Using Nanoinformatics to Predict Optimal Nano-formulations from Drug Structure

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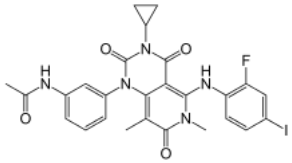
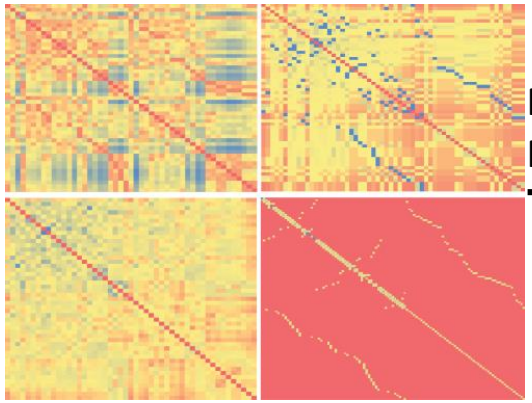
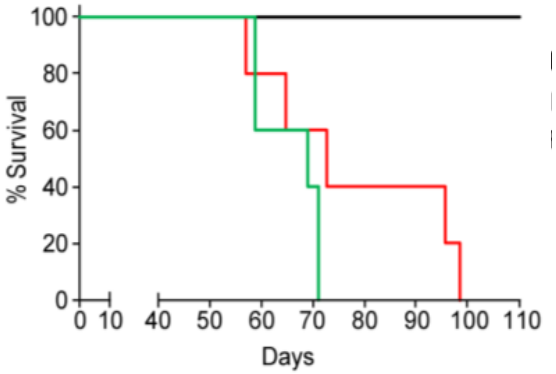
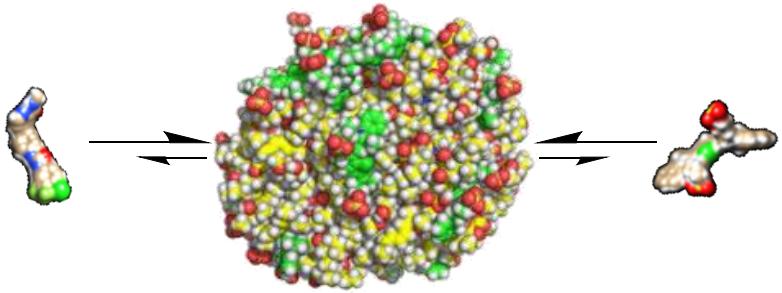


Chem-informatics

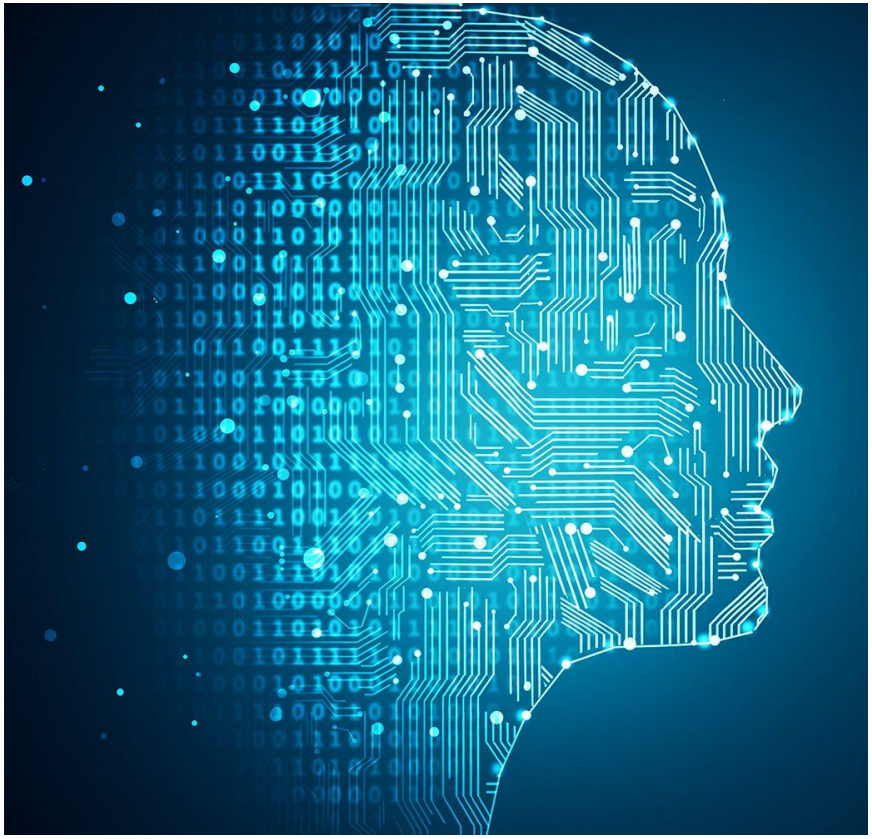


Personalized Nanomedicine





What is Machine Learning?



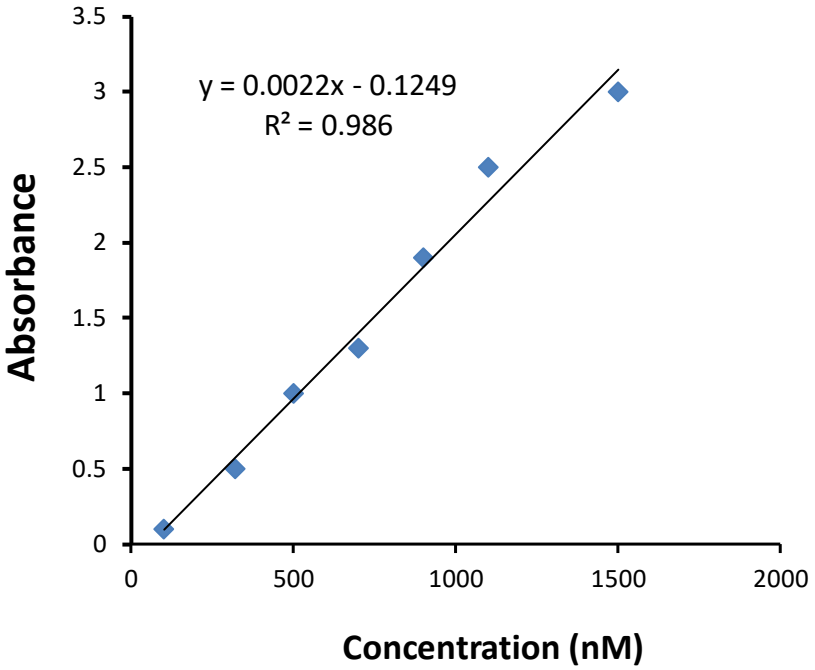
Is it Artificial Intelligence (AI)?

