École polytechnique fédérale de Lausanne

Institute of Materials - Institute of Bioengineering

sunmil.epfl.ch

SuNMIL Supramolecular NanoMaterials and Interfaces Laboratory

Virucidal Peptide-Based Drugs to Target Influenza

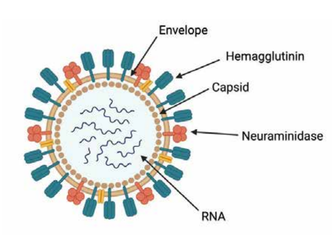
Shadi Kordbacheh, Francesca Olgiati, Francesco Stellacci

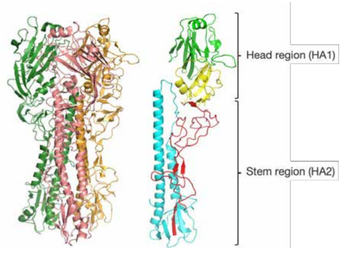
Institute of Materials Science & Engineering,
École polytechnique fédérale de Lausanne (EPFL), 1015-Lausanne, Switzerland

https://doi.org/10.17952/37EPS.2024.P1207

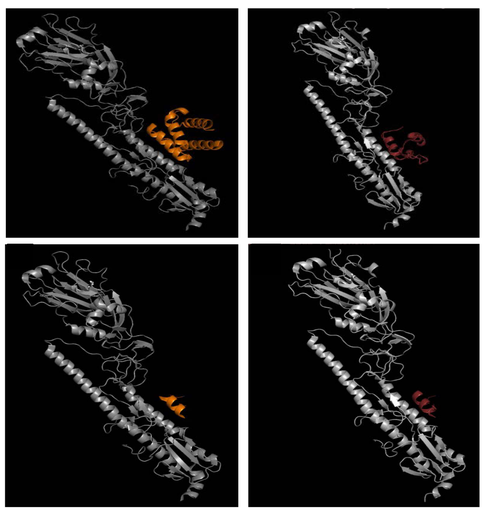
Aim of the Project

- Influenza viruses acquire point mutations in genes encoding the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA).
- In case of HA, mutation mainly happens at the head region of the protein.
- Compounds targeting other regions of HA than receptor binding domain (RBD) are needed to decrease the chance of mutation.
- Antibodies are the best natural antiviral drugs. Inspired by portions of antibodies against influenza, peptide sequences were chosen as the targeting moiety.





Peptide Extracts from Antibody

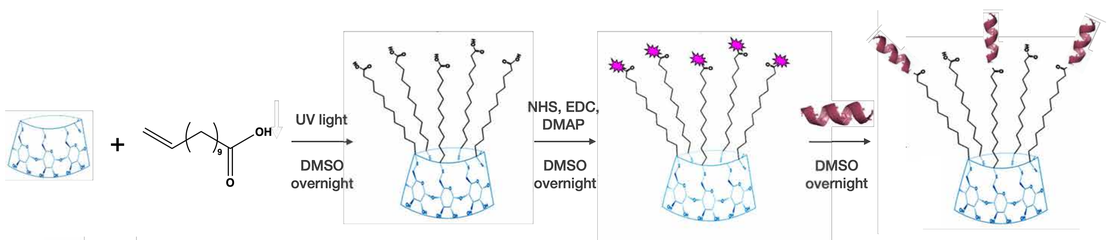


- Interaction of HB36.1 and HB80.4 Antibodies with HA
- Short Peptide Drives from Antibody:
  - ➢ Small portion of antibody is responsible for interaction with HA

Original protein	Peptide code	Peptide sequence
HB36.1	FW9	FDAAMRNMW
HB36.1	MF9	MRNMWAKVF
HB80.4	FA11	FSENIAKEIAA
HB80.4	EF11	ENIAKEIAASF

