absci®

```
from absci import de_novo_model
model = de_novo_model.load_latest()
antigen = model.load_pdb("7olz.pdb",
chain="A")
antibodies = model.predict(antigen, N=300000)
```

```
from absci_library import codon_optimizer
library
= codon_optimizer.reverse_translate(library)
library.to_csv("covid-antibody-designs.csv")
library.to_wet_lab(assay="ACE")
```

```
from absci import lead_opt_model
lead_optimizer = lead_opt_model.load_latest()
library.naturalness =
lead_optimizer.naturalness(library)
lead_optimizer.optimize(library).to_wet_lab(as
say="SPR")
```

DRUG CREATION

THERAPEUTIC ANTIBODY DESIGN USING GENERATIVE AI

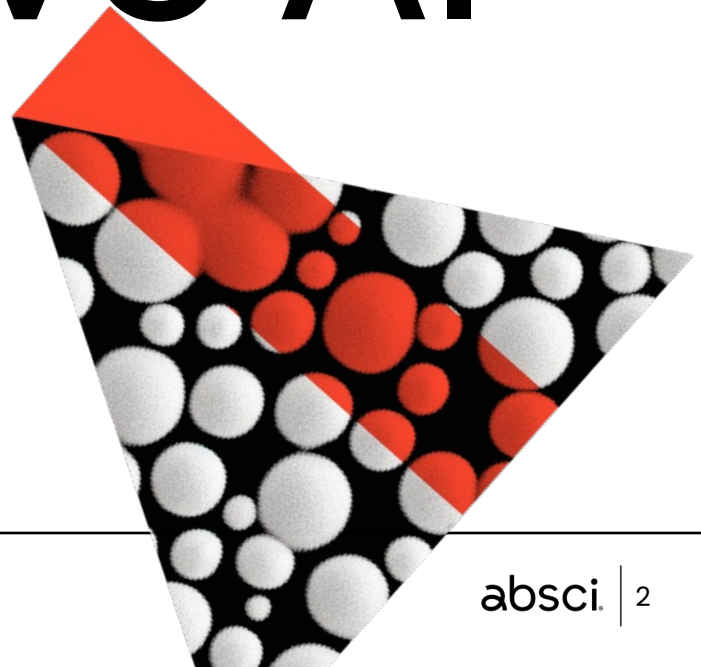
```
from absci import genetic_algorithm; parameters=["maximize|binding_affinity:pH=7.5", "minimize|binding_affinity:pH=6.0",
"maximize|human_naturalness"]; library = genetic_algorithm.multiparametric_optimization(library, parameters, evolutions=100);
library.to_wet_lab(assays=["ACE", "SPR", "Bioassays"])
```

```
absci_library import codon_optimizer
ary
odon_optimizer.reverse_translate(library)
ary.to_csv("covid-antibody-designs.csv")
ary.to_wet_lab(assay="ACE")
```

Therapeutic Antibody Design using Generative AI

```
from absci import lead_opt_model
lead_optimizer = lead_opt_model.load_late
library.naturalness =
lead_optimizer.naturalness(library)
lead_optimizer.optimize(library).to_wet_l
say="SPR")
```

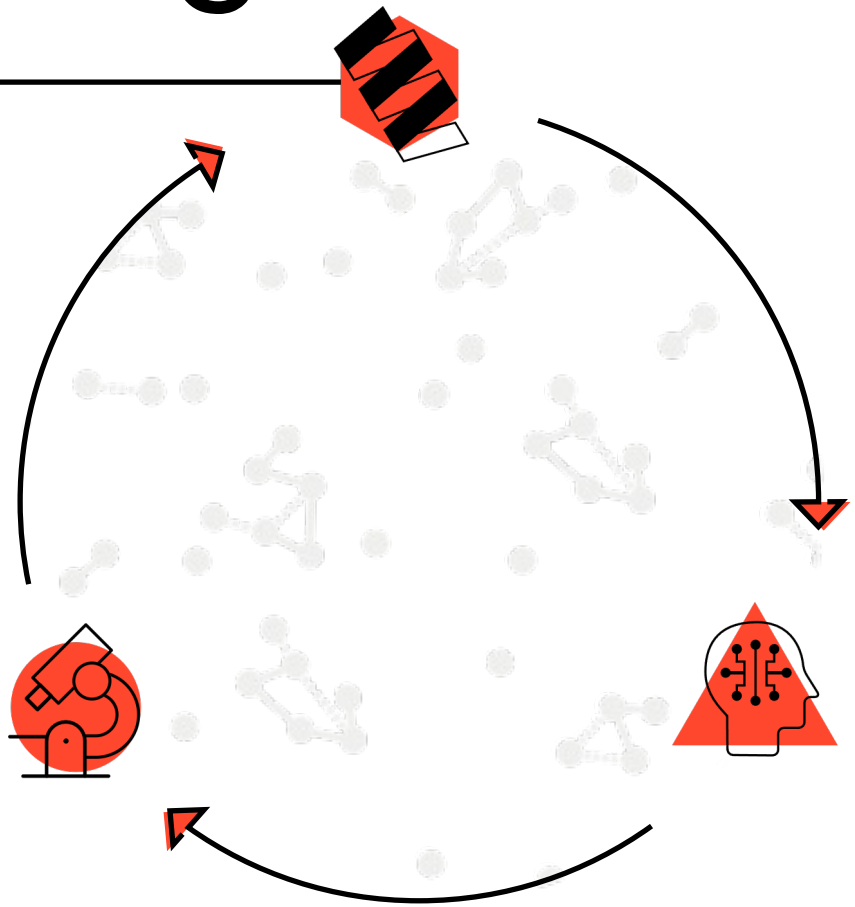
CARTERRA BOSTON SYMPOSIUM, JUNE 2023



Absci is leading the way with our Integrated Drug Creation™ platform

DATA TO TRAIN

Proprietary wet-lab assays capable of generating billions of protein-protein interactions a week for ML training



AI TO CREATE

Generative AI engine to create new antibodies and next-gen biologics

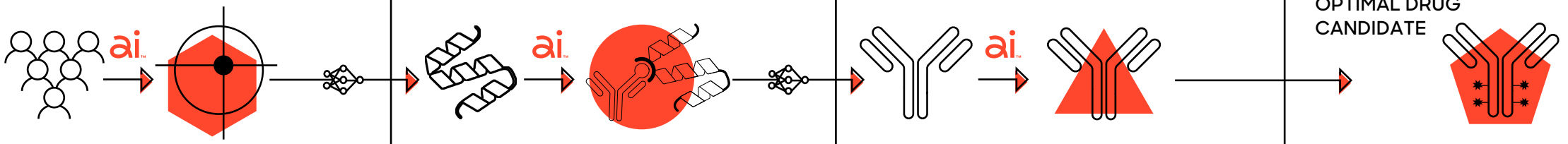
WET LAB TO VALIDATE

Scalable wet-lab infrastructure capable of validating 2.8 million unique AI-generated designs a week

ABSCI'S END-TO-END PLATFORM SOLUTION

The leading full-stack AI platform for biologics drug creation

Find patient cohort specific targets	Discover novel antibodies for selected target	Optimize antibodies' characteristics	Incorporate site-specific chemical handles
Novel target discovery	*De novo* discovery *in silico*	Lead optimization *in silico*	Bionic SoluPro™ strain



DE NOVO DESIGN

Absci's 'zero-shot' *de novo* design creates novel therapeutic leads

Find patient cohort specific targets

Novel target discovery

Discover novel antibodies for selected target

De novo discovery *in silico*

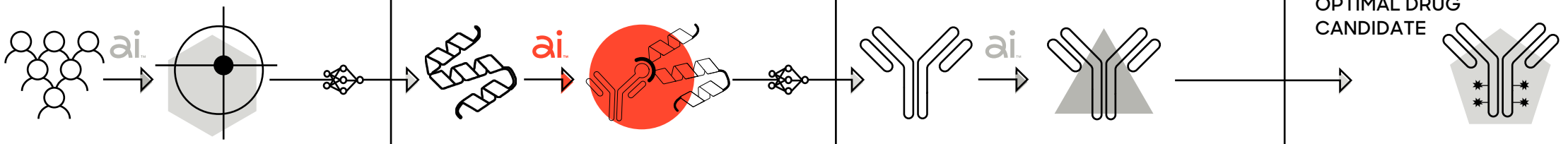
Optimize antibodies' characteristics

Lead optimization *in silico*

Incorporate site-specific chemical handles

Bionic SoluPro™ strain

OPTIMAL DRUG CANDIDATE



Absci is the first to design and validate novel CDRs using zero-shot generative AI

