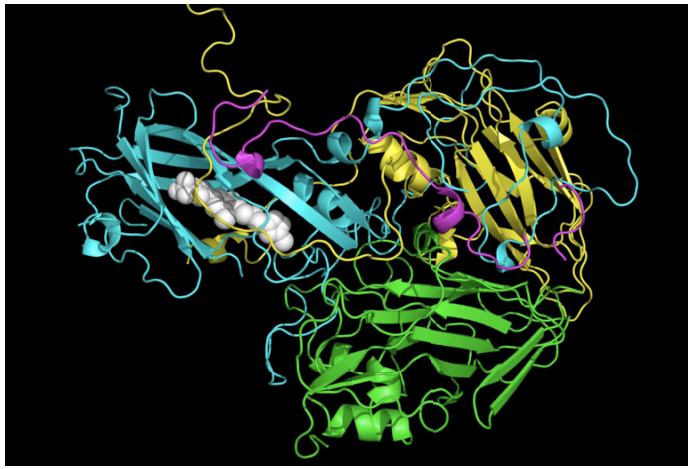
"UNDERSTANDING THE BASIS OF DISEASE AND FINDING RELIABLE, DRUGGABLE TARGETS"

Arthur Weininger and Susan Weininger

FROM DATA

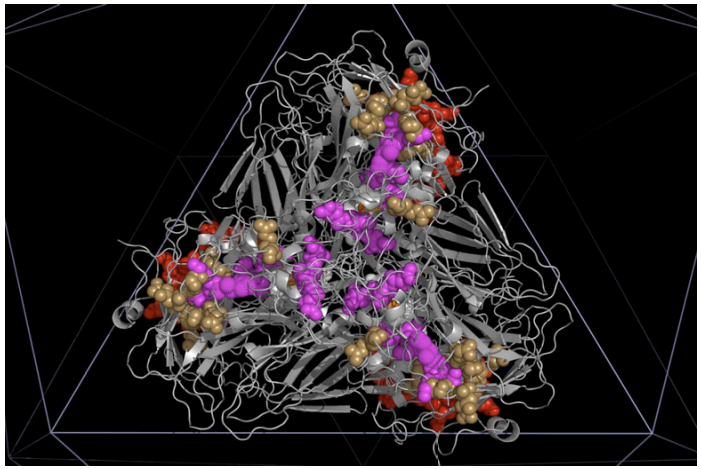
sequences/structure



EV-D68 Structure
(4WM7.PDB)

TO UNDERSTANDING

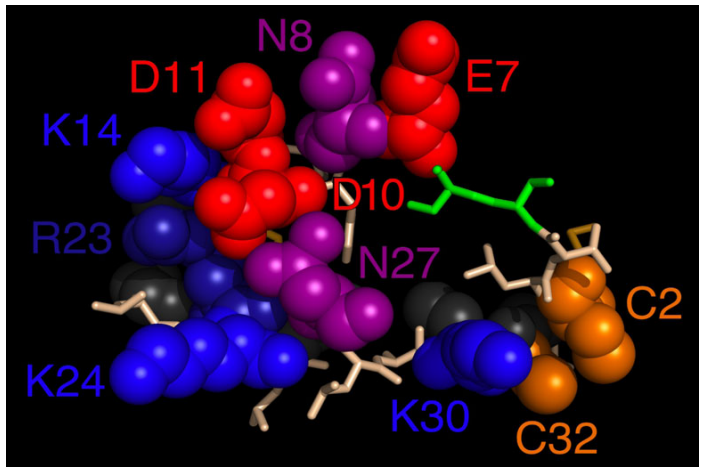
structural correlates of disease



Weininger Theory of
EV-D68 Induction of
MS and Paralysis

TO DESIGN

drug candidates



MS-BLOCK
Candidate Drug
and Diagnostic

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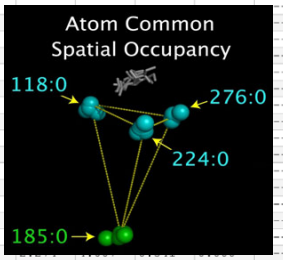
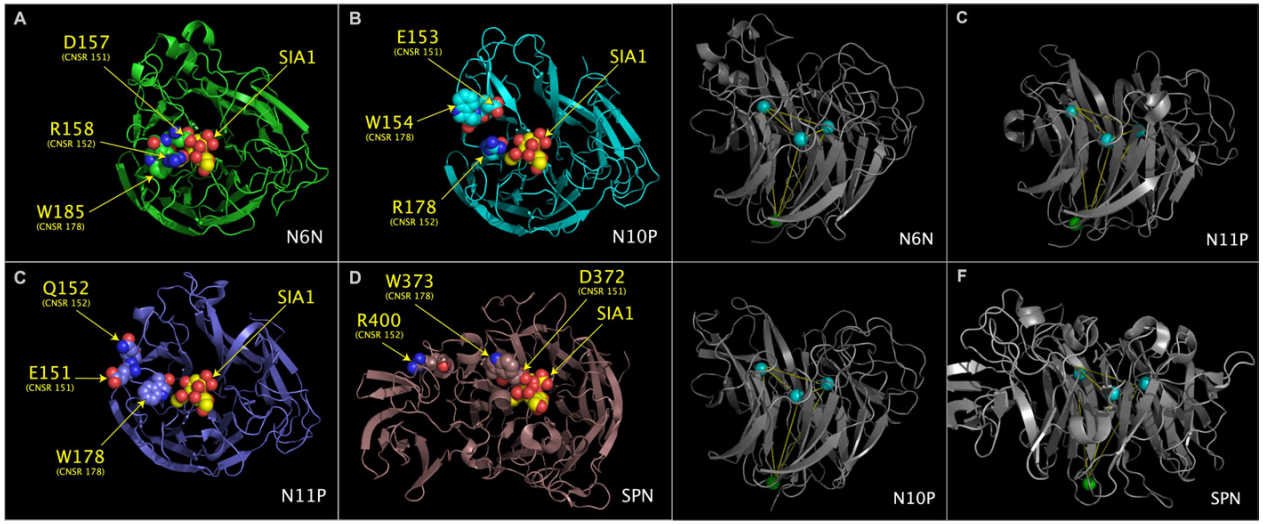
IDENTIFICATION OF SPATIALLY INVARIANT ATOMS TO RELATE STRUCTURES

Weininger A, Weininger S. (2015) Using Common Spatial Distributions of Atoms to Relate Functionally Divergent Influenza Virus N10 and N11 Protein Structures to Functionally Characterized Neuraminidase Structures, Toxin Cell Entry Domains, and Non-influenza Virus Cell Entry Domains. PLoS One 10(2):e0117499. doi: 10.1371/journal.pone.0117499

