



# Developing Predictive ML Models to Inform TPD Lead Optimization

Paul Novick, Mridula Bontha

TPD Europe

London

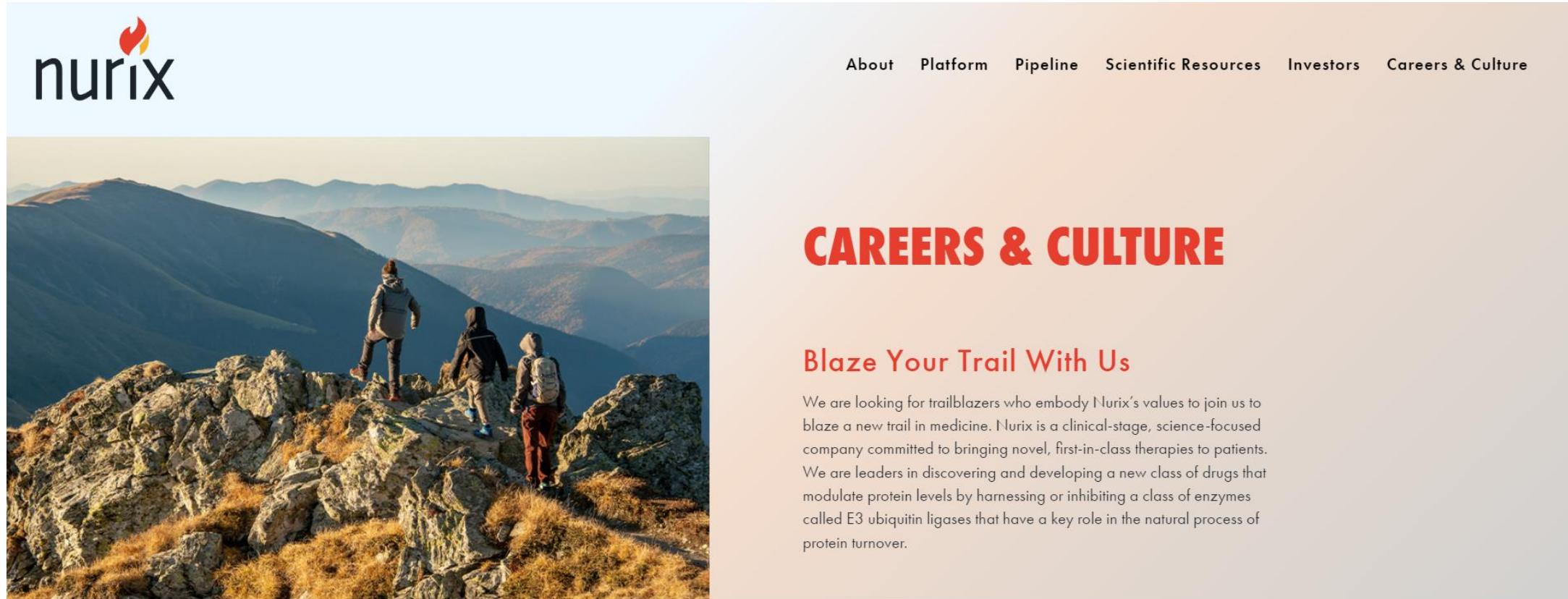
March 30, 2023

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# The Nurix Machine Learning Team



Mridula Bontha  
Primary ML Scientist on the project



Paul Novick  
Director Cheminformatics and Machine Learning



Elena Caceres



Heta Gandhi



Jen Bone

# Talk Outline

Introduction	Evaluation of existing tools in predicting molecular properties for Targeted Protein Degradation (TPD) molecules
Methods/Results	Performance and generalizability of Nurix Machine Learning (ML) models for Solubility and Permeability
Discussion	Interplay between model learnings and human interpretability

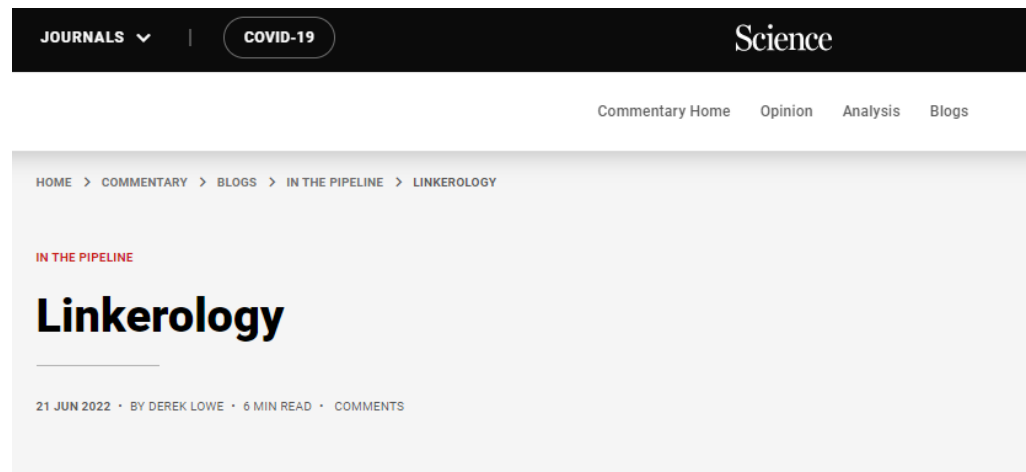
# Introduction

Evaluation of existing tools in predicting molecular properties for TPD molecules

# Degrader Optimization Remains Largely Empirical

...We're still in the "try 'em and see" stage of optimization. ... It would be much, much nicer if we could stand at the whiteboard or look at a screen, pursing our lips thoughtfully and then pointing purposefully at The Compound To Make, but we ain't there yet.

Derek Lowe  
*In The Pipeline*  
6/21/22



The screenshot shows the top navigation bar of the Science magazine website. It includes a 'JOURNALS' dropdown menu, a 'COVID-19' filter button, and the 'Science' logo. Below the navigation bar, there are links for 'Commentary Home', 'Opinion', 'Analysis', and 'Blogs'. The main content area shows a breadcrumb trail: 'HOME > COMMENTARY > BLOGS > IN THE PIPELINE > LINKEROLOGY'. The article title 'Linkerology' is prominently displayed, followed by the author 'BY DEREK LOWE', the date '21 JUN 2022', and a '6 MIN READ' indicator. There is also a 'COMMENTS' link.

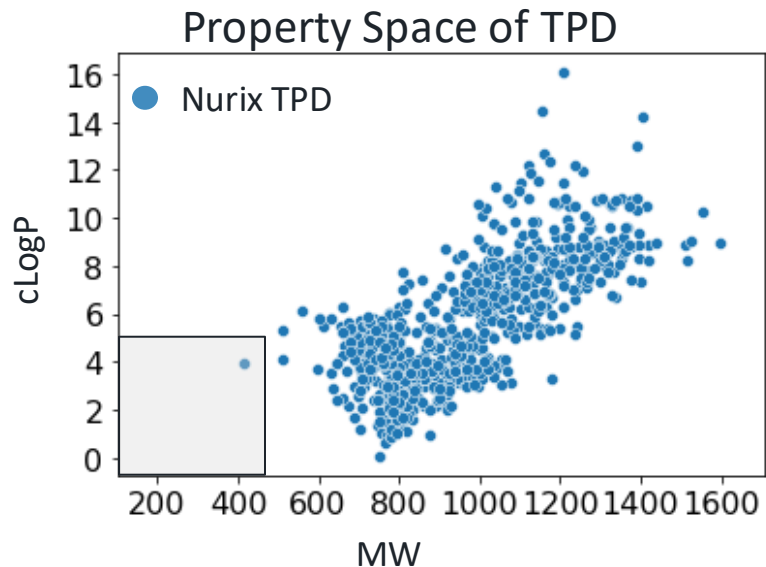
I've written a number of times here about bifunctional protein degraders, which have been a big topic in drug discovery for the past few years. There's a [new paper](#) that illustrates some of the challenges in this area, and it's worth using as an example.

*For those outside the field, the idea behind these things is pretty straightforward, at least in principle. You find a protein that you think is involved in a disease process, one whose activity you would like to dial down. You find a small-molecule ligand that binds that protein - you may already have some inhibitors around, in house or from the literature, and for these purposes your small molecule doesn't even have to be an inhibitor, just a binder. (Of course, the way we run assays means that most of the time we're not set up to detect silent binders, so those are thinner on the ground). Now you break out your synthetic organic chemistry skills and build out a linker group from that known ligand, and at the other end of that linker you attach a known ligand for an "E3 ligase" enzyme. There are several possibilities, but so far the well-established ones for the enzymes cereblon and VHL are the ones that get used the most, by far.*

# Degrader Molecules Are Outside the Domain of Applicability for Commonly Applied Intuition and Rules

Targeted Protein Degrader molecules occupy a property space well beyond traditional Lipinski RO5 molecules.

As a result, intuition and rules for predicting physicochemical properties developed based on RO5 small molecules do not generalize well when applied to TPD molecules.

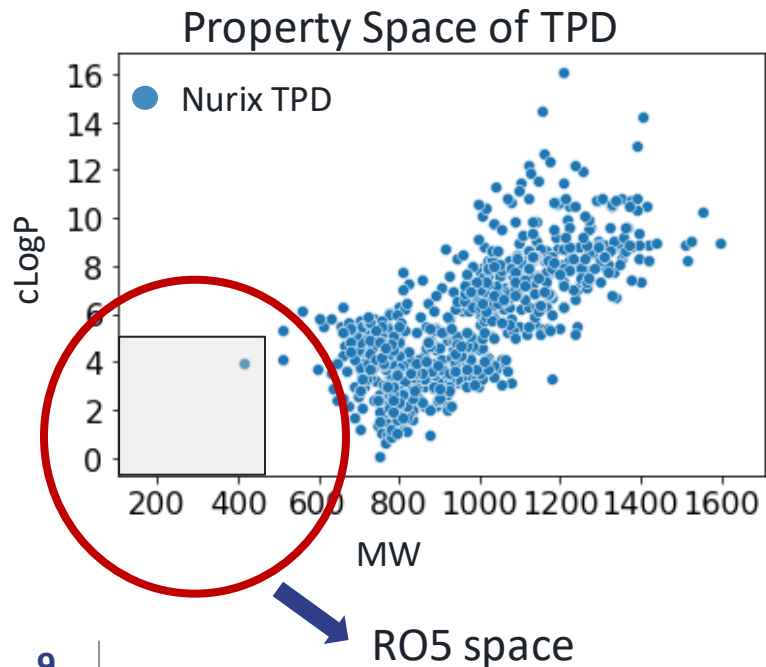




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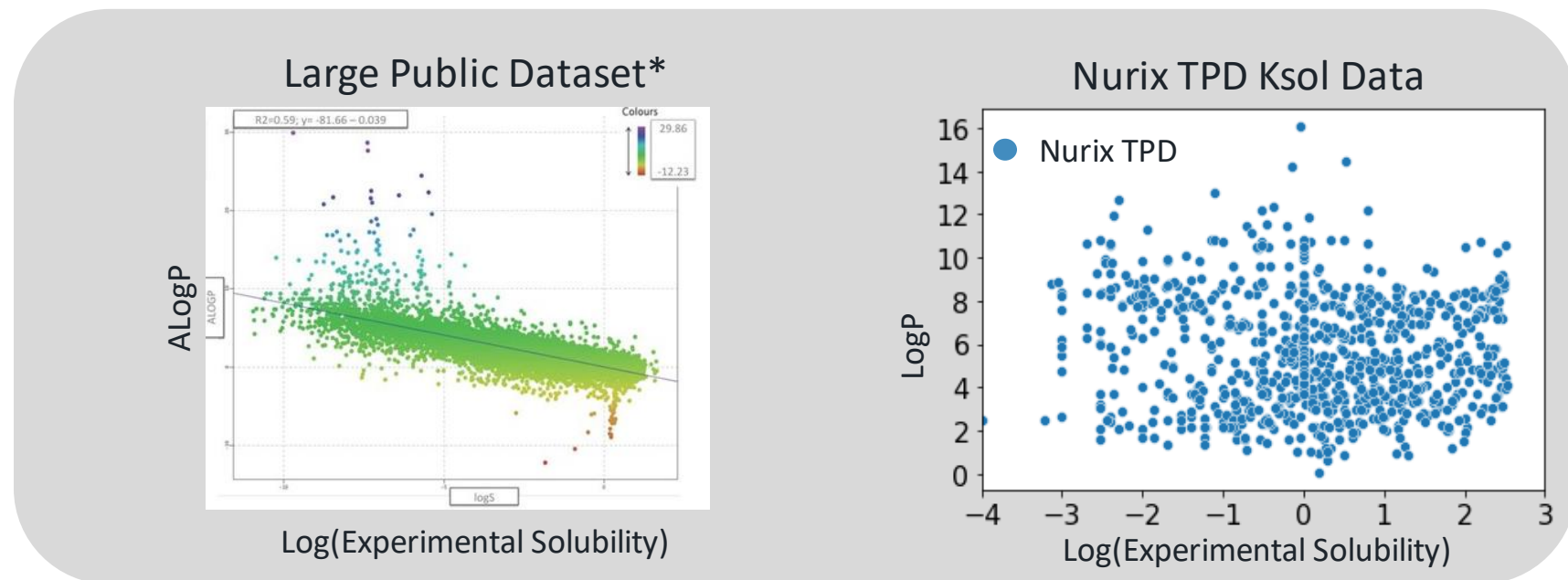
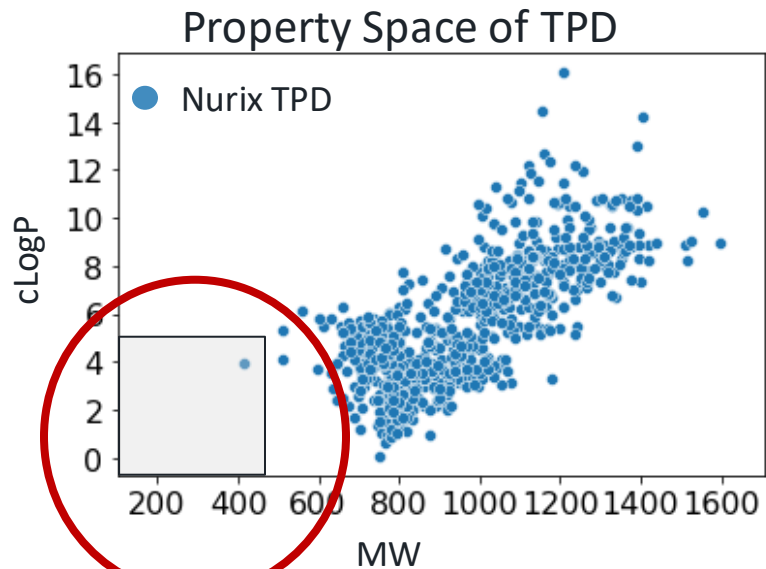
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# Degrader Molecules Are Outside the Domain of Applicability for Commonly Applied Intuition and Rules

Targeted Protein Degradator molecules occupy a property space well beyond traditional Lipinski RO5 molecules.

