




Virulence of the H1N1 2009 pandemic influenza virus

Prasert Auewarakul

Faculty of Medicine Siriraj Hospital

Mahidol University

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- The 2009 H1N1 pandemic is a mild virus?
 - It lacks most of the known genetic virulence determinants: HA cleavage site, PB1F2, NS1 PDZ domain, etc.
 - It induced low levels of proinflammatory cytokines from human cells in vitro.

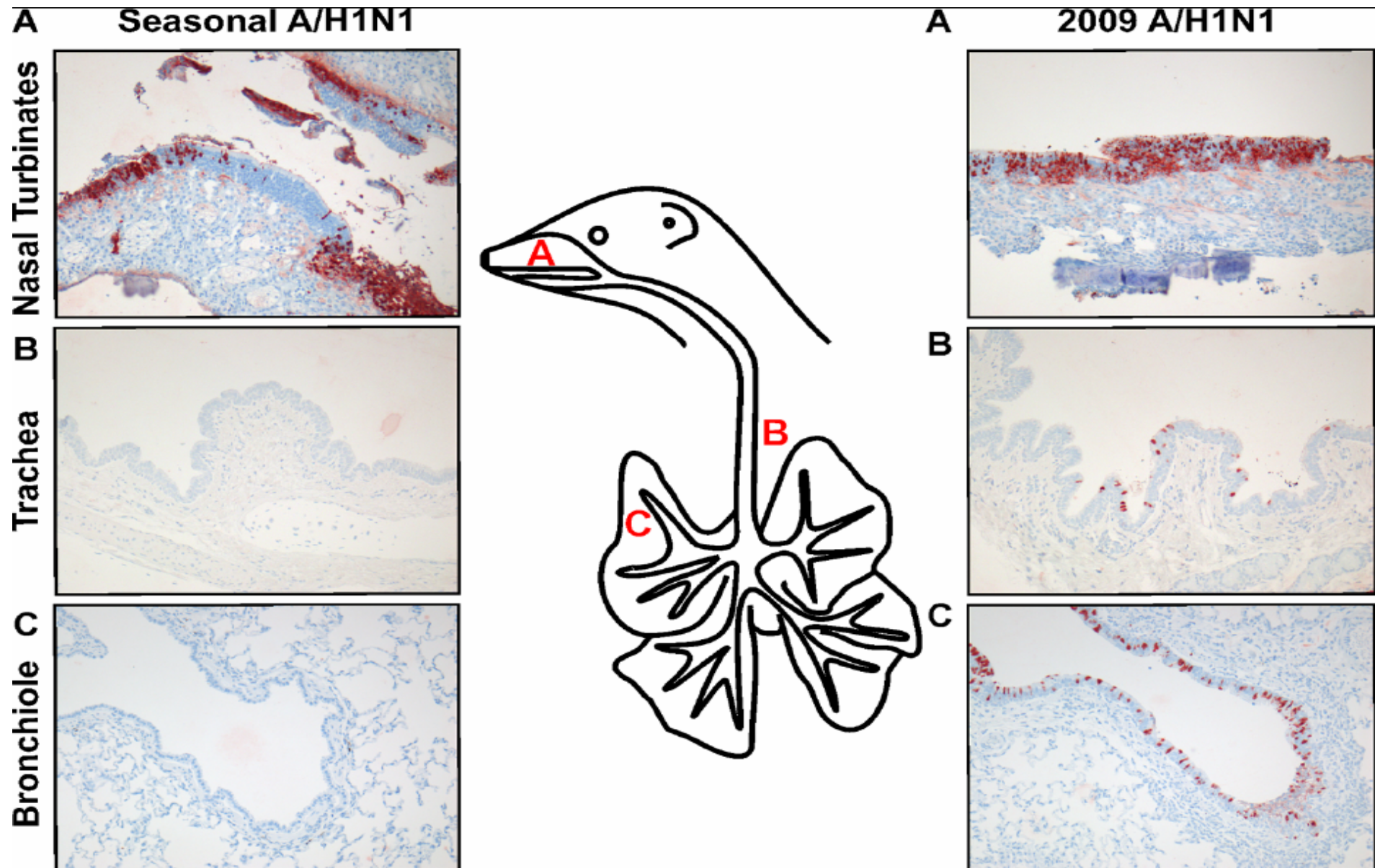
The 2009 pandemic was a mild one.

- Is the 2009 H1N1 pandemic a mild virus?
- It lacks most of the known genetic virulence determinants: HA cleavage site, PB1F2, NS1 PDZ domain, etc.
- It induced low levels of proinflammatory cytokines from human cells in vitro.

