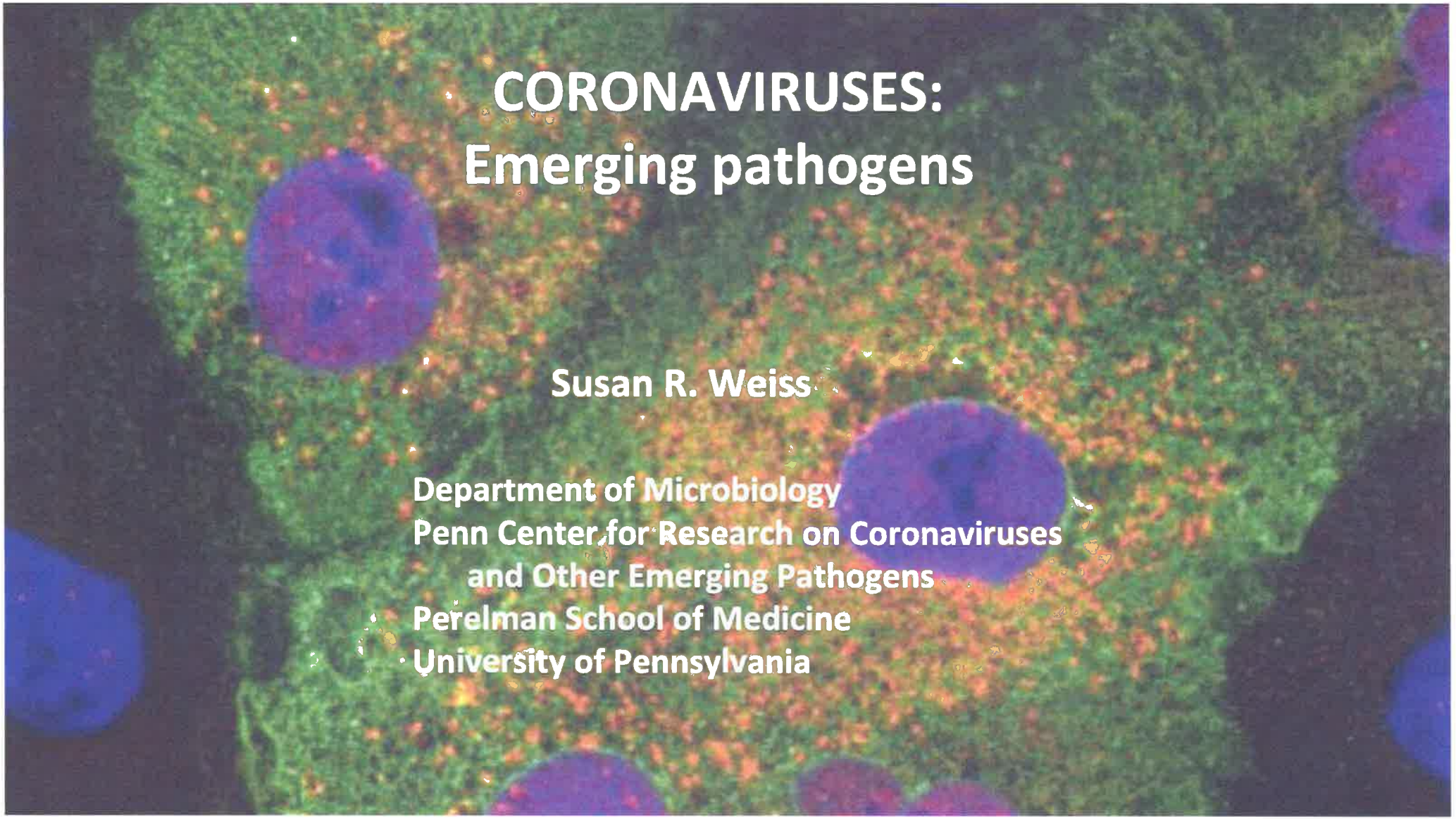
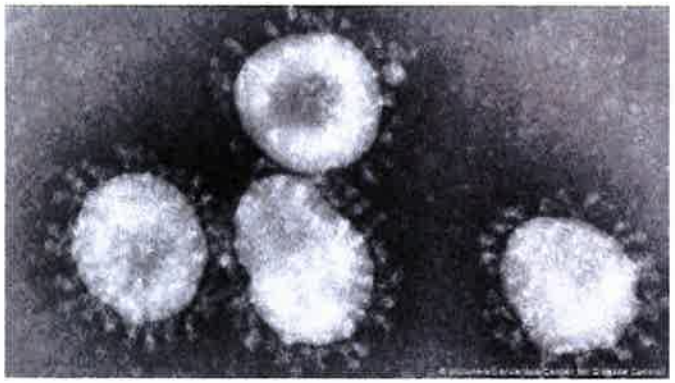


