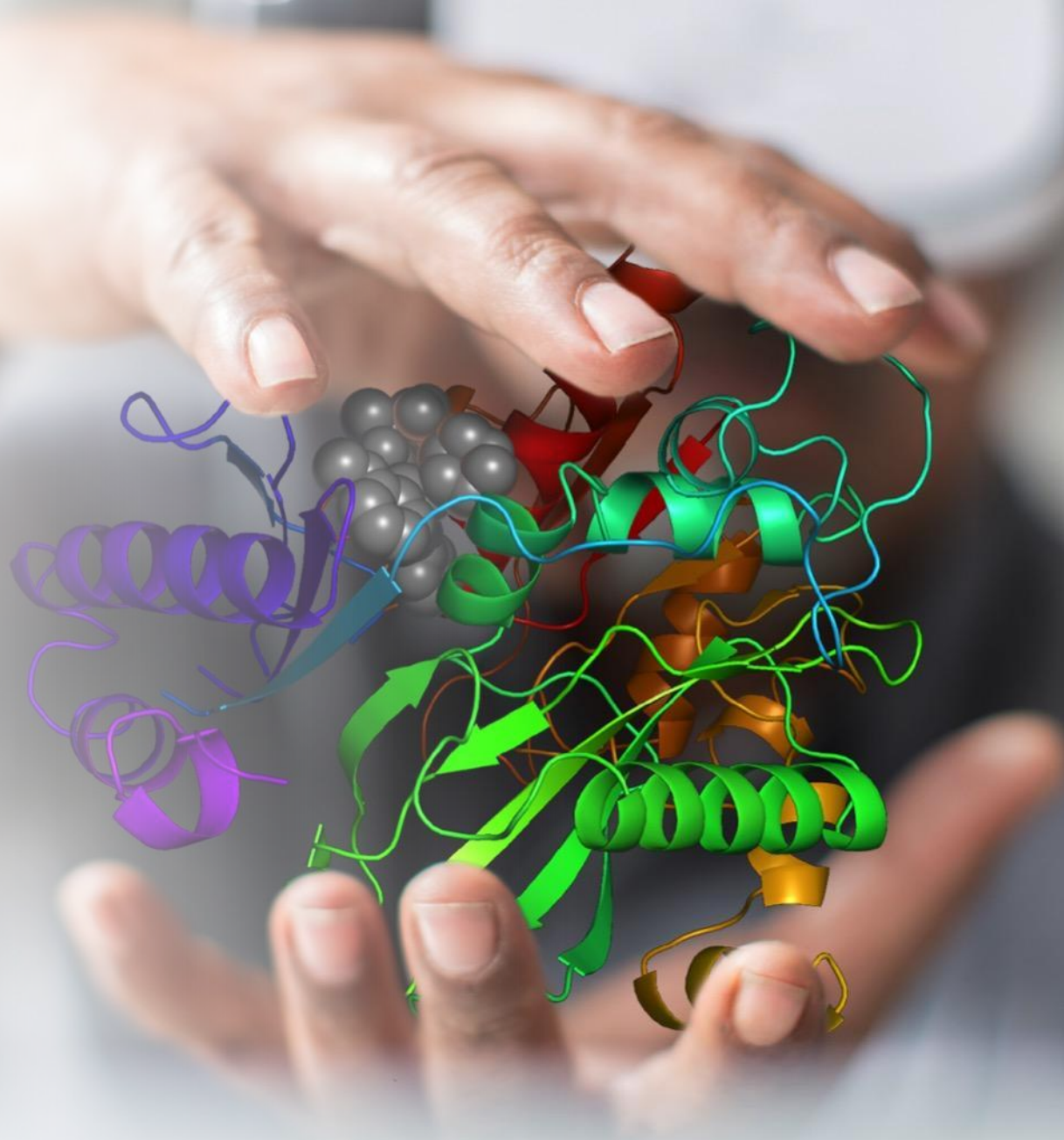
SCHRÖDINGER®

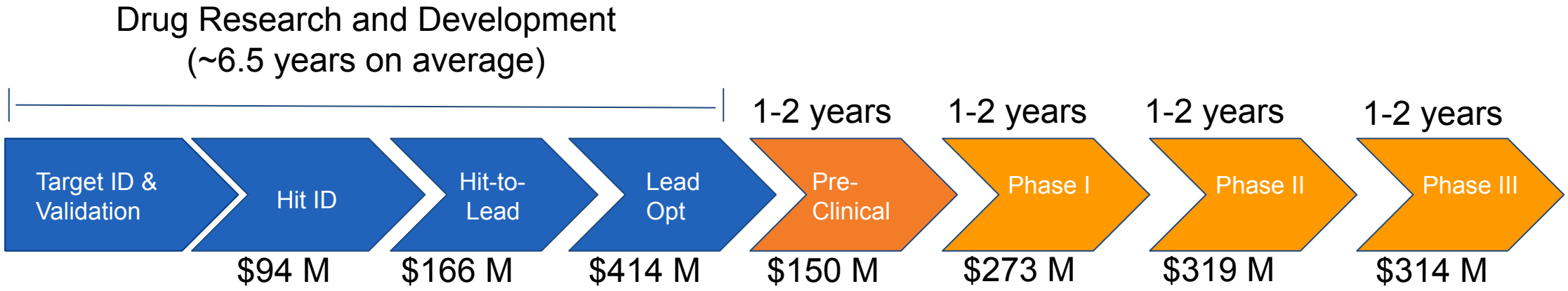
Molecular Modeling in Drug Discovery



By the end of this module you should be able to...

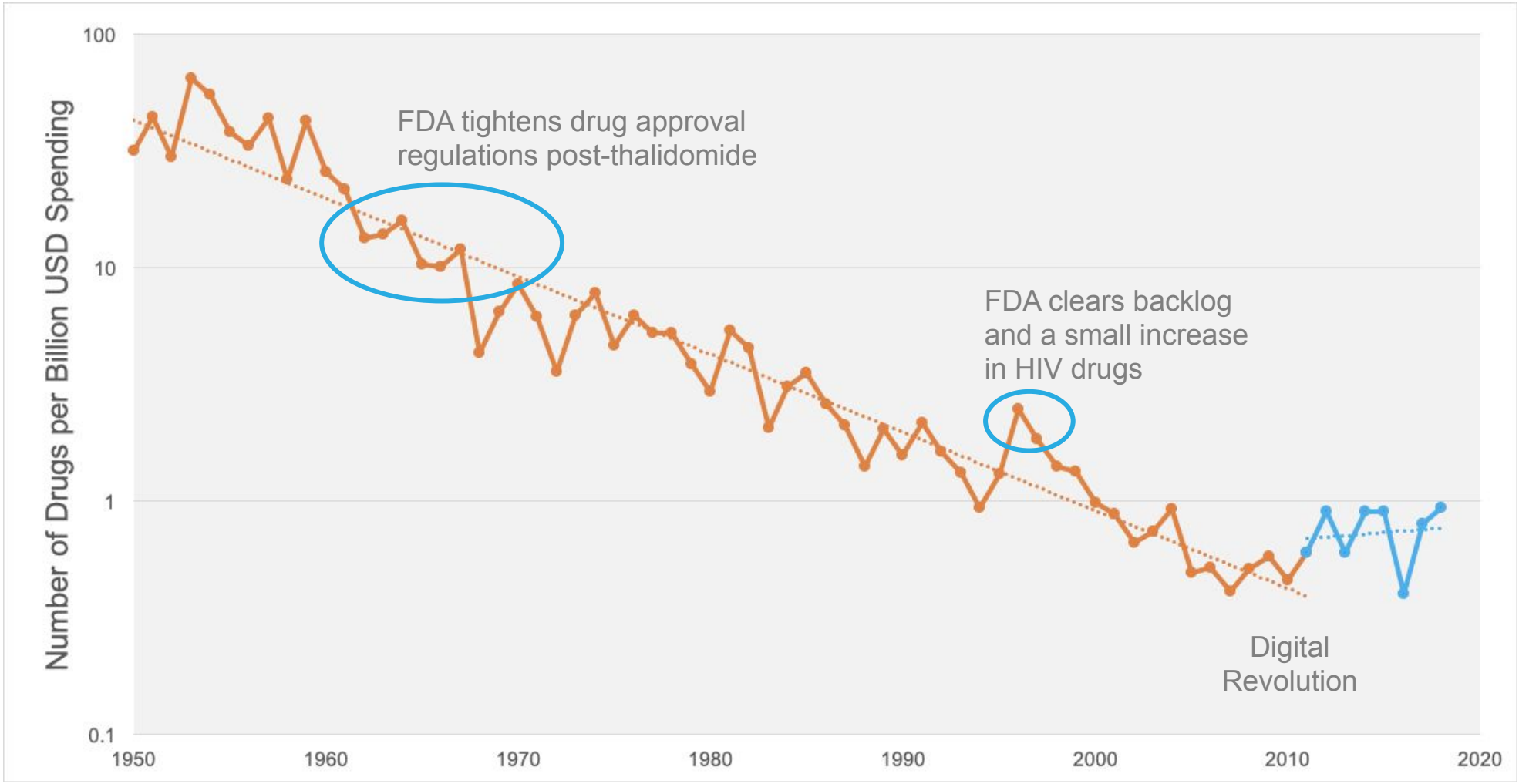
- Know more about the structure of this course and the computational strategies we will use
- Describe the difference between structure-based and ligand-based virtual screening
- List examples of how molecular modeling approaches have helped to identify and advance compounds to the clinical trials and beyond

The Drug Discovery pipeline has many steps



Paul SM et al., *Nat. Rev. Drug Discov.*, 2010, *9*, 203-214
Schuhmacher et al. *Value Creation in the Pharmaceutical Industry: The Critical Path to Innovation, First Edition*, 2016

