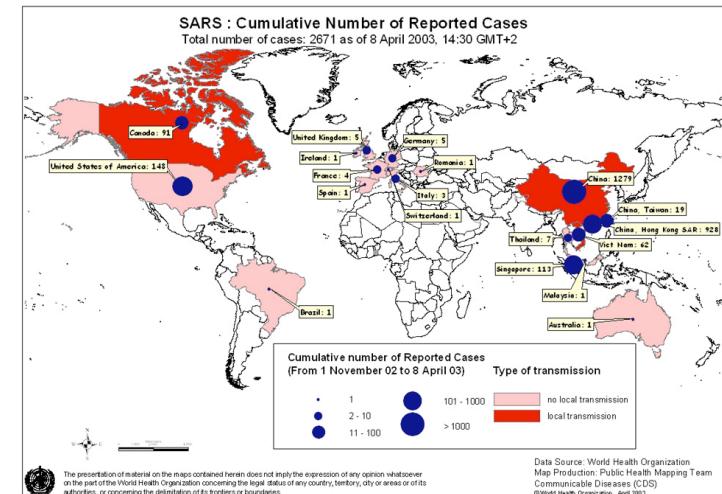


Structure of SARS coronavirus spike protein receptor-binding domain complexed with receptor

Fang Li

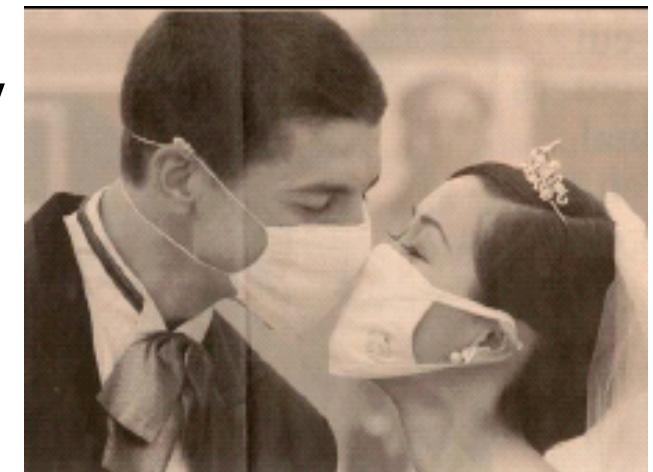
Harvard Medical School
Boston Children's Hospital

ALS user meeting
October 20, 2005

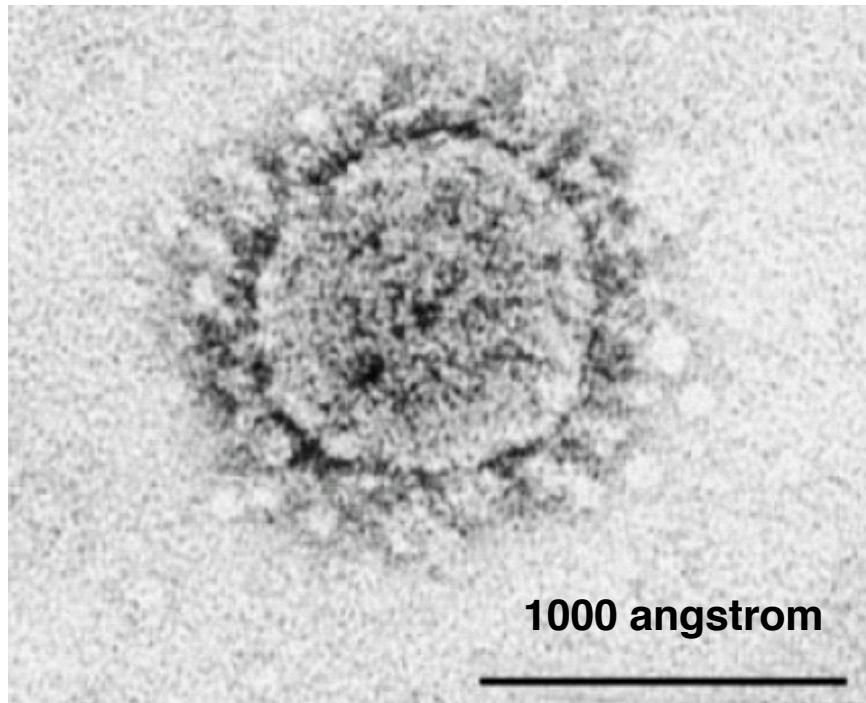


SARS: an open scar

- 2002-2003
 - Over 8000 people infected; 10% fatality
- 2003-2004
 - 4 infections; no fatality
- World still on alert
- No cure



The pathogen behind it all: SARS coronavirus (SARS-CoV)

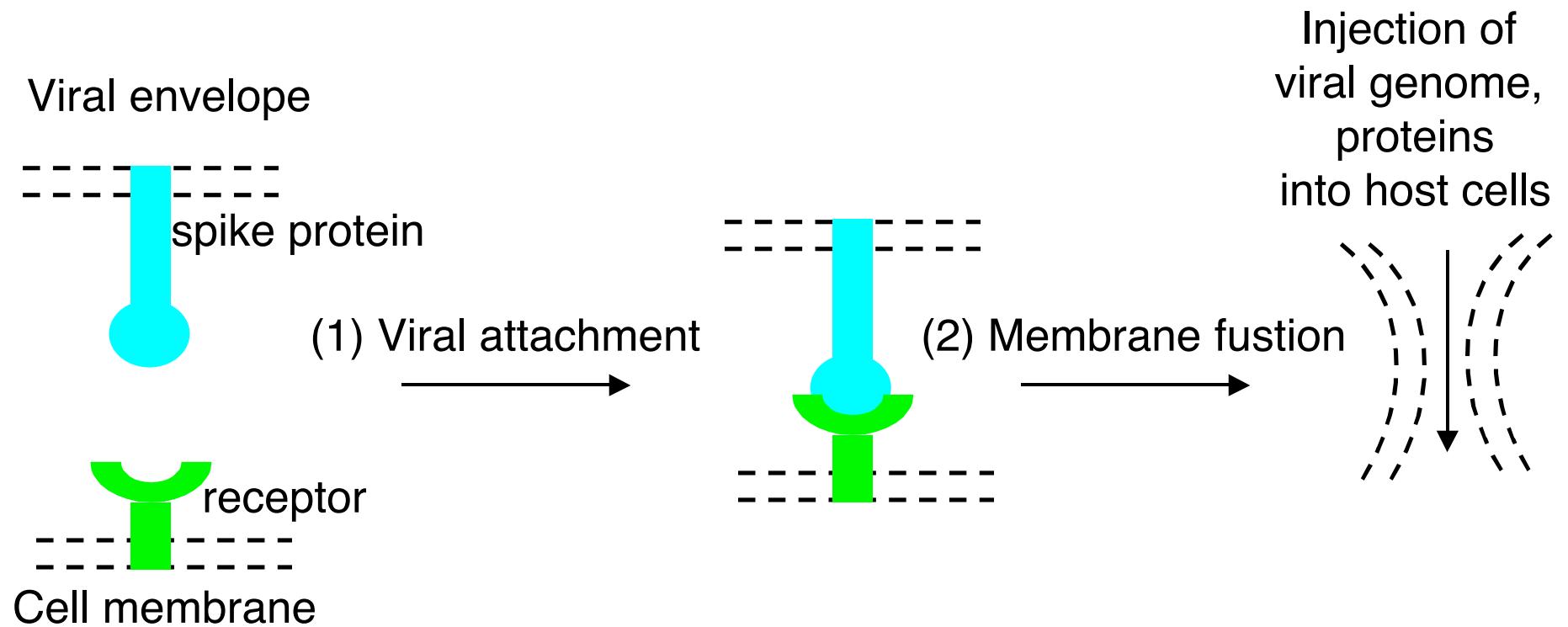


- Large, enveloped, positive-stranded RNA virus
- Originated from animals (palm civets? bats?)
- Large spikes on the surface (corona = crown)

