Viral infections and Alzheimer's Disease: Implications for COVID-19 and AD patients

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"Alzheimer's disease from all angles"
32nd Annual Southern California AD Research Conference
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Experimental goals for lab

A prominent experimental goal for our lab is to determine if Coronavirus infection increases neurologic disease in 1) Alzheimer's disease (AD) mouse models and 2) COVID-19-infected AD patients

Talk outline

- Coronavirus background, COVID-19, and neurologic disease
- How does Coronavirus infection affect neurologic disease in mouse models of Alzheimer's disease?
- Does COVID-19 affect neuropathology in patients with dementia/Alzheimer's disease?

Coronavirus: A virus we've been living with for decades….

Neurotropic Animal Coronavirus

- Murine Coronavirus
- Feline Infectious Peritonitis Virus
- Porcine Hemagglutinating Encephalomyelitis virus

Four Human CoV usually associated with mild seasonal respiratory Illnesses

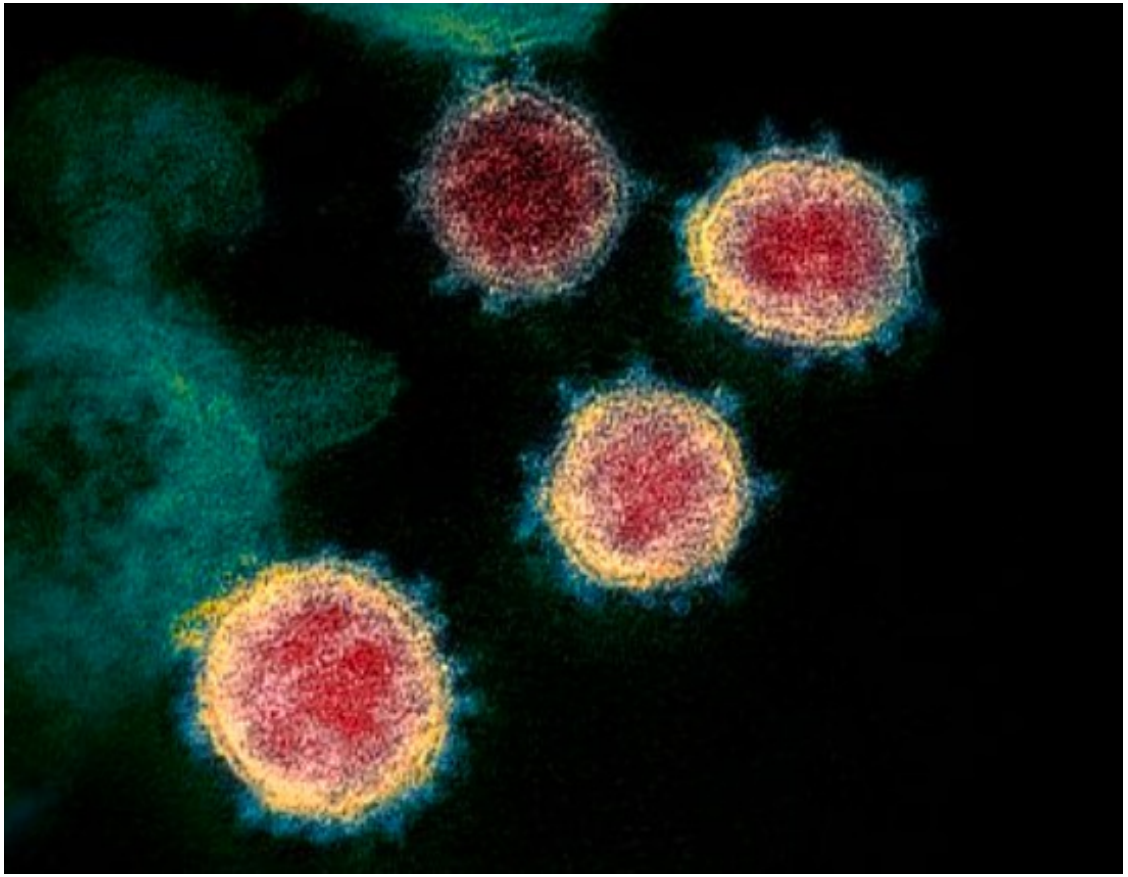
- 229E, OC43 -> 1960's
- HKU1, NL63 -> after SARS-CoV-1
- Referred to as Common Cold CoV's (CCC)

Another Decade, Another Coronavirus

Stanley Perlman, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

February, 2020



Source: NIH

Infection by SARS-CoV-2 causes the Coronavirus Disease 2019 (COVID-19)

COVID-19 – Unusual clinical manifestations

- Heart disease
- Kidney damage
- Inflammation of blood vessels
- Thrombosis (Stroke)
- Hyperinflammatory syndrome (children)
- Asymptomatic spreaders
- **Increased frequency of neurologic disease/ conditions**

COVID-19: Long Haulers

HEALTH

Long after the fire of a Covid-19 infection, mental and neurological effects can still smolder

STAT

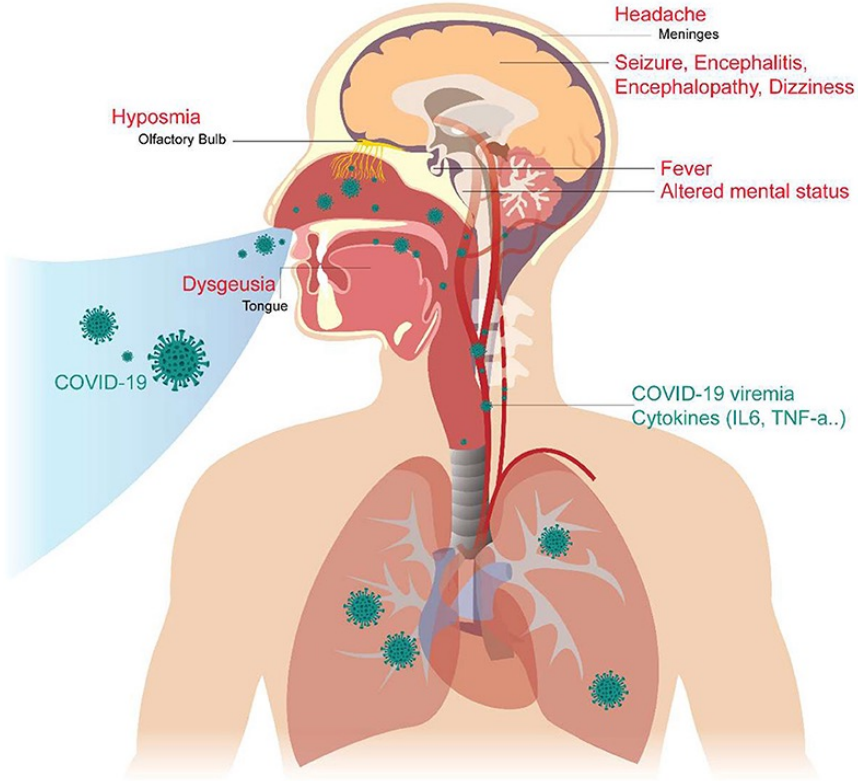
By ELIZABETH COONEY @cooney_liz / AUGUST 12, 2020

- Novel coronavirus symptoms can last weeks or months for some people.
- These individuals – referred to as **"long haulers"** have recovered from COVID-19 and test negative for virus.
- ~10-15% of COVID-19 patients become long haulers; can affect anyone *e.g.* young and old, healthy or with other co-morbidities.
- It has been detected in patients who were hospitalized or those with mild symptoms
- Neurological symptoms include **headaches**, **loss of taste/smell** (even if not previously had) and **"brain fog", memory loss,** and **difficulty concentrating.**
- A recent study indicated that within the brains of COVID-19 patients, there is altered expression of genes associated with i) **cognition**, ii) **schizophrenia**, and iii) **depression** (Yang *et al*., *Nature*, 2021)

COVID-19: Neuropathological Observations

Clinically:

- Headache/anosmia/dysgeusia commonly reported in non-hospitalized individuals (Meng, X. et al. Am. J. Otolaryngol. 2020)
  - Estimated 30% of symptomatic COVID19 patients
- Global incidence of neurological symptoms in ~80% of hospitalized patients (Chou, S. et al. JAMA Neurol. 2021) (Cohort: 3744 patients)
  - Correlated with increased risk of in-hospital death
- Non-hospitalized individuals with "brain fog" 6+weeks after infection perform worse in attention and working memory tasks (Graham, E., et al. *Ann. Clin. Trans. Neuro. 2021) (Cohort: 100 individuals)*
- Loss of gray matter post-infection in non-hospitalized individuals identified in large MRI study (Douaud, G. et al. MedRxiv 2021) (Cohort: 782 *individuals*)

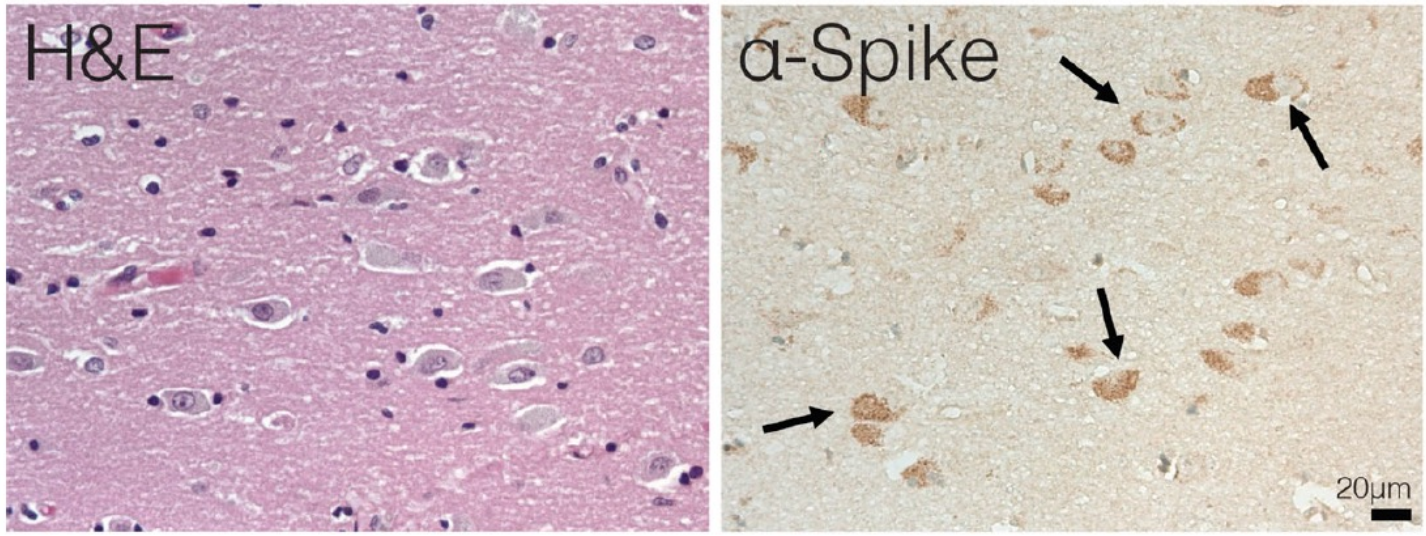


COVID19: Neurological Symptoms

Tsai, S. et al. Front. Neurol. 2020

Neuropathology of COVID-19

Viral presence by RT-PCR	**53.5% (54/101)**
Viral presence by IHC	**27.7% (23/83)**

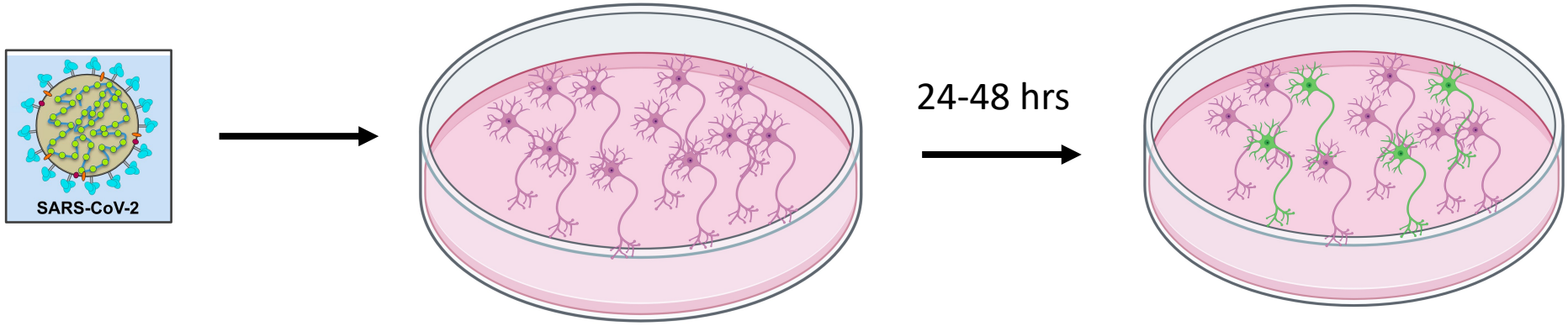


Prominent Neuropathological findings: Microglial activation/nodules, lymphocyte infiltration, acute hypoxic-ischemic changes, and astrogliosis

Song et al., 2020; Lou et al., 2021

Question 1

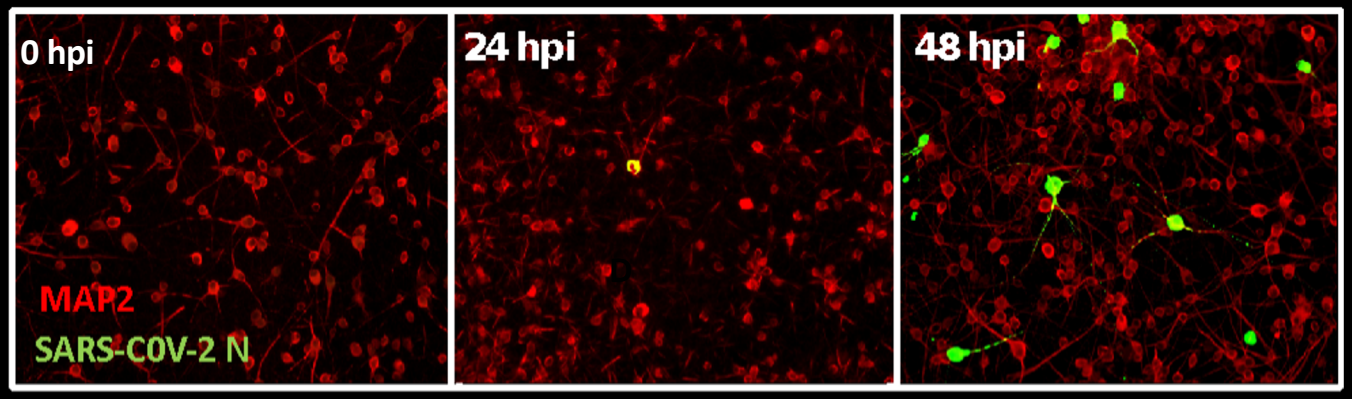
Is SARS-CoV-2 able to infect and replicate in human neurons?

