Independent undergraduate Research Project Screening of possible antiviral peptides to bind SARS Covid 19 spike protein

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### Introduction

#### SARS-CoV 2 Structure



- Single-stranded RNA-enveloped virus
- It bends to the angiotensin converting enzyme 2 (ACE2)
- Basic reproduction number (R0) is around 3,8<sup>[1]</sup>
- accumulates two single-letter mutations per month<sup>[2]</sup>

1 https://www.rki.de/DE/Content/InfAZ/N/Neuartiges\_Coronavirus/Steckbrief.html

#### Sructure of SARS-CoV-2 spike protein





- spike protein mediates the membrane fusion process
- Spike protein has 2 subunits –
  S1 and S2
- S1 catalyzes attachment,
  S2 -subunit fusion
- S2 forms a six-helical bundle via the two-heptad repeat domain, HR1 and HR2 ("fusion core region").

## Antiviral drugs



Classes:

- Spike maturation inhibitor
- Protease inhibitor
- Fusion inhibitor
- Polymerase inhibitor

Only Remdesivir was approved by FDA, but was later exluded from the guidline <sup>[4]</sup>

4. https://apps.who.int/iris/handle/10665/336729

#### (b) Most frequent drug targets or mechanisms



# Aim of the study

- to screen a list of peptides which were designed to bind the HR1 domains
- A peptide with the largest number of contacts with the HR1 domains would inhibit the membrane fusion, and therefore infection

## Methods

#### VMD - Visual Molecular Dynamics



- for structure visualization
- displaying, animating, and analyzing large biomolecular systems using 3-D graphics

![](_page_8_Picture_4.jpeg)

#### **CABS** Dock

- for protein-peptide docking
- coarse-grained model (it decreases a time of long simulations)
- advantages:
- 1. Can be used without knowing the binding site and peptide conformation
- 2. Peptide conformation is allowed to be fully flexible
- 3. It is possible to simulate significant conformational changes

![](_page_9_Figure_7.jpeg)

#### **Coarse-grained Model**

![](_page_9_Picture_9.jpeg)

### **CABS Dock**

![](_page_10_Figure_1.jpeg)

Steps:

- 1. Generating random structures
- 2. Simulation of binding and docking
- 3. Selection of the final models

### Results

HR1

HR2

Chain A and B

Chain C

Chain D

- Original structure:
- Fraction of contacts 51 % (cutoff 5Å)
- number of residues in chain D, that are in contact 20
- Chain D of HR2 has 41 amino acids
- The docking was run with a shorten version of the peptide HR2 (chain D): VVNIQKEIDRLNEVAKNLNESLID:CCCHHHHHHHHHHHHHHHHHHHHHHHH
- 24 amino acids, 18 of them form helices,
- The docking was run 2 times, first time with a number of cycles 100, second time 200, chain C was excluded.
- Parameters (100 cycles): model 5 (fraction 62, contacts 15), model 6 (fraction 70, contacts 17).
- Parameters (200 cycles): model 4 (fraction 75, contacts 18), model 6 (fraction 66, contacts 16), model 9 (fraction 54, contacts 13).
- Parameters (200 cycles+residues beside helix exluded): model 1 (fraction 62, contacts 15),
  model 4 (fraction 70, contacts 17)

![](_page_12_Figure_0.jpeg)

![](_page_12_Figure_1.jpeg)

Residues of chain A after docking in contact with chain D (within 5): 17 ASN 20 ILE 21 GLY 23 ILE 24 GLN 27 LEU 28 SER 30 THR 31 ALA 34 LEU 35 GLY 38 GLN 39 ASP Residues of chain B after docking in contact with chain D (within 5):

90 GLN 93 SER 94 ALA 97 LYS 98 ILE 100 ASP 101 SER 104 SER 105 THR 108 ALA 111 LYS

Blue amino acids mean the same contacts as in original structure. 200 cycles were also chosen for docking the derivatives.

- 10 derivatives were tested (additional parameter all amino acids form helices)
- Best peptide structures need to have higher fraction of contacts than in original peptide (>51)

models	218	1086	3200	3494	3630	6089	6154	7060	7407	9119
	7	-	-	-	-	-	-	-	-	-
model_full-0:	0 0.00 1	14 66.00 1	10 47.00 1	1 3.00 1	17 73.00 1	3 13.00 1	12 50.00 1	1 4.00 1	8 30.00 1	0 0.00 1
model_full-1:	5 20.00 1	0 0.00 1	2 9.00 1	0 0.00 1	1 4.00 1	0 0.00 1	6 25.00 1	16 64.00 1	0 0.00 1	3 12.00 1
model_full-2:	3 12.00 1	11 52.00 1	12 57.00 1	7 26.00 1	0 0.00 1	4 17.00 1	10 41.00 1	6 24.00 1	0 0.00 1	0 0.00 1
model_full-3:	13 52.00 1	0 0.00 1	0 0.00 1	22 84.00 1	18 78.00 1	11 47.00 1	0 0.00 1	1 4.00 1	0 0.00 1	16 64.00 1
model_full-4:	1 4.00 1	15 71.00 1	13 61.00 1	13 50.00 1	16 69.00 1	16 69.00 1	14 58.00 1	10 40.00 1	12 46.00 1	0 0.00 1
model_full-5:	13 52.00 1	0 0.00 1	0 0.00 1	5 19.00 1	0 0.00 1	14 60.00 1	0 0.00 1	0 0.00 1	17 65.00 1	4 16.00 1
model_full-6:	0 0.00 1	0 0.00 1	3 14.00 1	2 7.00 1	0 0.00 1	10 43.00 1	14 58.00 1	8 32.00 1	2 7.00 1	0 0.00 1
model_full-7:	18 72.00 1	10 47.00 1	5 23.00 1	15 57.00 1	1 4.00 1	0 0.00 1	12 50.00 1	18 72.00 1	15 57.00 1	11 44.00 1
model_full-8:	18 72.00 1	0 0.00 1	12 57.00 1	5 19.00 1	7 30.00 1	6 26.00 1	3 12.00 1	0 0.00 1	16 61.00 1	13 52.00 1
model_full-9:	0 0.00 1	8 38.00 1	9 42.00 1	0 0.00 1	8 34.00 1	1 4.00 1	3 12.00 1	6 24.00 1	13 50.00 1	0 0.00 1

First number-number of contacts Second number-fraction of contacts

![](_page_14_Figure_0.jpeg)

- Ranking according to the predicted number of models, fractions and position of a modal in a rank:
- ► 1. DERIVATIVE\_3630
- ► 2. DERIVATIVE\_1086
- ► 3. DERIVATIVE\_3200
- ► 4. DERIVATIVE\_3494
- **5**. DERIVATIVE\_6089
- ► 6. DERIVATIVE\_7060
- ► 7. DERIVATIVE\_9119
- ► 8. DERIVATIVE\_6154
- 9. DERIVATIVE\_218
- ► 10. DERIVATIVE\_7407

# **PPI-Affinity**

#### Peptide Affinity (kcal/mol)

![](_page_16_Figure_2.jpeg)

The most promising candidates:

- 1. DERIVATIVE\_1086
- 2. DERIVATIVE\_3200
- 3. DERIVATIVE\_3630

Vmd images of top 3 candidates

![](_page_17_Picture_1.jpeg)

DERIVATIVE\_3630, Model\_full 0 (73%, 17 contacts)

![](_page_17_Picture_3.jpeg)

#### DERIVATIVE\_1086, Model\_full 0 (66%, 14 contacts)

DERIVATIVE\_3200 Model\_full 2 (57%, 12 contacts)

# Tnanks you for attention!