<table>
<thead>
<tr>
<th>SPIN ID</th>
<th>Opportunity Title</th>
<th>Sponsor Name</th>
<th>Sponsor Number</th>
<th>Deadline Date</th>
<th>Funding Amount</th>
</tr>
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<tbody>
<tr>
<td>09627</td>
<td>Emergency Awards: Rapid Investigation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease 2019 (COVID-19) (R21 Clinical Trial Not Allowed)</td>
<td>National Institute of Allergy and Infectious Diseases/NIH/DHHS</td>
<td>PAR-20-177</td>
<td>29-Apr-2021</td>
<td>275,000.00 USD</td>
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<tr>
<td></td>
<td>Contact Name: Diane Post, Ph.D.</td>
<td>Contact Telephone: 240-627-3348</td>
<td>Contact Email: <a href="mailto:postd@niaid.nih.gov">postd@niaid.nih.gov</a></td>
<td>Program URL: <a href="https://grants.nih.gov/grants/guide/pa-files/PAR-20-177.html">https://grants.nih.gov/grants/guide/pa-files/PAR-20-177.html</a></td>
<td>Deadline Dates (ALL): 29-Apr-2021</td>
</tr>
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<td>Synopsis: The purpose of this Funding Opportunity Announcement (FOA) is to provide an expedited funding mechanism for research on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease 2019 (COVID-19). NIAID is issuing this FOA in response to the declared public health emergency issued by the Secretary, HHS, for 2019 Novel Coronavirus (COVID-19).</td>
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| 09630   | Emergency Awards: Rapid Investigation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease 2019 (COVID-19) (R01 Clinical Trial Not Allowed) | National Institute of Allergy and Infectious Diseases/NIH/DHHS | PAR-20-178     | 29-Apr-2021  | Not Available |
|         | Contact Name: Diane Post, Ph.D.                                                   | Contact Telephone: 240-627-3348        | Contact Email: postd@niaid.nih.gov | Program URL: https://grants.nih.gov/grants/guide/pa-files/PAR-20-178.html | Deadline Dates (ALL): 29-Apr-2021 |
|         | Synopsis: The purpose of this Funding Opportunity Announcement (FOA) is to provide an expedited funding mechanism for research on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease 2019 (COVID-19). NIAID is issuing this FOA in response to the declared public health emergency issued by the Secretary, HHS, for 2019 Novel Coronavirus (COVID-19). |
### 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></th>
<th>China as of February 11, 2020</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of deaths (% of total)</td>
<td>Case-fatality rate, %&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No. of deaths (% of total)</td>
<td>Case-fatality rate, %&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>All</td>
<td>1625 (100)</td>
<td>7.2</td>
<td>1023 (100)</td>
<td>2.3</td>
</tr>
<tr>
<td>Age groups, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10-19</td>
<td>0</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>20-29</td>
<td>0</td>
<td>0</td>
<td>7 (0.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>30-39</td>
<td>0.3</td>
<td>0.3</td>
<td>18 (1.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>40-49</td>
<td>0.6</td>
<td>0.4</td>
<td>38 (3.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>50-59</td>
<td>0.7</td>
<td>1.0</td>
<td>130 (12.7)</td>
<td>1.3</td>
</tr>
<tr>
<td>60-69</td>
<td>8.6</td>
<td>3.5</td>
<td>309 (30.2)</td>
<td>3.6</td>
</tr>
<tr>
<td>70-79</td>
<td>35.5</td>
<td>12.8</td>
<td>312 (30.5)</td>
<td>8.0</td>
</tr>
<tr>
<td>≥80</td>
<td>52.3</td>
<td>20.2</td>
<td>208 (20.3)</td>
<td>14.8</td>
</tr>
</tbody>
</table>
T cell-mediated immune response to respiratory coronaviruses

Airway Epithelium

rDCs migrating to draining LN

DLN

Naive T cell
Effector T cell
Respiratory dendritic cell (rDC)
Virus
MHC-Peptide complex

