# Navigating IBD with Evotec: From Discovery to Cure

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## Introduction

Evotec is a life science company with a unique business model that delivers on its mission to discover and develop highly effective therapeutics and make them available to the patients. The Company's multimodality platform comprises a unique combination of innovative technologies, data and science for the discovery, development, and production of first-in-class and best-in-class pharmaceutical products. Evotec leverages this "Data-driven R&D Autobahn to Cures" for proprietary projects and within a network of partners including all Top 20 Pharma and over 800 biotechnology companies, academic institutions, as well as other healthcare stakeholders.

Evotec has strategic activities in a broad range of currently underserved therapeutic areas such as neurology, oncology, inflammation & immunology as well as metabolic, cardiovascular, renal and infectious diseases. Within these areas of expertise, Evotec aims to create the world-leading co-owned pipeline for innovative therapeutics and has to-date established a portfolio of more than 200 proprietary and co-owned R&D projects from early discovery to clinical development.

IBD is a collective term for a range of clinical phenotypes caused by chronic, idiopathic and remitting inflammation of gastrointestinal tract. Crohn's disease and ulcerative colitis are the two most common forms. Despite many advancements in the treatment of IBD, there remains a high unmet medical need to provide patients with an early intervention of highly effective therapy, preferably with curative potential.

Evotec is currently engaged in several drug discovery programs tackling various aspects of the disease such as restoration of epithelial barrier function, modulation of inflammation and intestinal fibrosis.

Given the heterogeneity of the disease, we actively invest into efforts leading to increased disease understanding and stratification of patients based on the disease endotypes.

## Our strategic starting points to co-create pipelines with partners in I&I

| Focus Area | Project | Approach | MoA | Indication space | Target validation | Hit ID-H2L | LO | Collaborator |
|---|---|---|---|---|---|---|---|---|
| Immuno-modulation | Target 1 | AI/ML & ligand/ structure driven design | *Gut selective immuno-modulation* | Gastroenterology | Lead compound optimization | | | Internal R&D |
| | Target 2 (TM-S063) | Blocking antibody | *Macrophages polarization & Th17 inhibition* | Gastroenterology Dermatology Rheumatology | Lead antibody optimization | | | Internal R&D |
| | Target 3 | Bi-specific antibody | *Immune cell modulation* | Gastroenterology SLE | Lead antibodies identified | | | Biotech |
| | Target 4 | FFmAb ($T_{EM}$ screen) | *Co-stimulatory receptor inhibition* | Rheumatology Gastroenterology Dermatology | Lead antibodies identified | | | Internal R&D |
| | Target 5 (KDE4) | Small molecule inhibitor | *NETosis & citrullination* | Rheumatology Gastroenterology Fibrotic diseases | Hit identification | | | Internal R&D |
| | Target 6 | Small molecule agonist | *Immune cell modulation* | Gastroenterology | Hit identification | | | Foundation |
| | Target 7 | Protein-protein interaction inh. | *Restoration of barrier function* | Gastroenterology | Hit identification | | | Foundation |
| | HPF screen | Phenotypic screen/transcriptomics | *Reversion of fibrosis* | Fibrotic diseases | Hit identification | | | Internal R&D |
| Tissue regeneration | Target 8 | Small molecule agonist | *Mucosal healing* | Gastroenterology | Hit to Lead | | | Academic bridge |
| | Target 9 | CAR-iNK | *Elimination of fibrogenic myofibroblasts* | Fibrotic diseases Gastroenterology | *In vitro* PoC | | | Internal R&D |
| | Target 10 | CAR-iMAC | *Elimination of fibrogenic myofibroblasts* | Fibrotic diseases Gastroenterology | *In vitro* PoC | | | Internal R&D |

PanOmics | iPSC cell therapy

**Legend:** Internal R&D programs are available for partnering. Evotec is open to broad range of collaboration models for Evotec's platforms and assets.