As a result, intuition and rules for predicting physicochemical properties developed based on RO5 small molecules do not generalize well when applied to TPD molecules.



Calculated LogP vs Experimental Solubility for small molecules (left) and Nurix TPD (right)

\*Falcon-Cano, G., et al., ADMET & DMPK, 2020

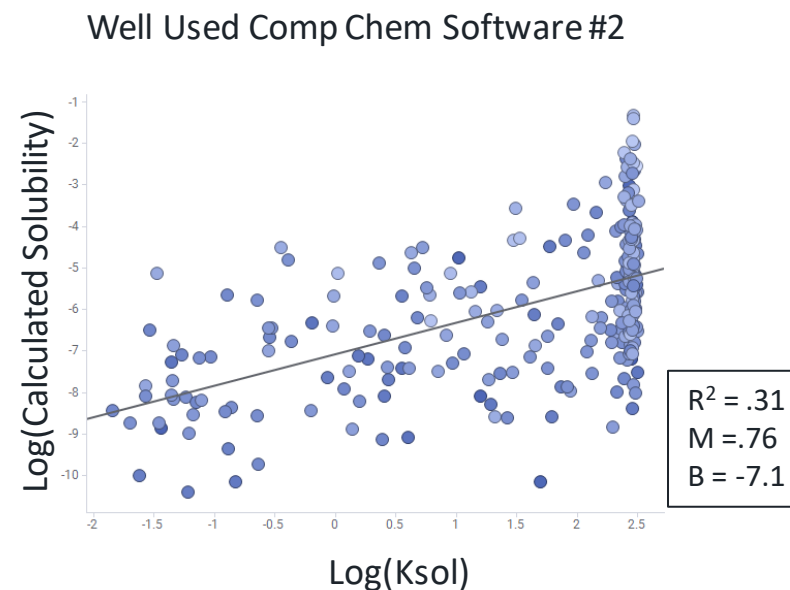
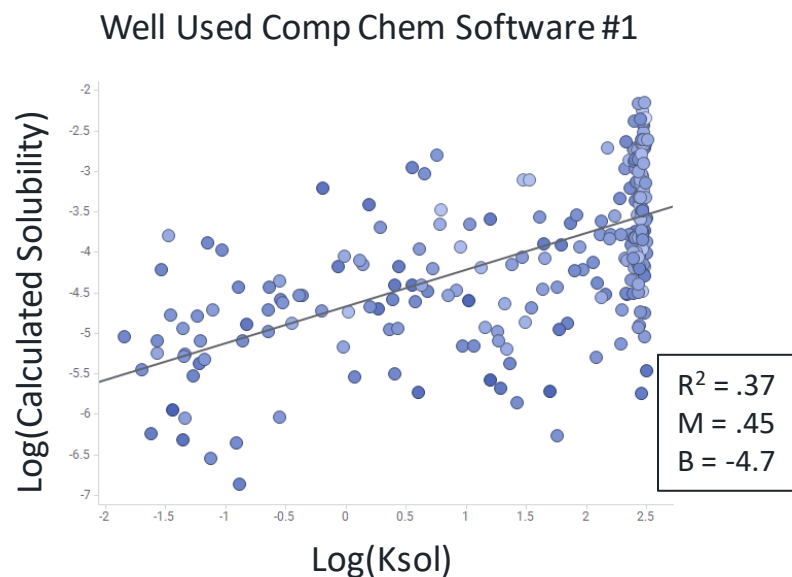
# Poor Correlation Between Ksol and 1D Molecular Properties

Extended view of weak correlation between molecular descriptors and solubility.

	R-squared
Kinetic Solubility X	1.000000
MolWt	0.117218
LogP	0.130907
NumHAcceptors	0.047313
NumHDonors	0.022847
NumHeteroatoms	0.079500
NumRotatableBonds	0.009230
NumHeavyAtoms	0.117752
NumAliphaticCarbocycles	0.016792
NumAliphaticHeterocycles	0.062368
NumAliphaticRings	0.085996
NumAromaticCarbocycles	0.032745
NumAromaticHeterocycles	0.044656
NumAromaticRings	0.132261
RingCount	0.185393
FractionCSP3	0.002377
TPSA	0.056036

A more thorough evaluation of 1D properties commonly thought to affect or relate to the solubility of small molecules shows very low correlation to experimental data.

# More Sophisticated Cheminformatics Calculators Similarly Struggle to Generalize to Degraders



Popular CompChem and Cheminformatics software struggle to accurately predict relevant properties of Degradable compounds.

# Active Literature Addressing Property Prediction in BR05 Space

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## Impact of Dynamically Exposed Polarity on Permeability and Solubility of Chameleonic Drugs Beyond the Rule of 5

Matteo Rossi Sebastiano, Bradley C. Doak, Maria Backlund, Vasanthanathan Poongavanam, Björn Över, Giuseppe Ermondi, Giulia Caron, Pär Mattsson\*, and Jan Kihlberg\*

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Publication Date: April 2, 2018  
https://doi.org/10.1021/acs.jmedchem.8b00347  
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Article Views: 7022 | Altmetric: 3 | Citations: 111

PDF (3 MB) | Supporting Info (2) | SUBJECTS: Conformation, Crystal structure, Peptides and proteins, Permeability, Solubility

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## Use of 3D Properties to Characterize Beyond Rule-of-5 Property Space for Passive Permeation

Cristiano R. W. Guimarães\*, Alan M. Mathioveztz, Marina Shalaeva, Gilles Goetz, and Spiros Liras

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Publication Date: March 6, 2012  
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Article Views: 2749 | Altmetric: 8 | Citations: 72

PDF (2 MB) | Supporting Info (1) | SUBJECTS: Interface engineering, Molecules

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## How Beyond Rule of 5 Drugs and Clinical Candidates Bind to Their Targets

Bradley C. Doak, Jie Zheng, Doreen Dobritzsch, and Jan Kihlberg\*

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Cite this: *J. Med. Chem.* 2016, 59, 6, 2312–2327  
Publication Date: October 12, 2015  
https://doi.org/10.1021/acs.jmedchem.5b01286  
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Article Views: 13630 | Altmetric: 41 | Citations: 200

PDF (6 MB) | Supporting Info (1) | SUBJECTS: Interfaces, Ligands, Macrocycles, >

**Abstract**

To improve discovery of drugs for difficult targets, the opportunities of chemical space beyond the rule of 5 (bRo5) were examined by retrospective analysis of a comprehensive set of structures for complexes between drugs and clinical candidates and their targets. The analysis illustrates the potential of compounds for beyond rule of 5 spaces to modulate novel and

Chemistry & Biology  
Review

CellPress

## Oral Druggable Space beyond the Rule of 5: Insights from Drugs and Clinical Candidates

Bradley Croy Doak,<sup>1</sup> Björn Över,<sup>2</sup> Fabrizio Giordanetto,<sup>3</sup> and Jan Kihlberg<sup>1,\*</sup>

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<sup>2</sup>CVMD iMed, AstraZeneca R&D Mölndal, 431 83 Mölndal, Sweden  
<sup>3</sup>Medicinal Chemistry, Taros Chemicals GmbH & Co. KG, Emil-Figge-Strasse 76a, 44227 Dortmund, Germany  
\*Correspondence: jan.kihlberg@kemi.uu.se  
http://dx.doi.org/10.1016/j.chembiol.2014.08.013

The rule of 5 (Ro5) is a set of in silico guidelines applied to drug discovery to prioritize compound increased likelihood of high oral absorption. It has been influential in reducing attrition due to poor pharmacokinetics over the last 15 years. However, strict reliance on the Ro5 may have resulted in lost opportunities particularly for difficult targets. To identify opportunities for oral drug discovery beyond the Ro5 we have comprehensively analyzed drugs and clinical candidates with molecular weight (MW) > 500. We conclude that oral drugs are found for bRo5 and properties such as intramolecular hydrogen bonding, macrocyclization, dosage, and formulations can be used to improve bRo5 bioavailability. Natural and structure-based design, often from peptidic leads, are key sources for oral bRo5 drugs. These should help guide the design of oral drugs in bRo5 space, which is of particular interest for difficult

Opportunities and guidelines for discovery of orally absorbed drugs in beyond rule of 5 space

Vasanthanathan Poongavanam<sup>1,3</sup>, Bradley C. Doak<sup>2,3</sup>, Jan Kihlberg<sup>1</sup>✉

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## Drug discovery beyond the 'rule-of-five'

Ming-Qiang Zhang ✉, Barrie Wilkinson

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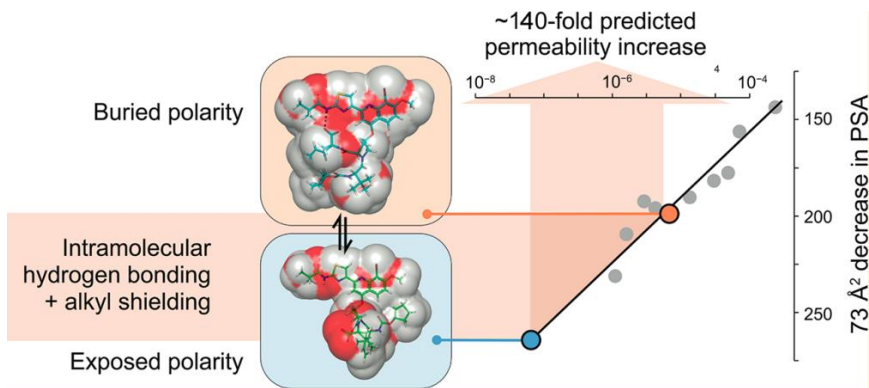
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Although a very useful guideline for orally bioavailable small-molecule drug design, the 'rule-of-five' (also known as 'Lipinski's rule of drug-likeness') has to some extent been overemphasized. Firstly, only 51% of all FDA-approved small-molecule drugs are both used orally and comply with the 'rule-of-five'. This does not even include the increasing number of biologicals of which several have reached 'blockbuster' status. Secondly, it does not cover natural product and semisynthetic natural product drugs, which constitute over one-third of all marketed small-molecule drugs. A more balanced and programmatic approach to drug discovery should be more productive than to rely on an overemphasis of 'rule-of-five' compliance. Rather it should consider proactively the

a dramatic increase in the number of drugs space outside of Lipinski's rule of 5, that is in what is now the beyond rule of 5 (bRo5) space. The development of orally absorbed drugs that treat HIV and HCV infections and that novel, difficult targets can be accessed has to understanding design of drugs displaying cell permeability and ultimately oral bioavailability in bRo5 space. A consistent outer property limit for a reasonable number of orally bioavailable drugs. In addition, several lines, along with incorporation of chameleonic drugs as strategies to aid design in bRo5 space. A more

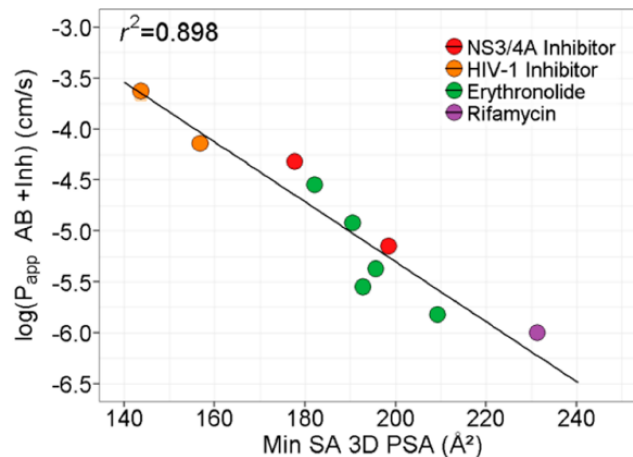
# Literature BRO5 Models Struggle to Predict Nurix Internal Degradation Experimental Data



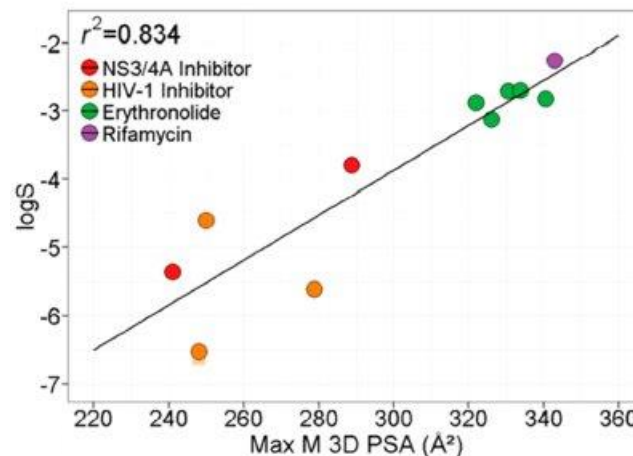
## Impact of Dynamically Exposed Polarity on Permeability and Solubility of Chameleonic Drugs Beyond the Rule of 5