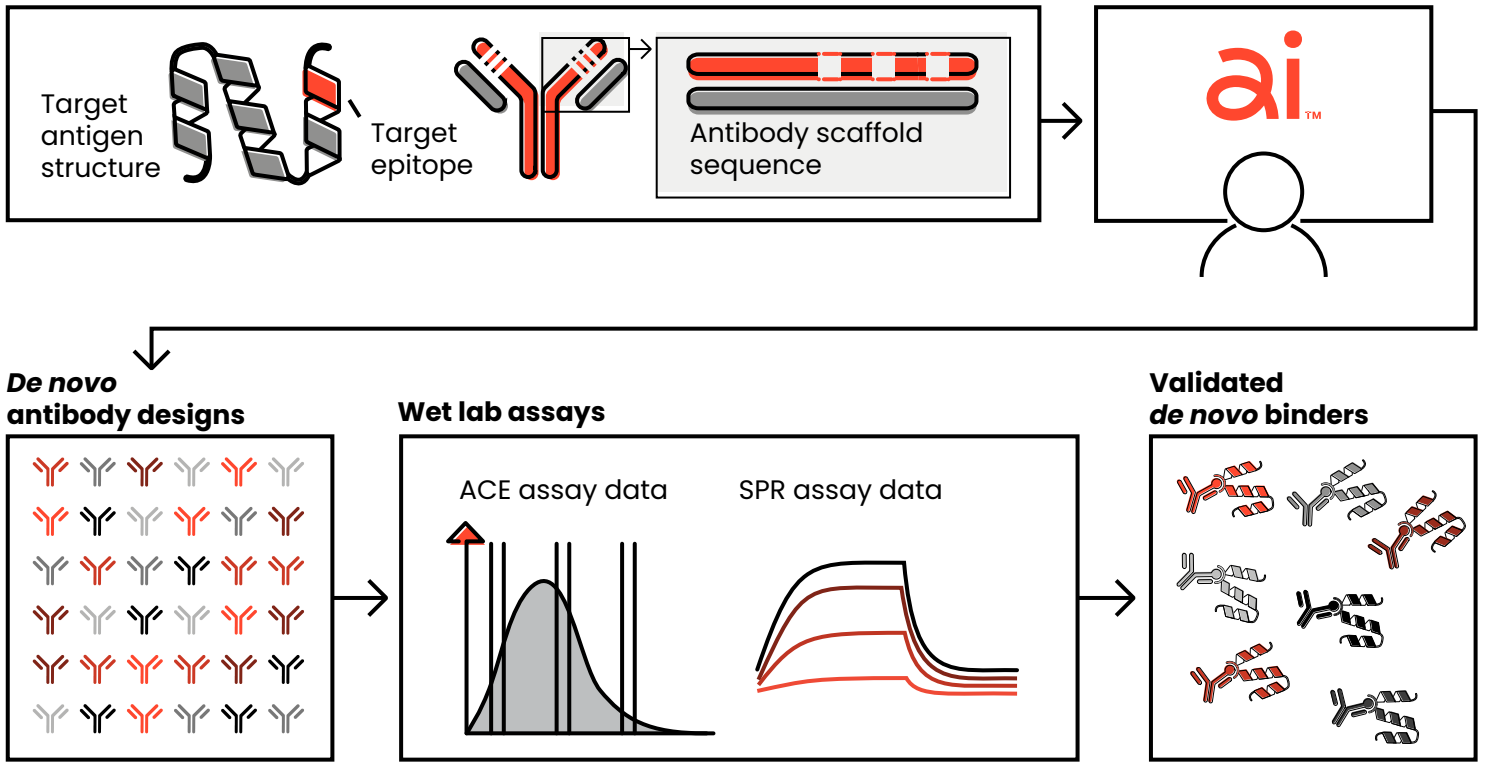
Zero-shot: a machine learning technique in which a model is trained to recognize and classify new objects without explicitly being trained on those objects' examples.

For *antibodies, this means designing an antibody to bind to an antigen with no previous demonstrations of binders to said antigen.*

Shanehsazzadeh A., Bachas, S., McPartlon, M. *et al.* (2023) pre-print in bioRxiv.

DE NOVO DESIGN *IN SILICO*

De novo drug creation with ‘zero-shot’ generative AI

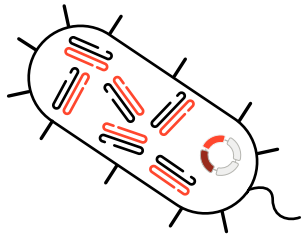


Shanehsazzadeh A., Bachas, S., McPartlon, M. *et al.* (2023) pre-print in bioRxiv.

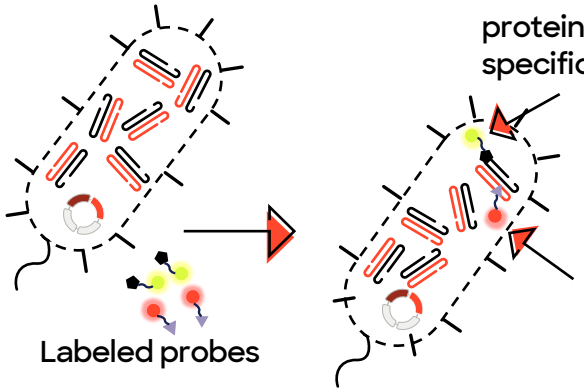
DE NOVO DESIGN *IN SILICO* REQUIRES LOTS OF HIGH-QUALITY TRAINING DATA

Highly validated ACE Assay generates high-quality and high-throughput data

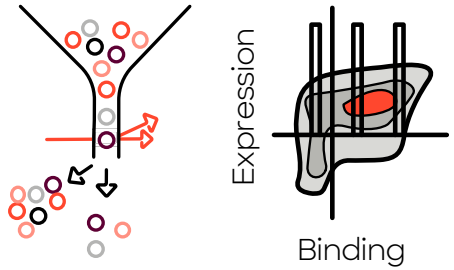
1. Strains expressing unique antibody sequence variants



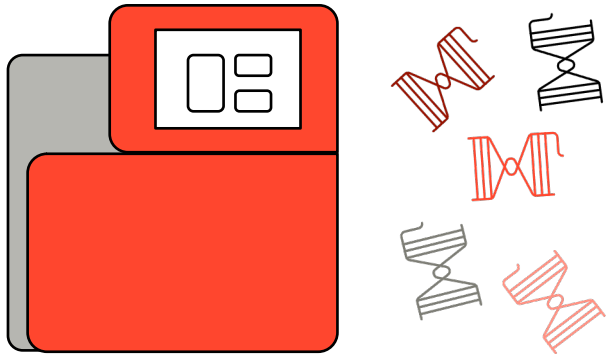
2. Fix and permeabilize cells and add labeled probes



3. Screen and sort by flow cytometry



4. NGS



5. ACE Assay scores (binding classification)

Metric	HCDR3 score	HCDR123 score
Accuracy	95.52%	95.3%
Precision	95.39%	95.65%
Recall	94.83%	92.91%
F1-score	0.951	0.943

~5K controls included in libraries of 400k in size:

- ~800 positive controls
- ~1000 negative controls

Each included with multiple codon optimized variants

Bachas, S., Rakocevic, G. *et al.* (2022) pre-print in bioRxiv. Shanehsazzadeh A., Bachas, S., McPartlon, M. *et al.* (2023) pre-print in bioRxiv.

CASE STUDY: *DE NOVO* DESIGN *IN SILICO*

AI designs of all HCDRs achieve high binding rates and outperform biological baselines

		HER2 Binding Rate (%) measured via ACE assay	
		HCDR3	HCDR123
Zero-shot *de novo* generated			
Matched input antigen	Human HER2	10.6	1.8
Mis-matched input antigen	Rat HER2	2.8	0.5
Mis-matched input antigen	HER3	2.9	0.2
Mis-matched input antigen	VEGF	2.5	0.0
Biological baseline			
	OAS	2.68	0.16
	OAS-J	5.25	0.32
	SAbDab	3.16	0.06
Random baseline			
	Permuted sequences	0.33	N/A

AI designs are specific

- Inputting a mis-matched undesired antigen (e.g. Rat HER2, HER3, VEGF) into the model results in significant performance decrease towards desired antigen
- Indicates the model's use of antigen information for sequence designs

AI models outperform biological baselines

- *De novo* designed HCDR3s achieve a 4-fold improvement over random OAS baseline
- *De novo* designed HCDR123s achieve an 11-fold improvement over random OAS baseline

Shanehsazzadeh A., Bachas, S., McPartlon, M. *et al.* (2023) pre-print in bioRxiv.

