Structure Based Prediction of Influenza Drug-Resistant Mutations

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Baloxavir Marboxil (Xofluza)

ORIGINAL ARTICLE FREE PREVIEW

Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

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September 6, 2018
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(650) 467-6800

xofluza™
(baloxavir marboxil) tablets

About XOFLUZA

XOFLUZA™ is approved by the U.S. Food and Drug Administration (FDA) as a single-dose, for acute, uncomplicated influenza in people 12 years of age and older.[1] A single dose of X be taken orally within 48 hours of symptom onset.[1]

October 06, 2018

Baloxavir Marboxil Safe and Effective for High-Risk Influenza Patients

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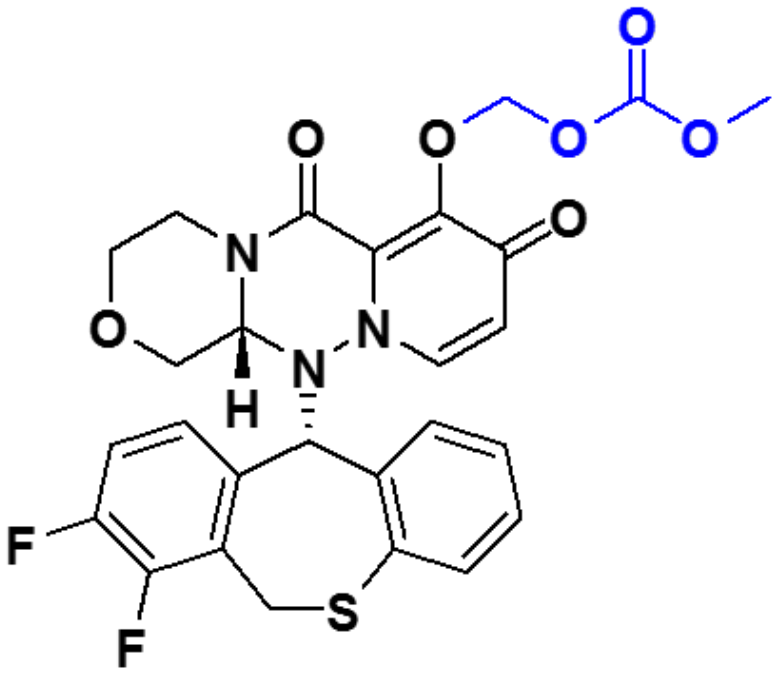
This article is part of *Infectious Disease Advisor*'s coverage of IDWeek 2018, taking place in San Francisco, CA. Our on-site staff will be reporting on the latest breaking research and clinical advances in infectious diseases. Check back regularly for highlights from IDWeek 2018.

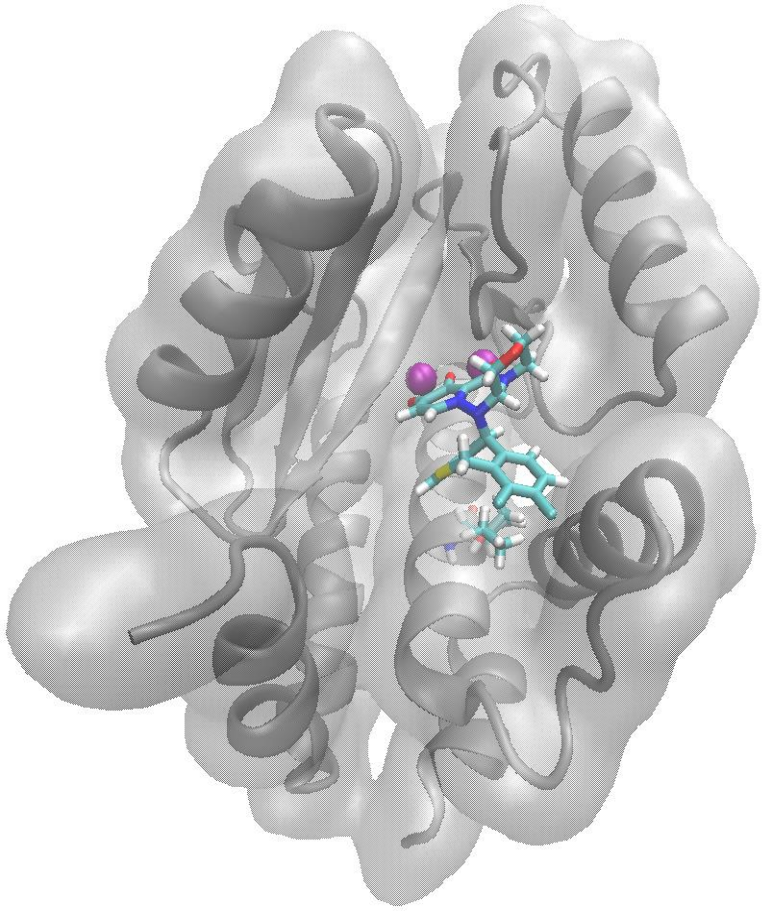
SAN FRANSISCO — When compared with a placebo, the oral selective, cap-dependent,

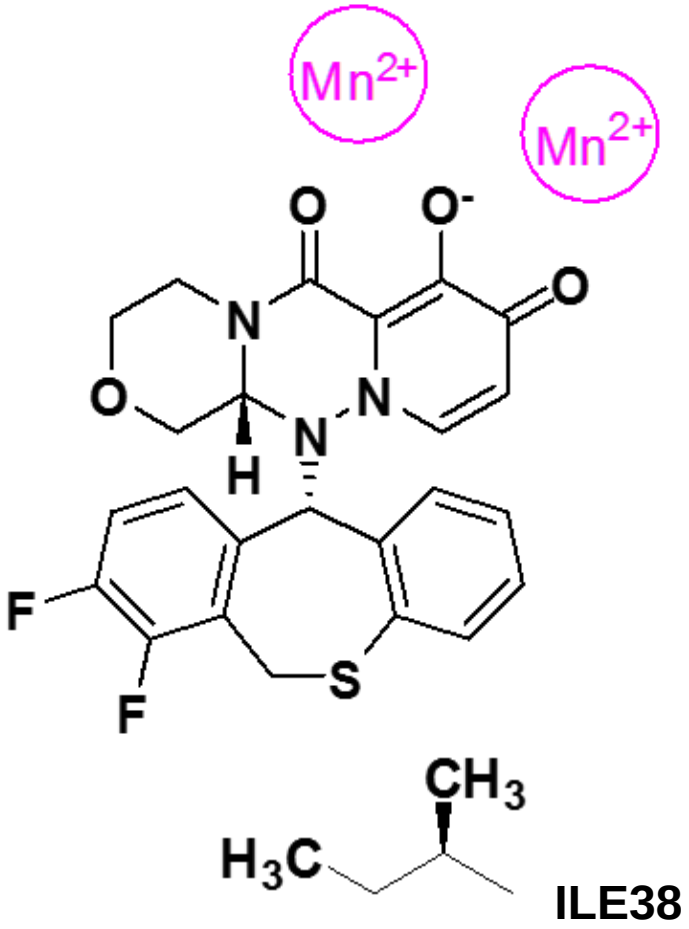
Baloxavir proved superior to oseltamivir in shortening the



