

GENERATIVE AI

DRUG CREATION

Corporate Presentation
May 2026

absci[®]

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From Code to Clinic

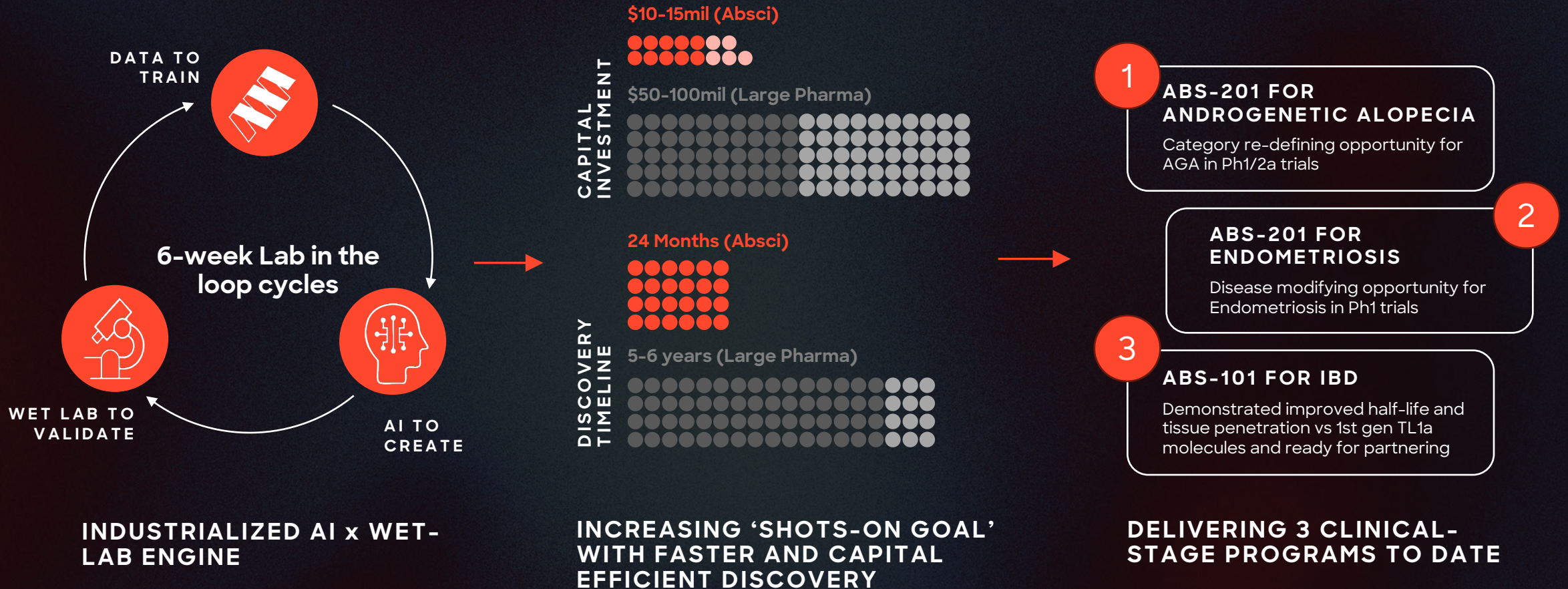
1. AI NATIVE PLATFORM

- Interdisciplinary Team with 10+ approved drugs and AI expertise
- Integrated Lab-in-the-Loop leveraging 77k ft² automated wet-lab
- Leading AI platform for *de novo* design and AI optimization of antibody-based therapeutics

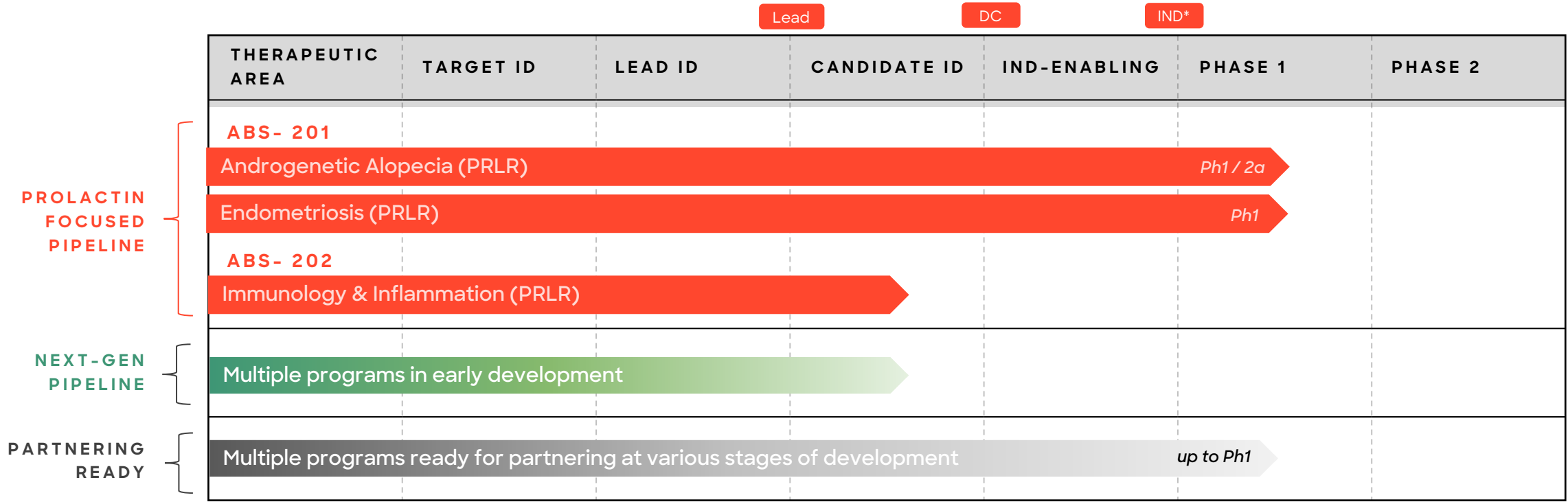
2. DIFFERENTIATED PIPELINE

- ABS-201 (anti-prolactin receptor)
 - Androgenetic Alopecia (AGA): Accelerated Ph1/2a trial on track to initiate December 2025, with interim POC readout 2H 2026
 - **Endometriosis (Endo)**: Indication expansion into endometriosis with anticipated Ph2 initiation in 4Q2026 with PoC readout as early as 2H 2027
- **Preclinical pipeline** focused on metabolism and I&I

Industrializing Drug Discovery



Advancing and expanding our pipeline of novel & differentiated assets designed using AI



*or equivalent ex-US filing

ABS-201 has the potential to unlock a wholly new category of therapy in hair “re-growth”

1. Significant clinical and commercial unmet need in androgenetic alopecia
2. Strong scientific rationale, with validated target, de-risked Mode of Action, and pharmacology
3. Straightforward development path with objective endpoints



Underserved patient population looking for therapeutic innovation

~80 million Americans live with androgenetic alopecia (AGA)



MALE AGA

~50M men in the U.S.

Only 2 FDA approved drug therapies

FEMALE AGA

~30M women in the U.S.

Only 1 FDA approved drug therapy for women

Growing patient population with limited therapeutic options and concerns of adverse side-effects

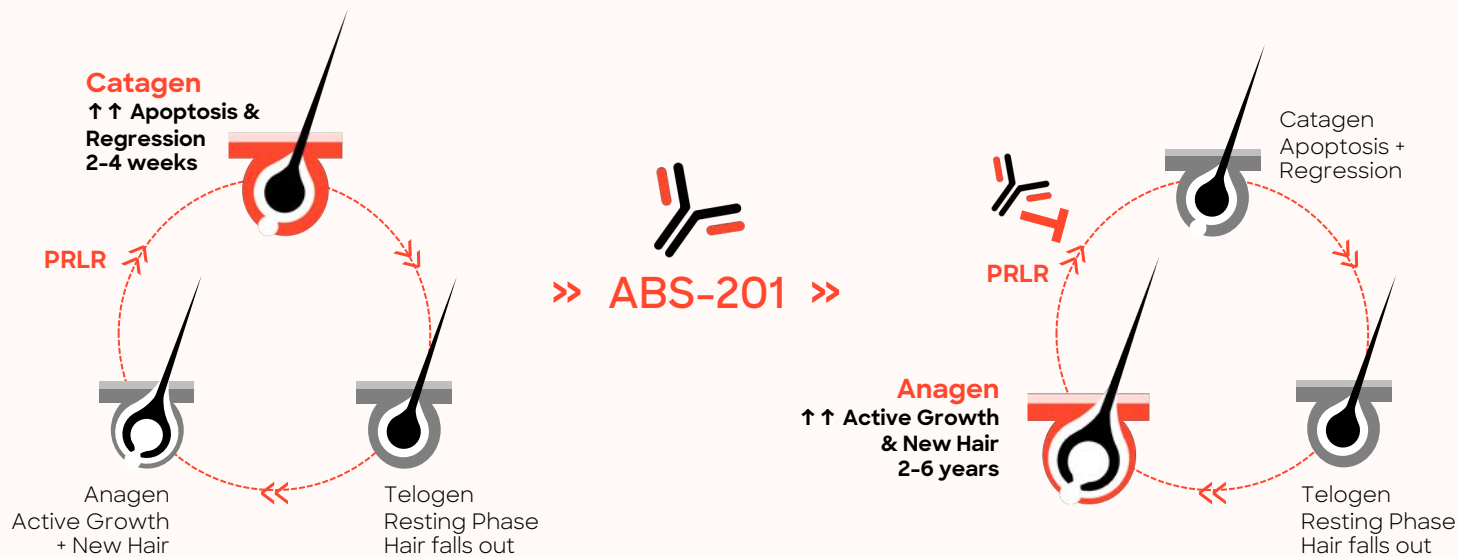
Last FDA approved therapy for androgenetic alopecia was in the 1990s

Patients and clinicians need better treatment options for “hair re-growth”

- › Hair re-growth, not just slowing of hair loss
- › Safe and minimal side effects
- › Durable effect
- › Convenient administration frequency
- › FDA approved

PRLR inhibition for androgenetic alopecia is an innovative alternative to current treatment options

PROPOSED DIRECT IMPACT OF ABS-201 ON HAIR CYCLE STAGES

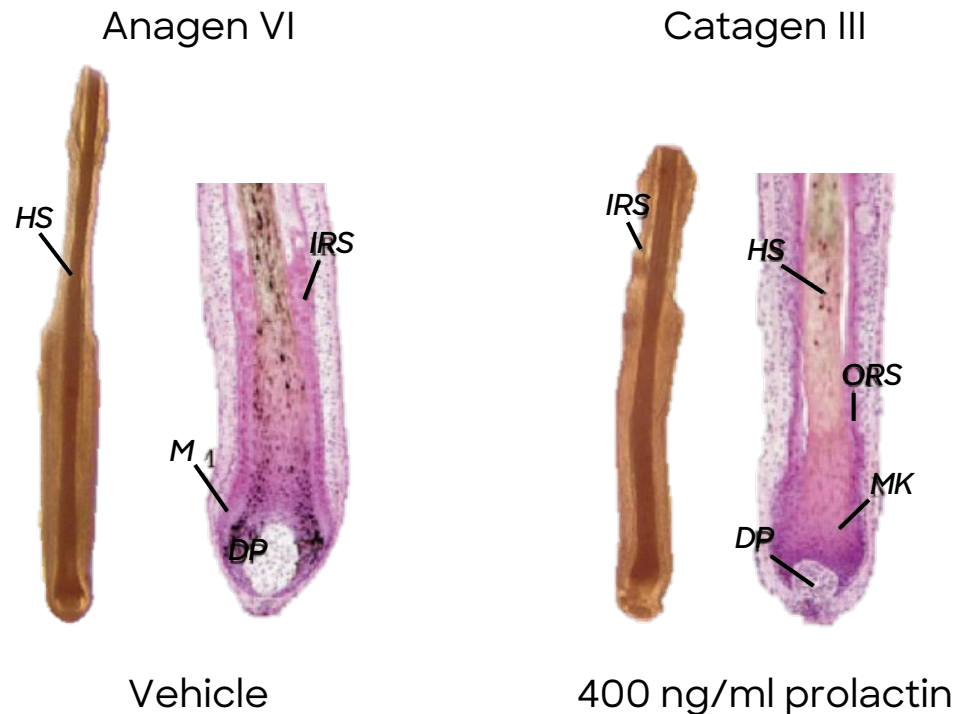


ABS-201 HAS THE POTENTIAL TO:

- Shift the balance in hair cycle stage towards anagen phase^{1,2} with:
 - Active and new hair growth
 - Prevention of telogen effluvium
- Promote a long-lasting effect after treatment cessation
- Block cessation of pigmentation, which may lead to the restoration of hair pigmentation²

Prolactin impacts on organ-cultured human hair follicles

Prolactin drives hair follicle regression in human ex vivo culture

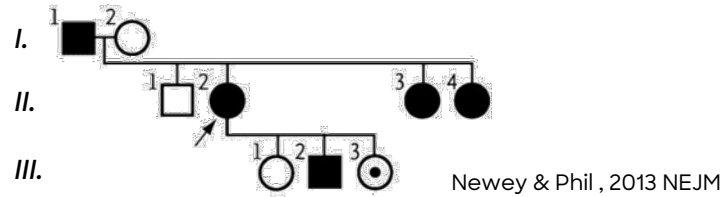


Prolactin prematurely induces a catagen-like stage in organ-cultured human hair follicles¹ characterized by:

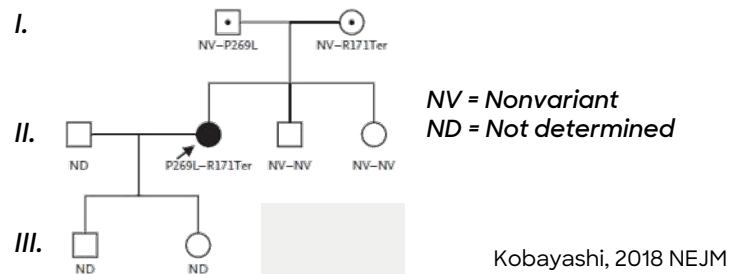
- › Condensed shape of the dermal papilla (DP)
- › Diminishment of the hair matrix volume
- › Apparent cessation of pigmentation
- › Inhibition of hair shaft elongation

PRLR inhibition anticipated to be safe & well tolerated as supported by human genetics

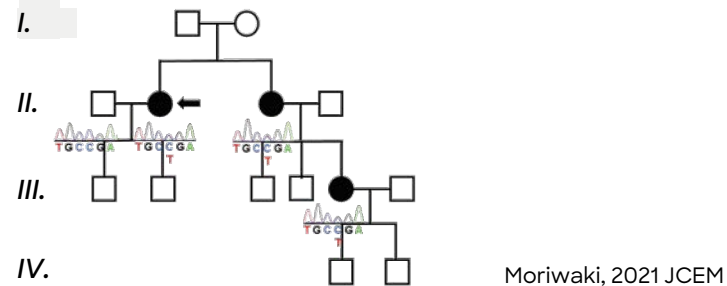
Dominant negative
PRLR loss-of-function



Compound heterozygous
PRLR loss-of-function



Dominant negative
PRL loss-of-function



Reduced/Loss of PRL or PRLR Signaling

- › Postpartum agalactia
- › Otherwise in good health:
 - No apparent impact on fertility
 - No report on erectile dysfunction in male
 - Normal breast development and menses in females
 - Normal serum electrolytes and hormone levels (except elevated PRL in PRLR mutation carrier)
 - No reported abnormalities of other hypothalamic-pituitary axes

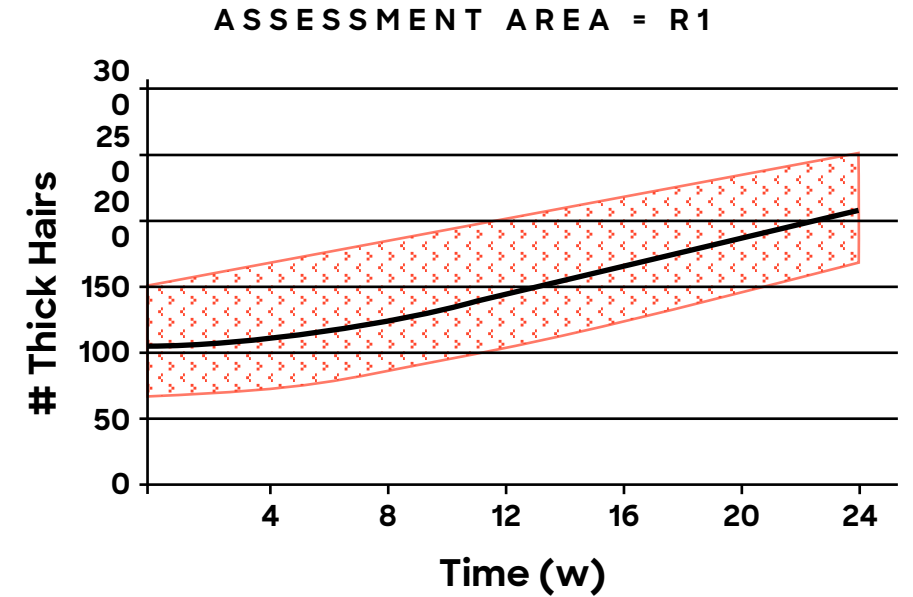
Top head view of Stumptailed Macaque's showing phenotypic change over time

	TREATMENT			POST-TREATMENT		
	BASELINE	12 WEEKS	28 WEEKS	6 MONTHS	2 YEARS	4 YEARS
MALE						
FEMALE						

40mg/kg s.c. Q2W for 28 weeks

Study commissioned by Absci CIO Andreas Busch while at Bayer.
Disclosure from competitor