Sebastiano, et al., J Med Chem, 2018

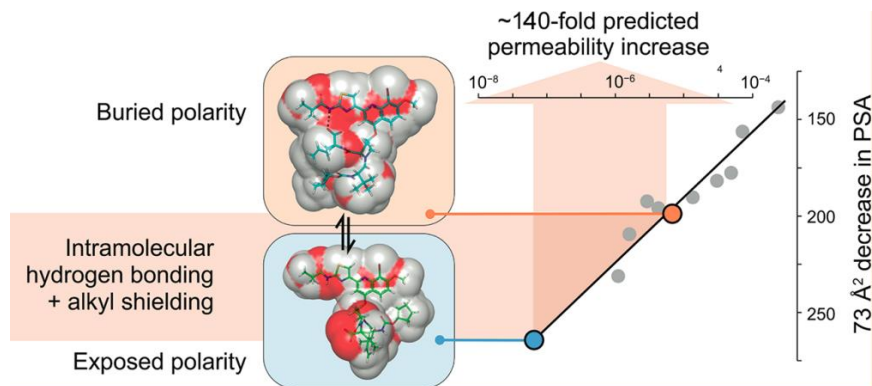
Literature model for predicting permeability and solubility of BRO5 compounds as a function of 3D polar surface area struggle to track with Nurix experimental data



## Publication Data



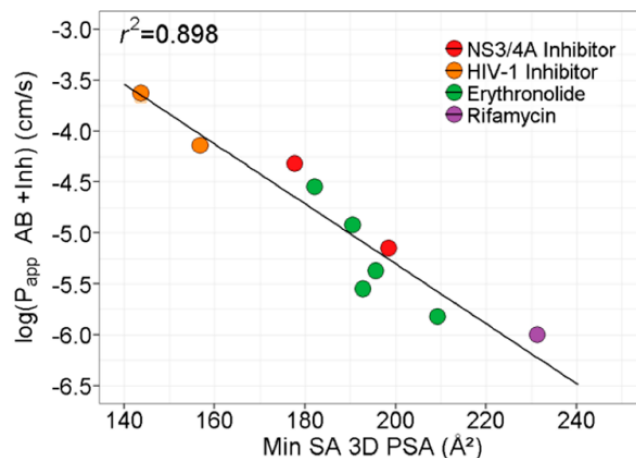
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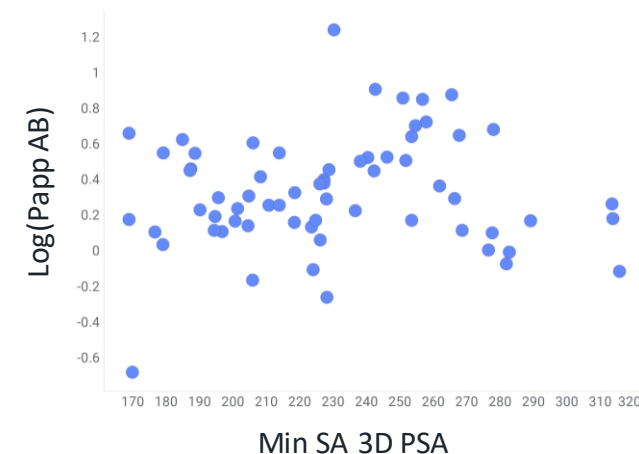
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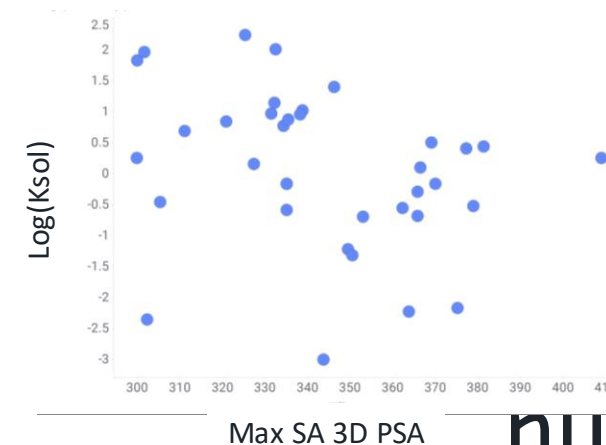
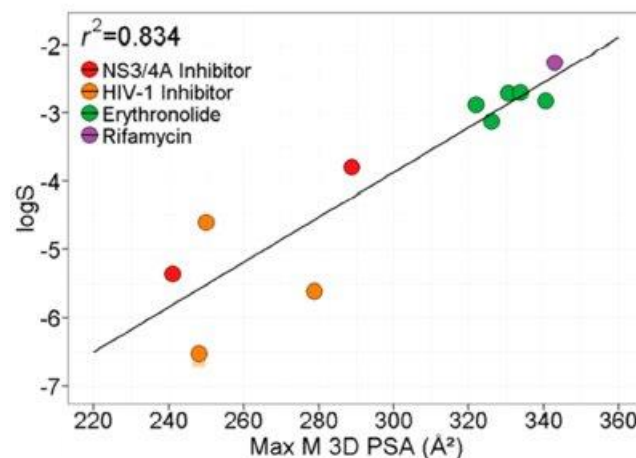
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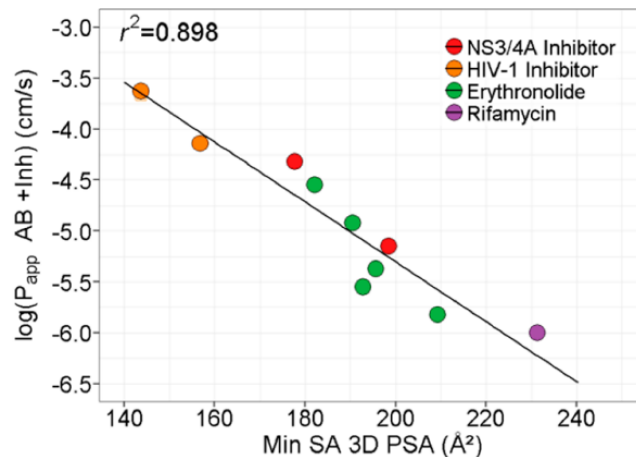
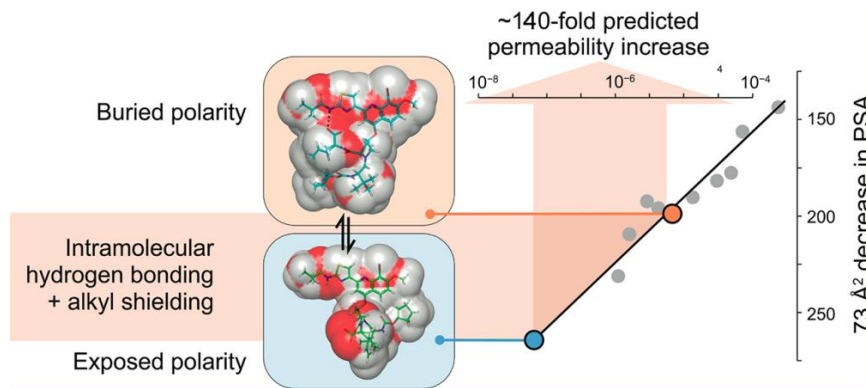
Publication Data



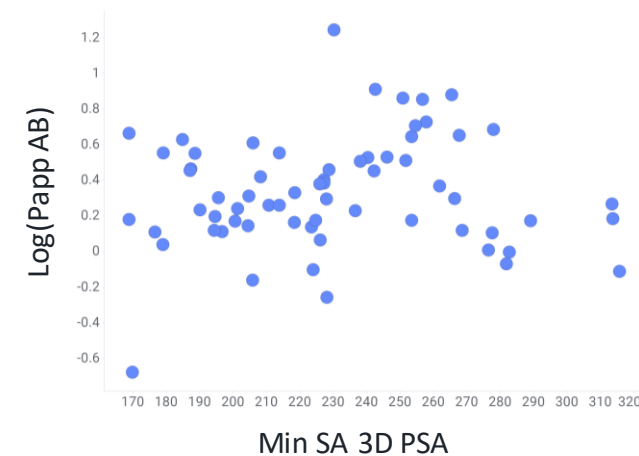
Nurix Data



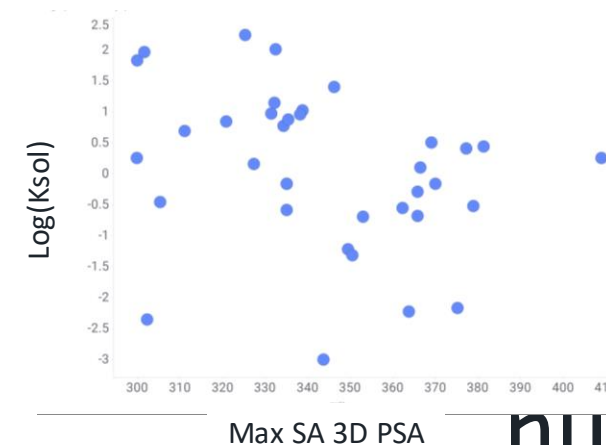
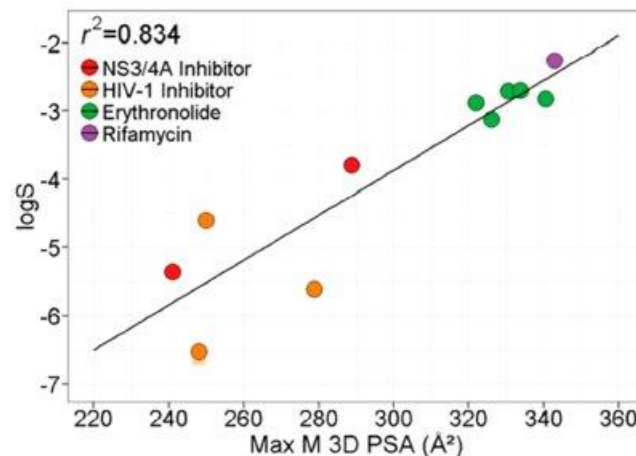
# Literature BRO5 Models Struggle to Predict Nurix Internal Degradation Experimental Data



Publication Data



Nurix Data



**Impact of Dynamically F...**  
**Permeability and Solubility of**  
**Drug Molecules**  
 Results representative of all  
 published methods tried  
 Se... chem, 2018

Literature model for predicting permeability and solubility of BRO5 compounds as a function of 3D polar surface area struggle to track with Nurix experimental data



# Moving Away from the Streetlight

1. TPD compounds occupy a completely different region of chemical space than historical drugs
2. Tools and intuition developed for RO5-like compounds largely fail to be predictive for TPDs



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Machine learning offers the opportunity to re-learn the rules and create models that are actually predictive.

# Methods/Results

Performance and generalizability of Nurix Machine Learning models for Solubility and Permeability

# Nurix Is Applying Automation to Better Define the Parameters of Degradation Design

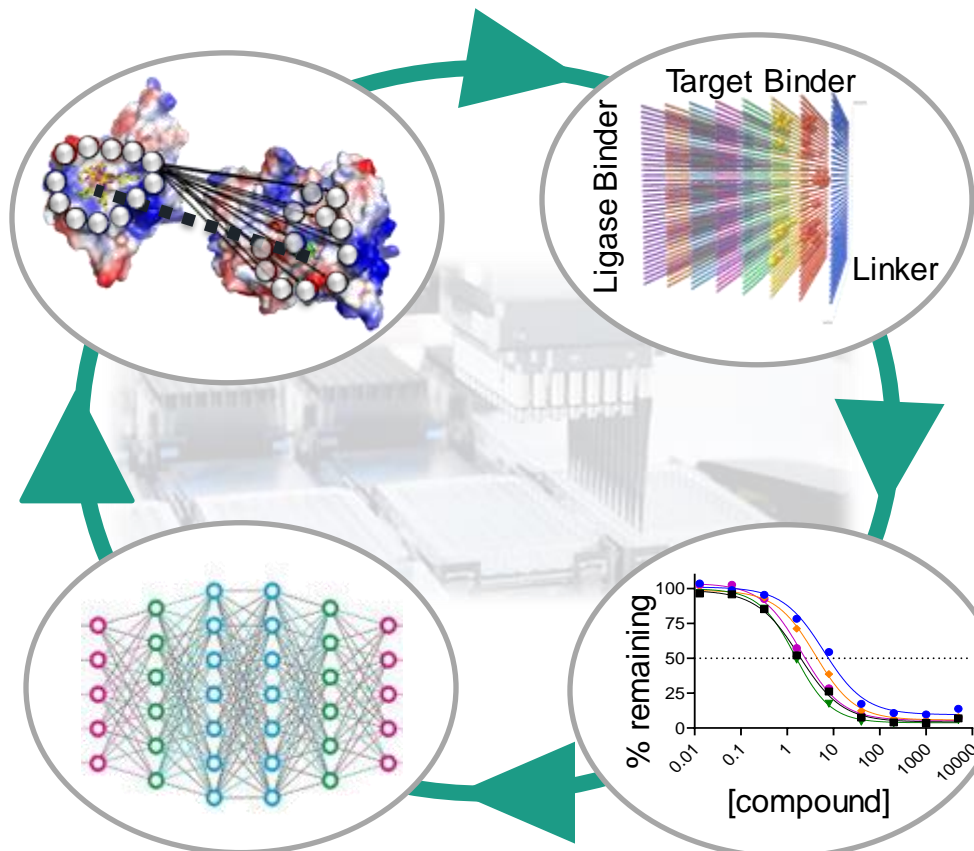
- Challenge: Identifying and optimizing degraders remains largely an empirical process.
- Nurix platform is scaled to enable evaluation of broad and unique search spaces to identify and optimize degraders.

