Development of ABS-101 - A potential best-in-class anti-TL1A antibody for the treatment of inflammatory bowel disease

Emily Gage, Douglas Ganini da Silva, Amer-Denis Akkad, Mario Sanches, Matthew Waugh, Daniele Biasci, Sharrol Bachas, Marcin Ura, Amir Shanehsazzadeh, Matt McPartlon, Simon Levine-Gottreich, Alec Jaeger, Jibran Khan, Dalton Chapman, Gaelin Kopec-Belliveau, Zheyuan Guo, Kaitlin Witherell, Emily Marsh, Curtis Orona, David Spencer, Shaheed Abdulhaqq, Miles Gander, Nick Smith, Abigail Ventura, Rebecca Viazzo, Kerianne Jackson, Jenn Stanton, Jubair Hossain, Andrea Steiger, George Kasun, Amber Brown, Brea Luton, Nic Diaz, Chelsea Chung, Robel Haile, Cailen McCloskey, John Sutton, Christa Kohnert, Rebecca Consbruck, Hayley Carter, Azeem Jimoh, Anand Sastry, Vincent Bla, Matthew Saunders, Chase LaCombe, Lichen Xiu, Masoud Zabet-Moghaddam, Paul Bringas, Pat Vilaychack, Zahra Hannani, Kuldeep Kumawat, Tiffany Devine, Engin Yapici, Alex Dubrovskyi, Elaine Hart, Samuel Yiu Huen Tsang, Namita Varudkar, Joshua Bennet, James Hickman, Luka Topalovic, Thomas Wrona, Byron Olson, Amaro Taylor-Weiner, and Christian Stegmann

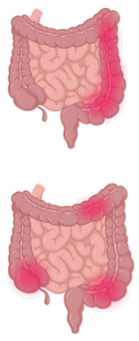
ABSTRACT

The application of generative artificial intelligence (generative AI) for the discovery and design of novel biologics holds substantial potential for the biopharmaceutical industry, although practical implementations are still limited. Here we introduce the development of ABS-101, a potential best-in-class antibody targeting TL1A for the treatment of inflammatory bowel disease and other indications with hallmarks of inflammation and fibrosis. Absci's Integrated Drug Creation™ Platform, featuring generative AI models, was leveraged to design antibodies against desired epitopes with the aim of achieving an optimized target product profile, including reduced immunogenicity risk and binding to both monomeric and trimeric forms of TL1A. Top leads were selected for AI-guided lead optimization, resulting in several high-affinity candidates with high cellular potency, desirable developability properties, and cross-reactivity to non-human primate (NHP) species to facilitate pre-clinical development.

Recently, we demonstrated that our development candidate ABS-101 exhibits a 2-3-fold extended half-life in NHPs compared to selected clinical competitors MK-7240 and RVT-3101. Coupled with achieving a high concentration formulation at 200 mg/mL, this data supports the potential for subcutaneous injections with extended administration intervals, projected at every 8 to 12 weeks (Q8W-Q12W).

TL1A AS A THERAPEUTIC TARGET IN ULCERATIVE COLITIS (UC) AND CHRON'S DISEASE (CD)

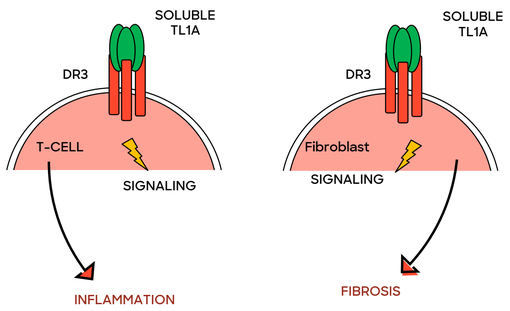
- Inflammatory Bowel Disease (IBD), which primarily includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic condition that affects the gastrointestinal tract. In 2017, there were 6.8 million cases of IBD globally[1,2,3].
- Large remaining unmet need: A significant number of IBD patients remain underserved, with about 30% being primary non-responders and 40% losing response over time (secondary non-responders).
- Current treatment options such as anti TNF-alpha blockers have limited efficacy and do not adequately address the fibrotic components of ulcerative colitis.
- TL1A inhibition is a promising novel mechanism for treatment of IBD that may additionally address fibrotic complications in IBD.
- Phase 2 data from Prometheus (now Merck's MK-7240) and Roivant (RVT-3101, now Roche) validate the MoA with clinical remission in UC and CD patients[4].



