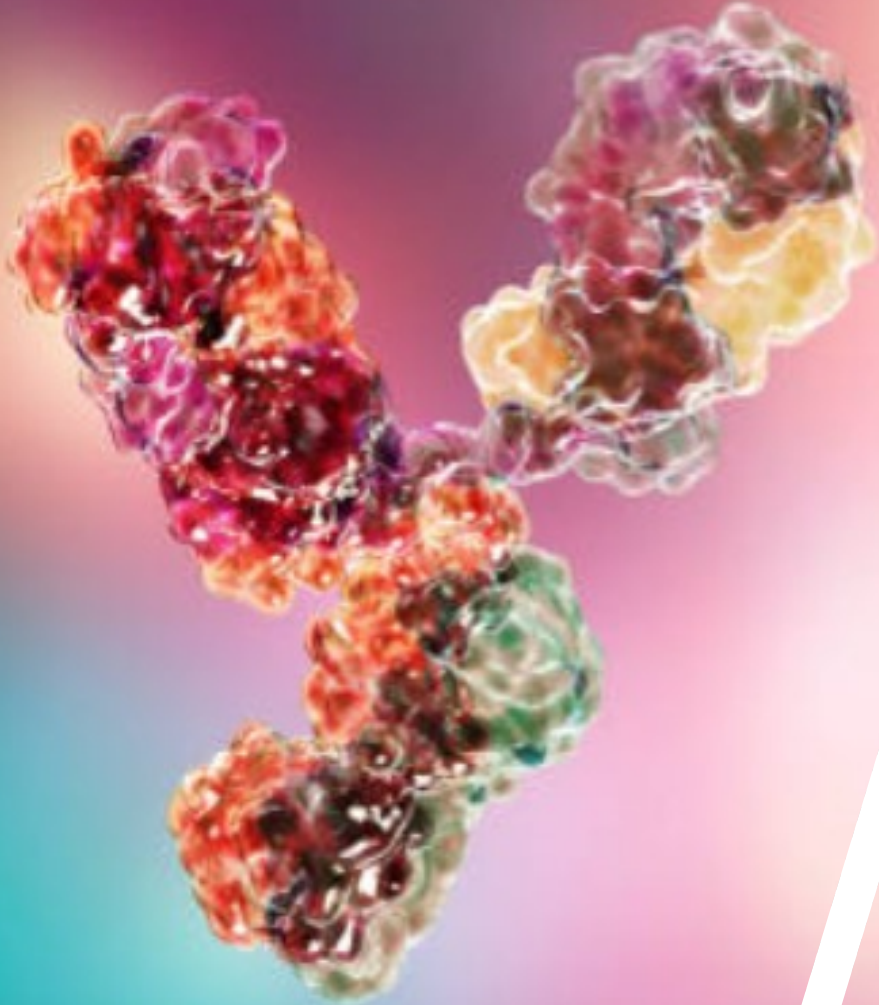# Protein-protein interactions using Deep Learning: application in antibody design

Sara Joubbi, 10 Mar 2023

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Agenda

- Protein-protein interactions

- Antibody-antigen interactions

- Reverse vaccinology 2.0

- Deep Learning for antibody-antigen interactions

- Applications of deep learning in antibody design

- Problems & Discussion

Protein-protein interactions (PPI) are a fundamental aspect of biological systems

- PPIs are physical interactions between two or more proteins

- PPIs are involved in a wide range of cellular processes (e.g., immune response).

- Dysregulation of PPIs can lead to a range of diseases (e.g., autoimmune disorders)

