SPIN ID	Opportunity Title	Sponsor Name	Sponsor Number	Deadline Date	Funding Amount
093627	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)	National Institute of Allergy and Infectious Diseases/NIH/DHHS	PAR-20-177	29-Apr-2021	275,000.00 USD
	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-20-177.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).			
093630	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).			

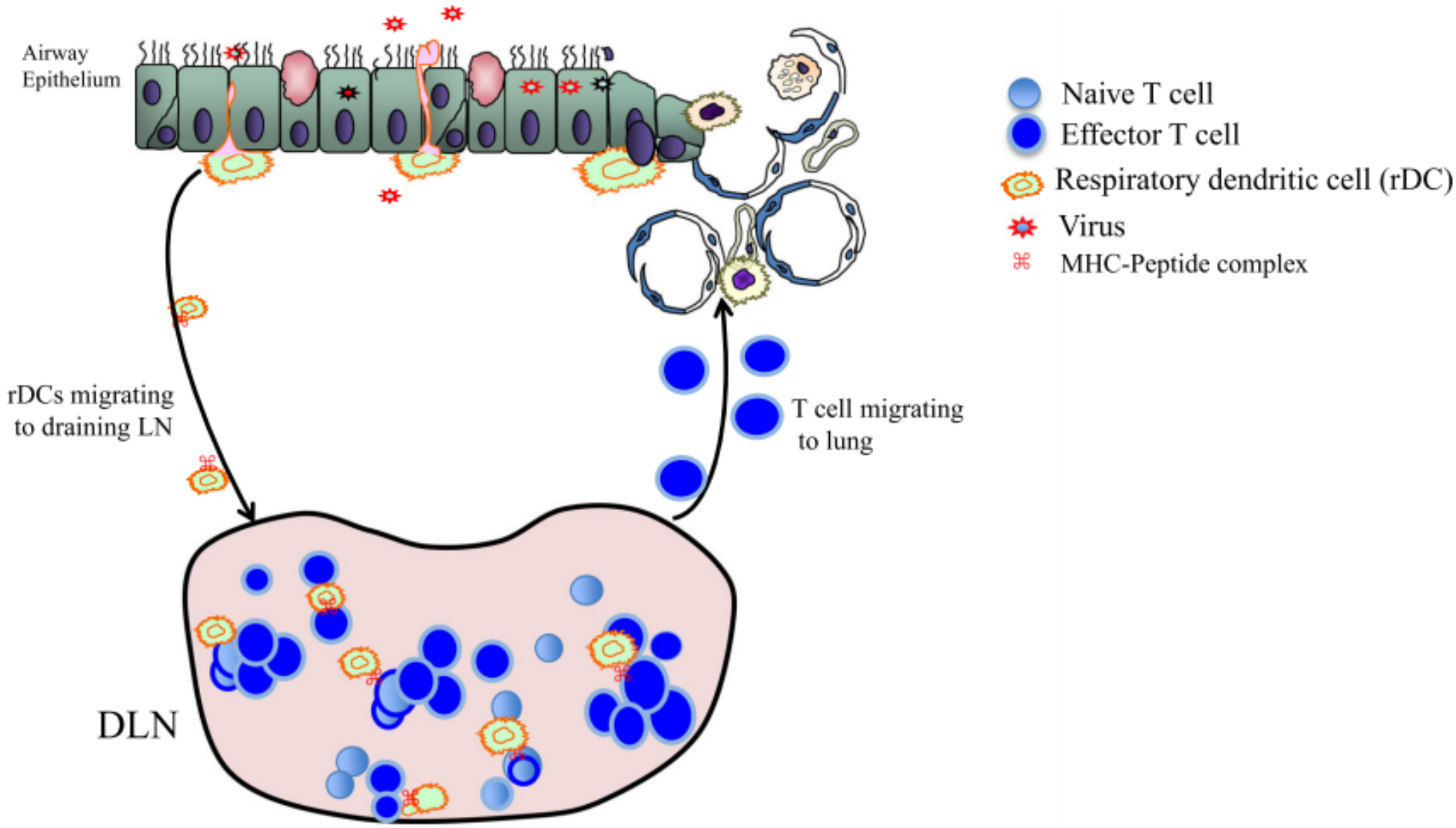
Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy

