Interpretable prediction of T cell receptor binding

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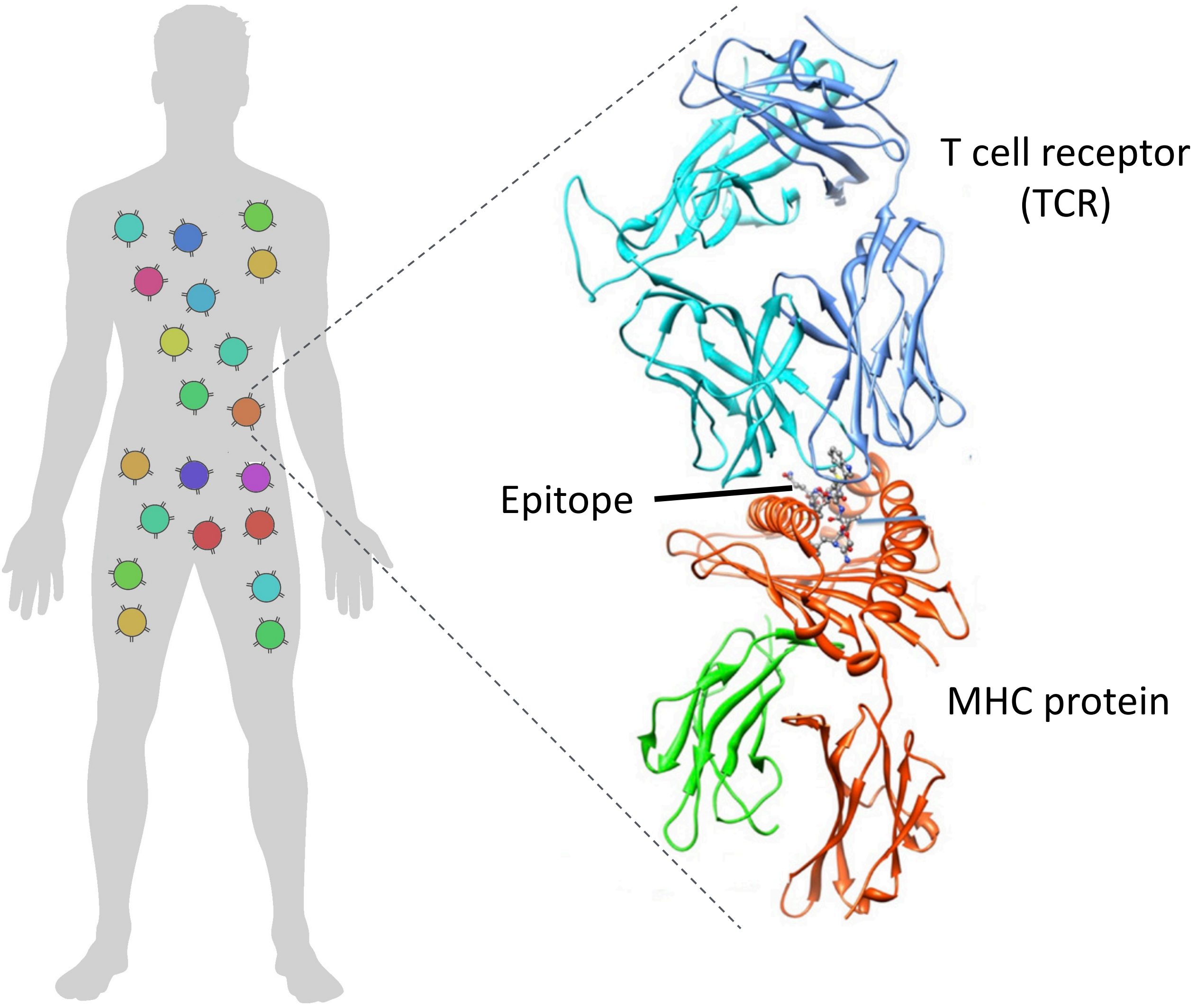
*https://precise-project.eu/

T cells are essential for adaptive immune responses



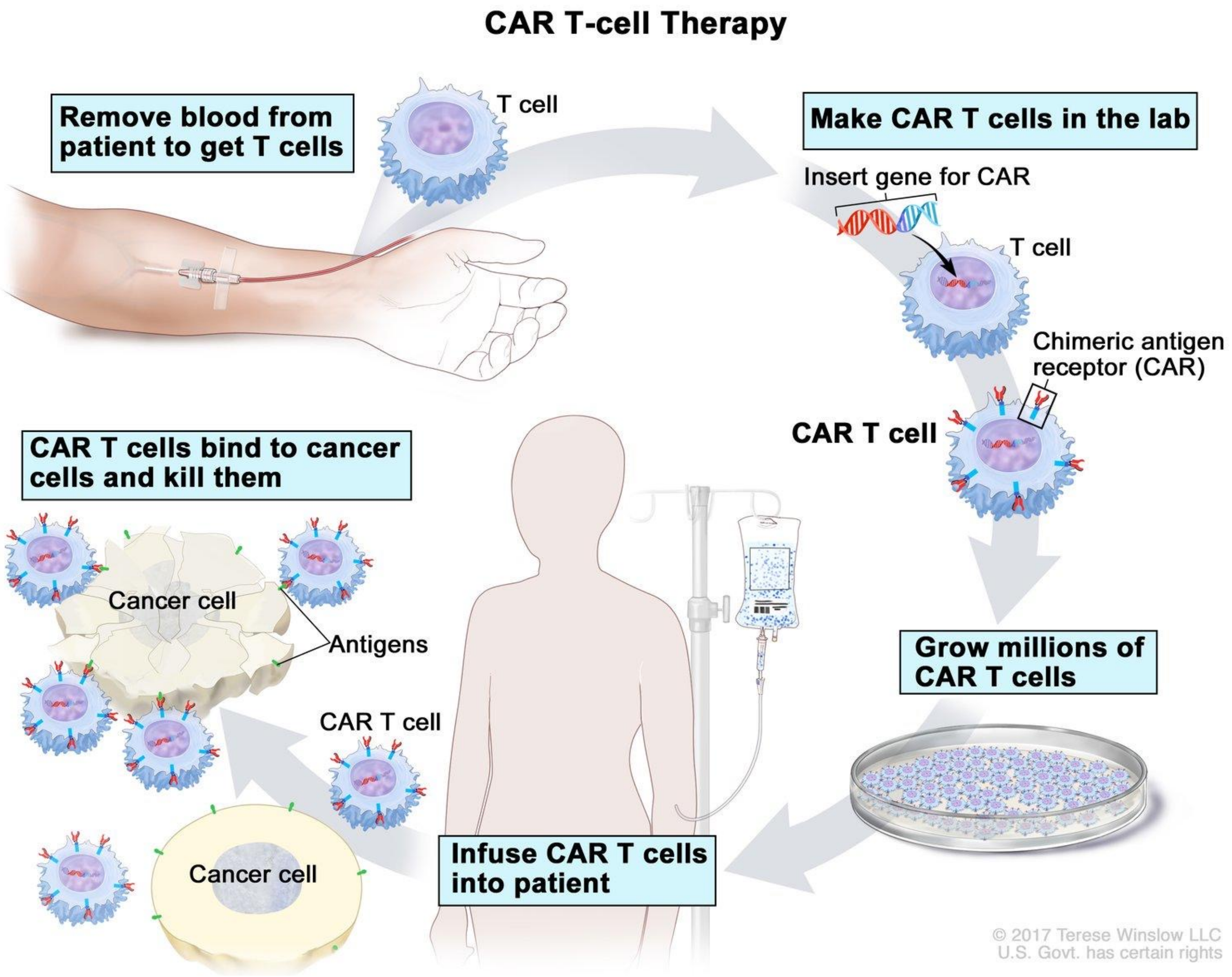
Immense Diversity of T Cells

Highly Specific Binding to Foreign Epitope

- T cells
  - → distinct T cell receptor (TCR)
  - → selectively recognize foreign epitopes
  - → cross-reactive
  - → regulate adaptive immune responses

Modeling adoptive cell transfer therapies

- Chimeric Antigen Receptor (CAR) T cell therapies
- T cell-based therapies



- Extract T cells from a patient
- (Engineer them to express a CAR)
- Expand them in vivo
- Reinfuse them into the patient