Peptide as the Targeting Moiety in the Virucidal Drug

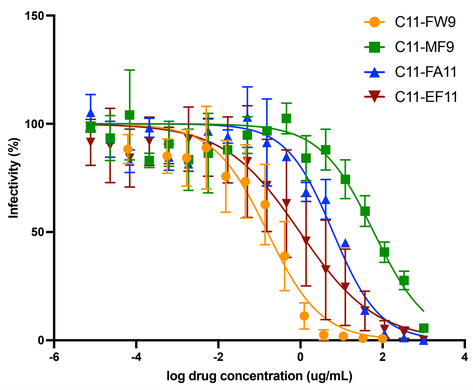
- Synthesis of Peptide-Based Drugs



: Peptide

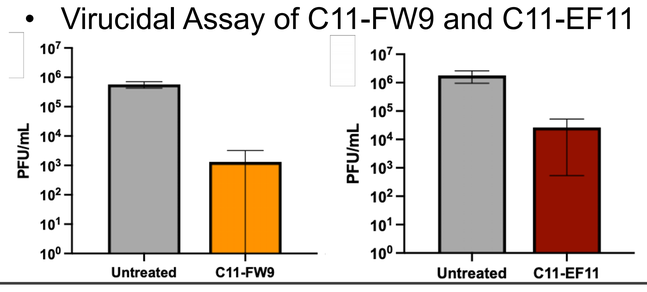
: Activated carboxylic acid

- Antiviral Activity of C11-Peptides Against A/Netherlands/602/2009



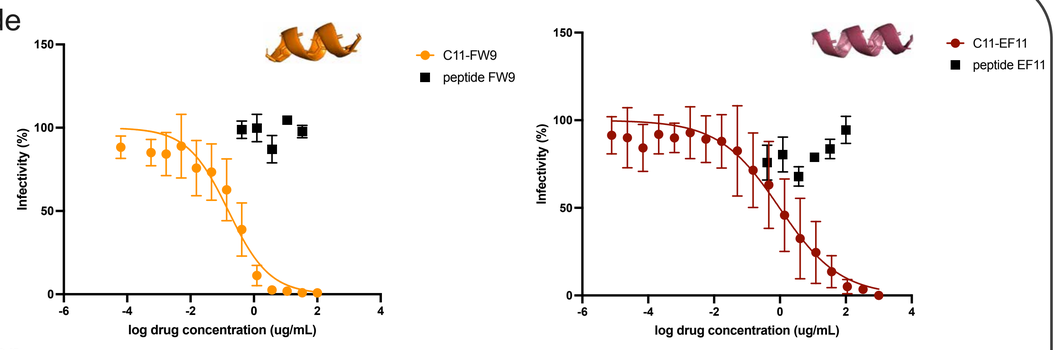
Molecule	Peptide sequence	EC50 (μg/mL)
C11-FW9	**FDAAMRNMW**	**0.16 (0.11-0.22)**
C11-MF9	MRNMWAKVF	60.9 (36.63-101.4)
C11-FA11	FSENIAKEIAA	6.19 (3.95-9.55)
C11-EF11	**ENIAKEIAASF**	**0.96 (0.60-1.55)**