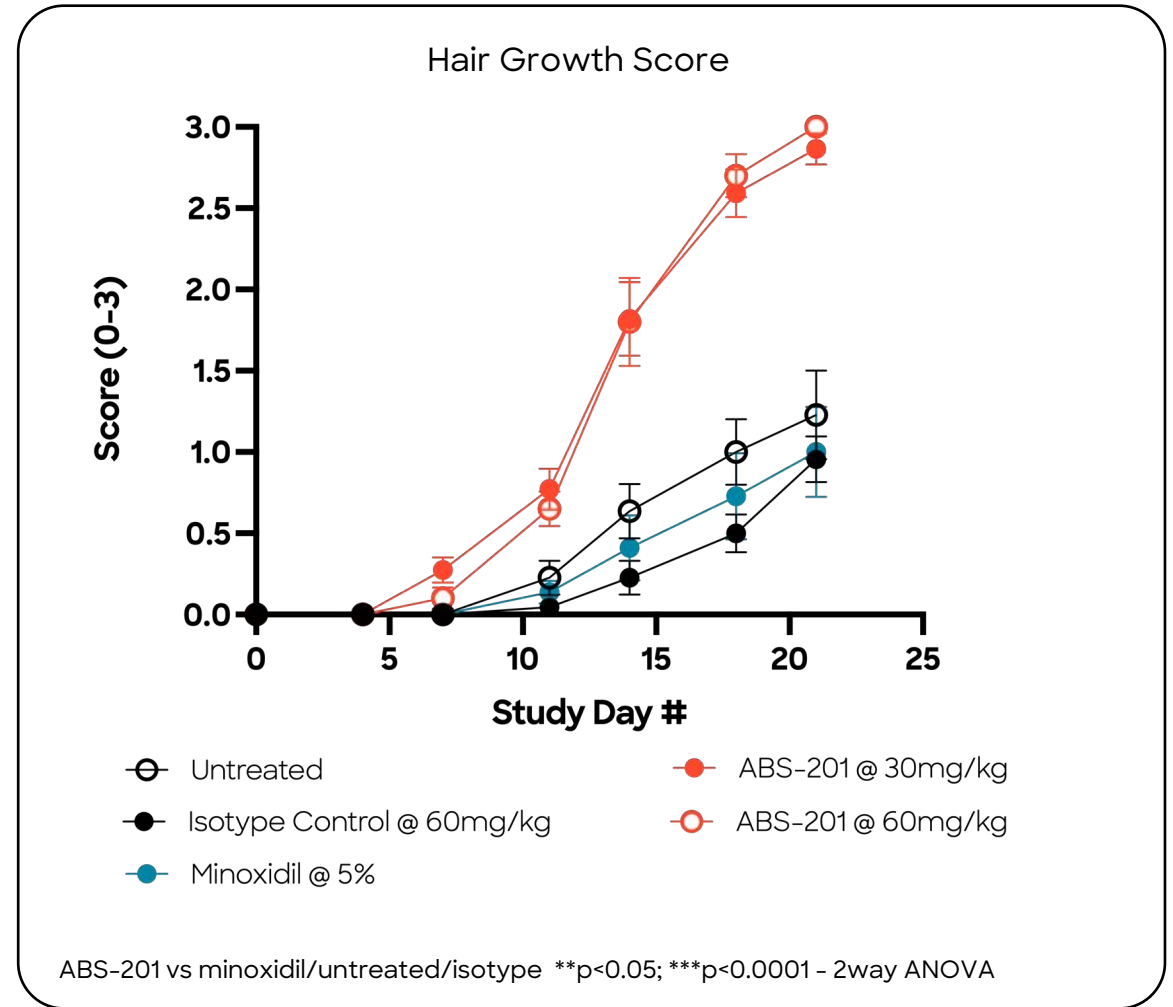
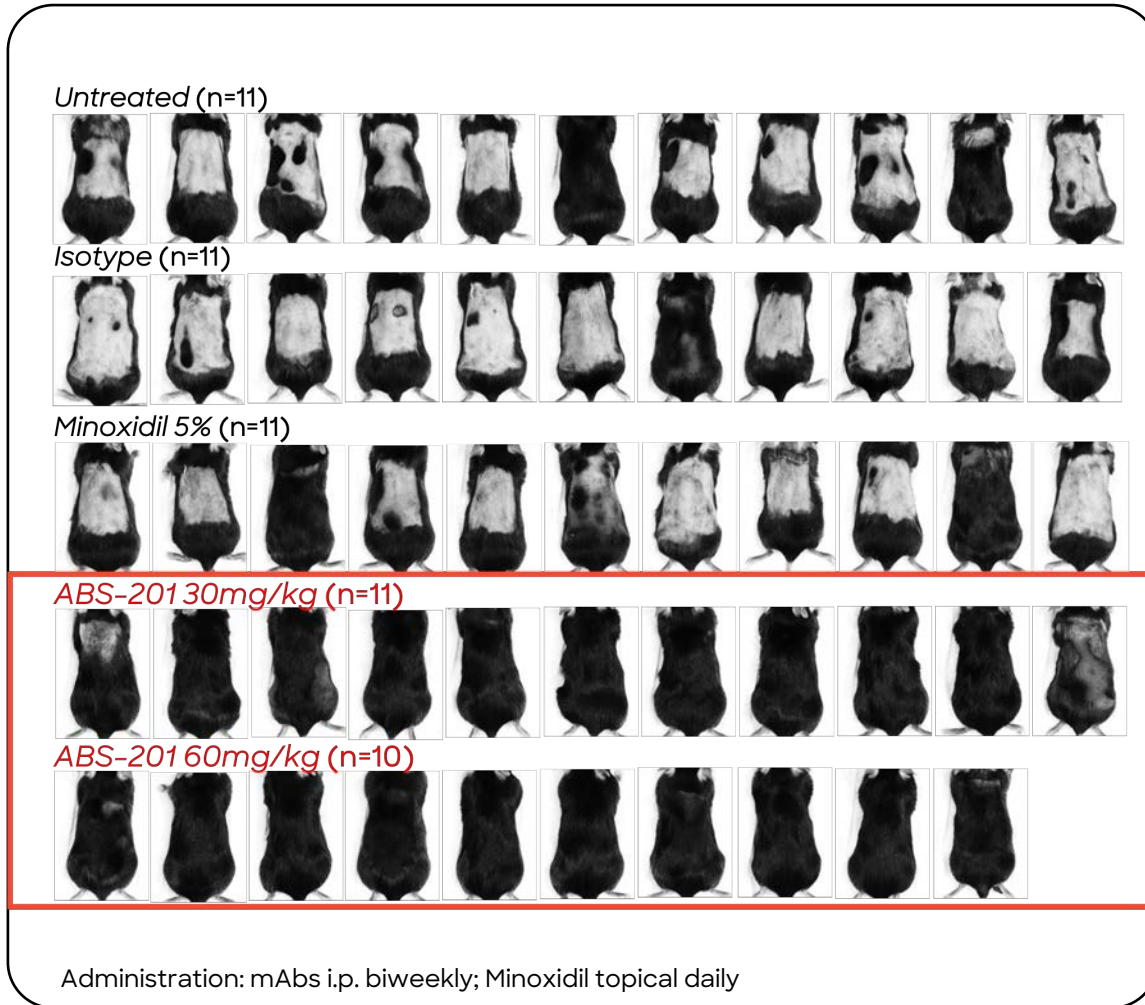
Terminal hair count "Thick Hairs" in prior bald areas



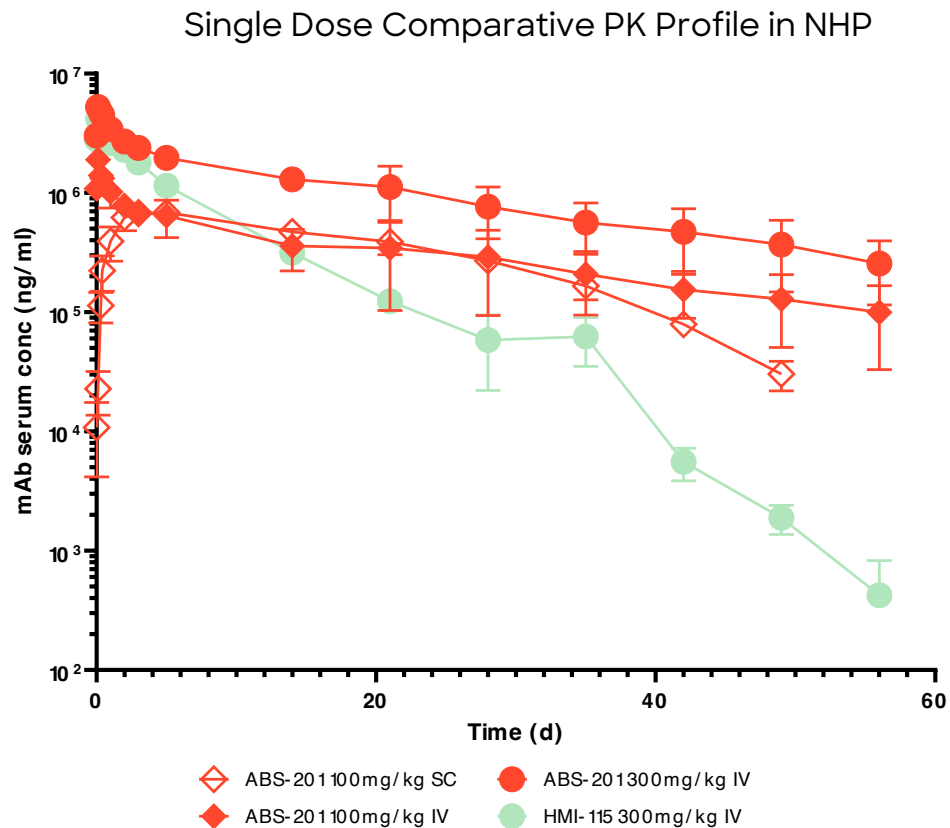
- Hair density & thickness improved with short treatment duration in primate model of androgenetic alopecia
- Hair growth remains and improves several years post cessation

- Hair regrowth observed for both male and female animals (>100 hairs/cm² increase in bald area at week 28 of treatment*)

ABS-201 shows superior efficacy vs 5% topical minoxidil in 21d hair regrowth model



56 Day NHP PK data confirms extended half-life profile and high SC bioavailability



Datapoints of animals with positive ADA rates impacting PK were excluded at corresponding timepoints onwards

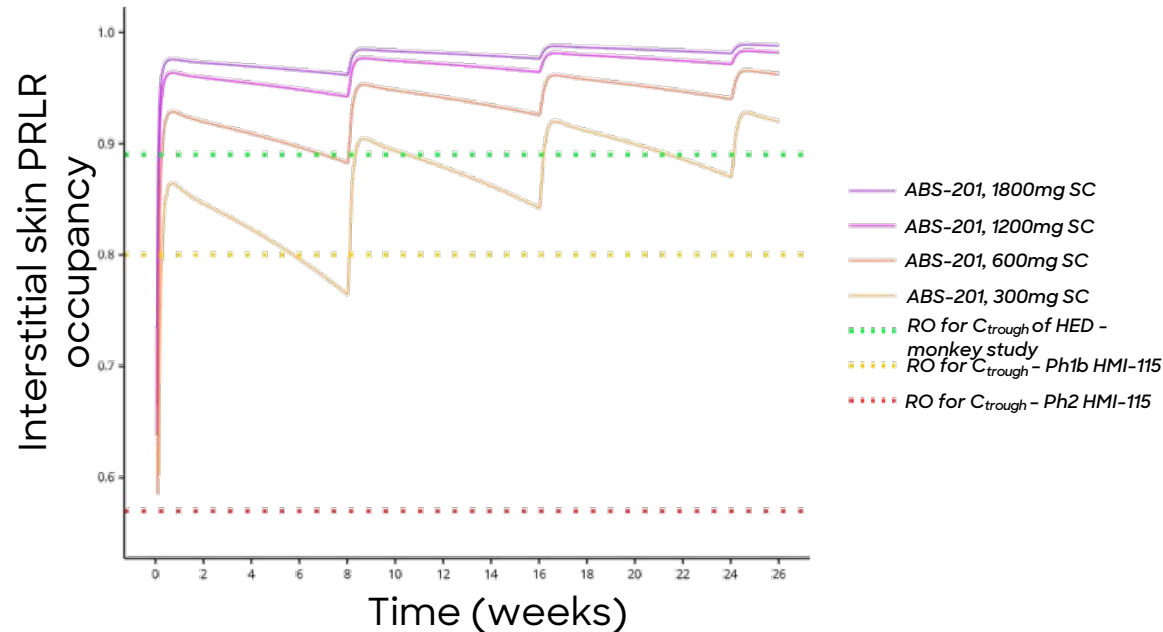
NHP-PK 56 Day Results

- >3x extended half-life in NHPs compared to HMI-115
- High subcutaneous bioavailability in NHPs at >90%
- In silico prediction of Q8W-Q12W dosing intervals anticipated in humans
- Manufacturability & developability profile believed to enable future high concentration formulation targeting >150mg/mL

Based on PK/PD modeling, ABS-201 is anticipated to likely require only 2-3 doses over a 6-month treatment period, compared to HMI-115, which would likely require 6-12+* doses in the same period, assuming the AGA indication is pursued.

*assumption on HMI-115: 60mg/mL formulation and Q2W or Q4W dosing interval

Modelling shows superiority of ABS-201 vs HMI-115 on PK & Receptor Occupancy

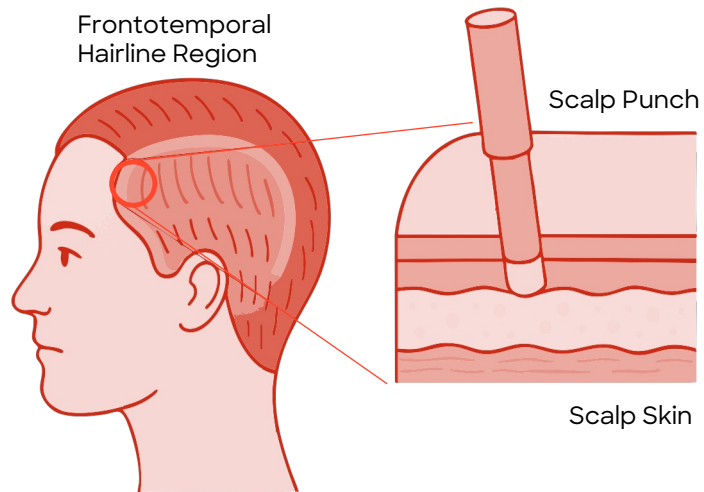


Preliminary in Silico Modeling

- > 3x extended half-life in NHPs predicted to translate in humans to Q8W-Q12W dosing intervals
- PK profile predicted to translate into higher interstitial skin concentrations resulting in higher receptor occupancy

Modelling assumptions include published NHP and Ph1b PK data on HMI-115 (formerly BAY 1158061), as well as in house generated in vitro and in vivo data. Parameters incl. 0.2 skin exposure coefficient, 2.6×10^{-2} nM interstitial PRLR concentration

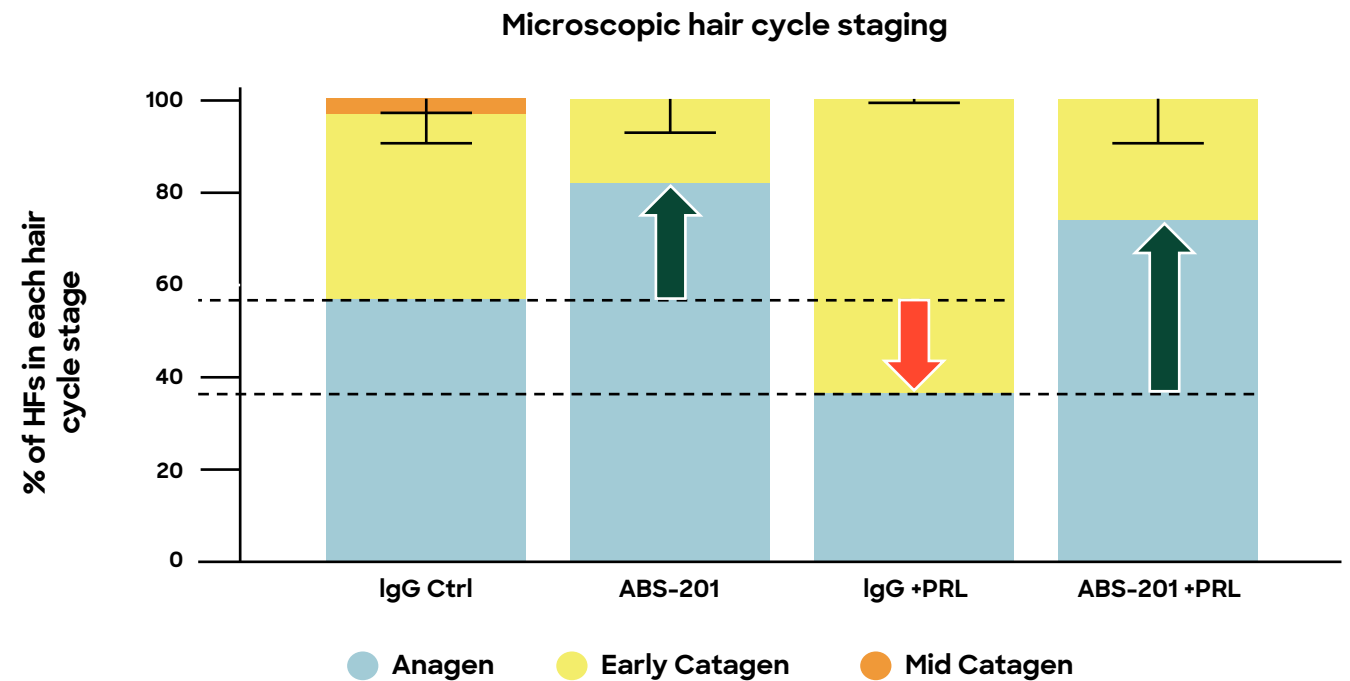
ABS-201 in human ex vivo culture study supports MOA in human scalp follicles

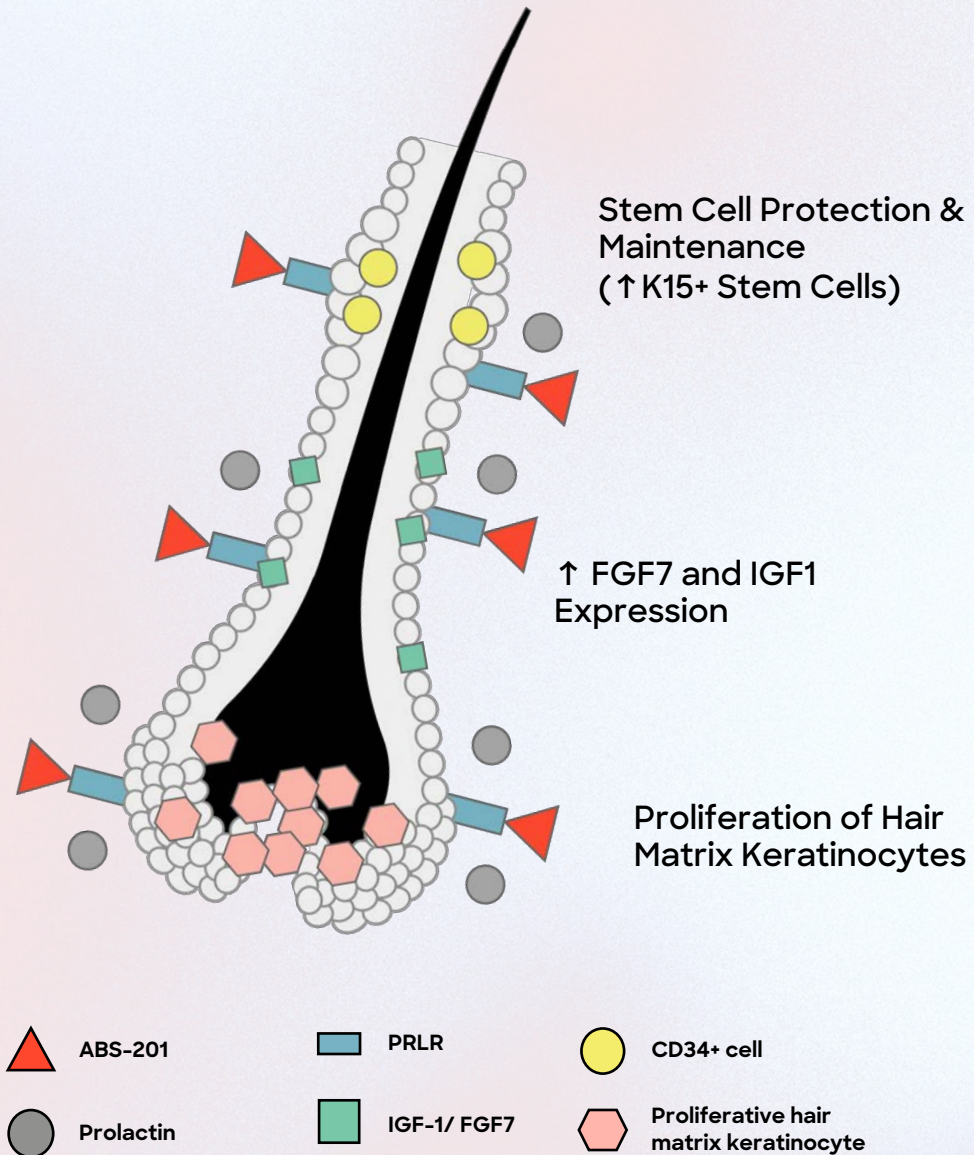


MODEL SYSTEM:

- Frontotemporal male scalp skin is the most androgenetic alopecia affected skin region
- Organ culture is the most relevant human preclinical hair research tool ex vivo

ABS-201 significantly prolongs anagen/inhibits catagen and stimulates hair matrix proliferation





Additional ABS-201 *ex vivo* study found:

- Prolonging anagen phase and blocking catagen, thereby inhibiting telogen effluvium
- Protecting and promoting hair follicle stem cells and restoring CD34+ progenitor cells
- Stimulating key hair growth factors (IGF1, FGF7)
- Decreasing catagen driver TGFβ-2
- Increasing hair shaft and hair shaft keratin production

Phase 1/2a trial designed to provide readouts on safety, tolerability, and PoC in AGA

HEADLINE

Design Elements:

- Double-Blind, Placebo-controlled, FIH
- Multi-site study in Australia
- Dose range ensures predicted >90% RO

Population:

- Up to 227 male & female healthy participants
- SAD; n= 32 healthy volunteers
- MAD; n= 147 AGA subjects (Norwood Scale IIIv-V)
- Optional AGA cohorts in SAD/MAD; n= 48
- 3:1 randomization

Endpoints:

- **Primary:** Safety & Tolerability
- **Secondary:**
 - PK/PD
 - Efficacy readouts include target area hair count, width, and darkness (pigmentation)



Single Ascending Dose

Cohort 1 150mg IV n=8	Cohort 2 450mg IV n=8	Cohort 3 900mg IV n=8	Cohort 4 1800mg IV n=8
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- All planned SAD cohorts dosed
- **Dec 2025:** Initiated
- **1H 2026:** PK and interim safety expected



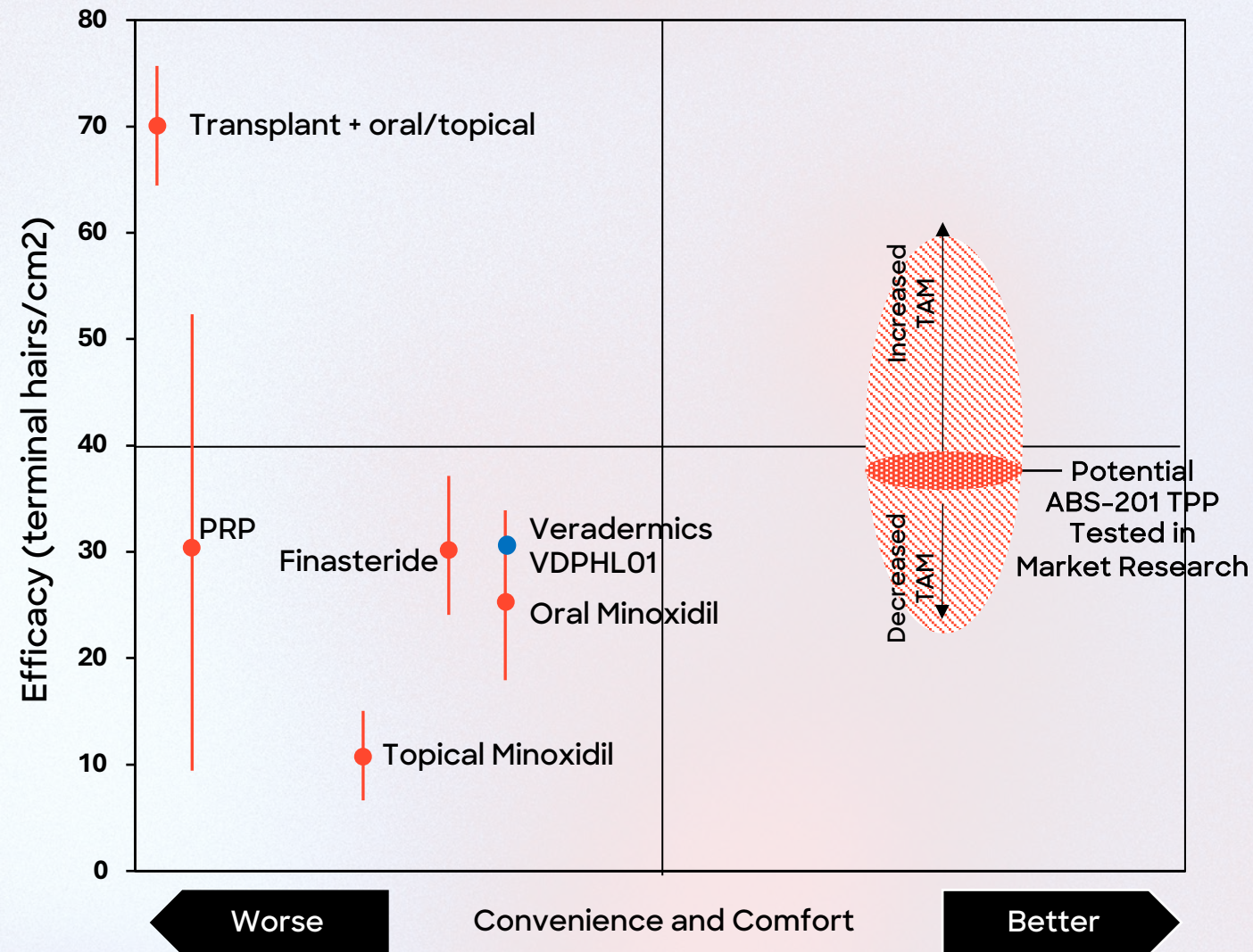
Multiple Ascending Dose (26 weeks)

Cohort 1 300mg SC n=49	Cohort 2 600mg SC n=49	Cohort 3 1200mg SC n=49
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- MAD design enabling **PoC for AGA**
- **MAD Cohort 1 enrolling**
- **2H 2026:** Expected 13-week interim PoC readout
- **Early 2027:** Expected 26-week topline PoC readout

ABS-201 TPP aims to offer a new treatment category in AGA based on efficacy and convenience

- Novel, targeted regenerative hair follicle mechanism
- Convenient, infrequent pulse therapy: 2-3 subcutaneous injections over six-month period
- Potential for durable efficacy: may provide 2-3 years of hair growth
- TPP tested in market research supports total addressable market >\$25B



* Based on 2-3 injections during first 6 months for >2 years of hair growth
 Efficacy at 24w for Vertex terminal hair count in male subjects: Oral Minoxidil (5mg/day); Panchaprateep 2020 (10.1007/s13555-020-00448-x) and Penha 2024 (doi:10.1001/jamadermatol.2024.0284); PRP: Dervishi 2019 (10.1111/jocd.13113); Finasteride and Topical Minoxidil: Gupta 2022 (doi:10.1001/jamadermatol.2021.5743), Transplant: based on KOL interviews.

Consumer Research Commissioned by Absci Validates Market Potential of ABS-201

Significant Unmet Need:

Driven by psycho-social impacts (loss of confidence, self-esteem) from AGA

Strong Commercial Demand:

Nearly all men and roughly 90% of women are inclined to ask their doctors about ABS-201

High Value Proposition:

Significant share of respondents willing to pay a premium for the ABS-201 TPP

Disruptive Potential:

Over 1/3 of respondents would select ABS-201 before their current treatment, suggesting ABS-201 can effectively compete as first-line therapy

610 Participants:

306 Men | 304 Women

*ALL PARTICIPANTS EXPERIENCING HAIR LOSS

UP TO
97%
MEN

UP TO
88%
WOMEN

**EXTREMELY OR VERY
LIKELY TO ASK HCP
ABOUT ABS-201**

37%
MEN

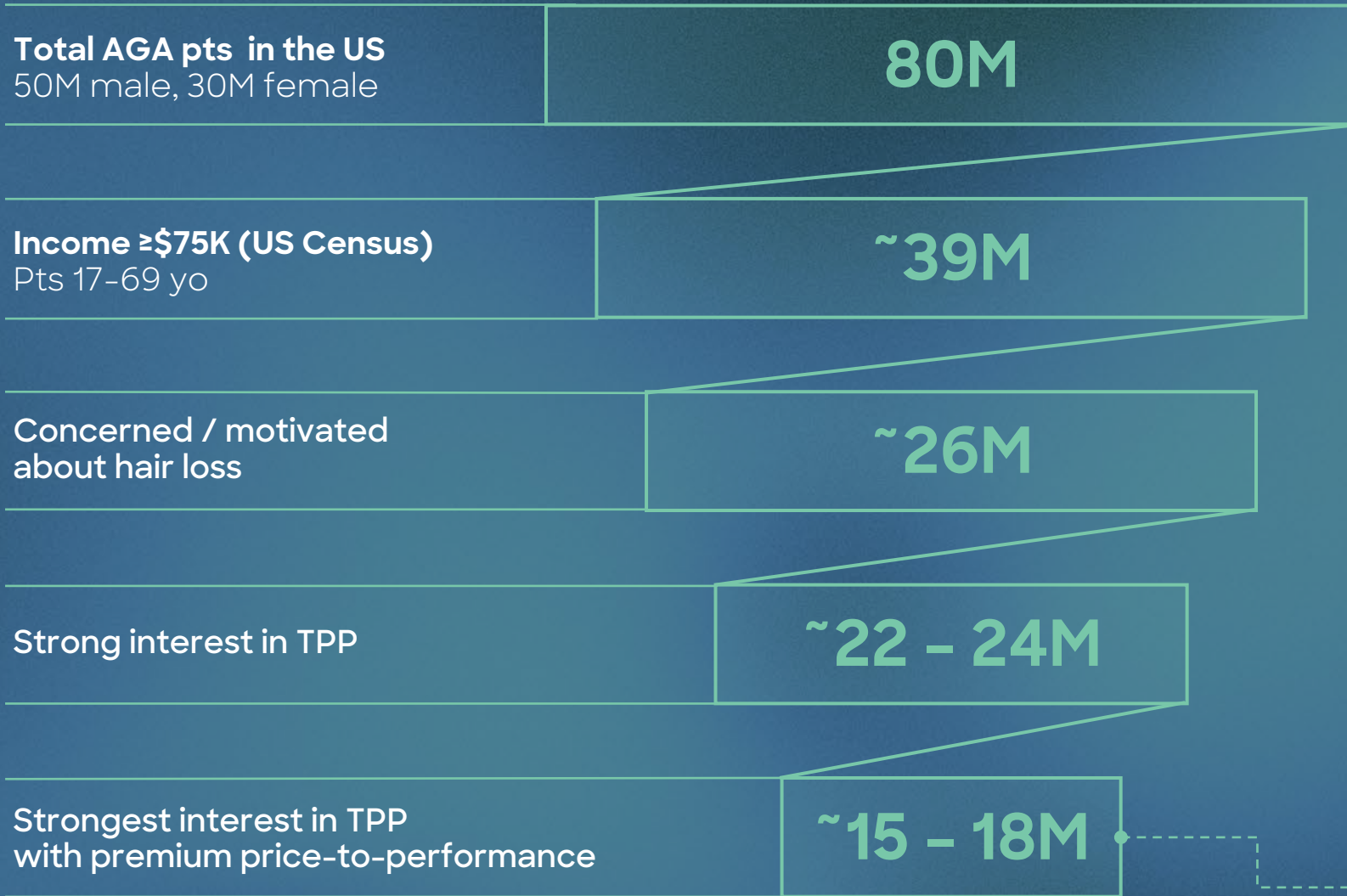
36%
WOMEN

**WOULD TRY ABS-201
FIRST (FIRST LINE)**

80%
MEN

81%
WOMEN

**REPORT NEGATIVE
PSYCHOLOGICAL
IMPACT**



Patient Funnel

> \$25B

ESTIMATED U.S. TAM

> \$40B

POTENTIAL GLOBAL TAM

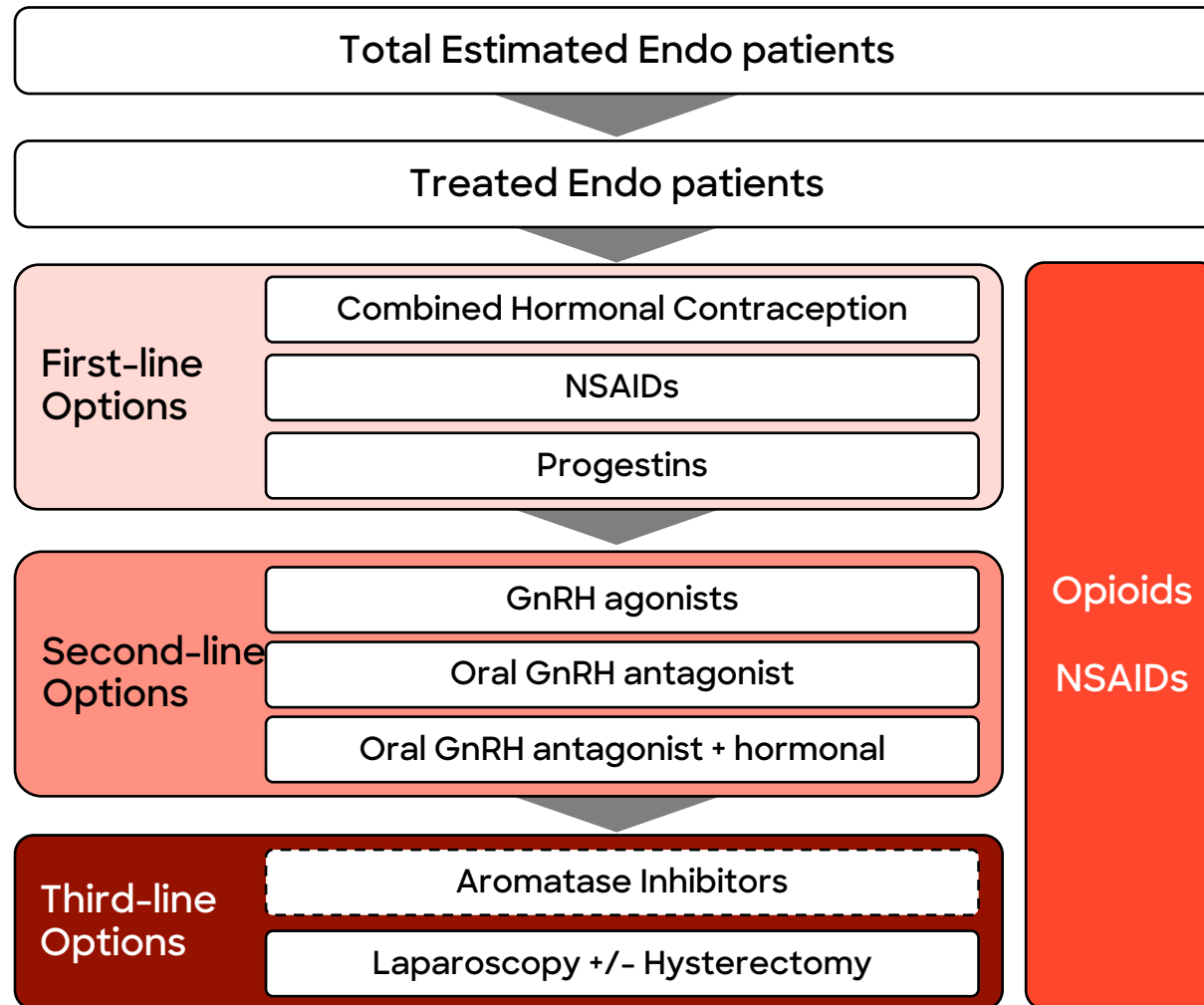
5-9M Pts Treated/Year
Assuming 2-3 Year Durability

Development of **ABS-201** in **Endometriosis**

1. Addresses Long-standing Unmet Medical Need and Poor standard of care
2. Strong Biological And Clinical Rationale: Including POC for PRLR mechanism in humans
3. Large, untapped market offers significant upside potential

Hormonal therapies and surgical intervention make up the treatment paradigm for Endo

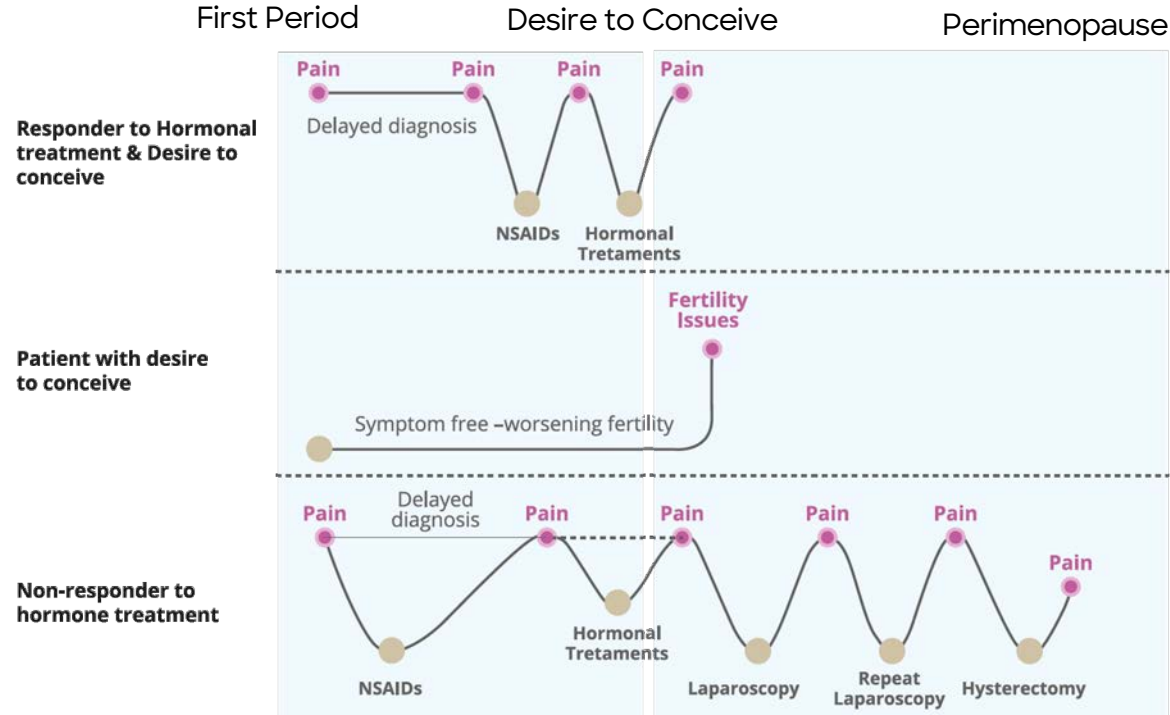
Current Treatment Paradigm (US)



