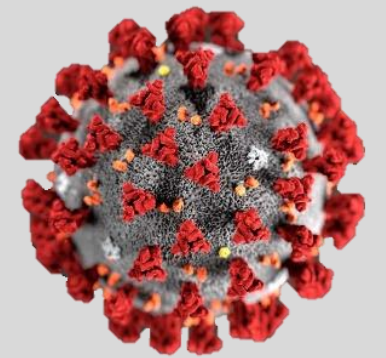
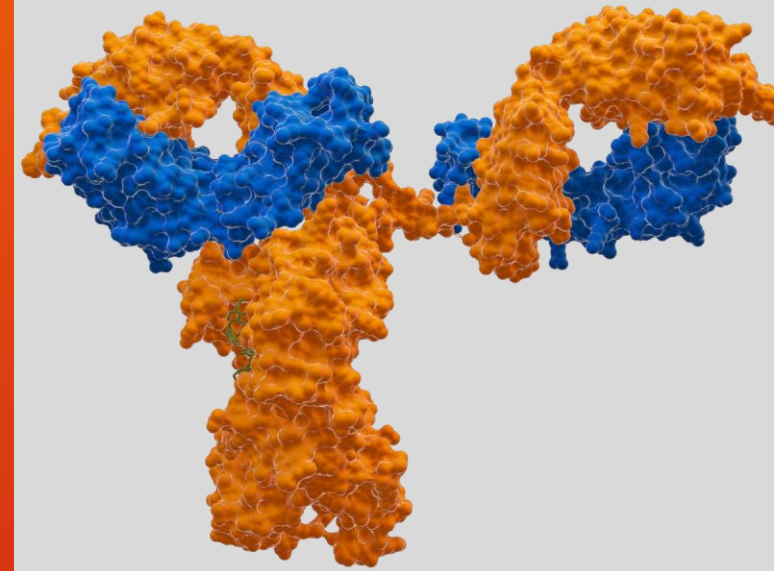


Glycosylering van IgG tegen bloed cellen

en envelopped virussen inclusief COVID-19:
een belangrijke kwalitatief parameter

Gestur Vidarsson, PhD.

Head Immunoglobulin Research
laboratory



Sanquin

Disclosures

Funders:



Projects discussed today

Sanquin
Bloedvoorziening



ZonMw

LSBR
Landsteiner Foundation for Blood Transfusion Research



Other projects

Genmab

argenx

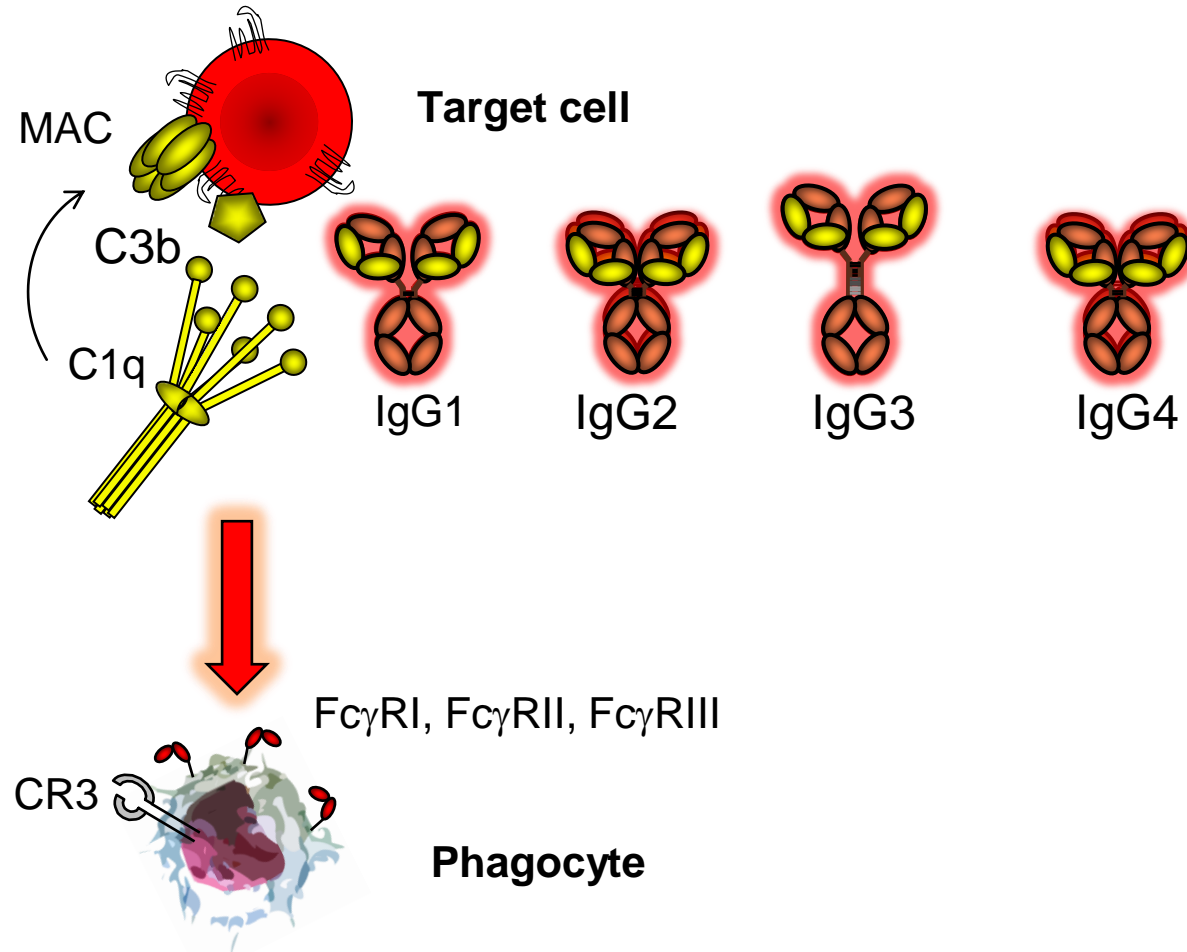


No other personal financial incentives

Humoral Immunity & memory

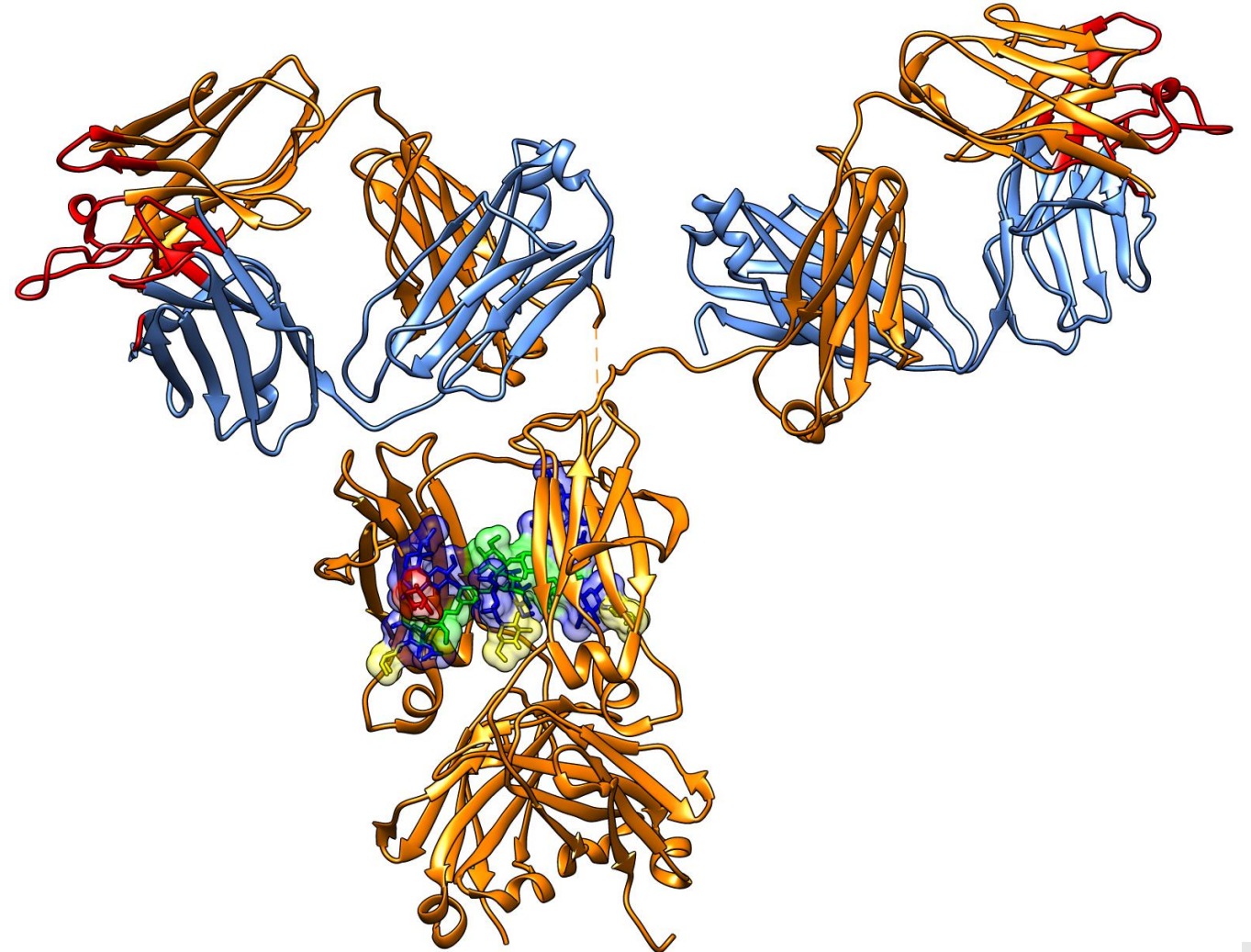
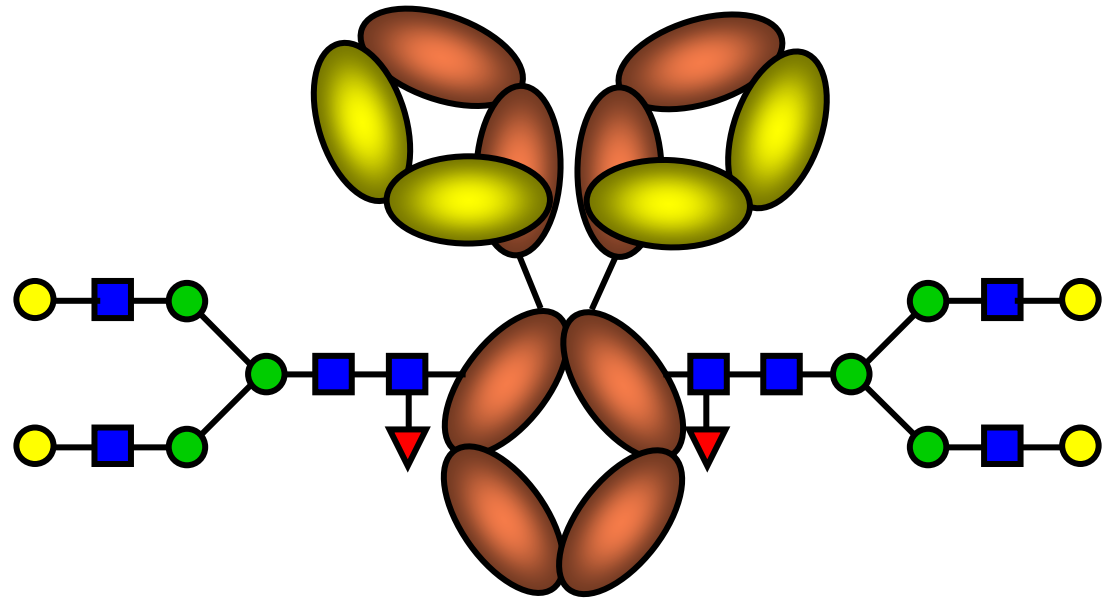
Memory