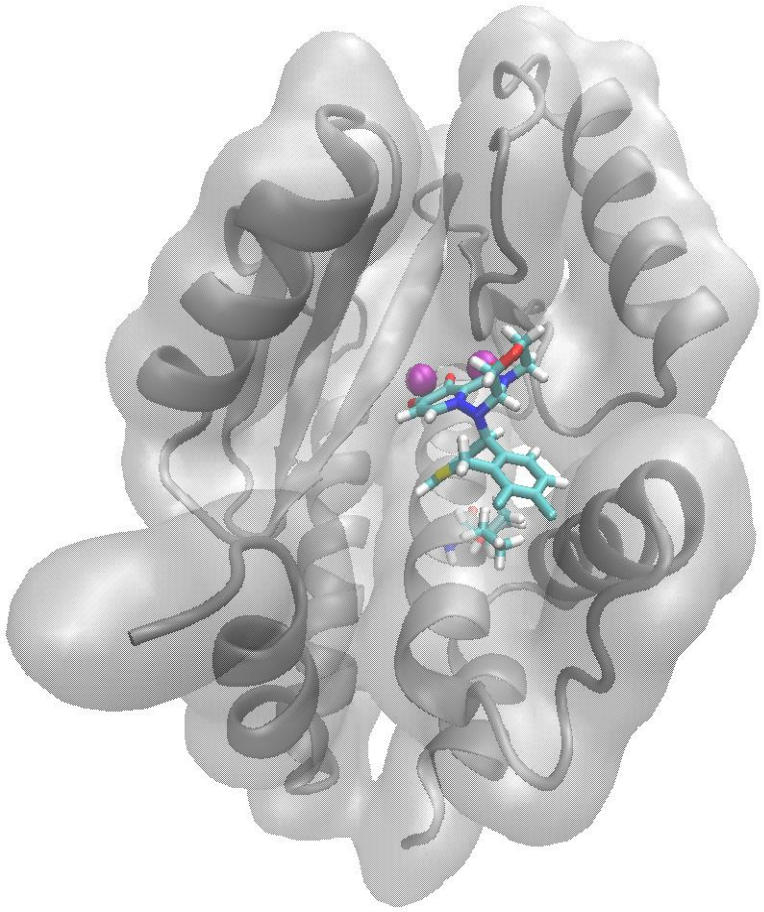
Baloxavir Marboxil - *Xofluza*
(Roche, Shionogi)

