Development of Targeted Nanomedicines via Machine Learning Processes

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Associate Member, Memorial Sloan Kettering Cancer Center
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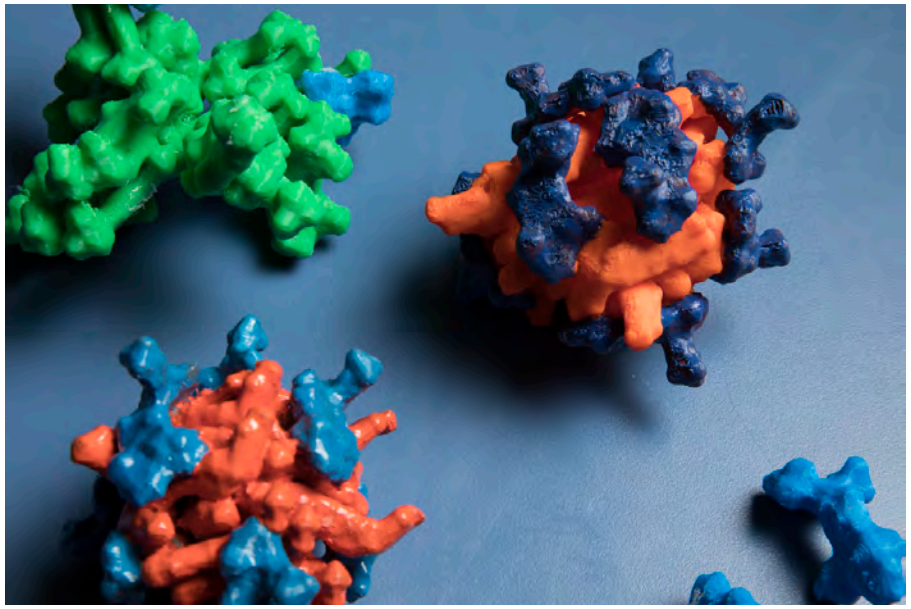


Nano WG
February 21, 2019

Memorial Sloan Kettering Cancer Center

Cancer Nanomedicine Laboratory
at Memorial Sloan Kettering Cancer Center

Sloan Kettering Institute

Memorial Sloan-Kettering Cancer Center

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

Upcoming Symposium:

Nanoinformatics: Information and Data Sciences Applied to Nanomaterials Synthesis, Properties, and Biological Effects

258th ACS National Meeting & Exposition, August 25 - 29, 2019, San Diego, CA.

Division of Colloid and Surface Chemistry [COLL]

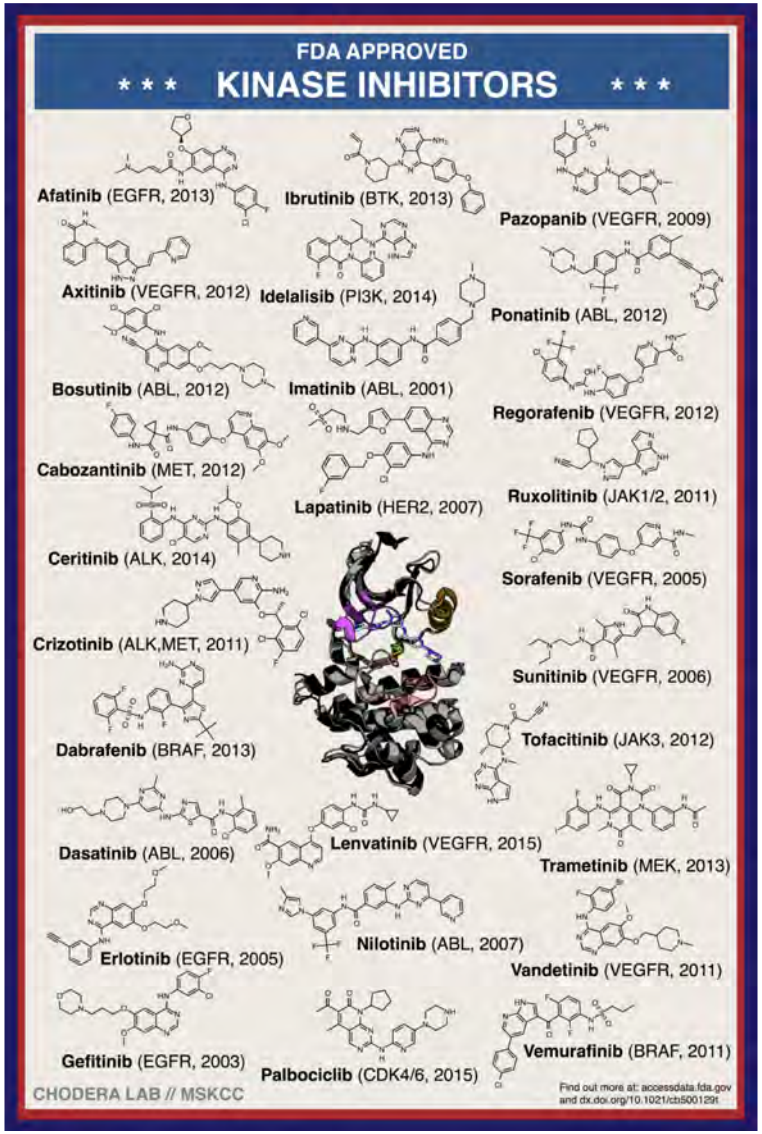
Submission site: https://www.acs.org/content/acs/en/meetings/national-meeting/abstract-submission.html?sc=natlmeeting_180116_mtg_BO18_od

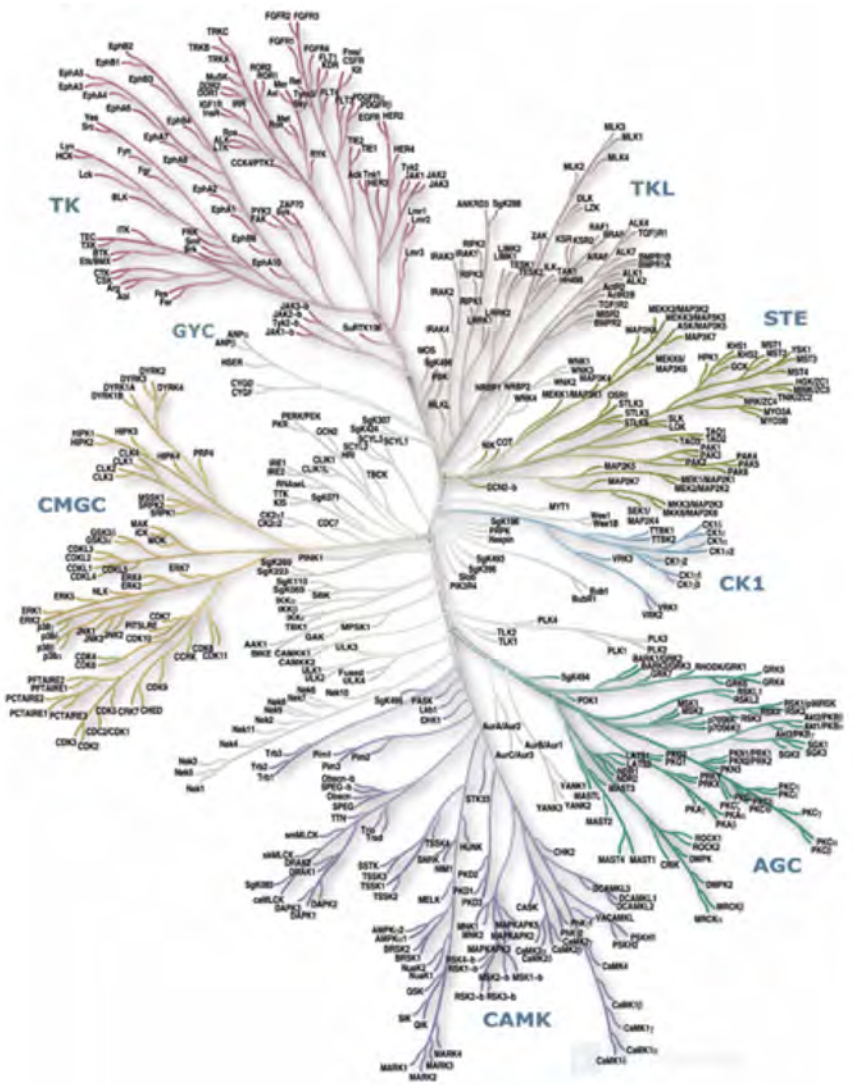
The deadline for abstract submission is Monday, March 25.

Synopsis: Recent work in nanotechnology and nanomedicine has benefitted from the use of data science and information science to optimize, standardize, and understand the synthesis, characterization, and biological effects of nanomaterials. Machine learning has been used to predict and inform nanoparticle synthesis and pharmacokinetics. Information science has been applied towards nanomedicines to standardize heterogeneous information related to nanoparticle characterization and toxicity. This session will focus on the use of data science and information science in the development and understanding of nanomaterials and nanomedicines. Appropriate topics include, but are not limited to:

- **Machine learning applied to nanotechnology**
- **Information management related to nanomaterials**
- **Data mining approaches**
- **Data standardization in nanotoxicology**
- **Data homogeneity in nanomaterials characterization**
- **Chemical information applied to nanoscience**

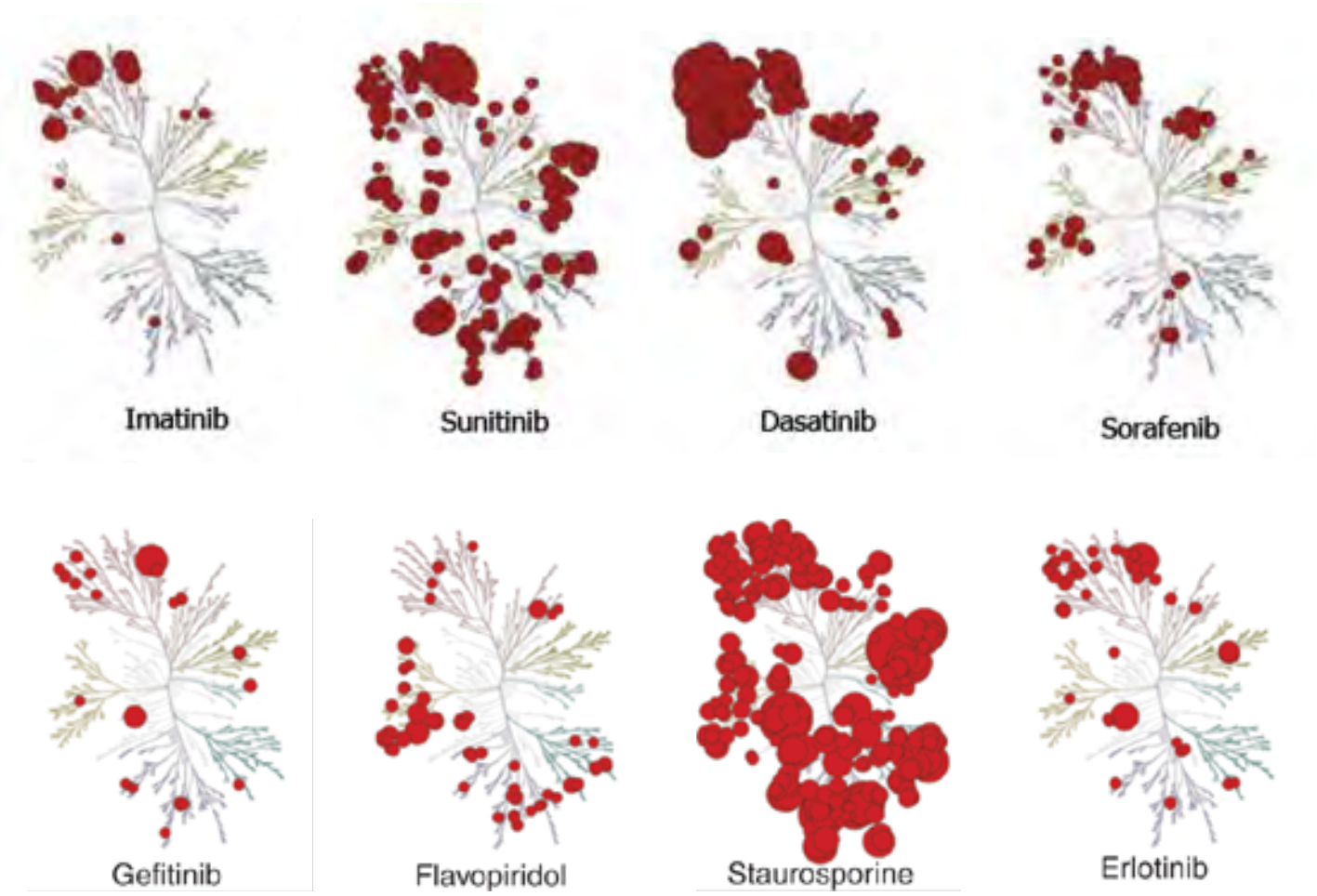
Fixing Personalized Medicines





G Manning, Science 2012, 298:1912-1934 Chodera Lab, 2015

Most Small Molecule Inhibitors Exhibit On- and Off-Target, Dose-Limiting Toxicities



Wilson, *Cancer Research*, 2018 *Nature Biotechnology* 26, 127 – 132, 2008

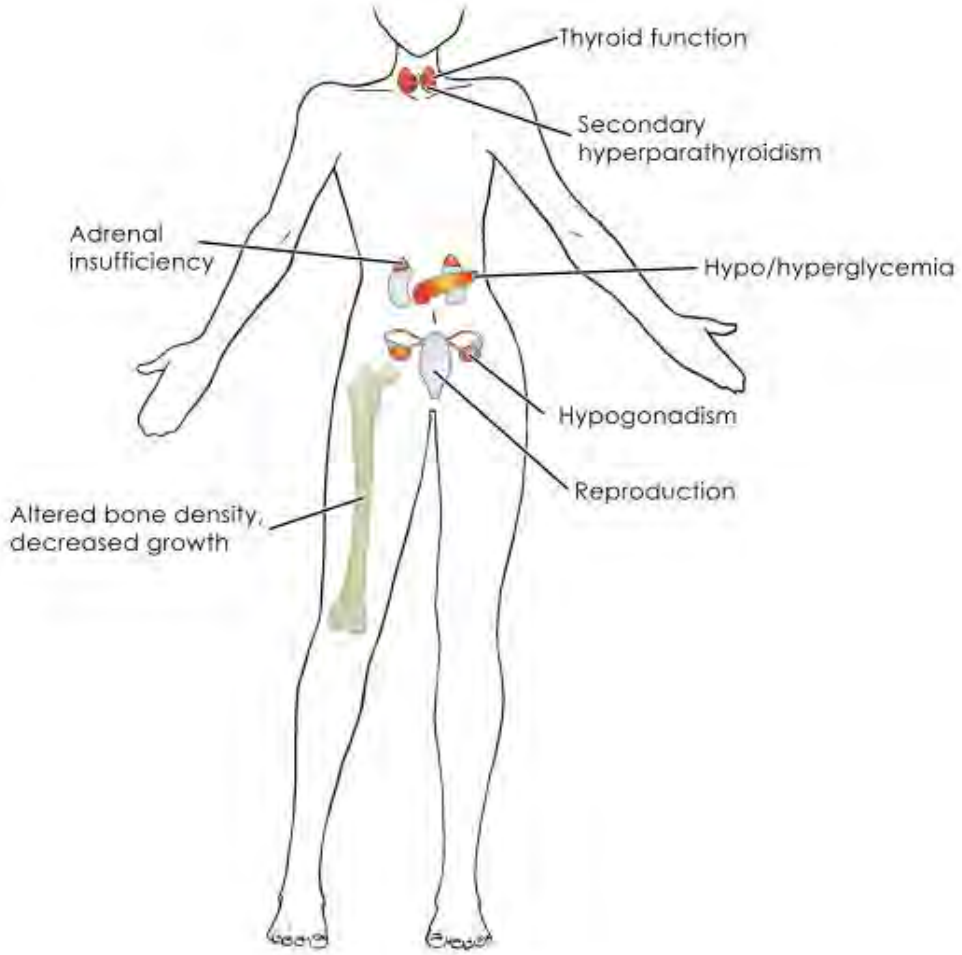
Dose Limiting Toxicities of Kinase Inhibitors

