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De nouveaux coronavirus de chauve-souris similaires à SARS-CoV-2 éclairent l'origine de la pandémie de COVID-19.

Sarah Temmam^{1,2,*}, Khamsing Vongphayloth^{3,*}, Eduard Baquero Salazar^{4,*}, Sandie Munier^{5,*}, Massimiliano Bonomi^{6,*}, Béatrice Regnault^{1,2}, Bounsavane Douangboubpha⁷, Yasaman Karami⁶, Delphine Chrétien^{1,2}, Daosavanh Sanamxay⁷, Vilakhan Xayaphet⁷, Phetphoumin Paphaphanh⁷, Vincent Lacoste³, Somphavanh Somlor³, Khaithong Lakeomany³, Nothasin Phommavanh³, Philippe Pérot^{1,2}, Océane Dehan^{5,8}, Faustine Amara⁵, Flora Donati^{5,8}, Thomas Bigot^{1,9}, Michael Nilges⁶, Félix A. Rey⁴, Sylvie van der Werf^{5,8}, Paul T. Brey³, Marc Eloit^{1,2,10,+}

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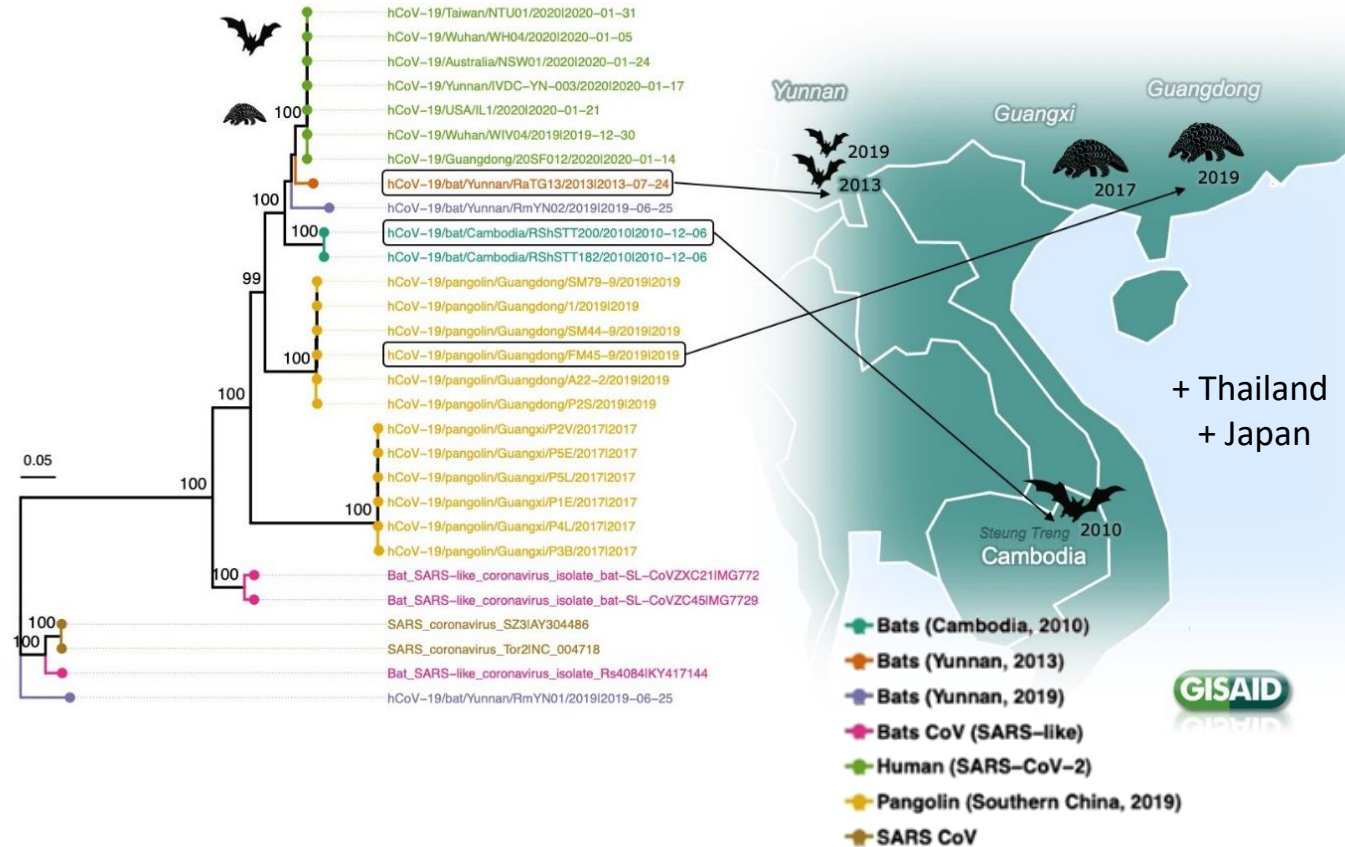
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* co-first authors

+ corresponding author

Context

- Numerous SARS-CoV-2-related viruses identified in **bats & pangolins**
- First cases detected in **Wuhan** (Huanan seafood market & elsewhere) *Worobey M. 2021 Science*
- First case 8th **December 2019**



- Animal reservoir?
- Intermediate host?
- Routes of introduction into human populations?
- Silent circulation in humans before detection?

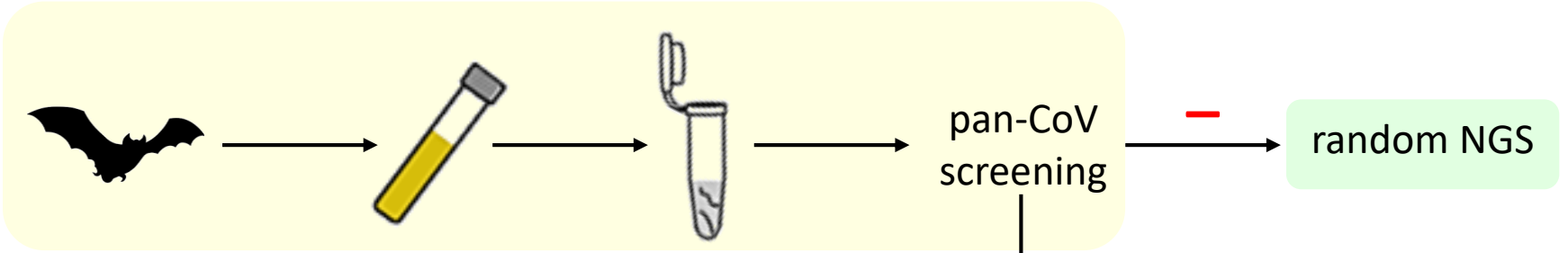
Objectives

- To improve the understanding of the **origins, natural history** and **dissemination** of SARS-CoV-2 and SARS-like coronaviruses **in their natural environment**
 - Identify natural reservoir(s) of SARS-CoV-2
 - Decipher interspecies transmission (bat-to-bat, bat-to-mammals, bat-to-humans)
- To detect **past coronavirus infections** in humans exposed to animal reservoirs
 - Identify early circulation of SARS-CoV-2 or SARS-CoV-2-like viruses before global spread

Ecological factors
that lead to
SARS-CoV-2
emergence

Workflow & consortium

- IP-Laos
- IPP-Pathogen discovery
- IPP-Structural virology
- IPP-Structural bioinformatics
- IPP-Molecular Genetics of RNA Viruses
- IPP-Mouse genetics



Characterization of the virus

Ecological studies

- Hosts spectrum
- Seasonality
- Persistence in environment
- Virus tropism in bats
- etc.

