

A NEXT-GENERATION ARTIFICIAL INTELLIGENCE-DESIGNED ANTIBODY AGAINST TUMOR NECROSIS FACTOR-LIKE LIGAND 1A FOR INFLAMMATORY BOWEL DISEASE: CURRENT STATUS AND FUTURE PERSPECTIVES

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DOI: <https://doi.org/10.63001/tbs.2026.v21.i04.pp185-217>

KEYWORDS

*Inflammatory bowel disease;
 Crohn's disease;
 Ulcerative colitis;
 TL1A; DR3 (TNFRSF25);
 Anti-TL1A antibody; ABS-101;
 Generative AI;
 Antibody engineering;
 Intestinal fibrosis; Biologic therapy*

Article Info

Received: 22.09.2026

Accepted: 09.10.2026

Published: 19.10.2026

Abstract

Inflammatory bowel diseases (IBD), which includes Crohn's diseases and ulcerative colitis, it is a chronic condition whose burden keeps growing worldwide, especially in Asia. Many patients still respond poorly to current therapies, and none of the available drugs can reliably reverse intestinal fibrosis. The TL1A-DR3 pathway has drawn attention because it drives both mucosal inflammation and fibrotic tissue remodelling. Phase 2 trial of first-generation anti-TL1A antibodies, such as tulusokibart and Afimkibart, have reported meaningful remission and endoscopic improvement. Their intravenous dosing and potential immunogenicity, however, remain concerns. This review looks at the epidemiology and socioeconomic burden of IBD, the immunological and genetic basis of the disease, and the molecular biology of TL1A and its therapeutic blockade. We then focus on ABS-101, a fully human anti-TL1A antibody created with AbSci's generative AI platform and taken from target identification to a clinical candidate in about 14 months. Preclinical work, including a 13-week primate toxicology study, suggests high potency, low immunogenicity, a long half-life and subcutaneous bioavailability. A first-in-human Phase 1 trial began in 2025. Although clinical efficacy in patients is yet to be shown, ABS-101 illustrates how AI-guided design could speed up and streamline biologic drug development in IBD.

1. INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a collection of chronic, immune-mediated gastrointestinal disorders characterized by a relapsing-remitting course of complications such as strictures, fistulae, abscesses, and colorectal cancer. Although CD and UC

differ in anatomical distribution and histology (Fig. 1), both share similar pathogenic elements, including gut microbiome alteration, genetic vulnerability, dysregulated mucosal immunity, and environmental triggers[1], [2]. A central driver of persistent inflammation and fibrosis in IBD is the

pathway formed by tumor necrosis factor-like ligand 1A (TL1A, encoded by TNFSF15) and its receptor death receptor 3 (DR3, encoded by TNFRSF25). TL1A, produced by epithelial and immune cells, binds to DR3 on T cells and other leukocytes to amplify Th1/Th17 responses and promote fibroblast activation, thereby driving both chronic mucosal inflammation and tissue scarring. This positions TL1A as an attractive upstream target that may modify disease course rather than merely suppress active inflammation[3]. Current IBD treatments, such as steroids, mesalamine and immunomodulators, relieve symptoms but have a delayed onset and incomplete efficacy, and carry long-term side effects including osteoporosis, diabetes, infections, bone marrow suppression, hepatotoxicity, and lymphoma. Biologics that target tumor necrosis factor (TNF), integrins, and the IL12/23 pathway improve outcomes, but up to one-third of patients show primary non-response, up to half of initial responders

lose response over time, and these drugs are expensive and carry an increased risk of infection. Furthermore, current agents primarily control inflammation and are poorly effective in the prevention or reversal of fibrosis, so many patients experience repeated flares and need surgery.[4] 4]

Next generation therapies target the TL1A–DR3 axis in an effort to meet these needs. Absci Corporation (Vancouver, WA, USA) has developed a fully human anti-TL1A monoclonal antibody called ABS-101, which was designed using a generative artificial intelligence (AI) drug-design platform. In about 14 months, Absci went from target identification to a candidate in Phase 1, ABS-101, the first AI-designed antibody to enter clinical testing for IBD. Previous anti-TL1A antibodies have shown encouraging Phase 2 results, including significant clinical remission rates, endoscopic improvement and histologic healing rates, and acceptable safety profiles, such as tulisokibart (PRA023;

Merck) and afimkibart (PF-06480605/RVT-3101; Roche). However, their long-term use may be limited by dosing frequency and by the potential for immunogenicity, which remain to be defined in longer-term studies. This review focuses on ABS-101, the first AI-designed anti-TL1A antibody to enter clinical testing, and on what its

development path shows about AI-directed biologic design. We review the biology of the TL1A–DR3 pathway, current challenges in IBD therapy, the preclinical and early clinical data for ABS-101, its change in development status, and the broader implications of AI-directed antibody design for biologic drug development.[5], [6], [7], [8].

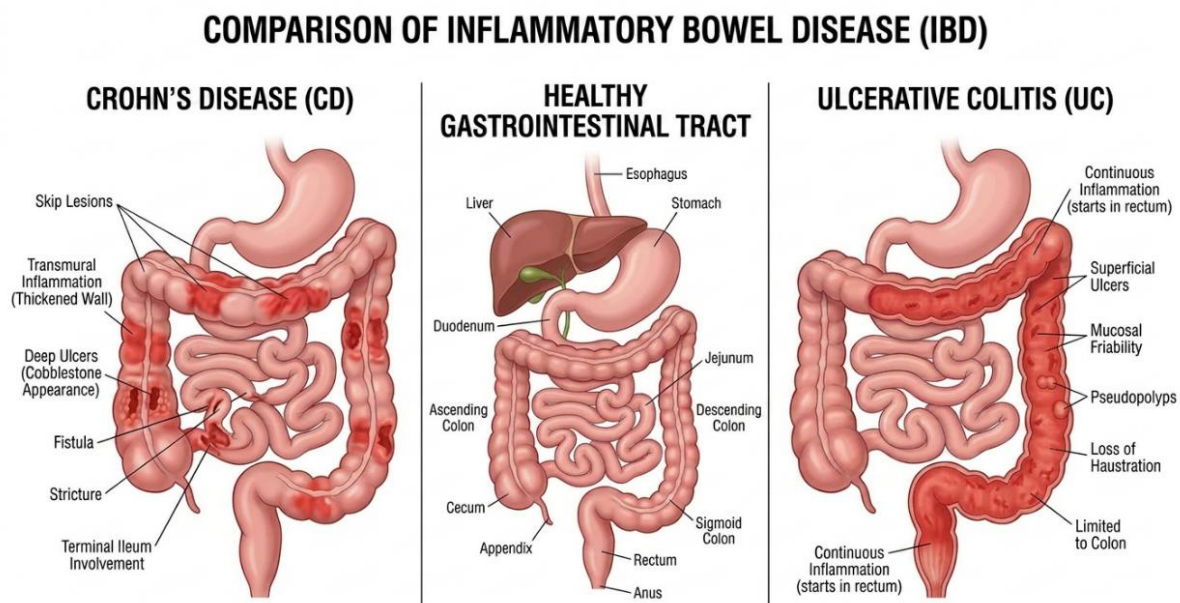


Fig. 1. Comparison of Crohn's disease, the healthy gastrointestinal tract and ulcerative colitis.