What is Machine Learning?

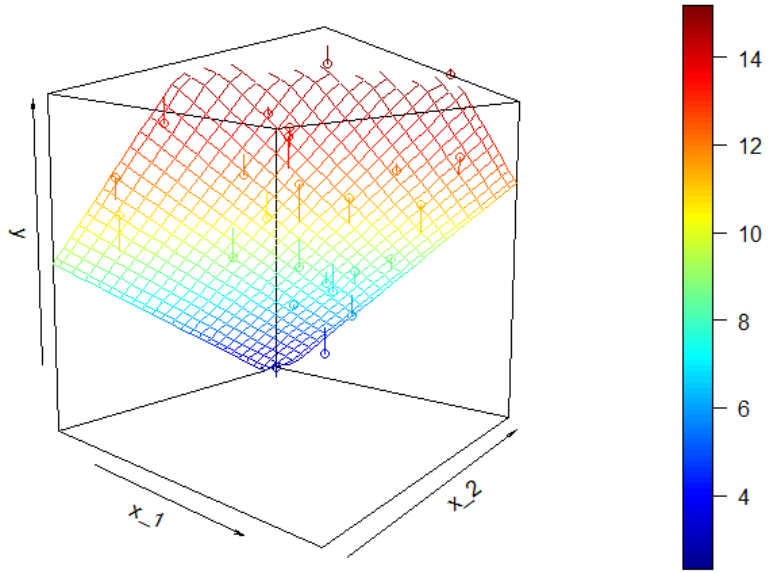
Basic Definition:

A method of **automated data analysis** which enables a computer program to 'learn' from data, improve models and then make a **prediction** about something in the world.

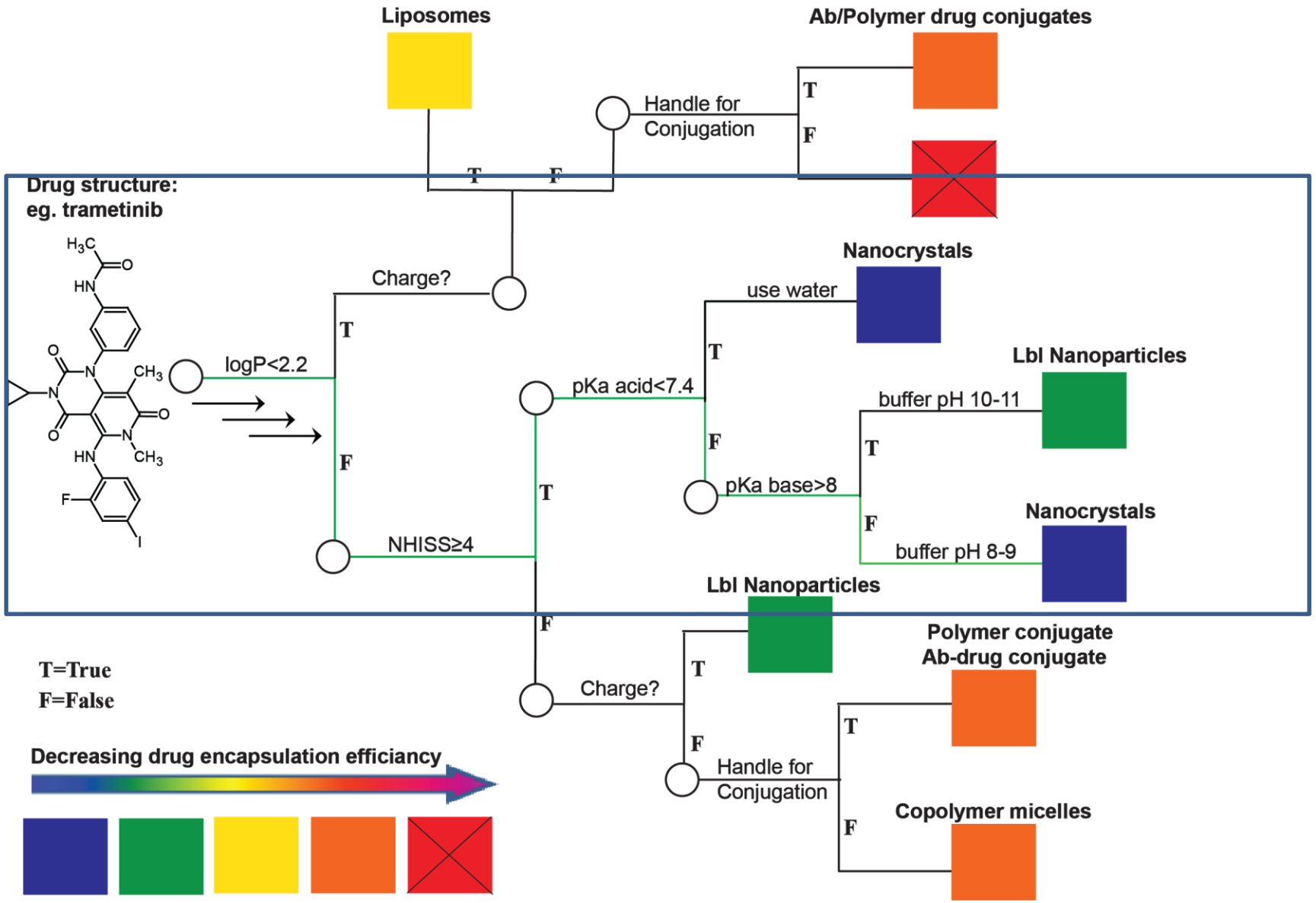
Linear Regression



Multiple Linear Regression



My Proposal for Machine Learning in Nanomedicine: Formulation Assistant



Modified from : Shamay et al Nature Materials 2018

Drug Nanocrystals

Features and Advantages

1) Hydrophobic drugs (eg KI's)

2) Can work with multiple drugs

3) High drug loading efficiency(>80%)