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

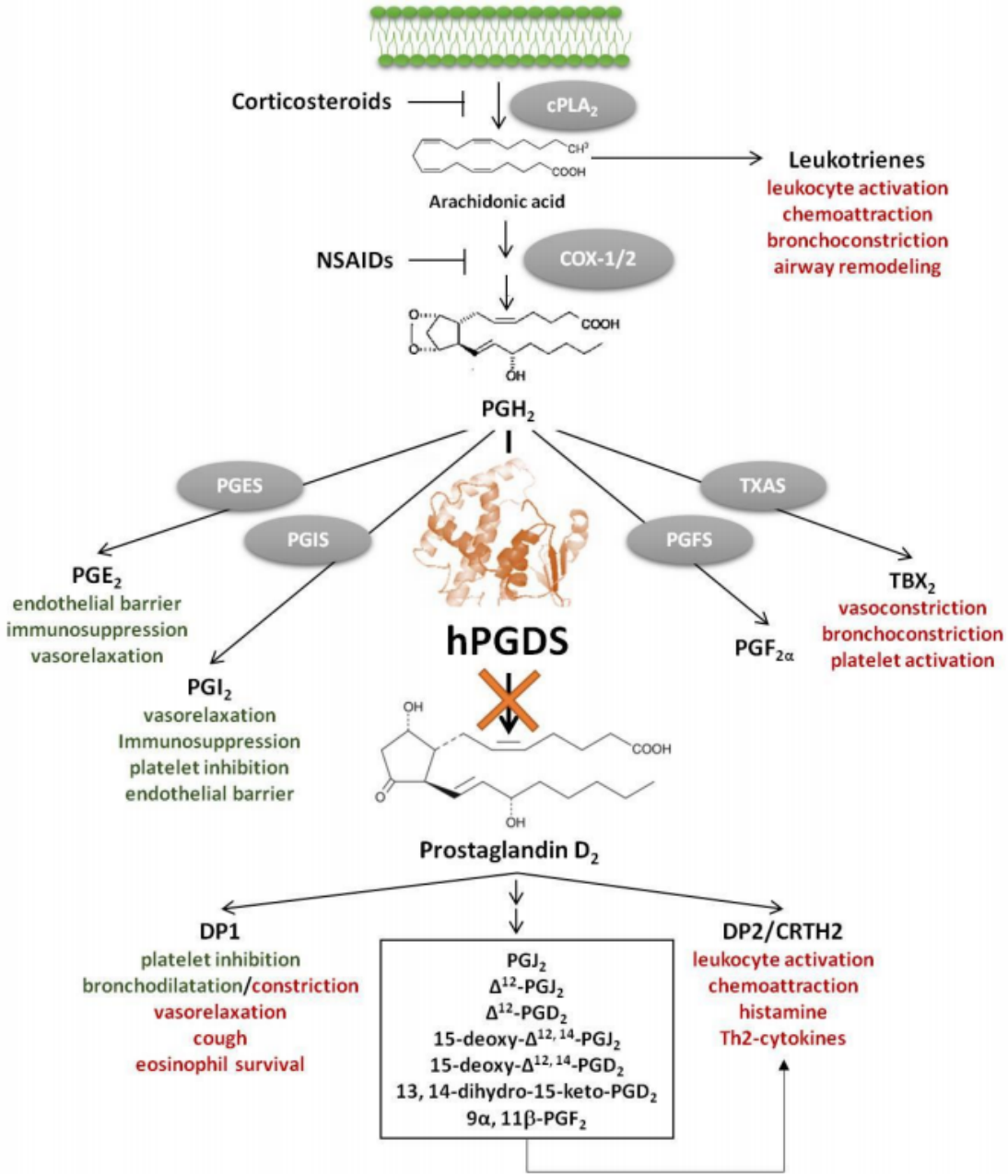
	Italy as of March 17, 2020		China as of February 11, 2020	
	No. of deaths (% of total)	Case-fatality rate, %[b]	No. of deaths (% of total)	Case-fatality rate, %[b]
All	1625 (100)	7.2	1023 (100)	2.3
Age groups, y				
0-9	0	0	0	0
10-19	0	0	1 (0.1)	0.2
20-29	0	0	7 (0.7)	0.2
30-39	4 (0.3)	0.3	18 (1.8)	0.2
40-49	10 (0.6)	0.4	38 (3.7)	0.4
50-59	43 (2.7)	1.0	130 (12.7)	1.3
60-69	139 (8.6)	3.5	309 (30.2)	3.6
70-79	578 (35.6)	12.8	312 (30.5)	8.0
≥80	850 (52.3)	20.2	208 (20.3)	14.8

