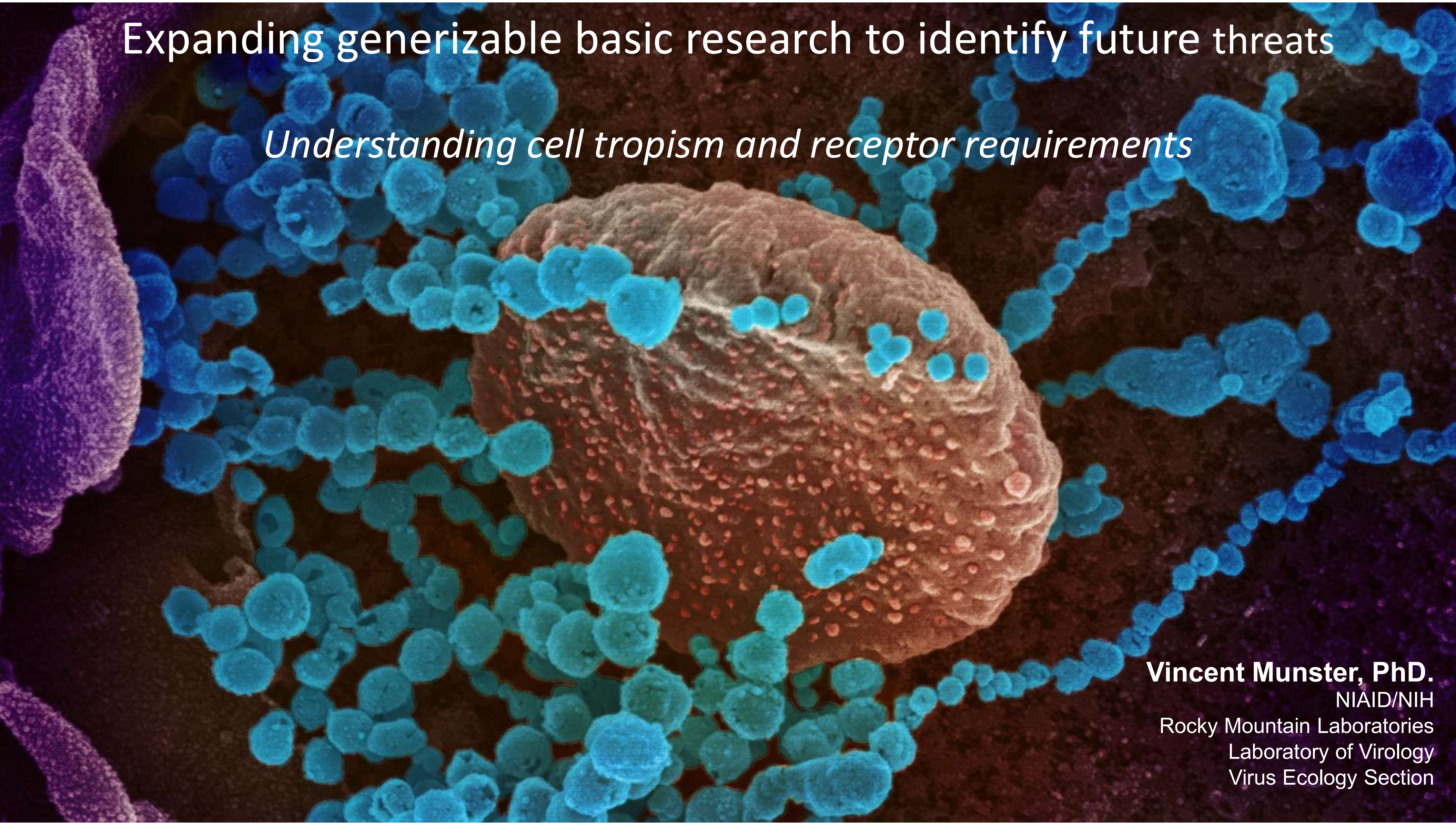
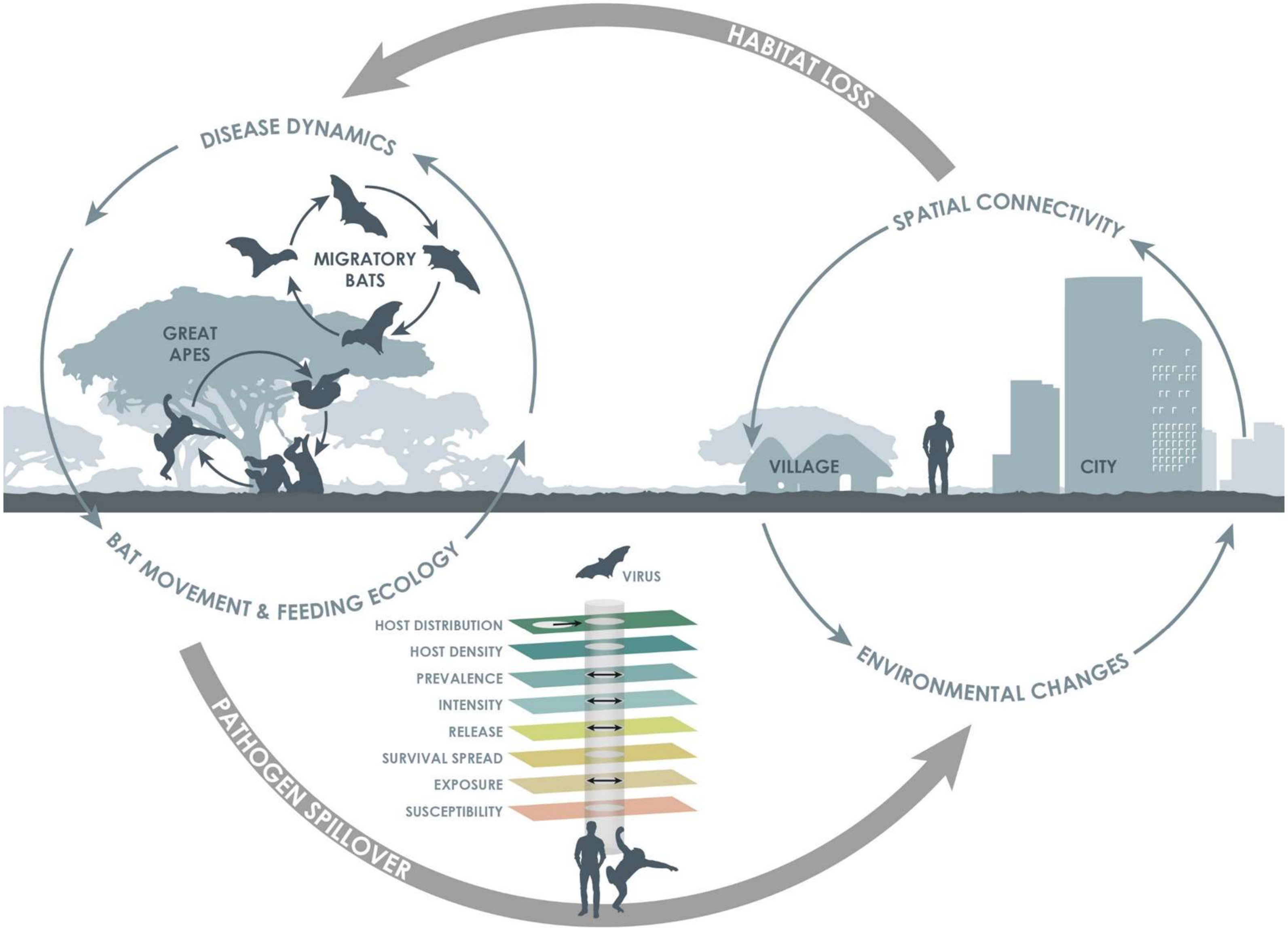


