Targeting Viral Envelope Proteins: An Application to the Zika Virus

Arul Prasad
Mentor: Dr. Gil Alterovitz
May 22nd, 2016
MIT PRIMES Conference

Motivation

Zika is part of an emerging trend of infectious diseases that we have witnessed in recent years: drug resistant TB, MRSA, SARS, H1N1, etc.

We need a quick, automated solution, that can quickly filter and select molecules for testing immediately as new infectious diseases arise.
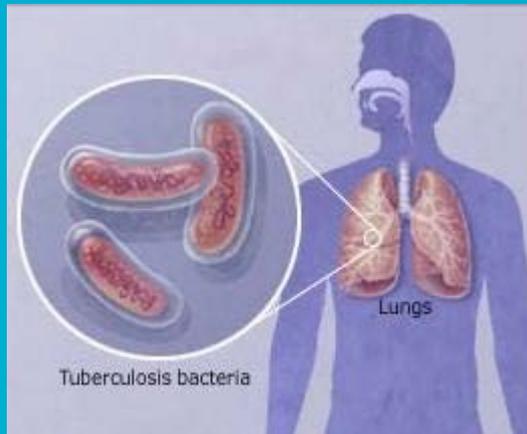
Background

➢Zika is transmitted through mosquito bites (*Aedes*)

➢Flavivirus genus

➢Connected to microcephaly and Guillain-Barre syndrome

The Spread Of The Zika Virus
Countries and territories with active Zika virus transmission* and reported cases

- Reported active transmission
- Zika case(s) currently reported
- Zika reports prior to 2015
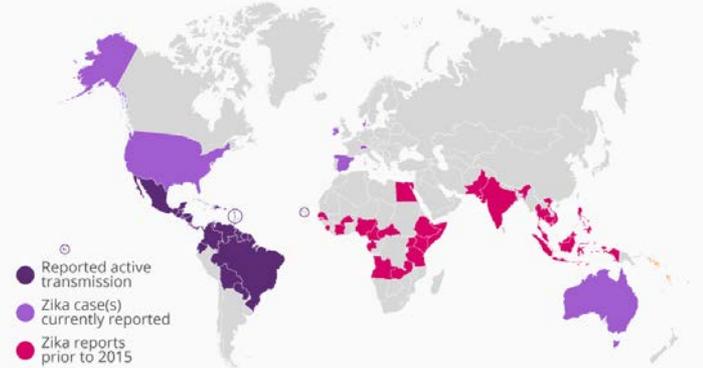
Source: Centers for Disease Control and Prevention
*As of February 2016
@Statista_com

statista

Zika virus transmission cycle

Symptoms
- Fever
- Rash
- Joint pain
- Conjunctivitis (red eyes)

Person infected with Zika virus

Possible transmission from mother to baby during pregnancy

Infected mosquito bites another person and transmits virus

Aedes mosquito bites infected person
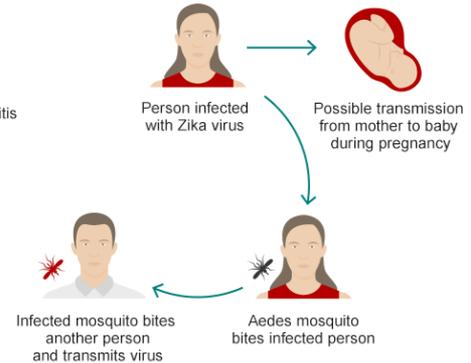
Zika can be transmitted through blood, but this is an infrequent mechanism.
The virus has also been isolated in semen, but person-to-person sexual transmission is unconfirmed.

