Study of various synergistic drug mechanisms in disordered protein-related diseases

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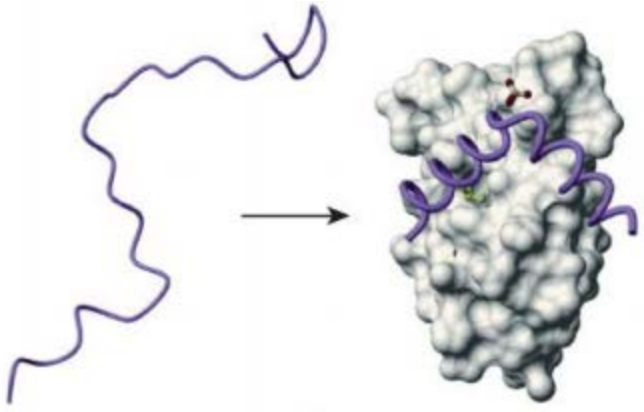
Intro – Disordered Proteins & Disease

- Intrinsically Disordered Proteins are highly prevalent in certain diseases, especially:
  - Cancer
  - Neurodegenerative Disease
  - Cardiovascular disease (CVD)
  - Diabetes
- The Molecular Recognition Feature (MoRF) is a disordered region involved w/ binding

A 3-D model of hemagglutinin, an IDP

Intro – Drug Synergy

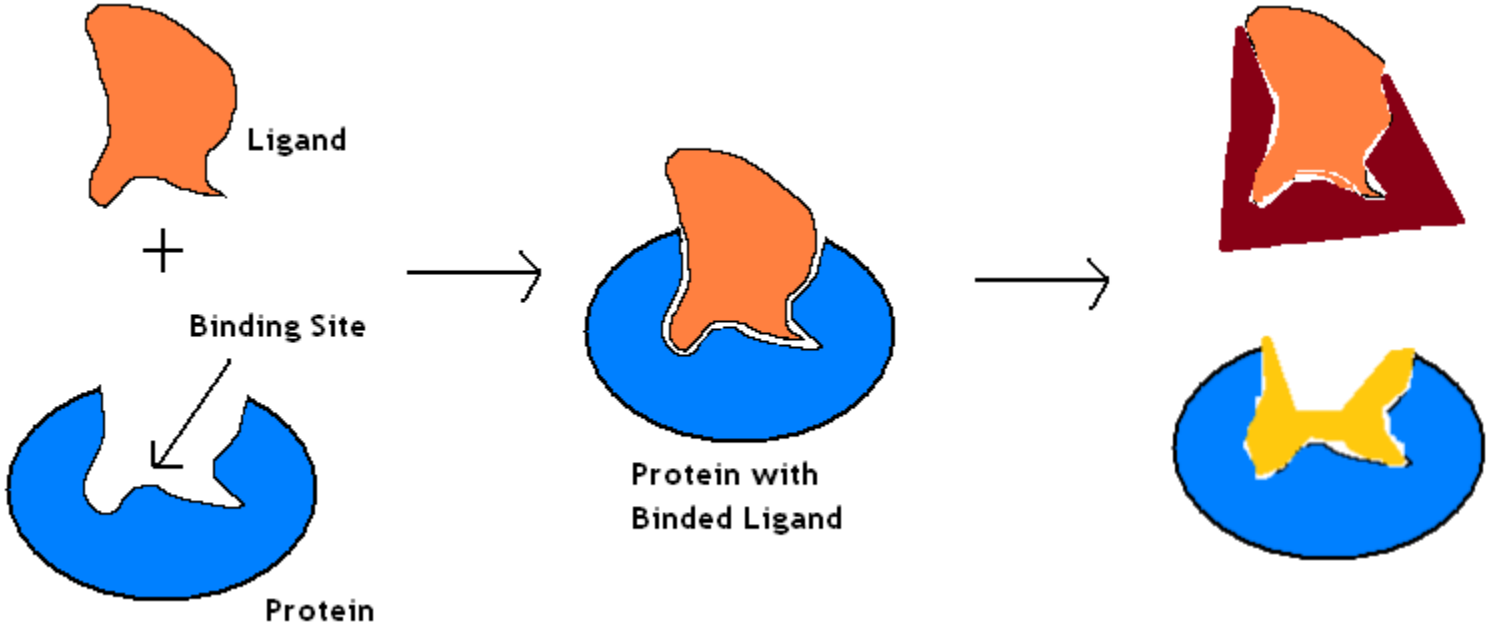
- Administering many drugs together doesn't always produce additive effect
- Drug Synergy is when two or more administered drugs have a more than additive effect.