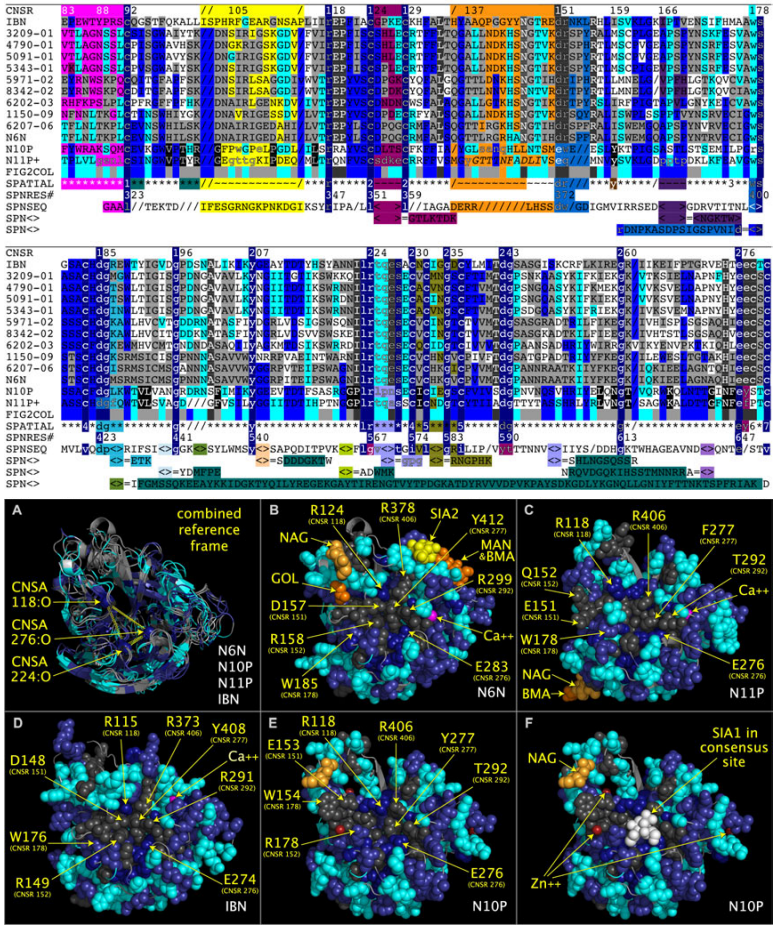
1. Align structures with Common Spatial Occupancy.

	ARG124	TRP185	SER186	ASP192	GLY203	TYR214	LEU230	ARG231	SER235	GLY242	ASP250	GLY251	GLY267	GLU283	ASP331	ARG334	TRP368	ARG378	GLY380	SER413	GLU433	TRP466
1W1X-->	ARG118	TRP154	SER179	ASP185	GLY196	TYR207	LEU223	ARG224	SER228	GLY235	ASP243	GLY244	GLY260	GLU276	ASP324	ARG327	TRP361	ARG406	GLY373	SER407	GLU425	TRP458
4FVK-->	ARG118	TRP154	SER179	ASP185	GLY196	TYR207	LEU223	ARG224	SER228	GLY235	ASP243	GLY244	GLY260	GLU276	ASP324	ARG327	TRP361	ARG406	GLY373	SER407	GLU425	TRP458
4K3Y-->	ARG118	TRP178	SER179	ASP185	GLY196	TYR207	LEU223	ARG224	SER228	GLY235	ASP243	GLY244	GLY260	GLU276	ASP324	ARG327	TRP361	ARG406	GLY373	SER407	GLU425	TRP458
1A4G-->	ARG115	TRP176	SER177	ASP183	GLY194	TYR205	LEU221	ARG222	SER226	GLY233	ASP241	GLY242	GLY258	GLU274	ASP323	ARG326	TRP363	ARG373	GLY375	SER409	GLU427	TRP455
3H72-->	ARG347	TRP373	ASP417	ASP423	GLY441	TYR540	LEU566	GLY567	THR572	GLY583	TYR590	THR591	GLY613	GLU647	ASP684	ARG687	TYR710	ARG721	GLY724	ASN753	GLU768	TRP786
CNSR#-->	CNSR118	CNSR178	CNSR179	CNSR185	CNSR196	CNSR207	CNSR223	CNSR224	CNSR228	CNSR235	CNSR243	CNSR244	CNSR260	CNSR276	CNSR324	CNSR327	CNSR361	CNSR406	CNSR373	CNSR407	CNSR425	CNSR458
CNSR118	0.000	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
CNSR178	2.581	0.000	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
CNSR179	0.410	3.789	0.000	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
CNSR185	0.485	3.293	0.530	0.000	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
CNSR196	0.601	0.686	1.357	1.027	0.000	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
CNSR207	1.174	1.800	0.525	**0.276**	1.410	0.000	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
CNSR223	0.908	3.665	0.729	0.600	1.639	0.473	0.000	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
CNSR224	**0.287**	3.954	**0.112**	**0.189**	1.234	**0.140**	**0.069**	**0.000**	---	---	---	---	---	---	---	---	---	---	---	---	---	---
CNSR228	1.331	5.232	1.125	0.730	2.121	**0.230**	1.348	1.091	0.000	---	---	---	---	---	---	---	---	---	---	---	---	---
CNSR235	**0.198**	3.937	0.407	0.950	1.559	2.002	0.580	0.304	0.916	0.000	---	---	---	---	---	---	---	---	---	---	---	---
CNSR243	1.369	2.445	1.559	1.629	1.488	1.598	1.389	1.787	0.867	1.615	0.000	---	---	---	---	---	---	---	---	---	---	---
CNSR244	0.434	2.990	**0.148**	0.892	1.341	0.450	0.328	0.558	**0.219**	1.294	0.452	0.000	---	---	---	---	---	---	---	---	---	---
CNSR260	0.648	3.367	0.676	0.940	2.324	0.988	**0.128**	0.484	0.587	0.367	0.865	0.366	0.000	---	---	---	---	---	---	---	---	---
CNSR276	**0.253**	4.215	0.377	**0.296**	1.260	0.398	0.506	**0.212**	0.331	0.730	0.856	0.878	0.369	0.000	---	---	---	---	---	---	---	---
CNSR324	3.899	5.631	1.155	1.464	1.529	0.507	0.604	**0.180**	0.311	3.839	0.872	1.287	1.697	0.924	0.000	---	---	---	---	---	---	---
CNSR327	1.626	3.984	**0.224**	2.437	1.108	1.489	0.443	0.646	1.667	4.032	0.853	1.014	1.813	0.882	1.182	0.000	---	---	---	---	---	---
CNSR361	1.689	5.235	1.174	2.340	1.664	1.897	1.163	0.988	1.909	3.186	0.847	0.863	1.690	1.376	1.924	0.664	---	---	---	---	---	---
CNSR406	2.016	2.881	2.706	4.175	1.658	3.482	2.589	2.825	4.132	3.838	2.114	0.768	3.993	2.552	6.523	3.326	---	---	---	---	---	---
CNSR373	1.079	3.556	0.820	1.119	1.163	1.463	1.258	0.593	0.834	1.379	0.685	1.294	0.520	0.308	6.475	2.795	---	---	---	---	---	---
CNSR407	0.996	3.871	1.271	0.969	1.045	1.803	0.314	**0.177**	0.556	0.970	1.204	0.480	0.656	0.618	4.304	1.281	---	---	---	---	---	---
CNSR425	0.902	3.463	0.875	**0.189**	0.772	1.206	1.152	0.664	0.854	0.444	1.212	1.024	0.695	0.469	6.065	2.731	2.566	1.299	0.881	0.349	0.000	---
CNSR458	3.766	5.358	2.040	2.053	3.172	1.541	2.494	1.613	1.667	2.802	1.083	1.810	1.265	1.257	3.204	0.462	3.052	4.388	1.706	1.600	4.617	0.000