- Understanding the mechanisms to develop treatments and therapies for these diseases
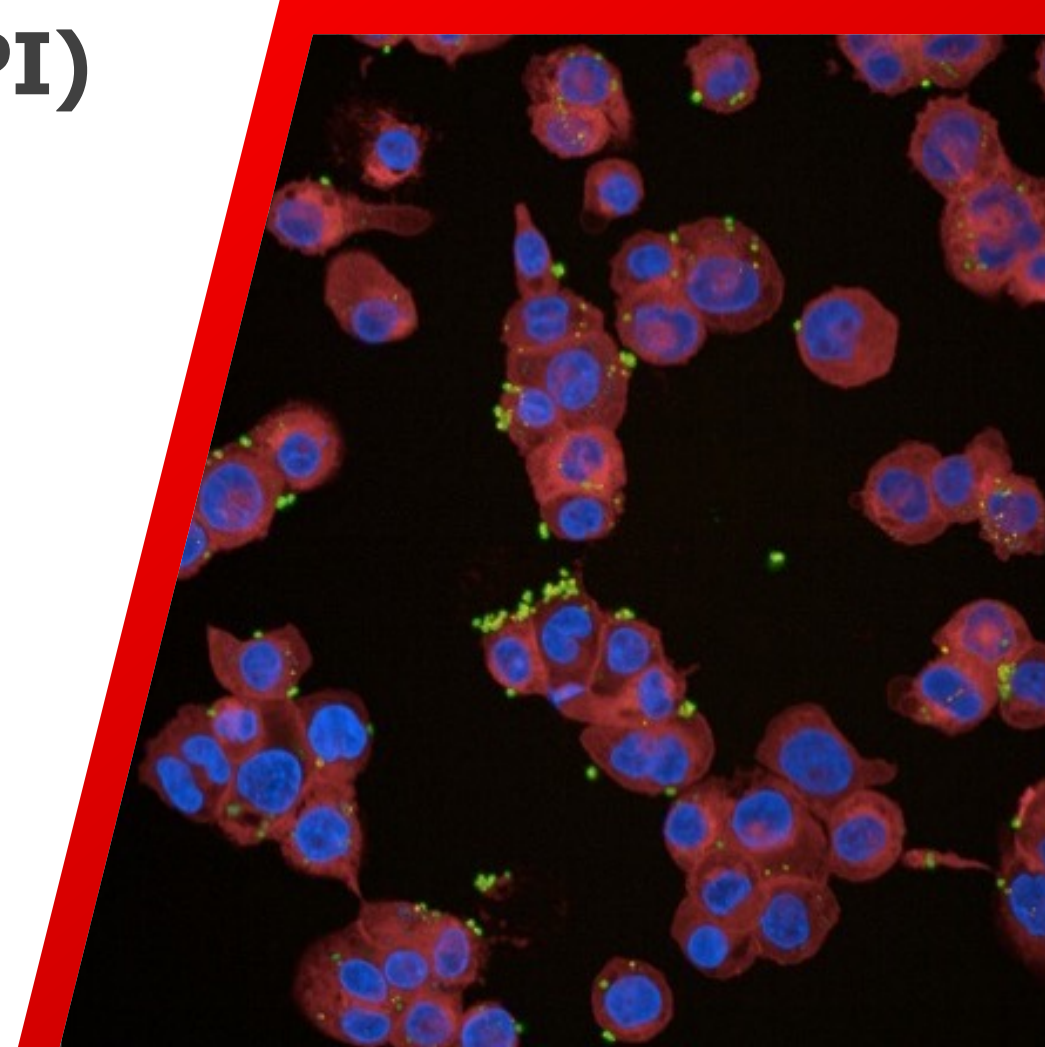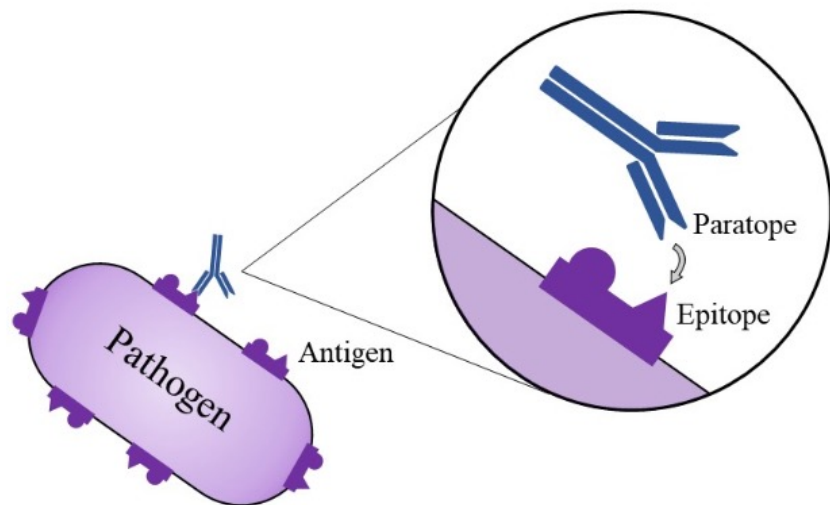
Antibodies recognize and bind to specific molecules, known as antigens