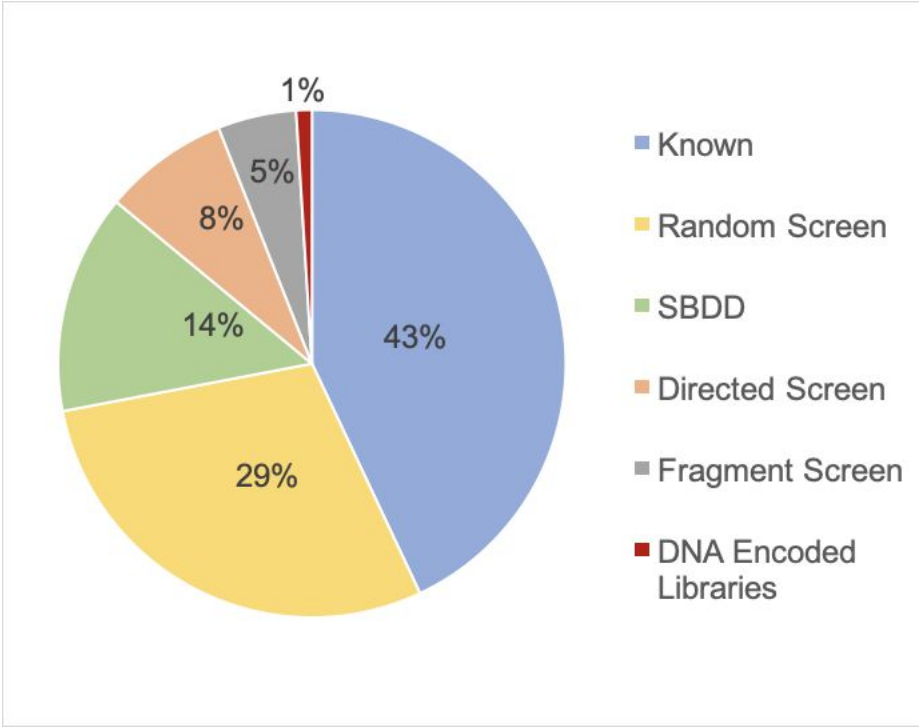
Drug discovery is expensive and slow



Scannell JW et al., *Nat. Rev. Drug Discov.*, 2012, *11*, 191-200
Ringel MS, Scannell JW, Baedeker M, Schulze U., Nat Rev Drug Discov (2020) *https://doi.org/10.1038/d41573-020-00059-3*

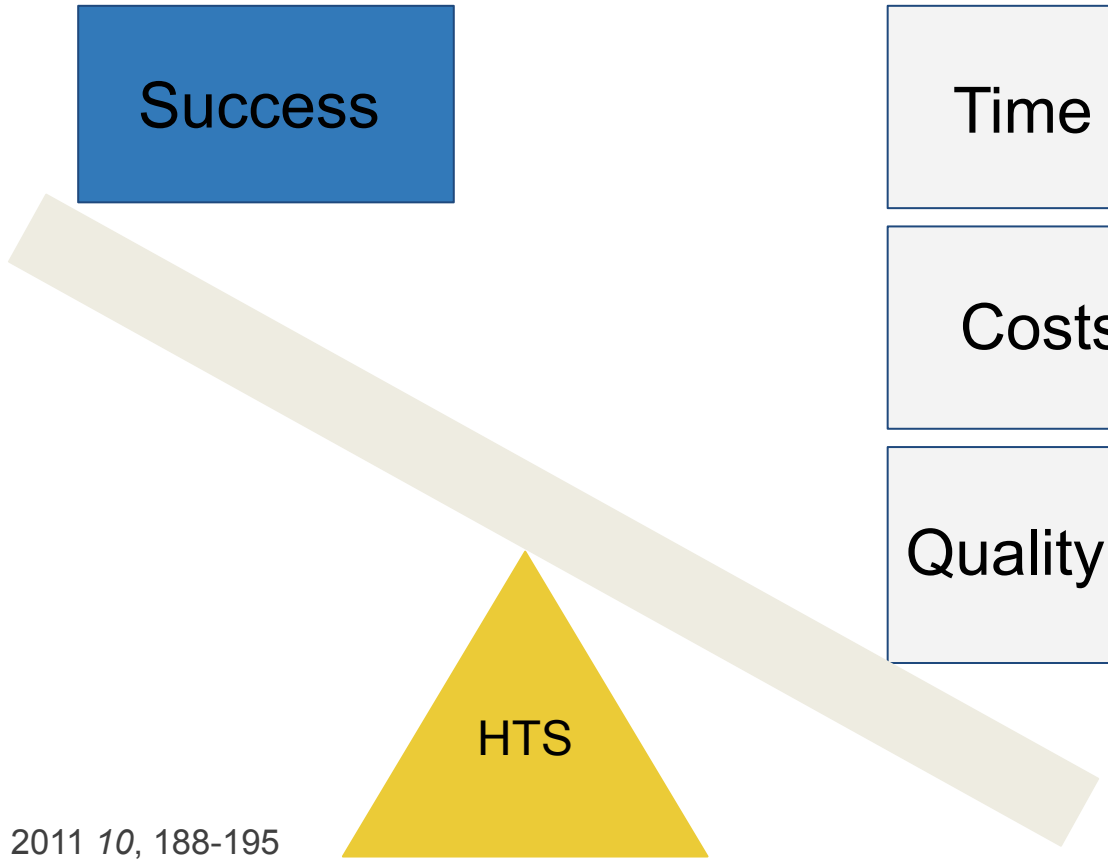
There are many strategies to identify hit compounds

Hit Identification Strategy % for Clinical Candidates in 2015-2016



Macarron R et al., *Nat. Rev. Drug Discov.,* **2011** *10*, 188-195
Brown D et al., *J. Med. Chem.* **2018**, *61*, 9442-9468

High-throughput virtual screening (HTVS) has advantages over traditional high-throughput screening



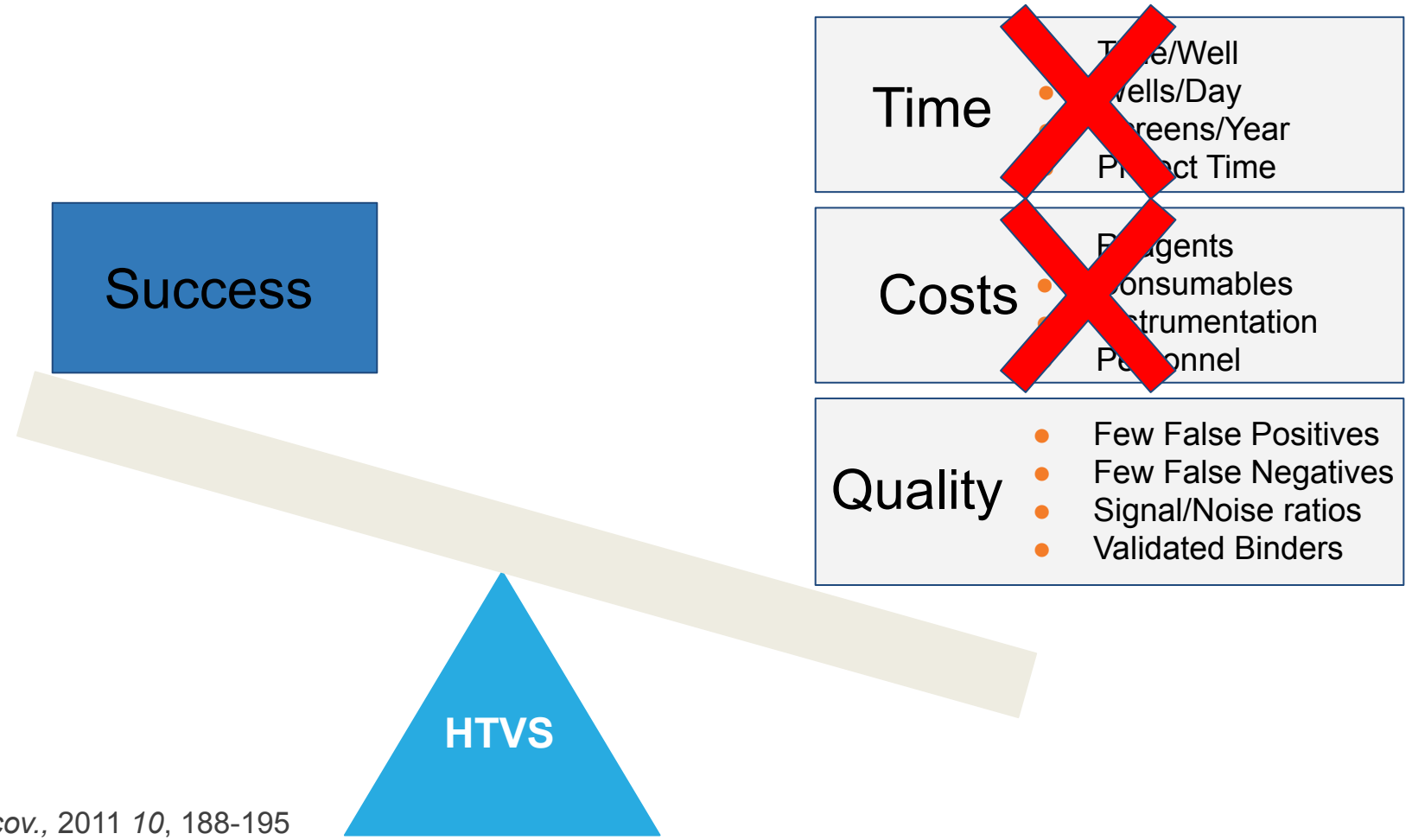
Time
- Time/Well
- Wells/Day
- Screens/Year
- Project Time

Costs
- Reagents
- Consumables
- Instrumentation
- Personnel

Quality
- Few False Positives
- Few False Negatives
- Signal/Noise ratios
- Validated Binders

Macarron R et al., *Nat. Rev. Drug Discov.,* 2011 *10*, 188-195
Lyu et al., *Nature,* 2019, *556,* 224-229
Mayer et al, *J. Biomol. Screening.* 2008, *13*

High-throughput virtual screening (HTVS) has advantages over traditional high-throughput screening



Macarron R et al., *Nat. Rev. Drug Discov.,* 2011 *10*, 188-195
Lyu et al., *Nature,* 2019, *556,* 224-229
Mayer et al, *J. Biomol. Screening.* 2008, *13*