Source: PAHO/WHO

BBC

Virus attachment
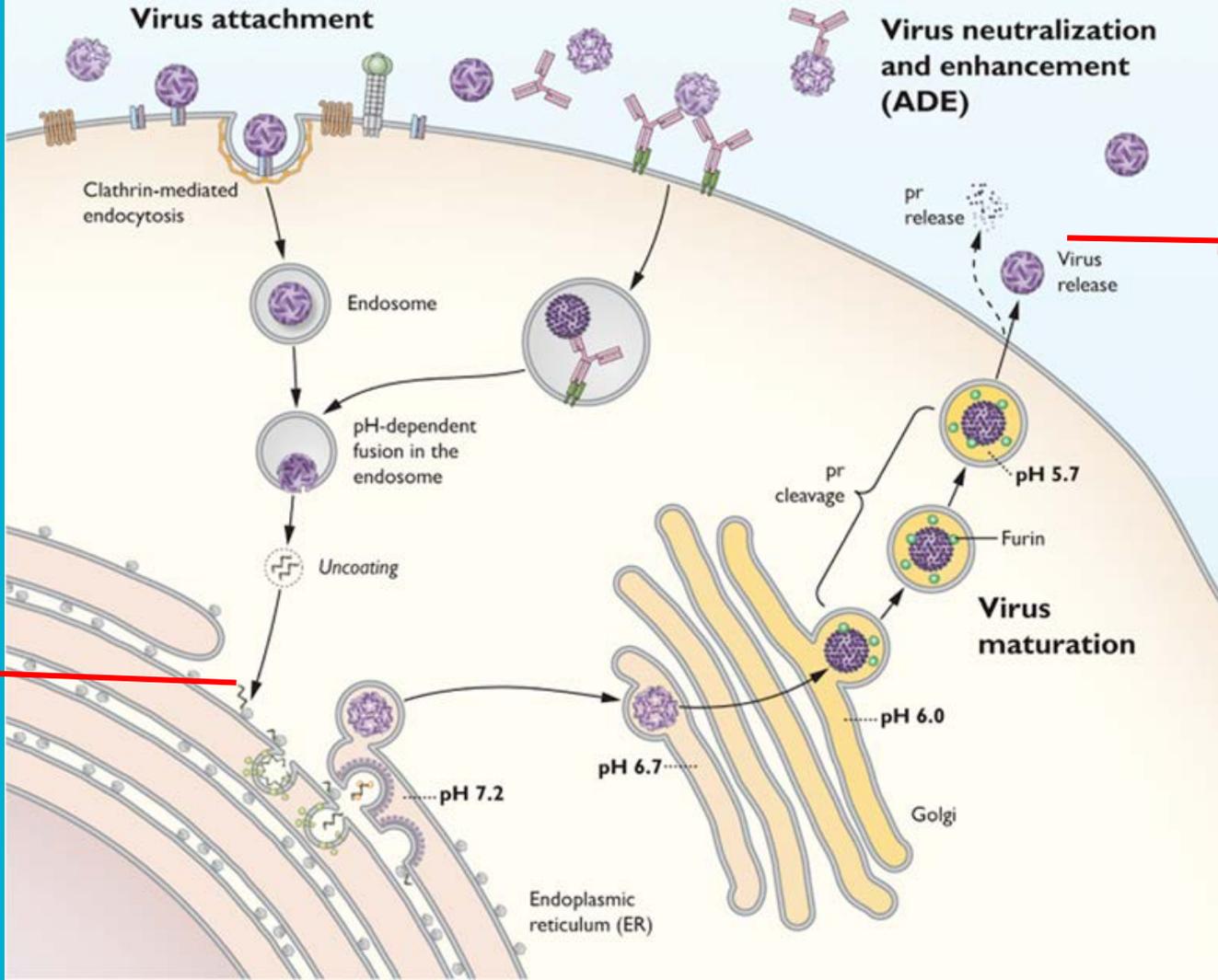
Virus neutralization and enhancement (ADE)

