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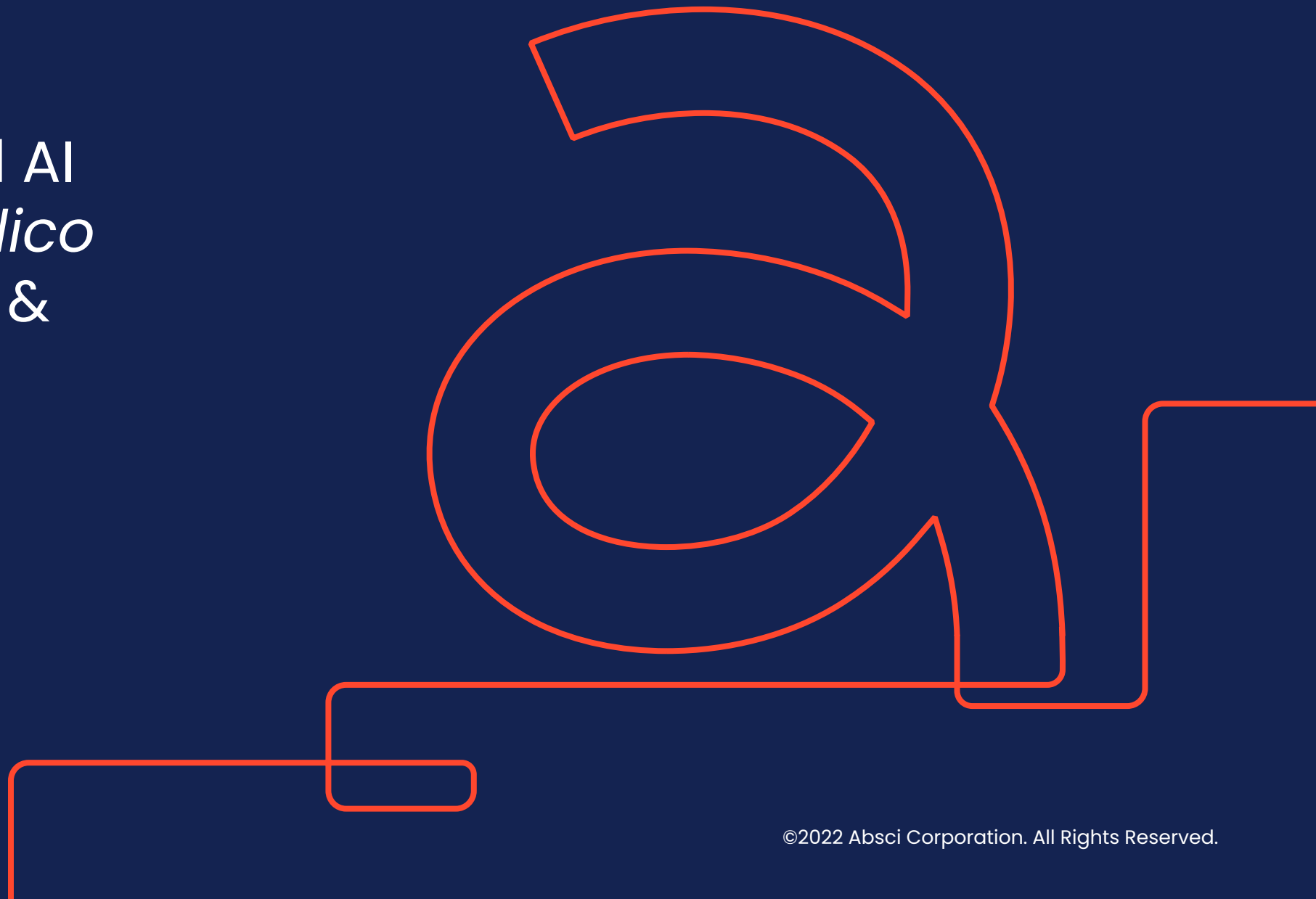
Absci's data and AI platform for *in silico* antibody design & optimization



October 2022

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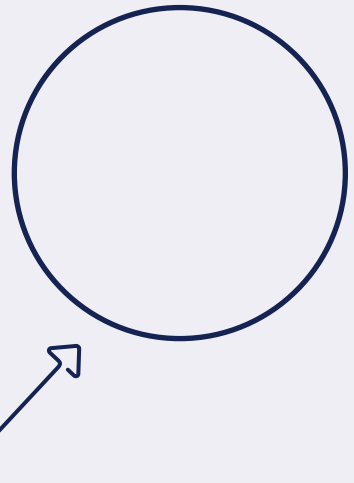
Biologic drug discovery is a complex combinatorial challenge

~20^{62} mAb CDR variants[1] *exceeds* **~10^{80}** atoms in the universe[2]

[1]Assuming 62 positions (6 unique CDRs of approximately 7-13 residues in length) to vary with 20 possible amino acids per position
[2]https://www.thoughtco.com/number-of-atoms-in-the-universe-603795

Biologic drug discovery fails too often

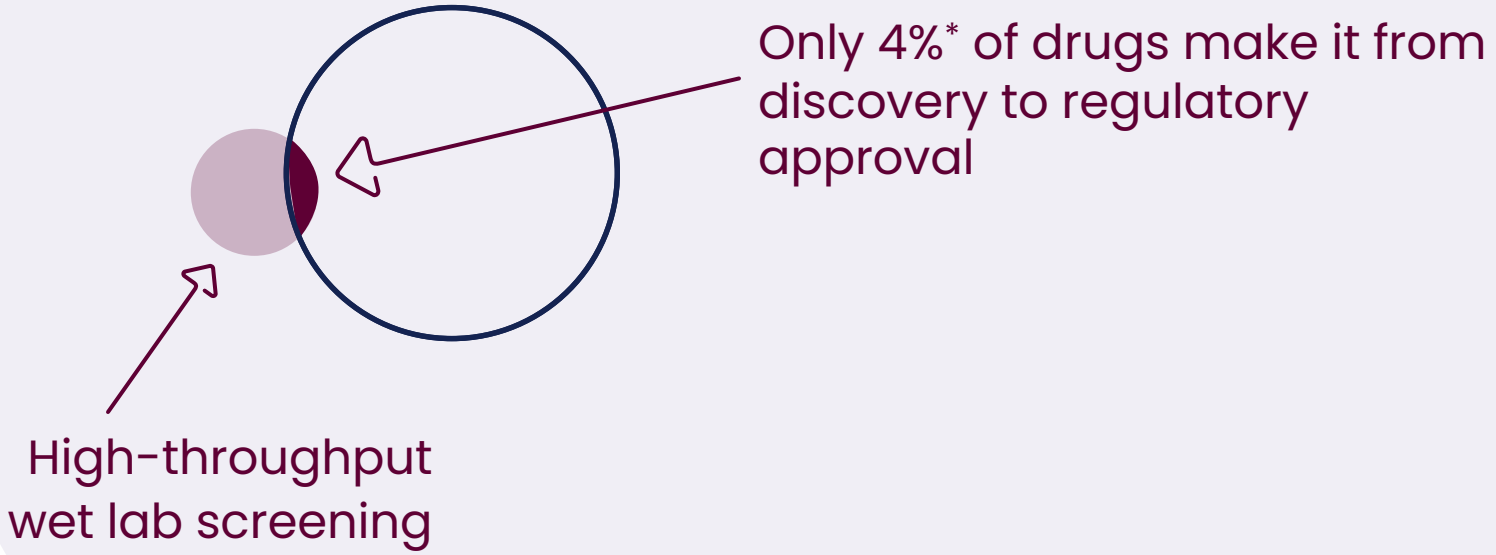
Only a subset of these sequences are biologically viable
(i.e., sequences that are developable, non-immunogenic, etc.)



Subset of biologically viable mAbs

Biologic drug discovery fails too often

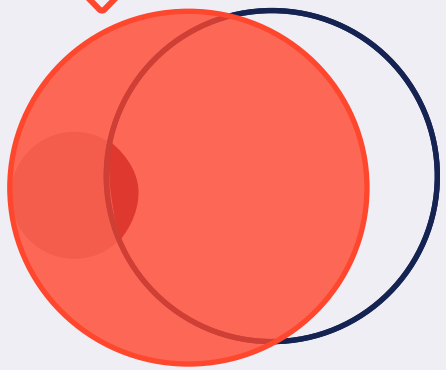
High throughput wet lab screening samples a very small fraction of possible sequences, many of which are not suitable drug candidates



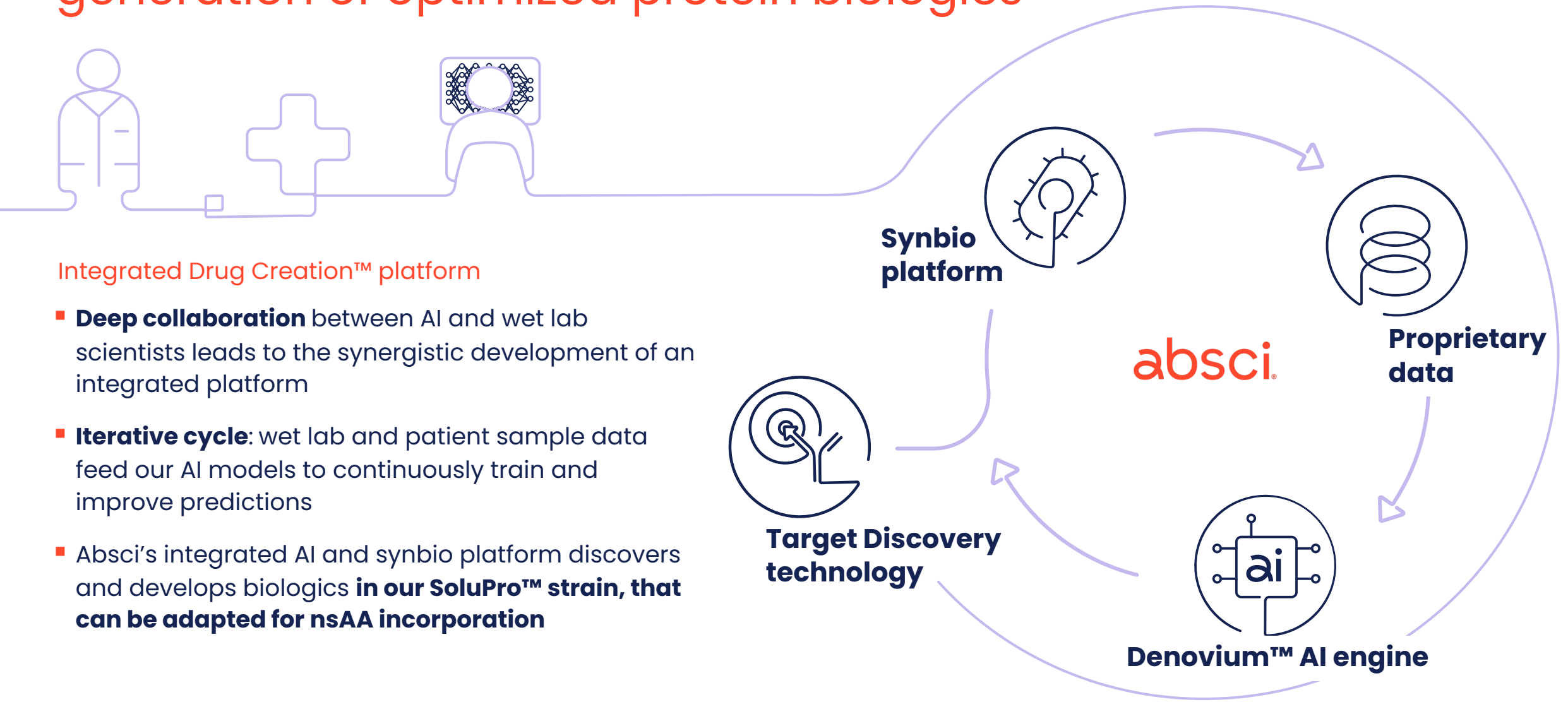
*Paul, S., Mytelka, D., Dunwiddie, C. et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov 9, 203–214 (2010).