Dermatologic Side-Effects

Hand–foot skin reaction

Skin rash

Endocrine Side-Effects

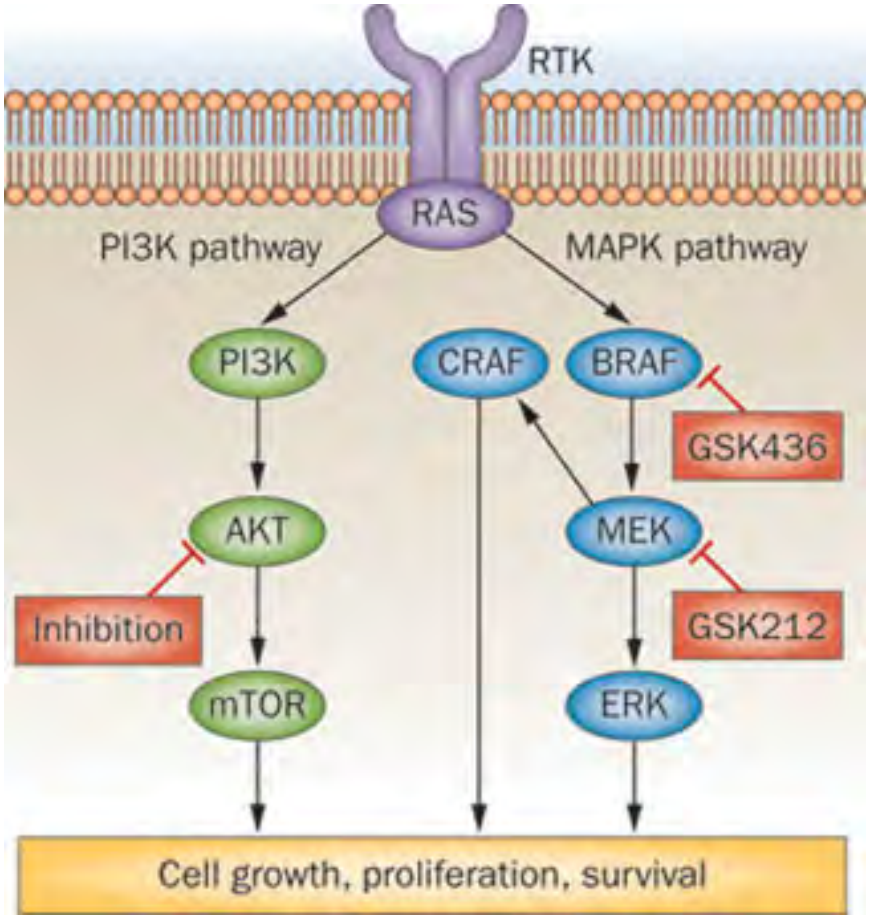


Joensuu, et. al., Cancer Treatment Reviews, 2011

Lodish, Endocr Relat Cancer, 2010

Targeting Targeted Therapies

Targeting the Pathway



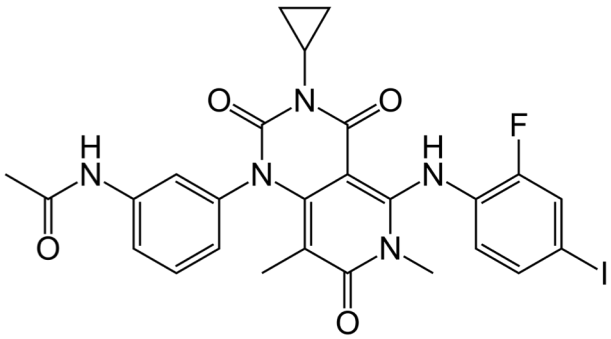
Targeting the Location

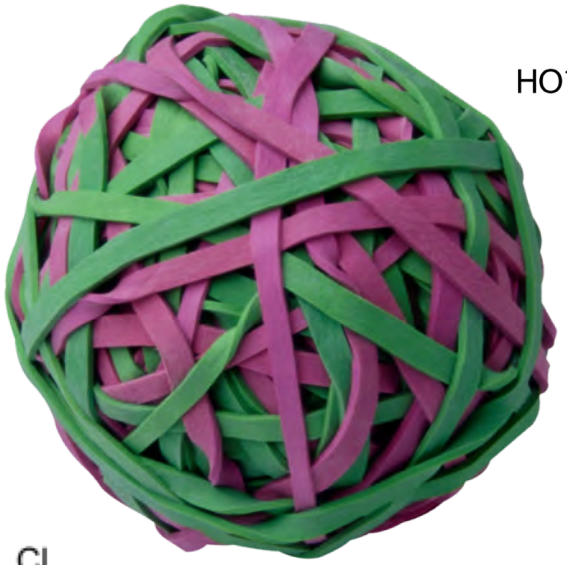
Avoiding Problem Tissues

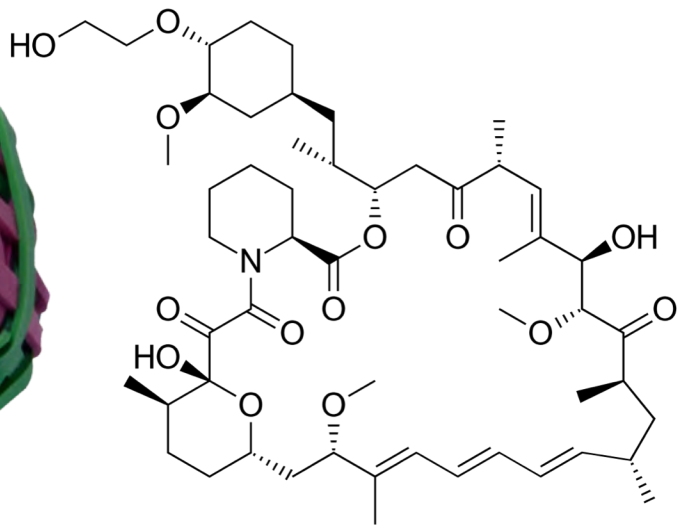
Shamay, et al. *Science Translational Medicine,* 2016
Mizrachi, et. al., *Nature Communications*, 2017

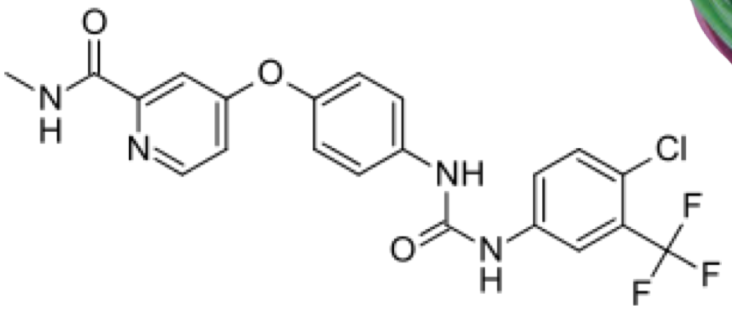
Problem:

The encapsulation of the diverse range of small molecule therapeutics into nanoparticles with high drug loadings.

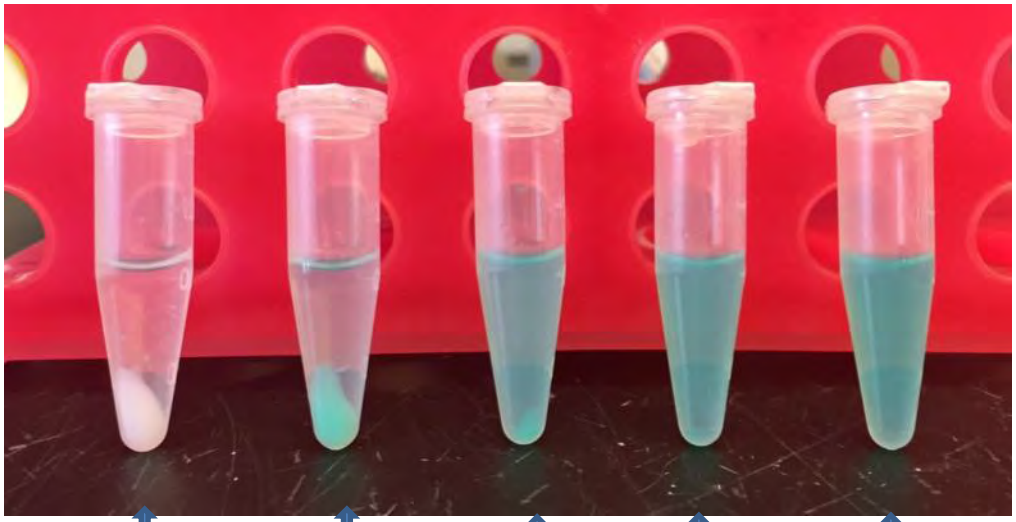






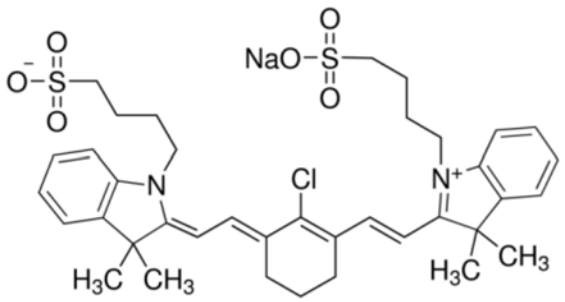


NIR Indocyanine Dyes Self-Assemble with Certain Hydrophobic Drugs to Form Nanoparticles

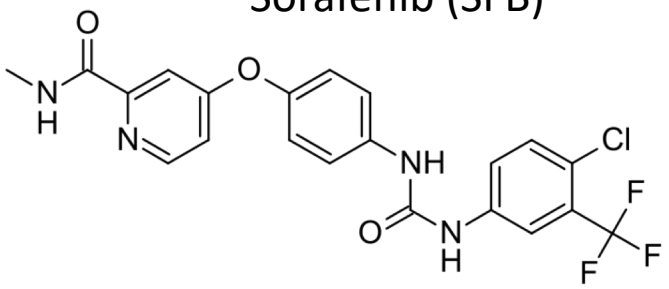


IR783 (1mg/ml)	0µg	5µg	10µg	30µg	40µg
Sorafenib (10mg/ml)	1mg	1mg	1mg	1mg	1mg

IR783

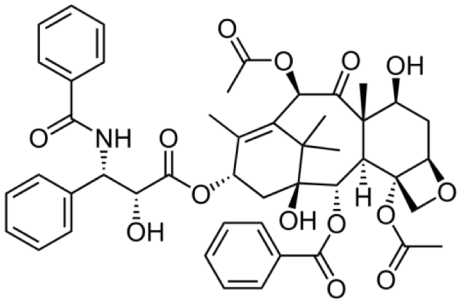


Sorafenib (SFB)

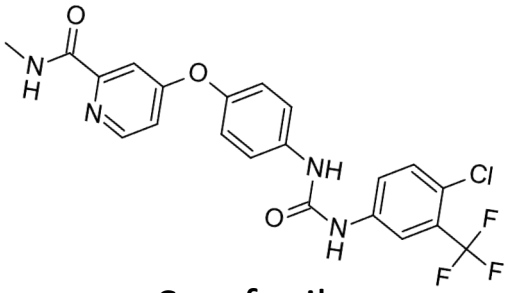


Shamay, et. al., *Nature Materials*, 2018

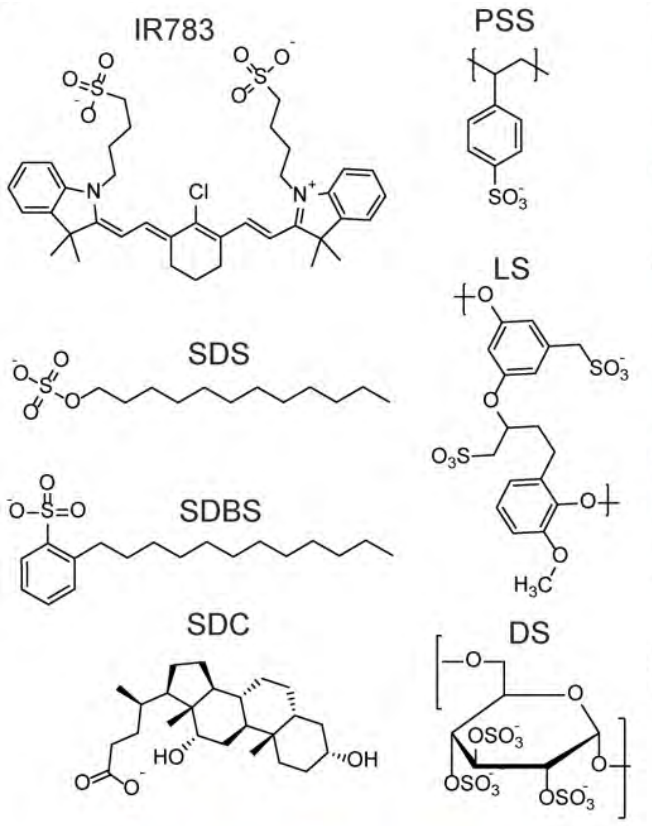
Few Small Molecule Excipients Suspend Hydrophobic Drugs

