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WIV Bat Coronavirus Collection Efforts

- WIV possesses a large bank of Bat Coronaviruses isolated from various bat species in Yunnan Province ChinaGe et al., 2013Yang et al., 2016Hu et al., 2017Five-year longitudinal study to isolate Bat Coronaviruses (April 2011 – October 2015)Only a few sequences have been published

Table 1. Summary of SARSr-CoV detection in bats from a single habitat in Kunming, Yunnan.

Sampling time	Sample type	Sample Numbers			SARSr-CoV + bat species (No.)
		Total	CoV +	SARSr-CoV +	
April, 2011	anal swab	14	1	1	*R. sinicus* (1)
October, 2011	anal swab	8	3	3	*R. sinicus* (3)
May, 2012	anal swab & feces	54	9	4	*R. sinicus* (4)
September, 2012	feces	39	20	19	*R. sinicus* (16)
					R. ferrumequinum (3)
April, 2013	feces	52	21	16	*R. sinicus* (16)
July, 2013	anal swab & feces	115	9	8	*R. sinicus* (8)
May, 2014	feces	131	8	4	*A. stoliczkanus* (3)
					R. affinis (1)
October, 2014	anal swab	19	4	4	*R. sinicus* (4)
May, 2015	feces	145	3	0	
October, 2015	anal swab	25	6	5	*R. sinicus* (5)
Total		***602***	***84***	***64***	***R (61) A (3)***

Extracted from Hu et al., 2017

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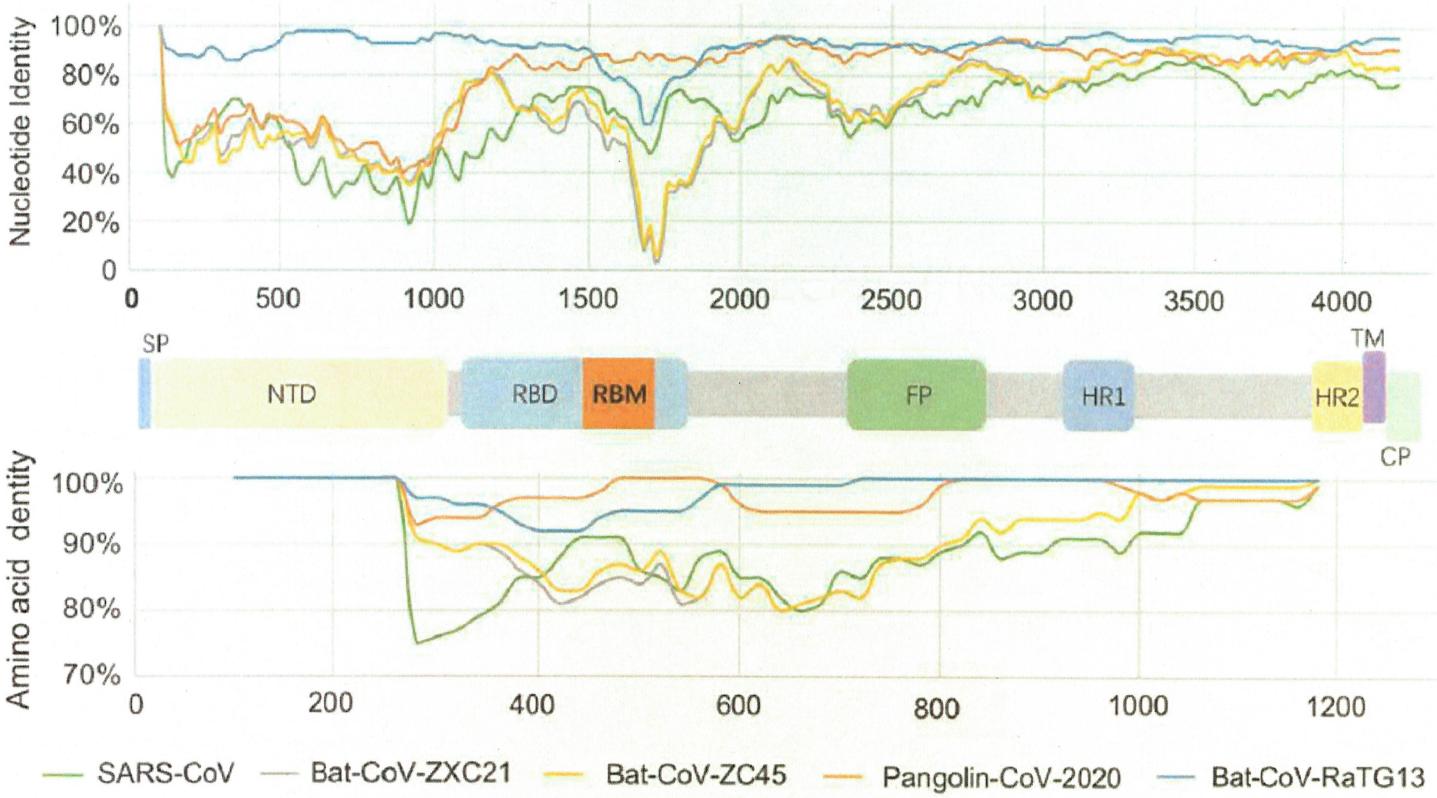
SARS-CoV-2 SimPLOT