CORONAVIRUSES: Emerging pathogens

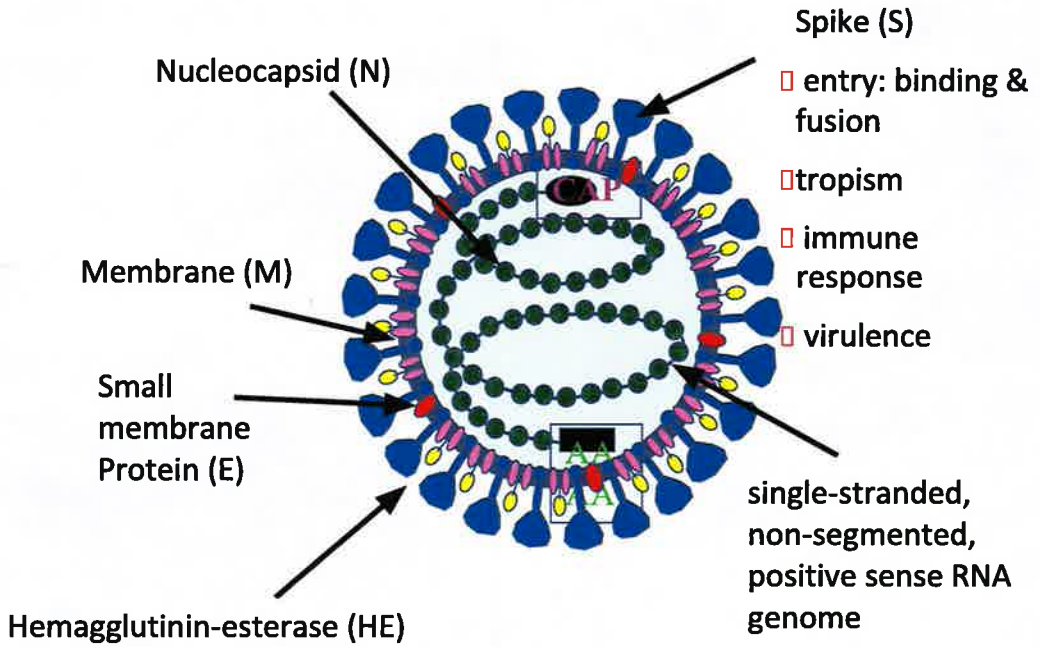
Susan R. Weiss

Department of Microbiology
Penn Center for Research on Coronaviruses
and Other Emerging Pathogens
Perelman School of Medicine
University of Pennsylvania

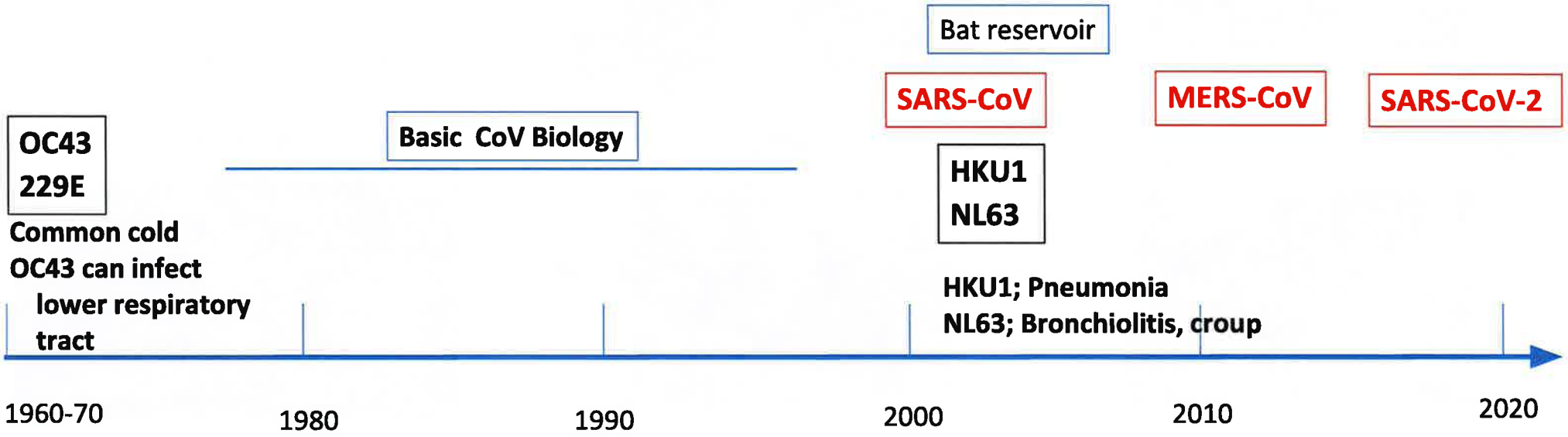
Coronavirus virion



Coronaviruses are a family within the Nidovirus order



Coronavirus Timeline



Severe acute respiratory disease

Coronavirus disease-2019 or COVID-19

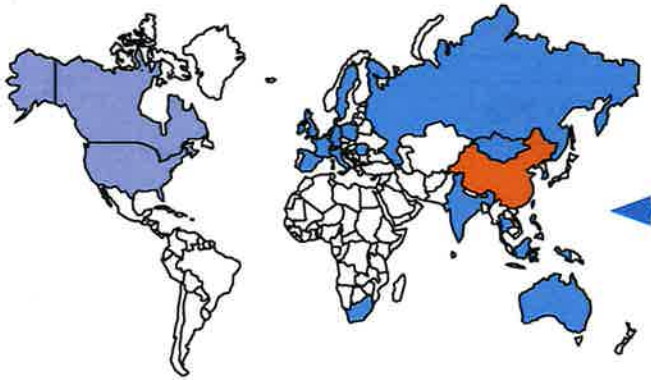
SARS-CoV interspecies transmission (2002)

Horseshoe bat

Civet

Human

Human to human close contact



How many times did this happen?

