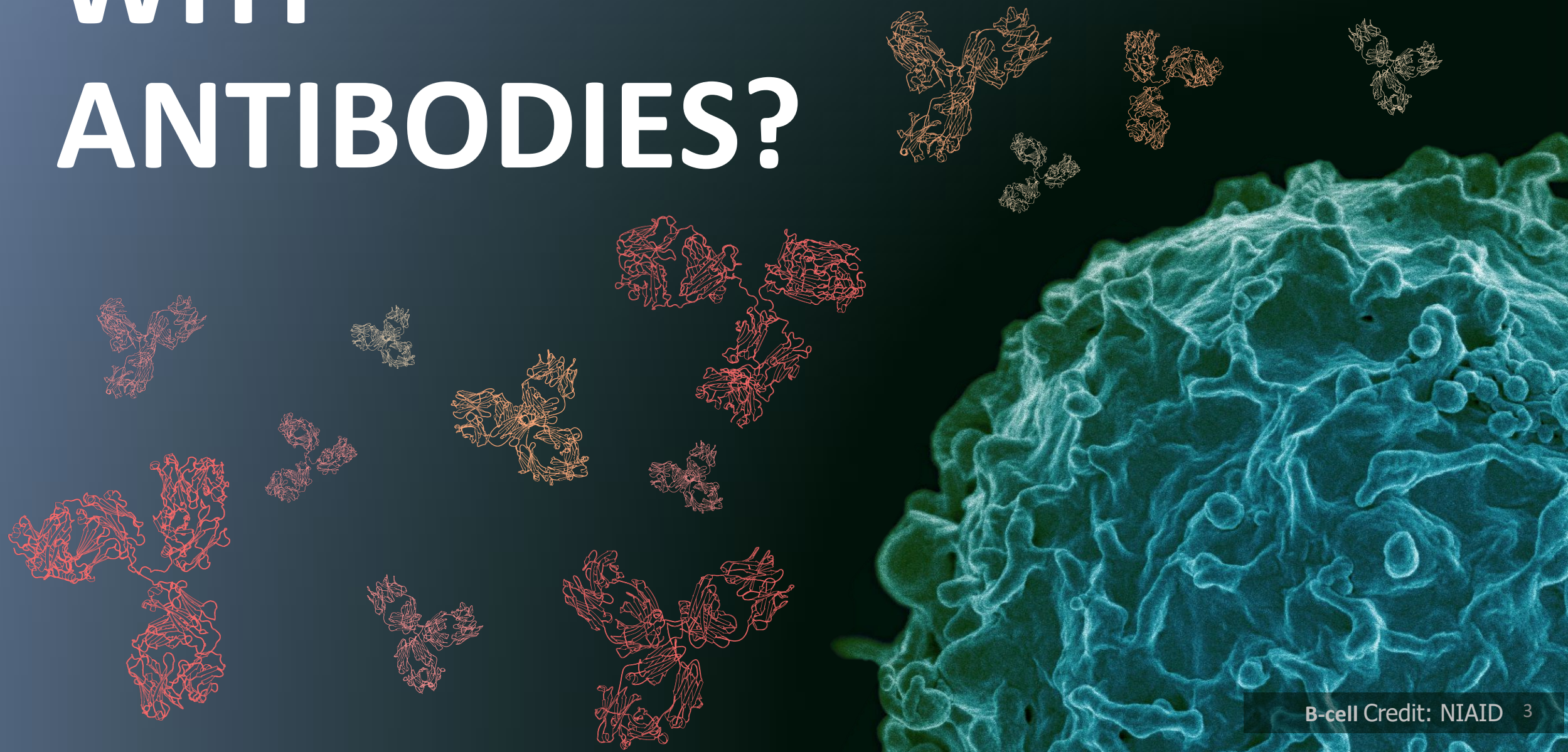
Bio-Health:
Using AI to Engineer Human Antibodies

Macromoltek

Revolutionizing antibody design

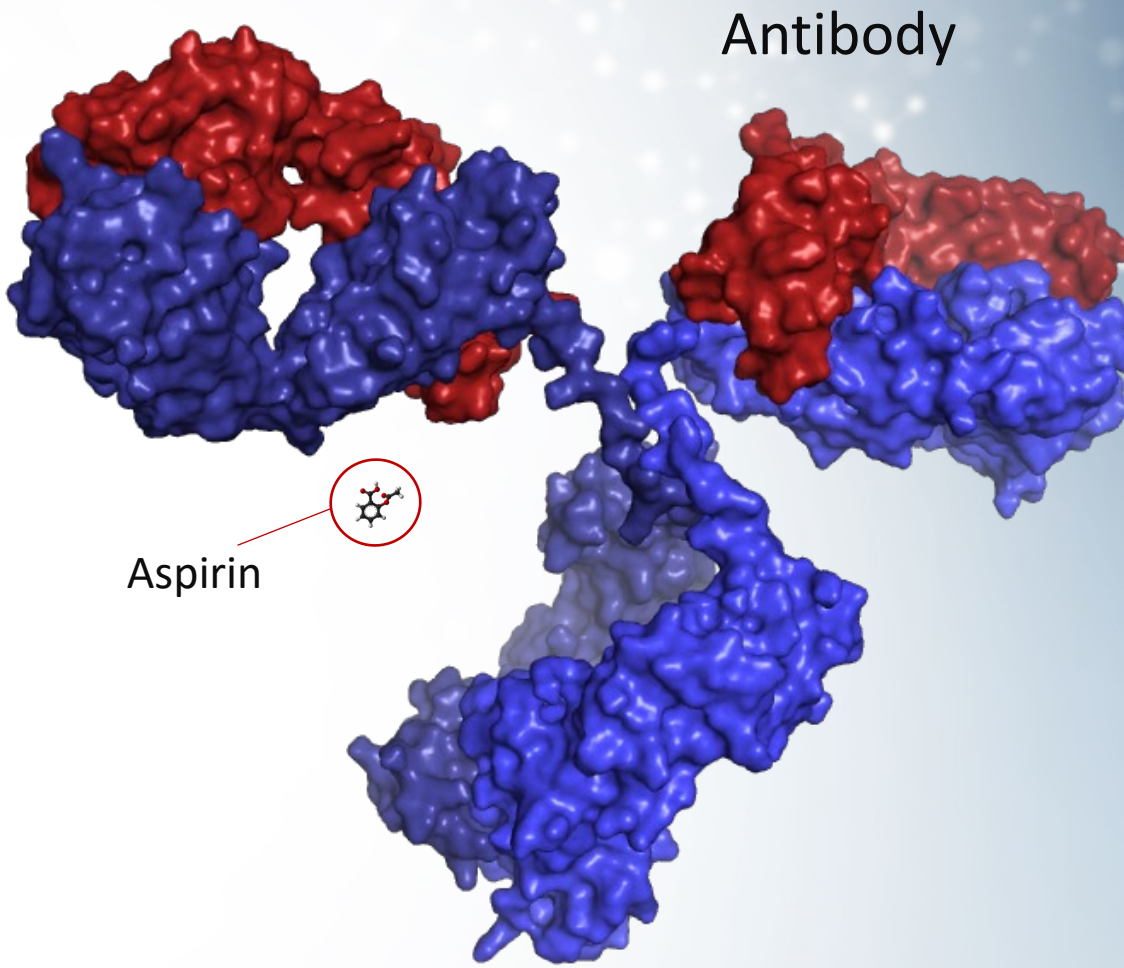
Monica Berrondo, PhD
CEO and Co-founder

WHY ANTIBODIES?



B-cell Credit: NIAID

ANTIBODIES ARE PROVEN SUPERIOR DRUGS



Advantages of antibodies over small molecules

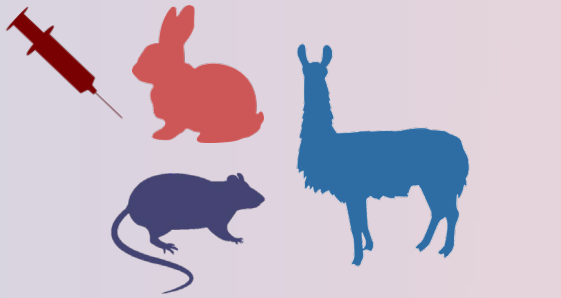
- Drugging “undruggable” targets
- Higher specificity and fewer side effects

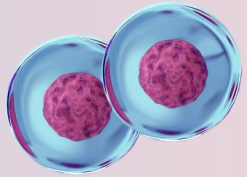
Clinical trial success rates

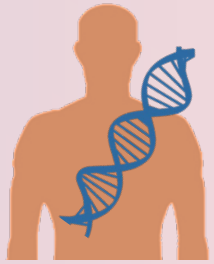
- 2X small molecule rate
- Highest of any drug modality