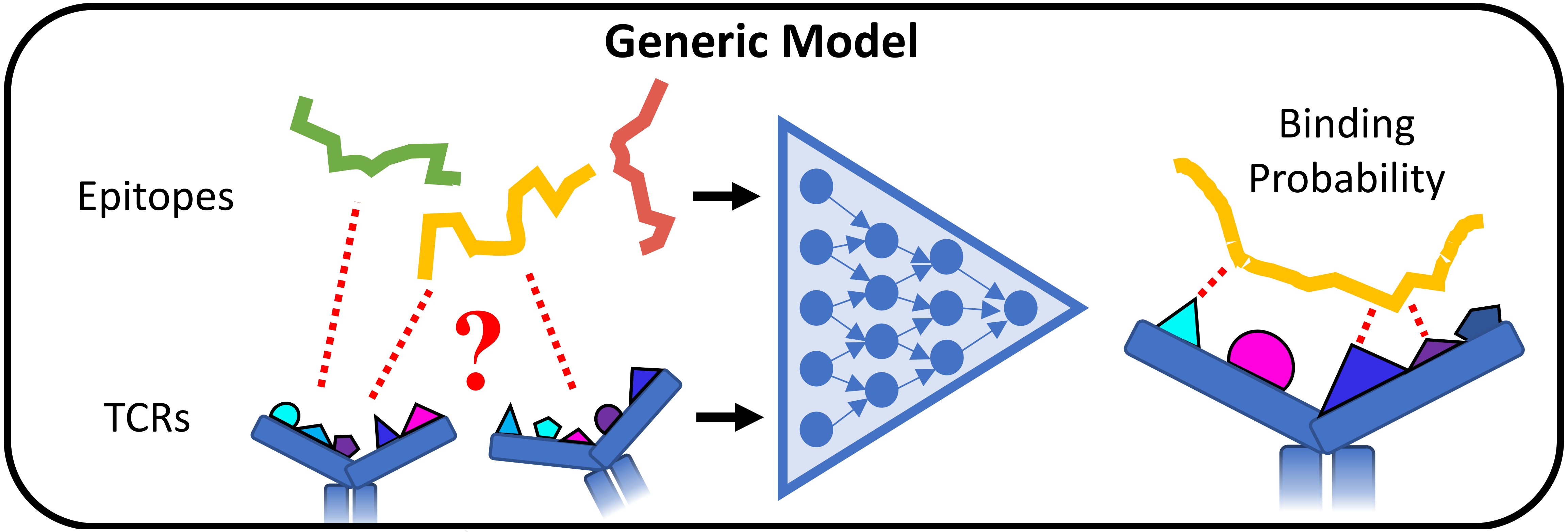
Credit: US National Cancer Institute

TITAN, an interpretable model to predict T cell receptor – antigen binding.

*https://precise-project.eu/

TITAN: AI model to predict T cell receptor – antigen binding

- TITAN: multimodal neural network to predict TCR binding



- 10^{15}-10^{20} theoretical diversity of TCRs
- Binding data of very few epitopes

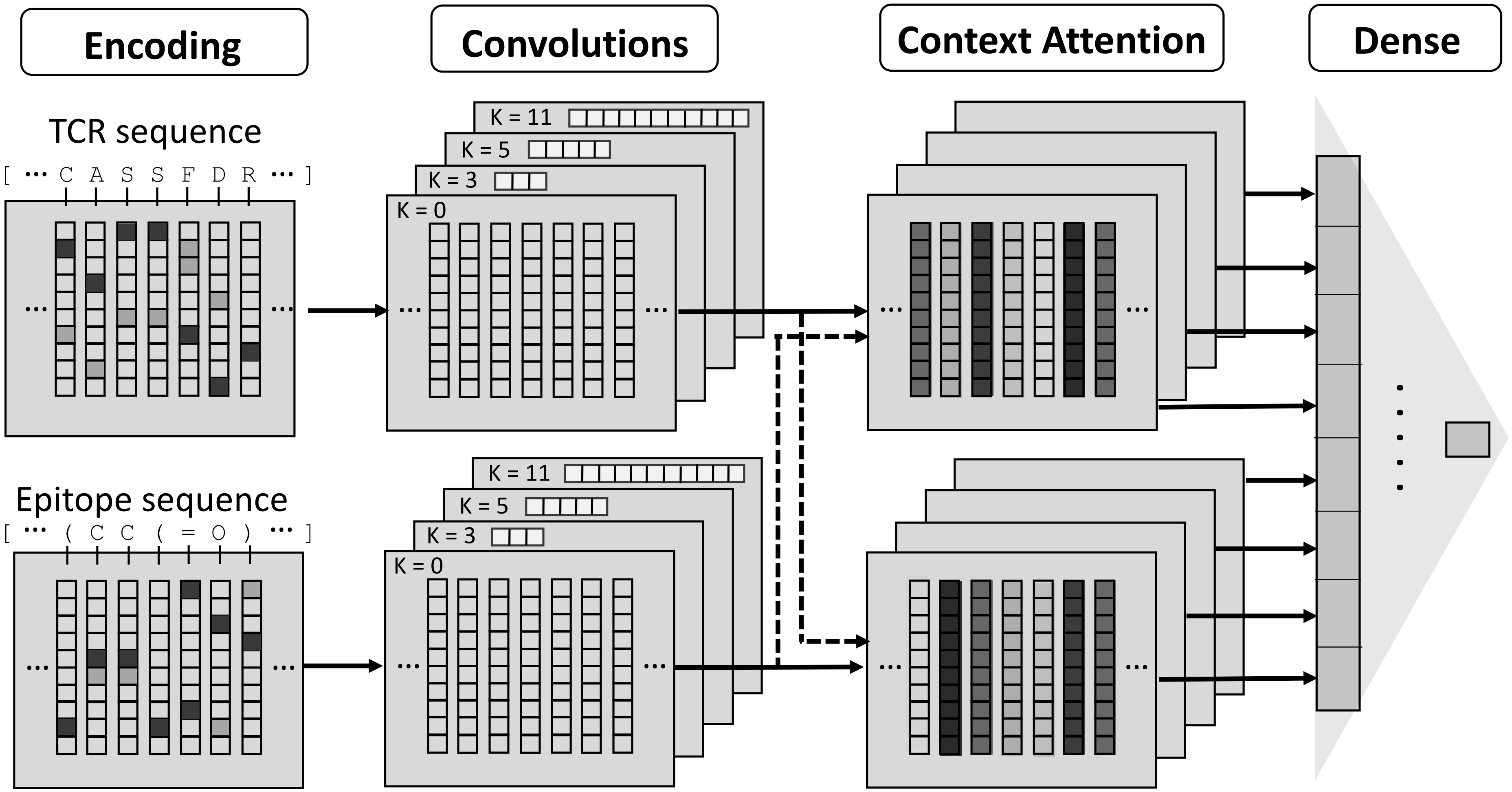
Weber et al, Bioinformatics, 2021.