Graziano Onder, et al. JAMA Published online March 23, 2020

T cell-mediated immune response to respiratory coronaviruses

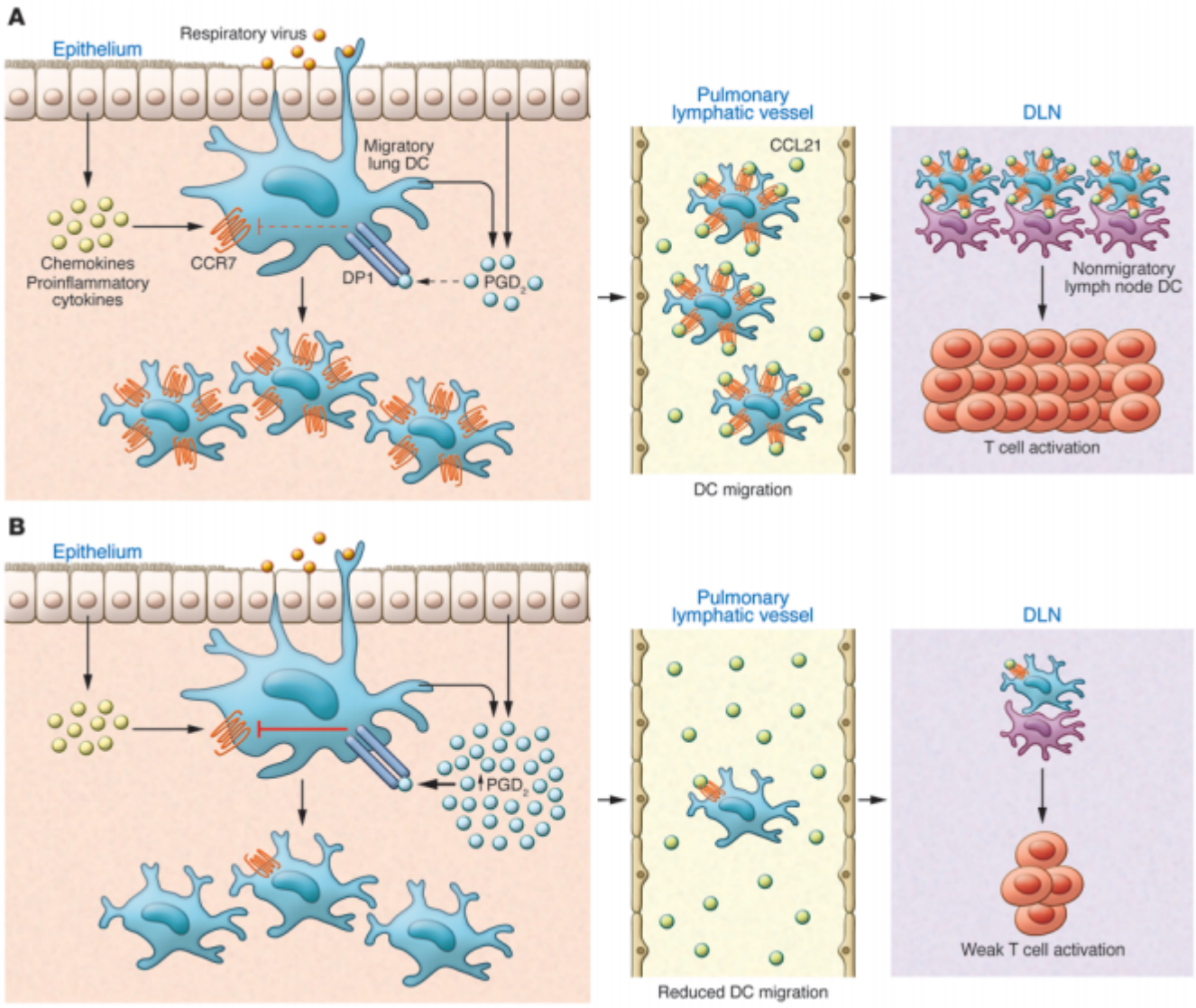


R. Channappanavar, J. Zhao, S. Perlman. Immunol Res (2014) 59:118–128. DOI 10.1007/s12026-014-8534-z



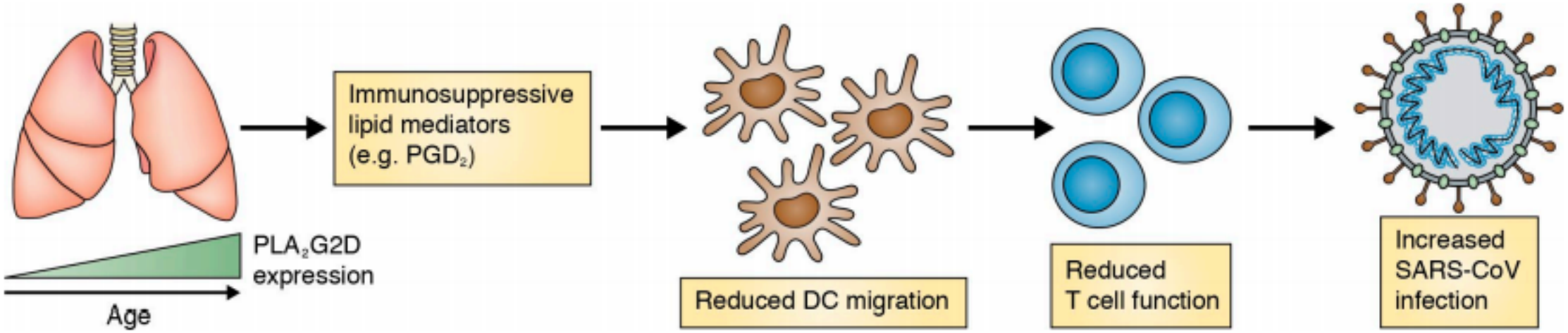
Sonja Rittchen and Akos Heinemann. Cells 2019, 8, 619; doi:10.3390/cells8060619

Slowing down with age: lung DCs do it too



Thomas J. Braciale, Taeg S. KimJ Clin Invest. 2011; 121(12):4636–4639. doi:10.1172/JCI61367.

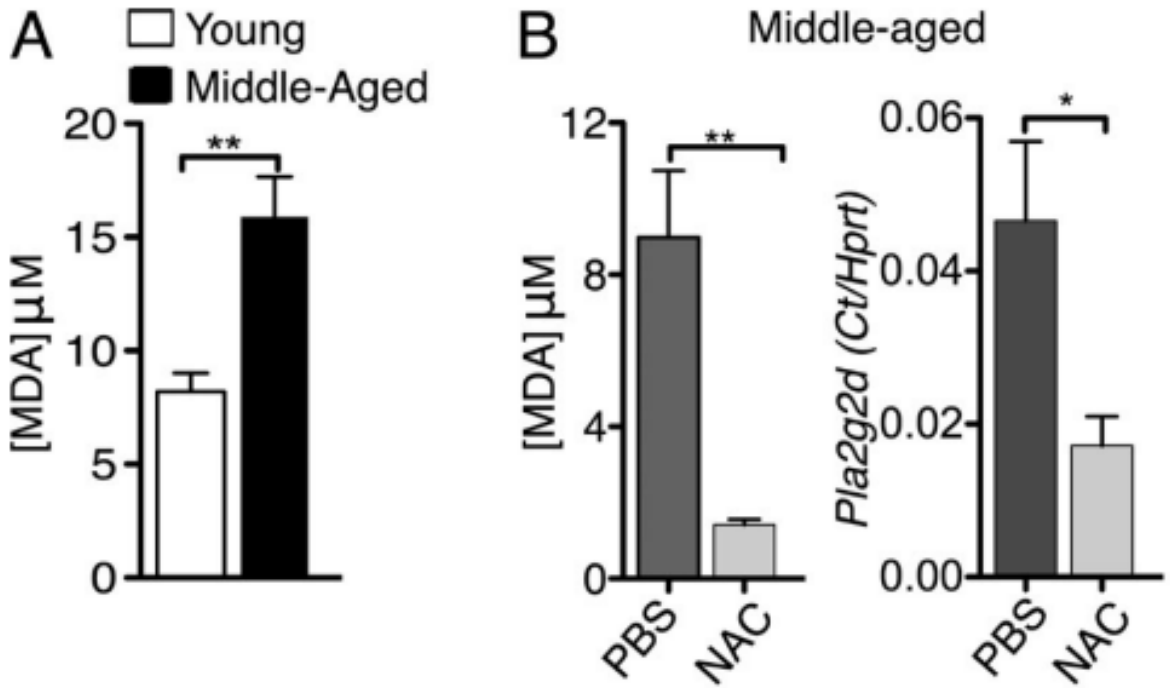
A phospholipase linkAGE to SARS susceptibility