Full genome sequencing

↓

Evolution history

Structural modelling

↓

Interaction with receptor

Pseudotyped lentiviruses

↓

Virus entry

Virus isolation

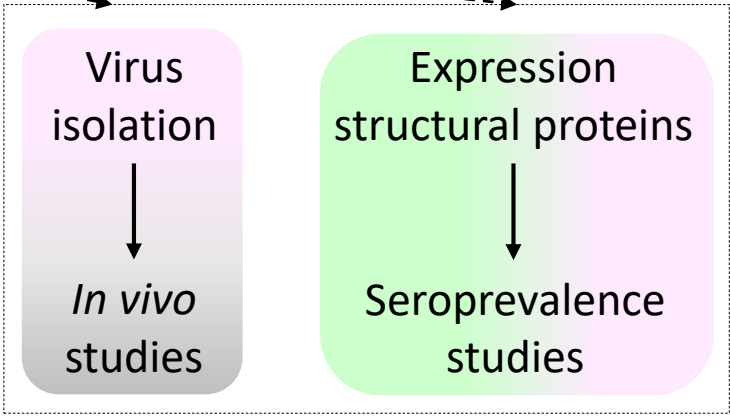
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In vivo studies

Expression structural proteins

↓

Seroprevalence studies



Field work



Khamsing
Vongphayloth
IP-Laos



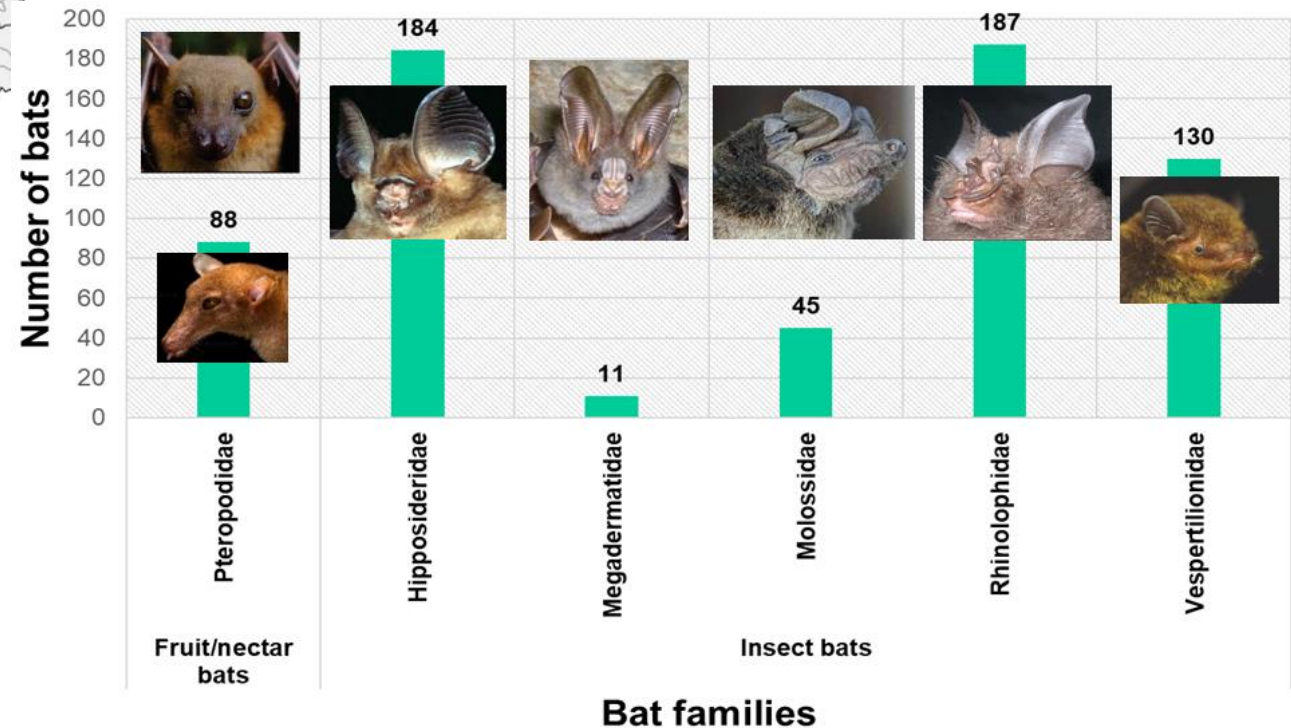
Harp trap



Mist net

- **645 bats**
 - 48 species
 - 6 families

- **Sample types**
 - Oral swabs (608)
 - Rectal swabs (539)
 - Urine (157)
 - Blood (246)



pan-CoV screening



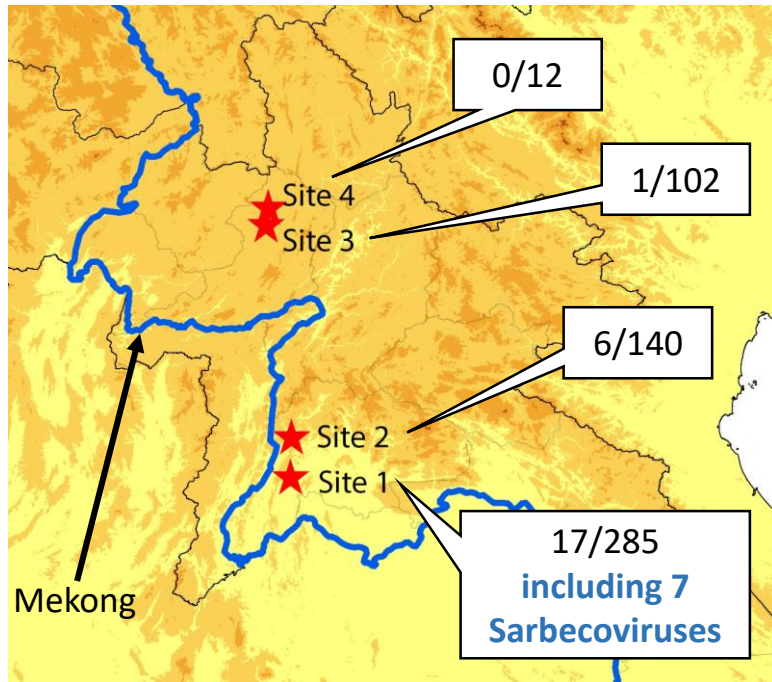
Vincent Lacoste
IP-Laos
(former member)

JOURNAL OF VIROLOGY, Dec. 2011, p. 12815–12820
0022-538X/11/\$12.00 doi:10.1128/JVI.05838-11
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Vol. 85, No. 23

Avian Coronavirus in Wild Aquatic Birds^{†‡}

Daniel K. W. Chu,¹ Connie Y. H. Leung,¹ Martin Gilbert,² Priscilla H. Joyner,² Erica M. Ng,¹
Tsemay M. Tse,¹ Yi Guan,¹ Joseph S. M. Peiris,^{1,3*} and Leo L. M. Poon^{1*}