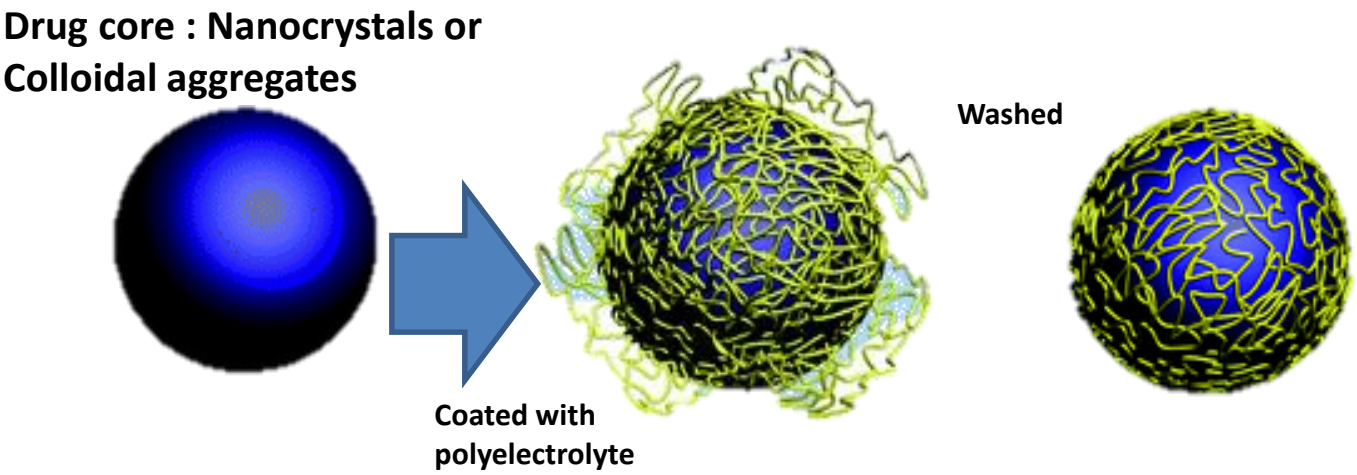
4) Rapid, scalable synthesis

Weakness

1) Unpredictable stability

2) Only good for some drugs

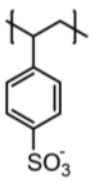
3) Lack of tissue specificity



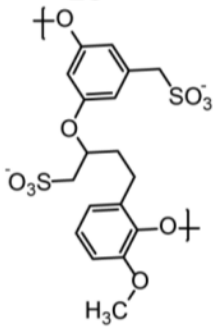
Which Molecule Is The Best Stabilizer For Nanocrystals ?

Polymers

PSS



LS



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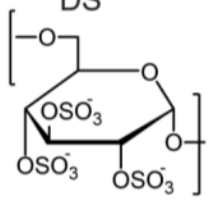
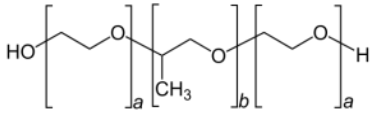
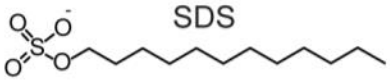