Data

- VDJ database contains 40,438 TCR sequences binding 191 epitopes
- COVID dataset with 154,320 TCR sequences binding 269 epitopes
- Generate negative examples by shuffling

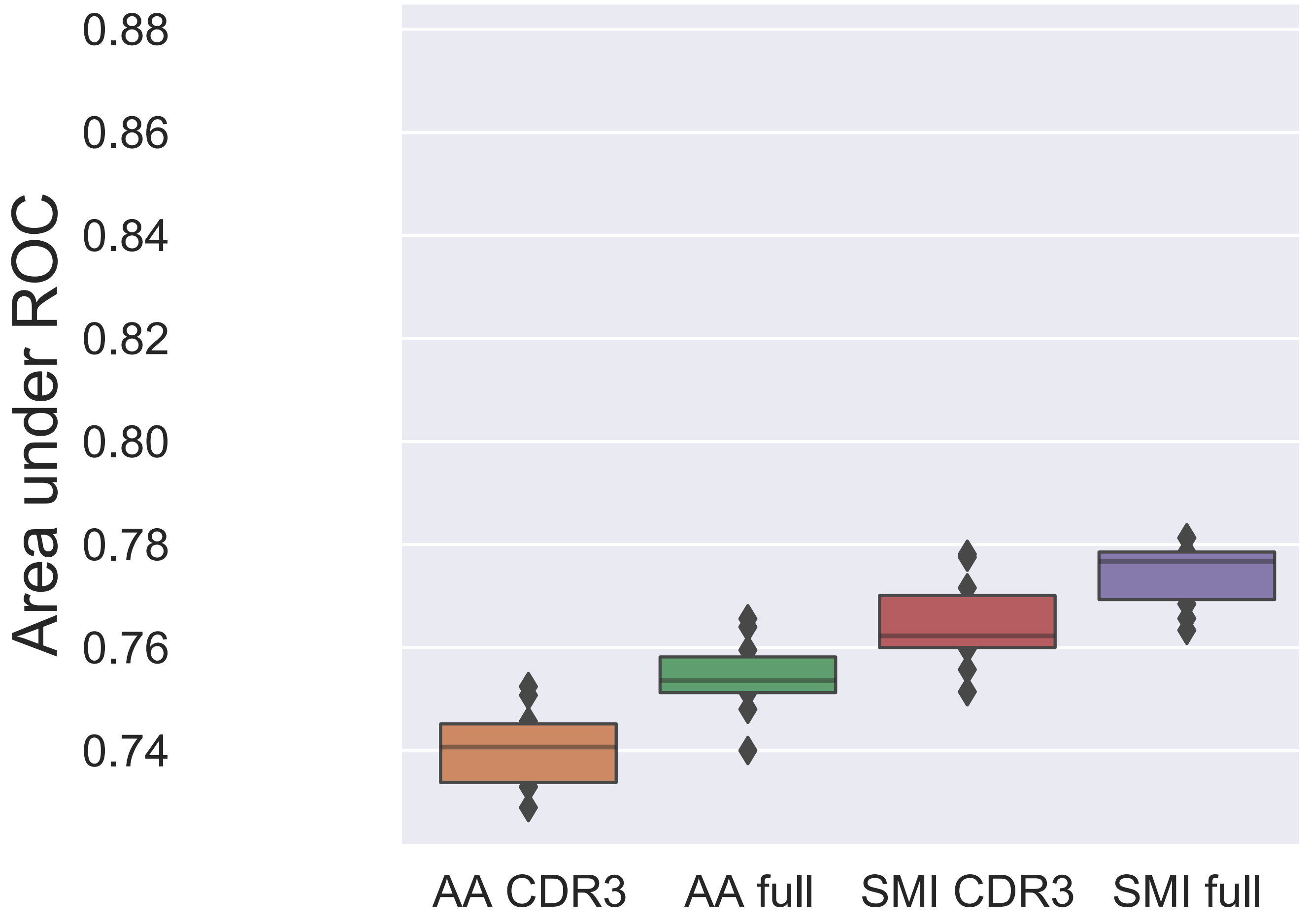
- Final data:
    - **46,290 TCRs binding 192 epitopes (15 – 400 TCRs/epitope)**

TITAN: predicting TCR- epitope binding affinity



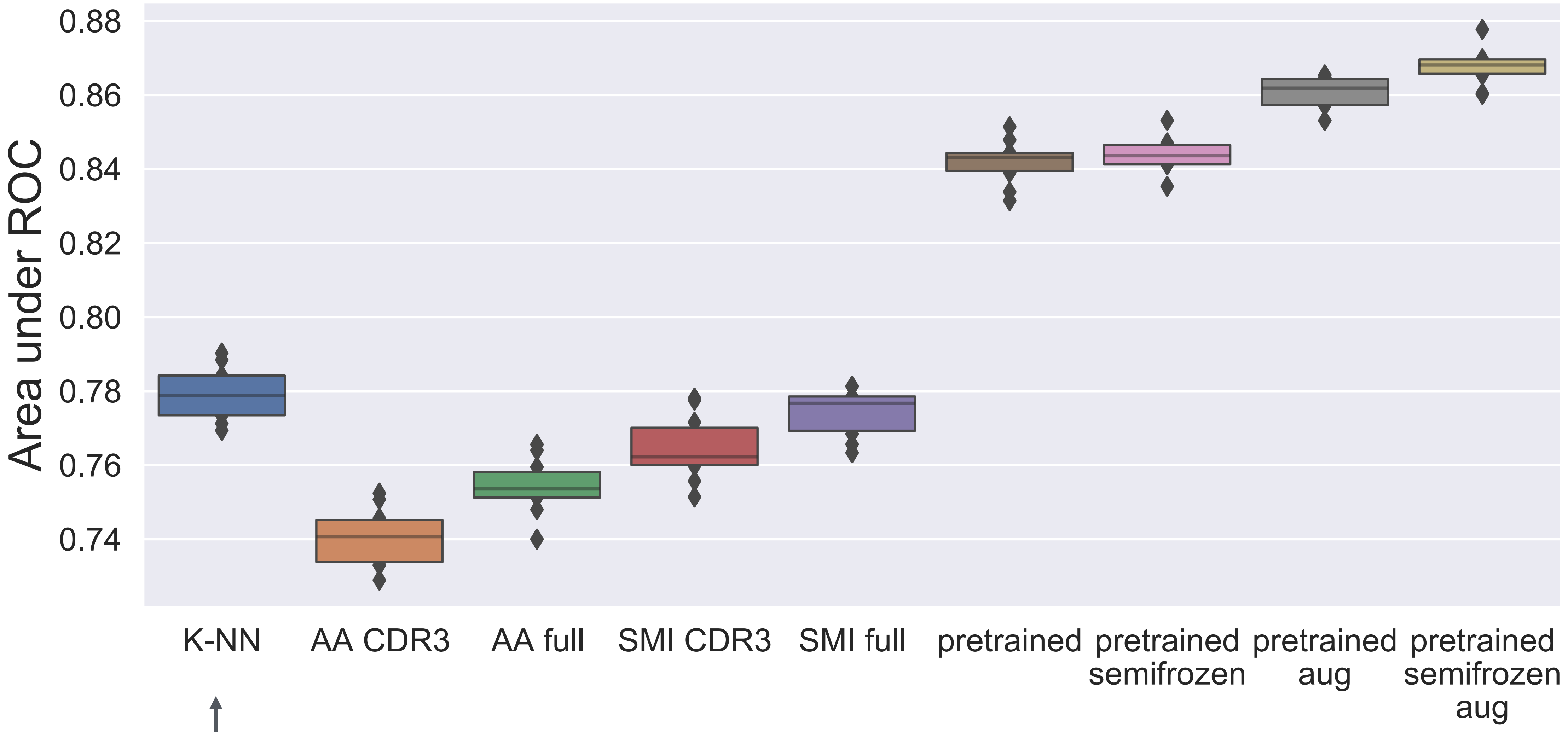
Weber et al, Bioinformatics, 2021.

TITAN performance



Weber et al, Bioinformatics (2021)