2. Align sequences by structure even w/o sequence homology.



3. Evaluate identified druggable targets.

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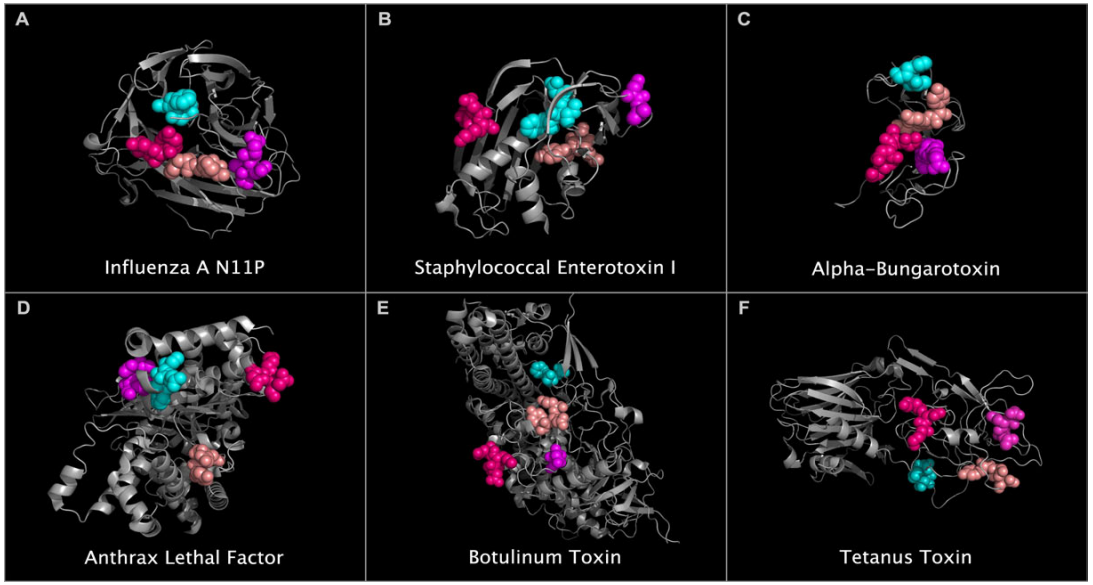
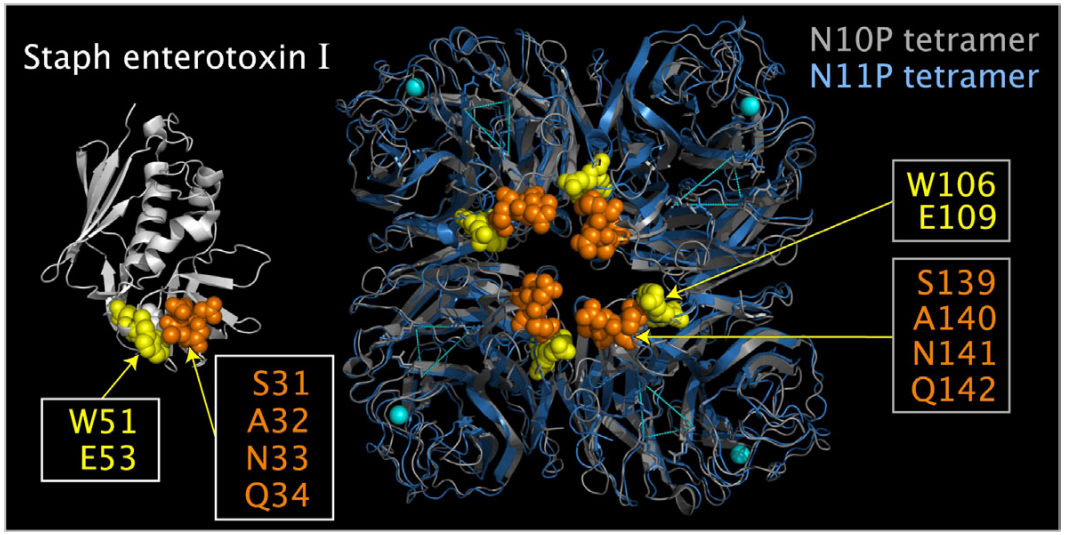
ISOLATING THE STRUCTURAL CORRELATES OF FUNCTION

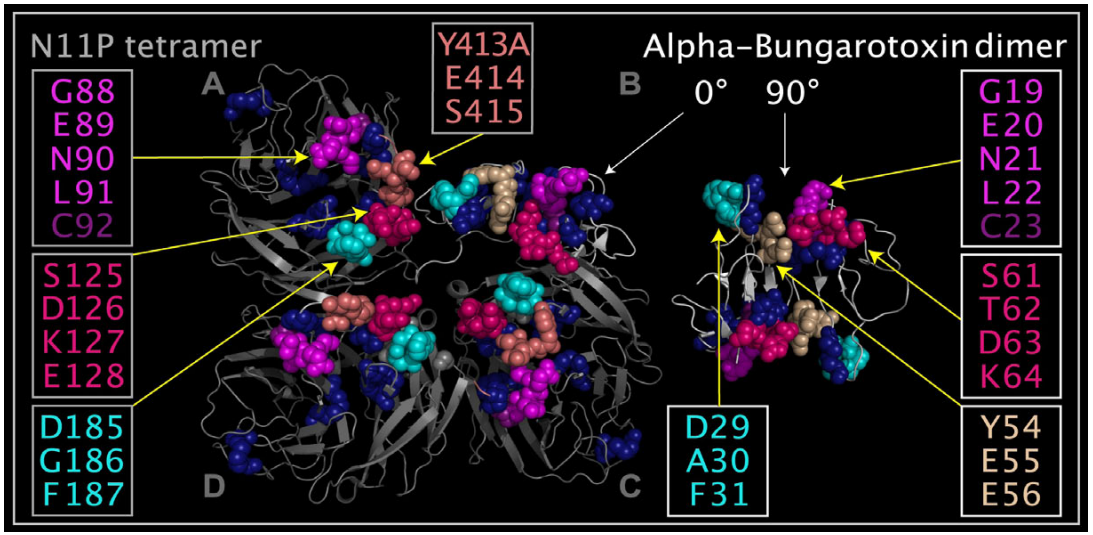
Weininger A, Weininger S. (2015) Using Common Spatial Distributions of Atoms to Relate Functionally Divergent Influenza Virus N10 and N11 Protein Structures to Functionally Characterized Neuraminidase Structures, Toxin Cell Entry Domains, and Non-infuenza Virus Cell Entry Domains. PLoS One 10(2):e0117499. doi: 10.1371/journal.pone.0117499

Presentation of chemical groups in a domain can be checked by using the interatomic distance standard deviation.

N10P E109 / SEI E53	N10P W106 / SEI W51													
	N	CA	C	O	CB	CG	CD1	CD2	NE1	CE2	CE3	CZ2	CZ3	CH2
N	1.228	0.612	0.813	1.193	0.116	0.424	0.625	0.453	0.738	0.655	0.278	0.698	0.355	0.565
CA	0.910	0.251	0.554	1.143	0.424	0.193	0.059	0.121	0.053	0.032	0.187	0.113	0.078	0.067
C	0.284	0.240	0.187	1.017	0.978	0.722	0.621	0.542	0.452	0.385	0.485	0.212	0.266	0.152
O	0.843	1.271	0.761	0.199	1.849	1.451	1.251	1.194	0.980	0.905	1.140	0.621	0.761	0.544
CB	1.350	0.546	0.743	1.220	0.110	0.063	0.035	0.138	0.020	0.071	0.264	0.103	0.293	0.201
C	1.348	0.542	0.623	1.125	0.122	0.006	0.056	0.033	0.111	0.106	0.004	0.152	0.054	0.130
CD	3.705	0.511	0.724	1.242	0.122	0.055	0.060	0.127	0.059	0.042	0.264	0.069	0.294	0.185
OE1	3.563	0.719	0.998	1.600	0.045	0.175	0.293	0.164	0.344	0.277	0.056	0.298	0.078	0.205
OE2	3.913	0.262	0.488	0.931	0.295	0.325	0.174	0.531	0.268	0.468	0.773	0.594	0.911	0.799