Aging lungs have higher PLA_2G2D 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.

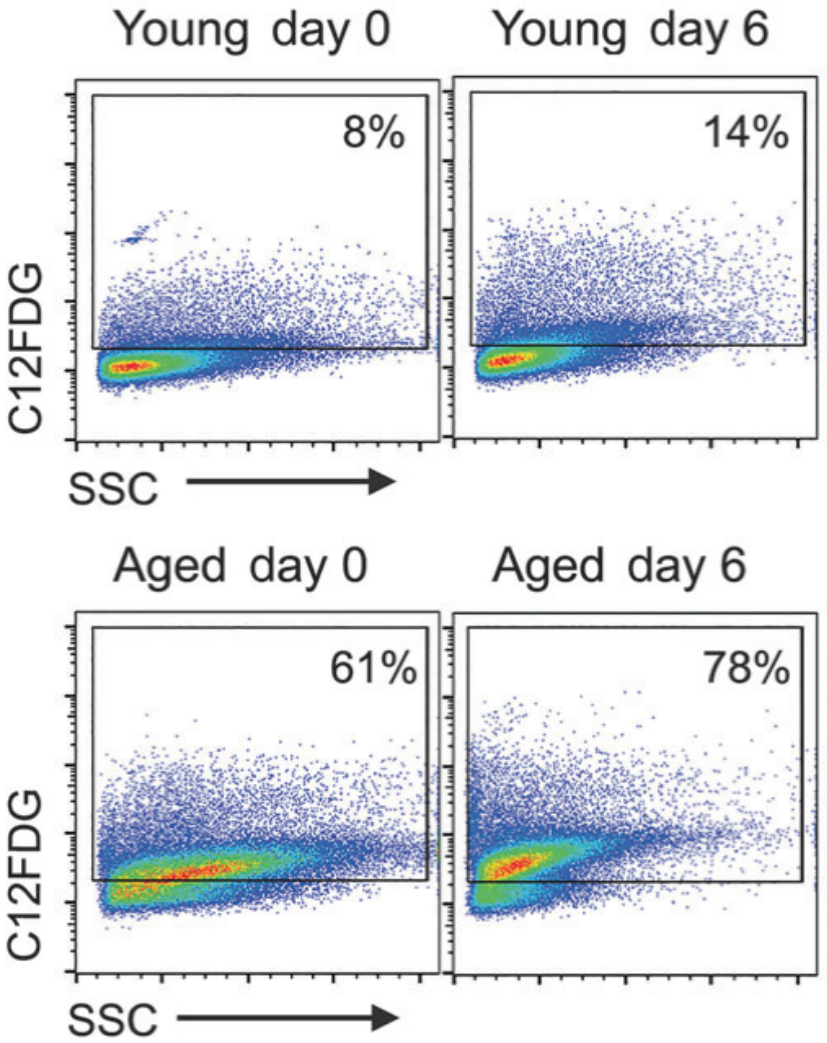
Vijay, R., et al. 2015. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.20150632

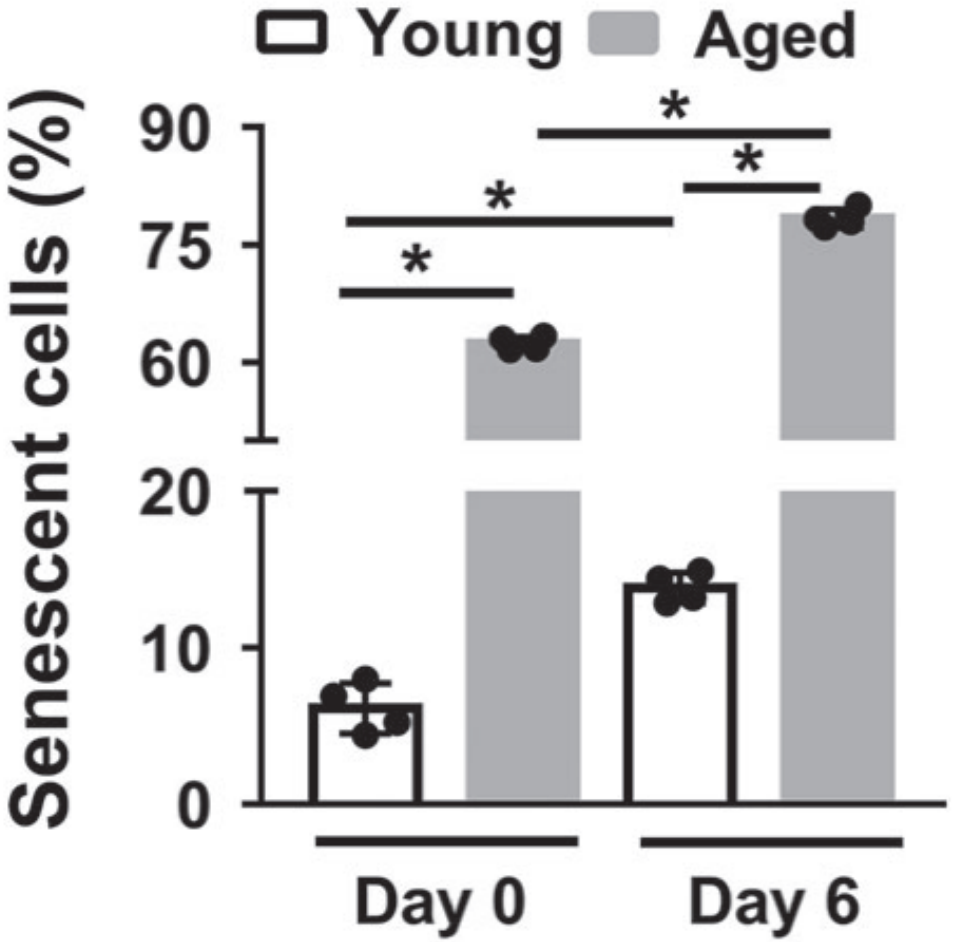
John W. Schoggins, University of Texas Southwestern Medical Center: john.schoggins@utsouthwestern.edu



