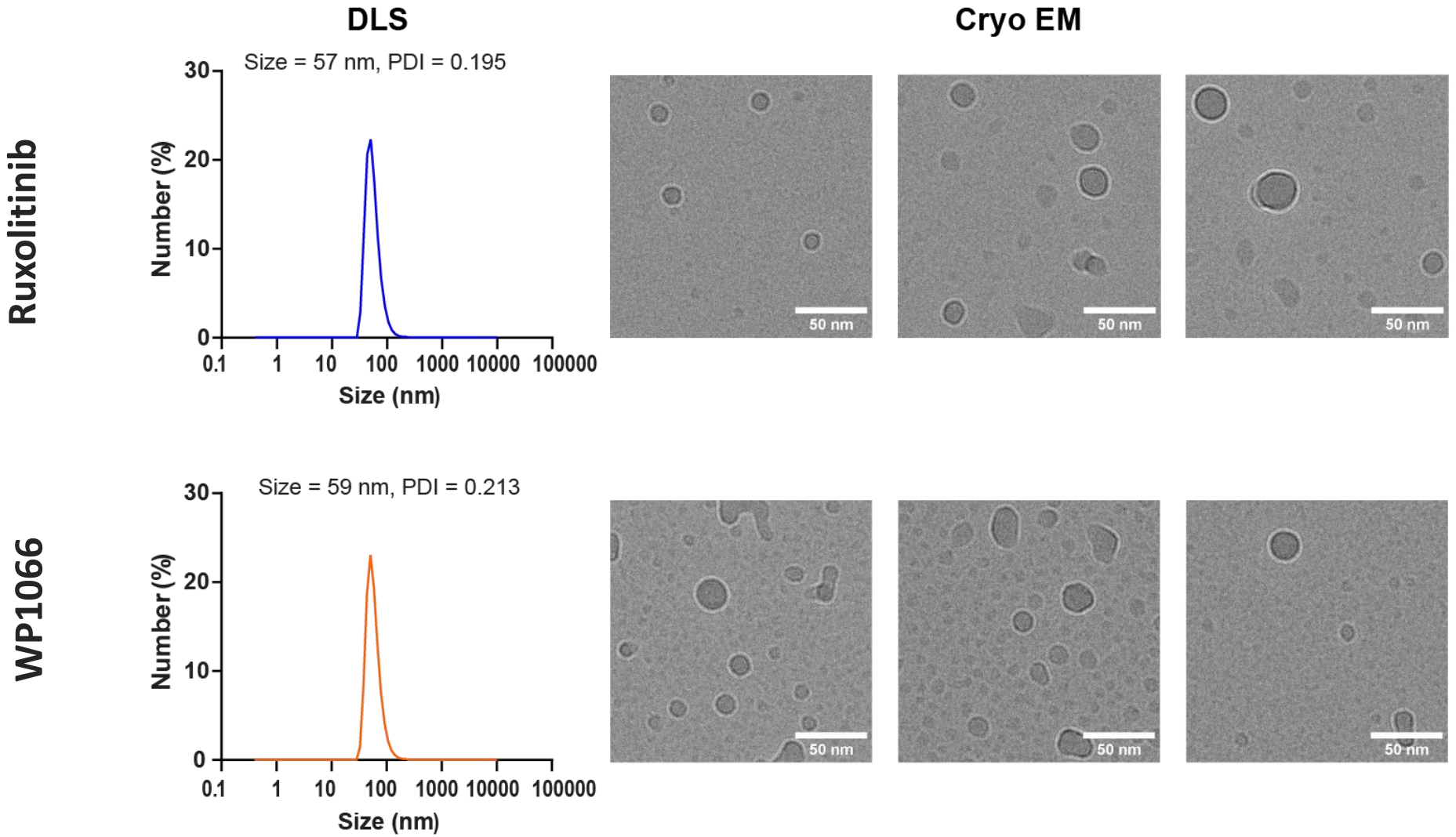
Henderson et al., Am J Pathol, 2008

Gordon-Alonso et al., Nat Commun, 2017

Shamay et al., Sci. Transl. Med., 2016

Tylawsky et al., Nat. Mater., 2023

Drug Core Lipid Nanoparticles with Small Sizes and High Encapsulation Efficiency



Panagiotakopoulou et.al, unpublished

Descriptor/Machine Learning Analysis

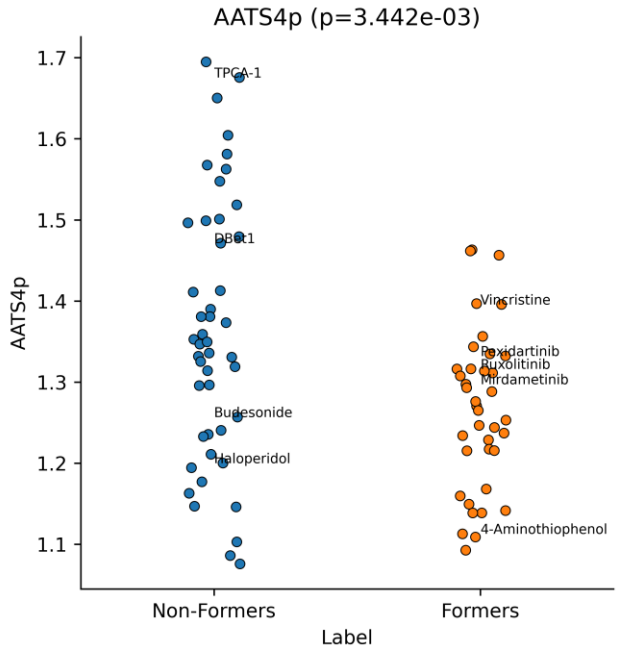
1. Experimental Data:

LNPs with **90 different drugs, 3 different targeting lipids**

2. Drug Labelling:
Clustering into *formers* and *non formers* (size, PDI, etc)

+

3. Cheminformatics Data:
Calculation of **1500 molecular descriptors** for each drug

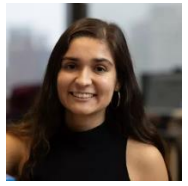


4. Descriptor selection:
Identify descriptors significantly different between formers and non formers

5. Machine Learning

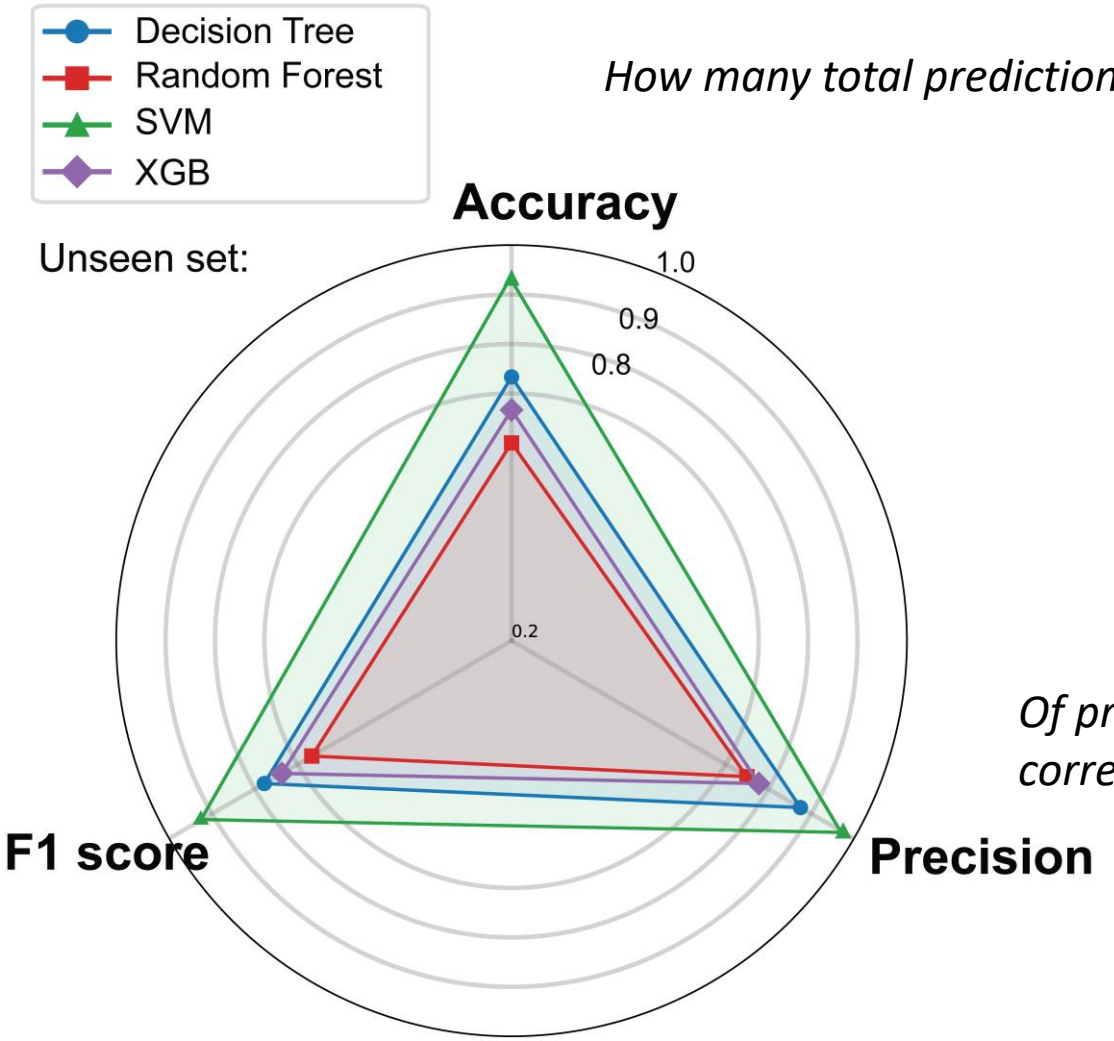
- **Decision Tree (DT)**
- **Random Forest (RF)**
- **Support Vector Machine (SVM)**
- **XGBoost (XGB)**