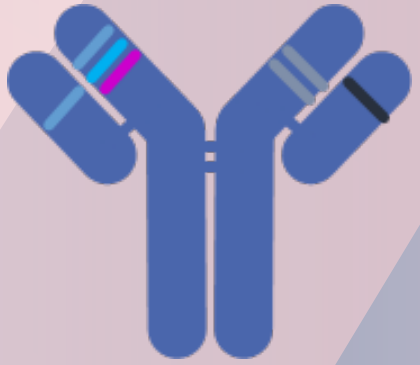
Current antibody discovery comes from two main sources:

Animal immunizations

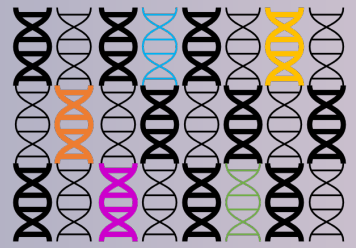


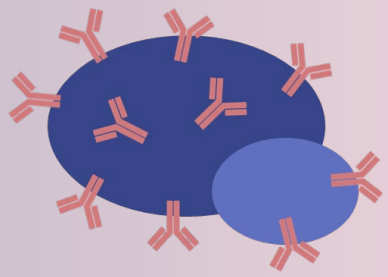






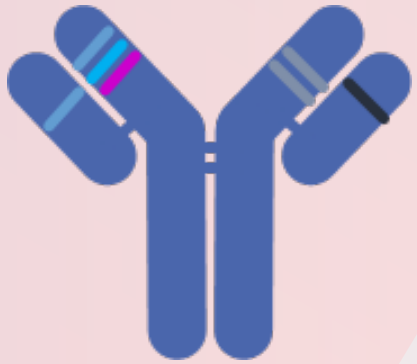
Display Technologies





Pitfalls of animal derived antibodies

Animal immunizations



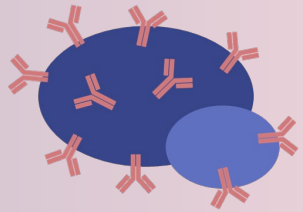
Time, labor, and capital intensive

Antibodies can cause negative immune response in humans

Extremely expensive to produce mice with human immune cells

Pitfalls of display derived antibodies

Display Technologies



Difficult to manufacture

Antibody diversity is limited by the cells in which they are produced

Further optimization necessary

DISCOVERY VS *DESIGN*

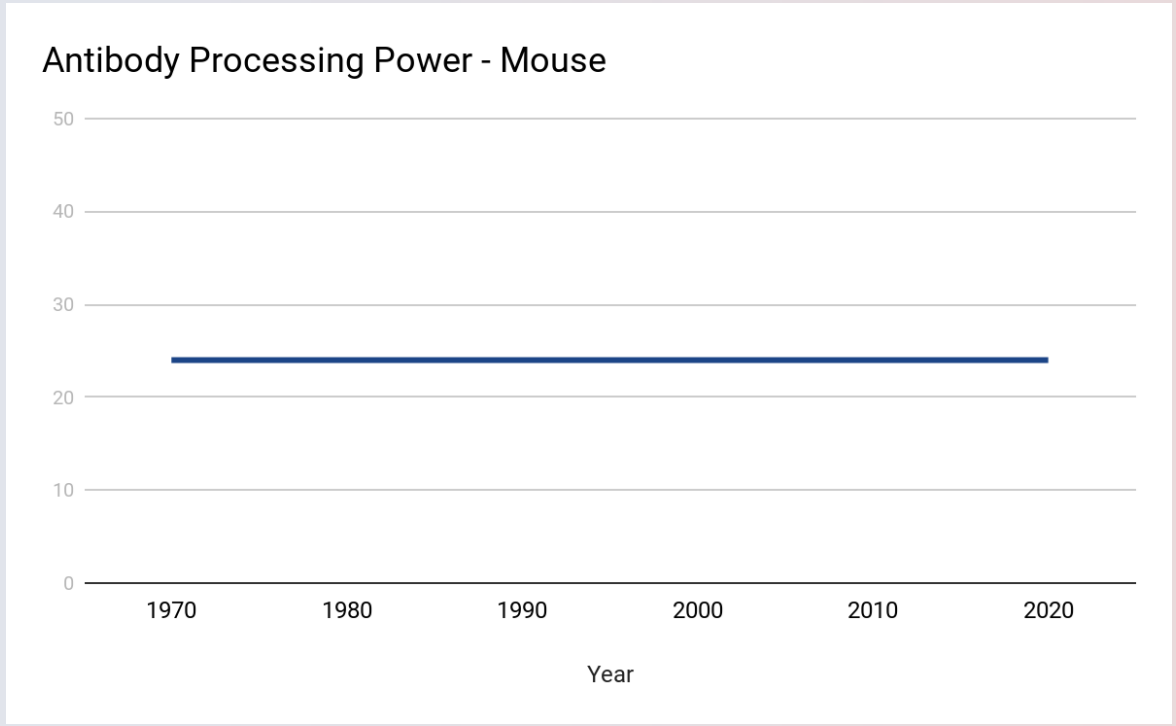
Discovery Platforms are unable to target specific mechanisms of action

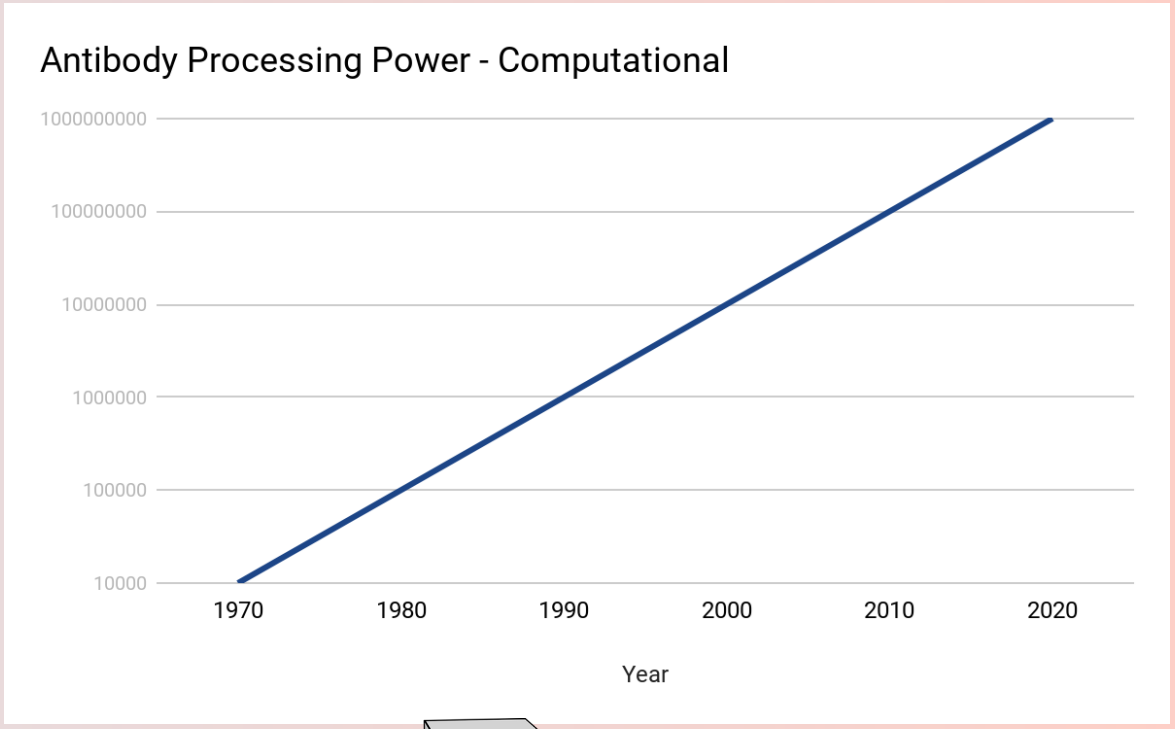
Current platforms blindly generate “hits” to be tested down the pipeline

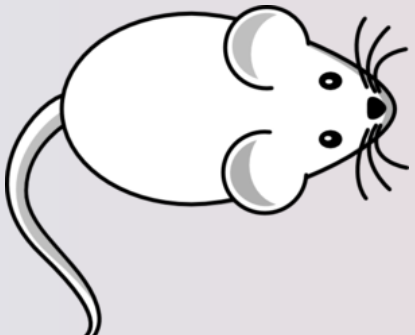
How the antibody interacts with its target is identified after discovery

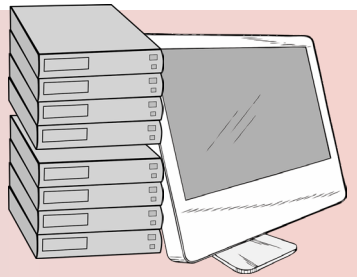
Our DESIGN software uses information about how the target causes disease to create antibodies that directly address the problem.

