Receptor Recognition by the Novel Coronavirus from Wuhan:an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus

Wan, Y., Shang, J., Graham, R., Baric, R. S., & Li, F. (2020). Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. Journal of virology, 94(7). DOI: 10.1128/JVI.00127-20.

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BIOL 386: Bioinformatics Laboratory

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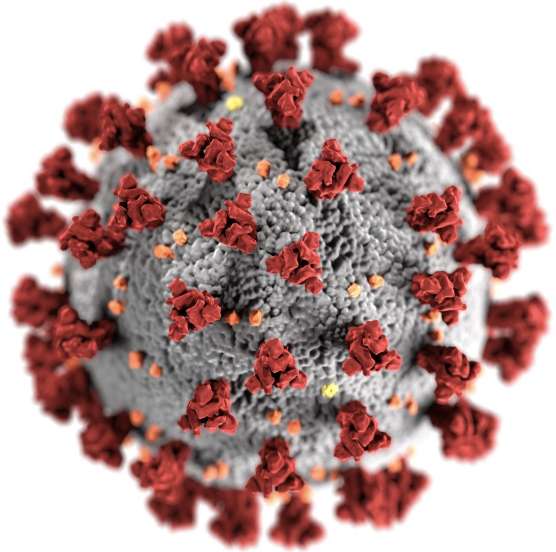
Outline

- 2019-nCoV and SARS-CoV present similarities
- 2019-nCoV is most related to the β-genus lineage b bat SARS-like coronaviruses
- SARS-CoV and 2019-nCoV share sequence similarities in their spike proteins
- SARS-CoV and 2019-nCoV spike proteins are 77% similar
- SARS-CoV contains a core structure as well as a receptor binding motif (RBM)
- Mutations in the RBM spike protein affect binding to the host ACE2 protein
- Amino acid positions that enhance viral binding of SARS-CoV to ACE2
- They built a model of 2019-nCoV binding to ACE2 based off of the previous structure
- Five amino acids in ACE2 that are important for spike protein binding
- Optimal Viral Binding Between Civet SARS-CoV RBD and Civet ACE2
- Model of Viral Binding Between 2019-nCoV RBD and Civet ACE2
- Using the information presented, future work could help researchers make predictions and prepare ways to fight the virus

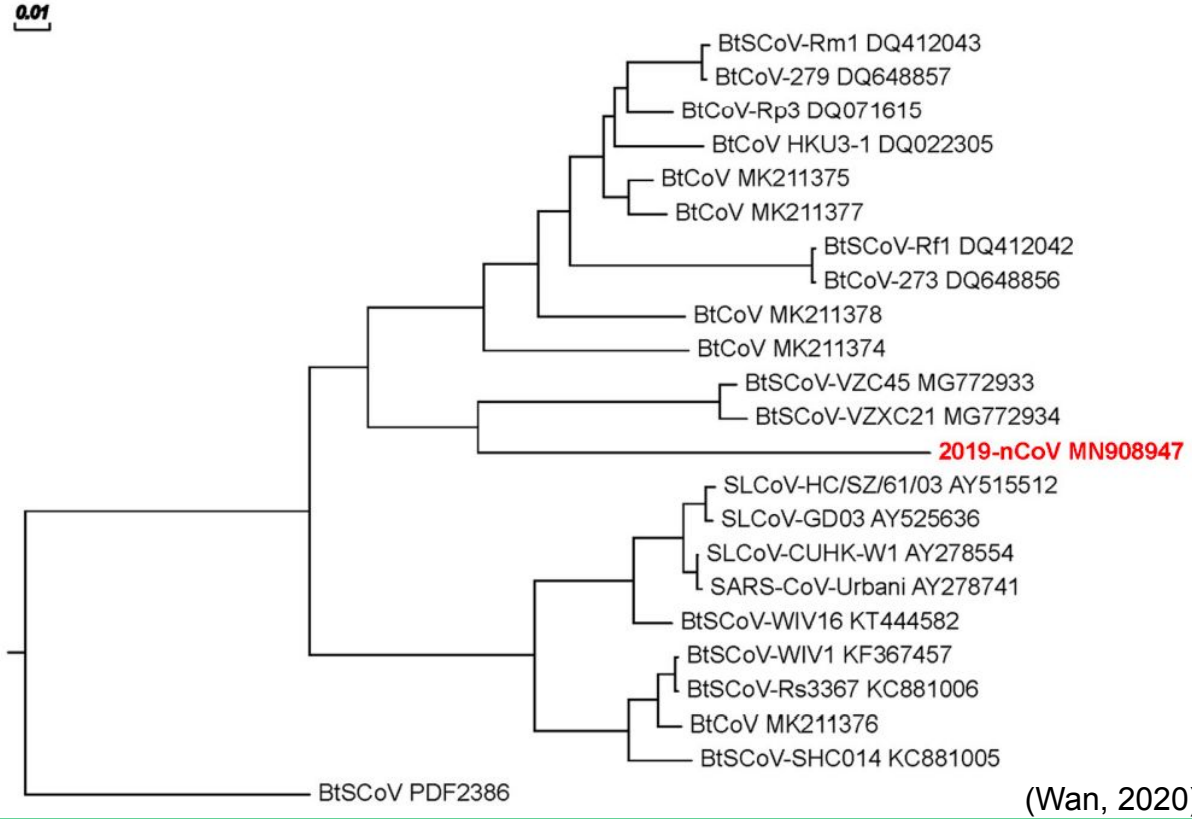
2019-nCoV has many similarities to SARS-CoV