- 1) Specificity
- 2) Isotype/Subclass
- 3) *Sugar switches*

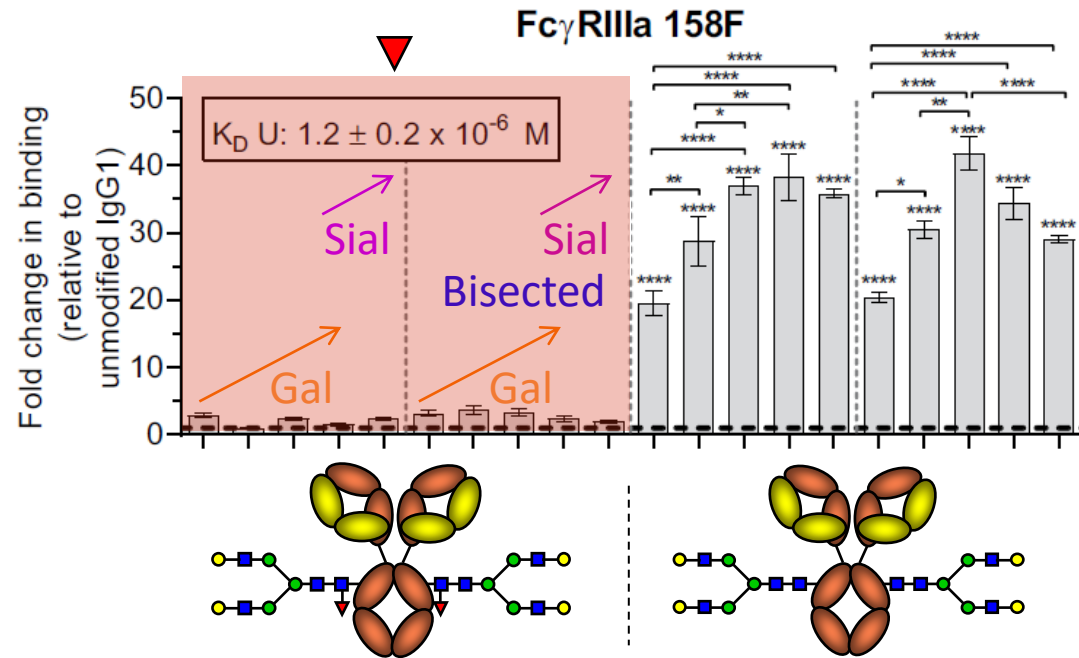


- A. What are these switches
- B. When are they turned ON/OFF
(types of target)
- C. How do they affect antibody biology
and human Immunology in health and disease

Fucosylation as molecular switch



Afucosylated IgG has elevated binding and activity for the human FcγRIII family



- Even larger (all- nothing) FcγRIII-mediated differences in enhanced **ADCC** and **phagocytosis** activity by **NK, Monocytes, Macrophages and Neutrophils**

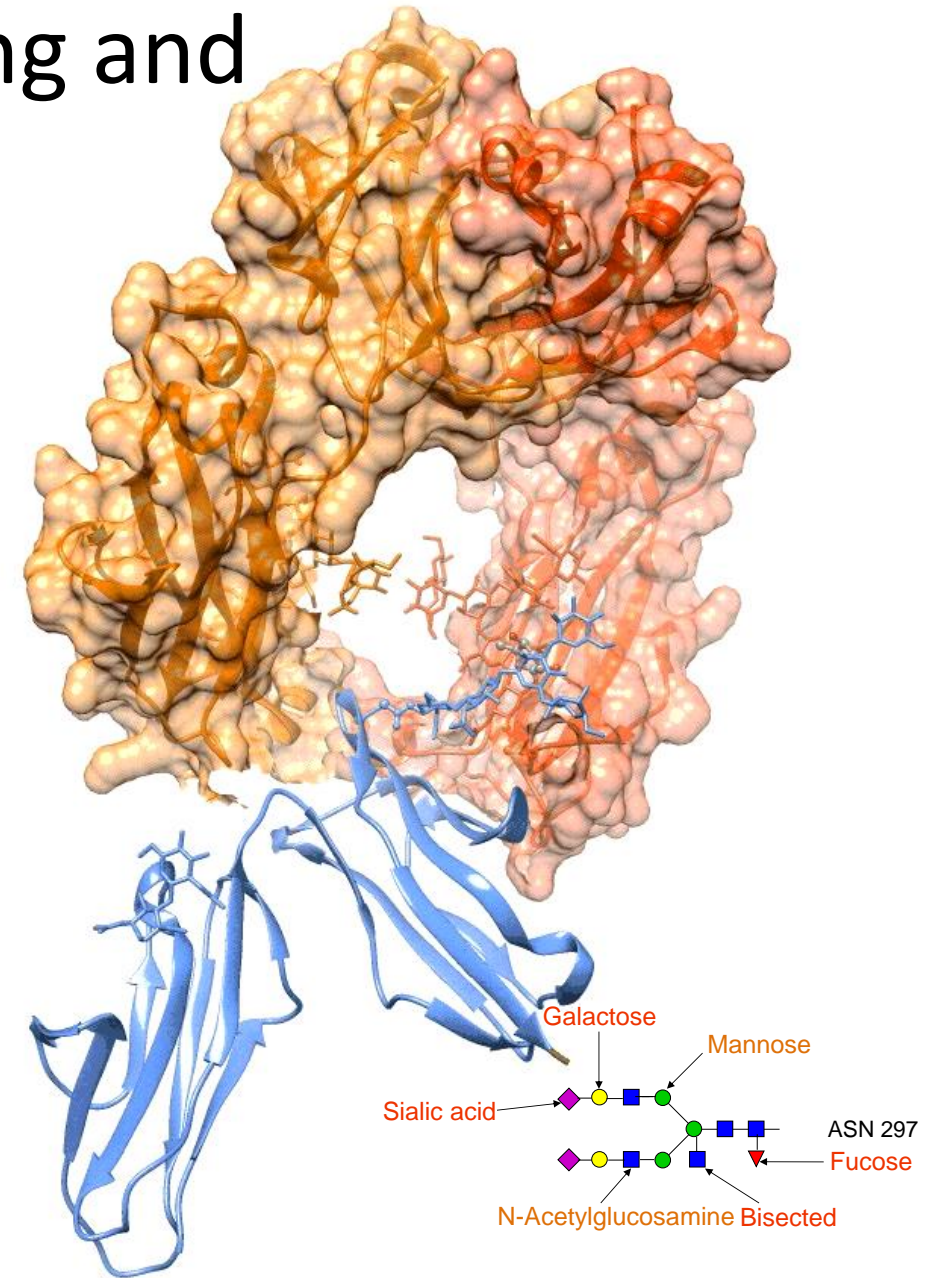
Dekkers et al *Frontiers in Immunology* 2017;8:877