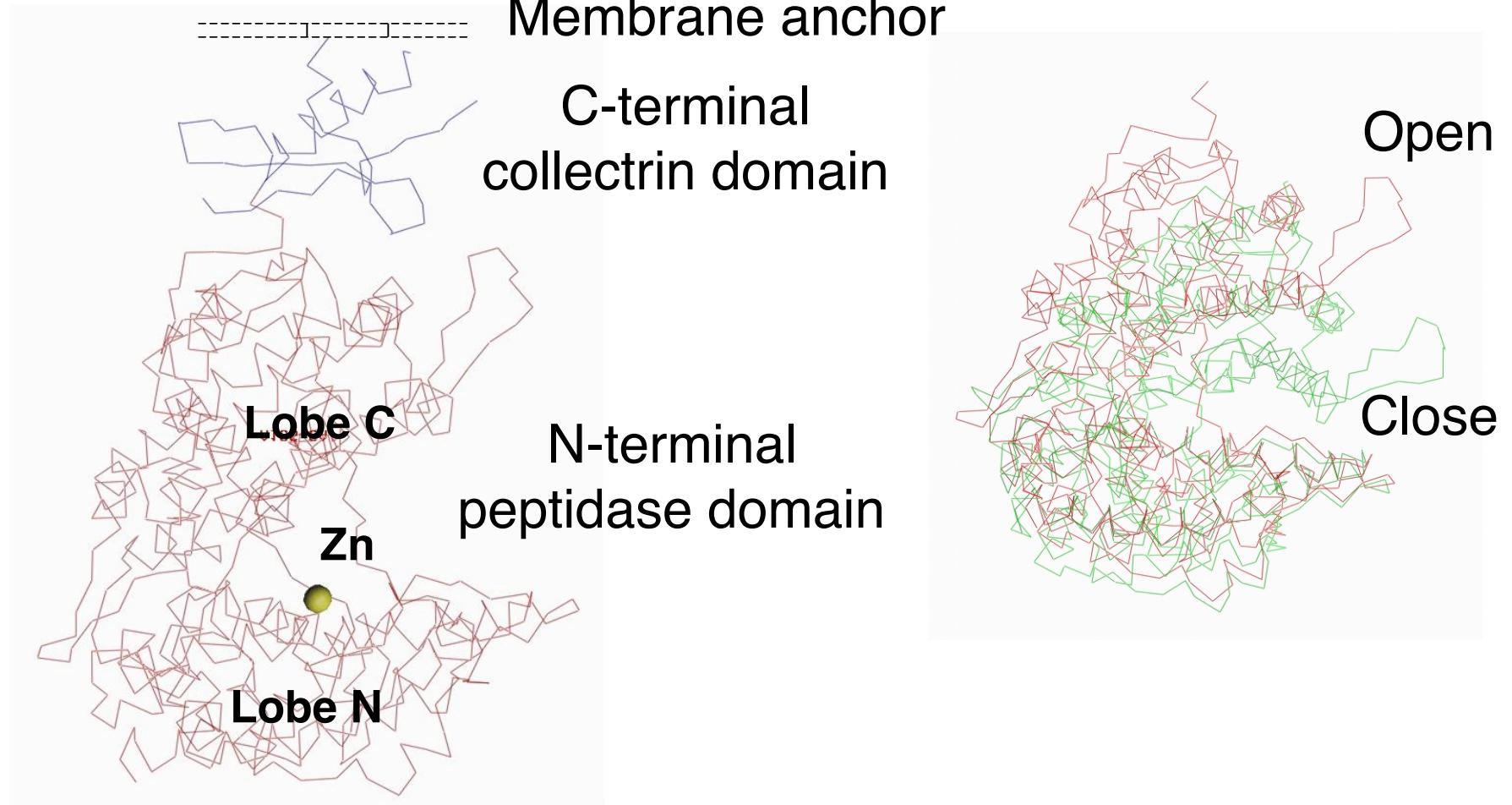
T. G. Ksiazek *et al.*, *N. Engl. J. Med.*
348, 1953 (2003)

The coronavirus spike protein

Virus-receptor interactions, viral host range, viral tropism,
viral entry, host immune responses



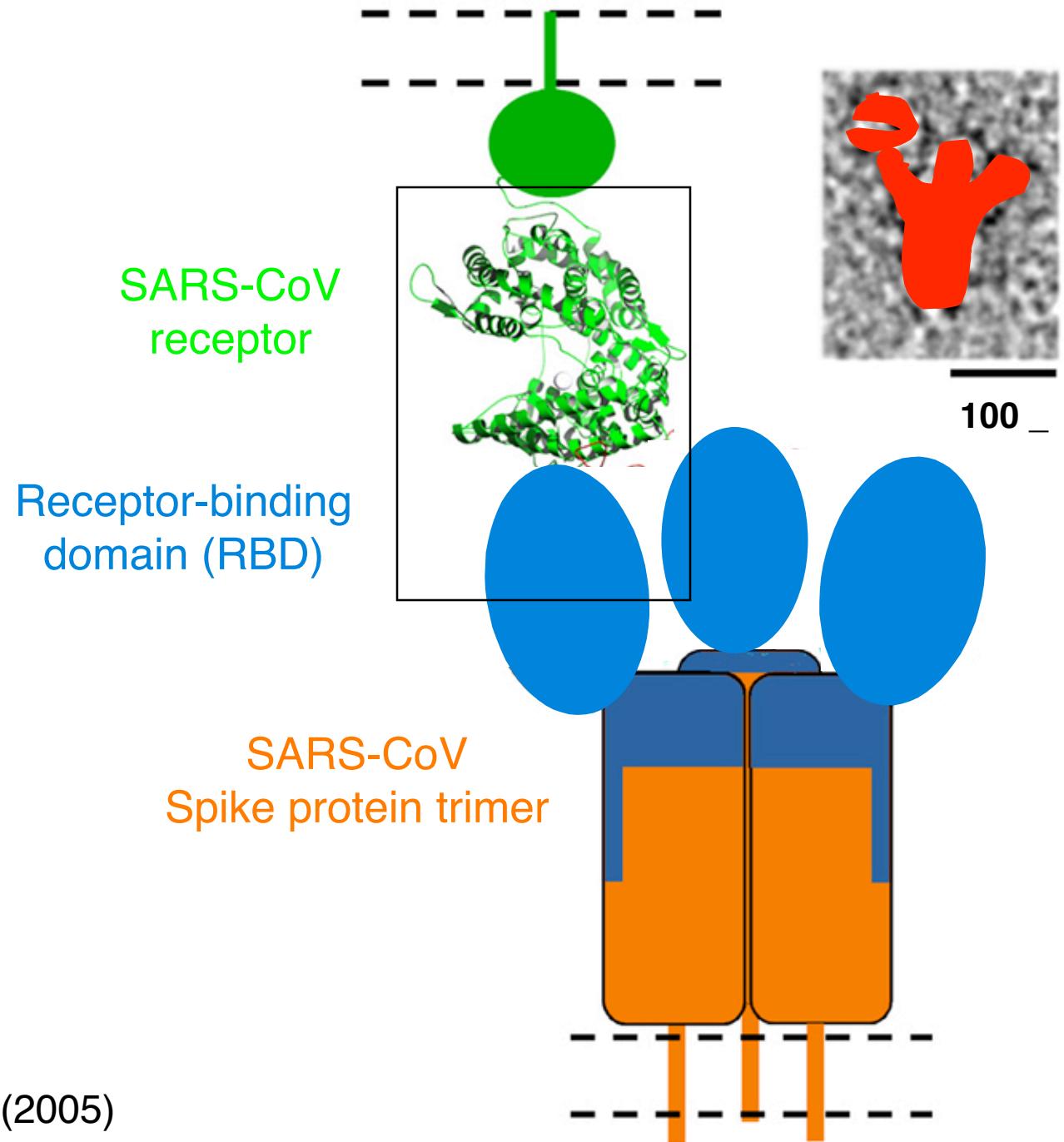
The SARS-CoV receptor – ACE2



W. Li *et al.*, *Nature* **426** (2003)

P. Towler *et al.*, *J Biol Chem* **279** (2004)

SARS-CoV attachment machinery

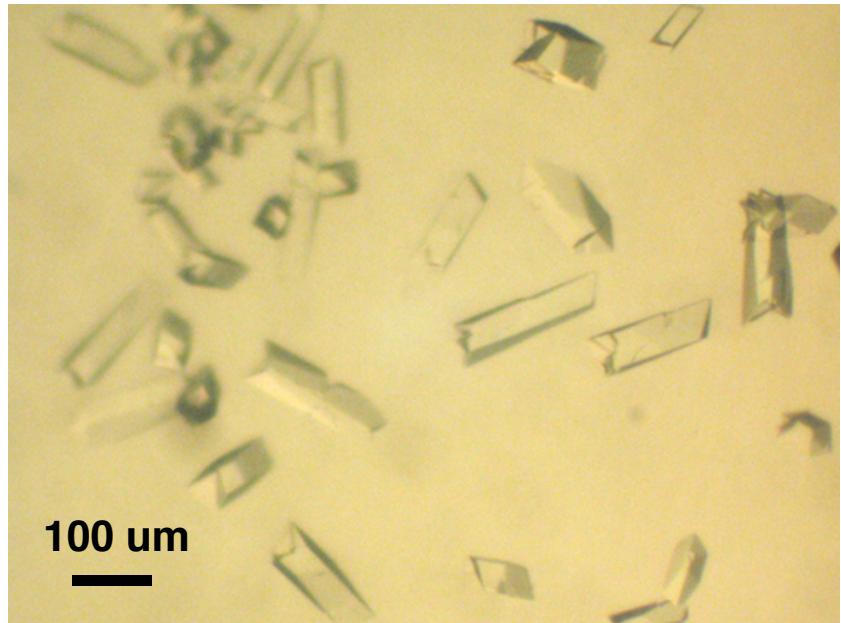


F. Li *et al.*, *in preparation* (2005)

Outline

- Structure of SARS-CoV-RBD complexed with ACE2
- Species specificity of SARS-CoV
- Structure-based vaccine design
- Lesson from SARS