Computational Drug Design – Huge Potential

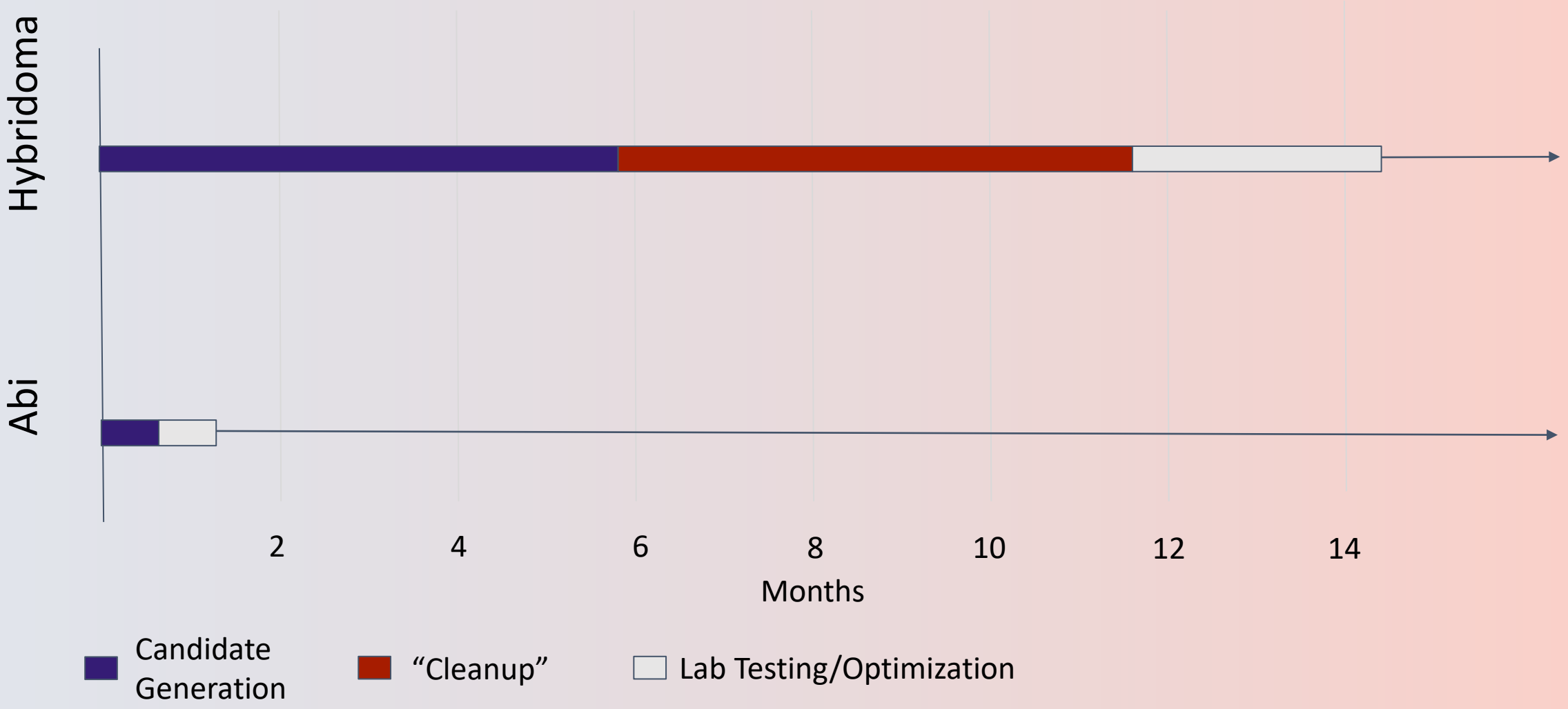








Antibody Development Timeline

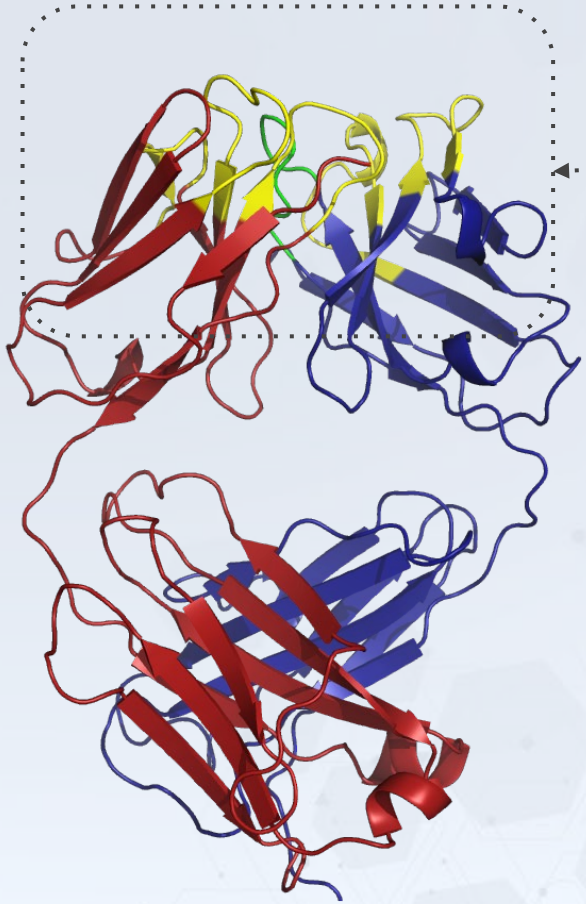


Computational Antibody Design

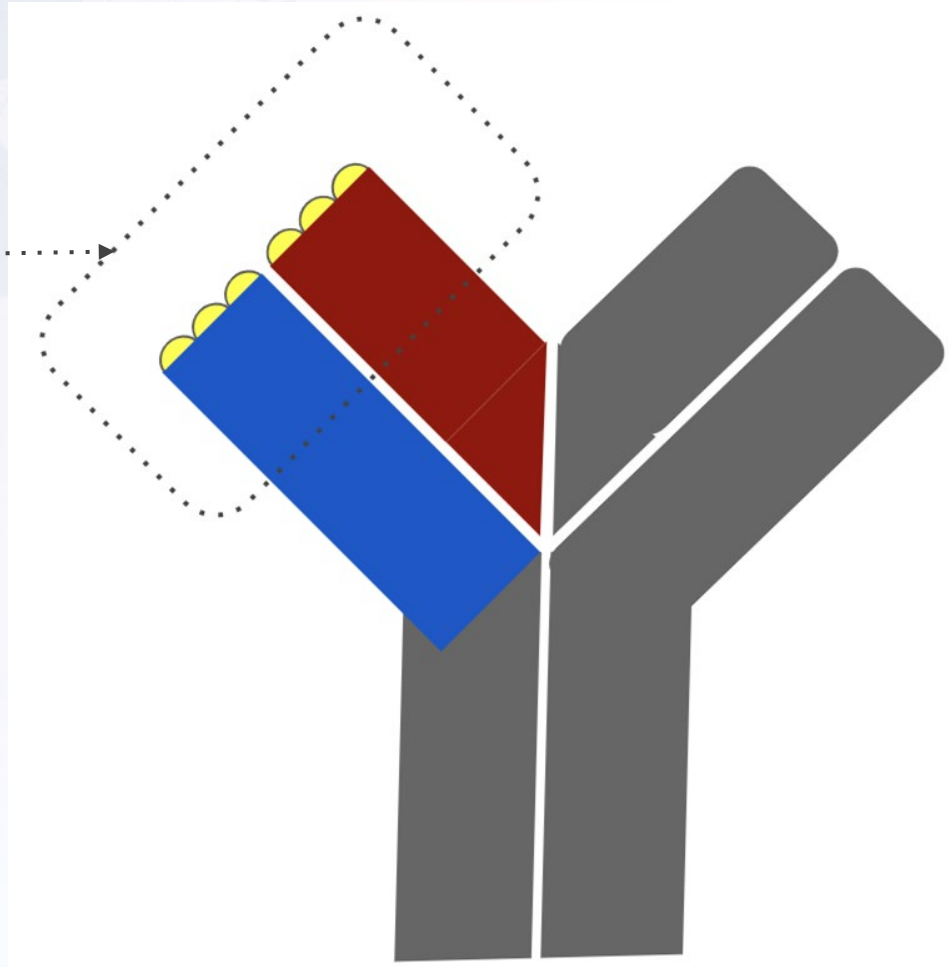
Advantages of Computational Antibody Design

- **Ability to target “undruggable” targets**
  - Inaccessible epitopes, alternate states, autoimmune targets
  - *In silico* design: target can be isolated and designed without interference from the system
- **Antibodies built on human scaffolds**
  - Less likely to be rejected than mouse antibodies
  - No need for extra humanization steps

What is an antibody?