Ashley Sullivan


Ana Marie Perea Del Angel

QSNAP-ML Predicts Formability of an Unseen Drug

Unseen set:
20 recently FDA-approved drugs

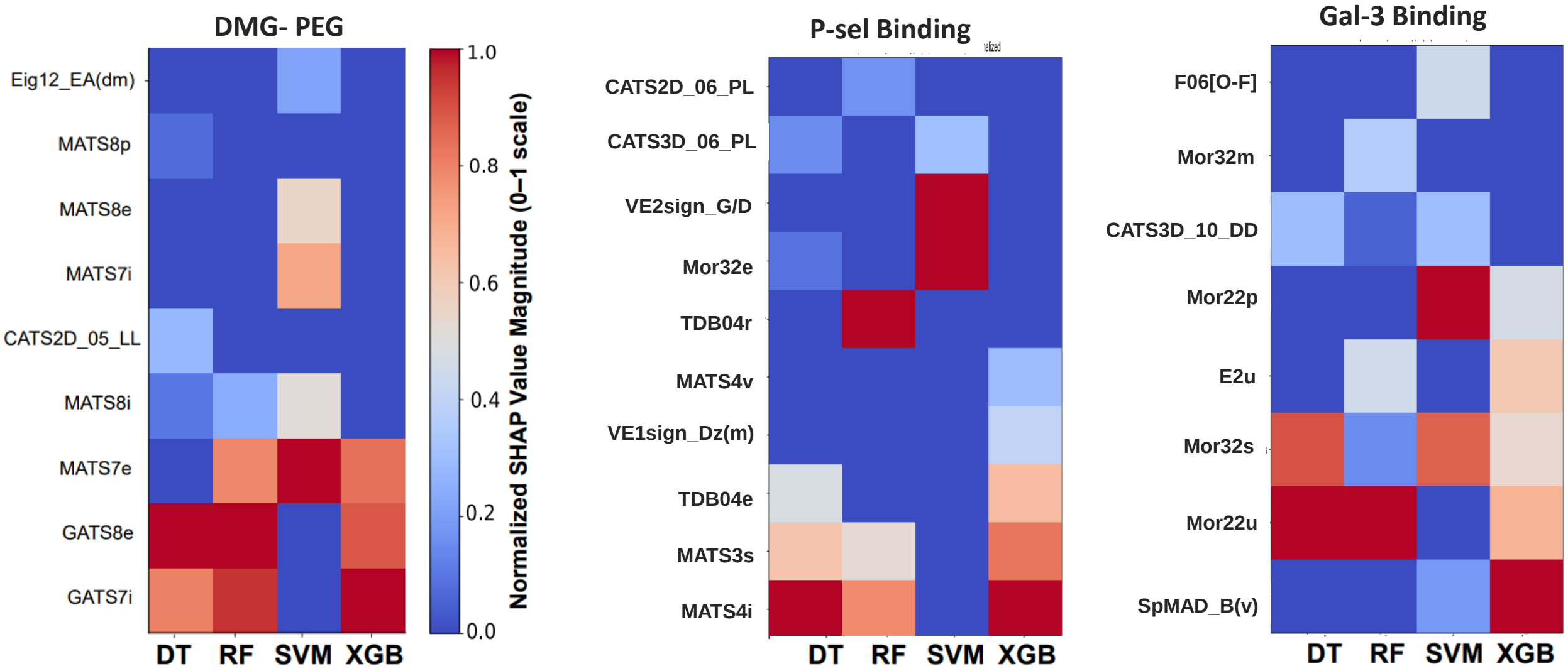


How many total predictions were correct?

An overall metric of the model performance, taking into account false negatives and false positives

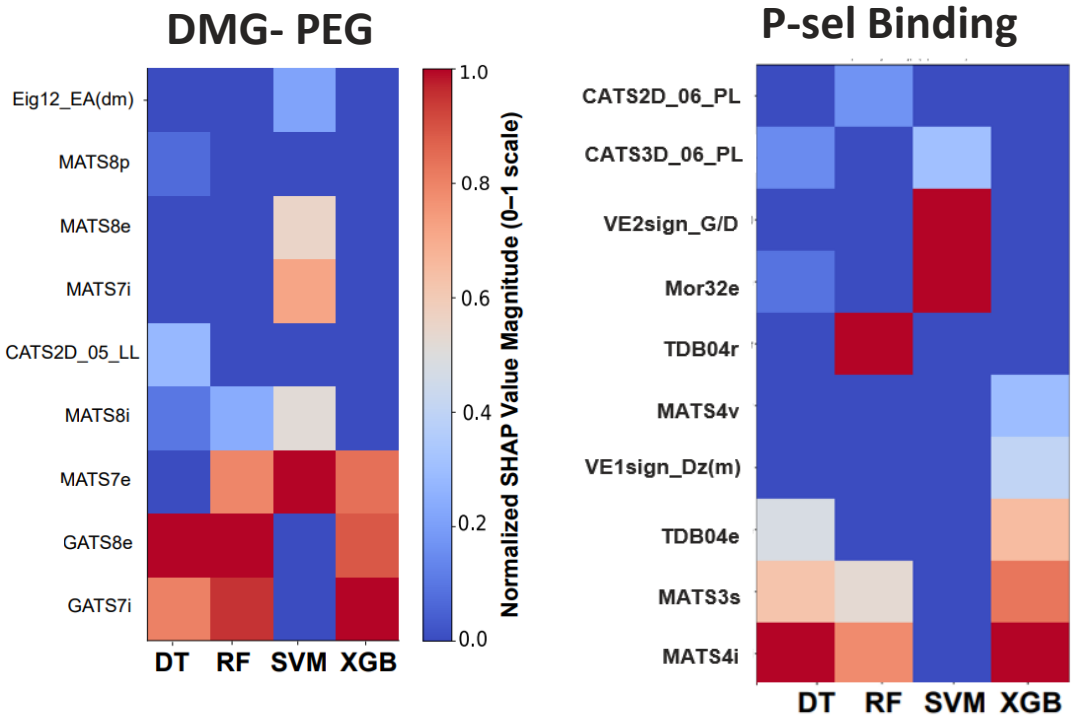
Of predicted positives, how many were correct?

