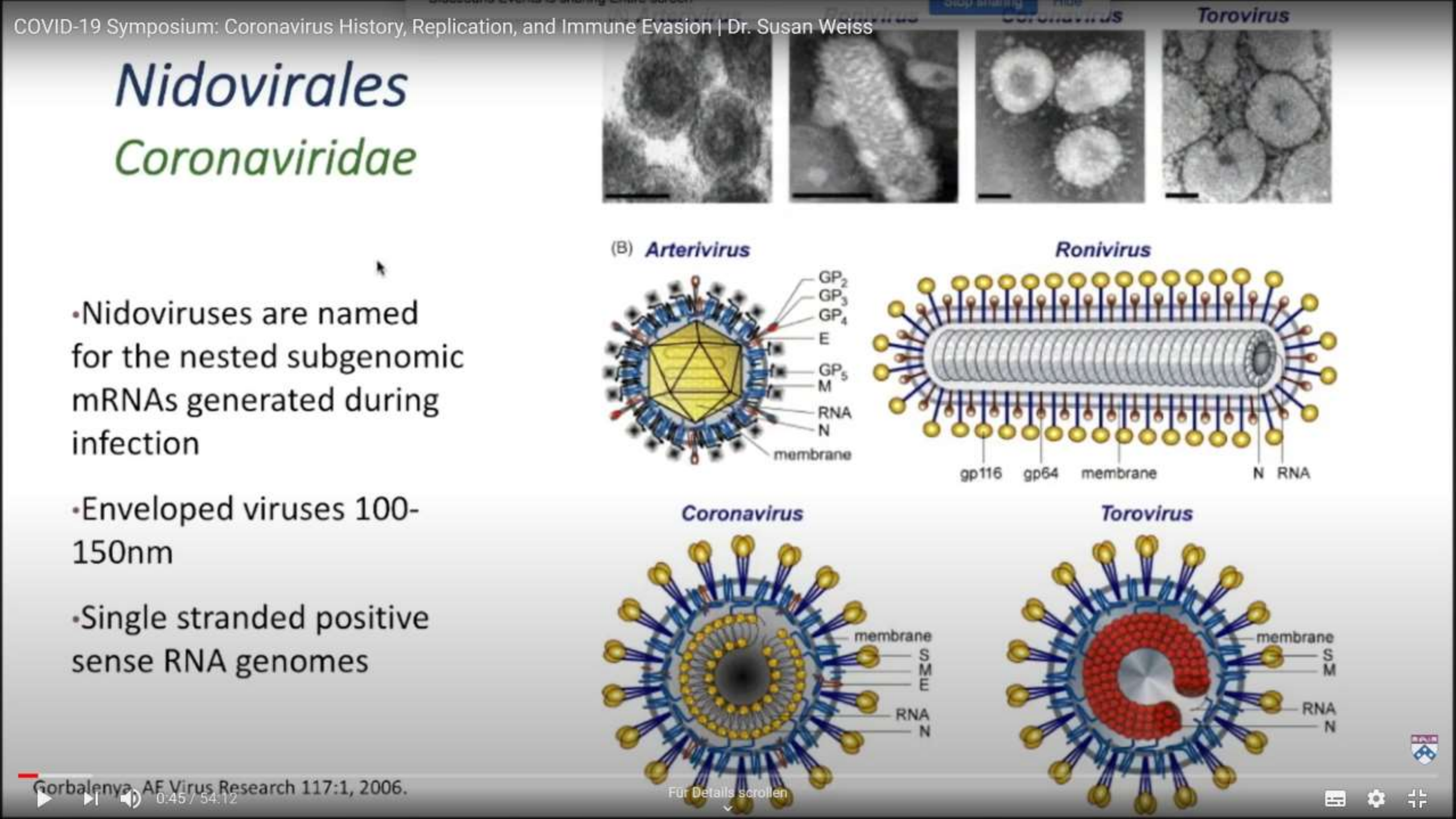

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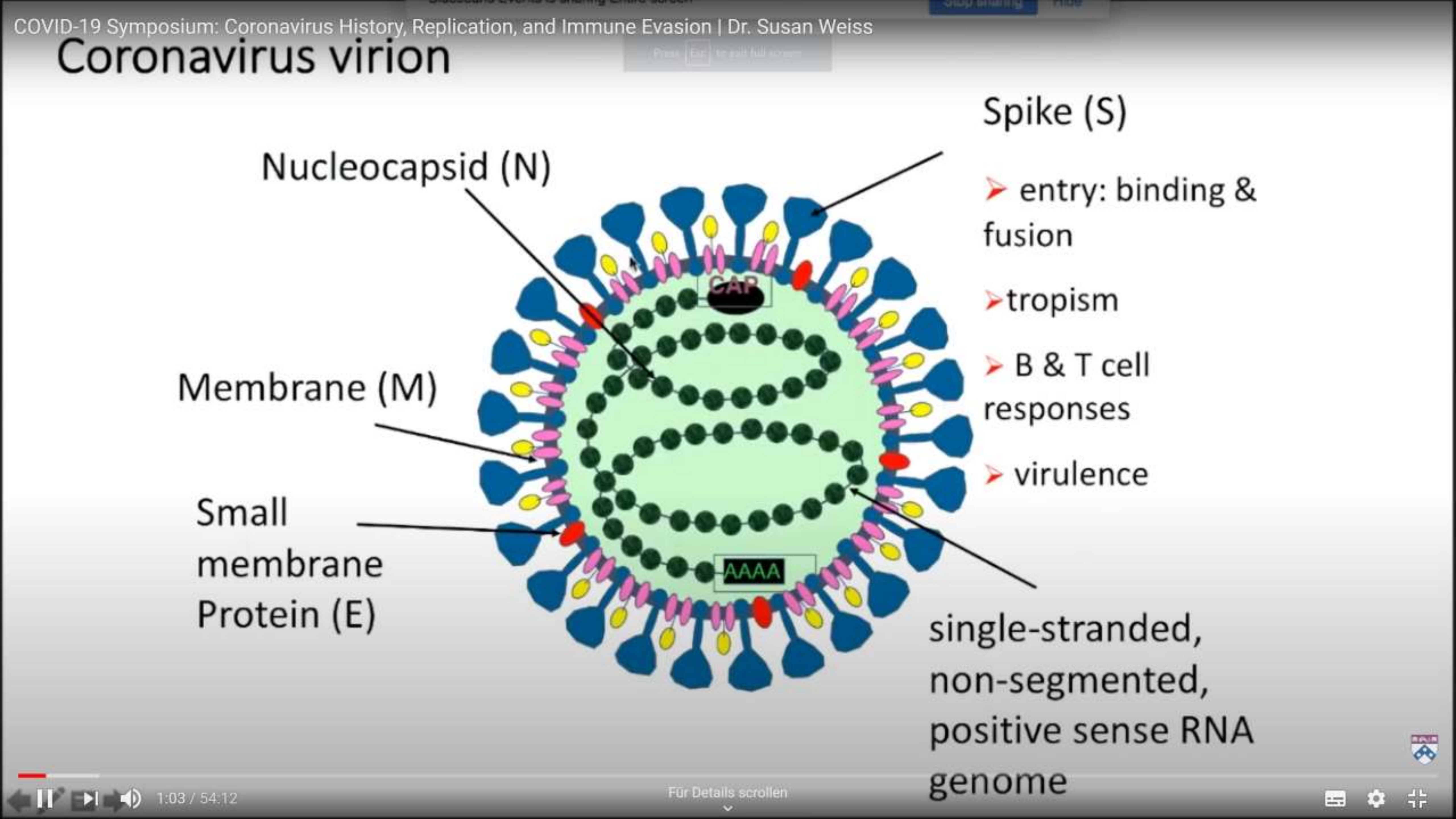
Nidovirales

Coronaviridae

- Nidoviruses are named for the nested subgenomic mRNAs generated during infection
- Enveloped viruses 100-150nm
- Single stranded positive sense RNA genomes

Gorbalenya, AE Virus Research 117:1, 2006.



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Coronavirus virion

Nucleocapsid (N)

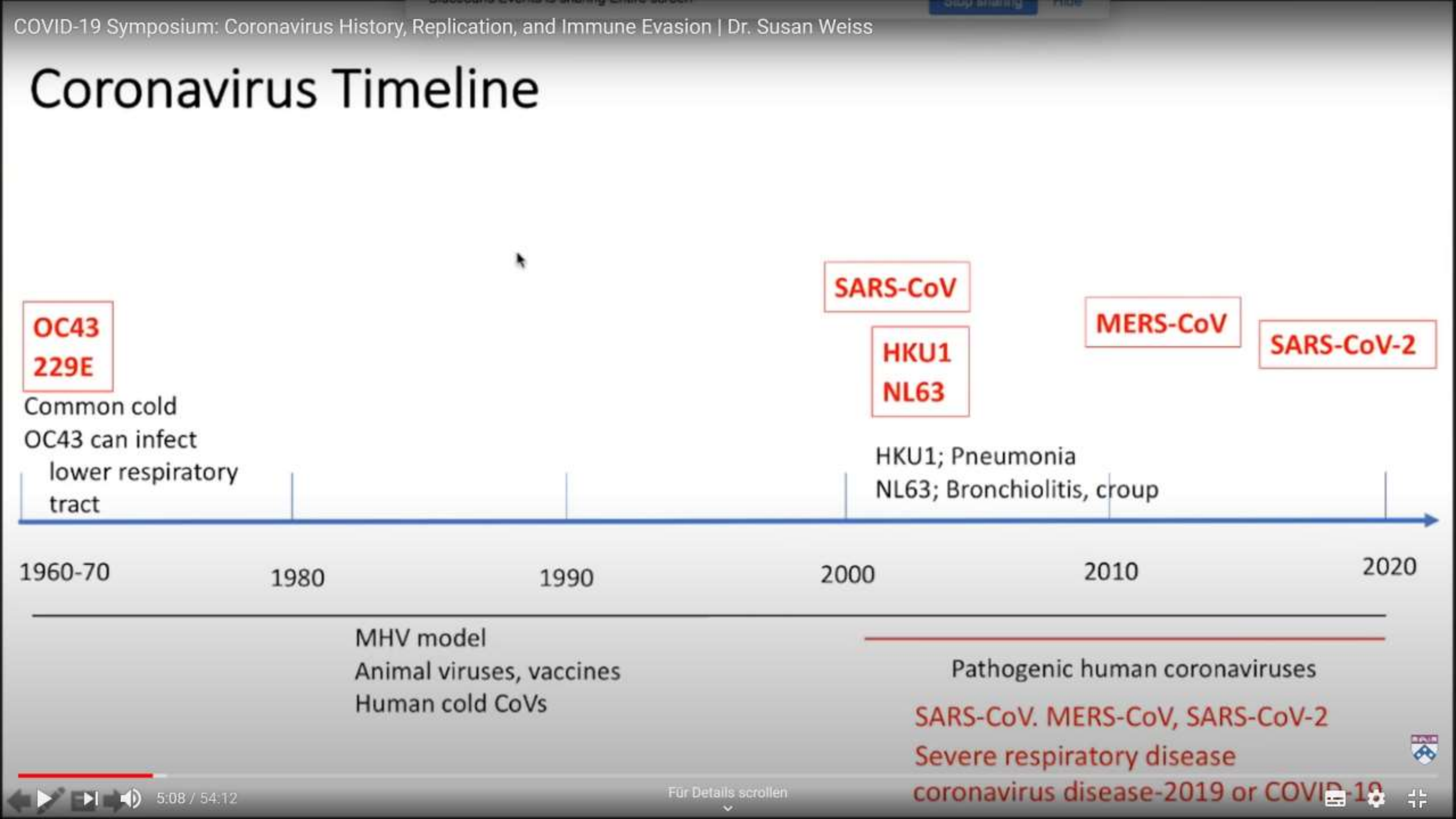
Membrane (M)