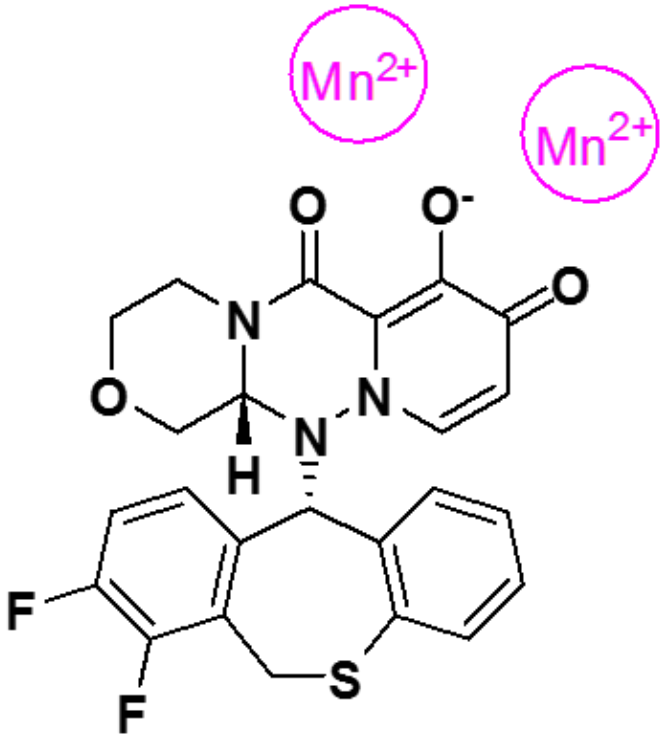
Baloxavir Marboxil (Xofluza) Resistance



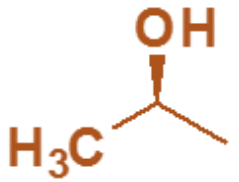


Baloxavir Marboxil (Xofluza) Resistance



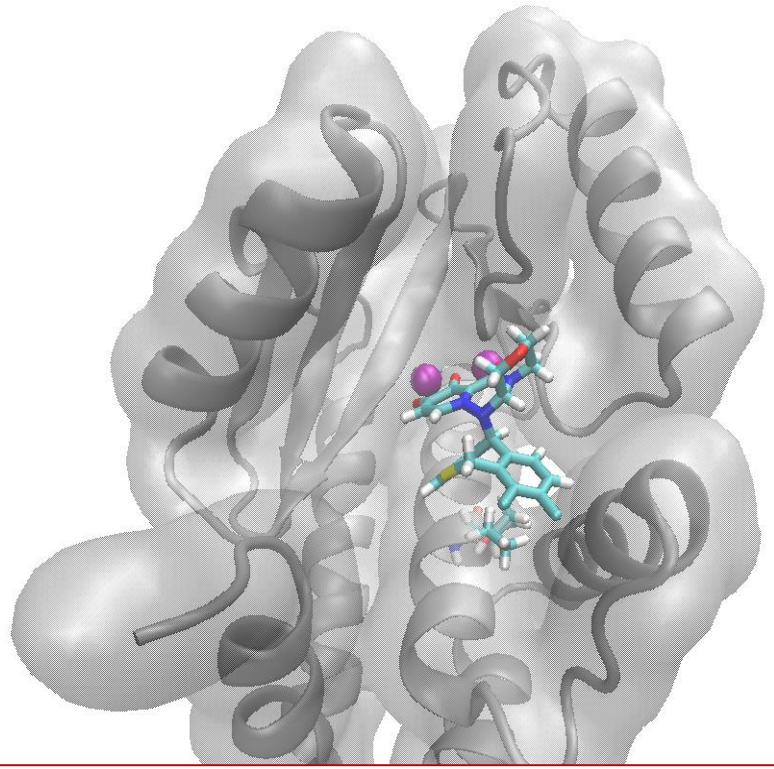


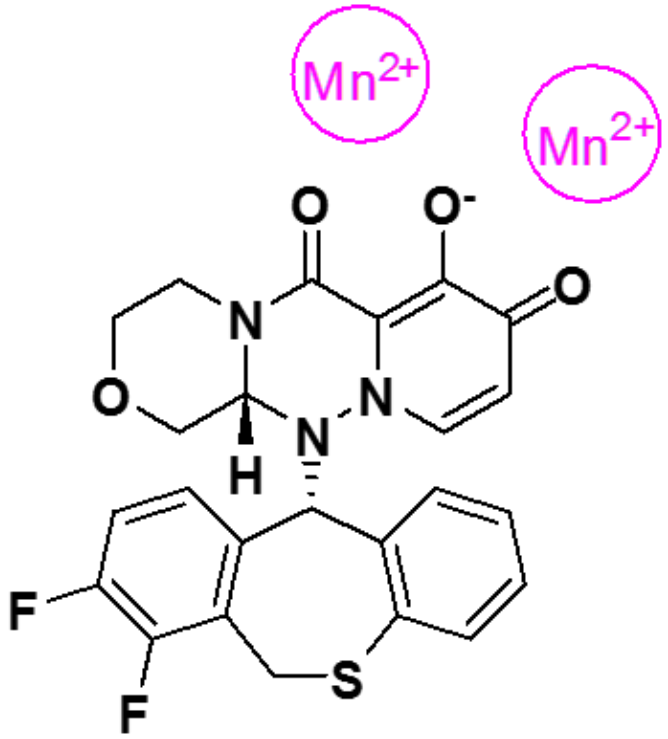
30-50X Decreased Activity



ILE38THR

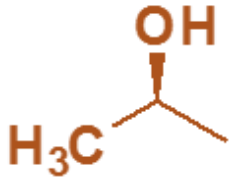
Baloxavir Marboxil (Xofluza) Resistance





30-50X Decreased Activity

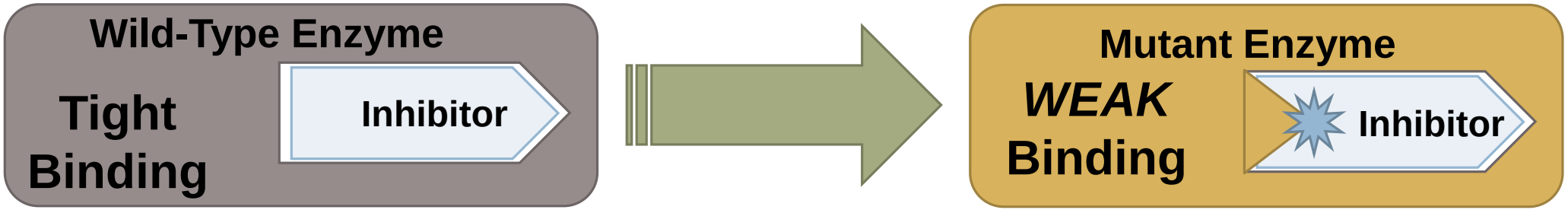
IF WE ONLY HAD THE BOUND STRUCTURES,
COULD WE PREDICT BALOXAVIR RESISTANCE MUTATIONS?