Pluronic

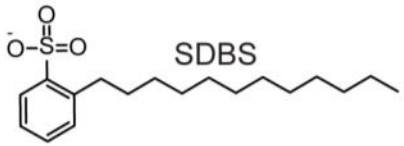


Surfactants

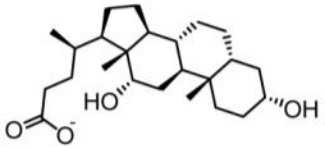
SDS



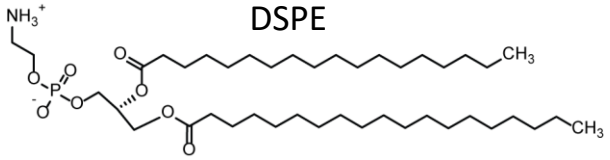
SDBS



SDC

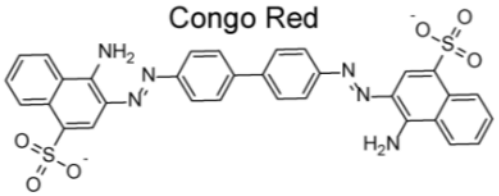


DSPE

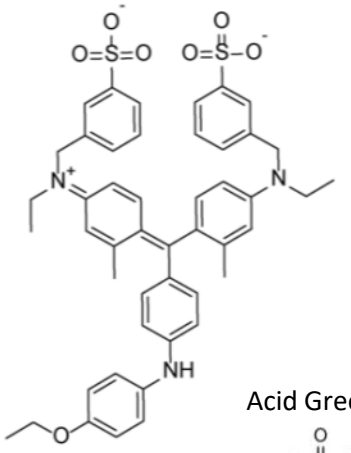


Water soluble organic dyes

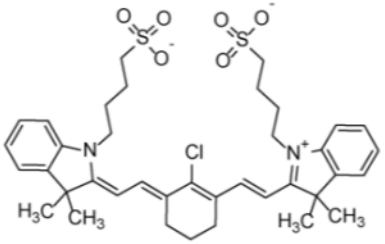
Congo Red



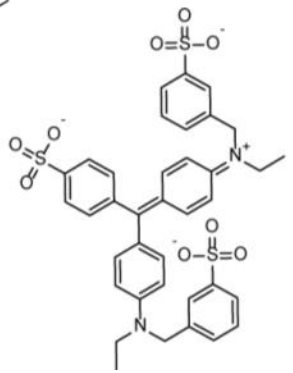
Biliant Blue G



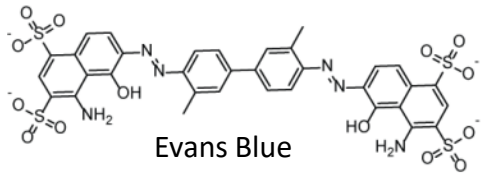
IR783



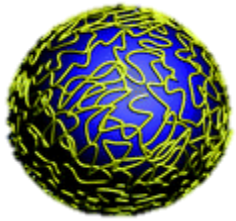
Acid Green5



Evans Blue



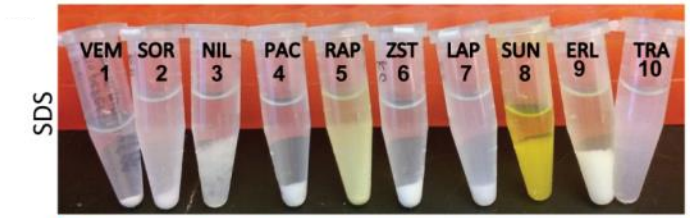
Drugs and Stabilizer Screen

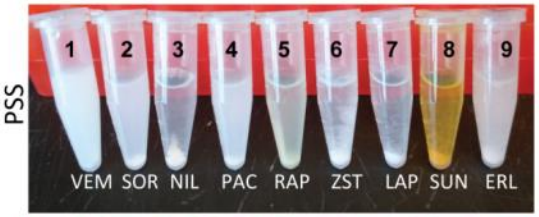


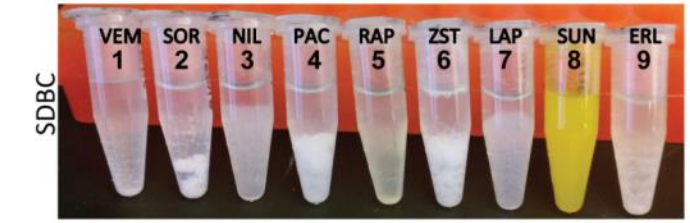
Selection criteria:
Excipient needs to stabilize a hydrophobic drug (water sol<1ug/ml) at 2mg/ml in water with a 1:10 ratio=> **90% loading efficiency**

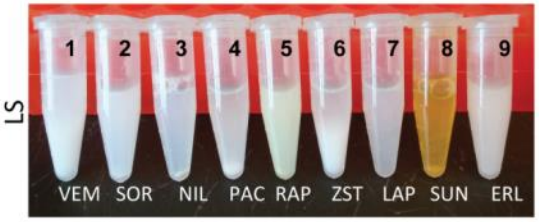
Tested 9 drugs with 20 amphophilic molecules

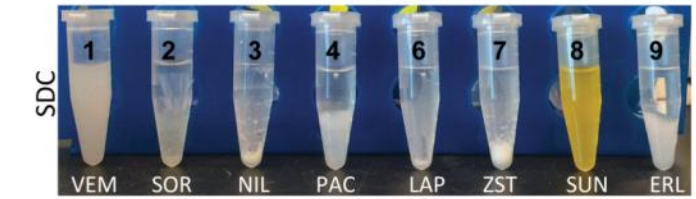
1.VEM=Vemurafinib, 2.SOR=Sorafenib, 3.NIL=Nilotinib, 4.PAC=Paclitaxel, 5.PAC=Paclitaxel, 6.ZST=ZSTK474, 7.LAP=Lapatinib, 8.SUN=Sunitinib, 9.ERL=Erlotinib, 10.TRA=Trametinib.