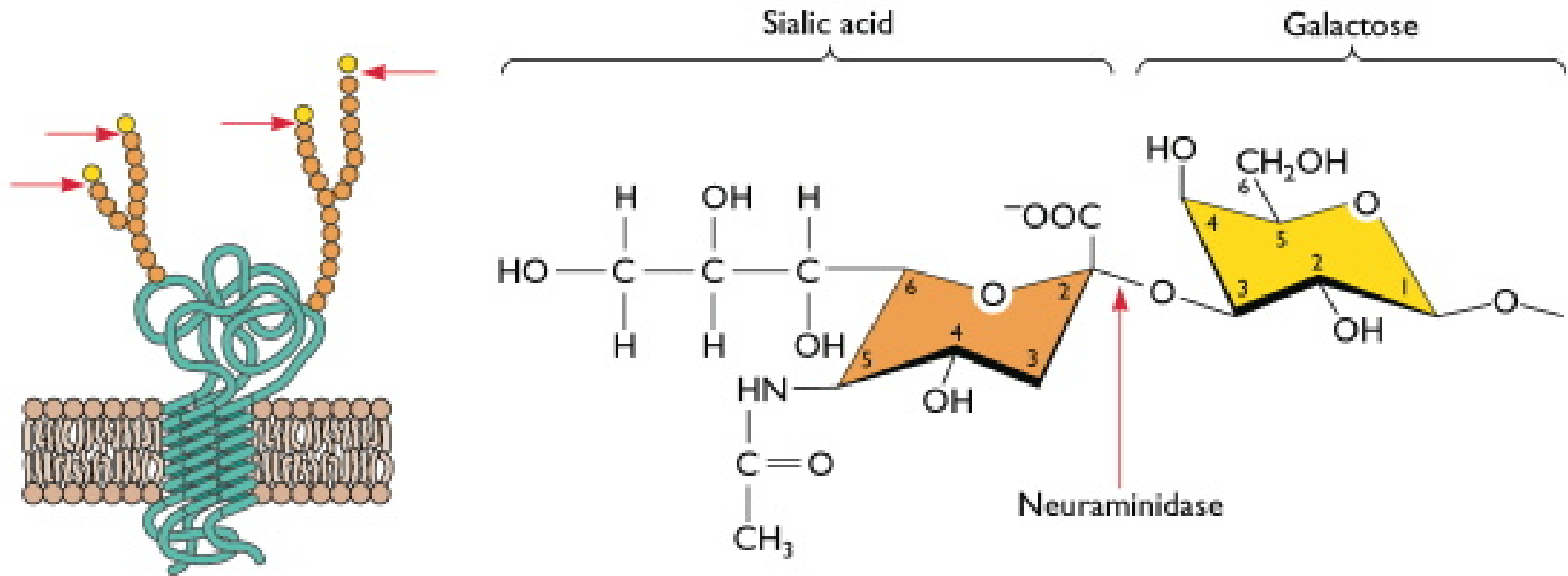
But

- Severe cases have been more often observed than in seasonal outbreaks.
- Studies comparing pandemic and seasonal influenza in the same outbreak showed increased mortality in pandemic influenza.
- Severe cases showed clinical picture quite similar to those caused by H5N1 avian influenza.

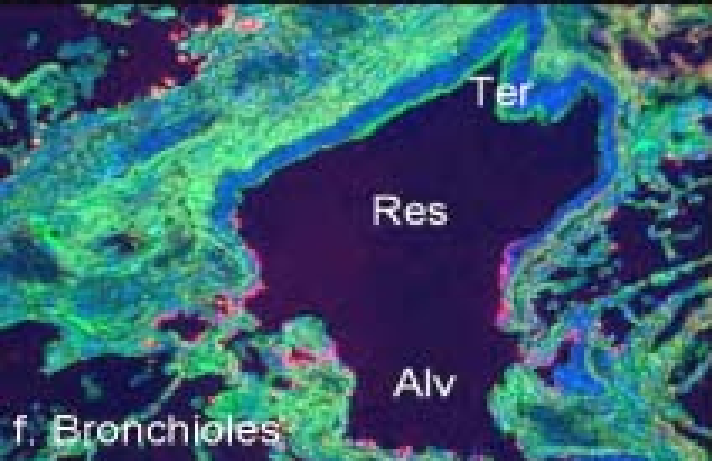
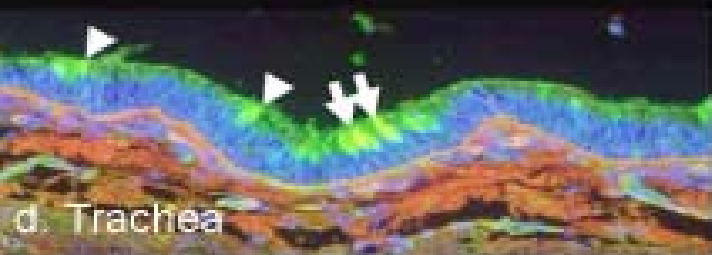
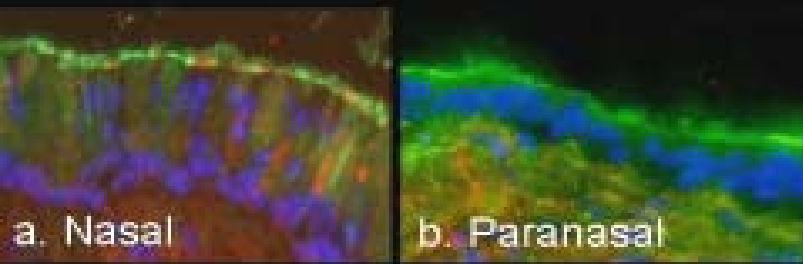
H1N1 pandemic influenza virus is more pneumotropic than seasonal influenza viruses.



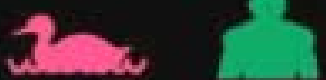
Sialic acid structure



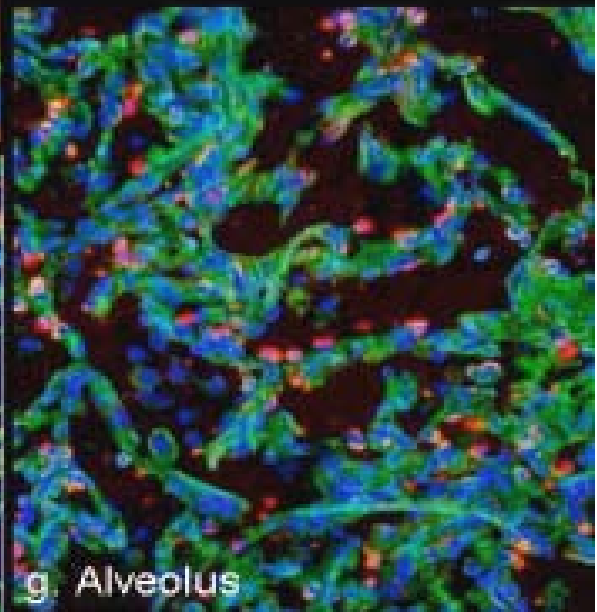
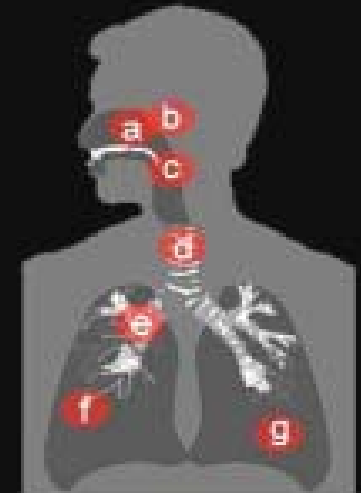
SA α 2,3Gal or SA α 2,6Gal