Over in eight months,
8098 infections, 9.6% mortality
87% in China and Hong Kong

Images from various internet sites

MERS-CoV interspecies transmission (2012)

Neoromicia capensis

Camel

Mostly in Arabian peninsula

Camels are a reservoir for MERS-CoV

Still new cases 2020

2562 cases, 35% mortality

Human

limited human to human spread

Korea

SARS-CoV-2 interspecies transmission (2019)

Bat

Intermediate species
Malayan pangolin

Human

Human to human spread

40.1 M infections

1,114,750 deaths

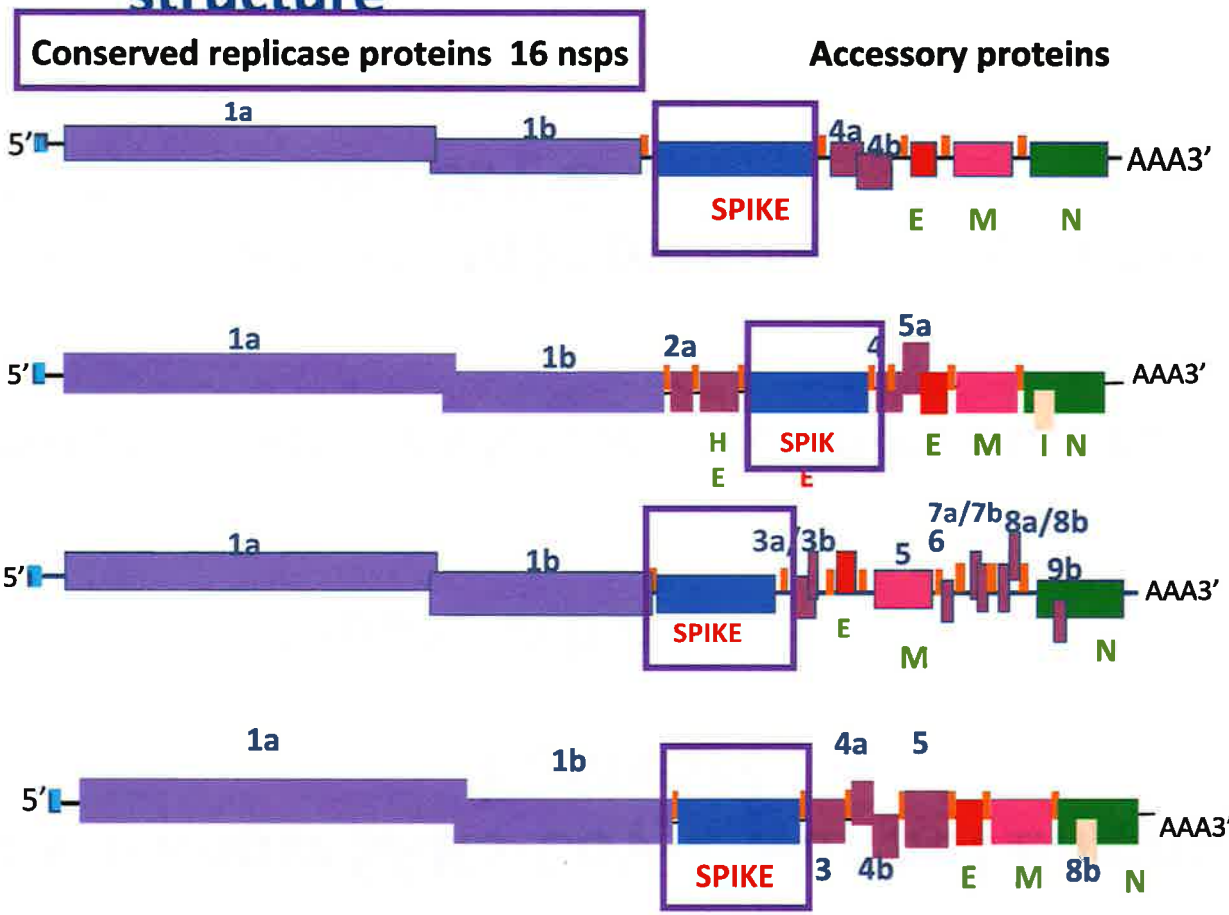
(10.19.20)