- Endo is a chronic condition with currently no medical or surgical cure
- Roughly, 75% of patients are estimated to use opioids and/or NSAIDs throughout their disease course
- Up to 33% of patients do not respond to hormonal treatment alone
 - Additionally, patients will pause treatment when seeking pregnancy
- GnRH therapies are typically prescribed by Gynecologist and often require formal Dx (surgical confirmation)
 - Due in part to higher cost, and AE profile which limit long-term use
- Notably, aromatase inhibitors are not FDA approved for Endo, but are used off-label
- Up to 40% of Endo patients undergo a laparoscopy and 12% receive hysterectomies
- Even after hysterectomy ~15% of patients still report pain symptoms

Pain remains a persistent, chronic issue for women with endometriosis

Illustrative Endometrial Patient Journeys



[PMID 40323608](#), [PMID 17498711](#), ARTEMIS 2024 Report

Patients with Endo report ineffective pain management as a number one unmet need

Additionally, patients are seeking the ability to have children

- › The condition itself carries a higher risk for infertility
- › Current therapeutic interventions prevent pregnancy or mimic a post-menopausal state

There has been little advancement in novel targets for endometriosis

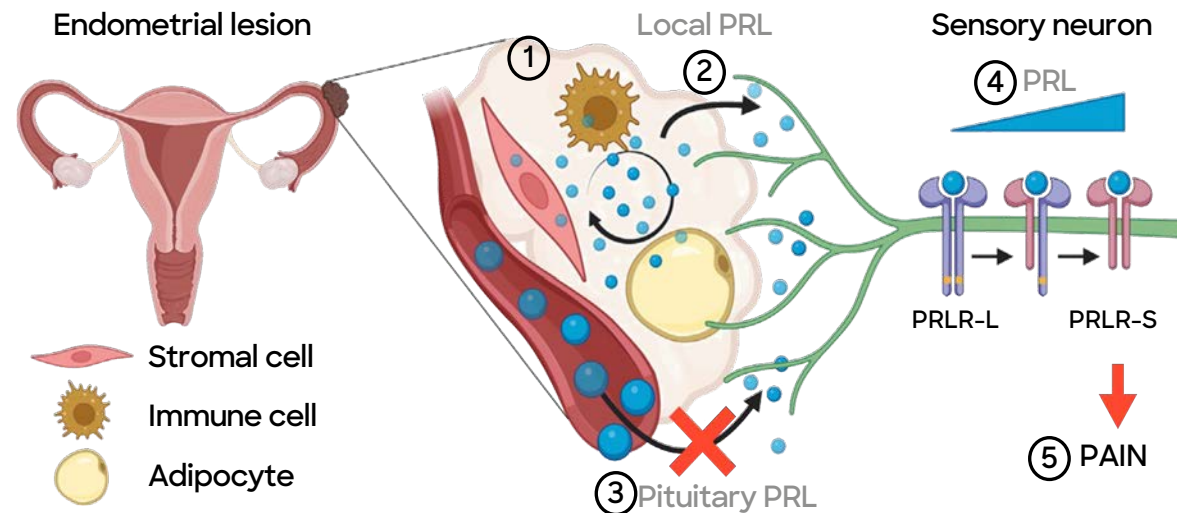
- › Contraceptive hormonal therapy has remained unchanged for decades
- › GnRH therapy, while effective for some needs to be stopped after 2 years due to AE risks (e.g., loss in bone density)

Endo remains underdiagnosed, which is predicted to improve with a disease-modifying therapy

- › Mean age of symptom onset is typically early 20s, while mean age of diagnosis is typically mid-30s

PRLR antagonism is a novel and differentiated MoA in Endometriosis

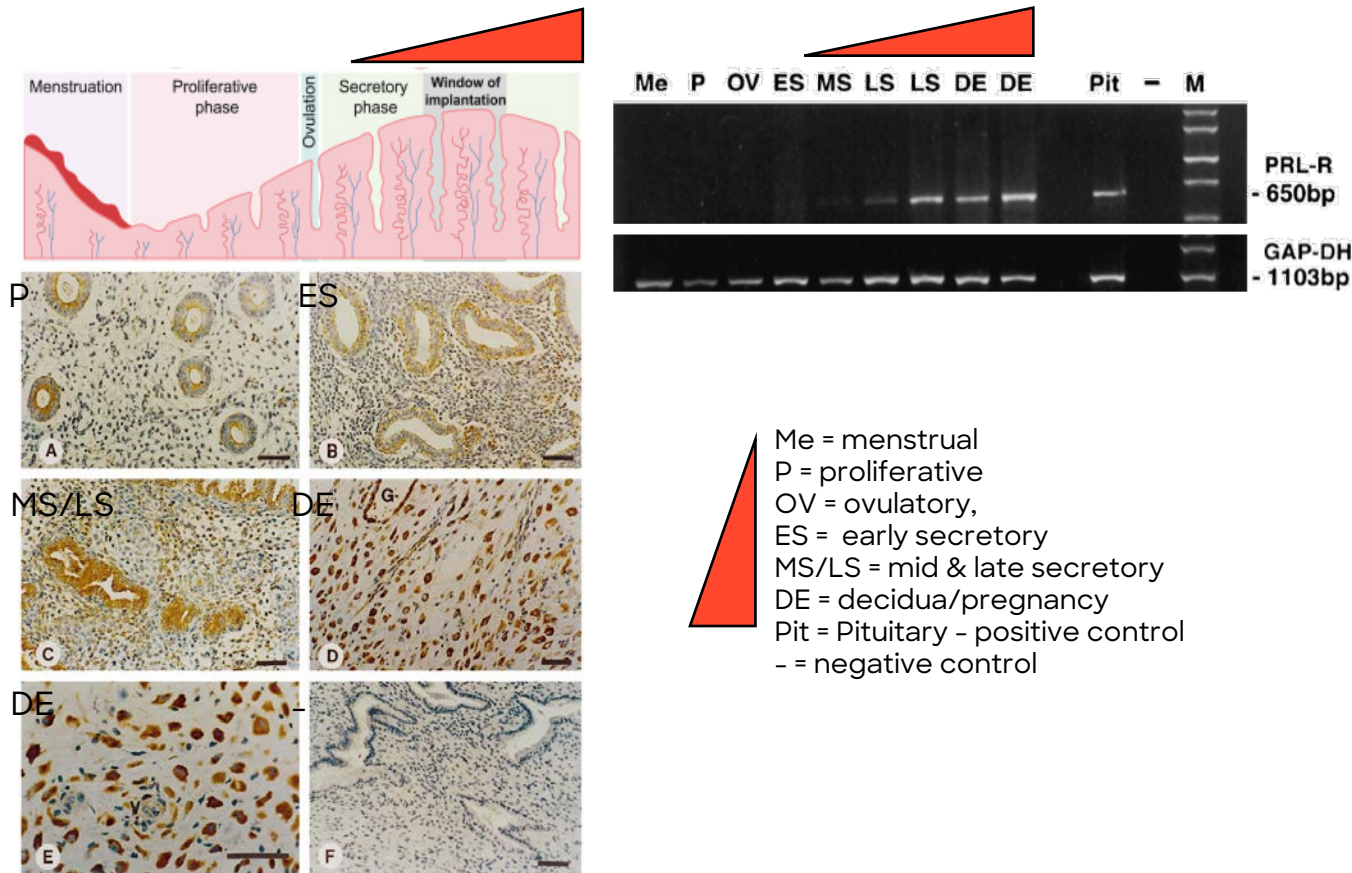
PRL and PRLR play a dual role in endometrial lesion development and pain response



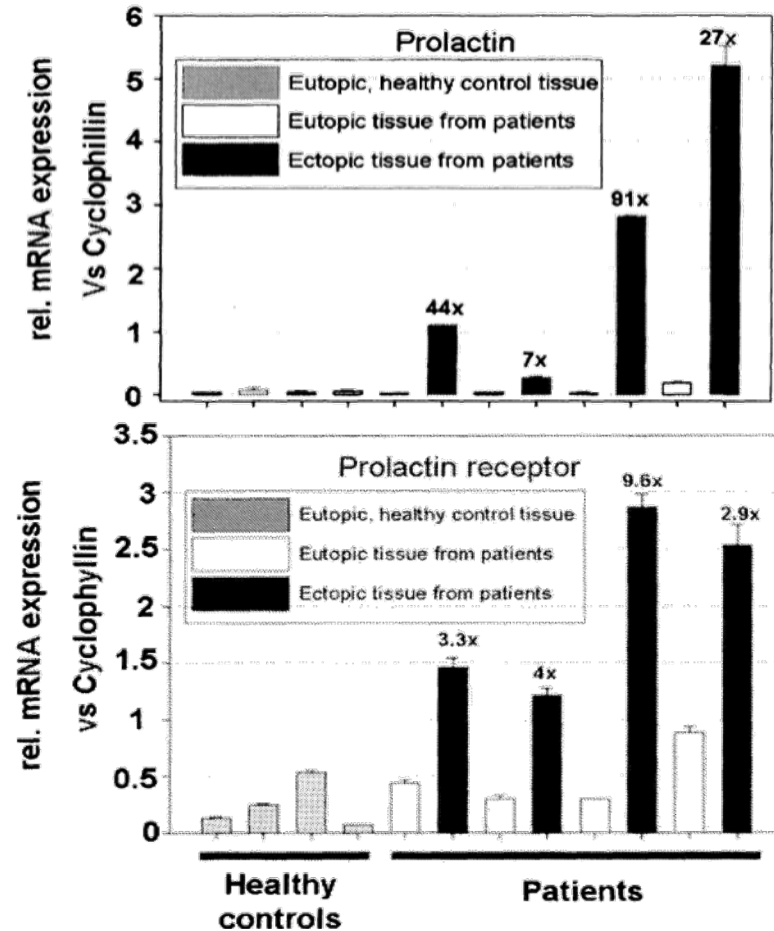
- Endometriotic lesions produce prolactin under estrogen/progesterone control.
- Excess prolactin promotes lesion growth and sensitizes pain-sensing nerves, contributing to chronic pelvic pain.
- Prolactin signaling is independent of sex-hormone pathways, offering a differentiated, non-hormonal treatment modality vs current therapies.

PRL and PRLR increase during secretory phase in healthy tissue, and is overexpressed in endometrium of patients with endometriosis

Localization And Temporal Expression Of Prolactin Receptor In Human Endometrium



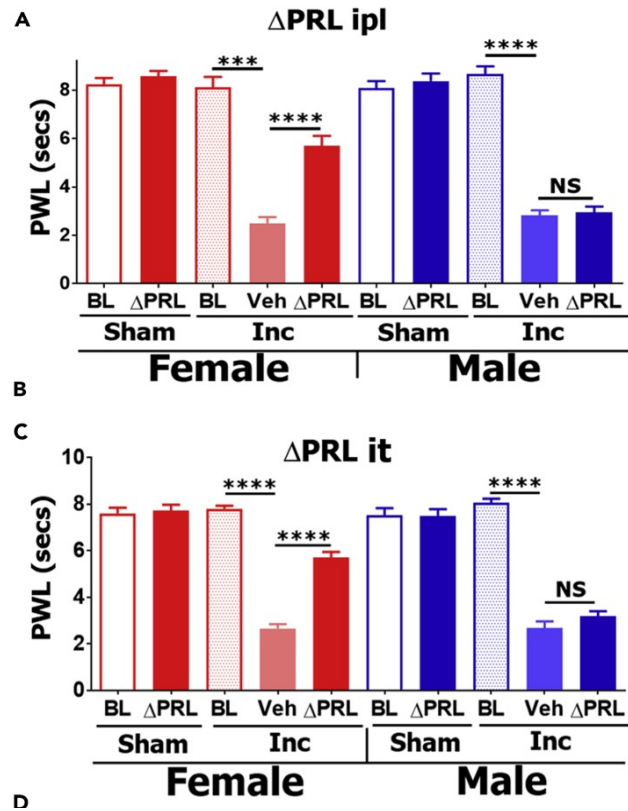
PRL & PRLR is Elevated Ectopic Endometriotic Lesions



Jones et al. Journal of Clinical Endocrinology and Metabolism, 1998; Otto et al. WO 2011/069795 A4

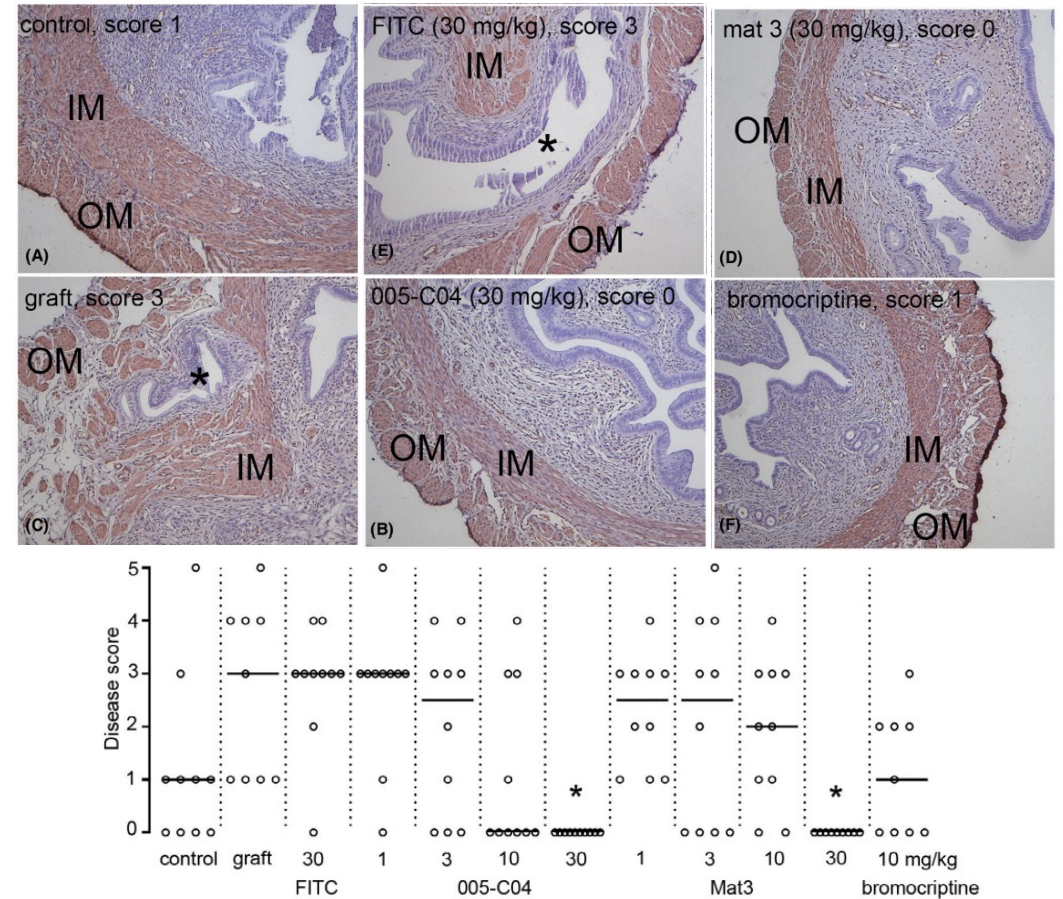
PRLR antagonism suppresses postoperative pain in female mice and inhibits endometriosis interna formation

Prolactin Regulates Pain Responses via a Female-Selective Nociceptor-Specific Mechanism



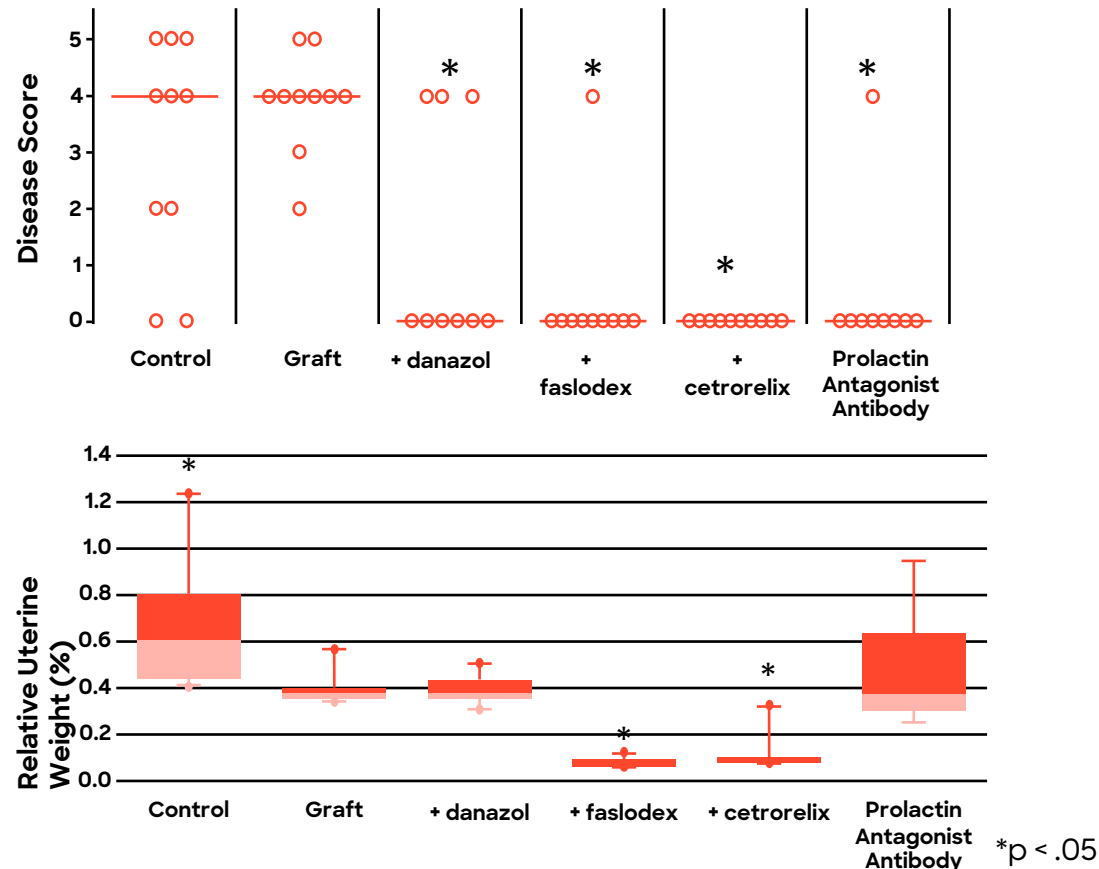
Depicted: pain incision (Inc) model for heat sensitivity & Δ PRL administration