Made with BioRender.

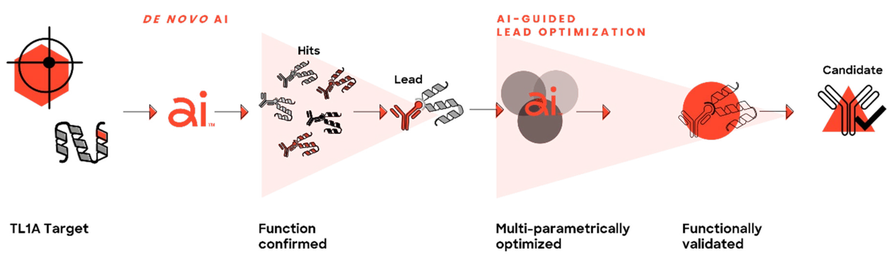
TL1A:DR3 SIGNALING CLINICALLY SHOWN TO INDUCE PROINFLAMMATORY RESPONSES

Figure adapted from reference 1.



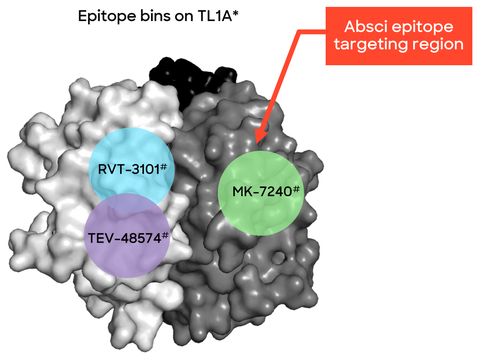
- TL1A is a member of the TNF-receptor superfamily that binds to Death Receptor 3 (DR3), initiating signaling cascades leading to pro-inflammatory and pro-fibrotic responses.
- TL1A is implicated in multiple inflammatory and fibrotic diseases beyond IBD including: rheumatoid arthritis, atopic dermatitis, lupus erythematosus, psoriasis, intestinal fibrosis, pulmonary fibrosis, and liver fibrosis.

ABSCI'S INTEGRATED DRUG CREATION™ PLATFORM



Schematic of Absci's Integrated Drug Creation™ platform, used to generate anti-TL1A lead candidates, that unlocks the potential to accelerate time to clinic and increase the probability of success by simultaneously optimizing multiple drug characteristics important to both development and therapeutic benefit.

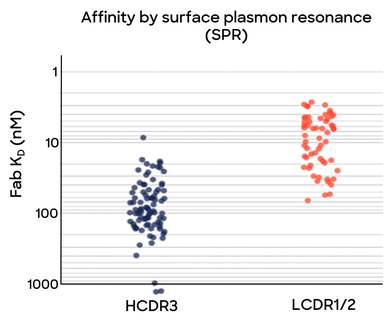
SUCCESSFUL AI *DE NOVO* DESIGN AND AI-GUIDED LEAD OPTIMIZATION FOR AN IMPROVED ANTI-TL1A THERAPEUTIC

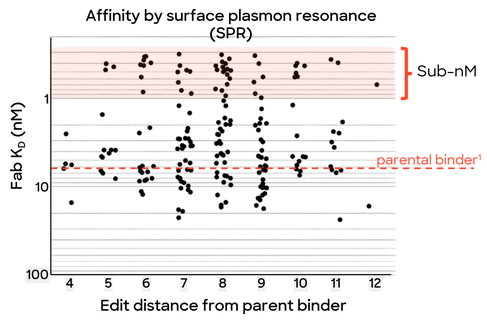


* Epitope binning by BLI competition experiment.
# Estimated performance of a putative clinical competitor molecule generated for in house comparison.