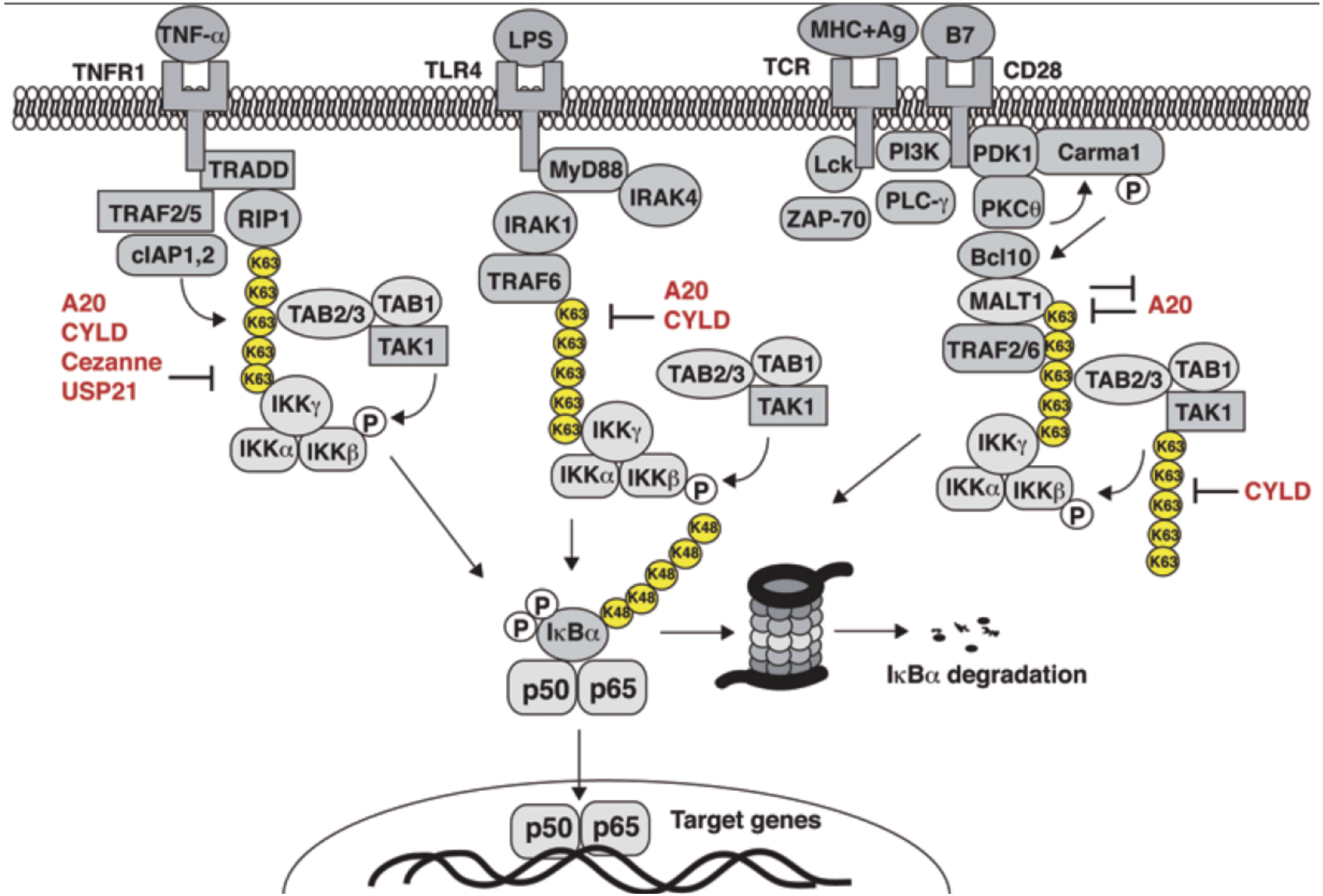
R. Vijay, et al. J. Exp. Med. 2015 Vol. 212 No. 11 1851–1868