Temming & de Taeye et al *Journal of Immunology* 2019;203(12):3126-3135

Bruggeman et al *Journal of Immunology* 2017;199(1):204-211

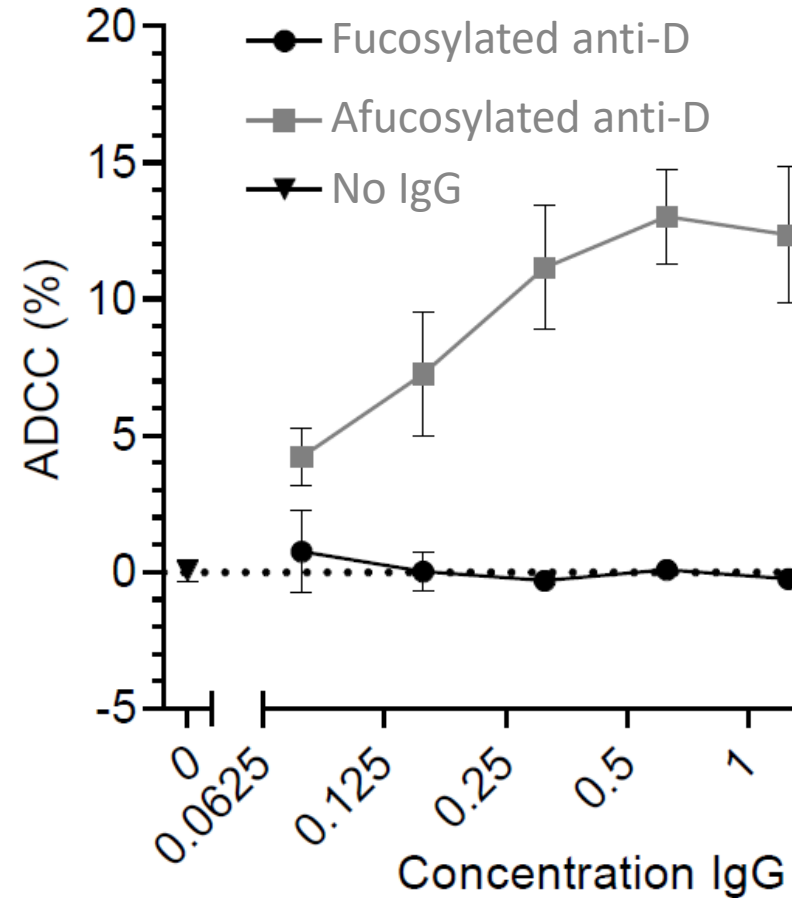
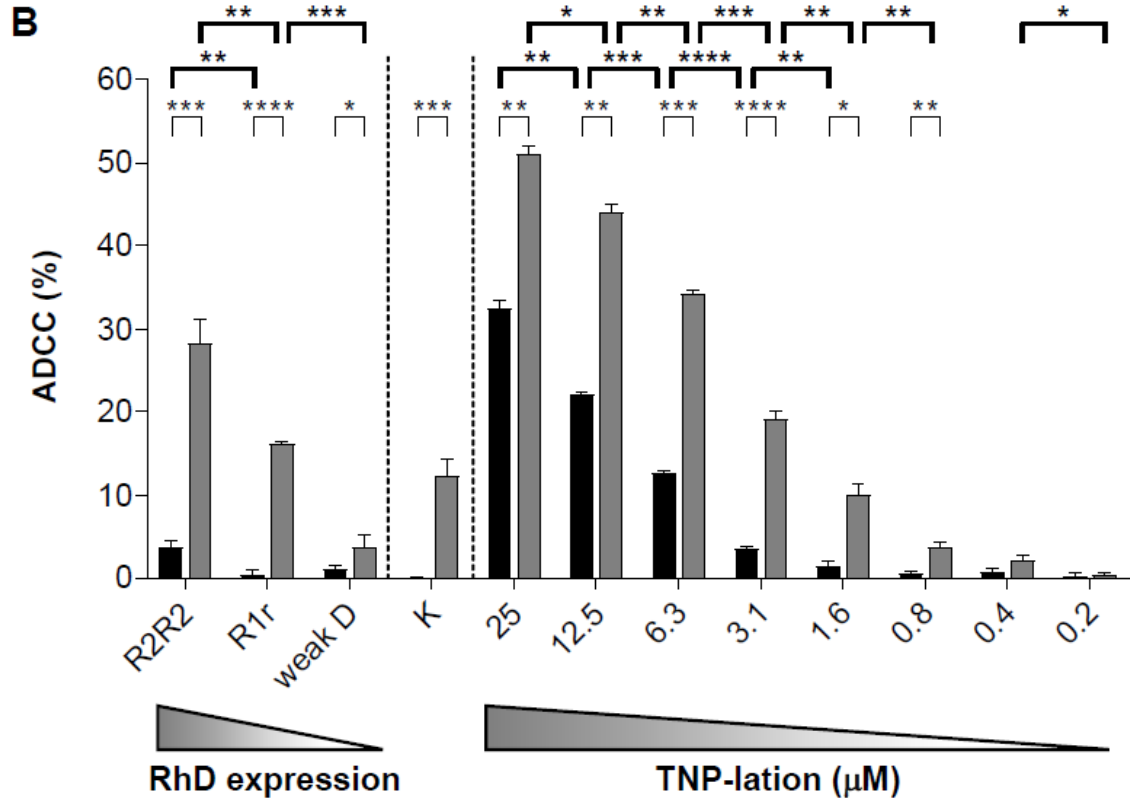
Shields et al *J Biol Chem* 2002;277:26733-40

Shinkawa *J Biol Chem* 2003;278:3466-73

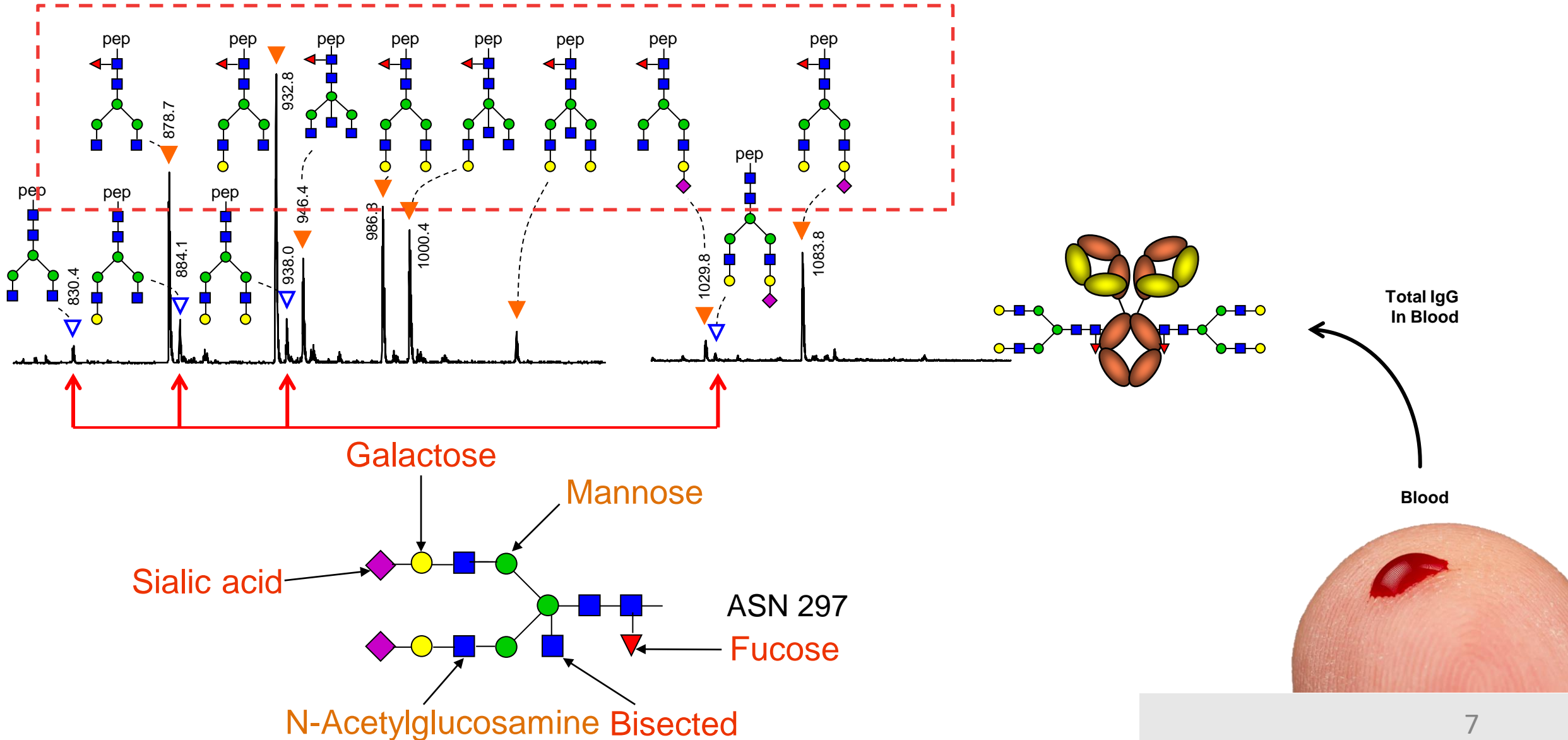


Afucosylation enhances NK-cell mediated ADCC

Functional activity



Fucose is seemingly invariably present in plasma IgG

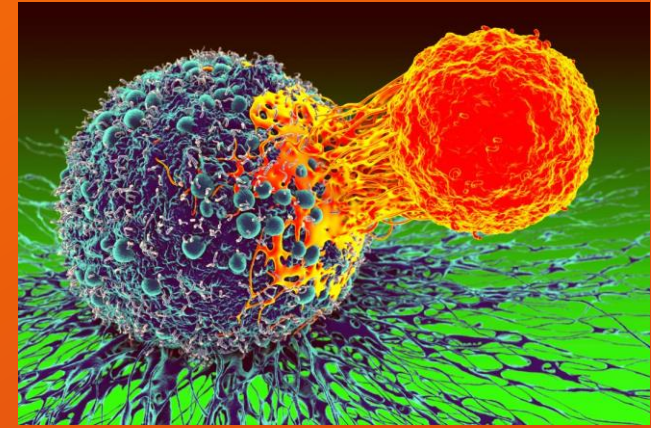


So why would afucosylation be important?