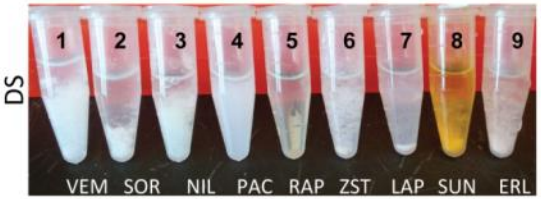


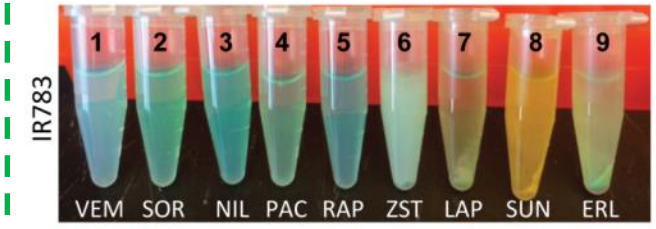


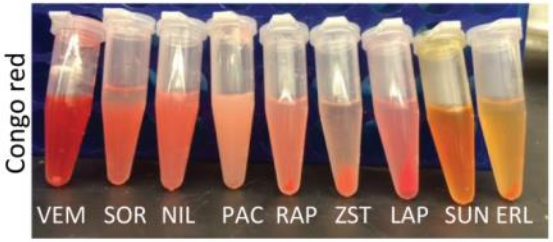


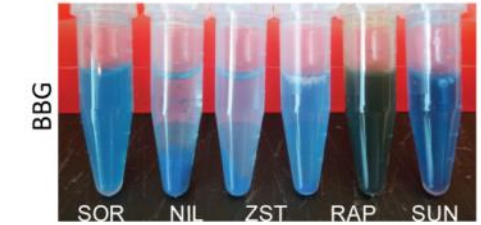


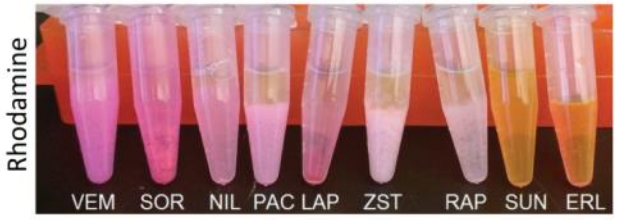




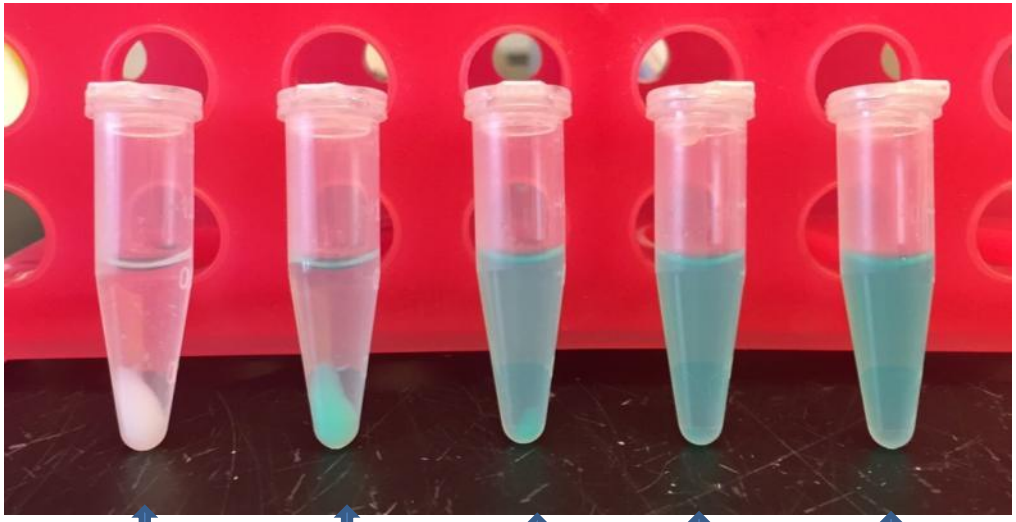






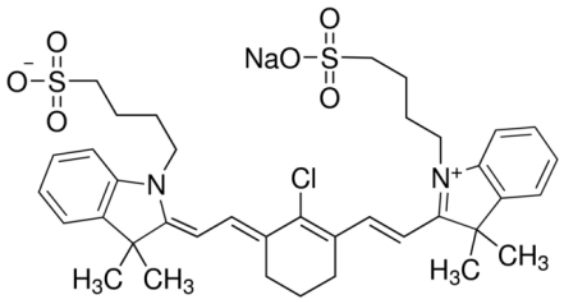


IR783 Co-Assemble with a Hydrophobic Drug

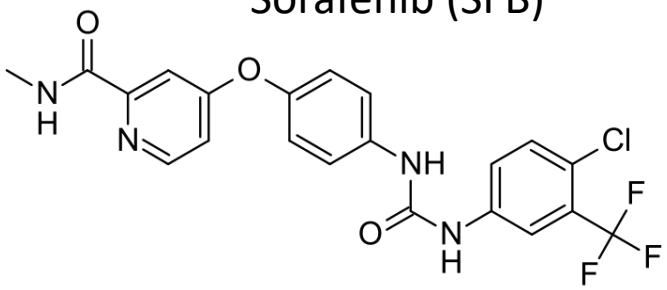


IR783	0μg	5μg	10μg	30μg	40μg
Sorafenib	2mg	2mg	2mg	2mg	2mg

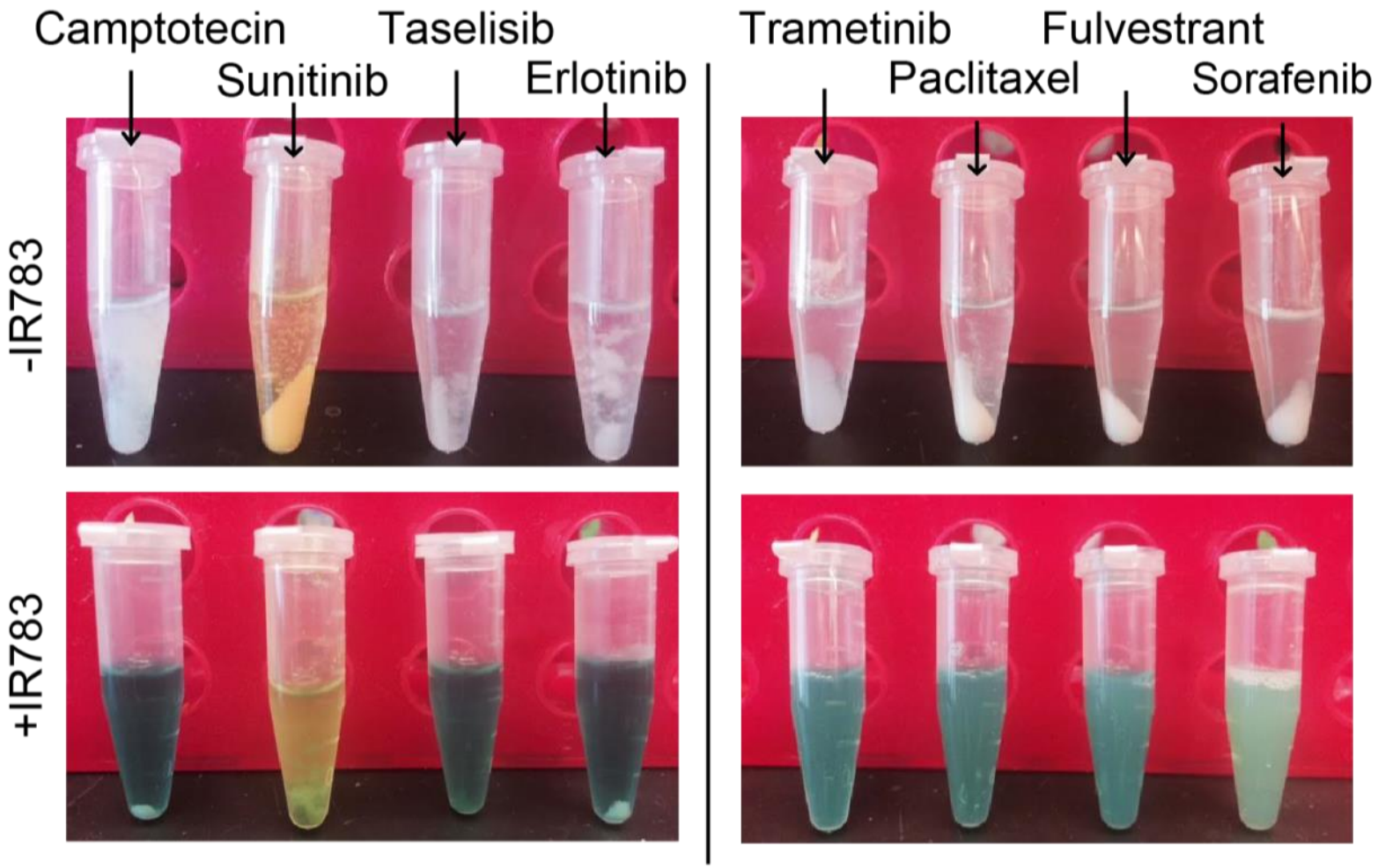
IR783



Sorafenib (SFB)