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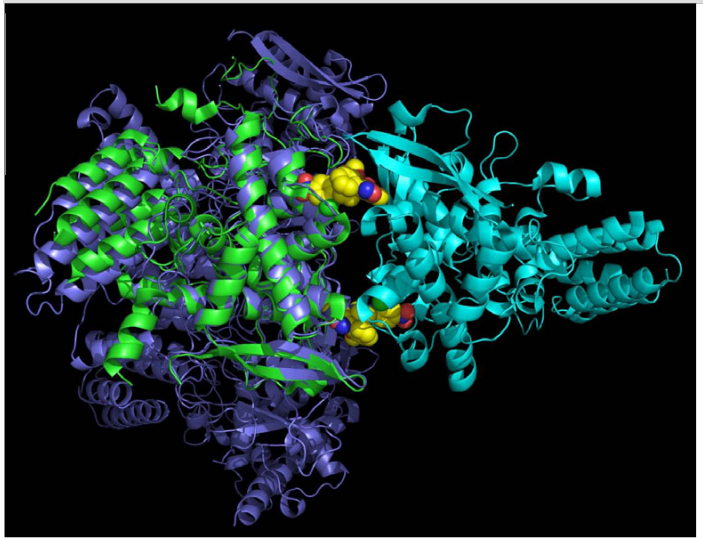
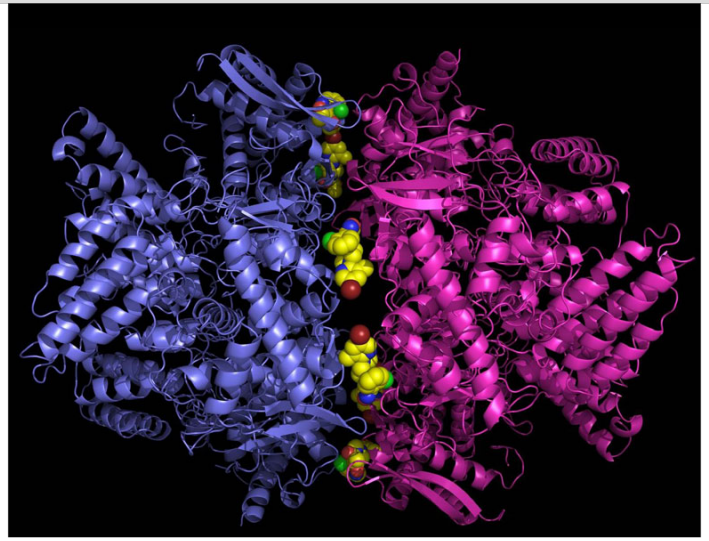
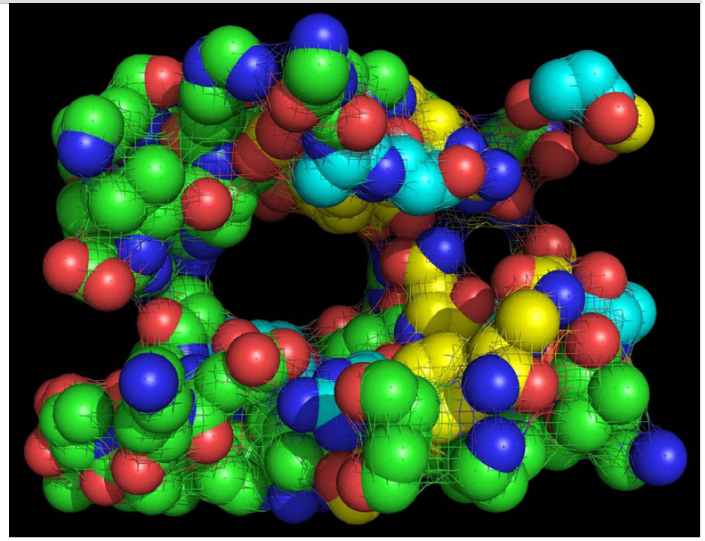
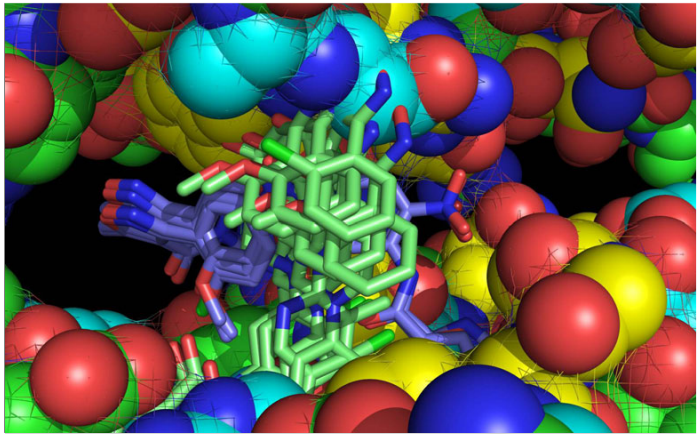
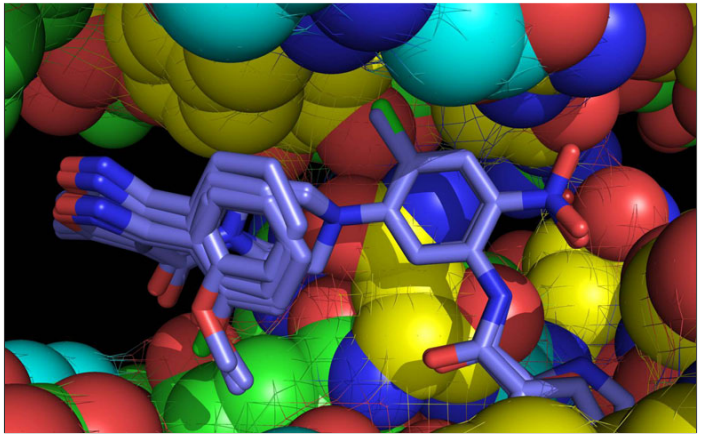
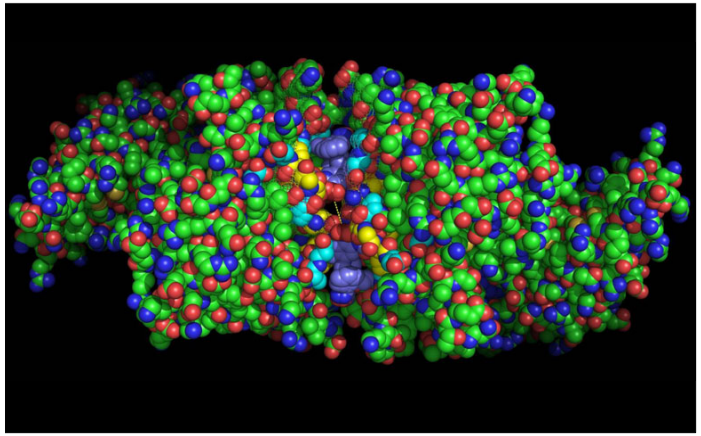
DRUGGABLE TARGET EVALUATION

“Finding an alternate binding site in a nucleoprotein trimer-trimer interface”

We used the dimer (green/cyan) and trimer (purple) influenza nucleoprotein structures to build the trimer-trimer (purple/magenta) interface and the interface's (target) surface.

We mapped mutational data onto the target surface and allowed the side chains of the surface to move. This suggested a binding site for the nucleozin derivatives that was orthogonal to the x-ray crystal structure positions and in the same density, coordinated as in other structures in the database, with no atomic van der Waals incursions, and that is chemically reasonable. Despite this positioning, the target was discarded due to the lability of the target. The impact of target lability could only partially be diminished by enhanced binding of a compound that represented a condensation of adjacent binding groups. From Weininger Works Technical Notes: WWave Output Example #4.

