"Corona viruses 101: Focus on Molecular Virology"
by Britt Glaunsinger
https://www.youtube.com/watch?v=8_bOhZd6ieM

Questions & Answers to guide you through the video:

- *The current pandemic is caused by what is commonly called "the corona virus". Is there only one kind of corona virus?*
  No! There are 7 known Coronaviruses that infect humans. HCoV-NL63, HCoV-229E, HCoV-OC43, HCoV-HKU1 are circulating, cause some fraction of common colds. In addition, SARS, MERS, SARS-CoV-2 (which causes COVID-19).

- *What animals are suspected in the origin and transmission of corona viruses?*
  Origin is likely bats, which harbor thousands of coronaviruses. For SARS transmission via civet cats; for MERS transmission via camels. For CoV-2 not yet sure how transmission occurred precisely.

- *How (in what form) do Corona viruses store their genetic information?*
  Single-stranded RNA, plus sense strand (which means that they can be directly read by ribosomes). RNA packaged by nucleocapsid protein and surrounded by lipid envelope.

- *Where on the virus is the "Spike" protein located and what is its role?*
  Spike is located in and protruding from the lipid envelope. Trimeric protein. Two domains: S1, upper part, is the receptor binding domain, which is highly variable. S2, lower part, is very conserved and involved in fusion to the host cell. Spike engages the cellular receptor.

- *What feature on human cells does Spike attach to?*
  ACE2 = angiotensin converting enzyme 2
  It also interacts with TMPRSS2, a protease that cleaves spike protein and triggers a series of conformational changes that ultimately lead to cell entry. Spike is a class I fusion protein (= resembles influenzavirus hemagluttinin).

- *What other host membrane protein is involved in viral entry and what is its role?*
  TMPRSS2, a protease that cleaves spike protein.

- *What is the main difference in the Spike protein between SARS-CoV-2 and the "original" 2002 SARS? How does it make the new SARS variant more infectious?*
  1) Critically conserved amino acids in the RBD are mutated in SARS-CoV-2. 2) In addition, SARS-CoV-2 has a polybasic cleavage site that can –likely– be cleaved by other cellular proteases in addition to TMPRSS2, which makes it more transmissible.

- *How does SARS-CoV-2 enter the host cell?*
  After conformational changes, Spike forms a hairpin and inserts into the host membrane, which eventually leads to endocytosis.

- *What are strategies that corona viruses use to encode multiple proteins using a single RNA?*

27 different proteins, only 1 RNA!
Three approaches: 1) ORF1 is large open reading frame that gets translated into polyprotein, which is later protealyzed (by viral proteases!) into the individual proteins. 2) Frameshifting, triggered by "slippery" sequence. 3) Discontinuous transcription: Nested set of sub-genomic RNAs.

- *What is thought to be the limit of genome size for RNA viruses and what sets that limit?*
  Mutations! If there are too many mutations per genome, replication is not viable.

- *What is proofreading in biology?*
  Error-correcting processes, for example in replication, transcription, or translation. Classical argument by Hopfield. CoV have proofreading.

- *What are nucleotide analogues and how can might they help fight corona viruses?*
  Block / inhibit RdRP (RNA-dependent RNA polymerase). Example with a lot of media attention is remdesivir (originally developed against Ebola virus).

- *What are replication-transcription complexes (RTCs)? Why is it beneficial for the virus to have separate compartments?*
  RTCs are interconnected double-membrane vesicles. Derived from ER. Likely where translation and transcription of the virus occurs. Benefits: 1) Protect viral genome, e.g. from nucleases. 2) Concentrate components. Helps assemble replicated viruses.

- *What does the viral protein nsp1 do? How? Why?*
  Nsp1 is a CoV pathogenicity factor. Restricts gene expression from the host cell, by i) interacting with the ribosome and blocking translation and ii) triggering degradation of mRNA. "Host shut off" is good for the virus, since i) it takes away resources from the host to the virus and ii) helps immune evasion, delays interferon response.

- *For the "original" 2002 SARS, how long do patients typically have neutralizing antibodies?*
  Typical time scale: ~years. It is big questions, both scientifically and for practical reasons, it is a very interesting question to what extent people develop immunity against the new SARS-CoV-2.