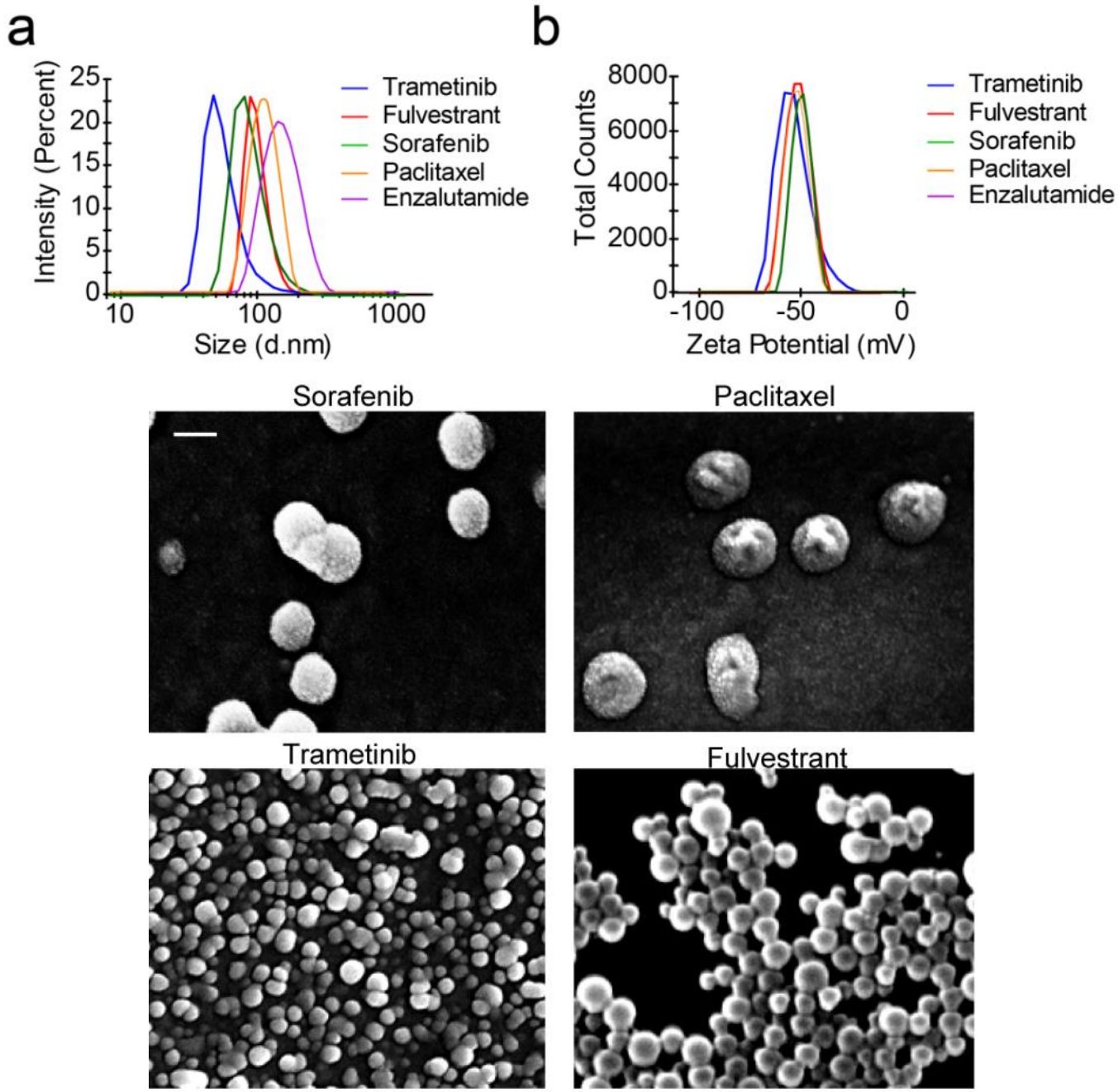


Only Certain Drugs Self-Assemble with IR783



Shamay et al . Nature Materials 2018

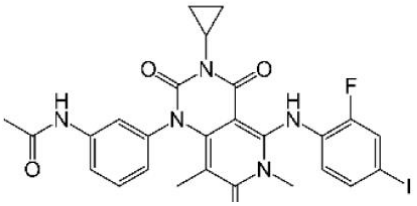
Indocyanine Nanoparticle (INP) Characterization



Can we predict which drugs will form stable nanoparticle?

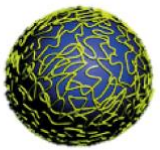
Quantitative structure–activity relationship (QSAR)

Drug Structure



?

Nanoparticle
Properties/Activity



QSAR: Correlation of Descriptors with Self-Assembly

Training Set

molecule	Rank
Idelalisib	0
Camptothecin	0
Sunitinib	0
Erlotinib	0
Taselisib	0
Silvesterol	0
Lapatinib	0
MEK162	0
ABT 199	1
Rapamycin	1
Docetaxel	1
Trametinib	1
Sorafenib	1
Enzalutamide	1
BYL719	1
Fulvestrant	1

Don't form nanoparticles

Calculation of 5000 molecular descriptors

Correlation of descriptor scores with training set

Form nanoparticles

Descriptor	Correlation
SpMax5_Bh(s)	0.9881
SpMax4_Bh(s)	0.9444
SM2_B(s)	0.8819
ATS2s	0.8778
HyWi_B(s)	0.8769
HTs	0.8761
SM3_B(s)	0.8669
Eig03_AEA(dm)	0.8444
H4s	0.8378
ZM1Kup	0.8334
SM03_EA(dm)	0.8304
ATSC2e	0.8279
RTs	0.8272
SM4_B(s)	0.8209

SpMAX Bh(s):
Leading eigenvalue of the **Burden matrix** weighted by the **I-state**

What is the Burden Matrix?

Burden matrices **B(w)** are augmented adjacency matrices derived from a molecular graph defined to account for heteroatoms and bond multiplicity

What is the Intrinsic State?

