Presentation by Sean Leng, MD, PhD

WEBINAR: COVID-19: Can the Science of Aging move us Forward?
March 24, 2020
COVID-19 pandemic and older adults

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COVID-19: A global pandemic


HIGHLIGHTS
- Three new countries/territories/areas from the African Region [1], Region of the Americas [1], and Eastern Mediterranean Region [1], have reported cases of COVID-19.
- The number of COVID-19 cases surpassed 300,000 globally.
- Data reported are based on information received from national authorities by 10:00 AM CET, 23 March 2020.
- Diagnostic testing for COVID-19 is critical to tracking the virus, understanding epidemiology, informing case management, and to suppressing transmission. WHO has updated the Laboratory Testing Strategy document according to the 4Cs transmission scenarios. All technical guidance can be found here.

SITUATION IN NUMBERS

<table>
<thead>
<tr>
<th>Region</th>
<th>Total (new) cases in last 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Globally</td>
<td>332,930 (40,788)</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>95,637 (850)</td>
</tr>
<tr>
<td>European Region</td>
<td>171,424 (20,131)</td>
</tr>
<tr>
<td>South-East Asia Region</td>
<td>177,806 (519)</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td>25,375 (1706)</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>37,016 (17,331)</td>
</tr>
<tr>
<td>African Region</td>
<td>990 (251)</td>
</tr>
</tbody>
</table>

WHO RISK ASSESSMENT

Global Level: Very High

Johns Hopkins Coronavirus Resource Center: https://coronavirus.jhu.edu/map.html

Baltimore Mayor begs residents to stop shooting each other so hospital beds can be used for coronavirus patients

March 18, 2020 at 11:30 pm

Friday, March 20, Palm Beach, FL
Older adults are most vulnerable
- Case-fatality data from China -

**Covid-19’s case fatality rate increases with age, according to China’s data**

*Estimated case fatality risk in Hubei, China, January-February 2020*

<table>
<thead>
<tr>
<th>Age group</th>
<th>Case fatality ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>.01%</td>
</tr>
<tr>
<td>10-19</td>
<td>.02%</td>
</tr>
<tr>
<td>20-29</td>
<td>.08%</td>
</tr>
<tr>
<td>30-39</td>
<td>.18%</td>
</tr>
<tr>
<td>40-49</td>
<td>.40%</td>
</tr>
<tr>
<td>50-59</td>
<td>1.3%</td>
</tr>
<tr>
<td>60-69</td>
<td>4.6%</td>
</tr>
<tr>
<td>70-79</td>
<td>9.8%</td>
</tr>
<tr>
<td>80+</td>
<td>18%</td>
</tr>
</tbody>
</table>

*Among all symptomatic and asymptomatic infections

Source: Adjusted age-specific case fatality ratio during the Covid-19 epidemic in Hubei, China, January and February 2020, medRxiv
Older adults are most vulnerable
- Data from EU -

Table. Case-Fatality Rate by Age Group in Italy and China

<table>
<thead>
<tr>
<th>Age groups, y</th>
<th>Italy as of March 17, 2020</th>
<th>China as of February 11, 2020</th>
</tr>
</thead>
</table>
|              | No. of deaths (% of total)  | Case-fatality rate, %
|              | Deaths                      |                              |
| 0-9          | 0                           | 0                             |
| 10-19        | 0                           | 0                             |
| 20-29        | 0                           | 0                             |
| 30-39        | 4 (0.3)                     | 0.3                           |
| 40-49        | 10 (0.6)                    | 0.4                           |
| 50-59        | 43 (2.7)                    | 1.0                           |
| 60-69        | 139 (8.6)                   | 3.5                           |
| 70-79        | 578 (35.6)                  | 12.8                          |
| ≥80          | 850 (52.3)                  | 20.2                          |

Proportion of older adults in the population

- Italy: 22.8%
- China: 11.9%

JAMA 3/23/2020
Older adults are most vulnerable
- Data in the US -

- First outbreak: Life care center, Kirkland, WA
- First death in New York: an 82 y/o in Brooklyn
- First death in Maryland: an 82 y/o in Howard county
COVID-19
... Clinical features & Geroscience approach ...