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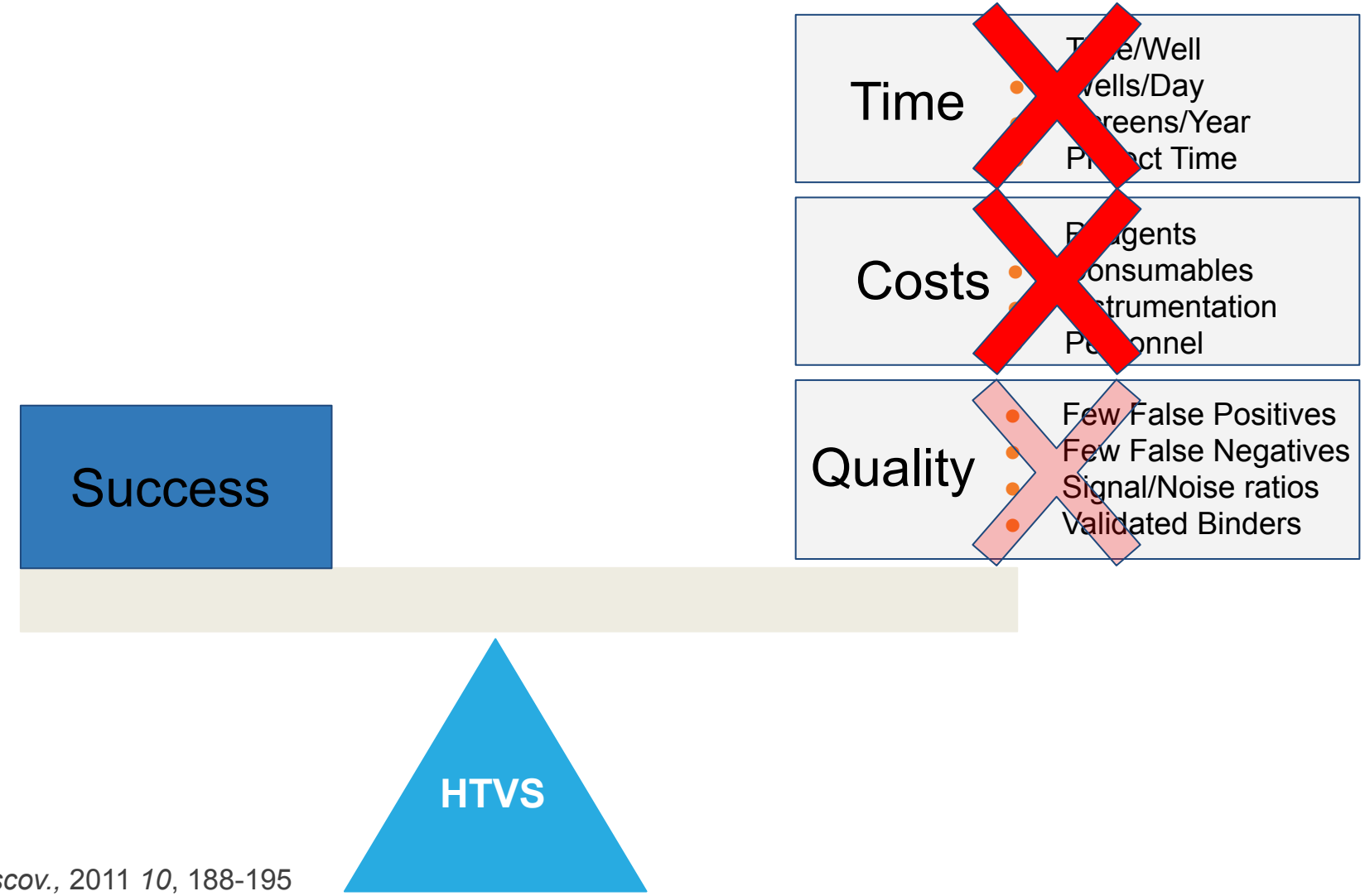
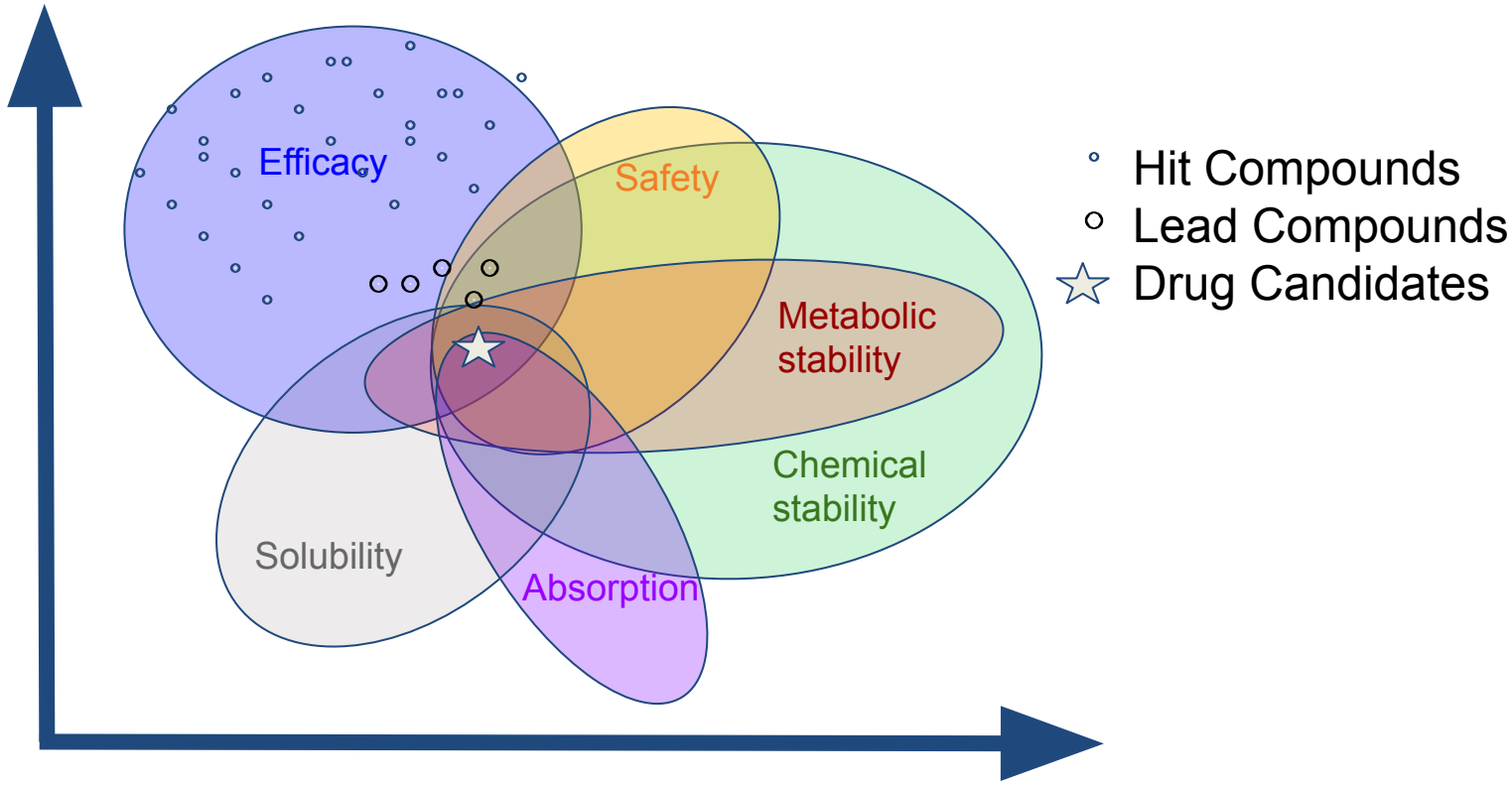


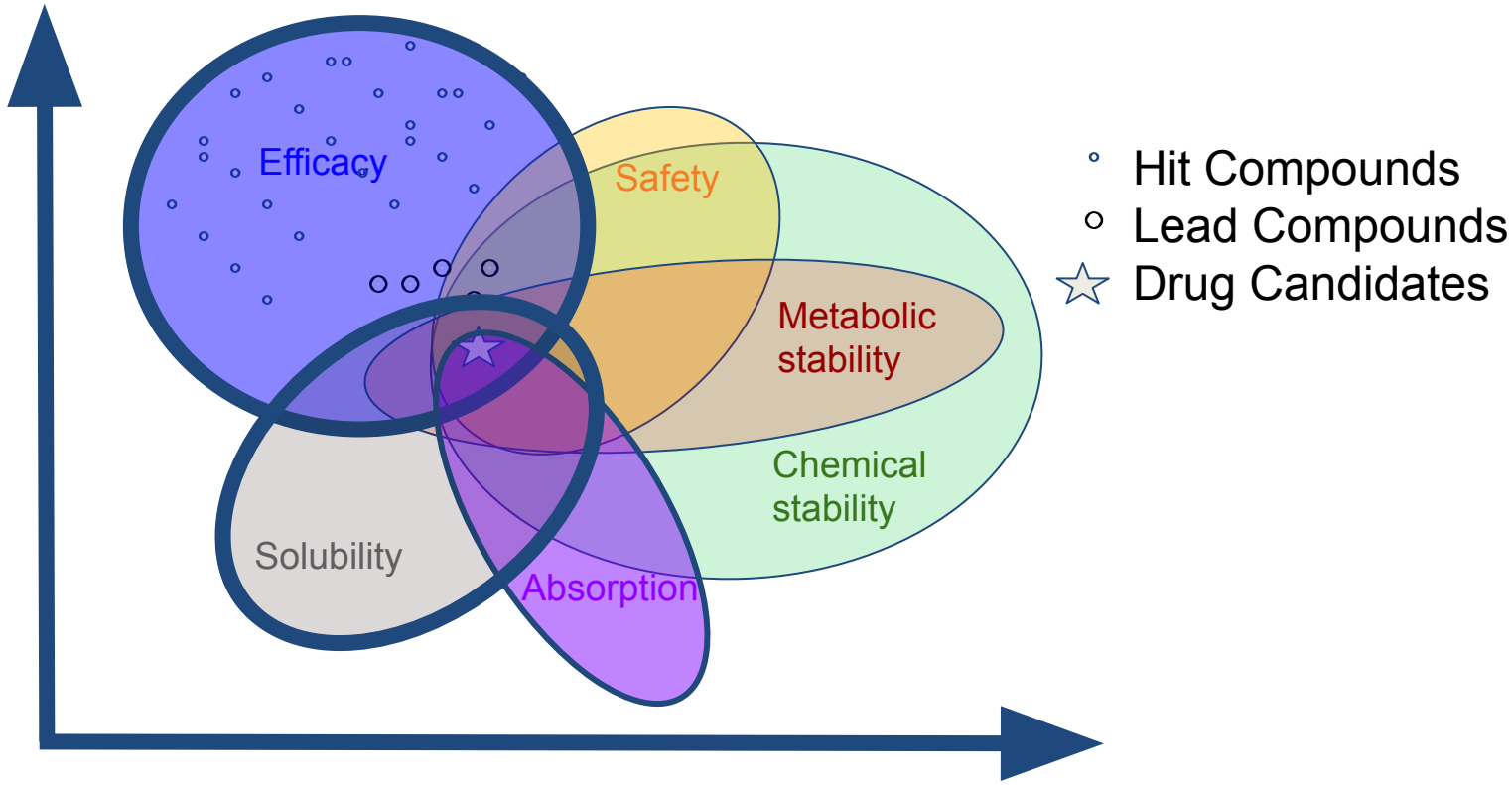
Macarron R et al., *Nat. Rev. Drug Discov.,* 2011 *10*, 188-195
Lyu et al., *Nature,* 2019, *556,* 224-229
Mayer et al, *J. Biomol. Screening*. 2008, *13*