- "A recent study found that a human ACE2-binding ridge in SARS-CoV-2 RBD takes a more compact conformation compared with the SARS-CoV RBD; moreover, several residue changes in SARS-CoV-2 RBD may also enhance its human ACE2-binding affinity [13]. The core residues in RBM which may related to higher human ACE2-binding affinity than SARS-CoV are 100% identical between SARSCoV-2 and CoV-Pangolin-2020. Therefore, pangolin-CoV-2020 (CoV-pangolin/GD) potentially recognizes human ACE2 better than the SARS-CoV."

Liu *et al.*, 2020

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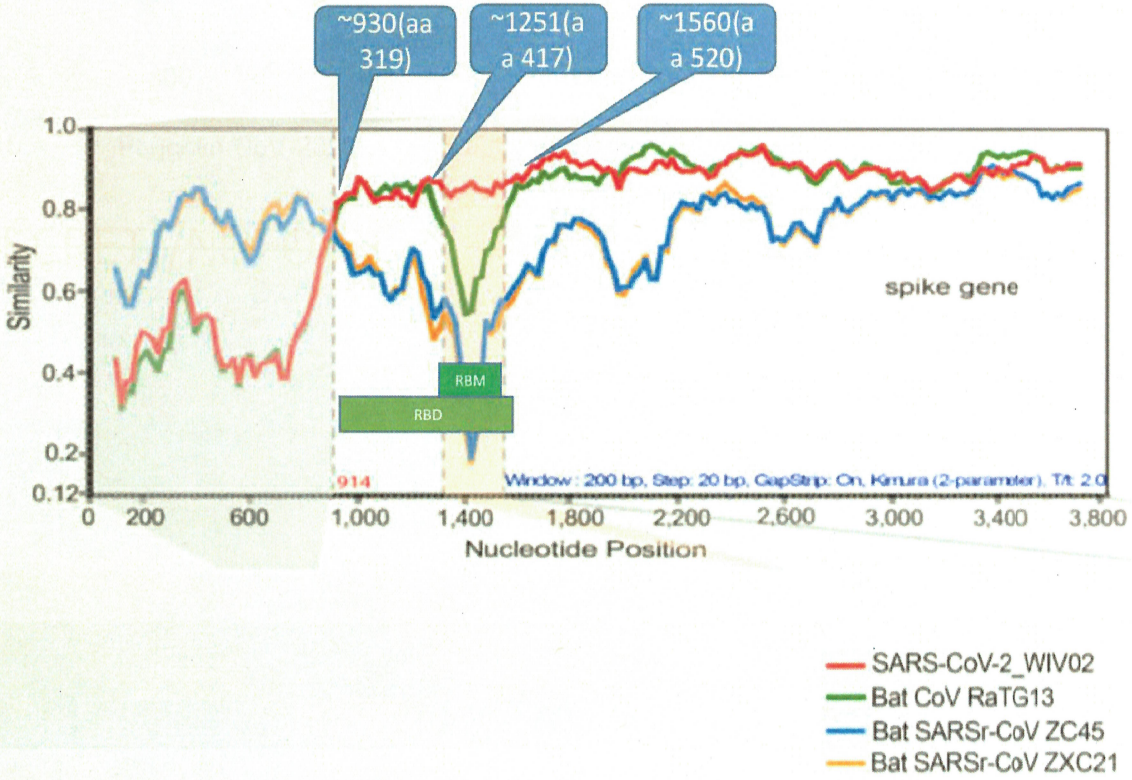
Minimal Receptor Binding Domain Cassette

- WIV scientists previously defined the minimal Receptor Binding Domain cassette that could functionally transfer ACE2 binding capability from one Spike protein to anotherSARS Nucleotide: 930-1554SARS Amino Acid: 310-518Receptor Binding MotifSARS Nucleotide: 1251-1482SARS Amino Acid: 417-494Homology cut points of SARS-CoV-2 coincide with WIV-identified borders of RBD and RBM