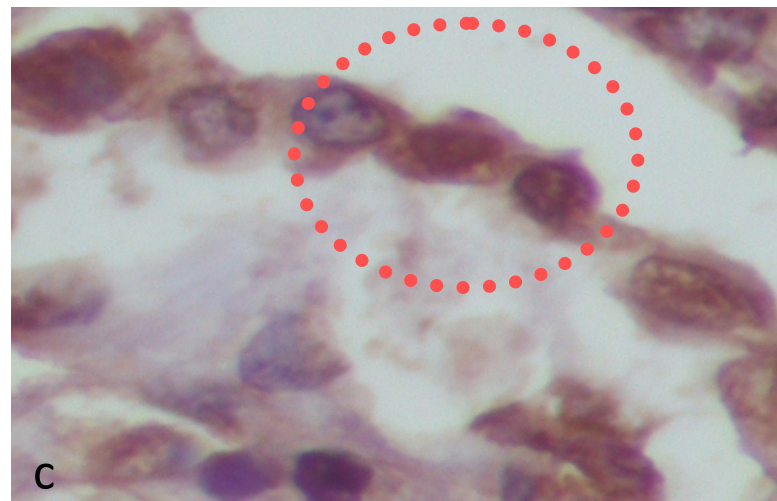
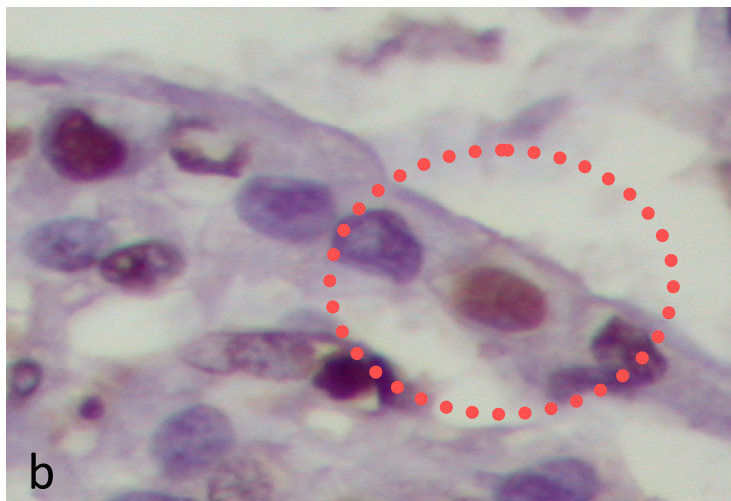
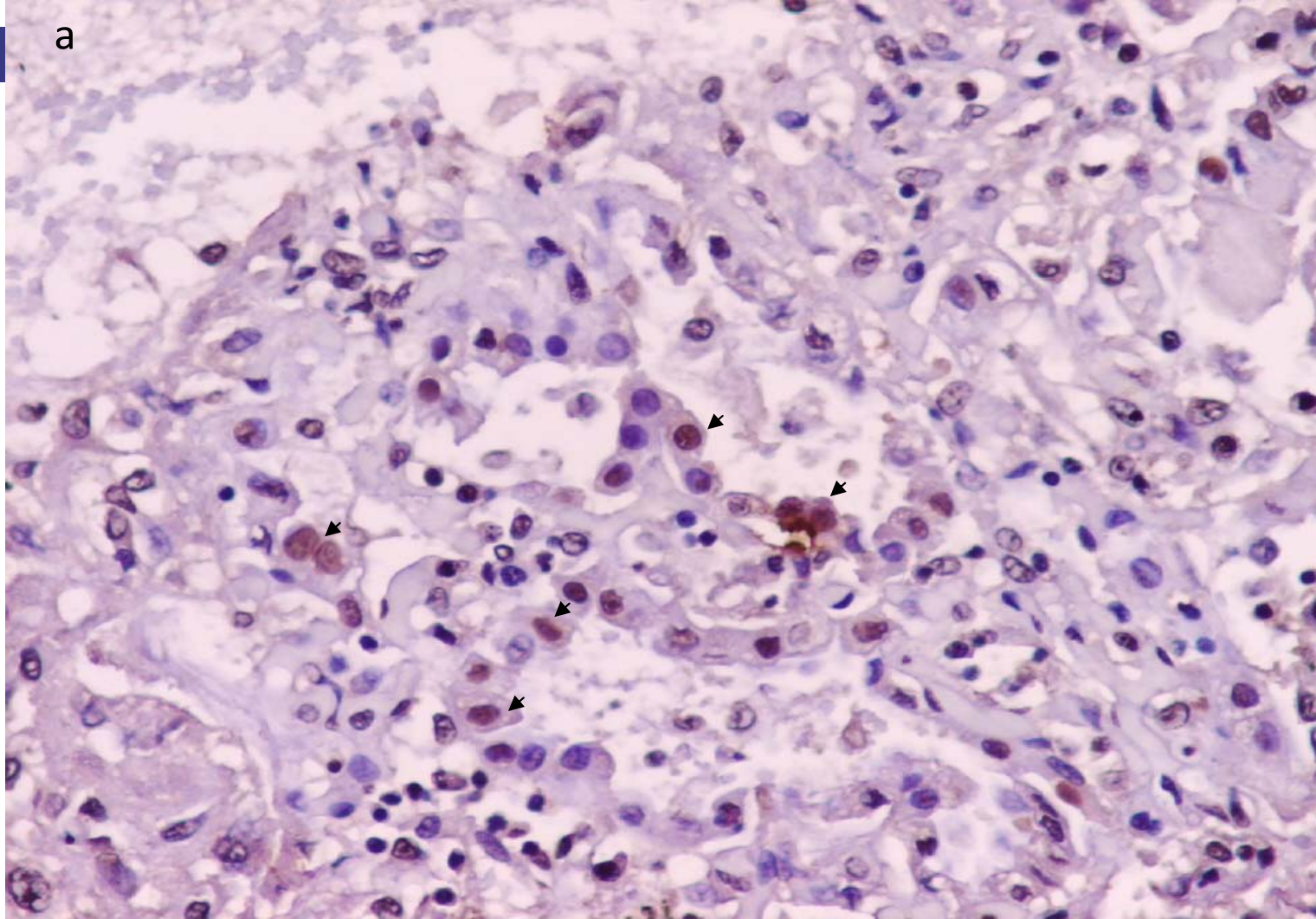