TITAN performance: good TCR generalization

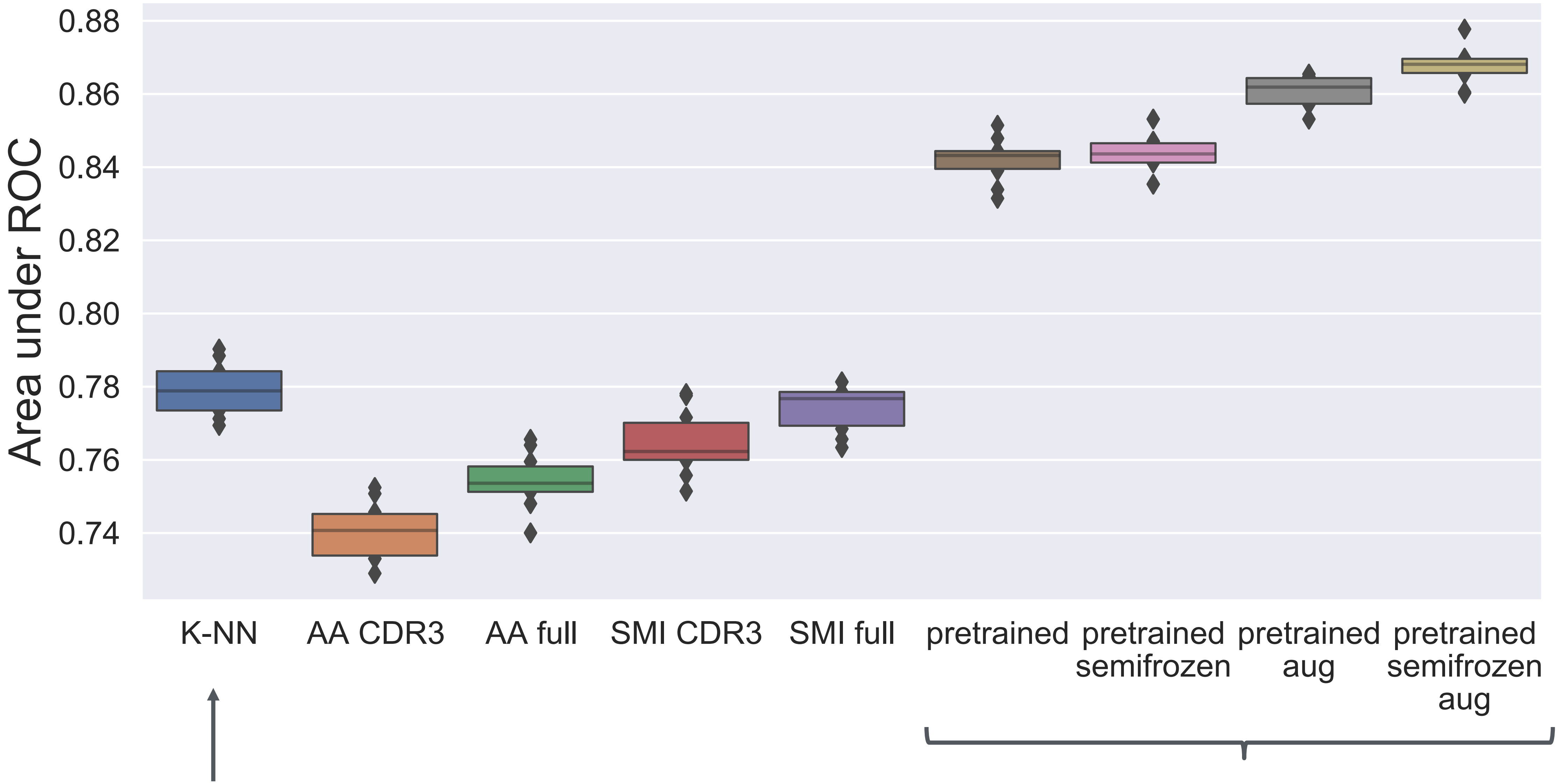


Baseline

TITAN models pretrained on BindingDB

Weber et al, Bioinformatics (2021)

TITAN performance: good TCR generalization

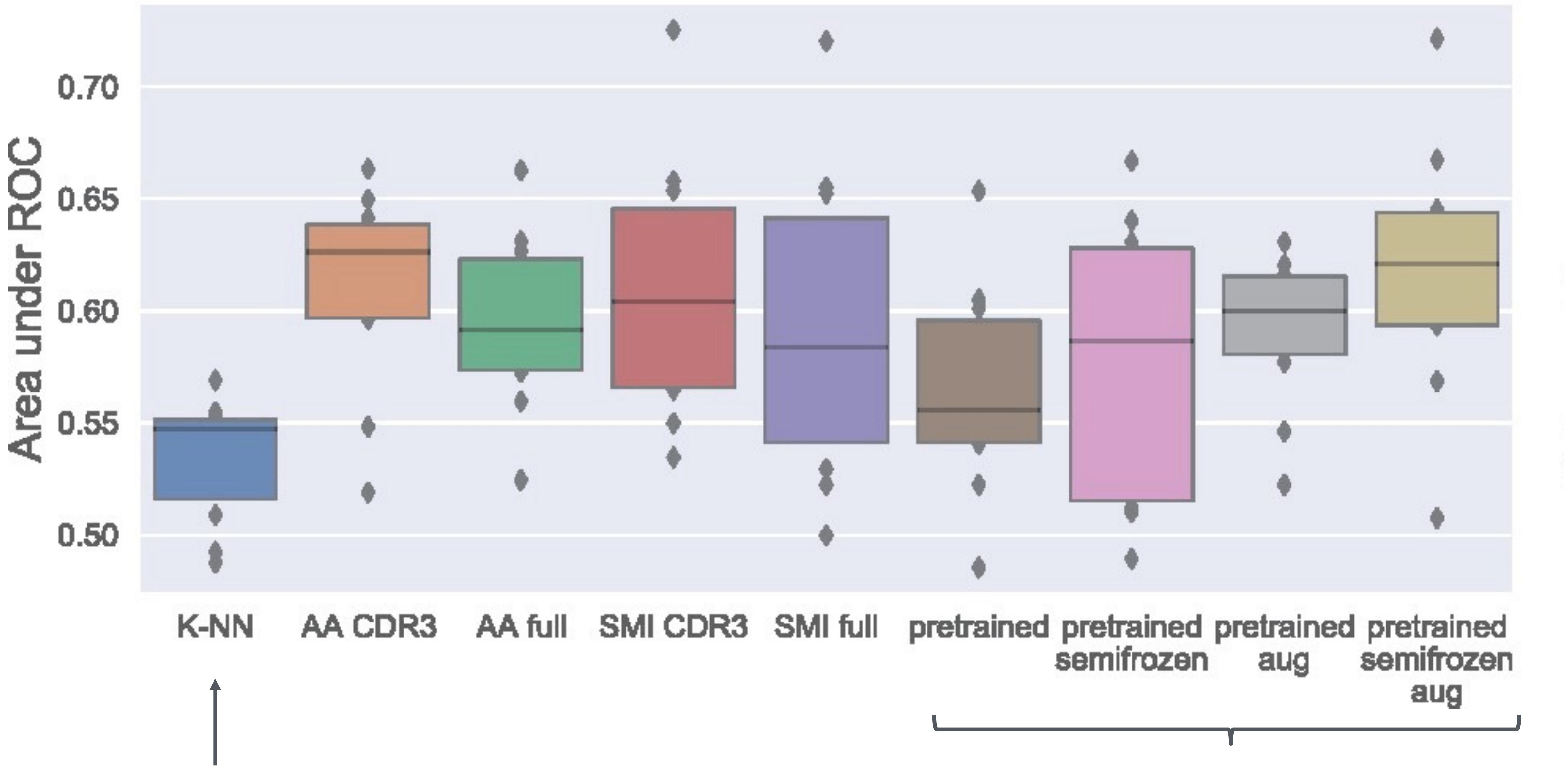


Baseline

TITAN models pretrained on BindingDB

Weber et al, Bioinformatics (2021)