ML Helps us Identify Top Features that Impact Drug Encapsulation



Panagiotakopoulou et.al, In preparation

ML Helps us Identify Top Features that Impact Drug Encapsulation



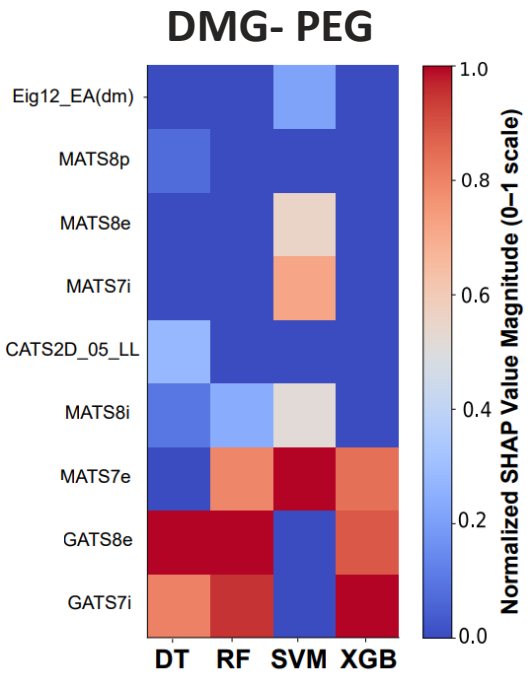
PEG, P-sel: :

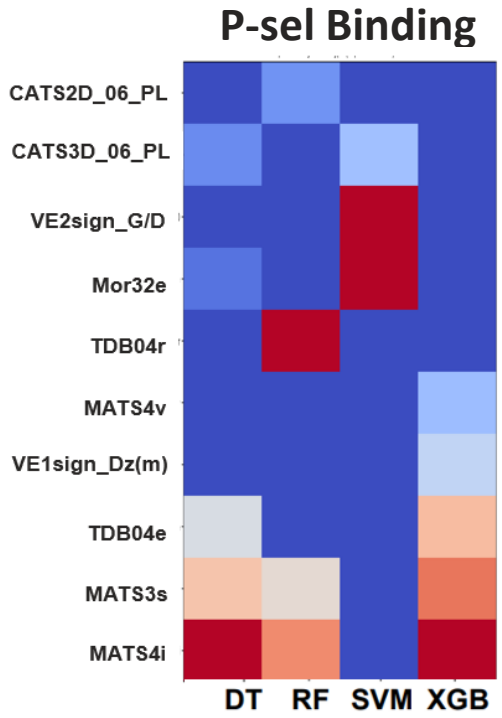
MATS(n)i
MATS(n)e
GATS(n)I
GATS(n)e

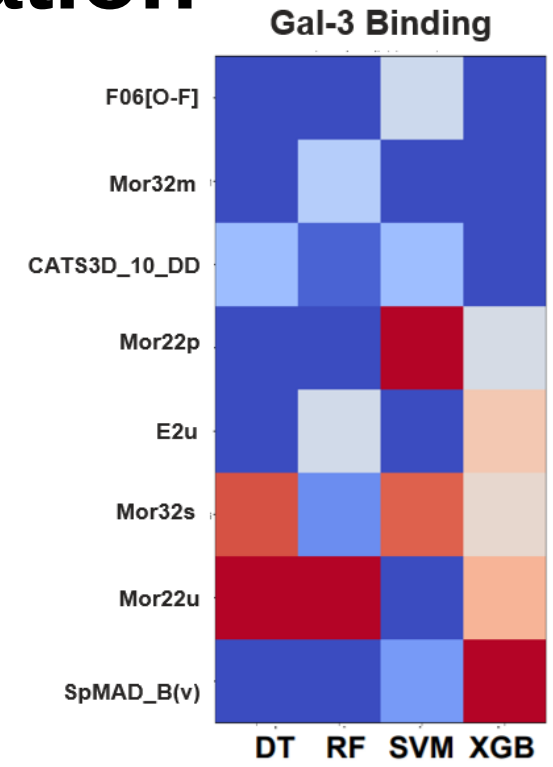
2D autocorrelation of **ionization potential (i), or electronegativity (e)**

Electronic properties over n bonds

ML Helps us Identify Top Features that Impact Drug Encapsulation







PEG, P-sel: :

MATS(n)i
MATS(n)e
GATS(n)I
GATS(n)e

2D autocorrelation of **ionization potential (i), or electronegativity (e)**

Electronic properties over n bonds

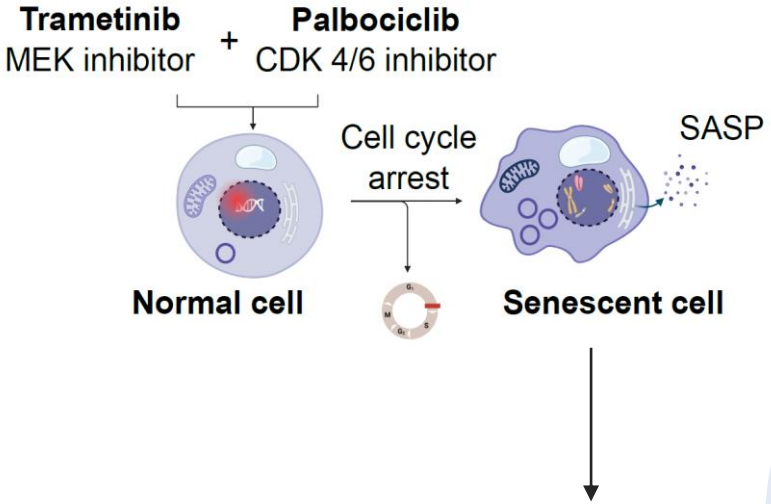
Gal-3:

Mor22u/p, SpMAD_B(v)

3D-MoRSE, Graph-based branching and density

3D geometry, **valence branching**, spatial organization of structure

Senescence Induction Followed by Senescent Cell Clearance as a treatment strategy



Reduce pro-tumorigenic inflammation

Enable re-entry to the cell cycle

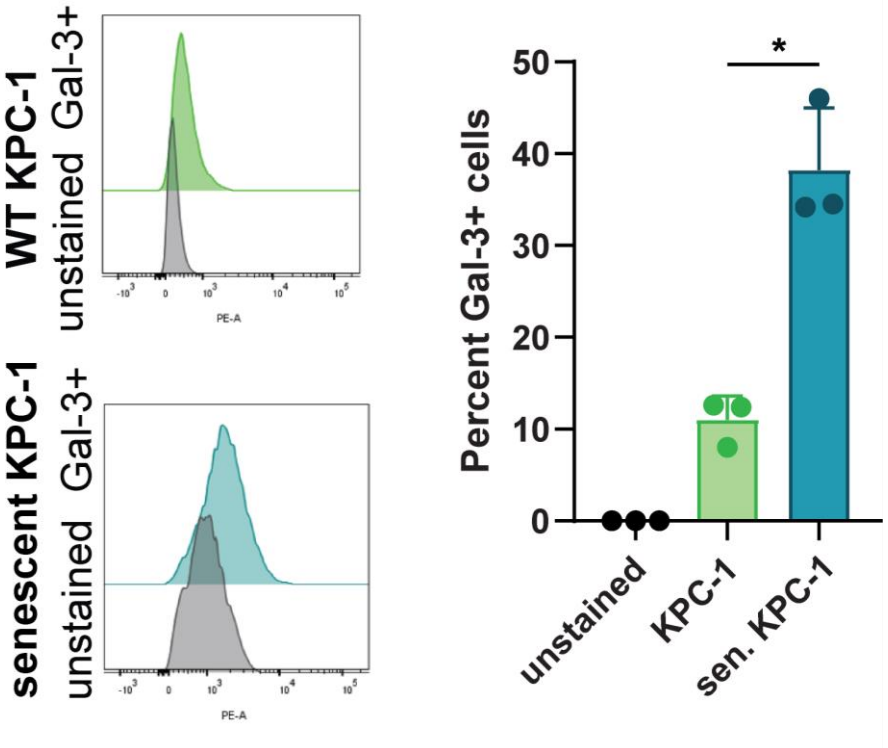
1. Inducing senescence

"One-two punch treatment"