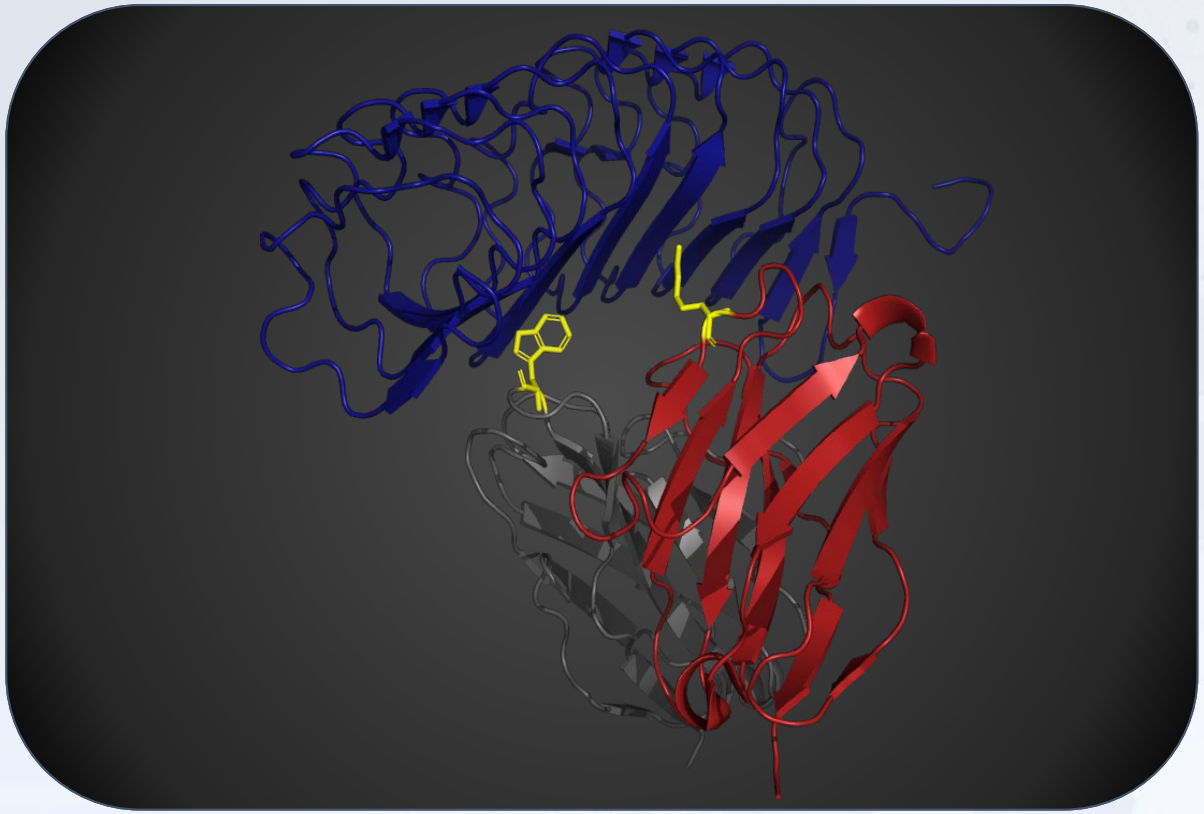
Special binding region



Modes of antibody design

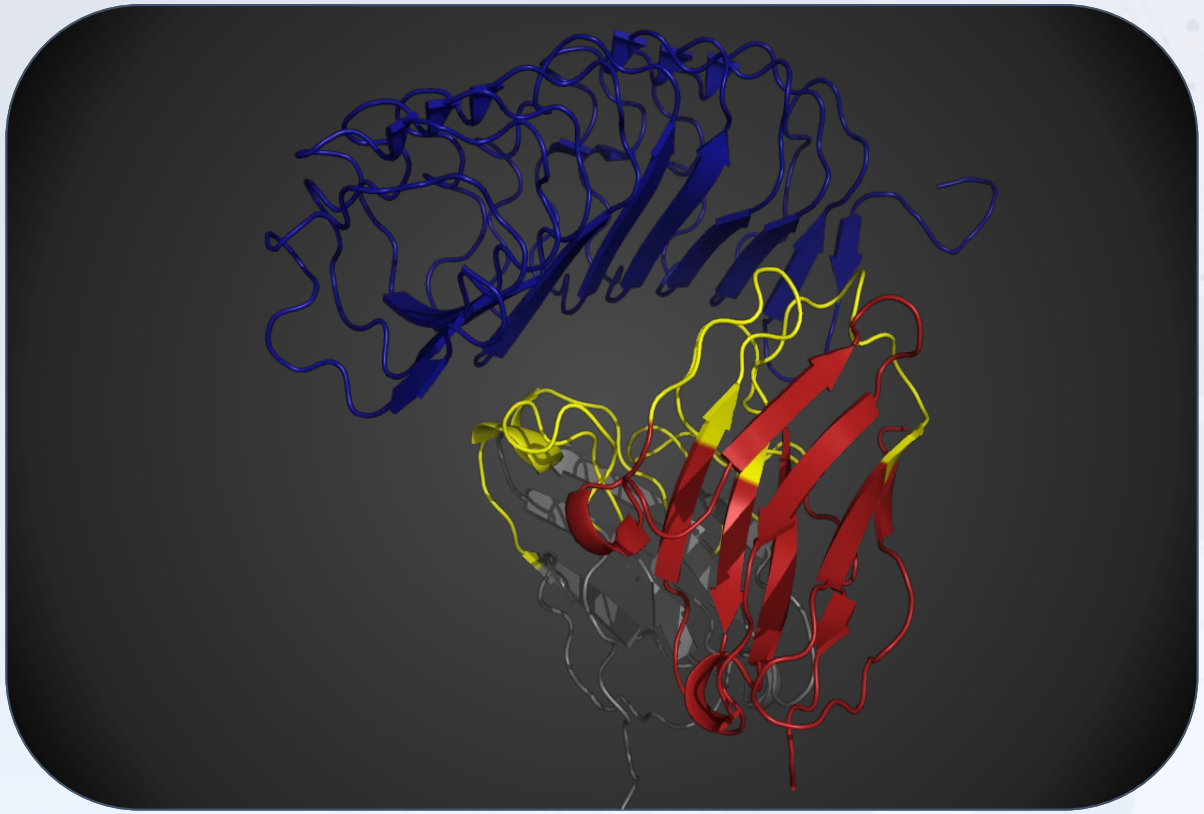
- **Most existing methods focus on improving the chemistry of an *existing* antibody-antigen complex**
- ***De novo* (from scratch) design is more complicated**
  - No starting-point antibody
  - Optimizes chemistry and topology simultaneously
- **New computational power and our proprietary software make it possible to do *de novo* antibody design**

Existing Computational Antibody Design Methods



- Series of individual amino acid changes to improve an existing antibody/antigen pairing
- Changes to make the antibody bind a similar epitope on another antigen
- High information requirement
  - Must know complete antibody and antigen complex structure

De novo Design Against a Selected Epitope



- "Holy Grail" of computational antibody design
- Design an antibody from scratch against a chosen epitope
- Low information requirement: all you need to start is an antigen structure
  - If a similar antigen exists, use homology modeling
    - In this case, only antigen sequence is needed

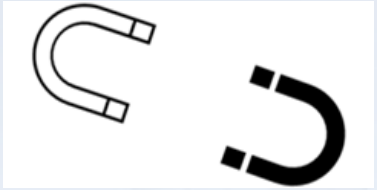
Key Considerations in Antibody-Antigen Interactions

- **Paratope topology: Is its shape complementary to that of the epitope?**
- **Chemistry**
  - Polar interactions: Do the paired amino acids attract or repel each other?
  - Hydrophobics: Are water-soluble amino acids exposed and water-repelling residues hidden?
  - Hydrogen bond formation: Structures which form more hydrogen bonds are more stable.
- **One change can affect everything!**
  - Altering an amino acid to improve chemical interactions might deform the paratope structure
  - Changes in structure can disrupt chemical interactions