Small membrane Protein (E)

Spike (S)

- entry: binding & fusion
- tropism
- B & T cell responses
- virulence

single-stranded, non-segmented, positive sense RNA genome



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Coronavirus Timeline

OC43
229E

Common cold
OC43 can infect
lower respiratory
tract

SARS-CoV

HKU1
NL63

MERS-CoV

SARS-CoV-2

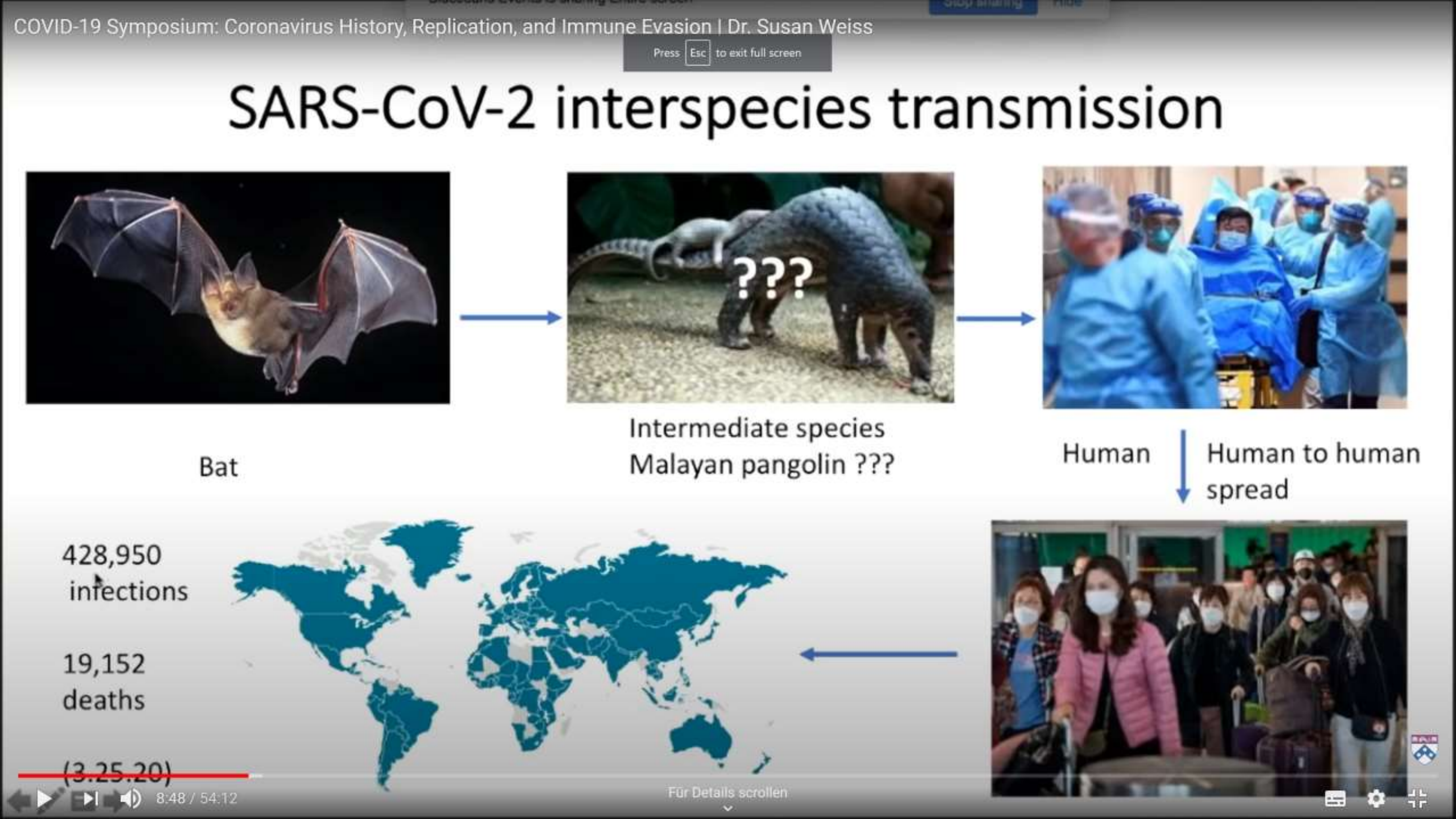
HKU1; Pneumonia
NL63; Bronchiolitis, croup

1960-70 | 1980 | 1990 | 2000 | 2010 | 2020

MHV model
Animal viruses, vaccines
Human cold CoVs

Pathogenic human coronaviruses

SARS-CoV. MERS-CoV, SARS-CoV-2
Severe respiratory disease
coronavirus disease-2019 or COVID-19



SARS-CoV-2 interspecies transmission

Bat

Intermediate species
Malayan pangolin ???

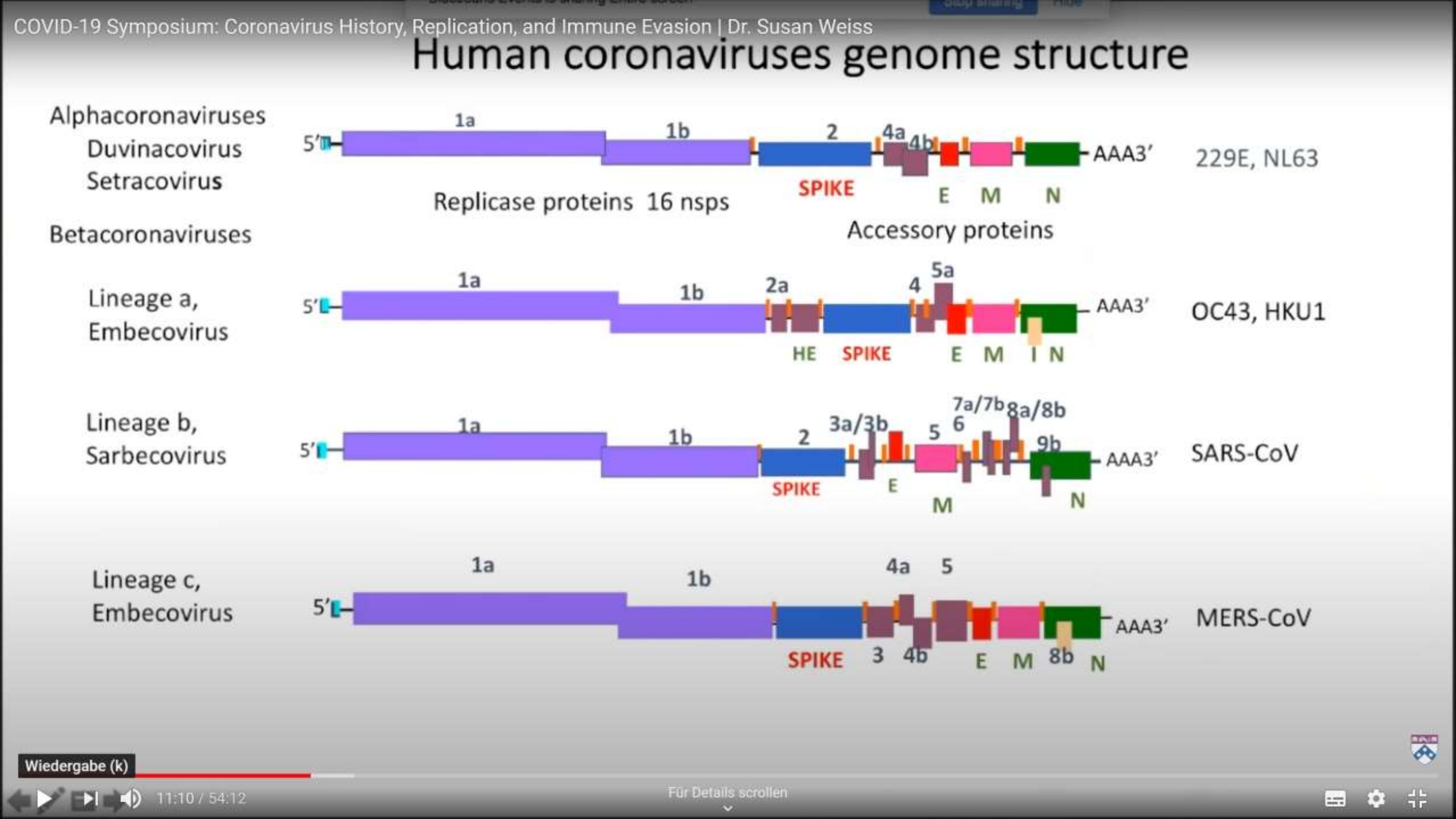
Human

Human to human spread

428,950 infections

19,152 deaths

(3.25.20)



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Human coronaviruses genome structure

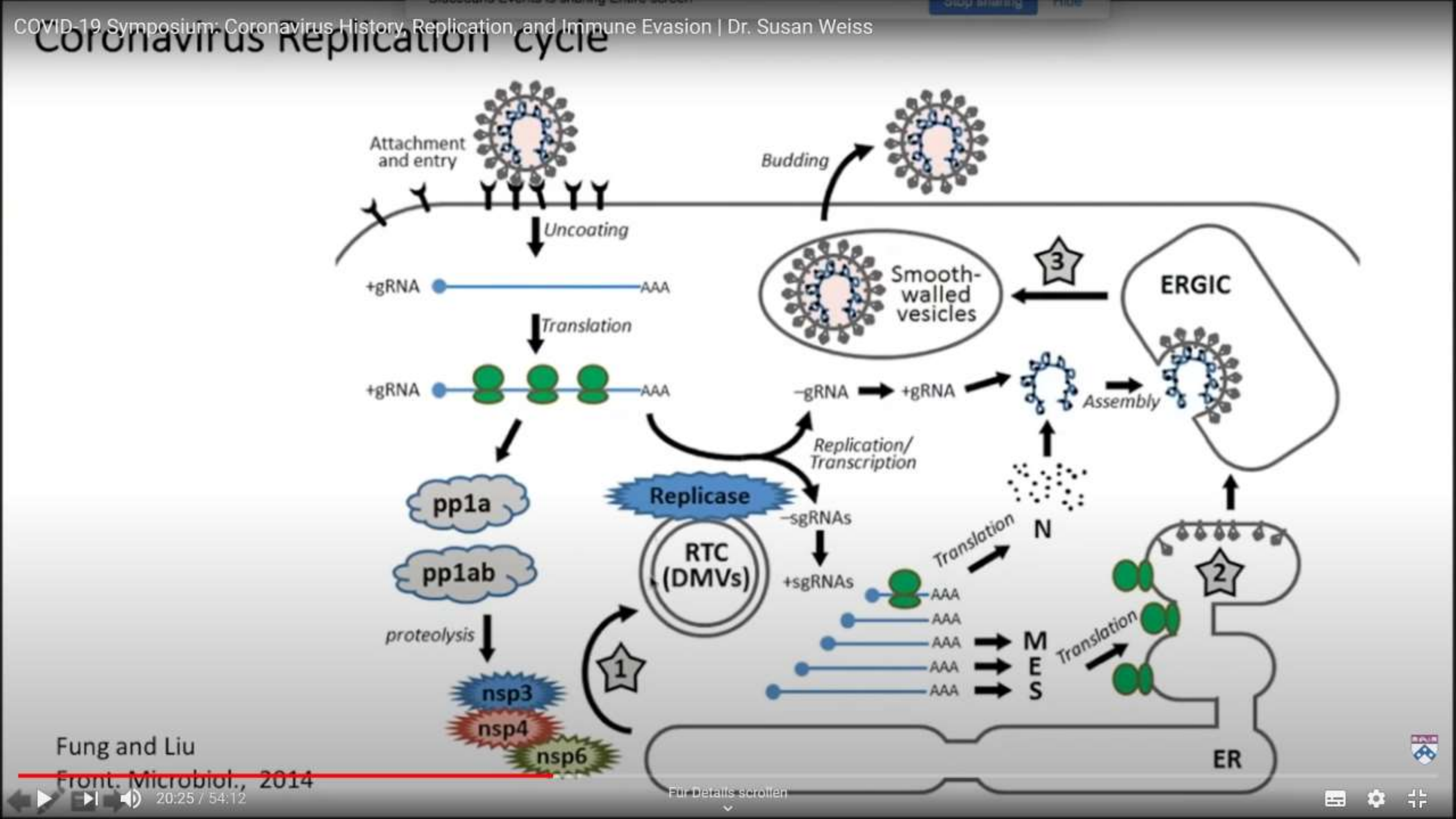
Alphacoronaviruses
Duvinacovirus
Setracovirus