(as it is hardly found in humans)

- Except perhaps for anti-tumour therapies...

(*Marcus et al NEJMed 2017;377:1331-44; Freeman & Sehn: BJH 2018;182:29-45*)



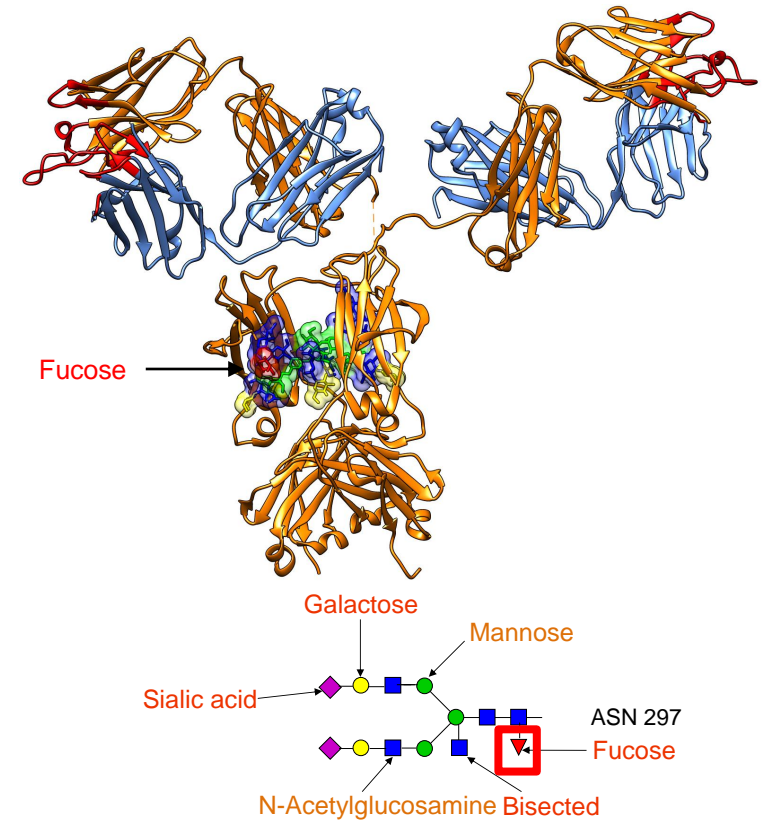
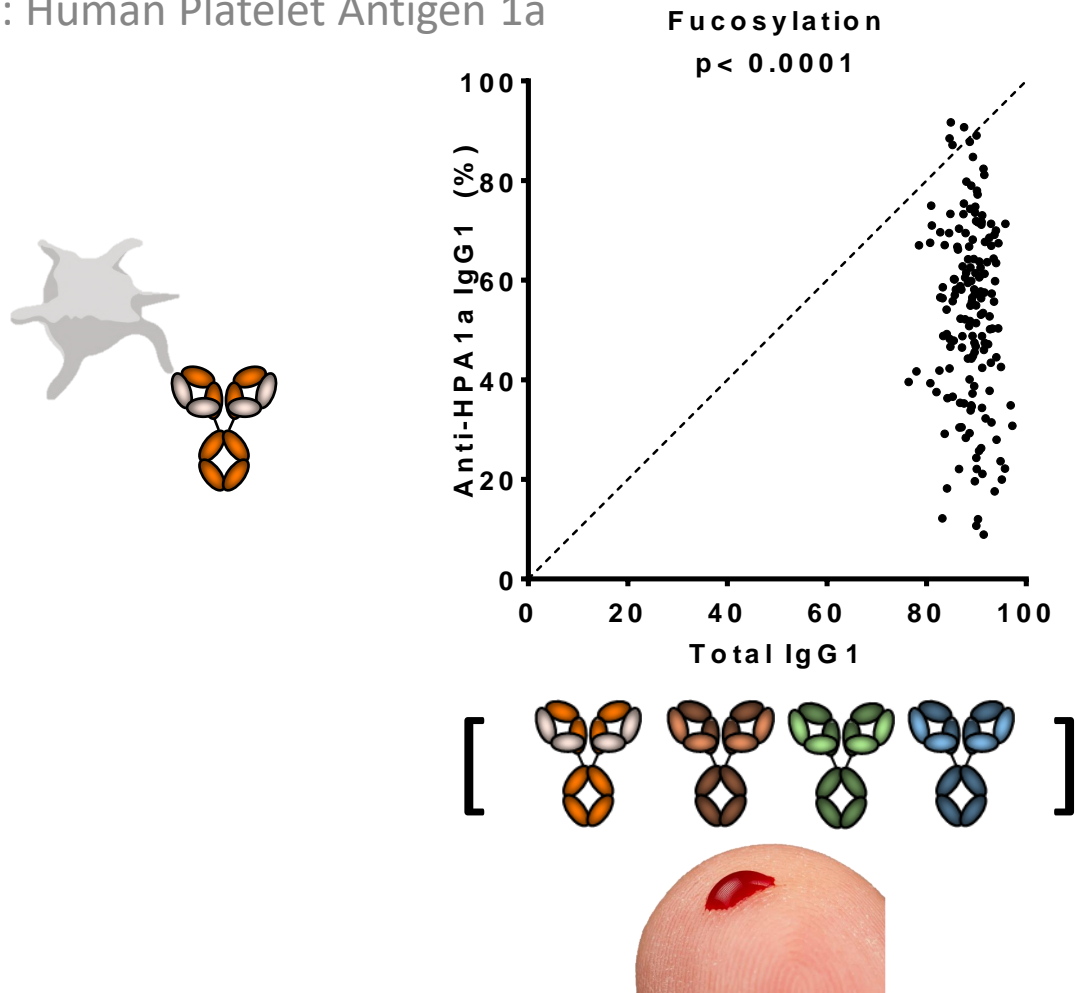
Glycosylation of IgG to blood cells in pregnancy (Platelets and RBC)



Antibody titer not strictly predictive of severity!

Anti-platelet and anti-RBC IgG-glycosylation show unique responses (alloimmune)

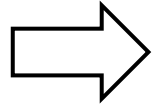
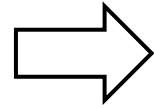
HPA-1a: Human Platelet Antigen 1a



Sonneveld et al Br J Haematol. 2017 Feb;176(4):651-660.
Kapur et al, Transfusion, 2015 ;55(3):553-62.
Kapur et al, Br J Haematol. 2014, 166(6):936-45.

Sonnefeld et al, Br J Haematol 2016;174(2):310-20.
Kapur et al, Blood 2014;123:471-80
Wuhrer et al J Proteome Res. 2009;8:450-6,

Afucosylated IgG appearing in immunity to blood cells



HDN (Rhesus)

RBC



FNAIT (HPA)

Platelets

Antibody titer not strictly predictive of severity!



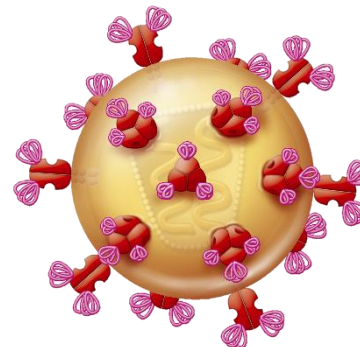
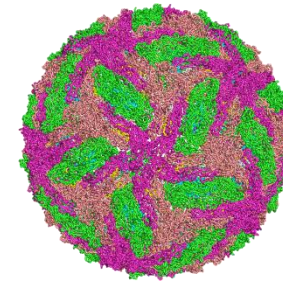
Also occurs after blood transfusion

Sonneveld et al Br J Haematol. 2017 Feb;176(4):651-660.
Kapur et al, Transfusion, 2015 ;55(3):553-62.
Kapur et al, Br J Haematol. 2014, 166(6):936-45.