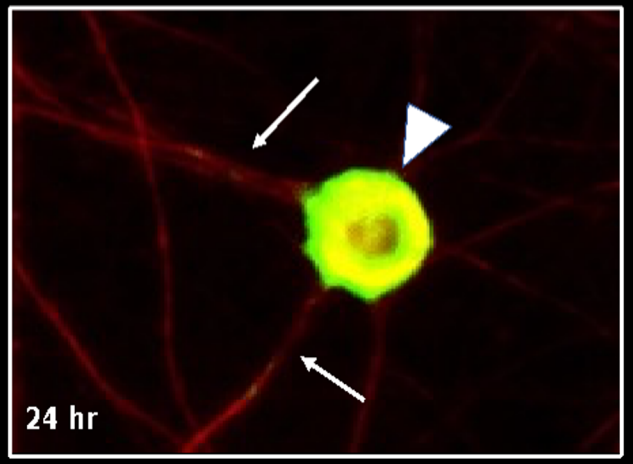


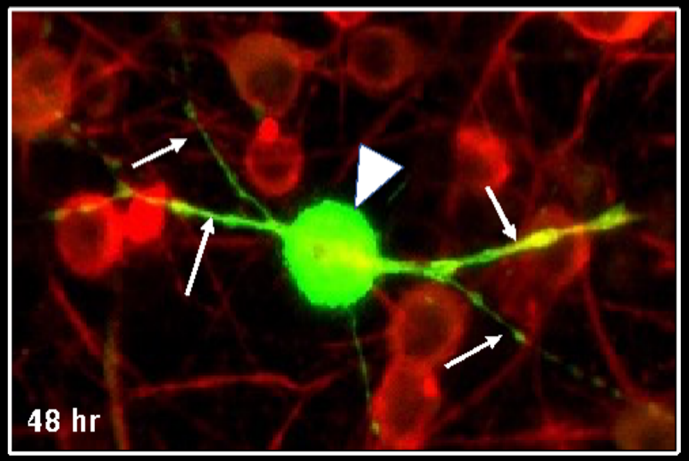
Infect cultured human neurons with SARS-CoV-2

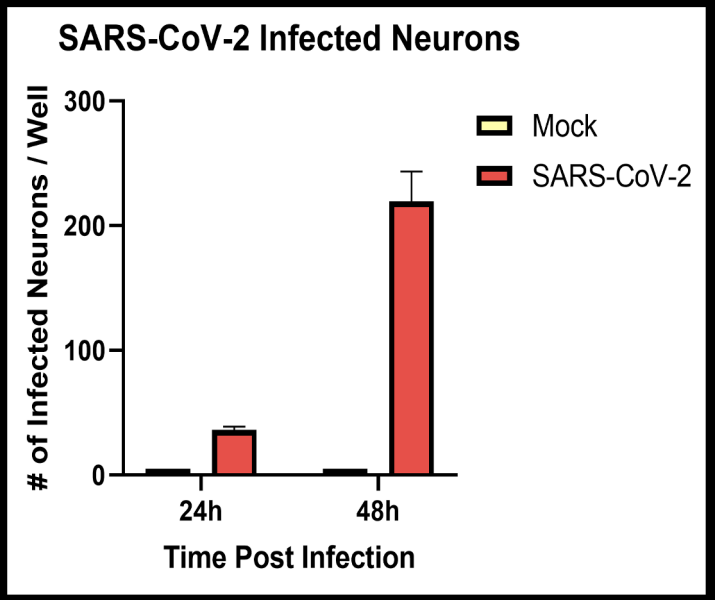
Determine if cells are infected with virus

SARS-CoV-2 Infects and replicates in human neurons (MOI = 0.1)









SARS2 infection of human neurons induces specific gene expression profiles associated with host defense

Charlene Smith-Geater, Ph.D., Leslie Thompson, Ph.D., Gema Olivarria UCI School of Biological Sciences

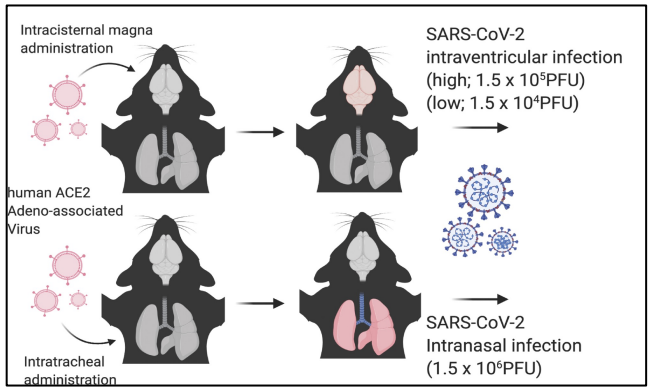
Question 2

Employ a mouse model of COVID-19 to understand mechanisms associated with disease progression and neurologic deficits

What are pre-clinical animal models for studying SARS2 pathogenesis?

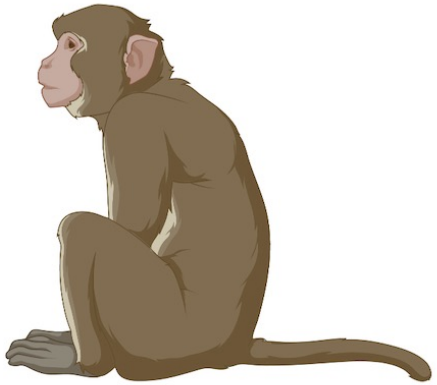
[Angiotensin converting enzyme 2 (ACE2) is receptor for SARS-CoV-2]

AAV-delivery of hACE2



Transgenic mice expressing hACE2

Rhesus macaque



Syrian hamster

Express SARS2-binding ACE2

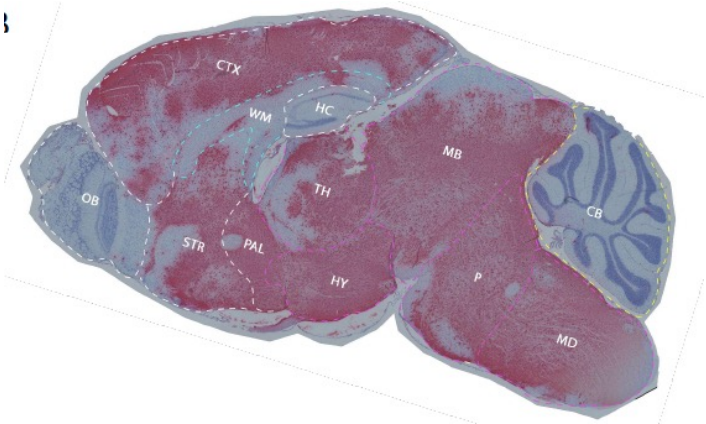
hACE2 = human ACE2

Experimental infection of mice with SARS-CoV-2

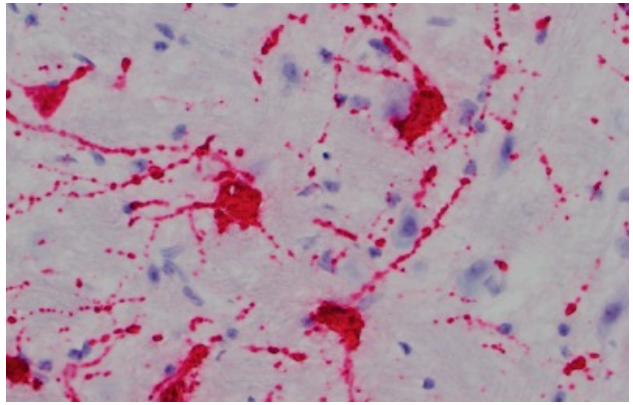
Transgenic mice that express human ACE2 -> susceptible to infection with SARS-CoV-2