- Antibodies (**Ab**) are composed by heavy (H) and light (L) chains.
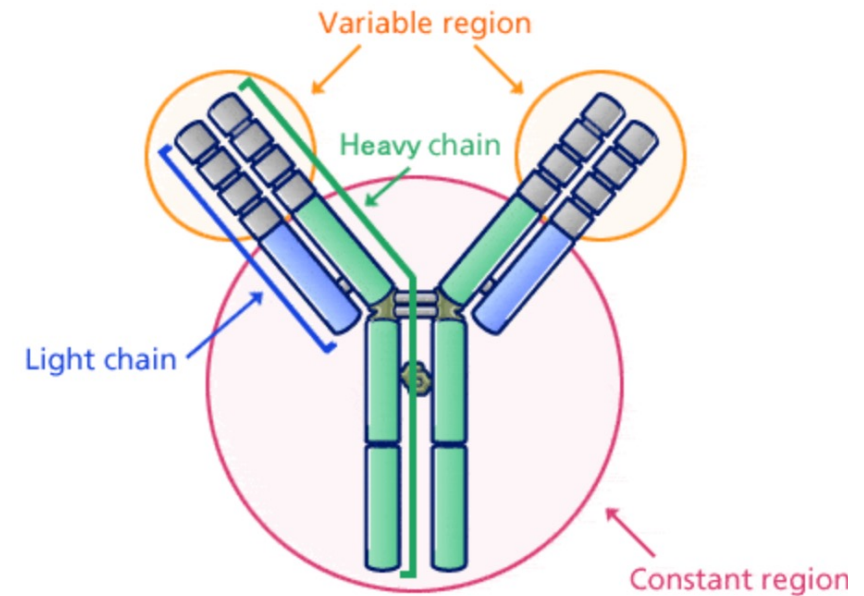
Antibody/Antigen interaction

- Each chain presents three variable domains containing the antibody's binding surface, or ***paratope*** (the corresponding antigen part is called ***epitope***).

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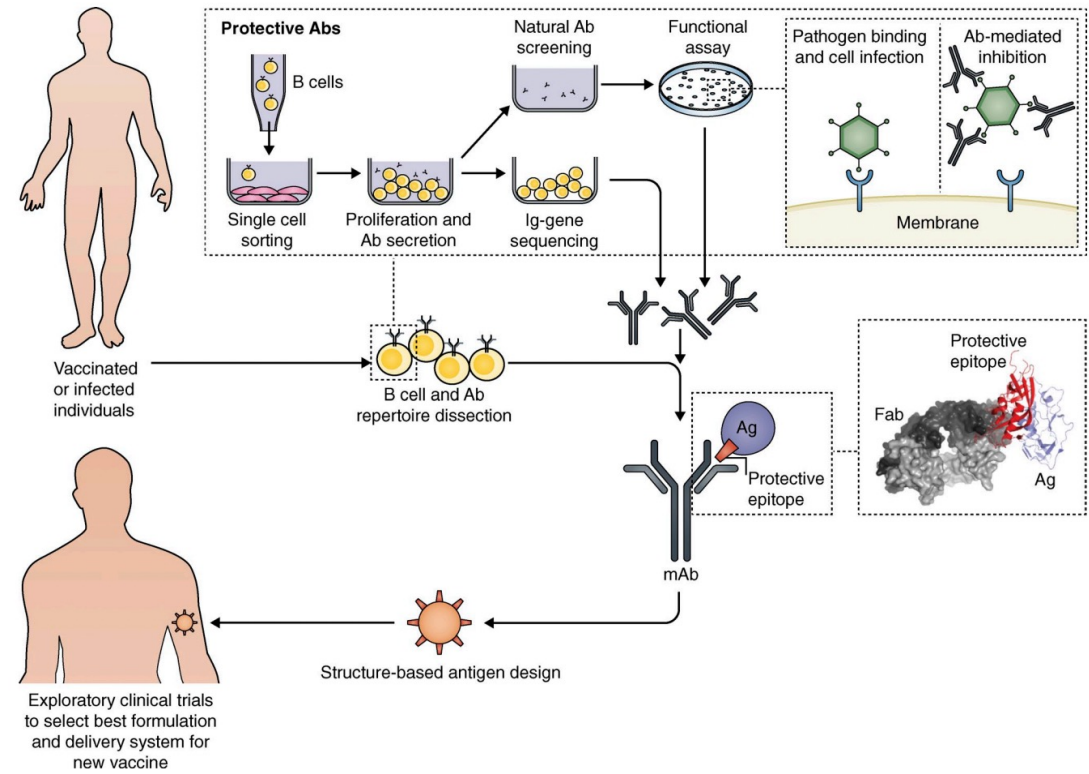# The interaction between an antibody and its specific antigen is highly specific, like a lock with a key