N=539 rectal swabs

Anal Swab ID	Bat Genus	Bat Species	CoV Genus	CoV Subgenus	Closest sequence	% blastN similarity
BANAL-20-27	<i>Rhinolophus</i>	<i>pusillus</i>	co-infection <i>Alpha/Betacoronavirus</i>	unclassified <i>Decacovirus/Sarbecovirus</i>	Rhinolophus bat coronavirus HKU32 / SARS-CoV-2	80%
BANAL-20-51	<i>Hipposideros</i>	<i>pomona</i>	<i>Alphacoronavirus</i>	<i>Decacovirus</i>	Bat coronavirus HKU10	98%
BANAL-20-52	<i>Rhinolophus</i>	<i>Malayanus</i>	<i>Betacoronavirus</i>	<i>Sarbecovirus</i>	SARS-CoV-2	99%
BANAL-20-103	<i>Rhinolophus</i>	<i>pusillus</i>	<i>Betacoronavirus</i>	<i>Sarbecovirus</i>	SARS-CoV-2	99%
BANAL-20-115	<i>Hipposideros</i>	<i>pomona</i>	<i>Alphacoronavirus</i>	<i>Decacovirus</i>	Bat coronavirus HKU10	98%
BANAL-20-116	<i>Rhinolophus</i>	<i>malayanus</i>	<i>Betacoronavirus</i>	<i>Sarbecovirus</i>	SARS-CoV-2	98%
BANAL-20-178	<i>Hipposideros</i>	<i>pomona</i>	<i>Alphacoronavirus</i>	<i>Decacovirus</i>	Bat coronavirus HKU10	98%
BANAL-20-191	<i>Chaerephon</i>	<i>plicatus</i>	<i>Alphacoronavirus</i>	<i>Pedacovirus</i>	Porcine epidemic diarrhea virus (PEDV)	93%
BANAL-20-197	<i>Chaerephon</i>	<i>plicatus</i>	<i>Alphacoronavirus</i>	<i>Pedacovirus</i>	Porcine epidemic diarrhea virus (PEDV)	93%
BANAL-20-212	<i>Chaerephon</i>	<i>plicatus</i>	<i>Alphacoronavirus</i>	<i>Pedacovirus</i>	Porcine epidemic diarrhea virus (PEDV)	93%
BANAL-20-213	<i>Chaerephon</i>	<i>plicatus</i>	<i>Alphacoronavirus</i>	<i>Pedacovirus</i>	Porcine epidemic diarrhea virus (PEDV)	93%
BANAL-20-236	<i>Rhinolophus</i>	<i>marshalli</i>	<i>Betacoronavirus</i>	<i>Sarbecovirus</i>	SARS-CoV-2	99%
BANAL-20-242	<i>Rhinolophus</i>	<i>malayanus</i>	<i>Betacoronavirus</i>	<i>Sarbecovirus</i>	SARS-CoV-2	99%
BANAL-20-247	<i>Rhinolophus</i>	<i>malayanus</i>	<i>Betacoronavirus</i>	<i>Sarbecovirus</i>	SARS-CoV-2	99%
BANAL-20-251	<i>Hipposideros</i>	<i>khaokhouayensis</i>	<i>Alphacoronavirus</i>	<i>Decacovirus</i>	Bat coronavirus HKU10	97%
BANAL-20-273	<i>Rhinolophus</i>	<i>pusillus</i>	<i>Alphacoronavirus</i>	unclassified <i>Decacovirus</i>	Rhinolophus bat coronavirus HKU32	92%
BANAL-20-289	<i>Rhinolophus</i>	<i>affinis</i>	<i>Alphacoronavirus</i>	<i>Rhinacovirus</i>	Rhinolophus affinis bat coronavirus HKU2-related / Swine acute diarrhea syndrome related coronavirus (SADS-CoV)	98%
BANAL-20-290	<i>Eonycteris</i>	<i>spelaea</i>	<i>Betacoronavirus</i>	<i>Nobecovirus</i>	Rousettus bat coronavirus GCCDC1	99%
BANAL-20-390	<i>Eonycteris</i>	<i>spelaea</i>	<i>Betacoronavirus</i>	<i>Nobecovirus</i>	Rousettus bat coronavirus GCCDC1	97%
BANAL-20-395	<i>Eonycteris</i>	<i>spelaea</i>	<i>Betacoronavirus</i>	<i>Nobecovirus</i>	Rousettus bat coronavirus GCCDC1	99%
BANAL-20-398	<i>Eonycteris</i>	<i>spelaea</i>	<i>Betacoronavirus</i>	<i>Nobecovirus</i>	Rousettus bat coronavirus GCCDC1	99%
BANAL-20-403	<i>Eonycteris</i>	<i>spelaea</i>	<i>Betacoronavirus</i>	<i>Nobecovirus</i>	Rousettus bat coronavirus GCCDC1	99%
BANAL-20-416	<i>Cynopterus</i>	<i>sphinx</i>	<i>Betacoronavirus</i>	<i>Nobecovirus</i>	Rousettus bat coronavirus GCCDC1	99%
BANAL-20-497	<i>Myotis</i>	sp.	<i>Alphacoronavirus</i>	<i>Pedacovirus</i>	Bat alphacoronavirus*	99%

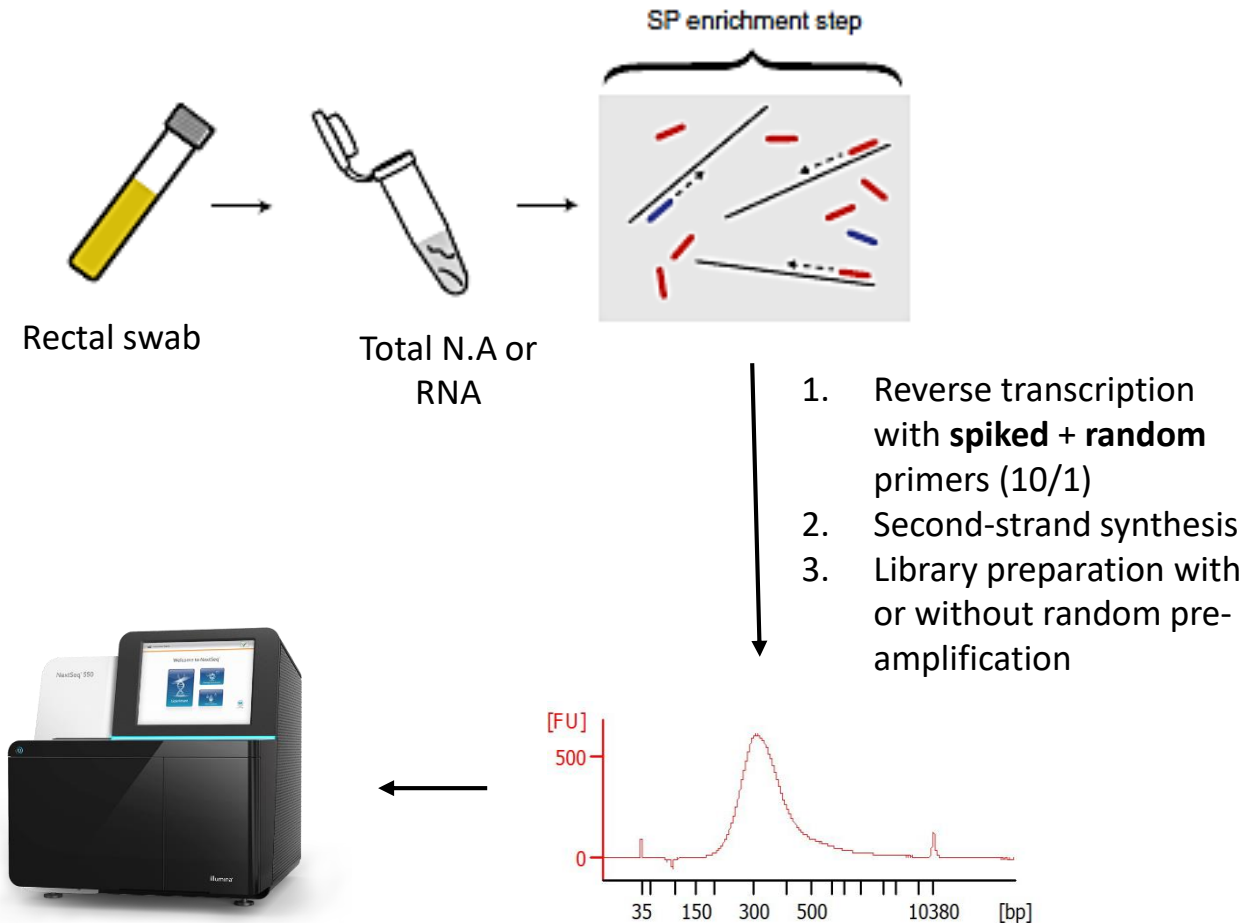
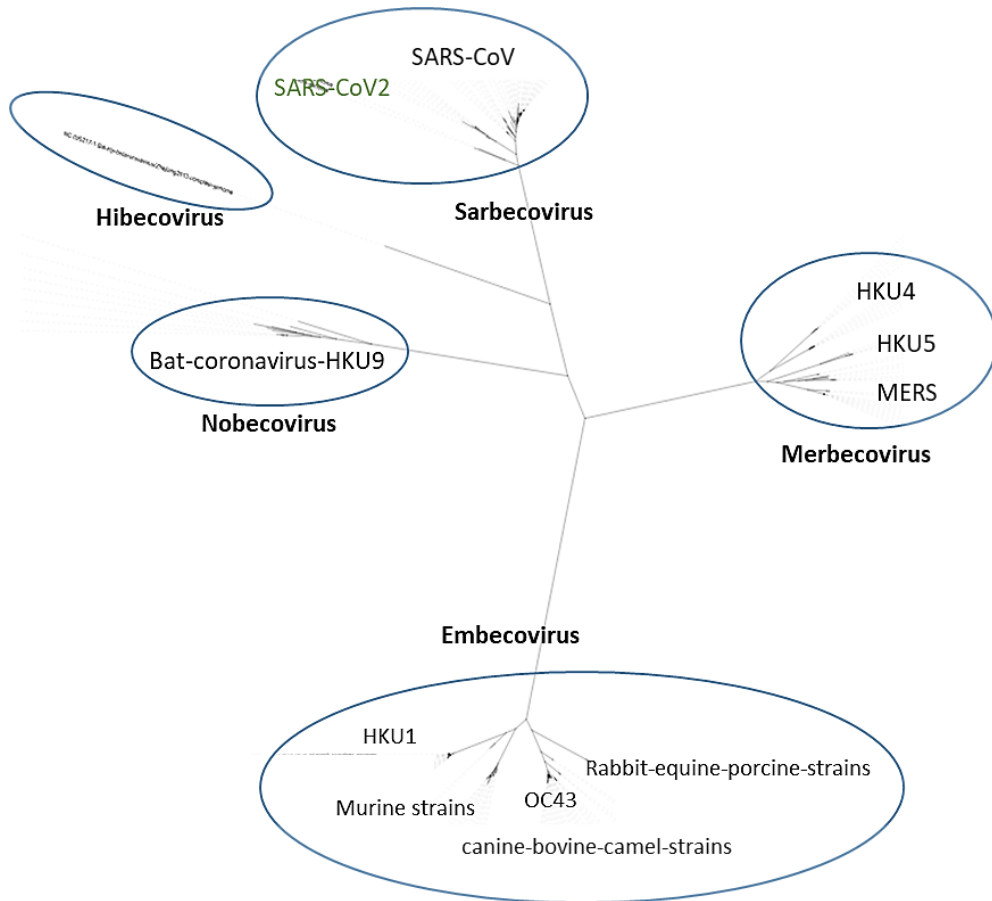