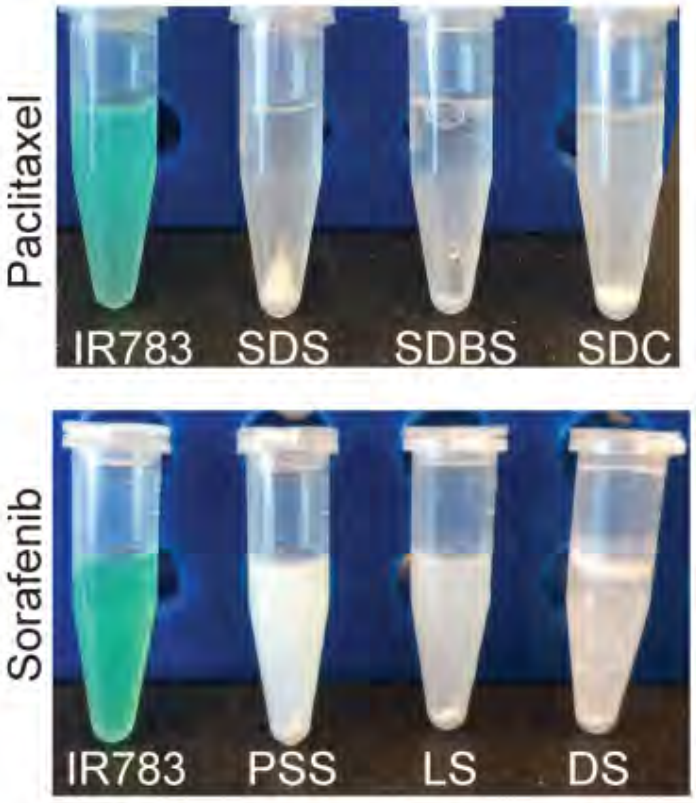


Paclitaxel



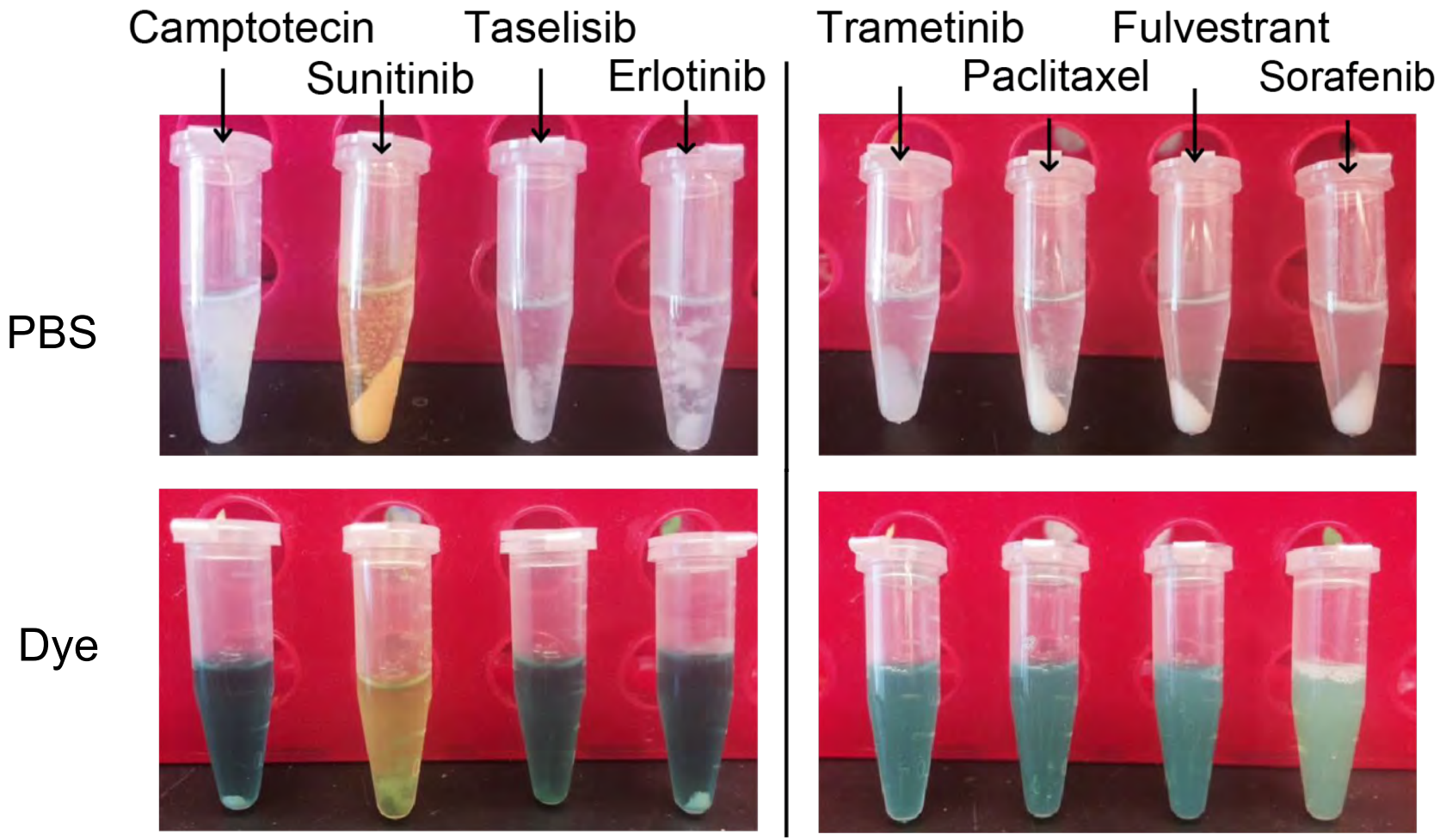
Sorafenib





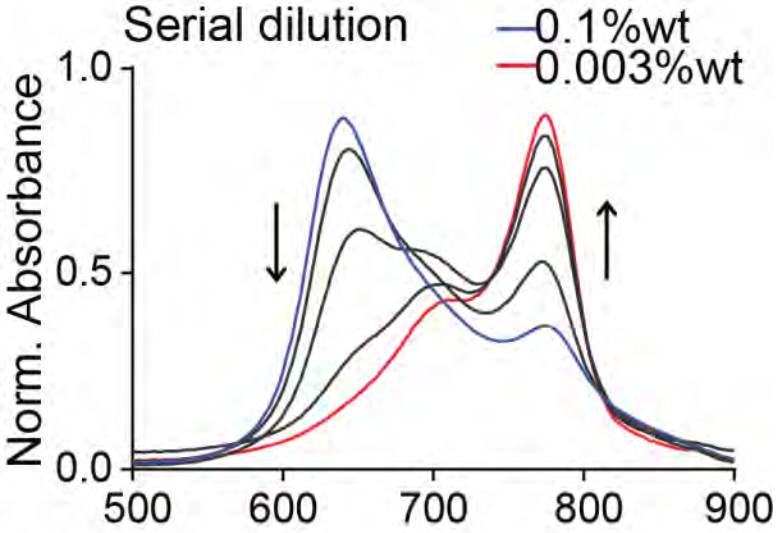
Shamay, et. al., *Nature Materials*, 2018

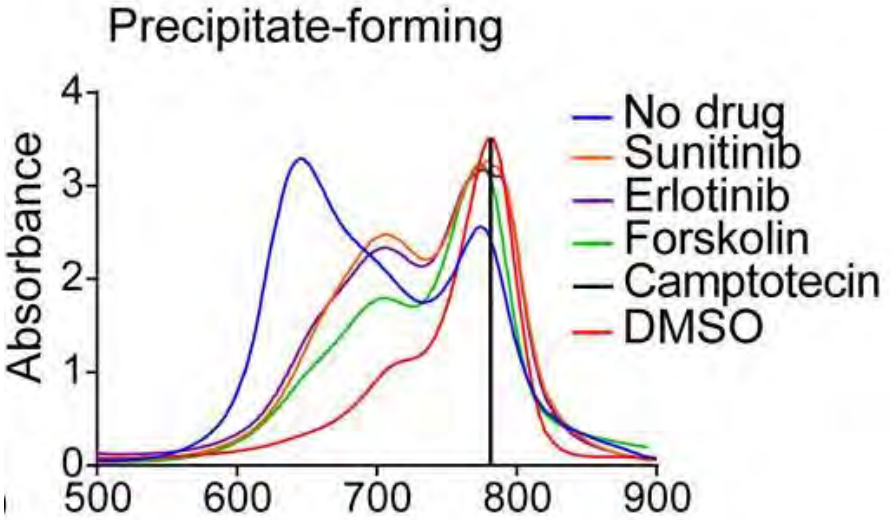
Certain Hydrophobic Drugs Self-Assemble with Indocyanines to Form Nanoparticles

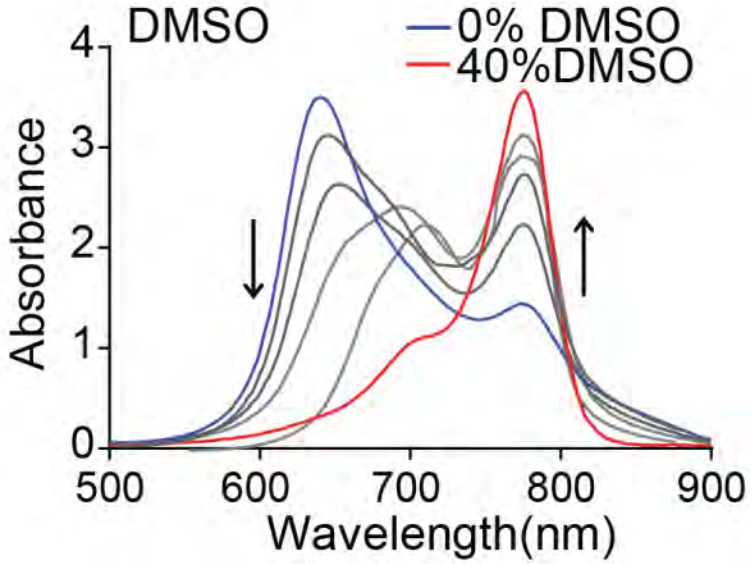


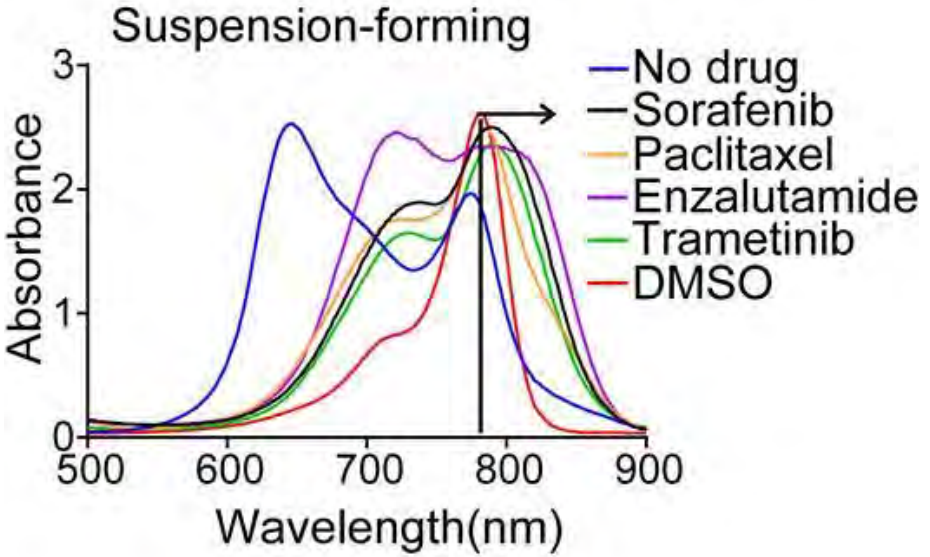
Shamay, et. al., *Nature Materials*, 2018

IR738 Forms an H-aggregate in Water
Spectrum Shifts upon Drug Solubilization



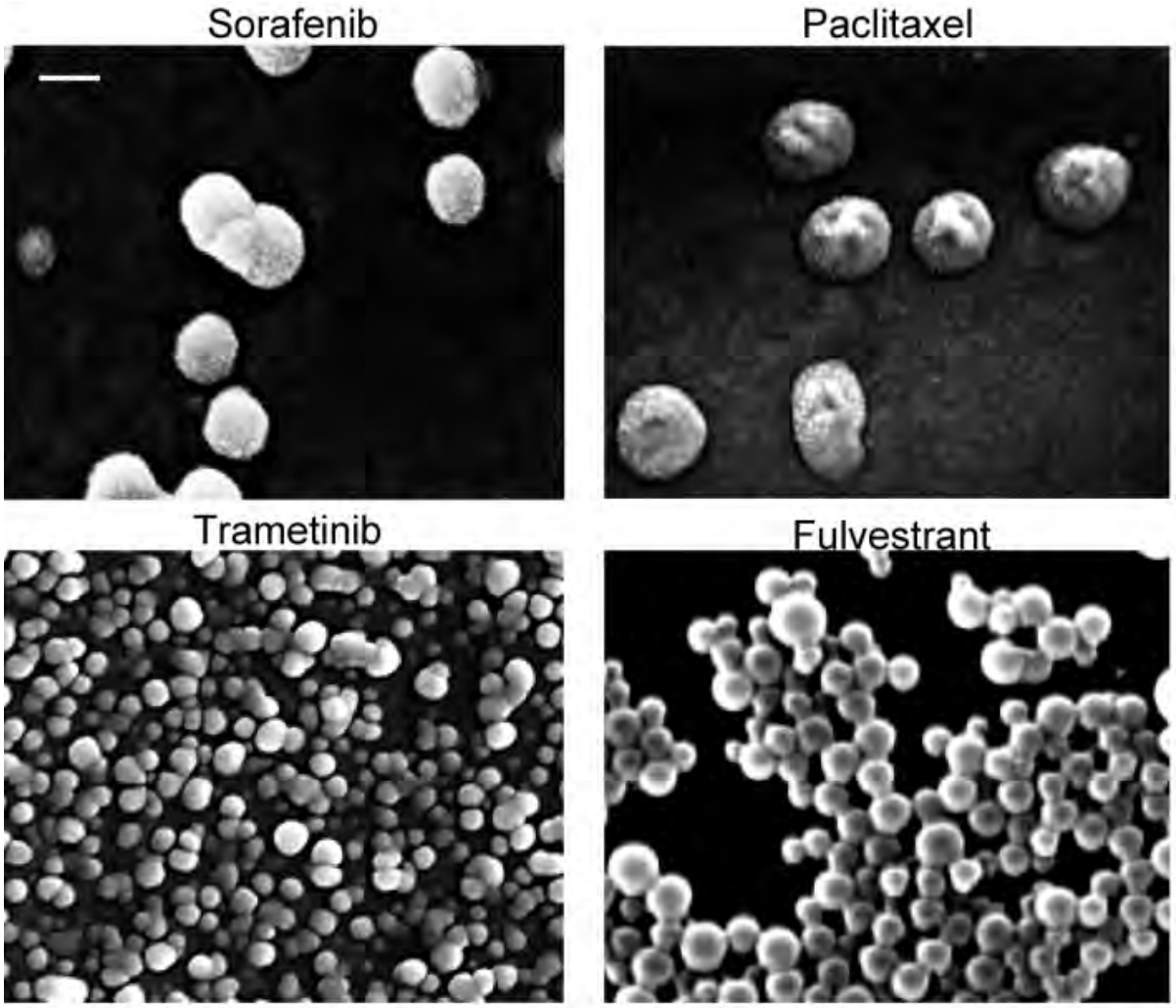






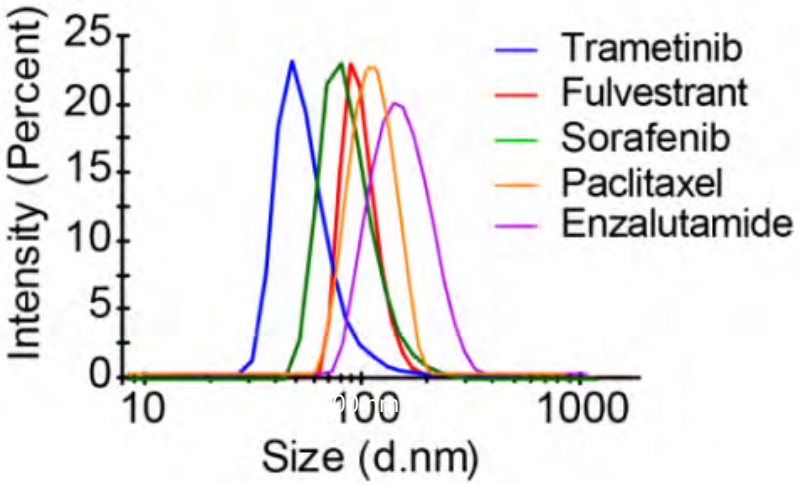
Shamay, et. al., *Nature Materials*, 2018

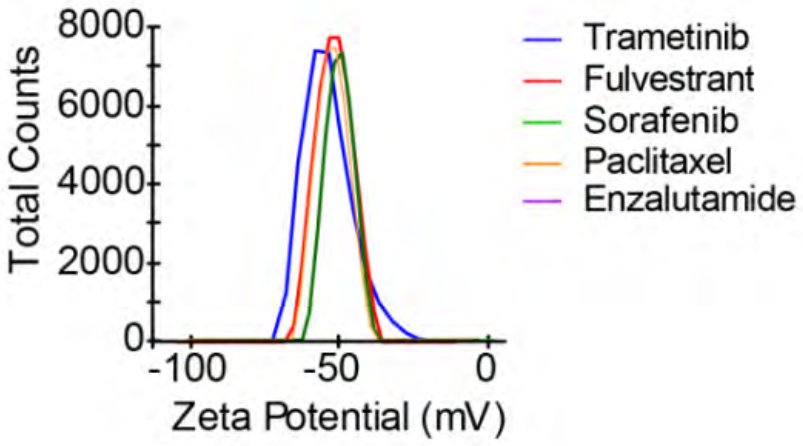
Indocyanine-Drug Suspensions Form Nanoparticles