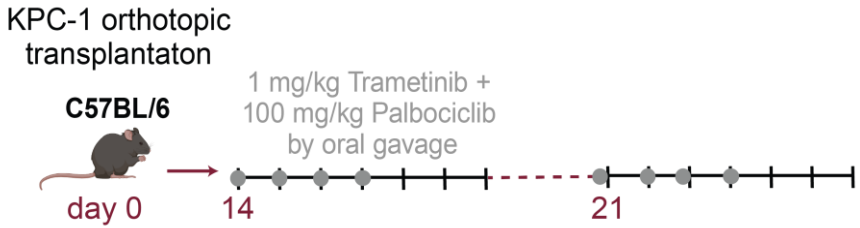
2. Clearing Senescent Cells

Galectin-3 Enables the Targeting of Senescent PDAC

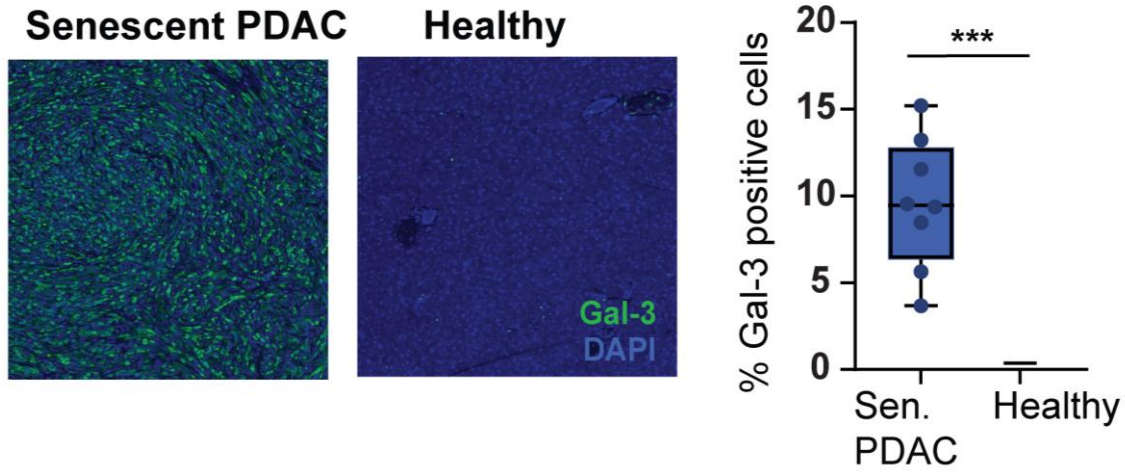
In vitro **overexpression on the cell surface of senescent KPC-1 cells**



In vivo **overexpression in senescent KPC-1 tumors**



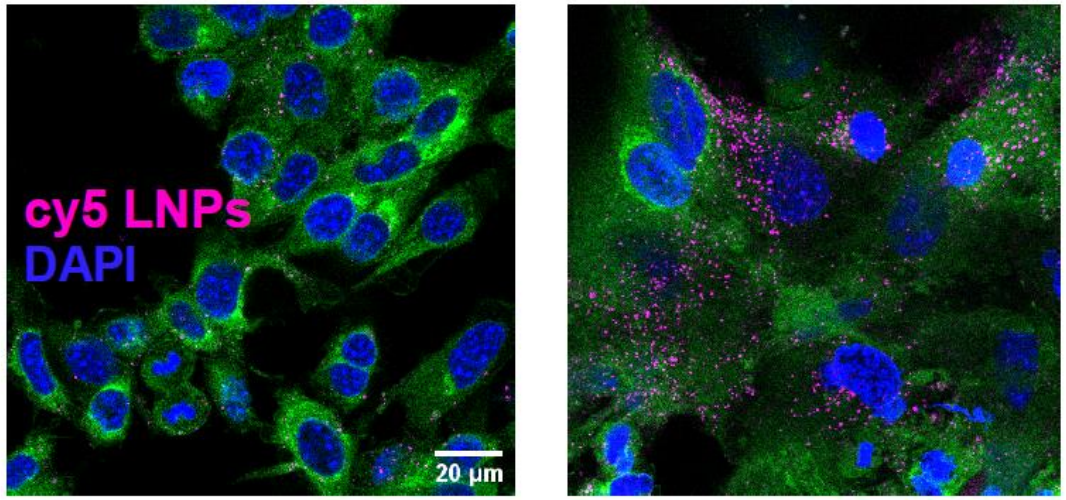
mouse tissue



Panagiotakopoulou et.al, In preparation

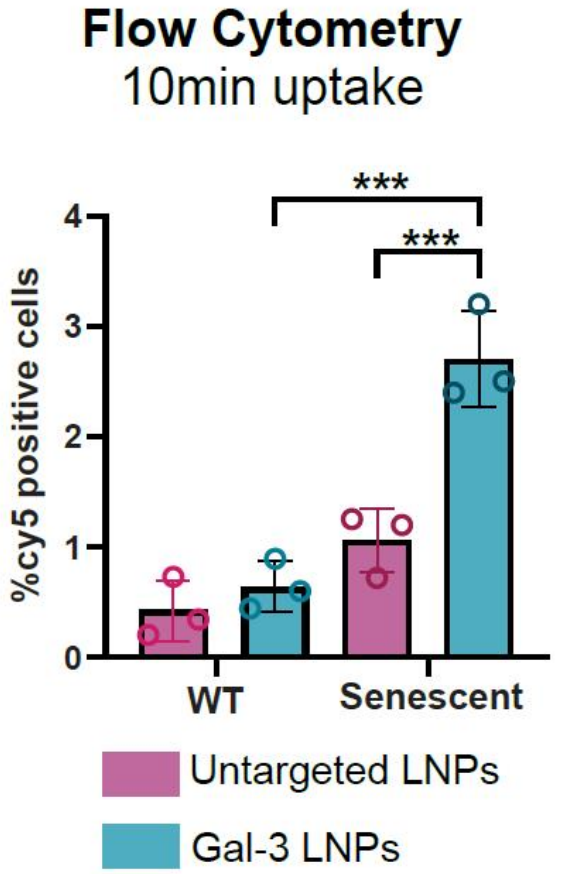
Senescent Tumor Cells Preferentially Take Up Galectin-3-Targeted Lipid Nanoparticles

Particles are conjugated to a **cy5 - fluorescent lipid,** uptake is measured by **microscopy** and **flow cytometry**



WT Senescent

Microscopy, 15 minute uptake



** p < 0.001, ordinary one-way ANOVA

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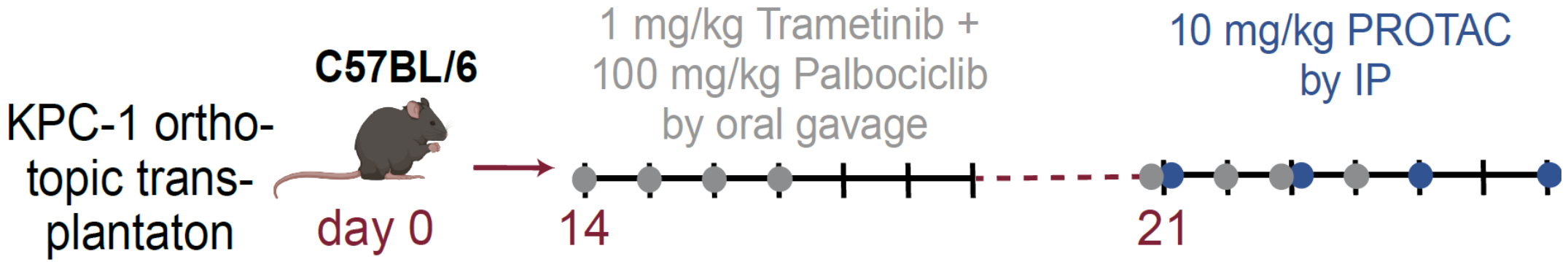
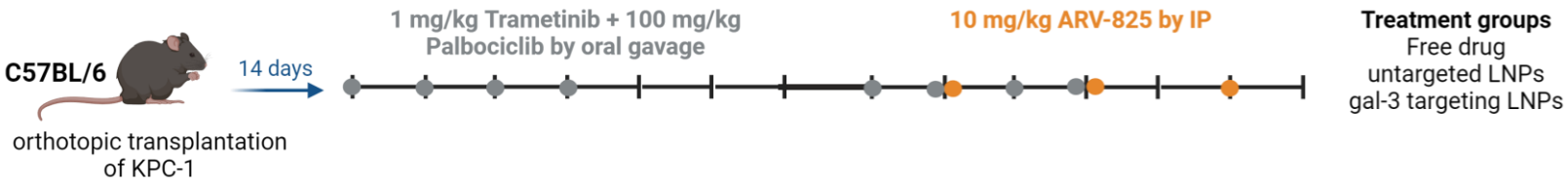
Senescence + Gal-3-Targeted Lipid BRD4 NanoPROTAC Efficacy Study