The Effects of Prolactin Receptor Blockade in a Murine Endometriosis Interna Model

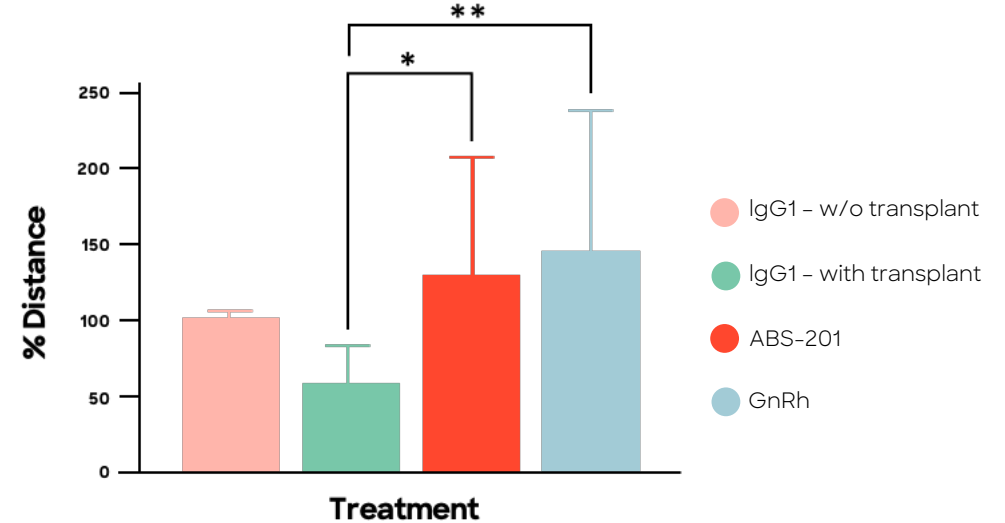


PRLR antagonism reduces lesion formation and pain in endometriosis mouse model

Prolactin inhibition decreases endometrial lesion formation in female mouse interna



% Distance travelled at Week 7 (compared to baseline)



○ ABS-201 and GnRh modulator increase distance travelled relative to placebo over time as surrogate for pain reduction

** p<0.01; *** p<0.001

ABS-201: a potentially differentiated profile targeting a large underserved market opportunity

NOVEL TREATMENT OPTION FOR ~9M PATIENTS
IN THE U.S. ALONE WITH ENDOMETRIOSIS

- **Novel Mechanism:** Non-sex-steroid (peptide) hormone
- **Potential for Improved Safety Profile:** Potential improved AE profile & longer use than GnRH
- **Dual Action:** Potential on both pain and lesion growth
- **Best-in-class Potential:** Superior developability and expected half-life
- **Disease Modifying:** Potential to treat cause
- **Clinically validated:** through HMI-115 Ph2 study

Potential to generate
>\$4.5B
at peak sales

Leading AI x Bio platform driving 2 Phase 2 readouts in the next 24 months

ABS-201 in AGA

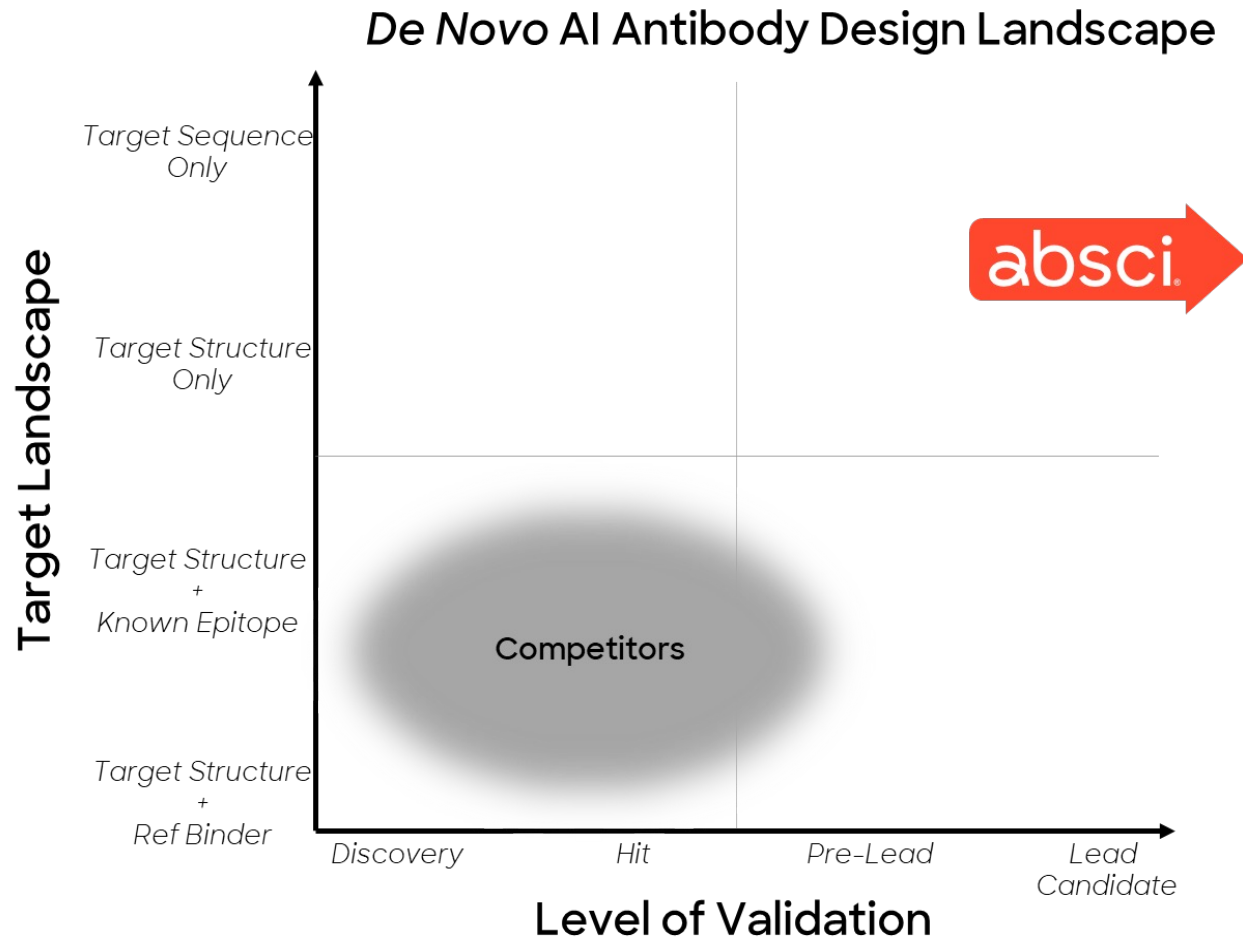
- Ph1/2a Study initiated Dec 2025
- Safety, Tolerability, and PK readout expected 1H 2026
- Interim PoC Readout - anticipated 2H 2026

ABS-201 in ENDO

- Ph1/2a Study initiated Dec 2025
- Phase 2 initiation expected in Q4 2026

Powered by Absci's Leading AI Platform

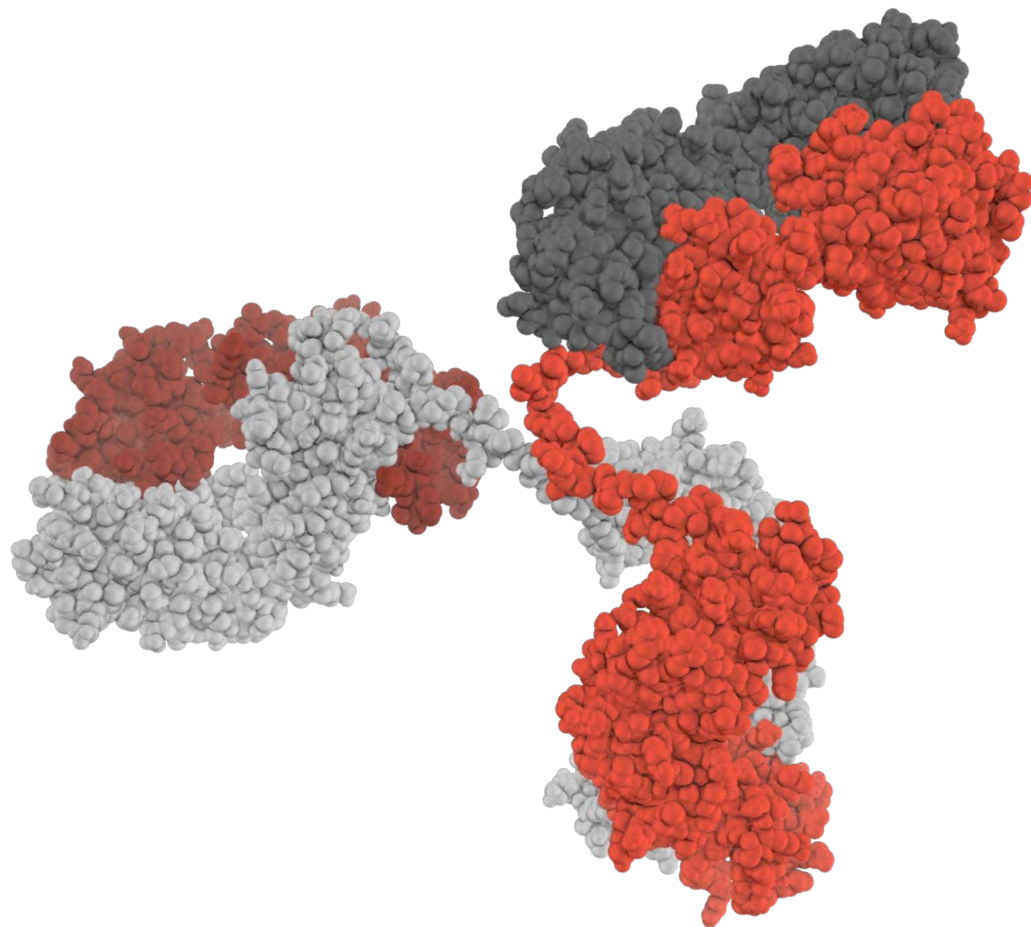
Absci's de novo AI models deliver differentiated lead candidates against challenging targets



ABSCI DIFFERENTIATION

- **Address challenging targets**
 - Only target structure or sequence required
- **Zero-Prior: Design against any epitope**
 - No known protein binder required
 - Interrogate multiple epitopes to achieve function (e.g. agonism)
- **Deliver mAbs that meet therapeutic criteria***
 - Specificity
 - Developability
 - Function

We use AI to create novel & differentiated therapeutics



✓ EPI TOPE-SPECIFIC DESIGN +
EPI TOPE INTERFACE OPTIMIZATION

✓ ENHANCED POTENCY AND MOA

✓ ABILITY TO ADDRESS DIFFICULT
TARGET CLASSES, E.G. GPCRS

✓ ENABLING FEATURES: MULTI-VALENCY,
pH-DEPENDENT BINDING

✓ POTENTIAL TO CREATE MEANINGFUL
IP: 100S TO 10,000S OF FUNCTIONALLY
VALIDATED SEQUENCES ENABLED BY
PROPRIETARY WET-LAB VALIDATION

We create experimentally validated AI technology that enables *de novo* antibody design

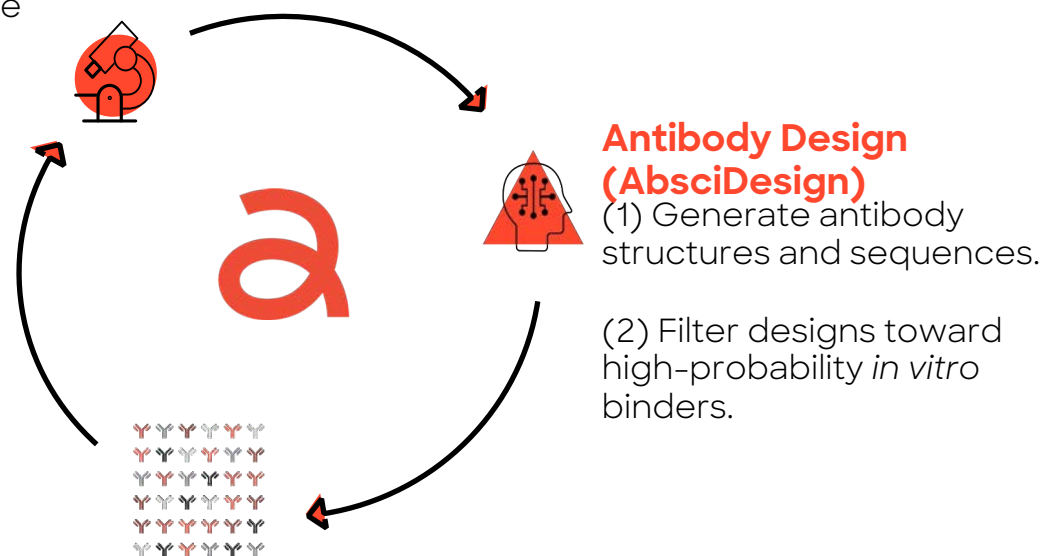
Wet Lab Validation

Wet Lab experiments confirm binding, epitope-specificity, developability, and function.

Wet Lab data enable assessment of model performance improvements.

Library Design

AbsciDesign generates “libraries” of sequences that encode putative antibody binders per disease target.



Origin AI models design and optimize therapeutic antibodies

INPUT

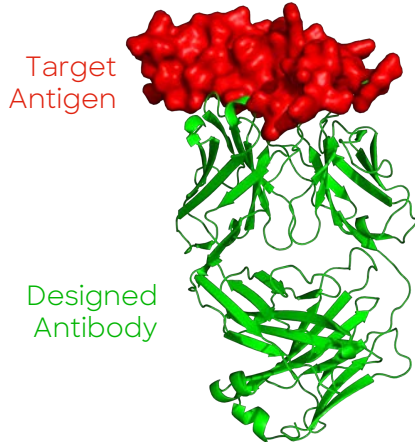


Target Antigen

1. Target structure(s)
2. Epitope(s)
3. Antibody framework(s)
4. CDR lengths

STRUCTURE & SEQUENCE DESIGN

Structure Design



Sequence Design

Design 1

HCDR1: GFNIKDTY
HCDR2: IYPTNGYT
HCDR3: SRWGGDGFYAMDY

LCDR1: QDVNTA
LCDR2: SAS
LCDR3: QQHYTTPPT

⋮

Design N

HCDR1: GFNIKDTW
HCDR2: IYPSNGYT
HCDR3: ARWGGDGFYAMDY

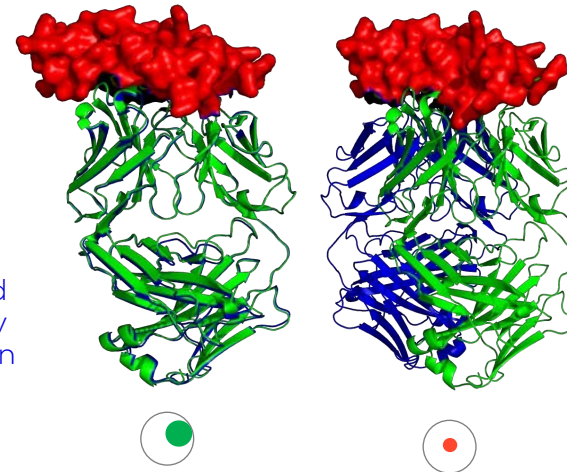
LCDR1: QDVNTA
LCDR2: SAS
LCDR3: QQHYTTPPT

DESIGN SCORING & FILTERING

Target Antigen

Designed Antibody

Designed Antibody Prediction



- Score, rank, and filter designs to optimize for diversity and binding likelihood
- Leverage quality confidence metrics, energy metrics, and molecular dynamics simulations to evaluate designs

OUTPUT LIBRARY

DESIGN LIBRARY

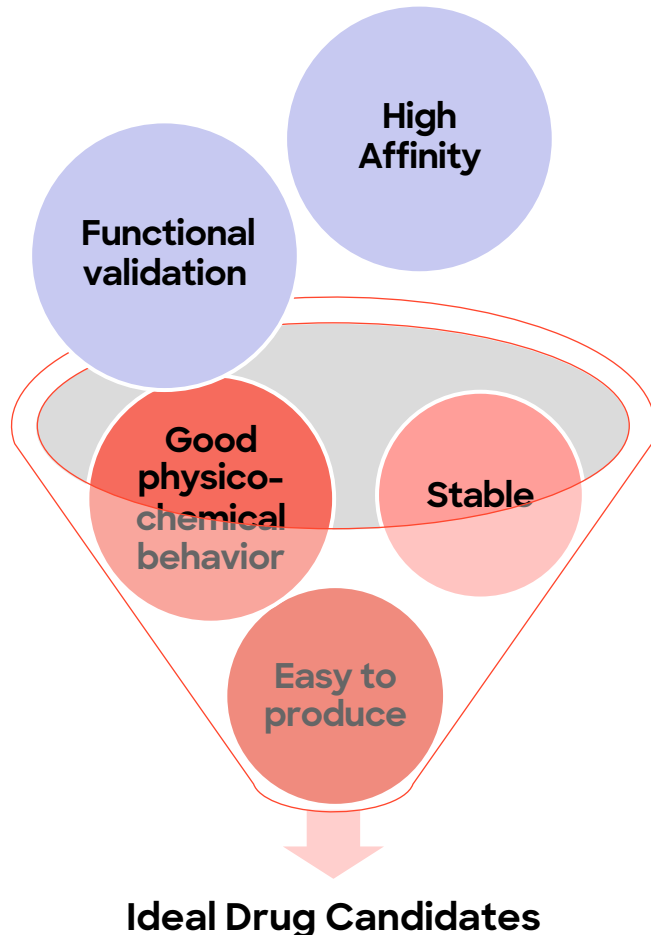
1. DESIGN 1
2. DESIGN 2
3. DESIGN 3
- ⋮
- ⋮
- ⋮
- N. DESIGN N

Output: library of amino acid sequences encoding antibody binders to therapeutic target-of-interest

CDR = Complementarity Determining Region

H = Heavy Chain; L = Light Chain

Lab-in-the-loop ensures AI-designed antibodies translate into drug-ready candidates



- **Screening** team confirms binding to target and affinity
- **Disease Biology** team validates functional activity
- **Analytical Development** team conducts developability assessment:
 - No self-association, hydrophobicity, or poly-reactivity
 - Appropriate melting temperature and colloidal profile, and stable upon stress conditions
- **Production team** evaluates manufacturability in CHO cells

Introducing Origin-1: an AI platform for *de novo* antibody design against **zero-prior epitopes**