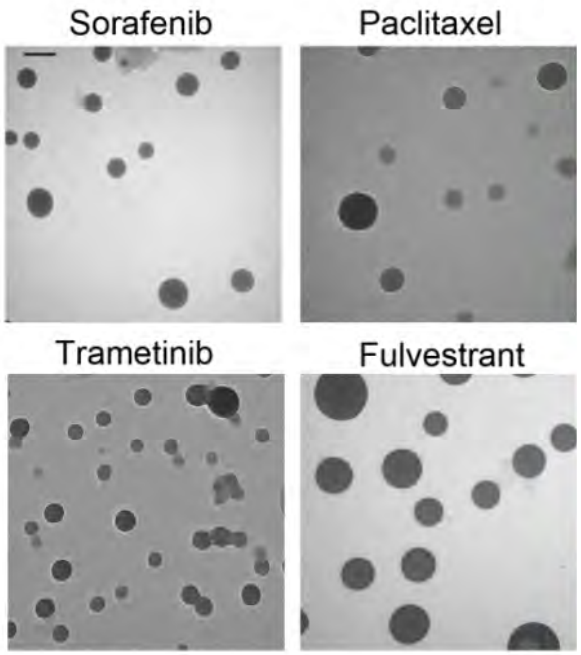


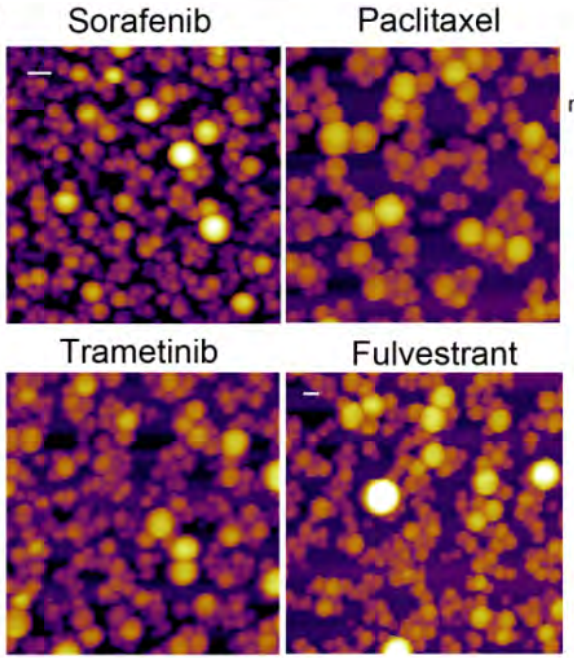
Shamay, et. al., *Nature Materials*, 2018

Indocyanine Nanoparticle (INP) Characterization



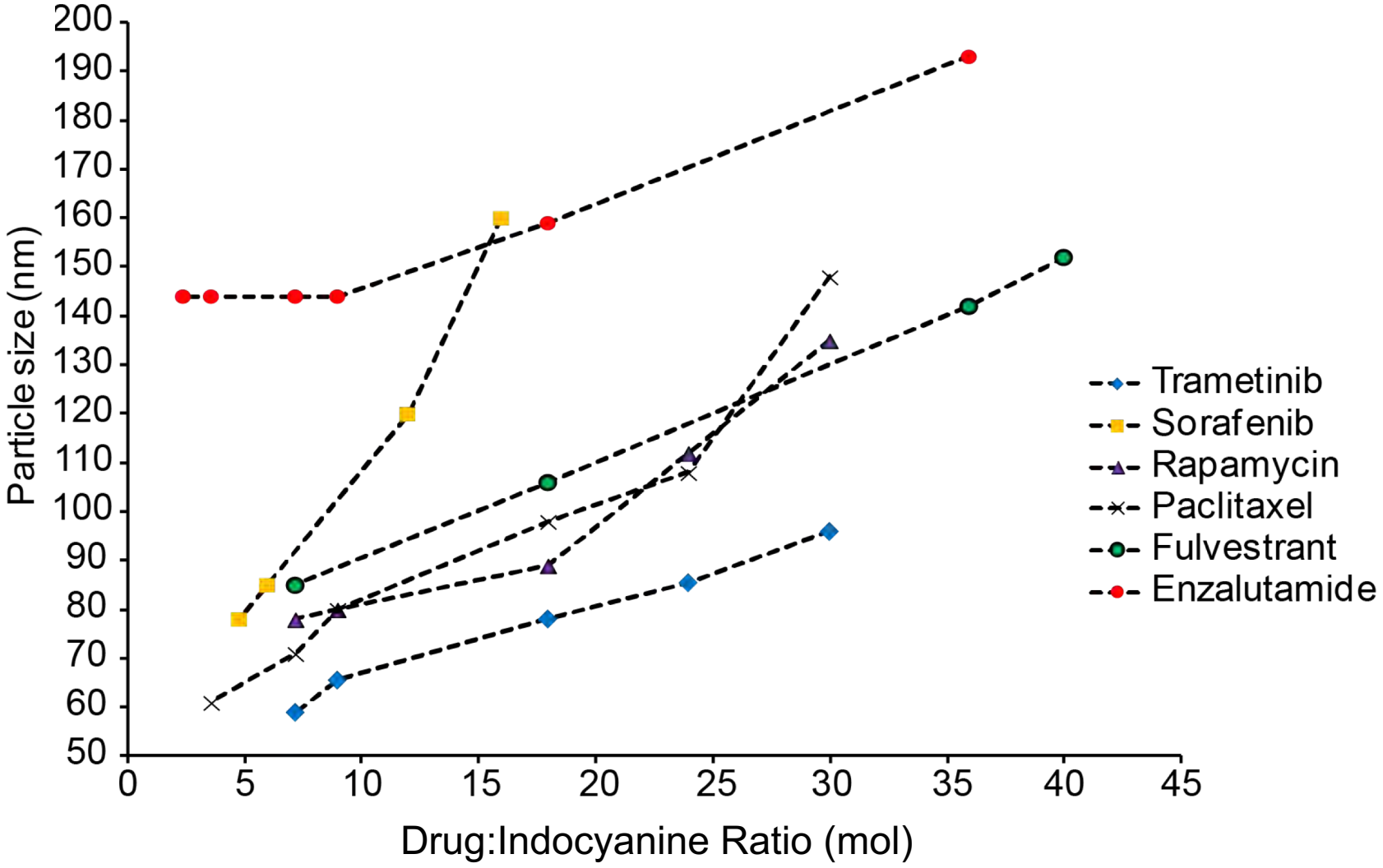






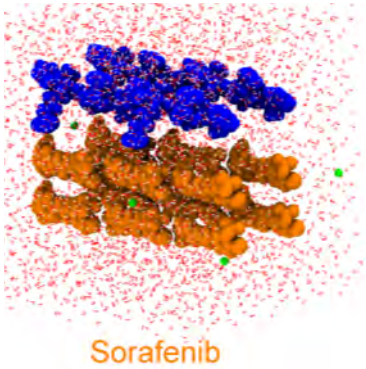
Shamay, et. al., *Nature Materials*, 2018

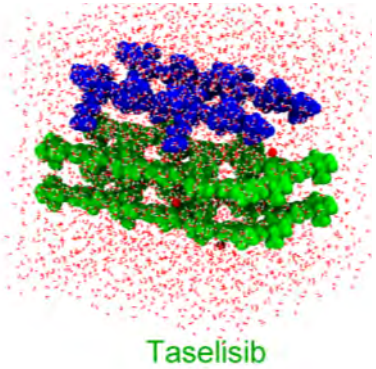
Particles Have Very High Drug Loading

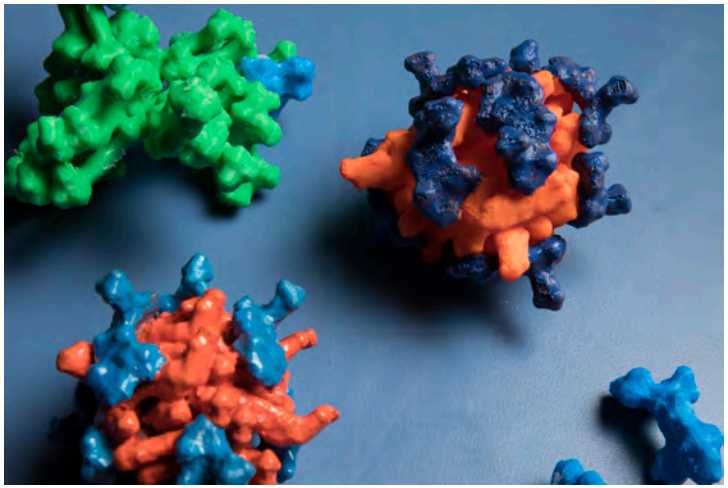


Shamay, et. al., *Nature Materials*, 2018

Molecular Dynamics Simulations

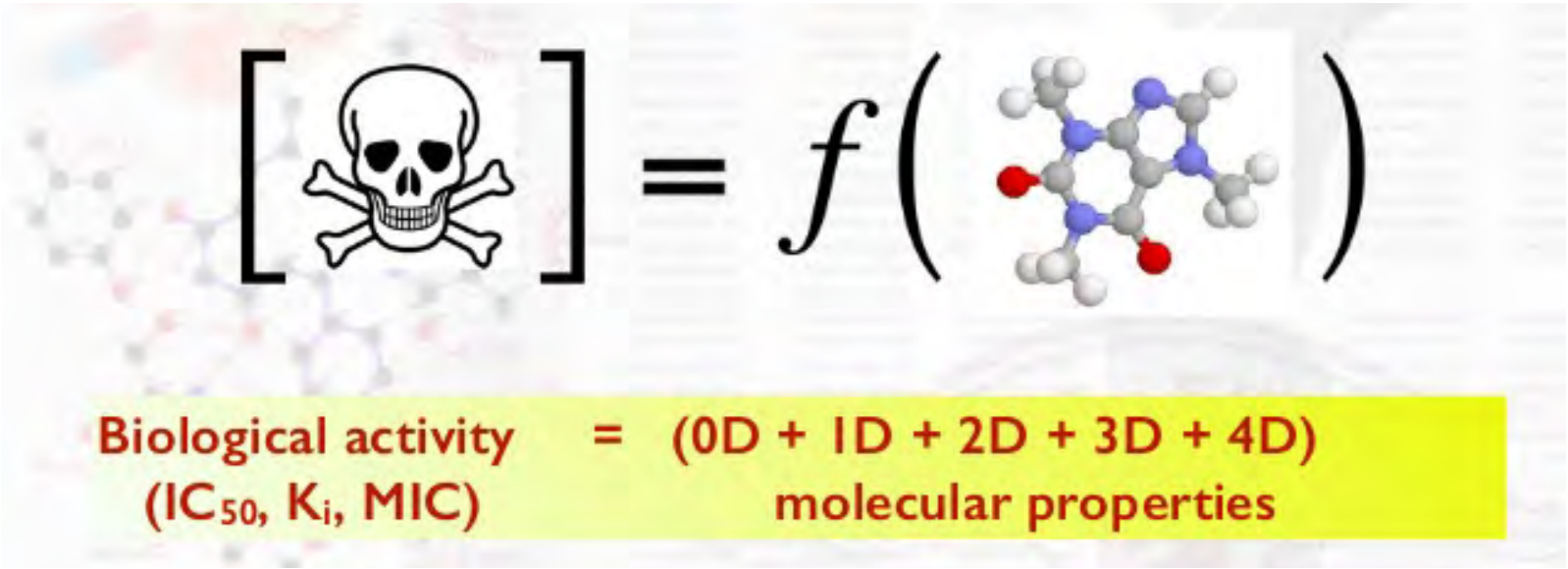






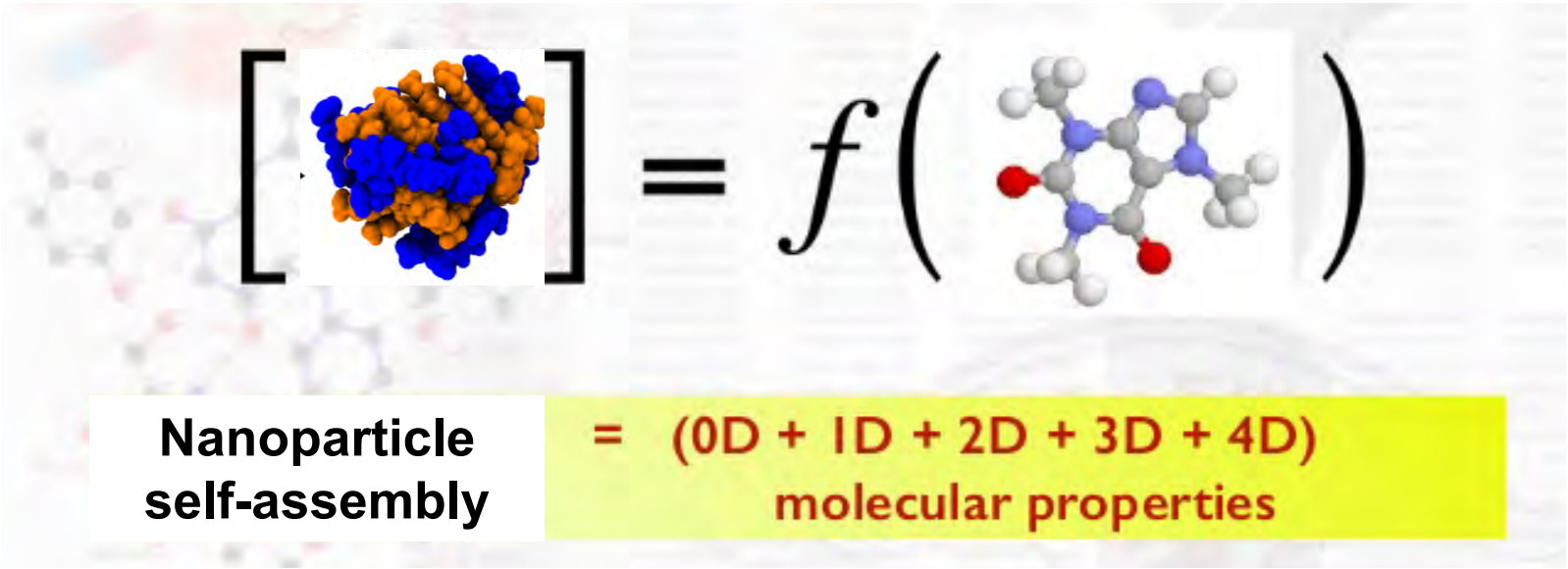
Shamay, et. al., *Nature Materials*, 2018

QSAR: Quantitative Structure-Activity Relationship



Shamay, et. al., *Nature Materials*, 2018

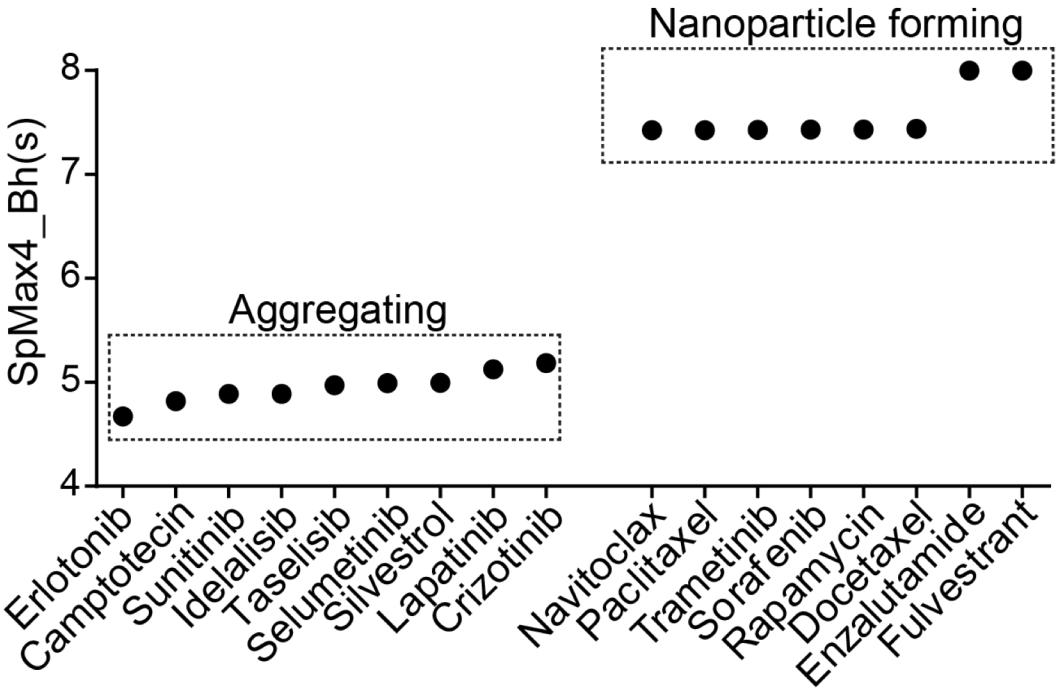
QSNAP: Quantitative Structure-Nanoparticle Assembly Prediction