- Viral infection of brain/spinal cord
- Neuropathology
- Neuroinflammation

SARS2 viral RNA in brain

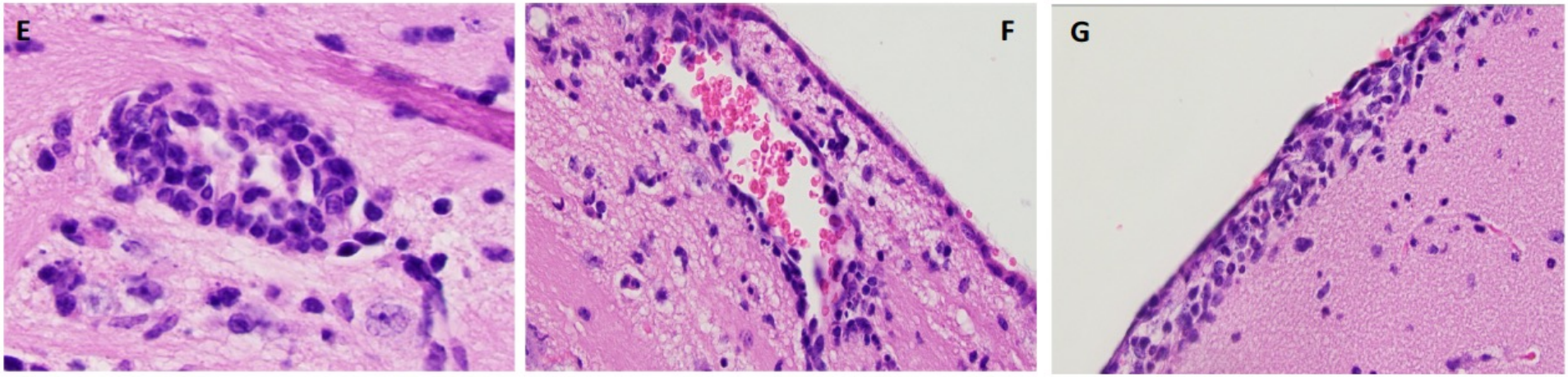


Neurons are infected by virus



Gema Olivaria, Yuting Cheng, Susana Furman, Robert Edwards, M.D., Ph.D.

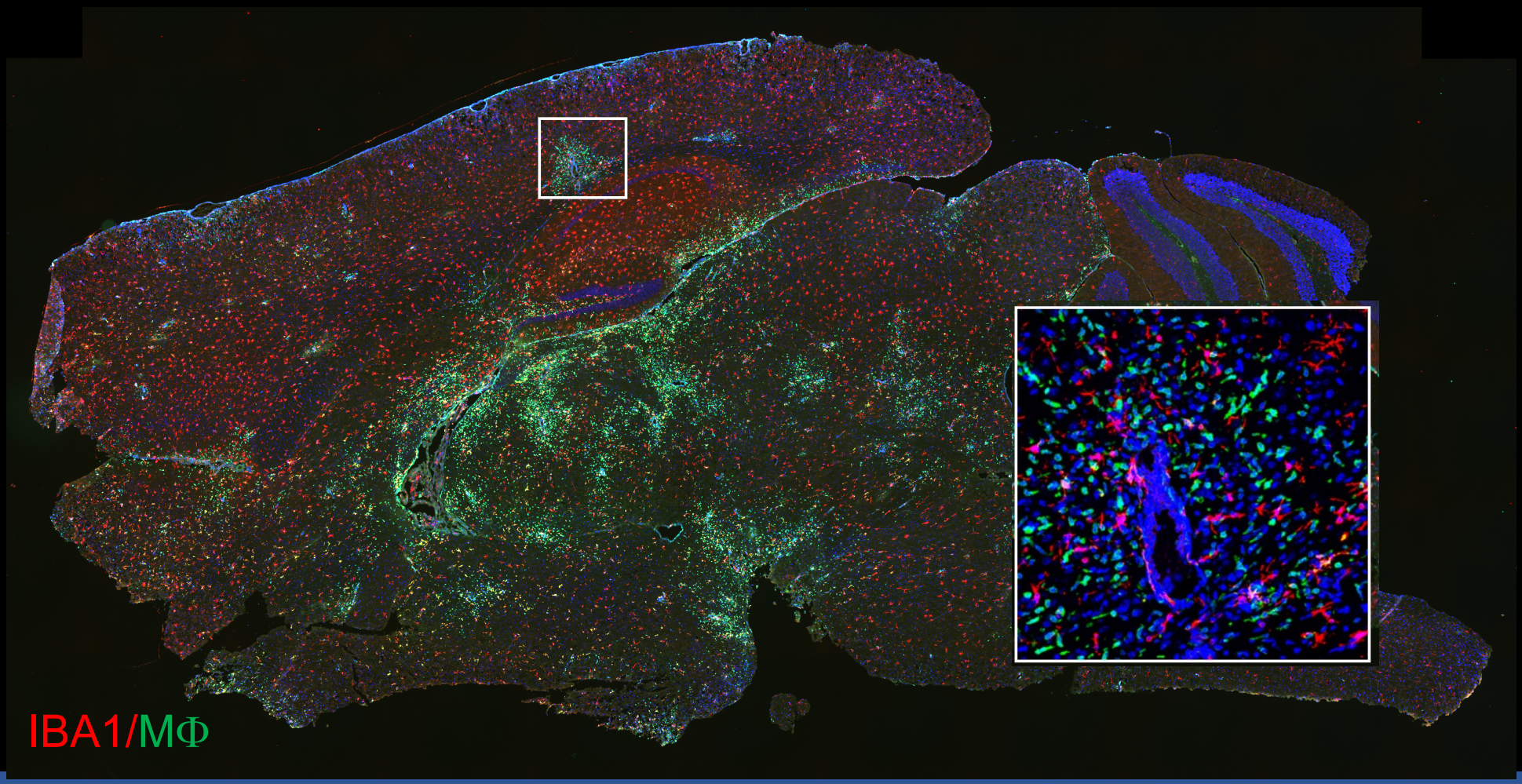
Neuroinflammation in response to SARS-CoV-2 infection of mouse CNS



Immune cells enter the mouse CNS in response to SARS-CoV-2 infection
(similar pathologic features to humans with COVID-19)

Gema Olivaria, Yuting Cheng, Susana Furman, Robert Edwards, M.D., Ph.D., William Yong, M.D.

Neuroinflammation in response to SARS-CoV-2 infection of mouse CNS

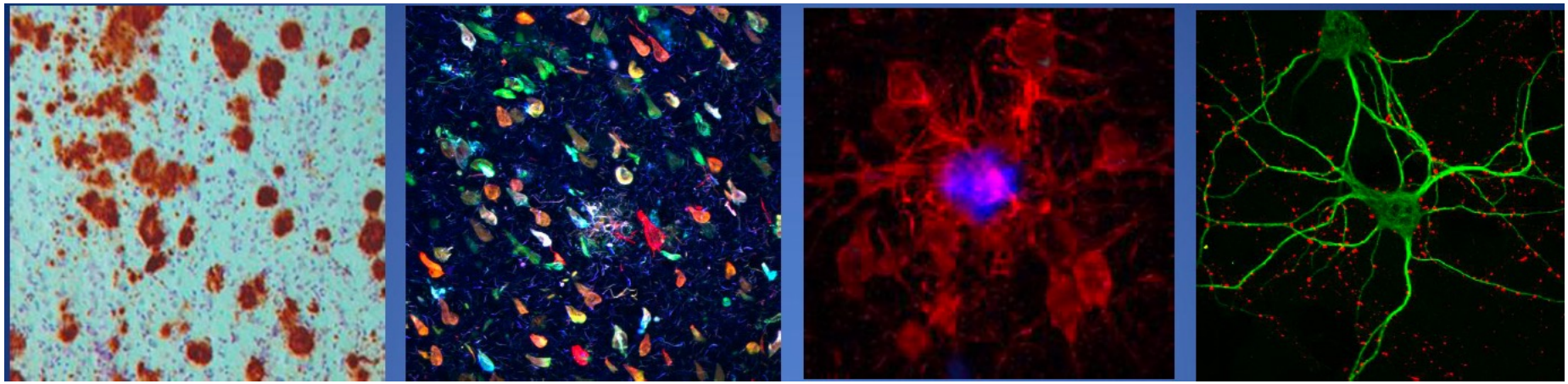


Lindsay Hohsfield, Ph.D., Kim Green, Ph.D.