2. EPIDEMIOLOGY AND GLOBAL BURDEN OF IBD:

The latest Global Burden of Disease (GBD) 2021 estimates indicate that, in 2021, there were 375,140 new cases of inflammatory bowel disease (IBD) and 3,830,119

prevalent cases worldwide. The global age-standardized incidence rate (ASIR) was 4.4 per 100,000 population (95% UI: 3.9–5.2). The age-standardized prevalence rate

(ASPR) was 44.9 per 100,000 population (95% UI: 38.8–52.9). Compared with 1990, the absolute global burden increased substantially. The number of prevalent cases increased from approximately 2.17 million (2,170,243.3) in 1990 to 3.83 million (3,830,119) in 2021, whereas incident cases increased from 199,235.9 to 375,140 during the same period. Despite the increases in absolute case numbers, the global ASPR decreased from 48.0 to 44.9 per 100,000 population, while the ASIR increased modestly from 4.2 to 4.4 per 100,000 population. This study shows that the global population growth and demographic shifts, in addition to changes in the occurrence of the disease, also contribute to the rising absolute burden of IBD.[9]

For comparison, the GBD 2019 study estimated 4.90 million prevalent cases of IBD worldwide in 2019. This is higher than the GBD 2021 figure of 3.83 million, but the two numbers come from different estimation cycles with different methods

and data inputs, so the difference should not be read as a real fall in prevalence. The GBD 2021 analysis is the most recent estimate available for global IBD (Fig. 2).[10] Over the past two decades, IBD has become much more common across Asia, one of the world's fastest-growing regions for the condition. Once considered rare in the region, both ulcerative colitis and Crohn's disease are rising rapidly due to urbanization, westernized diets, industrialization, and better diagnoses. China carries the largest burden, with over 1.5 million people living with IBD in 2025. Other nations like India, Japan, and South Korea report similar sharp increases[11], [12].

2.1. Socio-economics Burden:

Direct health care costs, medical expenses, loss of productivity, informal care, and reduced quality of life due to the disease are the significant economic and socio-economic burden of IBD. In a claims database analysis of 52,782 patients in the United States, it was found that there was

an average annual cost of US\$22,987 per patient suffering from IBD versus the matched control of US\$6,956 per patient without IBD. The costliest year was the first year after diagnosis, where the costs were mainly associated with biologic therapy, emergency service use, relapsing disease, anemia, and mental health comorbidities [13]. Similarly, IBD is a major economic burden in Europe too. An analysis of a questionnaire of 3,687 patients of IBD from 12 European countries reported major indirect costs due to loss of productivity and informal care. Mean annual costs of absenteeism varied from €1,253 in Bulgaria to €7,915 in Spain; costs of presenteeism varied from €2,149 in Bulgaria to €14,524 in Belgium, whereas costs of informal care varied from €1,729 in Poland to €12,063 in Italy. [14] The annual median cost of illness was reported to be INR 43,140 (IQR: INR 34,357–51,031) for UC and INR

43,763.5 (IQR: INR 32,202–57,372) for CD in remission. The costs of active disease increased to INR 52,436.5 (IQR: INR 49,229–67,567.75) for UC and INR 72,145 (IQR: INR 49,447–92,212) for CD [15].

The burden is growing in Asia, where the incidence and prevalence of IBD have risen significantly. As in other regions, higher healthcare costs, absenteeism, presenteeism and decreased quality of life were reported in patients with IBD in Japan and South Korea, with productivity losses estimated at 15.3% and 10.5% of costs, respectively[16], [17]. Indirect costs are also significant: a meta-analysis estimated 16.4% absenteeism, 35.9% presenteeism and 39.4% overall work impairment. Disease prevention and control can lead to cost savings for health care systems, productivity losses, and burden on caregivers, and and better quality of life [18].

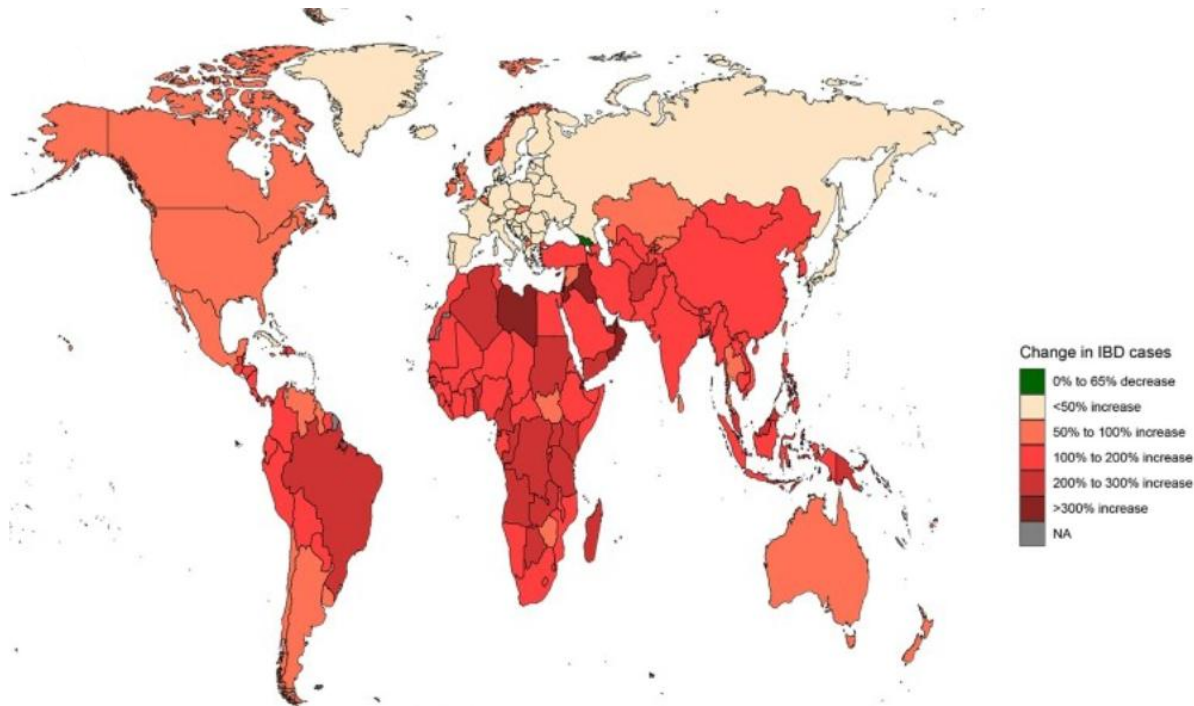


Fig. 2. Global prevalence of inflammatory bowel disease by country (cases per 100,000 population). [9]

3. MUCOSAL IMMUNITY AND HOMEOSTASIS:

The gastrointestinal tract, the largest immune organ in the human body, is continuously exposed to commensal microbes, potential pathogens, and food antigens. Under normal conditions, intestinal homeostasis is maintained through coordinated interaction between intestinal epithelial barrier, innate pattern recognition, and adaptive immune tolerance, involving intestinal epithelial cells, goblet cells, Paneth cells, dendritic cells, macrophages, innate lymphoid cells

(ILCs), and regulatory and effector T lymphocytes. Defects in the intestinal barrier allow bacteria and luminal antigens to enter the lamina propria, triggering abnormal innate and adaptive immune activation. The resulting chronic inflammation causes tissue damage, increased disruption of the epithelial barrier, and recruitment of immune effector cells (Fig. 3)[19].