=> Machine Learning

Shamay, et. al., *Nature Materials*, 2018

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

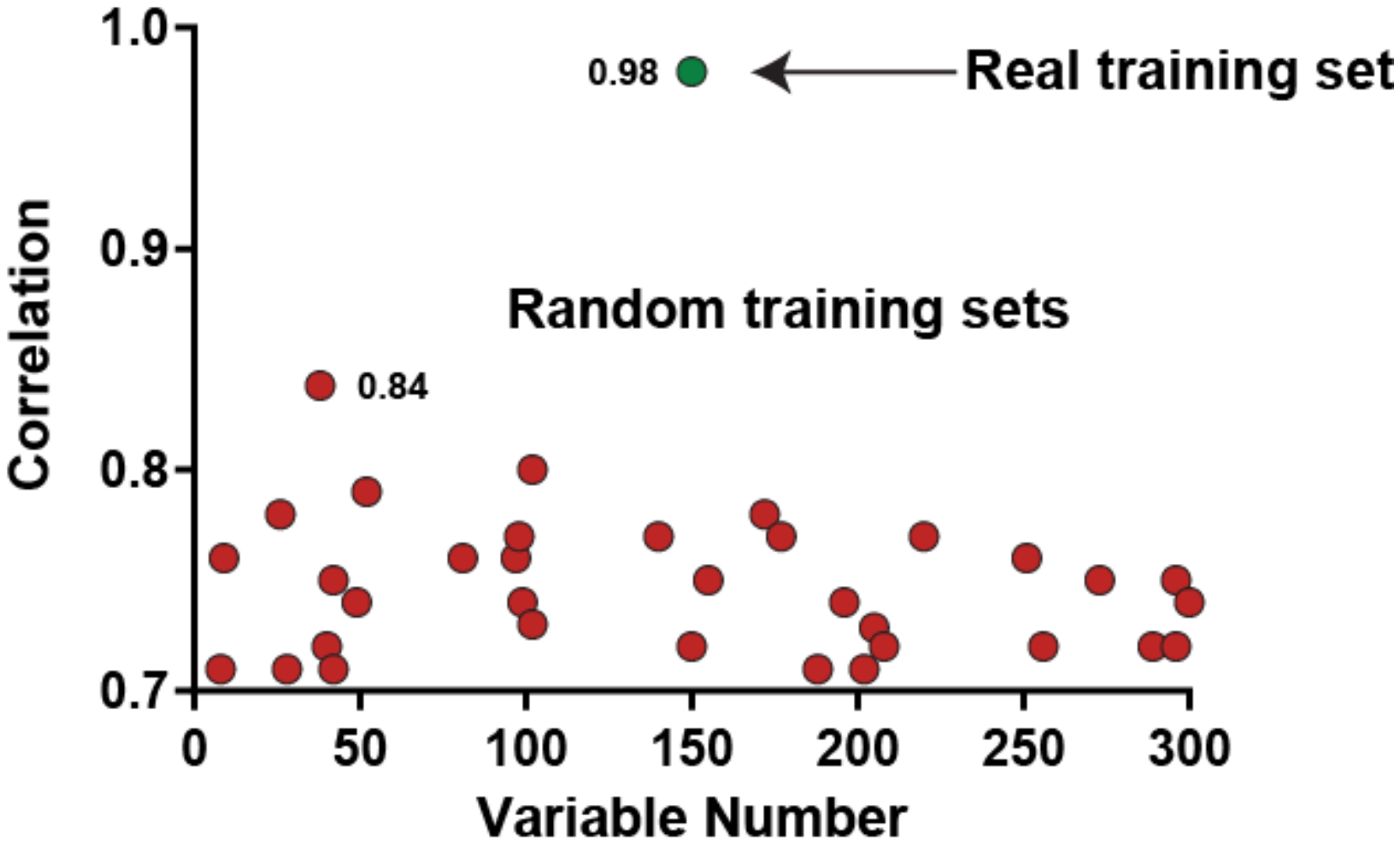


SpMAX4_Bh(s) Descriptor:

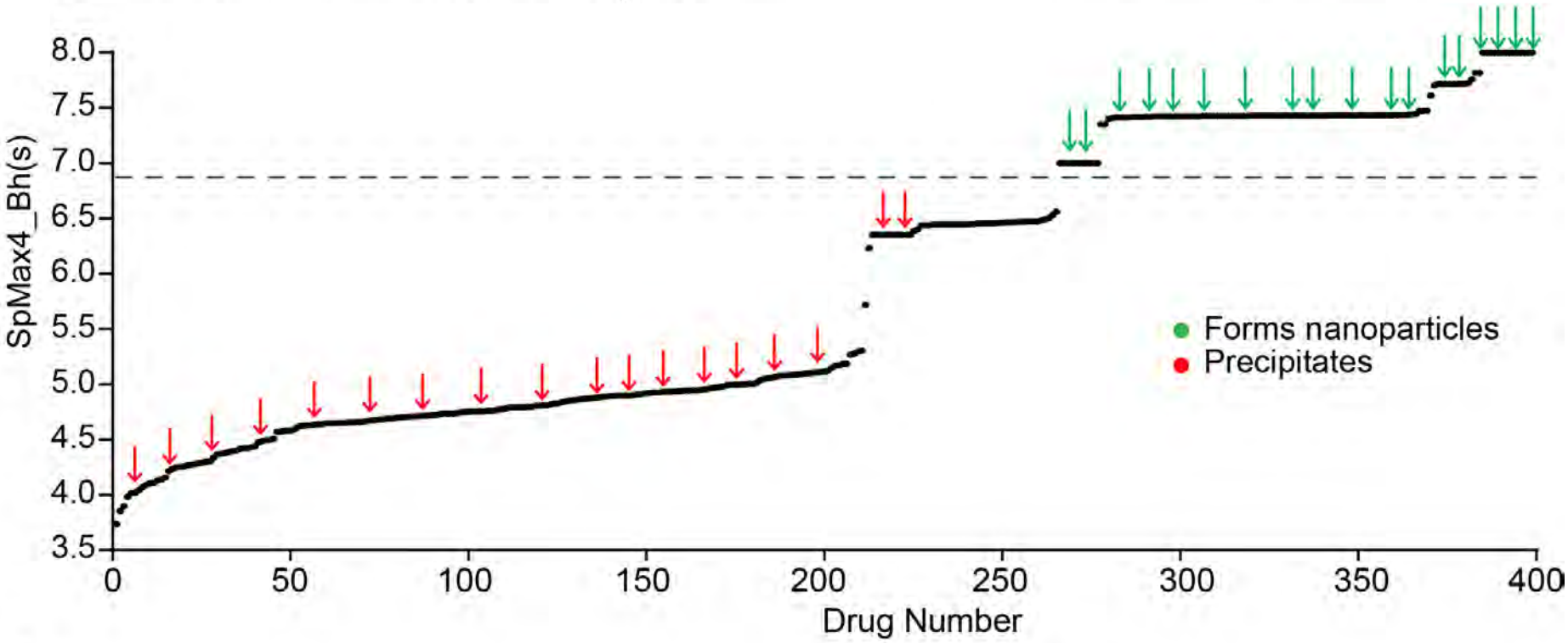
Leading eigenvalue of the Burden matrix *weighted by the intrinsic state*

Shamay, et. al., *Nature Materials*, 2018

Randomization of Training Set Shows that Correlation is Real

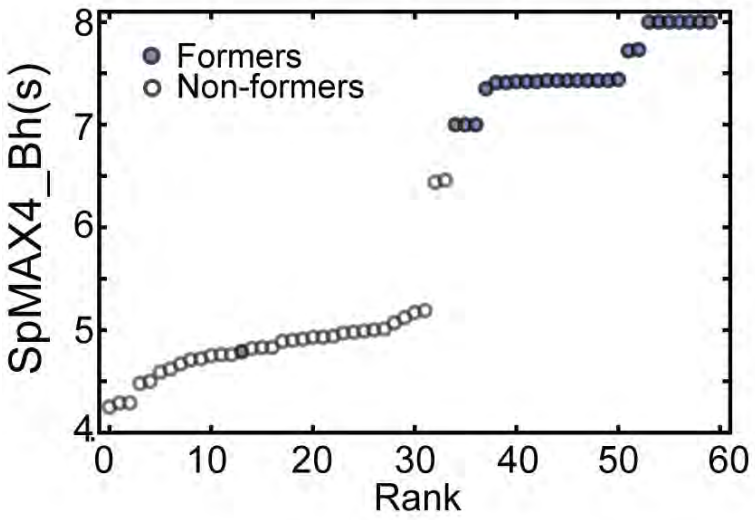


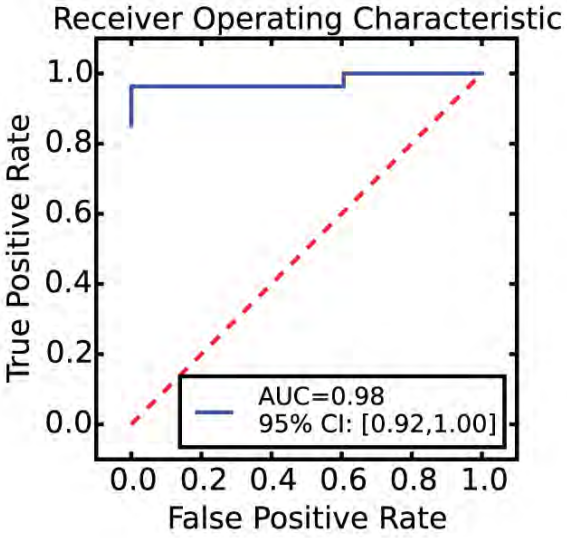
Validation Set: The Prediction was Accurate

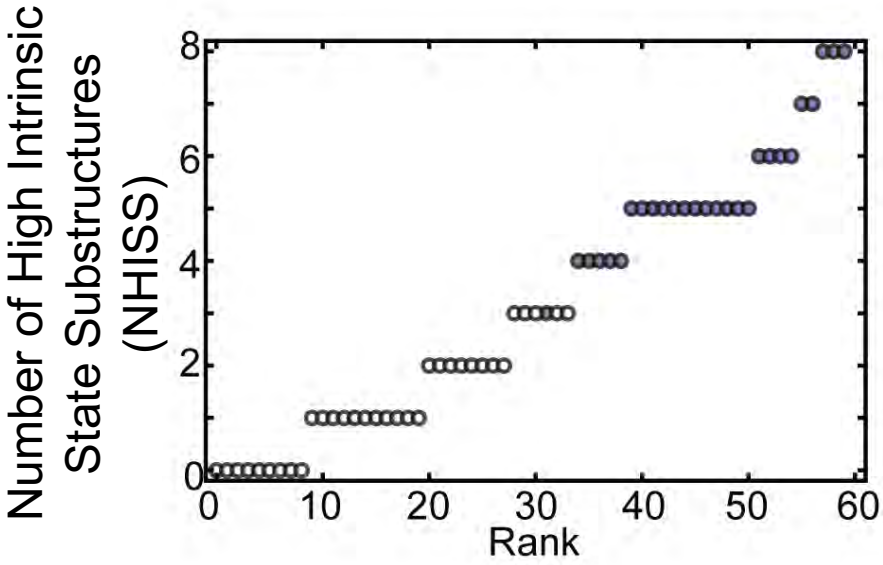


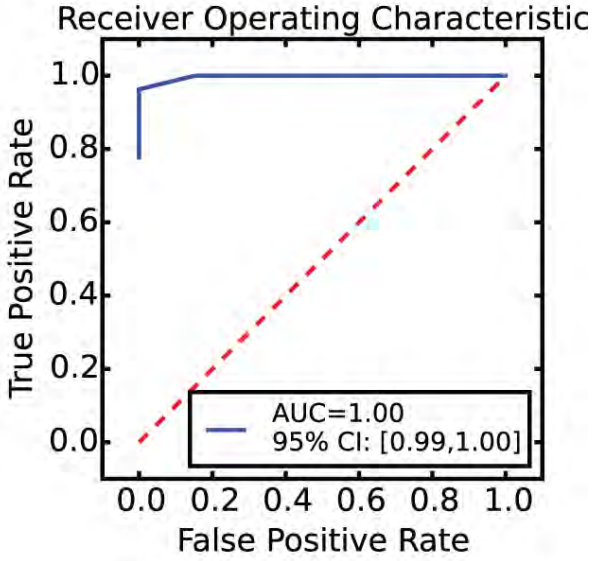
Shamay, et. al., *Nature Materials*, 2018