UCI School of Biological Sciences

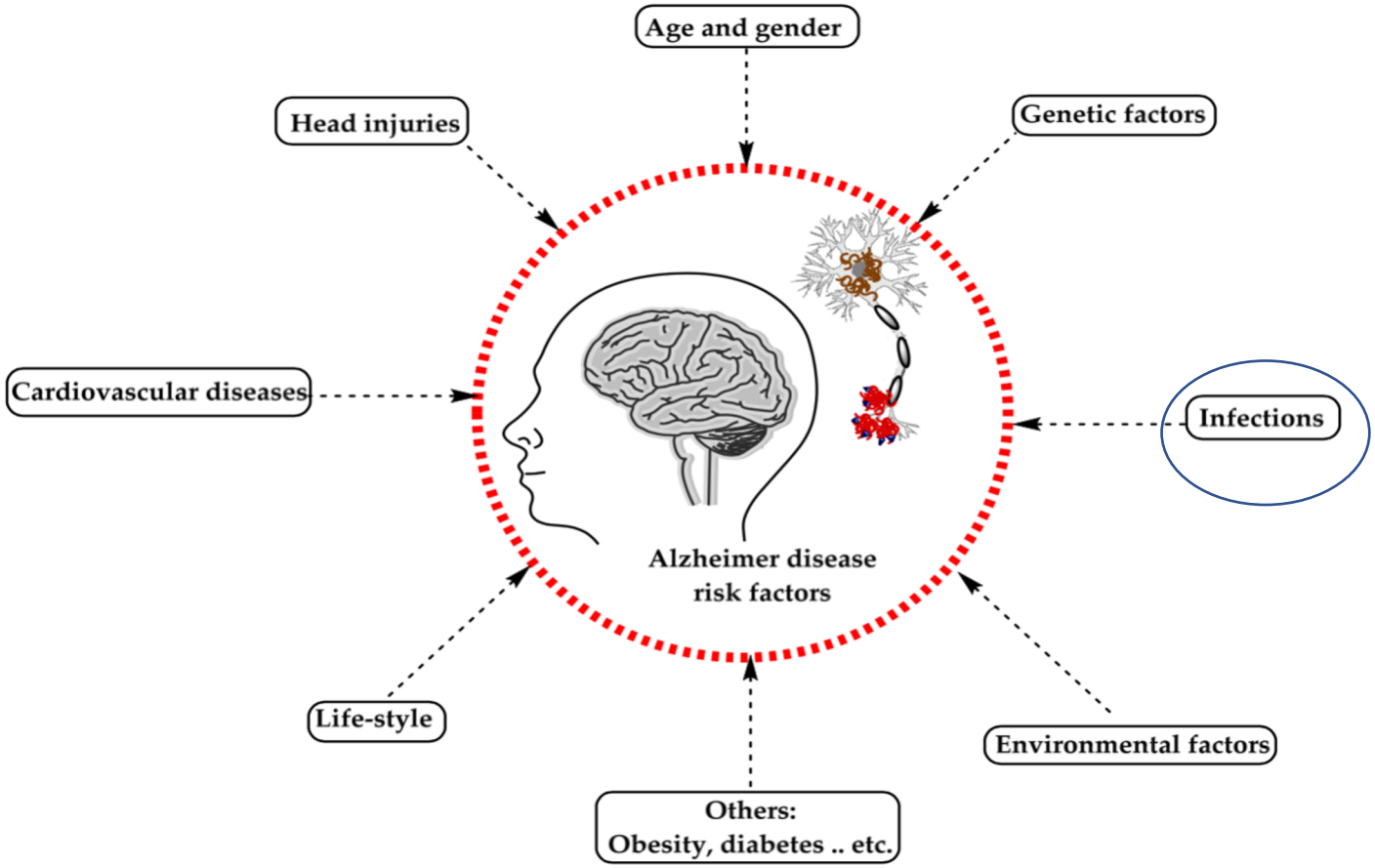
Question 3

Does infection of transgenic mouse models of Alzheimer's disease (AD) with a murine coronavirus affect AD-associated neuropathology?



- **Amyloid Plaques:** (β amyloid peptide)
- **Neurofibrillary tangles:** phosphorylated tau
- **Inflammation:** immune cells migrating into the brain
- **Neuronal and synaptic loss:** driven by all of the above

Risk factors and AD



Microbial infection

Infections to CNS have shown to lead to the accumulation of plaques and tangles (Holmes et al., 2009; Little et al.,2004;Wozniak et al., 2007).

(Breiyeh and Kamaran., Molecules 2020)

Does COVID-19 affect severity of AD/ dementia?

Review Article (Mini-Review)

Implication of COVID-19 on neurological complications with specific emphasis on alzheimer's and parkinson's disease

(E-pub Abstract Ahead of Print)

Author(s): Ankita Sood, Ravi Goyal, Harshdeep Singh, Tapan Behl, Sandeep Arora, Balraj Saini, Rajwinder Kaur*

Gathering evidence indicates SARS-CoV-2 infection exacerbates dementia-related clinical symptoms

Review

COVID-19 and Alzheimer's Disease

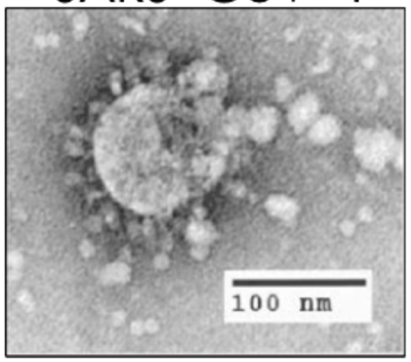
Marcello Ciaccio [1,2,*], Bruna Lo Sasso [1,2], Concetta Scazzone [1], Caterina Maria Gambino [1], Anna Maria Ciaccio [3], Giulia Bivona [1], Tommaso Piccoli [4], Rosaria Vincenza Giglio [1,†] and Luisa Agnello [1,†]

COVID-19 and Alzheimer's disease: how one crisis worsens the other

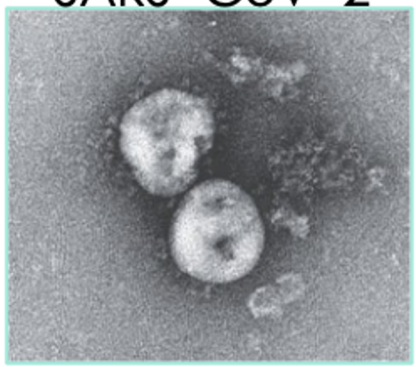
Xiaohuan Xia[1,2*], Yi Wang[1,2] and Jialin Zheng[1,2,3,4*]

Coronavirus: β subfamily

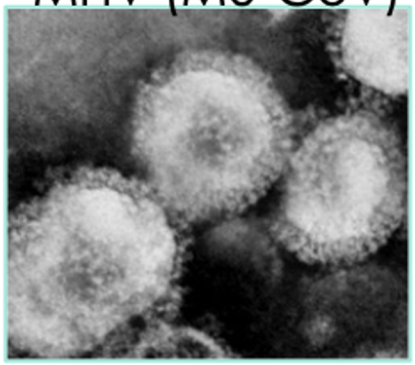
SARS- CoV- 1



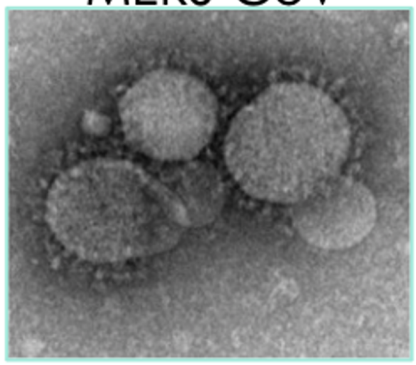
SARS- CoV- 2



MHV (Mu-CoV)



MERS-CoV



- Single-stranded positive-sense RNA virus
- RNA genome is 31 kilobases (among largest known)
- Beta-coronavirus family
- Wide-range of animal hosts including humans, pigs, cattle, rodents, bats, and camels
- Symptoms associated with infection are wide-ranging and include pneumonia, diarrhea, peritonitis, and **neurologic disease – neuroinflammation, encephalitis,** and **neurodegeneration**

Does coronavirus infection affect Alzheimer's disease neuropathology?