IDP binding to ordered protein

Intro – Drug Synergy

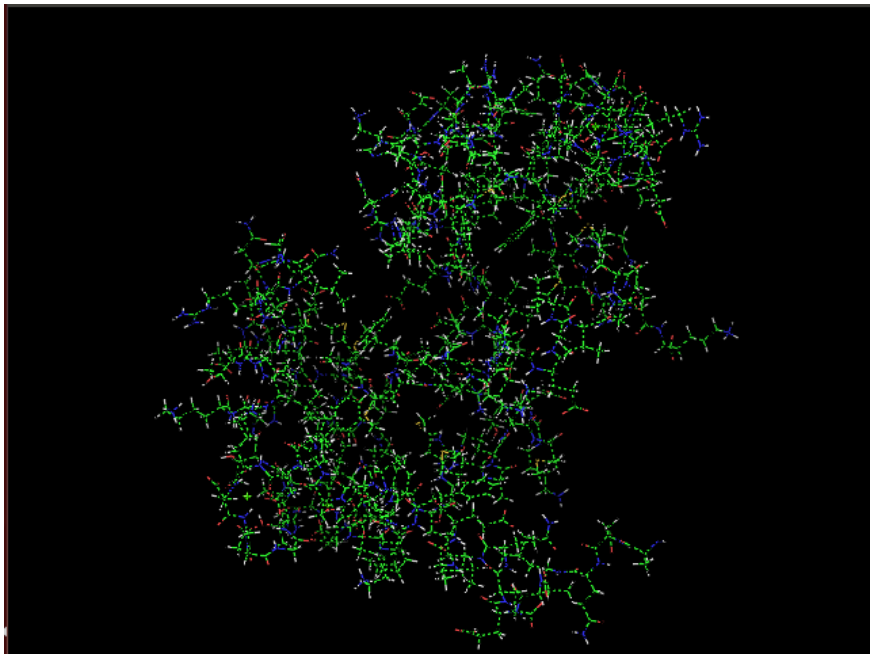
- Synergy by binding to both the MoRF and its interactor



- Also by attacking different steps of the disease

Methods – Drugs Mimicking MoRF

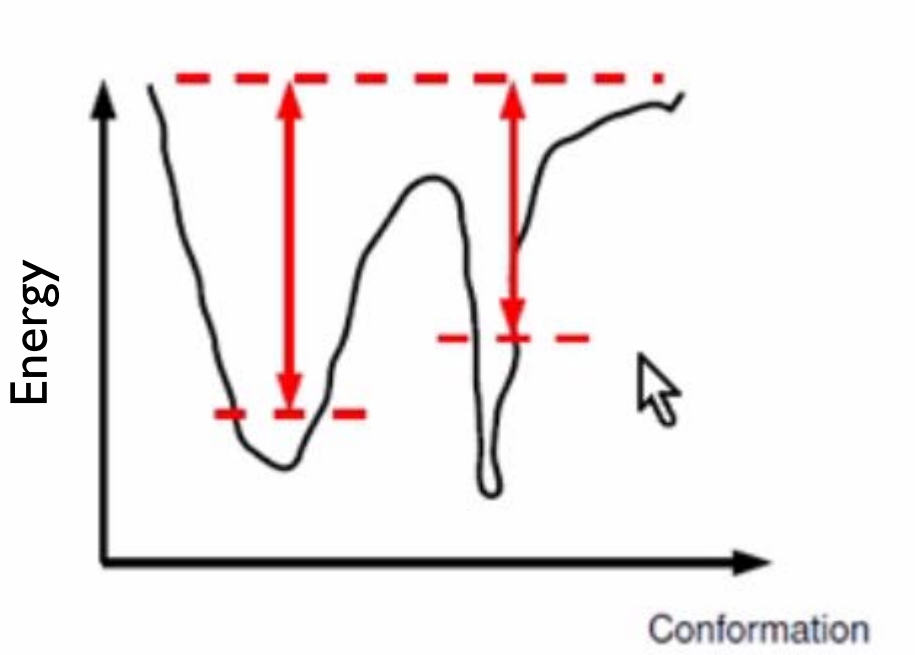
- How do you find drugs to mimic the MoRF?
  - Find 3-D Structure Model (Protein Data Bank) of IDP
  - Isolate MoRF
  - Compare drugs to MoRF (Spectrophore)
  - Sort drugs as effective or ineffective (Support Vector Machine)