$\alpha 2-3$ $\alpha 2-6$

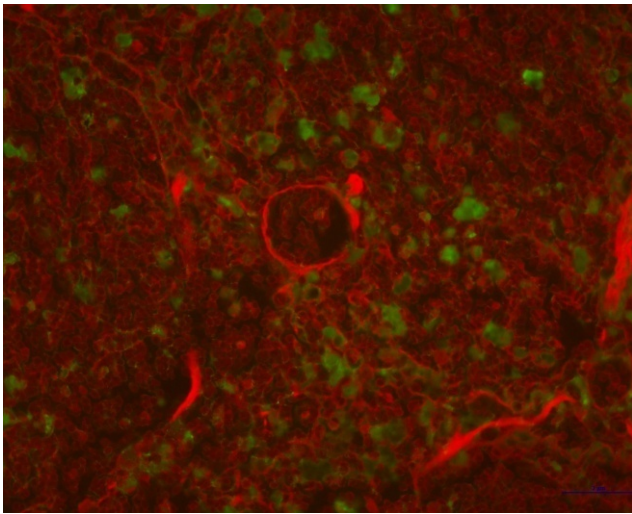


Swan icon (red) and human icon (green).

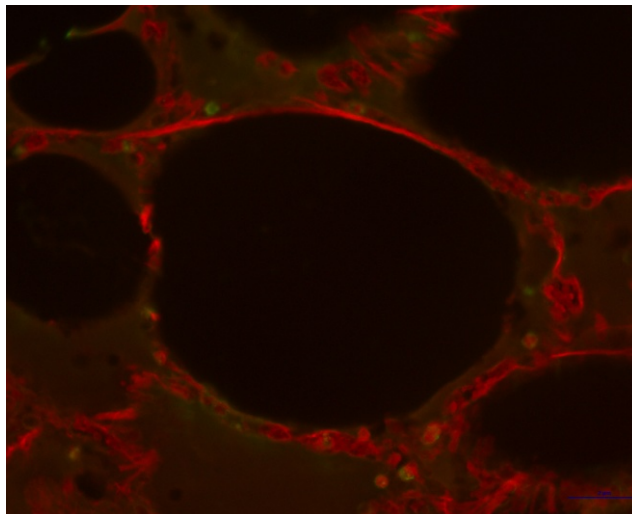




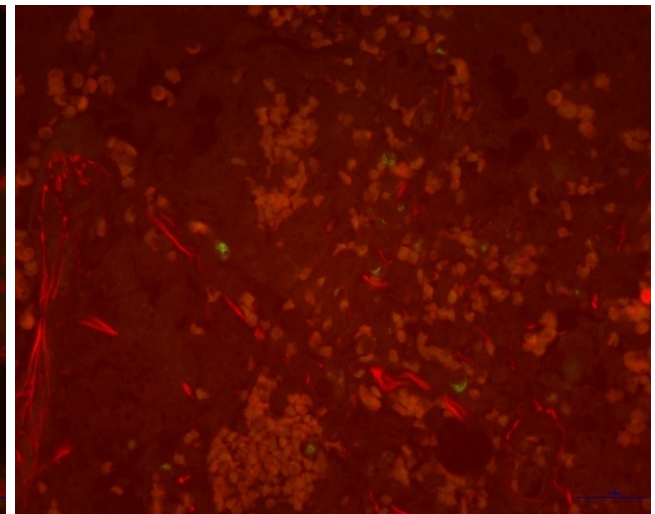
Lung of a H1N1
pandemic flu patient
with increased viral
receptor



Normal lung



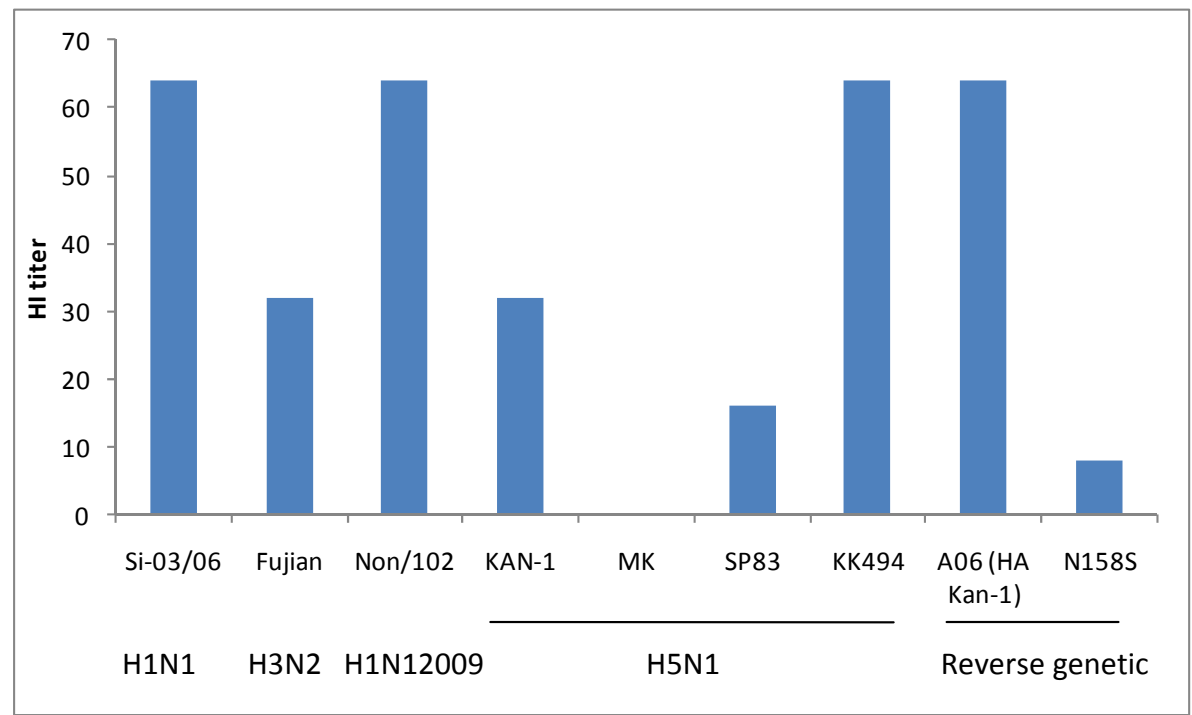
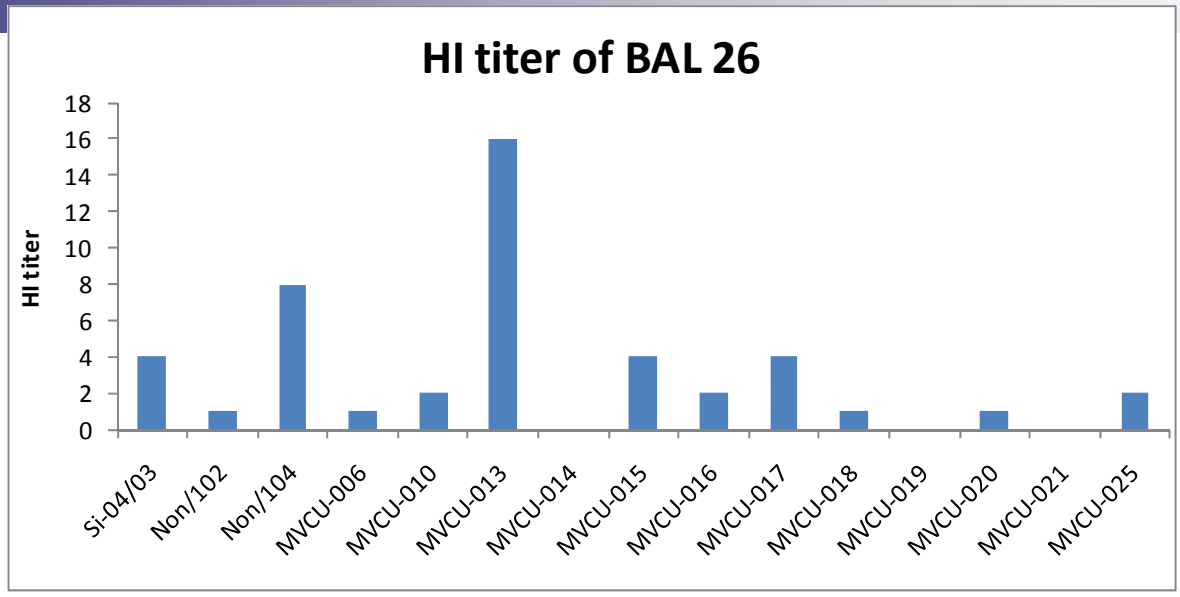
Lung of another
H1N1 pandemic flu
patient with normal
level of viral
receptor