## DESIGN SCOPE

Theoretical range of degrader chemical space more fortuitous than rational

## WRITE THE RULEBOOK

Machine Learning transforms large datasets into degrader rulebook for improved design



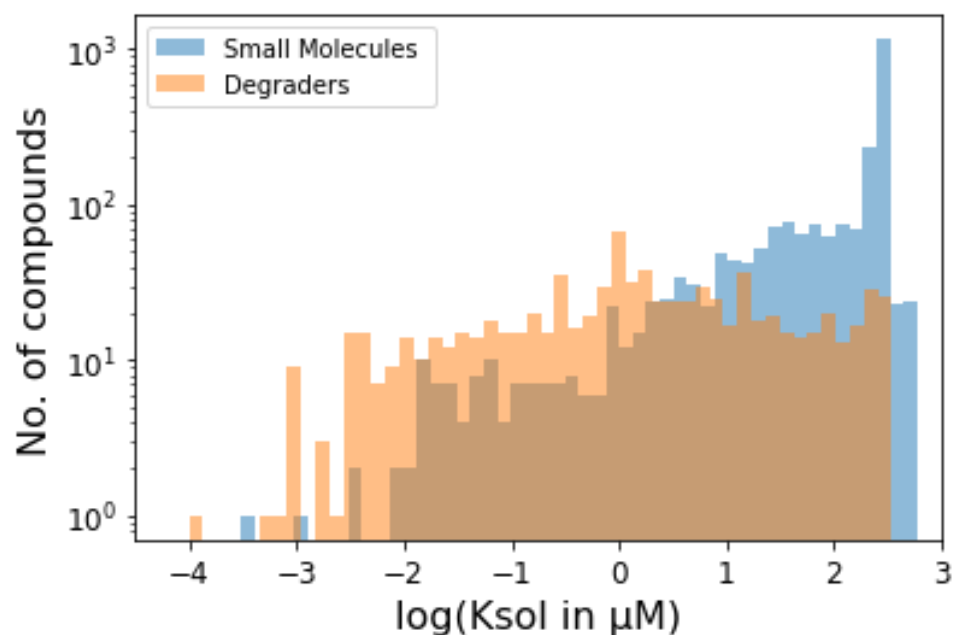
## SYNTHESIZE AT SCALE

Automation enables Nurix to sample unprecedented chemical space

## DISCOVER LEADS

Empirical data reveals degraders with optimal performance

# Nurix Kinetic Solubility Dataset and Framing the ML Problem



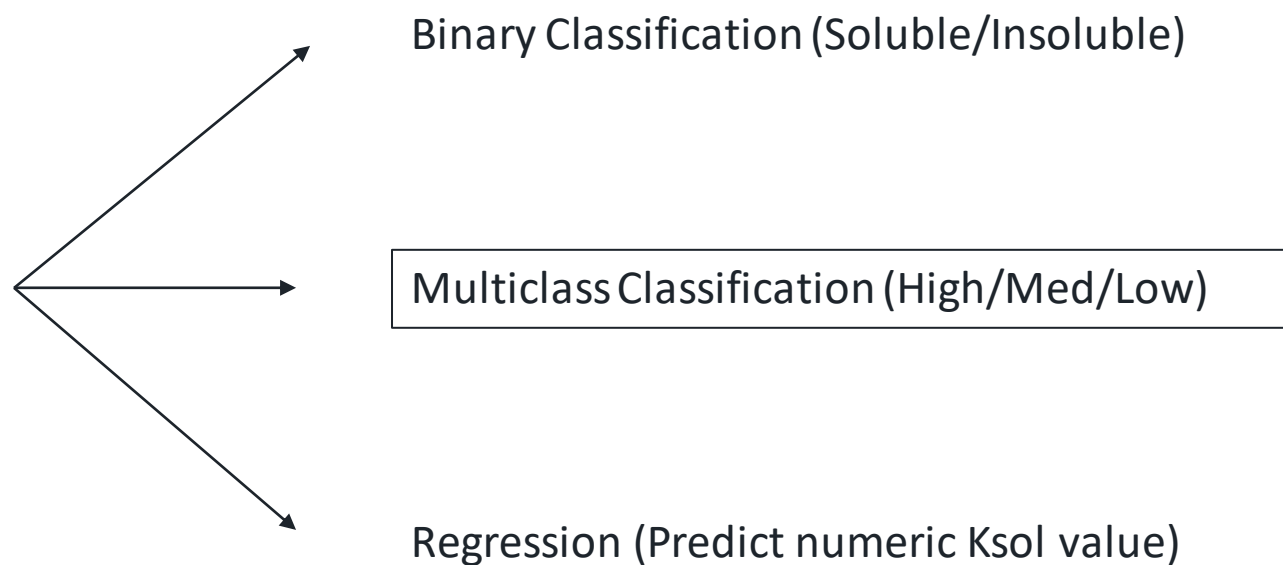
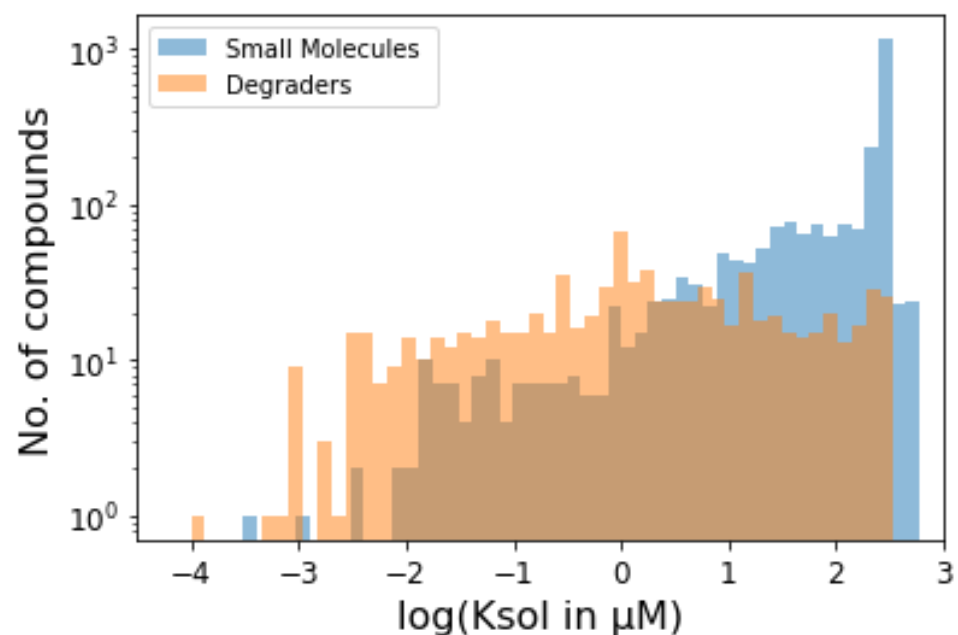
Binary Classification (Soluble/Insoluble)

Multiclass Classification (High/Med/Low)

Regression (Predict numeric Ksol value)

Leveraging the Nurix solubility dataset, we evaluated both Regression and Classification models (and a host of implementations and parameter sets) to identify the best performing models.

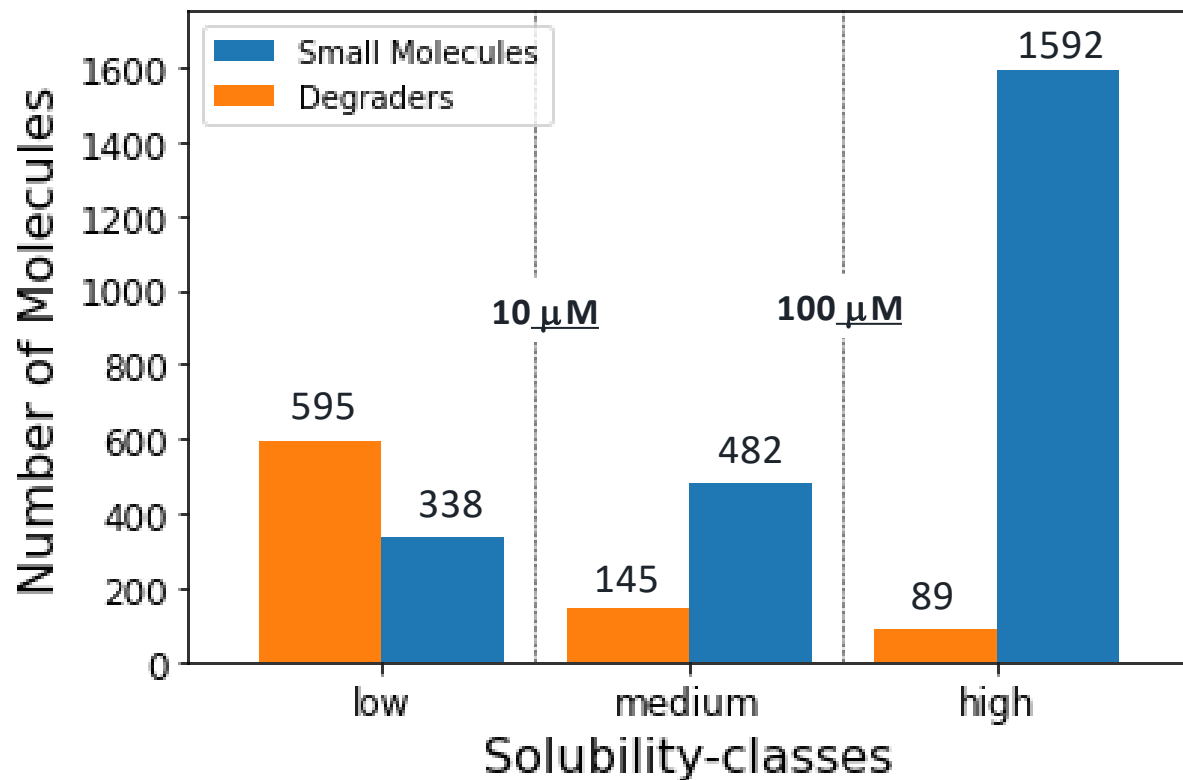
# Nurix Kinetic Solubility Dataset and Framing the ML Problem



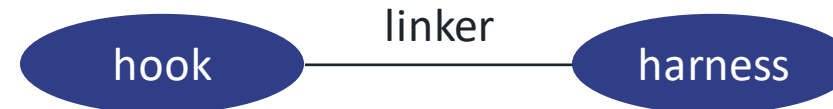
Leveraging the Nurix solubility dataset, we evaluated both Regression and Classification models (and a host of implementations and parameter sets) to identify the best performing models.

# Partitioning the Nurix Ksol Dataset to Enable Lead Optimization

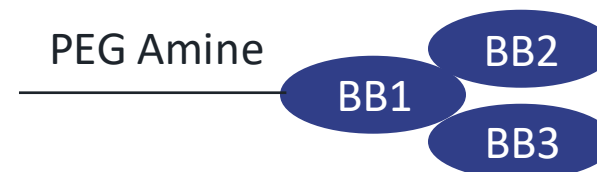
Multi-class Ksol distribution



TPD compound anatomy



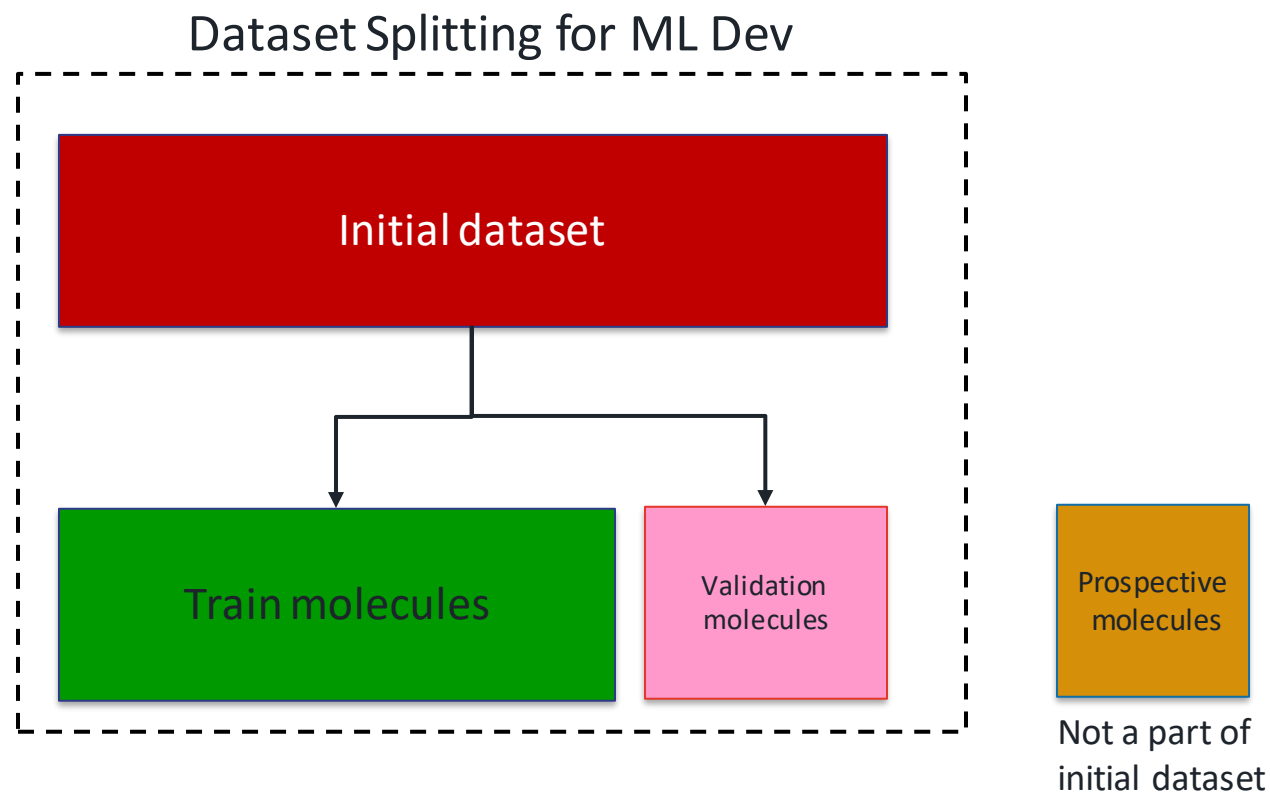
DEL 'Small Molecule'



Combined small molecule and degrader dataset to increase generalizability of models