Betacoronaviruses

Lineage a,
Embecovirus

Lineage b,
Sarbecovirus

Lineage c,
Embecovirus



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Coronavirus Replication cycle

Fung and Liu
Front. Microbiol., 2014

20:25 / 54:12

Für Details scrollen

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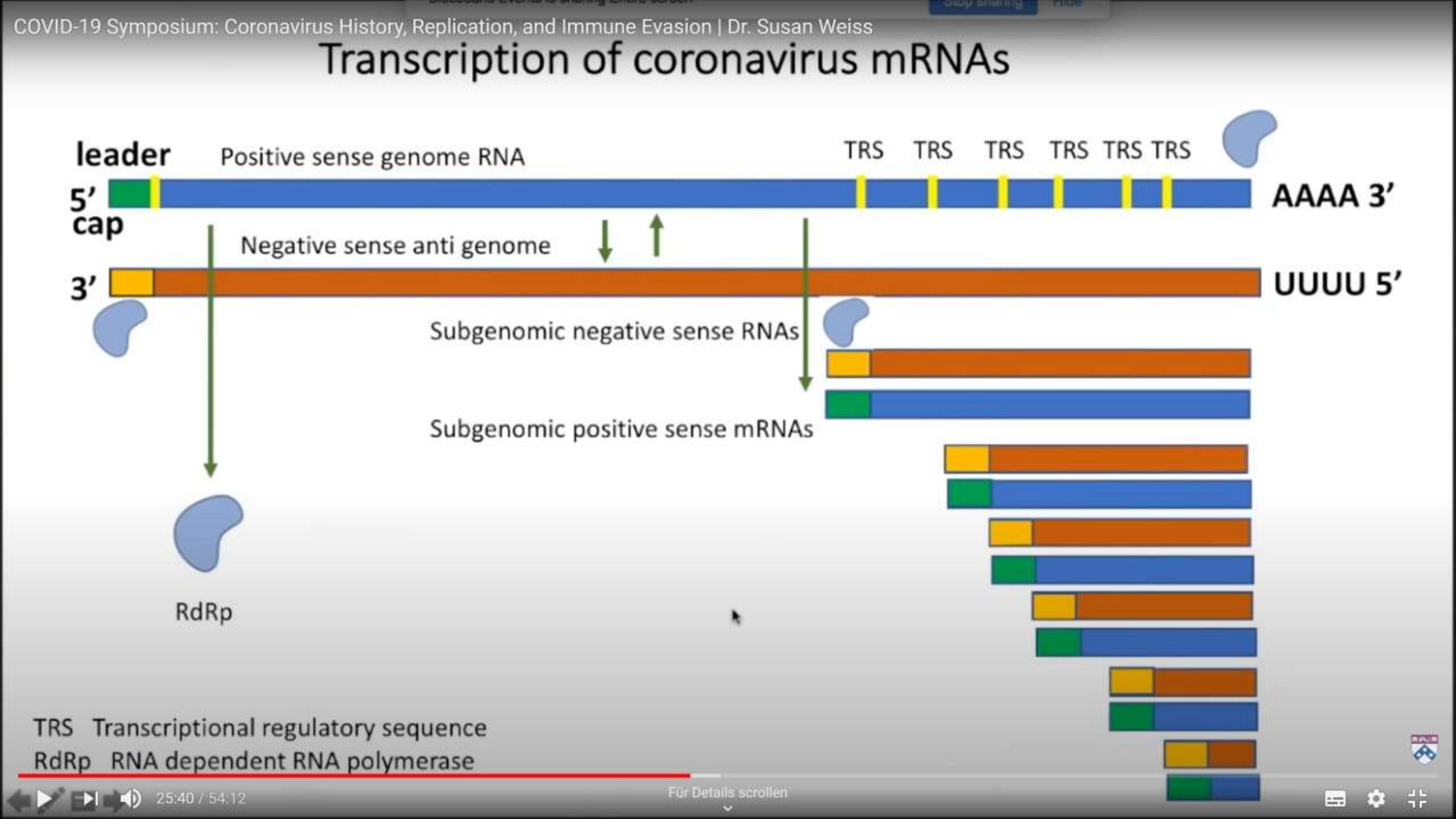

Transcription of coronavirus mRNAs

TRS Transcriptional regulatory sequence

RdRp RNA dependent RNA polymerase

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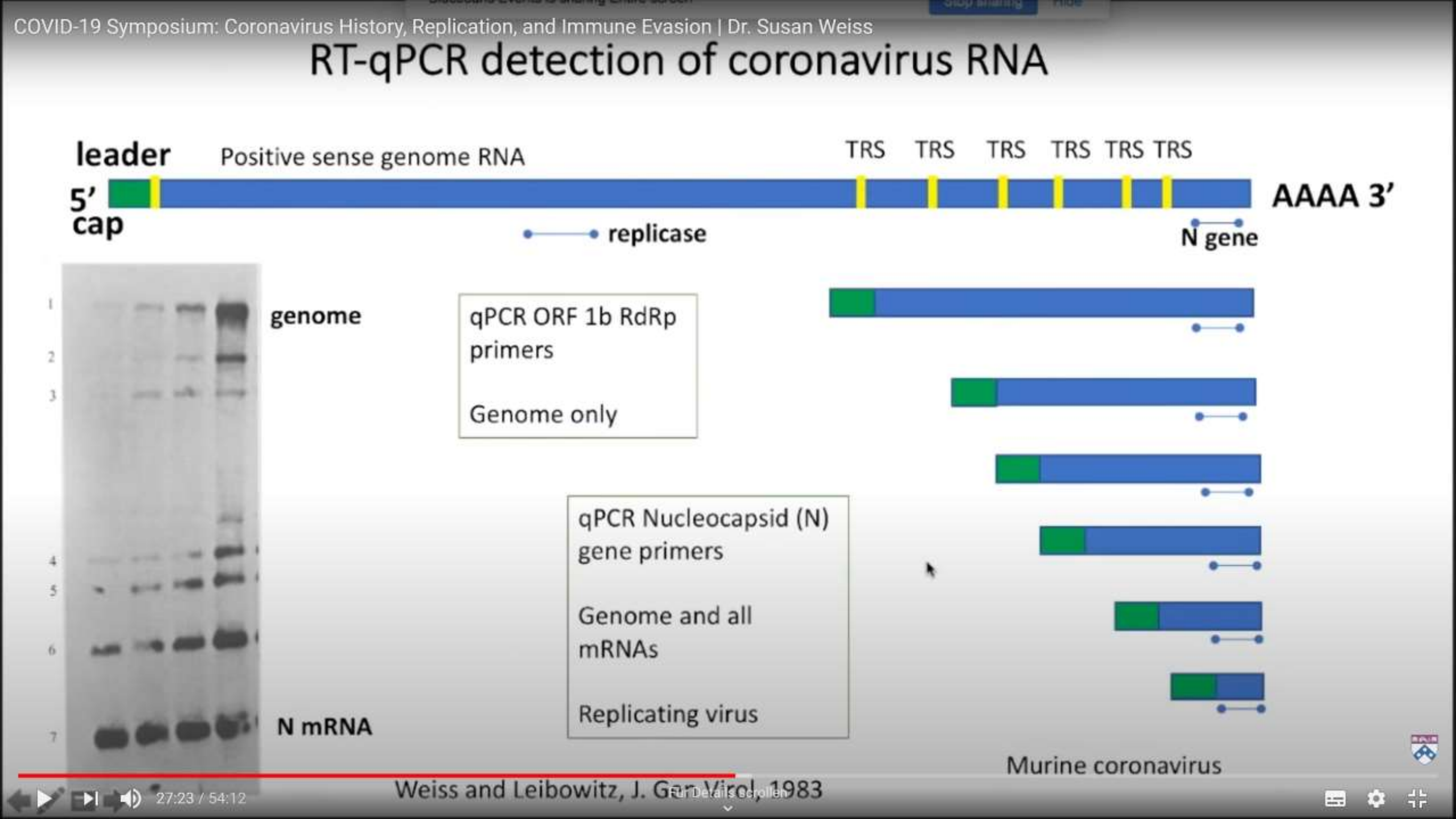
RT-qPCR detection of coronavirus RNA