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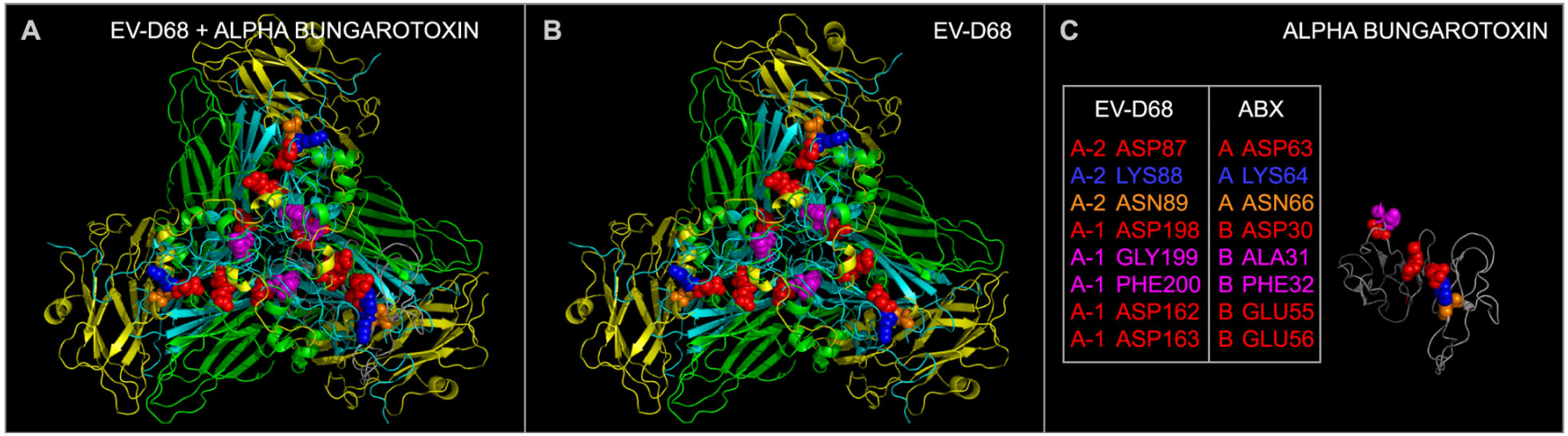
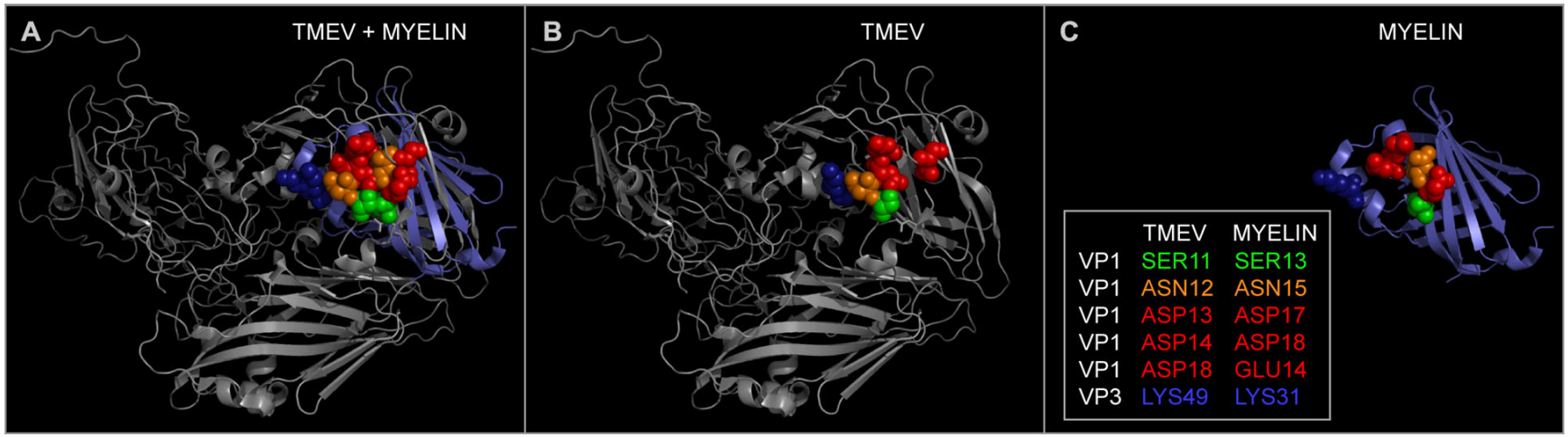
WHAT ARE THE STRUCTURAL CORRELATES OF DISEASE IN EV-D68?



EV-D68, Polio, and Alpha-bungarotoxin have the TOX domain and cause paralysis.

Weininger hypothesis: **EV-D68 induces paralysis by engaging cells with its TOX domain.**



Myelin P2, TMEV, and EV-D68 have an epitope in common, the “MS EPITOPE.”

Weininger hypothesis: **MS is induced by exposure of the MS epitope during EV-D68 viral uncoating.**

Weininger, A.; Weininger, S. (2015)

“Using Common and Divergent Structural Features of Picornavirus VP1, VP2, and VP3 Proteins and Non-Viral Proteins to Determine the Structural Basis for Multiple Sclerosis Induction by TMEV and Neuron Entry By EVD-68”

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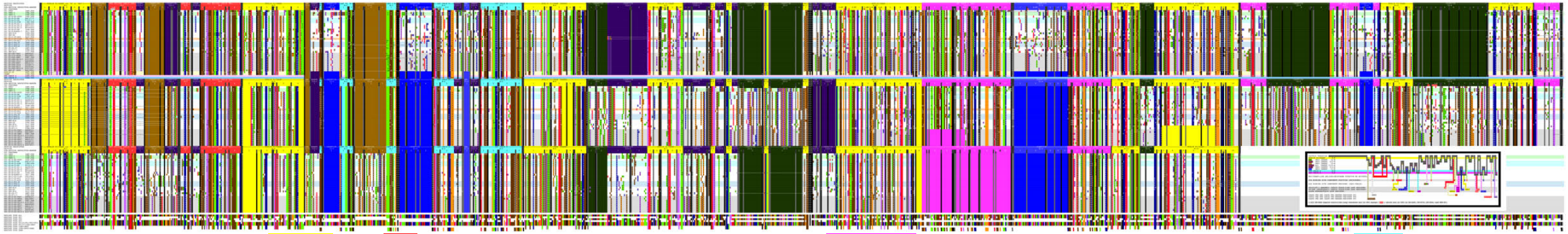
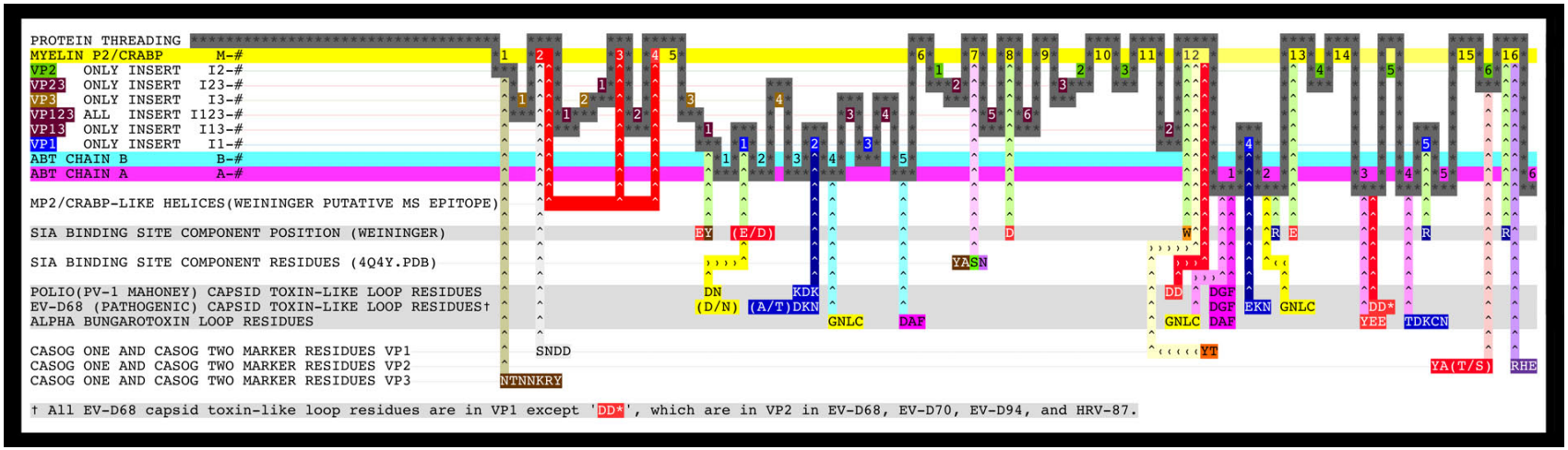
HOW EXTENSIVE IS THE STRUCTURAL CORRELATION?