Clathrin-mediated endocytosis

Endosome

pH-dependent fusion in the endosome

Uncoating

Endoplasmic reticulum (ER)

pH 7.2

pH 6.7

pH 6.0

Golgi

Furin

pr cleavage

Virus maturation

pH 5.7

pr release

Virus release

Mature virus infectious

Immature virus non-infecticus
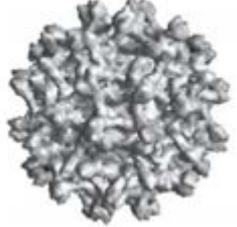
Virus Structure
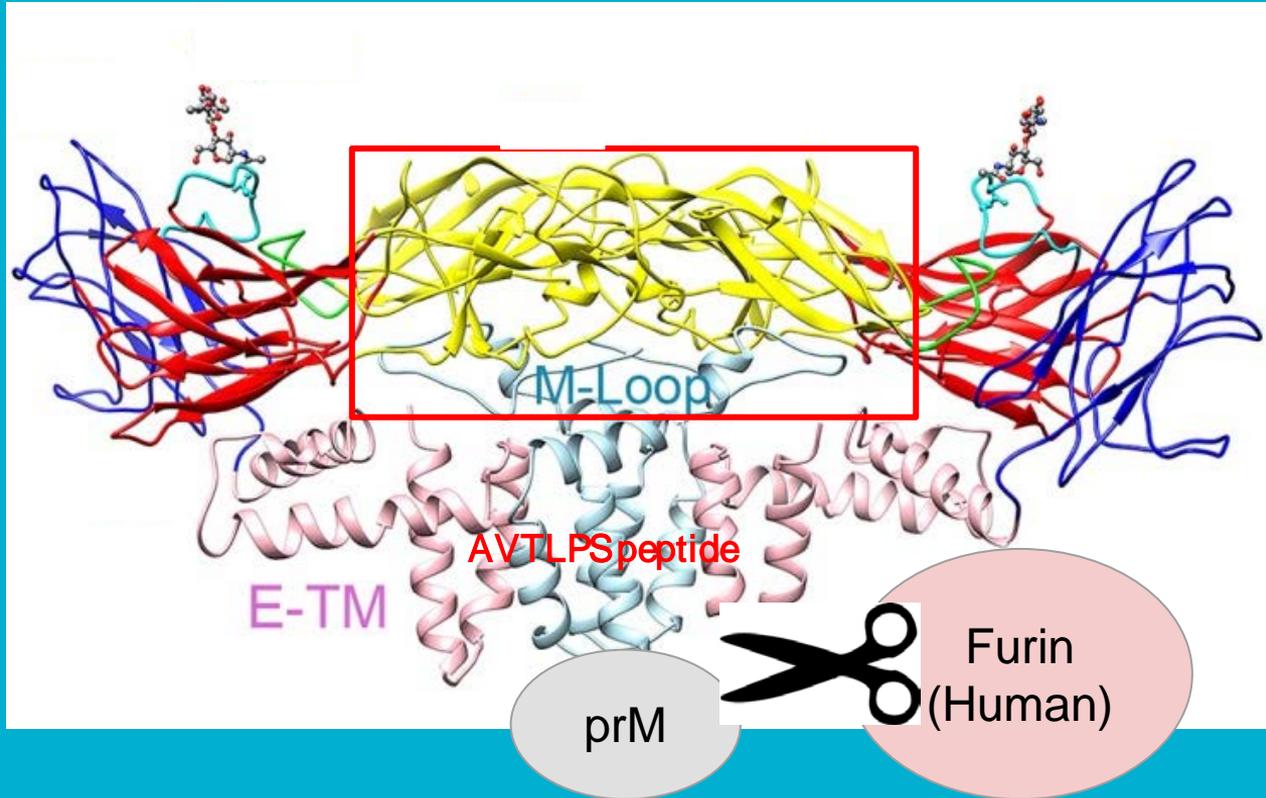
Solution

Inhibit the interaction between human Furin protein and the AVTLPSpeptide in the envelope protein of the Zika virus.