US
8.16 M infections
219,680 deaths

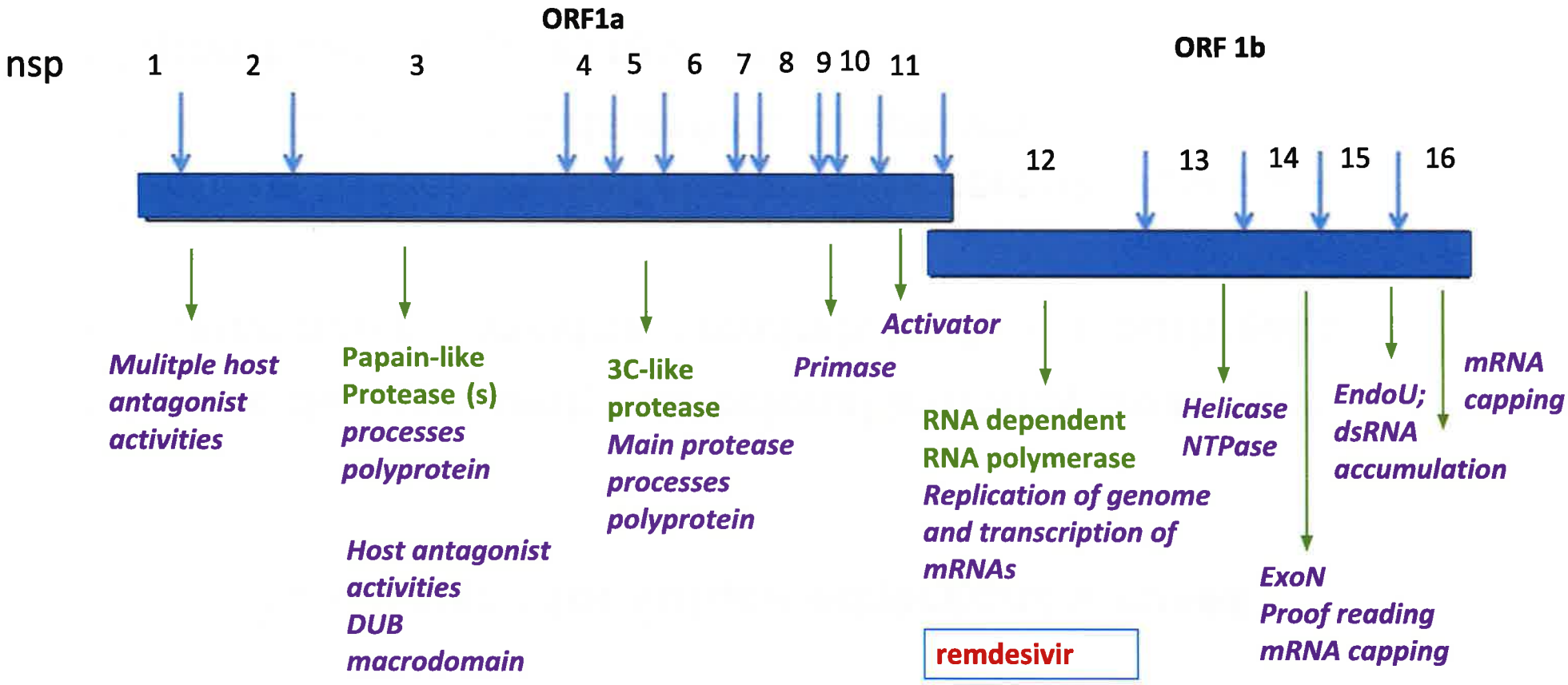
How do we know SARS-CoV-2 was not engineered by humans?

- Similar viruses are found in bats
- It does not resemble any known recombinant viruses
- Not possible for anyone to know how to design a virus with the properties of SARS-CoV-2

Coronavirus genome structure



Coronavirus conserved replicase proteins



To prepare for future emergent viruses

- Vaccine development; monoclonal antibody treatment
- Develop pan coronavirus antivirals for future outbreaks

- Continue to identify and characterize coronaviruses and other viruses from bats and other species
- Support basic virology research

ACKNOWLEDGEMENTS

Courtney Comar
Alejandra Fausto
Yize (Henry) Li
Erick Perez Jimenez
Rebecca Nusbaum
Nicholas Parenti
David Renner
Hanako Reyes
Nikki Tanneti
Jill Whelan
Iris Zhang

Funding NIH
NIAID/NINDS

PENN Center for Research on Coronavirus
and Other Emerging Pathogens

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: : Weiss, Susan R.

eRA COMMONS USER NAME (credential, e.g., agency login): SRWEISS

POSITION TITLE: Professor of Microbiology, Vice Chair, Department of Microbiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Brandeis University, Waltham, MA	BA	1971	Biology
Harvard University, Cambridge, MA	PhD	1975	Microbiology and Molecular Genetics
University of California, San Francisco, CA	Post doc	1976-1980	Molecular Virology; Retroviruses

A. Personal Statement. The overall goal of my lab over the last 40 years has been to understand the viral and host determinants of coronavirus tropism and virulence. Much of our work during the last approximately ten years has been on understanding the interactions of coronaviruses with the innate immune responses, primarily dsRNA induced anti-viral pathways. These include the canonical MAVS-dependent interferon synthesis and signaling system, the oligoadenylate synthetase-ribonuclease L (OAS-RNase L) pathway leading to limitation of virus replication and spread and the PKR pathway that leads to limitation of initiation of protein synthesis. We have extensively investigated activation the OAS-RNase L pathway and the antagonism of this pathway by coronavirus encoded phosphodiesterases. We worked with the human coronavirus severe acute syndrome coronavirus (SARS-CoV) in the past and have ongoing studies on the pathogenesis of the Middle East respiratory syndrome coronavirus (MERS-CoV). We have recently initiated investigation of the newly emerged severe acute respiratory coronavirus 2 (SARS-CoV-2) the agent of COVID-19. We need the equipment requested in this supplement application for BSL3 studies of SARS-CoV-2