Lead optimization requires getting all parameters right at once



Lead optimization requires getting all parameters right at once

Free Energy Methods and Machine Learning Enhanced QSAR



Computing power has increased over time

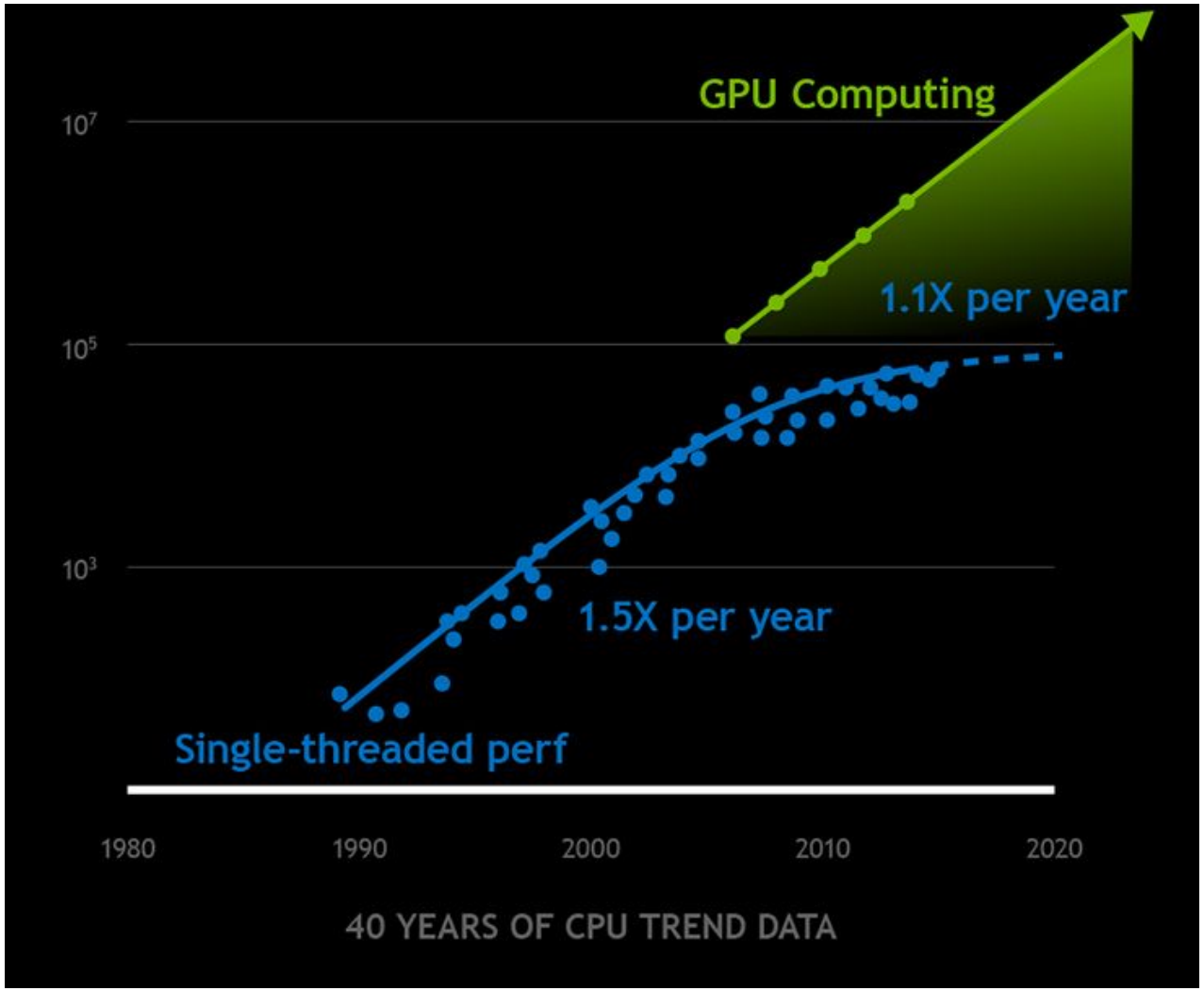
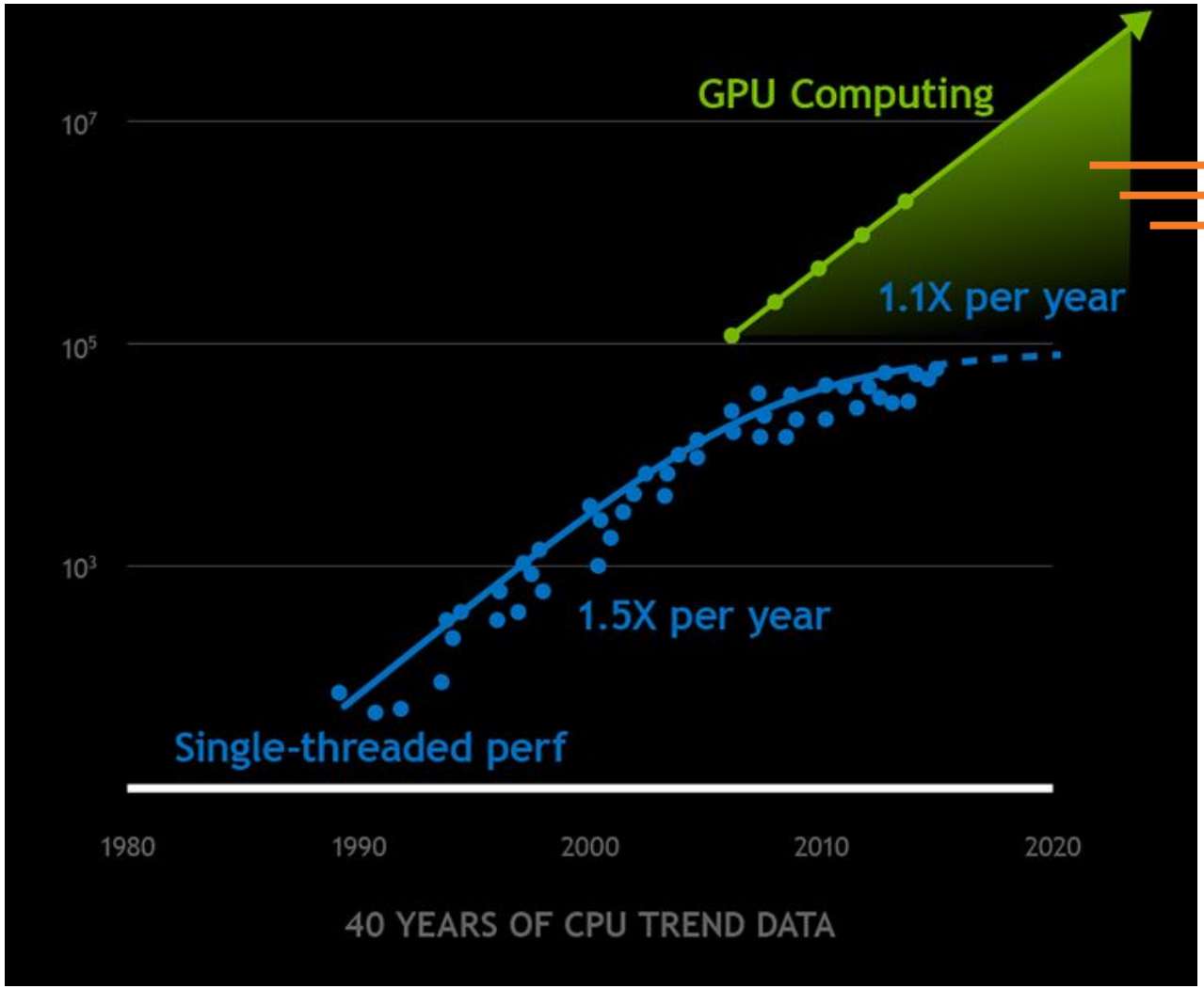