Corticosteroids → cPLA₂ → Arachidonic acid → COX-1/2 → Leukotrienes
Leukotrienes
leukocyte activation
chemoattraction
bronchoconstriction
airway remodeling

NSAIDs → COX-1/2 → PGH₂
PGH₂ → PGES → PGE₂ → endothelial barrier
immunosuppression
vasorelaxation
PGES → PGIS → PGI₂ → vasorelaxation
Immunosuppression
platelet inhibition
endothelial barrier
PGES → TXAS → TXA₂ → vasoconstriction
PGES → PGFS → PGF₂α → bronchoconstriction
platelet activation

hPGDS → Prostaglandin D₂

Prostaglandin D₂

DP1 → platelet inhibition
bronchodilatation/constriction
vasorelaxation
cough
eosinophil survival

DP₂/CRTTH2 → leukocyte activation
chemoattraction
histamine
Th2-cytokines

Slowing down with age: lung DCs do it too

Aging lungs have higher PLA₂G2D expression and elevated levels of lipid mediators, some of which naturally combat age-related oxidative stress by exerting immunosuppressive functions. The trade-off is an increased susceptibility to certain viral infections, including SARS-CoV and influenza A virus.

AECs from aged mice upregulate senescence-associated β-galactosidase activity

A20 is elevated in some but not all aged tissues

C57BL/6 mice at age 4, 10, 21 mo.

Fish oil lowers A20 levels and improves resistance to bacterial infection

Glutathione increase by the n-butanoxy glutathione derivative inhibits viral replication and induces a predominant Th1 immune profile in old mice infected with influenza virus.

Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment


Table 3. — Distribution of subjects as related to seroconversion towards A/H1N1, Singapore 6/86 influenza virus and to the presence or absence of symptomatology

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Treatment</th>
<th>Placebo</th>
<th>NAC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>29/122</td>
<td>(24)</td>
<td>36/126</td>
</tr>
<tr>
<td>Symptomatic episodes</td>
<td>23/29</td>
<td>(79)</td>
<td>9/36</td>
</tr>
<tr>
<td>No symptomatic episodes</td>
<td>6/29</td>
<td>(21)</td>
<td>27/36</td>
</tr>
<tr>
<td>No seroconversion</td>
<td>93/122</td>
<td>(76)</td>
<td>90/126</td>
</tr>
<tr>
<td>Symptomatic episodes</td>
<td>39/93</td>
<td>(42)</td>
<td>28/90</td>
</tr>
<tr>
<td>No symptomatic episodes</td>
<td>54/93</td>
<td>(58)</td>
<td>62/90</td>
</tr>
</tbody>
</table>

NAC: N-acetylcysteine. *: significantly different from the placebo group (p<0.0001), as assessed by Chi-squared analysis.
Where does this leave us?

- Very early events may be critical
  - Prophylactic treatment may be the best strategy
- Use of synolytic agents
- Anti-aging agents – resveratrol
- Possible interventions targeting redox:
  - N acetylcysteine?
  - Lipoic acid?
  - EPA or DHA? (Would these have adverse effects on DC migration?)
- Possible interventions targeting inflammation?
  - IL-1ra, anti-IL-1β, anti-TNFα
- Outcome measures for human studies?
Specific Aim #1. Interventions to reverse PLA2G2D and A20 expression in lungs of old mice. Westerns and QPCR to determine optimal dosing. Effect on senescent markers in airway epithelial cells. Dendritic cell migration. Response to lethal dose of flu to be evaluated with best options.

- Senolytic agents – rapamycin, dasatinib + quercetin or DPI-Foxo4
- Cytokine – IL1ra, anti-TNF
- Resveratrol
- Anti-oxidants – NAC, EPA

Specific Aim #2. Determine expression of PLA2G2D and A20 in healthy lung tissue for older vs. younger individuals. Surgical specimens old and new. We will use de-identified samples with information about diseases for archived specimens (immunohistochemistry) and signed consent before surgery (western, QPCR, immunohistochemistry).