1. Adedeji, A., Singh, K., Kassim, A., Coleman, C.M., Elliott, R., Weiss, S.R., Frieman, M., Sarafianos, S. 2014. SSYA10-001 Inhibits Replication of SARS, MHV and MERS Coronaviruses. Antimicrob Agents Chemother, 58:4894-8. PMCID:PMC4136041.
2. Thornbrough, J.M., Jha, B.K., Yount, B., Elliott, R., Li, Y., Goldstein, S.A., Sims, A.C., Baric, R.S., Silverman, R.H., Weiss, S.R. 2016. Middle East respiratory syndrome coronavirus NS4b protein inhibits host RNase L activation. MBio.7(2). pii: e00258-16. doi: 10.1128/mBio.00258-16. PMCID:PMC4817253
3. Comar, CE, Goldstein, SA, Li, Y, Yount, B, Baric, RS, Weiss, SR. 2019. Antagonism of dsRNA-induced innate immune pathways by NS4a and NS4b accessory proteins during MERS coronavirus infection. mBio10(2). pii: e00319-19. PMCID: PMC6437052.
4. Li, Y, Comar, CE, Renner, DM, Whelan, JN, Reyes, HM, Cardenas-Diaz, FL, Truitt, R, Tan, HL, Dong, B, Alysandratos, K, Huang, J, Kotton, DN, Silverman, RH, Yang,W, Morrissey, E, Cohen, N, Weiss, SR. SARS-CoV-2 induces double-stranded RNA-mediated innate immune responses in respiratory epithelial derived cells and cardiomyocytes, BioRxiv/2020/312553. PMCID: PMC7523129.

B. Positions and Honors

Professional Experience:

1971-1975 Graduate School. Laboratory of Dr. Michael Bratt, Department of Microbiology and Molecular Genetics, Harvard Medical School and Department of Microbiology, University of Massachusetts Medical School. Ph.D. thesis work: Studies on the messenger RNA and poly(A) of Newcastle

disease virus.

1976-1980 Postdoctoral training in the laboratory of Dr. J. Michael Bishop, Department of Microbiology and Immunology, University of California, San Francisco. Purification, characterization and cell-free translation of the messenger RNAs of avian sarcoma-leukosis viruses.

1980-present Assistant Professor, Associate Professor (1986), Professor (1992), Vice Chair (2018), Department of Microbiology, Perelman School of Medicine, University of Pennsylvania. Molecular Biology of coronaviruses, Pathogenesis of coronavirus CNS disease and hepatitis, MERS-CoV.

1994-1995 Sabbatical in the Department of Biochemistry, University of California, San Francisco with Dr. Robert Fletterick. Expression of the murine coronavirus papain like protease

2010-2019 Associate Dean for Postdoctoral Research Training and Director of Biomedical Postdoctoral Programs, School of Medicine, University of Pennsylvania.

2018-present Vice Chair, Department of Microbiology, Perelman School of Medicine, University of Pennsylvania

2020-present Co-Director of the Penn Center for Research on Coronaviruses and Other Emerging Pathogens

Honors

1971 Phi Beta Kappa

Professional societies

1975-present	American Society for Microbiology
1982-present	American Society for Virology
1994-present	Fellow of the American Academy of Microbiology
2019-present	Governor, American Academy of Microbiology
2008-present	Fellow of the American Association for the Advancement of Science

Grant reviews committees

1990-1994, 2001-2005	Virology Study Section
1995-1998	NIH Reviewers Reserve
1995-1999	National Multiple Sclerosis Society Study Section
1997, 1998	ASM/CDC Postdoctoral Fellowship review
1985-	Ad hoc NIH reviews- CSR, NINDS, NIAID
2012-2106	Ad hoc reviewer, CNBT study section, CSR
7/2016-present	Permanent member, CNBT study section, CSR
6/2018	Ad hoc external reviewer, NIAID RML

C. Contributions to Science

1. Establishment of murine coronavirus (MHV) animal model of acute encephalitis and chronic demyelinating disease. We established a mouse model of encephalitis, hepatitis and immune-mediated chronic demyelination, which we have used extensively for the mapping of viral determinants of virulence and for the study of coronavirus-host interactions. Using highly neurovirulent MHV-JHM.SD and weakly neurovirulent/hepatovirulent MHV-A59, this model formed the basis for numerous of our early studies and findings as detailed below and allowed we and others to compare infection of the CNS and the peripheral organ, the liver and to identify CNS specific aspects of virus-host interactions. We have used the A59 model, one of the few accepted animal models for Multiple Sclerosis, for studies of chronic demyelinating disease and viral persistence. We continue to use this animal model to investigate the CNS specific aspects of the host virus interactions most recently type I interferon responses as described below. We have recently used the demyelination model along with high throughput RNA sequencing to identify the host genes regulated in mice with MHV-induced demyelination.

a. Lavi, E., Gilden, D., Wroblewska, Z., Rorke, L. and Weiss, S.R. 1984. Experimental demyelination produced by the A59 strain of mouse hepatitis virus. Neurology 34:597-603.
b. Lavi, E., Gilden, D.H., Highkin, M.K. and Weiss, S.R. 1984. Persistence of MHV-A59 RNA in a slow virus demyelinating infection in mice as detected by *in situ* hybridization. J. Virol. 51:563-566.
c. Fishman, P.S., Gass, J.S., Swoveland, P.T., Lavi, E., Highkin, M.K. and Weiss, S.R. 1985. Infection of the basal ganglia by a murine coronavirus. Science 229:877-879.
d. Elliott R., Li, F., Dragomir, I., Chua M.W., Gregory, B.D., Weiss S.R. 2013. Analysis of the host transcriptome from demyelinating spinal cord of murine coronavirus-infected mice. PLoS One 8:| e75346. PMCID: PMC3776850.