Absci unlocks AI for biologics

Proprietary wet lab data combined with AI enables Absci to explore **more** of the **right** sequences



Absci's active learning cycle accelerates the discovery and generation of optimized protein biologics

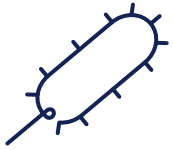


Integrated Drug Creation™ platform

- **Deep collaboration** between AI and wet lab scientists leads to the synergistic development of an integrated platform
- **Iterative cycle**: wet lab and patient sample data feed our AI models to continuously train and improve predictions
- Absci's integrated AI and synbio platform discovers and develops biologics **in our SoluPro™ strain, that can be adapted for nsAA incorporation**

Active AI learning improves cycle time and success rates

SoluPro® strain



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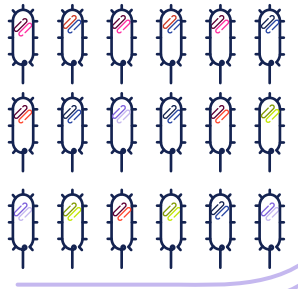
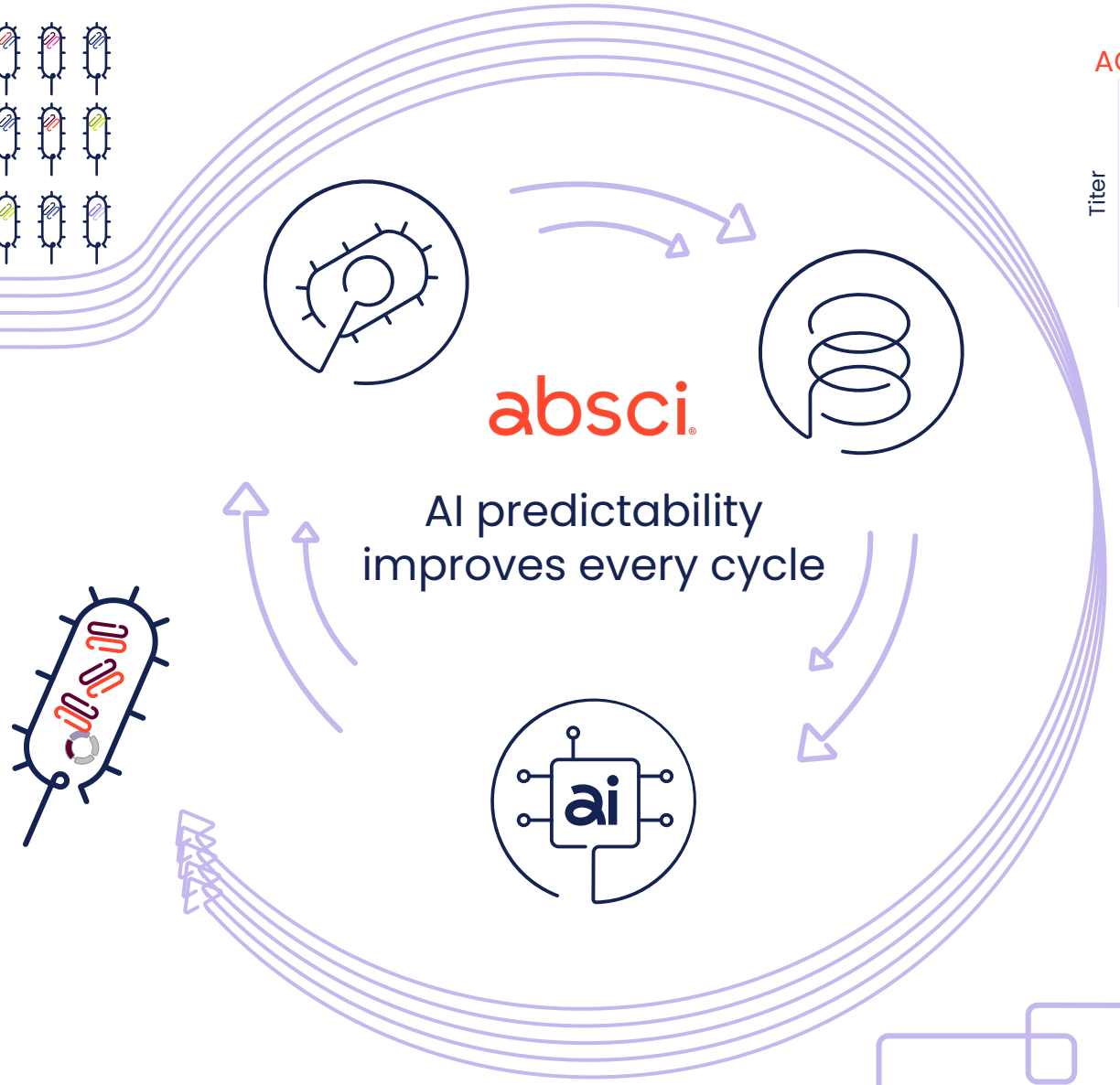
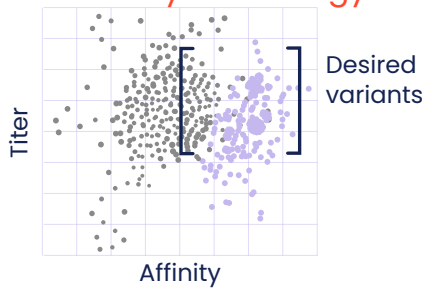
AI guided library of molecule variants

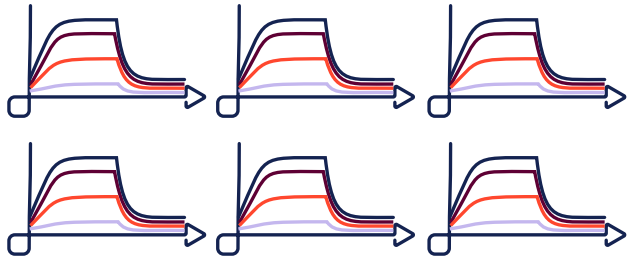




ACE Assay technology



Mid-throughput biophysical characterization



Absci has built an industry-leading data-centric platform for scalable, AI-enabled protein biologic discovery

Find patient cohort specific targets

Discover novel antibodies for your selected target

Optimize your antibodies characteristics

Incorporate site-specific chemical handles

Novel antibody and target discovery

patient immune response -> lead

De novo discovery *in silico*

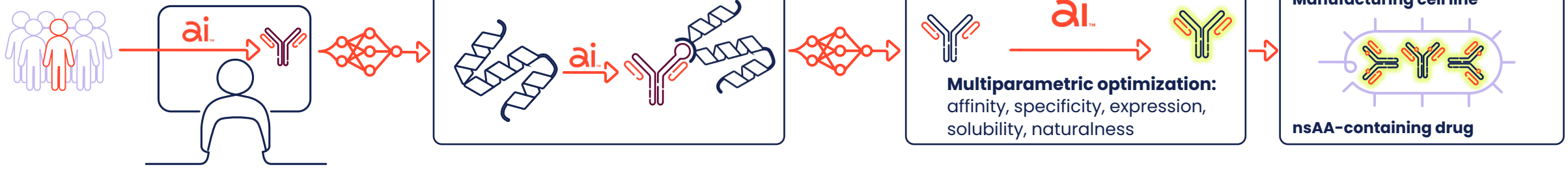
target -> lead

Lead optimization *in silico*

lead -> drug candidate

Bionic SoluPro™ strain

drug -> incorporate nsAA

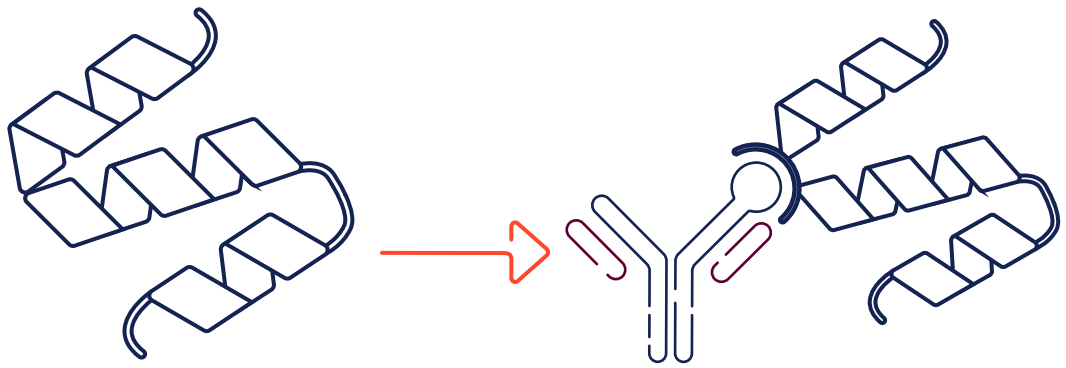


Our end-to-end platform uniquely positions us to support the needs of our partners in multiple ways to overcome increasing drug complexity and develop the best drugs for patients

Absci's AI models for *in silico* biologic drug design

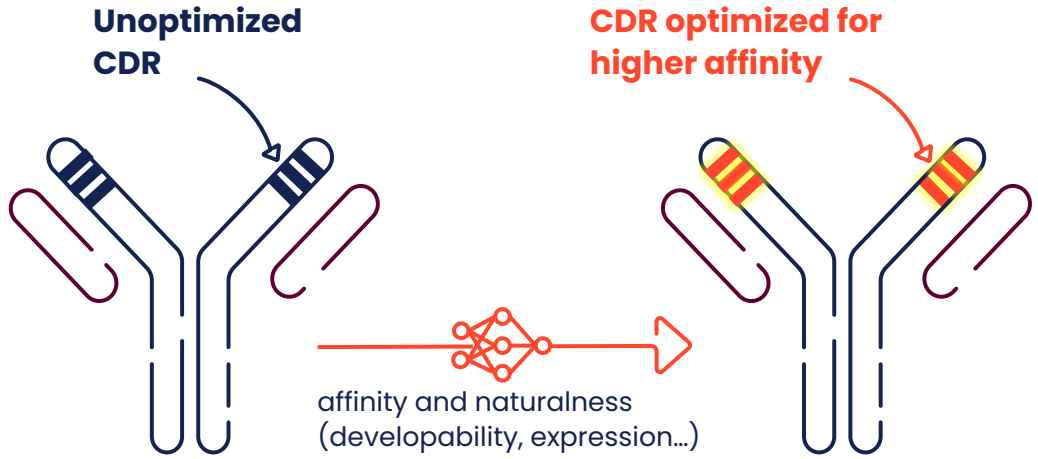
De novo discovery *in silico*

target -> lead



Lead optimization *in silico*

lead -> multiparametric optimization -> drug candidate



Absci's AI models for *in silico* biologic drug design

De novo discovery *in silico*

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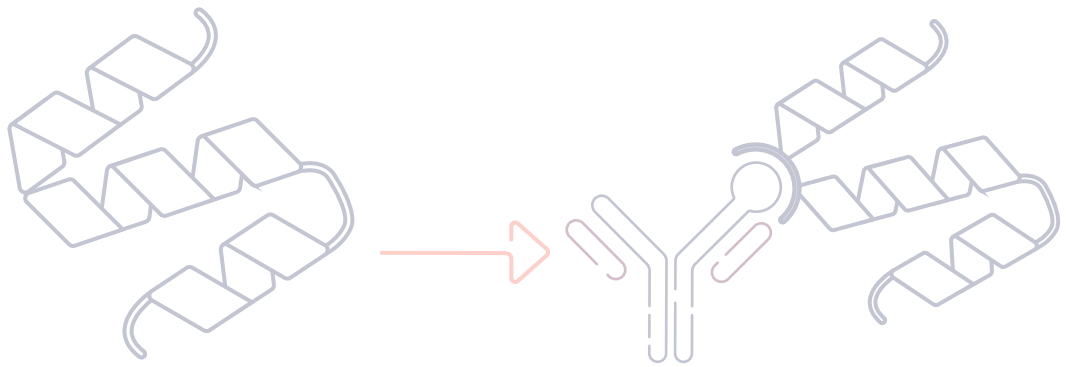
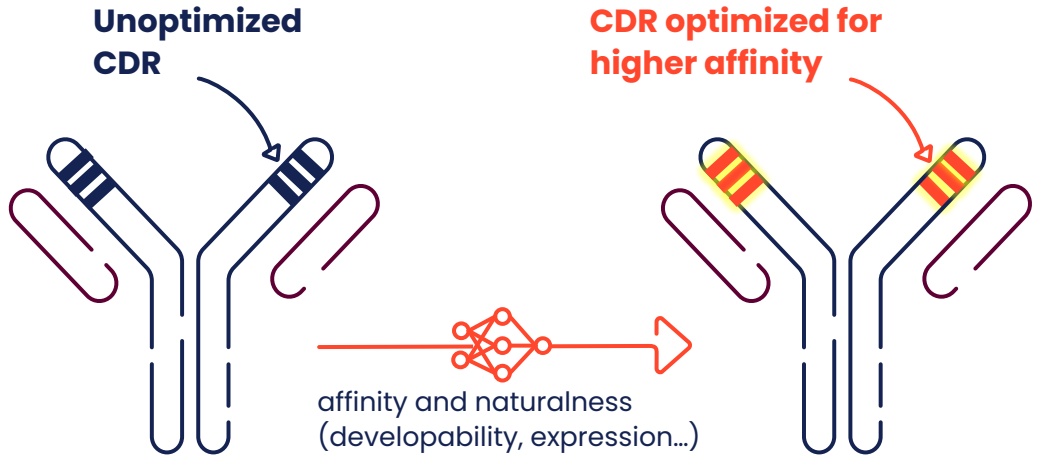