• Aging is the greatest risk for severe COVID-19 and deaths
• Immunosenescence may be a major mechanism for this risk (Dr. George Kuchel)
• Adverse impact on immunity:
  – Cytokine storm
  – Kills CD4 and CD8 T cells (lymphopenia nadir at Day 4-6) (Some on the frontline consider COVID-19 as SARS+HIV?)
• Lung damage and fibrosis early on (CT scan characteristic ground-glass opacification)
• Multi-organ failure, virus no longer detected
• Traditional paradigm:
  – Focusing only on individual pathogens or diseases
• Geroscience approach:
  – Address healthy aging, resilience, and older adults’ ability to fight against infections and diseases
Geroscience going global

International Geroscience Symposium in China
May 24-25, 2019

American Federation for Aging Research (AFAR), NIA Nathan Shock Center, and Milstein Medical Asian American Partnership (MMAAAP) Foundation
WEBINAR: COVID-19: Can the Science of Aging move us Forward?
March 24, 2020
Aging is the strongest risk factor for all age related diseases...

Geroscience

Hallmarks of Aging

- Metabolic Dysregulation
- Epigenetic Changes
- Inflammation
- Proteostasis failure
- Immune Dysfunction

Targeting the Hallmarks

- Bitech:
  - Restorbio
  - Lifebiosciences
  - CohBar

- Juvenescence
- Cambrian
- Apollo

Pharmaceuticals
- (more…)
- Pharmaceuticals
- Regeneron
- (Calico?)
• **Healthspan & lifespan** has been extended in numerous animal models.
• Relevant gero-protectors have been used in humans.  
  (Metformin, Rapamycin, ….)

Rapamycin (mTOR inhibitor)

Rapamycin + metformin
How to translate these achievements to humans?

Biotech & Pharmaceuticals: Developing drugs

Biological discoveries in areas of diseases

Drugs targeting disease

FDA and aging

If aging is not considered as a preventable condition:
1) Healthcare insurers would not pay for their clients.
2) Pharmaceuticals will not develop other, better and combination of drugs.
Targeting Aging with Metformin (TAME) (Launched by AFAR and friends)

• (Proof of concept) To show that composite of age-related diseases can be prevented by metformin

• (FDA regulation) To obtain a new indication for the delay of age-related morbidities.
We are frustratingly behind!

- Elderly adults account for most of the mortality due to COVID-19
- The biology of aging drives diseases of aging, underlying the cause for this excess mortality
- Hallmarks of aging are targets for gero-therapeutics.
- Metformin and mTOR inhibitors may be modulating response to viral infection in older adults
- They can target immune decline and inflammation and increase whole body resiliency to severe illness.
- FDA, CDC, BARDA needs to rush into action!

- This is relevant to future pandemics, blinded to cause!
Presentation by George Kuchel, MD, FRCP, AGSF

WEBINAR: COVID-19: Can the Science of Aging move us Forward?

March 24, 2020
Vulnerability of Older Adults to COVID-19:
Importance of frailty, biological aging and geroscience-guided therapies

George A. Kuchel, MD, FRCP, AGSF
Travelers Chair in Geriatrics and Gerontology
Director, UConn Center on Aging, University of Connecticut
Chief, Geriatric Medicine, UConn Health
kuchel@uchc.edu
Vulnerability of Older Adults to COVID-19: 
*Importance of frailty, biological aging and geroscience-guided therapies*

According to CDC highest Risk Populations for COVID-19 deaths include:
- Older adults
- All individuals (but especially older adults) with chronic diseases
- These may include heart and lung disease, diabetes and others
- Older men are at greater risk than older women
- What does this all mean?