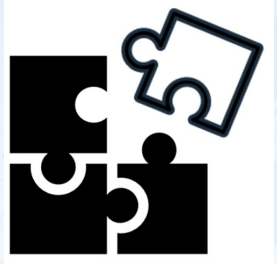
The Biochemistry of Antibodies

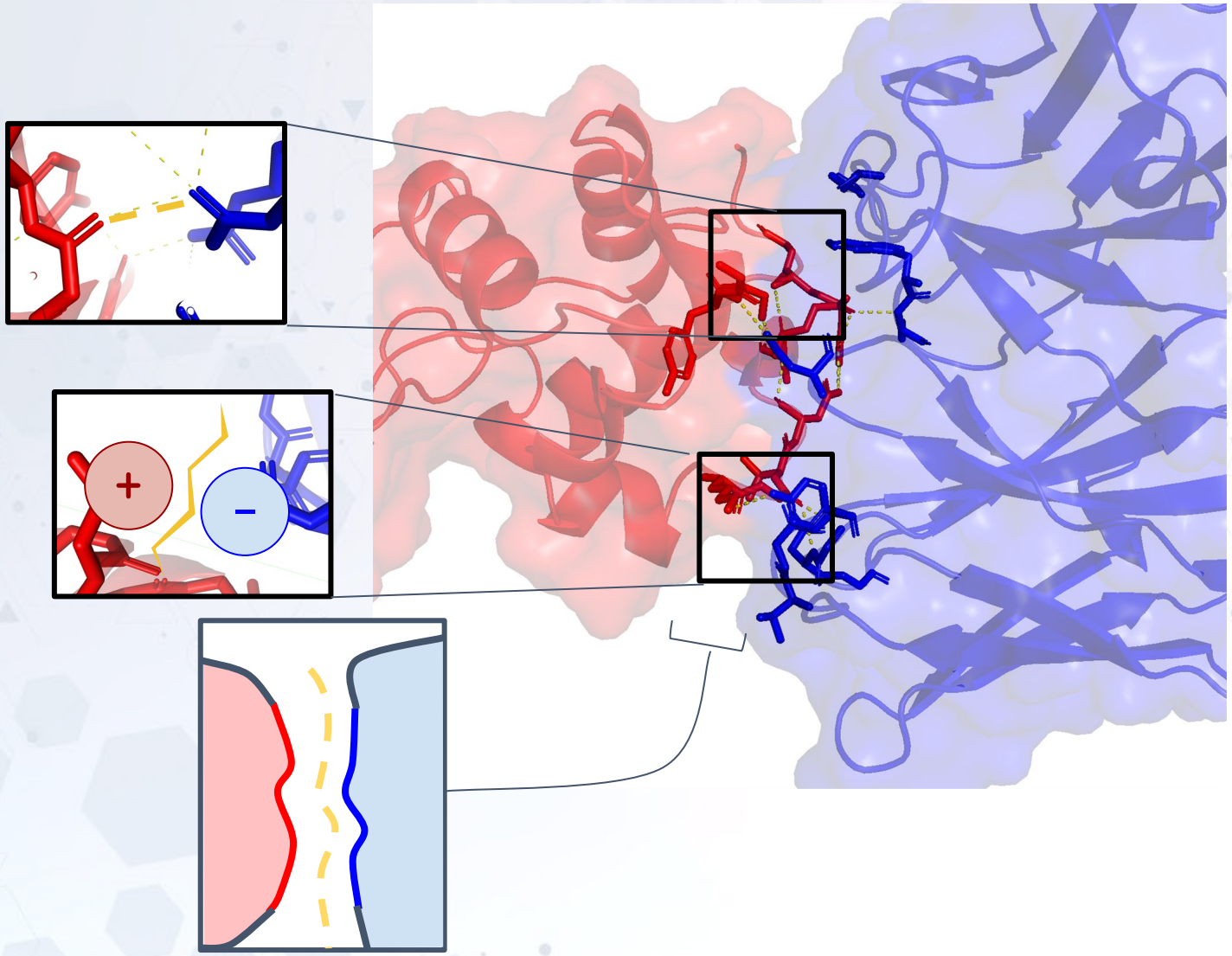
1. **Hydrogen bonding**

2. **Charge interactions**



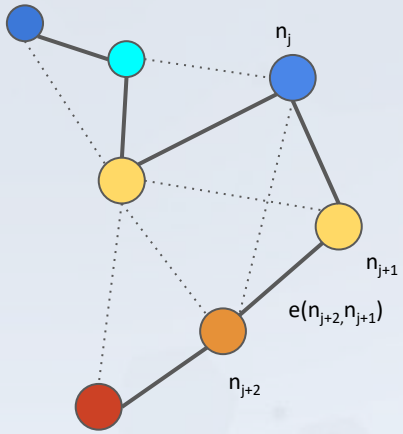
3. **Shape complementarity**



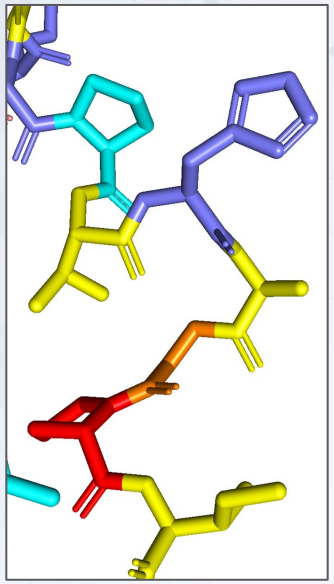


Data Representation

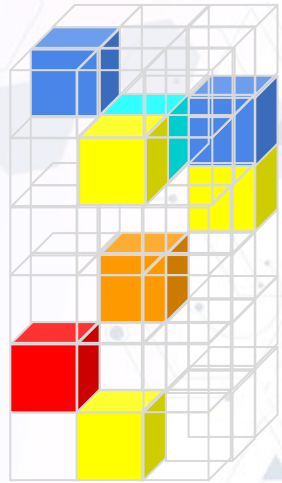
Graph



Protein Structure



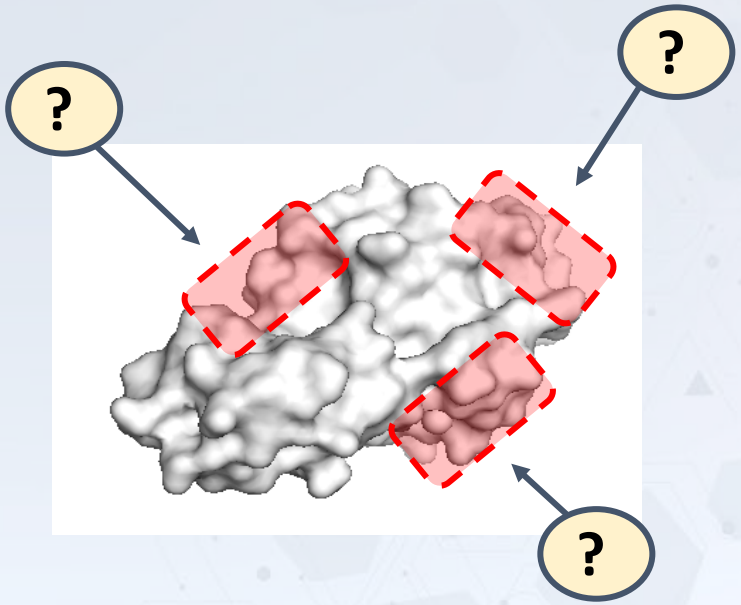
Voxel



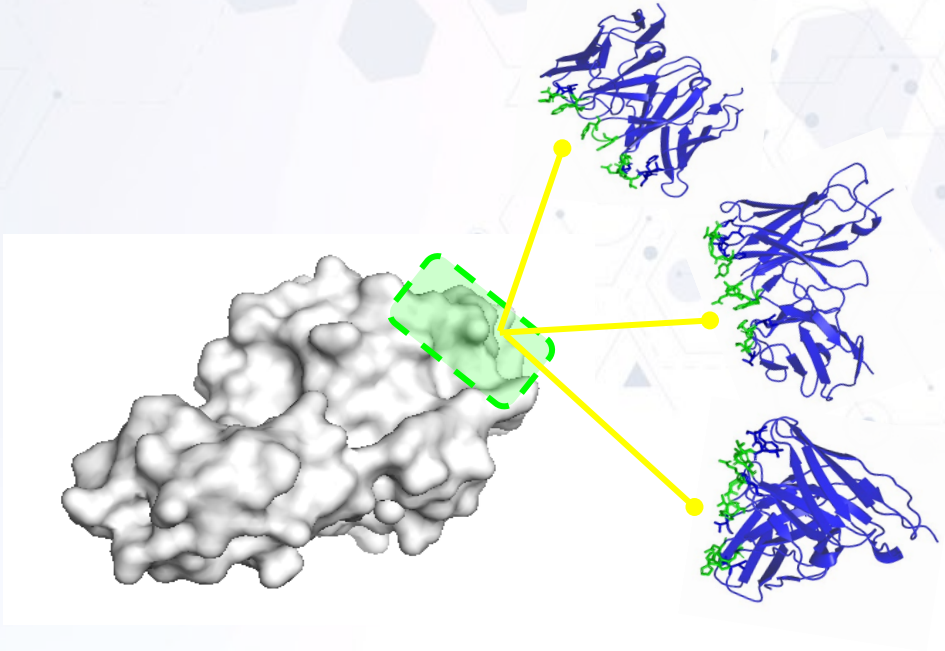
- Transforms into a complex computer vision problem
- Allows us to use build powerful convolutional neural networks
- GPUs are needed to train and infer using these representations

Problems in Computational Design

Where do we target our designs?



Which designs will work?