CD is characterized by transmural inflammation, granuloma development, and involvement of any part of the gastrointestinal system, particularly the

colon and terminal ileum. The inflammatory response is primarily driven by Th1 and Th17 pathways, with increased production of IFN- γ , TNF- α , IL-17 and IL-22. Excessive secretion of IL-12 and IL-23 by dysregulated macrophages and dendritic cells promotes Th1 and Th17 differentiation, respectively, and these cells further amplify intestinal inflammation through cytokine secretion. TNF- α contributes to endothelial activation, barrier failure, and epithelial apoptosis. UC is confined to the colon and rectum and presents with continuous mucosal inflammation extending from the rectum proximally. Although traditionally characterized by a Th2-type immune response involving IL-4, IL-5, and IL-13, recent evidence also implicates Th1, Th17, and innate immune pathways. Neutrophil infiltration into intestinal crypts leads to crypt abscesses formation, while activated macrophages, natural killer T cells, and ILC2s further intensify inflammation,

resulting in bleeding, ulceration, and epithelial erosion[20].

A major long-term complication of Crohn's disease is intestinal fibrosis, which affects approximately 30–50% of patients and can lead to strictures and bowel obstruction. Unlike inflammation, established fibrosis is virtually irreversible, and there is no approved anti-fibrotic treatment. Fibrosis develops through persistent activation of intestinal myofibroblasts and sub-epithelial fibroblasts by mediators including TGF- β , IL-33, TNF- α and TL1A. Through its interaction with death receptor 3 (DR3), TL1A promotes fibroblast activation, proliferation, collagen synthesis and extracellular matrix deposition, driving tissue remodeling and stricture formation. Consequently, the TL1A/DR3 signaling pathway has emerged as a promising therapeutic target, with the potential to address both inflammation and fibrosis[21], [22].

Pathophysiology of Inflammatory Bowel Disease (IBD)

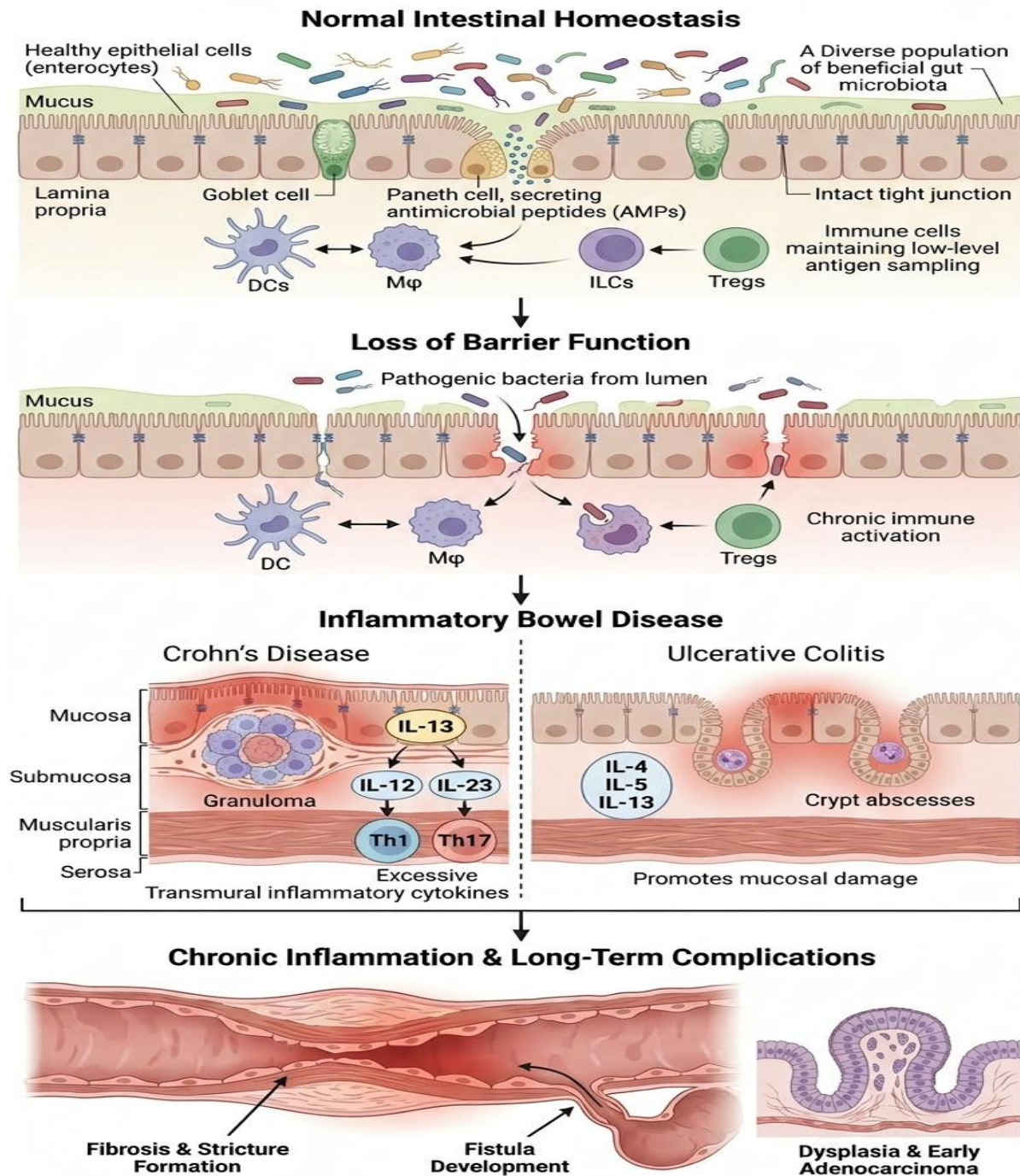


Fig. 3. Pathophysiology of inflammatory bowel disease.

4. FACTORS INVOLVED IN IBD DEVELOPMENT

4.1. Genetic and Environmental Factors:

IBD develops through a complex interaction between genetic susceptibility and environmental exposures. Genome-wide association studies (GWAS) have identified more than 200 susceptibility loci, including TNFSF15 (TL1A), ATG16L1 (autophagy pathway), IL23R (Th17 pathway), and NOD2 (Table 1). NOD2

mutations impair bacterial recognition and innate immune defense, while HLA-DR and HLA-DQ alleles are strongly associated with UC. Among environmental factors, a Western diet high in processed foods, refined sugars and saturated fats but low in fruits, vegetables and dietary fiber is one of the main risk factors. Reduced microbial exposure during childhood, as proposed by the hygiene hypothesis, may also contribute to IBD development [23].