➢Prevent activation of the virus

➢This can be applied to many other viruses as well (Dengue)

Methods

1. Isolate AVTLPS peptide and surrounding envelope protein from Zika protein structure

2. Implement Support Vector Machine (svm) pipeline to screen through 7,863 FDA approved drug compounds with high binding probabilities to the region

3. Determine docking score of proposed drugs with envelope protein

Primary protein structure
is sequence of a chain of amino acids

Amino Acids

Phe Leu Ser Cys

Amino group
NH₂
H—C—COOH
R
R group
Acidic
carboxyl
group

Amino Acid

SVM Pipeline

| Implement Machine Learning Model	→	Train using Pubchem Bioassay Database	→	Determine 3D similarity of drug compounds	→	Determine binding probabilities to Virus Envelope target
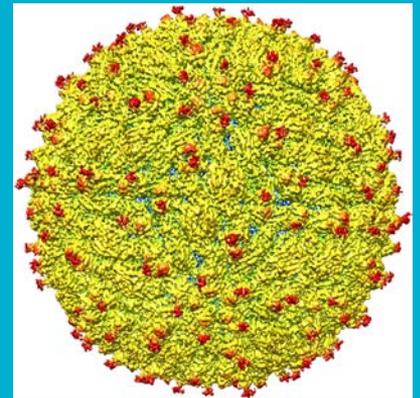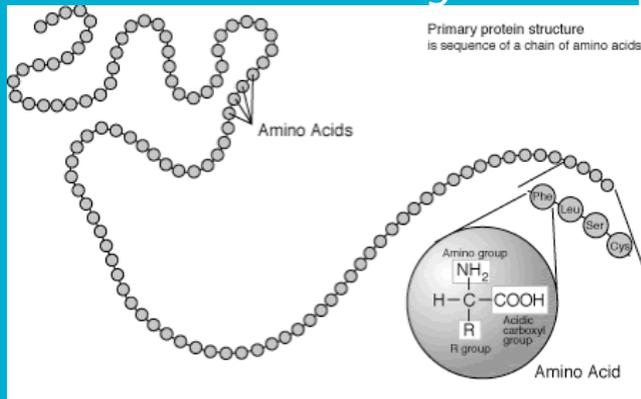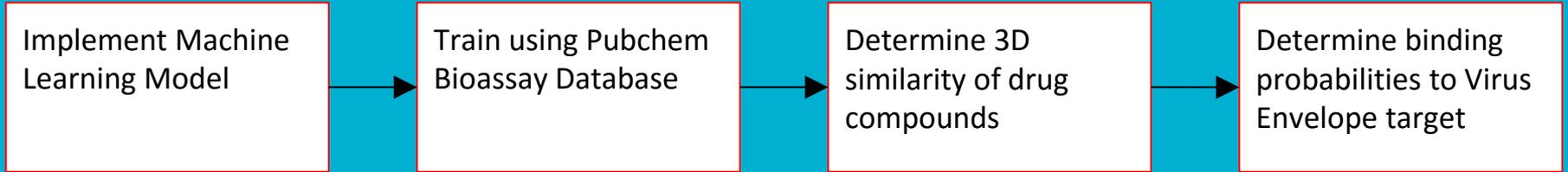
Results (Binding Probability)

➢Previously for TB, a 0.897 binding probability was successful in lab testing

Drug	Binding Probability	Name	Toxicity
	0.917	ZINC96006099	None
	0.895	ZINC96006113	None
	0.890	ZINC53683653	None
	0.888	AZINC08214629	None
	0.887	AZINC03830276	None
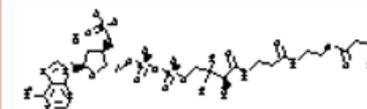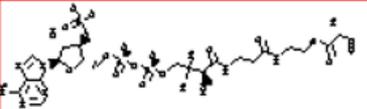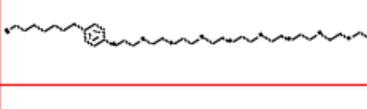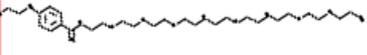
Docking