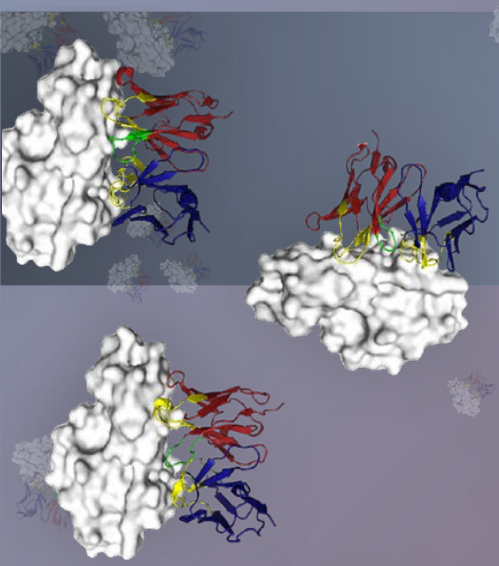


Computational Process

Antibody Design Process Taps into the FUTURE

Each cycle GOAL:

- Computation 1 week
- Testing Antibodies 1 week



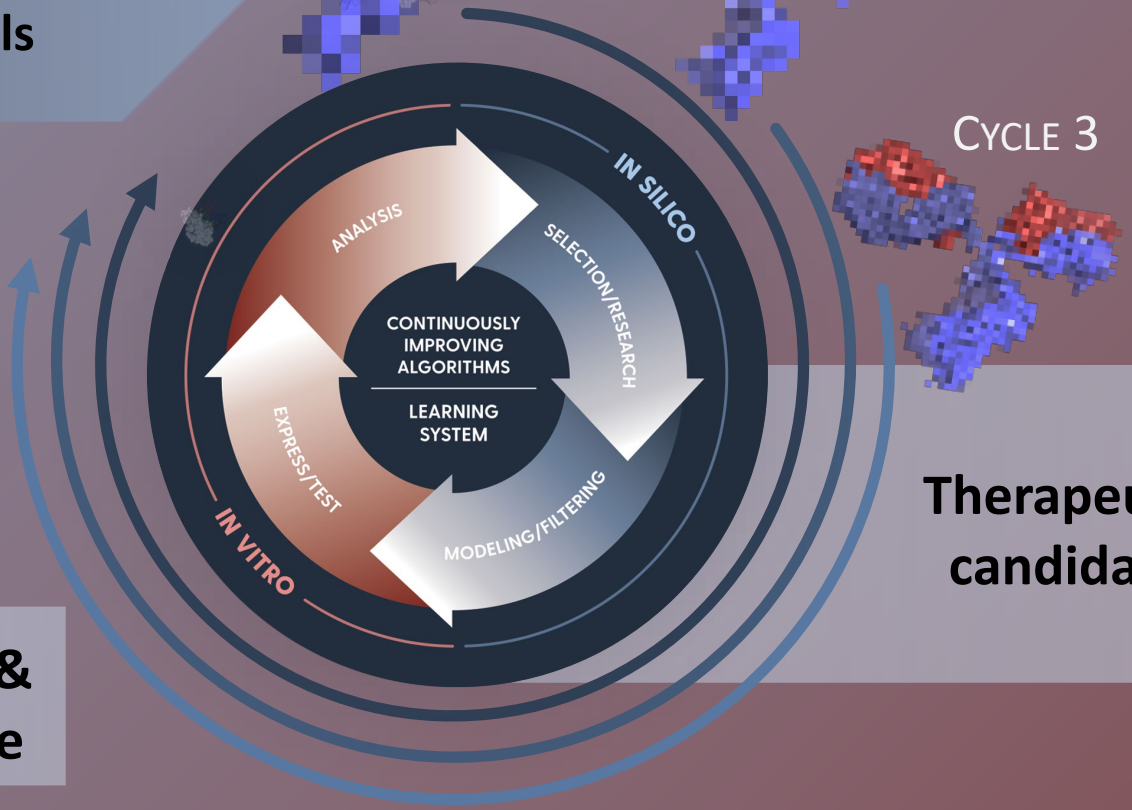
GENERATION OF THOUSANDS OF UNIQUE CANDIDATE ANTIBODY STRUCTURES

Neural Network Models

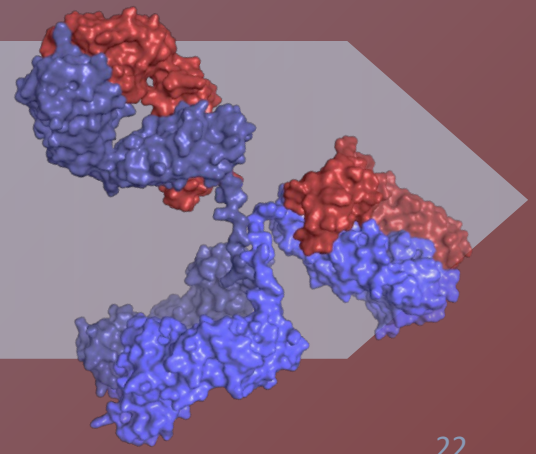
Cycle 1

Cycle 2

Cycle 3

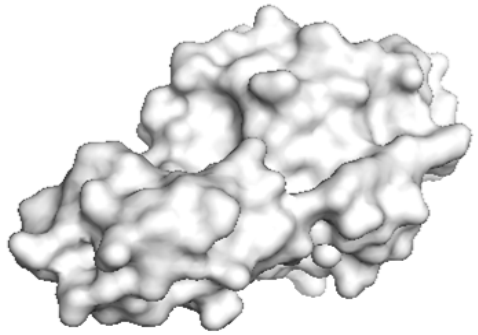


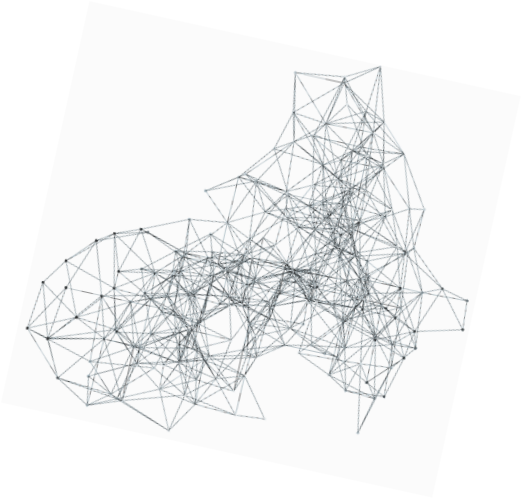
Therapeutic candidate

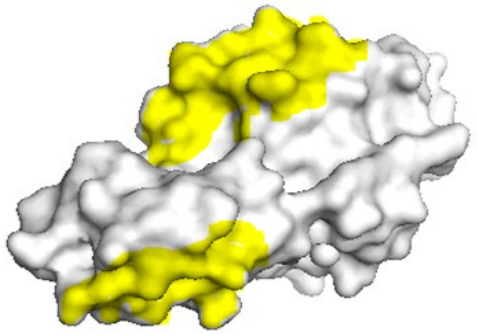


Antigen & Structure

STEP 1 - TARGET SELECTION/IDENTIFICATION







TARGET STRUCTURE

NEURAL NETWORK
*Proprietary IP

PROBABILITY MAP OF BEST REGIONS TO TARGET

SELECTED REGIONS SENT TO DESIGN ALGORITHM

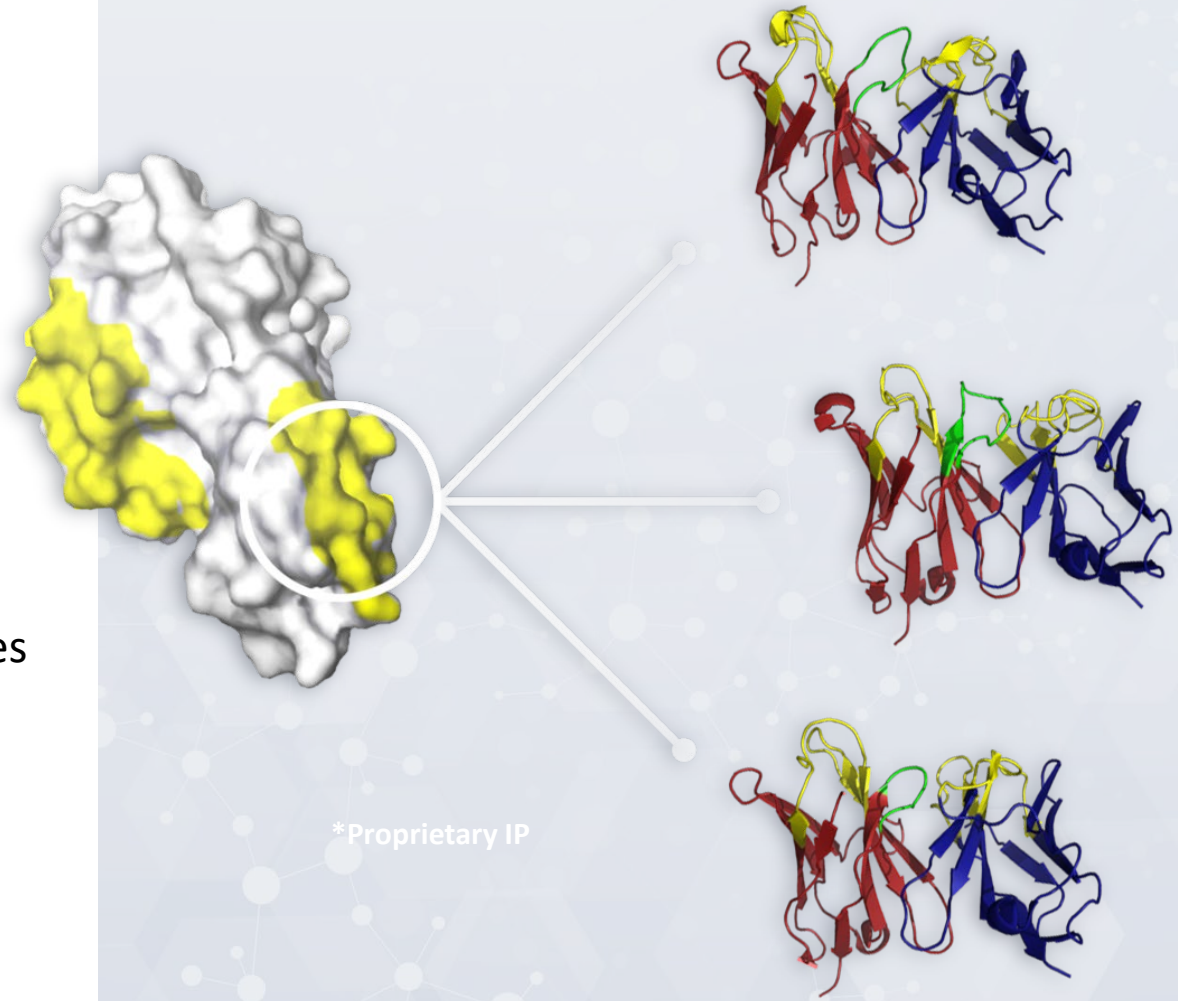
STEP 2 - RUN DESIGN ALGORITHM

Antibody specific algorithm

Antigen structure is fed into design algorithm

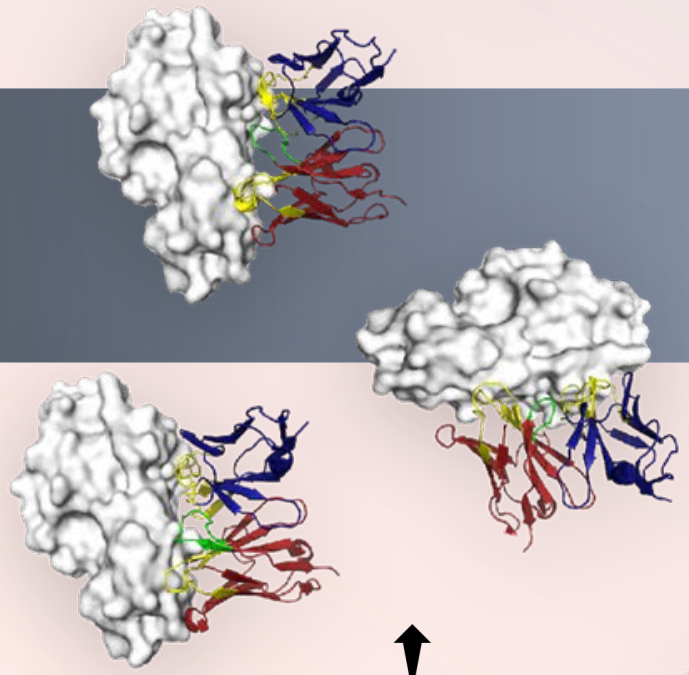
Template antibody is generated
Determines sequence of non-binding antibody regions

Algorithm generates large pool of predicted candidates with unique binding sequence