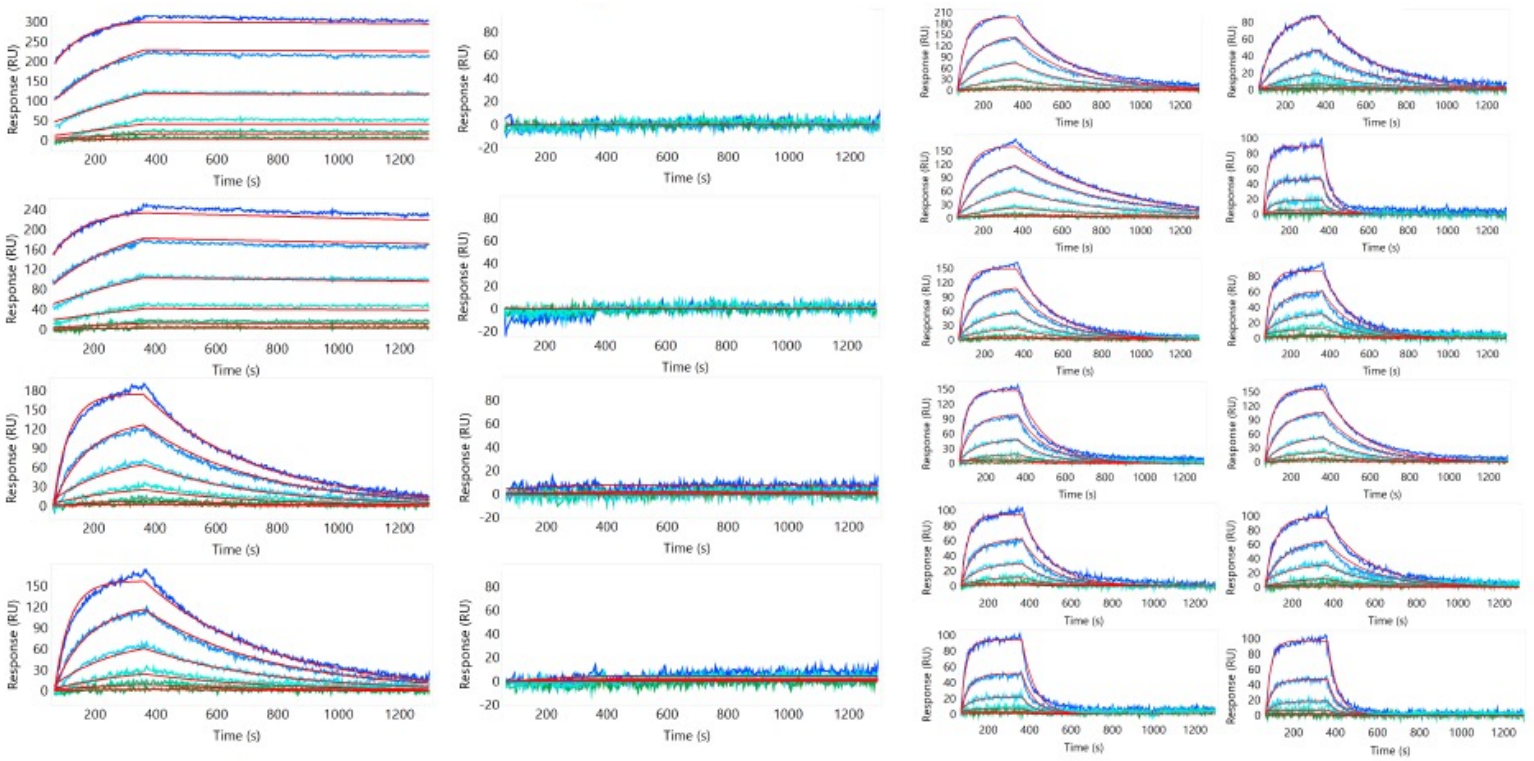
CASE STUDY: *DE NOVO* DESIGN *IN SILICO*

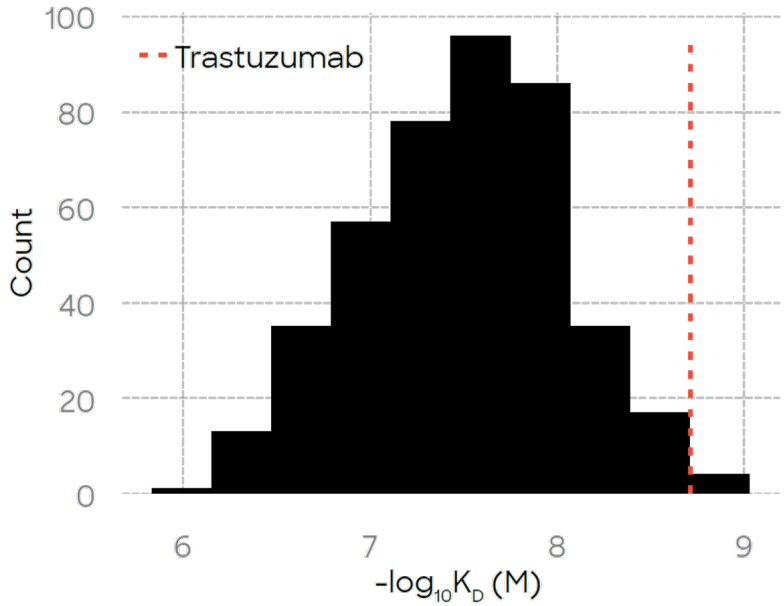
Binders validated using Carterra LSA kinetics

Positive controls

Negative controls

de novo binders



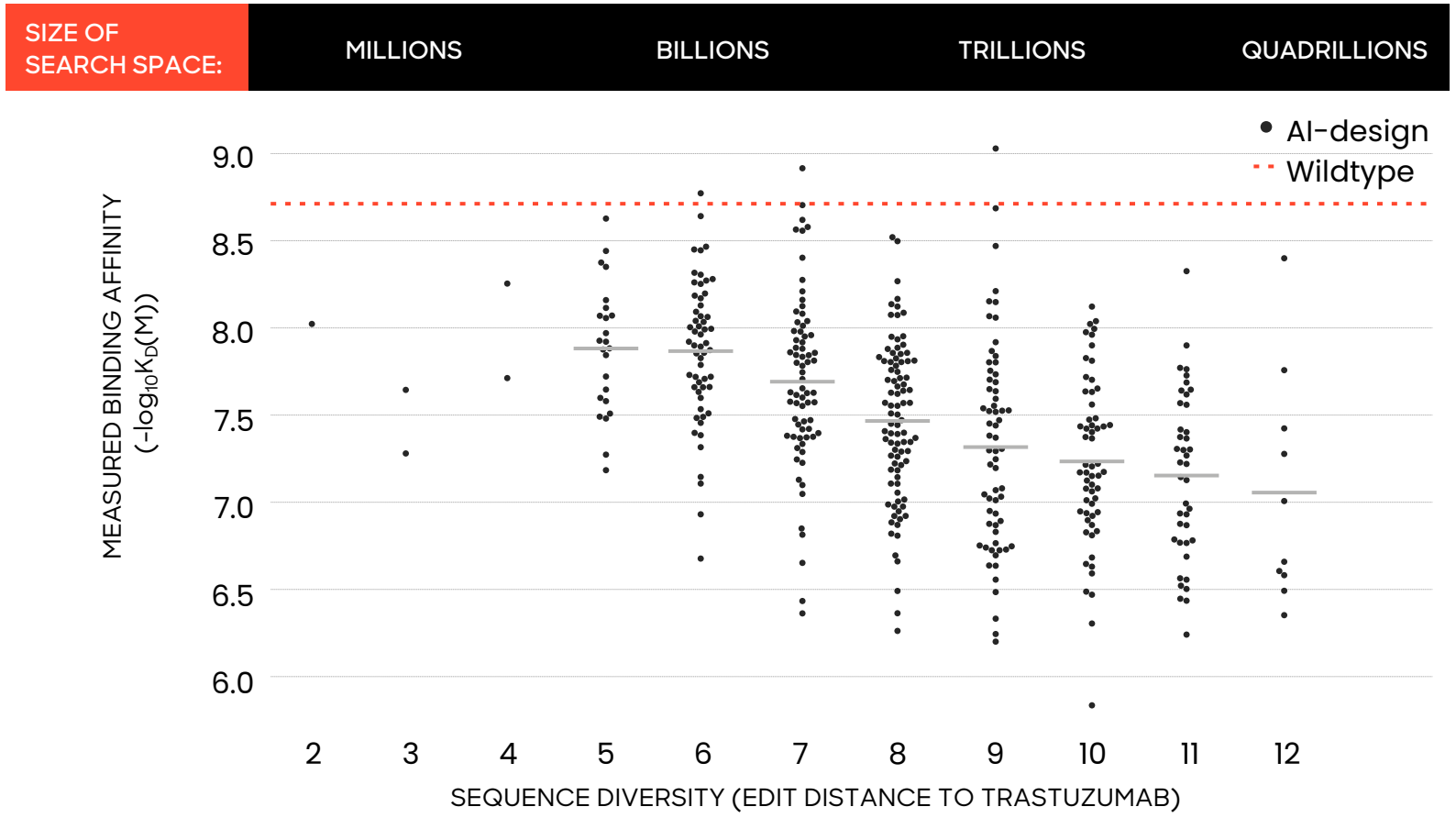


- 421 binders (HCDR3 designs) confirmed by SPR
- 71 exhibit <10 nM affinity
- 3 bind tighter than WT trastuzumab

Shanehsazzadeh A., Bachas, S., McPartlon, M. *et al.* (2023) pre-print in bioRxiv.