- The binding of an antibody to its antigen is known as an **antibody-antigen interaction**.

- This interaction plays a crucial role in the immune response to infection.

Epitope

VL

VH

Paratope

Epitope

Pathogen

Antigen
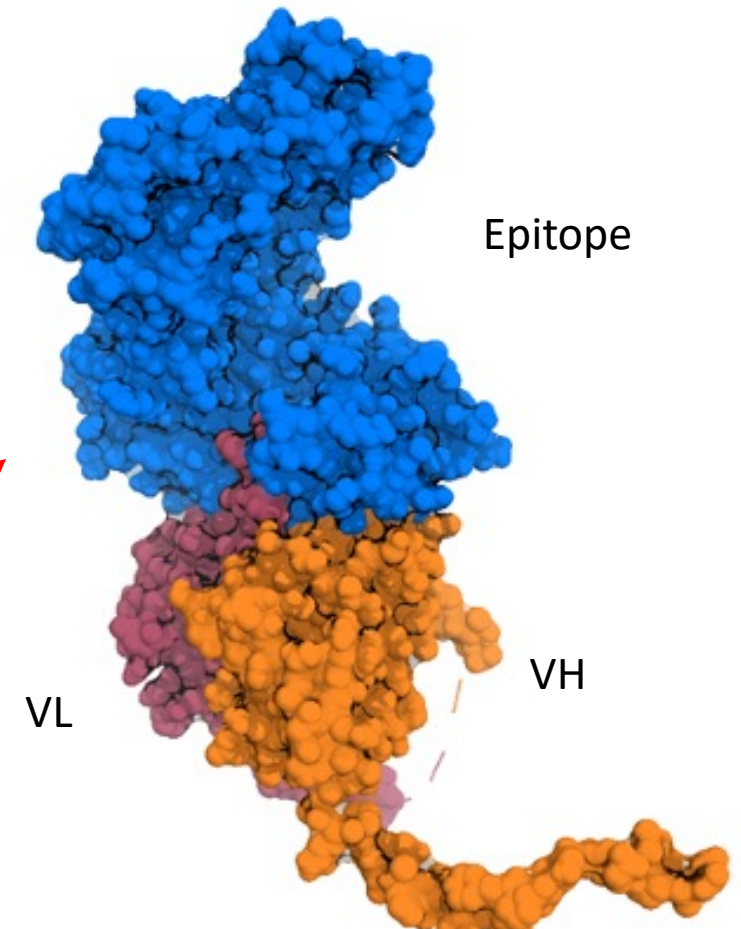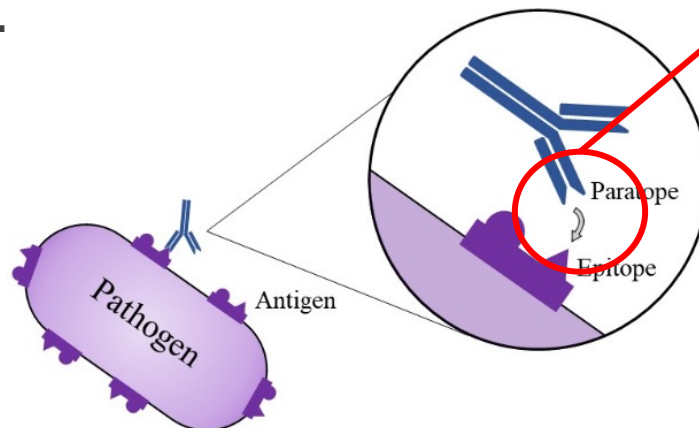
Reverse vaccinology 2.0 for vaccines and antibodies development