Crystals of SARS-CoV-RBD complexed with ACE2



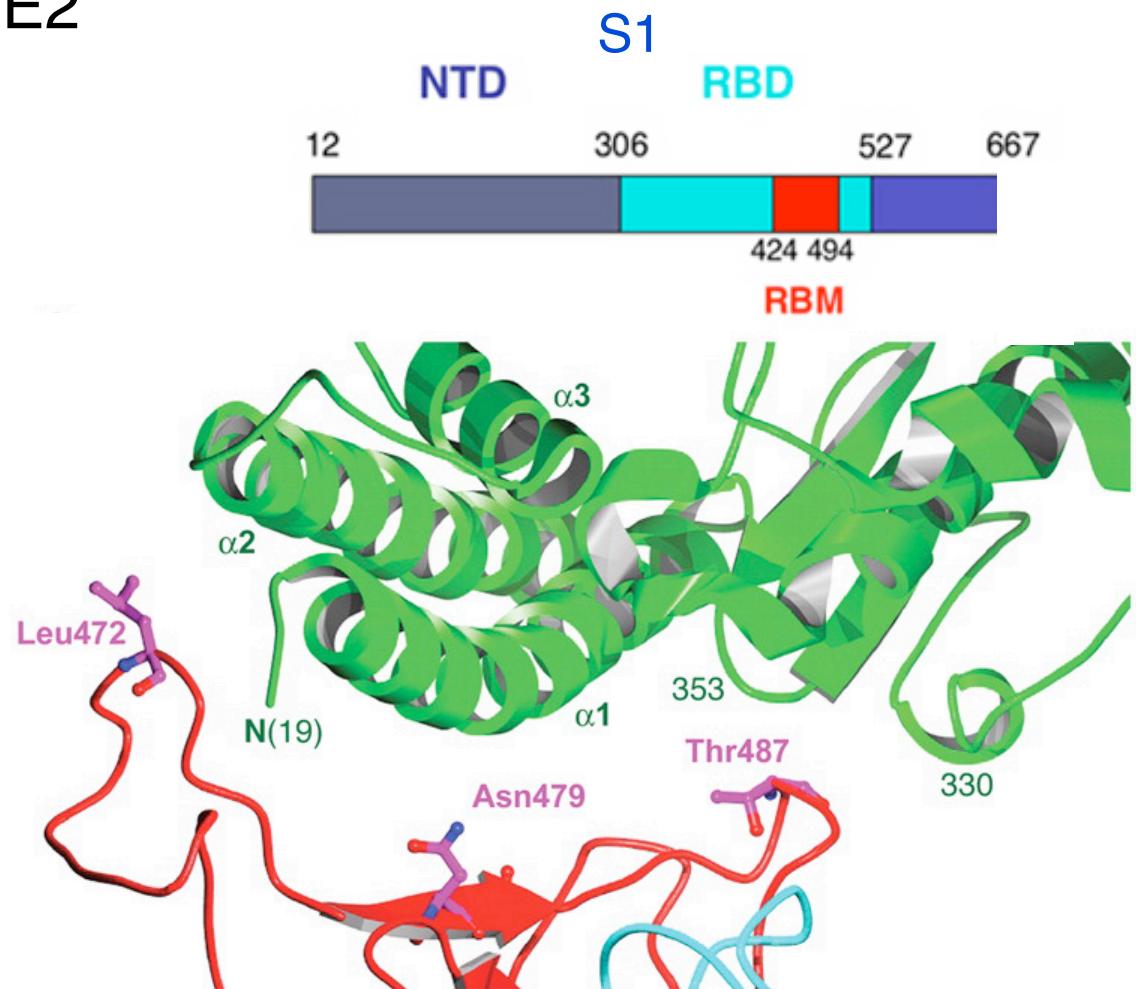
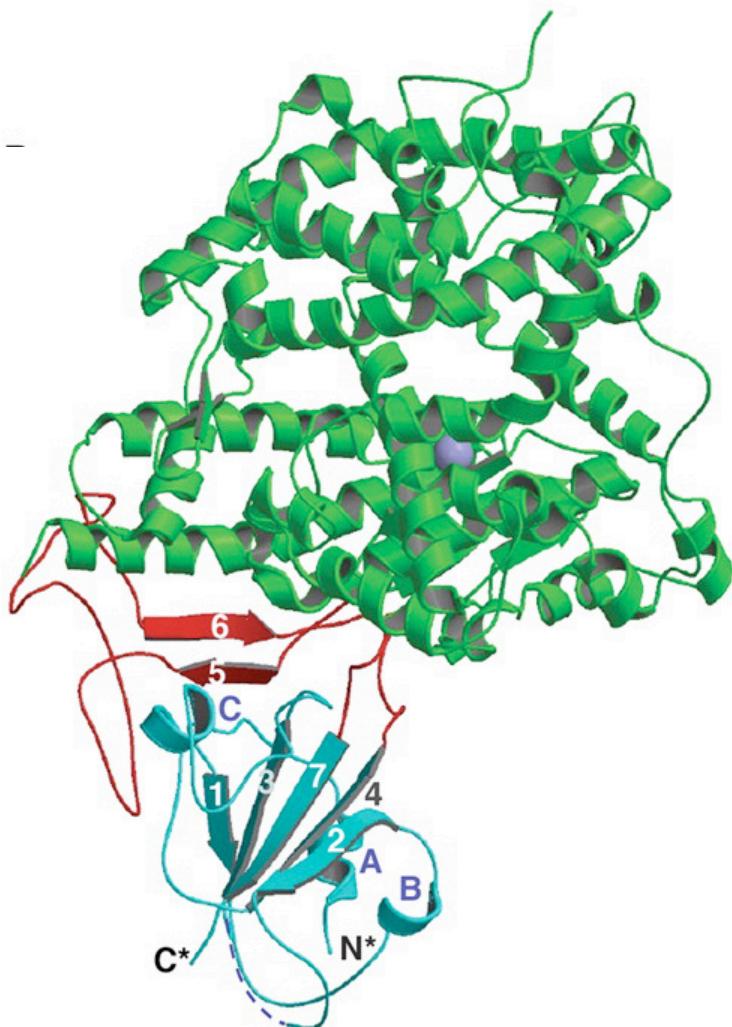
100 μm

24% PEG 6000
150 mM NaCl
100 mM Tris pH 8.2
10% ethylene glycol
Hanging drop
Room temperature

Space group	P2 ₁ (a=82.3, b=119.4, c=113.2, α =91.9)
Resolution (angstrom)	50 – 2.9
Observed (unique) reflections	291978 (48819)
Rsym (last shell)	8.2% (63%)
% completeness (last shell)	96.6 (73.9)
I/sigma (last shell)	23.9 (1.9)
Rwork (Rfree)	22.1% (27.5%)

2 complexes per asymmetric unit
Molecular replacement using ACE2 as the search model