CASE STUDY: *DE NOVO* DESIGN *IN SILICO*

AI model generates highly diverse and effective binders from a massive search space



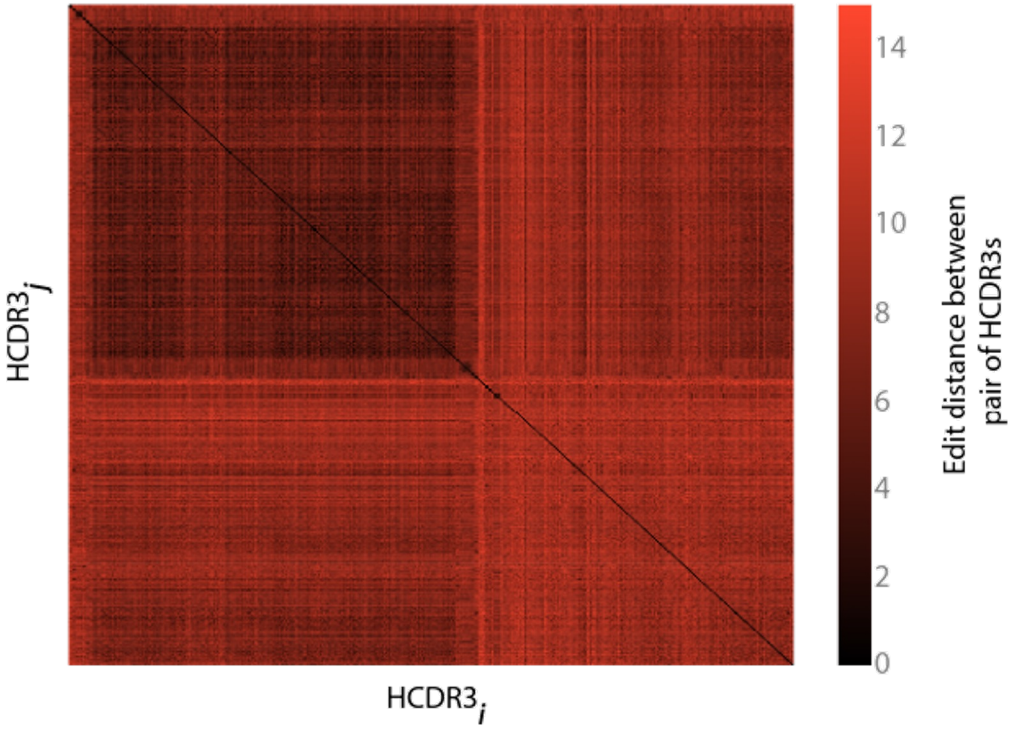
AI-Designed & Wet Lab Validated HER2 Binders

- Hundreds of binders created
- Ability to generate binders near to and far from trastuzumab
- Binding affinity maintained even when mutating >90% of the CDR3 region
- All binders to HER2 and HER2 homologs removed from the training dataset

Shanehsazzadeh A., Bachas, S., McPartlon, M. *et al.* (2023) pre-print in bioRxiv.

CASE STUDY: *DE NOVO* DESIGN *IN SILICO*

High sequence diversity supports patent estate expansion and differentiation



Designs are sequence diverse from one another, with a mean edit distance of 7.7 ± 2.1 SD

Shanehsazzadeh A., Bachas, S., McPartlon, M. *et al.* (2023) pre-print in bioRxiv.

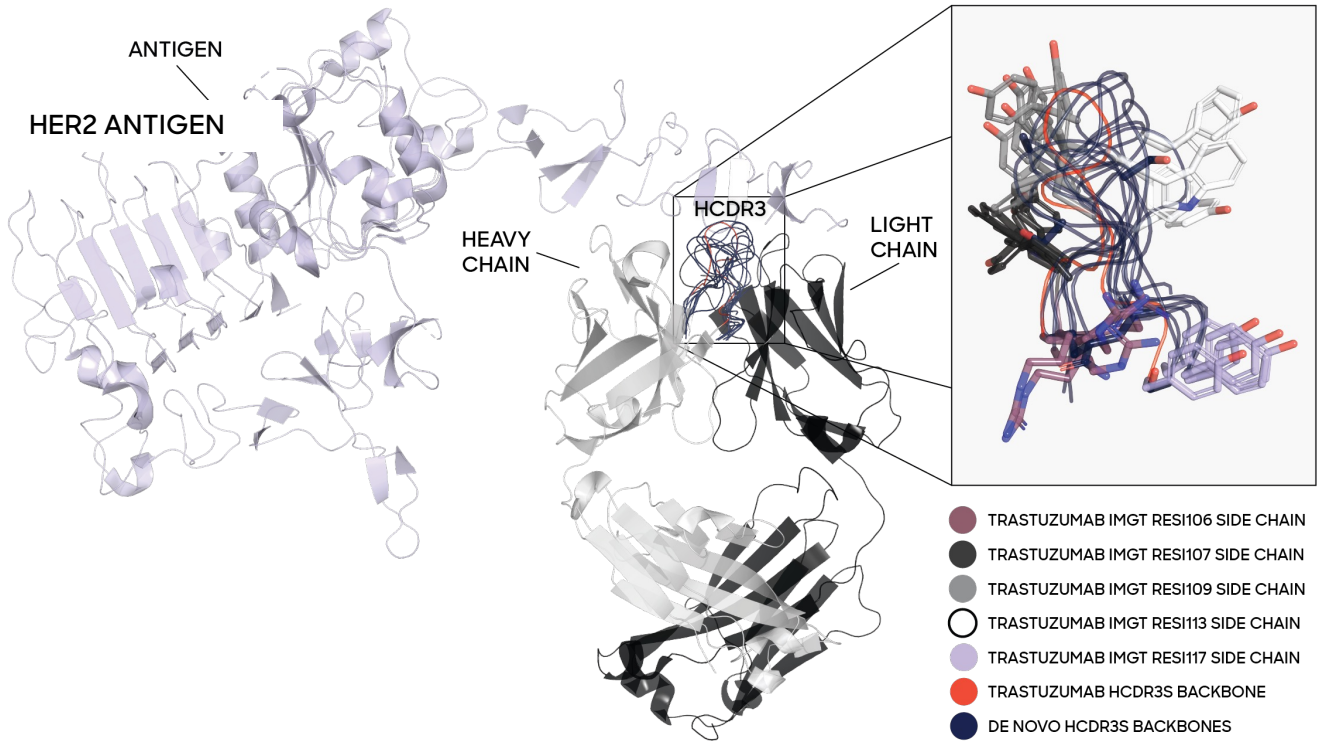
Example HCDR3 designs (edit distance)	-Log$_{10}$ (K_D)
S R W G G D G F Y A M D Y (Wildtype)	8.71
A R W G N Y Y Y Y M D Y (6)	**8.77**
A R Y Y Y G F Y Y F D Y (7)	**8.92**
A R Y A G V E R P G S F A Y (11)	6.24
T R Y F F N G W Y Y F D V (9)	**9.03**
A F A D S G A Y G I W S F (12)	7.0
A N D I Y I Q G Y D L N R (12)	8.4
A R G Y S G D W P Y E T F Y V (10)	7.01
A R Y D Y G Y Y I Y V S (10)	8.02

Key: Amino acids of the same color belong to the same class

CASE STUDY: *DE NOVO* DESIGN *IN SILICO*

Structural models of *de novo* designed HER2 antibodies

- We constructed structural models of 8 diverse binders.
- Alignment of 8 models with trastuzumab highlights large conformational flexibility between HCDR3 designs.
- Spatial conservation of aromatic residues is observed at discrete locations that are critical for epitope engagement.
- HCDR3 designs make novel contacts with domain IV epitope of HER2.
- Structural differences may allow for the design of HER2 binding antibodies with unique properties such as ortholog cross-reactivity and higher potency.



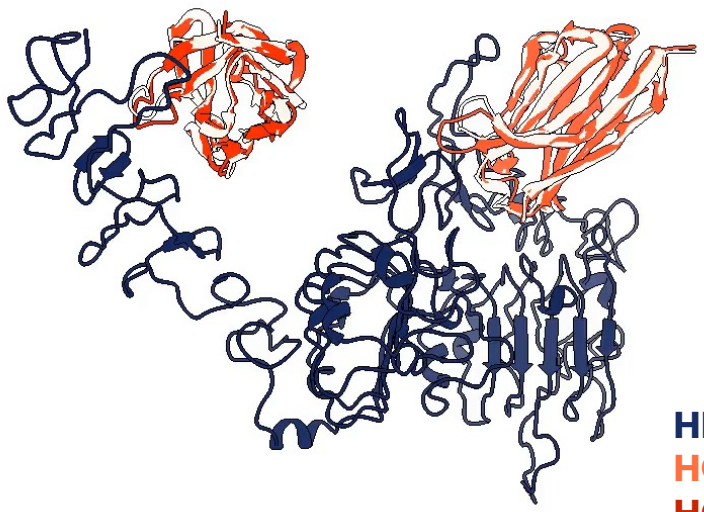
Shanehsazzadeh A., Bachas, S., McPartlon, M. *et al.* (2023) pre-print in bioRxiv.