Xiao *et al.*, 2020 & Ren *et al.*, 2008

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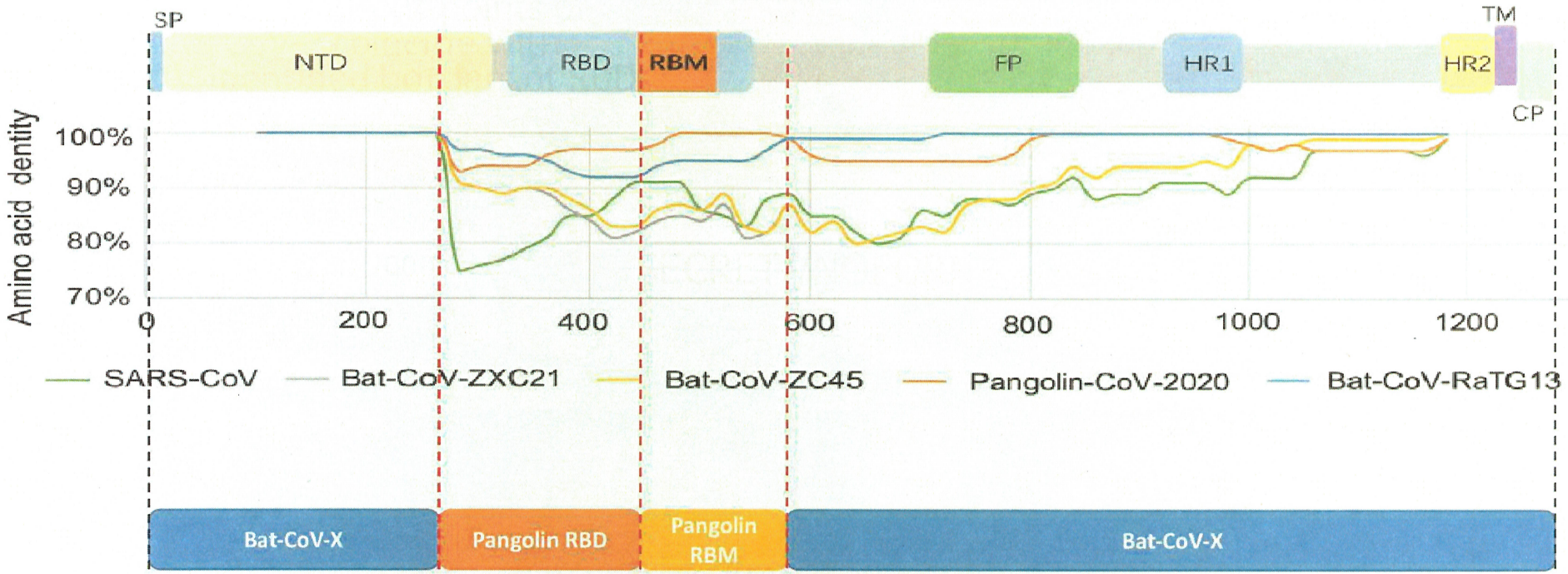
SARS-CoV-2 Spike Appears to be a Chimera



Break points align with those identified by WIV Scientists in 2008 (Ren *et al.*, 2008)

Liu *et al.*, 2020

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Perez, 2020 Scientific Challenges

- None of the six proposed regions are identical at either the nucleotide or amino acid level with the corresponding HIV/SIV segmentsNone of the six peptides are related to identified immunosuppressive regions of HIV and SIV (Retroviral ISU Domains)The HIV gp41 Immunosuppressive (ISU) Domains sequence is KQLQARILAVERYLKDQQLLGG - this sequence does not match any of the sixFour of the six regions either perfectly or almost perfectly match corresponding peptides in multiple Pangolin CoVs - Perez did not account for Pangolin genomes in the paperSeveral are only found in Pangolin CoV Spike sequences and not in Bat CoV Spike sequences, indicating that the SARS-CoV-2 Spike NTD region originated from a Pangolin CoV template