Expanding generizable basic research to identify future threats

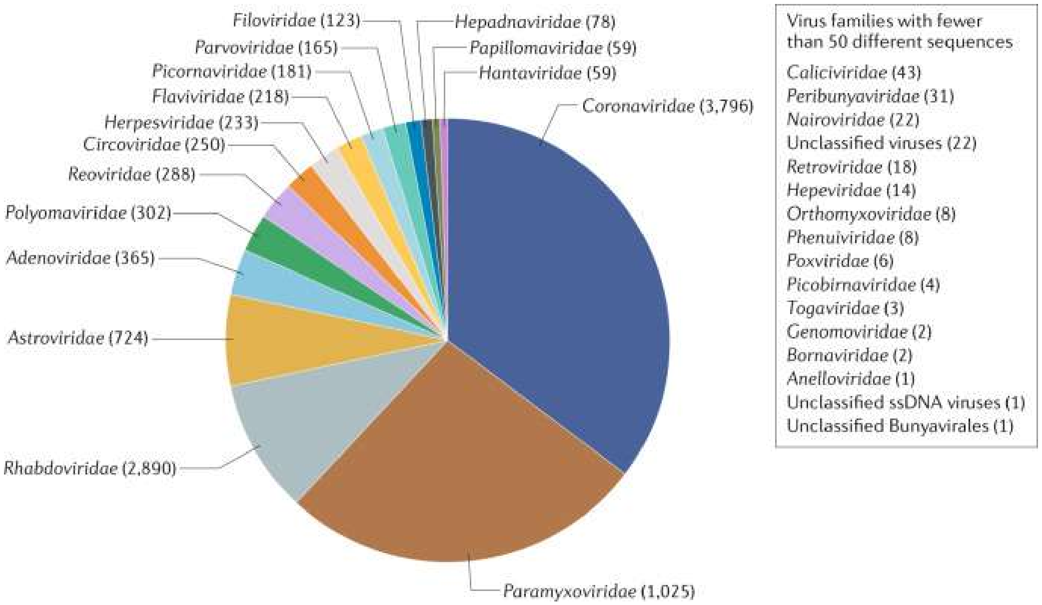
Understanding cell tropism and receptor requirements

Vincent Munster, PhD.
NIAID/NIH
Rocky Mountain Laboratories
Laboratory of Virology
Virus Ecology Section



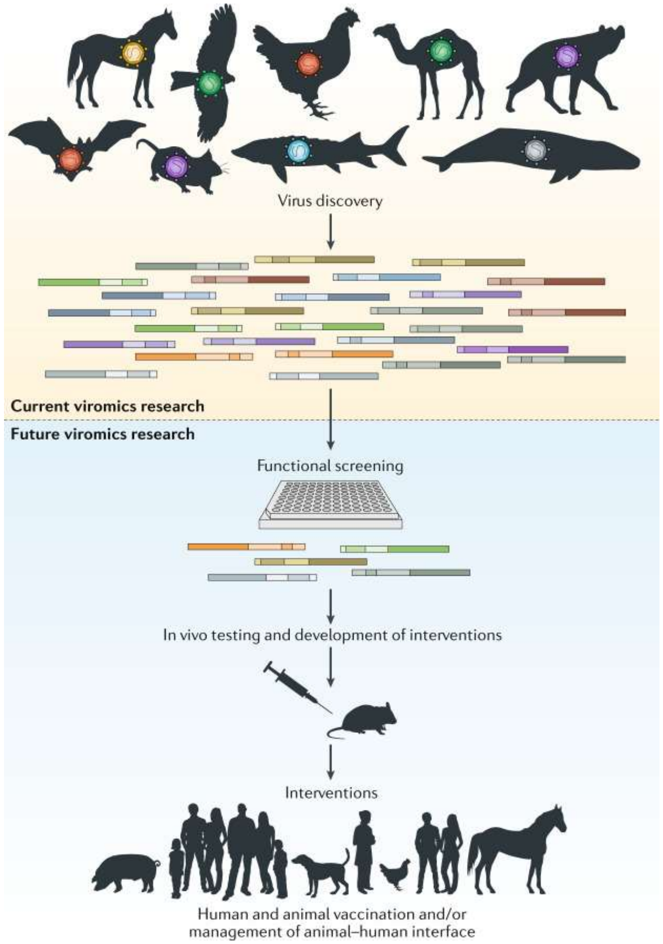
Adapted from Plowright *et al., 2017*

Functional Viromics



Virus families with fewer than 50 different sequences

Caliciviridae (43)
Peribunyaviridae (31)
Nairoviridae (22)
Unclassified viruses (22)
Retroviridae (18)
Hepeviridae (14)
Orthomyxoviridae (8)
Phenuiviridae (8)
Poxviridae (6)
Picobirnaviridae (4)
Togaviridae (3)
Genomoviridae (2)
Bornaviridae (2)
Anelloviridae (1)
Unclassified ssDNA viruses (1)
Unclassified Bunyavirales (1)