qPCR ORF 1b RdRp primers

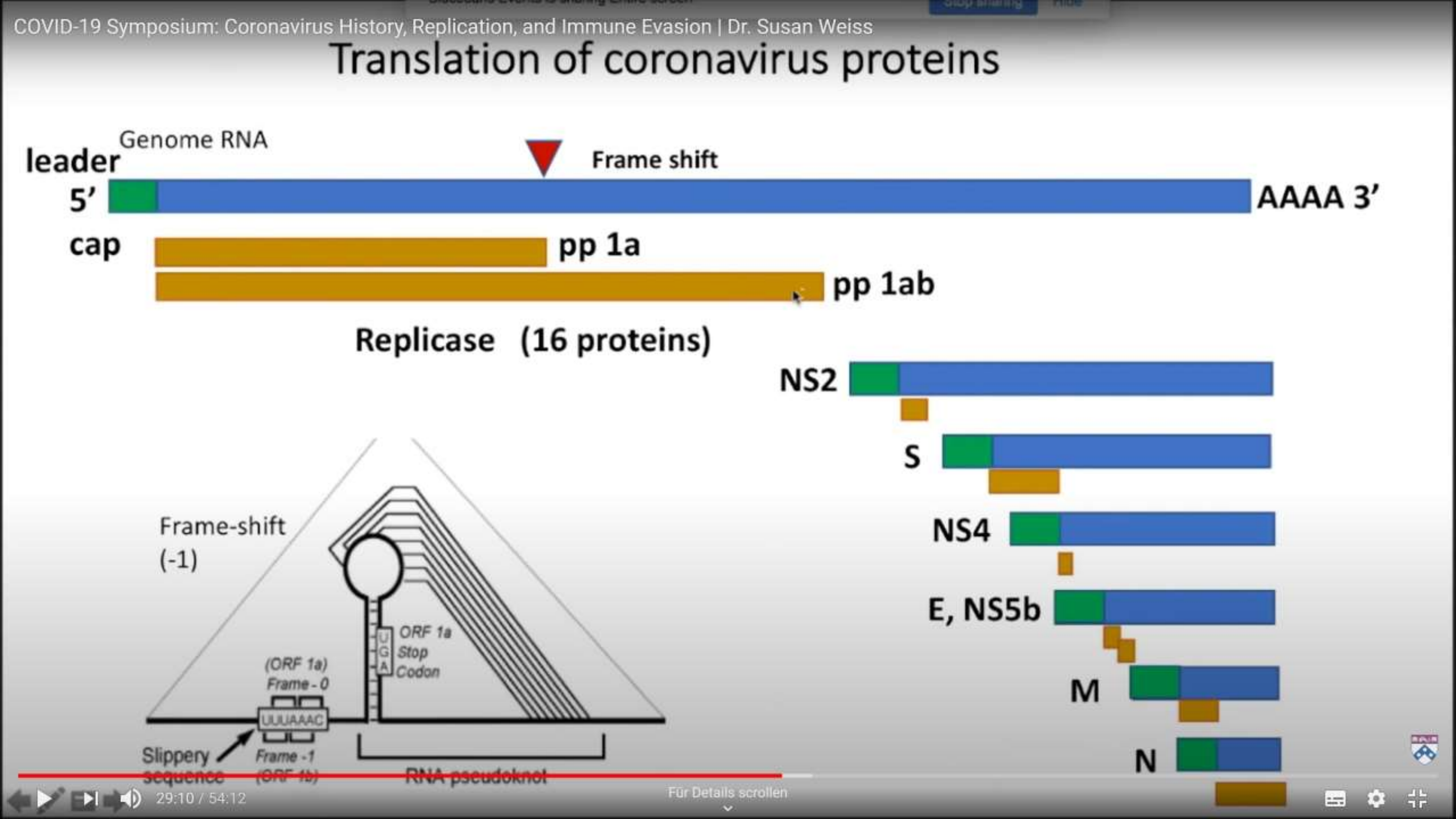
Genome only

qPCR Nucleocapsid (N) gene primers

Genome and all mRNAs

Replicating virus

Weiss and Leibowitz, J. Gen Virol, 1983



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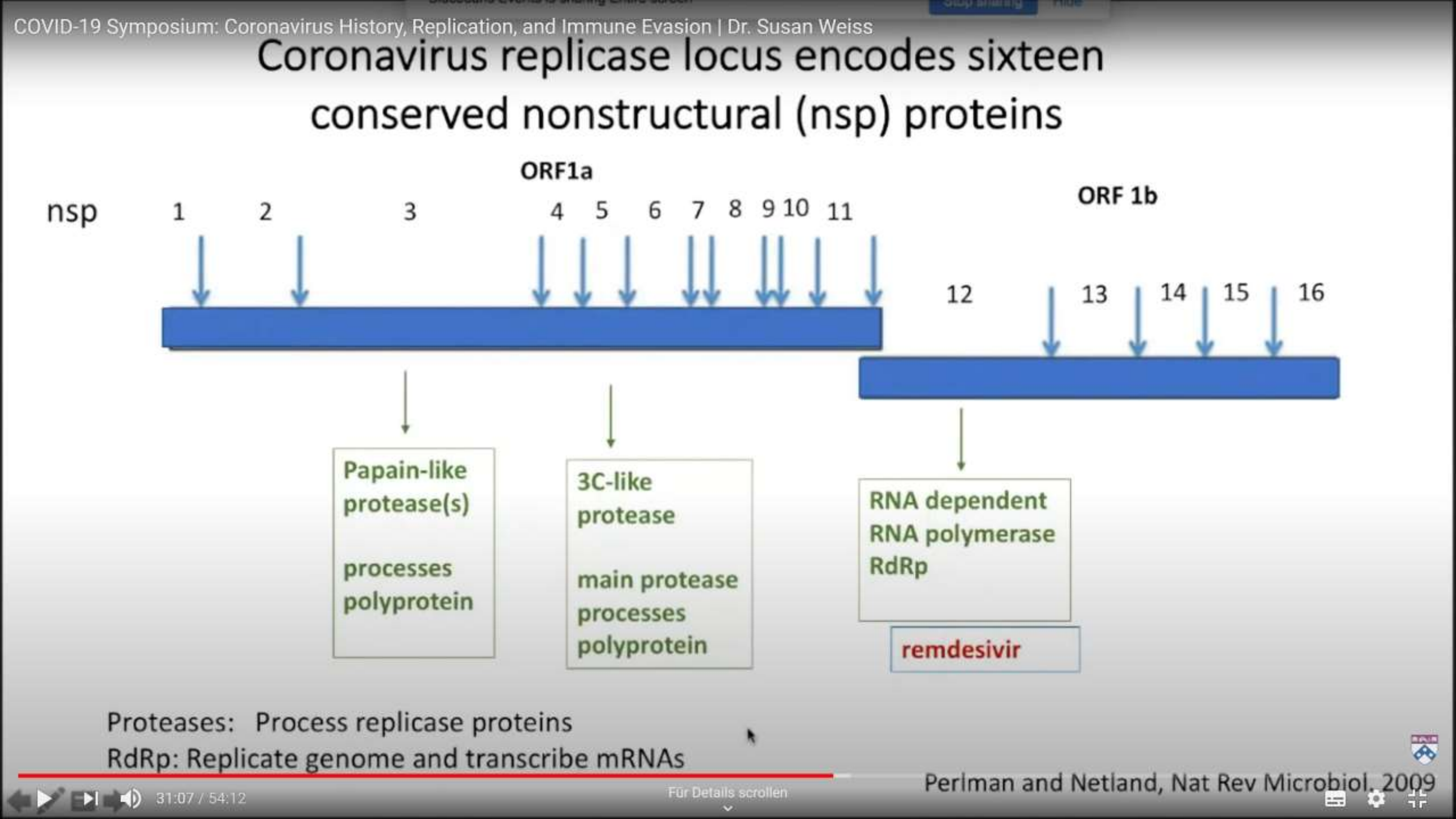
Translation of coronavirus proteins



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Coronavirus replicase locus encodes sixteen conserved nonstructural (nsp) proteins

Papain-like protease(s)