AI-OPTIMIZED LEAD CANDIDATES SPAN A DIVERSE SET OF EPITOPES

- Target epitope space is contained within one TL1A subunit to promote both monomer and trimer binding.
- The epitope for RVT-3101 was excluded during design due to high ADA observed in the clinic and to avoid binding at the interface between two subunits (exclusive trimer binder).





1Parental binder is the Heavy Chain AI *de novo* designed variant.

AI *DE NOVO* DESIGN GENERATED MANY HCDR3 AND LCDR1/2 HITS WITH DESIRED RANGE OF K_D FOR FURTHER OPTIMZATION

- Deep learning docking models, a crystal structure of TL1A, and a predicted structure of the antibody framework were used to generate *in silico* structural models of antibody-antigen complexes predicted to represent TL1A:DR3 blockade.
- Predicted complex structures were used in inverse folding models that were used to generate HCDR3 variants or LCDR1/2 variants.
- AI-designed HCDR3 variants were assessed for binding to TL1A via the ACE assay™. HCDR3 hits identified by the ACE assay™ were confirmed by SPR.
- LCDR1/2 hits were confirmed directly by SPR.

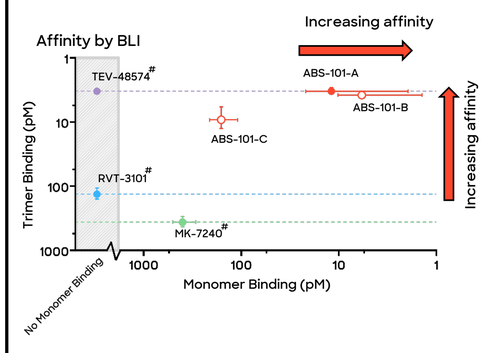
AI-GUIDED LEAD OPTIMIZATION GENERATED >50 NOVEL AI-OPTIMIZED VARIANTS WITH SUB-NANOMOLAR AFFINITY AND NO *IN SILICO* DEVELOPABILITY FLAGS

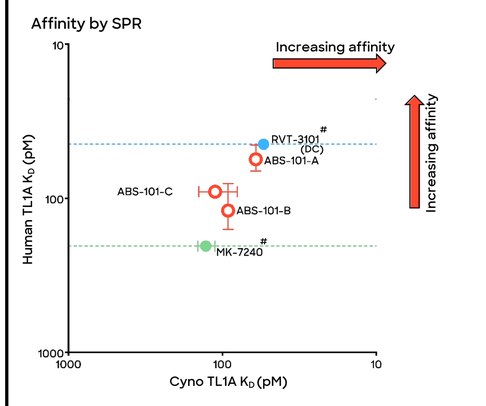
- Top AI *de novo* designed HCDR3 hits were selected for AI-guided lead optimization where HCDR123 variants were screened using the ACE Assay™ platform to generate data to train affinity-prediction models.
- AI-guided lead optimization models were optimized to produce diverse, high affinity heavy chain variants with suitable developability.
- A combinatorial library of top AI-optimized heavy chain variants and top *de novo* designed light chain variants was generated and assessed by SPR.