ILE38THR

Predicting Resistance: Central Hypothesis

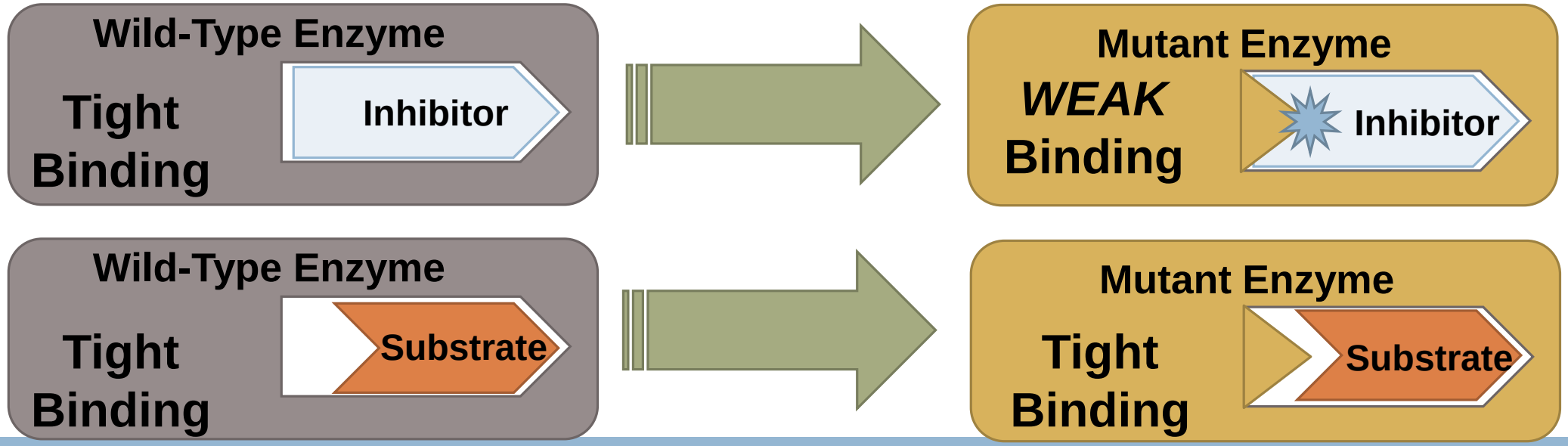
I. Decrease Binding of Inhibitor



Predicting Resistance: Central Hypothesis

I. **Decrease Binding of Inhibitor**

II. **Maintain Affinity of Substrate**

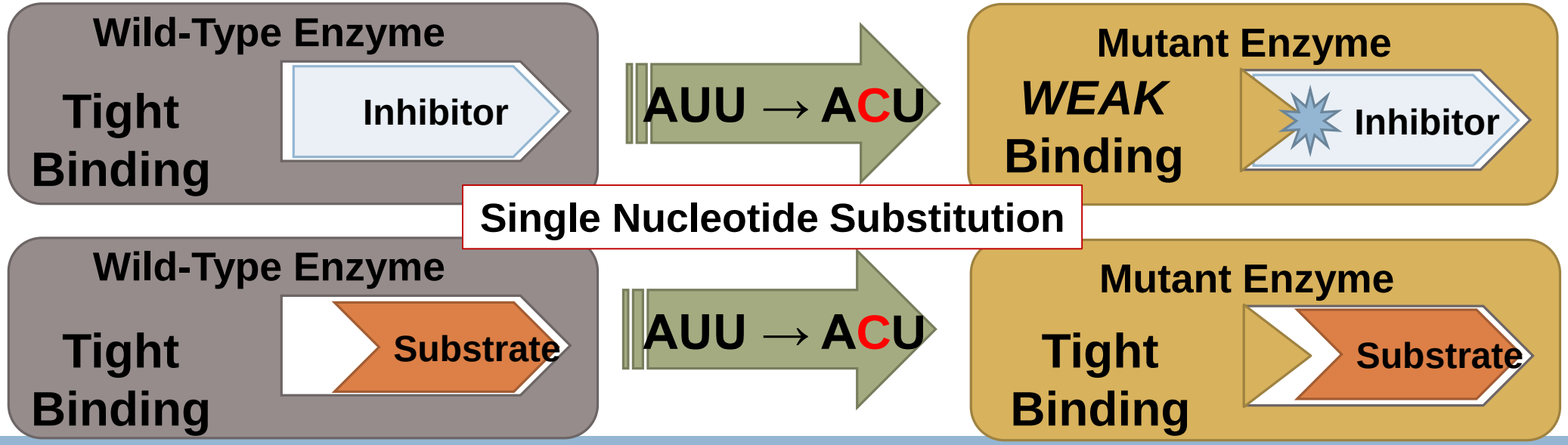


Predicting Resistance: Central Hypothesis

I. **Decrease Binding of Inhibitor**

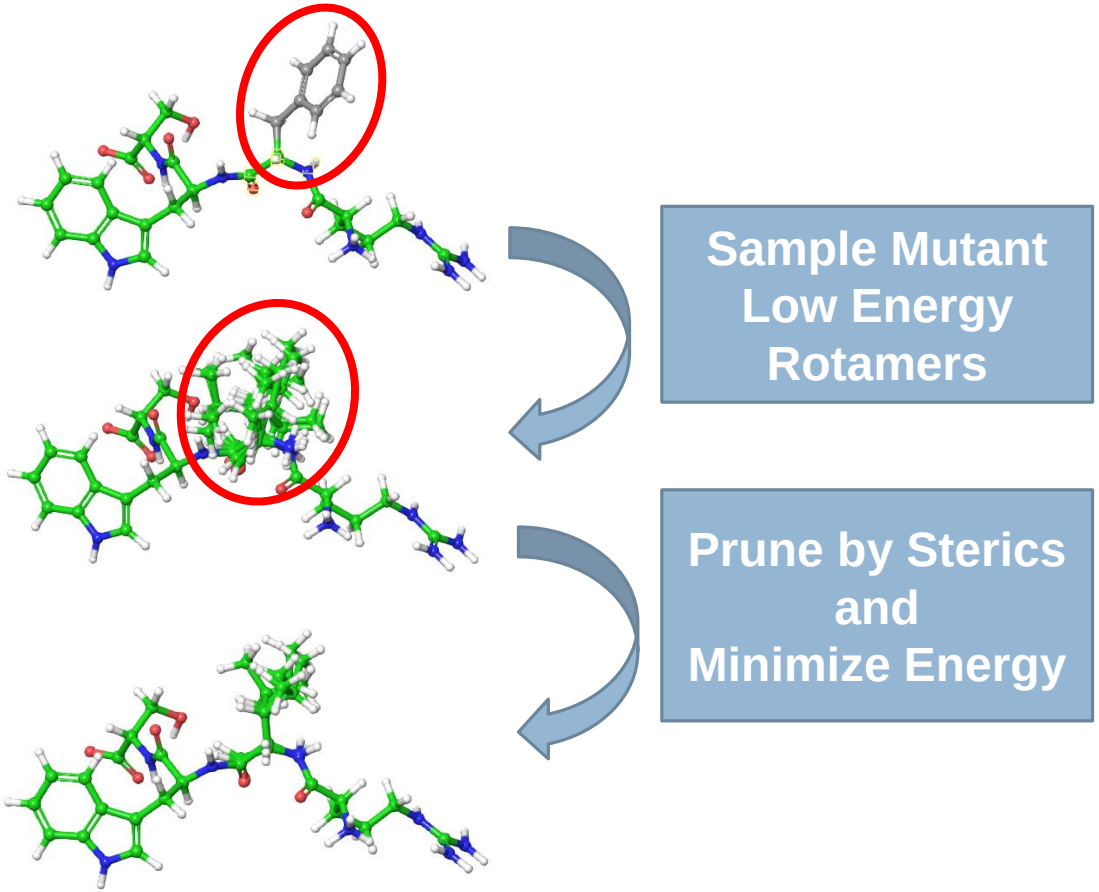
II. **Maintain Affinity of Substrate**

III. **Low Genetic Barrier**



Hao, et. al, *Drug Discovery Today* (2012) 17: 1121-1126.

Simulation of All I38 Mutations: OSPREY / K* Protein Design Algorithm



Sample Mutant Low Energy Rotamers

Prune by Sterics and Minimize Energy

Reeve, SM, et. al. *Proc Nat Acad Sci* (2015) 112(3): 749-754.
Gainza, P, et. al. *Methods Enzymol* (2013) 523: 87-107

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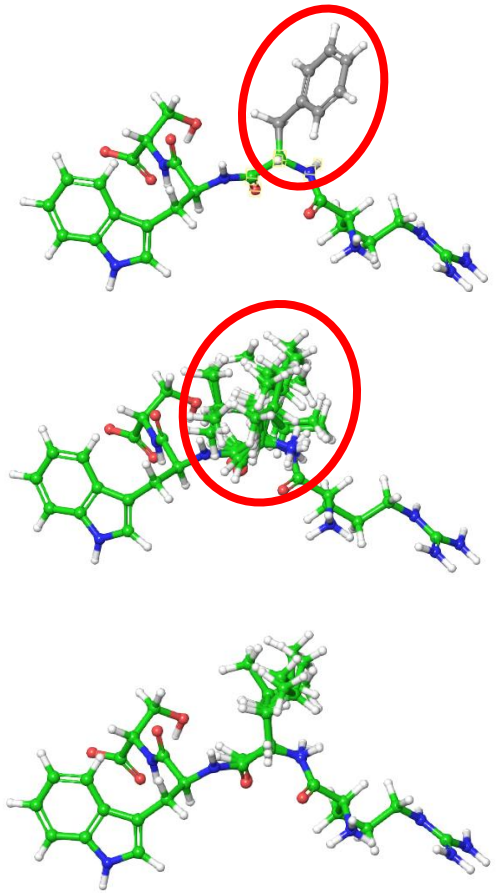

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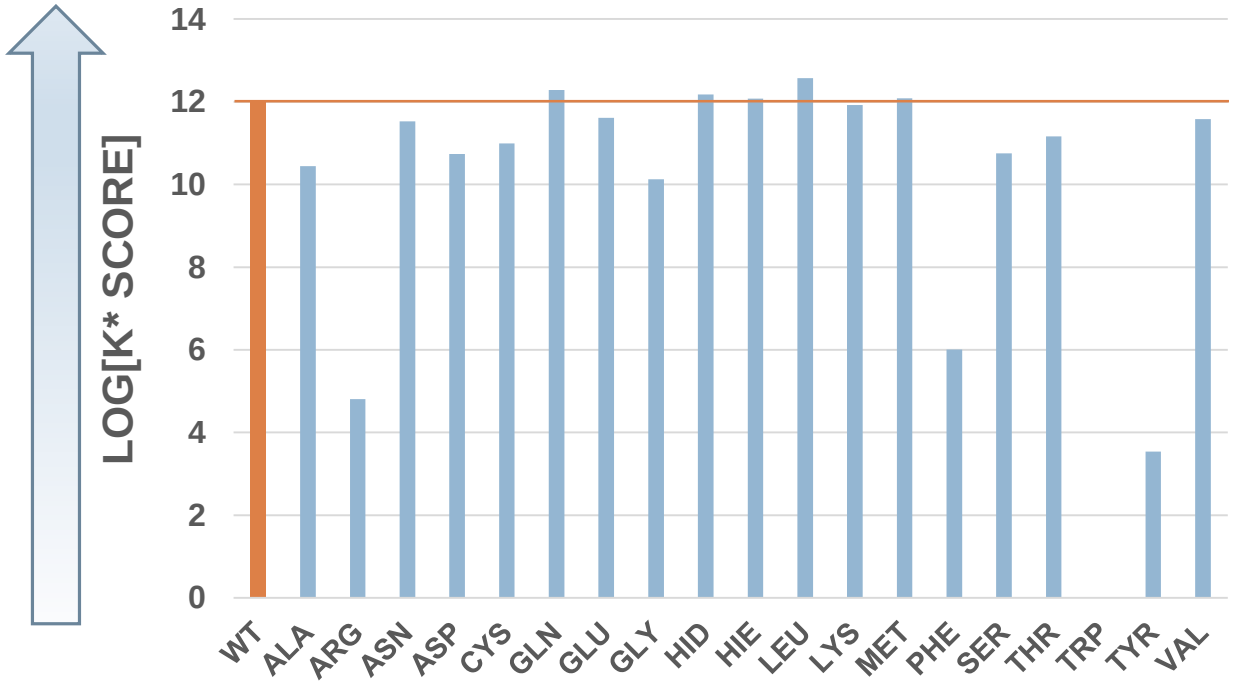
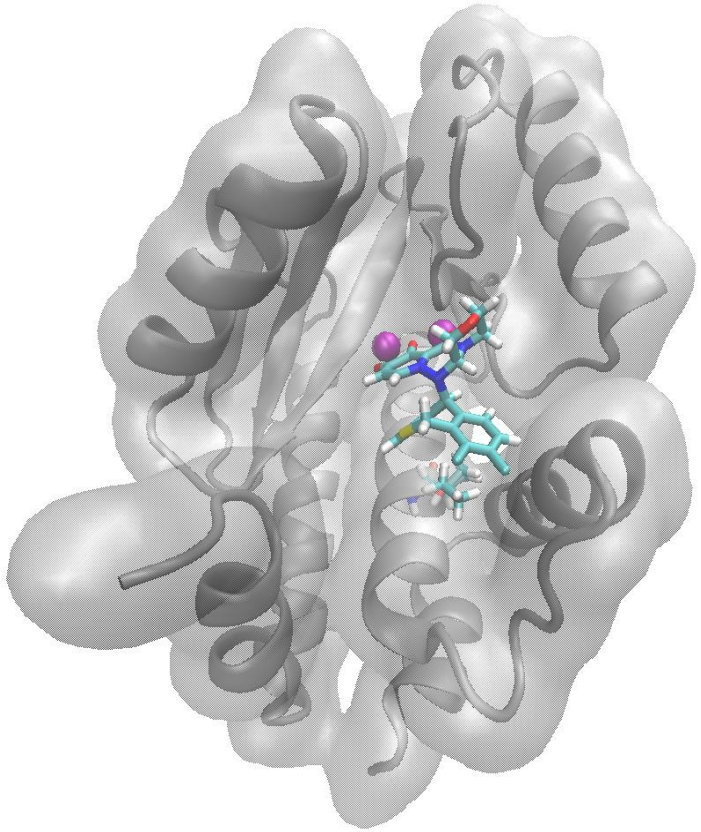