3-D rendering of an IDP

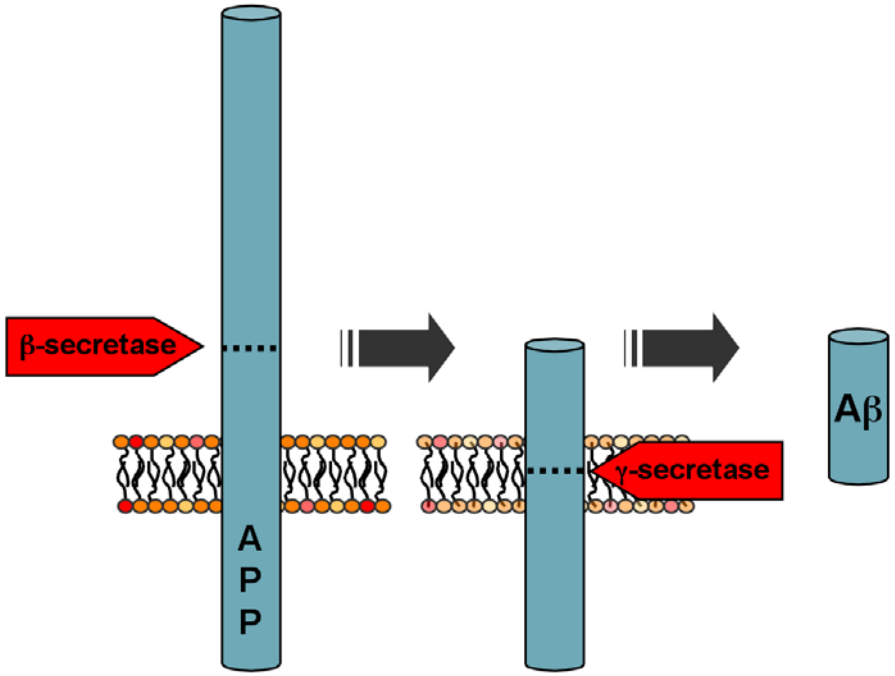
Methods – Docking

- Finding Drugs that will bind
  - Find 3-D Structure (PDB) of Protein & Drug
  - Calculate binding affinity: how much energy is released



Results – Alzheimer's Disease

- Alzheimer's is a neurodegenerative disease that causes memory loss
- Amyloid-beta (Aβ) is an IDP highly implicated in the disease



Production of Amyloid-β with β-secretase from Amyloid Precursor Protein (APP)

Results – Alzheimer's Disease

- Beta-secretase binds to GGA1 for transport
- Amyloid-β binds to leukocyte

immunoglobulin-like receptor B2 (LilrB2)

- <u>Results for Synergy</u>

Beta-secretase & GGA1

Mimicking Beta-secretase (c-terminus), binding to GGA1 VHS site

Drug Name	Predicted Similarity	Binding Affinity
RU83876	0.912	-7.2

Mimicking Amyloid-β, binding to LilrB2

Drug ID	Predicted Similarity	Binding Affinity
ZINC_16051964	0.917	-7.6

Results – HIV

- Human Immunodeficiency Virus (HIV) is a STD, global epidemic

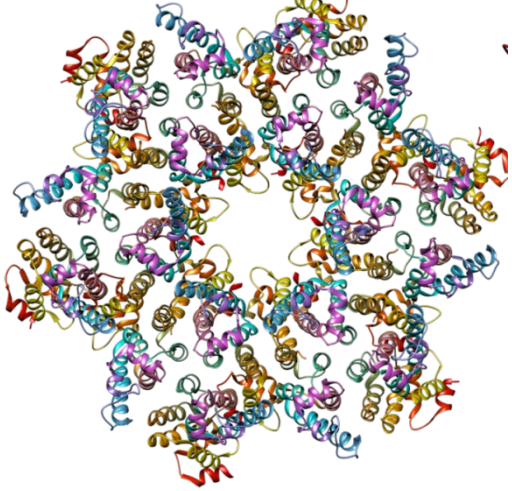


Diagram of HIV-1 nucleocapsid

- HIV-1 nucleocapsid is a disordered protein
  - Binds to DNA and RNA strands to propagate disease

- <u>Results for Synergy</u>

Mimics c-TAR DNA and binds to hiv-1 nucleocapsid (NC)