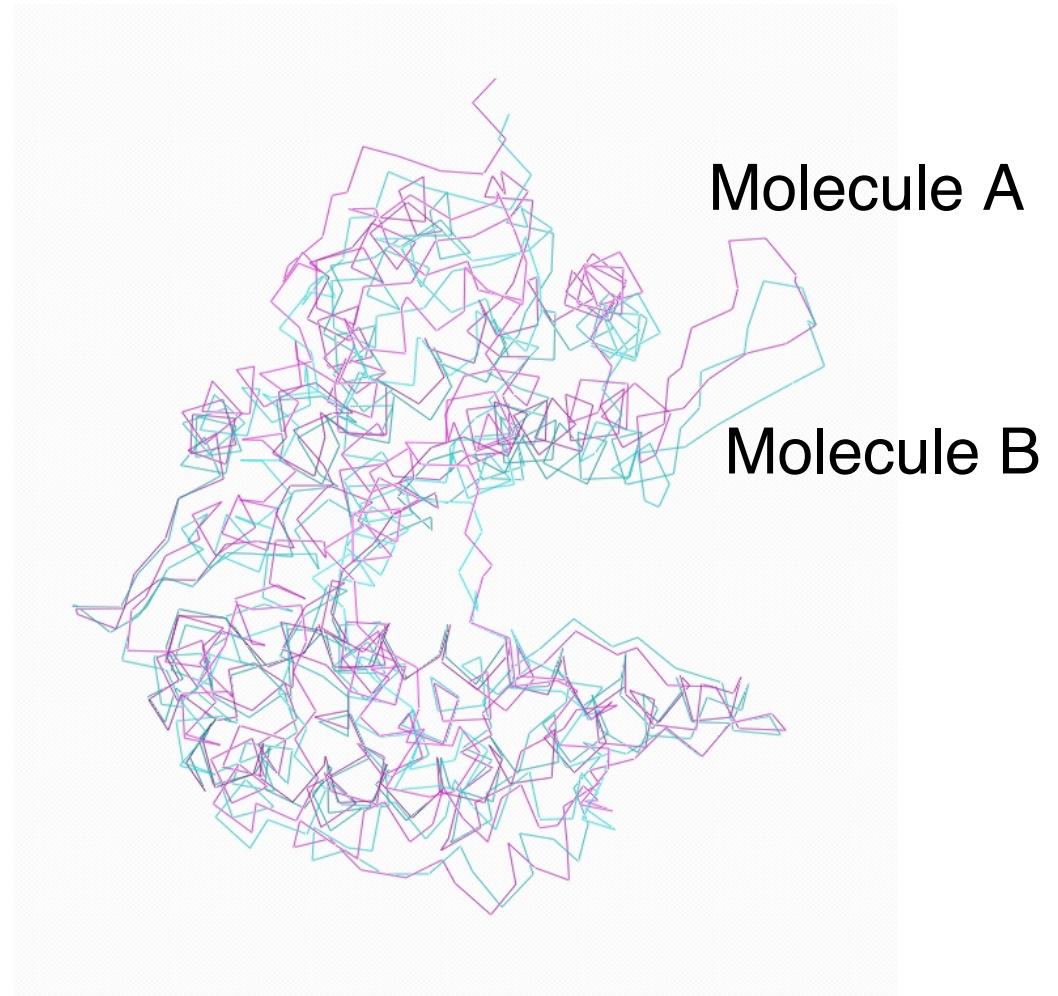
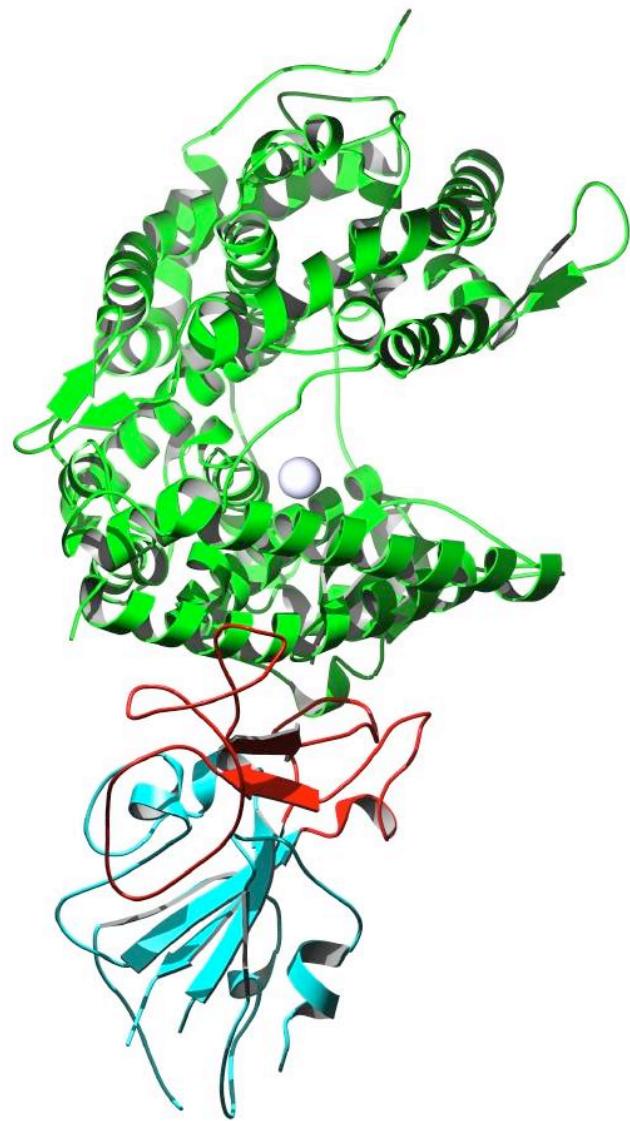
2.9 angstrom crystal structure of SARS-CoV RBD complexed with ACE2



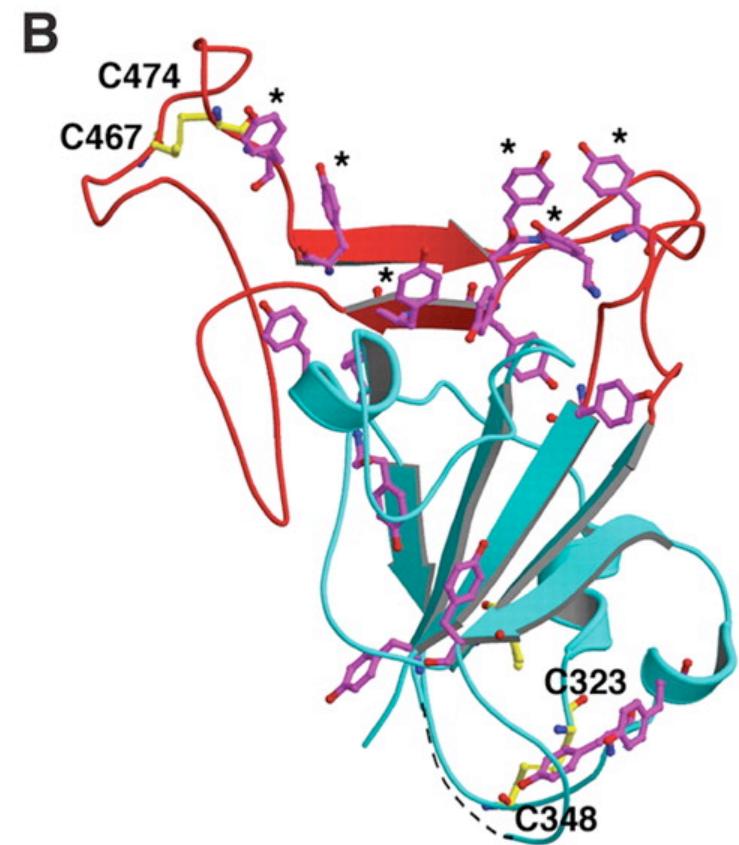
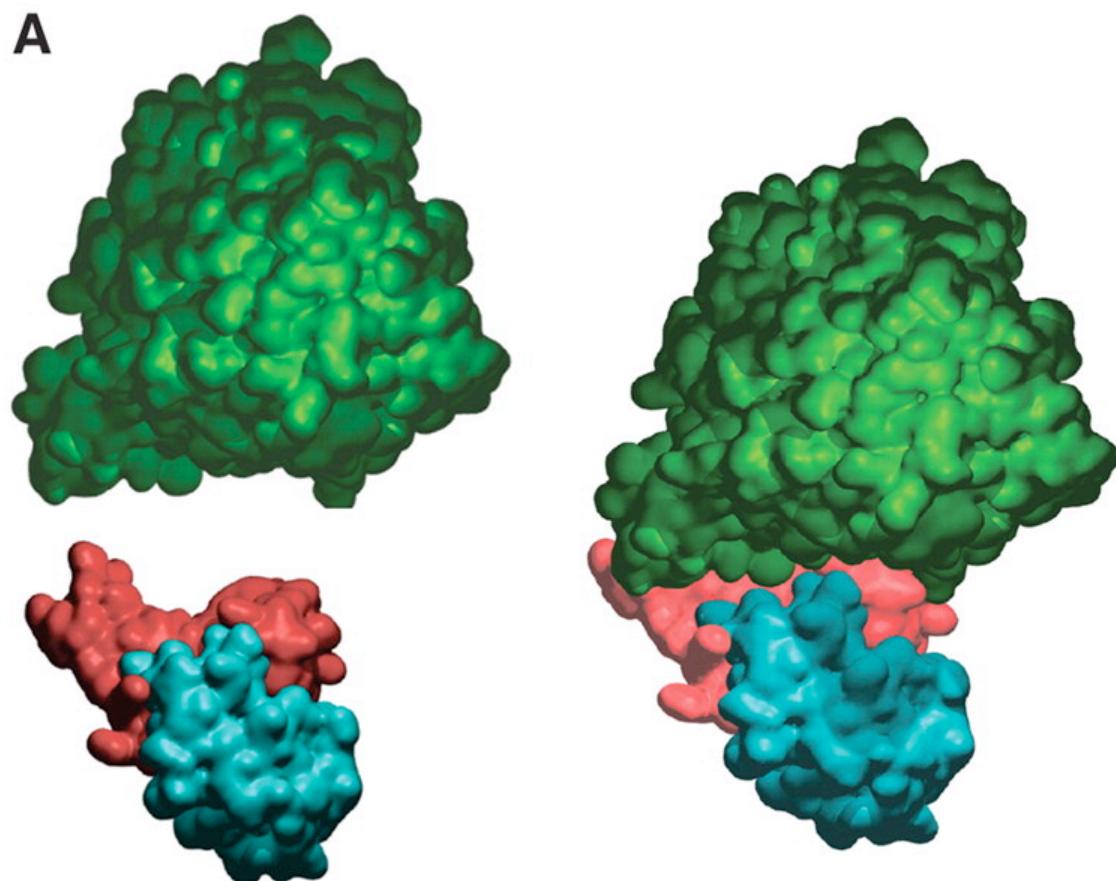
RBM - Receptor-binding motif