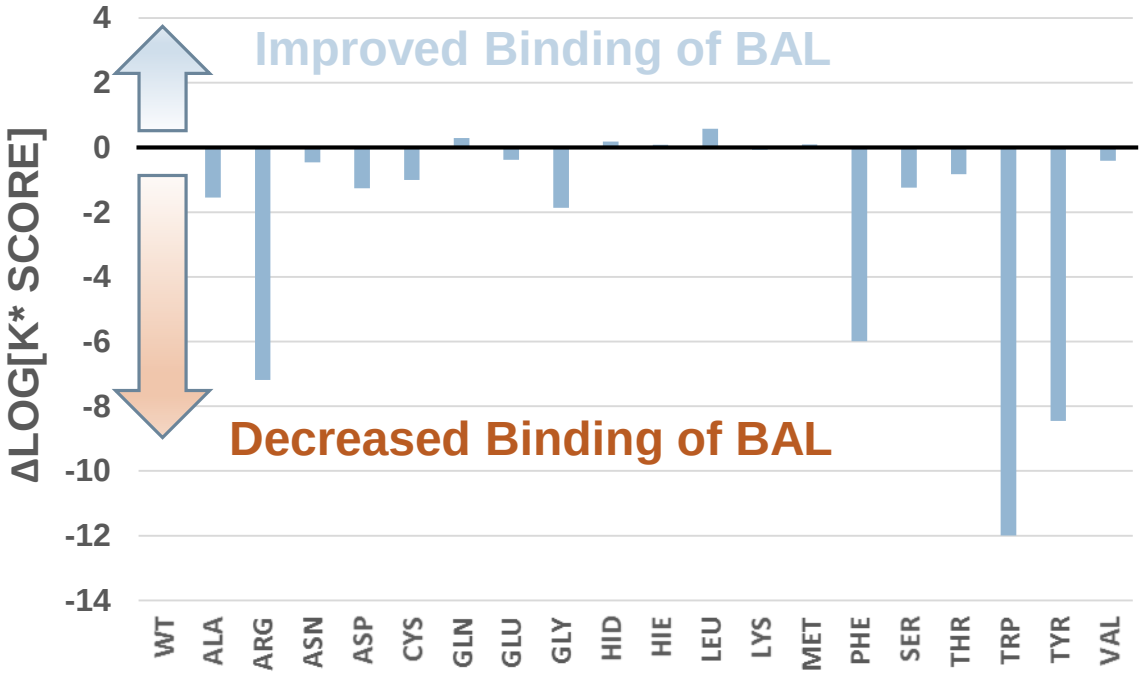
More Favorable Complex Energy

Reeve, SM, et. al. *Proc Nat Acad Sci* (2015) 112(3): 749-754.
Gainza, P, et. al. *Methods Enzymol* (2013) 523: 87-107