PICORNAVIRUSES SEQUENCES CAN BE PARSED INTO MYELIN P2, TOXIN, AND INSERT DOMAINS.

Precise structural alignment establishes that the inserts are non-random and can be unique to a protein.
VP1, VP2, and VP3 were not formed by simple gene duplication.



Myelin P2/CRABP (yellow and red sections), Alpha-bungarotoxin A chain (magenta sections) and B chain-residues 1-48 only (cyan sections)
Insert Sections - VP1 only (blue), VP2 only (green), and VP3 only (brown), mixed protein (purple)



Weininger, A.; Weininger, S. (2016)
"Common Features in Picornaviruses, Alpha-bungarotoxin, Myelin P2, and CRABP Suggest Structural Bases for Multiple Sclerosis, Guillain-Barre Syndrome, and Paralysis Induction"
http://www.weiningerworks.com/picornavirus_monograph.html

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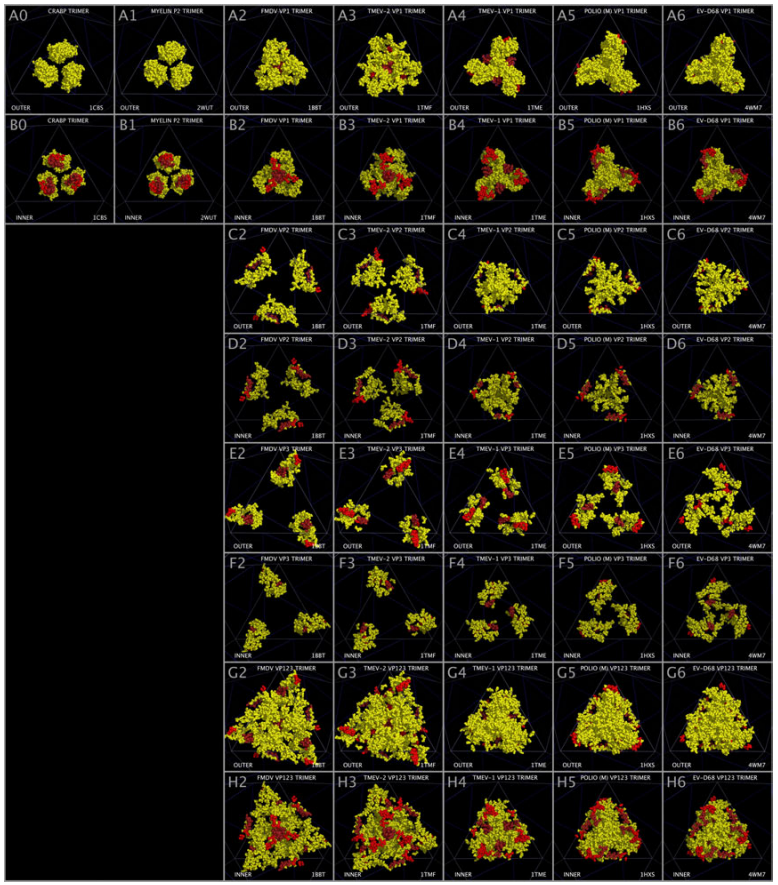
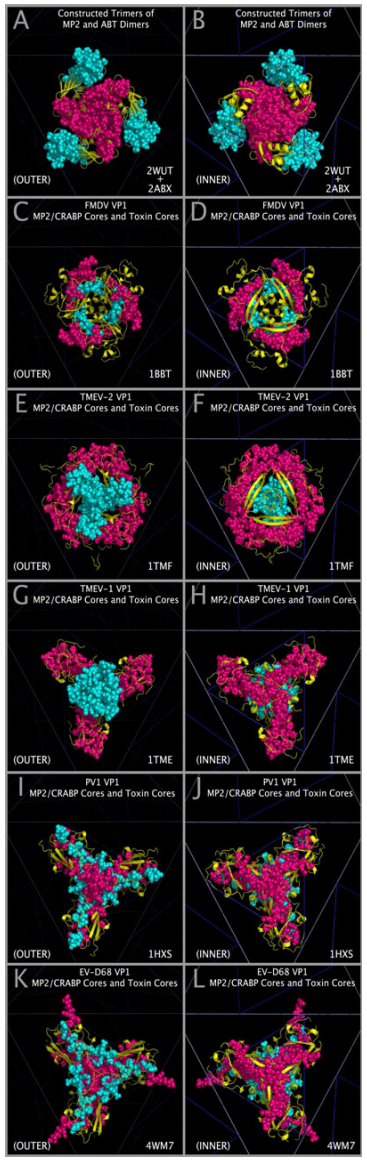
PICORNAVIRUS MYELIN P2-LIKE,TOXIN-LIKE, AND INSERT DOMAINS