Intrinsic State Predictive Value Approaches 100%



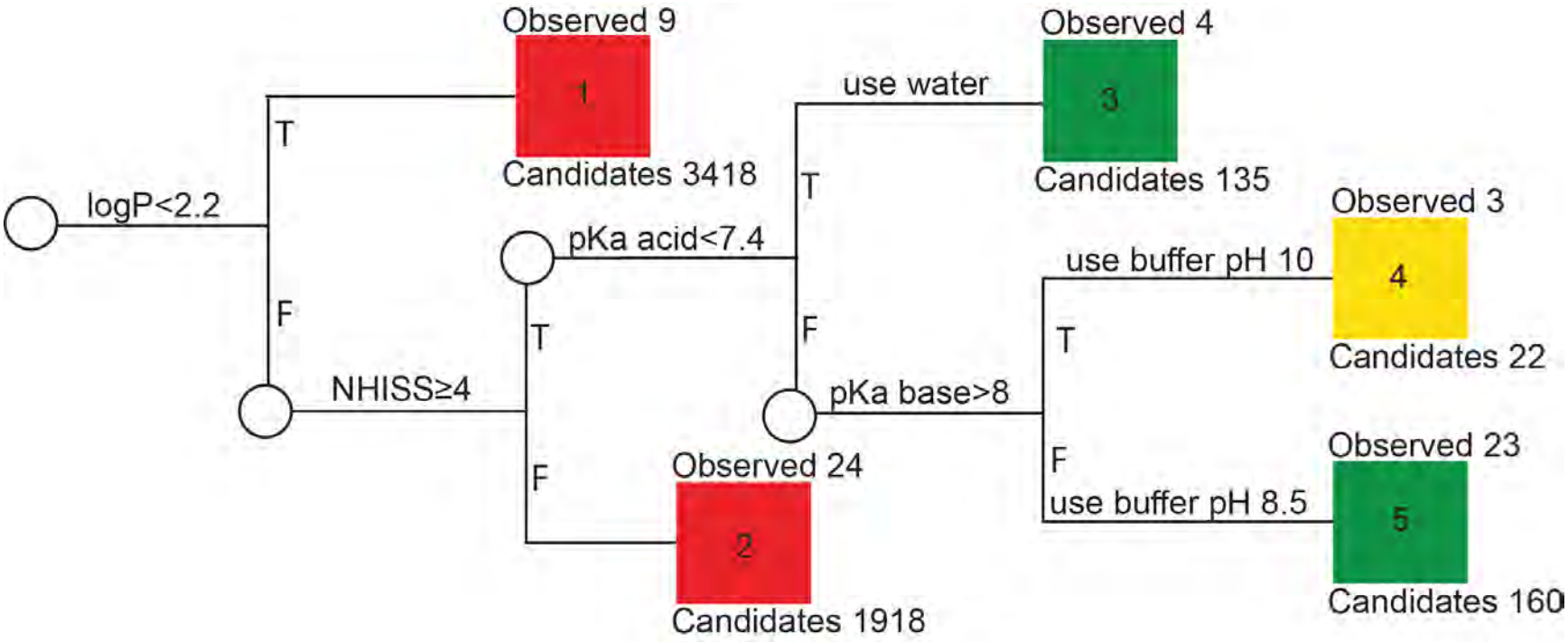






Shamay, et. al., *Nature Materials*, 2018

Decision Tree Summarizes the Process of Encapsulating Many Drugs

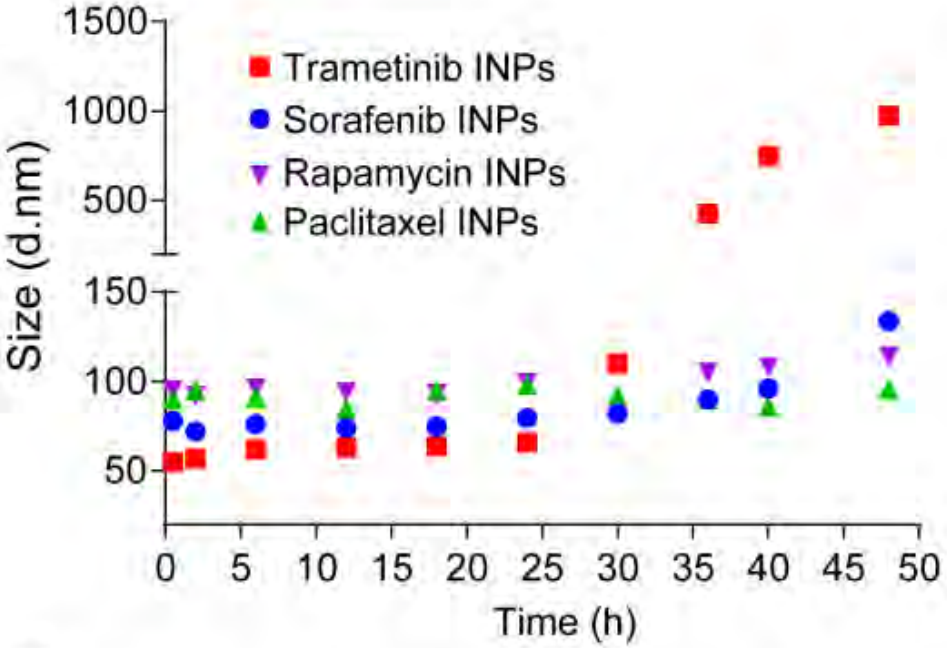


292 FDA approved drugs should form good nanoparticles with ~100% confidence

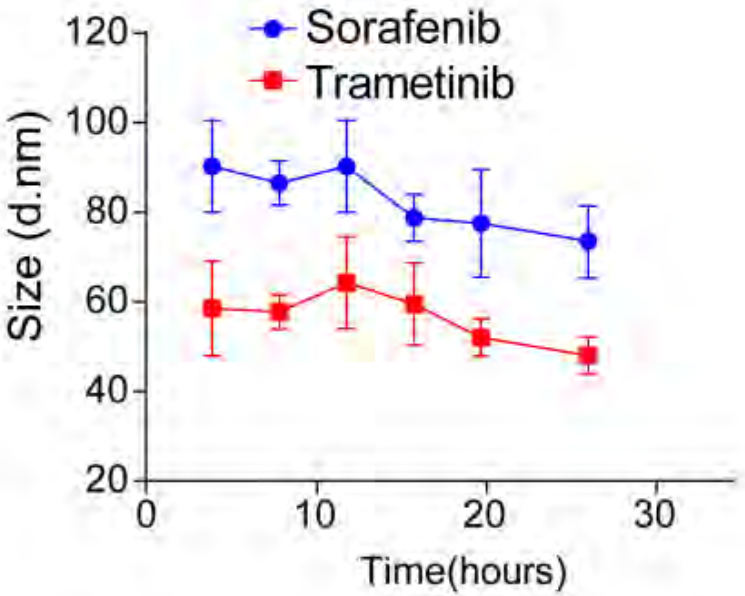
Shamay, et. al., *Nature Materials*, 2018

Are Uncoated Drug-Indocyanine Nanoparticles (INPs) Useful?

Stability in High Dilution (sink)

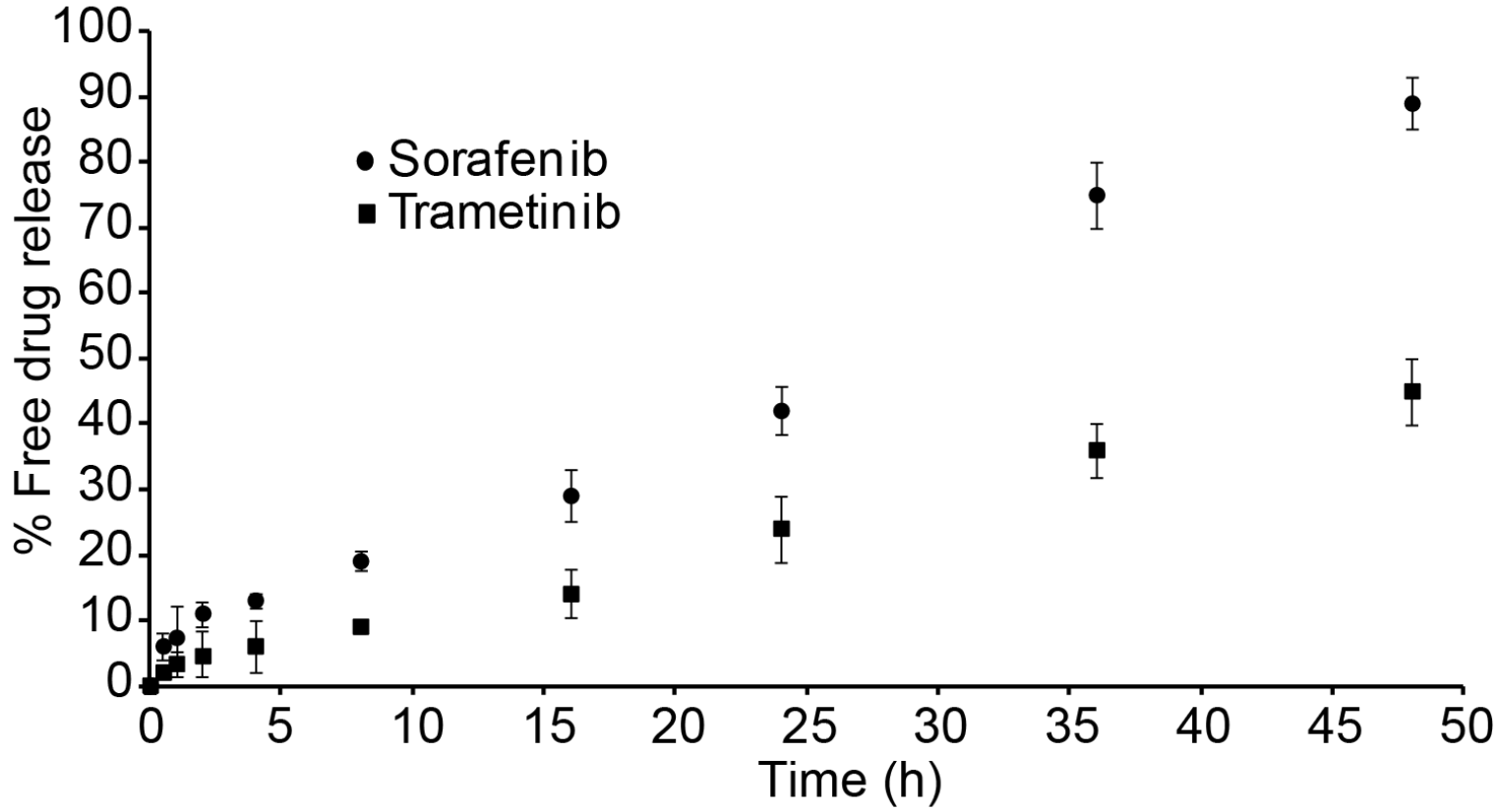


Stability in Serum



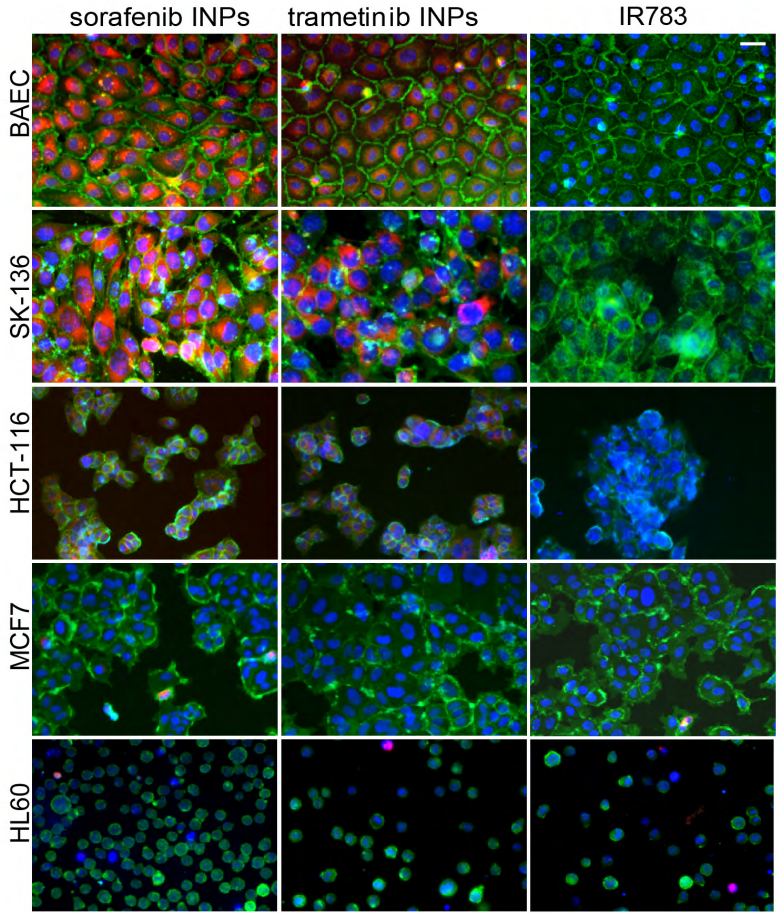
Shamay, et. al., *Nature Materials*, 2018

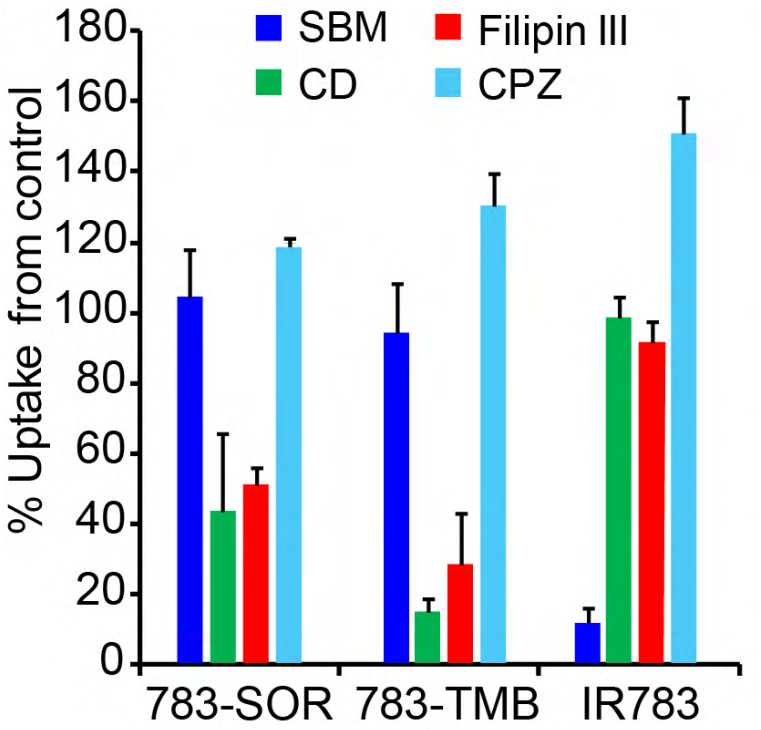
Release Rate and Other Parameters Depend on the Drug



Shamay, et. al., *Nature Materials*, 2018

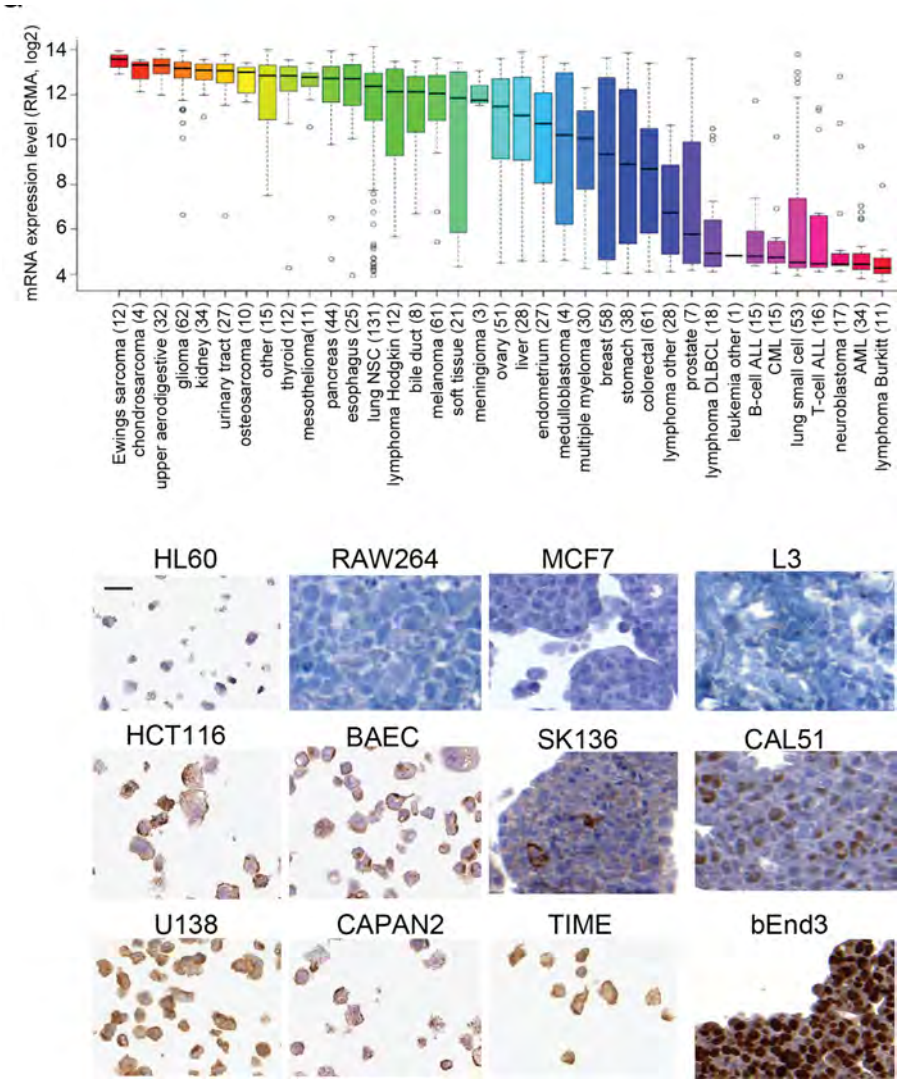
Inhibitors Suggest Nanoparticle Internalization via Caveolin-Mediated Endocytosis