Zero-Prior Epitope Targeting

Designed full-length mAbs against epitopes with no known protein binders or structural data in <100 designs per target



High Structural Fidelity

Cryo-EM confirmed designs at 3.0–3.1 Å resolution with DockQ 0.73–0.83, confirming high structure design accuracy



Functional Antagonist

AI-guided affinity maturation yielded 68x affinity gain for IL36RA, producing a functional antagonist at ~100 nM EC50

Origin Pipeline Components:

AbsciDiff
All-atom diffusion model



AbsciGen
CDR sequence design

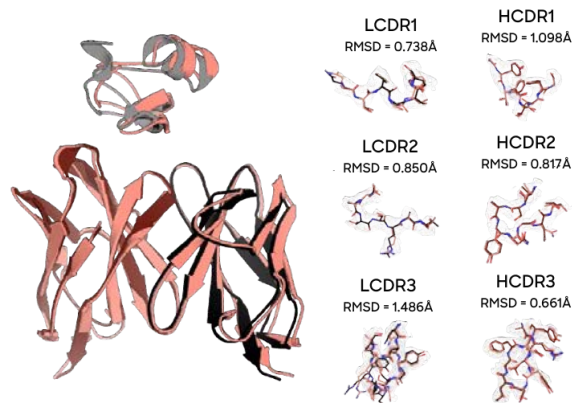


AbsciBind
Scoring & filtering

COL6A3

Experimental Structure
Designed Heavy Chain
Designed Light Chain
Designed Antigen

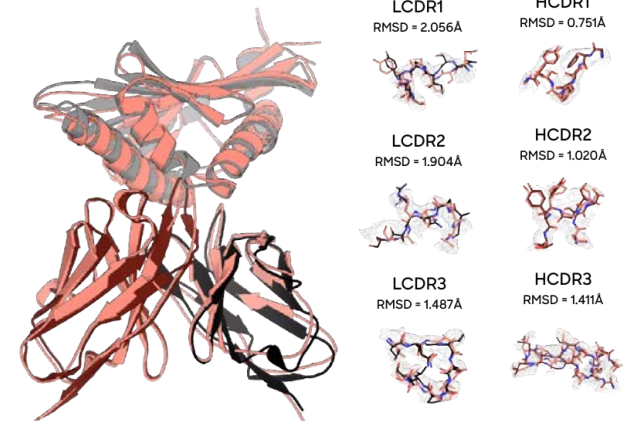
All-Atom Global RMSD = 2.56Å
Interface RMSD = 0.95Å
Ligand RMSD = 1.58Å
DockQ = 0.84



AZGP1

Experimental Structure
Designed Heavy Chain
Designed Light Chain
Designed Antigen

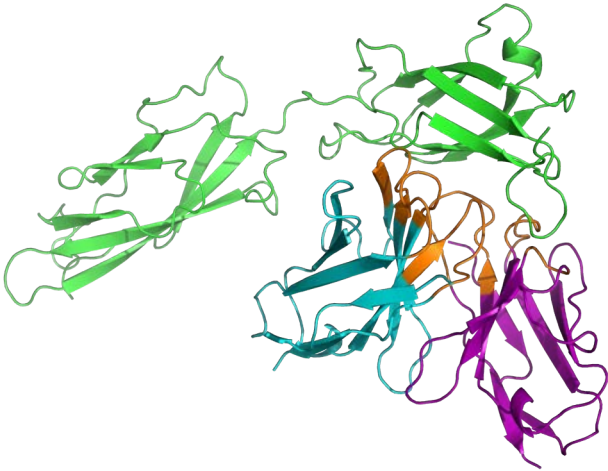
All-Atom Global RMSD = 1.79Å
Interface RMSD = 0.96Å
Ligand RMSD = 1.48Å
DockQ = 0.83



<https://www.absci.com/denovo/>

Absci's de novo AI models deliver differentiated lead candidates against challenging targets

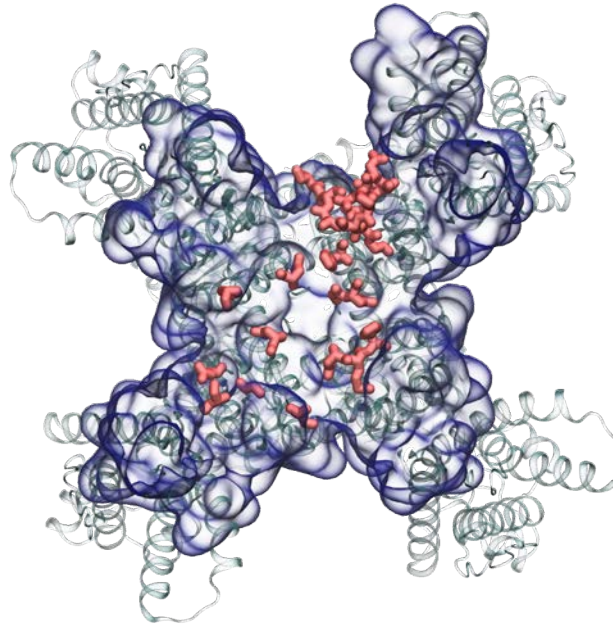
DE NOVO ANTIBODY DESIGN AGAINST TRANSMEMBRANE TARGET EPITOPE WITH NO KNOWN BINDER



Designed seven high-affinity antibodies against partner-specified epitopes on a transmembrane antigen without a known binder.

Pharma collaboration

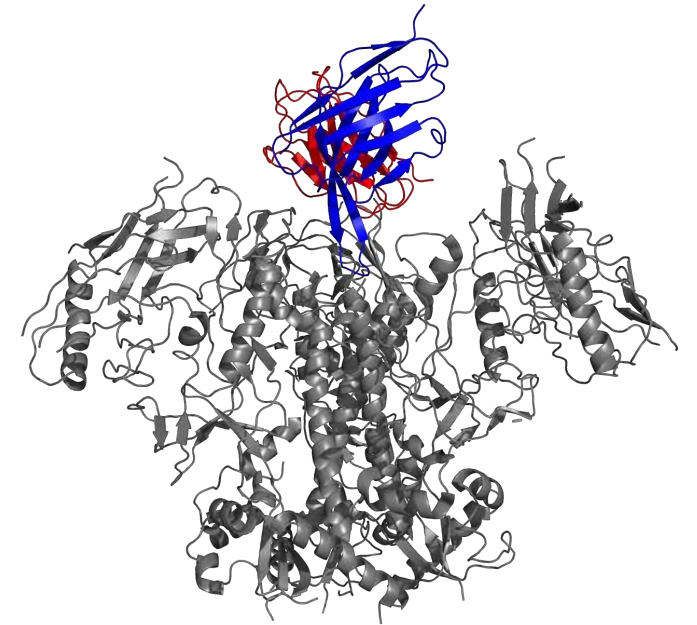
DE NOVO ANTIBODY DESIGN AGAINST CHALLENGING ION CHANNEL



Designed a pore-blocking, functional antagonist against a tetrameric membrane-embedded ion channel.

Pharma collaboration

DE NOVO ANTIBODY DESIGN AGAINST CONSERVED HIV-1 "CALDERA" EPI TOPE



Designed cross-reactive, conformation-specific antibodies against the HIV-1 "Caldera" epitope.

Caltech collaboration

We use high-fidelity, customized datasets with our own AI models to enrich for developable candidates

Generates **diverse**, **developable**, and **functional novel variants** within a desired target product profile (TPP):

Precise affinity tuning for bi-specific arms

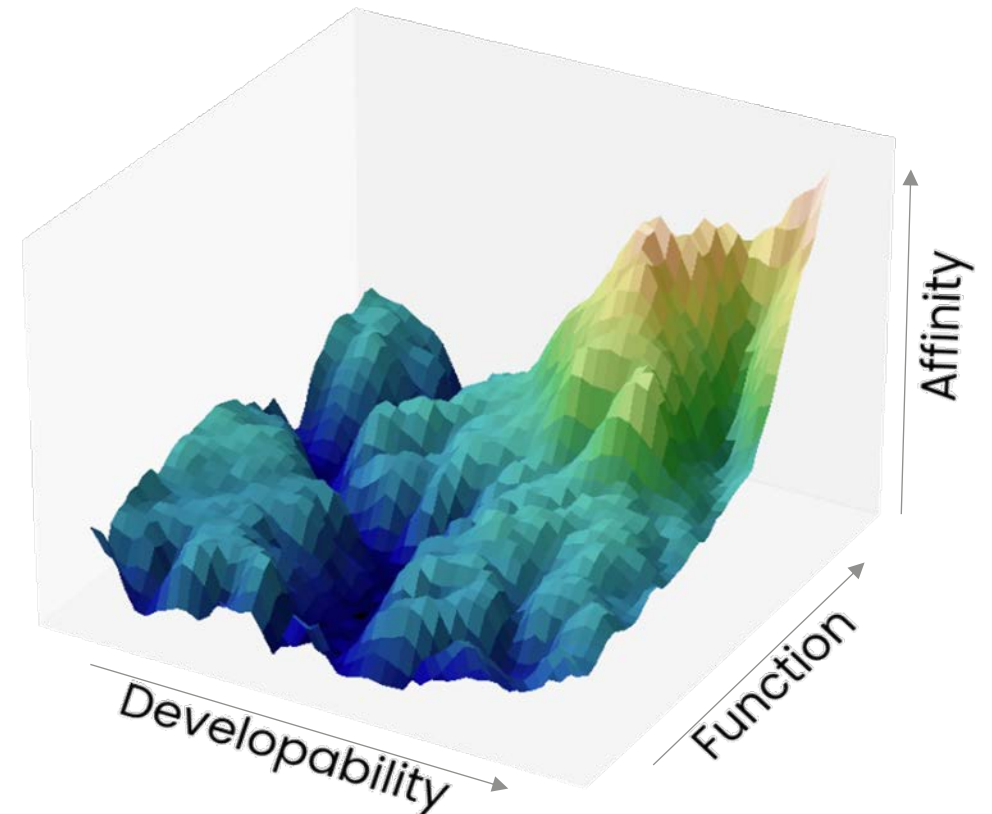
Cross-reactive leads to support *in vivo* testing

Conditional leads for optimal pharmacology

Lab-in-the-loop synergy provides strong model performance out to $>10^{18}$ combinatorial space*

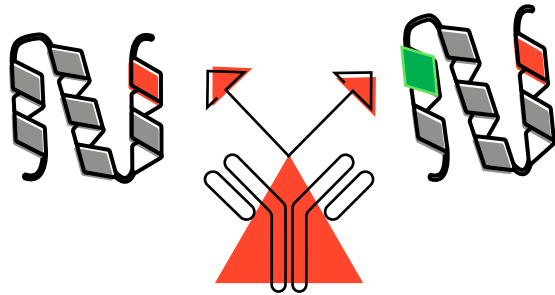
*derived from ≥ 10 amino acid changes at ≥ 24 CDR positions sampling all residues except cysteine

Landscape-wide scoring enables selection of optimal sets of sequences



Success in AI-design and optimization of multiple developability and pharmacological properties

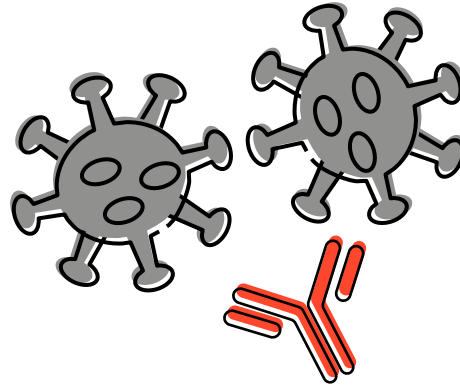
CROSS-SPECIES OPTIMIZATION



Successful design of antibodies binding to both mouse and human antigens

- Hits identified from 10^{19} combinatorial space
- Models identify hits with >175x tighter affinity and <500 pM KD to both antigens

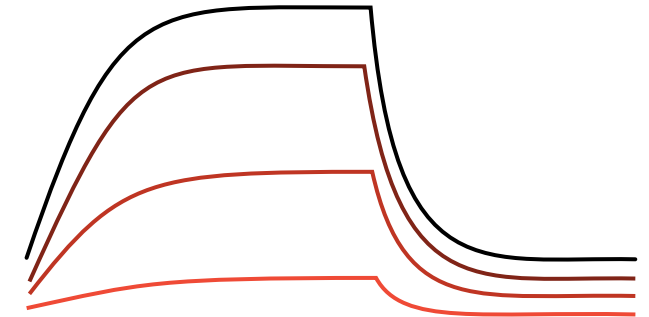
MULTI-VARIANT SPECIFICITY



Successful design of antibodies with expanded neutralizing activity vs three SARS-CoV-2 spike variants

- Tuned models identify developable hits with higher affinity to three variants, including >50x tighter affinity to previously resistant variant
- Potent neutralization activity to all three variants

PH-SENSITIVE BINDING



Successful design of pH-sensitive antibodies through sampling the entire relevant ionizable search space

- Hits show 20x to >100x pH sensitivity with favorable developability after one round

Track record of industry-leading partnerships

AI DRUG CREATION™ PARTNERSHIPS



SUPPORTING COMPUTE COLLABORATIONS



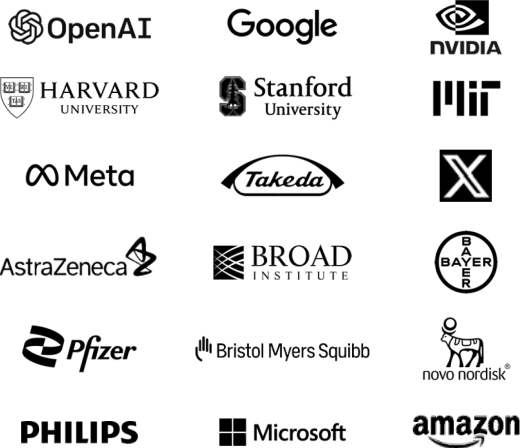
25+ PARTNERED PROGRAMS TO DATE

OUR PARTNERSHIP FOCUS

- Challenging Targets / Epitopes
- Differentiated TPPs
- Mono or Multi-specific Formats

”Multilingual”
team with
expertise in AI
and drug
creation

EXPERTISE AND
BACKGROUND FROM:



Leadership Team:



Sean McClain
Founder, CEO & Board
Director



Zach Jonasson, PhD
Chief Financial Officer
& Chief Business Officer



Ransi Somaratne, MD
Chief Medical Officer



Shelby Walker, JD
Chief Legal Officer



Christine Lemke
SVP, Portfolio & Growth
Strategy

Board Of Directors:



Frans Van Houten
Chairman of the Board
Former CEO, Royal
Phillips



Sean McClain
Founder, CEO & Board
Director



Sir Mene
Pangalos, PhD
Former EVP R&D
AstraZeneca



Mary Szela
CEO & President
TriSalus Life Sciences



Joseph Sirosh, PhD
Former CVP AI
Microsoft



Dan Rabinovitsj
VP Hardware
Engineering, Meta



Karen McGinnis,
CPA
Former Chief
Accounting Officer,
Illumina

Scientific Advisory Board:



Sir Mene
Pangalos, PHD
Co-Chair SAB
Former EVP R&D
AstraZeneca



Andreas Busch,
PHD
Co-Chair SAB
Chief Innovation Officer



Ian McInnes, PHD
Vice Principal and Head
of College
University of Glasgow



Luis Diaz, MD
Head, Division of Solid
Tumor Oncology
Memorial Sloan
Kettering Cancer
Center



John Wherry, PHD
Director, Institute for
Immunology & Immune
Health, University of
Pennsylvania



Victor Greiff, PHD
Associate Professor
University of Oslo



Hubert Truebel,
MD, PHD, MBA
Chief Medical Officer
AiCuris

Absci at a Glance

140

EMPLOYEES

“Multi-lingual” AI + Drug Discovery expertise AI team drawing on experience from tech leaders:



Biologics drug discovery expertise from:



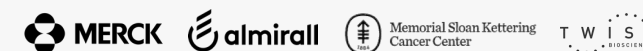
77,000

SQUARE FEET

- State-of-the-art wet and dry lab in Vancouver WA
- Absci AI Research (AAIR) lab in NYC
- Innovation Centre in Zug Switzerland

10+

PARTNERS, INCLUDING



3

CLINICAL STAGE PROGRAMS

In Androgenetic Alopecia, Endometriosis, and I&I

>\$650M

CAPITAL RAISED TO DATE

Generative AI Re(Generative) Biology

AI CASE STUDY I

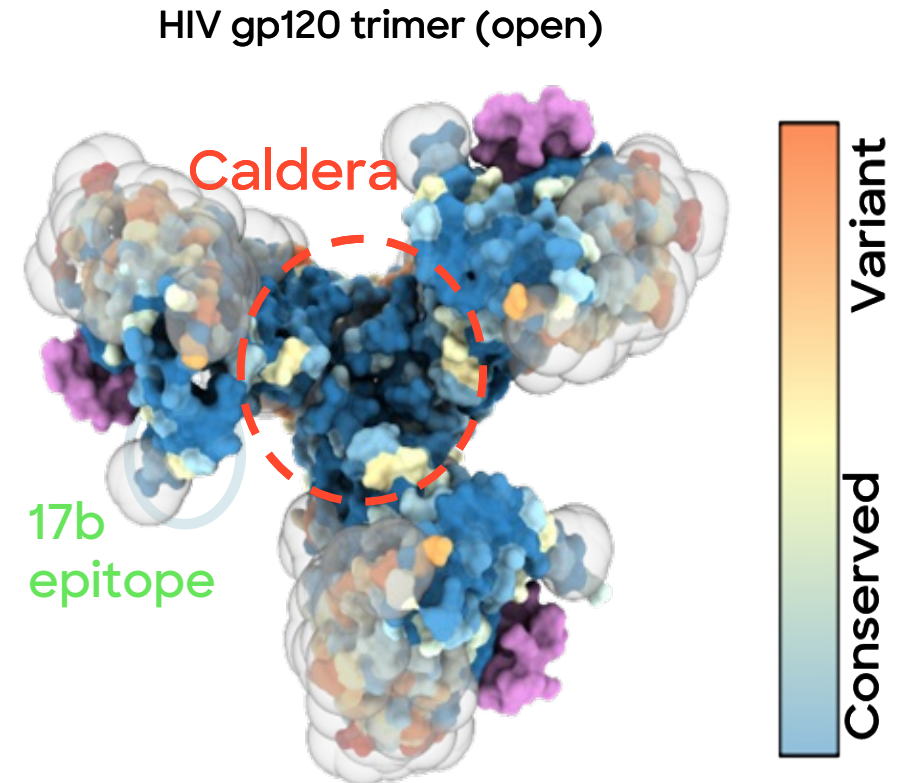
de novo design of an antibody that binds the Caldera region of HIV-1 trimer

Caltech **absci.** BILL & MELINDA
GATES *foundation*



de novo design antibody that binds to the highly conserved caldera region of HIV gp120

- No natural or synthetic antibody for HIV exists today because immune system cannot derive an antibody that is universally neutralizing against HIV
- Design challenge: create universally neutralizing HIV antibody by binding unique and conserved epitope within “caldera” of open conformation of gp120 to prevent HIV from entering host cells
- Numerous attempts to target this epitope have failed—previous efforts have identified antibodies, but none bind the “caldera” and none are universally neutralizing.