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

L : principal quantum number

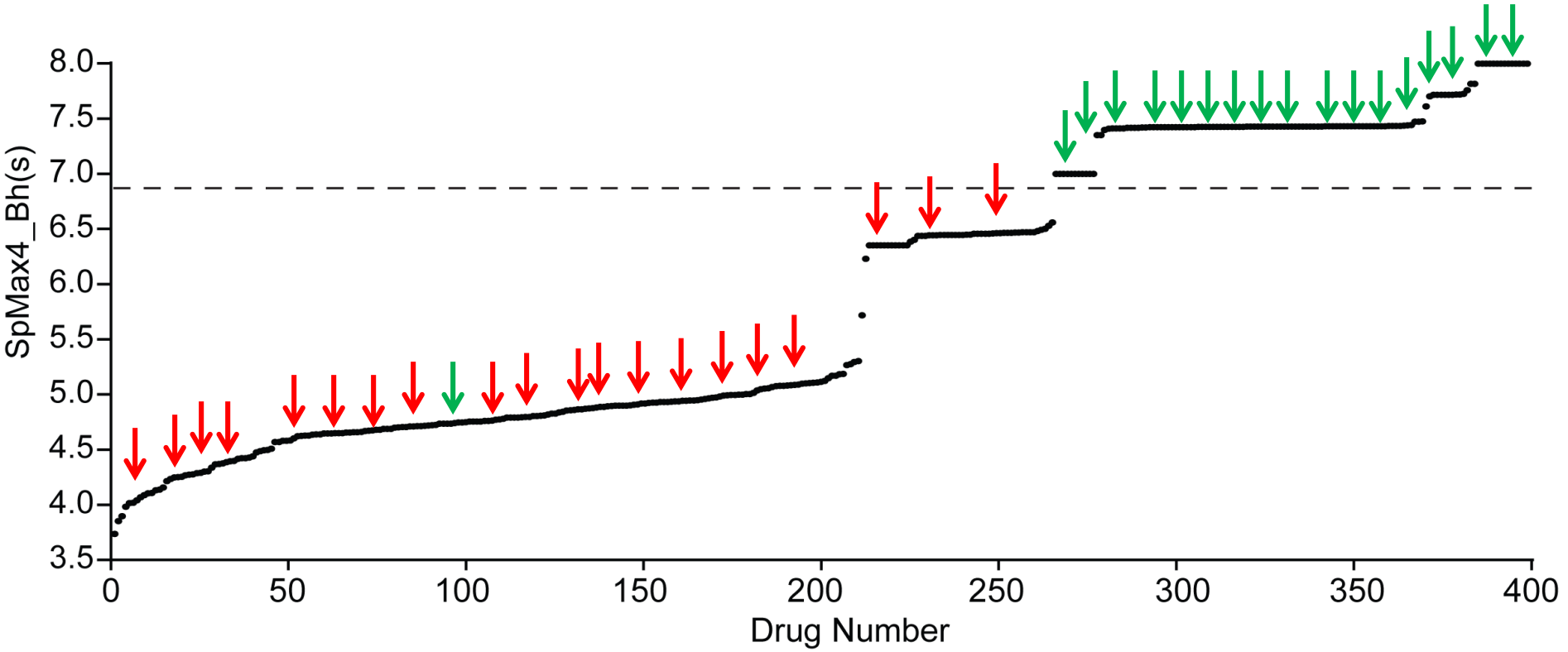
δ^v : number of valence electrons

δ : number of sigma electrons

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

Kier et al. Journal of Chemical Information. 1995

Validation of Predictions



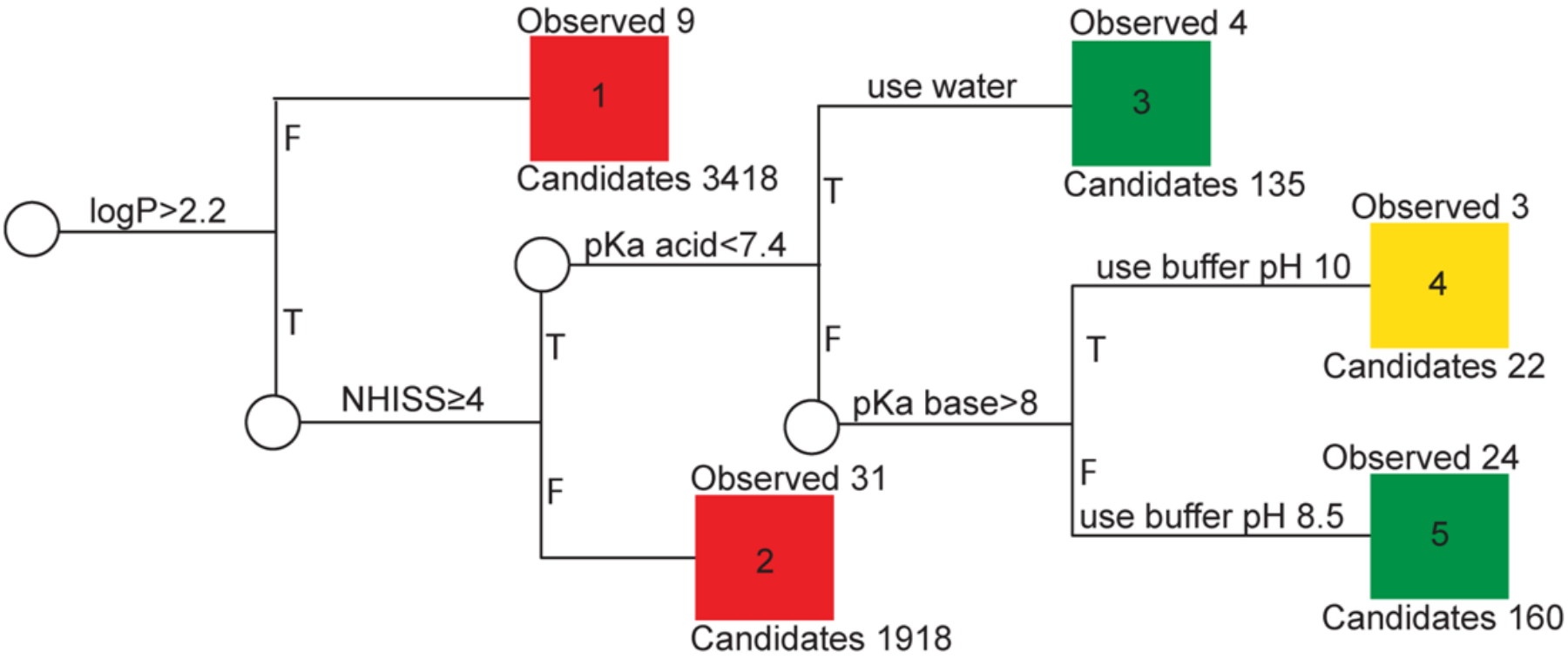
18 True Positive
25 True Negative
0 False positive
1 False negative

Forms stable nanoparticle

Precipitating

Quantitative Structure-Nanoparticle Assembly Prediction (QSNAP)

Decision Tree Summarizes QSNAP information applied to 6400 drugs:



No particle assembly

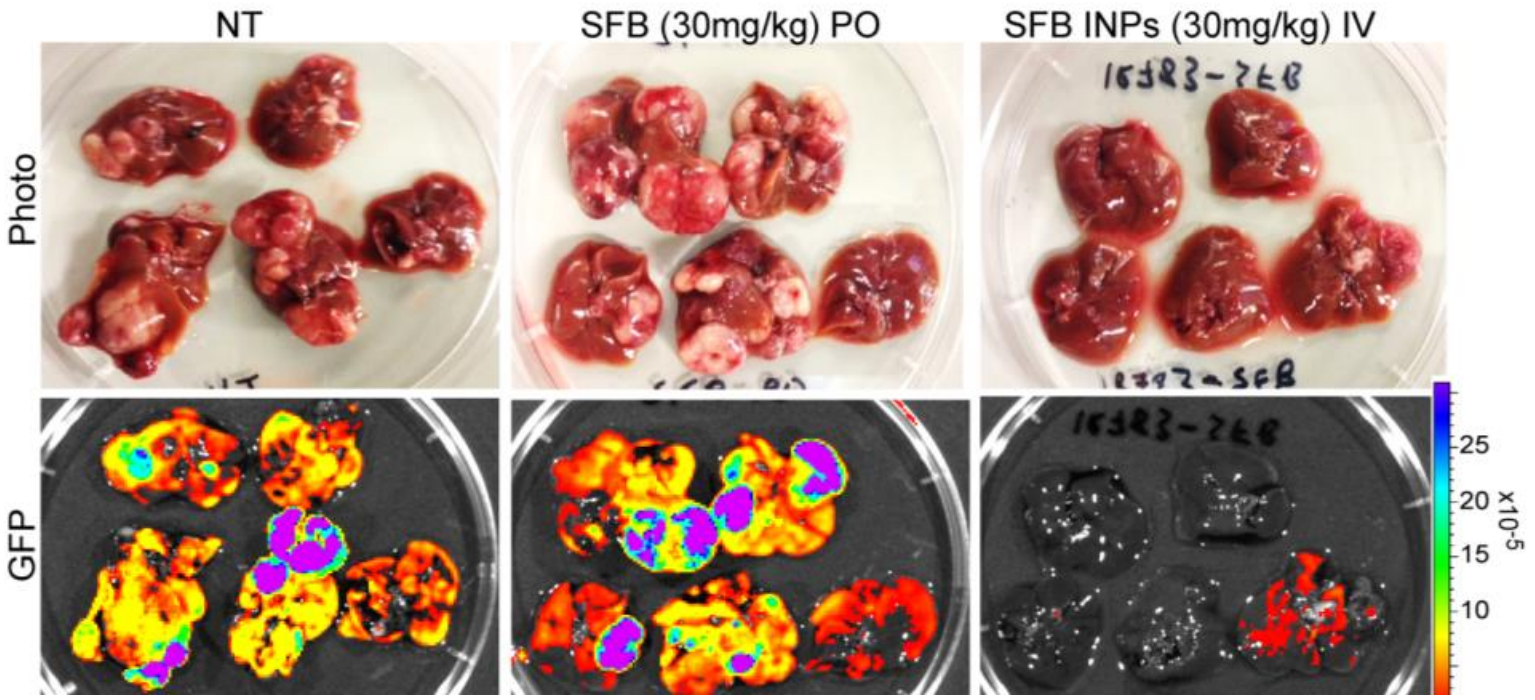
Stable particle assembly

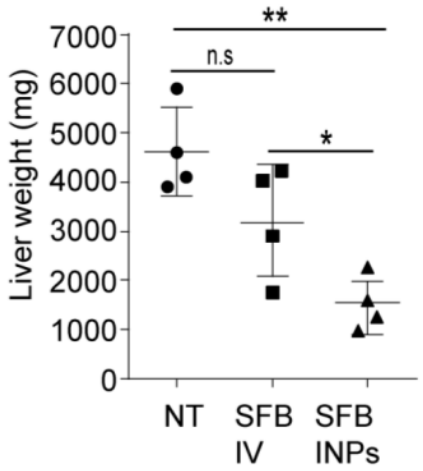
pH depended stability

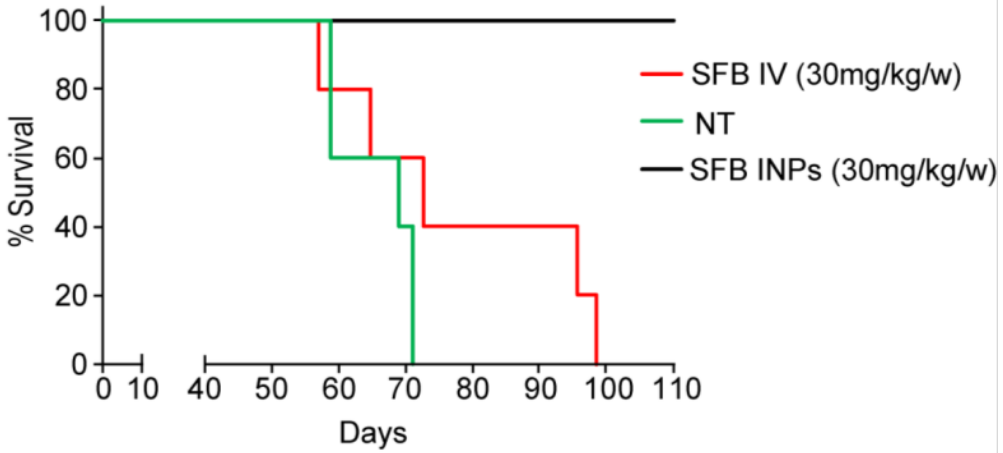
From 6400 drugs there are **292** FDA approved drugs should form good INP with ~98% confidence

This process could potentially save time and money for formulation processes

Sorafenib INPs Show Superior Anti Tumor Efficacy







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Conclusions

- IR dyes are new stabilizers for drug nanocrystals
- QSNAP is a predictive model for matching a drug to a unique nano-formulation
- High intrinsic state groups (=O and F) are required for self assembly.
- The stabilized nanoparticles are have therapeutic benefits without further polymer coating.

Please spread the word..

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Israel Institute of Technology

Is Looking for Students:

yshamay@technion.ac.il

Thank you ☺