1. *Mouse CoV infection*

Infect AD mouse models with mouse CoV and evaluate the effects on AD-pathology

- Amyloid beta (Aβ) formation
- Tau pathology
- Neuroinflammation

Mouse models

- 3xTg mice
- Human Aβ knock-in mice
- 5xFAD mice

2. *SARS-CoV-2 infection*

Infect AD mouse models with SARS-CoV-2 and evaluate the effects on AD-pathology

- Amyloid beta (Aβ) formation
- Tau pathology
- Neuroinflammation

Mouse models

- 3xTg mice
- Human Aβ knock-in mice
- 5xFAD mice

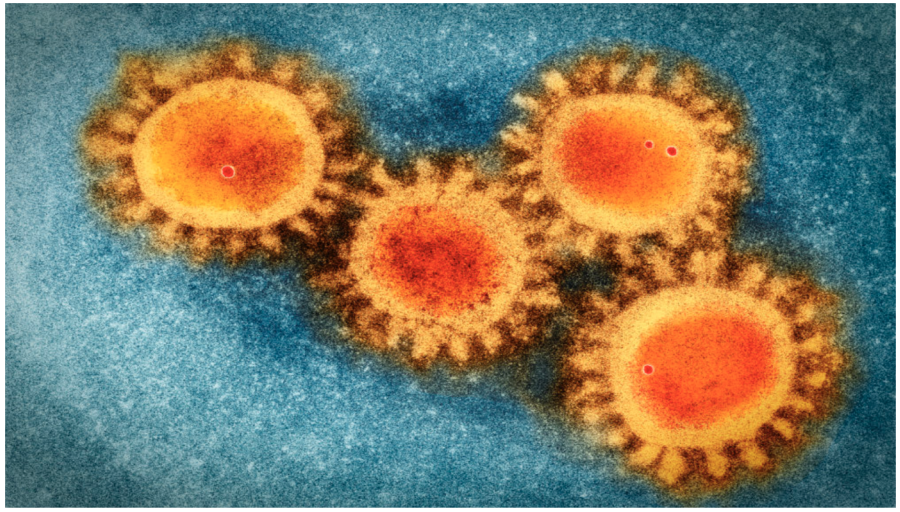
3. *Human Studies*

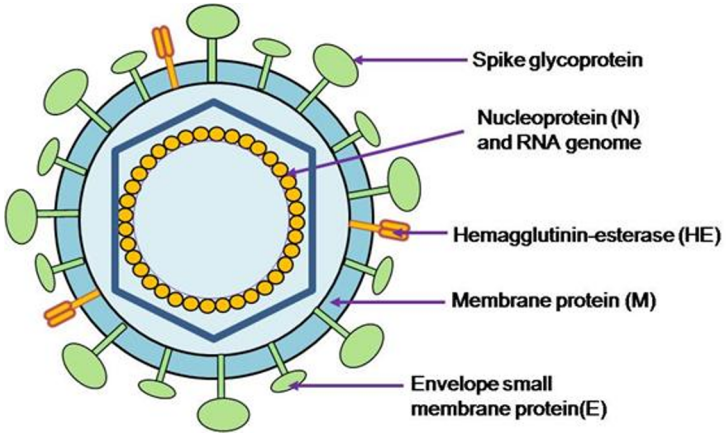
Post-mortem analysis from brains of AD patients that died from COVID-19 infection

- Is there detectable levels of virus in brain
- Is there evidence of increased AD pathology?
- Is there evidence of increased neuroinflammation?

Ongoing studies in the laboratory

Neuroadapted JHM strain of Mouse Hepatitis Virus (JHMV) – mouse coronavirus

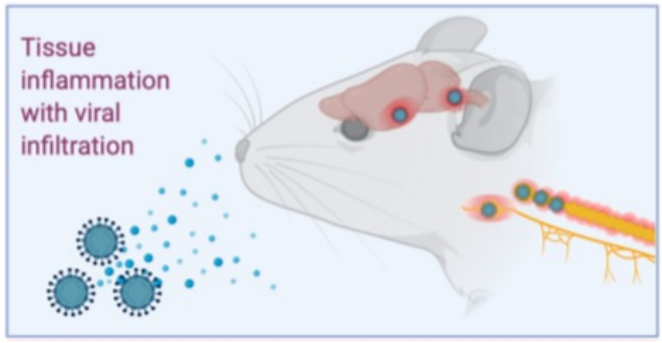




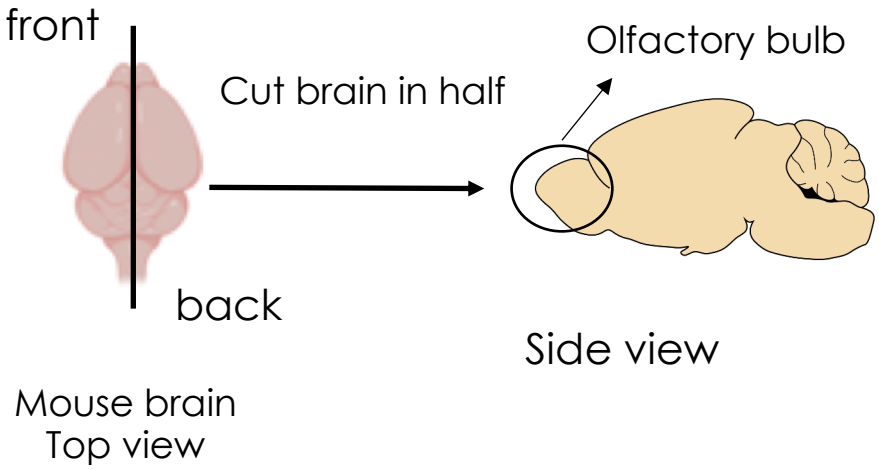
- Intracranial injection of JHMV leads to wide-spread viral infection throughout the brain.
- Targets of infection are astrocytes, oligodendrocytes, and microglia.
- Infection leads to neuroinflammation and neurodegeneration.

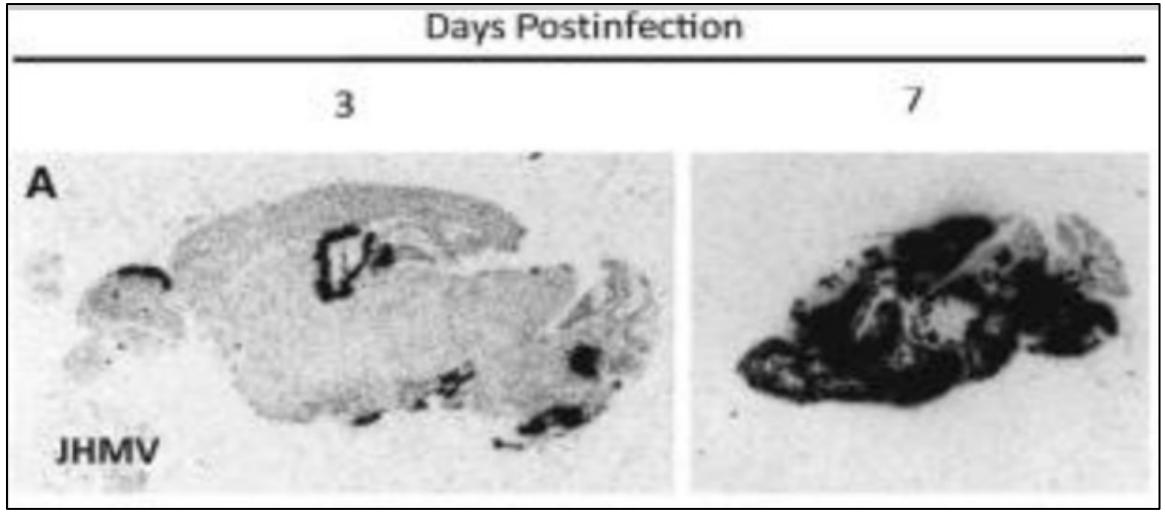
Adams, RA et al 2007 J Exp Med

Lessons learned from infection of mice with JHMV:



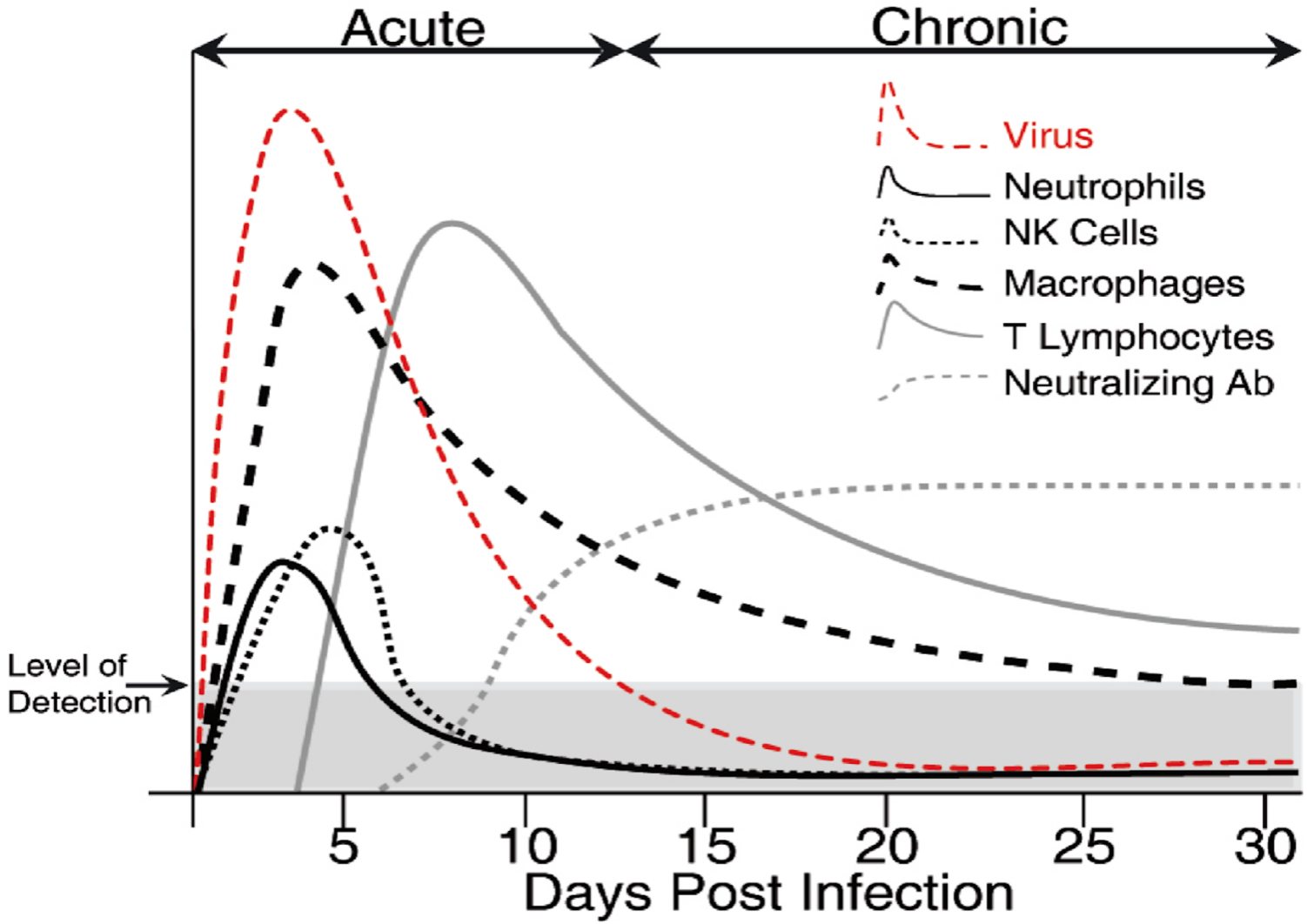
- Virus is able to infect & replicate in brain following intranasal administration.
- Immune cells rapidly accumulate in the CNS of infected mice that both control viral replication but also contribute to neurologic disease.





Lane *et al., J. Immunol.*, 1998

Mouse coronavirus (JHMV) and infection of the CNS



Lane *et al., J. Immunol.*, 1998; Skinner *et al., Viral Immunol.*, 2019

Infection of transgenic mouse models of AD with mouse coronavirus (JHMV)

Triple transgenic mice
(3x-Tg)

5x-FAD

Human Aβ knock-in mice
(hAβ-KI)

Infect with mouse coronavirus JHMV and assess effects on AD-associated neuropathology:

1. Tau formation
2. Amyloid β plaque deposition
3. Neuroinflammation

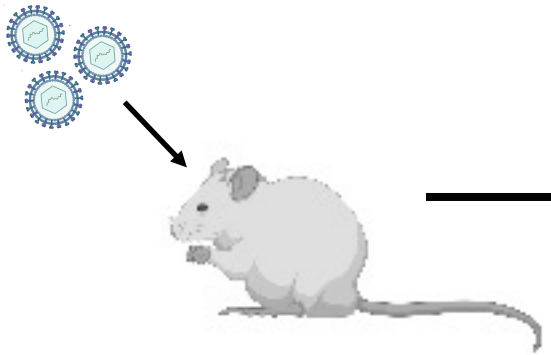
JHMV-infection of 3x-Tg mice

Inflammation Induced by Infection Potentiates Tau Pathological Features in Transgenic Mice

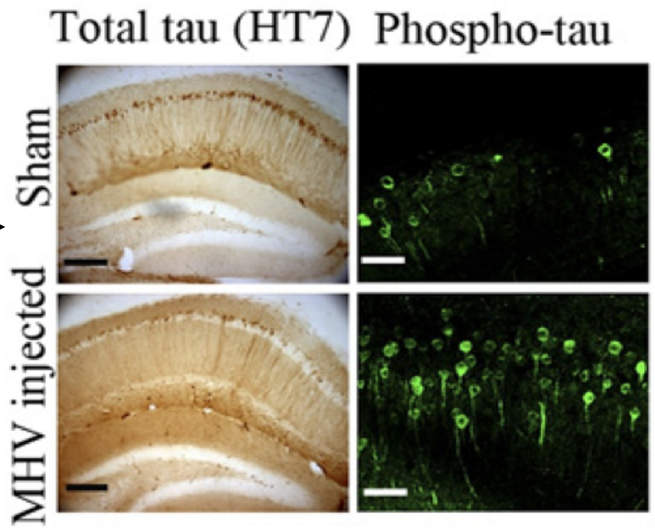
Michael Sy,*† Masashi Kitazawa,*†
Rodrigo Medeiros,*† Lucia Whitman,*‡
David Cheng,*† Thomas E. Lane,*‡
and Frank M. LaFerla*†

This study used the 3x-Tg transgenic model of AD to determine if infection by a mouse coronavirus (JHMV) either increased or decreased the severity of AD-associated neuropathology

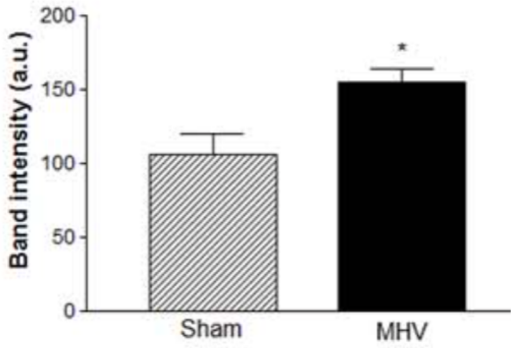
JHMV



Triple transgenic mice
(3x-Tg)