HIV-Caldera: Determine inputs and design

HIV Env Trimer Challenge :

- Highly glycosylated
- Extremely high sequence diversity among isolates
- High mutation rate at common neutralizing epitopes

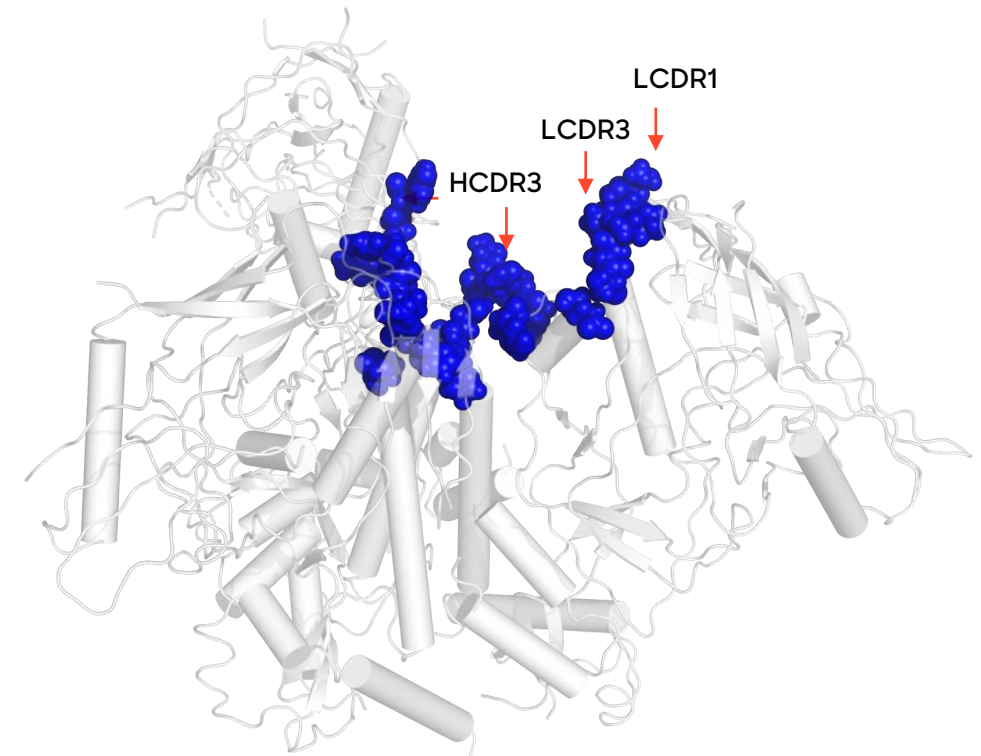
Model inputs:

1. Antigen structure
2. Framework of 17b
3. Epitope selected conserved across HIV strains (Clades A, B, and C)

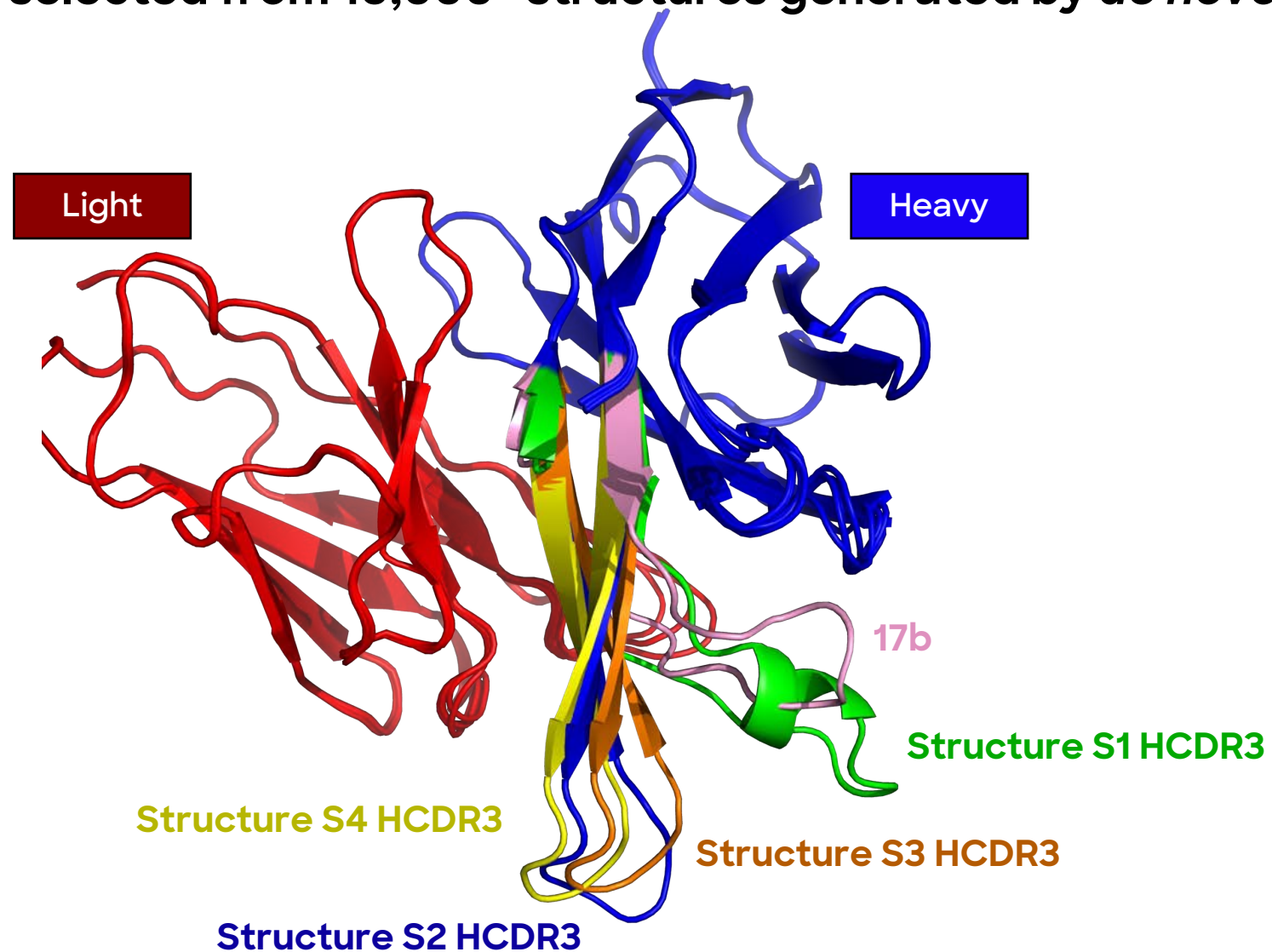
Design of CDRs:

- Condition the model to design long HCDR3s to reach into open caldera region (>20 residues)
- Designed HCDR2 and LCDR3 to bind to HIV surface

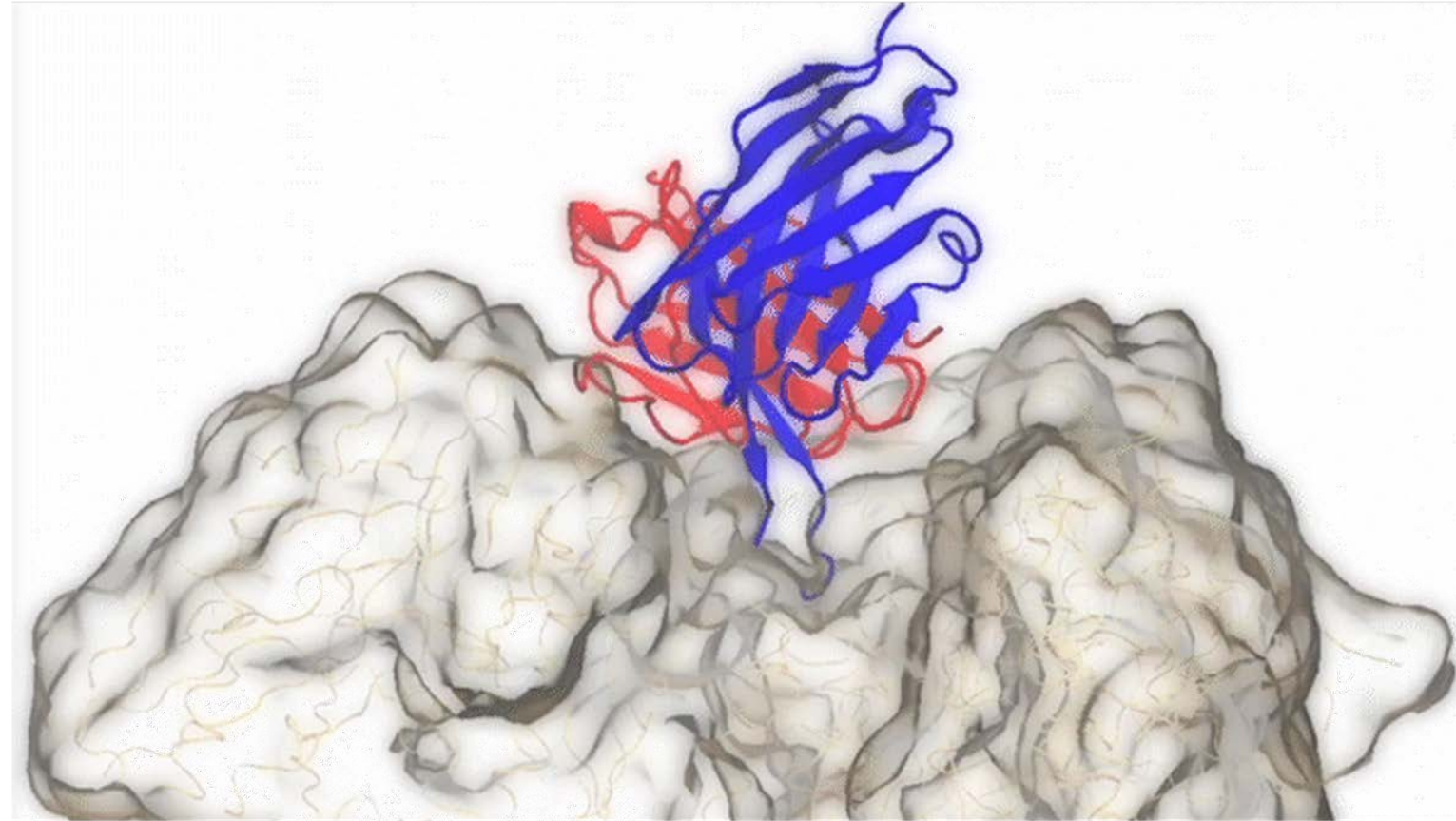
HIV Env trimer (open)