➢ Test drug compounds with top five binding probabilities

➢ Binding simulations of drug to structure
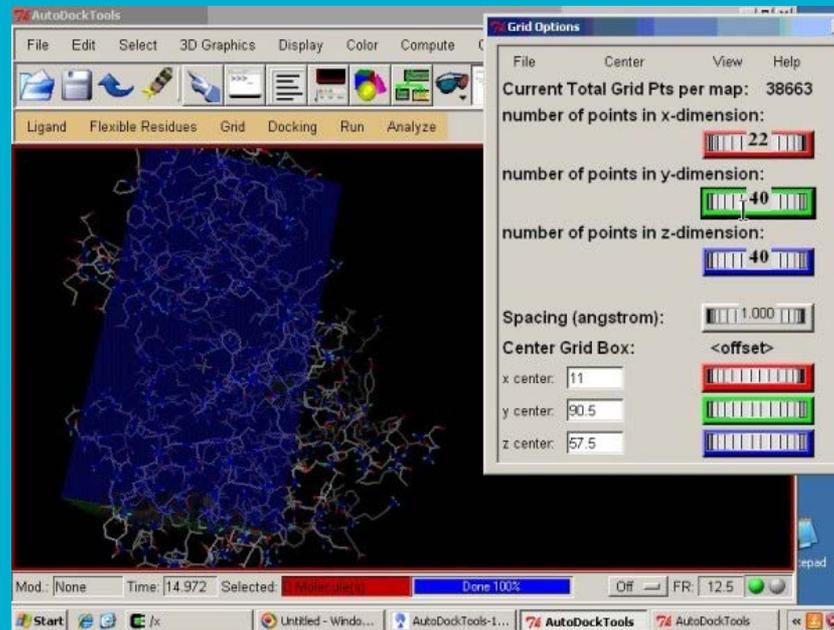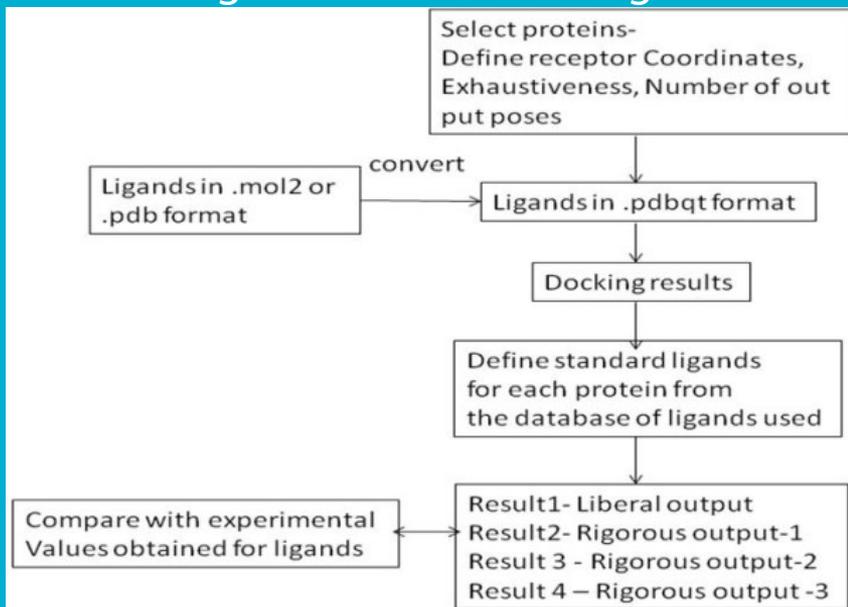
Results (Docking Score)

Drug	Binding Probability	Name	Docking Score
	0.917	ZINC96006099	-5.8
	0.895	ZINC96006113	-5.4
	0.890	ZINC53683653	-6.7
	0.888	AZINC08214629	-3.6
	0.887	AZINC03830276	-3.7
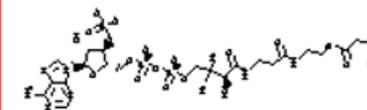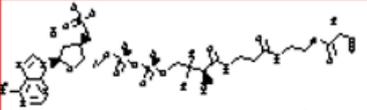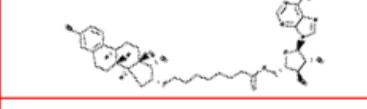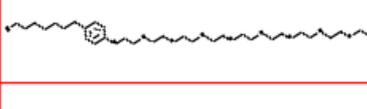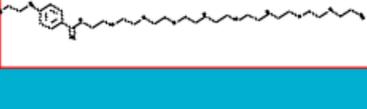
Discussion