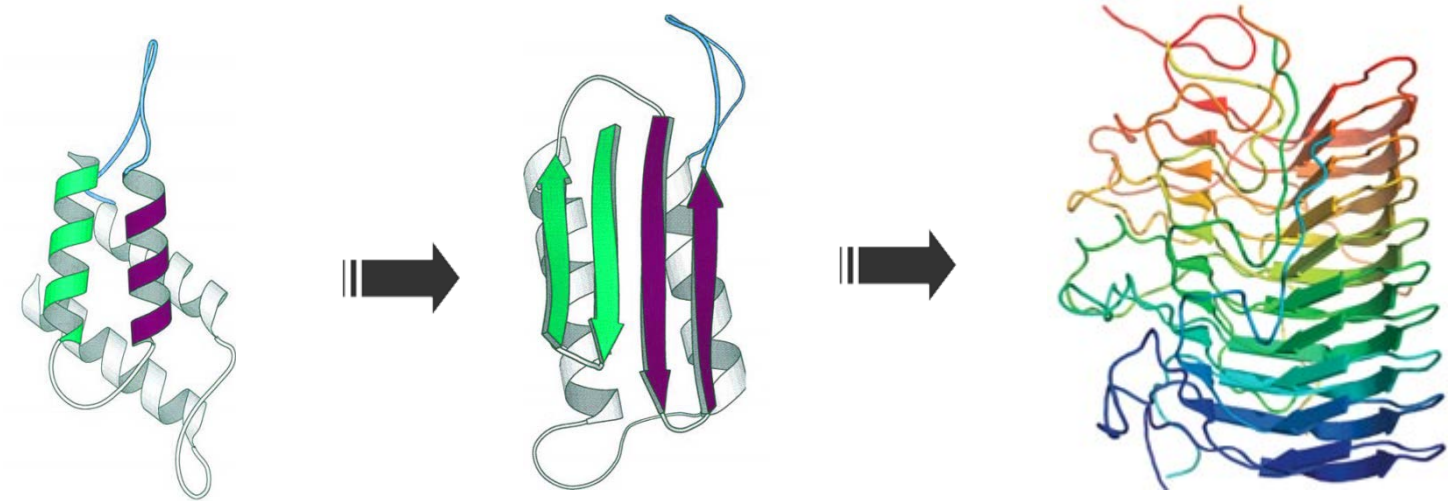
Drug Name	Predicted Similarity	Binding Affinity
Adenosine pentaphosphate	0.924	-6.7

Mimics zinc fingers of hiv-1 nucleocapsid (NC), binds to DNA

Drug Name	Predicted Similarity	Binding Affinity
RU83876	0.900	-6.5

Results – Prion diseases

- PrP (major prion protein)
  - PrP^{C} stands for Common or Cellular, properly folded
  - PrP^{Sc} stands for Scrapie, causes disease, protease-resistant
- PrP^{Sc} aggregate extracellularly, forming amyloid plaques



PrP^{C} PrP^{Sc} amyloid plaque

Mimics human prion 61-84 aggregation site to bind to whole human prion protein

Drug ID	Predicted Similarity	Binding Affinity
ZINC_53683321	0.917	-7.2

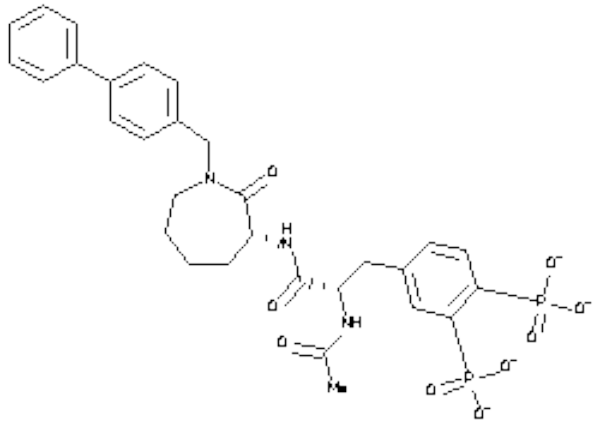
Full Results

Disease	Drug Name (ZINC_ID)	Structural Similarity (probability out of 1)	Binding Affinity (kcal/mol)
HPV	RU83876 (ZINC_53683662)	0.89398	-9.1
	4-(N,N-Dimethylamino) Cinnamoyl-Coa (ZINC_96006116)	0.89907	-8.2
Alzheimer's	RU83876 (ZINC_53683662)	0.91188	-7.2
	[1-Hydroxy-2-(1,1':3',1"-Terphenyl-3-Yloxy)Ethane-1,1-Diyl]Bis(Phosphonic Acid) (ZINC_16051964)	0.91684	-7.6
Myc-Max Cancer	10058-F4 (ZINC_2536881)	-proven-	-proven-
	Trans-6-(2-Phenylcyclopropyl)-Naphthalene-2-Carboxamidine (ZINC_6581941)	0.92263	-8.0
Influenza	Sialic Acid (ZINC_3793840)	-proven-	-5.5
	3-(3,5-Dibromo-4-Hydroxy-Benzoyl)-2-Ethyl-Benzofuran-6-Sulfonic Acid [4-(Thiazol-2-Ylsulfamoyl)-Phenyl]-Amide (ZINC_95544211)	0.91723	-8.6