TITAN performance: poor epitope generalization



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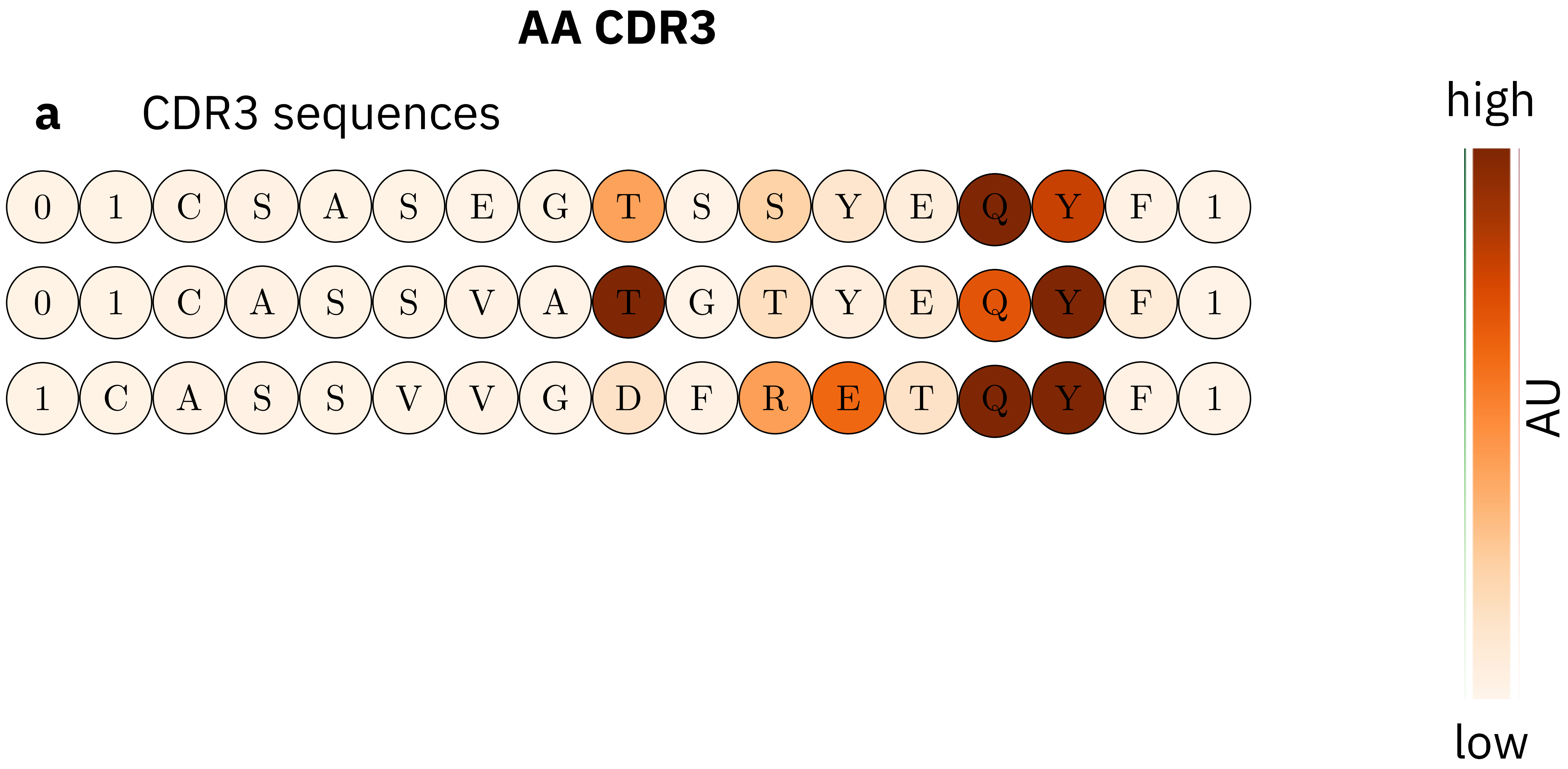
Extracting insights with attention mechanisms

Attention mechanisms:

→ Identify amino acids most important to predict the binding

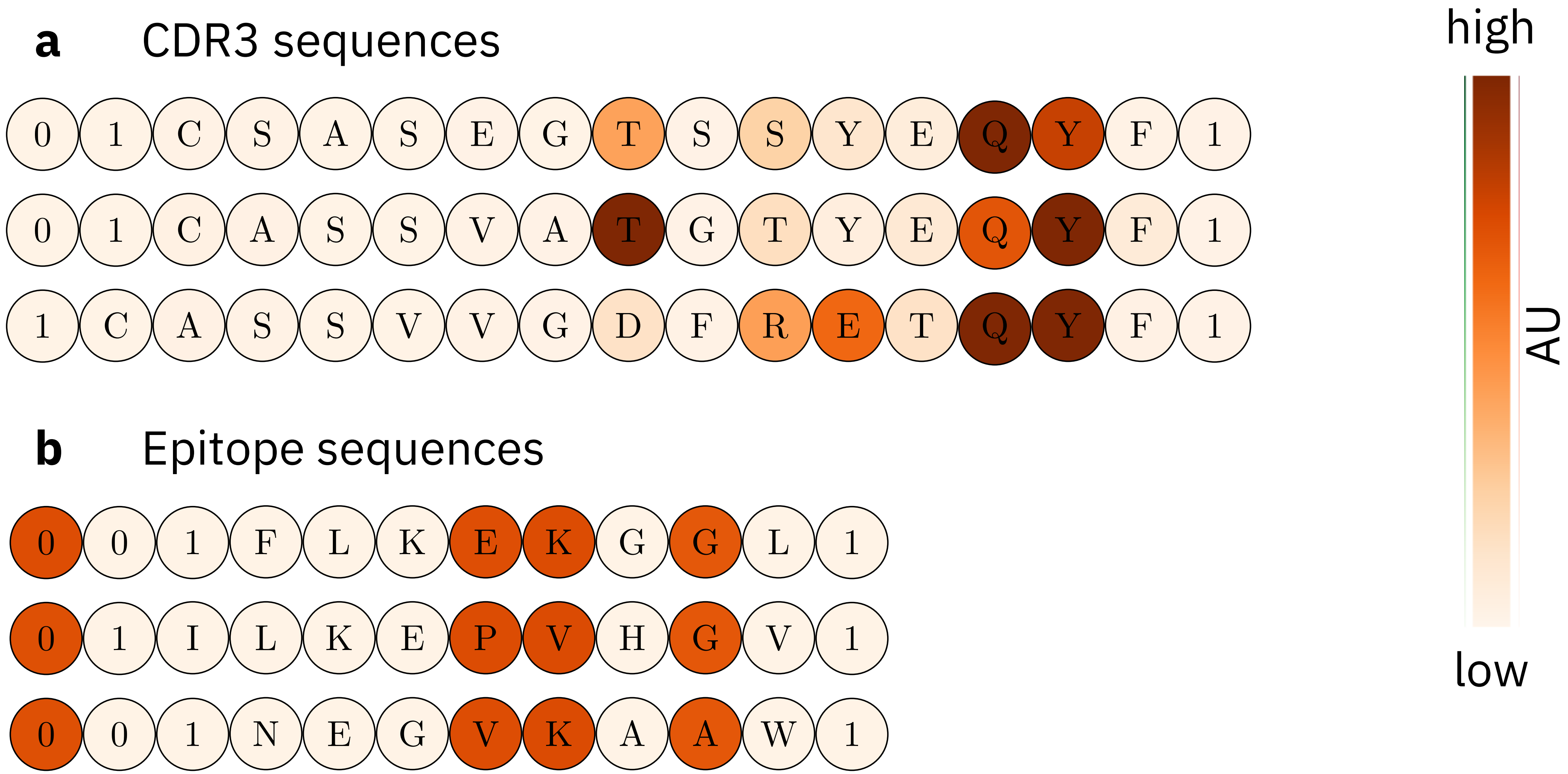


Extracting insights with attention mechanisms

Attention mechanisms:

→ Identify amino acids most important to predict the binding

AA CDR3



a CDR3 sequences

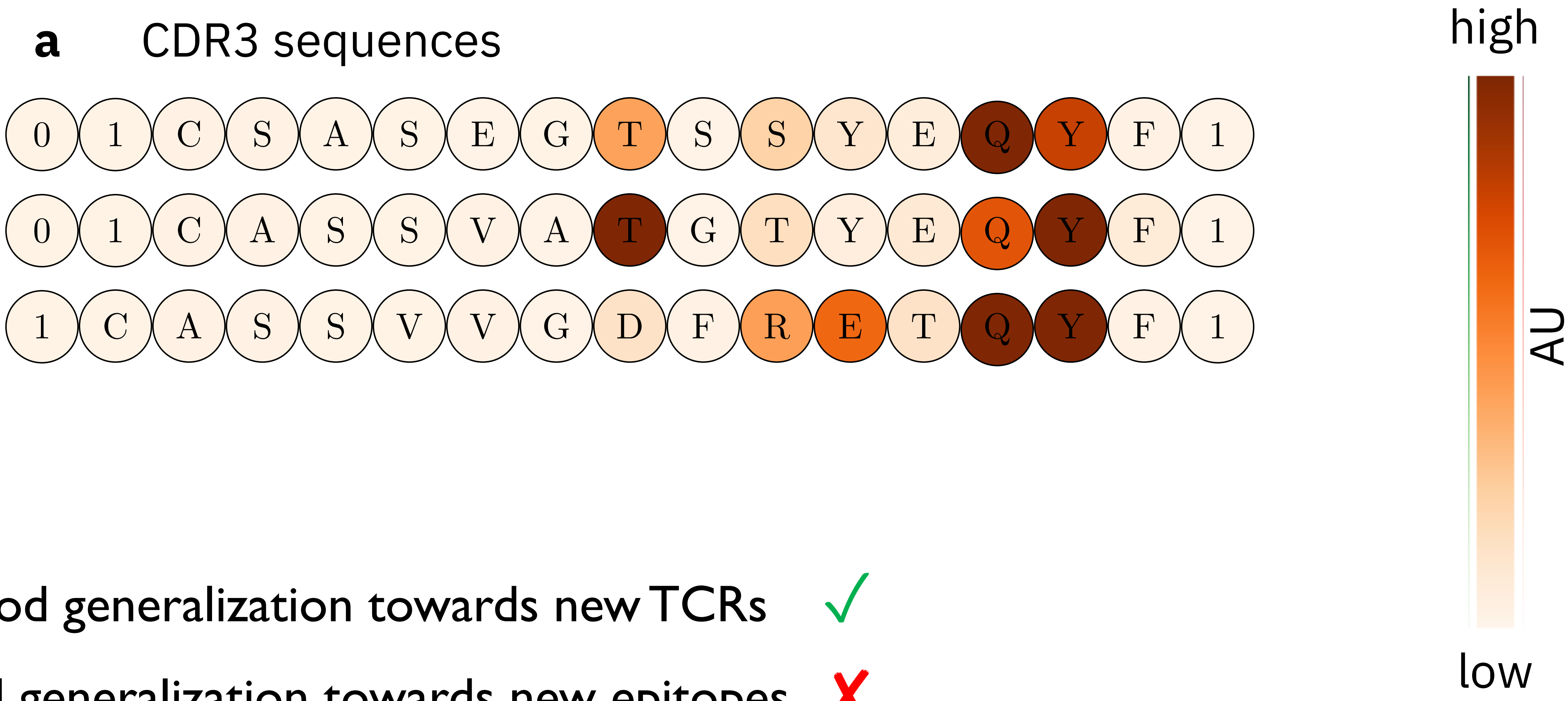
b Epitope sequences

Extracting insights with attention mechanisms

Attention mechanisms:

→ Identify amino acids most important to predict the binding

AA CDR3



- Good generalization towards new TCRs ✓
- Bad generalization towards new epitopes ✗

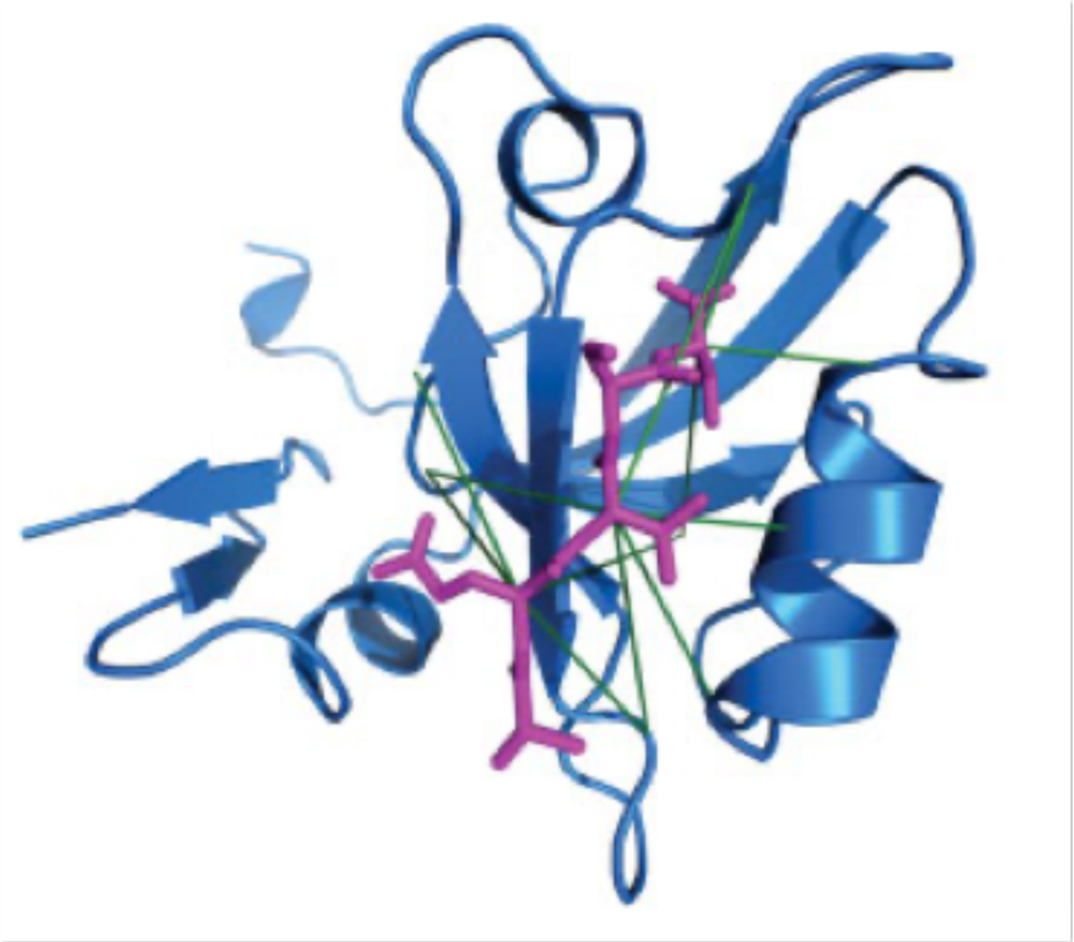
Unravelling TCR-antigen binding rules

Predict cross-reactivity:

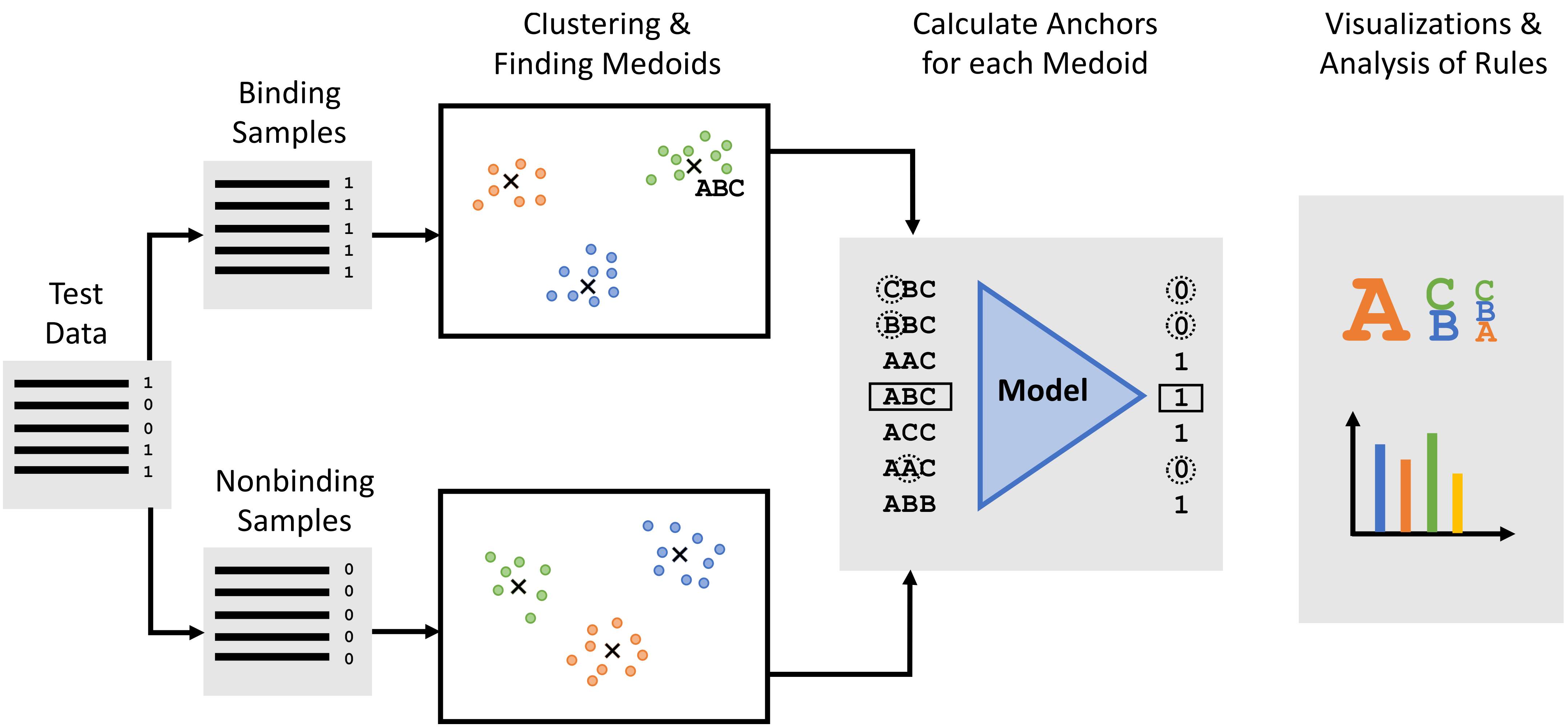
- A single TCR can recognize a million peptides
    - Off-target toxicities
    - Autoimmune diseases