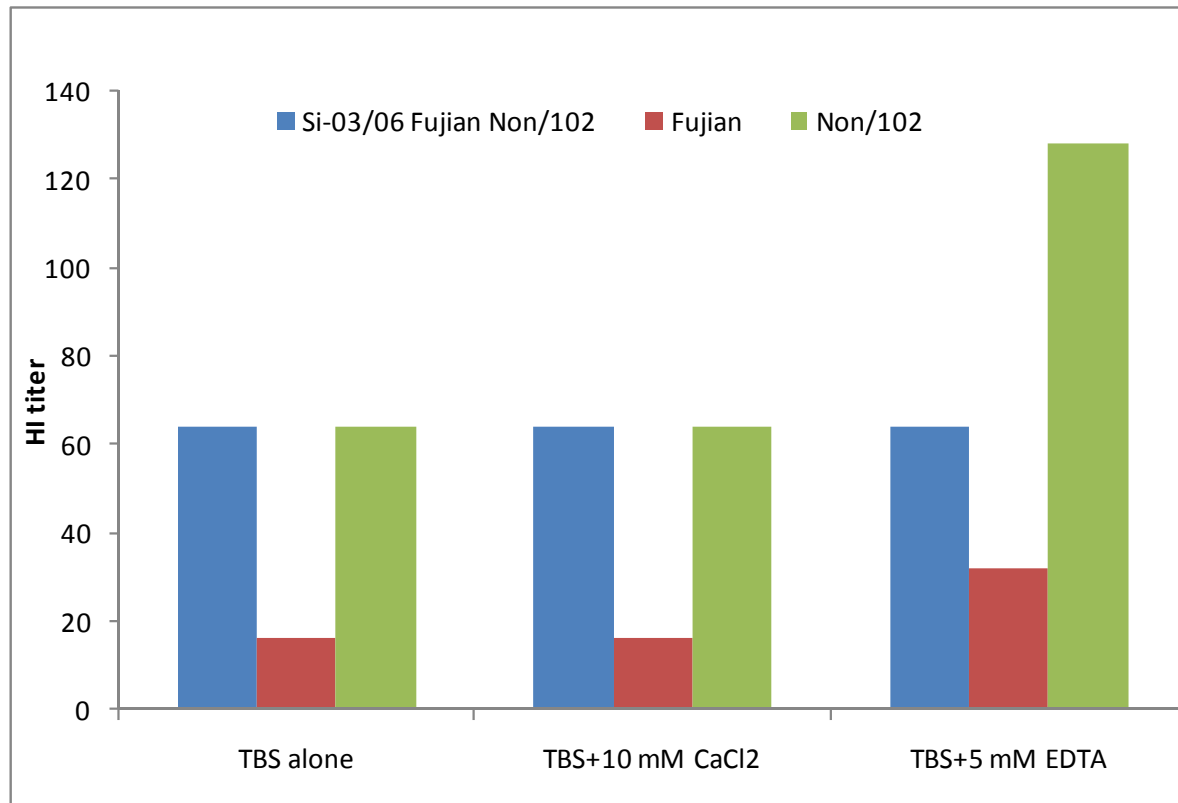
Innate defenses against influenza

- Interferon and cytokines
- Soluble factors: e.g.
 - Surfactant proteins (SPA and SPD)
 - Scavenger receptor gp340



BAL+RDE or normal saline → 37°C 18 hrs → 56°C 30 mins

Virus strain	Virus name	HI titer of pooled BAL (8+14+22)	
		BAL + normal saline	BAL+RD E
H1N1	Si-03/06	32	0
H3N2	Fujian	64	0
H1N1 2009	Non/102	32	0