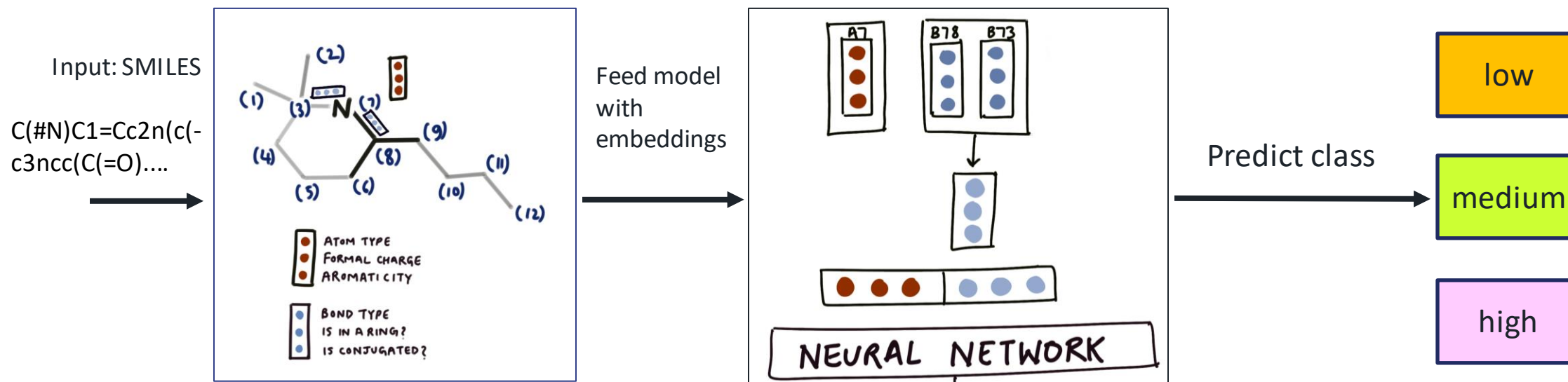


# Dataset Hygiene and Partitioning for the Multiclass ML Model



Proper dataset hygiene to ensure model is performant in prospective predictions

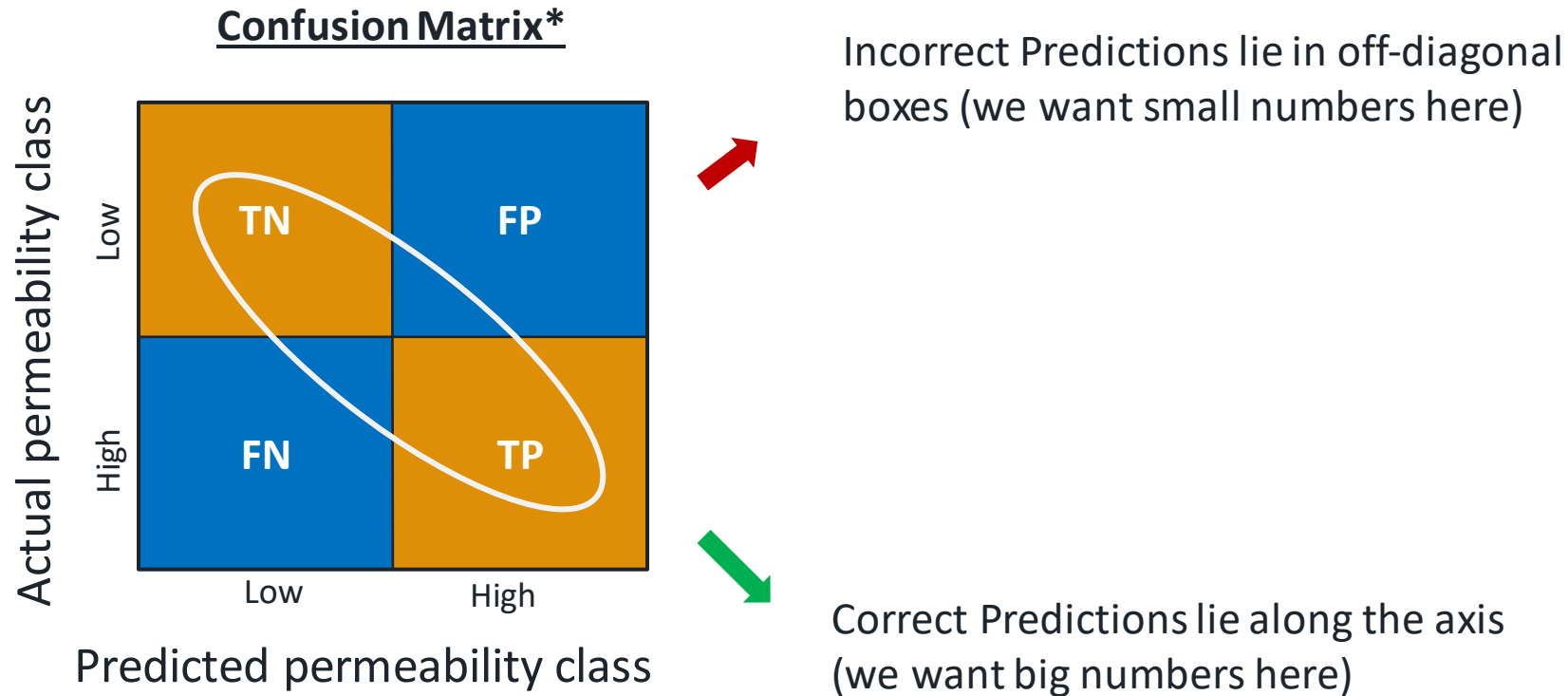
# Model Overview of Best Performing Ksol ML Model



- This is a variant of commonly used molecular property prediction ML model called **Chemprop**
- Represents a molecule as a graph made up of atoms and bonds, with associated properties

# Understanding Model Performance: Confusion Matrix

“All models are wrong, but some are useful” –George E. P. Box



\*Adapted From: Das, C., Sahoo, A.K. and Pradhan, C., 2022. Multicriteria recommender system using different approaches. In *Cognitive Big Data Intelligence with a Metaheuristic Approach* (pp. 259-277). Academic Press.

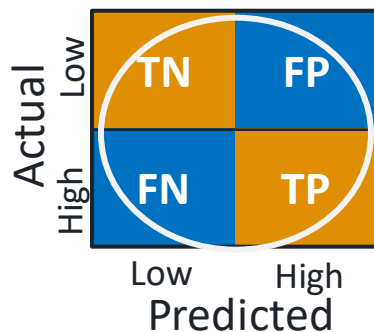
# Understanding Model Performance: Metrics

“All models are wrong, but some are useful” –George E. P. Box

## Accuracy

How many of the overall predictions were correct?

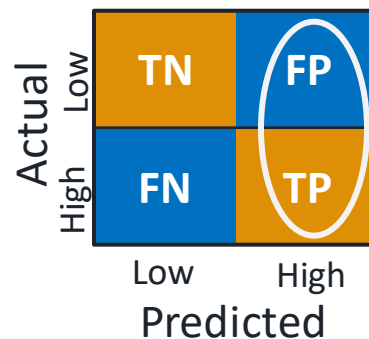
$$\frac{TP + TN}{TP + TN + FP + FN}$$



## Precision

How likely is a predicted active to be active?

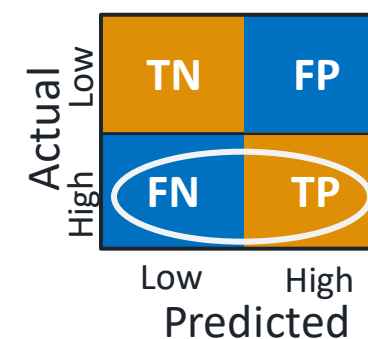
$$\frac{TP}{TP + FP}$$



## Recall

How many of the possible actives did our model find?

$$\frac{TP}{TP + FN}$$



# Prospective Performance Demonstrates the Best Performing Ksol Model Generalizes Well to Both SM and TPD

### Small molecules

	low	medium	high
low	28	7	6
medium	7	26	19
high	5	7	228

Actual Solubility class

Predicted Solubility class

### Degraders

	low	medium	high
low	69	5	0
medium	3	13	1
high	0	0	6

Actual Solubility class

Predicted Solubility class

**Overall Prospective Accuracy = 86%**  
Small Molecule Accuracy = 90%  
Degrader Accuracy = 85%

# Prospective Performance Demonstrates the Best Performing Ksol Model Generalizes Well to Both SM and TPD

### Small molecules

	low	medium	high
low	28	7	6
medium	7	26	19
high	5	7	228

Actual Solubility class vs Predicted Solubility class

### Degraders

low	69	5	0
medium	3	13	1
high	0	0	6

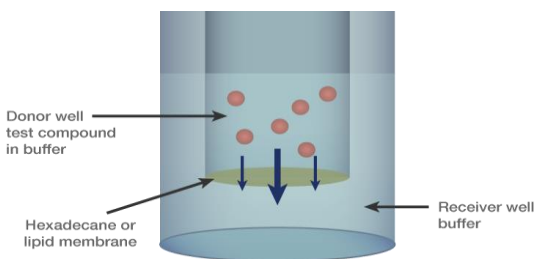
Actual Solubility class vs Predicted Solubility class

Overall Prospective Accuracy = 86%  
Small Molecule Accuracy = 90%  
**Degrader Accuracy = 85%**

High accuracy in prospective prediction of the true label of TPD compounds

# Introduction to Permeability ML: The Assay

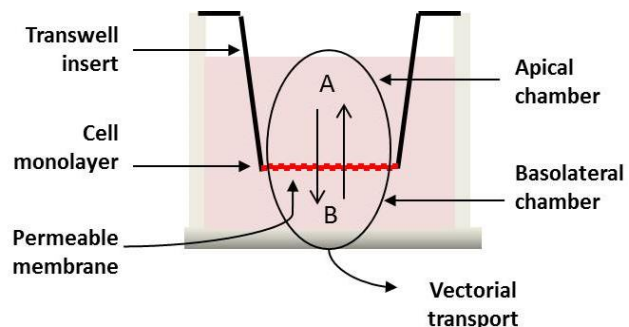
## Artificial membrane assays (PAMPA)



Measures passive diffusion across an artificial membrane.

Endpoints: logPe, Recovery

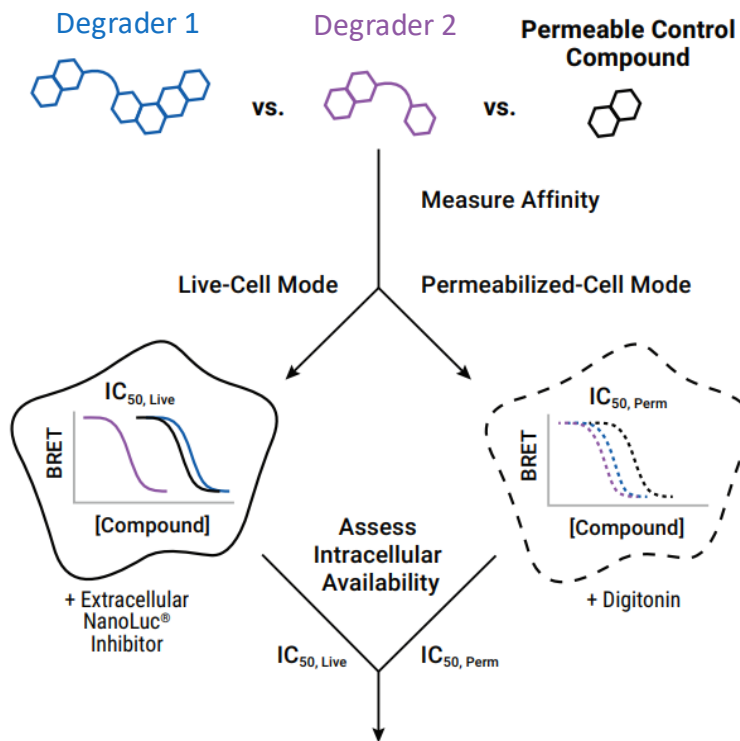
## Cell monolayer assays (MDCK, Caco-2)



Directional transport owing to transporter proteins

Endpoints: Papp A->B, Papp B->A, Efflux Ratio, Recovery, Leakage, TEER

## nanoBret Target Engagement assay



Evaluate shift in binding to intracellular target in live vs permeabilized cells

Endpoints: Relative Binding Affinity (RBA), Availability Index (AI)

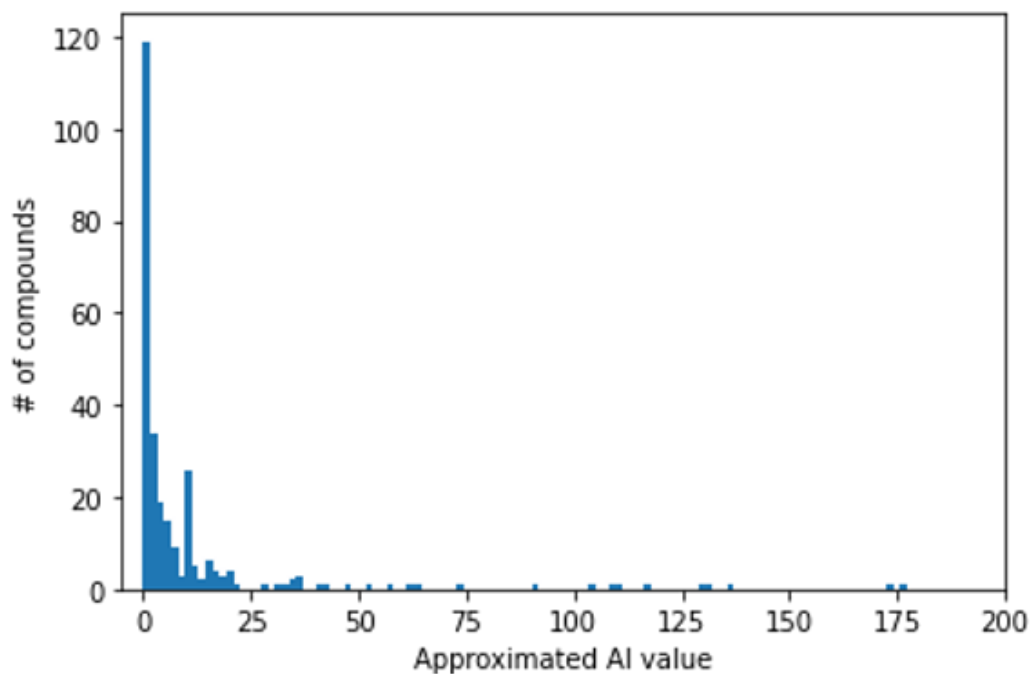
1. Relative Binding Affinity (RBA) =  $\frac{IC_{50, Live}}{IC_{50, Perm}}$