Is date of birth (chronological aging) the best measure? Frailty, chronic diseases, physiology, social factors and biology add essential clinical information

Acknowledgements to J McElhaney
Vulnerability of Older Adults to COVID-19: 
Importance of frailty, biological aging and geroscience-guided therapies

Experience from influenza (flu) vaccination:
• All older adults should be vaccinated
• Older adults represent over 90% of all flu-related deaths in most years
• Vaccine is 80% effective in preventing flu-related hospitalization in non-frail older adults, yet it is less effective in those who are frail (Andrew MK et al. J of Infectious Diseases 2017)
• Declines in antibody and cell-mediated responses seen with aging (Nikolich-Zugich, Nature Imm 2018)
• These are augmented by frailty, chronic diseases, physiological aging (McElhaney et al, Front Imm 2016)

Potential lessons for COVID-19 and future pandemics involving novel pathogens:
• Inevitable delays in vaccine and drug development impact mostly the most vulnerable
• A geroscience-guided approach designed to target biological drivers shared by aging and common chronic conditions could improve clinical outcomes against varied novel pathogens long before pathogen-specific vaccines and drugs become available (J. Mannick)
• COVID-19 vaccine will most likely be less effective in older adults with chronic conditions
Vulnerability of Older Adults to COVID-19: 
Impact of Immune Aging on Ability to Handle Familiar and Unfamiliar Pathogens

AFAR Webinar, March 24 2020

Acknowledgements to G Hargis & C Bonin

Nikolich-Zugich, *Nature Imm* 2018
Vulnerability of Older Adults to COVID-19:
Nearly all aspects of immune response and host defense are impacted by aging
Vulnerability of Older Adults to COVID-19:
Older men have more innate cell activity (inflammation) but less adaptive cell activity (T and B cell function) compared to older women

Marquez ...Kuchel, Banchereau, Ucar Nature Communications Feb 6;11(1):751, 2020
Vulnerability of Older Adults to COVID-19: Metformin and Emergence of Geroscience-Guided Therapies

Vulnerability of Older Adults to COVID-19:  
*TAME Trial (Targeting Aging with Metformin)*

- Metformin extends health span and life span in animals
- It is a first-line, generic drug to treat diabetes
- >60 year experience and outstanding safety record

Cumulative Survival

AFAR Webinar, March 24 2020
Vulnerability of Older Adults to COVID-19: 
*TAME Trial (Targeting Aging with Metformin)*

Inclusion Criteria: Age 65-80, nondiabetic, some comorbidities allowed; n = 3,000

Double blind placebo-controlled trial

**Primary Outcome:** TIME TO MAJOR DISEASES (FDA)

**Secondary Outcome:** FUNCTIONAL AGING

**Tertiary Outcomes:** BIOMARKERS (NIA)

Impact of Metformin on Flu Vaccine Responses (VEME-AFAR/NIA, Jenna Bartley, PhD - UConn)

Gordon *et al.* A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing.

- Not yet peer-reviewed but posted on bioRxiv (3/22) [https://www.biorxiv.org/content/10.1101/2020.03.22.002386v1](https://www.biorxiv.org/content/10.1101/2020.03.22.002386v1)
- AP-MS identification of 66 “druggable” human proteins or host factors targeted by 69 existing FDA-approved drugs, drugs in clinical trials and/or preclinical compounds. These include metformin and rapamycin.
- CAUTION!!..Mechanism?; Effects in cell infection assays?; Dose?; *In vivo* effects in animal models?; Human studies?
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TORC1 is an evolutionarily conserved pathway that regulates aging.

TORC1 inhibition has extended lifespan and healthspan in multiple preclinical species.
Inhibition of TORC1 has the potential to improve the function of multiple aging organ systems

**Improved Neurologic Function**
- Tain et al., *Nature Neuroscience*, 2009
- Malagelada et al., *J Neurosci*, 2010
- Spilman et al., *PLoS ONE*, 2010
- Halloran et al., *Neuroscience*, 2012
- Majumder et al., *Aging Cell*, 2012
- Neff et al., *JCI*, 2013

**Reversal of aging-related cardiac dysfunction**
- Flynn et al., *Aging Cell*, 2013
- Dai et al., *Aging Cell*, 2014
- Chiao et al., *Aging*, 2016

**Reversal of aging-related immune dysregulation**
- Chen et al., *Science Sig*, 2009
- Selman et al., *Science*, 2011
- Neff et al., *JCI*, 2013
- Hurez et al., *Aging Cell*, 2015

**Improvement in physical activity**
- Selman et al., *Science*, 2011
- Harrison et al., *Nature*, 2009
- Wilkinson et al., *Aging Cell*, 2014
- Flynn et al., *Aging Cell*, 2013
In Phase 2 clinical trials enrolling > 900 people 65 years of age and older, RTB101 was observed to decrease the incidence and/or severity of respiratory tract infections:

**Phase 2a trial**
- 264 healthy elderly
- RTB101 10 mg QD
- **42% reduction** in the rate of RTIs (p=0.006)
- Antiviral defense systems were upregulated in whole blood
- RTB101 was well-tolerated (Mannick et al, *Sci Transl Med*, 2018)

**Phase 2b trial**
- 652 high-risk elderly
- RTB101 10 mg QD
- **30.6% reduction** in the percent of patients with laboratory-confirmed respiratory tract infections (p=0.025)
- **52.1% reduction** in percentage of subjects with severe laboratory-confirmed respiratory tract infection symptoms (p=0.034)
- 5 day reduction in the time to alleviation of moderate to severe symptoms due to laboratory-confirmed RTIs (p=0.025)
- RTB101 was well-tolerated

QD = once daily
Phase 2b: RTB101 10mg QD was observed to increase expression of innate antiviral genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Placebo n (%)</th>
<th>RTB101 10mg QD n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISGs upregulated (mean ddCT ≤0)</td>
<td>5 (25%)</td>
<td>19 (95%)</td>
<td>0.00001</td>
</tr>
<tr>
<td>ISGs not upregulated (mean ddCT &gt;0)</td>
<td>15 (75%)</td>
<td>1 (5%)</td>
<td>-</td>
</tr>
</tbody>
</table>
Antiviral genes observed to be upregulated in subjects treated with RTB101 encode proteins that inhibit multiple steps in viral replication

Adapted from Schneider et al. *Annu Rev Immunol*, 2014
Phase 2b: RTB101 reduces the incidence of respiratory tract infections caused by multiple viruses including coronavirus

<table>
<thead>
<tr>
<th>Pathogen associated with laboratory-confirmed RTIs</th>
<th>RTB101 10mg QD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronavirus</td>
<td>7 had RTI</td>
<td>15 had RTI</td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td>3 had RTI</td>
<td>5 had RTI</td>
</tr>
<tr>
<td>Rhinovirus/Enterovirus</td>
<td>7 had RTI</td>
<td>16 had RTI</td>
</tr>
<tr>
<td>Influenza A</td>
<td>7 had RTI</td>
<td>9 had RTI</td>
</tr>
<tr>
<td>Influenza B</td>
<td>3 had RTI</td>
<td>7 had RTI</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>2 had RTI</td>
<td>2 had RTI</td>
</tr>
<tr>
<td>Respiratory Syncytial Virus</td>
<td>2 had RTI</td>
<td>7 had RTI</td>
</tr>
</tbody>
</table>
RTB101 was well-tolerated in high-risk elderly patients through Week 24

- Adverse events (AEs) were balanced between the RTB101 10 mg QD and placebo cohorts
- 1 unrelated death occurred in the RTB101 10mg QD cohort (patient was hit by car while riding a bicycle), 1 unrelated death occurred in the RTB101 10mg BID cohort and 1 unrelated death occurred in the placebo cohort (both from unknown causes)

<table>
<thead>
<tr>
<th></th>
<th>% of patients in treatment group</th>
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<tbody>
<tr>
<td></td>
<td>RTB101 10mg QD</td>
</tr>
<tr>
<td>Mild AEs</td>
<td>74.4%</td>
</tr>
<tr>
<td>Moderate AEs</td>
<td>38.1%</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>5.7%</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>4.5%</td>
</tr>
<tr>
<td>Discontinued study drug due to an AE</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

QD = once daily; BID = twice daily
Conclusions

• In preclinical species, TORC1 inhibition has been shown to improve the function of multiple aging organ systems including the immune system.

• Randomized, double-blind placebo-controlled clinical trials in almost 2,000 older adults have been completed to determine if TORC1 inhibition with RTB101 improves immune function in older adults.

• In a phase 2b trial, RTB101 10 mg once daily was observed to be well tolerated, upregulate innate antiviral gene expression, and reduce the incidence of laboratory-confirmed respiratory tract infections caused by multiple viruses including coronavirus in older adults age ≥65 years.

• RTB101 has the potential to decrease the severity of COVID-19 infections in adults age >65 years.