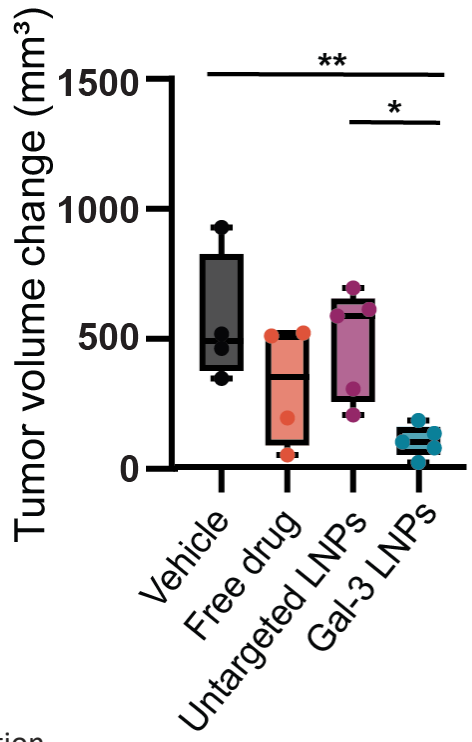
Treatment groups

Free drug
Untargeted LNPs
Gal-3 targeting LNPs
Vehicle

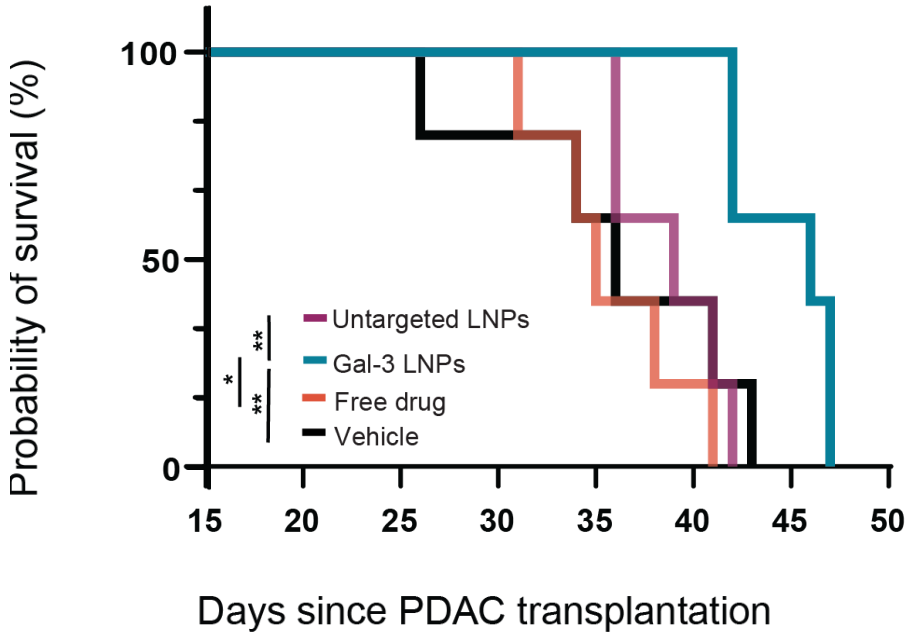
Senescence + Gal-3 LNP NanoPROTACs Reduce Tumor Growth and Prolongs Mouse Survival



Sen + targeted LNPs: lower growth



Sen + targeted LNPs: better survival



- Kaplan-Meier survival, ** $p < 0.01$, * $p < 0.05$ by Log-rank (Mantel-Cox) test, n=5

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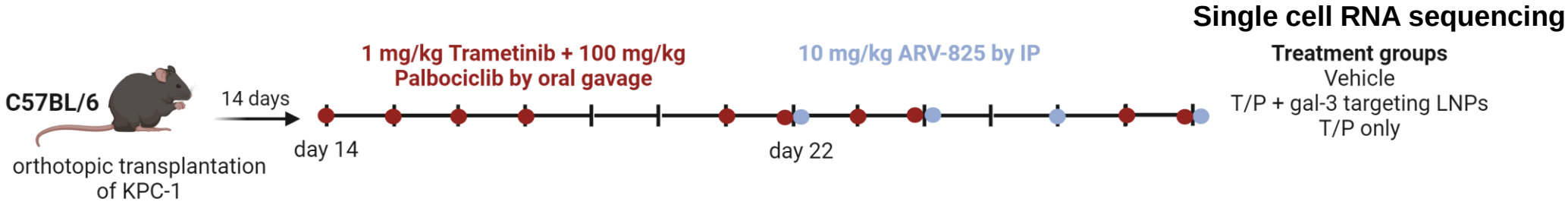
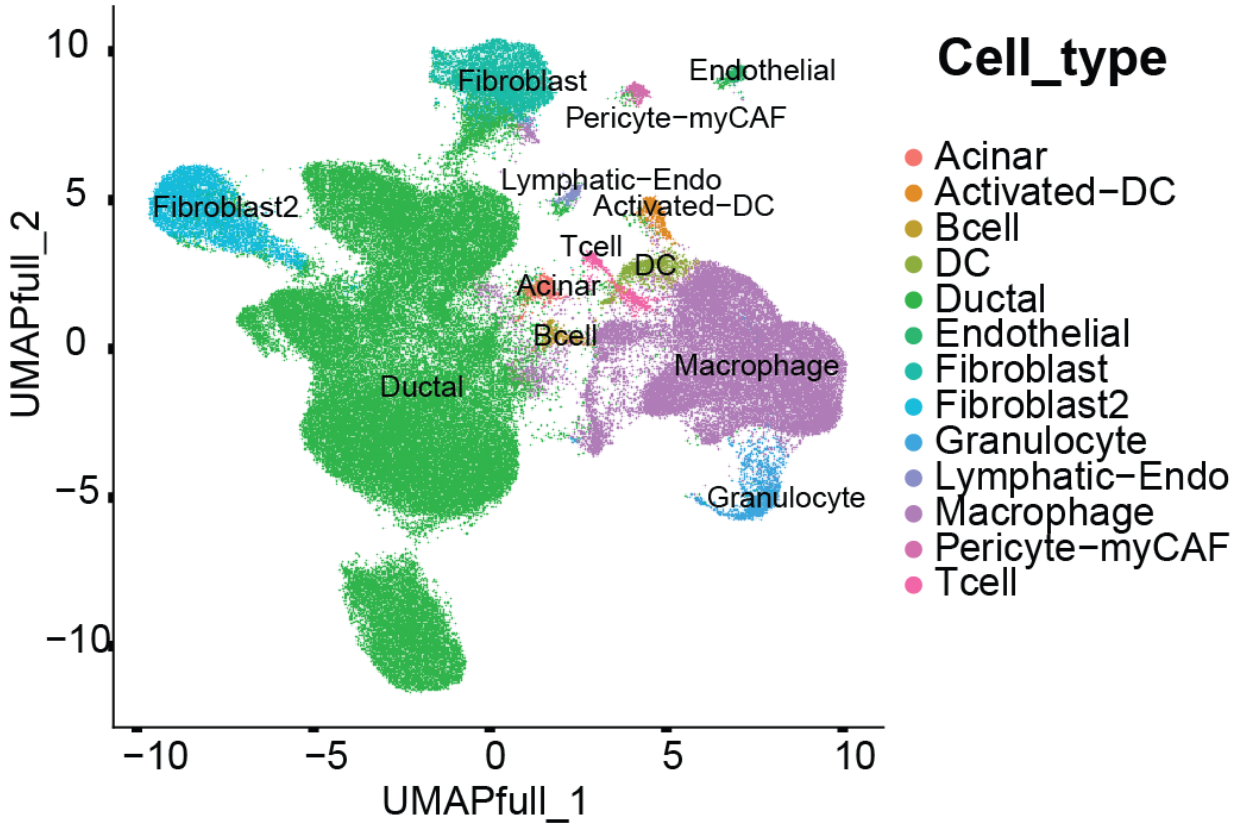
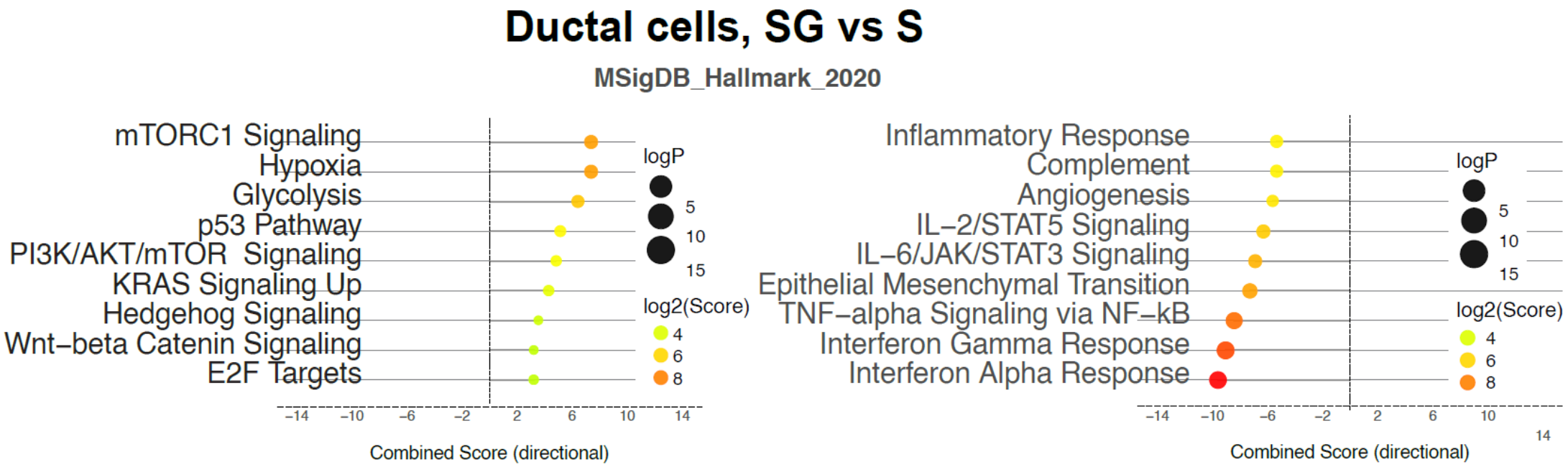
scRNA seq Investigation of Senolytic Effects in PDAC Cell Subpopulations