Table 1. Major genetic variants associated with IBD and their biological functions and clinical significance [24], [25], [26], [27], [28]

Gene	Major biological function	Example variant	Clinical significance
TNFSF15	Encodes TL1A; promotes inflammatory signaling through DR3	rs6478108, rs7869487 and haplotypes	Disease susceptibility; some variants associated with complicated CD
NOD2/CARD15	Intracellular bacterial sensing and innate immune signaling	R702W, G908R, L1007FS	Major CD susceptibility gene; effects strongly ancestry-dependent
ATG16L1	Autophagy and intracellular bacterial handling	rs2241880 (T300A)	Impaired autophagy/host-microbe interaction
IL23R	IL-23 receptor; regulates Th17/IL-23 immune pathway	rs11209026 (Arg381Gln)	Alters IL-23/Th17 signaling; the Arg381Gln variant is protective against IBD
HLA class II	Antigen presentation to CD4 ⁺ T cells	HLA-DRB1/HLA-DQB1 alleles	Strong disease/phenotype associations, particularly UC

STAT3	Cytokine signaling/transcription	Multiple regulatory variants	Regulates IL-6/IL-23-related immune responses
PTGER4	Prostaglandin E2 receptor signaling	rs4613763 etc.	Mucosal immune and epithelial responses

4.2. TNFSF15 variants in IBD:

TL1A, coded by TNFSF15, is a highly significant susceptibility gene in inflammatory bowel diseases (IBD) especially in Crohn's disease (CD). Several SNPs such as rs4263839, rs3810936, rs6478108, rs6478109, and rs7869487 have been implicated in IBD but their associations may be population-specific. The SNPs in TNFSF15 have been shown to confer susceptibility to CD in Japanese patients and have been examined in other populations as well [28], [29].]. Most of these SNPs affect TNFSF15/TL1A expression but not the sequence of the protein itself. The risk allele in rs6478108 has been found to increase TNFSF15 mRNA expression and membrane expression which can potentiate inflammation via TL1A-DL3 pathway.

SNP rs6478109 has been found to be closely linked to rs6478108 and may thus be part of a risk haplotype. [30], [31]. TNFSF15 variants have also been associated with clinical phenotypes of CD. In 906 Korean patients, rs6478108 was associated with intestinal stricturing and penetrating complications, whereas rs4574921 was associated with perianal fistulas [32]. These findings suggest that TNFSF15 variants may influence disease phenotype and therapeutic outcomes; however, their clinical utility remains investigational and requires validation in larger, prospective and ethnically diverse cohorts.

4.3. Gut Dysbiosis and Immune Dysregulation:

IBD is associated with the gut microbiome's composition and function (dysbiosis),

characterized by reduced microbial diversity, loss of beneficial bacteria such as *Faecalibacterium prausnitzii* and *Roseburia hominis*, and expansion of potentially harmful species including adherent-invasive *Escherichia coli* (AIEC). These changes promote barrier dysfunction and chronic intestinal inflammation. At the immune level, defective innate immunity, impaired autophagy, excessive Th1 and Th17 responses, and inadequate regulatory T-cell function result in persistent inflammation driven by cytokines such as TNF- α , IL-6, IL-12, IL-23, IL-17A, IFN- γ , and TL1A, which are key therapeutic targets in IBD[33], [34].

5. MOLECULAR BIOLOGY OF THE TL1A/DR3

5.1. TNFSF15 Gene structure and genetic variants:

TL1A (tumor necrosis factor-like ligand 1A), first identified in 2002, is encoded by the TNFSF15 gene located on chromosome 9q32. The gene produces TL1A, a 251

amino acid cytokine belonging to the TNF superfamily. Genetic studies have identified single nucleotide polymorphisms (SNPs), including *rs4263839*, *rs4979462*, *rs3810936*, *rs6478108*, and *rs6478109*, that are associated with increased risk of CD and UC. Certain variants are linked not only to disease susceptibility but also to more aggressive disease behavior, including stricturing and earlier bowel surgery[35].

5.2. Structure and Expression of TL1A and DR3:

TL1A is a type II transmembrane protein with a short cytoplasmic domain, a single transmembrane segment and an extracellular domain that contains a TNF homology domain at the C terminus. The extracellular domain comprises about 192 amino acids, forms a homotrimer and adopts the jelly-roll β -sandwich fold typical of the TNF superfamily. This trimeric extracellular architecture is the surface to which the receptor or a therapeutic antibody binds, so preserving conformational epitopes is important for blocking activity

(Fig. 4). TL1A exists in two forms, membrane-bound (mTL1A) and soluble (sTL1A). mTL1A is a biologically active precursor that can be cleaved by matrix metalloproteinases to produce sTL1A, which is also biologically active and can activate DR3. Both forms can trigger production of inflammatory cytokines, so both are targets of interest for anti-TL1A antibodies [34]. Under normal conditions, TL1A expression is low but is markedly increased in intestinal macrophages, dendritic cells, endothelial cells, infiltrating lymphocytes, and plasma cells. The

functional receptor for TL1A is Death Receptor 3 (DR3; TNFRSF25), a type 1 transmembrane receptor containing extracellular cysteine-rich domains and an intracellular death domain. DR3 is predominantly expressed on activated T cells, regulatory T cells, natural killer cells, and innate lymphoid cells (ILCs). Its expression is significantly increased in inflamed intestinal tissue. The soluble receptor DcR3 acts as a natural antagonist by binding TL1A and limiting TL1A/DR3 signaling [36], [37], [38].

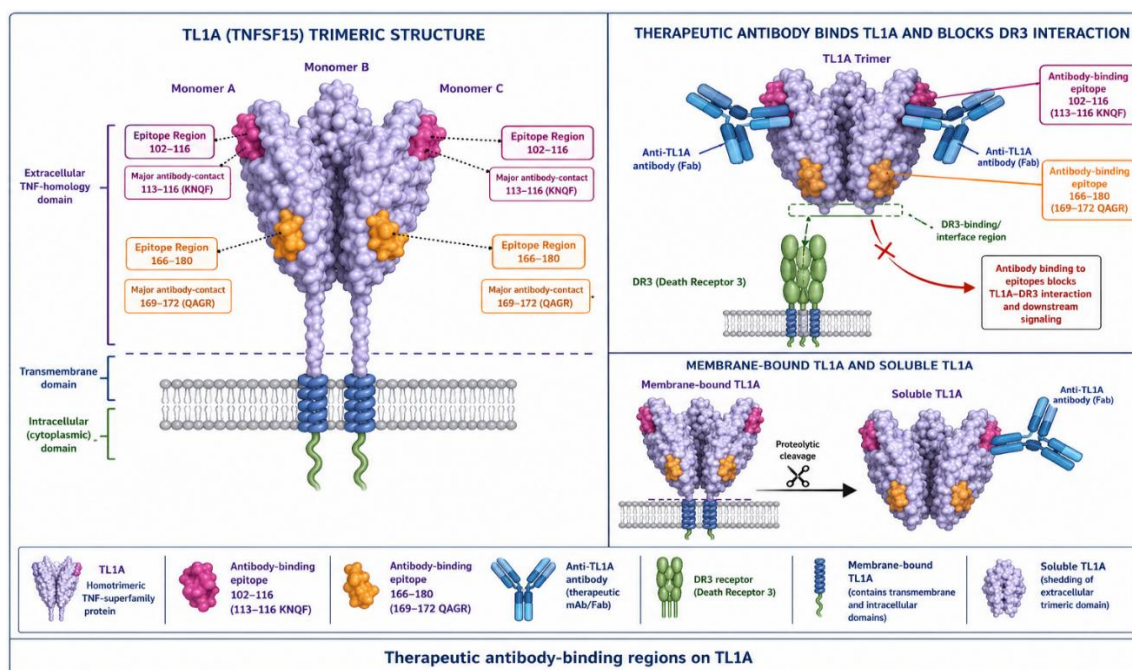


Fig. 4. Structure of TL1A and antibody-binding regions that block the TL1A–DR3 interaction. [39]