- 2019-nCoV has many similarities to SARS-CoV including:
  - Belonging to β-genus of coronaviruses
  - Similar symptoms (Wan, 2020)
- 2019-nCoV causes respiratory illness that is spread through respiratory droplets and has unknown animal origin (CDC, 2020)



(CDC, 2020)

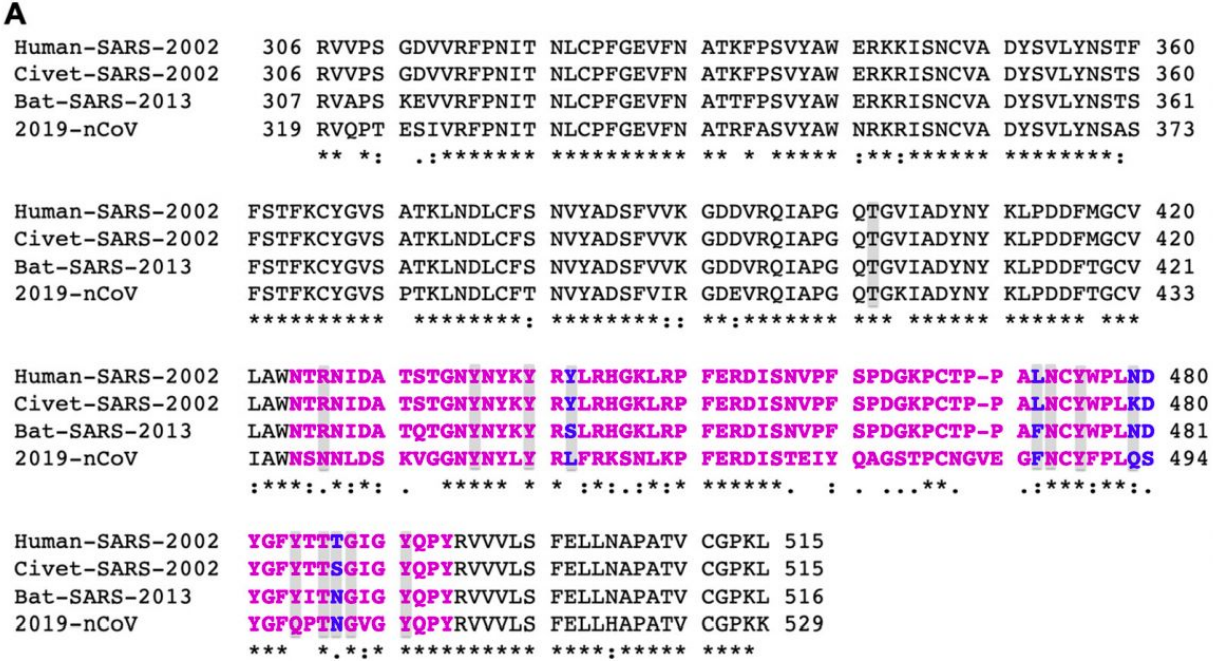
2019-nCoV is most related to the β-genus lineage b bat SARS-like coronaviruses



(Wan, 2020)

- These other viruses use ACE2 for entry into the cell

SARS-CoV and 2019-nCoV share sequence similarities in their spike proteins



- Suggest the possibility they share the same receptor

(Wan, 2020)