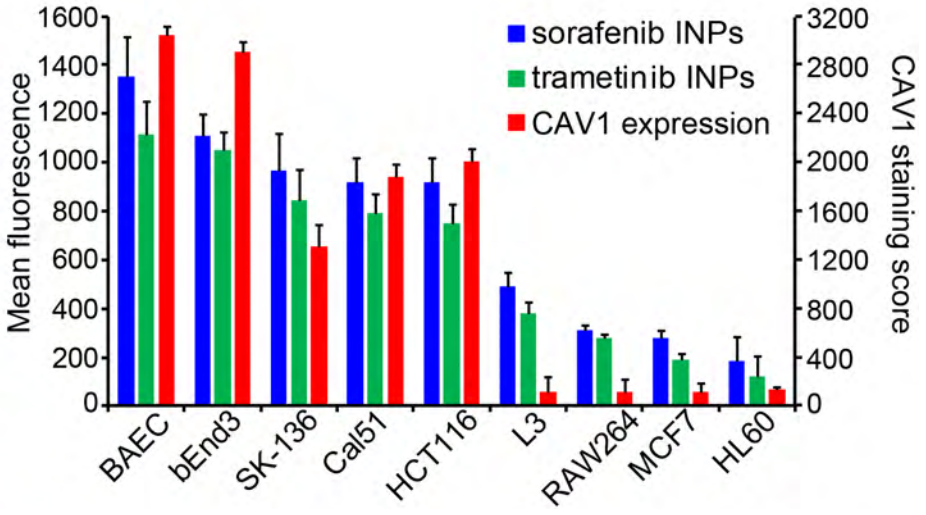




Shamay, et. al., *Nature Materials*, 2018

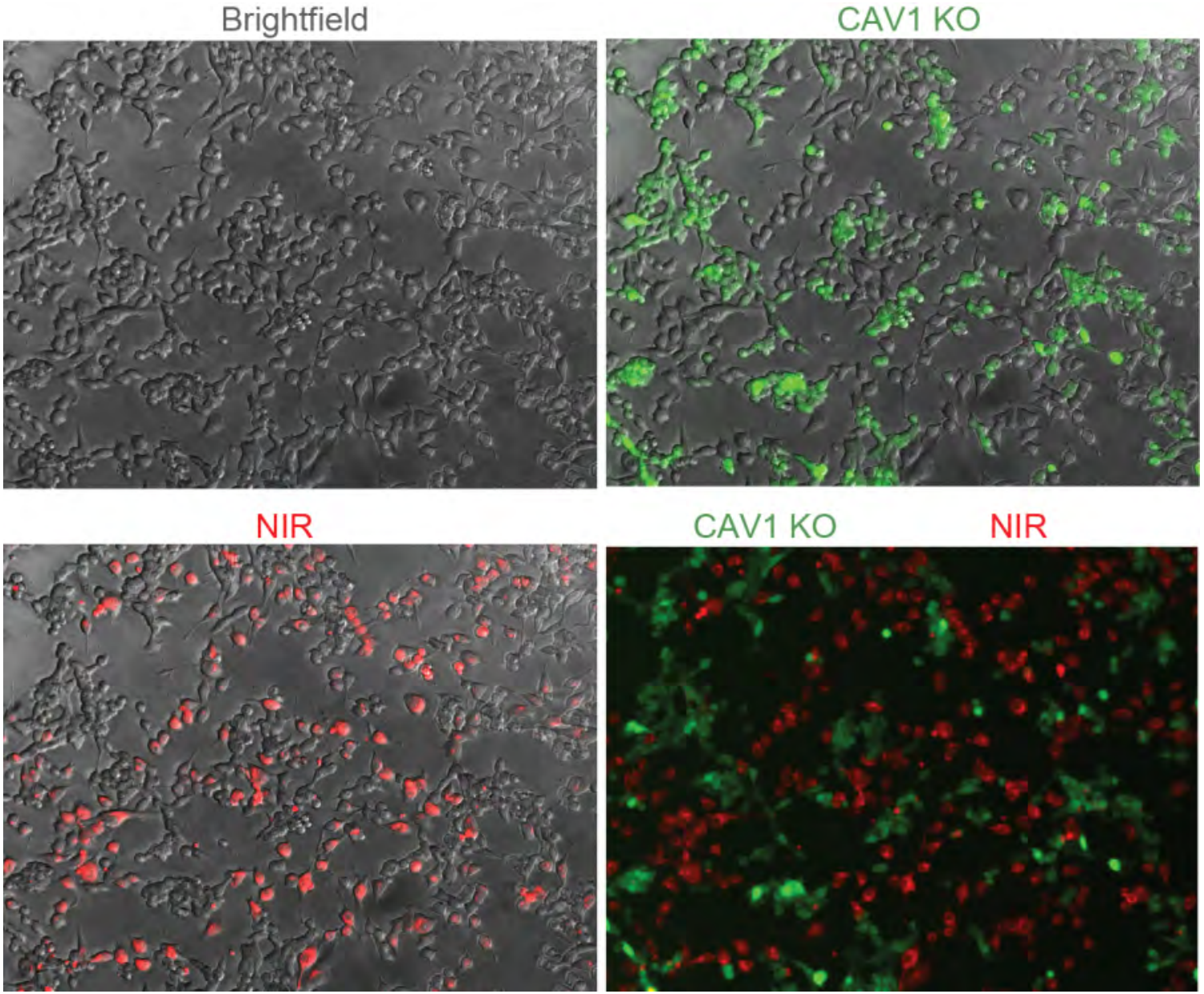
Cell Uptake Correlates with CAV1 Expression





Shamay, et. al., *Nature Materials*, 2018

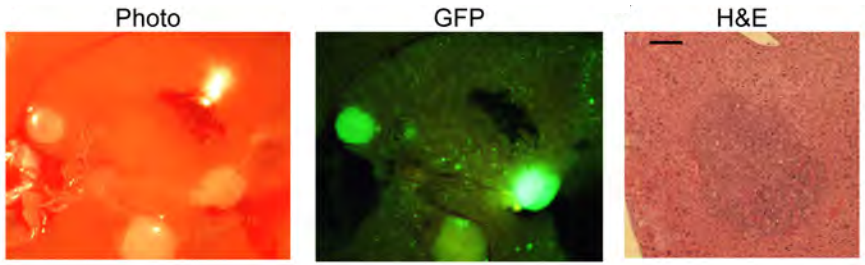
Nanoparticle Uptake is Low in CAV1 Knockout



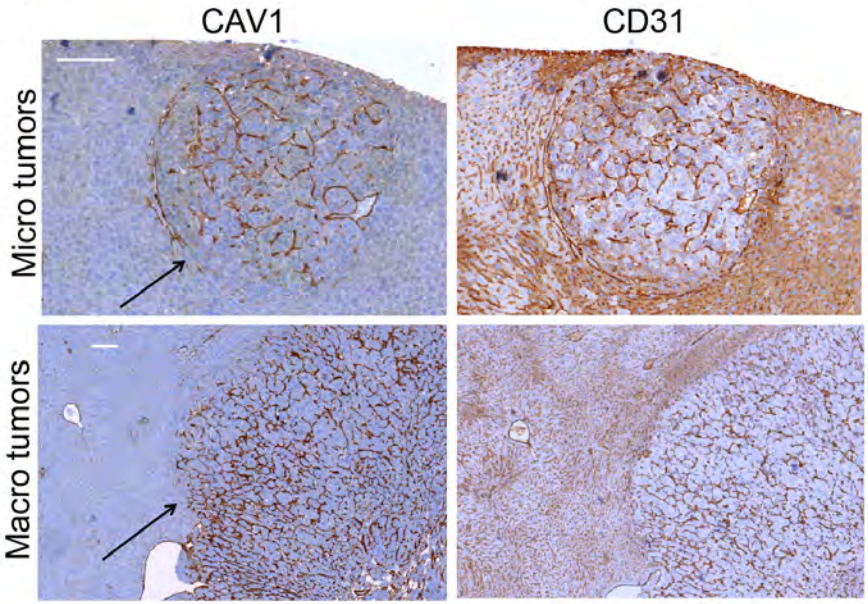
Shamay, et. al., *Nature Materials*, 2018

Nanoparticles Target Liver Tumors in Autochthonous Model

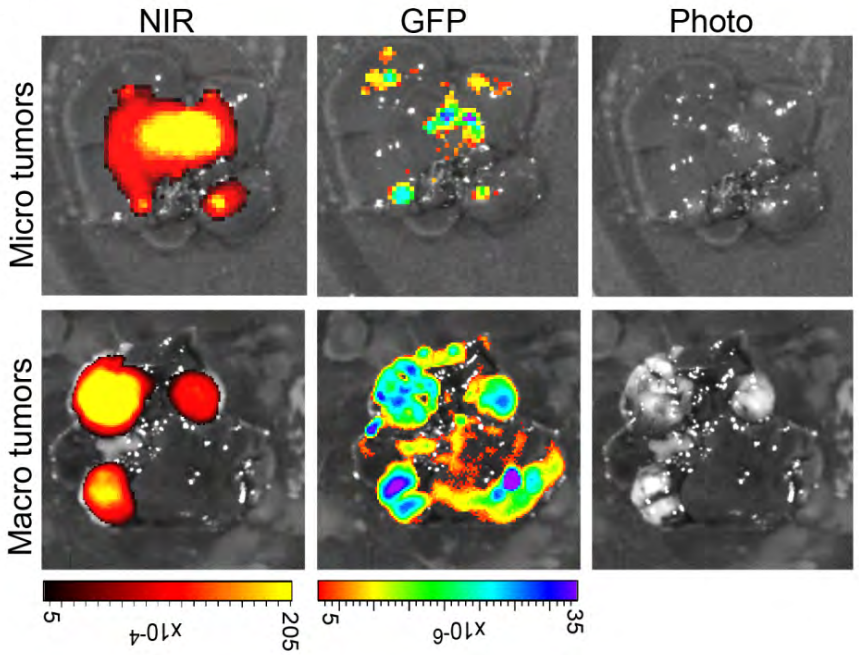
Hydrodynamic co-transfection of c-Myc/β-catenin oncogenes results in liver tumors



Tumors overexpress Cav1 in tumor vasculature

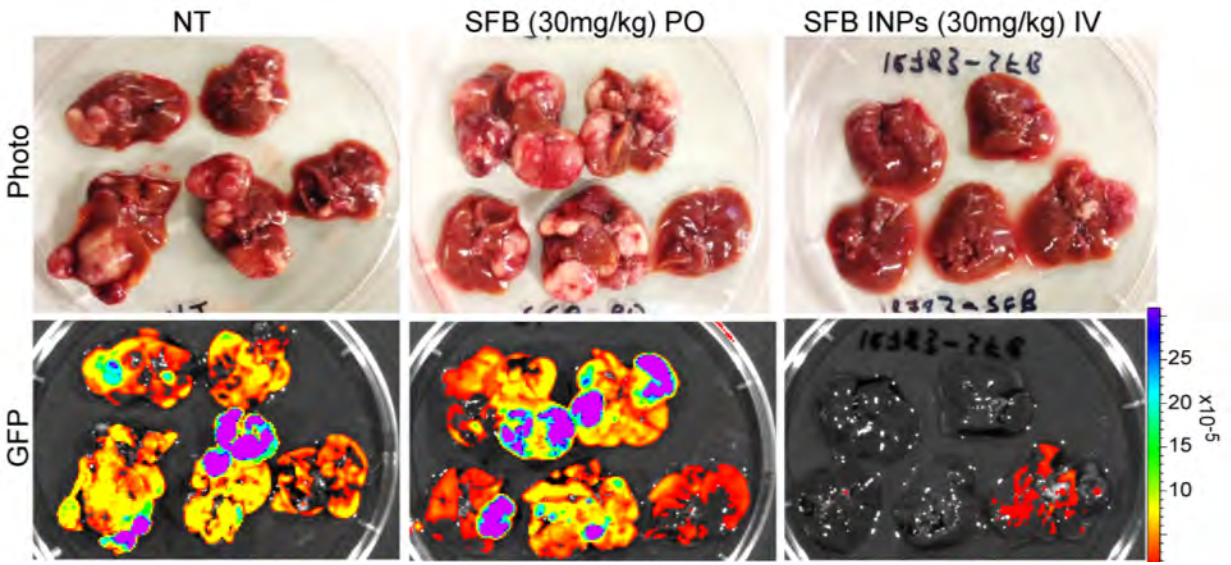


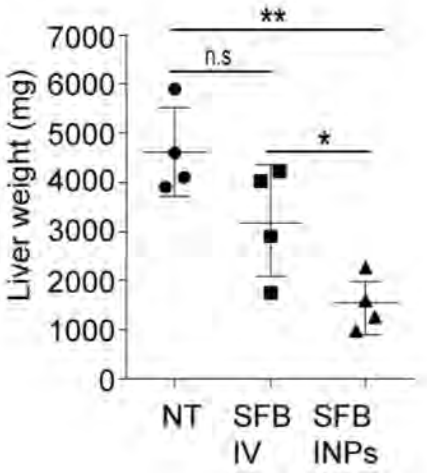
Nanoparticles localize in liver tumors

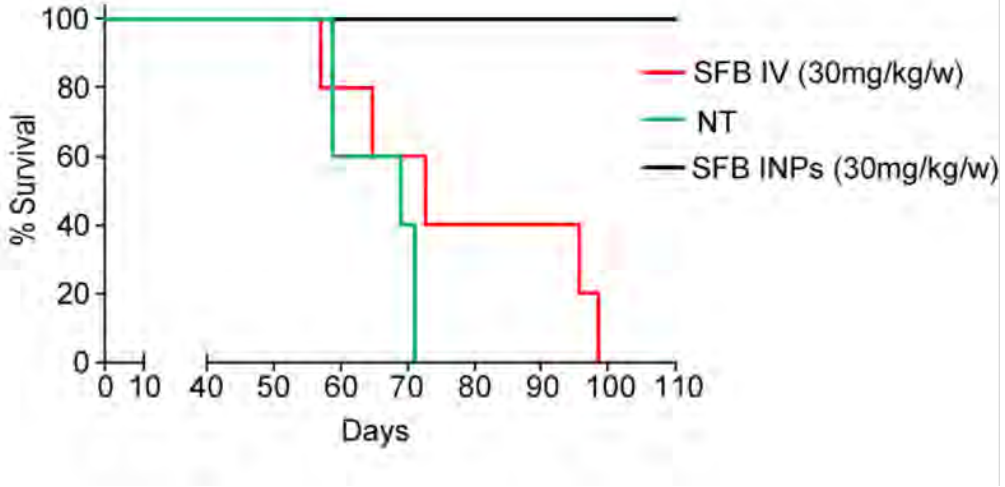


Shamay, et. al., *Nature Materials*, 2018

Sorafenib NPs Show Superior Anti Tumor Efficacy in an Autochthonous Liver Tumor Model