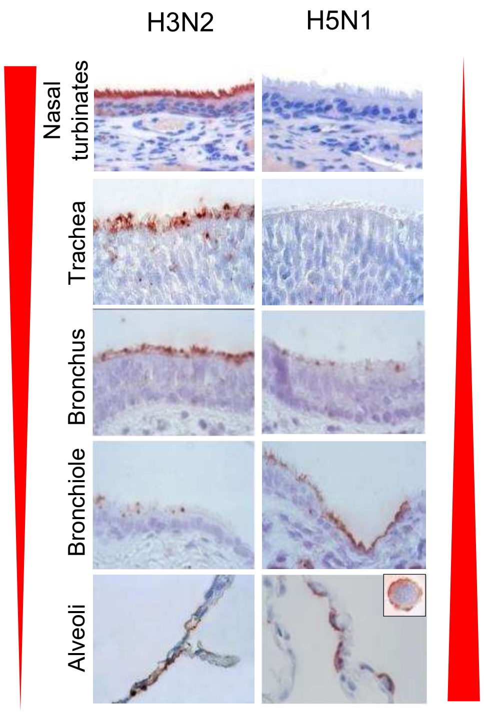


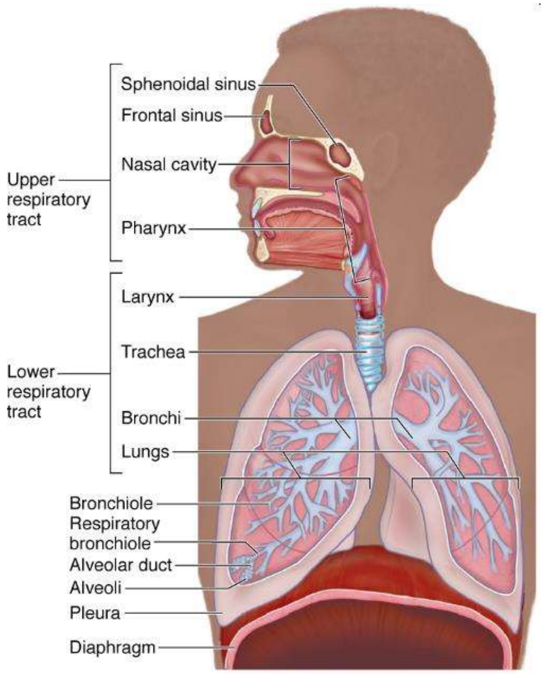
Increased sequencing efforts have resulted in a wealth of genetic data, but:

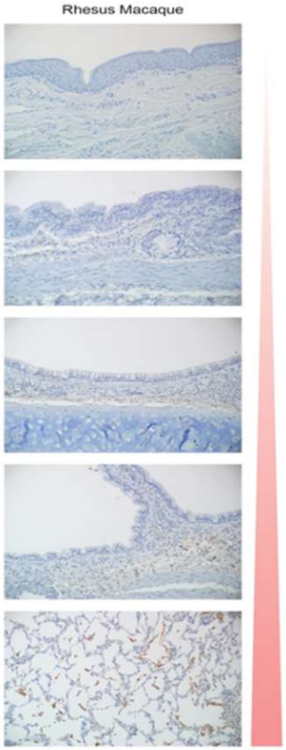
- Typically, no information on zoonotic potential
- Typically, no information on pathogenic potential

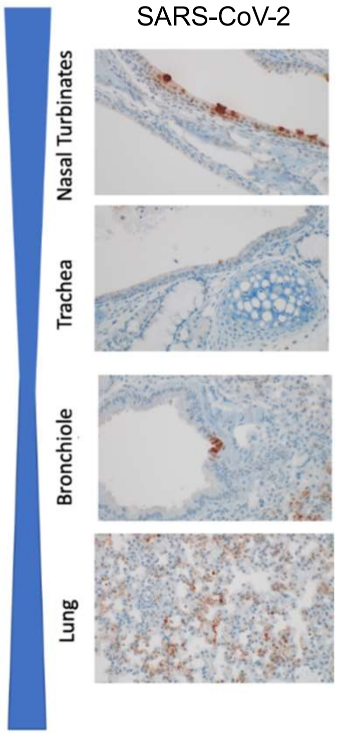
Letko, Seifert, Olival, Plowright and Munster. Nature Reviews Microbiology 2020