Lead optimization *in silico*

lead -> multiparametric optimization -> drug candidate



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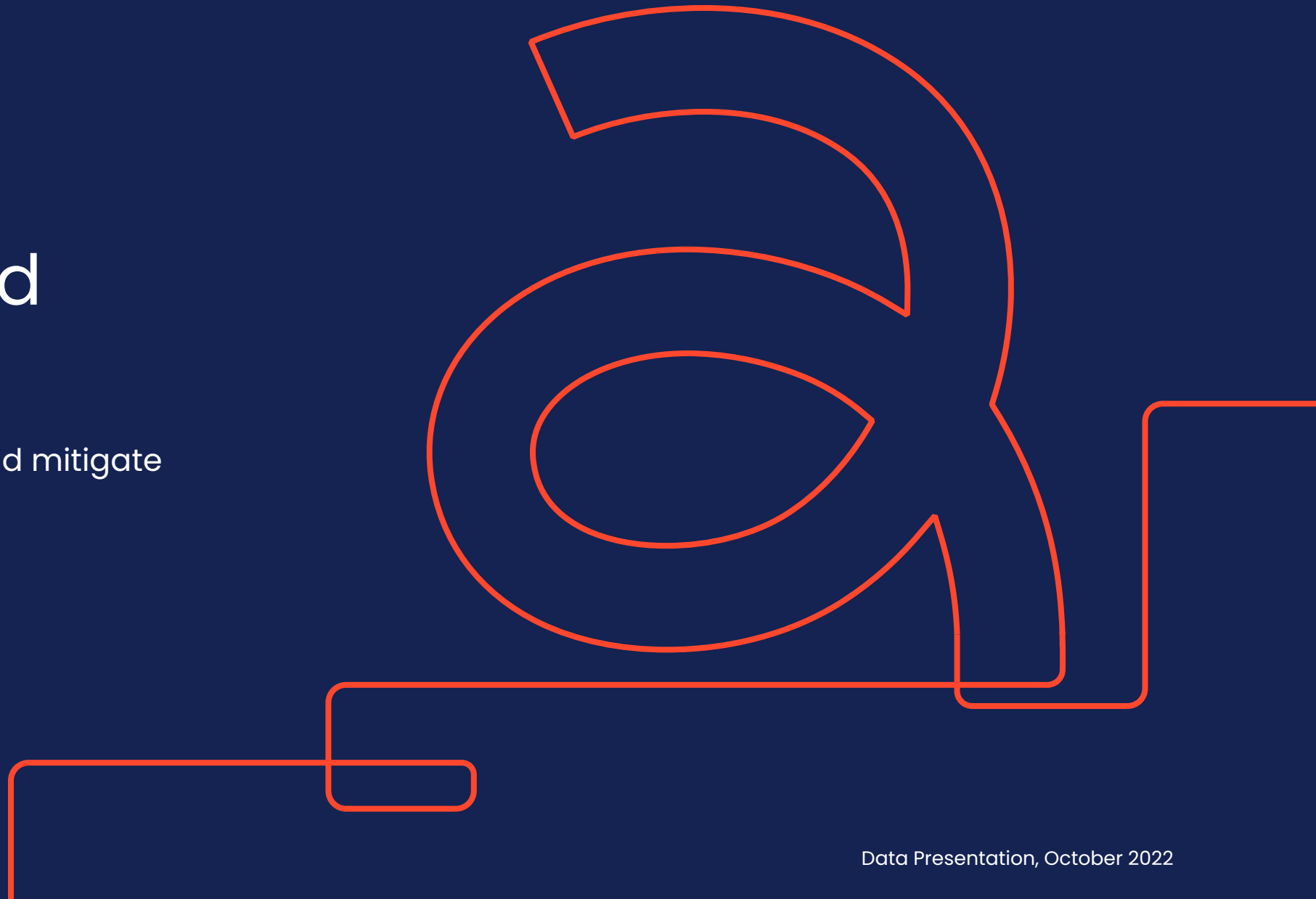
AI-guided lead optimization

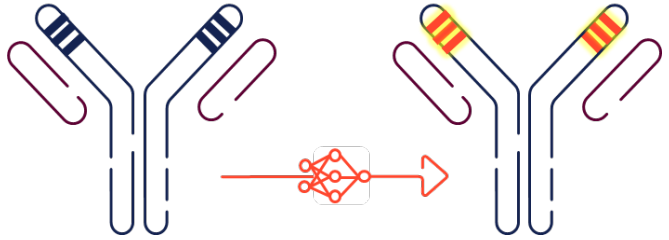
Solutions to optimize affinity and mitigate developability issues



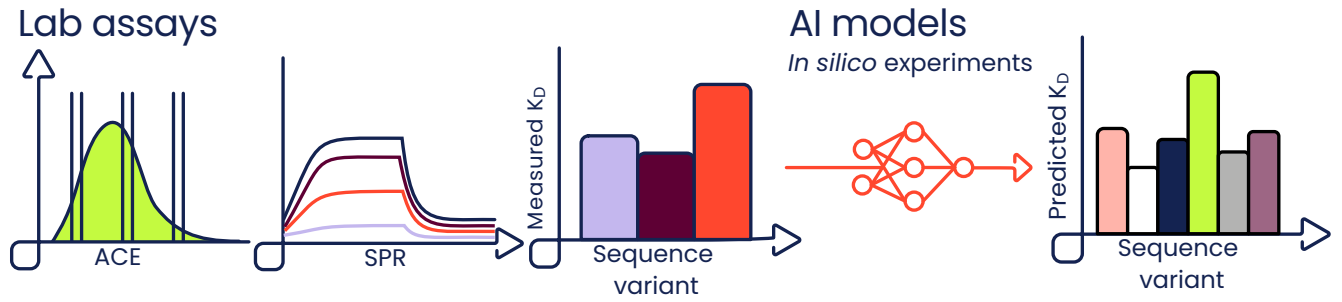
Data Presentation, October 2022

An academic publication illustrated the ability to predict binary binding of trastuzumab variants to Her2

Goal



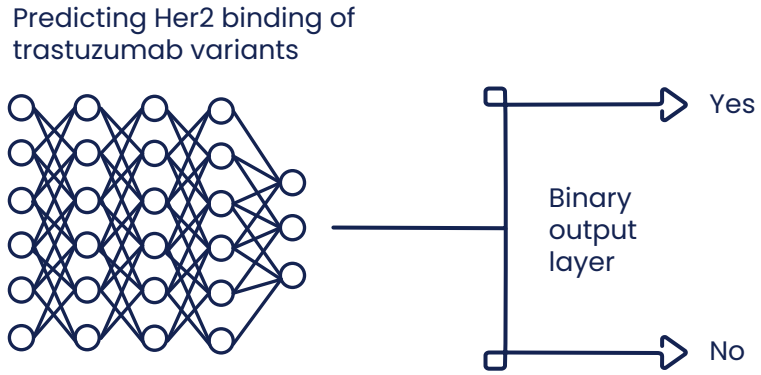
Overview of workflow



Binary binding predictions

Optimization of therapeutic antibodies by predicting antigen specificity from antibody sequence via deep learning

Derek M Mason[1,2], Simon Friedensohn[1,2], Cédric R Weber[1,2], Christian Jordi[1], Bastian Wagner[1], Simon M Meng[1], Roy A Ehling[1], Lucia Bonati[1], Jan Dahinden[1], Pablo Gainza[3], Bruno E Correia[3], Sai T Reddy[4]

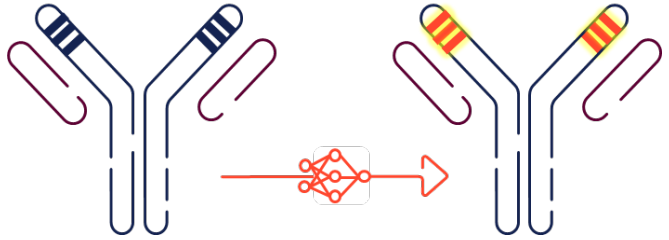


Publication demonstrated success of ML in classification of antigen binding by trastuzumab variants

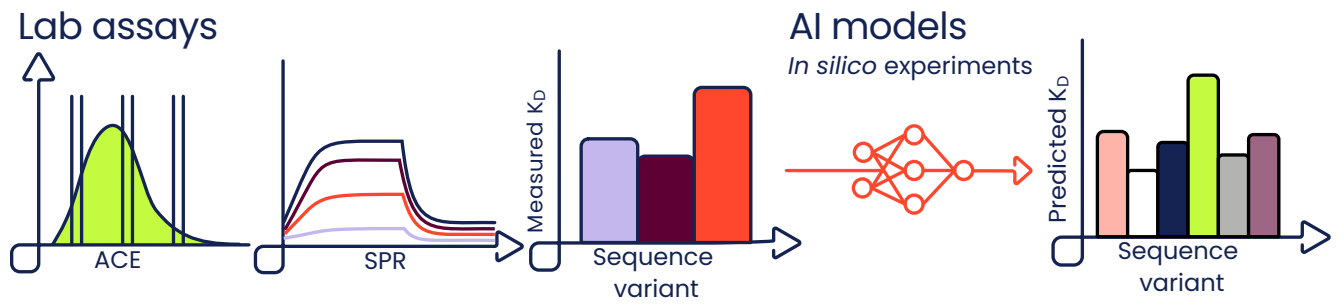
Nature Biomedical Engineering doi: 10.1038/s41551-021-00699-9. Epub 2021 Apr 15.