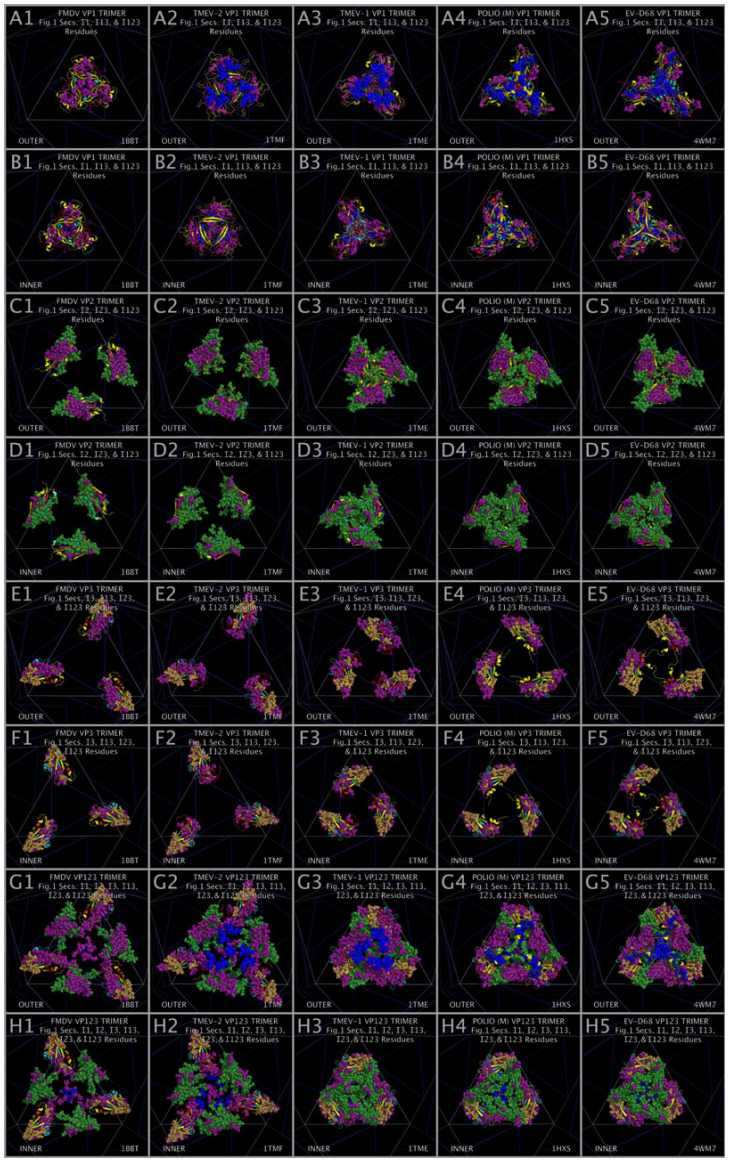
MYELIN P2/CRABP-LIKE RESIDUES



ABT-LIKE RESIDUES



INSERTS



http://www.weiningerworks.com/picornavirus_monograph.html

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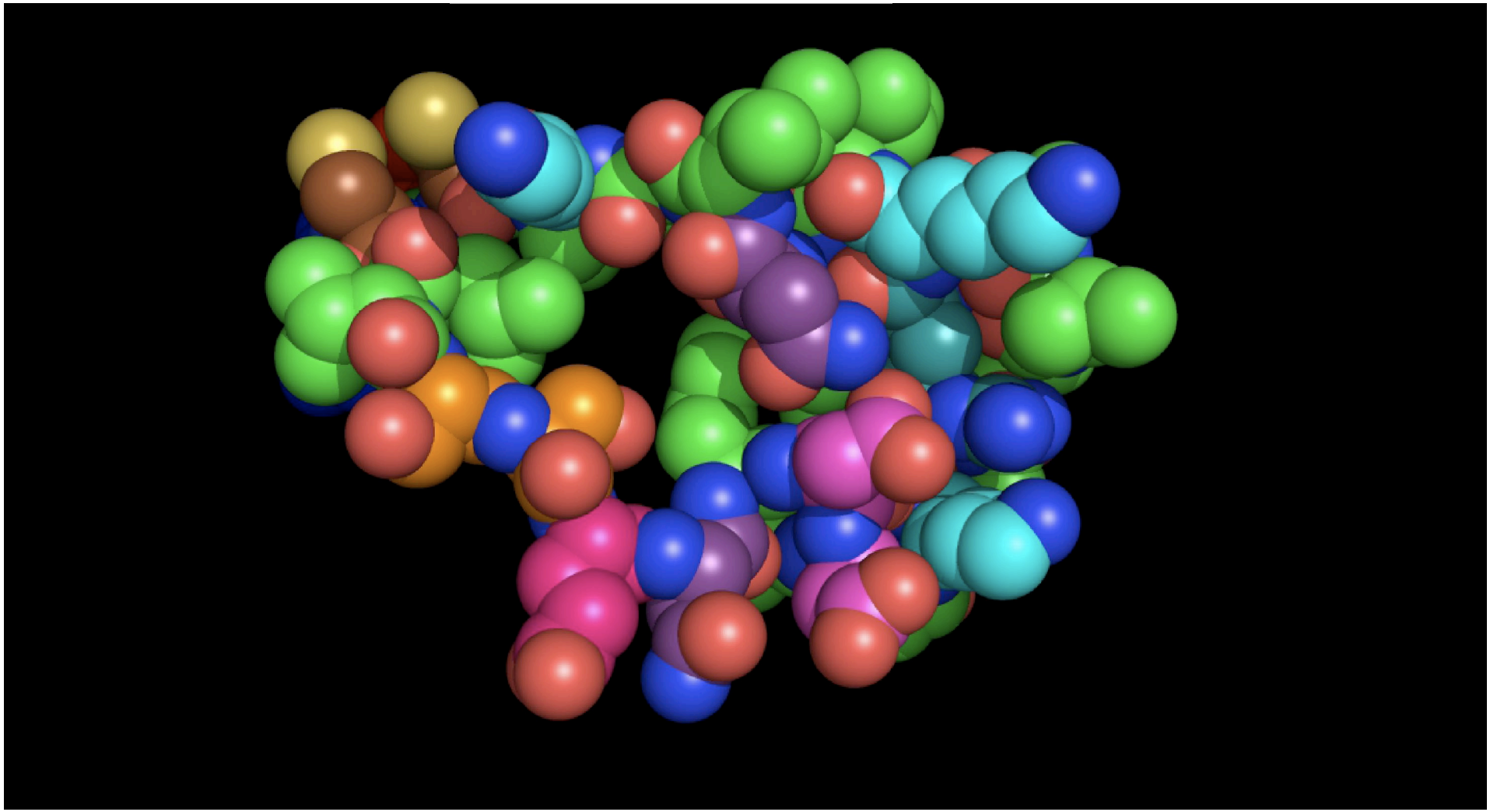
FROM ANALYSIS TO DRUG CANDIDATE: “OPEN ACCESS” MS-BLOCK



