WEININGER WORKS™ OPEN ACCESS MOLECULE: FLU-LOCK

FLU-LOCK Overview

We (Arthur Weininger and Susan Weininger) continue to be concerned about unusual emergent animal and human influenza viruses. We have published a structural analysis of a set of highly unusual influenza viruses, H18N11 and H17N10. We aligned the sequences (in the absence of sequence homology) and structures of the sialidases. Among other unusual features, we found toxin domains on the N11 and N10 proteins. We determined the structural bases in the N11 and N10 proteins for the alarming absence of sialidase activity and for the alarming absence of anti-viral binding group configurations where the normal sialic acid/drug binding site should be. We screened the influenza capsids and isolated non-active site regions (outside of the normally conserved sialic acid binding site) that could be used to bind anti-virals. We determined that small molecules in a set of nucleoprotein crystal structures presented better binding profiles if reoriented (rotated by ~90 degrees). We designed FLU-LOCK to bind tightly and specifically to one of the conserved sites in the nucleoprotein complex.

Emergent Influenza

New influenza viruses emerge regularly. For example, the H17N10 and H18N11 viruses isolated from bats in Guatelmala (H17N10) and Peru (H18N11) are highly divergent. The N10 and N11 neuraminidase proteins have no functional sialidase site and have no sequence homology to other neuraminidases.

Li, Q., Sun, X., Li, Z., Liu, Y., Vavricka, C. J., Qi, J., & Gao, G. F. (2012).
Structural and functional characterization of neuraminidase-like molecule N10 derived from bat influenza A virus.
Proceedings of the National Academy of Sciences, 109(46),18897-18902.
dx.doi.org/10.1073/pnas.1211037109

Garcia-Sastre, A. (2012). The neuraminidase of bat influenza is not a neuraminidase.
Proceedings of the National Academy of Sciences, 109(46), 18635-18636.
dx.doi.org/10.1073/pnas.1215857109

We studied the structural and sequence invariants and divergences of neuraminidases.

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.
dx.doi.org/10.1371/journal.pone.0117499