Absci developed models with quantitative binding predictions for tuning antibody binding affinity

Goal



Overview of workflow



Absci's quantitative binding predictions

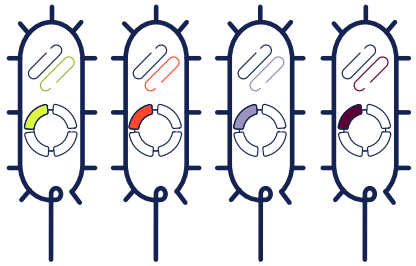
Absci has developed assays and AI models providing

quantitative

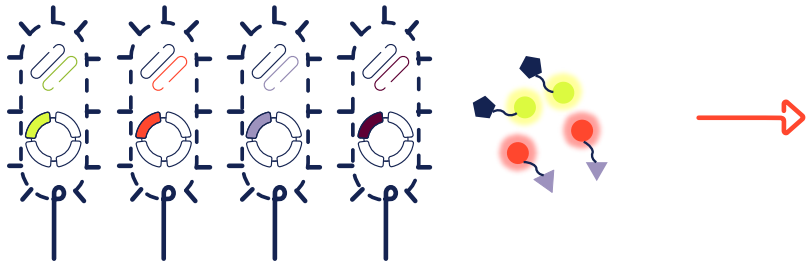
binding predictions, thereby enabling genuine *in silico* affinity maturation

We utilize our proprietary ACE Assay to train deep learning models for AI-augmented antibody optimization

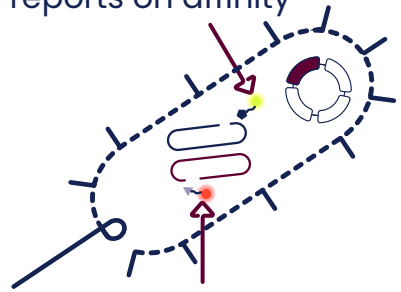
1. Strains expressing unique antibody sequence variants



2. Fix and permeabilize cells and add labeled probes

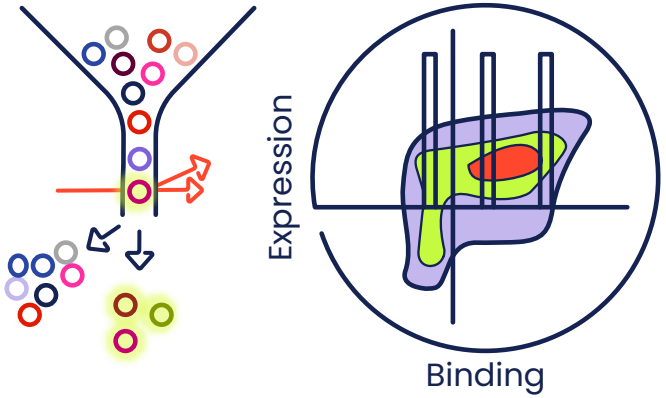


Labeled antigen reports on affinity

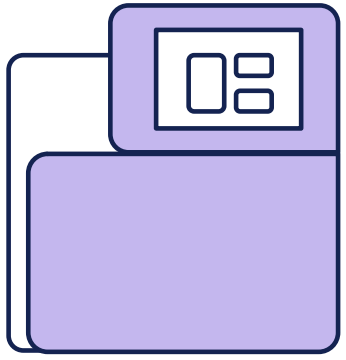


Labeled scaffold-binding protein reports specifically on titer

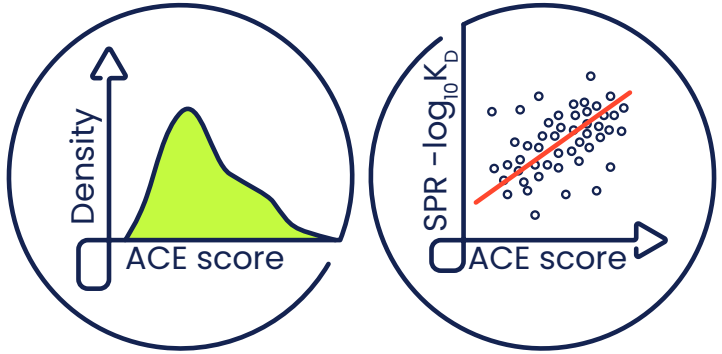
3. Screen and sort by flow cytometry



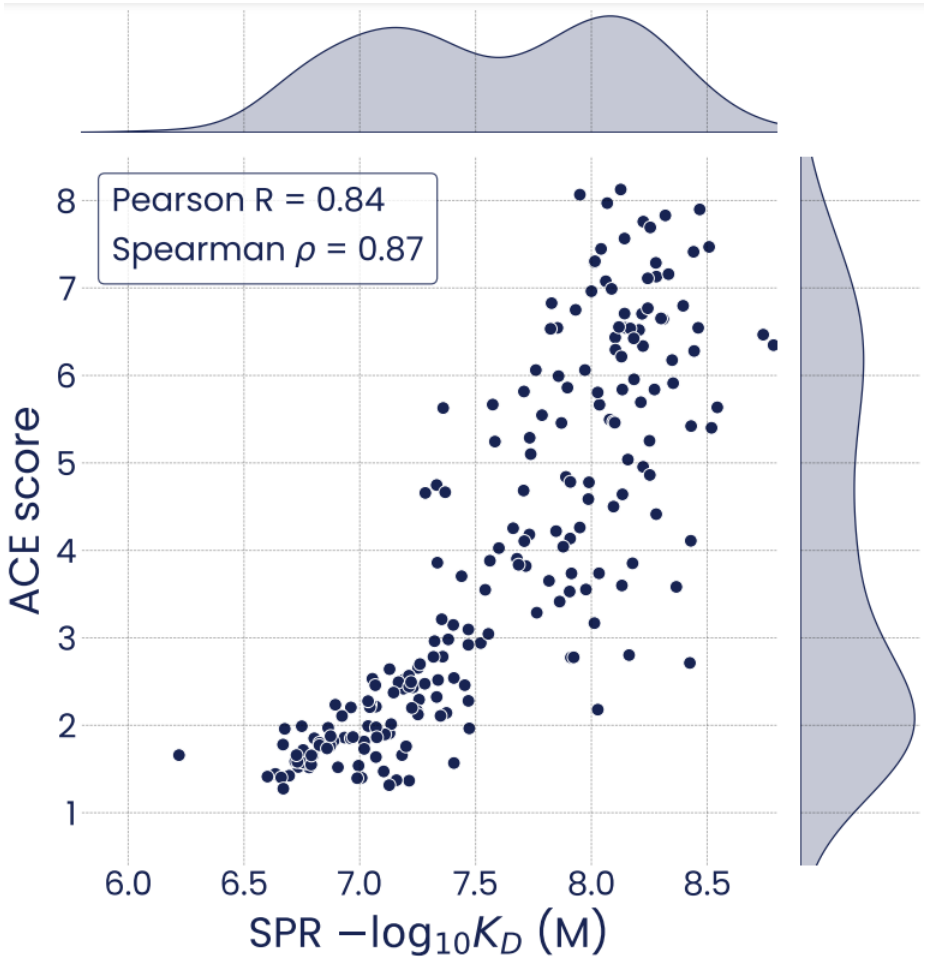
4. NGS

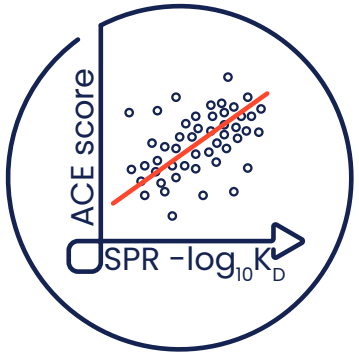


5. ACE Assay scores (affinity)



There is a strong agreement between our high-throughput ACE Assay scores and SPR-derived $-\log_{10} K_D$ (Pearson R = 0.84)





Accurate high-throughput experimental data required to successfully train a predictive AI model

Bachas, S., Rakocevic, G. *et al.* Antibody optimization enabled by artificial intelligence predictions of binding affinity and naturalness (2022) *pre-print in bioRxiv.*

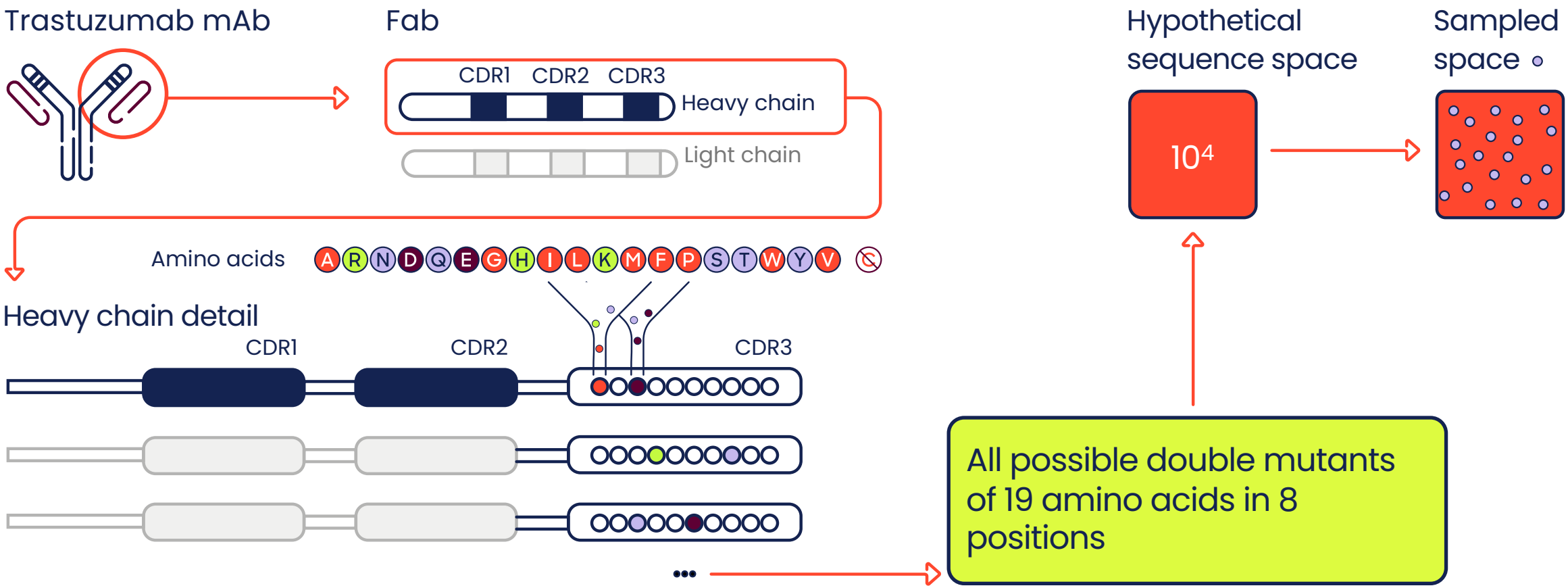
Three affinity prediction models were trained based on ACE Assay and SPR data

Dataset		trast-1	trast-2	trast-3
Design		Random sampling of combinatorial space	Uniform sampling by affinity from trast-1 dataset	Random sampling of combinatorial space per mutational load bin
Mutated CDRH2 positions		-	-	10 (55-66)
Mutated CDRH3 positions		8 (107-114)	8 (107-114)	10 (107-116)
Mutational load		Up to double mutations	Up to double mutations	Up to triple mutation
Allowed natural AAs		19 (no Cys)	19 (no Cys)	19 (no Cys)
Combinatorial space		9,217	9,217	6,710,401
Screening		ACE	SPR	ACE
Number of mutations in AA variants	**1** **2** **3** **4*** **5***	142 8,789 - - -	23 191 - - -	315 4,054 44,704 1,992 1,530

* denotes that sequences were not in the training set

Bachas, S., Rakocevic, G. *et al.* Antibody optimization enabled by artificial intelligence predictions of binding affinity and naturalness (2022) *pre-print in bioRxiv.*

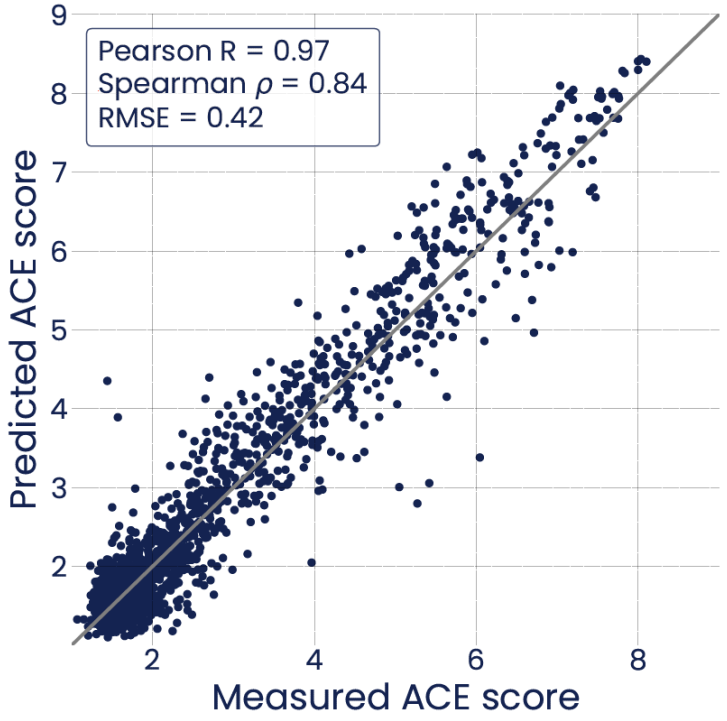
Deep learning models trained with the ACE-generated trast-1 dataset contained a 10^4 hypothetical sequence space