Engineer TCRs with improved affinity

Mechanistic insights



DECODE: Interpretable pipeline for TCR binding



Test Data

Binding Samples

Nonbinding Samples

Clustering & Finding Medoids

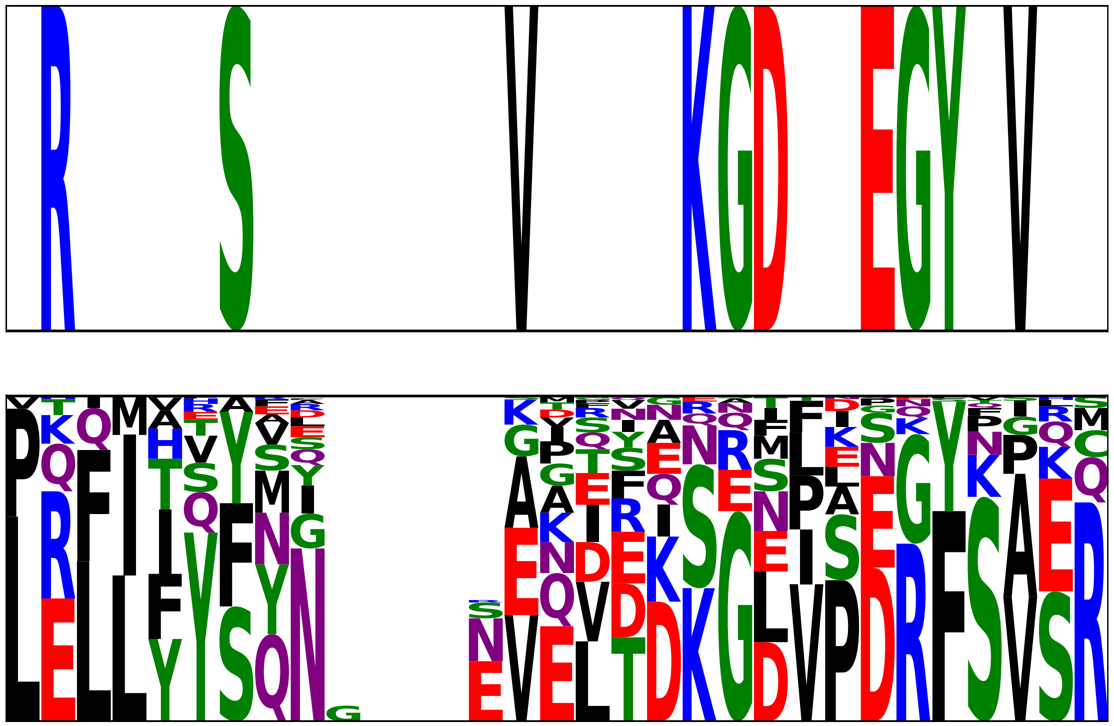
Calculate Anchors for each Medoid

Visualizations & Analysis of Rules

- Understand TCR binding rules
- Generate *if-then* rules

DECODE: Interpretable pipeline for TCR binding

Explanations can be visualized and evaluated



TITAN Anchor CDR2 Region

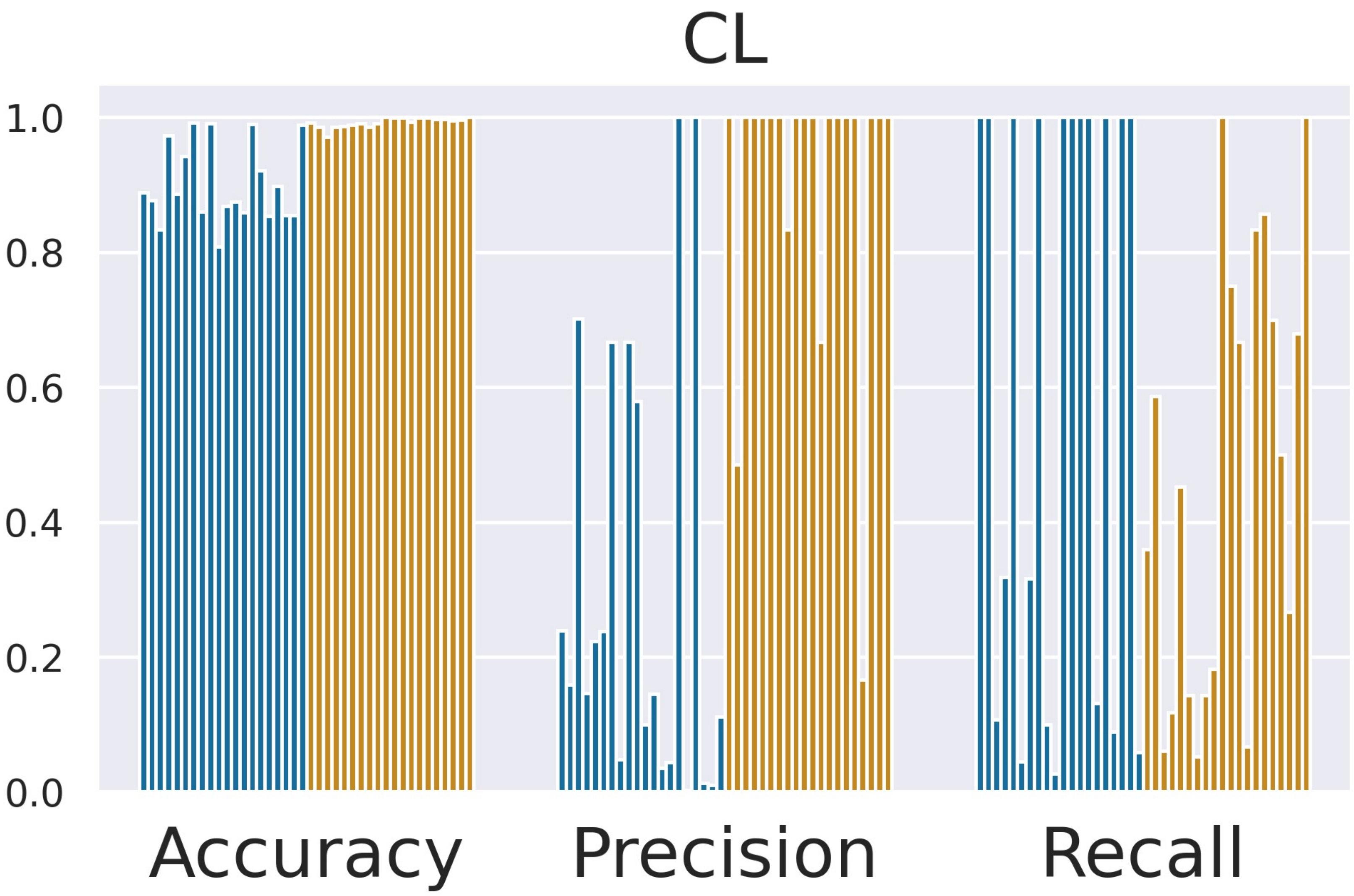
pMTnet Anchor CDR3 Region

Papadopoulou et al, Bioinformatics, 2022 (in press).