HIGH AFFINITY LEAD CANDIDATES DEMONSTRATE SUPERIOR OR EQUIVALENT POTENCY IN FUNCTIONAL ASSAYS COMPARED TO CLINICAL BENCHMARKS

HIGH AFFINITY MABS WITH MONOMER AND TRIMER BINDING AND EXCELLENT PRECLINICAL MODEL CROSS-REACTIVITY

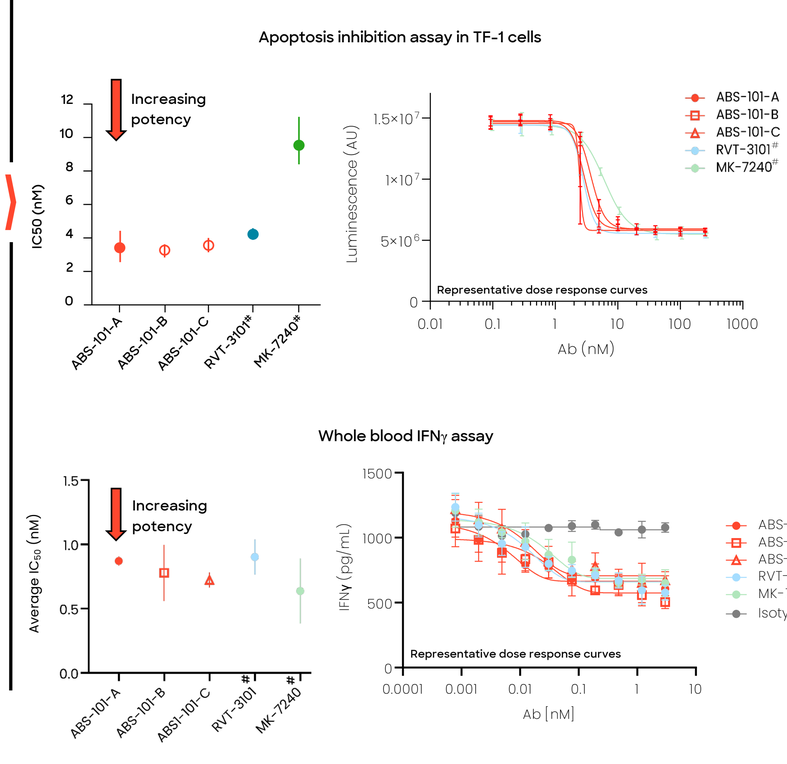
- Absci's lead candidates demonstrate binding to both TL1A monomer and trimer with high affinity (above).
- SPR TL1A binding assays demonstrate Absci's lead candidates have picomolar affinity for human TL1A and picomolar cross reactivity for cynomolgus TL1A (below).



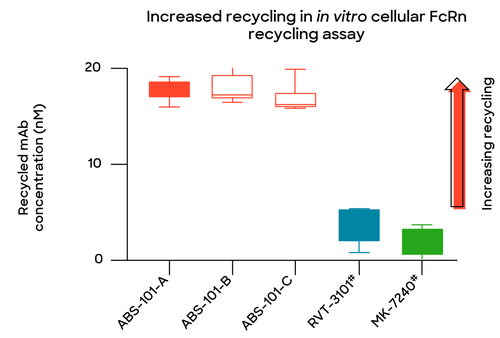


AI-OPTIMIZED LOW pM AFFINITY TRANSLATES TO SUPERIOR OR EQUIVALENT POTENCY

- AI-optimized lead candidates inhibit TL1A:DR3-driven apoptosis in TF-1 cells (top).
- AI-optimized lead candidates inhibit IFNγ release in whole blood stimulated with immune complex and IL-12/18 (bottom). IC_{50} is average of 3 donors.