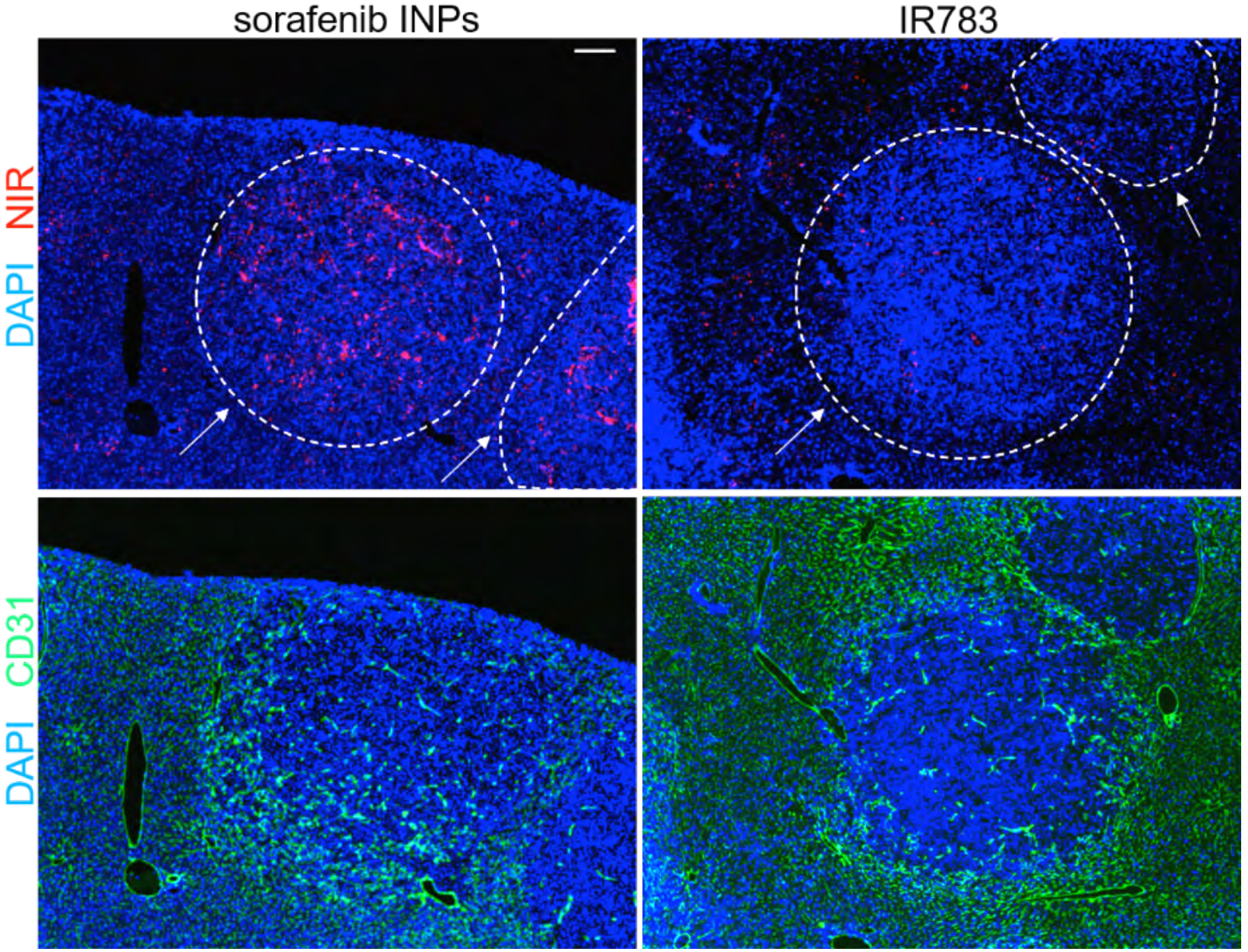






Shamay et. al., *Nature Materials,* 2018

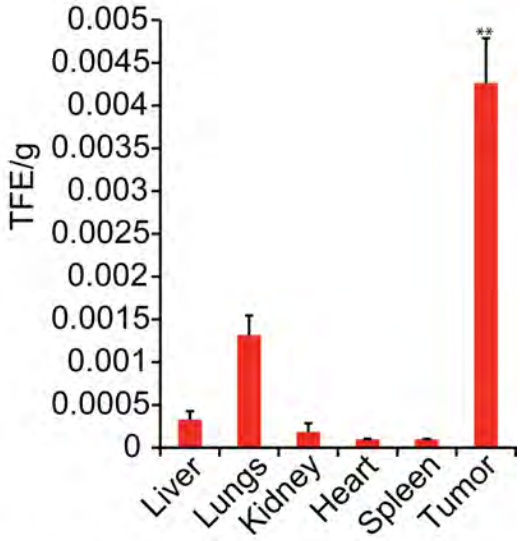
Nanoparticles Target Liver Tumors in Autochthonous Model



Shamay, et. al., *Nature Materials*, 2018

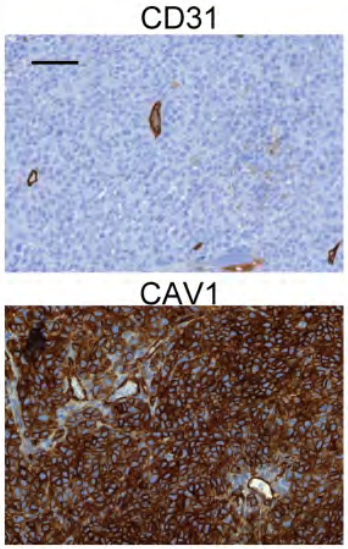
Nanoparticle/Drug Localization in Tumor

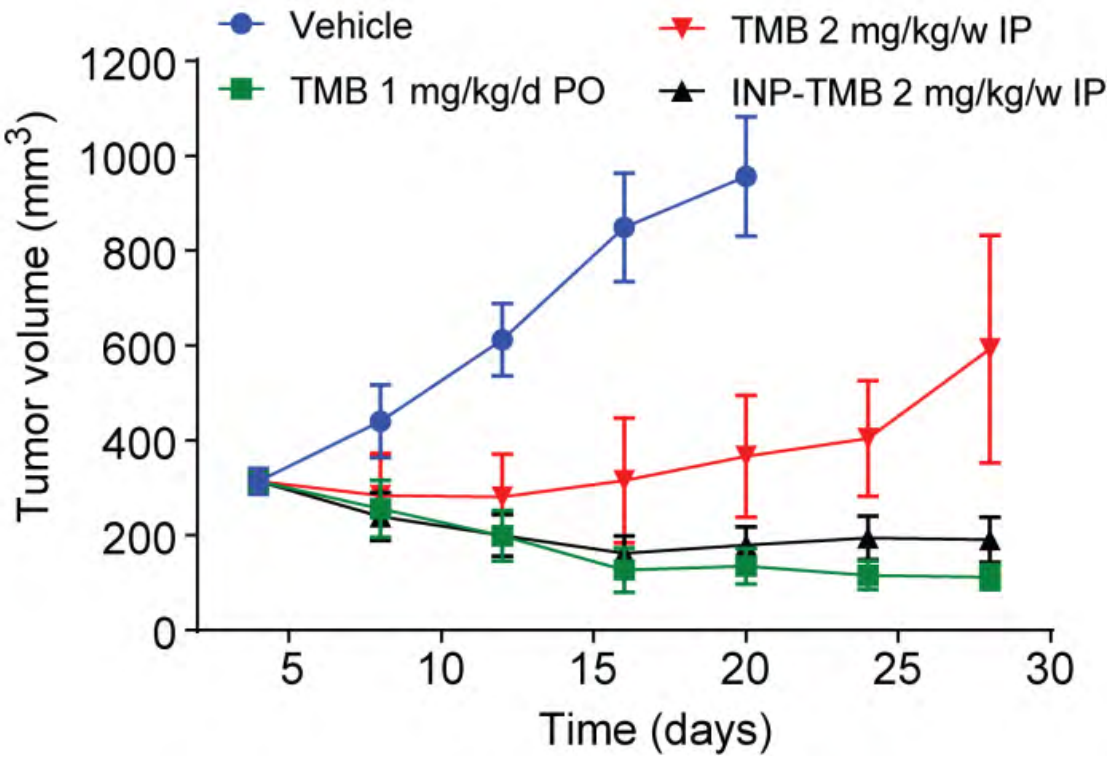
HCT116 SubQ



Shamay, et. al., *Nature Materials*, 2018

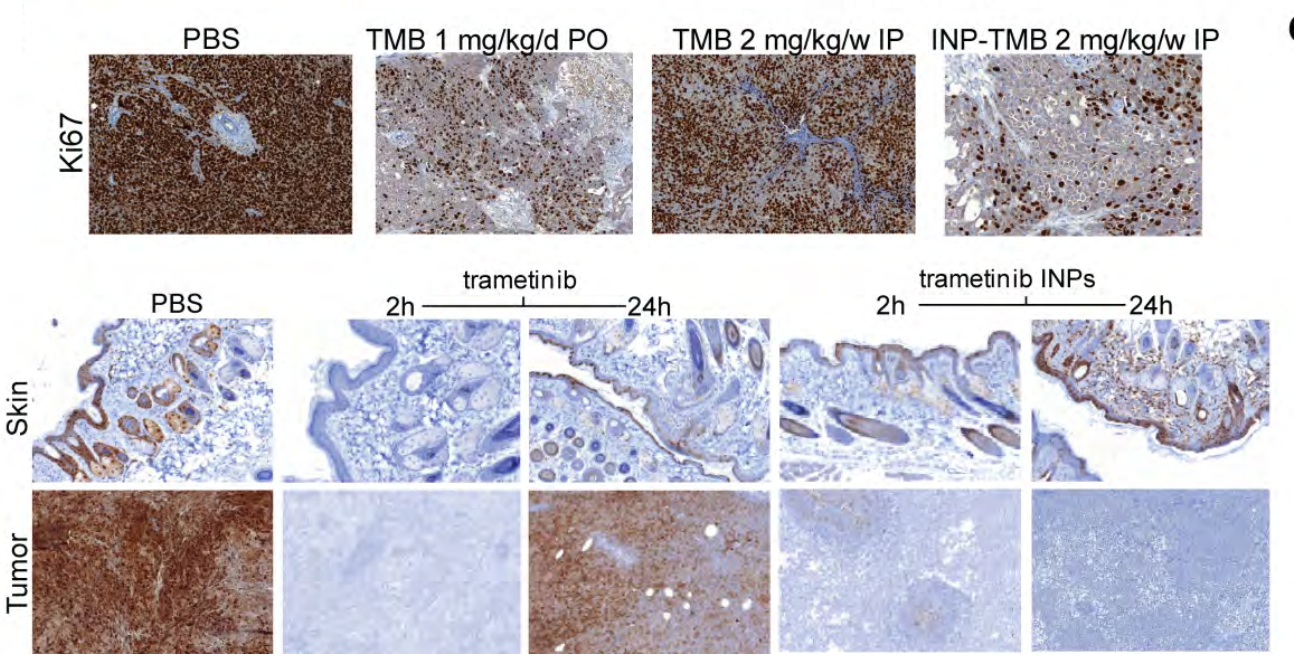
Trametinib-INPs Show Anti-Tumor Efficacy Over Free Drug

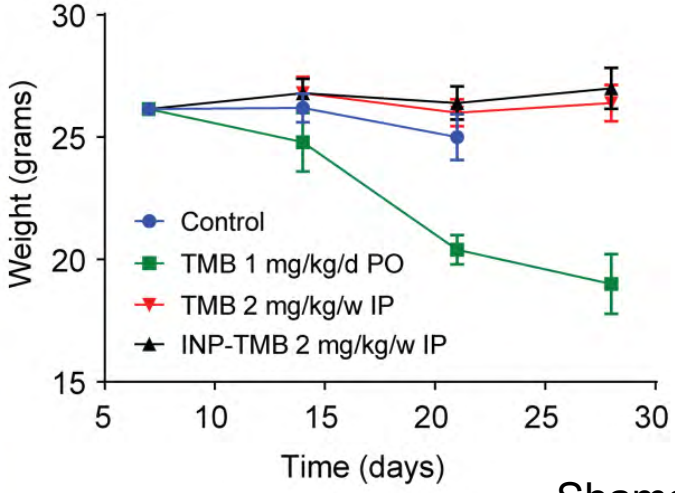




Shamay, et. al., *Nature Materials*, 2018

Trametinib-INPs Modulate Trametinib Pharmacodynamics





Shamay et. al., *Nature Materials,* 2018

Summary

- Targeted drugs have diverse dose-limiting toxicities that may be improved by nanomedicines.
- Nanoparticle delivery of kinase inhibitors enhances anti-tumor efficacy, prolongs target inhibition, and attenuates dose-limiting toxicities.
- Machine learning enables the prediction of nanoparticle self-assembly based on drug structure.
- Nanoinformatics = data sciences applied to nanomedicine

Shamay, et al. *Science Translational Medicine,* 2016
Mizrachi, et. al., *Nature Communications*, 2017
Shamay, et. al., *Nature Materials*, 2018

Upcoming Symposium:

Nanoinformatics: Information and Data Sciences Applied to Nanomaterials Synthesis, Properties, and Biological Effects

258th ACS National Meeting & Exposition, August 25 - 29, 2019, San Diego, CA.

Division of Colloid and Surface Chemistry [COLL]

Submission site: https://www.acs.org/content/acs/en/meetings/national-meeting/abstract-submission.html?sc=natlmeeting_180116_mtg_BO18_od

The deadline for abstract submission is Monday, March 25.

Synopsis: Recent work in nanotechnology and nanomedicine has benefitted from the use of data science and information science to optimize, standardize, and understand the synthesis, characterization, and biological effects of nanomaterials. Machine learning has been used to predict and inform nanoparticle synthesis and pharmacokinetics. Information science has been applied towards nanomedicines to standardize heterogeneous information related to nanoparticle characterization and toxicity. This session will focus on the use of data science and information science in the development and understanding of nanomaterials and nanomedicines. Appropriate topics include, but are not limited to:

- **Machine learning applied to nanotechnology**
- **Information management related to nanomaterials**
- **Data mining approaches**
- **Data standardization in nanotoxicology**
- **Data homogeneity in nanomaterials characterization**
- **Chemical information applied to nanoscience**

Upcoming Symposium:

Nanoinformatics: Information and Data Sciences Applied to Nanomaterials Synthesis, Properties, and Biological Effects

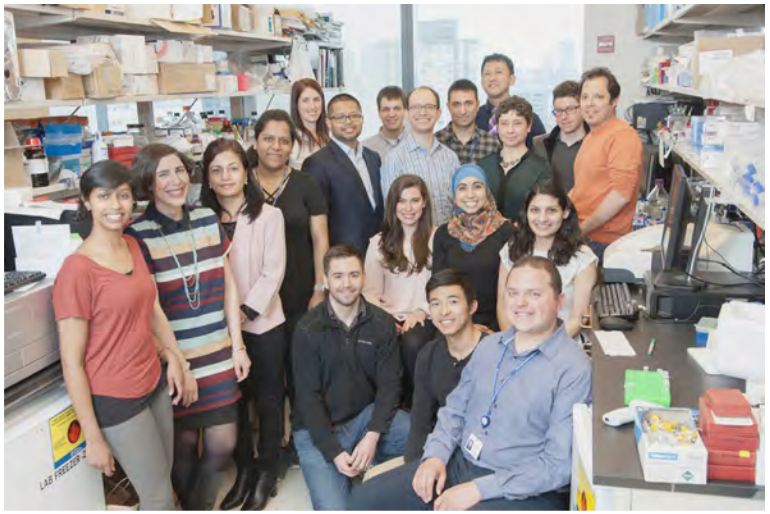
Organizers:

Daniel A. Heller, Memorial Sloan Kettering Cancer Center, Weill Cornell Medicine
James E. Dahlman, Georgia Institute of Technology, Emory School of Medicine
Shan Jiang, Iowa State University
Avi Schroeder, Technion—Israel Institute of Technology

Confirmed Invited Speakers:

Chad Mirkin – Northwestern University
Luisa Russell – National Cancer Institute
Bryce Meredig – Citrine Informatics
Aravind Asokan - Duke University
Korin Wheeler - Santa Clara University
Giuseppe Battaglia - University College London
Eric Shapiro - Michigan State University
Yosi Shamay – Technion - Israel Institute of Technology
Rein Ulijn – City University of New York

Acknowledgements



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Experimental Therapeutics Center
Metastasis and Tumor Ecosystems Center
Center for Mol. Imaging and Nanotechnology

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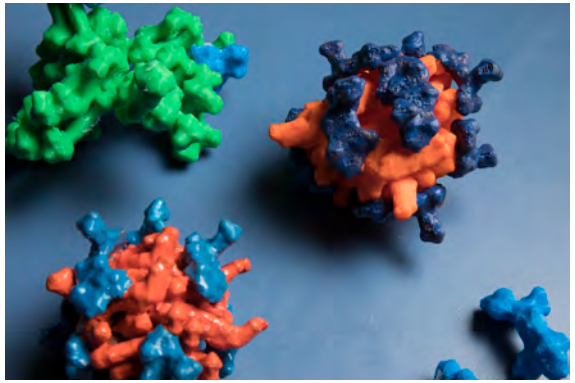

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