Béatrice Regnault
IPP – Pathogen
Discovery lab.

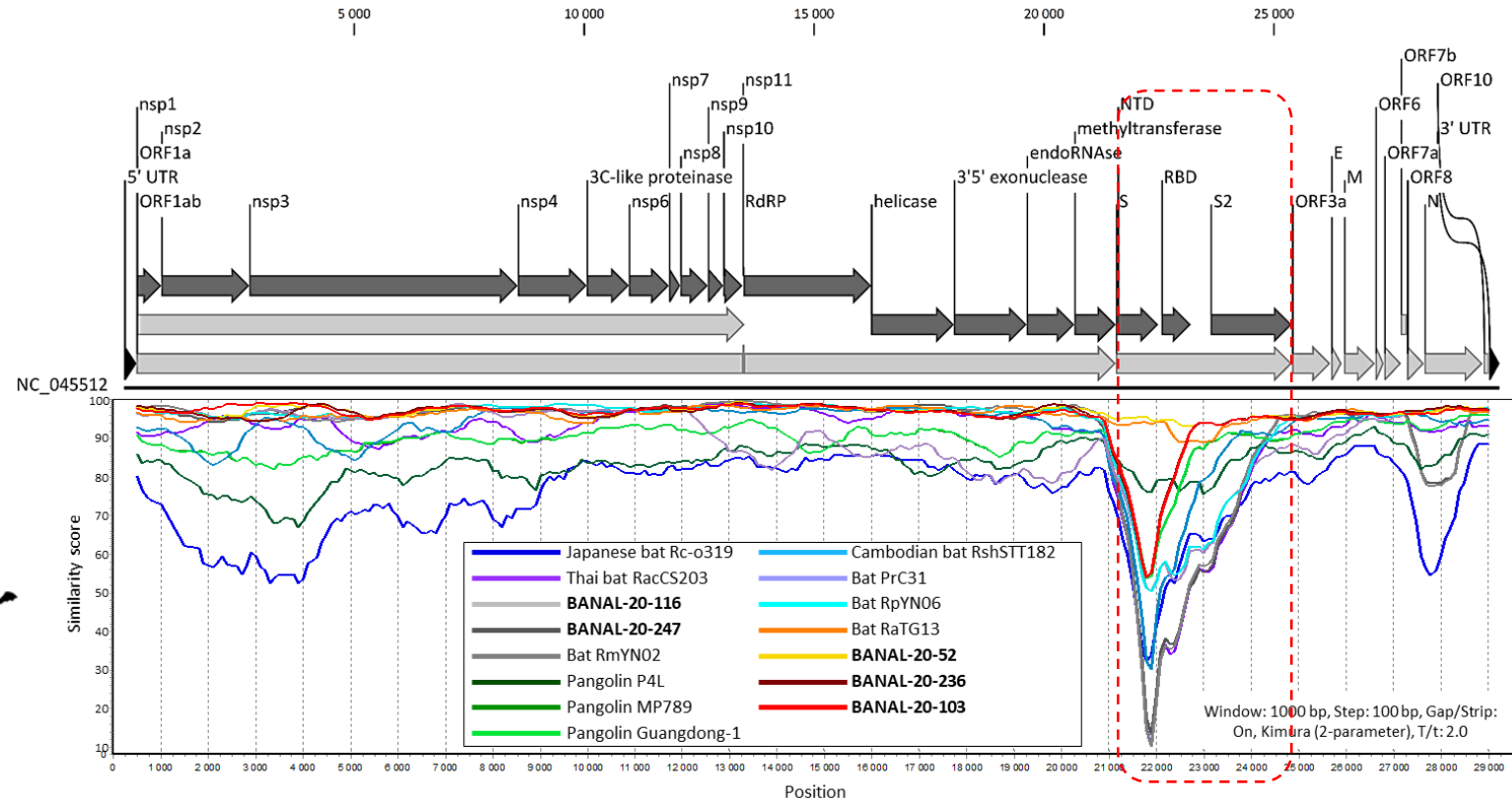
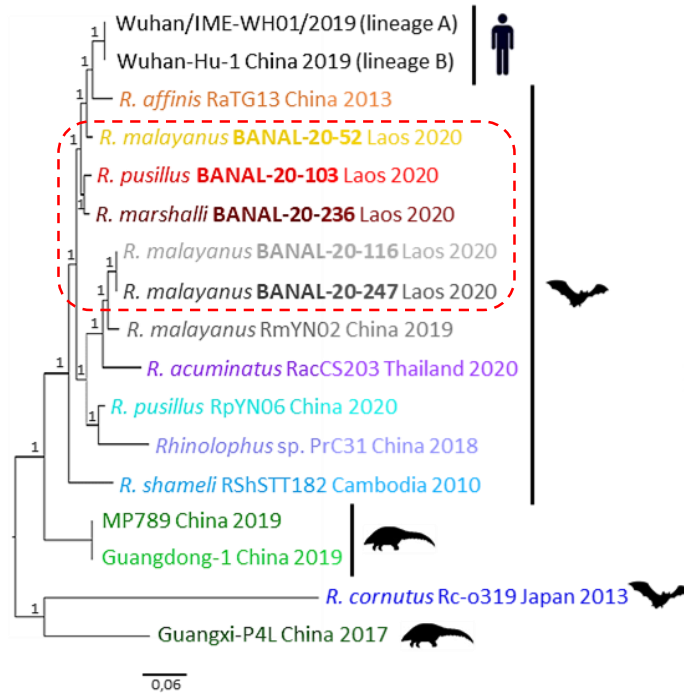
Betacoronavirus enrichment

➤ **In-silico probe design** from nucleotide sequence alignment of all *Betacoronavirus* subgenera

- 13-mer primers pan-generic or specific to each subgenus (MSSPE method) Deng X. et al., 2020 Nat. Microbiol. doi: 10.1038/s41564-019-0637-9
- 432 primers



Evolution history of bat CoVs



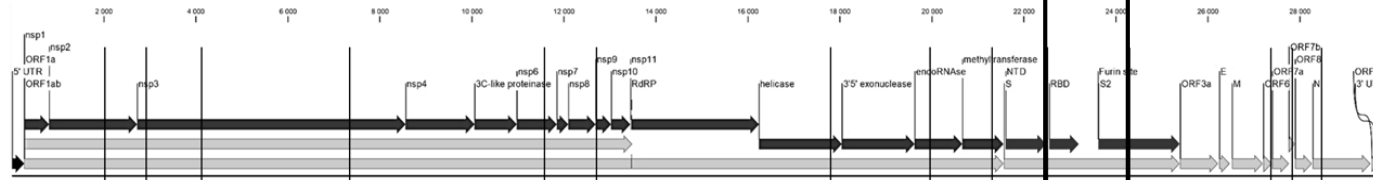
➤ At the whole genome level

- BANAL viruses close to SARS-CoV-2 early strains
- High degree of conservation between CoVs carried by different *Rhinolophus* species living in sympatry