NEW PROGRESS ON *DE NOVO* MODEL

Absci is progressing towards fully *de novo* antibody design

REPRESENTATIVE AI MODEL GENERATED STRUCTURES

HER2-ECD in complex with newly designed Fab Heavy Chains (HC)



AI-designed binders are identified, and lab verified for four therapeutic targets straight out of the model – no lead optimization applied and validated in the lab

- Model outperforms biological baselines
- Binders are antigen- and epitope-specific
- Binders confer natural sequence characteristics comparable or superior to known binders
- Binders are diverse and distinct from training set
- Structural modeling reveals important biological contacts

AI DRIVEN LEAD OPTIMIZATION

Multiparametric AI lead-optimization can enable higher potential therapeutics and increased PoS

Find patient cohort specific targets

Novel target discovery

Discover novel antibodies for selected target

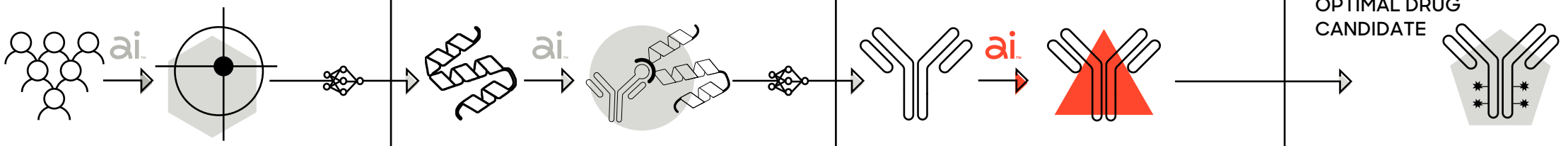
De novo discovery *in silico*

Optimize antibodies' characteristics

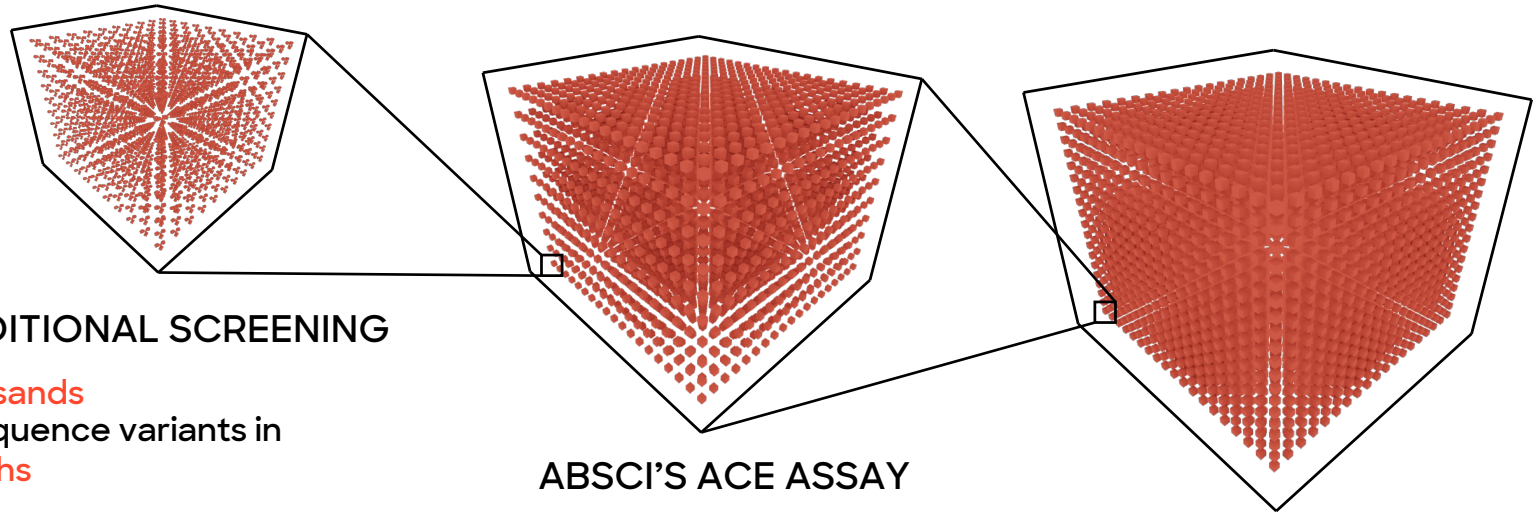
Lead optimization *in silico*

Incorporate site-specific chemical handles

Bionic SoluPro™ strain



Multiparametric AI lead-optimization unlocked by Absci's scalable biological data



TRADITIONAL SCREENING

Thousands
of sequence variants in
months

ABSCI'S ACE ASSAY

Hundreds of thousands
of sequence variants in
weeks

ABSCI'S AI

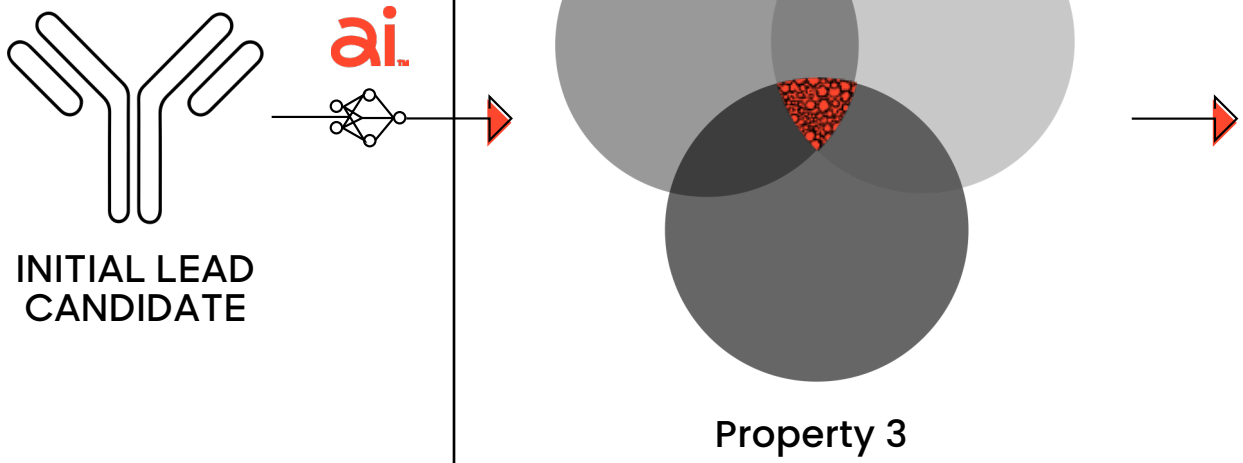
Millions
of sequence variants in
hours

Absci's AI lead-optimization is powered by high-quality and high-throughput data generation

Bachas, S., Rakocevic, G. *et al.* (2022) pre-print in bioRxiv.

CASE STUDY: AI-DRIVEN LEAD OPTIMIZATION

Multiparametric AI lead-optimization for increased success rates & higher potential therapeutics

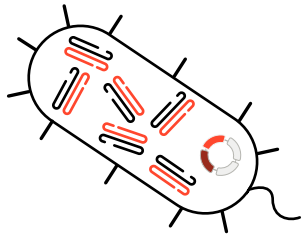


Higher potential therapeutics faster

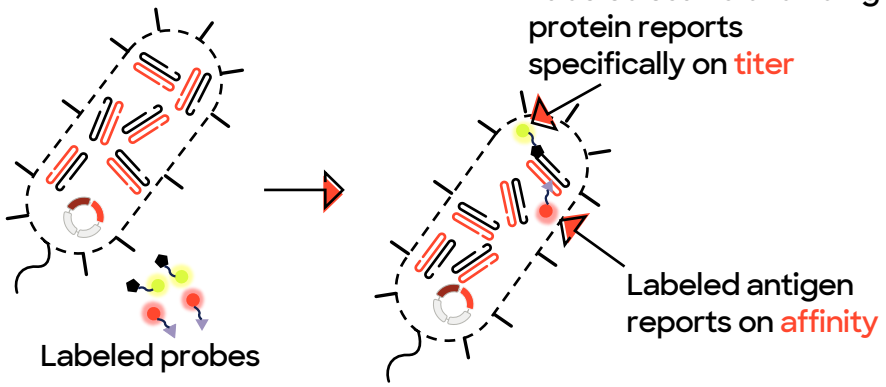
- Increased probability of success
  - Affinity tailored for desired application
  - Higher Developability
    - Thermostability
    - Self-association
    - Lower immunogenicity
    - S.c. formulation
  - Higher expression levels enabling lower COGS
- Higher potential with novel biology
  - Dual- or multi-valent binding
  - Conditional biologics

Highly validated ACE Assay generates high-quality and high-throughput data to train deep learning models

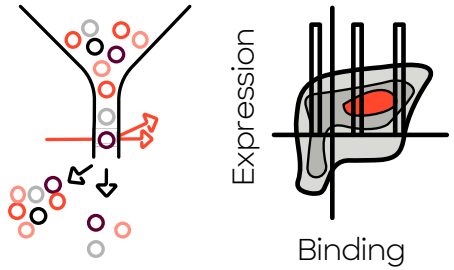
1. Strains expressing unique antibody sequence variants



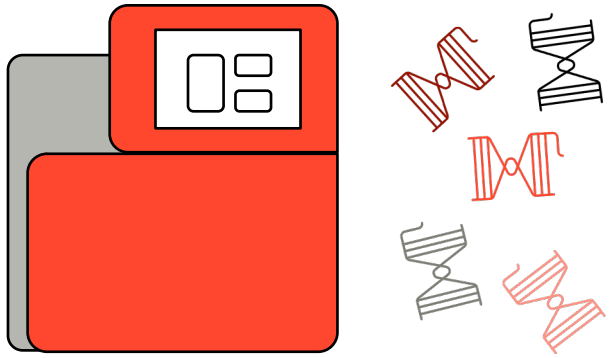
2. Fix and permeabilize cells and add labeled probes