www.weiningerworks.com/MSBLOCK.html

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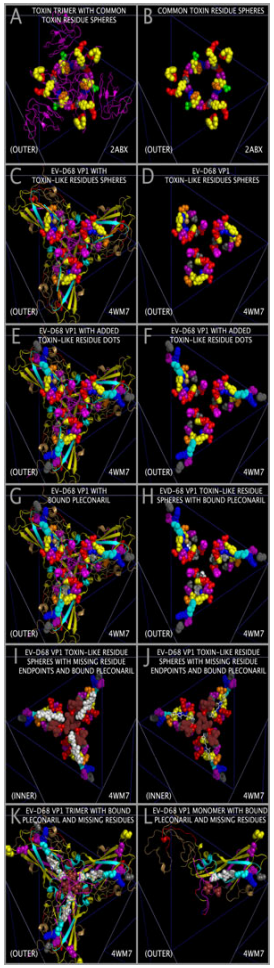
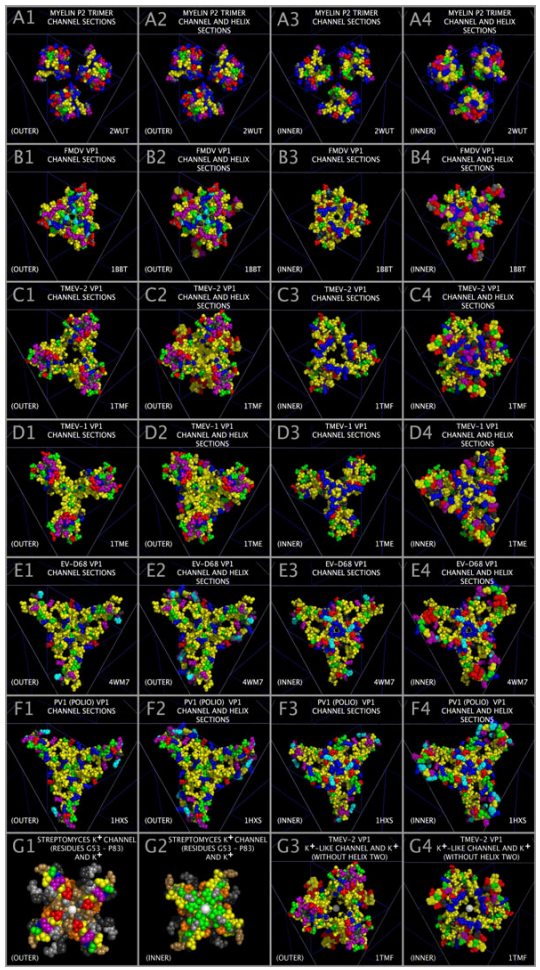
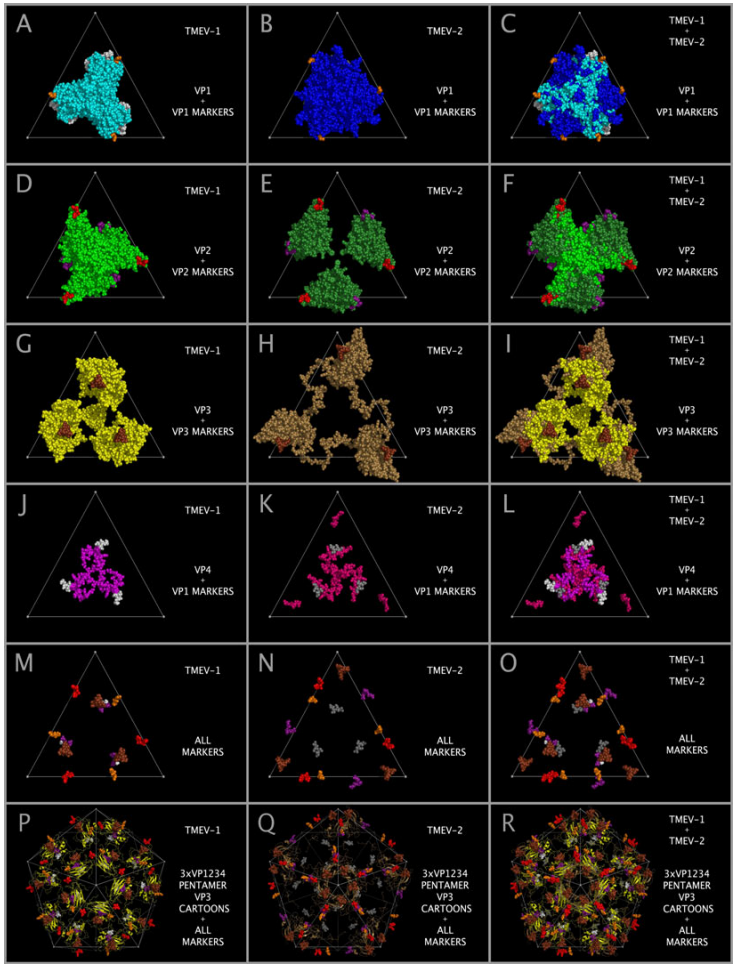
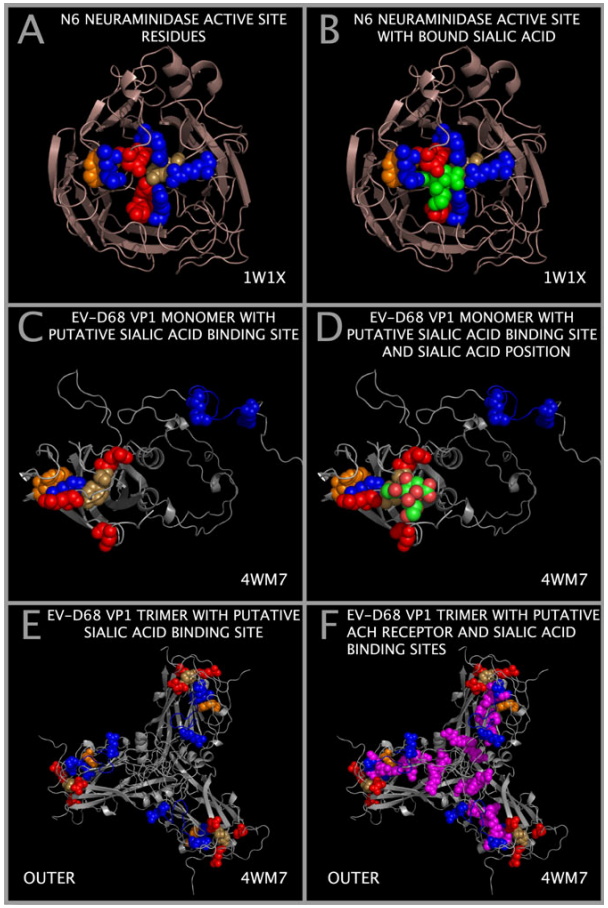
APART FROM THE ISOLATION OF DRUGGABLE TARGETS, WHAT ELSE IS LEARNED?

TOX. ANNULI CAPSID ION CHANNEL CAPSID DIAPHRAGM PORE CAPSID SIA BINDING SITE









Weininger, A.; Weininger, S. (2016)
"Common Features in Picornaviruses, Alpha-bungarotoxin, Myelin P2, and CRABP Suggest Structural Bases for Multiple Sclerosis, Guillain-Barre Syndrome, and Paralysis Induction"
http://www.weiningerworks.com/picornavirus_monograph.html

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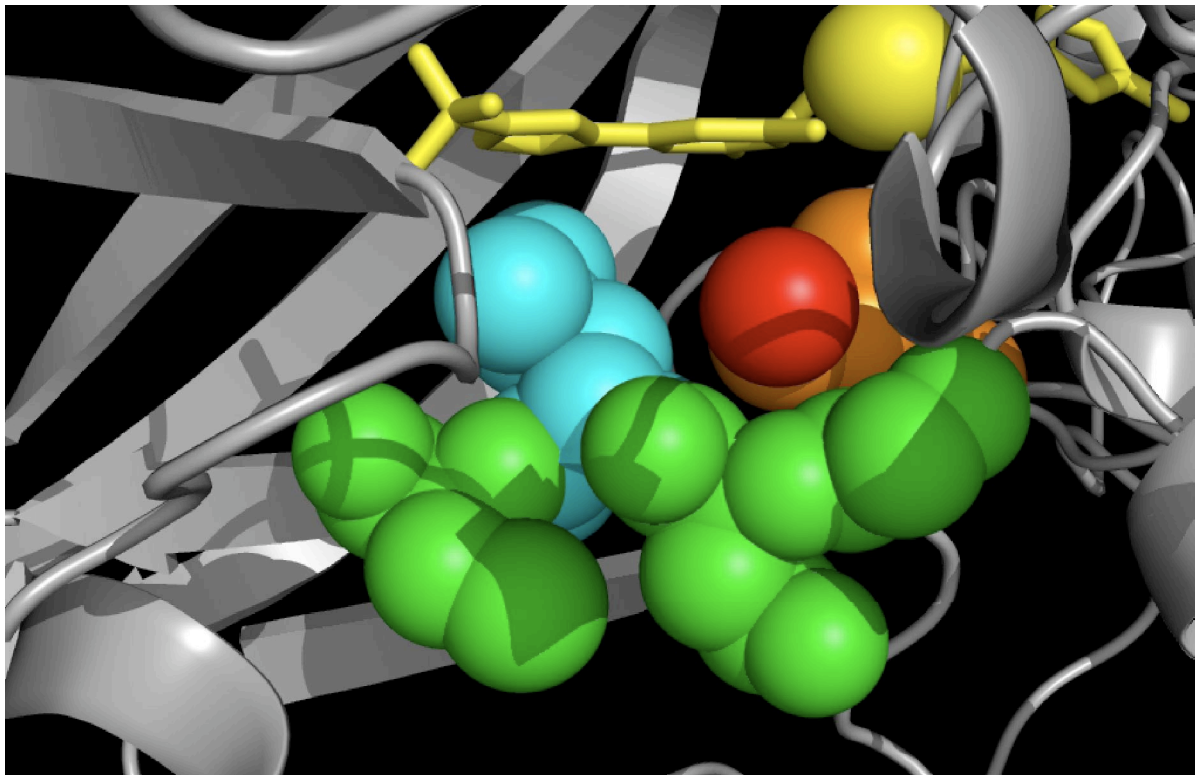
PRECISION IN ANALYSIS IS IMPORTANT – EVERY ATOM CAN COUNT
EXAMPLE: PLECORNARIL AND ILE95LEU



Certain compounds are expected to initiate mutations with single atom changes resulting in more fit EV-D68 species.

- Avoid using only one structure when making structural interpretations.
- Use all relevant databases to forge reliable, testable solutions.

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