Potent monoclonal antibodies can be **harnessed** from a human humoral response from individuals exposed to a specific pathogen:

- Beta cells are extracted from individuals
- Functional characterization identifies antigen-specific producing beta cells.
- Identified mAbs are then characterised and optimised

Rappuoli R., Bottomley, M.J., D'Oro U., Finco O., De Gregorio E. (2016) Reverse vaccinology 2.0: Human immunology instructs vaccine antigen design. *J Exp Med* (2016) 213 (4): 469–481

Deep learning has emerged as a powerful tool for predicting and analysing Ab-Ag interactions

- **Reverse vaccinology 2.0**: time- and resource-intensive, sampling many ineffective antibodies an route to identifying a feasible candidate.

- **Classical computational methods**: often require a deep understanding of biophysical principles and may not generalize well to different scenarios
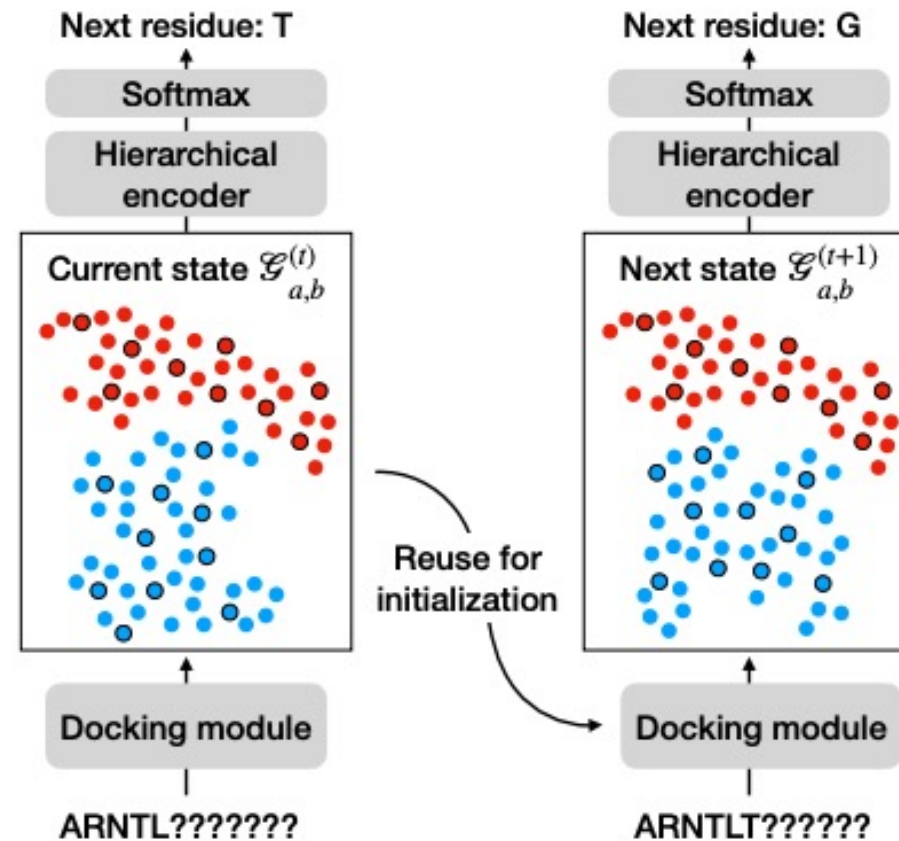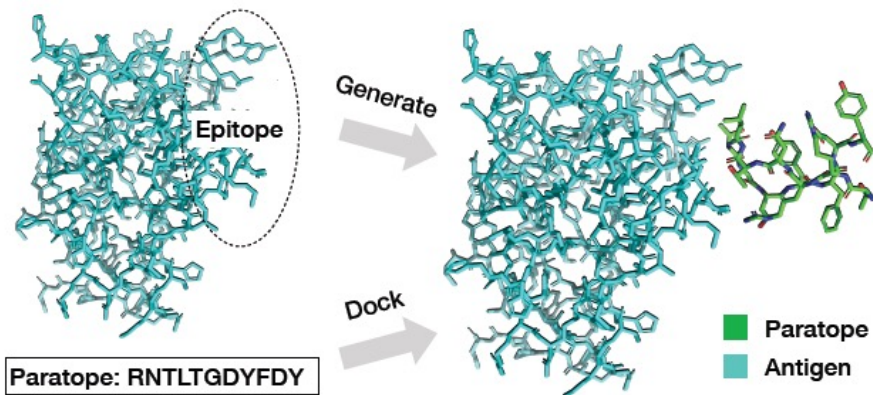
Deep learning is efficient and can handle large datasets, can be used to model complex interactions, predict interaction sites, and identify new interactions
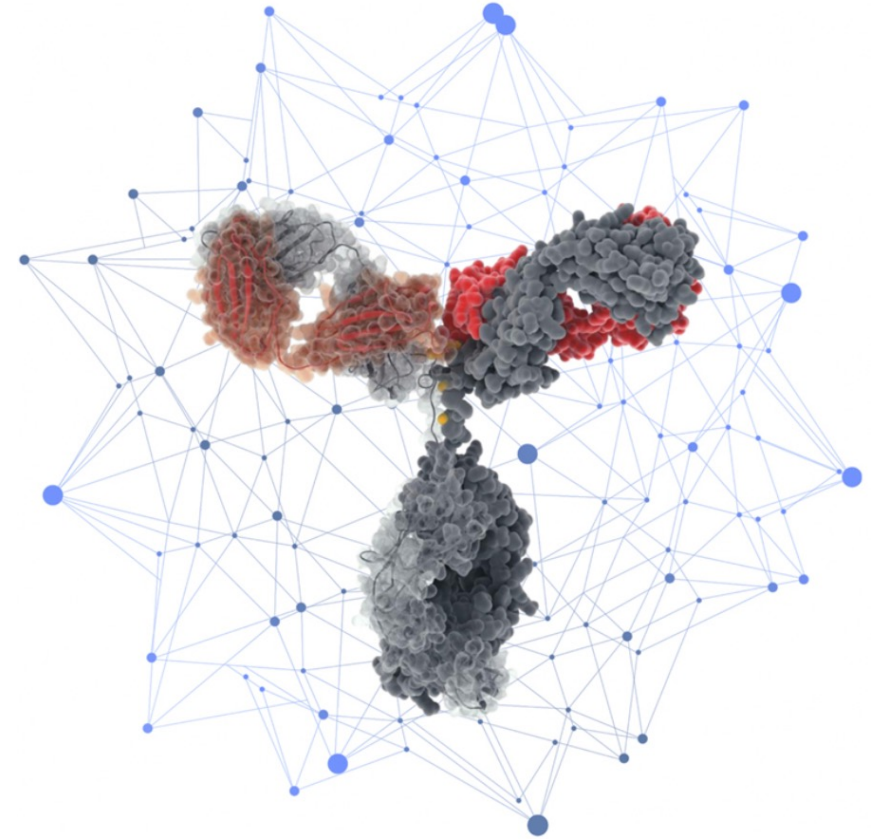
Applications of DL for Ab