Full Results continued…

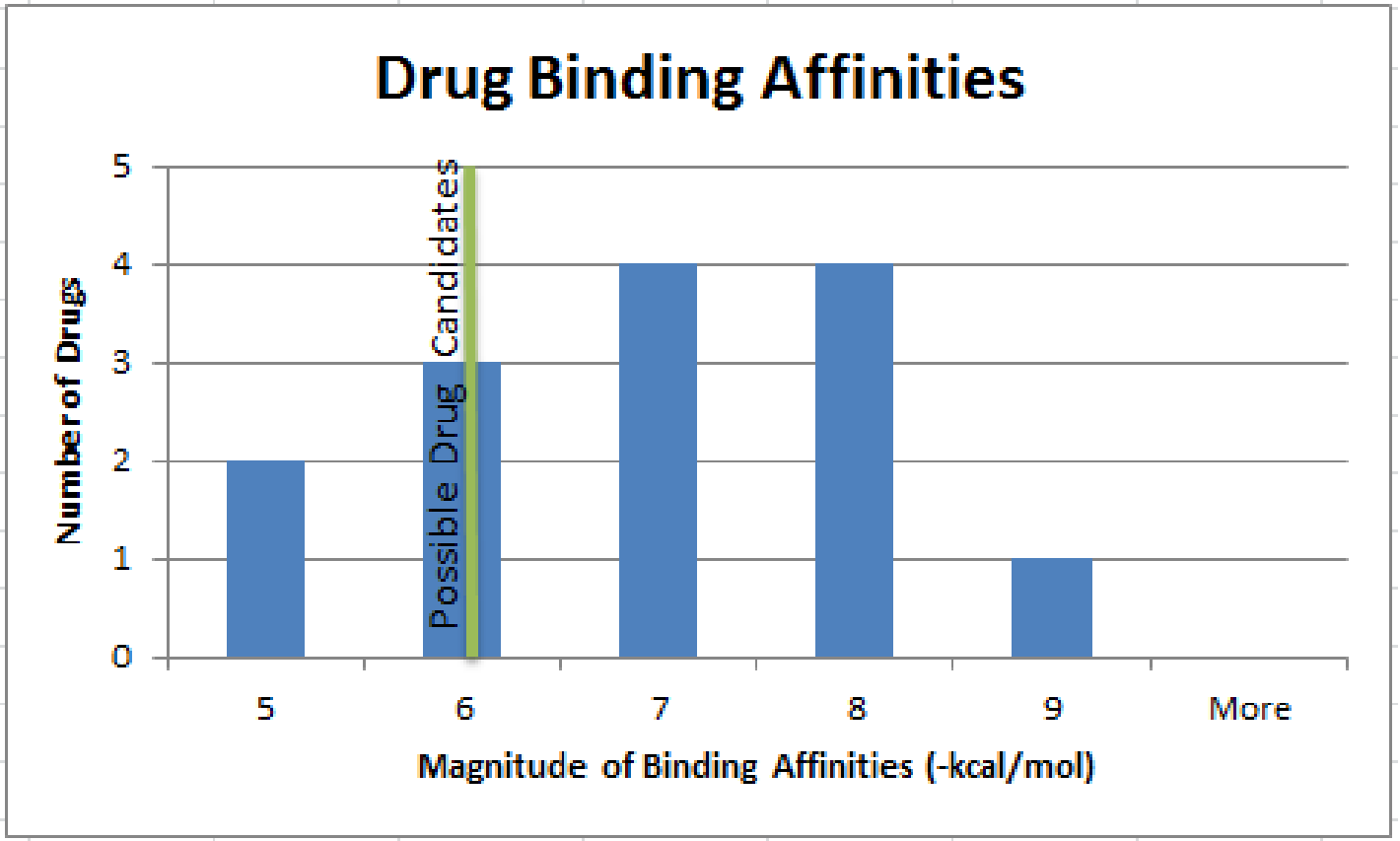
Disease	Drug Name (ZINC_ID)	Structural Similarity (probability out of 1)	Binding Affinity (kcal/mol)
HIV	Adenosine pentaphosphate (ZINC_58632138)	0.92387	-6.7
	RU83876 (ZINC_53683662)	0.89963	-6.5
E. Coli	Hexanoyl-Coenzyme A (ZINC_96006061)	0.91835	-6.3
	Uridine-5'-Diphosphate-N-Acetylmuramoyl-L-Alanine-D-Glutamate (ZINC_96006048)	0.89854	-8.8
Diabetes	P1-(Adenosine-5'-P5-(Uridine-5')Pentaphosphate (ZINC_96006101)	0.92460	-7.9
	Anthracene (ZINC_01586329)	0.92210	-5.8
Prion* Diseases (TSE's)	{4-[2-Acetylamino-2-(3-Carbamoyl-2-Cyclohexylmethoxy-6,7,8,9-Tetrahydro-5h-Benzocyclohepten-5ylcarbamoyl)-Ethyl]-2-Phosphono-Phenyl}-Phosphonic Acid (ZINC_53683321)	0.91683	-7.2