Cancer Ductal Cells:
Stress Pathways Up, Inflammation Pathways Down



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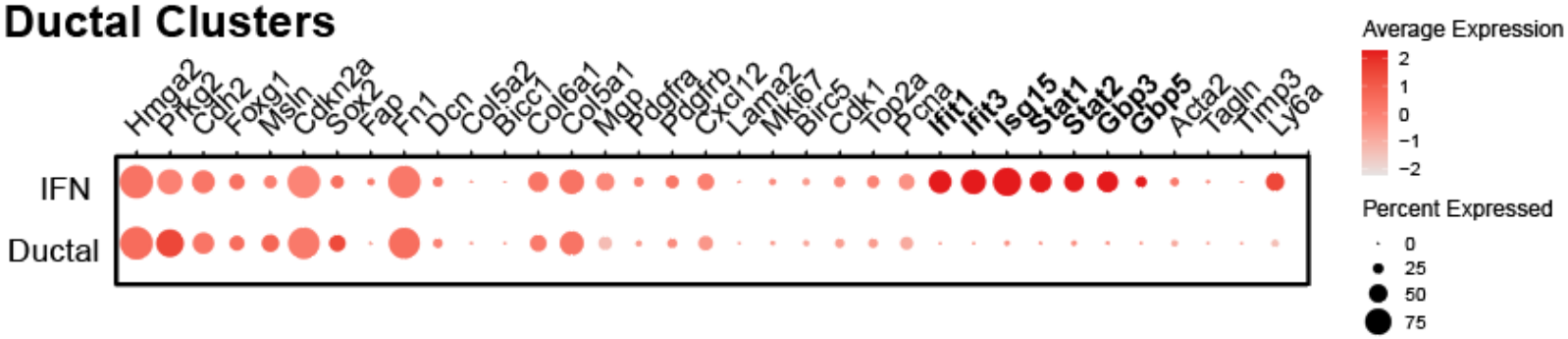
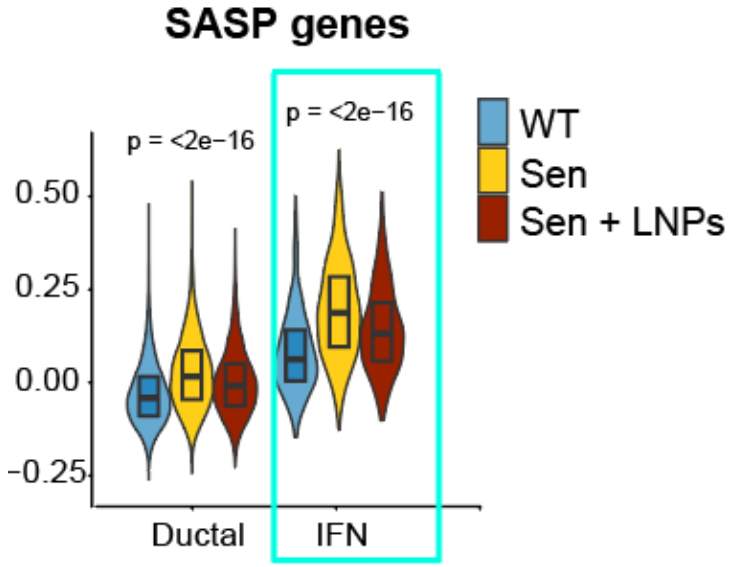
Gal-3 Targeted LNPs are Reducing SASP in IFN-γ Cell Clusters





Panagiotakopoulou et.al, In preparation

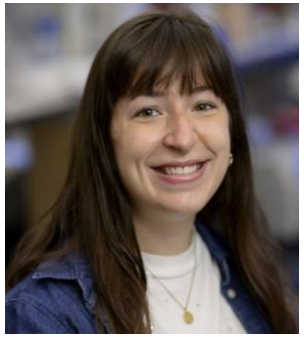
Summary & Next Questions

- Data analytics/AI can predict drug assembly into nanoparticles.
- Non-drug-like drugs can be predicted to self-assemble.
- Nanoparticles can improve drug pharmacokinetics/efficacy of PROTACs.
- Question: How can novel vehicles + novel cargoes be simultaneously advanced to the clinic?

Magdalini Panagiotakopoulou

Emma Grabarnik

Yosi Shamay

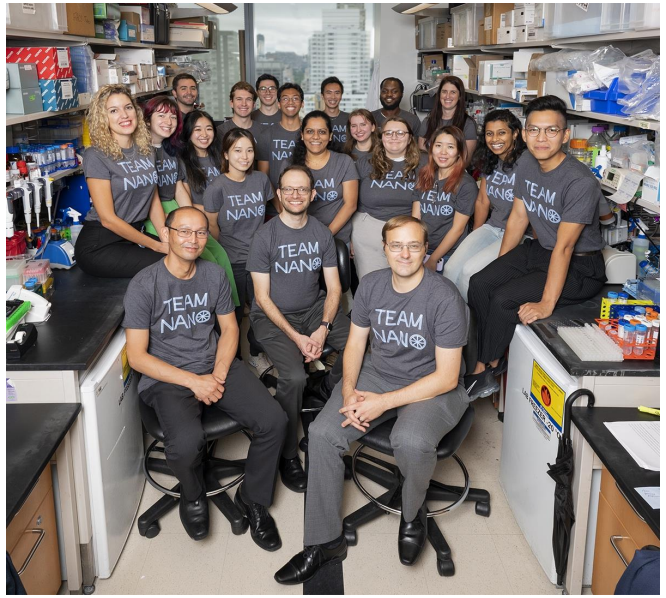


Kristen Vogt

Shamay, et al., *Nat Mater*, 2018
Chen, et al., *Nat Commun*, 2023
Berisha, et a., *Chem*, 2025
Vogt, et al., *Unpublished* 2025

Panagiotakopoulou, unpublished
Panagiotakopoulou, unpublished
Panagiotakopoulou, unpublished