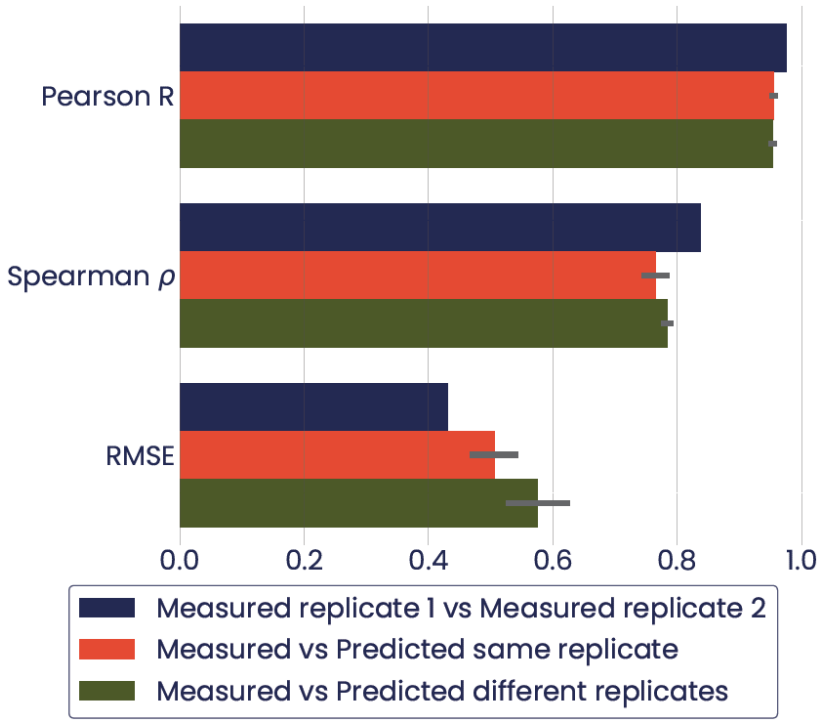


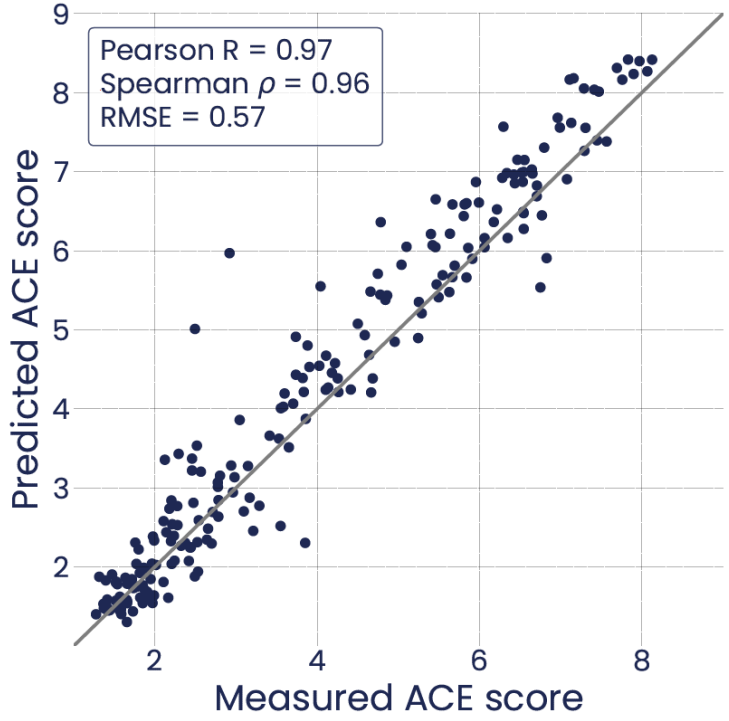
The following data slides on AI lead optimization are from a pending manuscript submission by Bachas, Rakocevic, *et al.*

Bachas, S., Rakocevic, G. *et al.* Antibody optimization enabled by artificial intelligence predictions of binding affinity and naturalness (2022) *pre-print in bioRxiv.*

Deep learning models trained with the ACE Assay-generated trast-1 dataset **quantitatively predict** antibody binding affinity







Predictive performance with a Pearson R correlation of 0.97

- trained on 90 % of trast-1 variants
- evaluated remaining 10 % of sequences

Comparing the inaccuracy of measurement to inaccuracy of predictions strongly illustrates the predictive ability of our models

Strong predictive performance against a hold-out set uniformly distributed with respect to binding affinity

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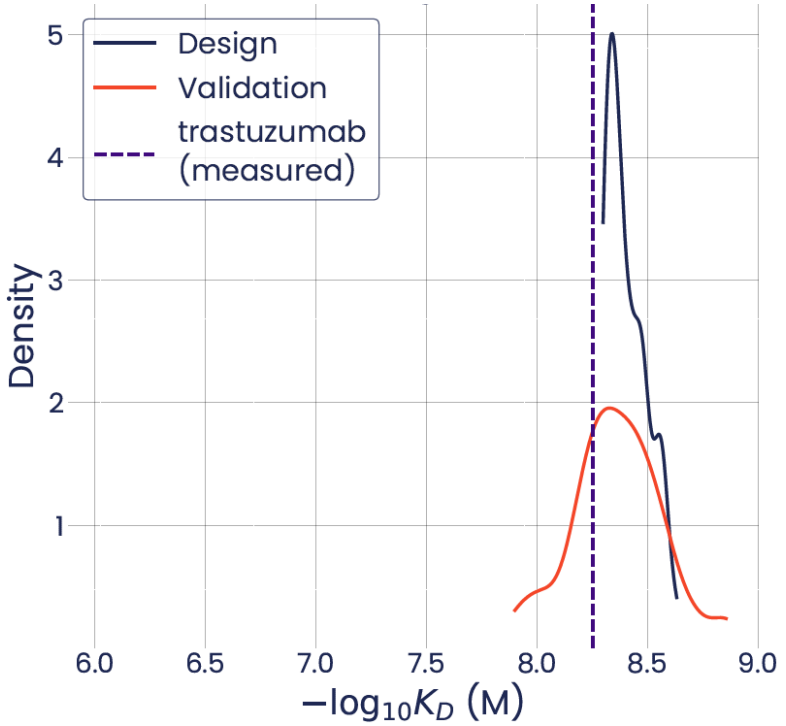
Bachas, S., Rakocevic, G. *et al.* Antibody optimization enabled by artificial intelligence predictions of binding affinity and naturalness (2022) *pre-print in bioRxiv.*

Models trained with the SPR-generated trast-2 dataset can design unseen sequence variants



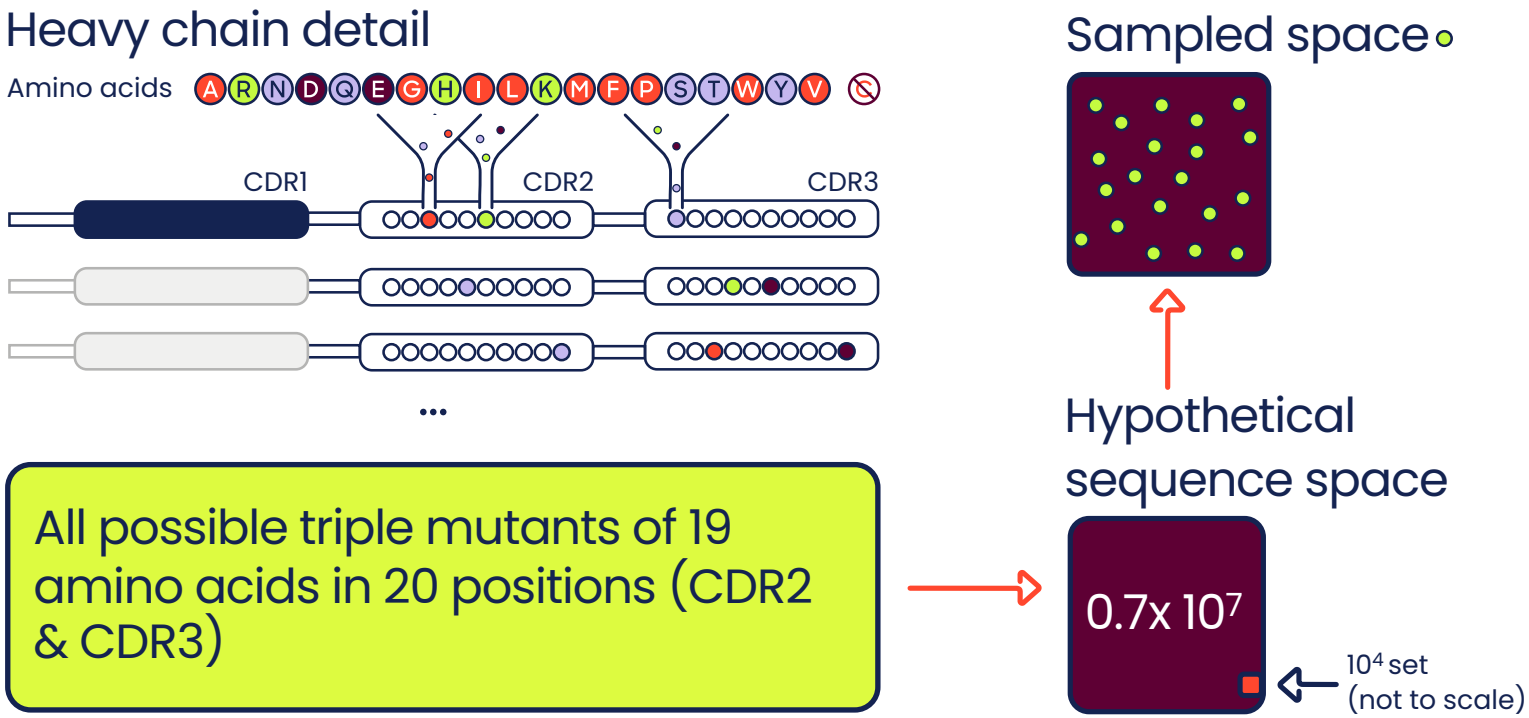
74% of variants were tighter binders than the parental antibody
- trained with the SPR-generated trast-2 dataset

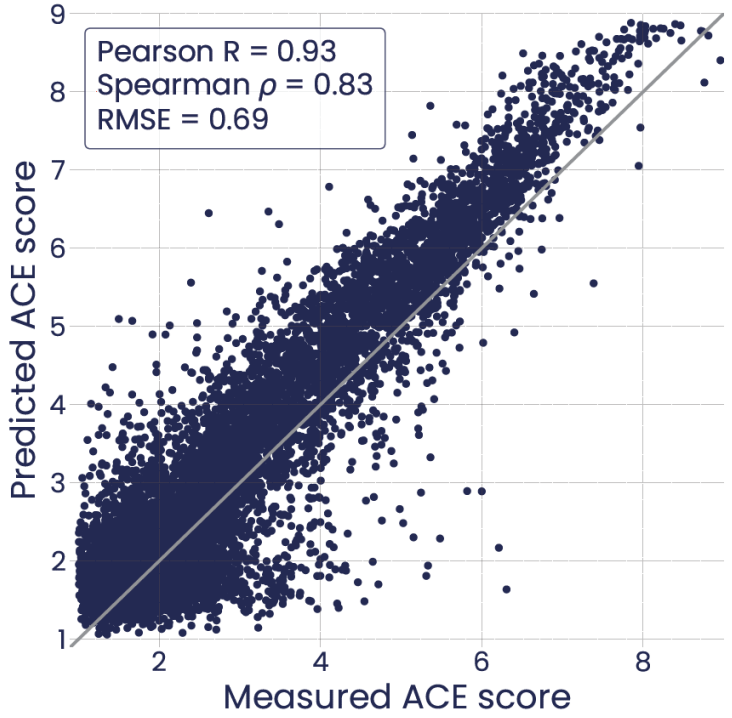
Evaluating the power of our AI models

1. tasked model trained with trast-2 dataset with designing sequences spanning 2-orders of magnitude of equilibrium dissociation constants
2. Found an agreement between predictions and validations
3. Assessed the model's ability to design variants with tighter binding than trastuzumab
4. Validated 50 sequences by SPR