BAL

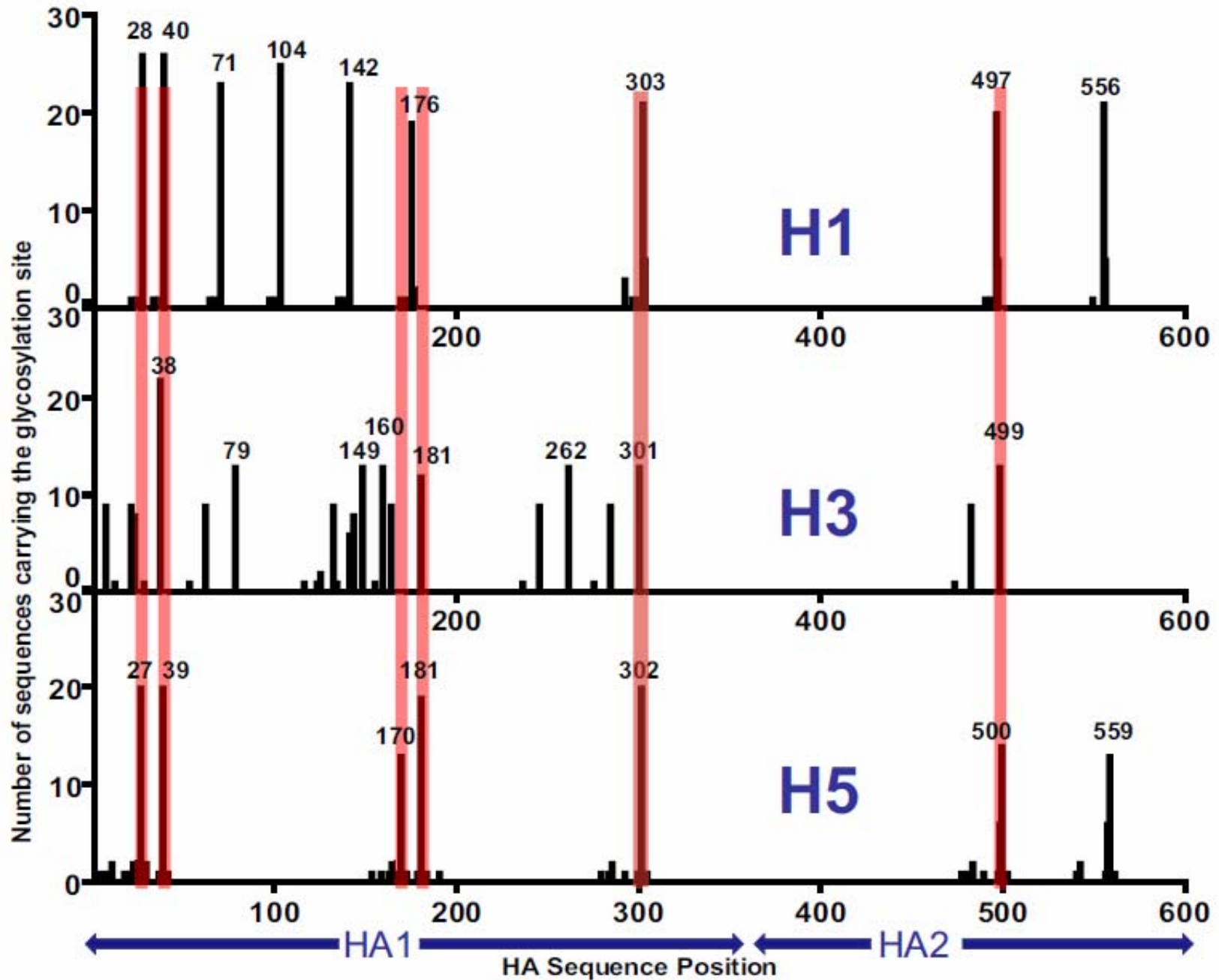
- α and γ inhibitors = sialic, e.g. gp340, SPA, serum α 2 microglobulin
- β inhibitors = lectins, e.g. SPD
- BAL seems to contain more α and γ ?
- H1N1 2009 is less sensitively to SPD and serum, and BAL γ inhibitor
- Determinant of this resistance?
- Effect on virulence?
- Variation? Risk groups?