Simulation of All I38 Mutations: Energy Relative to Wild-Type

Model of BAL Active Species Bound to Flu A H1N1 PA

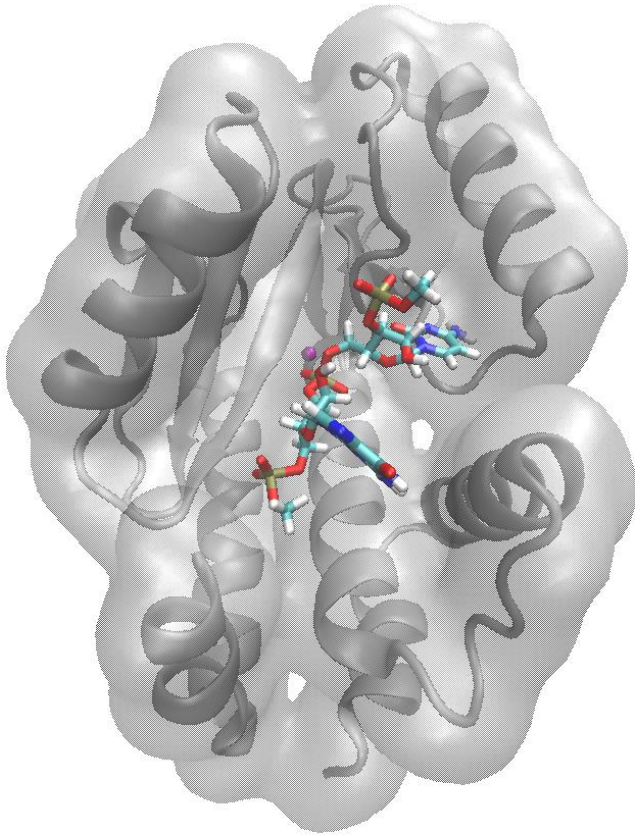


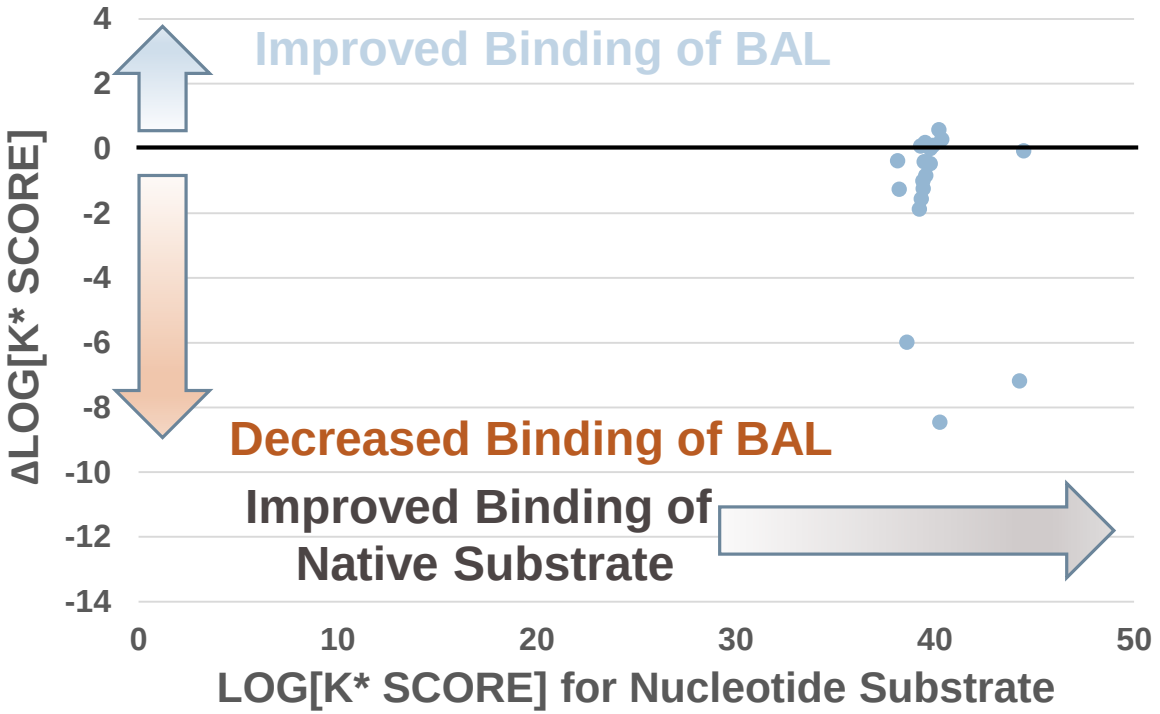


USEFUL TO PREDICT ACTIVITY AGAINST VARIANT STRAINS

Simulation of All I38 Mutations: Considering Native Substrate Affinity

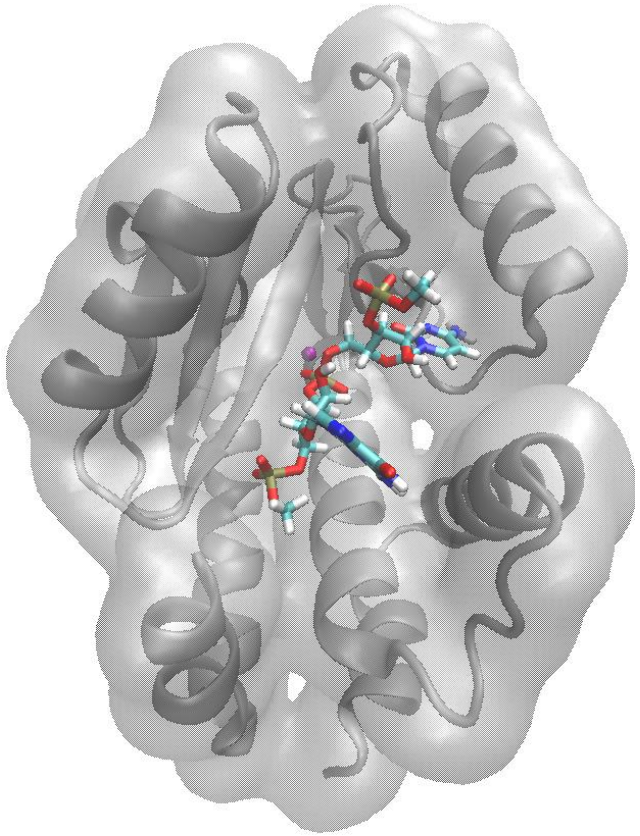
Model of Di-Nucleotide Substrate Bound to Flu A H1N1 PA