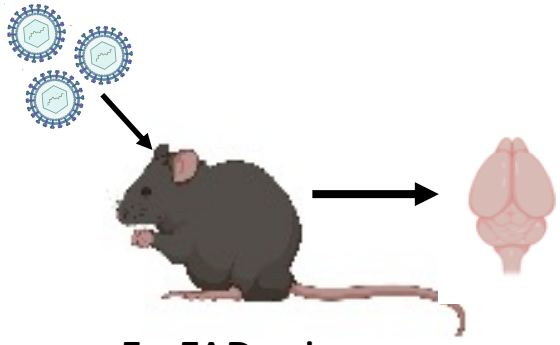


Phospho-tau

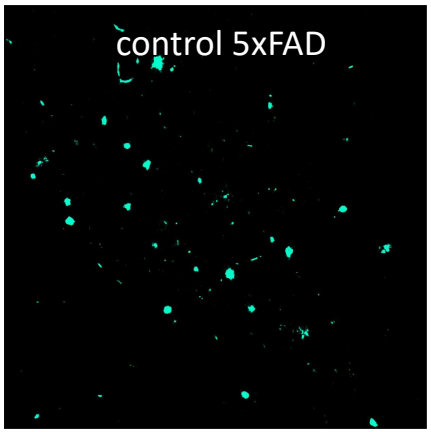


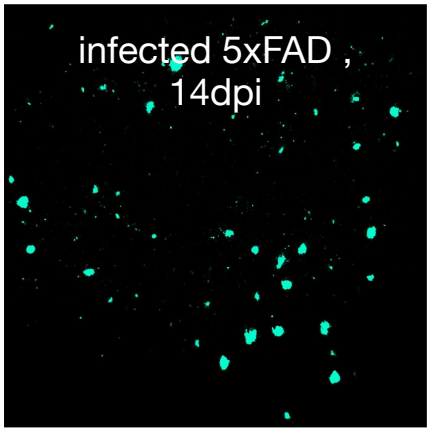
JHMV-infection of 5xFAD mice

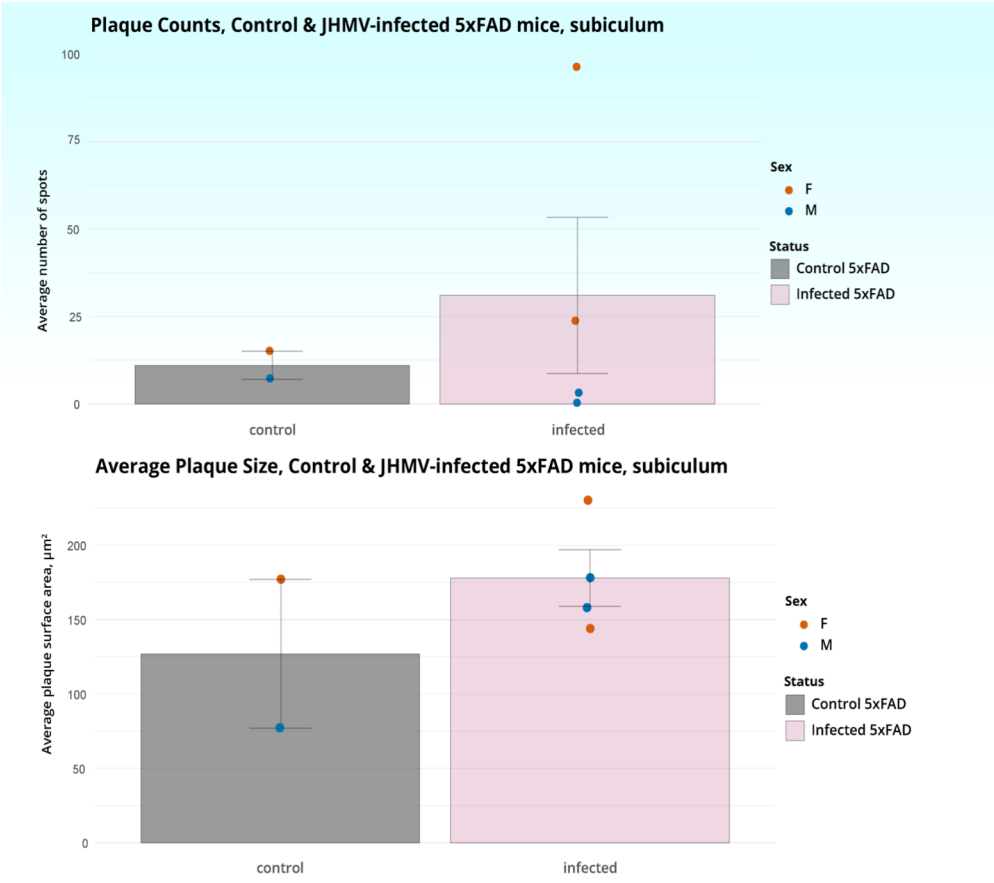
JHMV infection increases both the number and size of plaques in the brains of 5xFAD mice



5x-FAD mice







Susana Furman, Kate Tsourmas

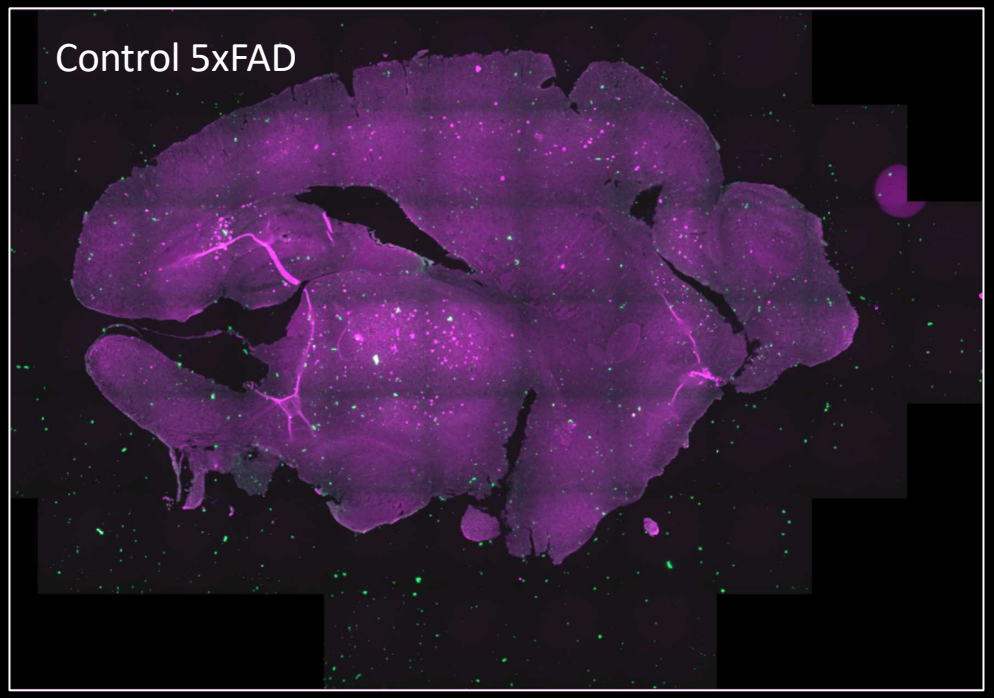
UCI School of Biological Sciences

JHMV-infection of 5xFAD mice

Immune cell entry into brains of JHMV-infected 5xFAD mice is increased and is associated with increased plaque burden

AmyloGlo (Aβ plaques)

Immune cells (monocytes)



Monocyte infiltration into brain

Susana Furman, Kate Tsourmas

UCI School of Biological Sciences

Perspectives - I

- Using different transgenic mouse models of AD, we've been able to show that infection of the CNS with a mouse coronavirus increases AD-associated neuropathology (phospho-Tau and Aβ accumulation).
- Increased AD pathology in infected brains was associated with immune cell infiltration suggesting a role for CNS-infiltrating cells in enhancing disease.
- We will attempt to block specific immune cells from entering CNS of infected mice to define potential mechanisms by which increased pathology is occurring.

Perspectives - II

Ongoing studies will also accomplish the following:

1) Determine if infection of AD mouse models of SARS-CoV-2 accelerates neuropathology as well as affects memory/cognition.
2) Examine brains from AD patients that succumbed to COVID-19 and determine i) is virus detected in the brain?, ii) is there an increase in neuropathology?, and iii) is there an increase in immune cell infiltration?

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RAY & TYE NOORDA FOUNDATION

MS National Multiple Sclerosis Society

NIH National Institute of Neurological Disorders and Stroke R35NS116835

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NIH National Institute of Neurological Disorders and Stroke R01NS091939

NIH National Institute of Neurological Disorders and Stroke R01 NS092042