Image source:
https://www.nvidia.com/es-la/data-center/hpc/

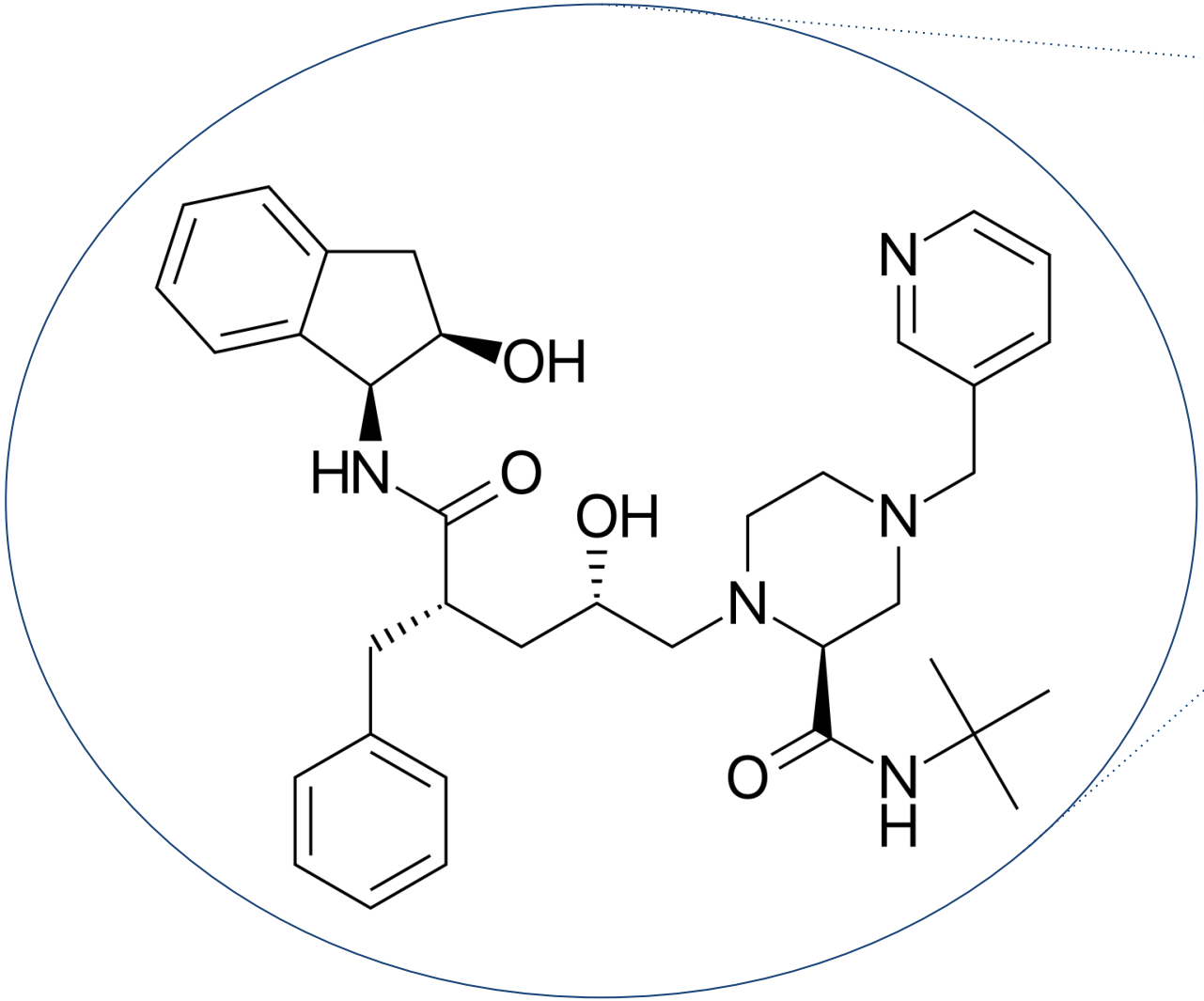
Computing power has increased over time

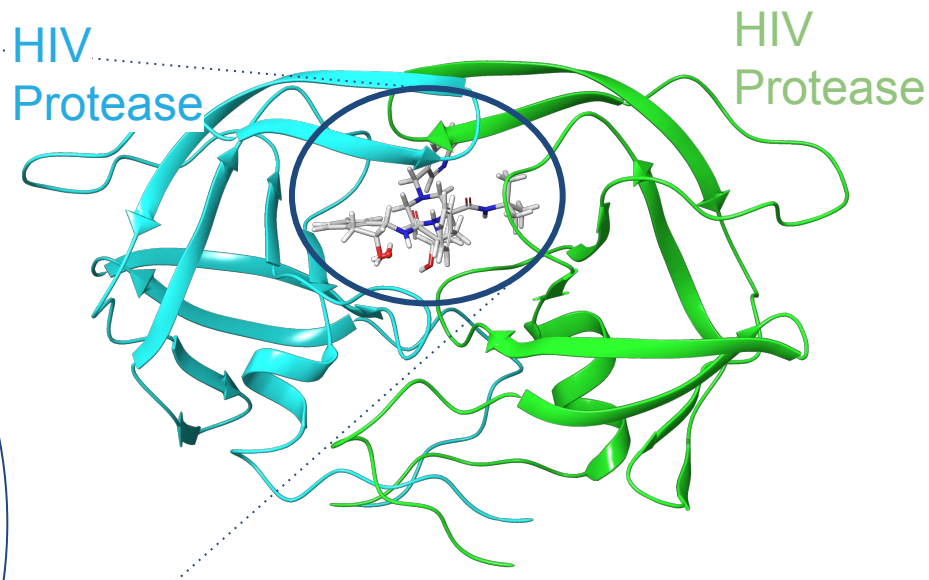


faster identification and optimization of drug candidates

Image source:
https://www.nvidia.com/es-la/data-center/hpc/

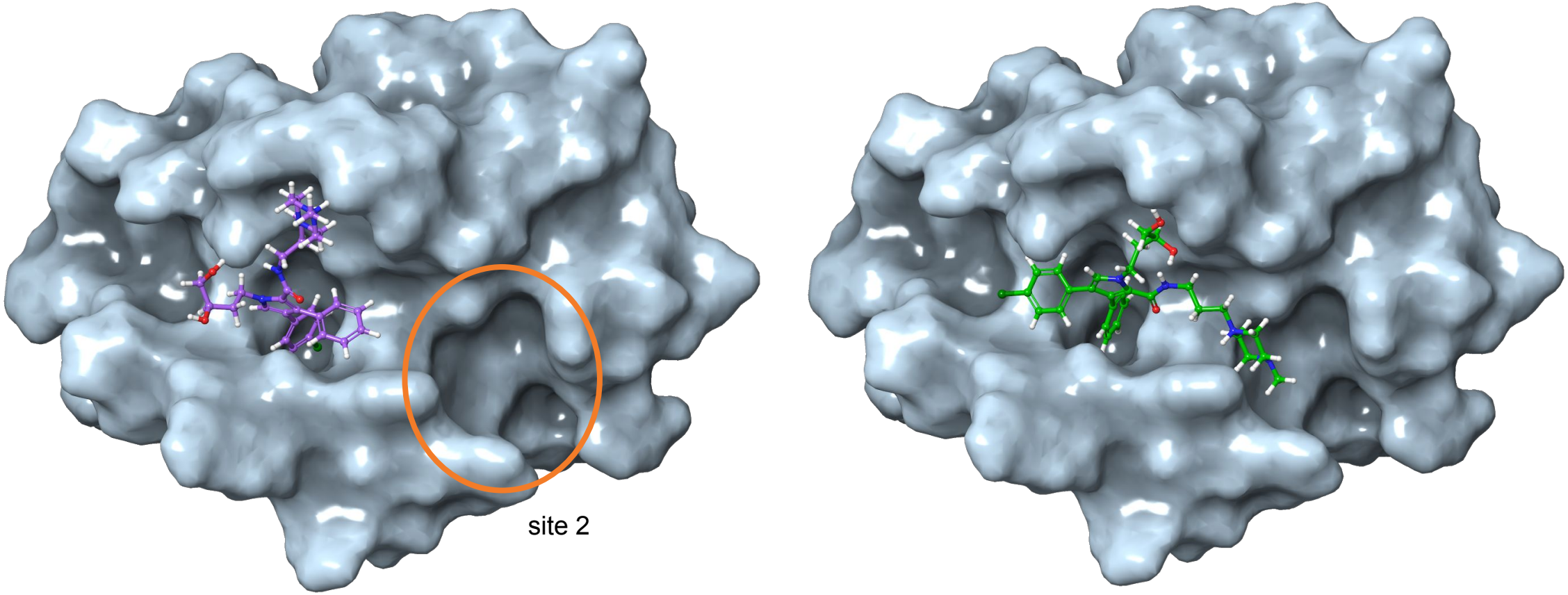
Success Stories in Molecular Modeling: Indinavir against HIV Protease





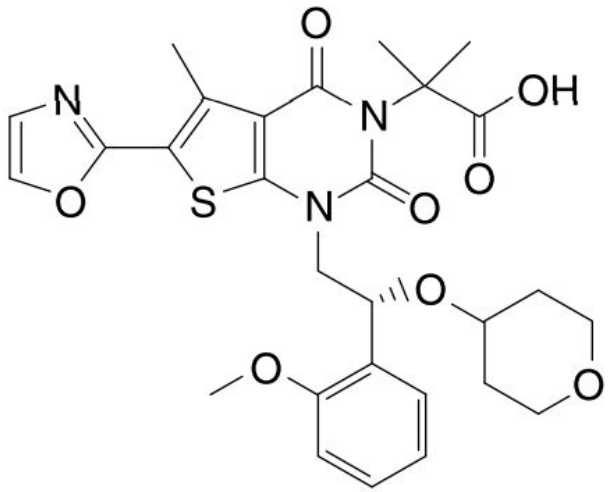
Rich et al., *J Med Chem.,* 1991 *34*, 1222-1225
https://pubs.acs.org/doi/pdf/10.1021/jm00107a049

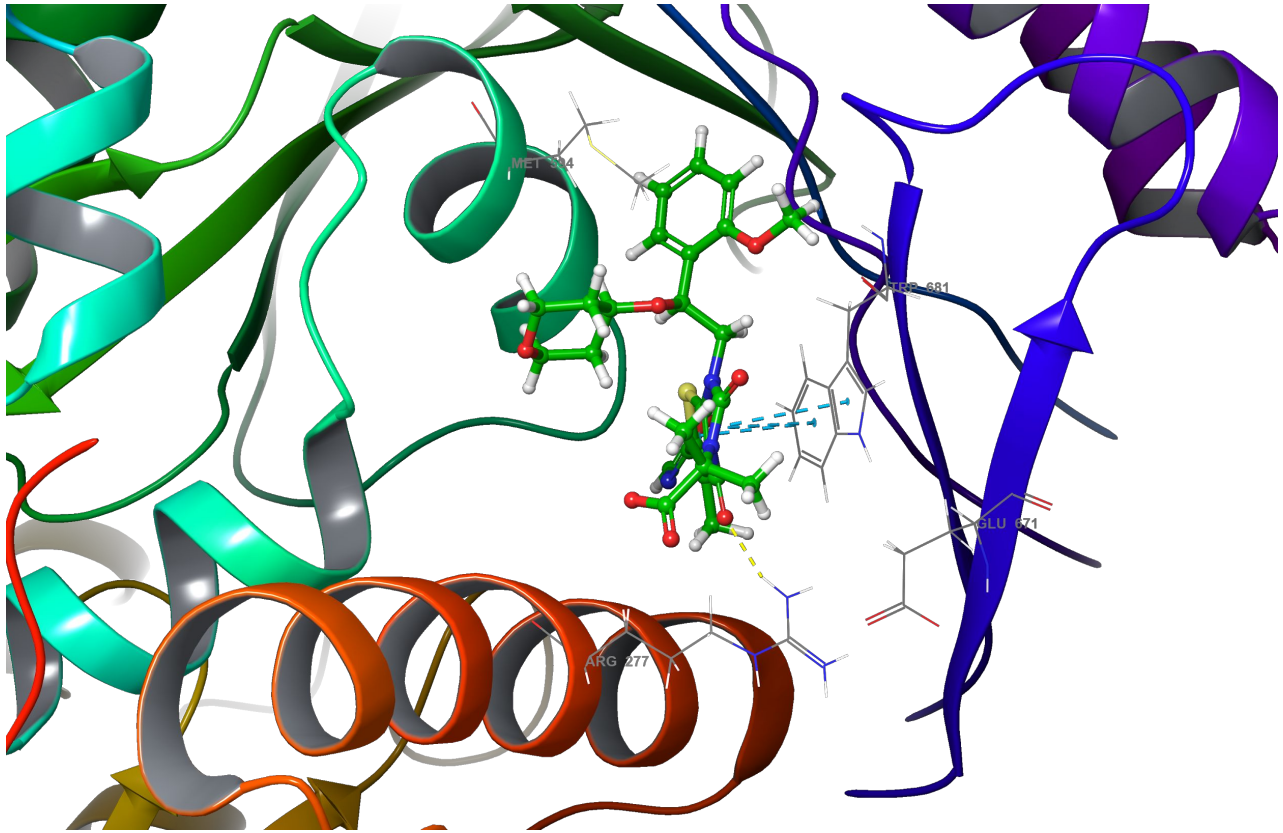
Success Stories in Molecular Modeling: Navitoclax and BCL2