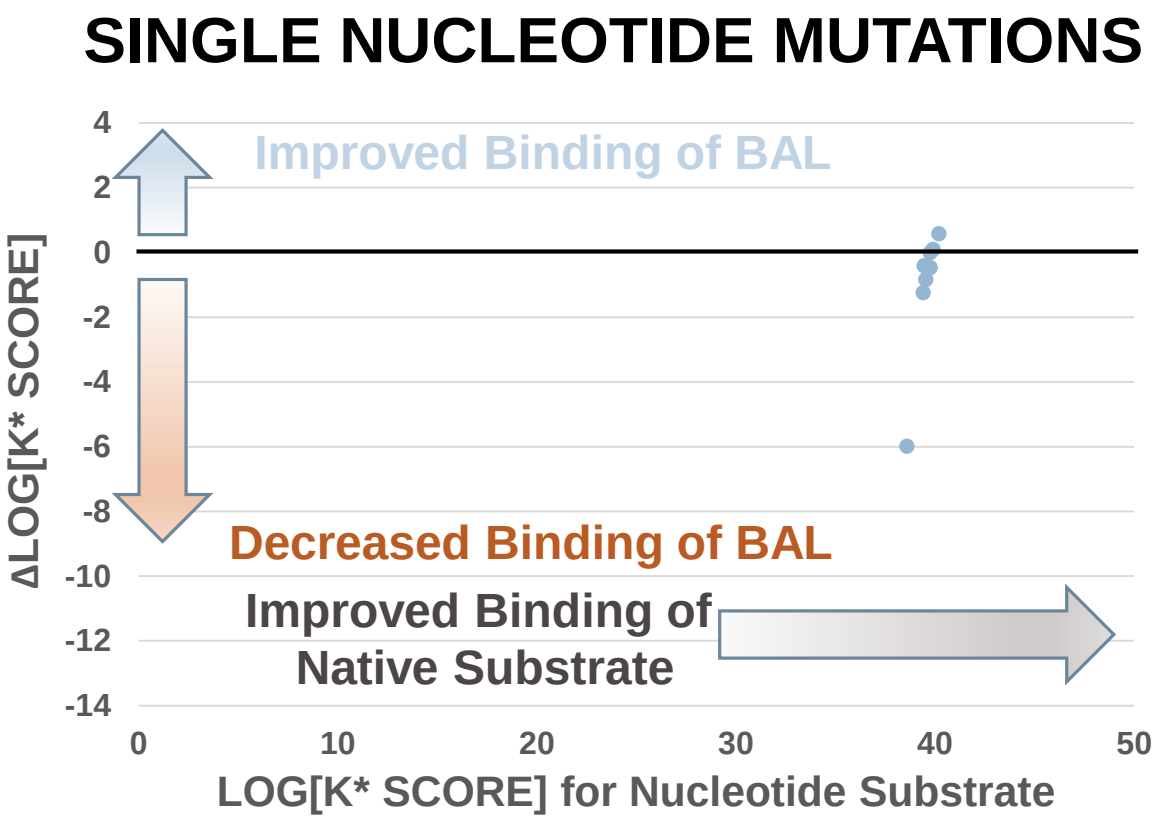




Simulation of All I38 Mutations: Accessible by Low Genetic Barrier

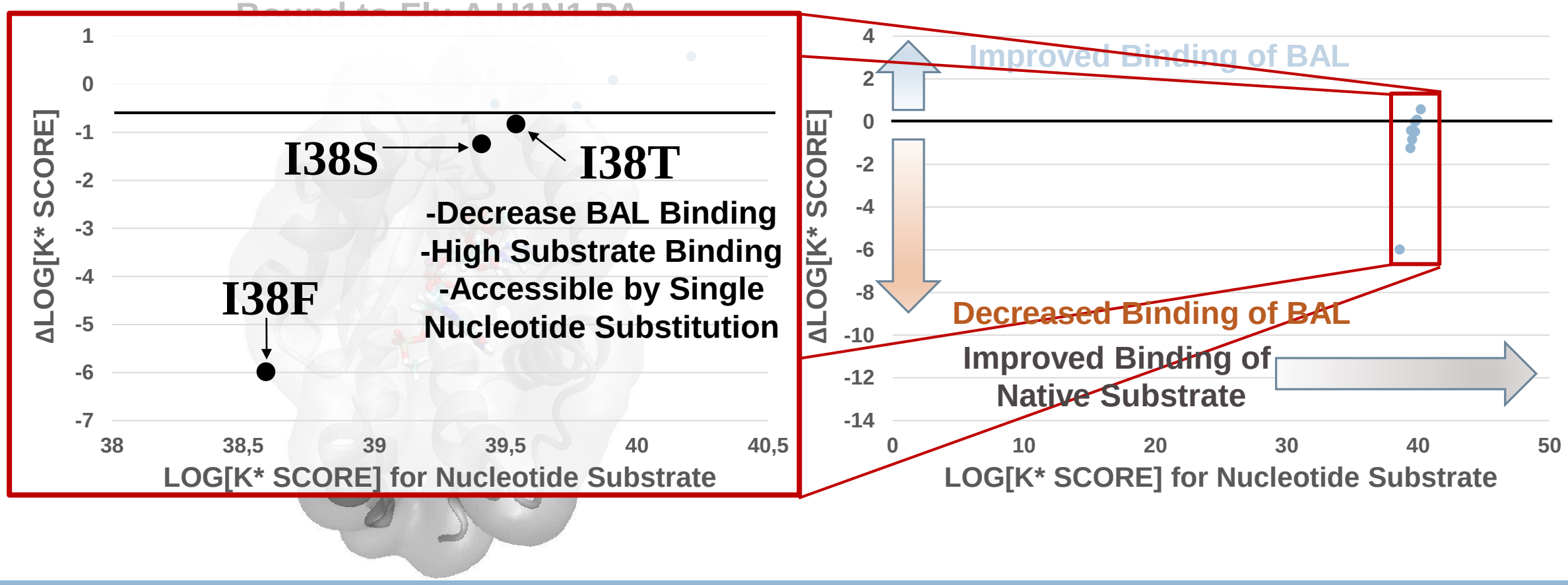
Model of Di-Nucleotide Substrate Bound to Flu A H1N1 PA



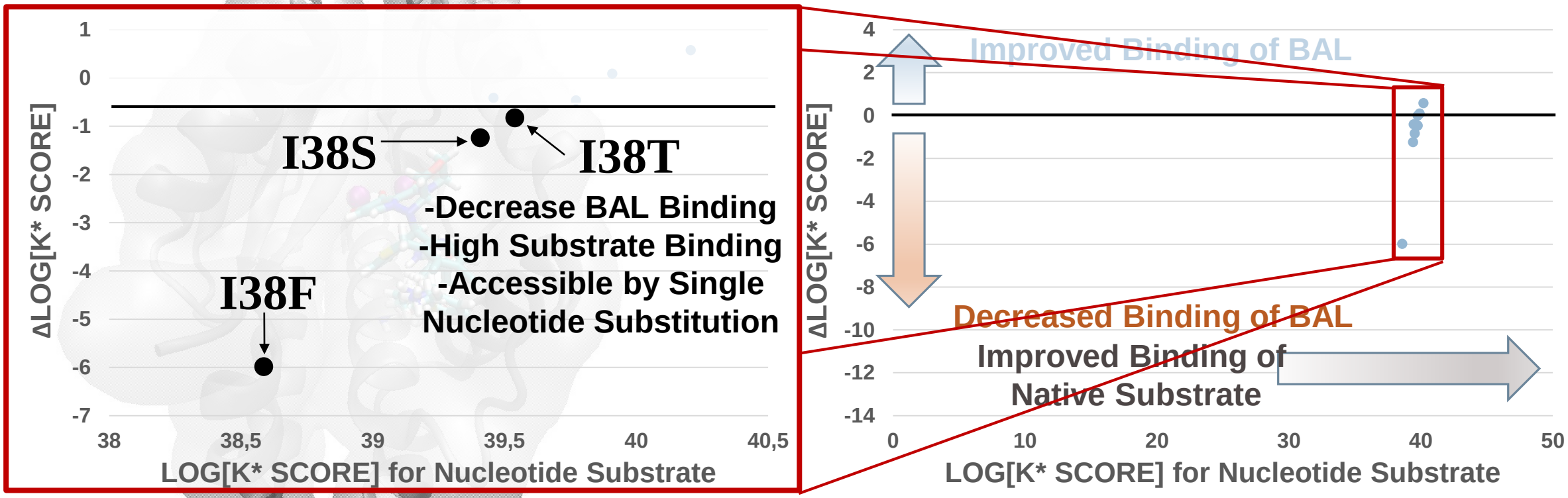


Simulation of All I38 Mutations: Single-Nucleotide Accessible Mutations

Model of Di-Nucleotide Substrate
Bound to Flu A H1N1 PA

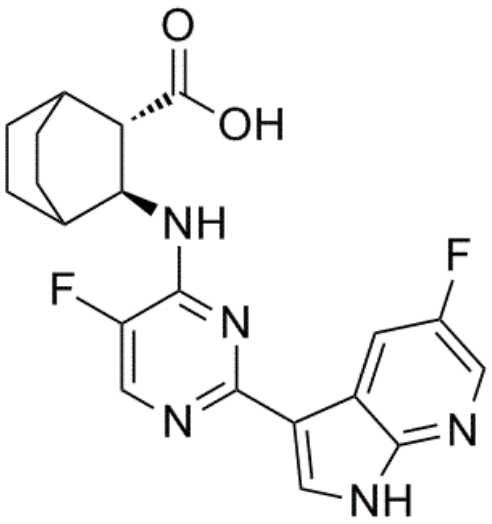


Simulation of All I38 Mutations: Single-Nucleotide Accessible Mutations

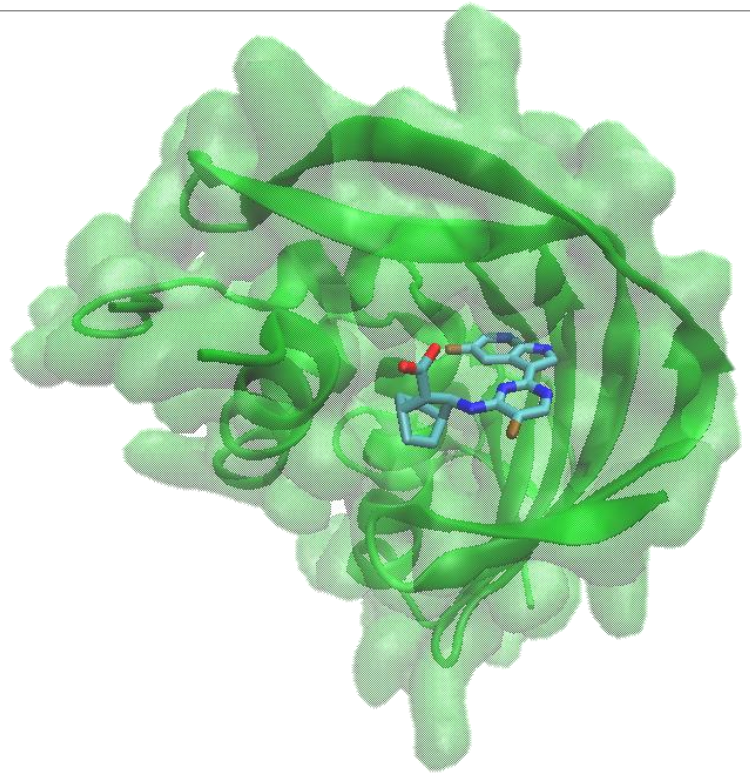


Correctly Identified I38T As a Likely Resistance Mutation for Baloxavir Marboxil

Predicting Resistance Mutations for Pimodivir - Influenza A PB2 Inhibitor



VX-787 (Pimodivir)