➤ Similarity along the genome

- BANAL viruses present >95% nt identity along the genome, BANAL-52 the closest known to date
- In the spike, BANAL viruses closer to SARS-CoV-2 than bat and pangolin CoVs
- No furin site

Evolution history of bat CoVs

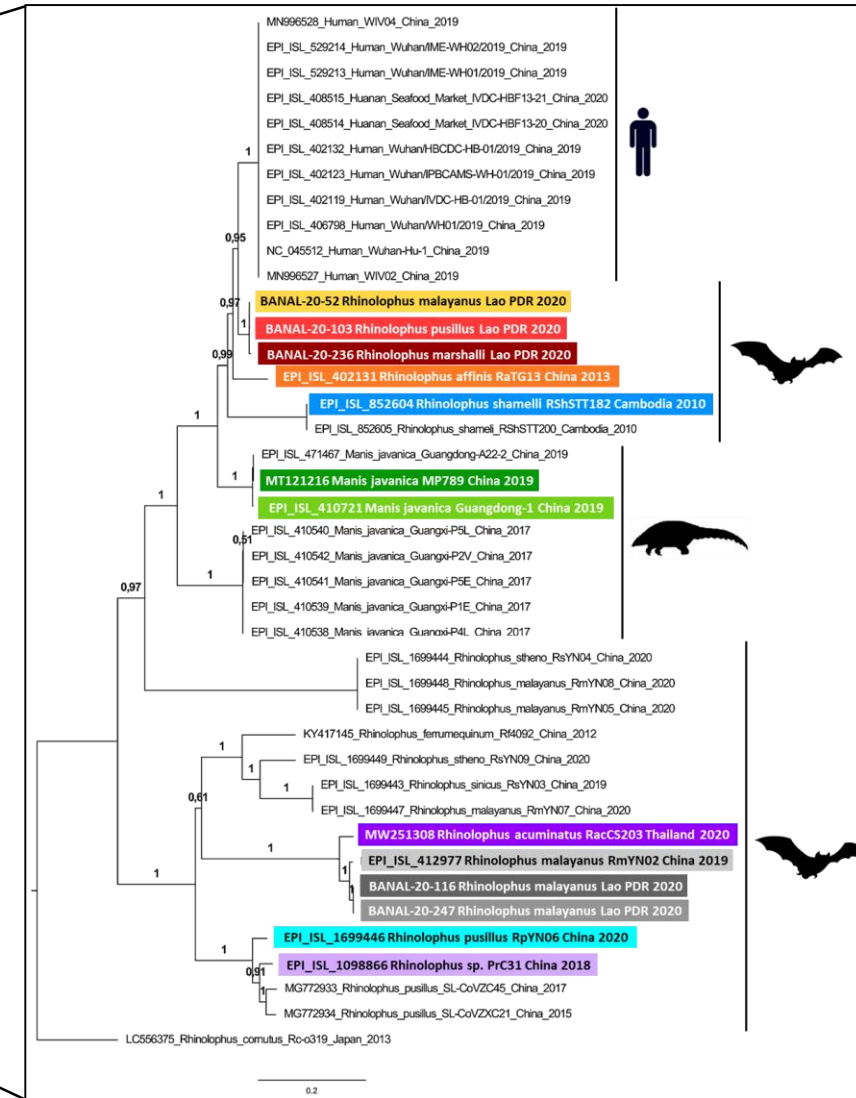


Fragment no:

Fragment no:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
SARS-CoV-2	RmYN02	BANAL 103	MULT	MULT	RpYN06	MULT	MULT	RmYN02	BANAL 52	RaTG13	MULT	MULT	BANAL 52	MULT	
Bat RaTG13	MULT	MULT	MULT	MULT	MULT	MULT	MULT	MULT	MULT	SARS CoV-2	MULT	MULT	MULT	MULT	MULT
BANAL-20-52	BANAL-236		BANAL-103		MULT		BANAL-236		MULT	MULT	MULT	MULT	SARS CoV-2	MULT	
BANAL-20-103	MULT	MULT	BANAL-52		MULT	MULT	MULT	MULT	MULT	BANAL-236	MULT	MULT	MULT	MULT	
BANAL-20-236	BANAL-52	RacCS 203	MULT		BANAL-247		BANAL-52		MULT	BANAL-103	MULT	MULT	MULT	MULT	
Pangolin Guangdong-1							MP789				MULT	MP789		MP789	
Pangolin MP789							Guangdong-1				Guangdong A22-2	Guangdong-1		Guangdong-1	
Bat PrC31	MULT		RmYN02		MULT	MULT	Rf4092		MULT	RpYN06	MULT	MULT		RpYN06	
Bat RpYN06	MULT	MULT	MULT	MULT	SARS-CoV-2		RmYN02		MULT	BANAL 236	PrC31	MULT	RmYN02		PrC31
Cambodian bat RShSTT182							RShSTT200								RShSTT200
BANAL-20-116			BANAL-247				MULT			BANAL-247					BANAL-247
BANAL-20-247			BANAL-116				BANAL-236			BANAL-116					BANAL-116
Bat RmYN02	SARS-CoV-2		PrC31		MULT		RpYN06		SARS-CoV-2	MULT	MULT	MULT	RpYN06	MULT	MULT
Thai bat RacCS203	MULT	MULT	BANAL 236		MULT		MULT		MULT	MULT	MULT	MULT	MULT	MULT	MULT

➤ Numerous recombinations in SARS-CoV-2 history

- No pangolin CoV as direct contributor
- One / multiple ancestors depending on the fragment of genome
- In the spike: RaTG13 CoV for the NTD, BANAL CoVs for RBD and N-terminal part of S2 (including the furin site)



Bat CoV RBD highly similar to SARS-CoV-2

SARS-CoV-2 lineage A	319	RVQPTESIVRFPNITNLCPFGVEVFNATRFASVYAWNRRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLDLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPDDFT	430
SARS-CoV-2 lineage B	319	RVQPTESIVRFPNITNLCPFGVEVFNATRFASVYAWNRRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLDLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPDDFT	430
BANAL-20-52	319T.....T.....V.....	430
Bat RaTG13	319D.....T.....T.....	430
Pangolin P4L	317I.....SK.....T.....VK.....V.....	428
BANAL-20-103	315D.....T.....T.....V.....	426
BANAL-20-236	315D.....T.....T.....V.....	426
Pangolin Guangdong-1	315T.....T.....V.....R.....	426
Pangolin MP789	315T.....T.....V.....R.....	426
Bat PrC31	315Q.V.....V.....HK.....P.....E.TK..D.I...T.F...T.....S..I...S...T.L.FS...V.....V.....	426
Bat RpYN06	315Q.V.....V.....HN.....P.....E.TK..D.I...T.F...T.....S..I...S...T.L.FS...V.....V.....	426
Cambodian bat RShSTT182	306	..TS..TQV.....T.....R.....TT.....V.....M.....	417
BANAL-20-116	298	..L.STEV.....F...DK.....FN...Q.TK..D.I...T...T.....S..I...S...T.L.FS...E...V.....	409
BANAL-20-247	298	..L.STEV.....F...DK.....FN...Q.TK..D.I...T...T.....S..I...S...T.L.FS...E...V.....	409
Bat RmYN02	298	..IL.STEV.....F...DK.....PN...Q.TK..D.I...T...T.....S..I...S...T.L.FS...E...V.....	409
Thai bat RacCS203	298	..L.STEV.....F...DK.....PN...Q.TK..D.I...T...T.....S..I...S...T.L.FS...E...V.....	409
Japanese bat Rc-o319	293QDTV.....S.....T.....R.....Q.....S.....V.....	404