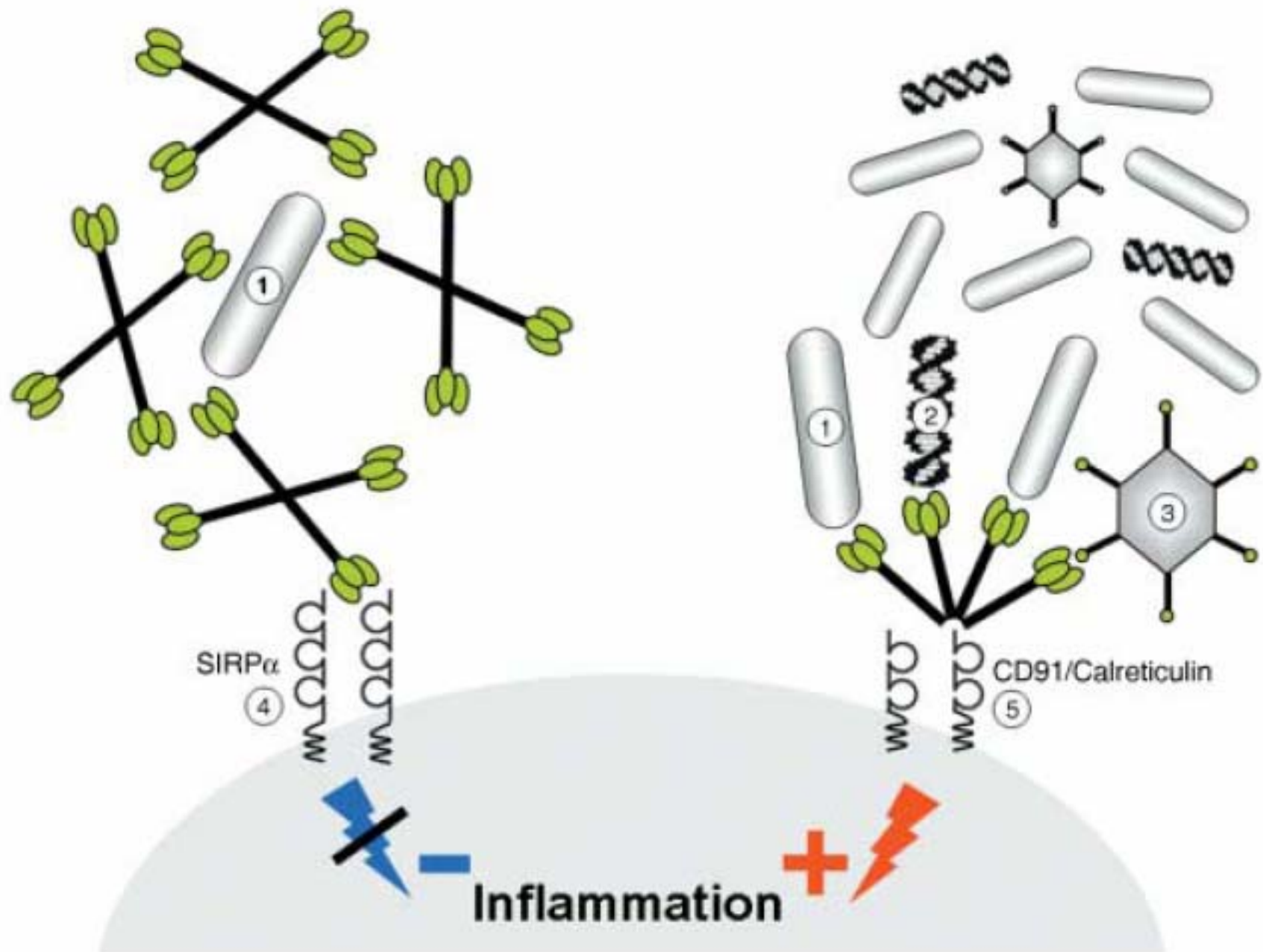


SPD

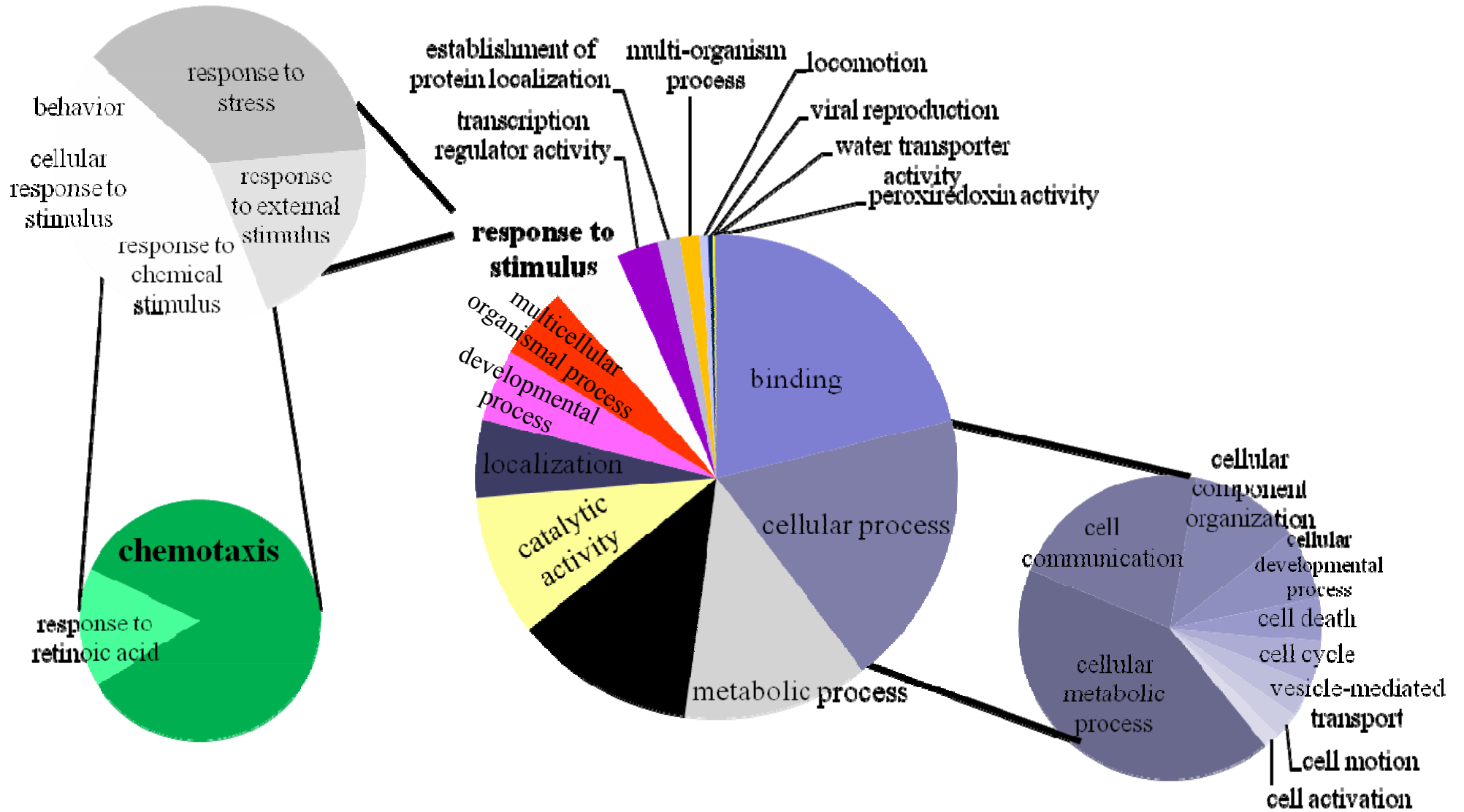
- Our data indicate that the main anti-viral activity in BAL was not contributed by SPD.
- A recent report has showed that the H1N1 2009 pandemic influenza was less sensitive to SPD due to their lack of glycosylation on HA (Job , 2010).