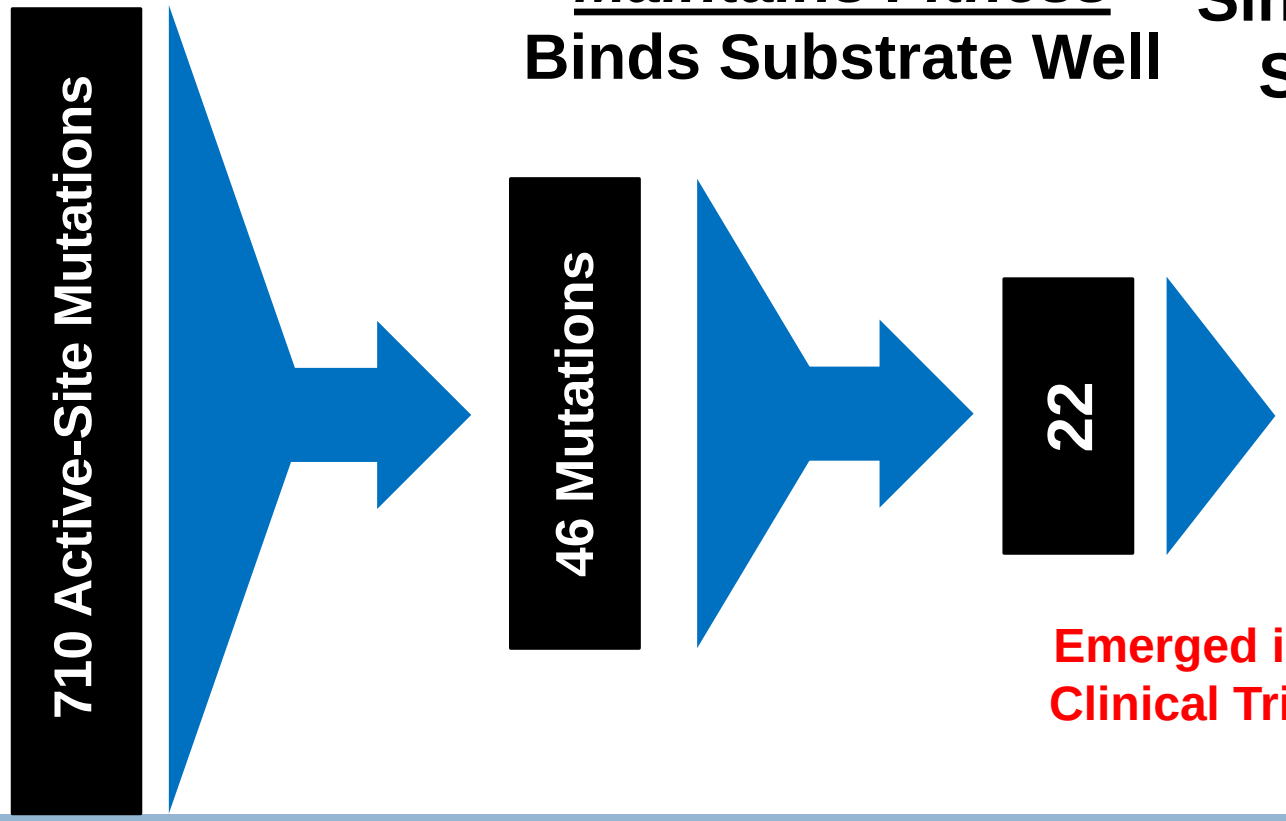
Model of Pimodivir Bound To Avian H5N1 FluA PB2

Predicting Resistance Mutations for Pimodivir - Influenza A PB2 Inhibitor

Reduced Inhibitor Binding from WT

Maintains Fitness
Binds Substrate Well

Low Genetic Barrier
Single Nucleotide Substitution?



Emerged in Clinical Trial →

Res	WT	Resistant
323	PHE	L M V
325	PHE	V
339	LYS	D E
357	HIS	D E
404	PHE	M Y
431	MET	I
510	ASN	I T Y

Incorporating Resistance Prediction into Drug Design Platform

COMPUTATIONAL DESIGN
In Silico Library Enumeration
Targeted Modifications
Virtual Screening/Docking
WT Potency Prediction (FEP)

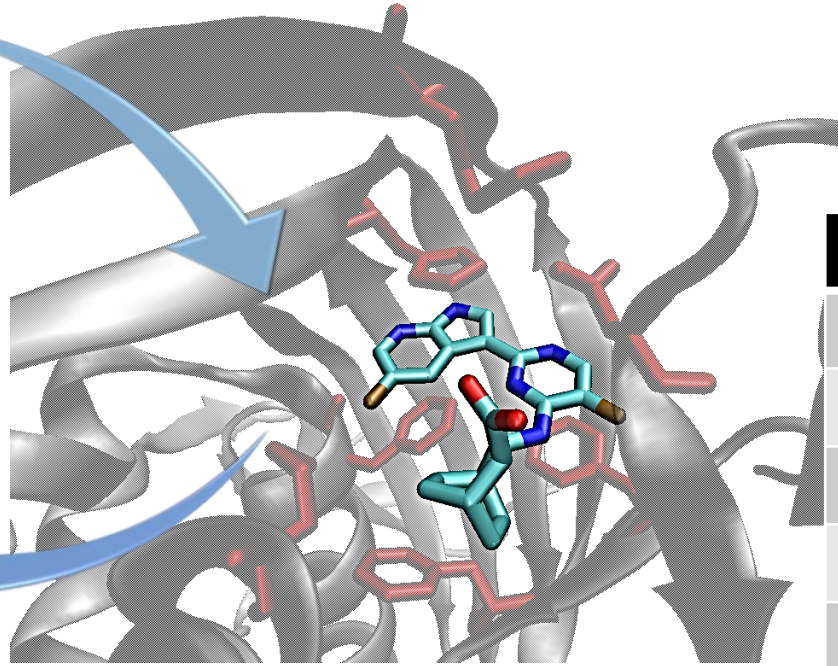
NO

Desired Resistance Profile?

YES

SYNTHETIC CANDIDATE

RESISTANCE MUTATION PROFILE



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431	MET	I
510	ASN	I T Y

Summary and Conclusions

Developed approach to *de novo* predict resistance mutations given only an inhibitor-bound structure

- Successfully applied to other viruses (HIV-1, HBV, HCV and ZIKV)
- Recapitulated resistance mutations for Baloxavir Marboxil and Pimodivir

Useful tool in antiviral drug design

- Rational design of broadly active agents against all strain variations
- Rational design of agents with improved resistance profiles
- Rational design of drug combinations that ensure no single mutation delivers cross-resistance to all agents

Future Directions and Other Applications

- Allosteric mutations not in direct contact with inhibitor
- Compensatory mutations that improve substrate binding
- Antibody escape mutations

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- Keivan Zandi, PhD

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