2. Availability Index (AI) =  $\frac{RBA_{PROTAC}}{RBA_{CONTROL}}$

3. Compare Values:

Compound	RBA	AI
Control	0.8	1.0
Degradation 1	16.0	20.0
Degradation 2	0.9	1.1

# Nurix Permeability Dataset and Framing the ML Problem



Binary Classification (Permeable/Impermeable)

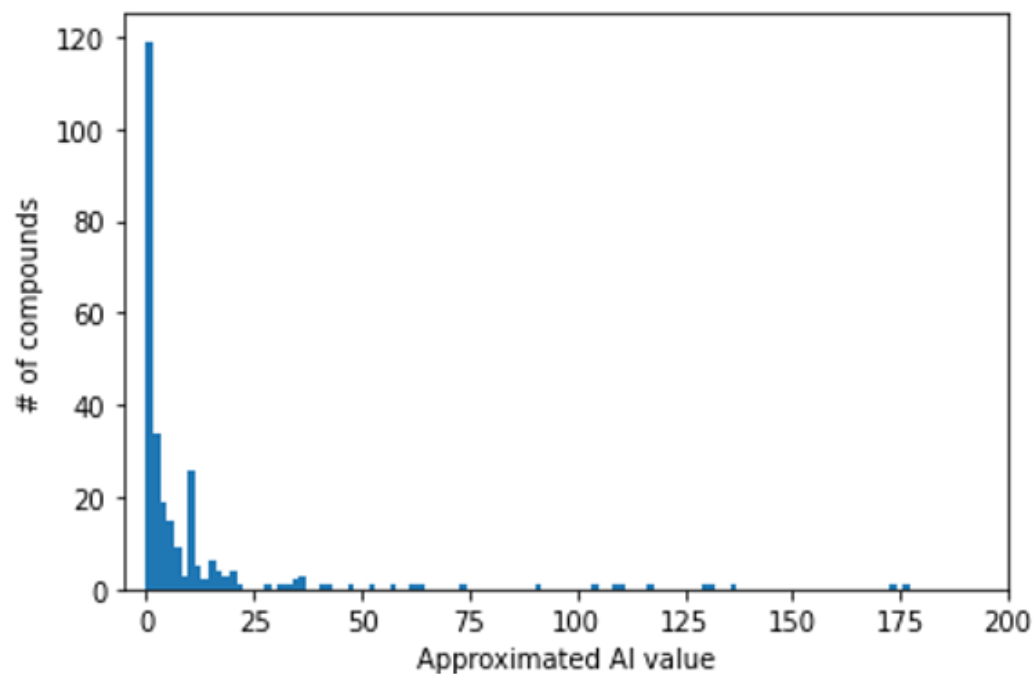
Multiclass Classification (High/Med/Low)

Regression (Predict numeric TE AI value)

Due to the small size of the Nurix permeability dataset, we evaluated a binary-classification model



# Nurix Permeability Dataset and Framing the ML Problem



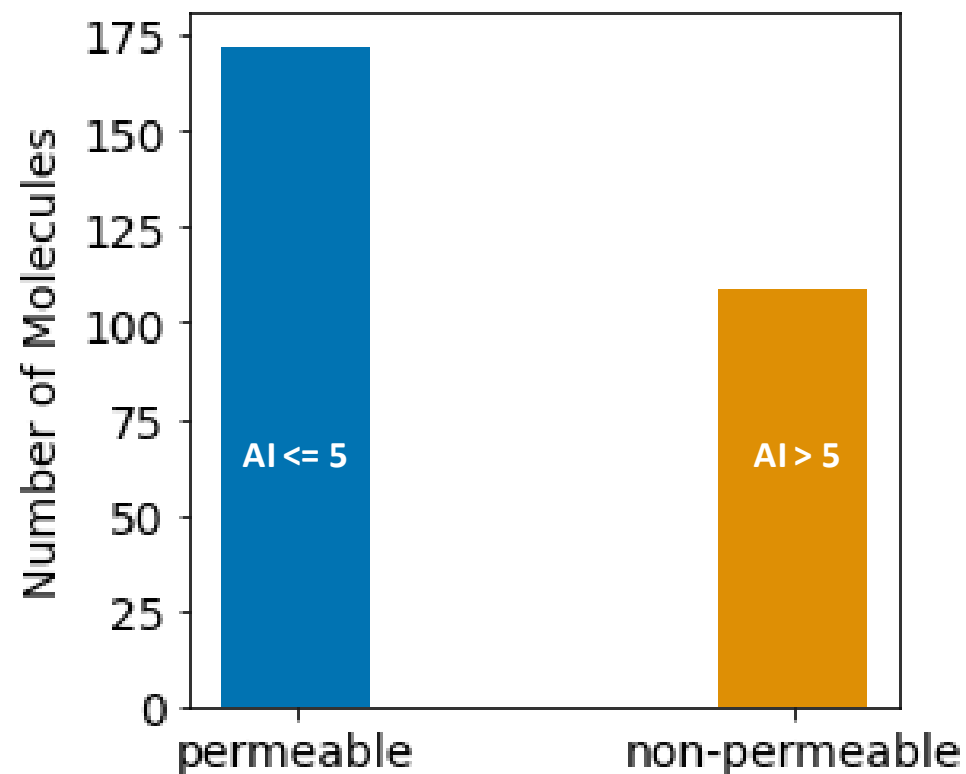
Binary Classification (Permeable/Impermeable)

Multiclass Classification (High/Med/Low)

Regression (Predict numeric TE AI value)

Due to the small size of the Nurix permeability dataset, we evaluated a binary-classification model

# Permeability Data as a Binary-Class ML Dataset

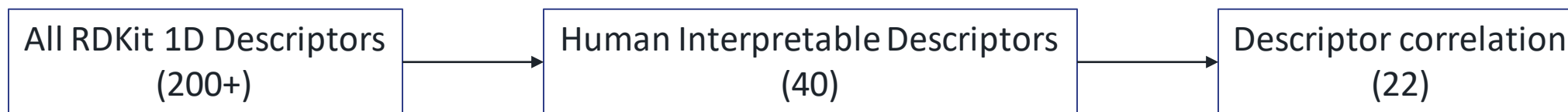


- Dataset distribution : 281 degraders representing multiple ligases
- Data labeling: If **Availability Index (AI) > 5**, then **non-permeable** else **permeable**.

# Feature Selection To Enable Human Interpretability

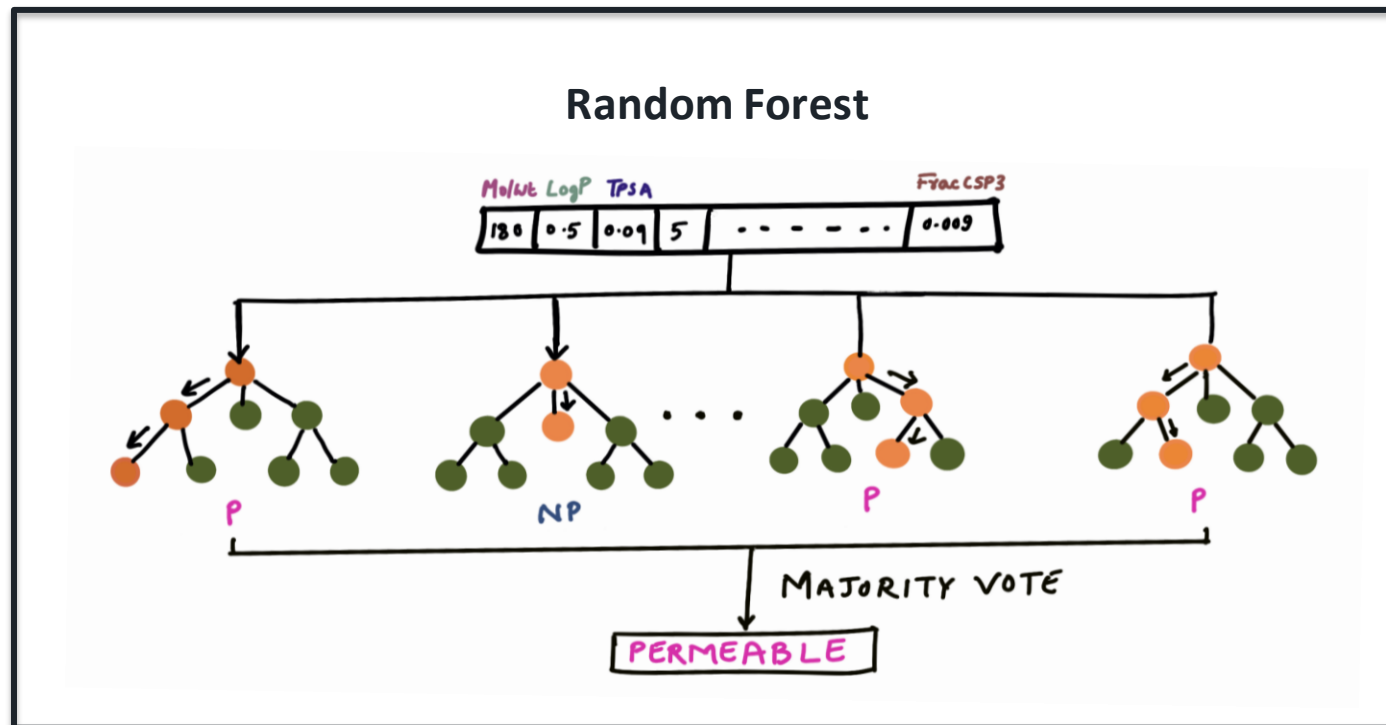
In determining how to featurize our molecules, we had a few considerations:

- Smaller dataset -> too many features can lead to overfitting
- Desire to enable human interpretability of ML model learned SAR



MW	#Rings
cLogP	FracSP3
#HBD	#HeteroAtoms
#HBA	TPSA

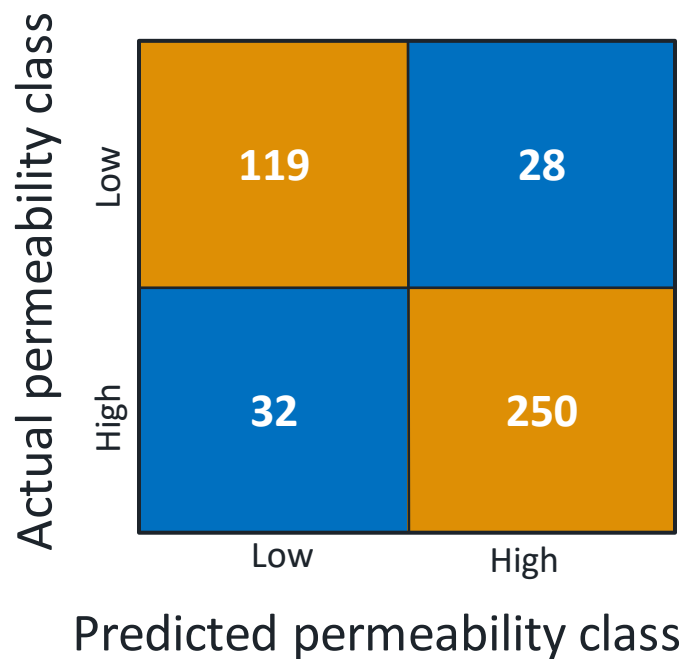
# Model Overview of Best Performing Permeability ML Model



A collection of decision trees that predicts permeability based on molecular properties

# Permeability Model Achieves High Levels of Accuracy in Prospective Predictions

RF Model achieves **86% accuracy and 90% precision** in prospective predictions generalizing across different ligases and protein targets



# Permeability Model Achieves High Levels of Accuracy in Prospective Predictions

RF Model achieves **86% accuracy and 90% precision** in prospective predictions generalizing across different ligases and protein targets