Tropism and transmission



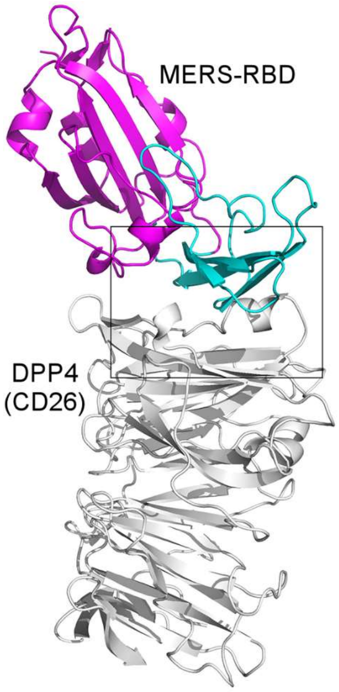


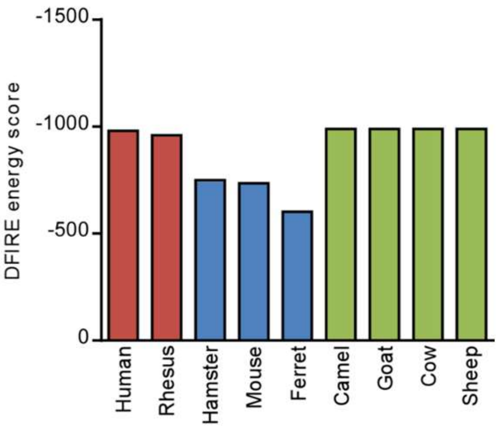


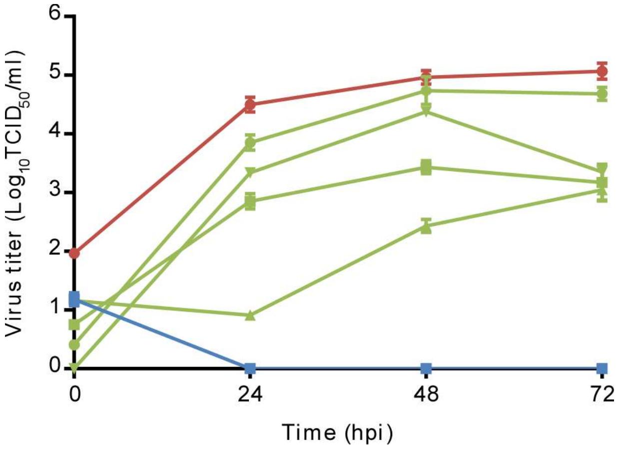


Van Riel, Munster, Science 2006
Munster, de Wit, Science 2009
Munster, NEJM 2013
Munster, Nature 2020

Receptor biology, structure and prediction



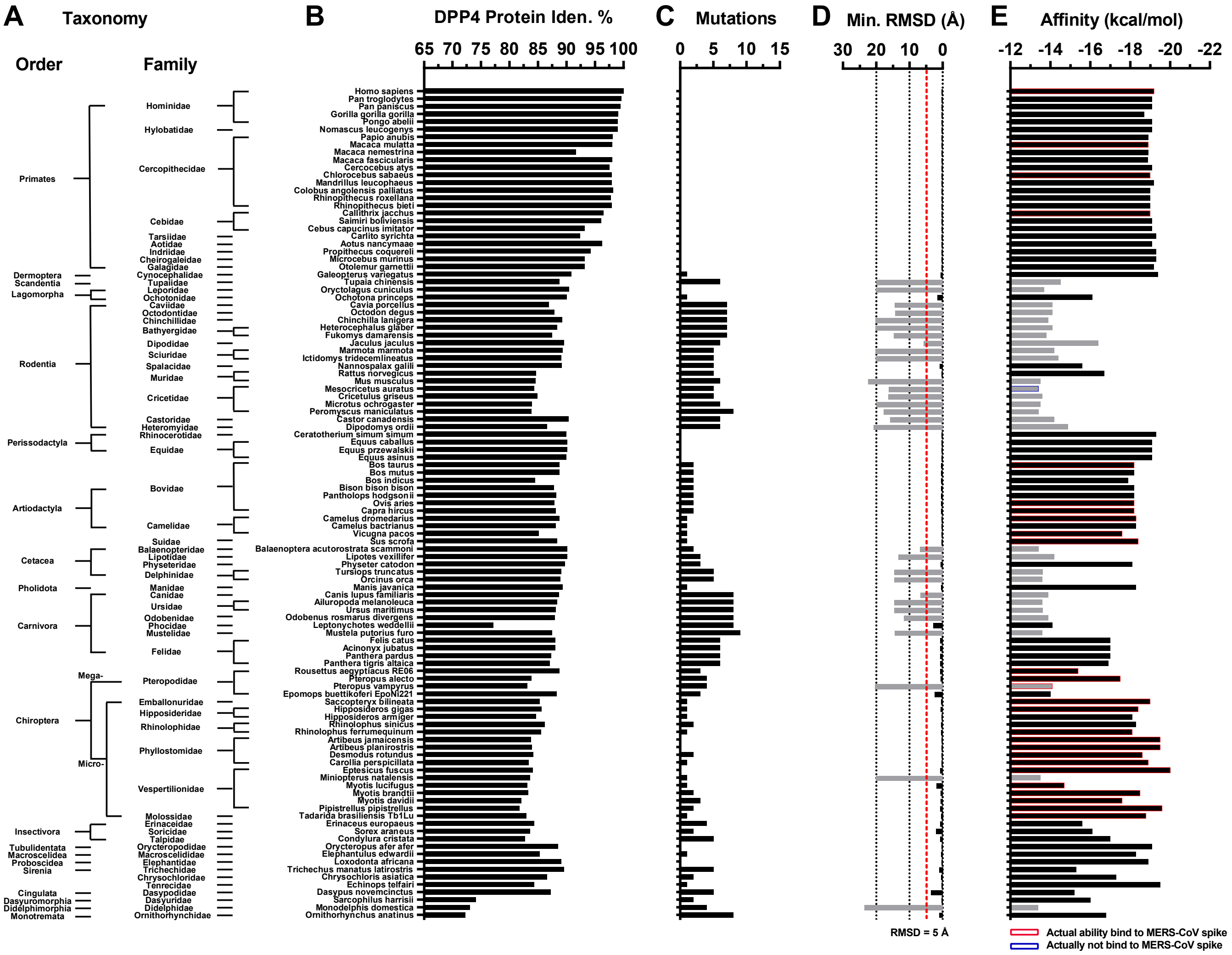




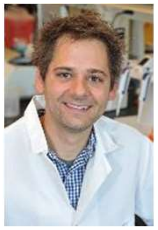
van Doremalen *et al.*, Journal of Virology 2014