HALF-LIFE EXTENSION MUTATION IMPROVE ANTIBODY PHARMACOKINETICS

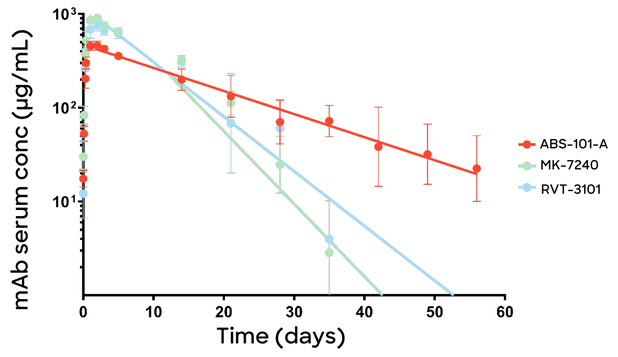


EXTENDED HALF-LIFE *IN VITRO* COMPARED TO CLINICAL COMPETITORS

- Cell-based FcRn recycling assay assessed in HMEC-1 cells[5].
- Half-life extension mutations introduced to improve antibody recycling compared to regular IgG by:
  - Increased affinity for FcRn at pH 6.0 to promote antibody recycling from endosomes.
  - Preserved low affinity at pH 7.4 to promote antibody release in the extracellular environment.

2-3X LONGER HALF-LIFE IN NHPs COMPARED TO CLINICAL COMPETITORS AND HIGH S.C. BIOAVAILABILITY

- Extended half-life of 2-3-fold over clinical competitors to support Q8W-Q12W dosing interval. Cynomolgus macaques (n=3 per arm) were dosed with 60 mg/kg s.c.
- ABS-101-A shows enhanced biodistribution in NHPs, compared to antibodies in clinical development. Potential therapeutic advantage due to faster tissue penetration, likely without the need for a loading dose.
- ABS-101-A achieves ~80% s.c. bioavailability (BA) in NHPs ($BA_{AUC336h}$ = 77%; BA_{AUCinf} = 86%)



PK Parameters	ABS-101-A	MK-7420#	RVT-3101#
$t_{1/2}$ (d)	8.5 (8.3-13.0)	2.6 (2.1-2.7)	3.3 (2.6-4.0)
CL/F (mL/hr/kg)	0.36 ± 0.08	0.26 ± 0.02	0.27 ± 0.03
$AUC_{0-\infty}$ (µg*h/mL)	175000 ± 45700	234000 ± 22400	225000 ± 26500
Vz/F (mL/kg)	118 ± 4.2	22 ± 3.8	31 ± 12.7
Cmax (µg/ml)	462 ± 52	909 ± 87	767 ± 107

Estimated performance of a putative clinical competitor molecule generated for in house comparison.

HIGH CONCENTRATION FORMULATION ENABLES SUBCUTANEOUS INJECTION

- Successful development of high-concentration drug substance formulation at 200mg/mL to enable subcutaneous injection.

ABS-101-A TIMELINE

JAN 2024

AI-Designed Advanced Leads have Demonstrated:

- ✓ High Affinity
- ✓ High Potency
- ✓ Long Half-Life
- ✓ Favorable Manufacturability

INITIATED FEB '24

IND-enabling studies to evaluate

- ✓Development candidate selected Feb '24
- ✓Sub-Q formulation
- ✓Favorable PK and long Hal-Life
- ✓High Bioavailability in NHPs
- • Low ADA
- • High Tolerability (low tox)

1H25

Initiating Phase 1 Trial

2H25

Phase 1 Interim Data Readout

IND-ENABLING STUDIES ONGOING FOR ABS-101, A POTENTIAL BEST-IN-CLASS ANTI-TL1A ANTIBODY *DE NOVO* DESIGNED USING GENERATIVE AI

Absci presented preclinical data on ABS-101 in January 2024, with three advanced leads showing properties consistent with a potentially superior product profile, including demonstrated high affinity, high potency, favorable developability, and extended half-life. Absci used its *de novo* AI model to design ABS-101 toward a specific epitope with the objective for superior potency and lower immunogenicity. This target product profile, combined with high concentration formulation, high bioavailability, and 2-3x half-life extension enables convenient, less frequent dosing. Absci expects to submit regulatory filing for ABS-101 in the first quarter of 2025. Subject to regulatory clearance, Absci expects to initiate Phase 1 studies for this program shortly thereafter.

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