SARS-CoV and 2019-nCoV spike proteins are 77% similar

B

Spike / RBD / RBM	SARS-human	SARS-civet	SARS-bat	2019-nCoV
SARS-human	100% / 100% / 100%			
SARS-civet	98.12% / 98.10% / 97.18%	100% / 100% / 100%		
SARS-bat	92.33% / 94.29% / 92.96%	92.75% / 94.76% / 91.55%	100% / 100% / 100%	
2019-nCoV	76.04% / 73.33% / 50.00%	76.78% / 74.29% / 50.00%	77.50% / 75.71% / 52.78%	100% / 100% / 100%

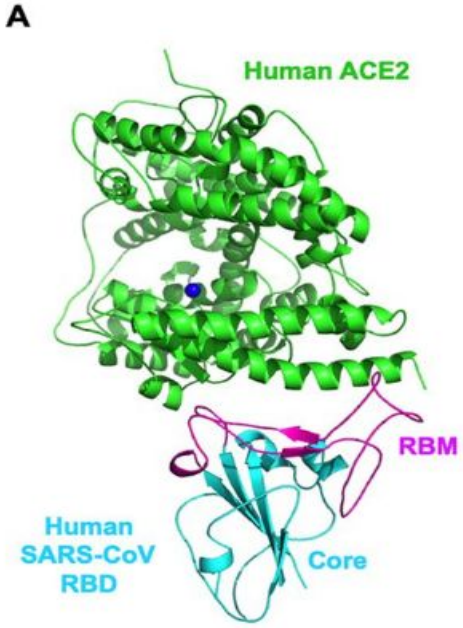
(Wan, 2020)

C

Spike /RBD /RBM	MERS-human
HKU4-bat	67.04% /57.69% /40.79%

- MERS and HKU4 have even fewer similarities but share the same receptor
- Sequence similarities strongly suggest SARS-CoV and 2019-nCoV share the same ACE2 receptor

SARS-CoV contains a core structure as well as a receptor binding motif (RBM)



(Wan, 2020)

- RBM binds to the human ACE2 receptor
- Does 2019-nCoV bind to ACE2 in the same way?

Mutations in the RBM spike protein affect binding to the host ACE2 protein

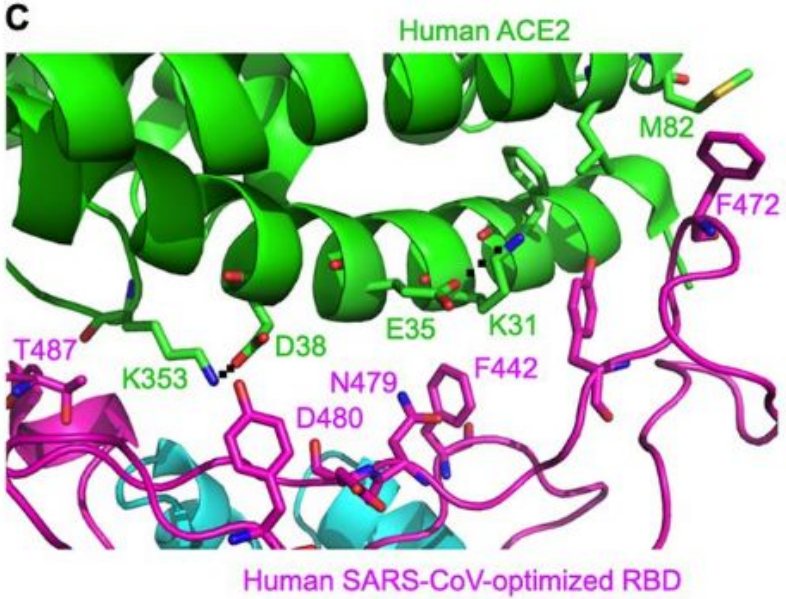
B

Virus	Year	442	472	479	480	487
SARS - human	2002	Y	L	N	D	T
SARS - civet	2002	Y	L	K	D	S
SARS - human/civet	2003	Y	P	N	G	S
SARS - civet	2005	Y	P	R	G	S
SARS - human	2008	F	F	N	D	S
Viral adaption to human ACE2		F > Y	F > L > P	N = R >>> K	D > G	T >>> S
Optimized - human	In vitro design	F	F	N	D	T
Viral adaptation to civet ACE2		Y > F	P = L > F	R > K = N	G > D	T > S
Optimized - civet	In vitro design	Y	P	R	G	T
SARS - bat	2013	S	F	N	D	N
2019-nCoV – human	2019	L (455)	F (486)	Q (493)	S (494)	N (501)