By Target

Target	Accuracy
1	88%
2	100%
3	92%
4	64%
5	78%

← No data in training set for this target

By Ligase

Ligase	Accuracy
CRBN	93%
VHL	81%
Others	60%

← Low representation in training set

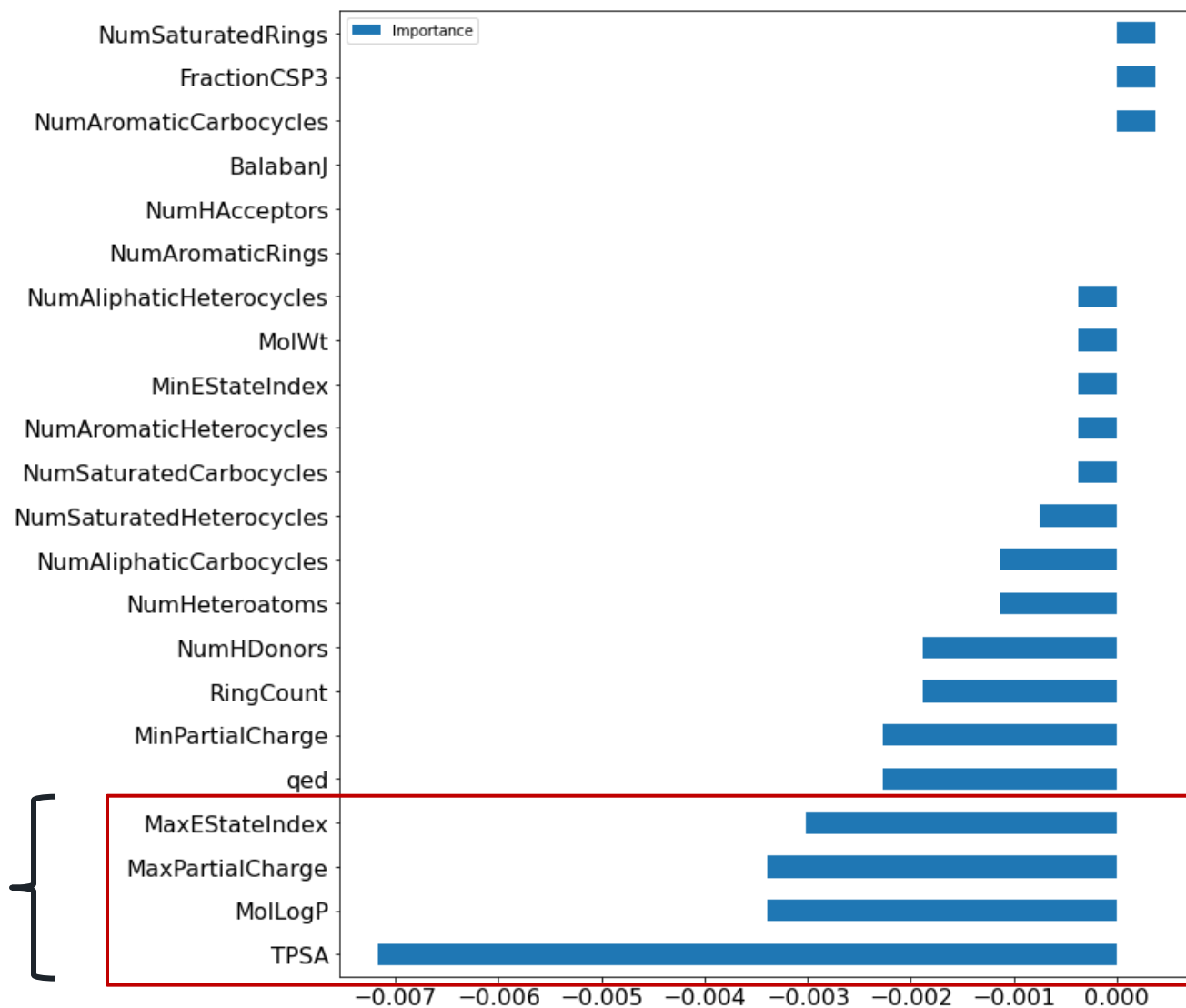
# Discussion

Interplay between model learnings and human interpretability

# Investigating What the Model Has Learned

- Feature importance tells which features contributed to model's learning process.
- Bars to the left are negatively correlated and to the right are positively correlated to permeability.
- **Interpretability analysis can allow chemists to build intuition and design better compounds.**

Important features



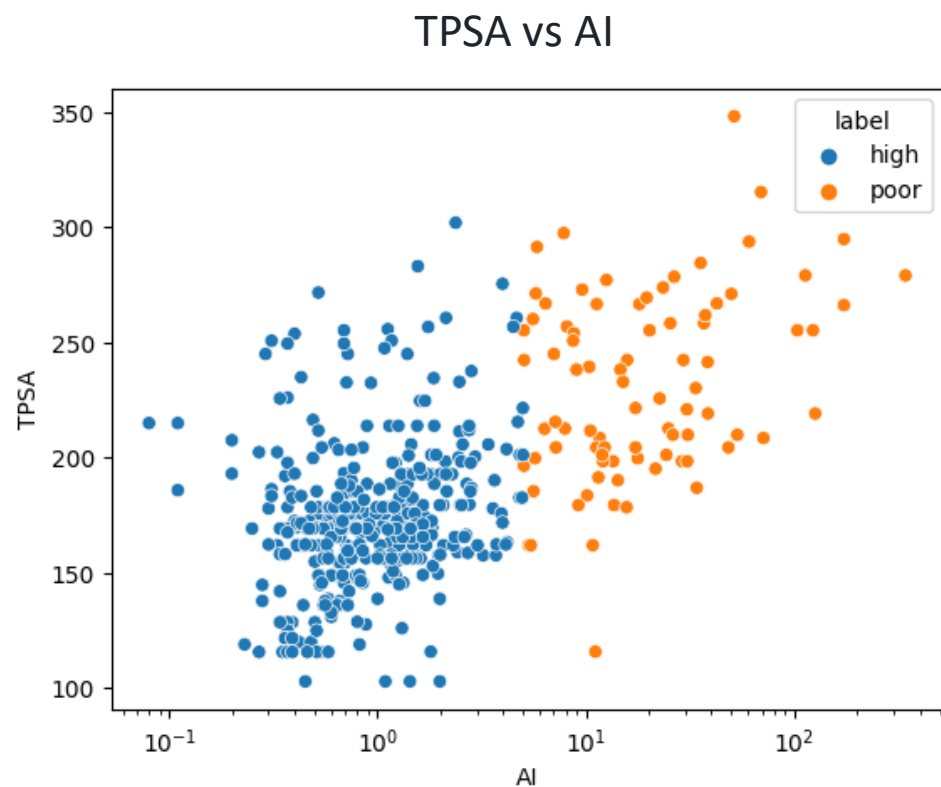
Positive correlation

Negative correlation



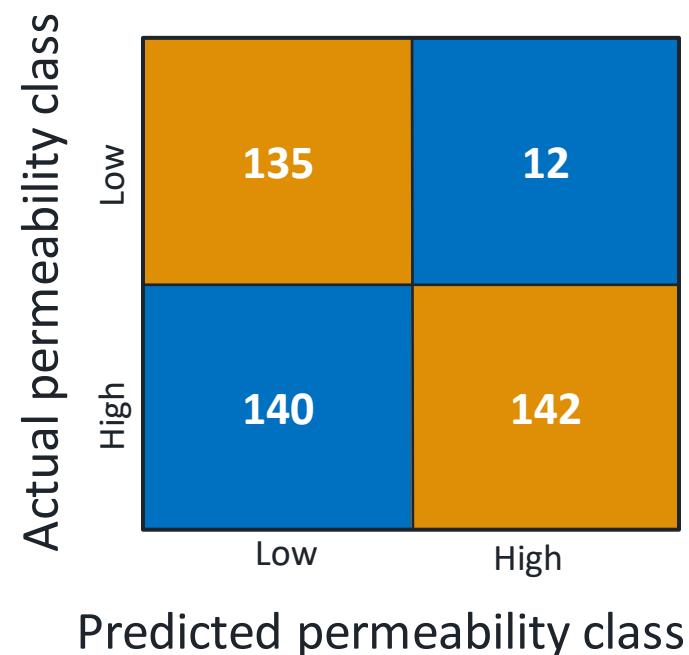
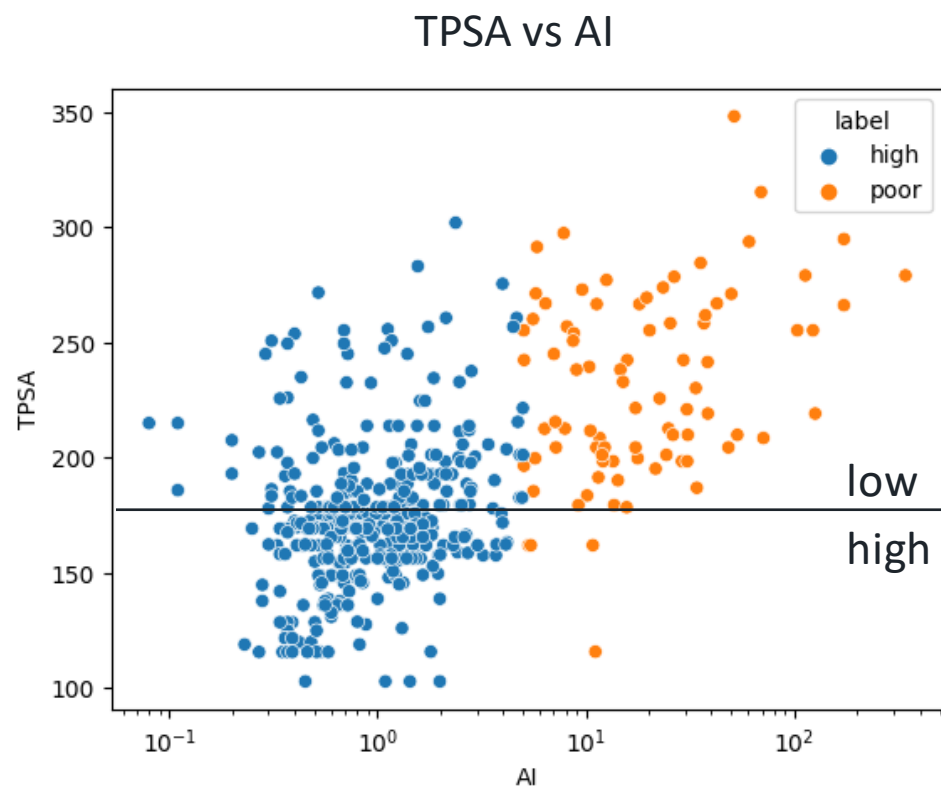
# Building Human Intuition Leveraging Feature Importance Analysis

Evaluating the features suggested as important offers learnings to inform human guided molecular design



# Building Human Intuition Leveraging Feature Importance Analysis

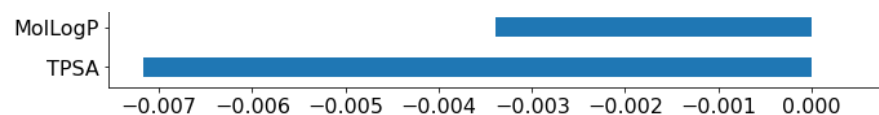
Evaluating the features suggested as important offers learnings to inform human guided molecular design



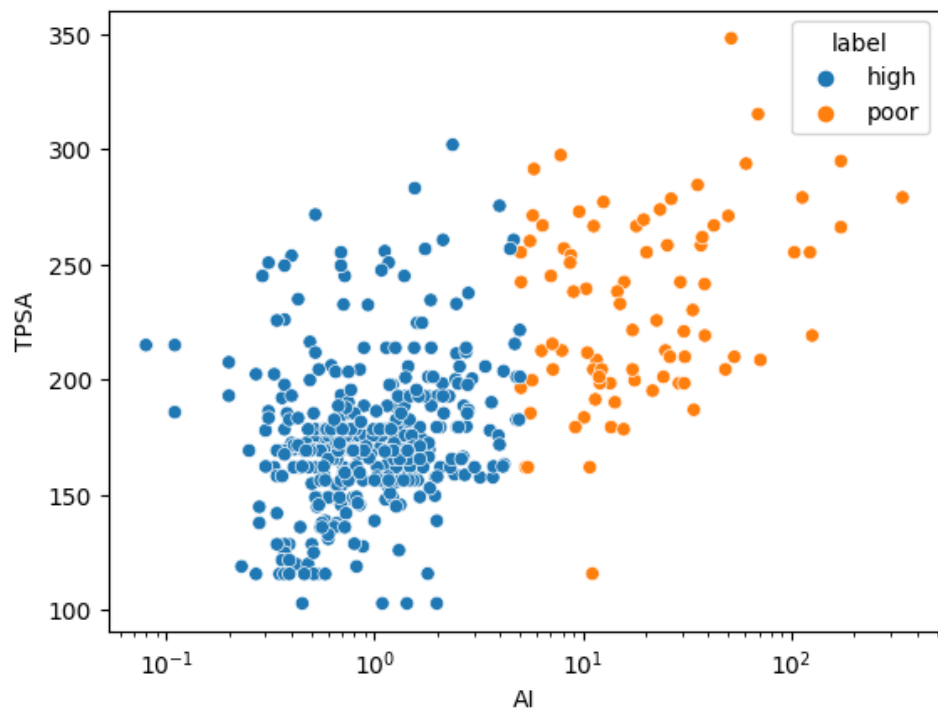
**65% accuracy and 92% precision** with a simple model based solely on TPSA

# Building Human Intuition Leveraging Feature Importance Analysis

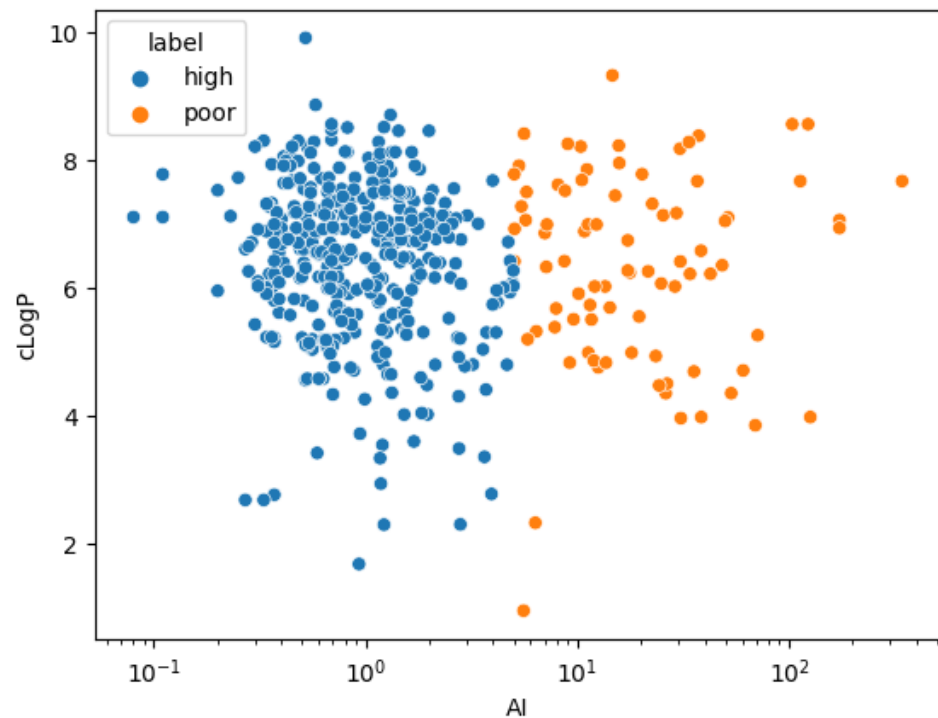
Evaluating the features suggested as important offers learnings to inform human guided molecular design