- Virucidal Assay of C11-FW9 and C11-EF11

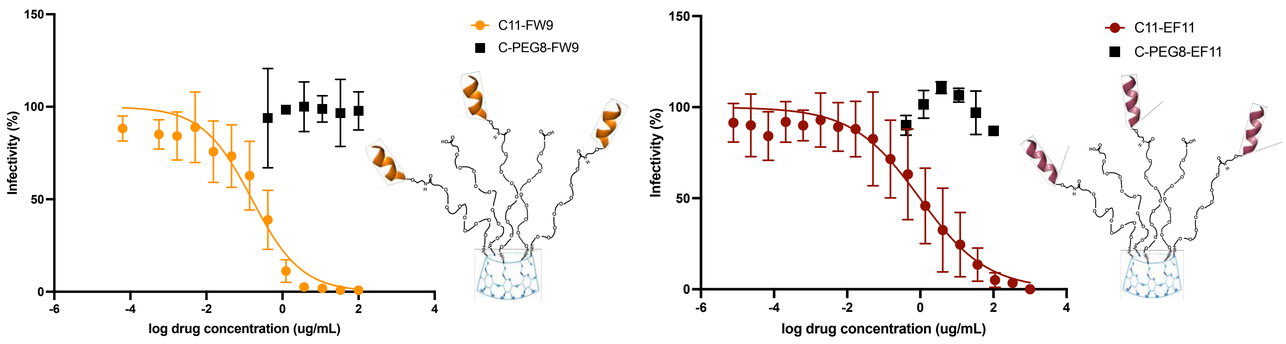


Mechanism of Action

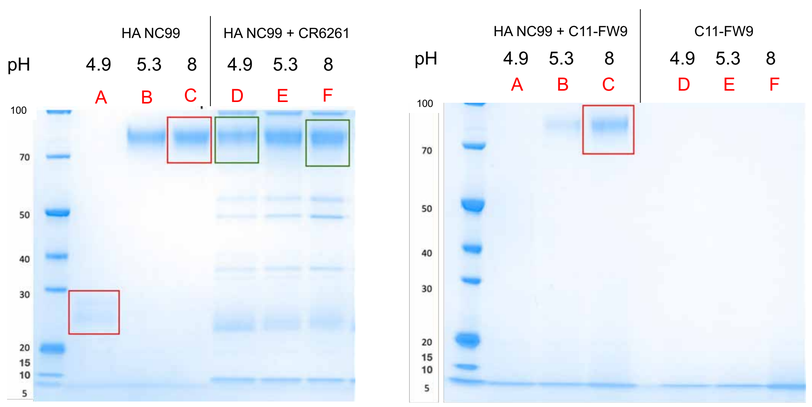
- Individual Peptide



- PEGylated Linker

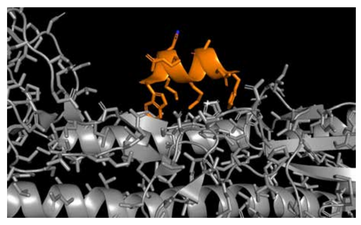


- Trypsin-Susceptibility Assay



Key Amino Acids for Interaction

- The contact comes from the side chains of FM and W



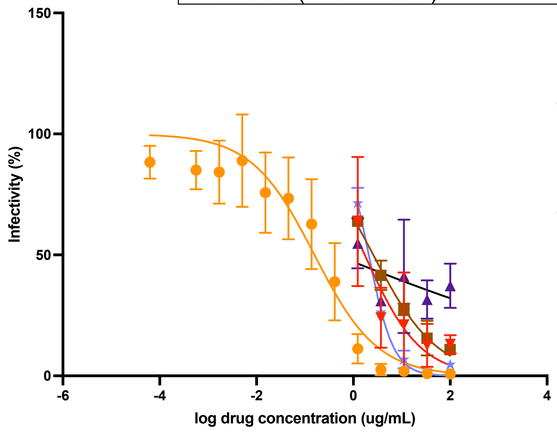
FDAAMRNMW

Peptide Code	Peptide sequence	Molecule	EC50 (μg/mL)
FW9	FDAAMRNMW	C11-FW9	0.16 (0.11-0.22)
EE9	EDAAARNAE	C11-EE9	34.31 (28.91-41.48)
SS9	SDAAARNAS	C11-SS9	>100
AA9	ADAAERNEA	C11-AA9	Not soluble

RBD is NOT the binding site

- Inhibition Assay with Mutants of the Original Virus

Mutation	EC50 (μg/mL)
No mutation (N09)	0.16 (0.11-0.22)
Cal09	2.09 (1.84-2.35)
G155E (N09 mutant)	1.72 (0.08-3.98)
N125D + D127E + A186D + S190R (N09 mutant)	0.43
K160E (N09 mutant)	2.58 (1.94-3.30)



- C11-FW9 inhibited the viral replication of all the mutants
- **This results demonstrates that the binding site of the molecule is not the receptor binding domain**

Summary

- Virucidal drugs can be obtained exploiting interactions between peptide and HA of influenza virus
- The original virus mutants with a different receptor binding domain demonstrated the peptides bind to a different region of hemagglutinin than RBD

reference

- Ghafoori, S.M., Petersen, G.F., Conrady, D.G. *et al., Sci Rep* 13, 6940 (2023)
- Fleishman, S. J. et al. Computational Design of Proteins Targeting the Conserved Stem Region of Influenza Hemagglutinin. Science 332, 816–821 (2011)