

Weaving the Threads of Memory: How Pre-existing Immunity Shapes B Cell Responses to Influenza A Virus

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i hörsal Arvid Carlsson, Medicinargatan 3, Göteborg, den 28. Februari 2025, klockan 9:00

av **Laura Reusch**

Fakultetsopponent:

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Avhandlingen baseras på följande delarbeten

- I. Danica F Besavilla, [Laura Reusch*](#), Josue Enriquez*, Karin Schön, Davide Angeletti. **Pre-existing CD4 T cell help boosts antibody responses but has limited impact on germinal center, antigen-specific B cell frequencies after influenza infection.** Front Immunol. 2023 Aug 30;14:1243164.
- II. [Laura Reusch](#), Nimitha R Mathew, Karin Schön, Danica F Besavilla, Ivan Kosik, James S Gibbs, Madeleine C Mankowski, Jonathan W Yewdell, Mats Bemark, Davide Angeletti. **The impact of pre-existing antibodies and memory B cells upon vaccination with influenza A virus depends on their antigenic site specificity and antigen valency.** Manuscript
- III. Sarah Wehrle*, Andreas Scheck*, [Laura Reusch*](#), Flavio Matassoli, Sandrine Georgeon, Karla M. Castro, Johannes Cramer, Wayne Harshbarger, Stéphane Rosset, Sarah Andrews, Karin Schön, Badiia Bouzya, Ronan Rouxe, Normand Blais, Enrico Malito, Adrian McDermott, Thomas Krey, Corey P. Mallett, Ventsislav Vassilev, Davide Angeletti**, Bruno E. Correia**. **Computationally designed stem-epitope mimetics elicit broadly reactive antibodies.** Manuscript

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Abstract

Influenza A virus (IAV) poses a persistent global health threat due to its ability to evolve rapidly, requiring annual updates to seasonal vaccines. Despite significant advancements, a universal vaccine capable of providing long-term and broad protection has not been developed yet. It was investigated here, how pre-existing immune components—antibodies (Abs), memory B cells (MBCs), and CD4 T cells—shape B cell responses to drifted IAV haemagglutinin (HA). We also explored innovative immunogen design strategies, targeting a conserved epitope to overcome immunodominance (ID) and enhance vaccine efficacy.

While pre-existing CD4 T cells accelerated Ab and GC responses, pre-existing Abs were shown to mask epitopes and exhibit feedback mechanisms, thereby reshaping ID patterns of B cell responses. The valency of antigens used for vaccination influenced the extent of Ab-mediated modulation, with multivalent antigens showing greater effects compared to monovalent counterparts. Whereas MBC rapidly differentiated into antibody-secreting cells (ASC) rather than re-entering secondary germinal center reactions (GCs), this localized Ab secretion contributed to secondary responses rather than the presence of serum-Abs. Finally, MBC and naïve B cells were regulated differently after vaccination with a multivalent particle.

To address challenges posed by antigenic variability and to induce broad immunity against IAV, a computationally designed HA stem mimetic was developed. This immunogen selectively engaged MBCs of IAV-experienced individuals and induced cross-reactive Ab responses against both group 1 and group 2 IAV strains after vaccination in mice.

By combining insights into ID, the effect of pre-existing immunity on secondary B cell responses and rational antigen design, this work highlights key mechanisms driving protective and broad B cell responses to IAV, thereby providing valuable insights to inform the development of a universal IAV vaccine. These findings also offer broader implications for combating other highly variable pathogens, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and human immunodeficiency virus (HIV).

Keywords: Influenza A virus, haemagglutinin, universal vaccine, memory B cells, immunodominance, computational vaccine design, antibodies, CD4 T cells