(Wan, 2020)

- Each amino acid number on the top row represents a different residue
- Red coloring indicates the differences

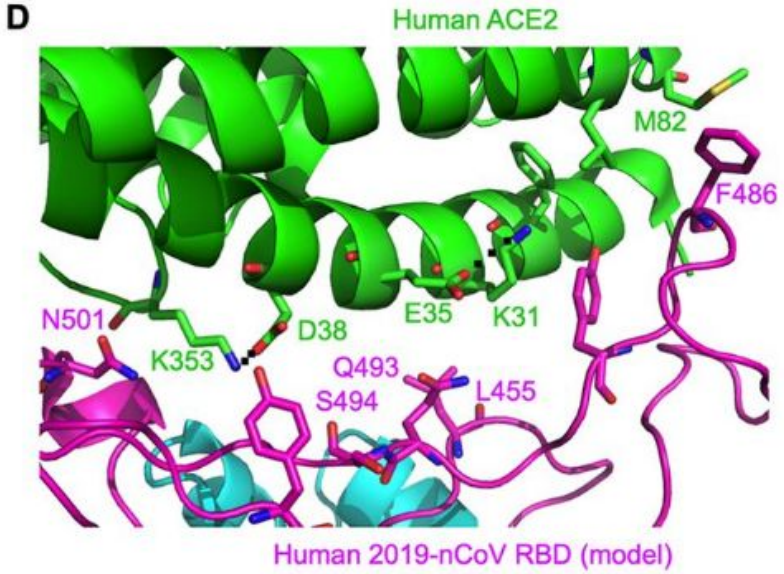
Amino acid positions that enhance viral binding of SARS-CoV to ACE2



(Wan, 2020)

- Receptor binding motif of Human SARS-Cov (magenta) binding to Human ACE2 (green)
- Specific amino acids at the 442, 472, 479, 480, and 487 positions enhance viral binding to ACE2
- When an RBD contains all of these residues, it will bind with high affinity allowing for the virus to enter human cells with high efficiency

They built a model of 2019-nCoV binding to ACE2 based off of the previous structure



(Wan, 2020)

- Receptor binding motif of Human 2019-nCoV (magenta) binding to Human ACE2 (green)
- Specific amino acids at the positions 455, 486, 493, 494, and 501 enhance the viral binding to ACE2