1. **Antibody-antigen docking**: to predict the structure of antibody-antigen complexes
2. **Epitope prediction**: predict the binding sites that are recognized by antibodies
3. **Antibody optimization**: optimize the affinity and specificity of antibodies by predicting the effects of mutations on the antibody-antigen complex
4. **De novo design**
5. **Virtual screening**: screen large libraries of potential antibody candidates for those with the best predicted binding affinity and specificity
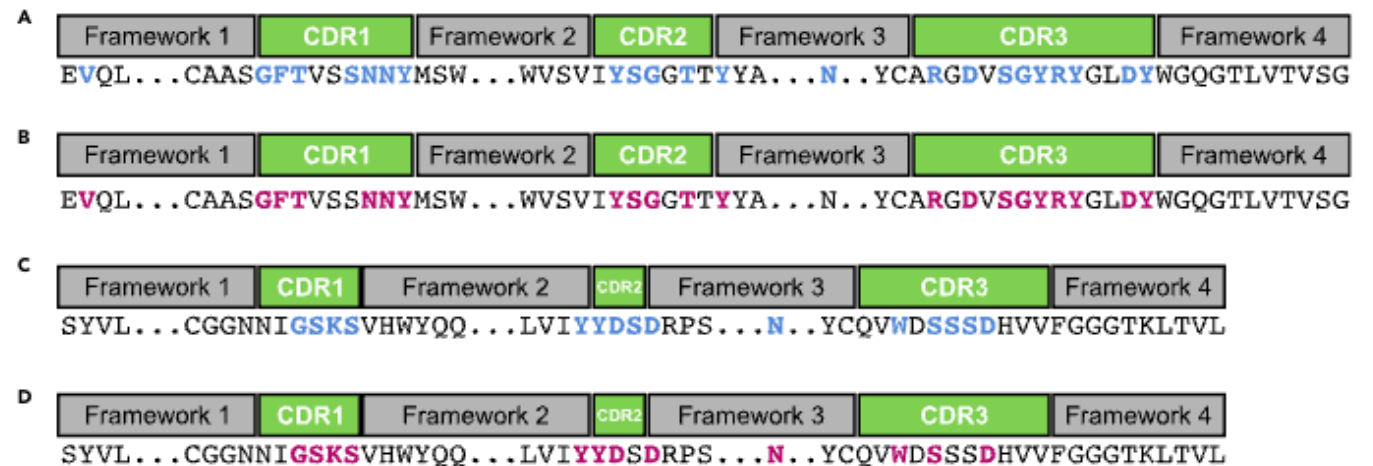
Paratope docking and design with Hierarchical Structure Refinement Network (HSRN)

Jin, W., Barzilay, R., & Jaakkola, T. (2022, June). Antibody-antigen docking and design via hierarchical structure refinement. In *International Conference on Machine Learning* (pp. 10217-10227). PMLR.