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



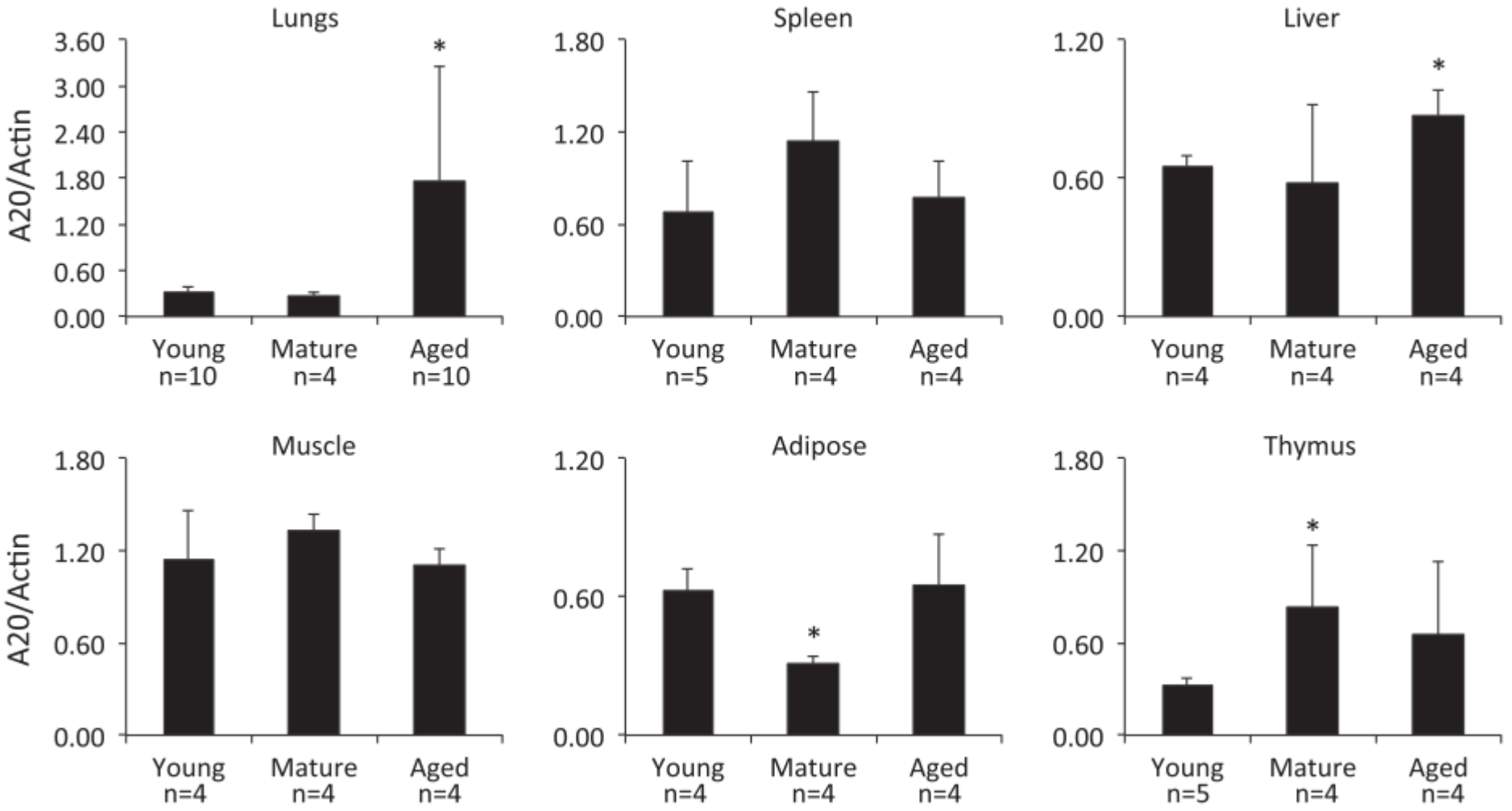


Upasana Kulkarni, et al. Mucosal Immunology (2019) 12:545–554



Edward W Harhaj, Vishva M Dixit. Cell