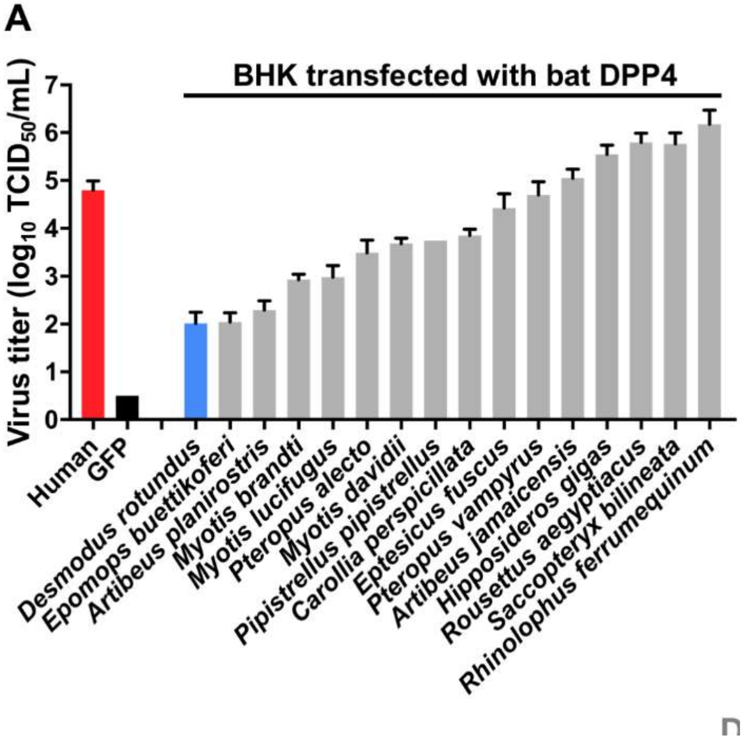
Future Directions

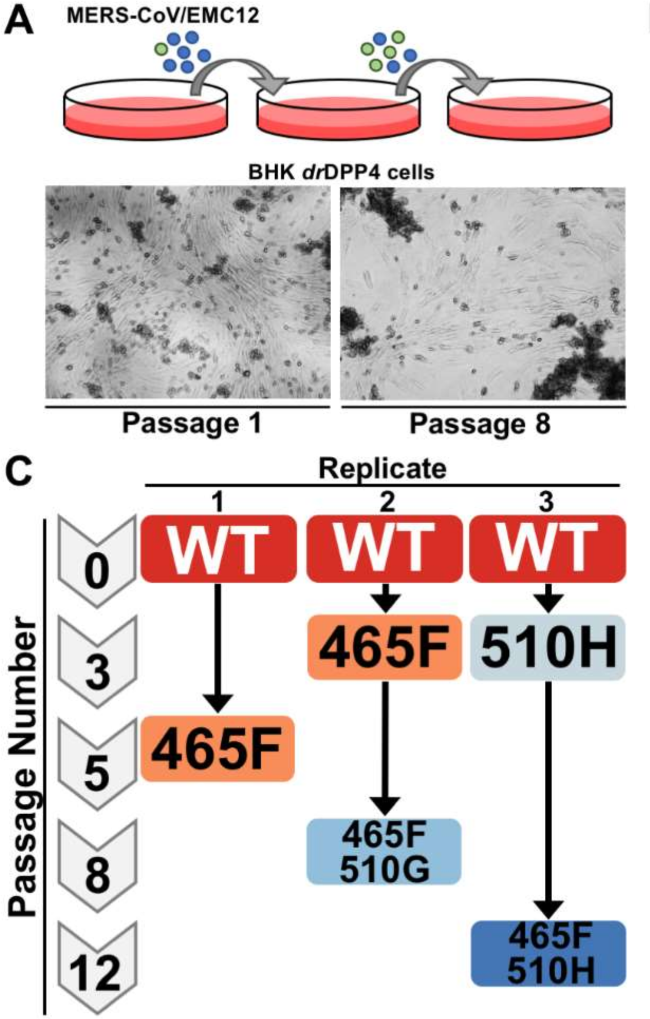
- Prediction reservoir, pathogen spillover and countermeasures -