F. Li *et al.*, *Science* **309** (2005)

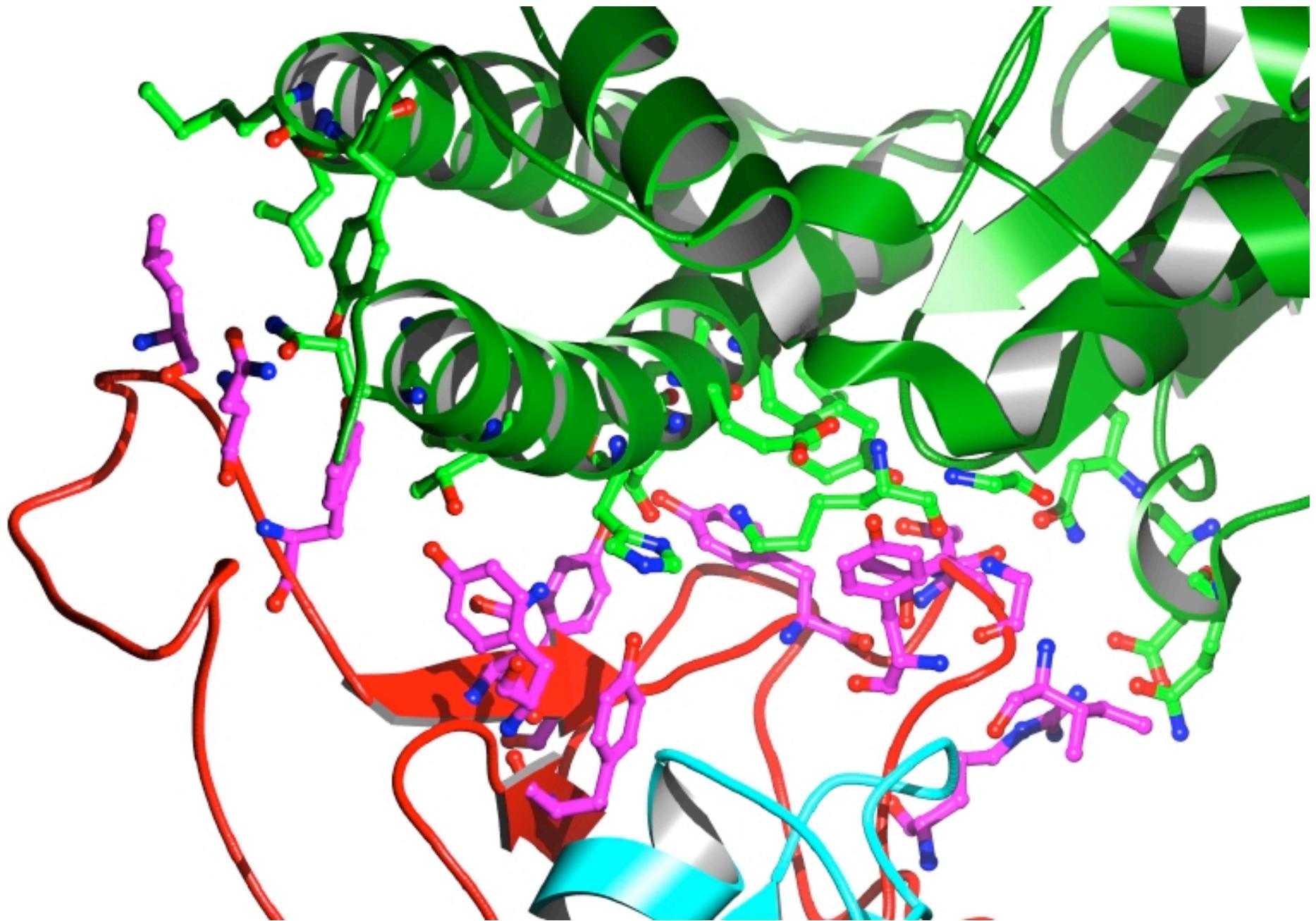
Different conformations of ACE2 in the crystal structure



Specific recognition of ACE2 by SARS-CoV



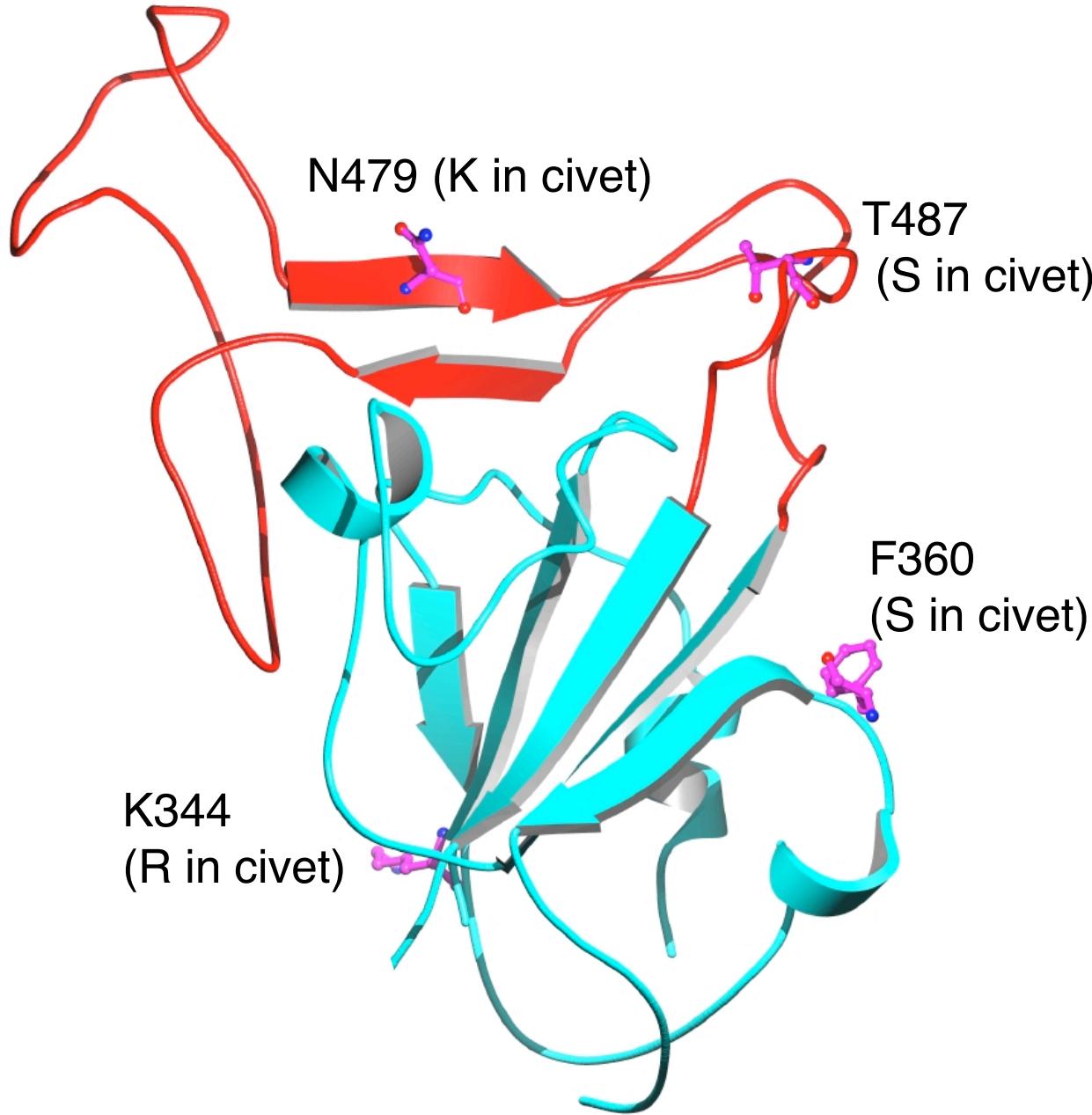
Extensive interactions at the SARS/receptor interface