2. The type I interferon response is both cell type and organ specific and less robust in the CNS than in the periphery. We found that, in the absence of type I interferon (IFN) signaling, MHV replicates to an extremely high titer and spreads to organs not usually infected in immunocompetent mice and is uniformly fatal even at low

dose. However, MHV does not induce type I IFN nor respond to IFN signaling in transformed cell lines nor in primary cultures of CNS parenchyma cell types including neurons, astrocytes or oligodendrocytes or hepatocytes. In contrast, MHV does induce IFN in myeloid cells, including microglia (brain) and Kupffer cells (liver), and this is dependent on MDA5 signaling. We also found that IFN signaling, both basal levels of IFN and basal levels of interferon stimulated genes (ISGs) including transcription factors, RNA sensors and antiviral genes, are much lower in the brain than in the liver, contributing to the weak IFN response in the brain as compared to the periphery. We have more recently found that MDA5 signaling is required for the survival in the mouse in vivo and for maintaining tropism barriers. We identified two IFN antagonists expressed by MHV, nsp1, antagonizes the induction of IFN and NS2 antagonizes activation of RNase L as described below. We have promoted the notion that host IFN signaling responses are less robust in the brain than the liver and that this is at least in part due to differences in basal ISG expression.

a. Roth-Cross, J.K., Roth-Cross, J.K., Bender, S.J., **Weiss, S.R.** 2008. Murine coronavirus mouse hepatitis virus (MHV) is recognized by MDA-5 and induces type I IFN in brain macrophages/microglia. J Virol 82:9829-9838. PMCID: PMC2566260.
b. Rose, K.M., Elliott, R., Martínez-Sobrido, L., García-Sastre, A., **Weiss, S.R**. 2010. Murine coronavirus delays expression of a subset of interferon-stimulated genes. J Virol 84:5656-69. Chosen as "spotlight" article. PMCID: PMC2876584.
c. Zhao, L., Rose, K.M., Elliott R., Van Rooijen, N., **Weiss, S. R.** 2011. Cell type-specific type I interferon. antagonism influences organ tropism of murine coronavirus. J Virol 85: 10058-10068. PMCID: PMC3196400.
d. Zalinger, Z.B., Elliott, R., Rose, K.M., **Weiss, S.R.** 2015. MDA5 is critical to host defense during infection with murine coronavirus. J Virol 89:12330 –12340. PMCID: PMC4665247.

3. Virus encoded phosphodiesterases (PDEs) as well as host AKAP7 antagonize the oligoadenylate synthetase-ribonuclease L (OAS-RNase L) pathway by a novel mechanism. We demonstrated, along with our collaborator Dr. Robert Silverman, that MHV accessory protein, NS2, is an RNase L antagonist with 2',5'-PDE activity that acts by cleaving 2',5'-oligoadenylates (2-5A), the inducer or RNase L. This has a profound effect on liver pathogenesis in the MHV model but little effect on CNS pathogenesis. This demonstrates that innate immune responses are much less robust in the brain than the liver, consistent with the notion of "immune privilege" of the CNS. In addition, we found that homologs of NS2 with PDE activity are encoded by other lineage A Betacoronaviruses including human coronaviruses OC43. Interestingly, group A rotaviruses, unrelated to coronaviruses, also encode homologous PDEs. Finally, the central domain of host AKAP7 also contains an homologous and active PDE domain. Importantly, these PDEs provide potential targets of antiviral therapies. We more recently found that MERS NS4b and related lineage C bat Betacoronavirus encoded homologs also encode PDE RNase L antagonists that differ from the other viral PDEs by having a nuclear localization signal and are localized primarily in the nucleus. Investigation of NS4b is ongoing.

a. Zhao, L., Jha, B., Wu, A., Elliott, R., Ziebuhr, J., Gorbalenya, A.E., Silverman, R.H., **Weiss, S.R.** 2012. Antagonism of the interferon-induced OAS-RNase L pathway by murine coronavirus NS2 protein is required for virus replication and liver pathology. Cell Host & Microbe 11: 607 - 616. PMCID: PMC3377938.
b. Zhang, R., Jha, B.K., Ogden, K.M., Dong, B., Zhao, Elliott, R., Patton, J.T., Silverman, R.H., **Weiss, S.R.** 2013. Homologous 2',5'-phosphodiesterases from disparate RNA viruses antagonize antiviral innate immunity. Proc Natl Acad Sci U S A 110(32):13114-9. PMCID: PMC3740845.
c. Gusho, E., Zhang,R., Jha B.K., Thornbrough, J.M., Dong, B., Gaughan , C., Elliott, R., **Weiss, S.R.,** Silverman, R.H. 2014. Murine AKAP7 has a 2',5'-phosphodiesterase activity that can restore the growth and virulence of an NS2 mutant murine coronavirus. mBio, Volume 5 Issue 4 e01312-14. PMCID: PMC4161237.
d. Thornbrough, J.M., Jha, B.K., Yount, B., Elliott, R., Li, Y., Goldstein, S.A., Sims, A.C., Baric, R.S., Silverman, R.H., **Weiss, S.R.** 2016. Middle East respiratory syndrome coronavirus NS4b protein inhibits host RNase L activation. mBio, vol 7(2). pii: e00258-16. PMCID: PMC4817253.