processes polyprotein

3C-like protease

main protease processes polyprotein

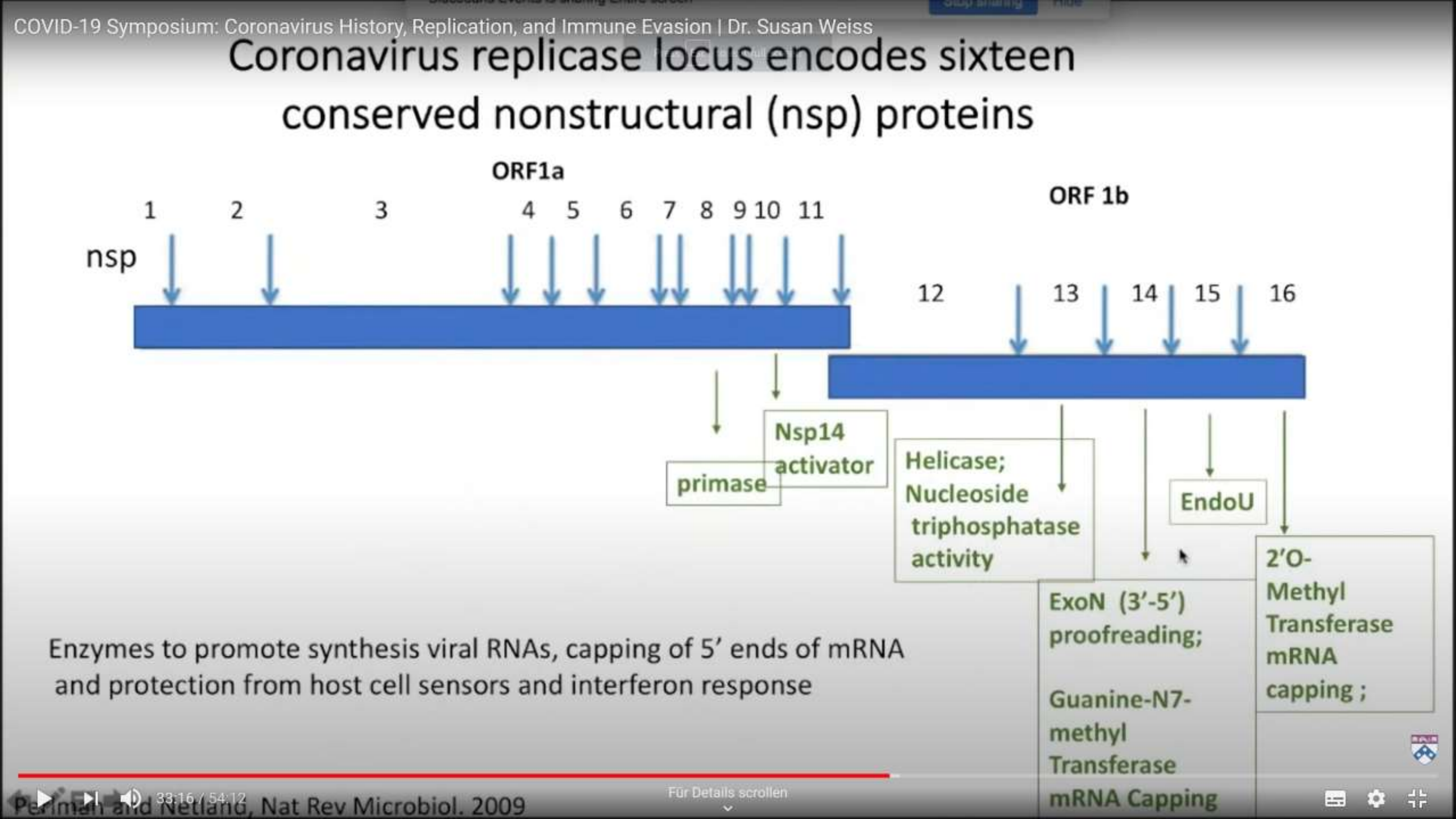
RNA dependent RNA polymerase RdRp

remdesivir

Proteases: Process replicase proteins

RdRp: Replicate genome and transcribe mRNAs

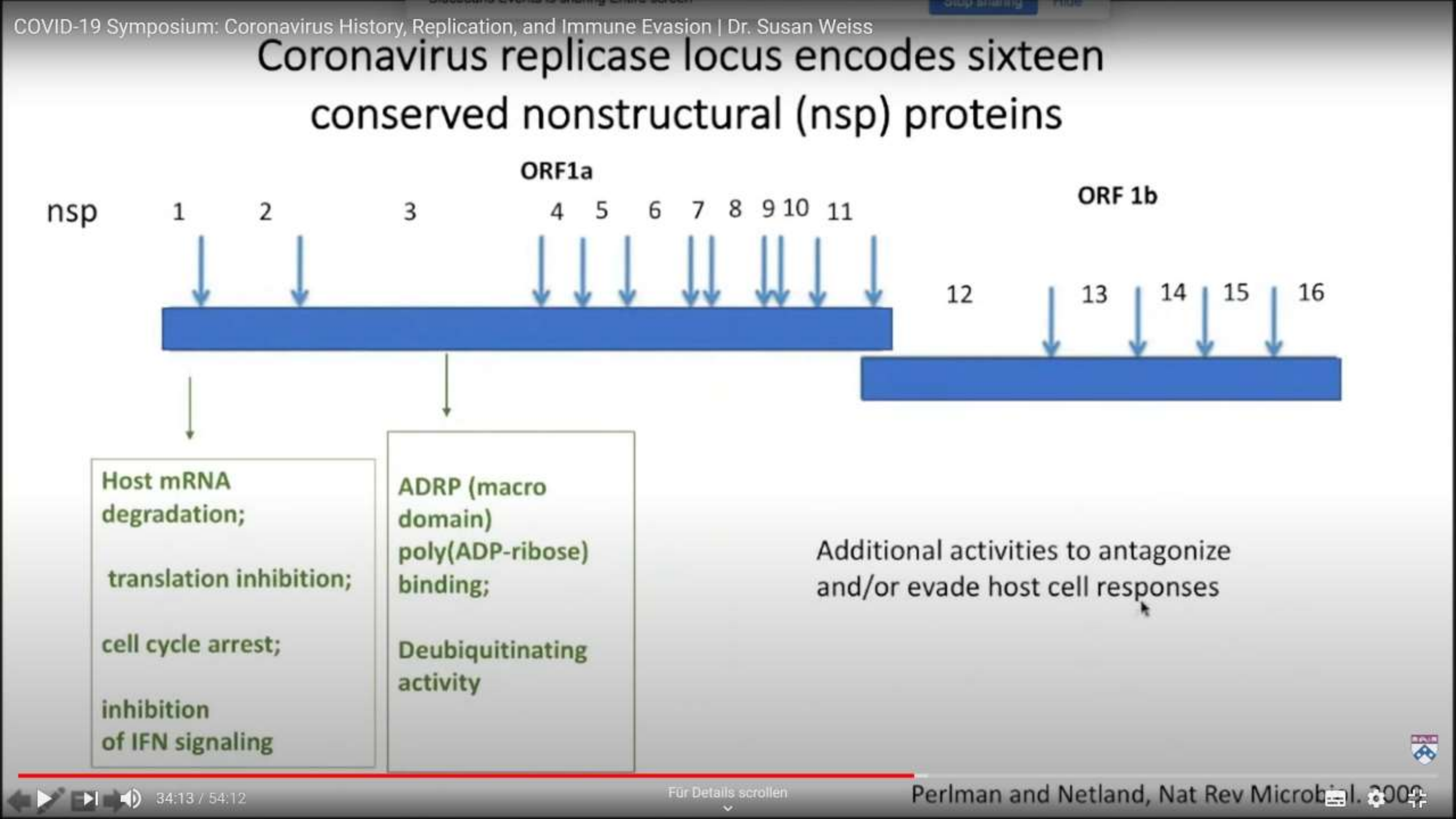
Perlman and Netland, Nat Rev Microbiol. 2009



Coronavirus replicase locus encodes sixteen conserved nonstructural (nsp) proteins

Enzymes to promote synthesis viral RNAs, capping of 5' ends of mRNA and protection from host cell sensors and interferon response

Perlman and Netland, Nat Rev Microbiol. 2009



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Coronavirus replicase locus encodes sixteen conserved nonstructural (nsp) proteins

Host mRNA degradation;

translation inhibition;

cell cycle arrest;

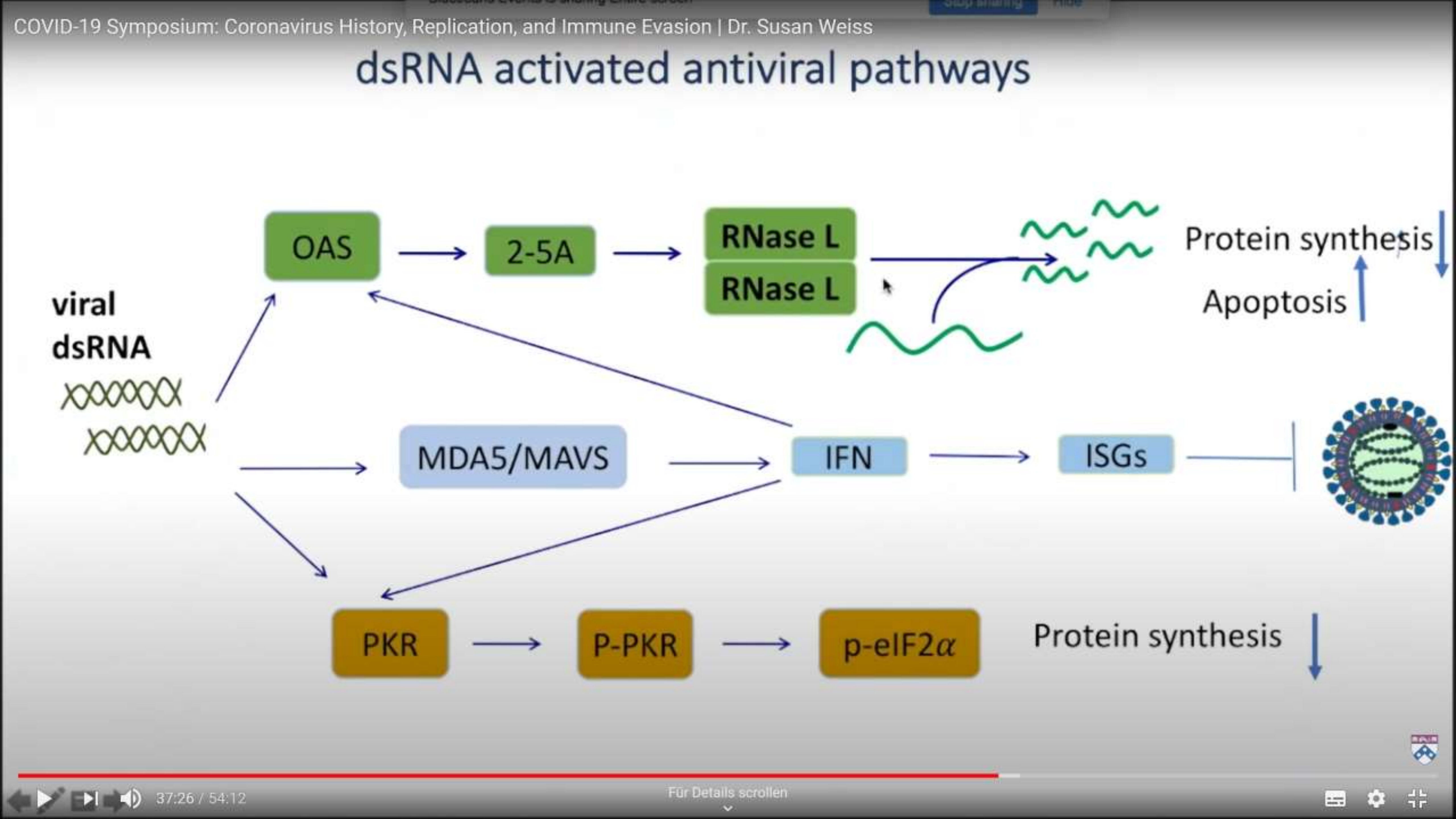
inhibition of IFN signaling

ADRP (macro domain) poly(ADP-ribose) binding;

Deubiquitinating activity

Additional activities to antagonize and/or evade host cell responses

Perlman and Netland, Nat Rev Microb l. 200



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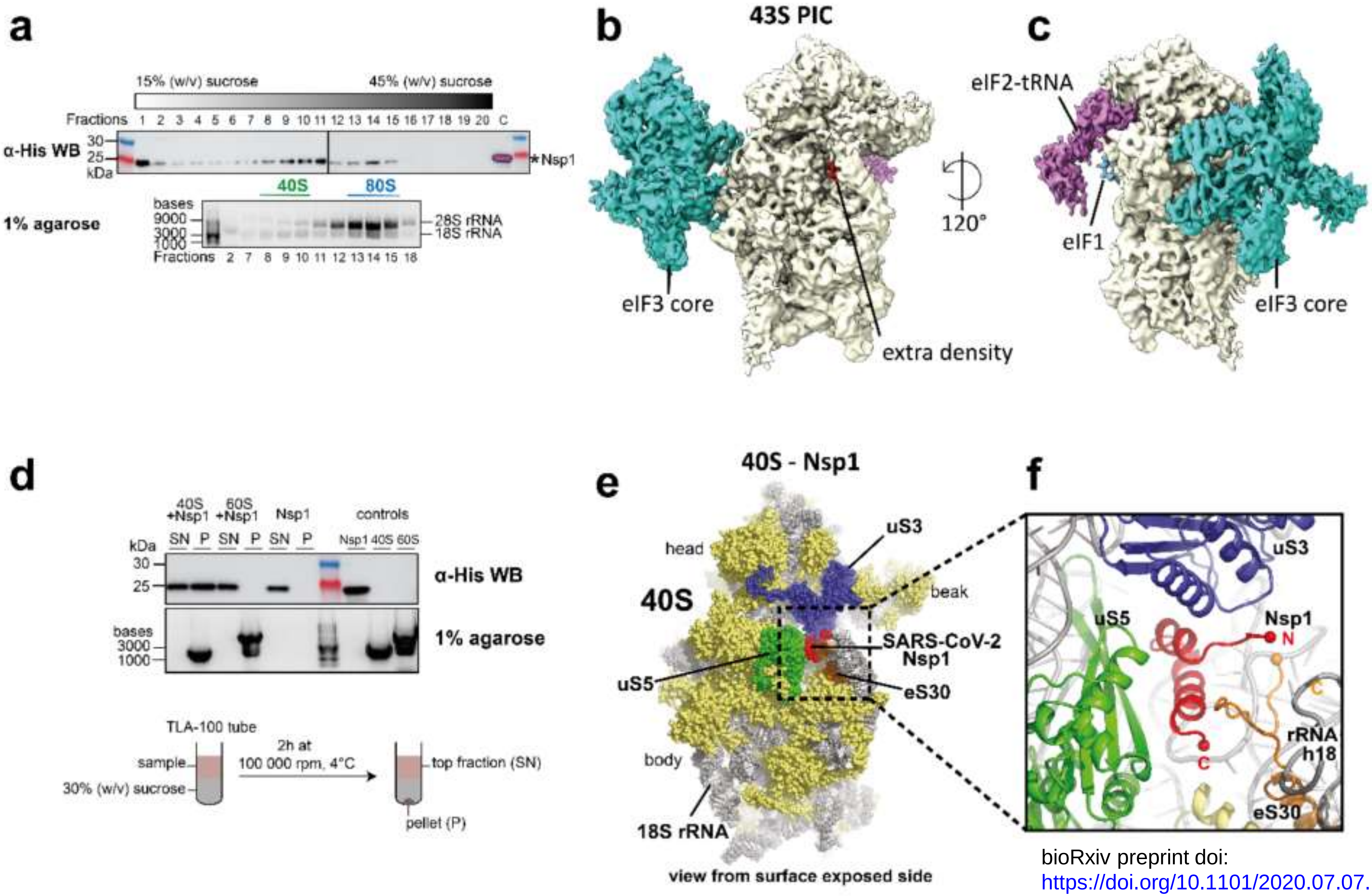
dsRNA activated antiviral pathways

viral
dsRNA

OAS → 2-5A → **RNase L** / **RNase L**
Protein synthesis ↓
Apoptosis ↑

MDA5/MAVS → IFN → ISGs ⊣

PKR → P-PKR → p-eIF2α
Protein synthesis ↓



bioRxiv preprint doi:
https://doi.org/10.1101/2020.07.07.191676

Figure 1: Structures of ribosomal complexes inhibited by SARS-CoV-2 Nsp1 solved by cryo-EM.