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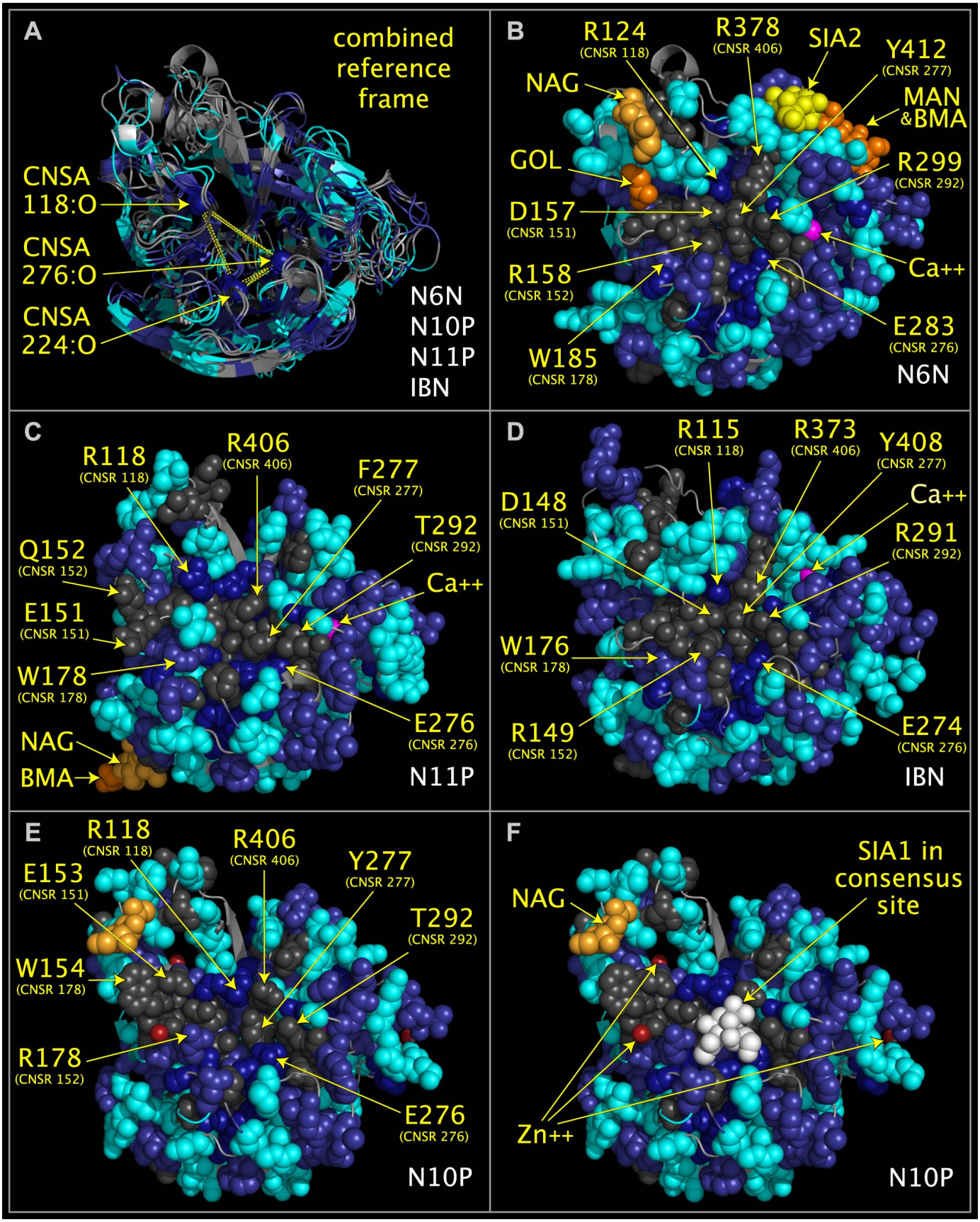
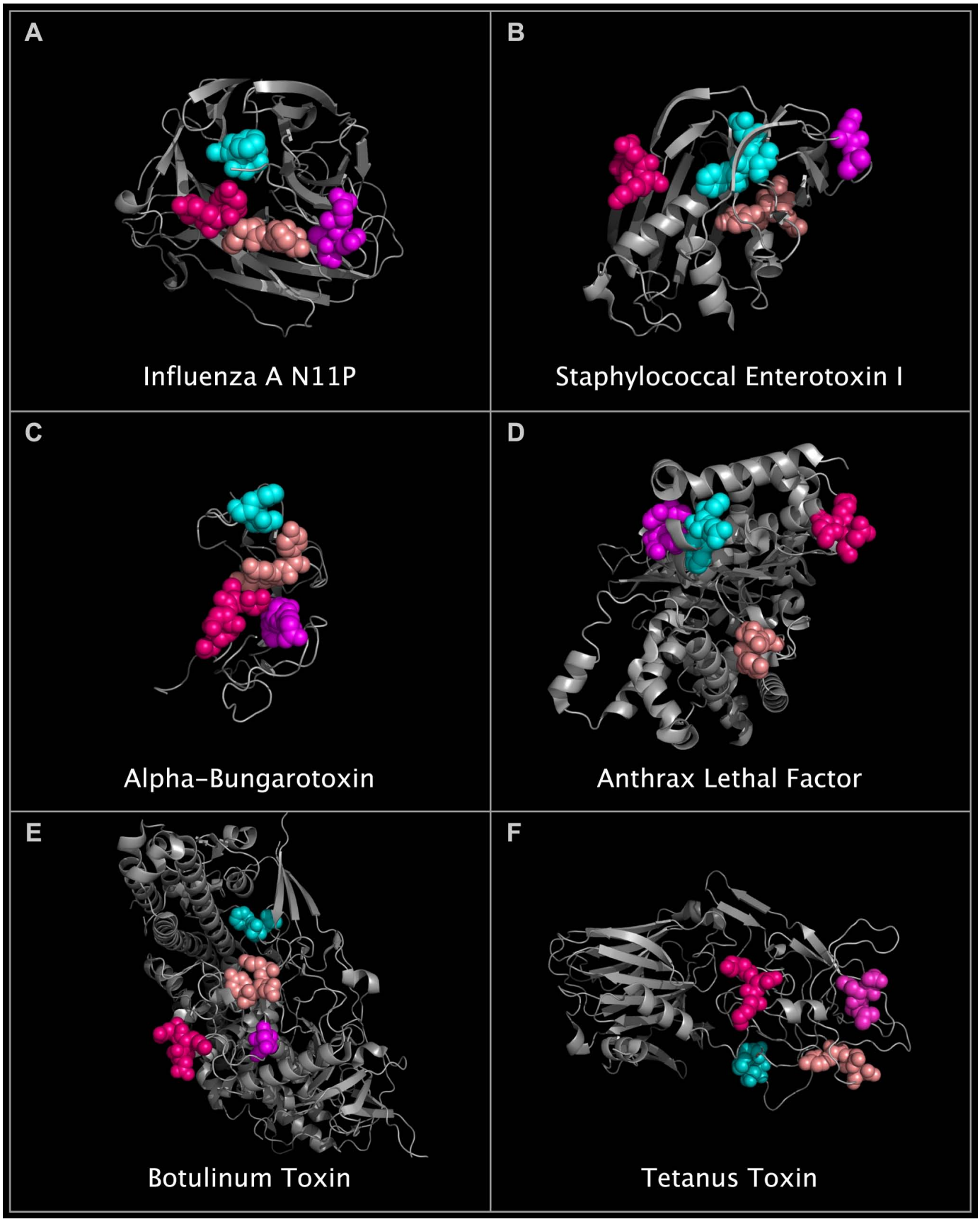
We aligned the structures and sequences of N10 protein (N10P), N11 protein (N11P), an influenza A neuraminidase (N6N), an influenza B neuraminidase (IBN), and a bacterial neuraminidase. This allowed us to compare the active and inactive sites of these proteins and to further evaluate the compatability of the inactive sites of the N10 and N11 neuraminidases with the structures of drug compounds that target the normally conserved sialic acid site. The following image shows aligned N6N, N10P, N11P, and IBN sialidases, both individually and in a combined superposition:



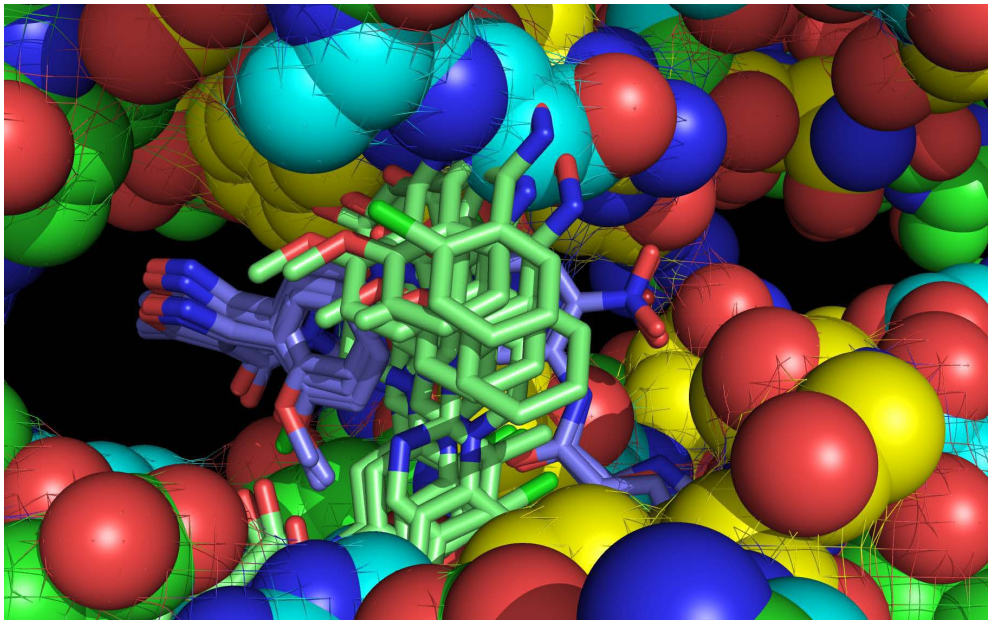
We found similarities between structures in the N10 and N11 virus capsid proteins and structures in non-neuraminidase proteins. Among other findings, we found that the N10 and N11 capsid proteins contain toxin-like domains. In N10 protein, we identified staphylococcal enterotoxin I-like domains. In N11 protein, we identified hepatitis E E2S-like domains, SARS spike protein-like domains, and toxin components shared by alpha-bungarotoxin, staphylococcal enterotoxin I, anthrax lethal factor, clostridium botulinum neurotoxin, and clostridium tetanus toxin. The following image shows the N11 protein, with its toxin-like domains highlighted, next to toxins containing structurally similar residue clusters.