Multiuse Drug - RU83876



RU83876
(ZINC_53683662)

Results – Drug viability



- -6.5 kcal/mol is considered "lead candidate for drug development"
- 11 out of 14 drugs meet this threshold

Discussion – statistical significance

Disease	Drug Name (ZINC_ID)	p-Value (successes/total random trials)
HPV	RU83876 (ZINC_53683662)	3.33067e-16 (95/100)
	4-(N,N-Dimethylamino) Cinnamoyl-Coa (ZINC_96006116)	7.77156e-16 (96/102)
Alzheimer's	RU83876 (ZINC_53683662)	3.33067e-16 (97/100)
	[1-HYDROXY-2-(1,1':3',1"-TERPHENYL-3-YLOXY)ETHANE-1,1-DIYL]BIS(PHOSPHONIC ACID) (ZINC_16051964)	3.33067e-16 (95/100)
Myc-Max Cancer	Trans-6-(2-Phenylcyclopropyl)-Naphthalene-2-Carboxamidine (ZINC_6581941)	3.33067e-16 (92/100)
Influenza	3-(3,5-Dibromo-4-Hydroxy-Benzoyl)-2-Ethyl-Benzofuran-6-Sulfonic Acid [4-(Thiazol-2-Ylsulfamoyl)-Phenyl]-Amide (ZINC95544211)	3.33067e-16 (100/100)

Discussion – statistical significance

Disease	Drug Name (ZINC_ID)	p-Value (successes/total random trials)
HIV	Adenosine pentaphosphate (ZINC_58632138)	6.88338e-15 (87/100)
	RU83876 (ZINC_53683662)	4.44089e-16 (89/100)
E. coli	Hexanoyl-Coenzyme A (ZINC_96006061)	3.33067e-16 (98/100)
	Uridine-5'-Diphosphate-N-Acetylmuramoyl-L-Alanine-D-Glutamate (ZINC96006048)	3.33067e-16 (100/100)
Diabetes	P1-(Adenosine-5'-P5-(Uridine-5')Pentaphosphate (ZINC96006101)	3.33067e-16 (100/100)
	Anthracene (ZINC_01586329)	6.54932e-12 (83/100)
Prion	{4-[2-Acetylamino-2-(3-Carbamoyl-2-Cyclohexylmethoxy-6,7,8,9-Tetrahydro-5h-Benzocyclohepten-5ylcarbamoyl)-Ethyl]-2-Phosphono-Phenyl}-Phosphonic Acid (ZINC53683321)	3.33067e-16 (90/100)

Conclusion

- Promising results for drug pairs
- Future Work
  - Additional tests for Statistical Significance
  - Expanding Functionality of Pipeline
  - Inhibiting Aggregation like Prion Proteins
  - Wet Lab Validation

Conclusion

The plushie army of diseases out to get us

- Promising results for drug pairs
- Future Work
  - Additional tests for Statistical Significance
  - Expanding Functionality of Pipeline
  - Inhibiting Aggregation like Prion Proteins
  - Wet Lab Validation

Acknowledgements

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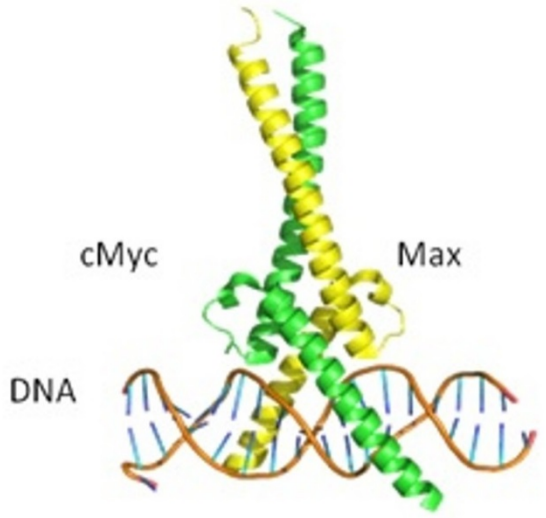
- Parents
- PRIMES & RSI alumni
- Other members of Dr. Alterovitz's PRIMES group

End

Drugs that Work



c-Myc-Max dimer recognizing DNA

- 10058-F4 with c-myc dimerization inhibition
- Sialic acid as an influenza inhibitor