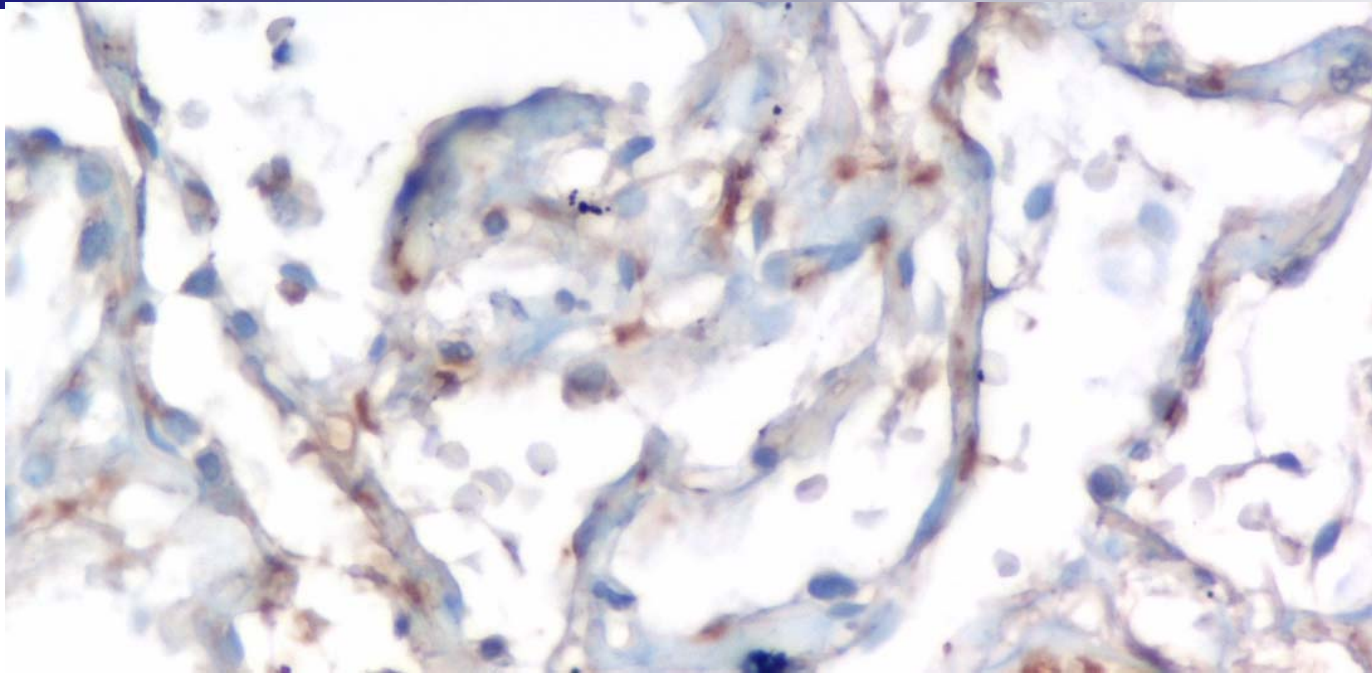
B





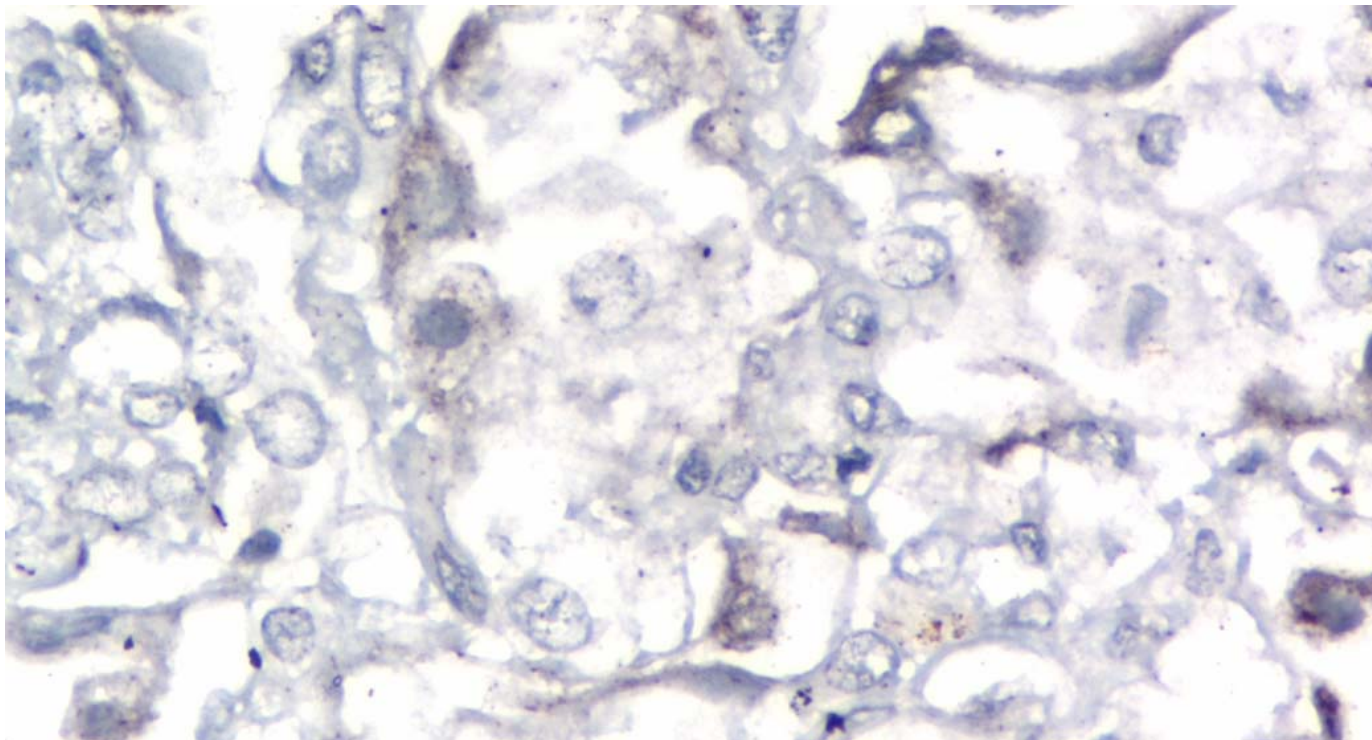
Down-regulated





SPD staining

Normal lung



H5N1-infected
Lung with ARDS



Conclusions

- H1N1 2009 pandemic influenza virus is less susceptible to soluble innate antiviral factors in the lung.
- The reduced sensitivity may explain the enhanced virulence of this virus.



Acknowledgements

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