SARS-CoV-2 lineage A	431	GCVIAWNSNNLDSKVGNGNYLYRFLFRKSNLKPFFERDISTEIQAGSTPCNGVEGFNCYFPLOS YGFQPTNGVGYQPYRVVVL SFELLHAPATVCGPKKSTNLVKNKCVNFN	541
SARS-CoV-2 lineage B	431	GCVIAWNSNNLDSKVGNGNYLYRFLFRKSNLKPFFERDISTEIQAGSTPCNGVEGFNCYFPLOS YGFQPTNGVGYQPYRVVVL SFELLHAPATVCGPKKSTNLVKNKCVNFN	541
BANAL-20-52	431H.....N.....I.....	541
Bat RaTG13	431KHI.A.E...F.....A.....K...QT.L...Y.YR...Y.D...H.....N.....	541
Pangolin P4L	429VKQ.ALT...G.....K.....QV.L...Y.ER...H.T.N...F.....NG...L.T...D.....	539
BANAL-20-103	427H.....N.....I.....	537
BANAL-20-236	427H.....N.....I.....	537
Pangolin Guangdong-1	427H.....N.....Q.....	537
Pangolin MP789	427H.....K.....Q.....	537
Bat PrC31	427TAKQ.VG---S.F..SH.STK.....L.SDE-----R---T.ST.D.N.NVPLE...AT.....N.....L.Q...Q.....	518
Bat RpYN06	427TAKQ.VG---F...SH.STK.....L.SDE-----R---T.ST.D.N.NVPLE...AT.....N.....L.Q...Q.....	518
Cambodian bat RShSTT182	418IS..A--...S.Y...V.....QL...DK..S---PD.....Y..S.....N.....H.V.....	523
BANAL-20-116	410	..L...TAQQ.IG---S.F..SH.AVK.....L.SDE-----R---T.ST.D.N.NVPLD...AT.....N.....L.Q...R.....	501
BANAL-20-247	410	..L...TAQQ.IG---S.F..SH.AVK.....L.SDE-----R---T.ST.D.N.NVPLD...AT.....N.....L.Q...R.....	501
Bat RmYN02	410	..L...TAQQ.IG---S.F..SH.AVK.....L.SDE-----R---T.ST.D.N.NVPLD...AT.....N.....L.Q...R.....	501
Thai bat RacCS203	410	..L...TAKQ.IG---S.F..SH.AVK.....L.SDE-----R---T.ST.D.N.NVPLD...AT.....N.....L.Q...R.....	501
Japanese bat Rc-o319	405	..L...R.Q.ASTS...E...Y...I.W.SEK.R.....AHYD..V..TQFKS---S.KN...YSSA.DSH.....N.....Q...E.I.....	506

➤ Alignment of the RBD region

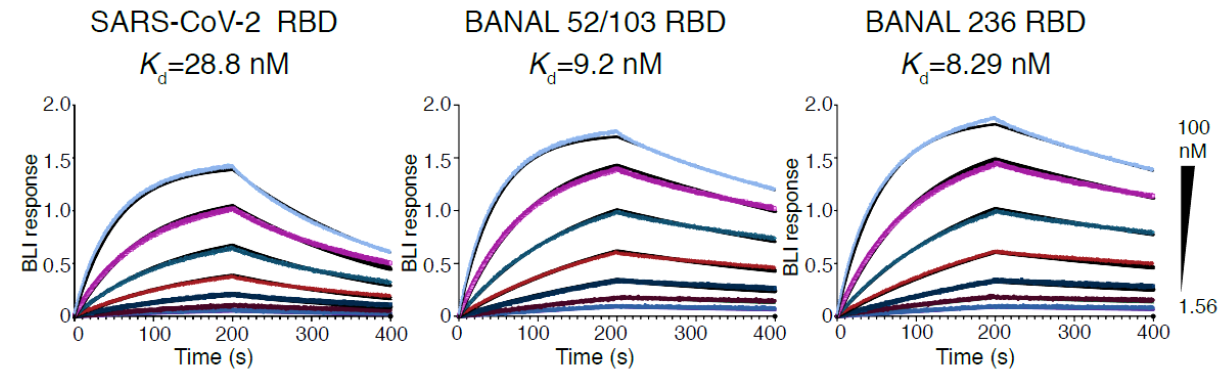
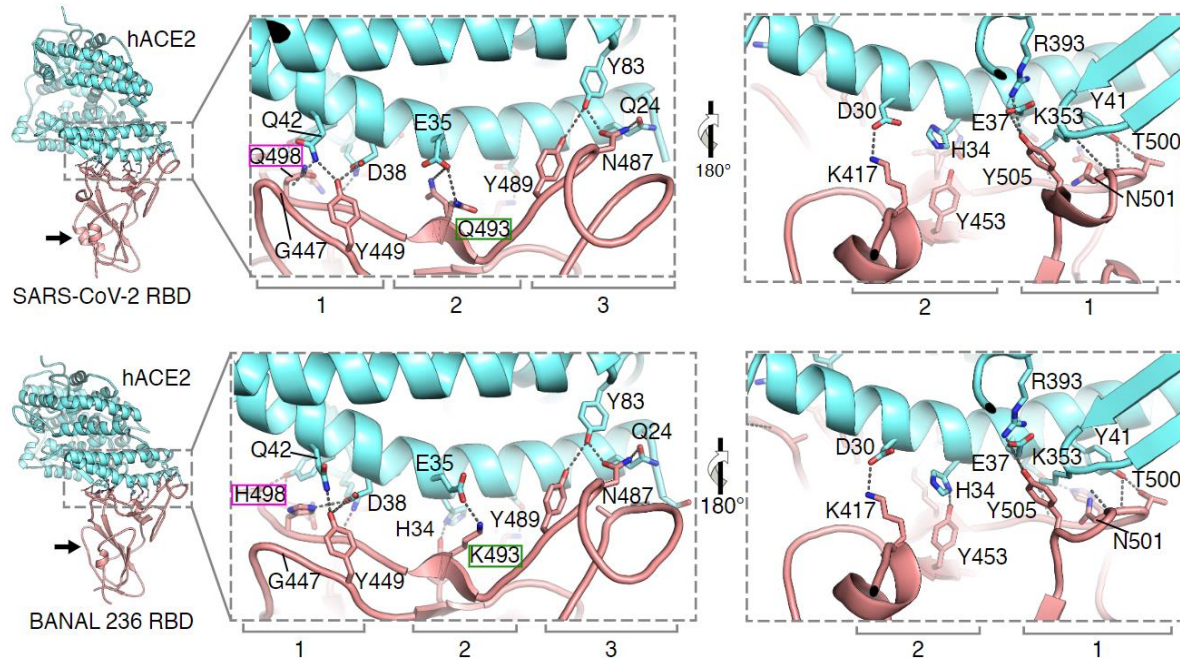
- BANAL-52 (*R. malayanus*) closer to SARS-CoV-2 than any bat / pangolin CoVs
- 15-16/17 aa residues interacting with hACE2 receptor conserved between BANAL viruses and SARS-CoV-2 (13/17 for Cambodian bat *R. shamelii* and 11/17 for Chinese bat *R. affinis* RaTG13)

Insights into RBD/hACE2 complex



Eduard Baquero-Salazar
IPP – Structural Virology

Massimiliano Bonomi
IPP – Structural Bioinformatics



➤ Determination of the crystal structure of BANAL RBDs

➤ Effects of mutations in RBD-hACE2 interactions

- BANAL mutation $H498^Q$ disrupt transient hydrogen bonds but is known to increase affinity of SARS-CoV-2 RBD for hACE2 *Huang et al., 2021 EBioMedicine*
- BANAL mutations $K493^Q \rightarrow$ 2 additional salt bridges formed between BANAL-236 RBD & ACE2 \rightarrow possible \nearrow affinity