Five amino acids in ACE2 that are important for spike protein binding

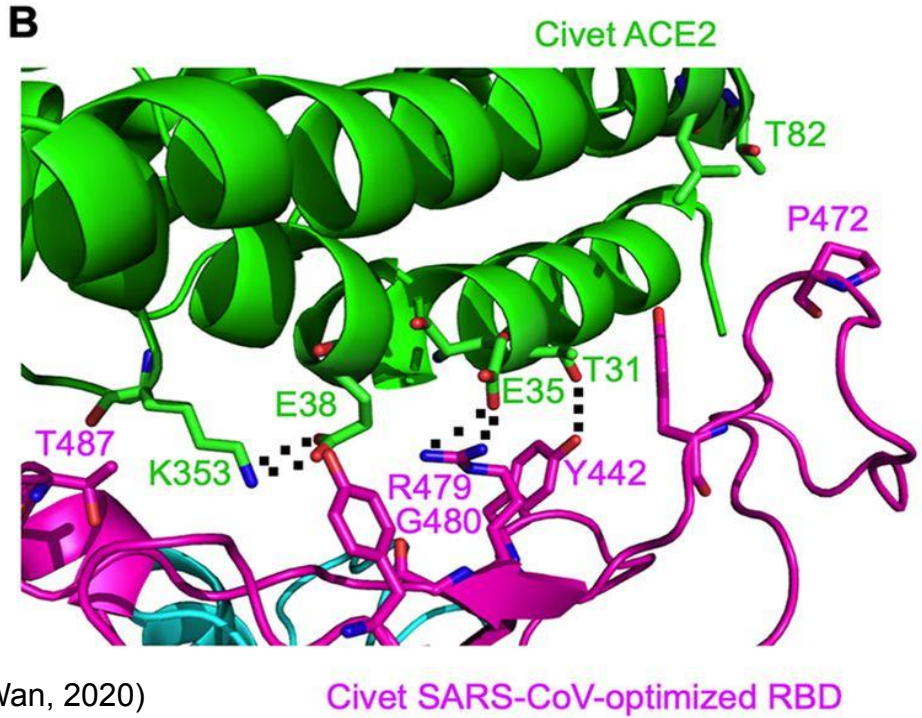
A

ACE2	31	35	38	82	353
Human	K	E	D	M	K
Civet	T	E	E	T	K
Bat	K	K	D	N	K
Mouse	N	E	D	S	H
Rat	K	E	D	N	H
Pig	K	E	D	T	K
Ferret	K	E	E	T	K
Cat	K	E	E	T	K
Orangutan	K	E	D	M	K
Monkey	K	E	D	M	K

(Wan, 2020)

- It is predicted that it would bind to all of these species except mice and rat

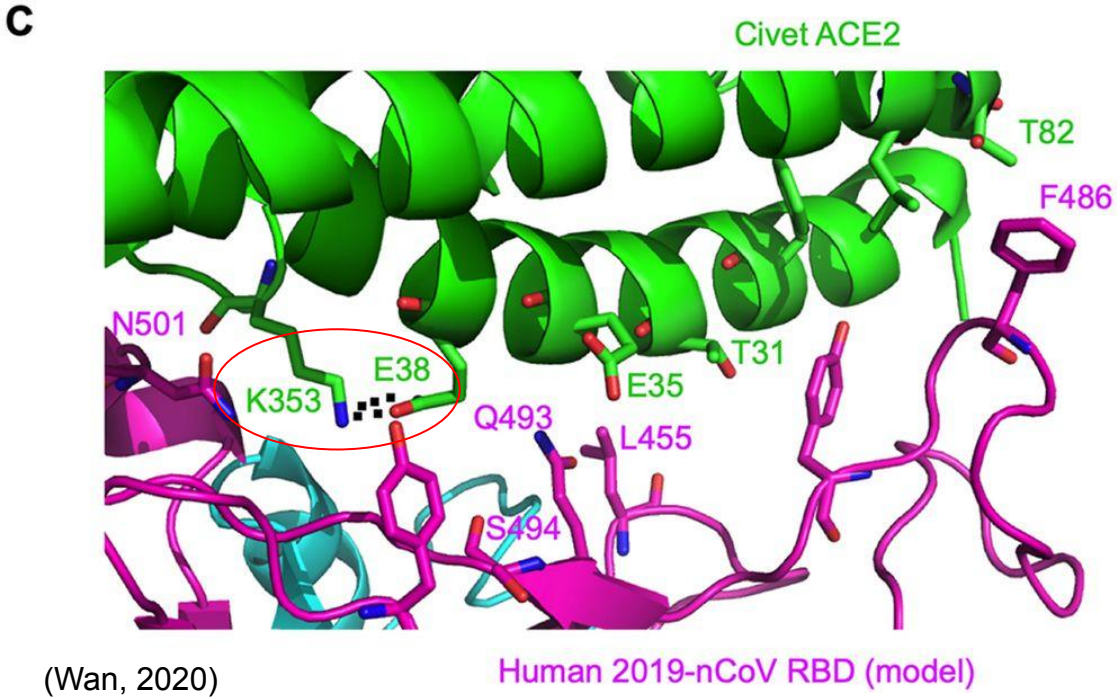
Optimal Viral Binding Between Civet SARS-CoV RBD and Civet ACE2



(Wan, 2020)

- Glu35 to Arg 479 is an ionic bond
- E38 to K353 is an ionic bond
- T31 to Y442 is a hydrogen bond
- Unfavorable interactions do not occur

Model of Viral Binding Between 2019-nCoV RBD and Civet ACE2



(Wan, 2020)

- Unfavorable interactions occur
- 2019-nCoV has not adapted to binding efficiently to ACE2
- But ACE2 is still likely used

Discussion

- 2019-nCoV shares sequence, structural, and binding similarities with SARS-CoV
- The authors used the same predictive framework to study 2019-nCoV as they did with SARS-CoV in 2003
- The main limitation of this study was that the authors do not actually know the structure yet
- Using the information presented, future work could help researchers make predictions and prepare ways to fight the virus

Summary

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References

CDC. (2020). Know the facts about coronavirus disease 2019. Center for Disease Control.https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/share-facts.html.

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Thank you to Dr. Dahlquist, Loyola Marymount University Biology Department, and the BIOL 368 class!