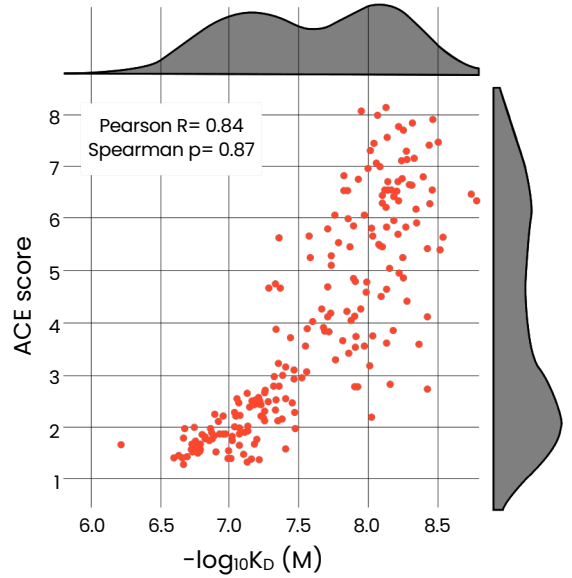
3. Screen and sort by flow cytometry



4. NGS



5. ACE Assay scores (affinity)

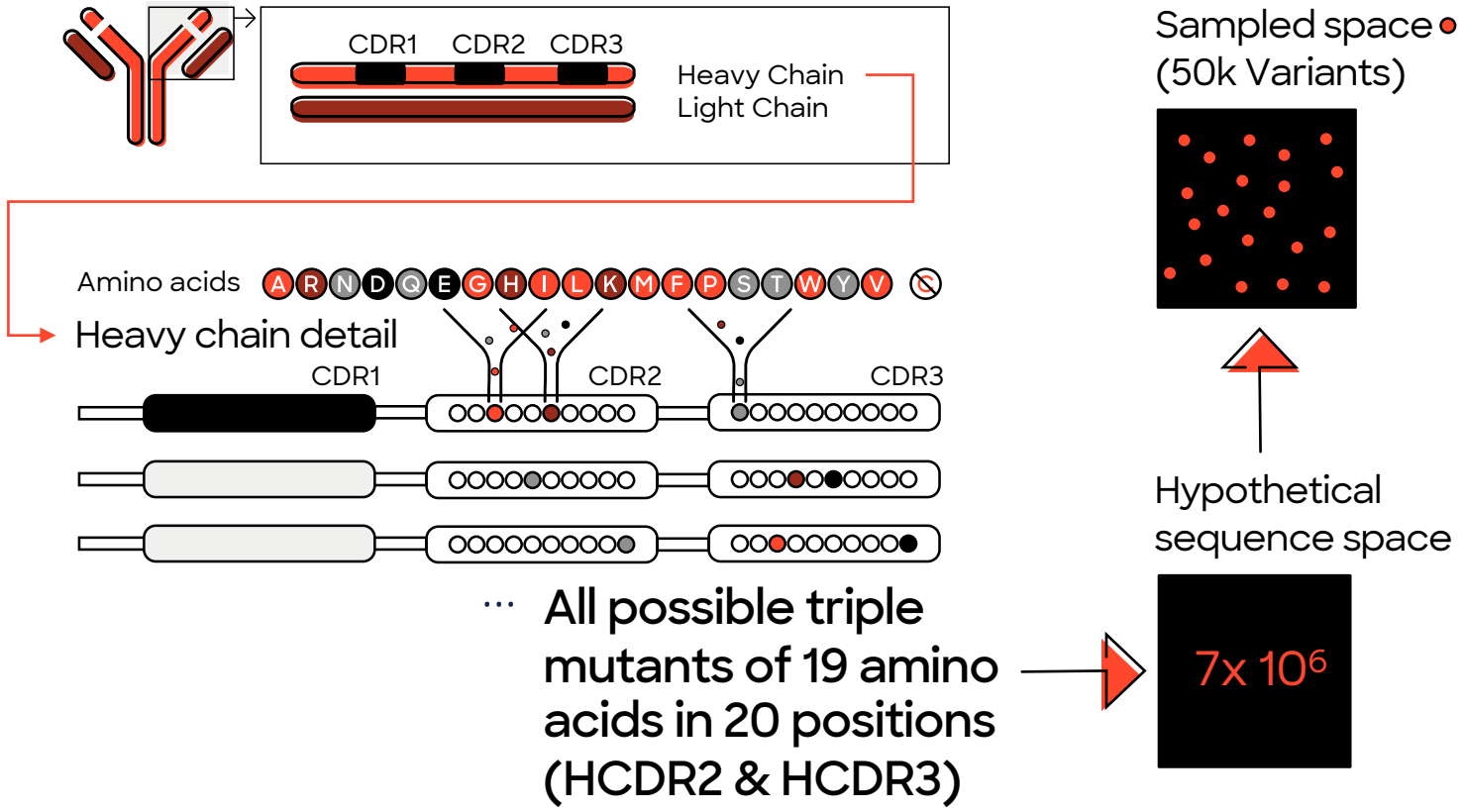


ACE Assay scores strongly correlate with SPR-derived -$\log_{10}$ K_D (Pearson R = 0.84) generating high-quality data for AI model training

Bachas, S., Rakocevic, G. *et al.* (2022) pre-print in bioRxiv.

CASE STUDY: OPTIMIZING HER2 BINDERS

AI models can expand search space by orders of magnitude

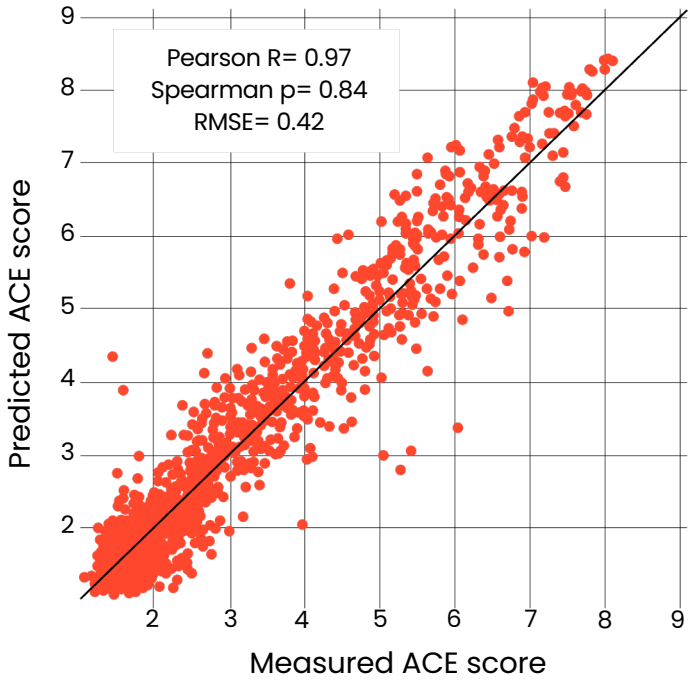


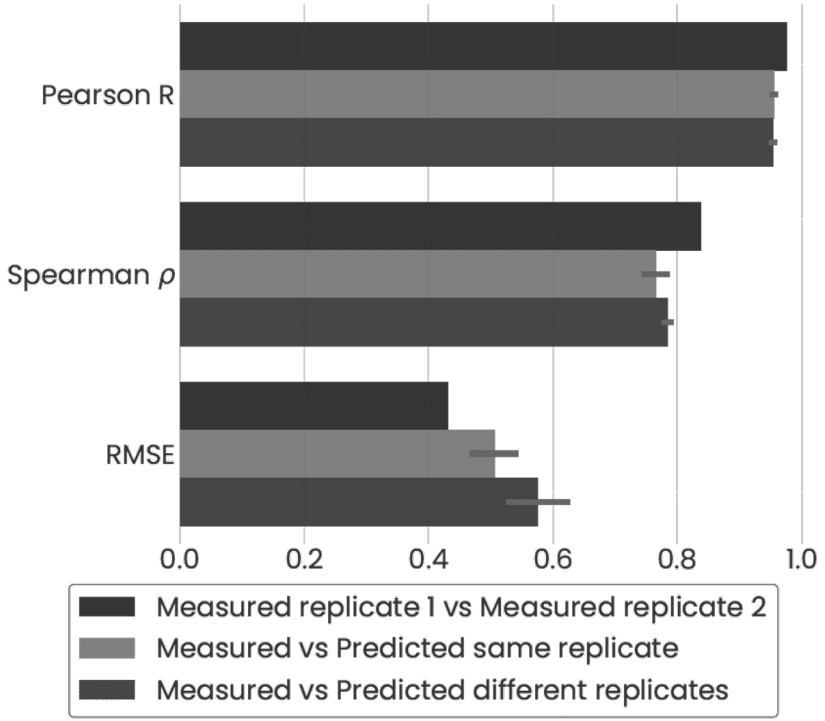
- Combinatorial mutagenesis of up to 3 mutations over ten amino acids each in HCDR2 and HCDR3
- Sampled less than 1% of the sequence space
- Measured binding affinity of nearly 50,000 sequence variants