Outline

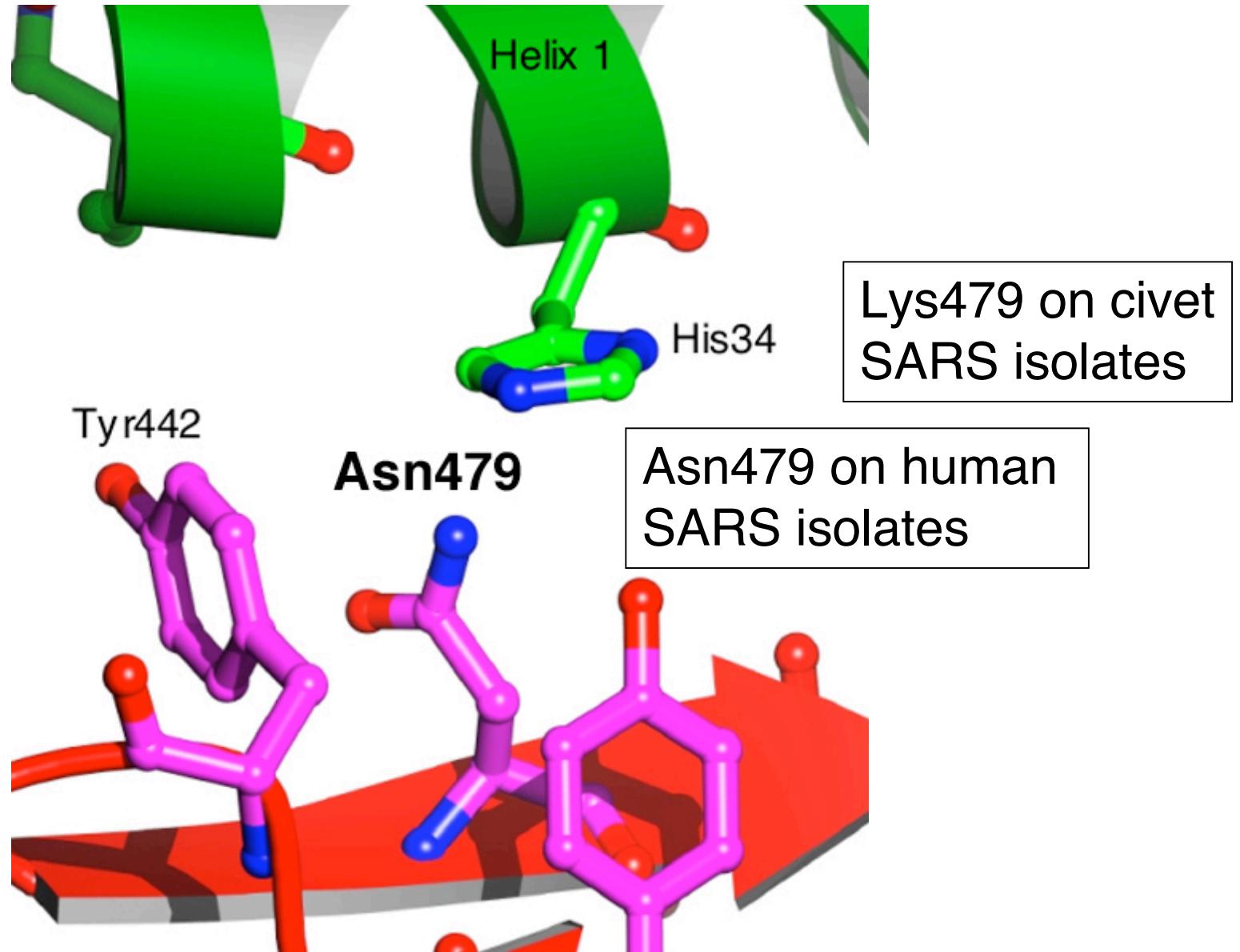
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Residues that differ in the RBDs of human and civet SARS

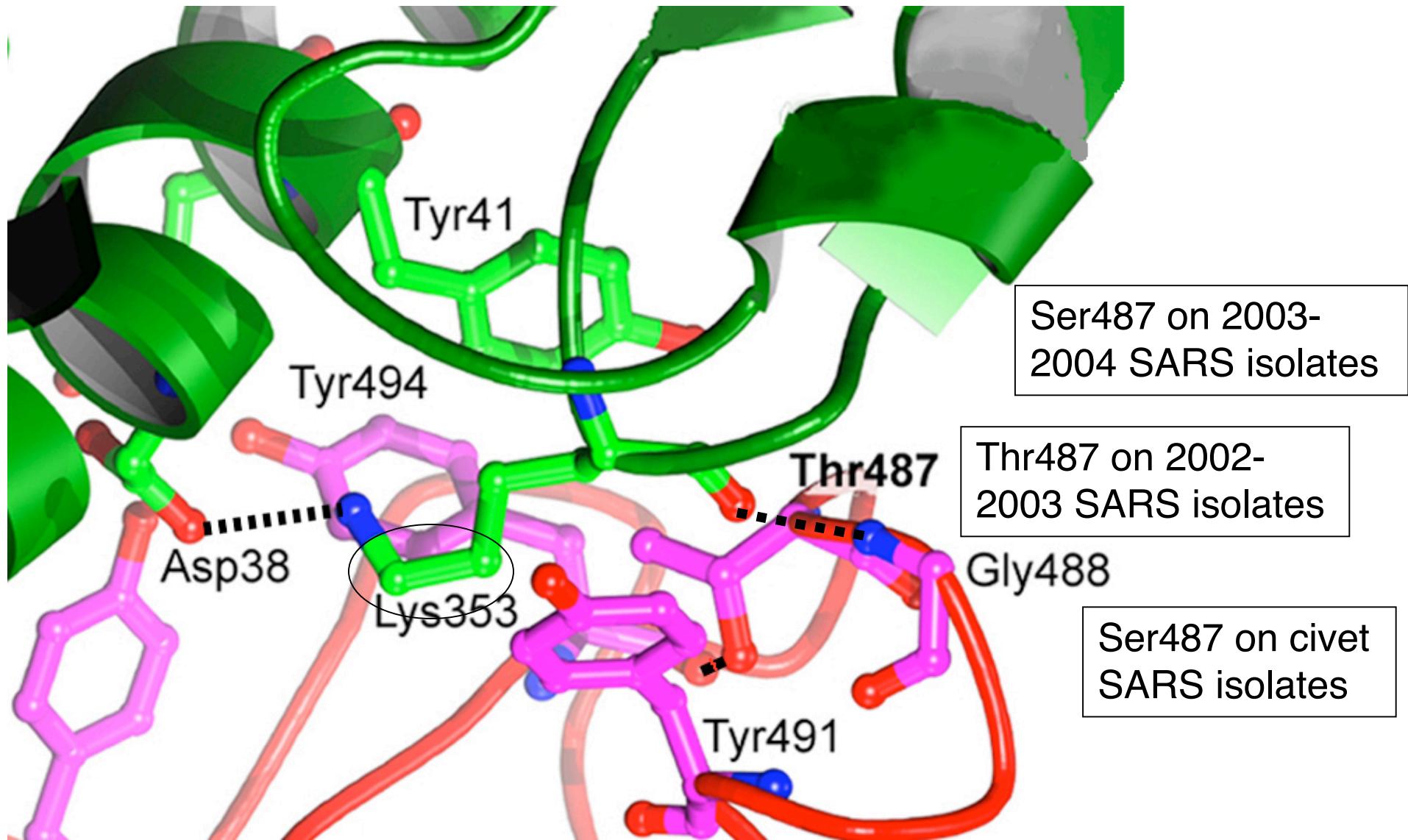


RBD	Kd (M) (hACE2)
human	1.6 $\times 10^{-8}$
SARS	1.6 $\times 10^{-8}$
K344R	1.6 $\times 10^{-8}$
F360S	1.4 $\times 10^{-8}$
N479K	4.8 $\times 10^{-7}$
T487S	3.5 $\times 10^{-7}$
civet SARS-like	5.5 $\times 10^{-4}$