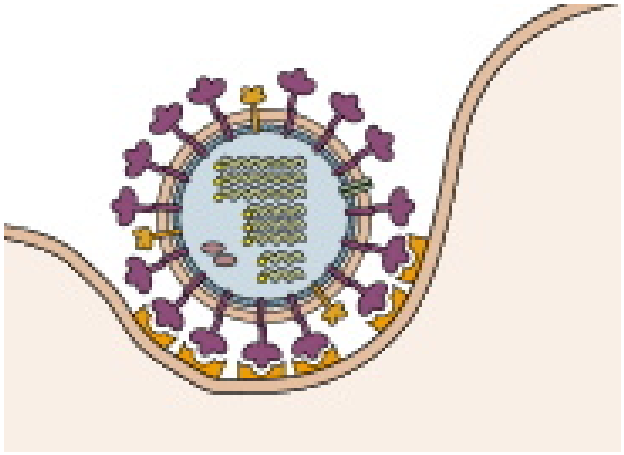


Diagram of hemagglutinin, an IDP for influenza

Extra Results – HPV

- Human Papillomavirus (HPV) is a STD, cancer
- E6 is an IDP of HPV
  - Interacts with E6-AP ubiquitin-protein ligase

- <u>Results for Synergy</u>

Mimicking E6, binding to E6AP

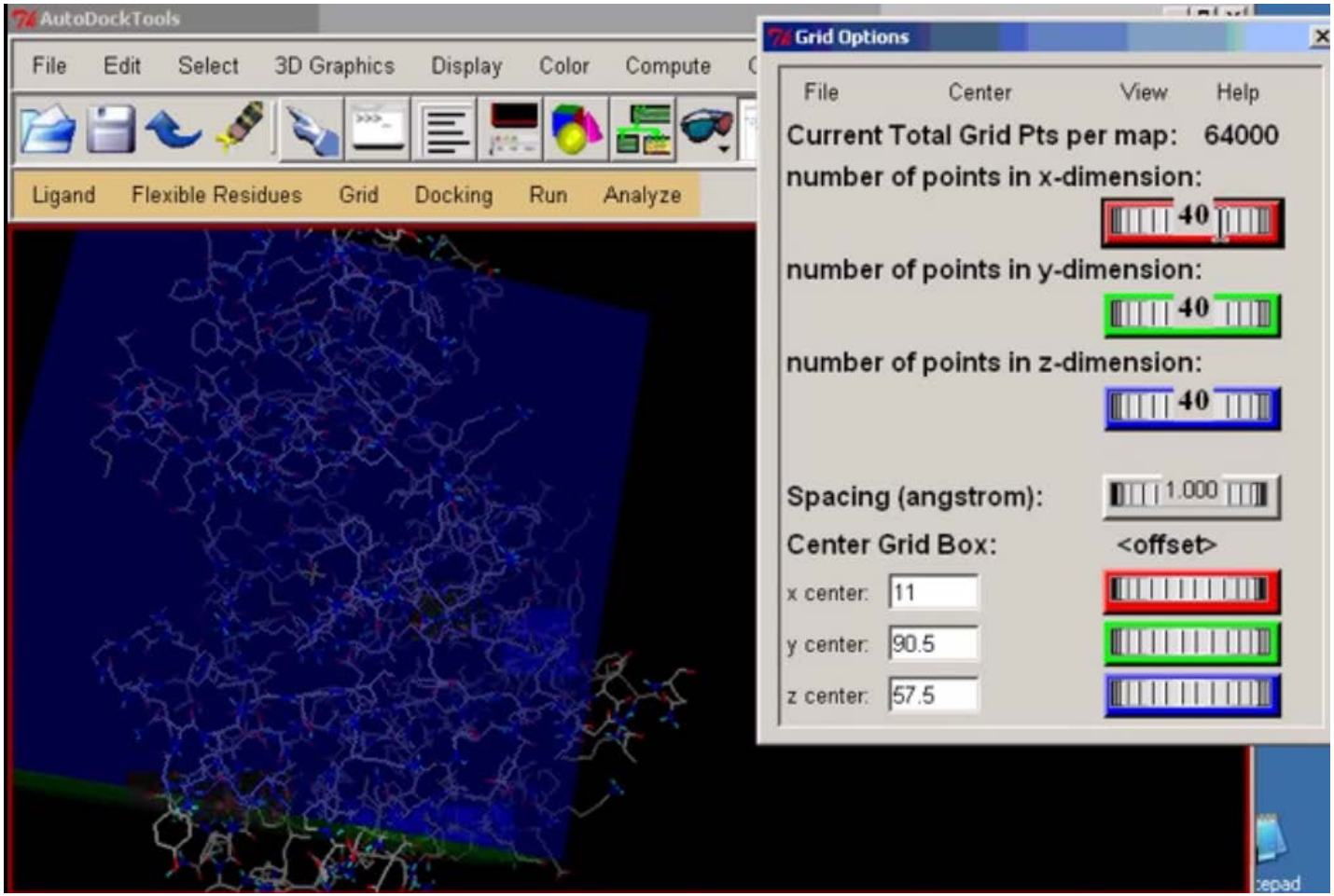
Drug Name	Predicted Similarity	Binding Affinity
RU83876	0.894	-9.1