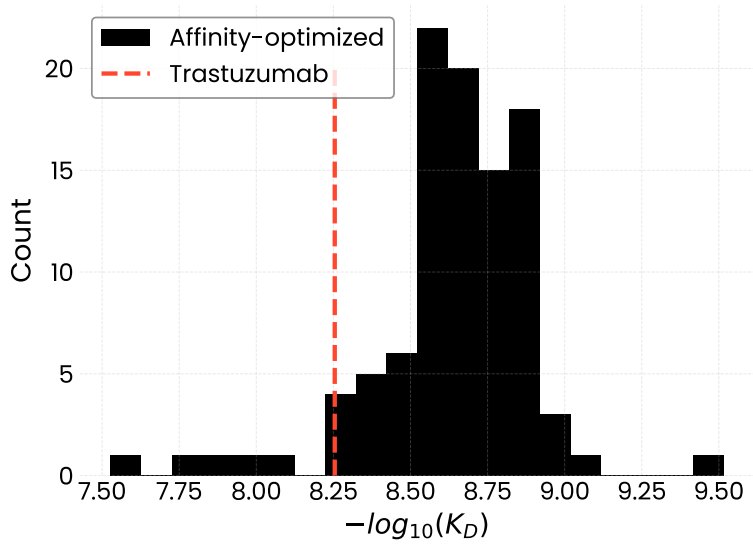
Bachas, S., Rakocevic, G. *et al.* (2022) pre-print in bioRxiv.

CASE STUDY: DESIGNING BETTER HER2 BINDERS

AI quantitatively predicts antibody affinity







HIGH PREDICTIVE PERFORMANCE

Pearson R correlation of 0.93

- Trained on 90 % of dataset
- Results shown for 10% of dataset not seen by model

HIGH QUALITY DATA

Models trained on one replicate can predict unseen data from a different replicate

HIGH AFFINITY PREDICTIONS

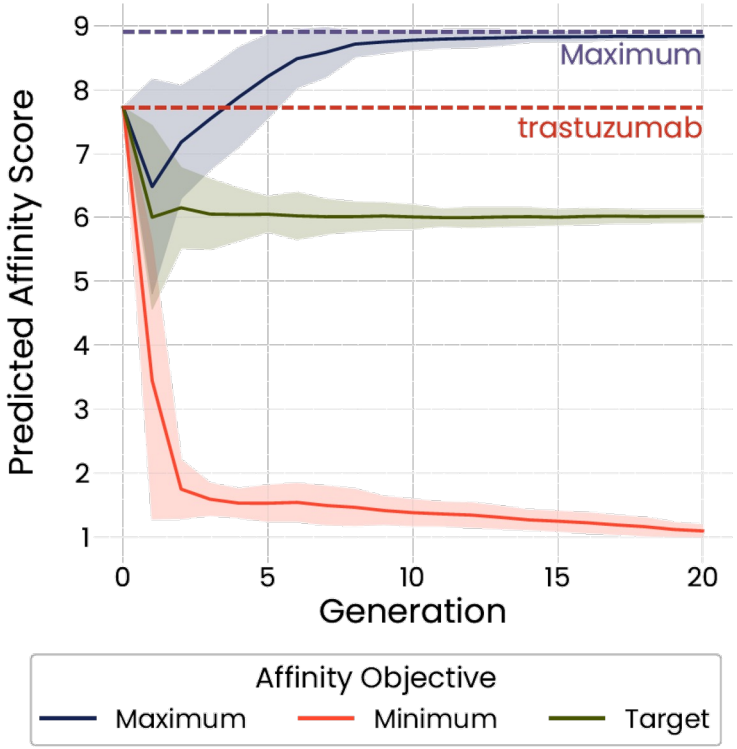
Models can find variants with higher affinity than seen in training data

- 92 of top 100 predicted high-affinity variants bind tighter than trastuzumab

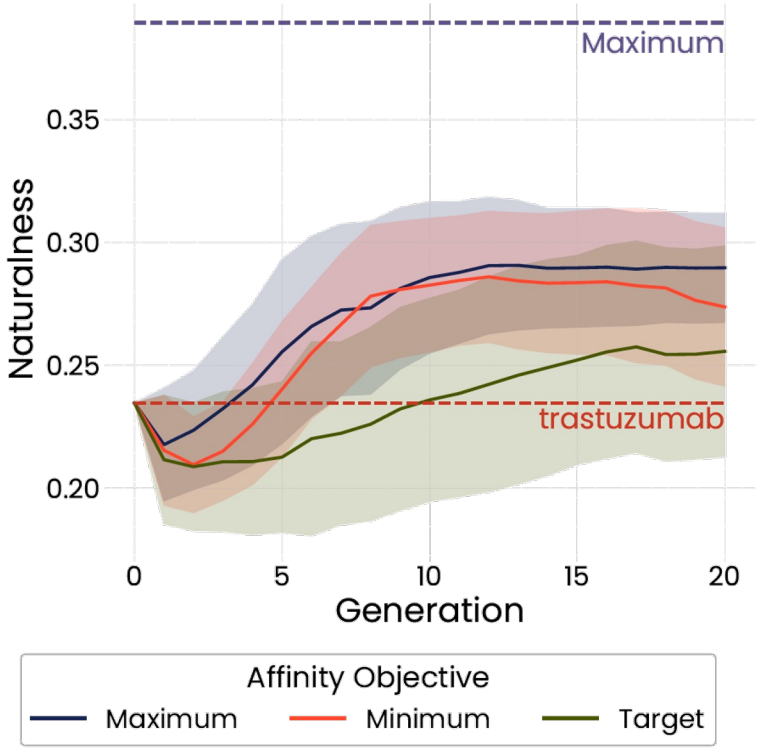
Bachas, S., Rakocevic, G. *et al.* (2022) pre-print in bioRxiv.

CASE STUDY: AI-DRIVEN LEAD OPTIMIZATION

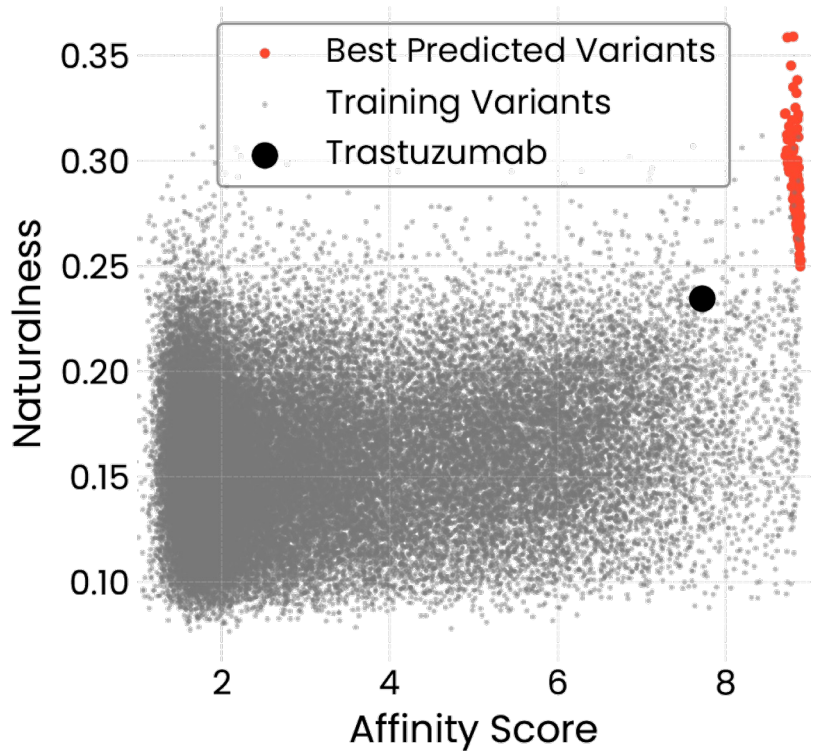
Simultaneous co-optimization of affinity and naturalness



Maximize, minimize, or tailor binding affinity



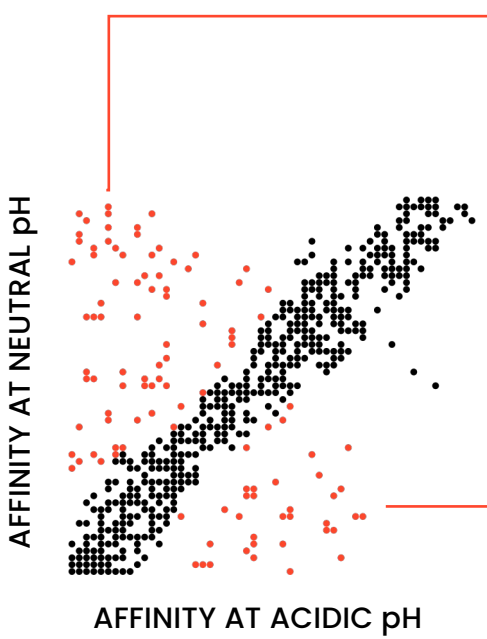
At the same time, ensure sequences appear to come from humans (naturalness)

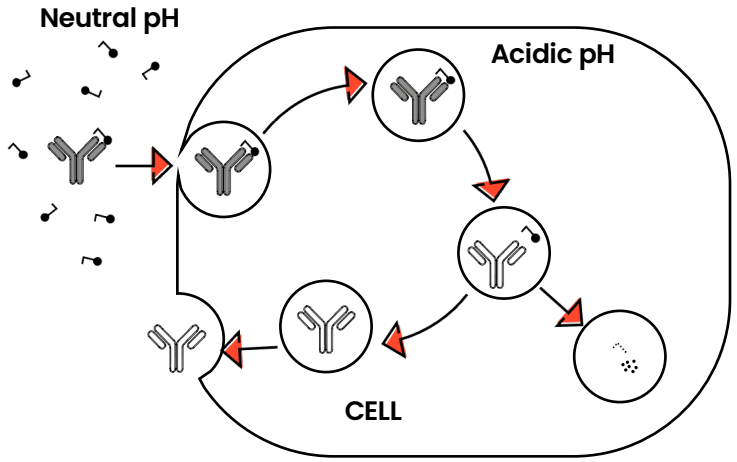


Models simultaneously tuning for affinity & maximizing naturalness

Bachas, S., Rakocevic, G. *et al.* (2022) pre-print in bioRxiv.