5.3. TL1A/DR3 Signaling pathways:

Binding of TL1A to DR3 recruits the adaptor protein TRADD, initiating downstream signaling. The major pathway activates RIP1, TRAF2, NF- κ B and MAPK, leading to production of pro-inflammatory cytokines such as TNF- α , IL-6 and IL-8 and promoting Th1, Th17 and Th9 responses. The signaling enhances production of IFN- γ , IL-17, IL-21 and IL-9, contributing to chronic intestinal inflammation. Under specific cellular conditions, DR3 can also activate a pro-apoptotic pathway through recruitment of FADD and activation of caspase-8, leading to programmed cell death. The inflammatory signaling can engage JAK/STAT pathways to further enhance immune-cell activation and maintain chronic intestinal inflammation. Beyond

inflammation, chronic TL1A–DR3 stimulation could also promote intestinal fibrosis through cross-talk with the TGF- β /SMAD pathway. TGF- β activates fibroblasts and induces myofibroblast differentiation and extracellular-matrix deposition, which are implicated in intestinal-wall remodeling and stricture. TL1A signaling could therefore contribute to chronic immune activation as well as tissue remodeling and fibrosis. Fig. 5 shows the TL1A→DR3 pathway with its NF- κ B and apoptotic branches; the JAK/STAT and TGF- β /SMAD links described here are not drawn. The balance between pro-inflammatory and apoptotic signaling depends on the cellular environment and the expression of regulatory proteins [32], [40], [41].

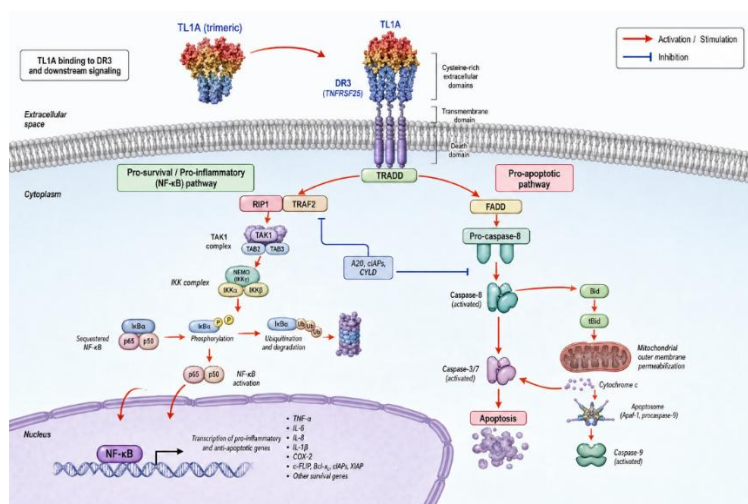


Fig. 5. TL1A/DR3 signaling pathway.

6. ANTI-TL1A ANTIBODY THERAPY: RATIONALE AND MECHANISM OF ACTION

6.1. Therapeutic rationale for TL1A blockade:

The scientific basis of anti-TL1A therapy in IBD is supported by convergent evidence from human genetics, translational immunology and preclinical animal models. First, several TNFSF15 variants are established susceptibility loci for IBD in ethnically diverse groups, directly implicating TL1A signaling in pathogenesis. Second, TL1A and DR3 are markedly more highly expressed in inflamed IBD tissue than in non-inflamed

mucosa or healthy controls, and their expression correlates with disease activity. Third, transgenic mice that express TL1A in lymphoid or myeloid compartments spontaneously develop ileitis and intestinal fibrosis resembling human CD, and anti-TL1A antibody treatment prevents colitis and reverses fibrosis in several murine models. TL1A is also an attractive target because it amplifies various T helper cell responses rather than acting through a single effector pathway. TL1A/DR3 signaling augments Th1, Th2, Th9 and Th17 responses and innate lymphoid cell subsets, so TL1A blockade is a broad intervention that can inhibit several inflammatory pathways at once. This

contrasts with more selective cytokine inhibitors (for example, anti-IL-12/23, which inhibits only Th1/Th17 pathways, or anti-IL-4/13, which inhibits only Th2 pathways) and may contribute to the clinical effect of anti-TL1A agents in CD and UC. In addition, inhibition of direct DR3 signaling on fibroblasts could give anti-TL1A therapy an anti-fibrotic effect, addressing a major unmet need that existing IBD therapies do not meet[41].

6.2. Anti-TL1A monoclonal antibodies overview:

Anti-TL1A monoclonal antibodies are humanized or fully human immunoglobulin G (IgG) antibodies that specifically bind TL1A with high affinity and specificity, preventing its binding to DR3 and, thus, inhibiting downstream pro-inflammatory and pro-fibrotic signaling. The main mode of action is steric blockage of the TL1A–DR3 interaction, which suppresses Th1 and Th17 differentiation, reduces production of pro-inflammatory cytokines (IFN- γ , TNF-

α , IL-17), supports regulatory T-cell function and inhibits fibroblast activation and collagen production (Fig. 6). Several anti-TL1A antibodies are in clinical development for IBD. Tulisokibart (previously PRA023) was developed by Prometheus Biosciences, which Merck acquired in 2023; it is a humanized IgG1 kappa monoclonal antibody that binds membrane-bound and soluble TL1A with high affinity and specificity.[42] Afimkibart (PF-06480605/RVT-3101) was originally developed by Pfizer, licensed to Roivant's subsidiary Telavant and has been held by Roche since its acquisition of Telavant in 2023; it has completed Phase 2b trials and is in Phase 3 development. Duvakitug (TEV-48574), developed by Teva and Sanofi, was evaluated in a Phase 2b study (RELIEVE UCCD) in both UC and CD. ABS-101, the focus of this review, is a next-generation candidate designed with generative AI to improve on the pharmacological profile of first-generation agents[43].

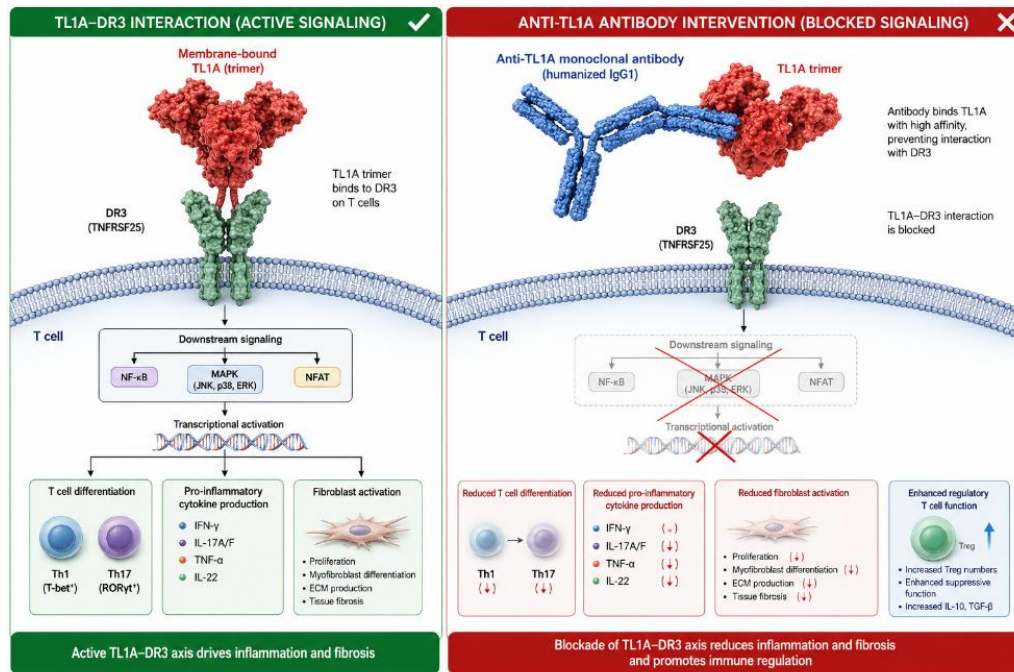


Fig. 6. Mechanism of action of anti-TL1A antibody therapy.