DECODE: Interpretable pipeline for TCR binding

Explanations can be visualized and evaluated:

→ Cluster level: a sample is a true positive if it fulfills *only* the anchor rule generated from the medoid of its cluster

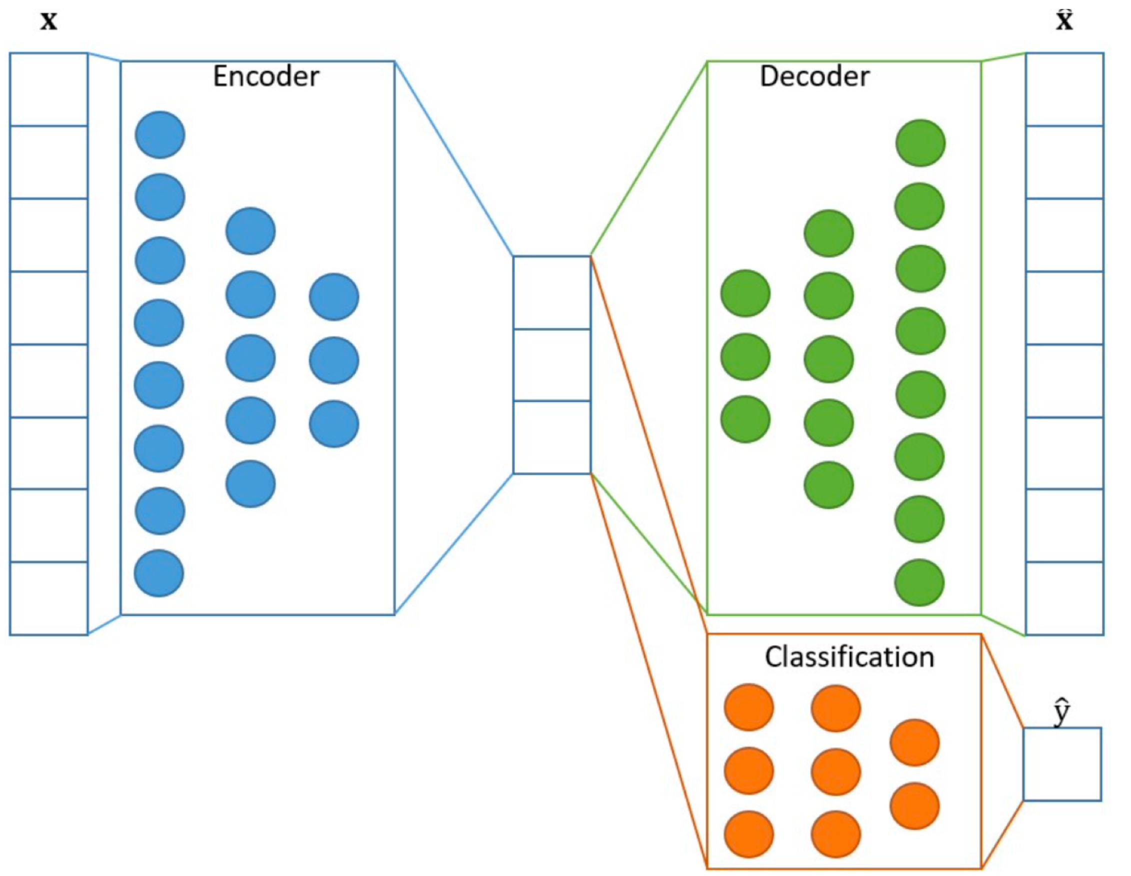


Blue – non-binding rules
Orange – binding rules

Ongoing work

Increasing the amount of epitope data

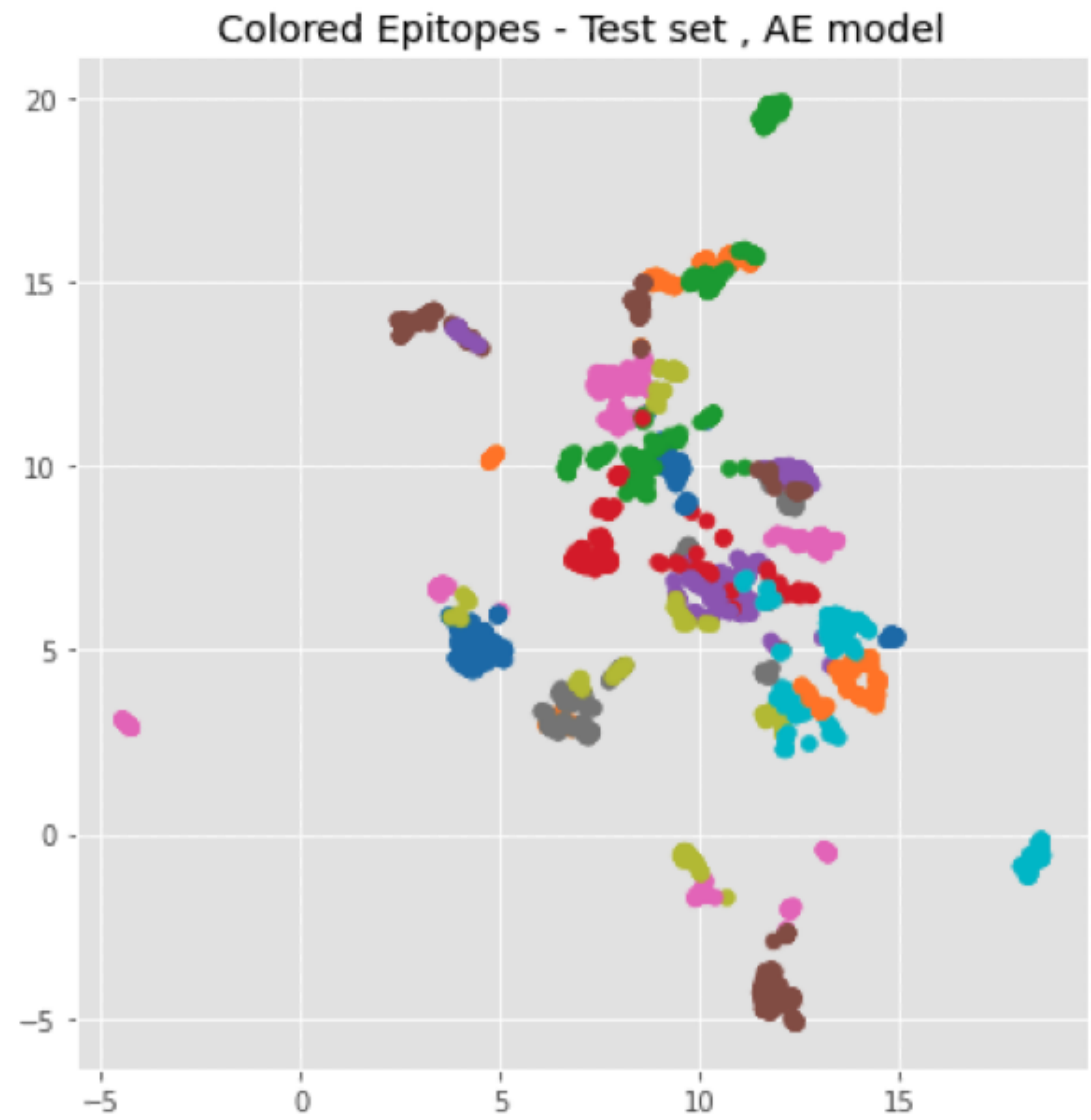
- Semi-supervised learning approaches
  - ➢ Exploit labelled and unlabelled data



Increasing the amount of epitope data

- Semi-supervised learning approaches
  - ➢ Exploit labelled and unlabelled data

- **Future work**: reinforcement learning for domain adaptation



Conclusions

- Goal
  - Predicting TCR binding is essential to understand the adaptive immune system and to engineer immune interventions
    - Optimization of cancer immunotherapies
- TITAN
  - Predicts the binding of TCRs and a small set of epitopes
    - Good accuracy when epitope is fixed
    - Interpretability through attention mechanisms
- DECODE
  - Interpretable pipeline to generate biochemical rules to explain TCR-epitope binding
- Future work
  - Predicting cross-reactivity when little epitope data
    - Semi-supervised learning approaches
    - Combination of molecular dynamics + AI

Thank you for your attention!

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