AntiBERTa for learning the language of Antibodies
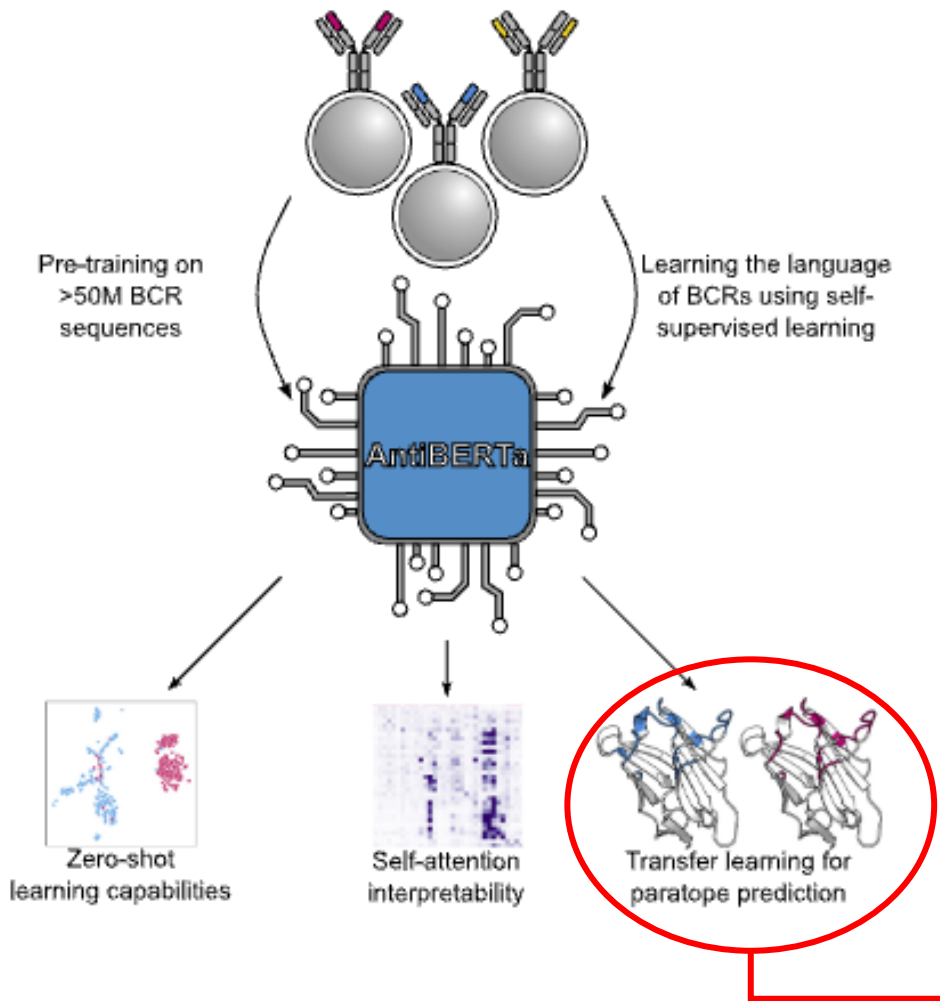
Paratope prediction: the probability that a position is part of the paratope of the antibody

Leem, J., Mitchell, L. S., Farmery, J. H., Barton, J., & Galson, J. D. (2022). Deciphering the language of antibodies using self-supervised learning. *Patterns, 3*(7), 100513.
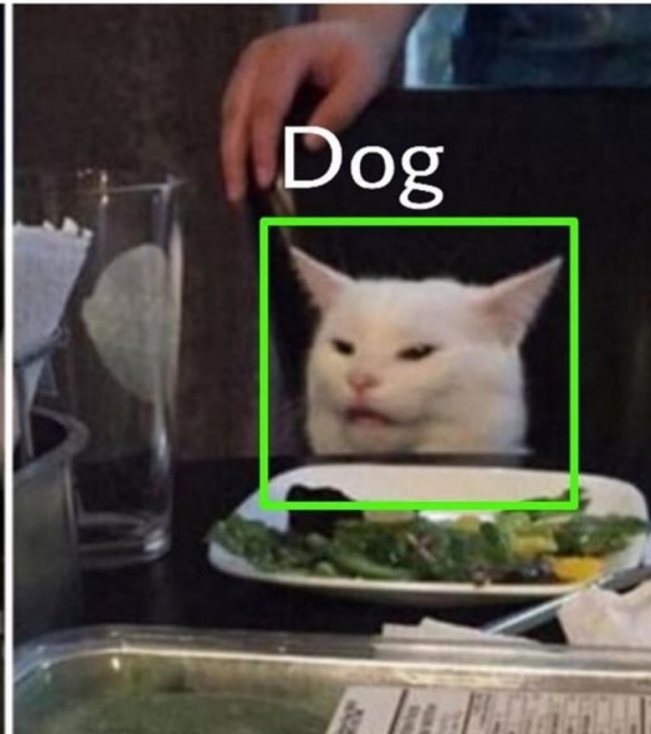
Reality check...

1. Data scarcity

2. Transferability

3. Complex nature of the interaction

4. Integration with experimental workflows

Thanks for your attention