TPSA vs AI

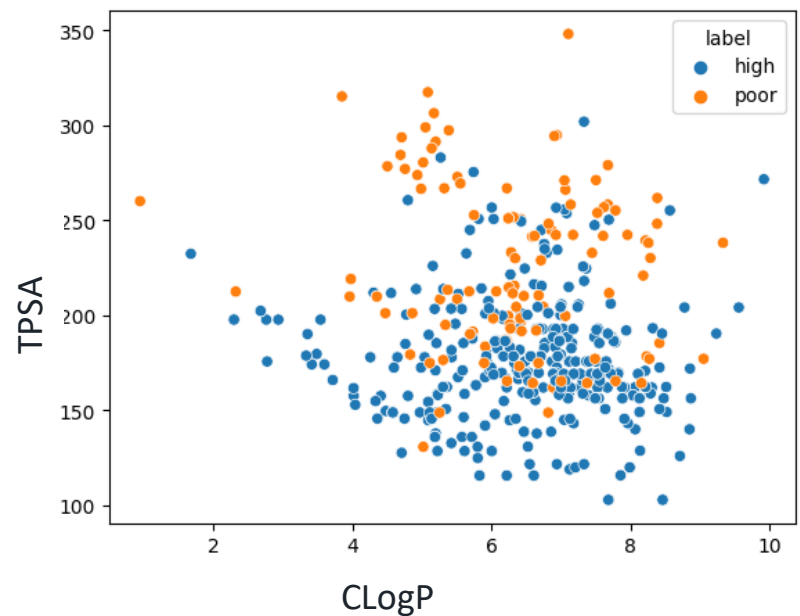


cLogP vs AI

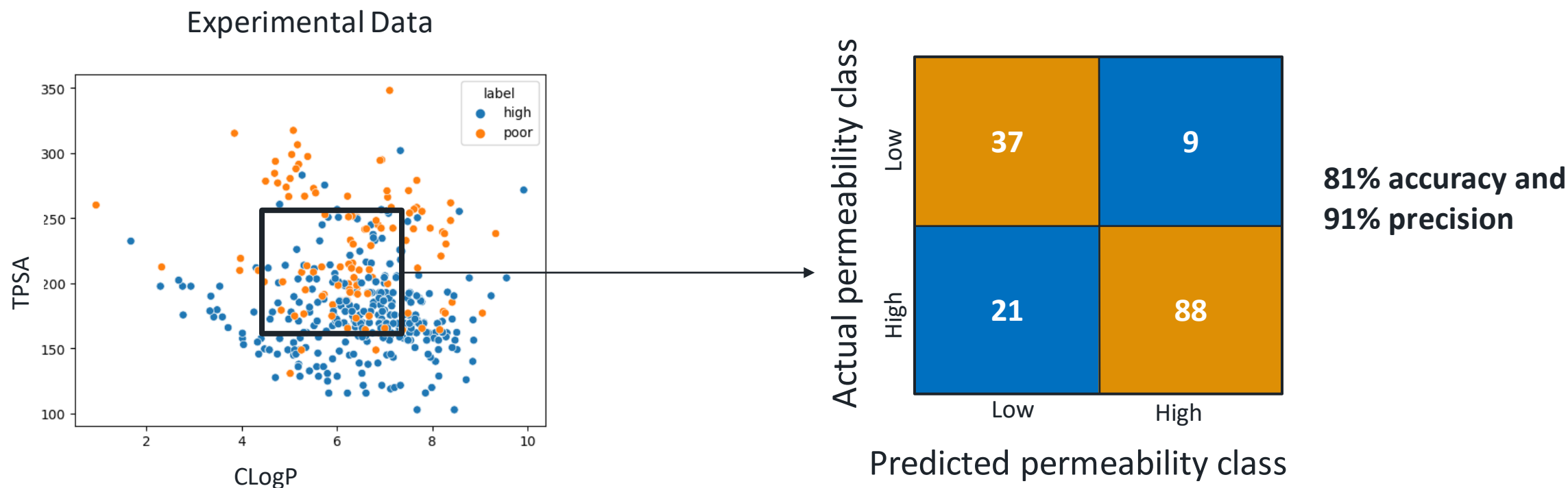


# ML Model Complements Intuition In Non-Obviously Separable Property Space

Experimental Data

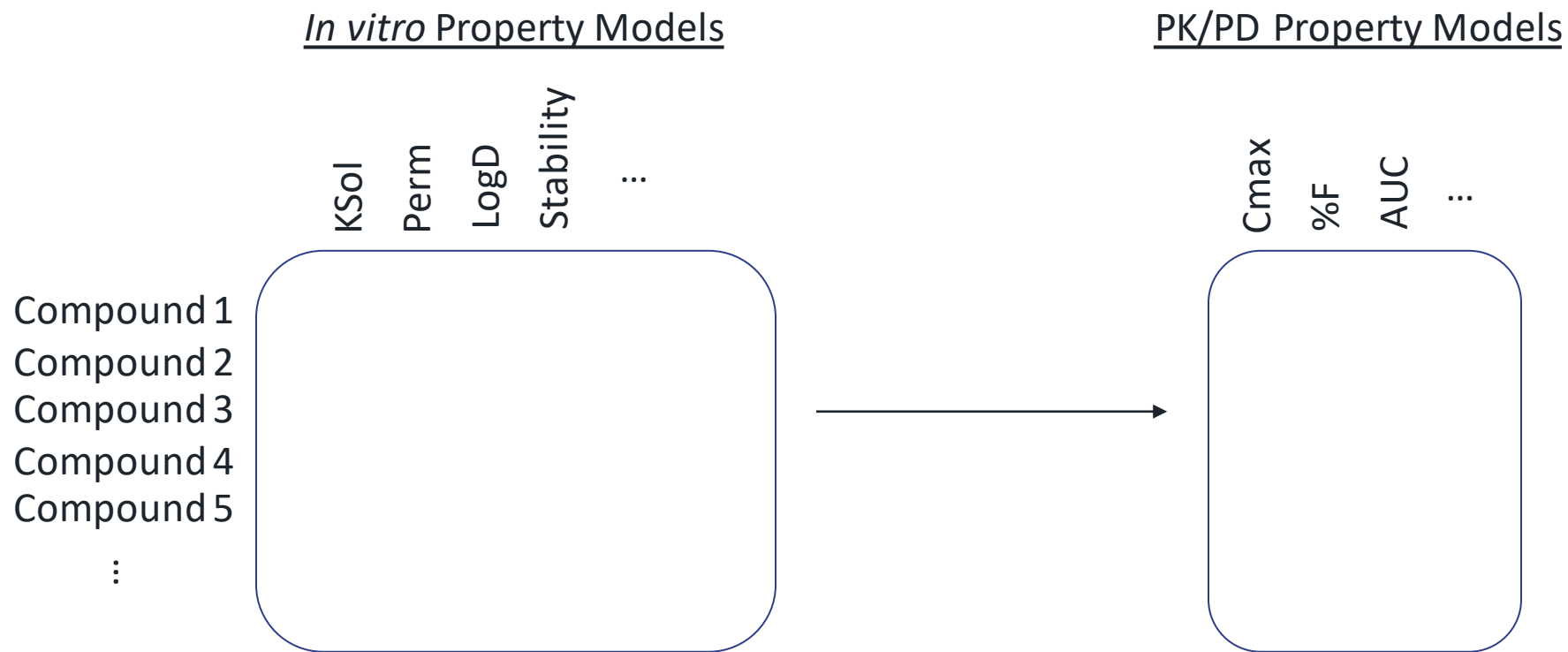


# ML Model Complements Intuition In Non-Obviously Separable Property Space



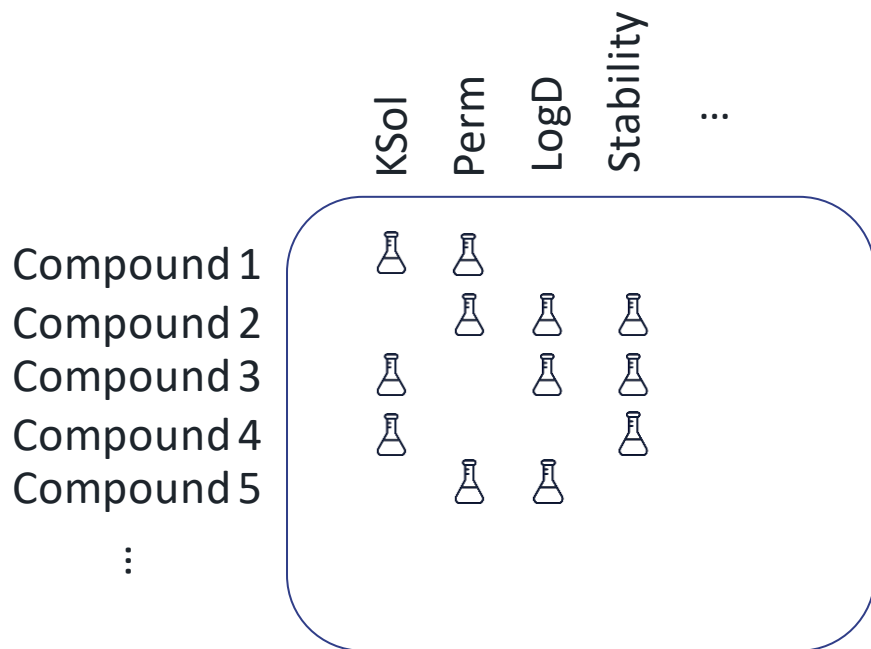
Permeability ML model predicts correct class membership despite no obvious separation of High/Low permeable compounds in property space defined by highest importance features.

# Rebuilding Understanding to Enable Improved Predictions

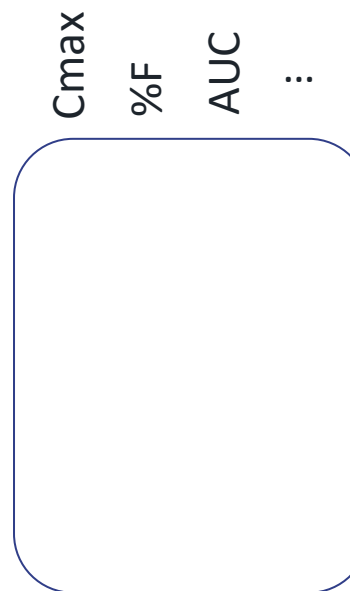


# Rebuilding Understanding to Enable Improved Predictions

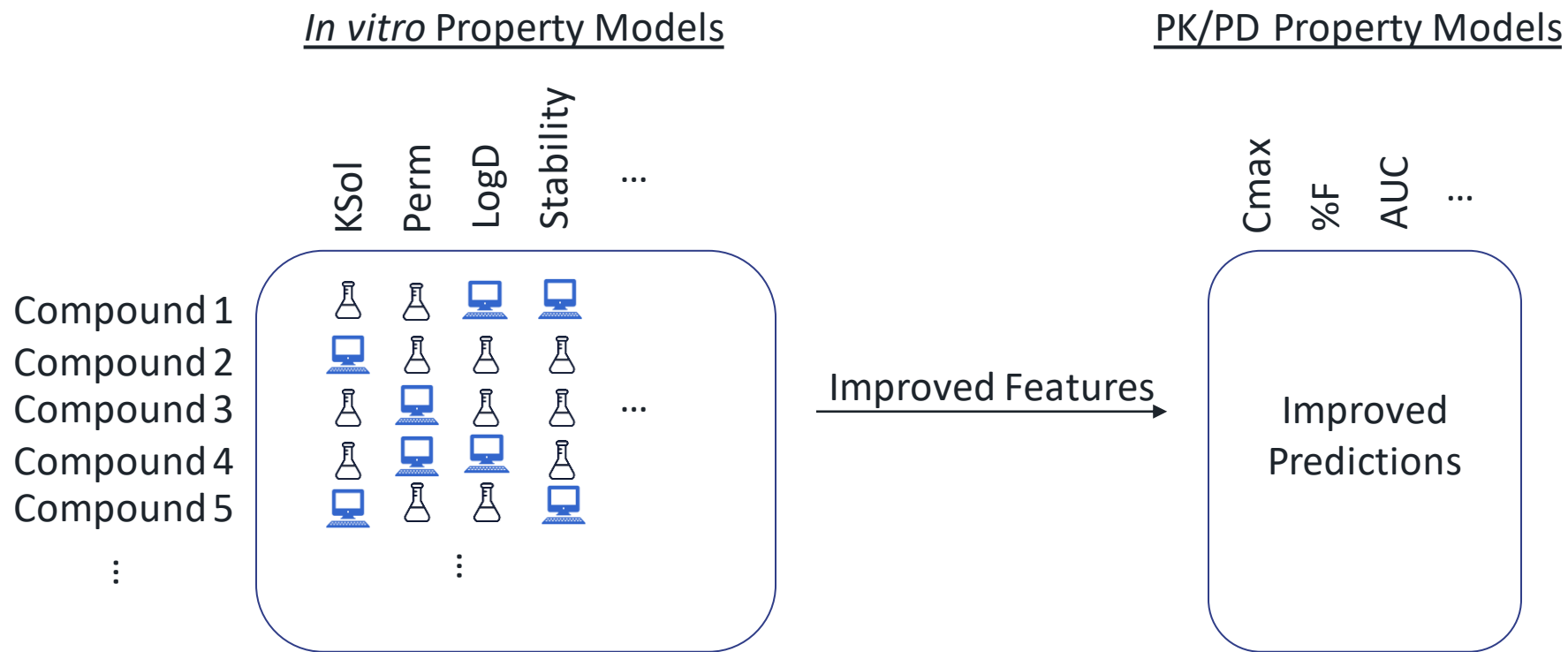
## In vitro Property Models



## PK/PD Property Models



# Rebuilding Understanding to Enable Improved Predictions





# Conclusions

- Many off-the-shelf property calculators do not generalize well to TPD molecules given the novel chemical space occupied by these compounds
- Machine Learning can re-learn the rules of structure-property relationships and offer a useful tool to inform molecular design during Lead Optimization
- ML models for structure-property prediction can enable and complement human understanding of learned SPR



Thank you