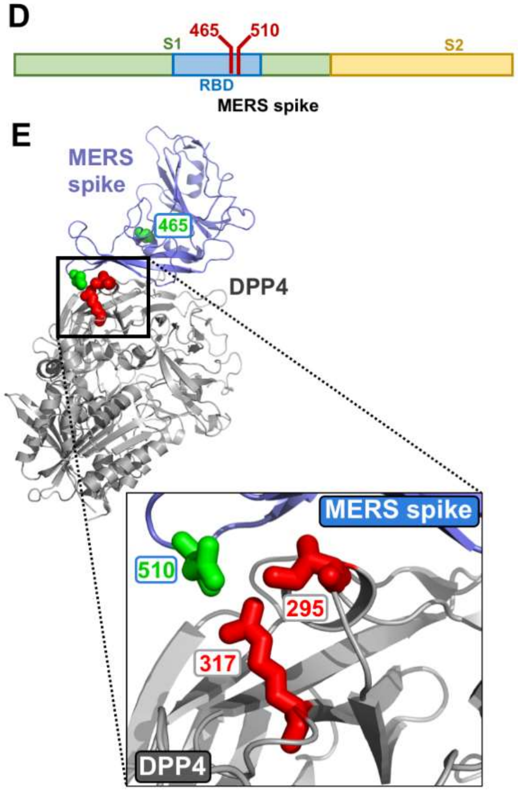


Adaptive evolution of MERS-CoV to bat species variation in DPP4



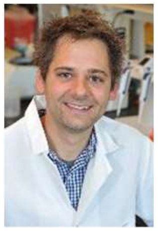


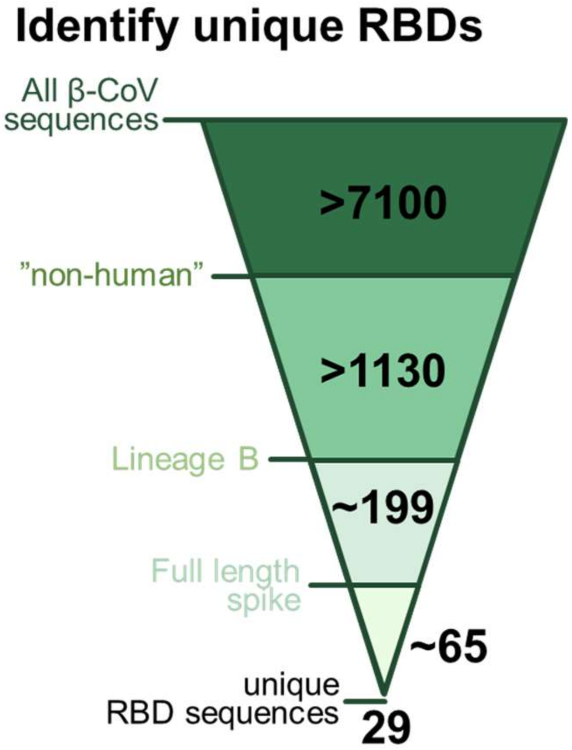


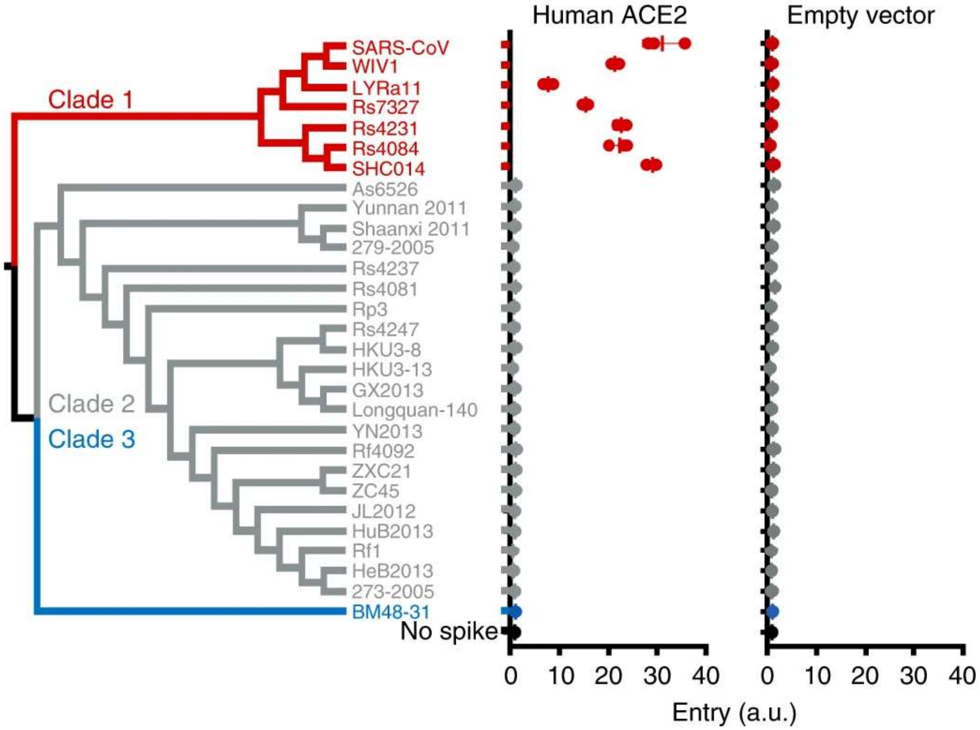


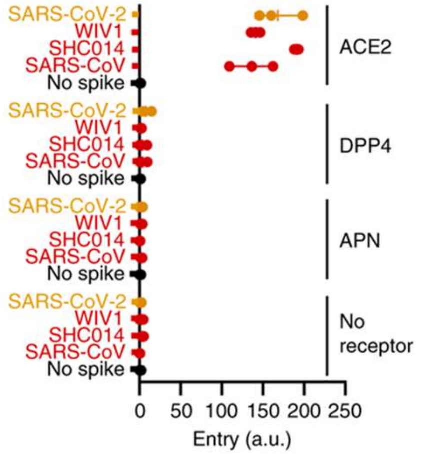
Letko *et al.*, Cell Reports 2018

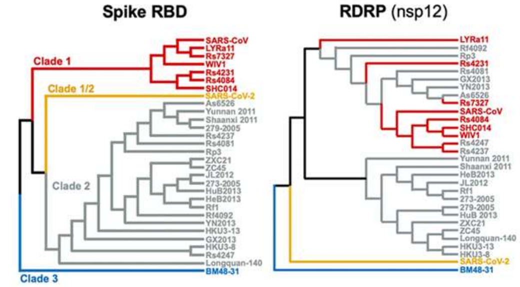
Rapid discovery of ACE2 as the receptor for SARS-CoV-2