4. Activation of the OAS-RNase L pathway and its impact on cell death. We found that in the murine system, activation of RNase L depends on relatively high basal levels of OAS gene expression. Our data suggest that cells such as murine myeloid and endothelial cells, with high basal OAS gene expression, serve as sentinels to detect virus infection. Other parenchymal cells such as hepatocytes and neurons do not activate RNase L and are thus protected from the potentially damaging effects of RNase L, which include apoptosis and inflammation. We found that human cell lines, however, express high basal levels of OAS genes and activate RNase L following infection with several viruses in the absence of virus induced IFN. Interestingly, we found that activation of RNase L during infection with diverse viruses is dependent on OAS3 only and not OAS1 or OAS2. We recently found that Zika virus (ZIKV) activates RNase L in an OAS dependent fashion but avoids its antiviral activities. Moreover,

ZIKV repurposes RNase L to establish replication factories and promote virus production. Finally, we found that RNase L activity induced by endogenous dsRNA as well as viral RNA promotes apoptosis. Thus, activation of RNase L protects the host from viral infection both by direct antiviral activity and by promoting apoptosis of infected cells to effect complete viral clearance.

a. Birdwell L.D., Zalinger, Z.B., Wright, P.W., Elliott, R., Rose, K.M, Silverman, R.H., **Weiss, S.R.** 2016. Activation of RNase L by murine coronavirus in myeloid cells is dependent on basal OAS gene expression and independent of virus-induced interferon. J Virol 90:3160–3172. PMCID: PMC3719824.
b. Li, H., Banerjee, S., Dong, B., Goldstein, S.A., Silverman, R.H., **Weiss, S.R.** 2016. Activation of RNase L is dependent on OAS3 expression during infection with diverse viruses. Proc Nat Acad Sci 113 (8): 2241-2246. PMCID: PMC4776461.
c. Li, Y., Banerjee, S., Goldstein, S.A., Rath, S., Donovan, J., Korennykh A., Silverman, R.H., **Weiss, S.R**. 2017. RNase L mediates the cell-lethal phenotype of adenosine deaminase ADAR1 deficiency. eLife;10.7554/eLife.25687. PMCID: PMC5404912.
d. Whelan, J.N., Li, Y., Silverman, R.H., **Weiss, S.R**. 2019. Zika virus production is resistant to RNase L antiviral activity. J.Virol., pii: JVI.00313-19. PMCID:PCM6675901.

5. **Human coronavirus-host interactions**. We worked on several SARS-CoV (2002) projects involving antivirals and accessory proteins but stopped working on this virus when it became a select agent. We have been working with MERS-CoV and found that this virus encodes two host antagonists in its accessory genes and shuts down dsRNA induced host antiviral pathways including interferon signaling, OAS-RNase and PKR pathways. We have more recently expanded our studies to include newly emerged SARS-CoV-2 as well as human coronaviruses that cause the cold or croup. Interestingly we found that SARS-CoV-2 is less effective at shutting down host innate immune pathways than MERS-CoV and activates RNase L and PKR, unlike either MERS-CoV or MHV. The work proposed by Tanneti represent our new studies of SARS-CoV-2 infection of the nervous system, and a return to research on neuropathogenic MHV.

a. Adedeji, A., Singh, K., Kassim, A., Coleman, C.M., Elliott, R., Weiss, S.R., Frieman, M., Sarafianos, S. 2014. SSYA10-001 Inhibits Replication of SARS, MHV and MERS Coronaviruses. Antimicrob Agents Chemother, 58:4894-8. PMCID:PMC4136041.
b. Thornbrough, J.M., Jha, B.K., Yount, B., Elliott, R., Li, Y., Goldstein, S.A., Sims, A.C., Baric, R.S., Silverman, R.H., Weiss, S.R. 2016. Middle East respiratory syndrome coronavirus NS4b protein inhibits host RNase L activation. MBio.7(2). pii: e00258-16. doi: 10.1128/mBio.00258-16. PMCID:PMC4817253
c. Comar, CE, Goldstein, SA, Li, Y, Yount, B, Baric, RS, Weiss, SR. 2019. Antagonism of dsRNA-induced innate immune pathways by NS4a and NS4b accessory proteins during MERS coronavirus infection. mBio10(2). pii: e00319-19. PMCID: PMC6437052.
d. Li, Y, Comar, CE, Renner, DM, Whelan, JN, Reyes, HM, Cardenas-Diaz, FL, Truitt, R, Tan, HL, Dong, B, Alysandratos, K, Huang, J, Kotton, DN, Silverman, RH, Yang, W, Morrissey, E, Cohen, N, Weiss, SR. SARS-CoV-2 induces double-stranded RNA-mediated innate immune responses in respiratory epithelial derived cells and cardiomyocytes. bioRxiv 2020.09.24.312553. PMCID: PMC7523129.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/susan.weiss.1/bibliography/40385908/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing research projects

Endogenous double-stranded RNA induced CNS damage in the absence of ADAR1 activity.
Principal Investigators: Susan R. Weiss and Yize Li (MPI)
Agency: National Institute for Allergy and Infectious Diseases
5R21AI138564-02 (MPI: Weiss, Li) 2/22/2018 – 1/31/2021 (no cost extension)
The goals are to use a mouse model to investigate the effects of ADAR1 knockout on IFN induction, interferon stimulated gene expression and RNase L activation, through experiments in primary CNS cell types and *in vivo* in mice. Effects 0f ADAR1 KO on the pathology in the CNS will also be investigated.