Research (2011) 21:22-39

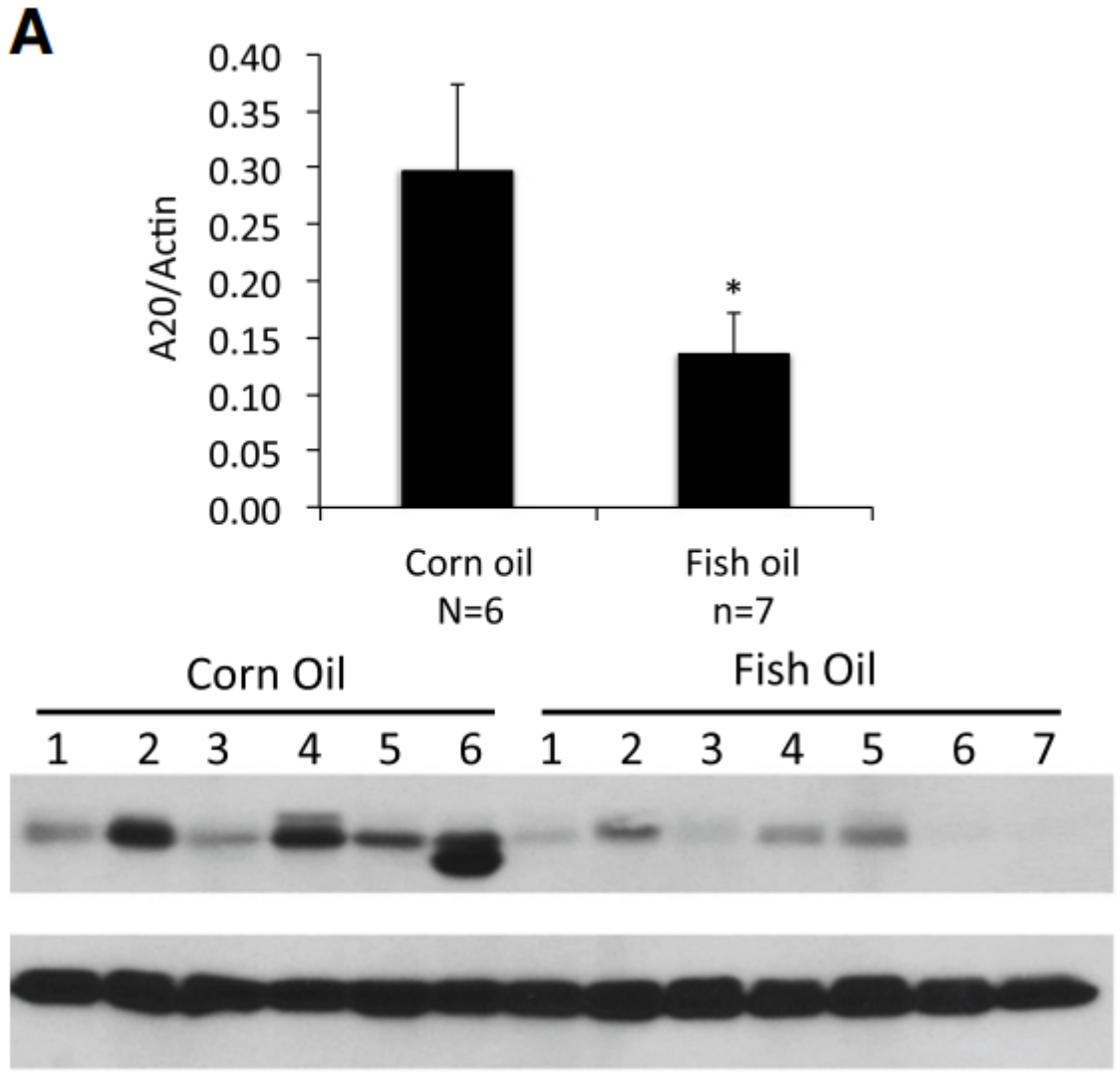
A20 is elevated in some but not all aged tissues

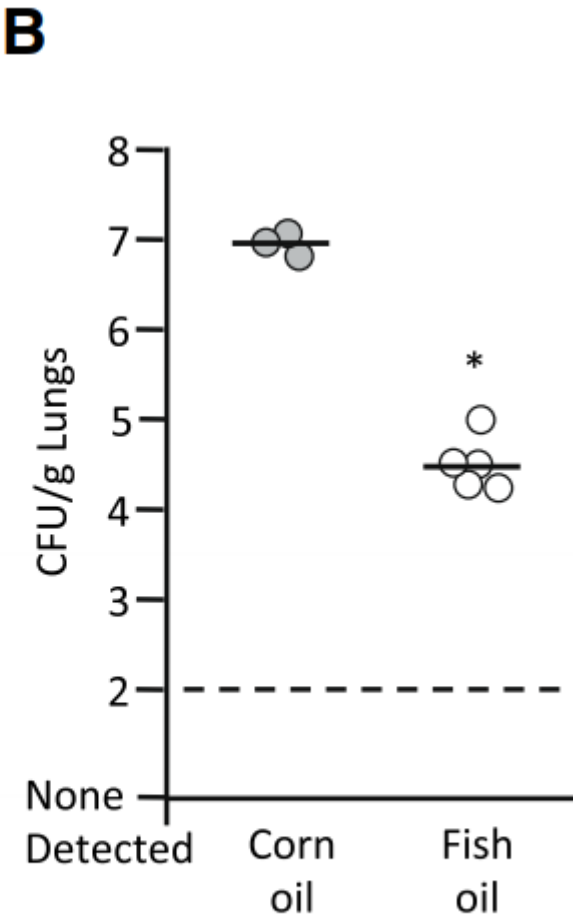


C57BL/6 mice at age 4, 10, 21 mo.