Acknowledgements



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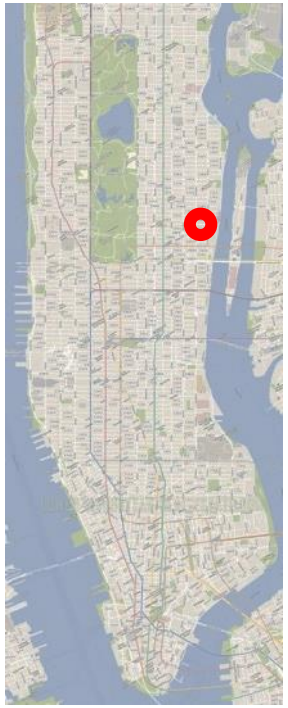
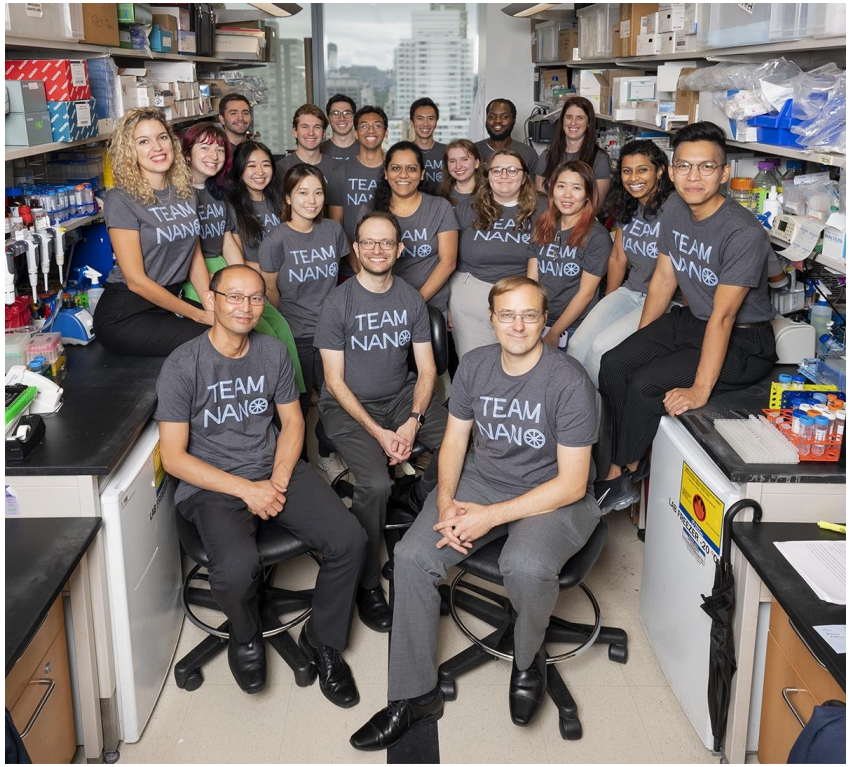
Experimental Therapeutics Center, MSKCC

A Biomedical Engineering Lab at Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine





Memorial Sloan-Kettering Cancer Center

Gerstner Sloan Kettering PhD Program in Cancer Engineering

Weill Cornell Medicine Graduate School of Medical Sciences
A partnership with the Sloan Kettering Institute

Tri-Institutional PhD Program Chemical Biology

Daniel A. Heller, PhD
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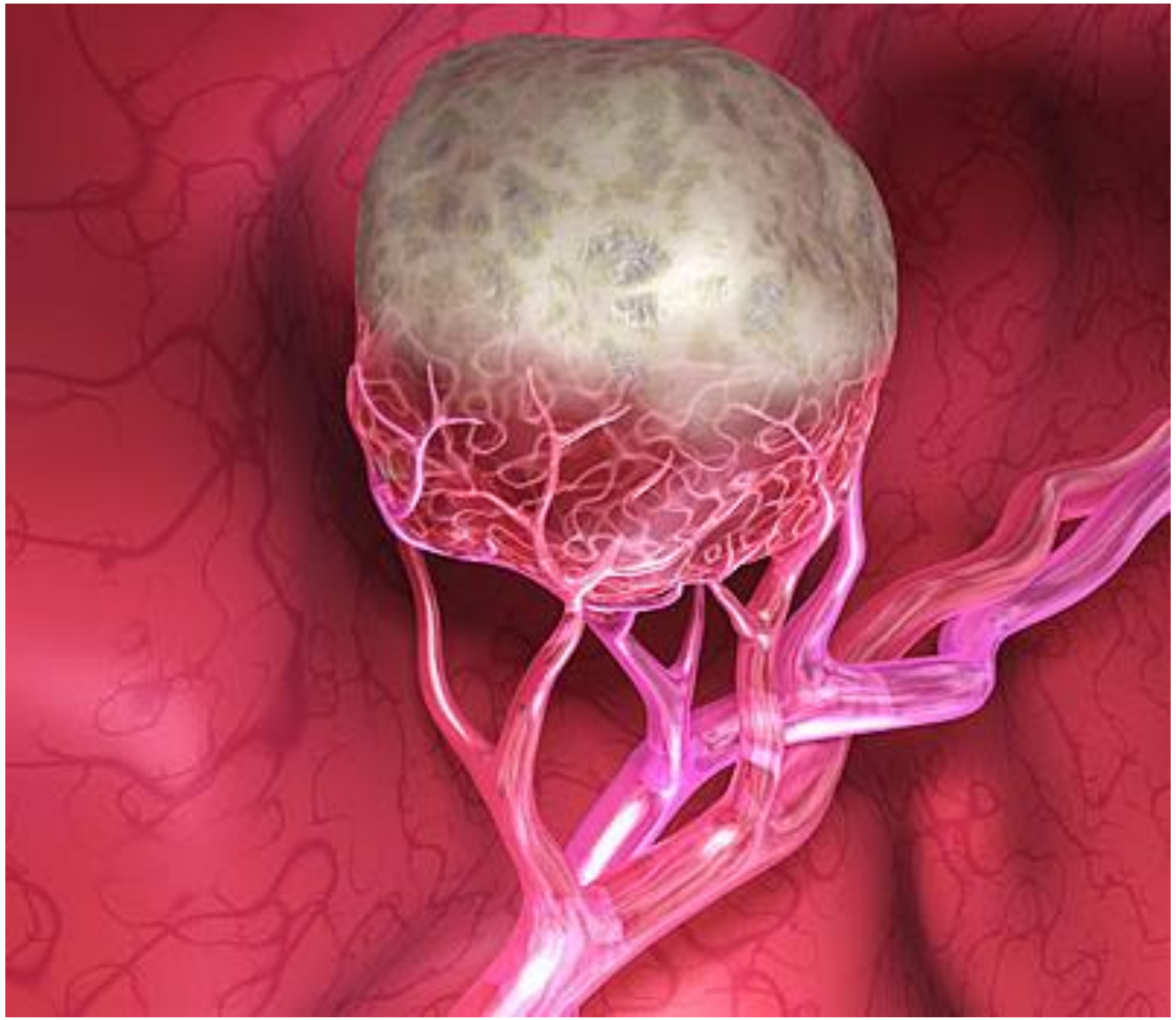
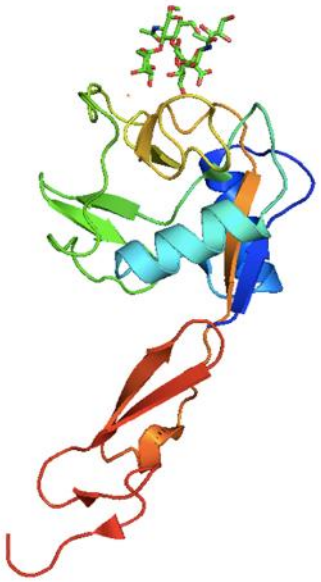
www.mskcc.org/research-areas/labs/daniel-heller
@HellerLab, @Dan_A_Heller