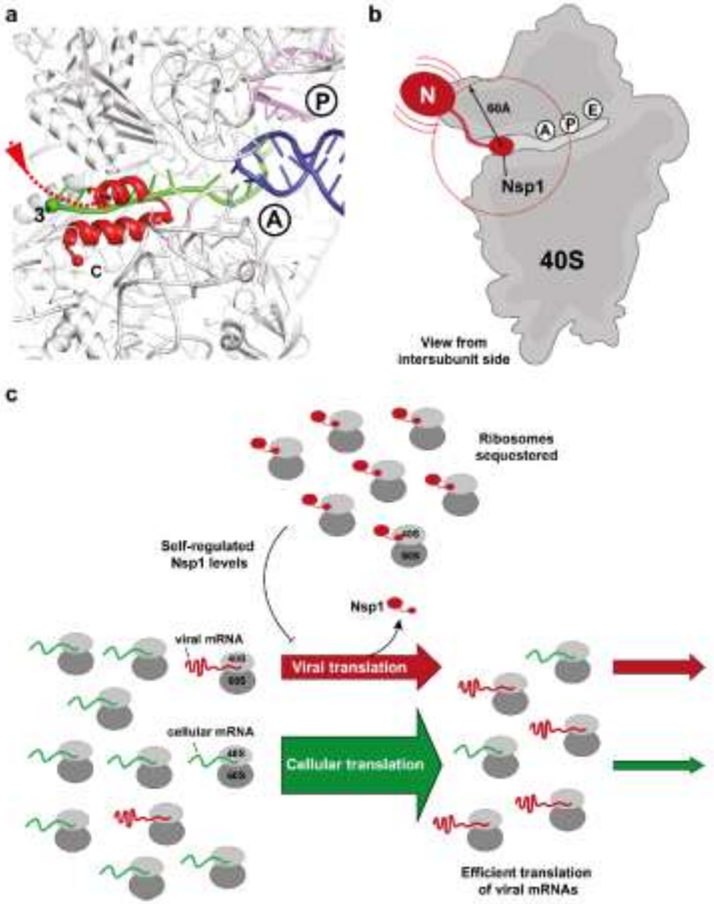
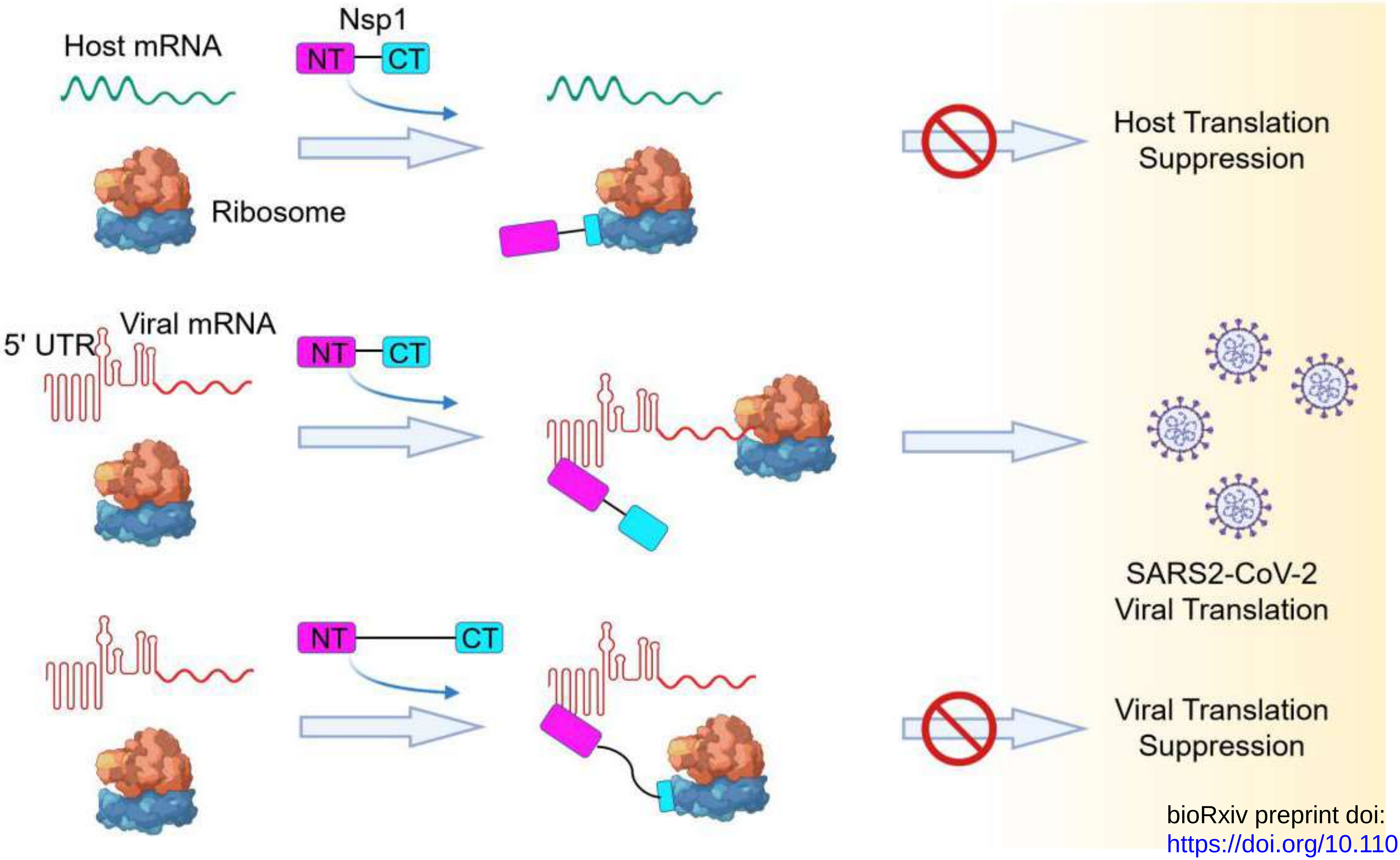


Figure 4: Binding of C-terminal domain of SARS-CoV-2 Nsp1 to ribosomal mRNA channel prevents classical mRNA binding by sterical hindrance.

(a) Superposition of canonically bound mRNA (green), A- (blue) and P-site (purple) tRNAs (pdb 6HCJ) reveals that Nsp1 (red) prevents classical binding of the mRNA at the entry site due to blockage. **(b)** Nsp1 binds *via* its C-terminus in proximity of the 40S mRNA entry site. Due to the flexible linker, the N-terminal domain can sample an area of ~60 Å around its attachment point (circle). **(c)** Model for translation inhibition by Nsp1. Upon viral infection and translation of viral genomic mRNA, Nsp1 acts as a translation inhibitor reducing the pool of ribosomes that can engage in translation. Under such ribosome-limiting conditions, viral mRNAs are translated with high efficiency.

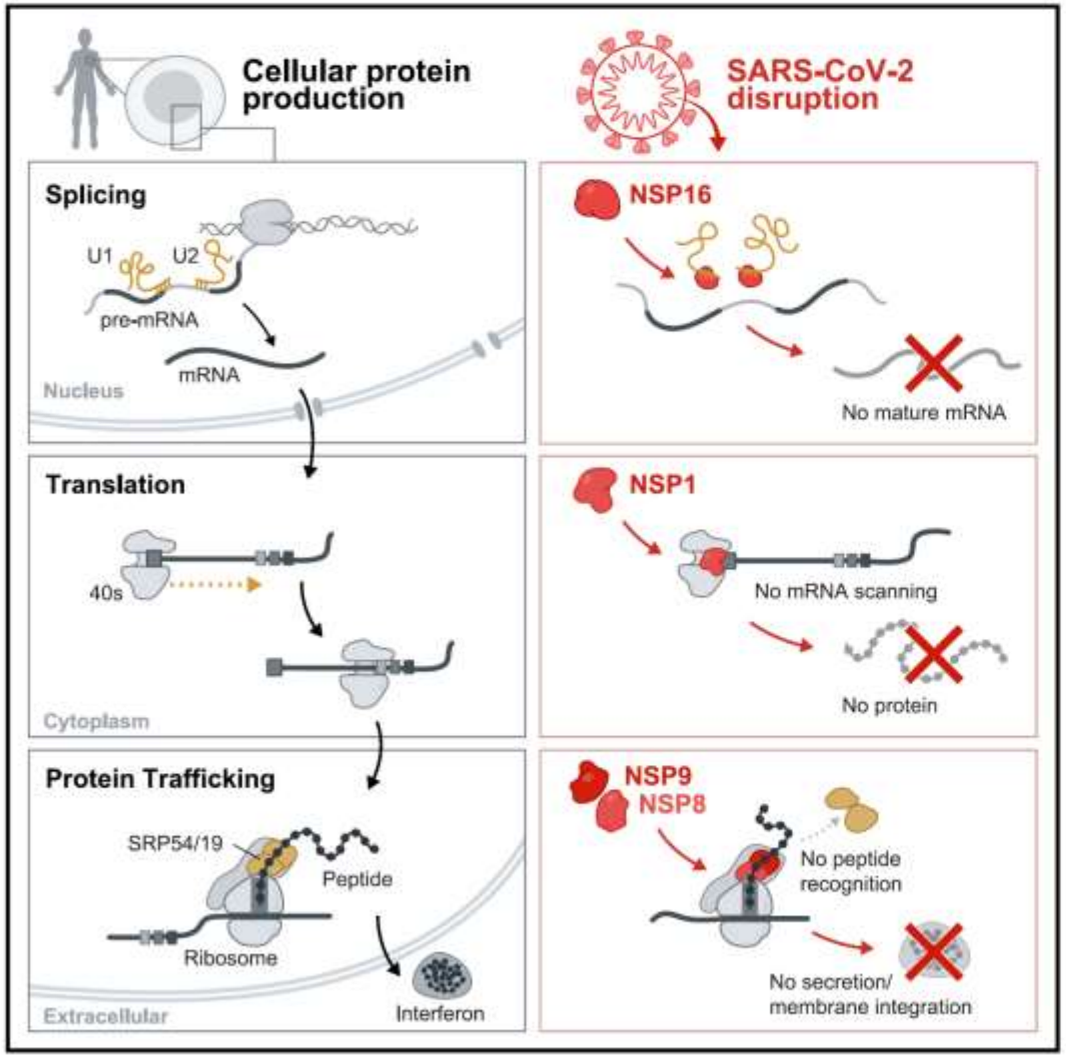
Model of a Bipartite Mechanism for Nsp1-Mediated Translation Inhibition and Evasion by SARS-CoV-2 5’ UTR



bioRxiv preprint doi:
https://doi.org/10.1101/2020.09.18.302901

SARS-CoV-2 Disrupts Splicing, Translation, and Protein Trafficking to Suppress Host Defenses

Graphical Abstract



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In Brief

SARS-CoV-2 proteins directly engage host RNAs to dysregulate essential steps of protein production and suppress the interferon response.