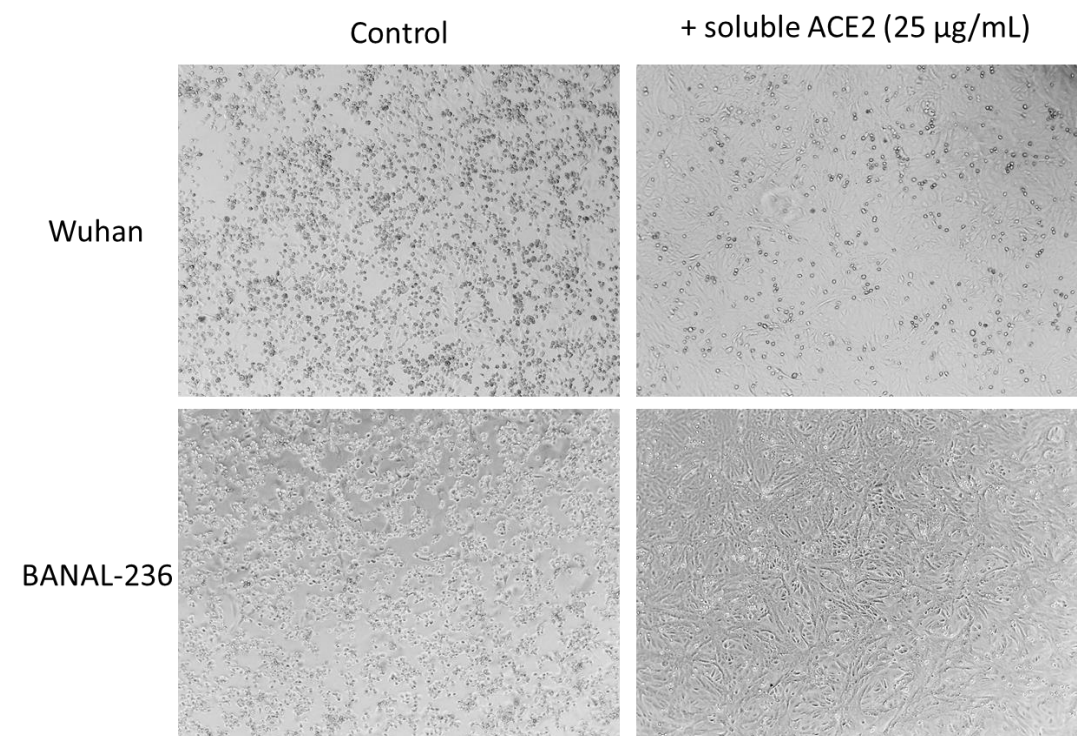
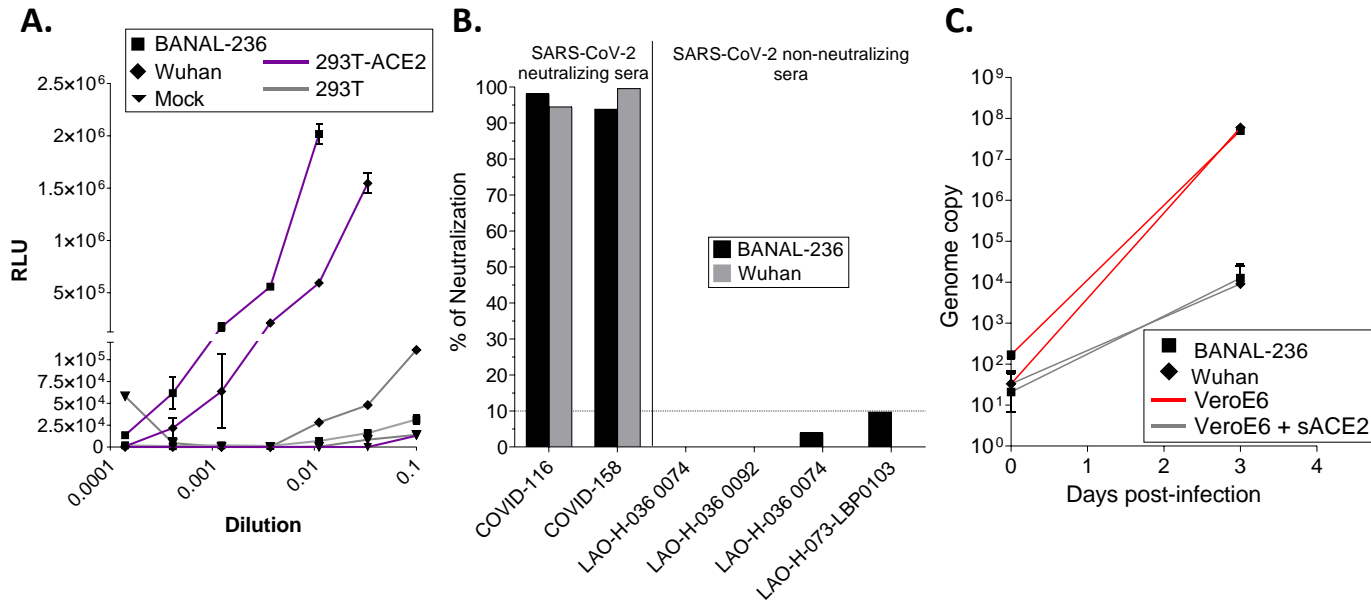
➤ Biolayer interferometry

- K_d BANAL viruses \ll SARS-CoV-2 \rightarrow \nearrow affinity of BANAL viruses compared to SARS-CoV-2 Wuhan strain

Cell entry through ACE2-dependent pathway



Sandie Munier
IPP – Molecular
Genetics of RNA
Viruses



➤ **Lentiviral pseudoparticles expressing Wuhan or BANAL-236 wild type spikes**

- Entry in 293T cells expressing hACE2
- Entry blocked by SARS-CoV-2 neutralizing sera

➤ **BANAL-236 virus isolation**

- Infection VeroE6 expressing endogenous ACE2
- Infection blocked by soluble ACE2 (-3,6 log₁₀) similar to Wuhan (-3,8 log₁₀)