*Proprietary IP

STEP 3 – DESIGN SELECTION



THOUSANDS OF UNIQUE
CANDIDATE ANTIBODY STRUCTURES

NEURAL NETWROK

***Proprietary IP**

SMALL POOL OF MOST LIKELY BINDERS

LAB TESTING

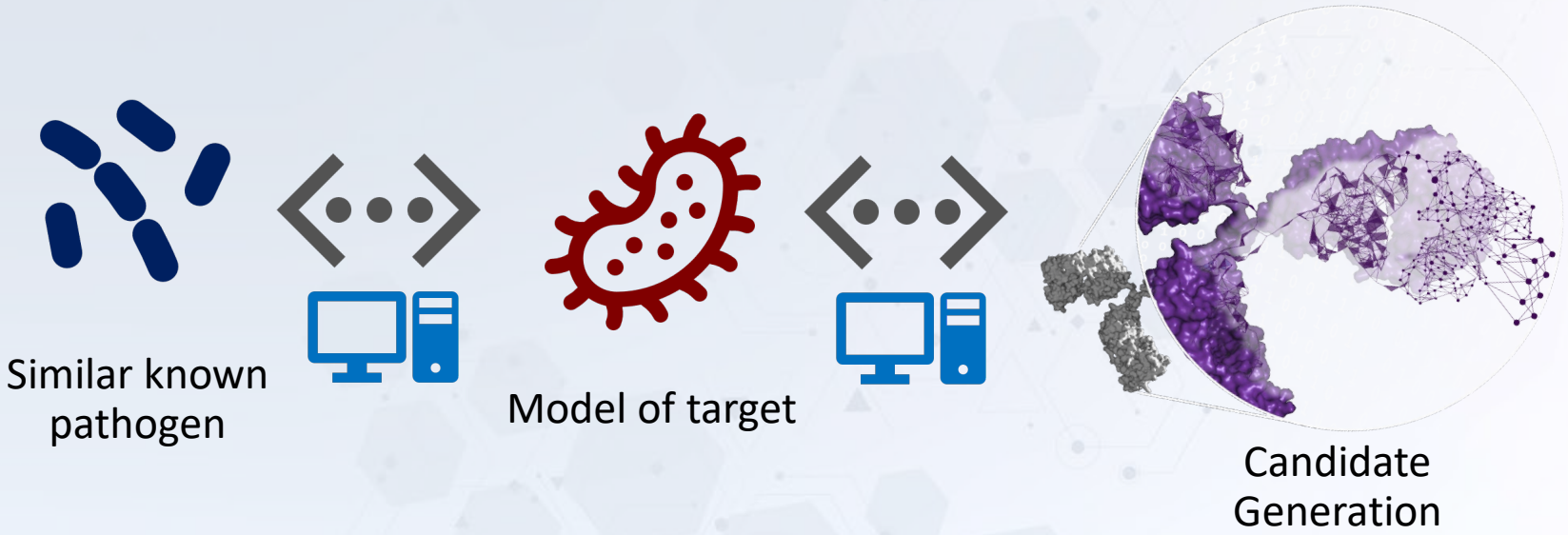
Case Studies

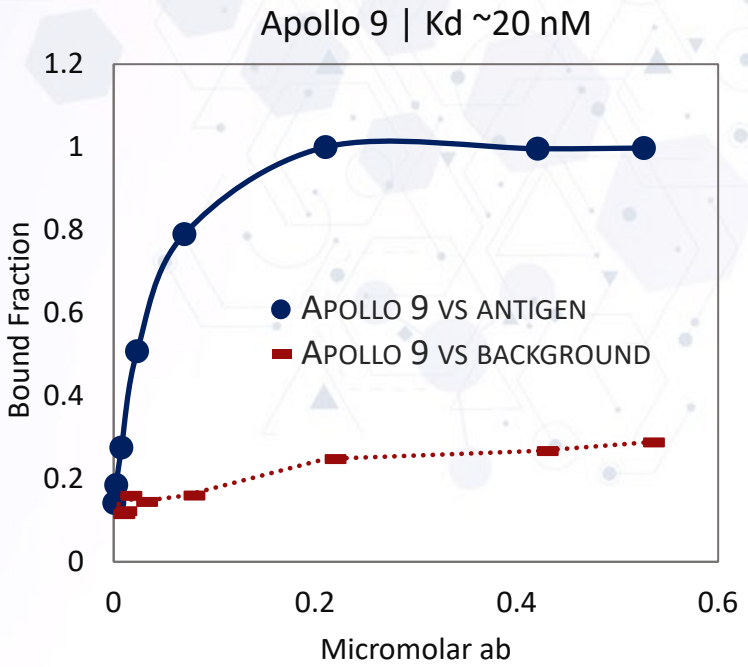
Case Study 1:
APOLLO

3 Designs undergoing biophysical characterization

TARGETING A **MEMBRANE PROTEIN** OF A MULTI-DRUG RESISTANT PATHOGENIC BACTERIA

UNDERGOING BIOPHYSICAL CHARACTERIZATION ANTIGEN-ANTIBODY COMPLEX





POTENT ANTIBODY DESIGNED USING MODELED TARGET

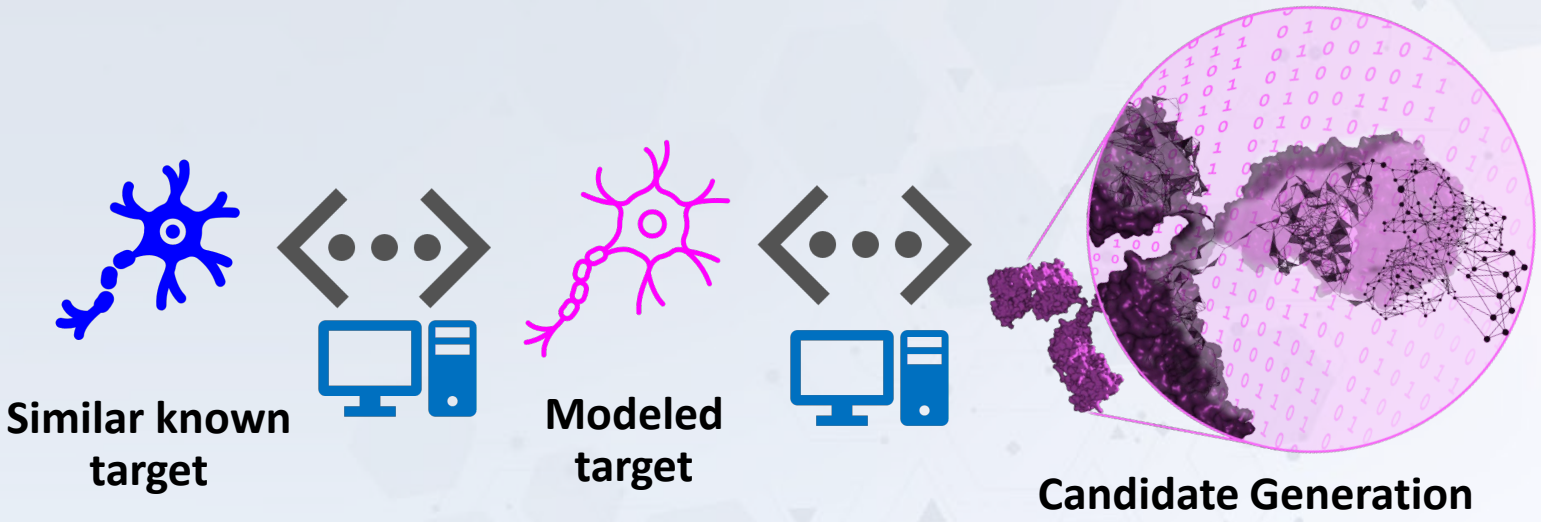
Case Study 2:

SARASWATI

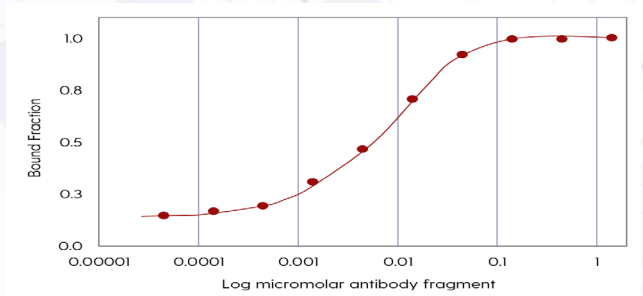
30nM antibody
Designed without preexisting crystal structure

POTENT ANTIBODY

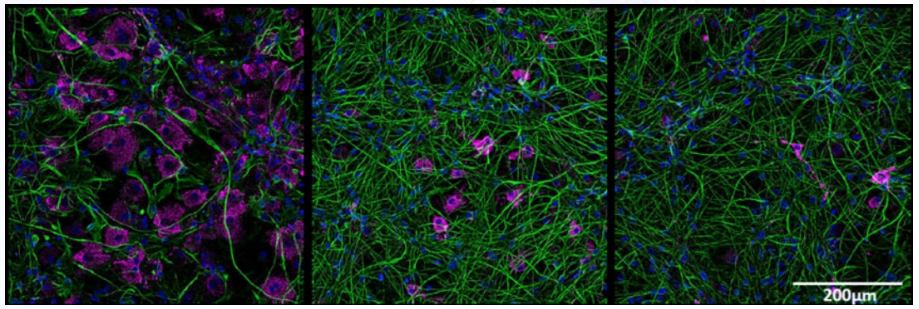
Tested in tissue culture and progressing toward animal studies



Purified antigen
EC50 = single digit nM



Cell binding at EC50 ~60 nM



Nuclei, Design Antibody, Cells

- Created a model for **understudied disease target**