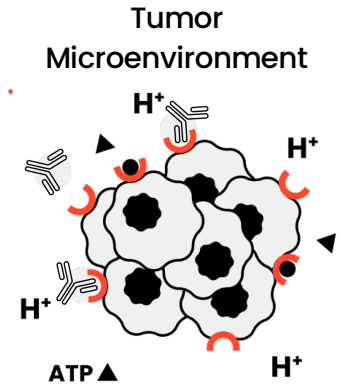
Absci's AI co-optimization enables novel conditional biologics

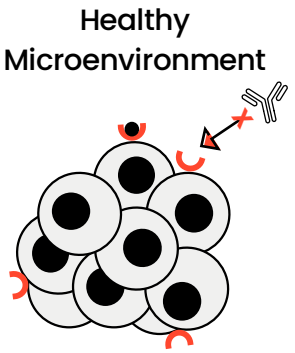




Recycling antibodies e.g. neutral pH binders for Recycling Antibodies

Immunological Reviews 2016 Vol. 270 270: 132-151 © 2016 John Wiley & Sons A/S. Published by John Wiley & Sons





Conditional Biologics e.g. low-pH binders for Oncology

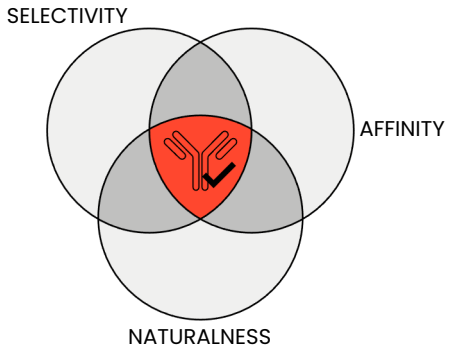
Current Opinion in Biotechnology 2022, 78: 102809

VALUE CREATION FOR PATIENTS AND PARTNERS - TODAY

Platform unlocks new and differentiated value drivers

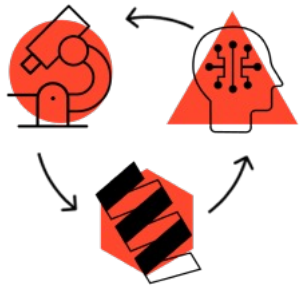
Higher Potential Biologics with Increased PoS

Multidimensional optimization in parallel creates higher quality biologics with an increased Probability of Success



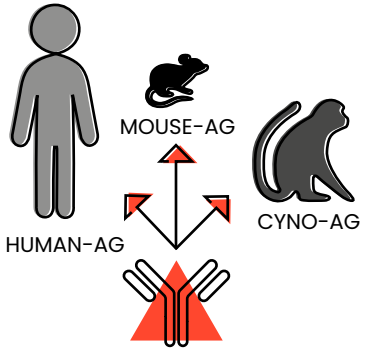
Reducing Time & Increasing Competitiveness

Drug creation process significantly shortened reducing research costs and increasing competitiveness



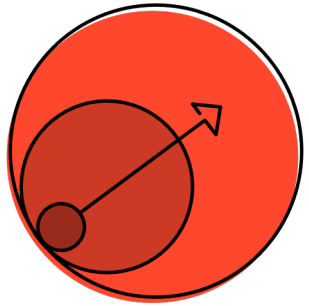
Novel biology: Multi-valent biologics & conditional biologics

Preclinical development: Cross-species binding to improve success rates & speed



Broadening Intellectual Property Space

AI-driven drug creation generates valuable IP



DRUG CREATION AT THE SPEED OF AI

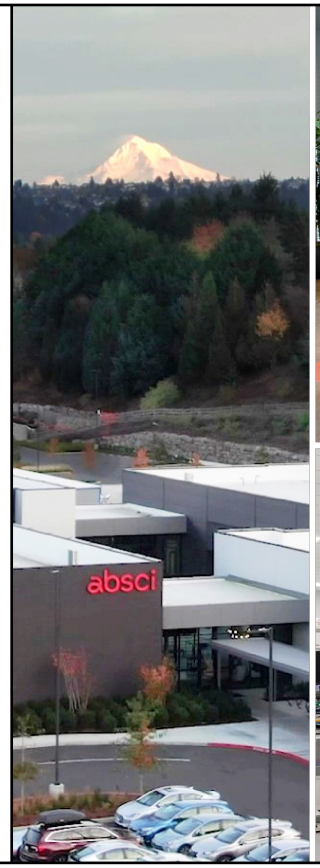
World-class team to accomplish the impossible

Antibody optimization enabled by artificial intelligence predictions of binding affinity and naturalness

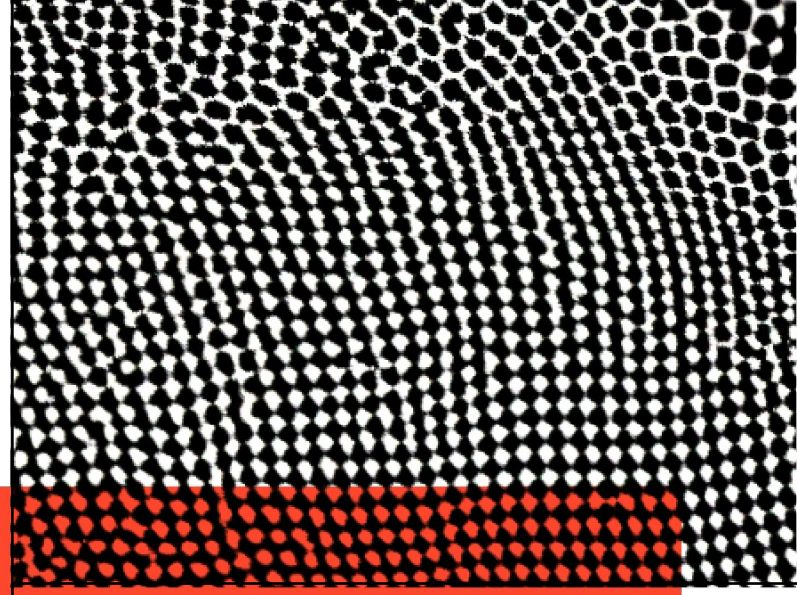
Sharrol Bachas*, Goran Rakocevic*, David Spencer, Anand V. Sastry, Robel Haile, John M. Sutton, George Kasun, Andrew Stachyra, Jahir M. Gutierrez, Edriss Yassine, Borka Medjo, Vincent Blay, Christa Kohnert, Jennifer T. Stanton, Alexander Brown, Nebojsa Tijanic, Cailen McCloskey, Rebecca Viazzo, Rebecca Consbruck, Hayley Carter, Simon Levine, Shaheed Abdulhaqq, Jacob Shaul, Abigail B. Ventura, Randal S. Olson, Engin Yapici, Joshua Meier, Sean McClain, Matthew Weinstock, Gregory Hannum✉, Ariel Schwartz, Miles Gander, Roberto Spreafico✉

Unlocking *de novo* antibody design with generative artificial intelligence

Amir Shanehsazzadeh*, Sharrol Bachas*, Matt McPartlon*, George Kasun, John M. Sutton, Andrea K. Steiger, Richard Shuai, Christa Kohnert, Goran Rakocevic, Jahir M. Gutierrez, Chelsea Chung, Breanna K. Luton, Nicolas Diaz, Simon Levine, Julian Alverio, Bailey Knight, Macey Radach, Alex Morehead, Katherine Bateman, David A. Spencer, Zachary McDargh, Jovan Cejovic, Gaelin Kopec-Belliveau, Robel Haile, Edriss Yassine, Cailen McCloskey, Monica Natividad, Dalton Chapman, Joshua Bennett, Jubair Hossain, Abigail B. Ventura, Gustavo M. Canales, Muttappa Gowda, Kerianne A. Jackson, Jennifer T. Stanton, Marcin Ura, Luka Stojanovic, Engin Yapici, Katherine Moran, Rodante Caguiat, Amber Brown, Shaheed Abdulhaqq, Zheyuan Guo, Lillian R. Klug, Miles Gander, Joshua Meier✉



Connect with us and let's create together!



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