Virus isolation

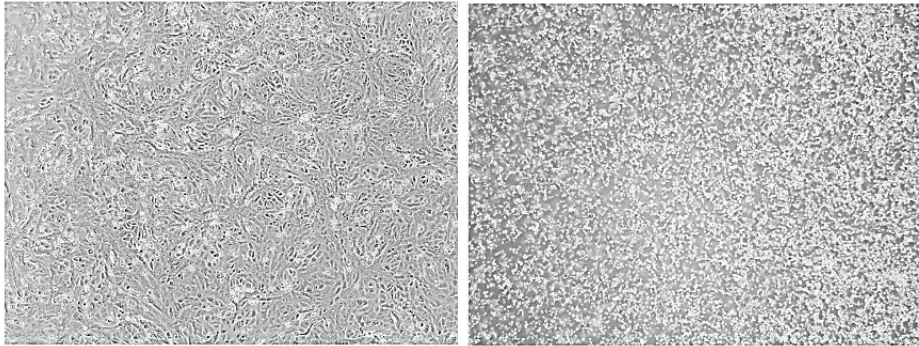


Flora Donati
IPP – Molecular
Genetics of RNA
Viruses

Neg control

BANAL-236

VeroE6

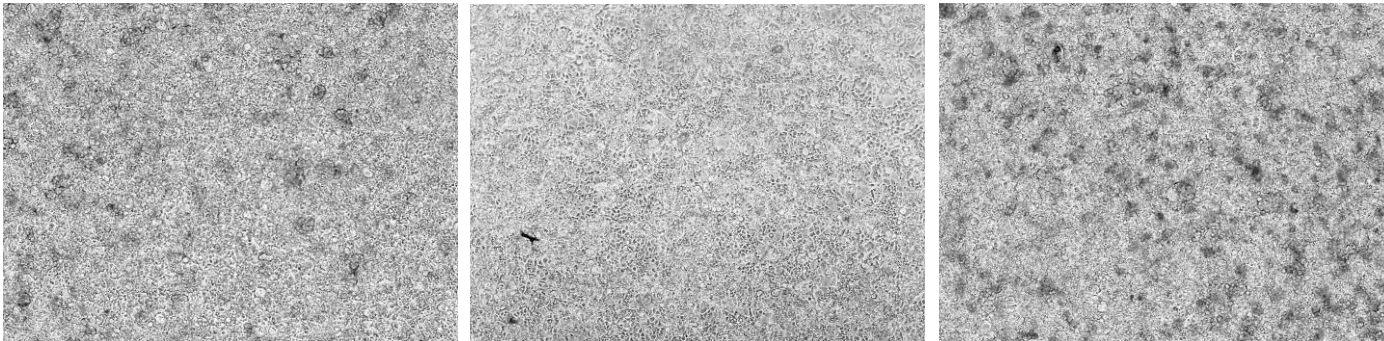


➤ BANAL-236 virus growth

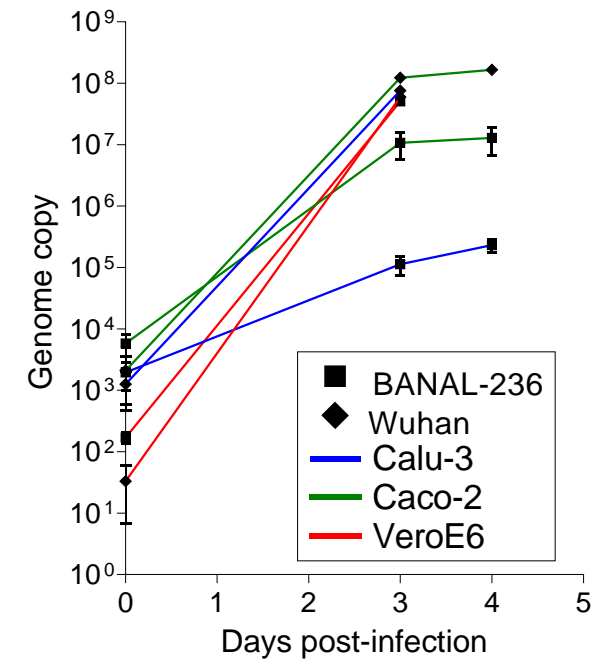
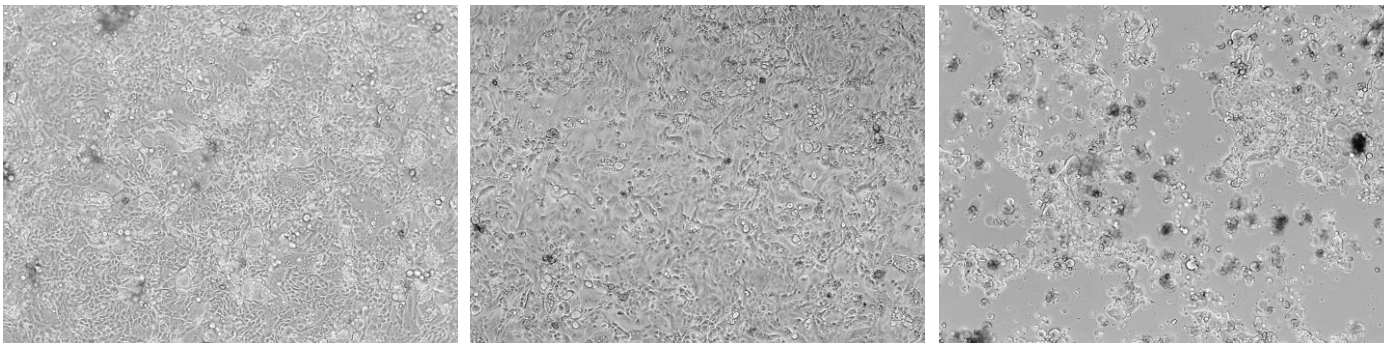
- Efficient replication in VeroE6, similar yield compared to Wuhan
- Lower replication in human cells expressing endogenous ACE2
 - No CPE observed compared to Wuhan

Wuhan

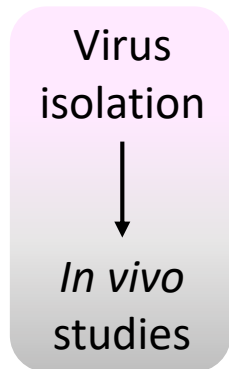
Caco-2



Calu-3



Ongoing studies

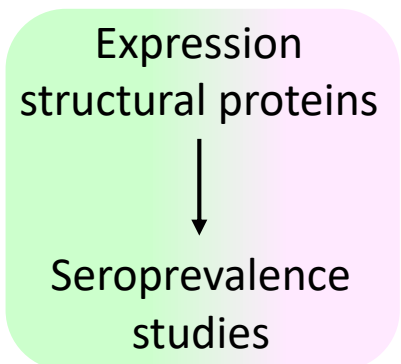


➤ Pathogenicity in animal model (mice + primates)

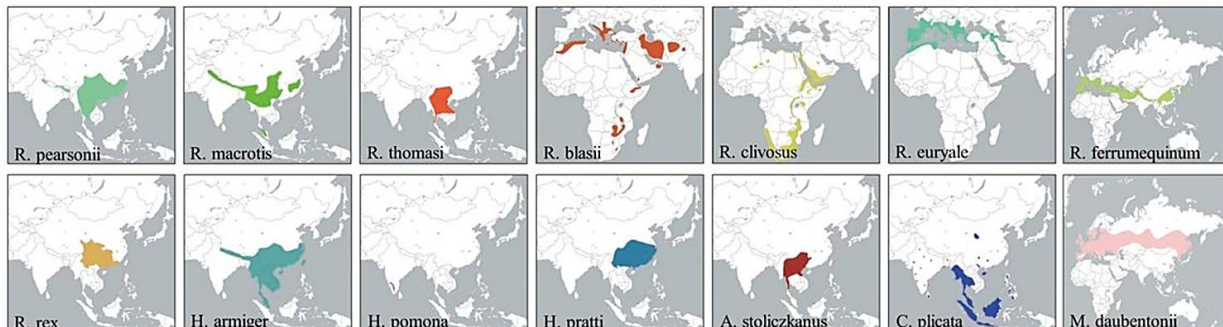
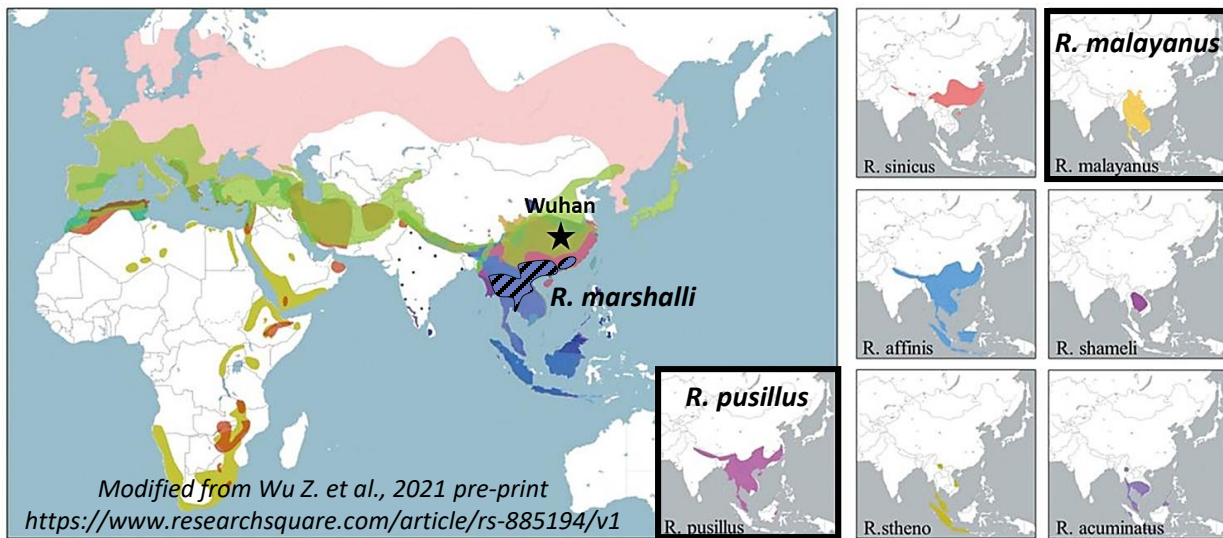
- Level of replication in classical or humanized mice
- Virus tropism in different organs
- Adaptation mutations
- Immune response to infection
- Cross-protection against SARS-CoV-2
- etc...

➤ Infection of Laotian populations?

- In 2020, low seroprevalence in humans Virachith et al., 2021 Lancet Reg Health West Pac.
 - Impact of governmental measures?
 - Young age population?
or...
 - Cross-protective immunity?
- Serosurvey of general vs bat-exposed populations
 - LIPS: RBD, N, full S
 - PNT



Conclusions



➤ SARS-CoV-2 origin

- **Recombination** from different *Rhinolophus* CoVs living in the limestone cave system of S-E. Asia
 - Rich diversity of bats living in sympatry → ↗ exchanges of viruses
 - Major route of transmission: feces (but oral swabs also >0 for BANAL-27)
- **No need for an intermediate host** to increase affinity for ACE2, but...
 - Origin of the furin cleavage site?
- **Route of introduction** to the human population?

➤ Risk of emergence of other bat CoVs?

- **Exposure** of guano collectors, religious communities, tourists?
- If yes, **symptomatic** infection? Cross-protection against SARS-CoV-2?

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