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Concluding Points

- WIV possesses a bank of Bat Coronavirus isolatesWIV has scientists experienced in Coronavirology and Coronavirus Infectious Clone generationWIV Scientists generated chimeric SARS CoV and Bat CoV Spike genes to identify minimal Spike Receptor Binding Domain cassette that could transfer receptor binding specificity (Ren et al., 2008)WIV possesses an existing and published Coronavirus Reverse Genetics System (Zeng et al., 2016) utilizing their pBAC-CMV plasmidWIV has utilized the pBAC-CMV-WIV1 Full-length clone to generate chimeras with Bat CoV spike genes (Hu et al., 2017)WIV has BSL2/BSL3/BSL4 animal facilitiesWIV has multiple in vitro assays (apoptosis, IFN-B induction, etc.) to characterize their Bat Coronaviruses and chimeric Bat CoronavirusesWIV and other Chinese researchers have conducted Gain of Function studies in SARS, MERS, IBV, and PEDV to add Furin Cleavage Sites to CoV Spike proteinThe absence of a published progenitor virus for SARS-CoV-2 only indicates that it has not been published, not that it does not existThe genomic sequence of SARS-CoV-2 has Type IIS restriction sites that are consistent with being generated by the Golden Gate Cloning system utilizing the published pBAC-CMV plasmidThe SARS-CoV-2 genome has several break points where homology jumps from Bat Coronaviruses to Pangolin Coronaviruses which is consistent with a synthesized chimeric virusThe SARS-CoV-2 Spike protein similarity with RaTG13 and Pangolin CoV Spike proteins may also be explained by use of cassettes swapped into the base virus – these break points align with those identified by WIV scientists (Ren et al., 2008)There are no other published Betacoronaviruses that possess a Furin Cleavage Site in their Spike protein (RmYN02 does not have an insertion)Zeng et al., 2016 stated that "All experiments using live virus was conducted under biosafety level 2 (BSL2) conditions" which would make an accidental release of a pathogenic Bat CoV capable of binding human ACE2 more likelyA chimeric virus comprised of segments from natural Bat CoV genomes would appear like a recombined virus

The molecular biology capabilities of WIV and the genome assessment are consistent with the hypothesis that SARS-CoV-2 was a lab-engineered virus that was part of a bank of chimeric viruses in Zhen-Li Shi's laboratory at WIV that escaped from containment

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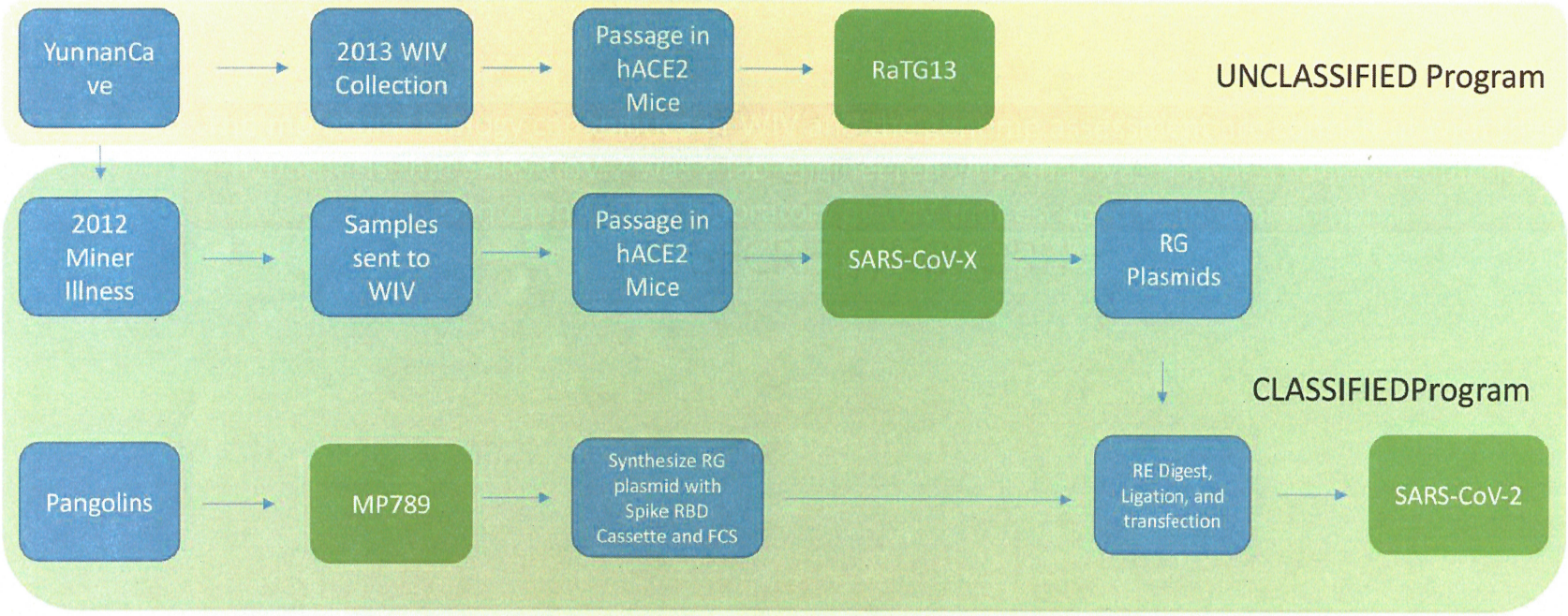
Hypothetical Origin of SARS-COV-2



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