Control of viral pathogenesis by regulation of 2-5A levels
Principal Investigator: Susan R. Weiss and Robert Silverman, multi-PI
Agency: National Institute for Allergy and Infectious Diseases
R01 AI104887-06 1/1/2013 – 12/31/2023
The goals are to investigate: how ADAR1 and host PDEs regulate levels of 2-5A and determine which OAS

isoforms are involved; how the antiviral, apoptotic and inflammatory roles of RNase L cooperate to effect viral clearance in an MHV mouse model; and 3) how the OAS-RNase L pathway is expressed and activated in bats, and the mechanism(s) underlying antagonism of OAS-RNase L activation by filovirus VP35.

Antiviral mechanisms of 2-5A-dependent RNASE L
Principal Investigator: Robert Silverman, Susan Weiss Co-Investigator
Agency: National Institute for Allergy and Infectious Diseases
9 R01 AI135922-33 9/25/2017 – 8/31/2022
The goals are to investigate: 1) the impact of the RNase L protein-kinase like domain on cells and viruses; 2) how the ATP-binding cassette member, ABCE1 (RLI), limits RNase L activity and; 3) the mechanism of NLRP3 inhibitor drugs on viral mediated inflammation in a mouse model.

MERS coronavirus: antagonism of double-stranded RNA induced host response by accessory proteins
Principal Investigator: Susan R. Weiss
Agency: National Institute for Allergy and Infectious Diseases
1R01AI140442-02 5/24/2018 – 4/30/2023
Supplement for SARS-CoV-2: 5/1/2020-4/30/2022
These studies will elucidate the likely multiple functions of the MERS NS4a and NS4b accessory proteins and in the long-term lead to identification of candidate therapeutic targets.

Double-stranded RNA during DNA virus infection
Principal Investigator: Matthew Weitzman, Susan Weiss Co-Investigator
Agency: National Institute for Allergy and Infectious Diseases
1R01AI145266-01 (PI: Weitzman) 3/1/2019-2/28/2024
This proposal is built upon our unexpected discovery of nuclear dsRNA during Adenovirus infection. These studies will provide unique knowledge into how compact DNA viral genomes prevent the deleterious effects resulting from accumulation of dsRNA.

Completed research projects during the last three years

Role of type I interferon signaling in Zika virus infection of the brain
Principal Investigator: Susan R. Weiss
Agency: National Institute for Neurological Diseases and Stroke
1R21NS100182-02 9/30/2016 – 8/31/2020
These studies will contribute to the understanding of the type I interferon response to ZIKV virus during infection of primary murine CNS cells and in the embryonic mouse brain in vivo.

Murine coronavirus neurovirulence: role of type Interferon response

Principal Investigator: Susan R. Weiss
Agency: National Institute for Neurological Diseases and Stroke
R01NS081008-05 9/01/2012-5/31/2019
The aims were to define the central nervous system (CNS) cell types that are responsible for the type I interferon (IFN) response to murine coronavirus infection, elucidate the activity and effectiveness of the antiviral OAS-RNase L pathway in individual CNS cell types and map the determinants of high neurovirulence..

Susan Weiss

My mini bio

SUSAN WEISS obtained her PhD in Microbiology from Harvard University working on paramyxoviruses and did postdoctoral training in retroviruses at University of California, San Francisco. She is currently Professor and Vice Chair, Department of Microbiology and Co-director of the Penn Center for Research on Coronaviruses and Other Emerging Pathogens at the Perelman School of Medicine at the University of Pennsylvania. She has worked on many aspects of coronavirus replication and pathogenesis over the last forty years, making contributions to understanding the basic biology as well as organ tropism and virulence. She has worked with murine coronavirus (MHV), MERS-CoV and most recently SARS-CoV-2. Her work for the last ten years has focused on coronavirus interaction with the host innate immune response and viral innate antagonists of double-stranded RNA induced antiviral pathways. Her other research interests include activation and antagonism of the antiviral oligoadenylate-ribonuclease L (OAS-RNase L) pathway, flavivirus- primarily Zika- virus-host interactions and pathogenic effects of host endogenous dsRNA.

History of human coronaviruses, including the three lethal human coronavirus epidemics and how this informs us to deal with future emerging coronaviruses

I will discuss the history of human coronaviruses including the common cold viruses that we have known about since the 1960s. I will then describe and compare the three epidemics caused by emergence of coronaviruses from bats into human population- lethal coronaviruses SARS-CoV, MERS-CoV and SARS-CoV-2. Finally, I will briefly discuss what we have learned from studying these viruses and how it helps us prepare for future coronavirus that may emerge.