Zhou, et al., *J Med Chem.,* 2012 *55*, 6149-6161
https://pubs.acs.org/doi/10.1021/jm300608w

Success Stories in Molecular Modeling: ND630 and ACC1/2





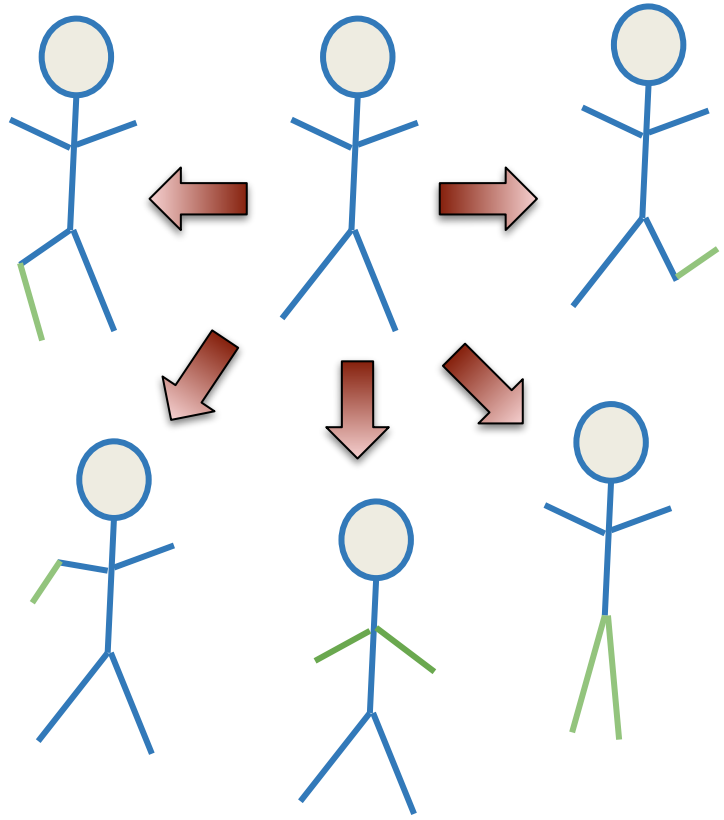
Harriman, et al., *PNAS.,* 2016 *13*, E1796-E1805.

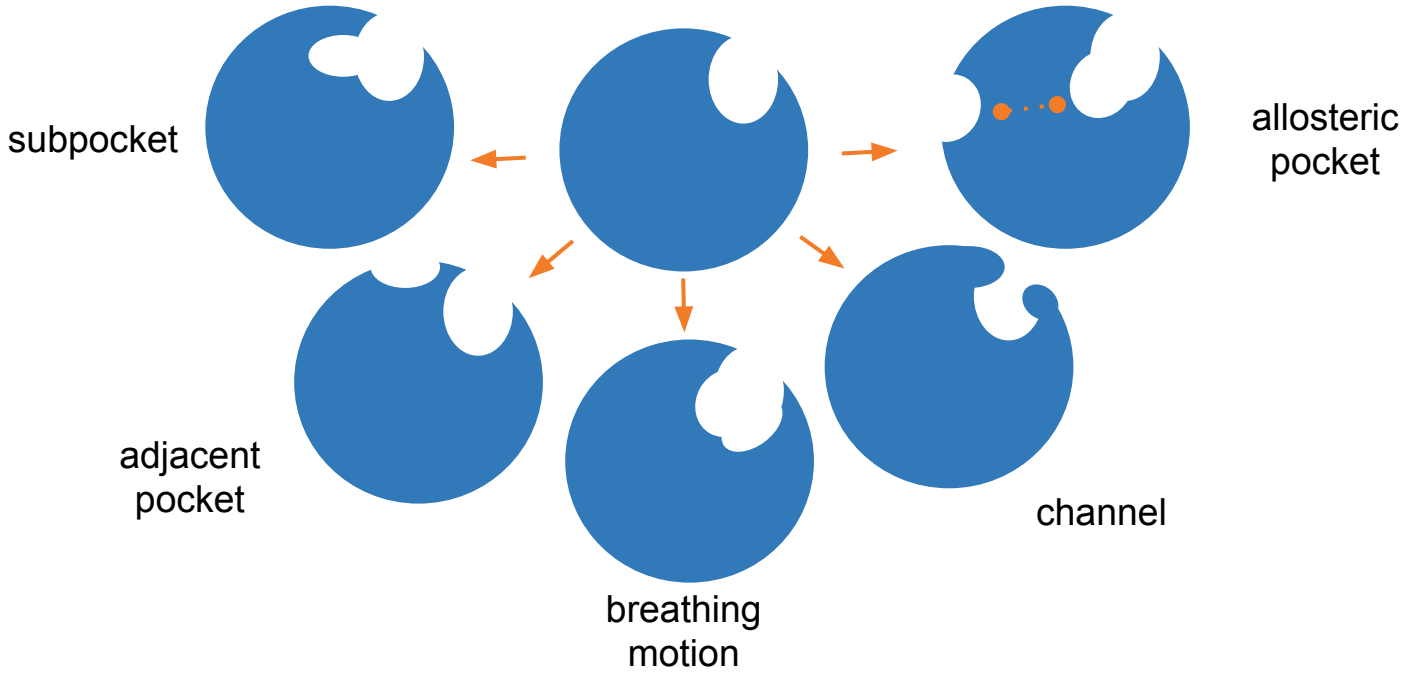
Success Stories in Molecular Modeling: From Concept to Clinic

Drug	Target	Stage	Chapter
Rucaparib	PARP-1, -2, -3	Approved	----
Pazopanib	VEGF kinase	Approved	Final Case Study
LY517717	Factor Xa	Approved	-----
Rofecoxib	COX2	Phase II	-----
1,2,4-Triazine Derivatives	A2A	Phase I	-----
NDI-010976	ACC	Phase II	-----

Talele, et al., *Curr Top. Med Chem.,* 2010 *10*, 127-141

Physics-based methods allow you to explore more





Stank et al., *Acc. Chem. Res.* 2016, 49, 5, 809–815.
https://doi.org/10.1021/acs.accounts.5b00516

There are different elements to the course modules

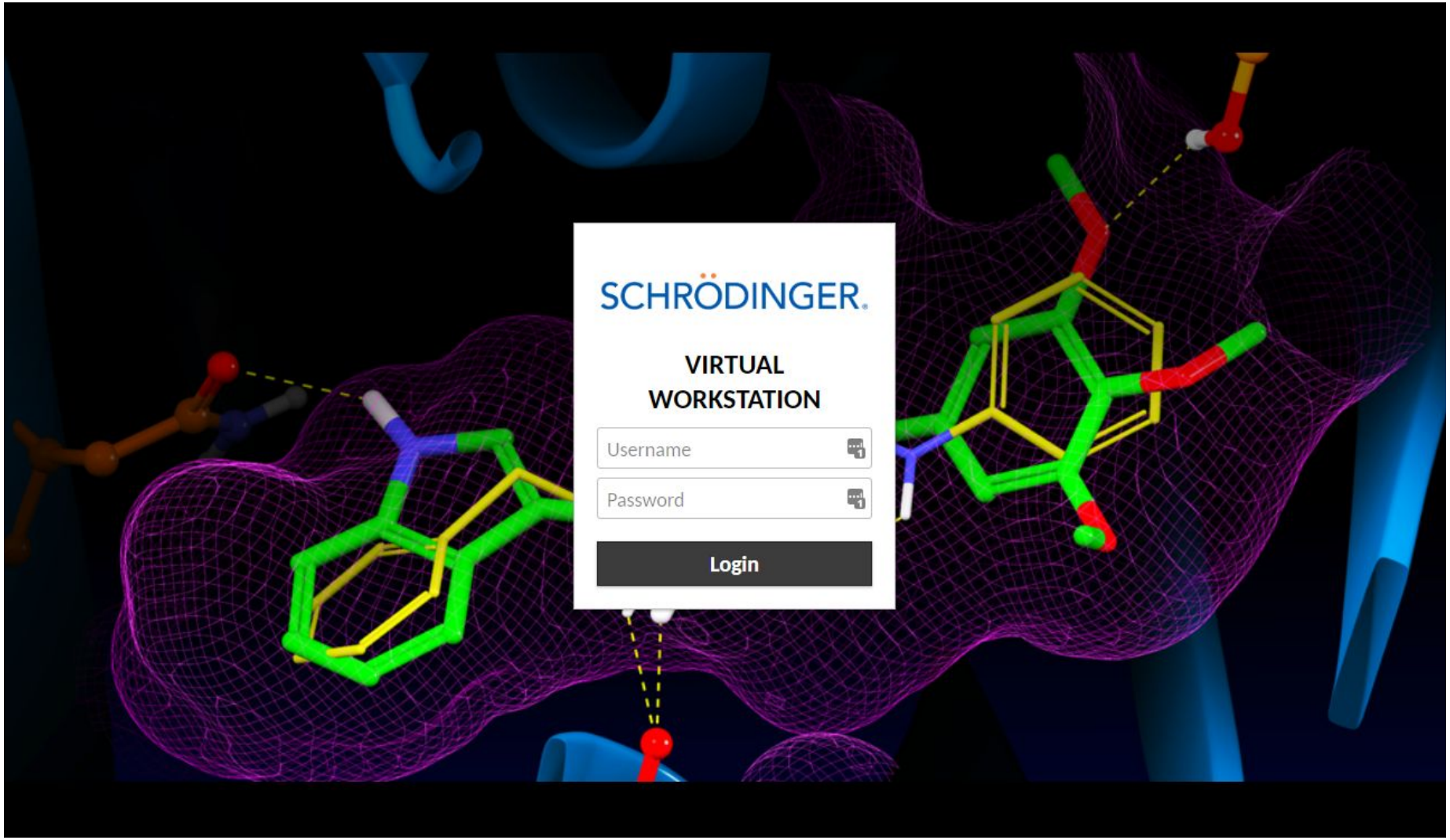
This Course Includes

- Introduction to molecular modeling concepts
- Using Schrödinger's modeling interface, **Maestro**
- Discussion of virtual screening methods and analyses
- Compound ideation in 3D using Schrödinger's web-based platform, **LiveDesign**