Sonnefeld et al, Br J Haematol 2016;174(2):310-20.
Kapur et al, Blood 2014;123:471-80
Wuhrer et al J Proteome Res. 2009;8:450-6,

Known hypofucosylated IgG Fc responses

- **Anti-Human Platelet Antigen-1a** (Wuhrer et al, J Proteom Res 2009; 8; Kapur et al Blood 2014; Sonneveld et al BJH 2016)
- **Anti-RBC antigens (Rhesus)** (Kapur et al, Br J Haematol 2014; Kapur et al Transfusion 2015, Sonneveld et al BHJ 2017, Sci Rep 2017, Front Immunol 2018)
- **Anti-dengue** (Wang et al. Science 2017; 355)
- **Anti-HIV** (Ackerman J Clin Invest 2013; 123)

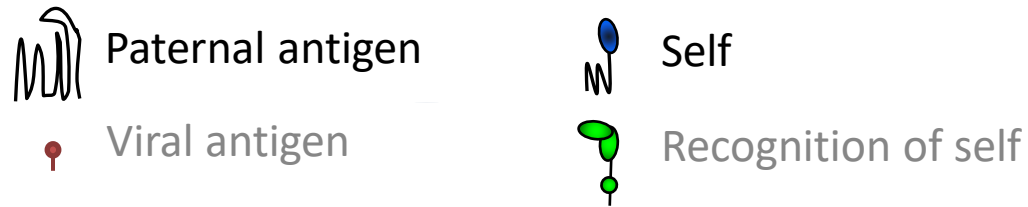
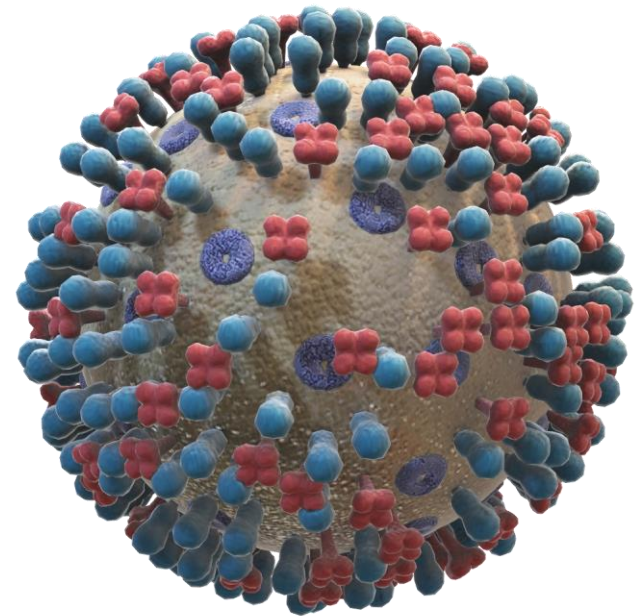
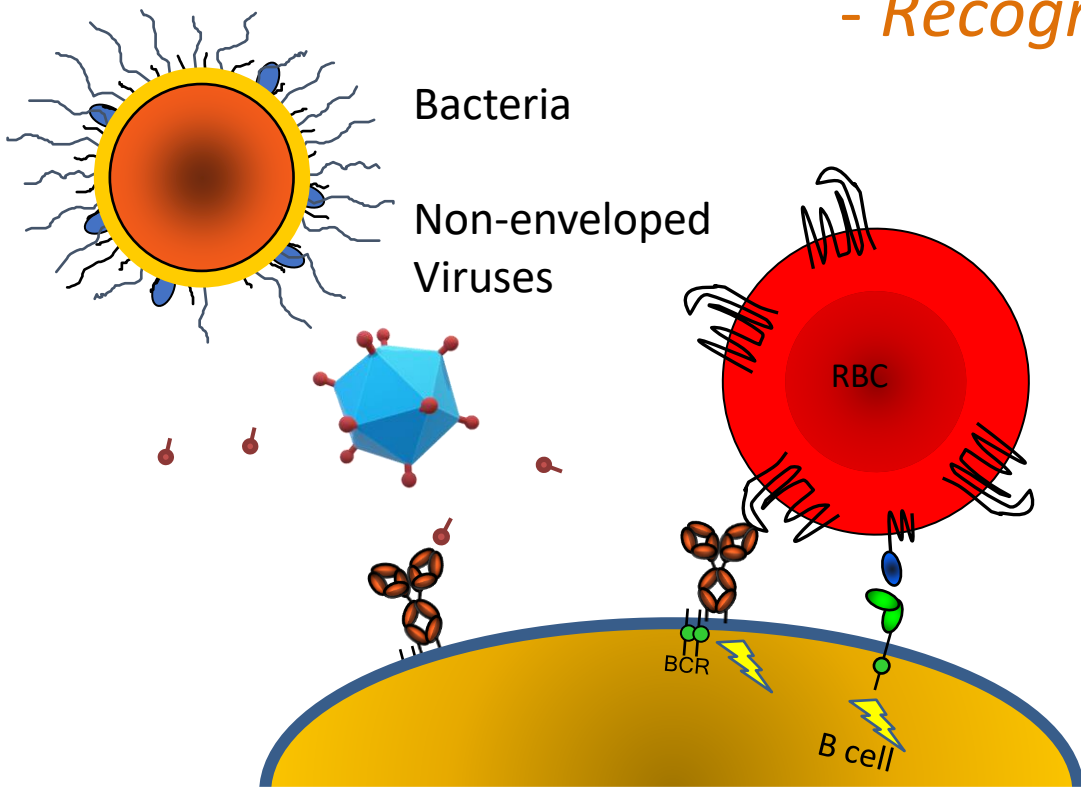


High fucose

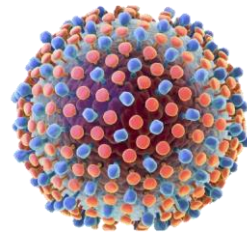
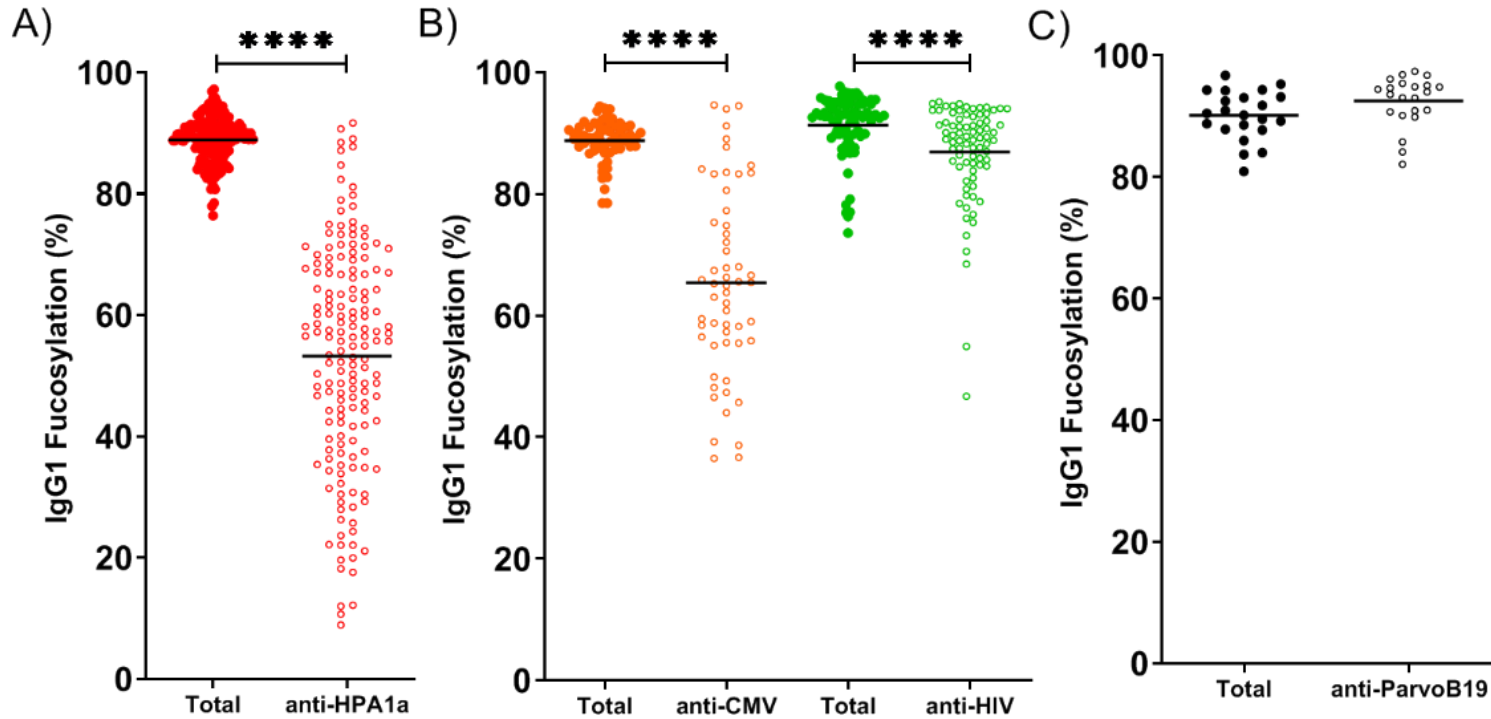
-Total IgG-

- Tetanus toxoid,**
- inactivated influenza,**
- Selman et al. 2012 *Mol Cell Proteomics*
- Inactivated influenza,**
- Meninococcal,**
- Pneumococcal,**
- Vestrheim et al 2014 *Immun Inflamm*
- Citrullinated proteins**
- Rombouts et al 2016 *Ann Rheum Dis*