6.3. Phase 2 clinical evidence: first-generation anti-TL1A antibodies.

The ARTEMIS-UC Phase 2 trial compared Tulisokibart with placebo in patients who had moderately to severely active UC and who had not responded to glucocorticoids or advanced therapies. Patients with a TNFSF15 biomarker indicating a higher likelihood of response showed significantly better clinical remission, endoscopic improvement, histologic improvement, and mucosal healing at 12 weeks compared with placebo. The TUSCANY-2 phase 2b trial assessed Afimkibart (PF-06480605) in

moderately to severely active UC. Afimkibart achieved higher rates of clinical remission and endoscopic improvement than placebo and demonstrated a favorable safety profile. Biopsy analyses also showed reduced expression of genes associated with fibrosis and extracellular matrix remodeling, providing the first clinical evidence of the anti-fibrotic effects of TL1A inhibition[44], [45]. Duvakitug (TEV-48574) was tested in the RELIEVE UCCD Phase 2b trial, which included both UC and CD. The study demonstrated clinical efficacy and good safety during induction therapy in both diseases. Overall,

these Phase 2 studies support the mechanism of action, clinical efficacy and short-term safety of anti-TL1A antibodies, establish TL1A as a promising therapeutic target in IBD and have led to Phase 3 development[46].

7. ABS-101: DEVELOPMENT, MECHANISM, AND CLINICAL TRIALS

7.1. Absci and Integrated Drug Creation Platform:

Absci Corporation (NASDAQ: ABSI) is a biotechnology company headquartered in Vancouver, Washington, with an AI research presence in New York and an innovation center in Zug, Switzerland. Its Integrated Drug Creation™ platform combines generative artificial intelligence with high-throughput synthetic biology and wet-laboratory validation to support iterative antibody design and optimization. The platform is structured around a data-to-design-to-validation cycle in which experimentally generated biological data

are used to train AI models, which subsequently generate or optimize antibody sequences for experimental testing. Two components of this platform were reported by Absci in the development of ABS-101: de novo antibody design and AI-guided lead optimization. In the de novo design process, the company uses a target antigen and selected epitope to generate novel antibody sequence variants without relying on an existing antibody as the starting template. For ABS-101, Absci reported that its de novo generative AI model was used to design antibodies against a selected TL1A epitope, after which AI-based lead optimization was applied to further refine candidate properties [46,47]. The company describes its multiparametric lead-optimization approach as simultaneously considering characteristics including affinity, potency, specificity, developability, manufacturability, safety-related properties, and pharmacokinetic characteristics [8], [47], [48].

7.2. Development of ABS-101:

ABS-101 was developed starting with an in-depth target analysis of TL1A, defining the molecular basis of its involvement in IBD pathogenesis and the most important therapeutic needs of a best-in-class anti-TL1A antibody. These criteria, which together formed the target product profile, included:

- (i) high affinity and potency to TL1A;
- (ii) capability to bind both monomeric and trimeric isoforms of TL1A;
- (iii) low risk of immunogenicity in comparison with first-generation agents;
- (iv) long pharmacokinetic half-life that supports infrequent dosing;
- (v) high subcutaneous bioavailability for patient convenience; and
- (vi) favorable developability and manufacturability.

Absci's de novo AI model was used to design antibodies directed at a specific epitope on TL1A, with the aim of achieving high potency and low immunogenicity,

both of which depend partly on the binding interface between antibody and antigen (Fig. 7 shows a Schematic representation of ABS-101, an AI-designed anti-TL1A antibody, illustrating antibody architecture and proposed interaction with TL1A. The representation is illustrative and does not depict an experimentally determined three-dimensional structure of ABS-101). According to Absci, the model generated millions of antibody lead sequences by sampling interface contacts across the antigen surface, and these were then characterized experimentally. A lead optimization model then refined the best candidates, balancing the desired pharmacological and developability properties. Three leads met the target product profile: all three showed high affinity and potency in cell-based assays, bound both TL1A monomer and trimer, had favorable developability profiles and a long half-life. The company also reported that each of the three matched or exceeded the potency of the comparator anti-TL1A

molecules (tulisokibart/PRA023 and afimkibart/RVT-3101) in several biophysical and functional assays. The development candidate was selected on the

best combined profile of binding affinity, in vitro potency, mouse pharmacokinetics, developability and manufacturability[37], [49].

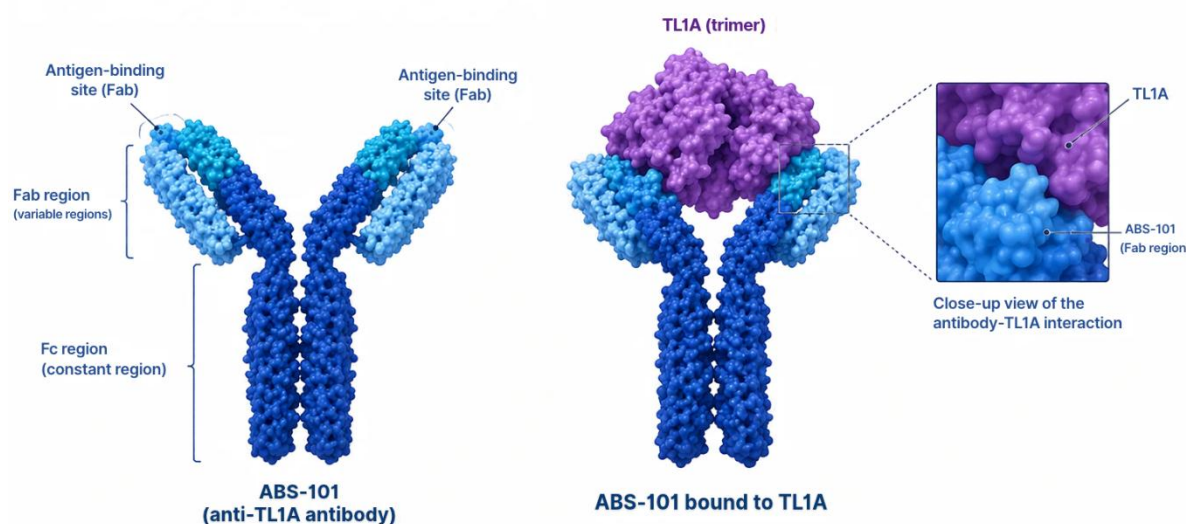


Fig. 7. Schematic representation of ABS-101, an AI-designed anti-TL1A antibody, illustrating antibody architecture and proposed interaction with TL1A.