- Antibody designed **without any pre-existing structural data**
- Currently **undergoing pre-clinical testing in human cells**
- Computational antibody targeting a **neurodegenerative disease**

Case Study 3:

OSIRIS

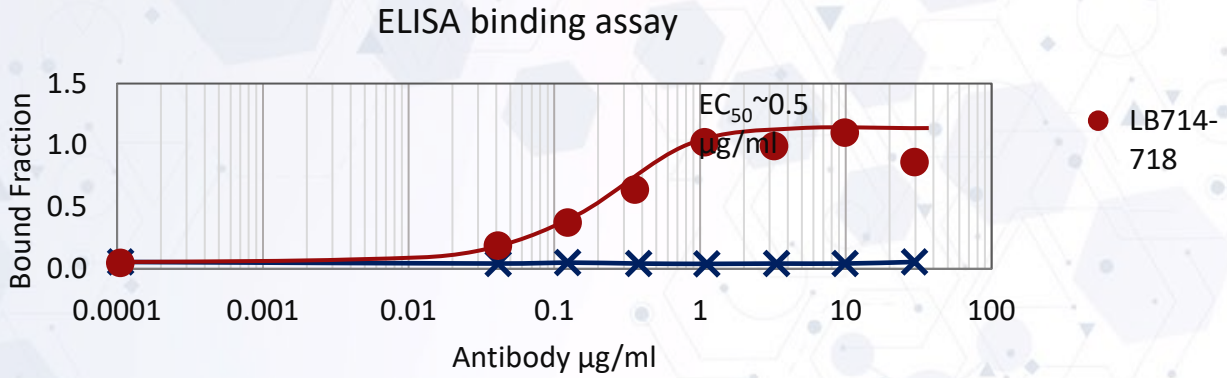
Antibody specifically binding to antigen generated in 2 weeks

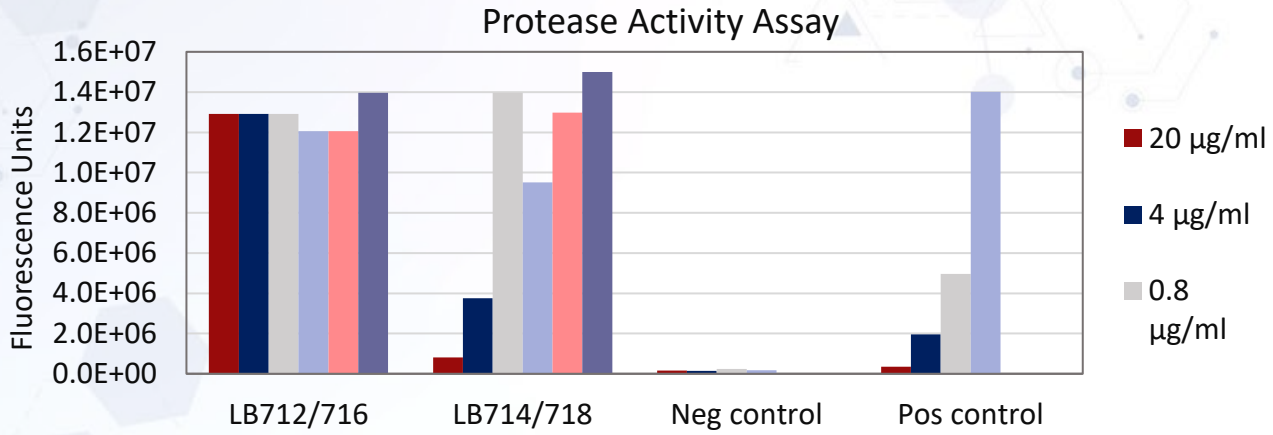
SUCCESSFUL BINDING TO ANTIGEN,

PREVIOUSLY NOT POSSIBLE!

Protease involved
in neonatal skin disease

Biotech partner failed to generate
antibodies with mice or phage display





WHAT'S NEXT IN AI DIRECTED ANTIBODY DESIGN?

- Increased speed of antibody generation
- Rational binding affinity design *de novo*
- Rational agonism/antagonism design *de novo*
- De-risking immunogenicity and safety issues*
- Harnessing Generative AI
- Bringing order to disorder → antibodies to floppy loops (GPCRs et al.)
- Improving hit rate of library

Macromoltek

Revolutionizing antibody design

monica@macromoltek.com
www.macromoltek.com