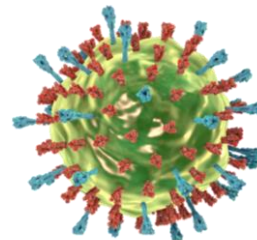
- Recognition of self hypothesis -



Alloantibodies and anti-viral responses: only enveloped viruses



HBV



Mumps
Measles

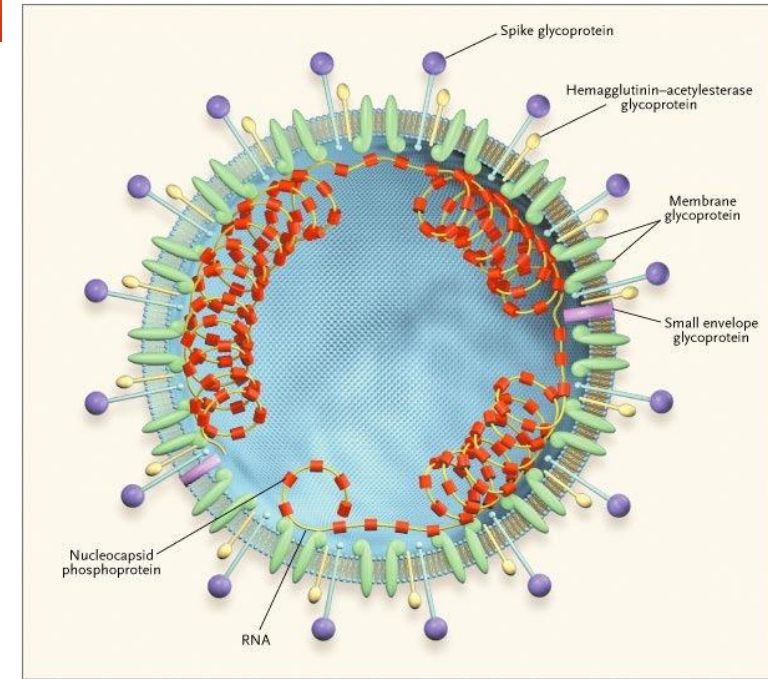
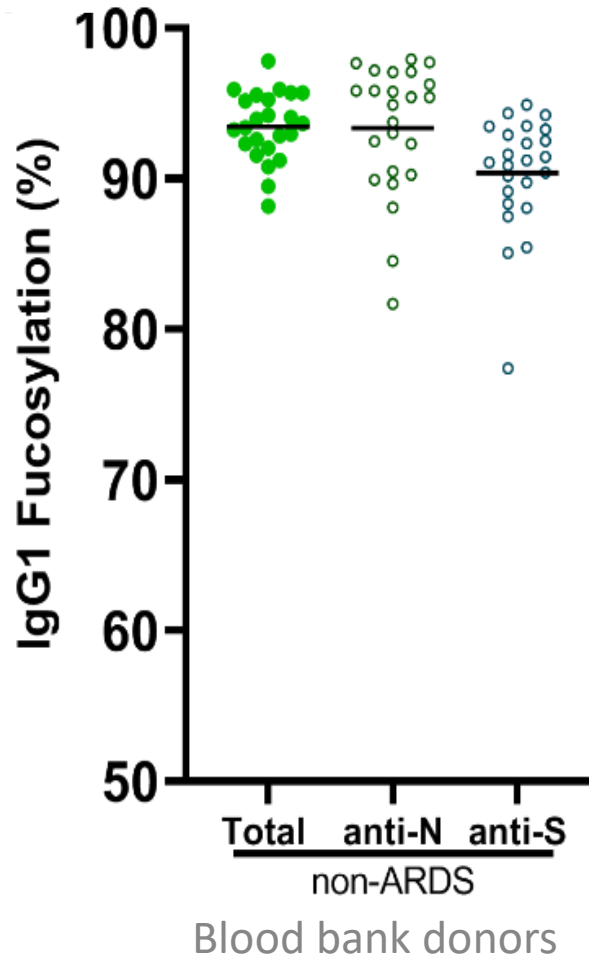
High fucose

- Total IgG-
- Tetanus toxoid,**
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- Inactivated influenza,**
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- Pneumococcal,**
- Vestrheim et al 2014 *Immun Inflamm*
- Citrullinated proteins**
- Rombouts et al 2016 *Ann Rheum Dis*

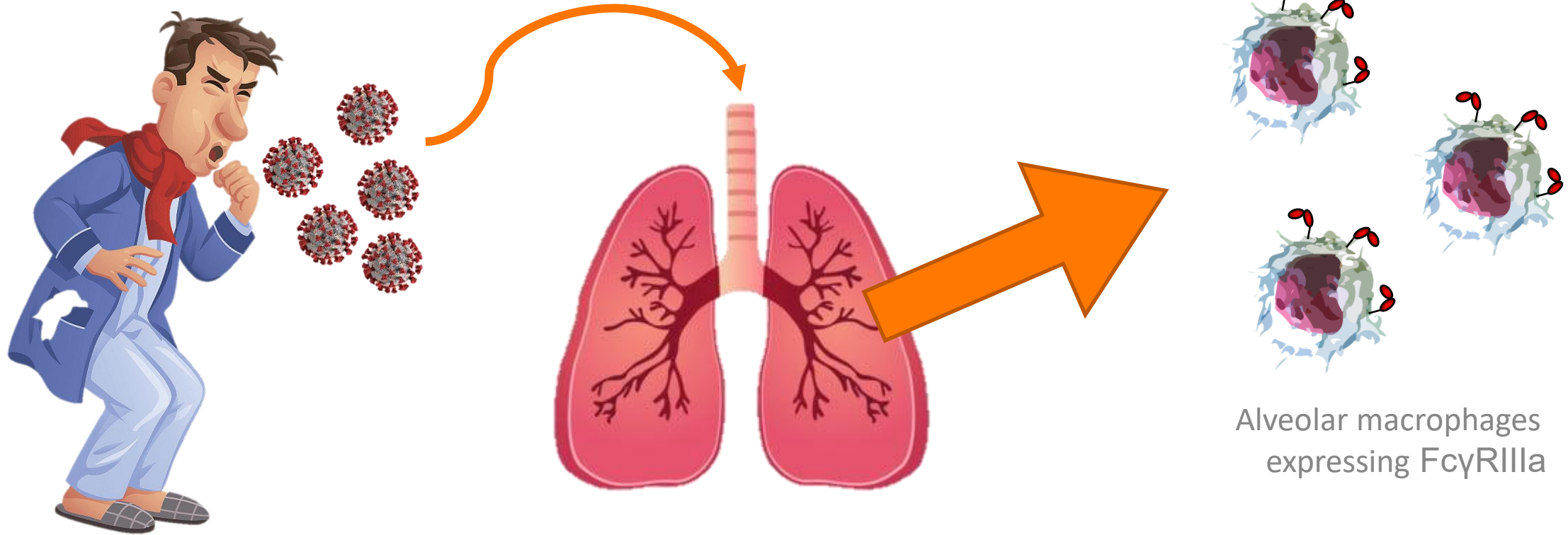
Low fucose

- Platelet antigens**
- Wuhrer et al 2009 *J Proteome Res*.
- Kapur et al *Blood* 2014
- Sonnevel et al 2016 *Br J Haematol*
- RBC antigens**
- Kapur et al 2014 *Br J Haematol*.
- Kapur et al 2015 *Transfusion*,
- Sonneveld et al 2017 *Br J Haematol*.
- Sonneveld et al 2018 *Front Immunol*
- HIV**
- Ackerman et al, 2013 *J Clin Invest*.
- Dengue**
- Wang et al, *Science* 2017

COVID-19 responses

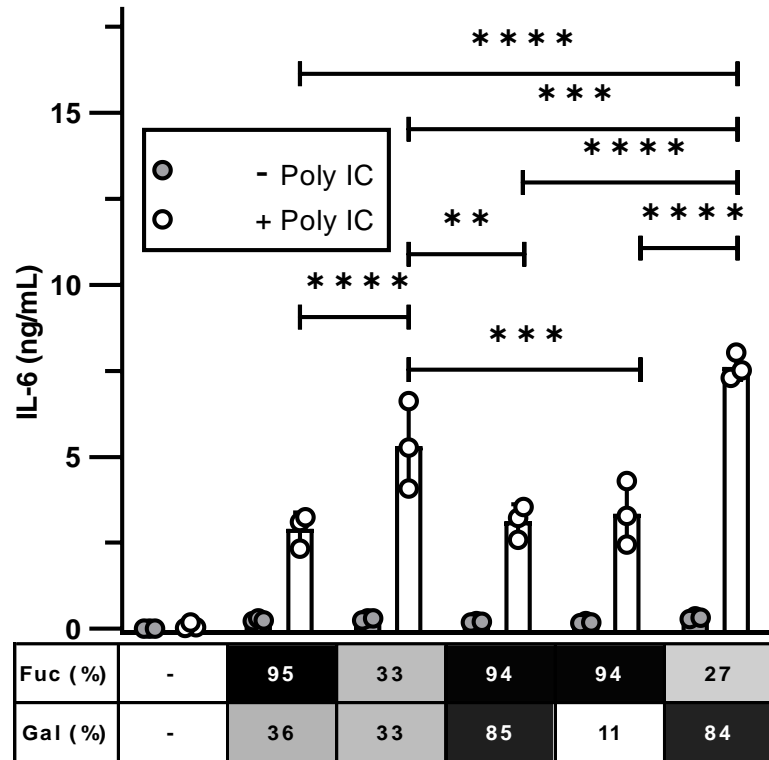


Where is this taking place?