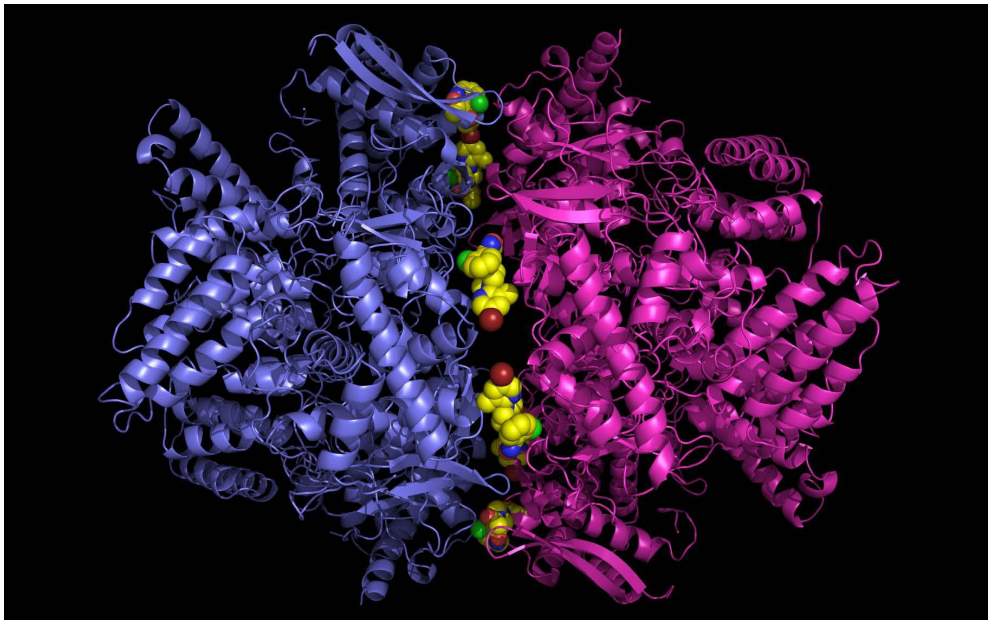
We concluded that the absence of demonstrated neuraminidase activity with the presence of new cell entry domain components in N10 and N11 proteins suggests that N10 and N11 protein-containing viruses may enter cells without a functioning sialidase, i.e., by binding to alternative receptors such as ACE2, acetylcholine, and MHC II receptors on an expanded receptive cell population, including cells such as neurons and T-cells.

FLU-LOCK Structural Basis

While screening protein surfaces presented by influenza virions, we noticed potential problems with structures containing a class of small molecules bound to nucleoproteins. We examined the nucleoprotein superstructure and found an alternative positioning (rotation in place) of small molecules bound to influenza nucleoproteins. This repositioning appears to resolve all chemical and structural issues that we noticed.



The rotation of the bound molecules provided a better physical and chemical fit and suggests an antiviral molecule, FLU-LOCK. Because FLU-LOCK is a dimer, it is expected to have much tighter affinity for the nucleoprotein site than single components.



Weininger, A.; Weininger, S.
"Finding an alternate binding site in a nucleoprotein trimer-trimer interface"
Weininger Works Technical Notes (2013) Sept 10;4:1-22 (HTML) (PDF – LOCAL COPY)

FLU-LOCK Open Access Molecule

FLU-LOCK is an Open Access Molecule.

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