Mimicking E6AP, binding to E6

Drug ID	Predicted Similarity	Binding Affinity
ZINC_96006116	0.899	-8.2

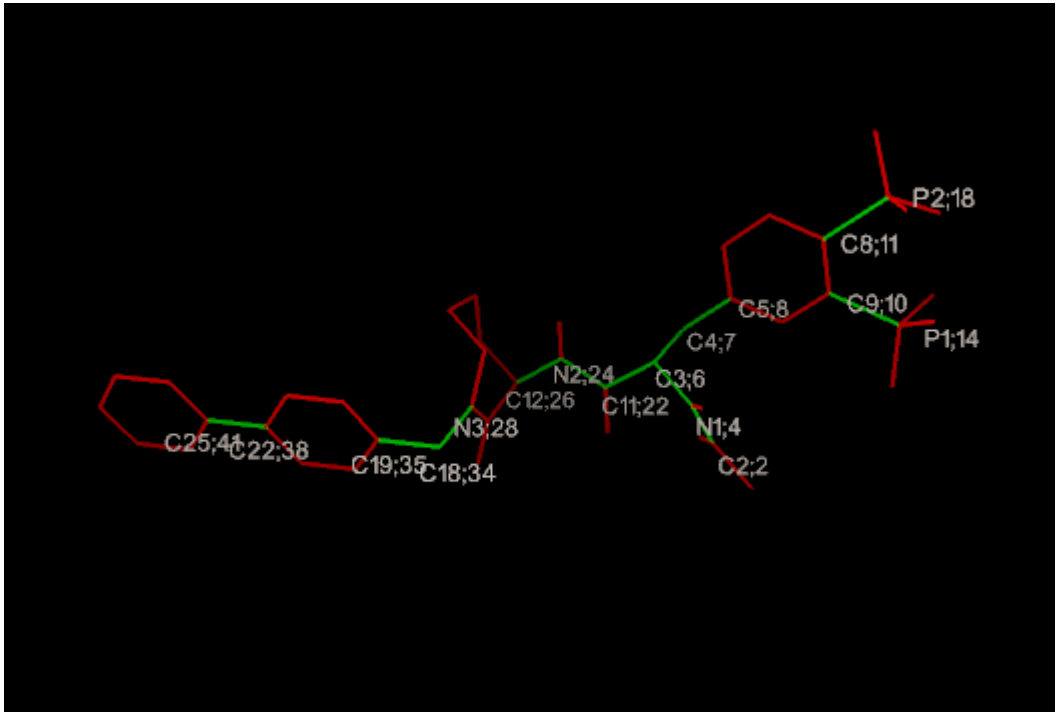
Extra Methods - Autodock

- Grid box determining binding region

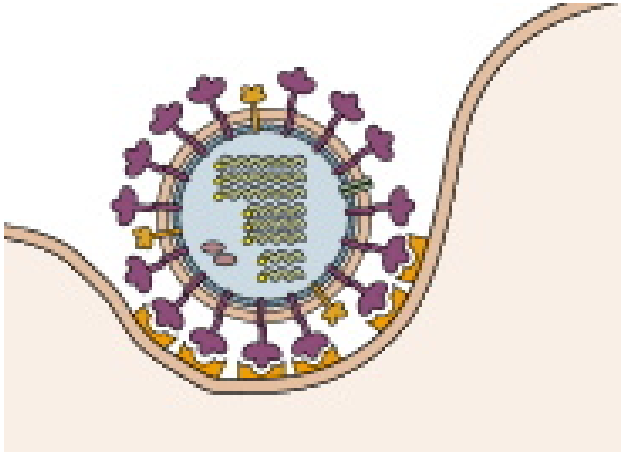


Extra Methods - Autodock

- Model of ZINC_53683662 with color-coded bonds
  - Green – rotatable Red – unrotatable



Extra Results – Influenza



Hemagglutinin, IDP/glycoprotein

- Binds to cell receptors to facilitate entry of the flu

- Results for Drug Synergy

Mimicking hemagglutinin binding to sialic acid

Drug Name	Predicted Similarity	Binding Affinity
ZINC_96006030	0.84422636989	--

Mimicking antibody binding to hemagglutinin

Drug Name	Predicted Similarity	Binding Affinity
ZINC_	--	--

Extra Results – Thrombin & Cancer

- Thrombin is a protein that increases metastasis of tumors
  - Binds to hirudin, an IDP
- Previous work by Anvita Gupta
- <u>Results for Drug Synergy</u>

Mimicking hirudin, binding to thrombin (Anvita's/FDA)

Drug Name	Predicted Similarity	Binding Affinity
Dabigitran	0.8911	-6.1

Mimicking thrombin, binding to hirudin