Cecilia Hinojosa, et al. Experimental Gerontology 54, 58-66, 2014

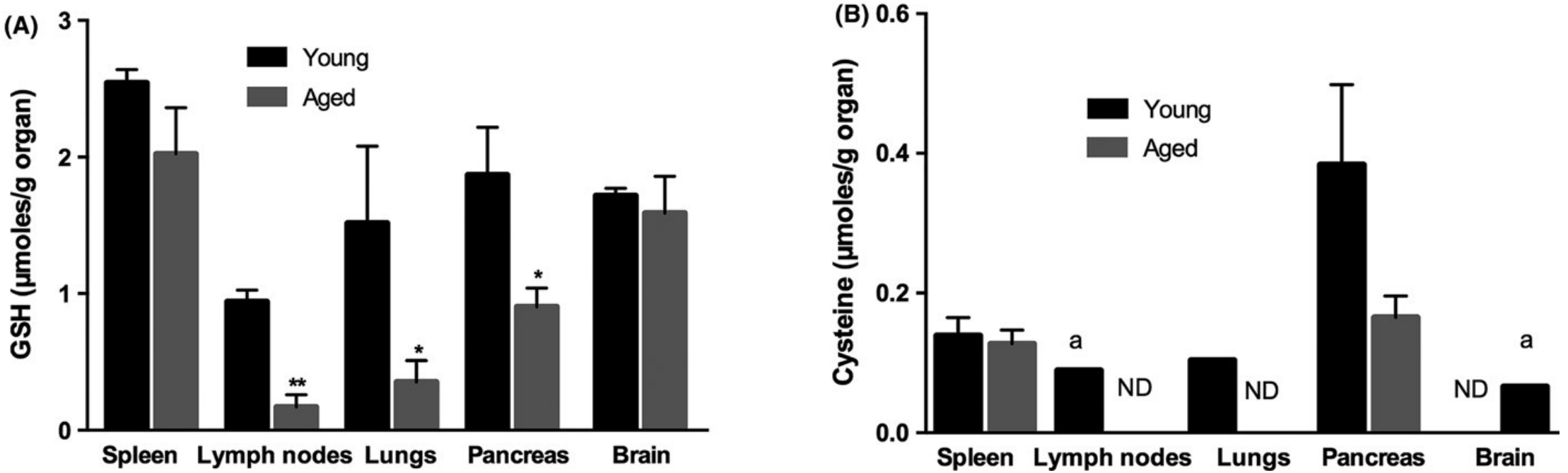
Fish oil lowers A20 levels and improves resistance to bacterial infection





Cecilia Hinojosa, et al. Experimental Gerontology 54, 58-66, 2014

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



D. Amatore, et al. FASEB BioAdvances. 2019;1:296–305

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

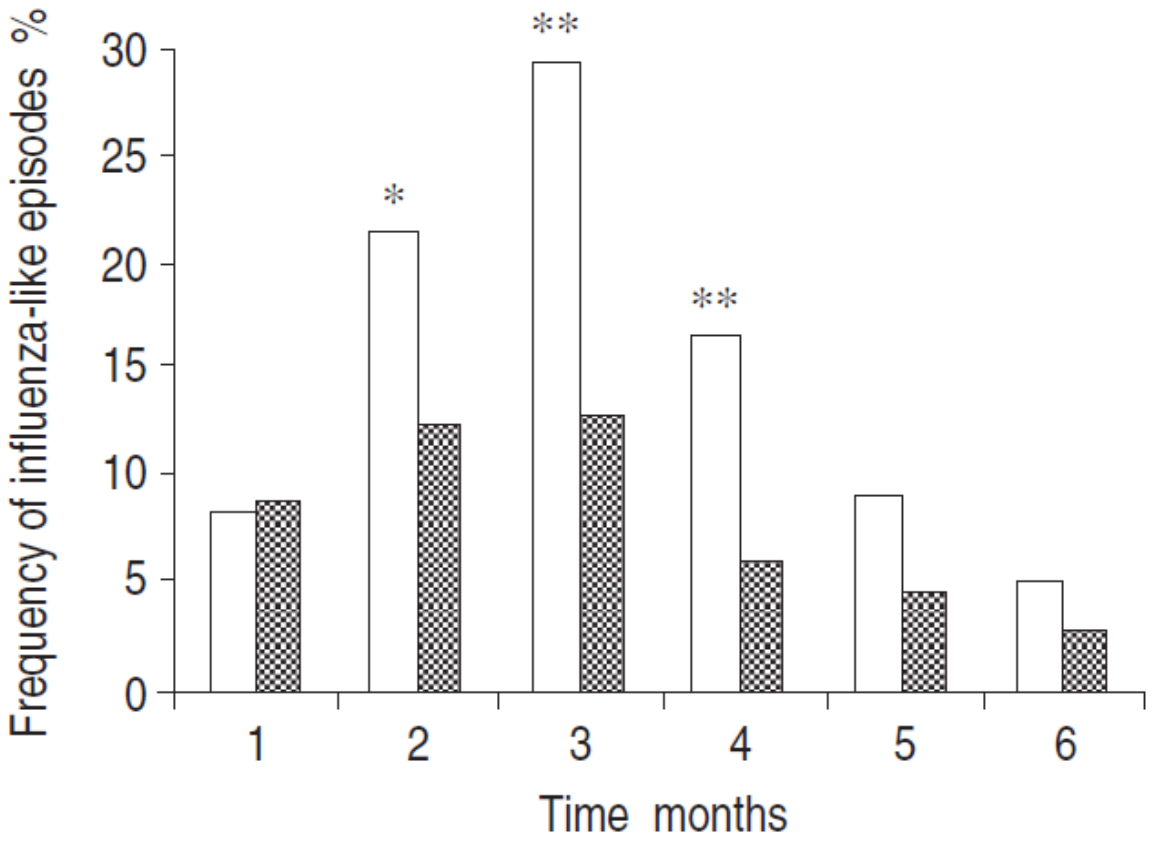


Table 3. – Distribution of subjects as related to seroconversion towards A/H_1N_1 Singapore 6/86 influenza virus and to the presence or absence of symptomatology

Subjects	Treatment			
	Placebo		NAC	
	n	%	n	%
Seroconversion	29/122	(24)	36/126	(29)
Symptomatic episodes	23/29	(79)	9/36	(25)+
No symptomatic episodes	6/29	(21)	27/36	(75)+
No seroconversion	93/122	(76)	90/126	(71)
Symptomatic episodes	39/93	(42)	28/90	(31)
No symptomatic episodes	54/93	(58)	62/90	(69)

NAC: N-acetylcysteine. +: significantly different from the placebo group ($p<0.0001$), as assessed by Chi-squared analysis.

D. De Flora, et al. Eur Respir J 1997; 10: 1535–1541 DOI: 10.1183/09031936.97.10071535

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).