Bachas, S., Rakocevic, G. *et al.* Antibody optimization enabled by artificial intelligence predictions of binding affinity and naturalness (2022) *pre-print in bioRxiv.*

High-throughput binding scores from ACE-generated trast-3 dataset expands predictive capabilities





- Combinatorial mutagenesis of up to 3 mutations over ten amino acids each in CDRH2 and CDRH3
- Sampled less than 1% of the sequence space
- Measured binding affinity of nearly 50,000 sequence variants
- **Predictive performance of triple-mutant dataset is comparable to the double-mutant library (Pearson R>0.9)**

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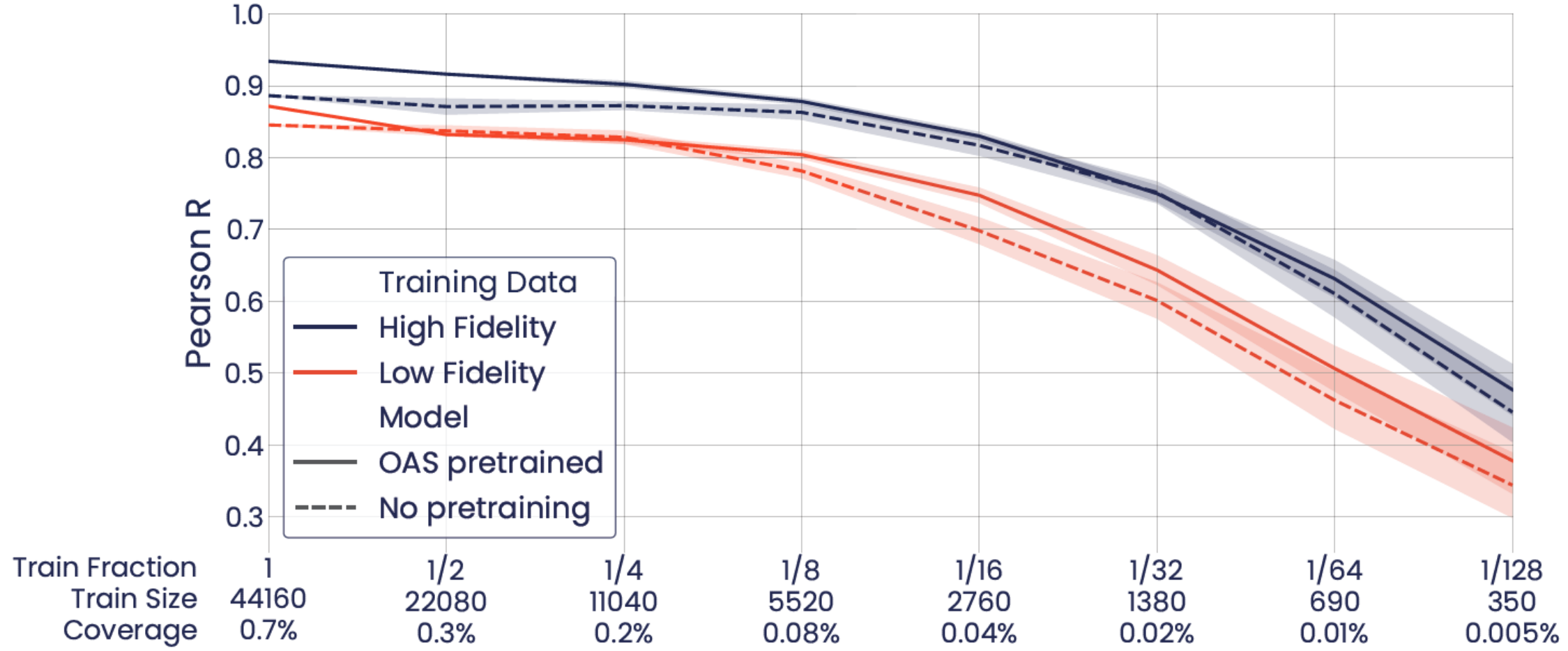
Bachas, S., Rakocevic, G. *et al.* Antibody optimization enabled by artificial intelligence predictions of binding affinity and naturalness (2022) *pre-print in bioRxiv.*

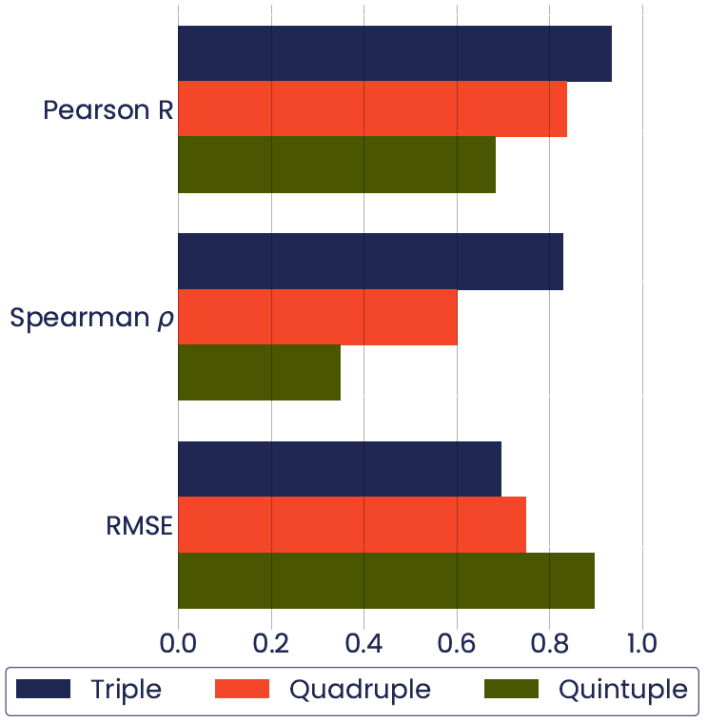
Models learned to predict roughly 2,500 sequences for every sequence in the training dataset

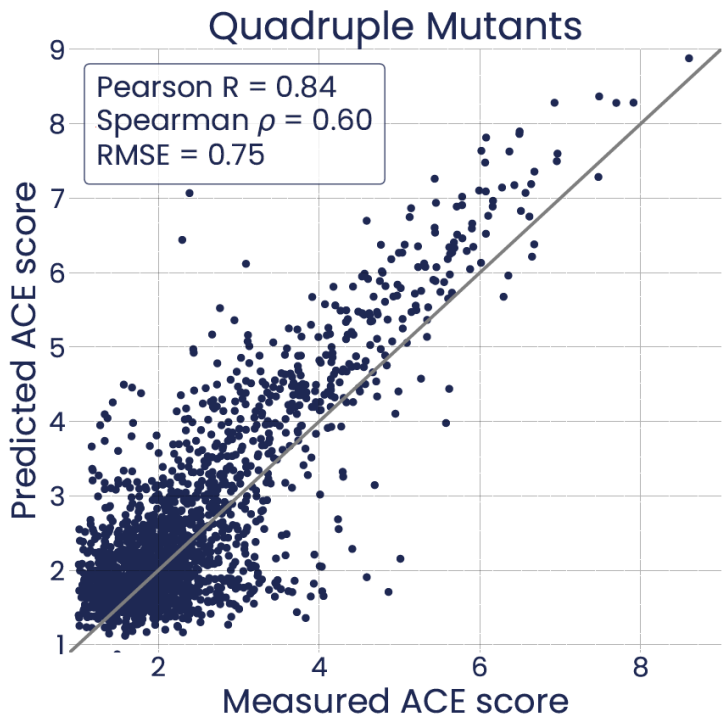


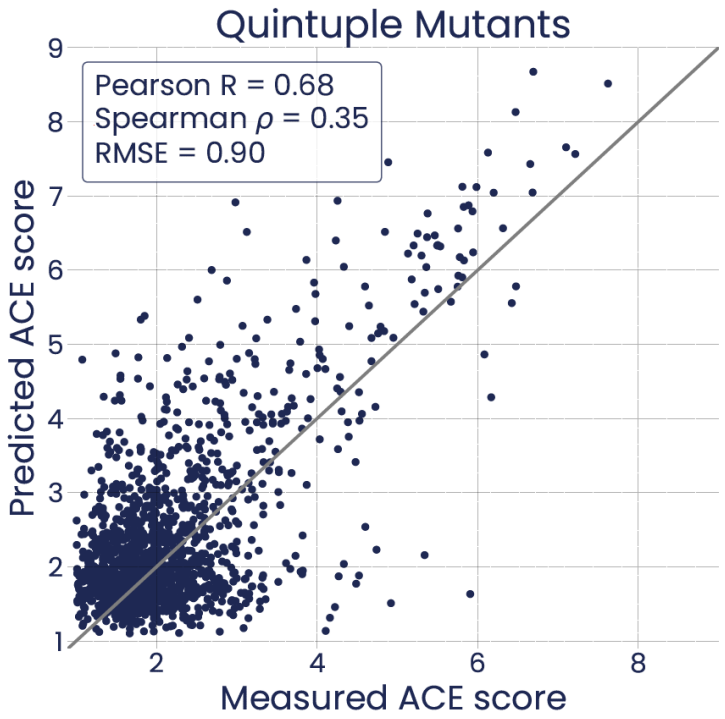
We can make predictions with actionable performance using <0.1% of the combinatorial sequence space as the training set

Bachas, S., Rakocevic, G. *et al.* Antibody optimization enabled by artificial intelligence predictions of binding affinity and naturalness (2022) *pre-print in bioRxiv.*

Predictive power is maintained when extrapolating to larger mutational load → access to a greater combinatorial space







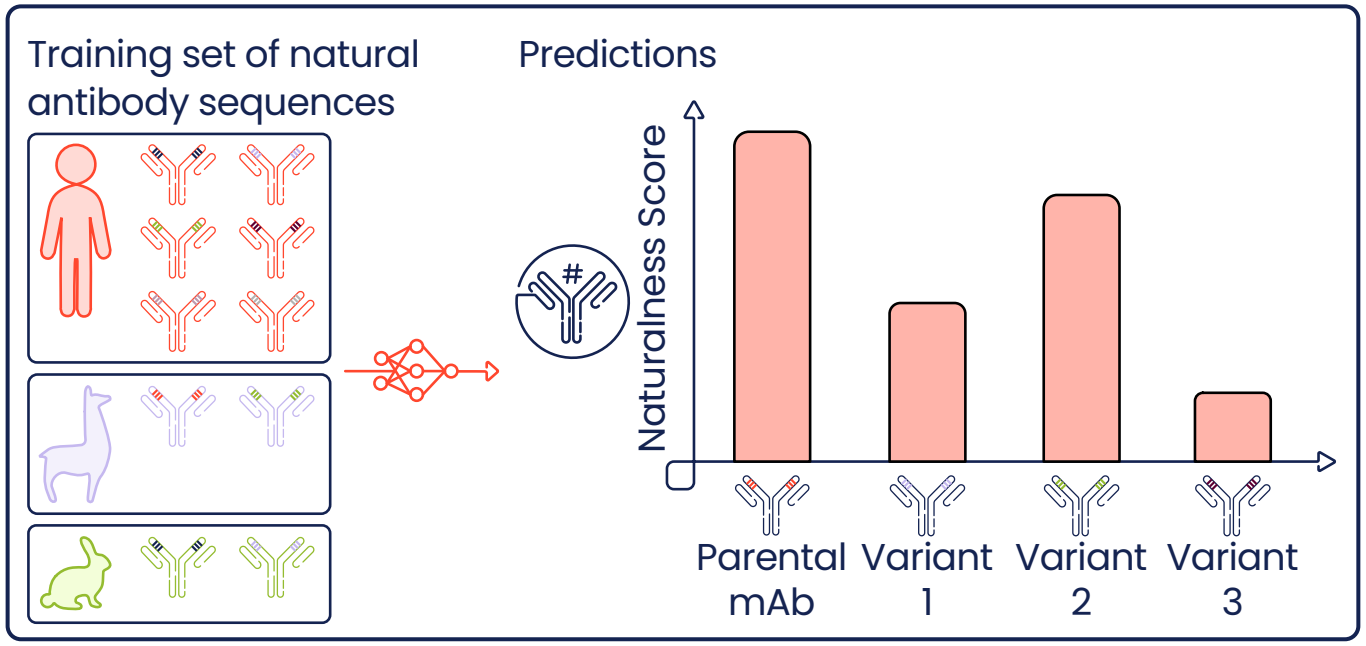
As the mutational load increases, the model accuracy degrades