7.3. Preclinical profile of ABS-101:

Absci has reported the following preclinical results for ABS-101:

- **High Affinity and Potency:** ABS-101 binds TL1A with sub-nanomolar affinity (KD). In cellular potency assays it inhibited TL1A-mediated cytokine production as well as or better than reference anti-TL1A molecules at similar concentrations. Inhibiting both monomeric and trimeric TL1A may be

relevant because different cell types can respond selectively to different TL1A forms.

- **Pharmacokinetics and Pharmacodynamics:** ABS-101 was well tolerated in a 13-week Good Laboratory Practice (GLP) toxicology study in cynomolgus monkeys, with no safety concerns reported. Non-human primate (NHP) pharmacokinetic/pharmacodynamic

(PK/PD) studies showed prolonged target occupancy after single and repeated dosing, consistent with the extended half-life built into the molecule. Target engagement was dose-dependent with a plateau at higher doses and exceeded that of competitor molecules at a comparable dosing regimen, which supports a possible dosing interval of 8 to 12 weeks or longer.

- **Immunogenicity:** Low immunogenicity was a design goal for ABS-101. In an in vitro THP-1 cell assay of TL1A immune-complex internalization, ABS-101 showed less internalization than a comparator molecule with a high clinical anti-drug antibody (ADA) rate. A lower tendency to induce ADAs could translate into more durable efficacy during long-term therapy, but this has not been shown in patients.
- **Subcutaneous Bioavailability:** In NHP studies ABS-101 showed high

bioavailability after subcutaneous administration, supporting subcutaneous delivery. Compared with intravenous infusion, subcutaneous dosing is more convenient, can improve adherence and may improve quality of life.[8], [47], [48]

7.4. Role of artificial intelligence in the design of ABS-101

Generative AI is a step toward computational design of biologics. Conventional antibody discovery relies on animal immunization or display systems (phage display, yeast display) to generate libraries of antigen-binding molecules, which are screened for the desired properties and improved through repeated rounds of mutagenesis. This process is slow, is limited in its ability to engineer several properties at once and depends heavily on the diversity of the starting library.

The generative AI approach of Absci treats antibody design as a generative problem:

given the desired functional and physical characteristics (epitope specificity, affinity, immunogenicity risk, half-life, developability), the AI model generates sequences that are expected to meet these criteria. The de novo model uses deep generative neural networks, which are similar in architecture to large language models but are trained using protein sequence and structure information, to sample the large space of possible antibody sequences and find the ones that are most likely to meet the desired product profile[36]. The synthetic biology wet lab then tests the AI predictions quickly and produces new data that are used to refine the models. While generative AI has the potential to facilitate biologic discovery at a faster rate, there are still several hurdles for AI-generated antibodies to become a standard part of clinical products. Some AI models work in a “black box” fashion, which can make them difficult to explain, making it hard to understand why a specific antibody sequence, structure, or target

interaction was chosen. Another issue is reproducibility, as the training sets, model architectures, parameters, and computation pipeline can vary and lead to different candidate molecules[50]. Therefore, more transparency should be provided regarding training data, model validation, sequence generation processes, and experimental verification when performing regulatory evaluation[51]. Unpredicted sequence liabilities, which include immunogenicity, aggregation, or diminished developability, may also occur as a result of generative AI. Therefore, AI-generated candidates need to undergo a series of experiments, clinical trials, pharmacological tests, and toxicology tests before they can be used in therapy[52].

According to Absci, this approach allowed ABS-101 to be designed for several features at the same time. Low immunogenicity was pursued by directing the antibody to an epitope intended to reduce immune-complex formation and ADA production, and the prolonged half-

life by optimizing the Fc region and biophysical characteristics [47] A main advantage of the generative approach is the simultaneous optimization of several properties in one discovery campaign, which is difficult with traditional sequential optimization.[37], [49]

7.5. ABS-101 Phase 1 clinical trial and current status:

On May 13, 2025, Absci announced that the first healthy volunteers had been dosed in a Phase 1 first-in-human trial of ABS-101, which moved the company into clinical-stage development and made ABS-101 the first AI-designed antibody to enter human trials for IBD. The trial is registered as ACTRN12625000212459p. The Phase 1 trial was a randomized, double-blind, placebo-controlled, single ascending dose (SAD) study of the safety, tolerability, pharmacokinetics and pharmacodynamics of ABS-101 in healthy adult volunteers. The registry lists about 40 healthy adults, subcutaneous injection, randomization to ABS-101 or placebo, a primary endpoint of

safety and tolerability, and secondary endpoints of pharmacokinetics, pharmacodynamics and immunogenicity (ADA formation).

A healthy-volunteer SAD design is standard for a first-in-human monoclonal antibody study because it allows the safety and pharmacology to be characterized closely before patients with the target disease are treated. Key pharmacokinetic parameters include maximum concentration (C_{max}), area under the concentration–time curve (AUC), terminal elimination half-life (t_{1/2}) and subcutaneous bioavailability.

Pharmacodynamic endpoints measure target engagement, such as free and total serum TL1A, to test whether the prolonged target engagement seen in NHP studies is reproduced in humans at relevant doses. The immunogenicity assessment detects anti-drug antibodies against ABS-101.the desired long target engagement profile in NHP studies at clinically relevant dose levels. This immunogenicity test will

determine the presence of anti-drug antibodies against ABS-101.

AbSci reported interim Phase 1 results in November 2025, together with its third-quarter 2025 financial results. According to the company, ABS-101 showed an extended half-life compared with first-generation anti-TL1A programs, a favorable safety profile with no serious adverse events, and no apparent impact of ADAs on pharmacokinetics. The half-life advantage was reported against first-generation programs, not against next-generation anti-TL1A programs. The company also announced a strategic decision not to start additional later-stage trials of ABS-101 internally, to explore partnership and out-licensing opportunities, and to redirect resources to other programs, notably ABS-201. These statements come from a company press release. ABS-101 therefore has no efficacy data in patients with IBD, and any further development, including Phase 2 trials in ulcerative colitis or Crohn's disease and the fibrotic and

immune-mediated indications once proposed for TL1A blockade, would depend on a future partner.[53], [54]

7.6. Differentiation of ABS-101 from first-generation anti-TL1A antibodies:

Table 2 compares the intended features of ABS-101 with those of the first-generation anti-TL1A antibodies tulisokibart and afimkibart. Most ABS-101 characteristics are company-reported design features and preclinical findings, not clinical comparisons.

- **Binding profile:** According to AbSci, first-generation agents such as tulisokibart and afimkibart bind the trimeric form of TL1A, whereas ABS-101 binds both monomeric and trimeric forms. Broader coverage could matter in disease states where monomeric TL1A predominates, but any effect on clinical efficacy is untested.
- **Immunogenicity:** Anti-drug antibodies are a recognized concern for biologic therapies, including some anti-TL1A

antibodies. ABS-101 was designed for low immunogenicity, and in vitro assays showed lower immune-complex internalization than a comparator with a high ADA rate. Interim Phase 1 data reported no apparent effect of ADAs on pharmacokinetics, but whether this gives more durable responses than agents with higher ADA rates is unknown.

- **Administration route:** ABS-101 was designed for subcutaneous delivery. In the Phase 2 trials, tulisokibart induction

was given intravenously, but subcutaneous regimens are also being developed for first-generation agents, so route of administration alone is unlikely to be a lasting advantage.