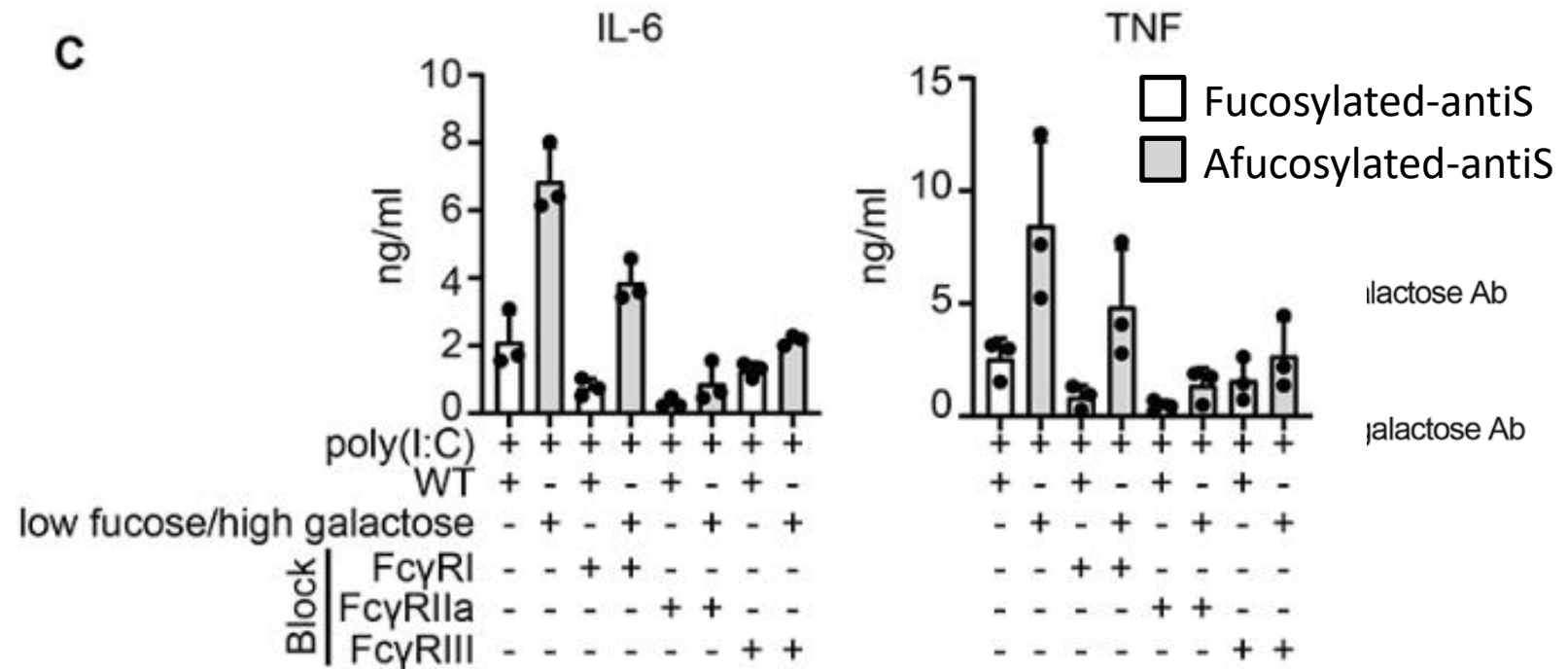
Alveolar macrophages
expressing FcγRIIIa

Afucosylated IgG create pro-inflammatory environment through FcγR on macrophages



Monocyte-derived Macrophages (alveolar)