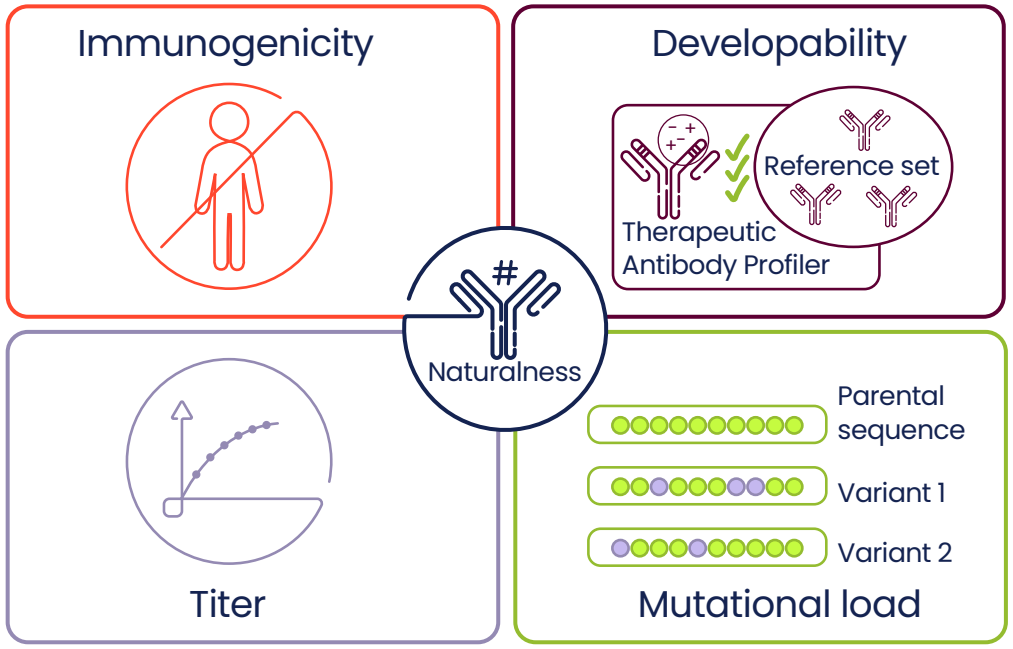
Predictions with quadruple mutants is slightly lower in accuracy than those of triple mutants, but still actionable

Model trained with triple mutants can qualitatively predict binding of quintuple mutant variants

Bachas, S., Rakocevic, G. *et al.* Antibody optimization enabled by artificial intelligence predictions of binding affinity and naturalness (2022) *pre-print in bioRxiv.*

Modeling the risk of production, formulation, efficacy, and adverse reaction has been a major challenge in the industry

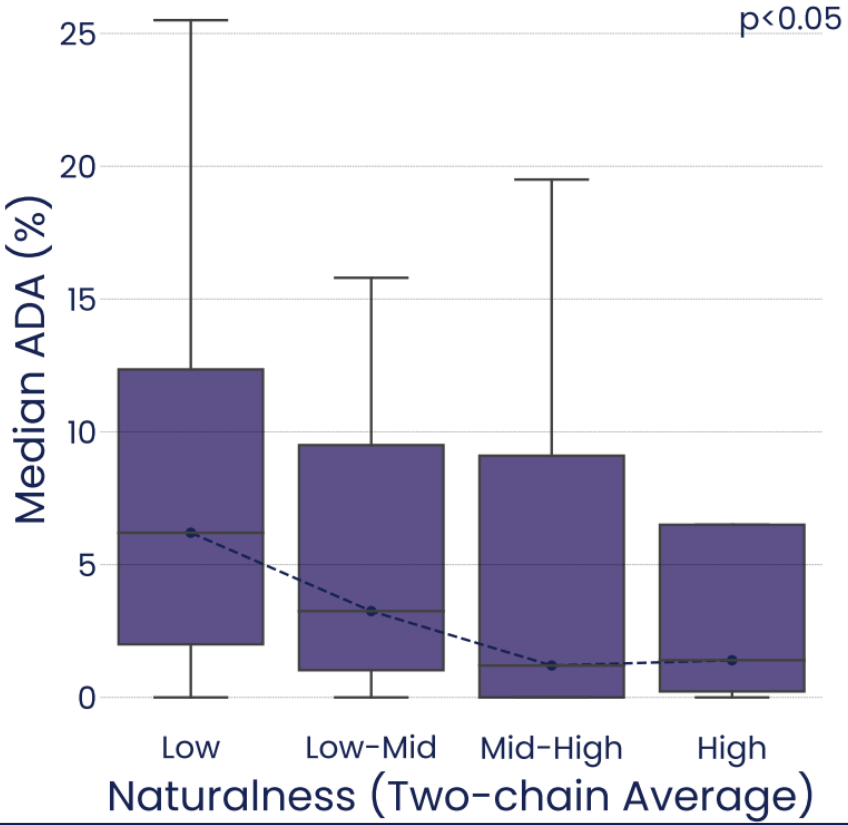




- Absci assessed four independent properties of therapeutic antibodies: i) immunogenicity, ii) developability, iii) expression levels, and iv) mutational load against naturalness score
- Naturalness is a score computed by pretrained language models that measures how likely it is for a given antibody sequence to be derived from an organism of interest, in our case human

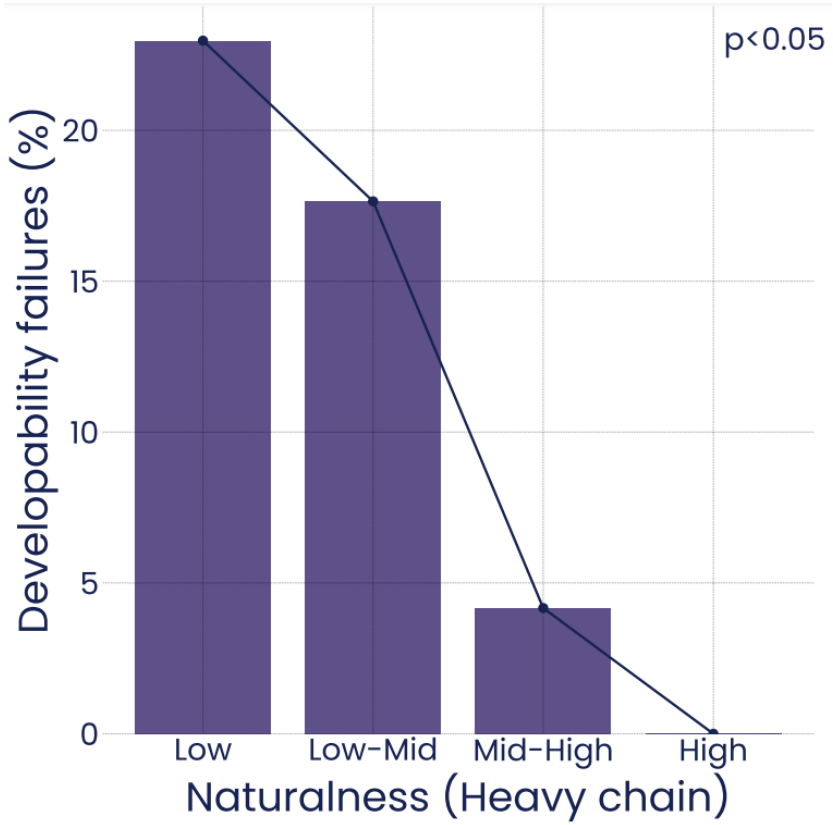
Bachas, S., Rakocevic, G. *et al.* Antibody optimization enabled by artificial intelligence predictions of binding affinity and naturalness (2022) *pre-print in bioRxiv.*

Average naturalness score correlates with lower antibody immunogenicity (ADA%) issues and developability success



Antibodies with higher average naturalness scores tend to have lower median immunogenicity values

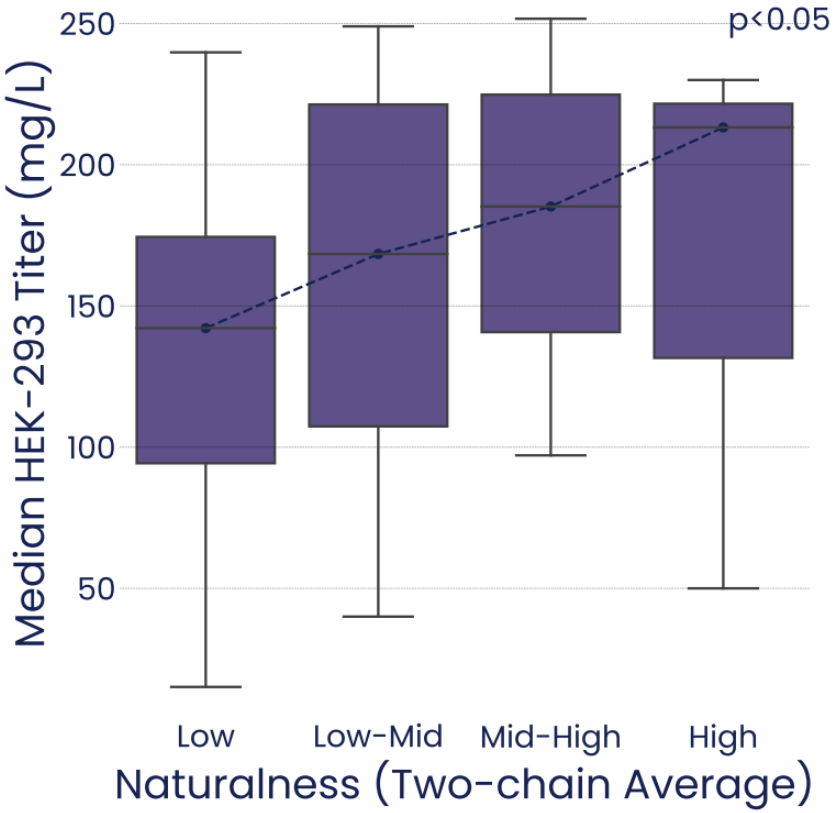
*Therapeutic antibodies and ADA responses from Marks et al, *Bioinformatics* 37:4041 (2021)