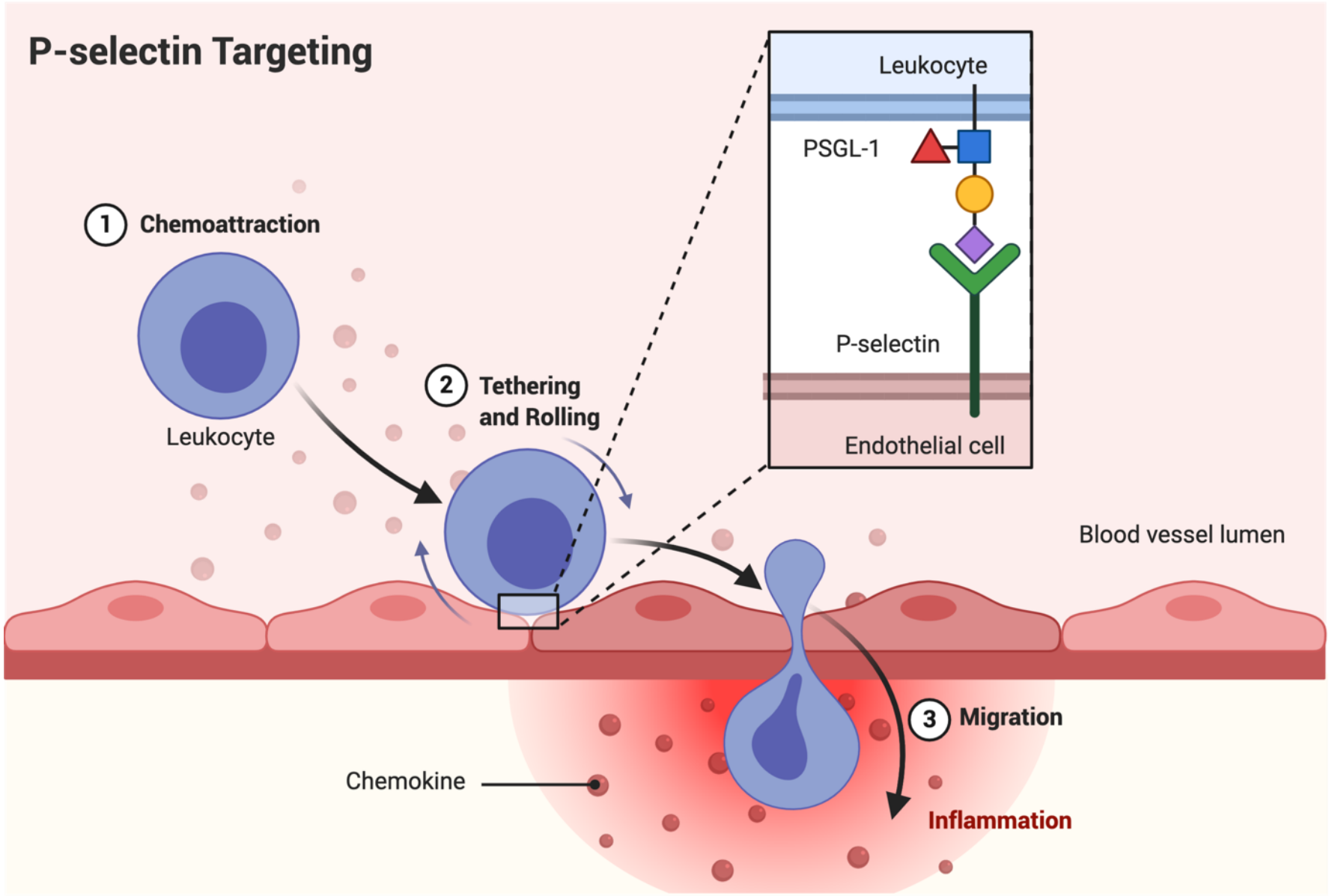
How Can We Target Tumor Endothelium?



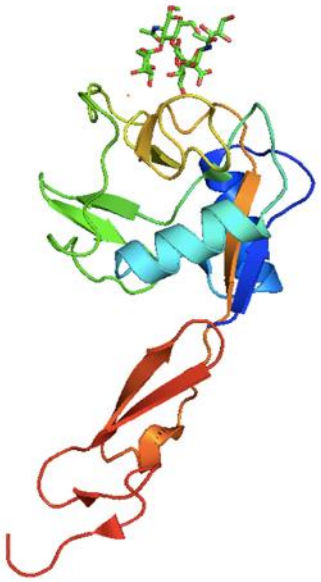
P-selectin is Released to Surface of Activated Endothelial Cells for Immune Cell Localization and Extravasation



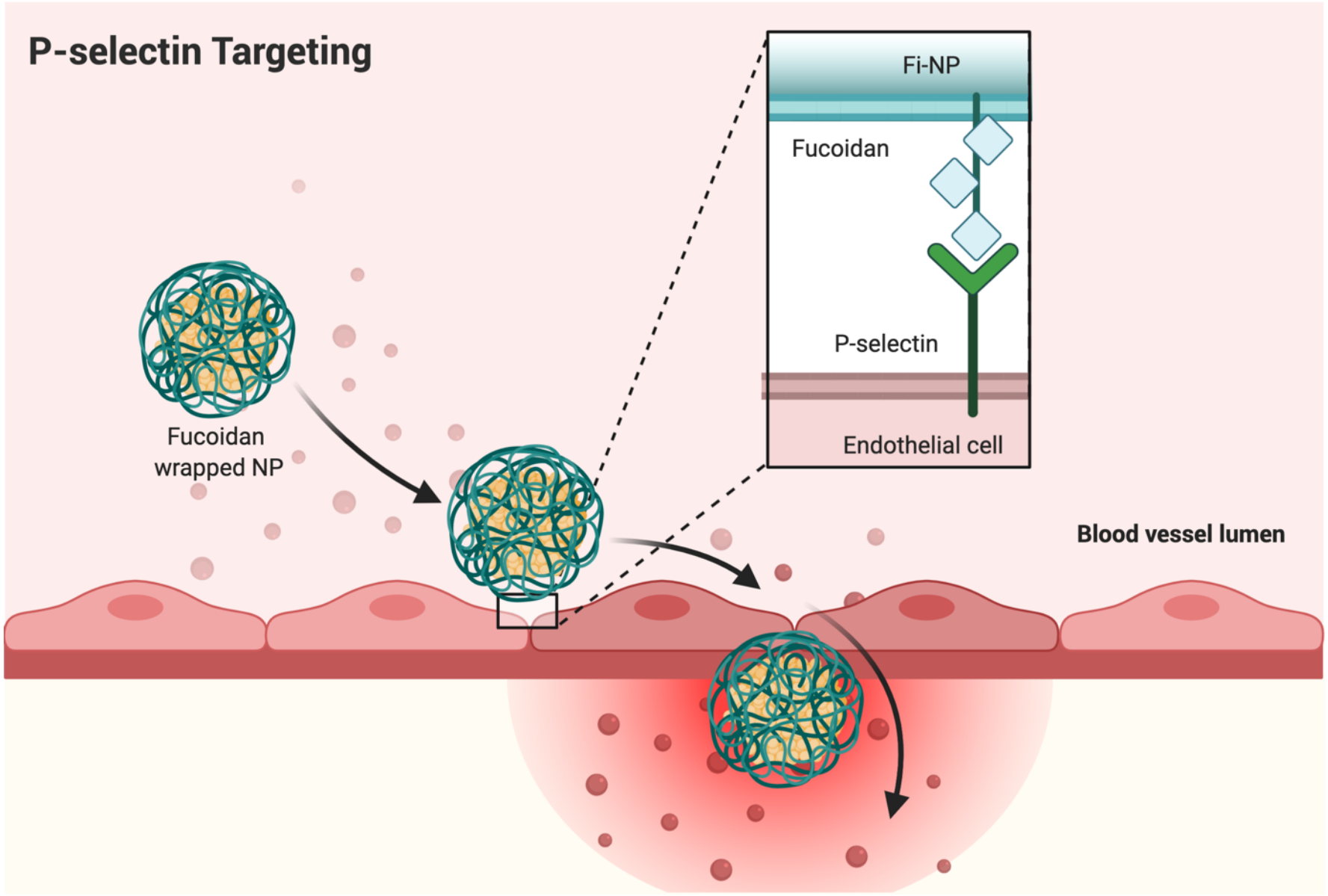
P-selectin



Can P-selectin-Targeting Facilitate Extravasation at Tumor Sites?

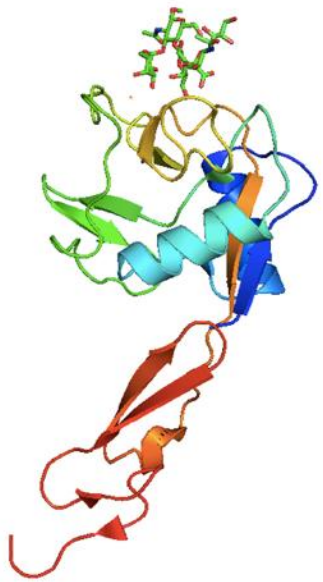


P-selectin

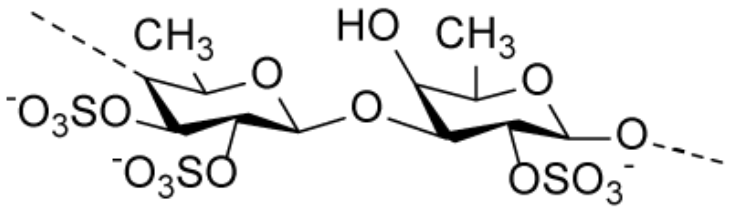


Polysaccharide Fucoidan Mimics Glycoprotein Binding Interactions to P-selectin

P-selectin



Fucoidan



Structural similarity to PSGL-1

Brown Algae

-High affinity binding to P-selectin (~20nM); mimics natural ligand PSGL-1

-Structural element for nanoformulation, derived from brown algae