4 best structures selected from 10,000+ structures generated by *de novo* model

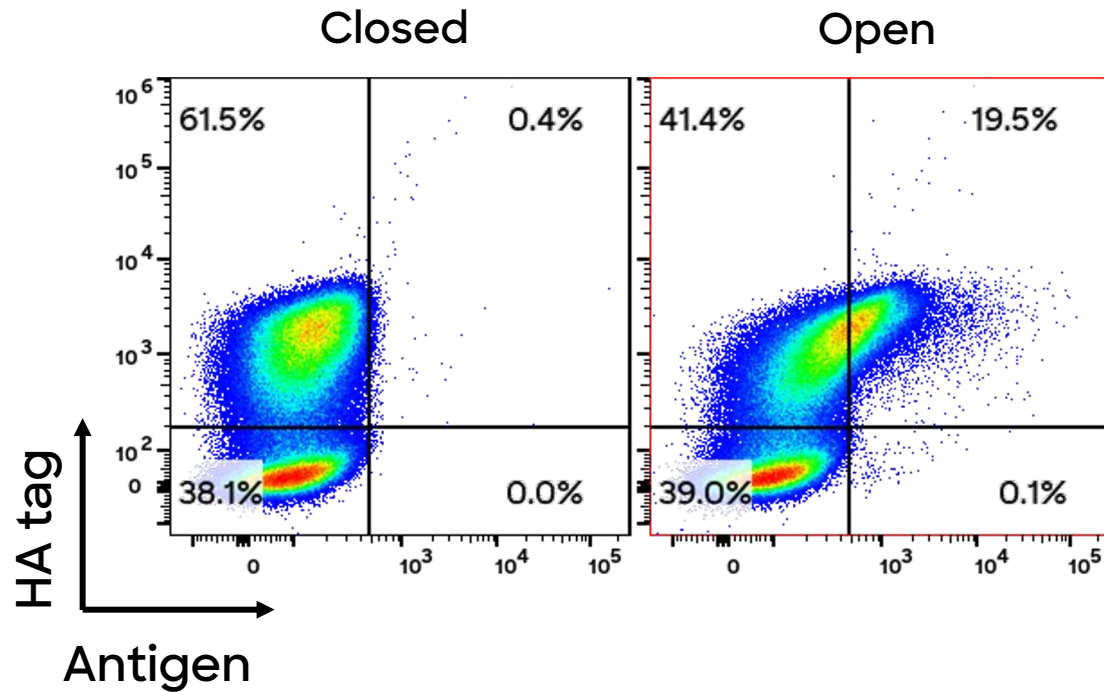


Applied molecular
dynamics simulation
to *de novo* designed
antibodies

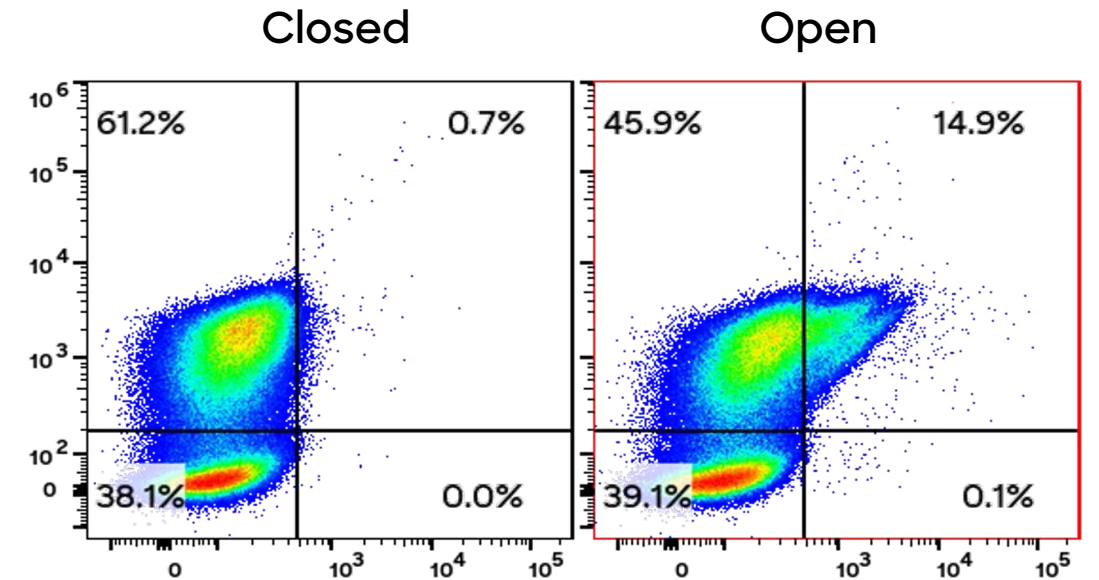


Enriched de novo library binds open, not closed, Env trimer conformation in YSD

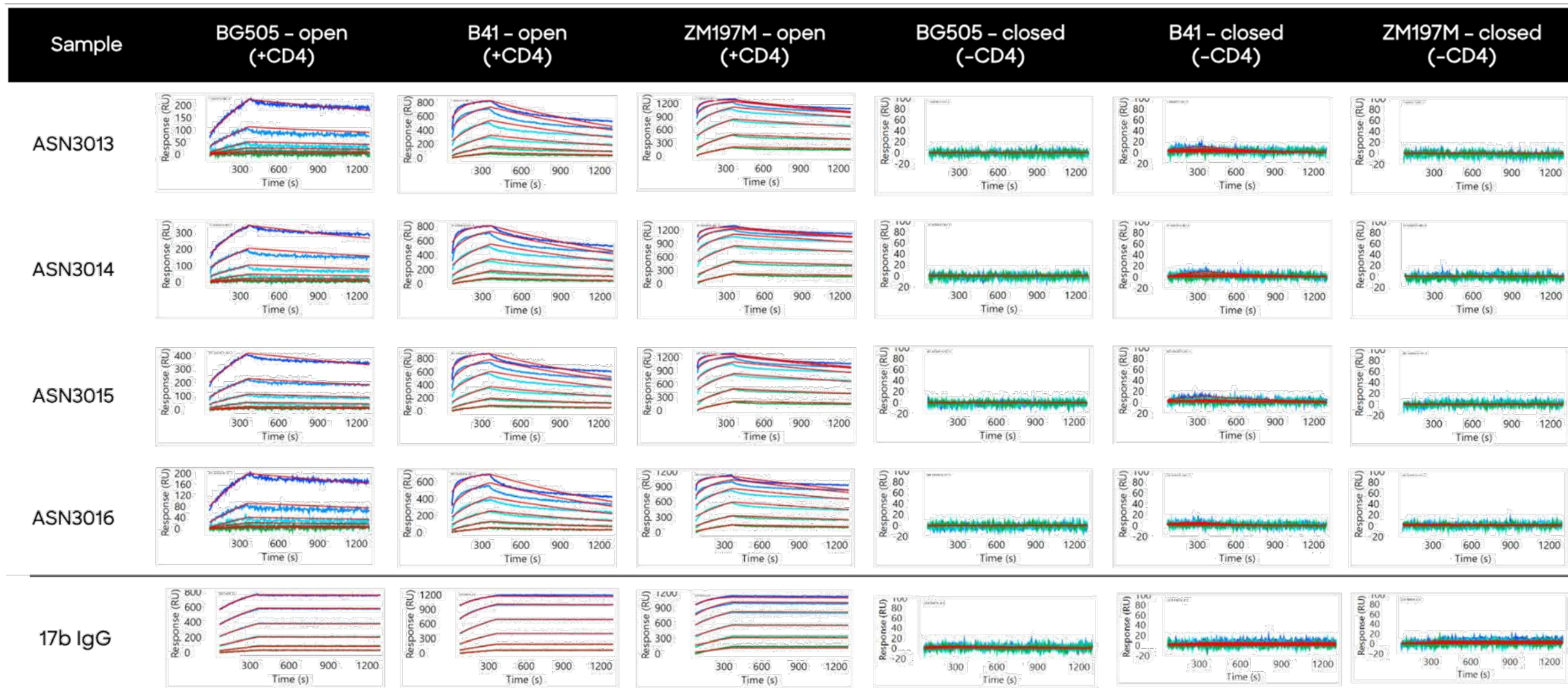
Clade A Env trimer



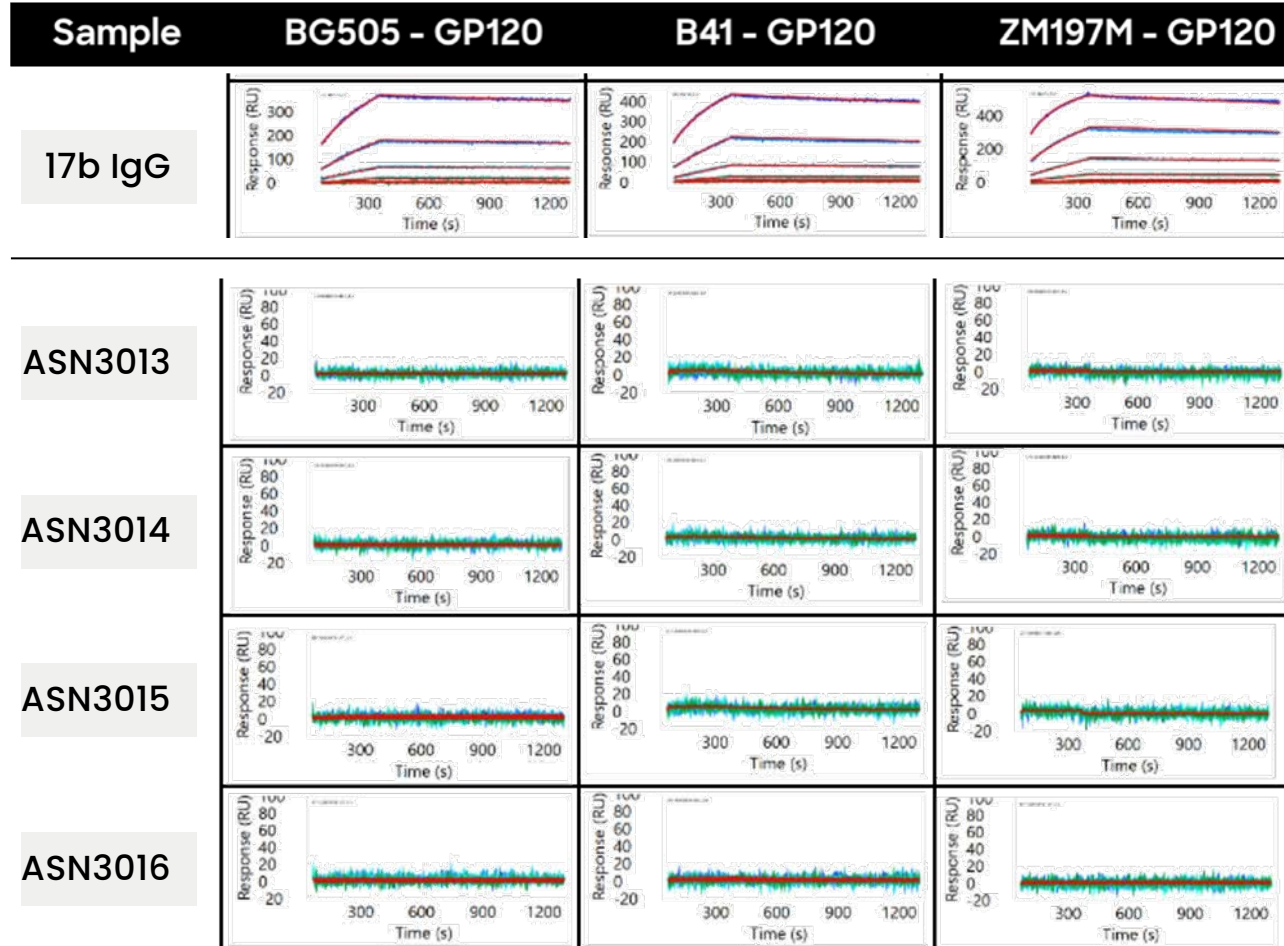
Clade B Env trimer



SPR data demonstrate binding characteristics consistent with binding of caldera



HIV-Caldera: SPR demonstrates no binding of de novo designs to GP120 monomer



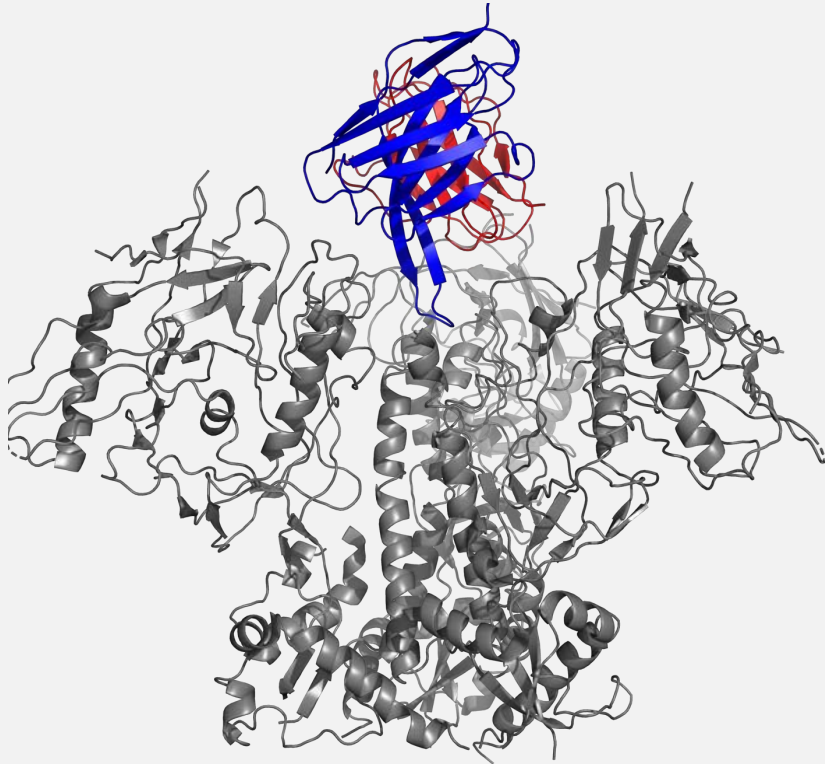
Hypothesis:

If the designed mAbs are binding to the caldera region we should not observe binding to monomeric GP120 since the caldera is only present in the Env trimer

Key results:

- ✓ **17b** showed high affinity binding to monomeric GP120 as expected
- ✓ **Absci mAbs** showed no binding to monomeric GP120, suggesting these binders are targeting an epitope that is only present in the Env trimer

HIV-Caldera: demonstrating AI de novo design for challenging target



SUMMARY

- *de novo* design model created a novel and diverse antibody which binds multiple clades of HIV indicating successful targeting of the caldera epitope
- Screening cascade enabled selection of differentially binding variants

NEXT STEPS

- Binders from this study will be selected for affinity maturation
- Structure of *de novo* binder and epitope specificity will be experimentally solved to confirm fidelity with designed structure and targeted epitope

AI CASE STUDY II

AI Optimization for pH sensitivity



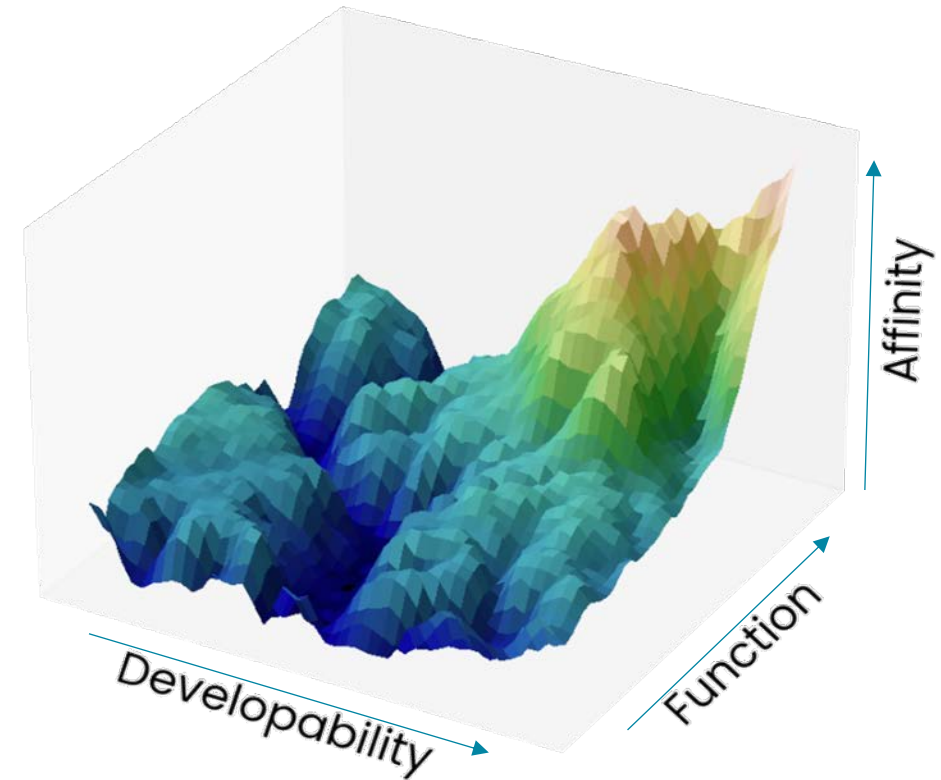
AI lead optimization platform for 'smart biologics'

The Challenge

The diversity of antibodies is vast, making it impossible for traditional methods to explore effectively.

Absci Solution

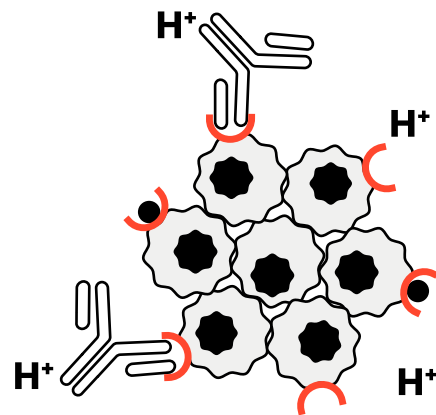
Our AI can search a space of $\sim 10^{19}$, a million times larger than traditional methods, identifying functional, developable antibodies in one step.



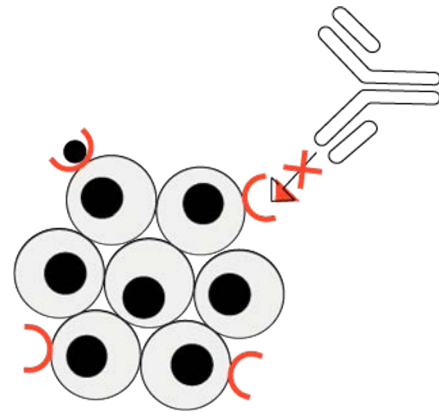
pH sensitivity may reduce toxicity and/or improve efficacy of therapeutic mAbs

Tumor specificity improves efficacy and reduces "on-target off-tumor" toxicities

Binding occurs in the acidic pH of the tumor microenvironment



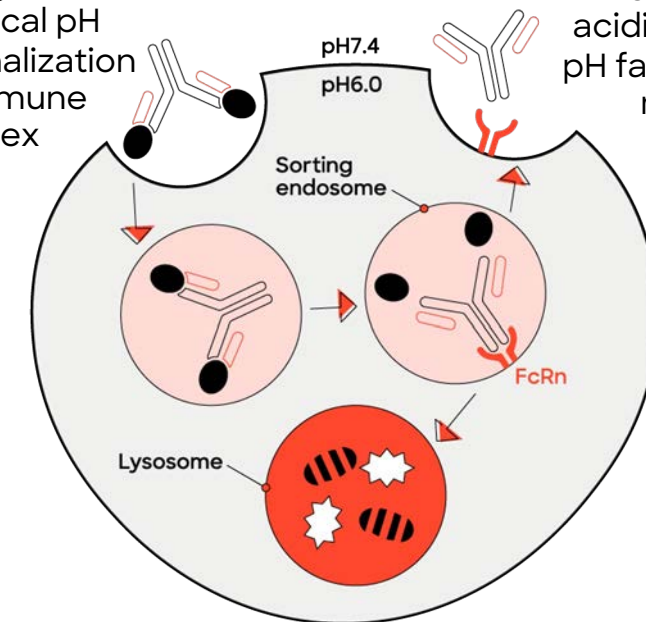
No binding occurs in the neutral pH surrounding healthy cells



Disassociation in the endosome drives antibody recycling and efficient clearance of soluble targets

Binding at physiological pH drives internalization of the immune complex

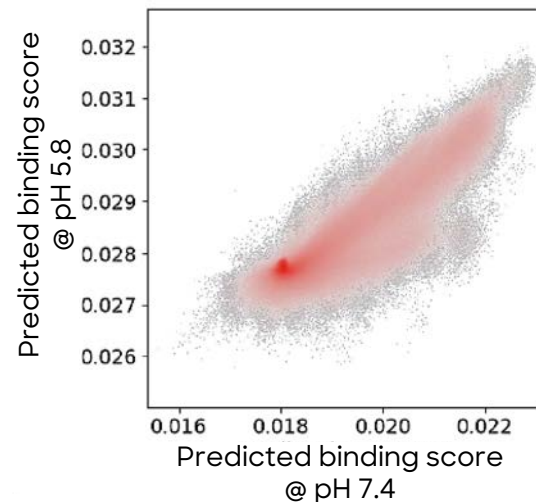
Dissociation at acidic endosomal pH favors antibody recycling



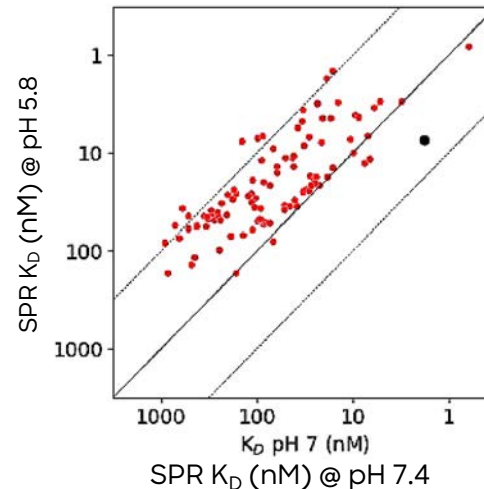
Models identify pH sensitive Fab variants from the same lead for either indication

1. Library for model training sampled 60 positions on heavy chain framework and CDRs with up to 7 substitutions biased for ionizable residues (H, K, R, D, E)
2. Library screened for antigen binding at pH 7.4 and pH 5.8
3. Model trained and used to generate antibodies with tuned pH dependency

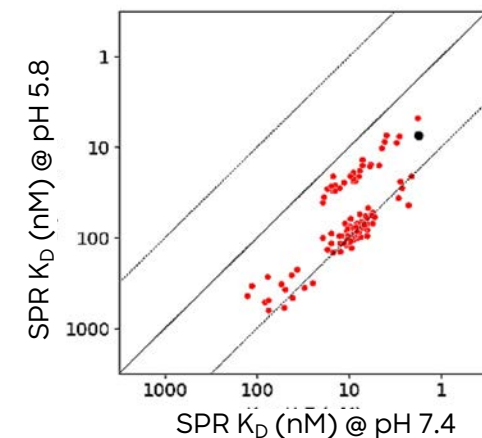
AI affinity scoring of variants within a large combinatorial space



Lab measured affinities of Fab variants predicted to have tighter binding at low pH



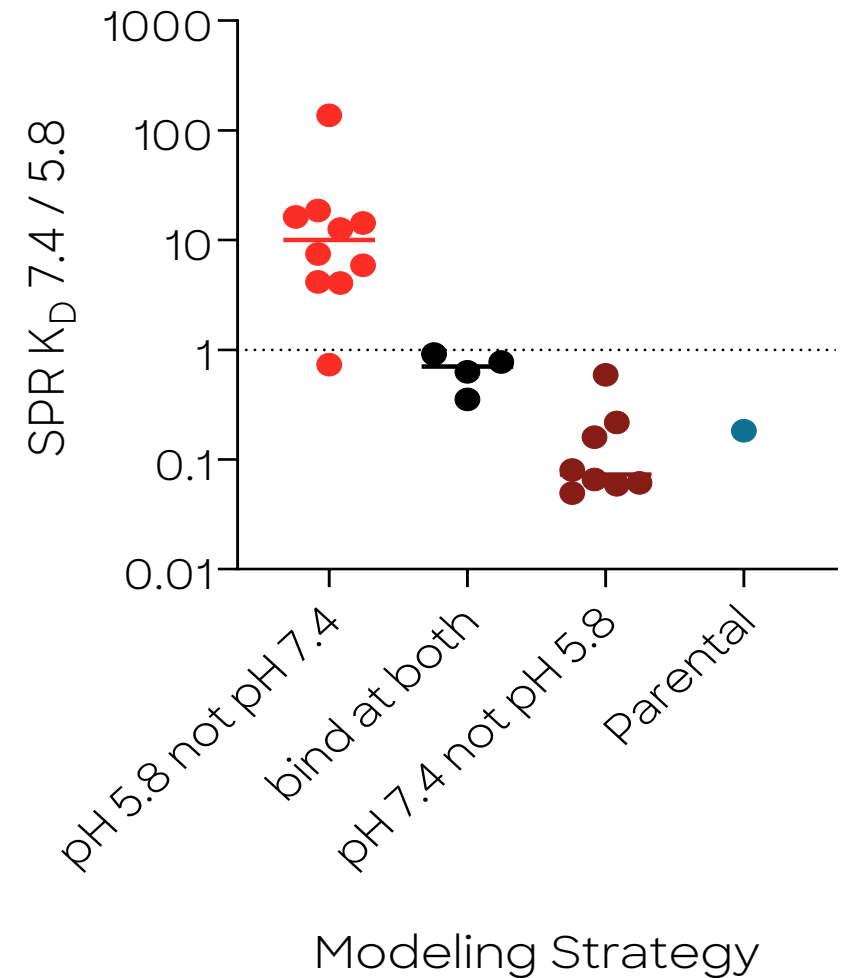
Lab measured affinities of Fab variants predicted to have tighter binding at neutral pH



Hits reformatted as mAbs show desired binding profiles

SUMMARY

- › AI optimized leads achieves variants with pH sensitive binding up to 100x differential
- › pH-sensitive leads had no liabilities for stability, aggregation and polyreactivity¹
- › Model proposed mutations use all 6 ionizing residues in heavy chain CDRs and framework region
- › Sequences were proposed from a >10¹³ combinatorial space



Summarized platform case studies

de novo Design

- › de novo design model created molecule binds multiple clades of HIV suggesting successful targeting of the caldera epitope
- ›
- › Represents second disclosed target success for our de novo platform in the 2nd half of this year

Absci's de novo design platform can successfully address difficult to drug target epitopes

AI Optimization

- › Models identify unseen variants with 10x-20x pH sensitivity in both directions, and up to 100x differential compared to parental molecule after only one round
- ›
- › Designed leads had no liabilities indicating the ability to successfully search a fitness landscape

Absci's lead optimization platform enables molecules with differentiated pharmacology