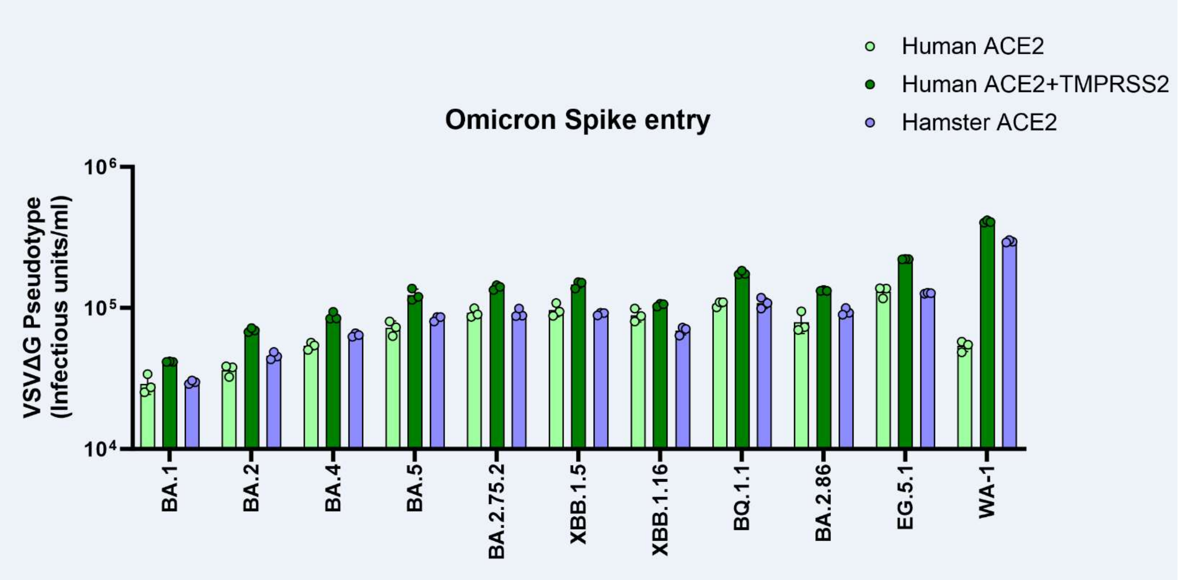


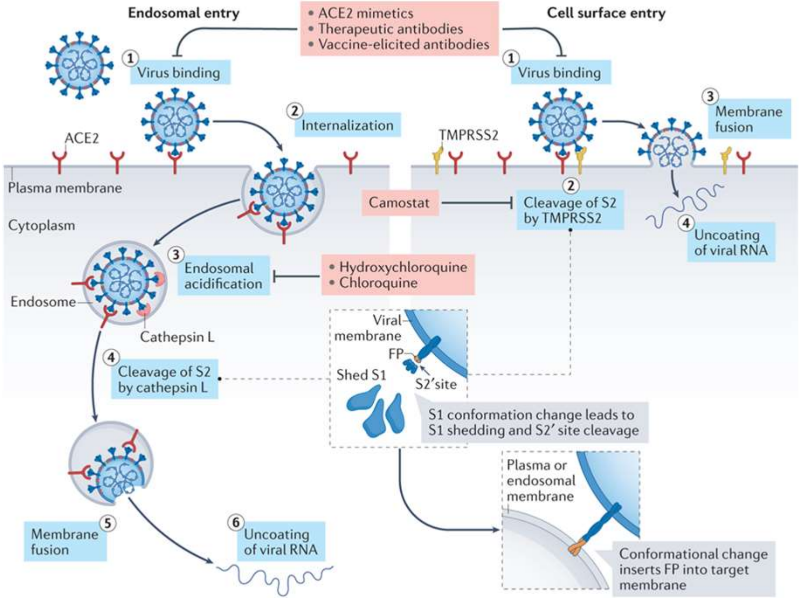




Letko, Marzi & Munster, Nature Microbiology 2020

ACE2 species specificity of SARS-CoV-2 & TMPRSII





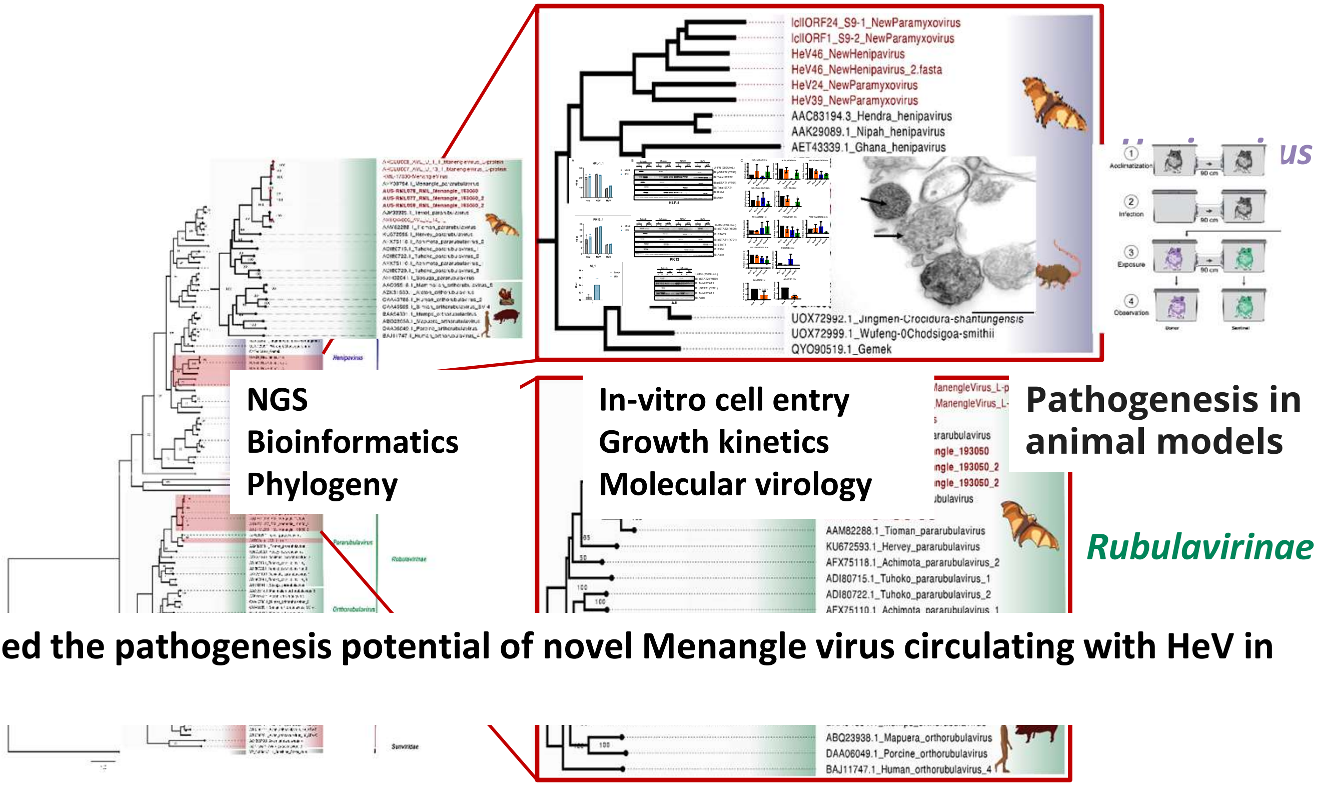
Wickenhagen et al, in preparation

Genotype to Phenotype

Molecular determinants of zoonotic and cross-species transmission

Genotype to phenotype

- Molecular determinants of zoonotic transmission
- Modelling zoonotic and human to human transmission
- Host - Pathogen Interactions