From civet to human: K479N



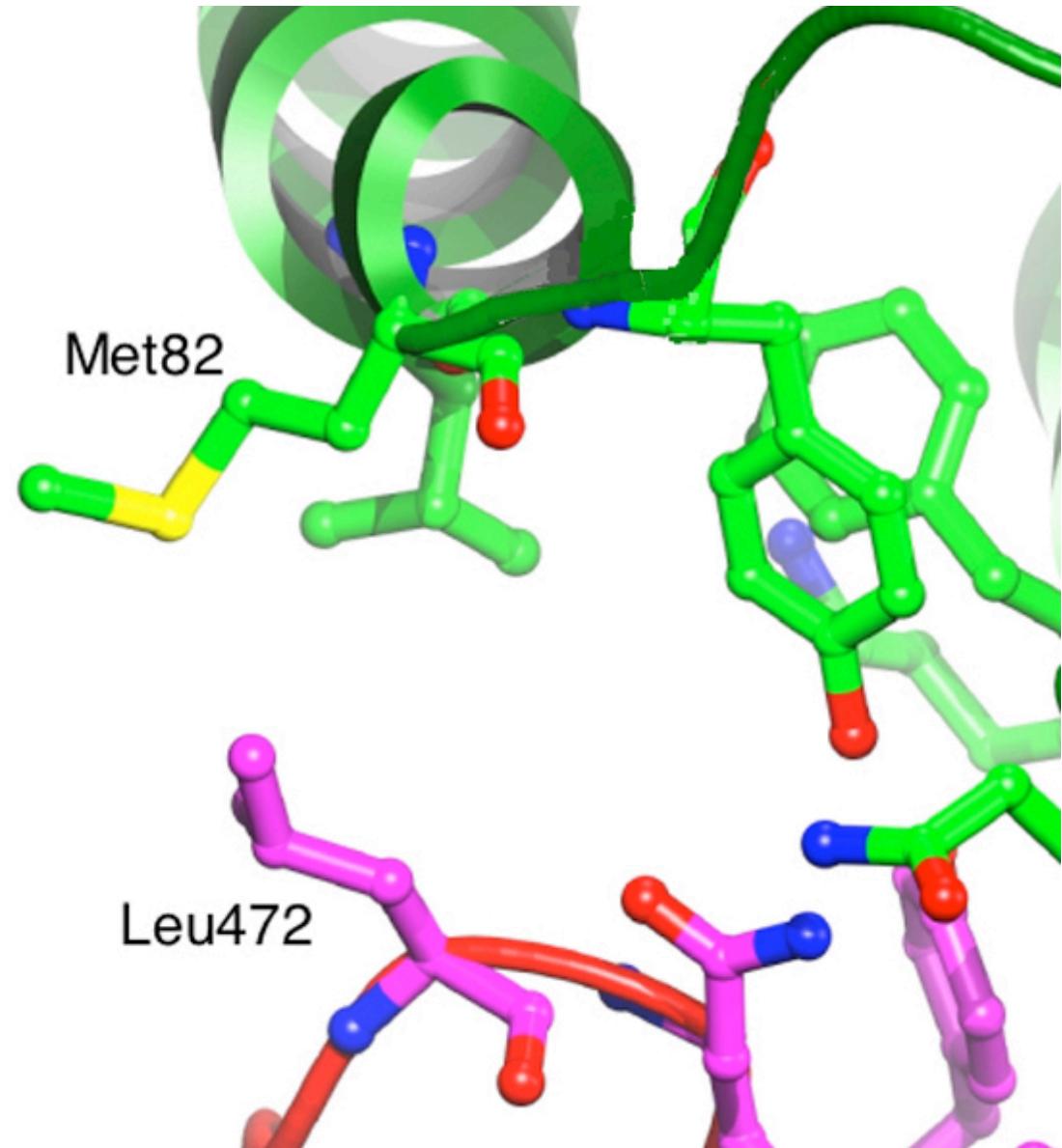
From human to human: S487T



A possible attenuation mutation: L472P

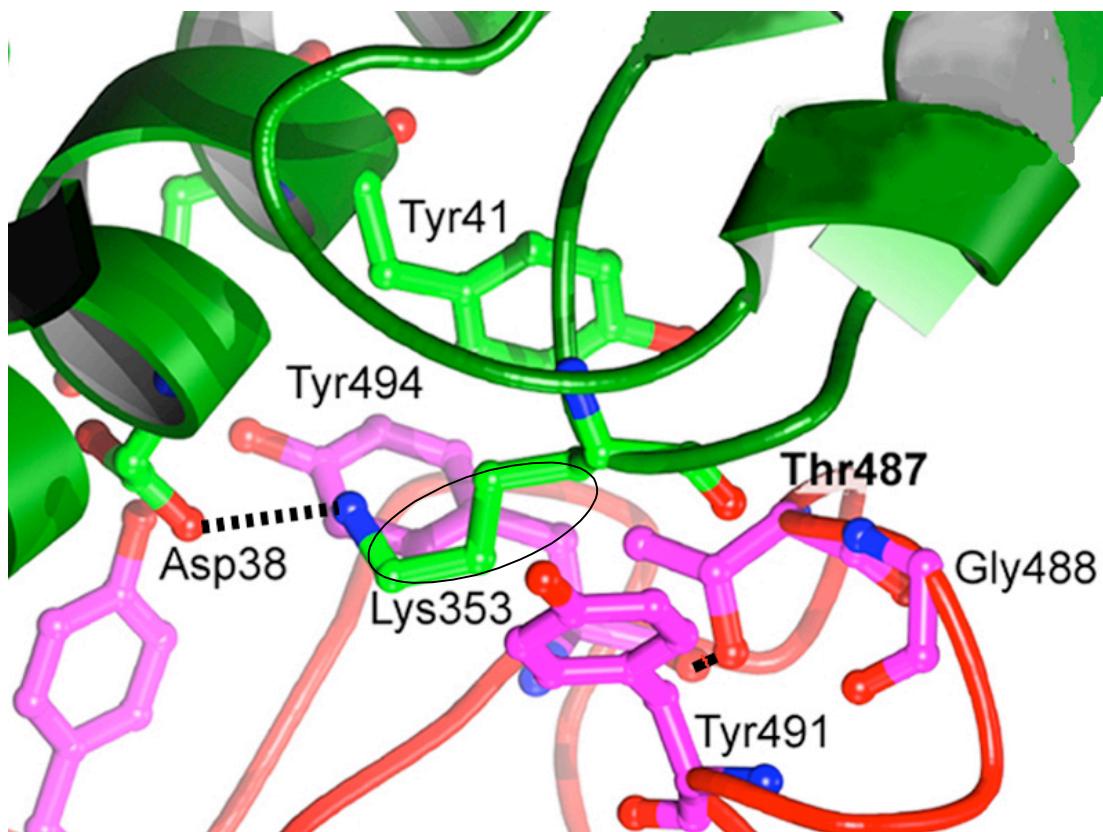
Pro472 on 2003-2004
SARS isolates

Leu472 on 2002-2003
SARS isolates

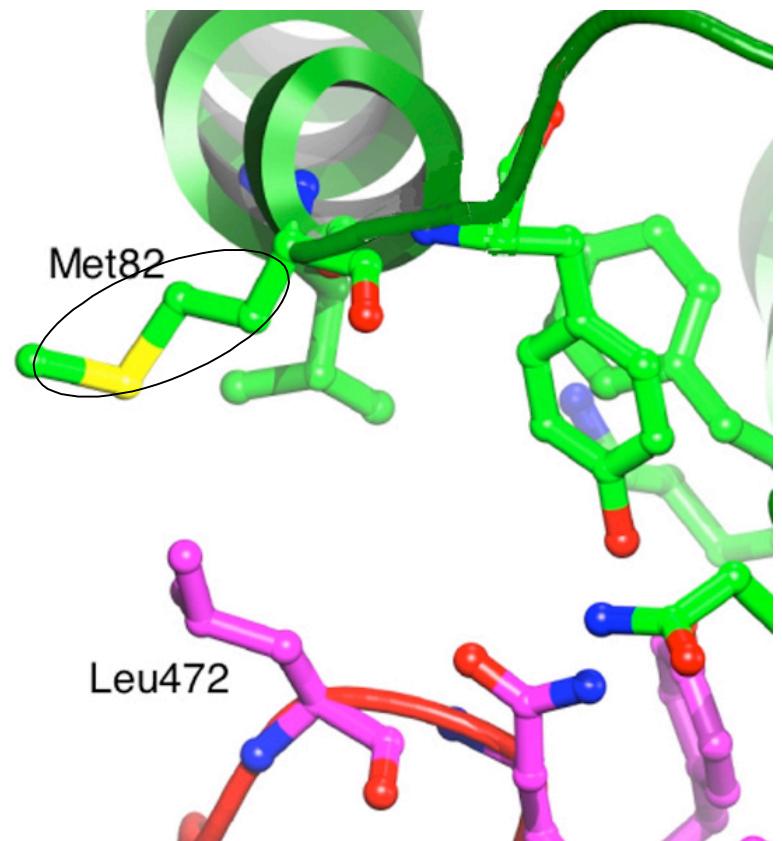


Why are rats safe from SARS?