Banerjee et al., 2020, Cell 183, 1–15
November 25, 2020 ª 2020 Published by Elsevier Inc.
https://doi.org/10.1016/j.cell.2020.10.004

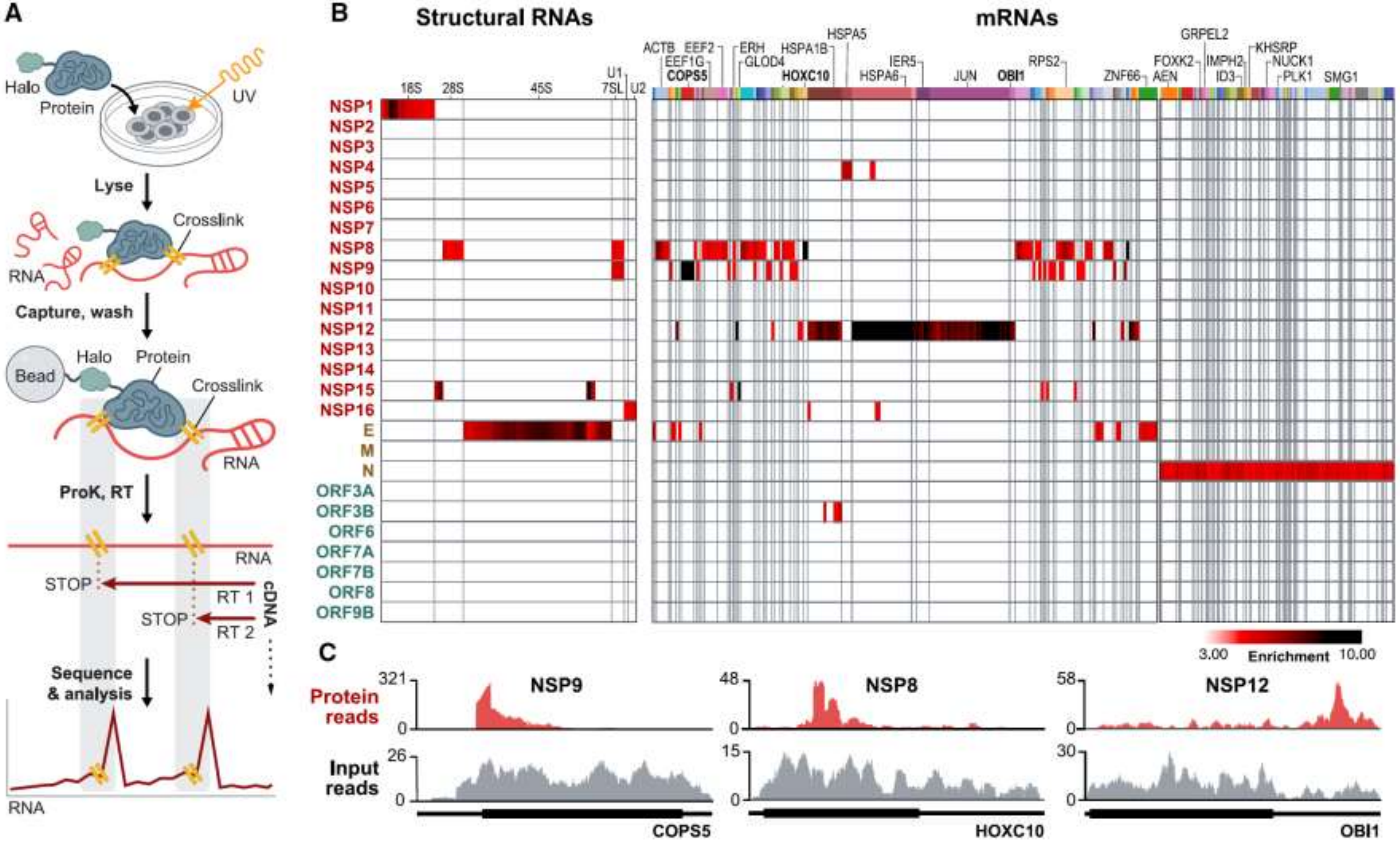


Figure 1. Global RNA Binding Maps of SARS-CoV-2 Proteins

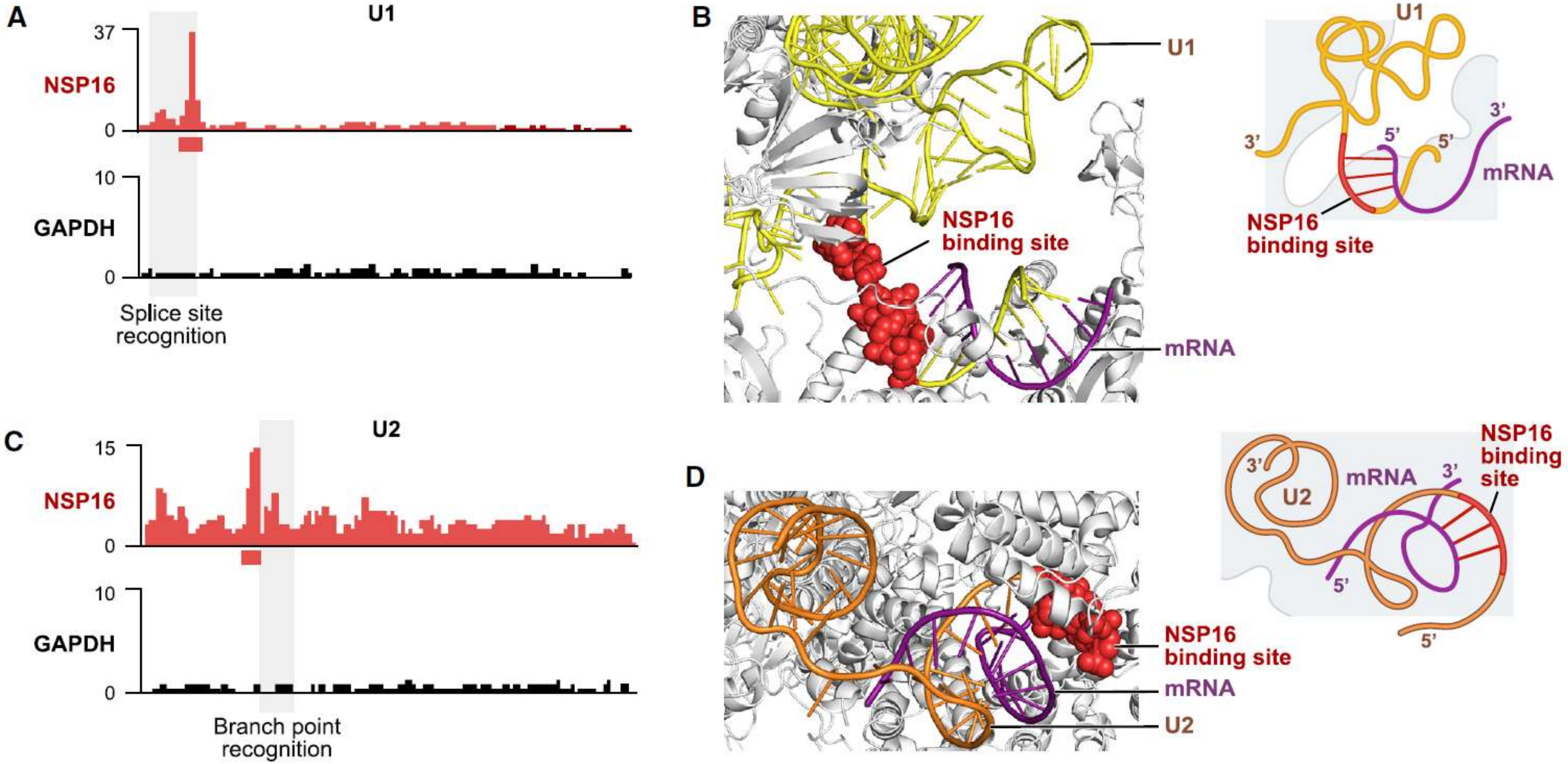
(A) Schematic of our approach.

(B) Enrichment heatmap of each SARS-CoV-2 protein (rows) by significantly enriched 100-nt RNA bins (columns; $p < 0.001$ and enrichment > 3-fold; STAR Methods). Shared colored bars indicate multiple bins within the same mRNA. For spacing reasons, the 82 mRNAs bound by N protein are displayed separately.

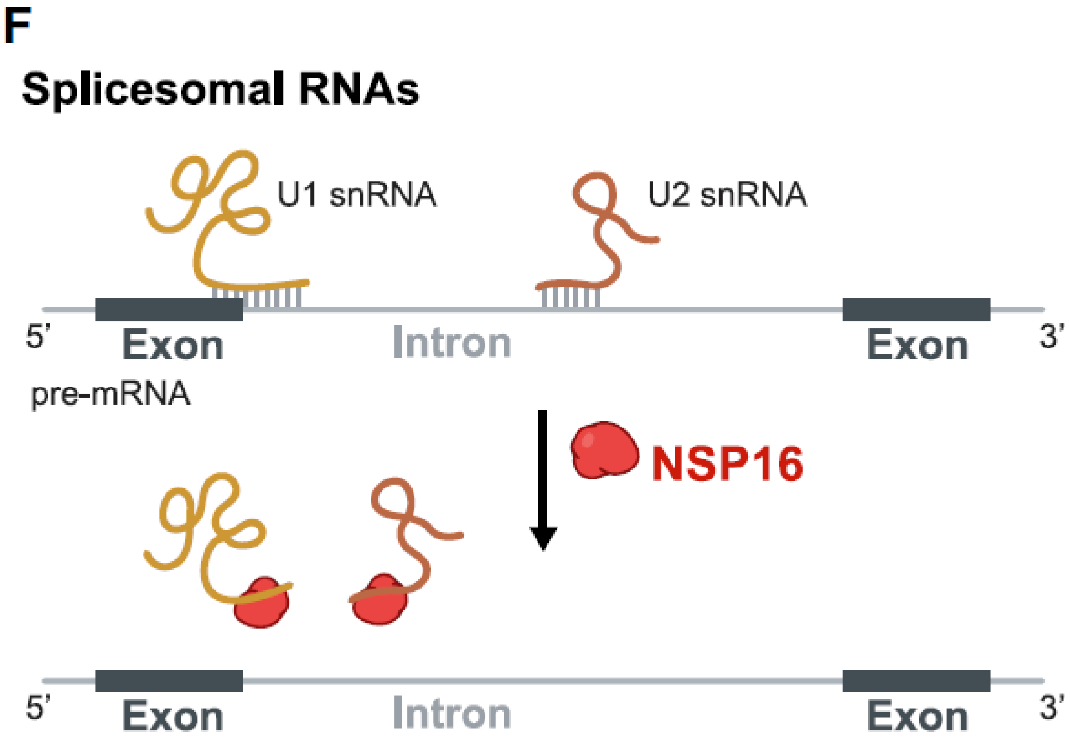
(C) Examples of sequencing reads over specific mRNAs for viral proteins (red) relative to input RNA coverage (gray) are shown. Coding regions (thick lines) and untranslated regions (thin lines) are shown for each mRNA.

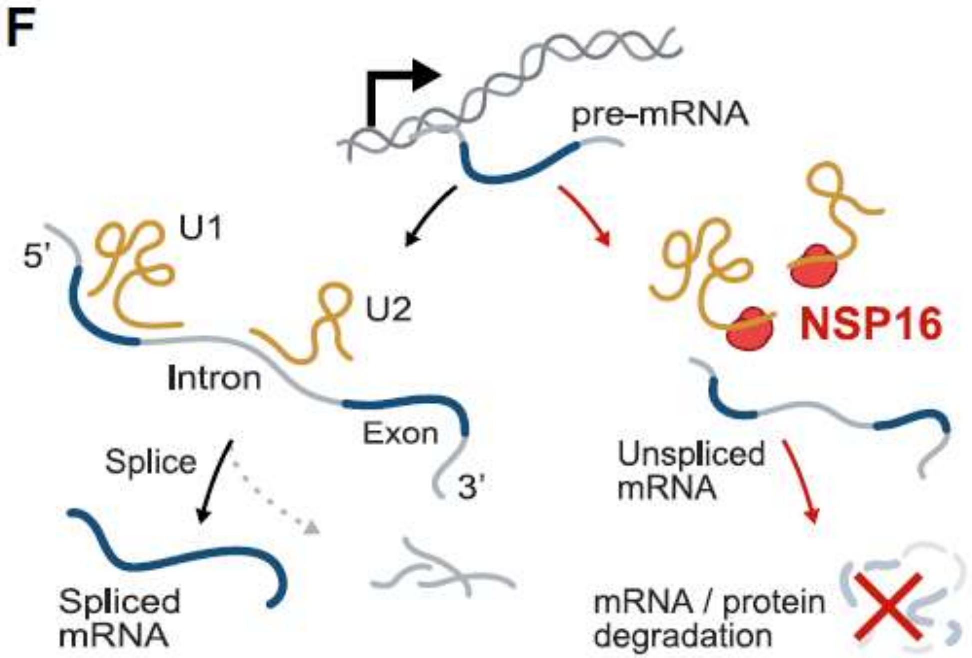
See also Table S1.