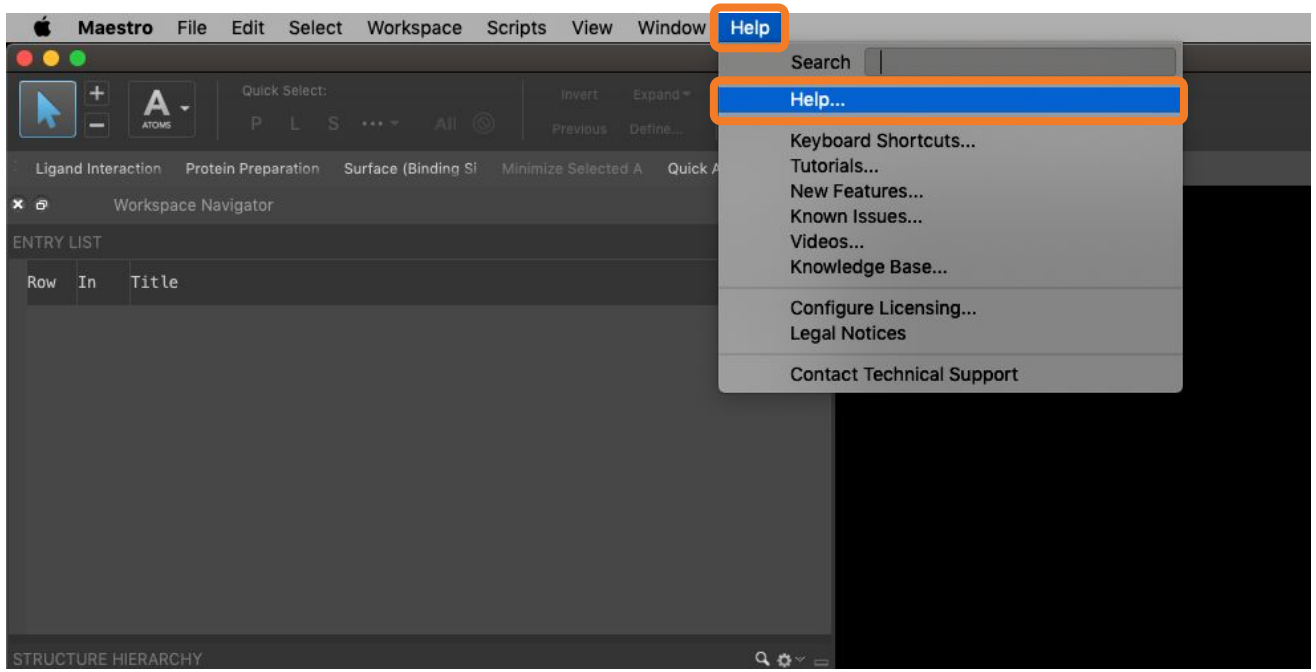
Types of Learning Modules

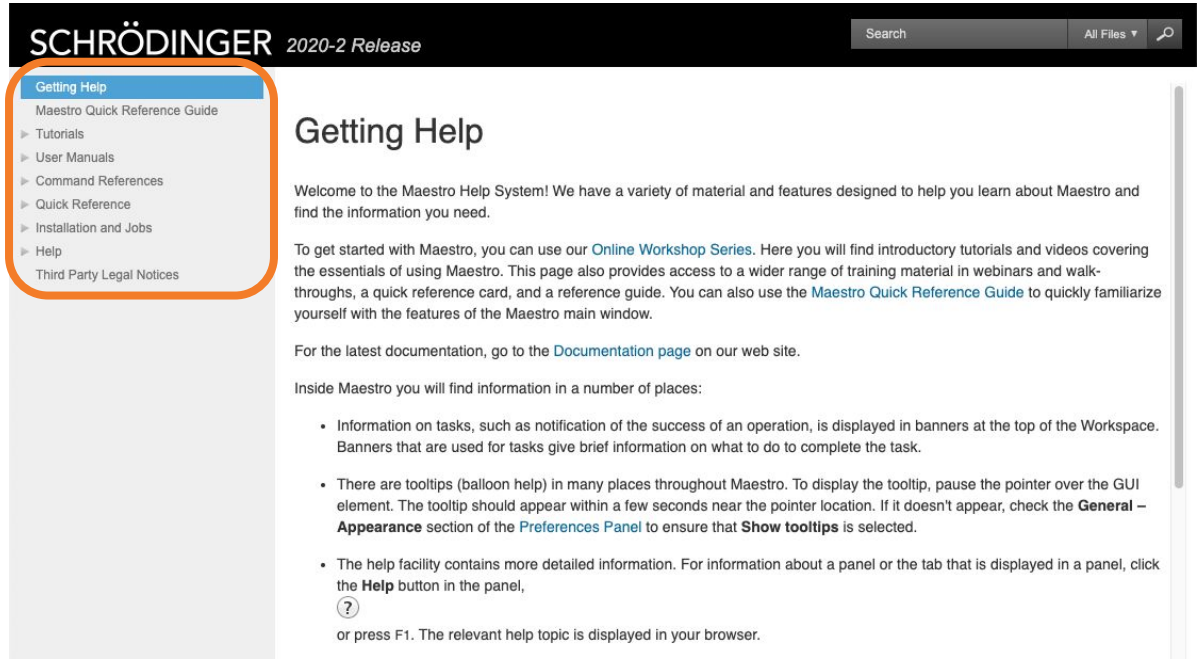
- Videos
- Journal articles
- Online resources
- Tutorials
- Case study