(1) His353



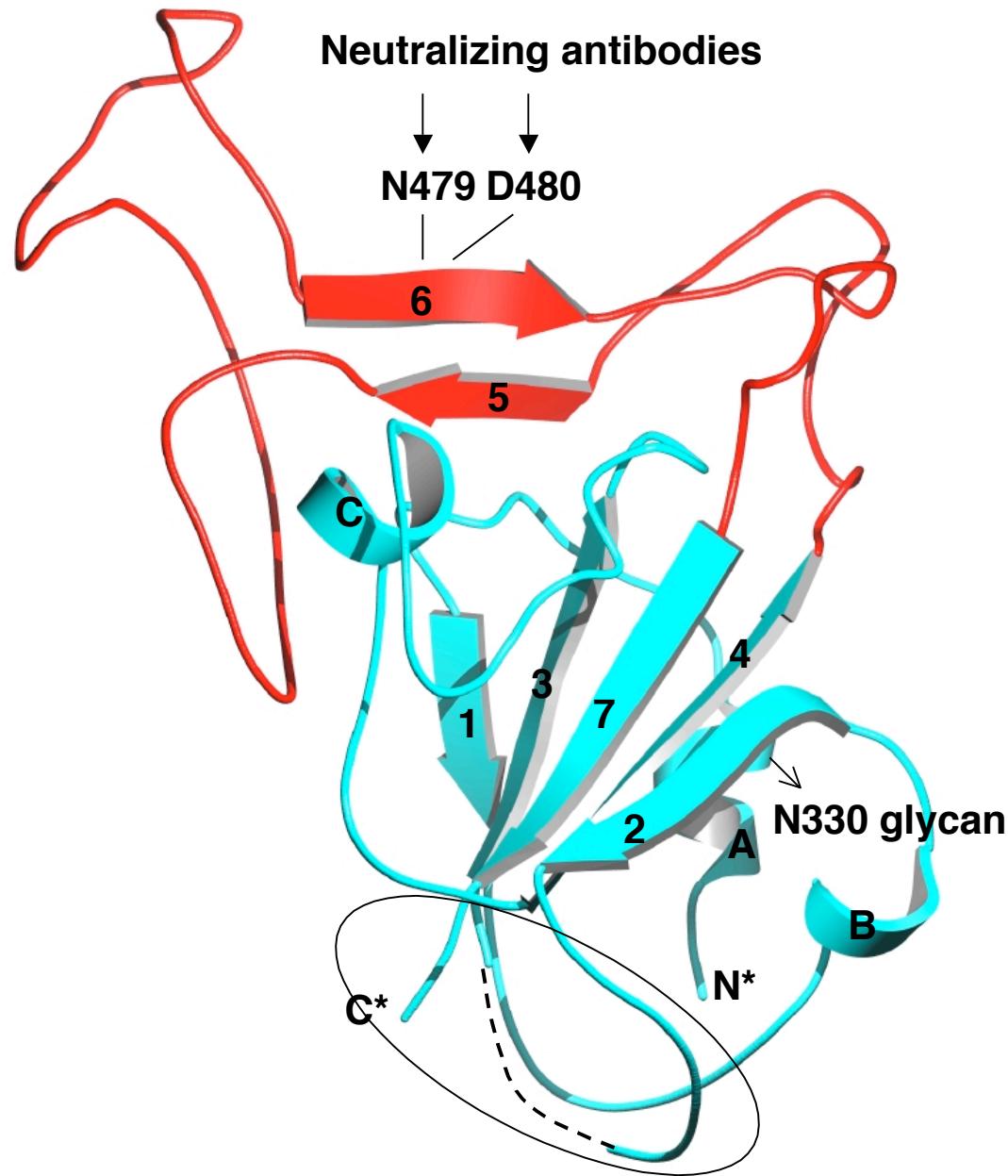
(2) Glycan at 82



Outline

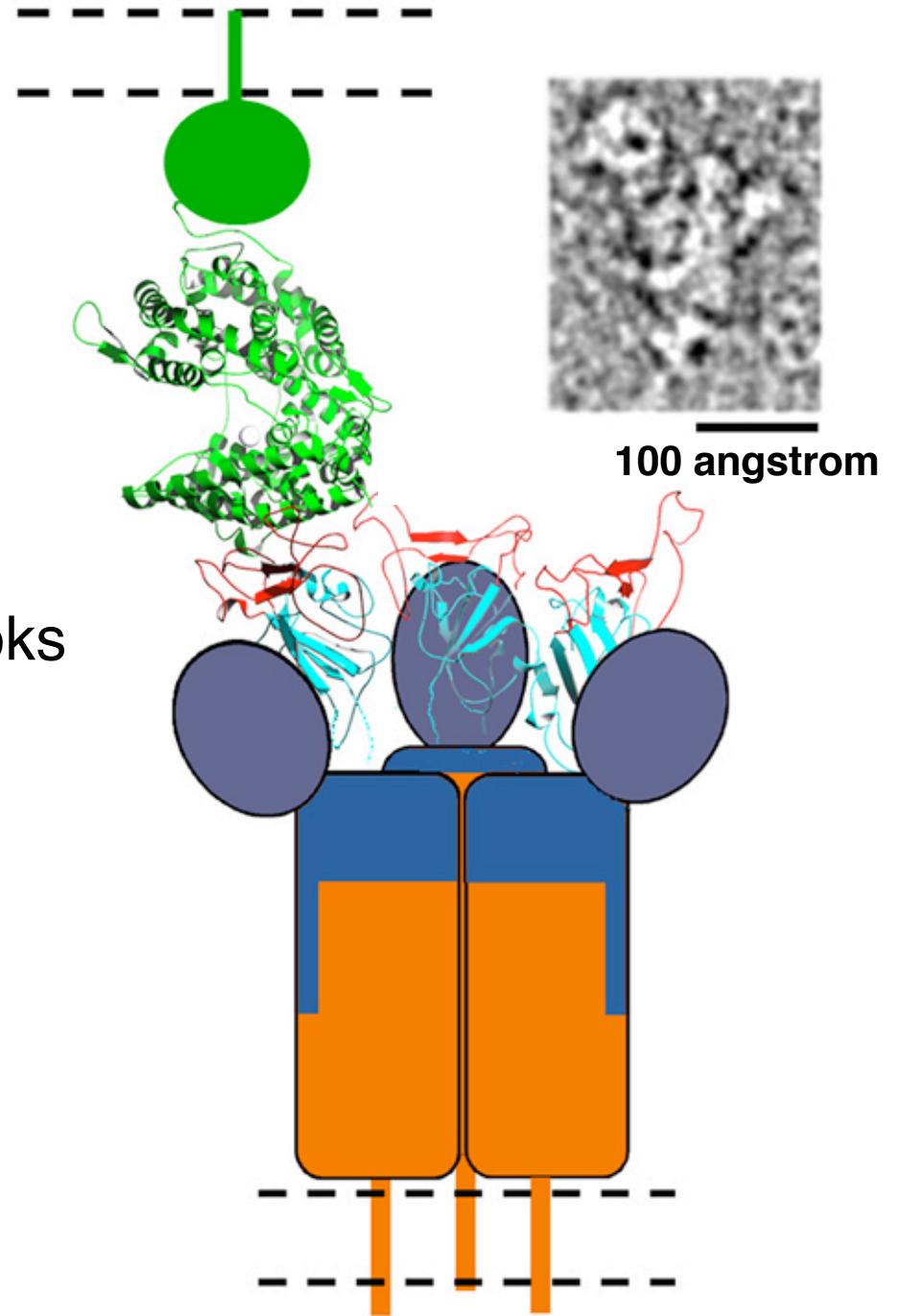
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Structure-based vaccine design



Outline

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“A dramatic epidemiological difference can result from what looks like an almost trivial mutation.”

Outline

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