NSP 16 binds U1 and U2 snRNA at their pre-mRNA recognition sites



NSP 16 binds U1 and U2 snRNA at their pre-mRNA recognition sites





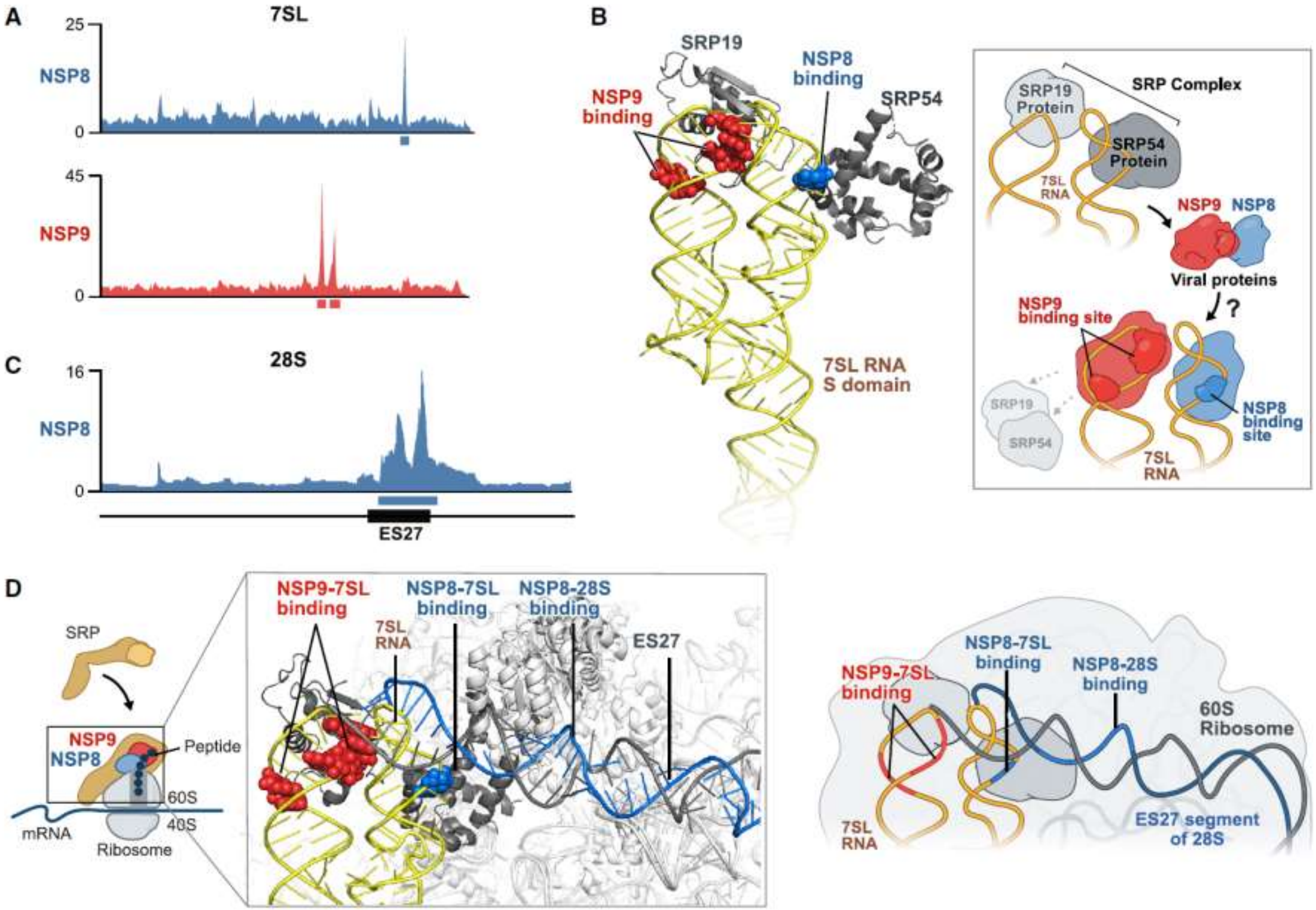
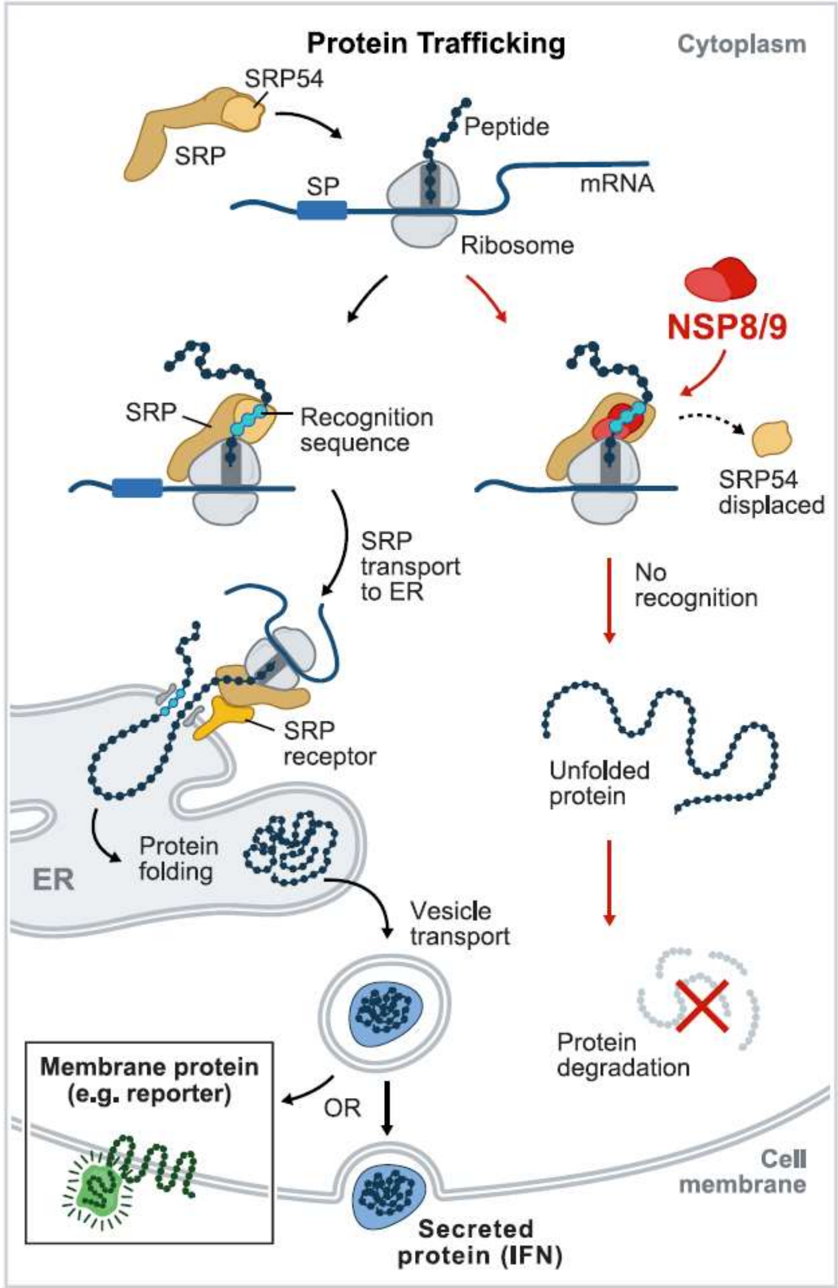
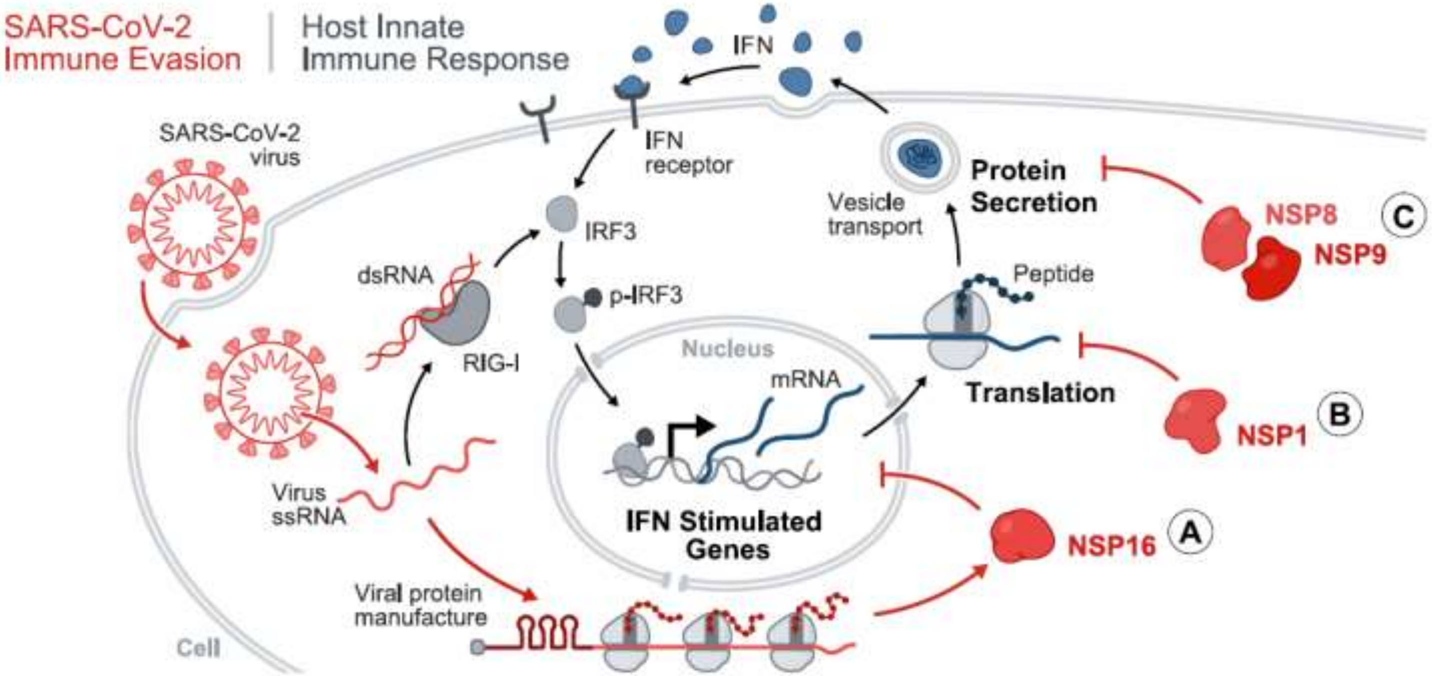


Figure 6. NSP8 and NSP9 Bind to 7SL RNA of the SRP


Protein Trafficking
Cytoplasm
SRP54
SRP
Peptide
SP
mRNA
Ribosome
NSP8/9
SRP
Recognition sequence
SRP54 displaced
SRP transport to ER
No recognition
SRP receptor
Unfolded protein
ER
Protein folding
Vesicle transport
Protein degradation
Membrane protein (e.g. reporter)
OR
Cell membrane
Secreted protein (IFN)


SARS-CoV-2 Immune Evasion
Host Innate Immune Response
IFN
IFN receptor
SARS-CoV-2 virus
IRF3
p-IRF3
dsRNA
RIG-I
Vesicle transport
Protein Secretion
NSP8
NSP9
C
Peptide
Nucleus
mRNA
Translation
NSP1
B
Virus ssRNA
IFN Stimulated Genes
NSP16
A
Viral protein manufacture
Cell