➢ ZINC53683653 has highest docking score of -6.7
  ○ Molecular weight: 677.843 g/mol

➢ ZINC96006099
  ○ Docking score: -5.8
 ○ Molecular weight: 849.599 g/mol

➢ ZINC96006113
 ○ Docking score: -5.4
  ○ Molecular weight: 862.574 g/mol
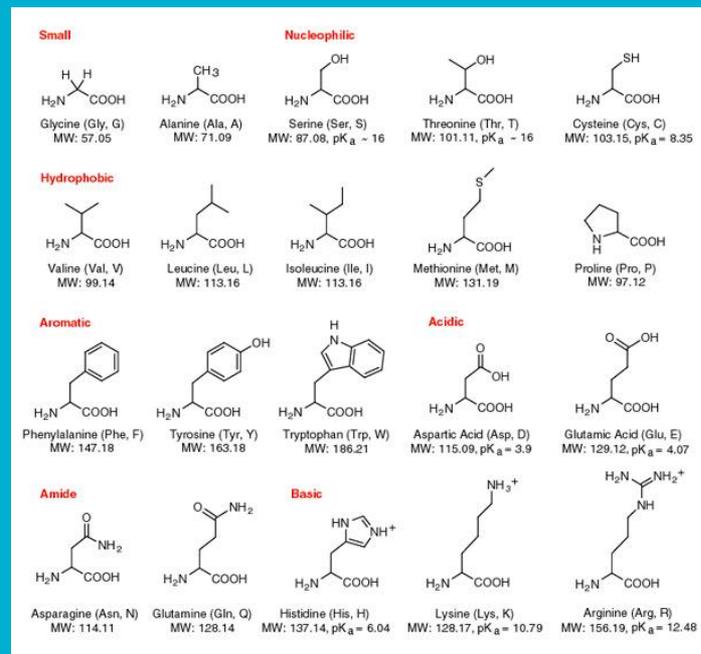
Conclusion

ZINC53683653 is the best candidate FDA approved drug compound available to fight the Zika virus.
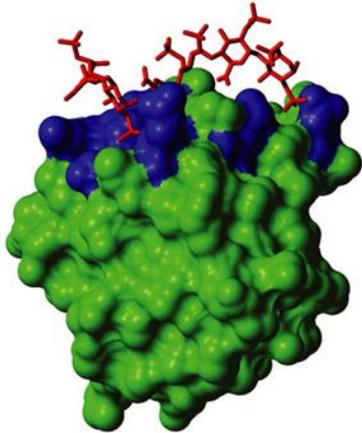
Nature Reviews | Cancer

Drug – Protein binding
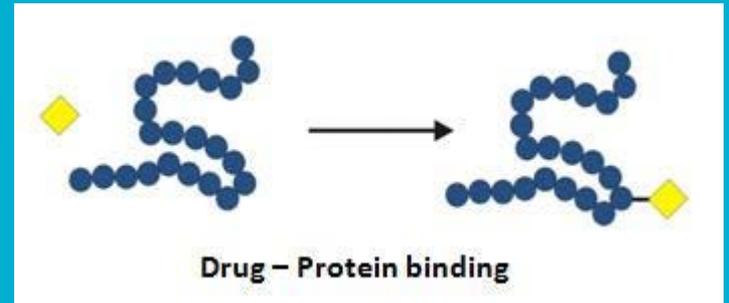
Future Work

➢Modify drug compounds to enhance docking score

➢Send proposed drug compounds to real life lab testing

➢Apply methods to other viruses

  ○ Furin used in many virus activation cycles

Acknowledgements

➢ MIT PRIMES program

➢ Mentor: Dr. Gil Alterovitz

➢ PRIMES group

➢ Previous RSI/PRIMES students

➢ Parents

THANK YOU