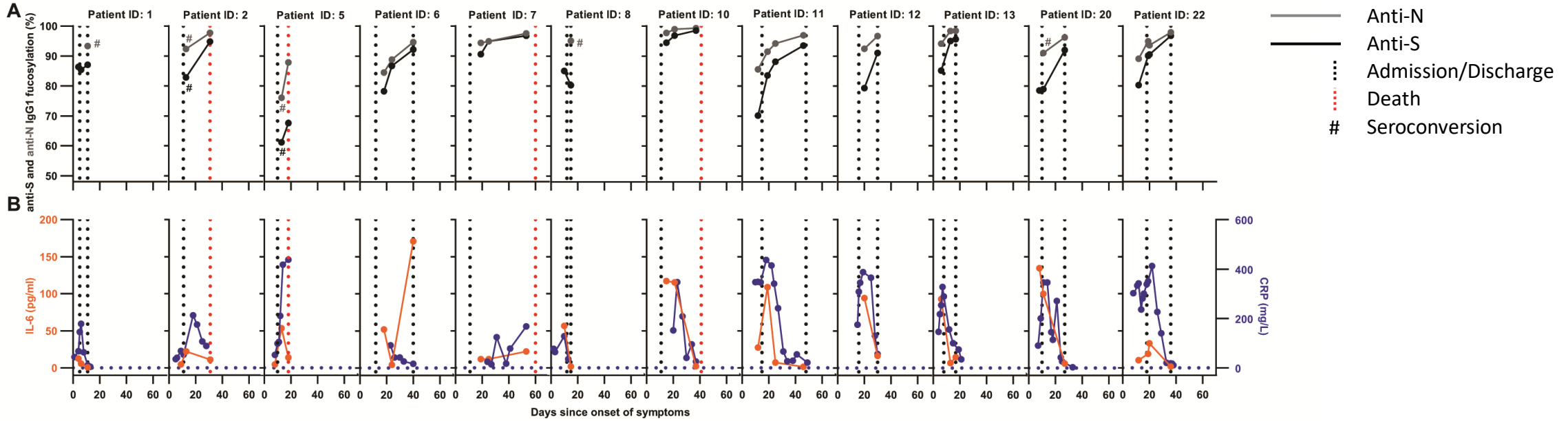
C

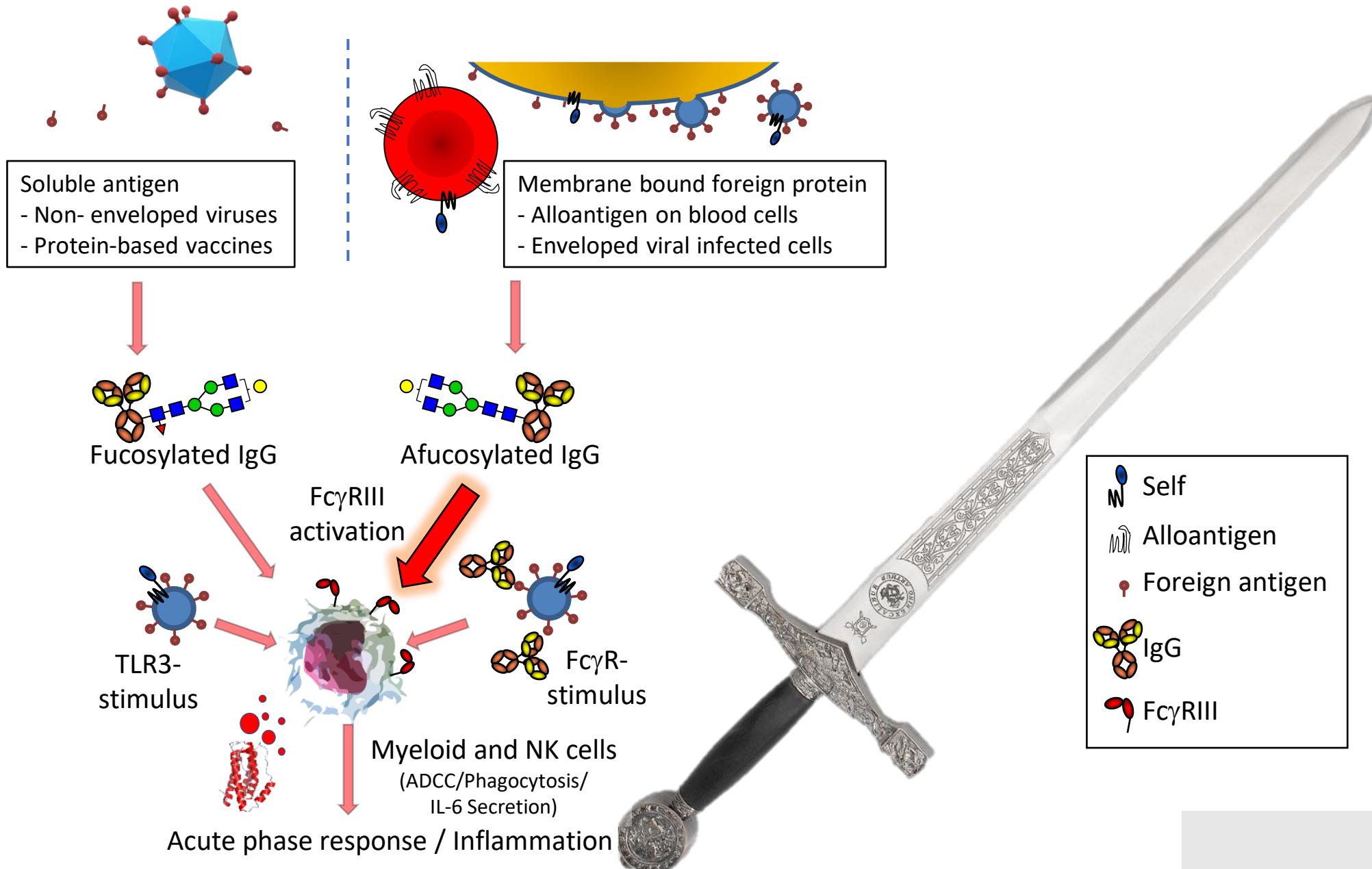


Also blocked by SYK inhibitor Fostamatinib

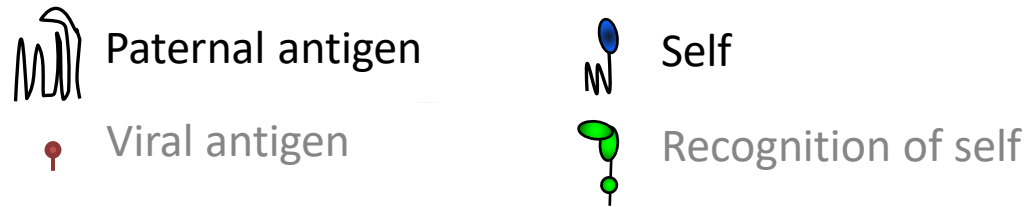
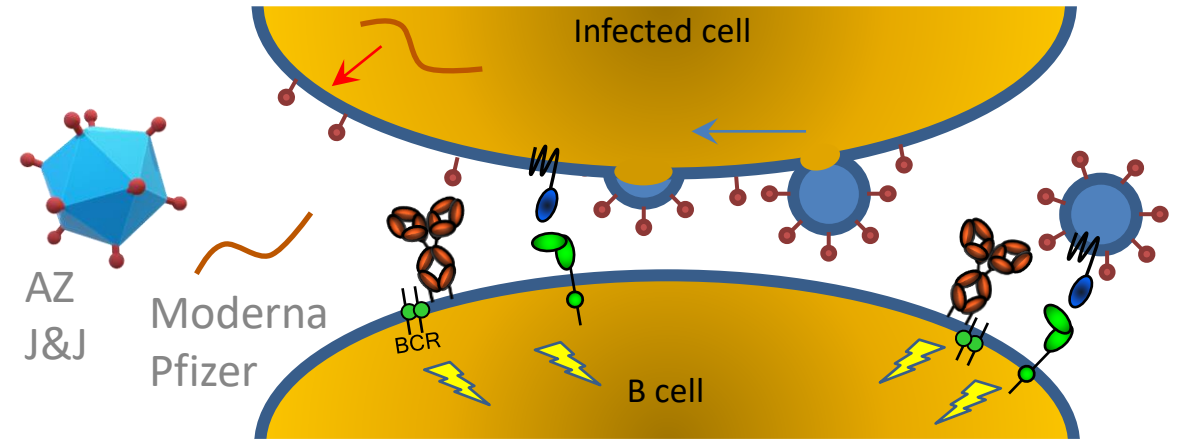
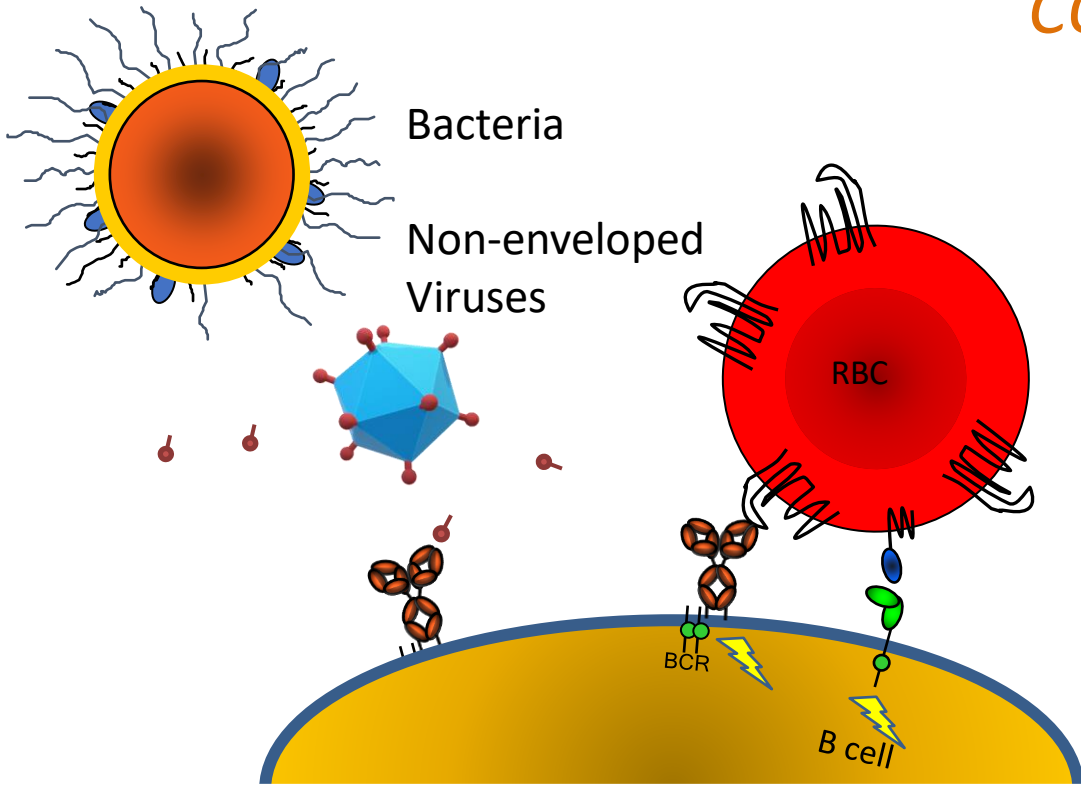
Hoepel et al Science translational medicine in press 2021
10.1126/scitranslmed.abf8654

ICU

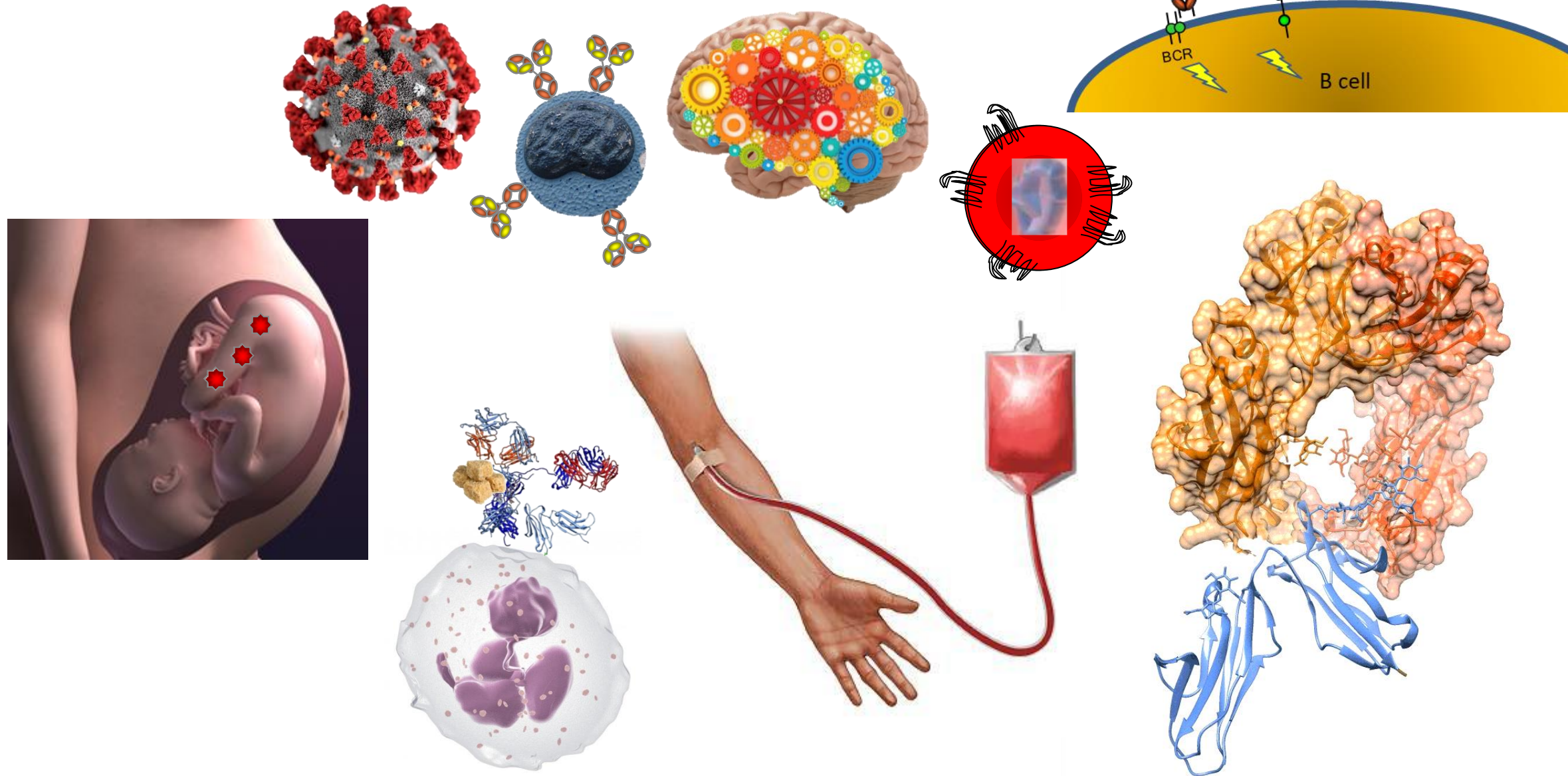




COVID-19 vaccines?



Afucosylated IgG responses in humans





Mads Larsen, Myrthe Sonneveld, Rick Kapur, Erik de Graaf, Robin Temming, Steven de Taeye, Federiece Linty, Arthur Bentlage, Gillian Dekkers, Maximilian Brinkhaus, Tonci Šuštić, Suvi Toivonen, Remco Visser, Ninotska Derksen, Gerjan Wolbink, Hans Zaaier, Leendert Porcelijn, Masja de Haas, Theo Rispens, Ellen van der Schoot



Neeltje Kootstra, Ineke ten Berge, Rogier Sanders, Menno de Winther, Sanne de Bruin, *Alexander Vlaar*, Philip Brouwer, *Marit van Gils, Williana Hoepel, Jeroen den Dunnen*, Amsterdam UMC COVID-19 biobank study group



Suvi Toivonen, Susanna Sainio



Lars Hviid, Mary Lopez-Perez

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Noortje de Haan,
Manfred Wuhrer



ZonMw