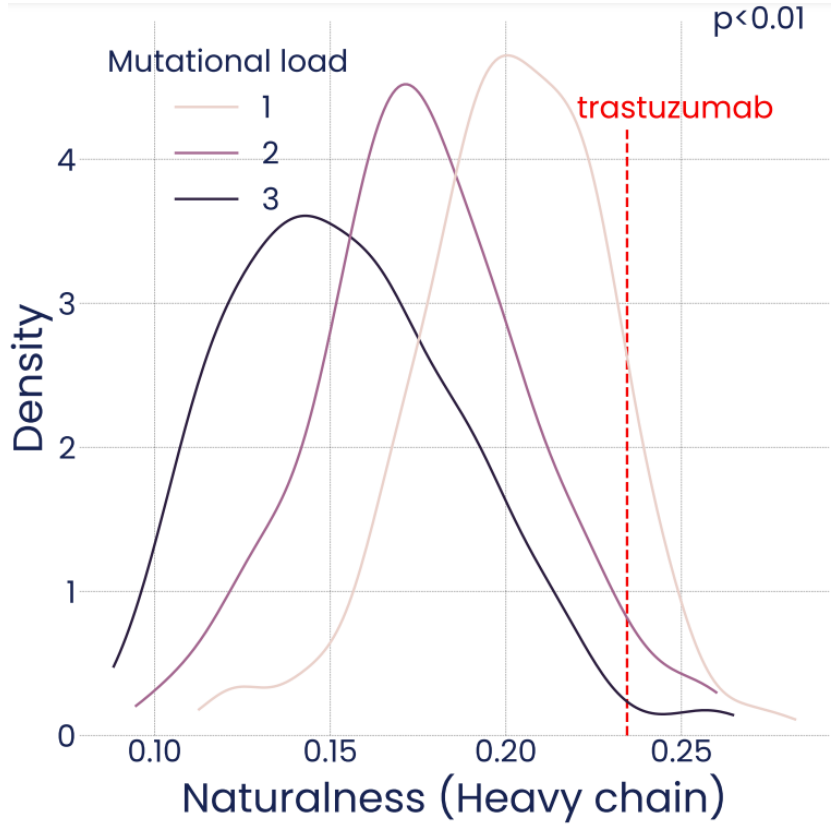


More natural antibodies have fewer developability failures than antibodies with lower naturalness scores

**Developability failures as predicted by the Therapeutic Antibody Profiler (TAP) for round 3-enriched phage display hits from the Gifford library, Liu et al, *Bioinformatics* 36:2126 (2020)

Naturalness is also associated with a higher level of expression in HEK-293 cells and lower mutational load





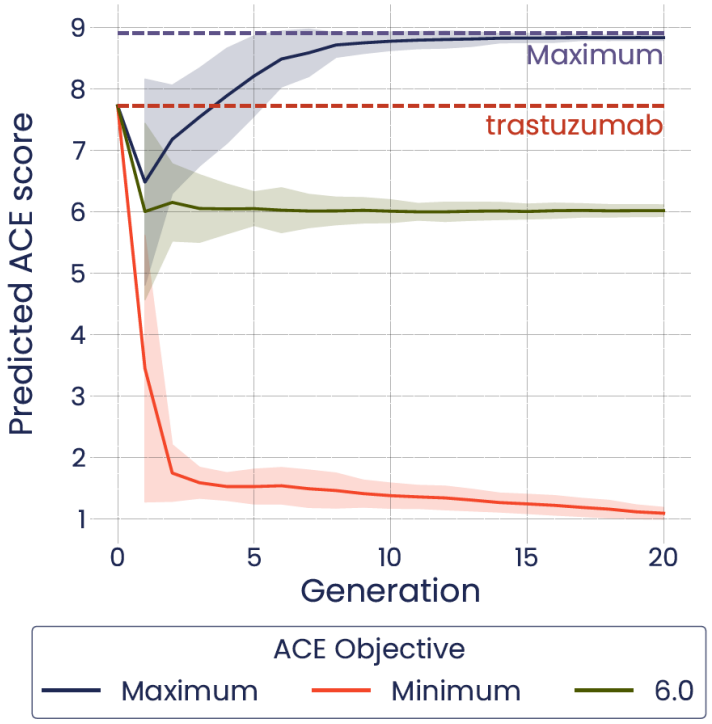
Antibodies with high naturalness scores were expressed at higher levels than antibodies with low scores

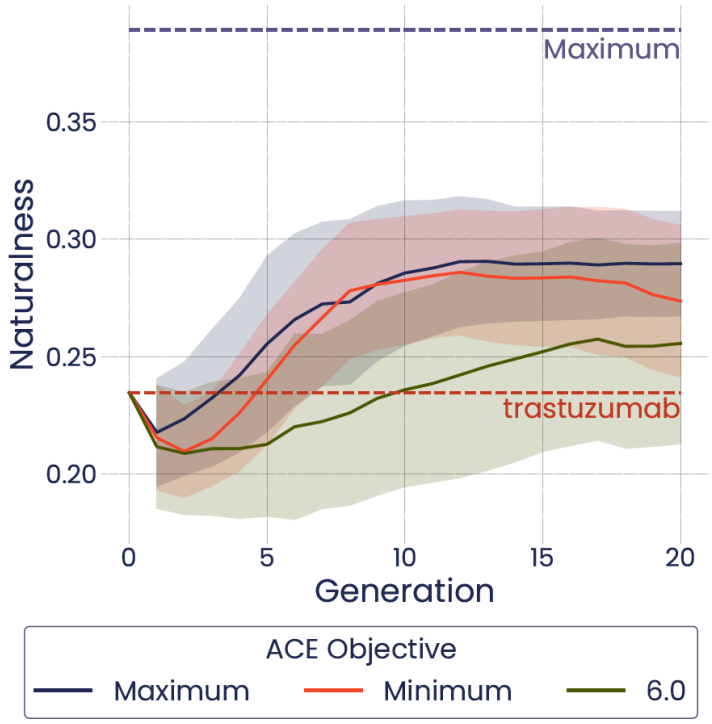
Naturalness has an inverse relationship to mutational load illustrating the need to actively optimize for naturalness

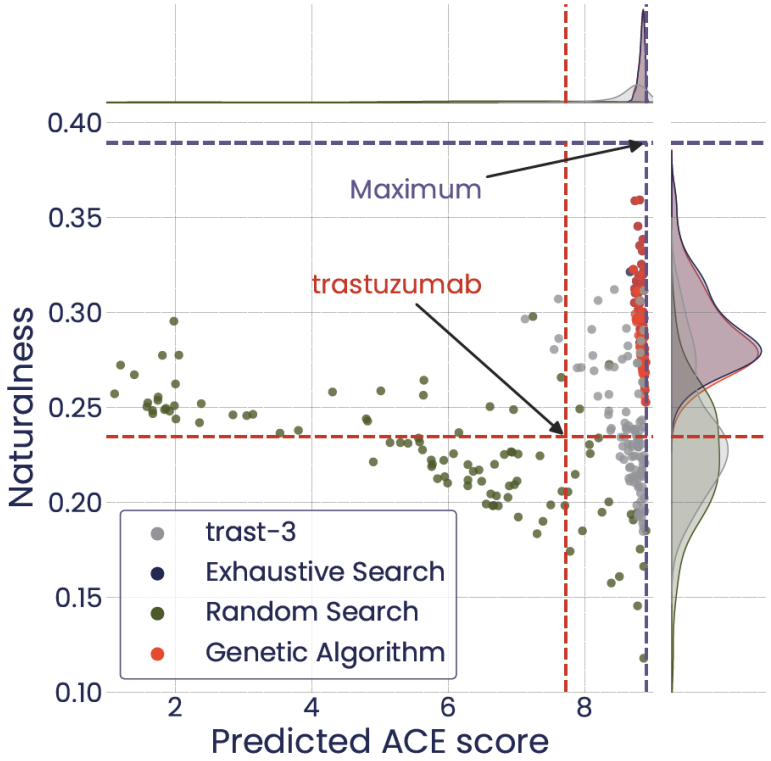
HEK-293 titers of clinical-stage antibodies (Ph2+) from Jain *et al.*, *PNAS* 114:944 (2017)

absci Bachas, S., Rakocevic, G. *et al.* Antibody optimization enabled by artificial intelligence predictions of binding affinity and naturalness (2022) *pre-print in bioRxiv.*

Identified variants with higher Her2 binding and naturalness than trastuzumab





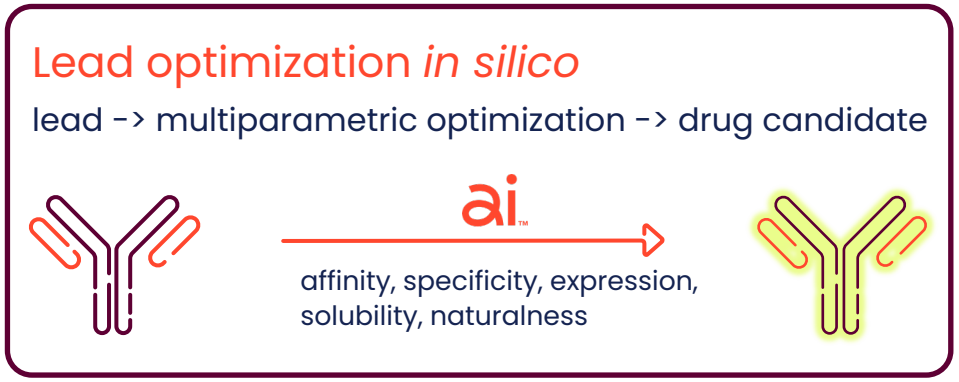


We employ pretrained language models to evaluate antibody sequences for their naturalness score and apply a genetic algorithm that enables simultaneous tuning of affinity while maximizing naturalness

Bachas, S., Rakocevic, G. *et al.* Antibody optimization enabled by artificial intelligence predictions of binding affinity and naturalness (2022) *pre-print in bioRxiv.*

Take-home messages

- AI predicted the affinity of unseen variants from libraries generated using diverse mutational strategies and combinatorial sequence space
- Our AI models make predictions with actionable performance using <0.1% of the combinatorial sequence space as training set
- Naturalness is associated with developability metrics and expression titer while it is inversely associated with immunogenicity metrics and mutational load
- It is conceivable to use naturalness as a risk mitigation strategy and prioritization metric for variant candidates



Together we can bring better drugs to patients faster by:

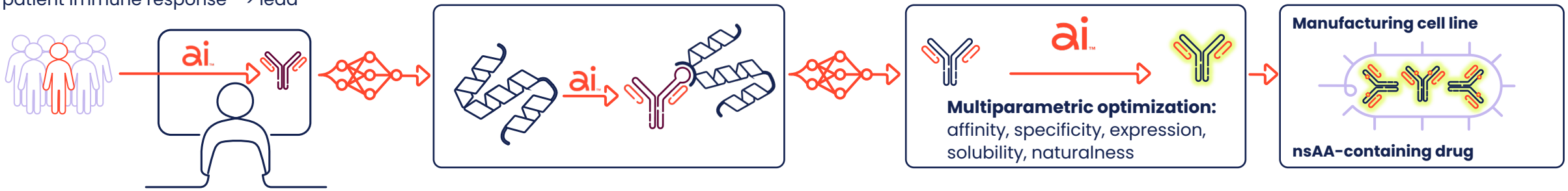
- Unearthing a new target to treat a currently untreatable disease
- Discovering and/or optimizing a biologic for a validated target
- Developing a known binder by enabling the addition of unique chemistries

Novel antibody and target discovery
patient immune response -> lead

De novo* discovery *in silico
target -> lead

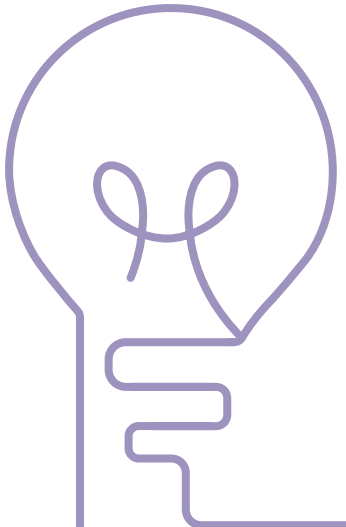
Lead optimization *in silico*
pead -> drug candidate

Bionic SoluPro™ strain
drug -> incorporate nsAA



Our end-to-end platform uniquely positions us to support the needs of our partners in multiple ways to overcome increasing drug complexity and develop the best drugs for patients

Just because something hasn't been done, doesn't mean it can't be done



Translate ideas into impact™