NGS
Bioinformatics
Phylogeny

In-vitro cell entry
Growth kinetics
Molecular virology

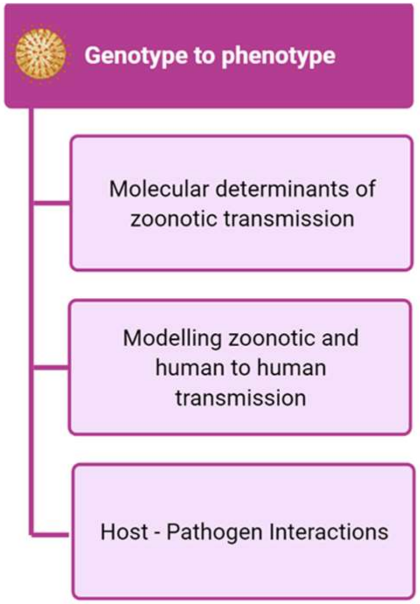
Pathogenesis in animal models

Demonstrated the pathogenesis potential of novel Menangle virus circulating with HeV in Australia.

Yinda et al, in preparation

Genotype to Phenotype

Molecular determinants of zoonotic and cross-species transmission



Genotype to phenotype

- Molecular determinants of zoonotic transmission
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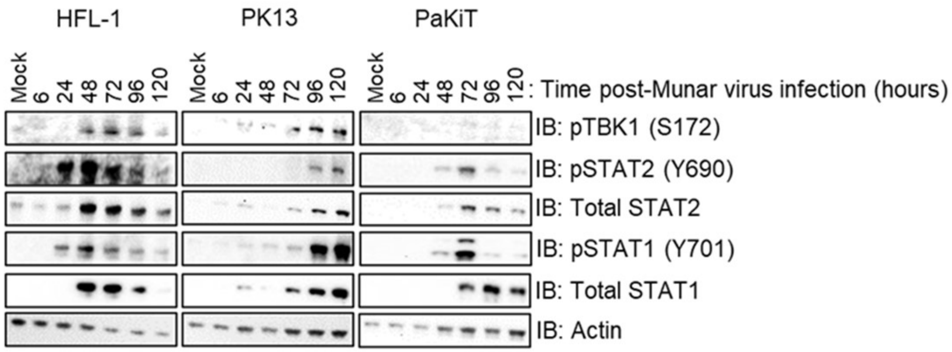
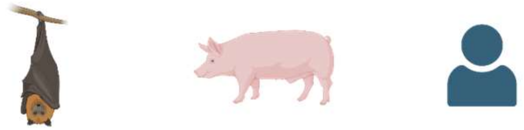


HFL-1 – human lung fibroblasts
PK13 – pig kidney
PaKiT – black flying fox kidney



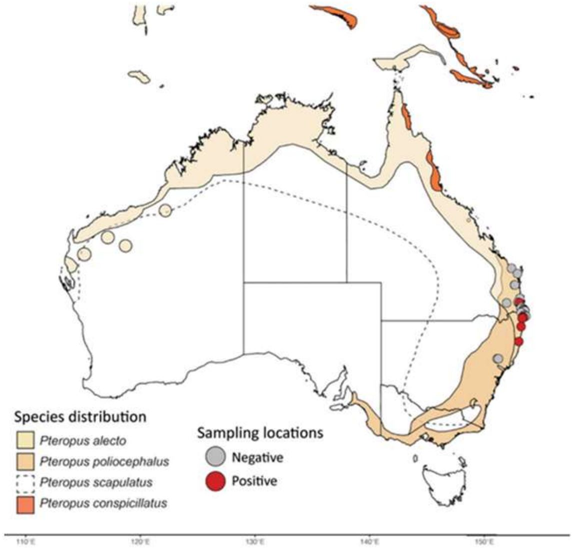
In vitro replication	☑	☑	yes, poor
IFN-I induction	delayed	delayed	yes, efficient

Yinda, Van Tol et al, in preparation

Hendra Virus Time-scale phylogeny

Multiple co-circulating lineages, limited antigenic variation

- Tree is based on HeV full genome
- Colored by host and sequence
- 3 major clades include a new clade

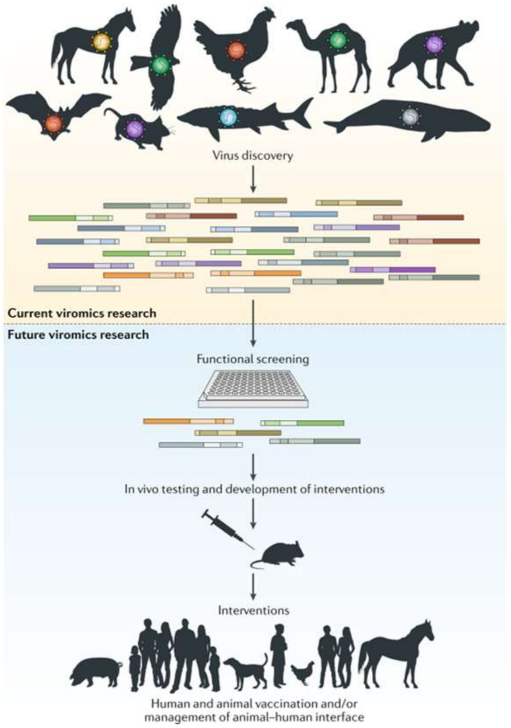


Yinda et al, in preparation

Expanding generizable basic research to identify future threats

Molecular determinants of zoonotic and cross-species transmission

- Wealth of genetic data, but limited full genome data
- Limited connection between surveillance / discovery and mechanistic work
- Mechanistic work currently limited by absence of generizable high throughput tools



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