Log in to web-based Maestro for the hands-on portions

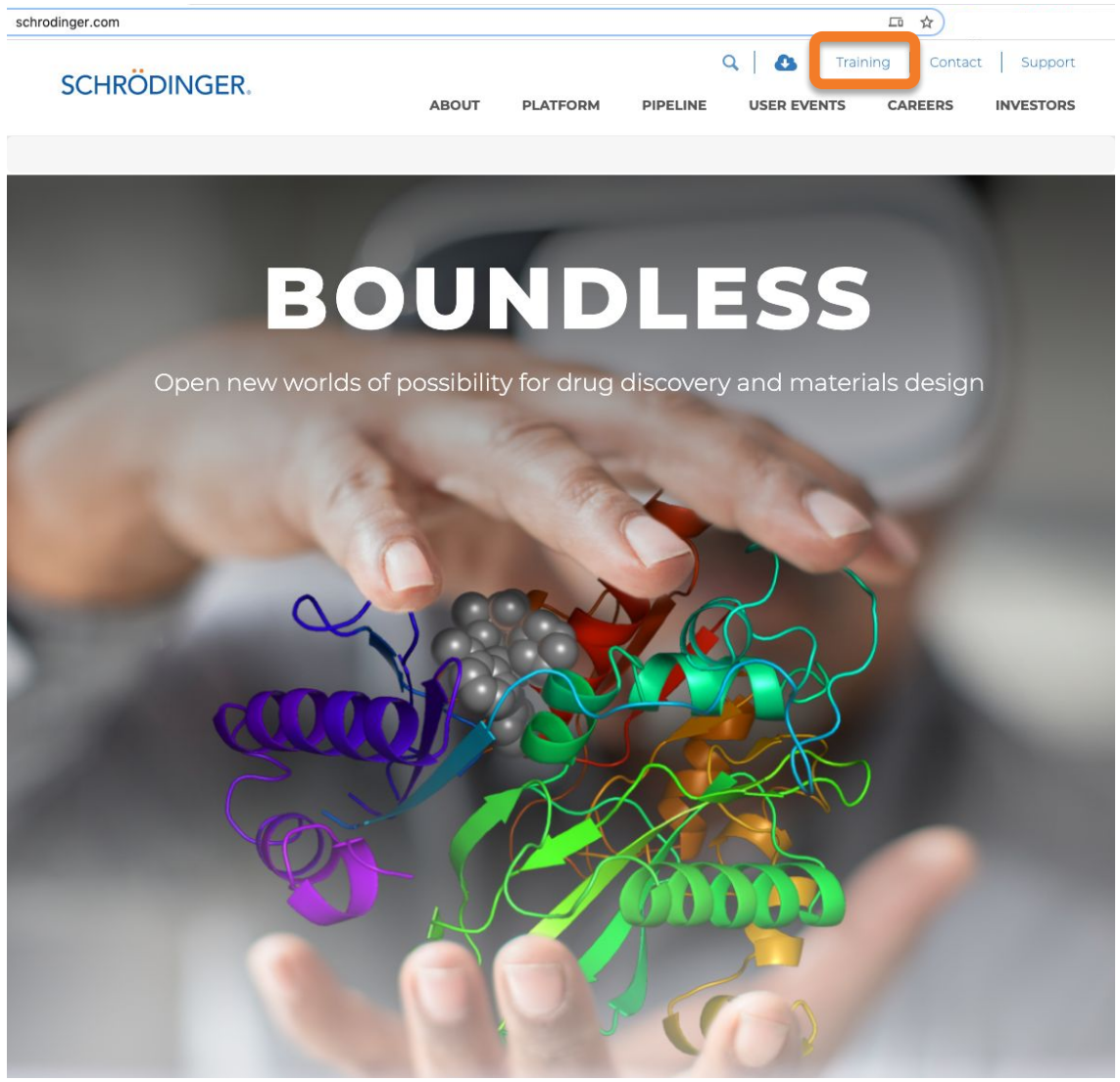


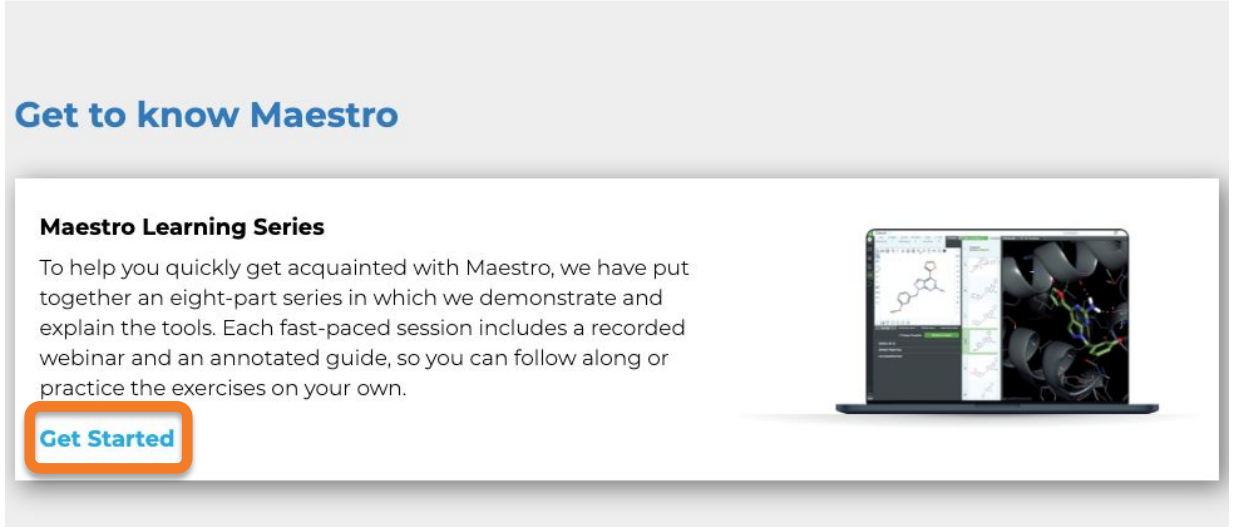
The Maestro Help menu contains more detail



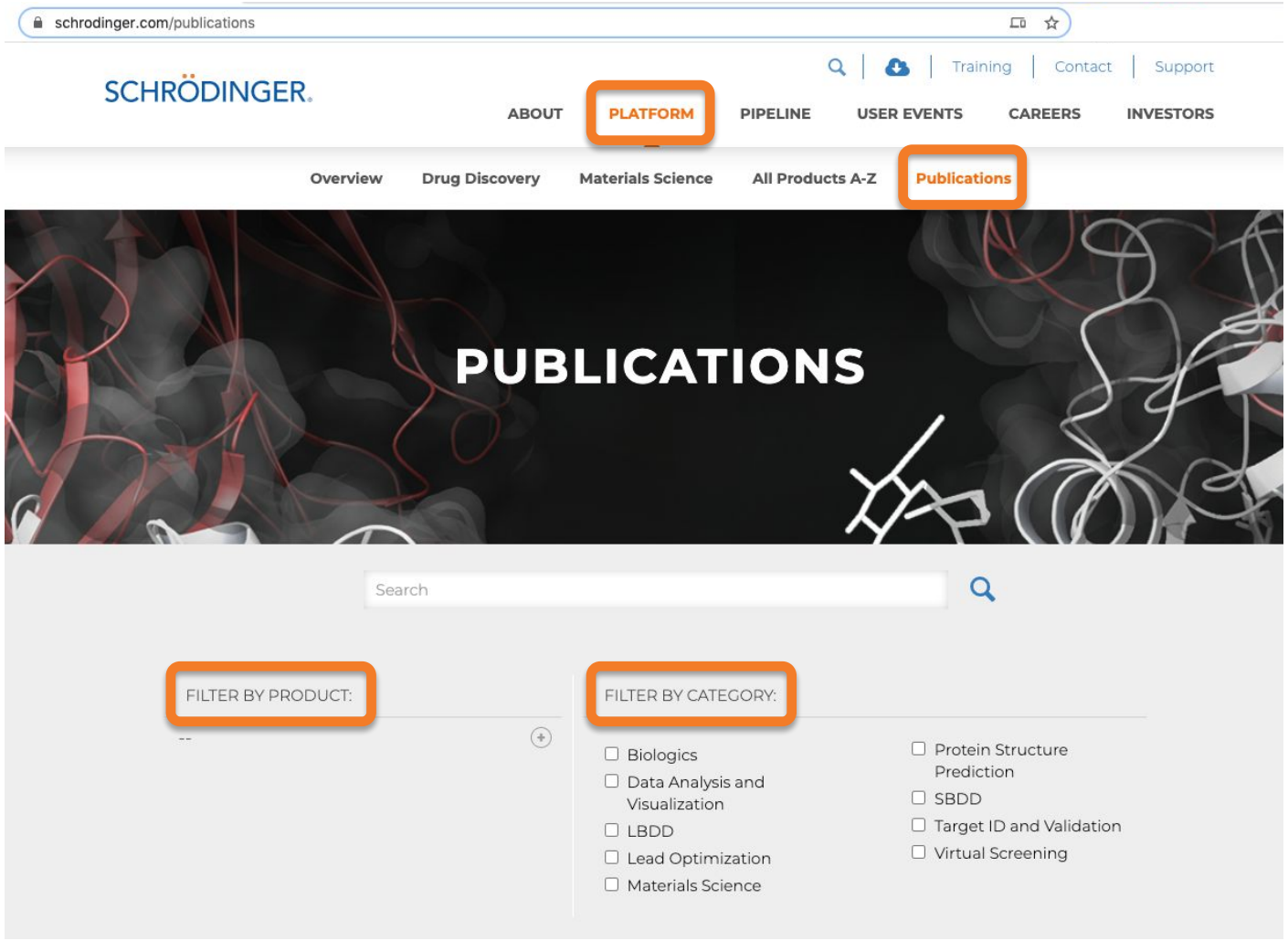


Learn more with the Training Portal





Use our list of publications to generate ideas



Results

	"Clobetasol Propionate Is a Heme-Mediated Selective Inhibitor of Human Cytochrome P450 3A5" Wright, W.C.; Chenge, J.; Wang, J.; Girvan, H.M.; Yang, L.; Chai, S.C.; Huber, A.D.; Wu, J.; Oladimeji, P.O.; Munro, A.W.; Chen, T., *J. Med. Chem., 2020, x, xx-xx*	Desmond, Glide, Maestro, Protein Preparation Wizard	**2020**
ö	"Large-Scale Assessment of Binding Free Energy Calculations in Active Drug Discovery Projects" Schindler, C.; Baumann, H.; Blum, A.; Böse, D.; Buchstaller, H-P.; Burgdorf, L.; et al. , *ChemRxiv., 2020, Preprint, xx-xx*	FEP+	**2020**
ö	"Combining Cloud-Based Free Energy Calculations, Synthetically Aware Enumerations and Goal-Directed Generative Machine Learning for Rapid Large-Scale Chemical Exploration and Optimization" Ghanakota, P.; Bos, P.; Konze, K.; Staker, J.; Marques, G.; Marshall, K.; Leswing, K.; Abel, R.; Bhat, S., *ChemRxiv, 2020, Preprint, xx-xx*	FEP+	**2020**
ö	"Large-Scale In Vitro Functional Testing and Novel Variant Scoring via Protein Modeling Provide Insights Into Alkaline Phosphatase Activity in Hypophosphatasia" Del Angel, G.; Reynders, J.; Negron, C.; Steinbrecher, T.; Mornet, E., *Hum Mutat., 2020, DOI: 10.1002/humu.24010,*	BioLuminate®	**2020**
ö	"A Free Energy Perturbation Approach to Estimate the Intrinsic Solubilities of Drug-like Small Molecules" Mondal, S; Tresadern, G.; Greenwood, J.; Kim, B.; Kaus, J.; Wirtala, M.; Steinbrecher, T.; Wang, L.; Masse, C.; Farid, R.; Abel, R., *ChemRxiv., 2020, preprint, https://doi.org/10.26434/chemrxiv.10263077.v1*	FEP+	**2020**
ö	"A Reliable and Accurate Solution to the Induced Fit Docking Problem for Protein-Ligand Binding" Miller, E.; Murphy, R.; Sindhikara, D.; Borrelli, K.; Grisewood, M.; Ranalli, F.; Dixon, S.; Jerome, S.; Boyles, N.; Day, T.; Ghanakota, P.; Mondal, S.; Rafi, S.B.; Troast, D.M.; Abel, R.; Friesner, R.A., *ChemRxiv, 2020, Preprint,*	Glide, Induced Fit, Phase, Prime, FEP+	**2020**
ö	"Impact of Different Automated Binding Pose Generation Approaches on Relative Binding Free Energy Simulations" Cappel, D.; Jerome, S.; Hessler, G.; Matter, H., *J. Chem. Inf. Model., 2020, 60 (3), 1432-1444*	FEP+	**2020**
ö	"Quantifying the Extent of Ligand Incorporation and the Effect on Properties of TiO2 Thin Films Grown by Atomic Layer Deposition Using an Alkoxide or an Alkylamide" Dufond, M.E.; Diouf, M.W.; Badie, C.; Laffon, C.; Parent, P.; Ferry, D.; Grosso, D.; Kools, J.C.S.; Elliott, S.D.; Santinacci, L., *Chem. Mater., 2020, 32 (4), 1393-1407*	MS Jaguar	**2020**
ö	"Discovery of Potent, Selective, and Orally Bioavailable Inhibitors of USP7 with In Vivo Anti-Tumor Activity" Leger, P.R.; Hu, D.X.; Biannic, B.; Bui, M.; Han, X.; et. al., *J. Med. Chem., 2020, XXX, XXX-XXX*	FEP+	**2020**

Other education resources are available online

- Knowledge Base: https://www.schrodinger.com/kb/
- Schrödinger Seminar Series:
  https://www.schrodinger.com/seminars/current
  https://www.schrodinger.com/seminars/archives
- Script Center: https://www.schrodinger.com/scriptcenter/

Here are some useful video Maestro links

- Maestro Quick Start Guide
  - https://www.schrodinger.com/training/maestro
- Maestro Short Videos
  - https://www.schrodinger.com/training/videos/maestro/all
- Protein Preparation Wizard
  - https://www.schrodinger.com/training/videos/protein-preparation
- Other Small-Molecule Drug Discovery Tools
  - https://www.schrodinger.com/training/videos/small-molecule-drug-discovery

Thanks for joining us!

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