- **Dosing interval:** Absci's non-human primate data suggest that a dosing interval of 8 to 12 weeks or longer may be possible. This has not been confirmed in patients, and the interim Phase 1 results do not establish a dosing interval.[55]

Table 2. Features of ABS-101 compared with first-generation anti-TL1A antibodies.

Feature	ABS-101	Tulisokibart and afimkibart
Binding profile	Designed to bind monomeric and trimeric TL1A (company-reported)	Reported to bind trimeric TL1A
Immunogenicity	Low immune-complex internalization in vitro; no apparent effect of ADAs on pharmacokinetics in interim Phase 1 data (company-reported)	ADAs reported for some anti-TL1A antibodies; rates depend on the agent
Route of administration	Subcutaneous	Intravenous induction in Phase 2 tulisokibart trials; subcutaneous regimens in development
Dosing interval	8 to 12 weeks or longer suggested by non-human primate data; not established in humans	Under evaluation in Phase 3 programs
Clinical status	Phase 1 in healthy volunteers completed; partner being sought	Phase 2 completed; Phase 3 programs under way

Since the late 1990s, the direction of IBD treatment has changed with the first anti-

8. DISCUSSION:

TNF biologics. Anti-TNF agents have delivered a significant benefit to moderate-to-severe disease patients, but their long-term results are not optimal: primary non-response rates of 20 to 30 percent, secondary loss of response in about half of initial responders over five years, and inability to reverse established intestinal fibrosis are critical unmet needs. One of the most promising recent advances in IBD therapeutics is the development of anti-TL1A therapies. TL1A acts as a co-stimulatory amplifier of several T effector and innate lymphoid cell responses rather than driving a single cytokine pathway. This wide immunological footprint offers theoretical advantages over more targeted cytokine inhibitors, particularly in an immunologically heterogeneous disease such as IBD. The finding that TNFSF15 is a genetic susceptibility locus across several ethnic groups further supports the target, because human genetic evidence is among the strongest indicators that a target is

relevant to disease pathophysiology.[37], [49]

The combined anti-inflammatory and anti-fibrotic potential of TL1A blockade could fill an important gap in IBD therapy. Intestinal fibrosis is an essentially irreversible complication of Crohn's disease with no approved drug treatment, so the potential of anti-TL1A agents to prevent fibrotic progression, supported by preclinical data and early biopsy findings from afimkibart trials, would be a significant step beyond current therapies. If this anti-fibrotic activity is confirmed in larger controlled studies, anti-TL1A therapy could change the natural course of Crohn's disease by reducing stricture formation and surgical resection. The ABS-101 program shows that generative AI can shorten early antibody discovery: Absci reports about 14 months from target selection to clinical candidate, compared with the four to six years often cited for conventional programs, while several properties were optimized together. This

speed applies to discovery, not to clinical success. Interim Phase 1 data showed an extended half-life and no serious adverse events, yet Absci chose not to take ABS-101 into later-stage trials itself, so whether AI-designed properties translate into a clinical advantage remains untested. The feedback loop between AI design and high-throughput wet lab testing allows exploration of antibody sequence space on a scale that is hard to reach with traditional methods[56].

ABS-101 was designed to address possible limitations of first-generation anti-TL1A agents, namely immunogenicity and the dosing frequency needed to maintain exposure. Its intended features were binding of both monomeric and trimeric TL1A, low immunogenicity and a longer dosing interval. These remain design goals supported by preclinical findings and limited interim human data. In principle, lower immunogenicity could sustain long-term response and allow retreatment in patients who have developed ADAs to

other biologics, and longer dosing intervals could reduce treatment burden and improve adherence. Genetically based biomarkers that predict response to anti-TL1A therapy, as shown in the ARTEMIS-UC trial of tulisokibart, point toward precision medicine in IBD. If TNFSF15-based patient selection proves sound, it could allow more tailored treatment, directing anti-TL1A therapy to patients most likely to respond and sparing others from ineffective treatment. Whether ABS-101 will be developed further now depends on a development partner, so biomarker-based selection for this molecule remains hypothetical[52].

9. FUTURE PERSPECTIVES:

Anti-TL1A antibodies such as tulisokibart, afimkibart and duvakitug are promising treatments for inflammatory bowel disease, and clinical trials in ulcerative colitis and Crohn's disease have given encouraging results[57], [58]. Phase 3 programs for several first-generation agents are under way, and their results, together with long-

term safety data and the first controlled data on fibrosis and stricture formation in Crohn's disease, will set the benchmark against which any newer molecule must be judged.

The outlook for ABS-101 itself has changed. After the interim Phase 1 results, Absci decided not to start later-stage trials internally and is seeking a partner. Whether ABS-101 reaches patients with IBD therefore depends on an external developer. Its proposed advantages (coverage of monomeric and trimeric TL1A, low immunogenicity, and an extended half-life that could support infrequent subcutaneous dosing) remain to be tested in patients. The interim data showed an extended half-life relative to first-generation programs, but no comparison with next-generation anti-TL1A programs was reported, and there are no efficacy data in IBD. Any Phase 2 development would need to show endoscopic healing, corticosteroid-free remission and sustained disease control in ulcerative colitis and Crohn's disease, with

particular attention to anti-fibrotic effects in Crohn's disease.

Biomarker-driven patient selection could improve outcomes for anti-TL1A therapy as a whole, since the link between TNFSF15 variation, TL1A expression, disease susceptibility and treatment response underpins precision-medicine approaches. TL1A blockade may also be relevant to other fibrotic and immune-mediated diseases, such as pulmonary fibrosis, liver fibrosis, rheumatoid arthritis, psoriasis and atopic dermatitis, although the evidence is preliminary. More broadly, ABS-101 is an instructive example of AI-enabled antibody discovery. It shows that AI can shorten the path from target to clinical candidate, and its fate shows that clinical and commercial success also depend on factors beyond the discovery stage. [57], [59].

10. CONCLUSION:

Inflammatory bowel disease is a growing global health problem with substantial

morbidity and few options for patients who do not respond to available biologics or who have fibrotic complications of Crohn's disease. TL1A, encoded by TNFSF15 on chromosome 9q32, is a clinically promising therapeutic target because of its central role in coordinating mucosal inflammation across several T helper and innate lymphoid cell pathways and its direct profibrotic action through DR3 signaling on intestinal fibroblasts. Phase 2 trials of tulisokibart (ARTEMIS-UC), afimkibart (TUSCANY-2) and duvakitug (RELIEVE UCCD) reported clinically meaningful remission and endoscopic improvement, together with early signals of anti-fibrotic activity. Absci Corporation created ABS-101 with its generative-AI-based Integrated Drug Creation platform as a next-generation anti-TL1A antibody designed to overcome limitations of first-generation agents by binding both monomeric and trimeric TL1A, with low immunogenicity and a long half-life. ABS-101 entered a first-in-human Phase 1 trial in May 2025, the first

AI-designed antibody to reach clinical testing in IBD. Interim results reported in November 2025 showed an extended half-life compared with first-generation anti-TL1A programs, a favorable safety profile and no serious adverse events, but Absci decided not to take ABS-101 into later-stage trials itself and is seeking a partner. These findings come from healthy volunteers and do not show efficacy in patients with IBD. Further clinical research would be needed to show whether the design features translate into benefits in disease activity, remission, safety and durability of response. Overall, AI-driven design is a promising way to speed the discovery of next-generation biologics, but it must be validated experimentally and, above all, in clinical development.

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