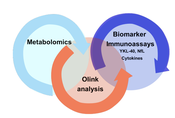
## Evotec's platforms for experimental characterization of human samples

**Within a pilot study, Evotec interrogates human samples from autoimmune disease (AID) patients – including IBD patients – for biomarker signatures, employing plasma and metabolomic analyses.**

Healthy volunteers (N=30) | IBD (CD N=7, UCC N=11) | Other AIDs (N=28)

**Evotec's human sample management** — Acquisition and aliquoting of human plasma samples, handling of clinical data

**Evotec's research expert teams**




| Measurement | | Platform application | |
|---|---|---|---|
| YKL-40 | Serum YKL-40 levels are significantly correlated with disease activity in Crohn's disease (CD) and ulcerative colitis (UCC)[1]. | MSD Sector SI6000 | High robust MSD platform |
| NfL | Neurofilament light chain (NfL) levels correlate with inflammatory disease activity in MS and may serve as therapeutic biomarker for autoimmune neurologic disorders[2,3]; NfL levels might be also affected in other autoimmune diseases such as IBD. | HD-X Simoa | High-sensitivity Quanterix platform |
| Cytokines | Cytokines play crucial roles in the pathogenesis of IBD and were identified as potential new targets for the therapy of intestinal inflammation[4]. | Luminex + Olink | Multiplexing platforms Luminex (bead-based) and Olink (based on Proximity Extension Assay (PEA) runs on fluidigm chips) |
| Metabolomics | Untargeted metabolomics | Metabolomic platform | Newly established platform |

1) Koutroubakis et al.; Int J Colorectal Dis. 2003. 2) Ning L, et al. PLoS One. 2022 3) Kammeyer et al.; Front Neurol. 2022. 4) Neurath; Nat.Rev.Immun. 2024

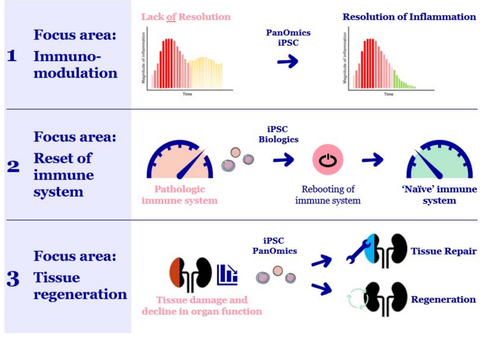
**Combining clinical data with experimental and leveraging data science approaches to identify potentially new biomarker signatures.**




## Evotec's approach to develop innovative and differentiated medicines

**I&I research focus areas for co-creation**

- Our focus is on three defined areas within the I&I space with high medical need and high probability for scientific and commercial success
- Our strategy is modality agnostic, utilizing Evotec's entire technology platforms for drug candidate development
- We are driving development of innovative I&I therapeutics through Evotec's PanOmics-driven drug discovery for precision medicine
- We believe that the cell therapy will have a major impact in I&I field, and we are building a portfolio of iPSC-derived immune cell product candidates




**Evotec's key expertise in autoimmune diseases enables development of I&I therapeutics for:**

**Gastroenterology**
- Ulcerative Colitis
- Crohn's Disease
- IBD

**Lung fibrosis**
- Idiopathic Pulmonary Fibrosis
- Interstitial Lung Disease

**Rheumatology**
- SLE, Lupus Nephritis
- RA
- Sjögren's Syndrome
- Ab-driven diseases

**Kidney fibrosis**
- Diabetic Kidney Disease
- Chronic Kidney Disease
- FSGS

**Dermatology**
- Psoriasis
- Atopic Dermatitis
- Alopecia
- Ab-driven diseases

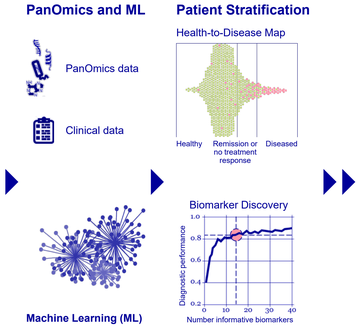
**Legend:** PanOmics: high performance Omics data generation; iPSC: iPSC-derived immune cell therapy

## First in class discovery starts with patient data

**Portfolio of molecular patient databases (MPD) and Health-to-Disease Maps and biomarker discovery**

EVOgnostic – Evotec's panOmics driven diagnostics is a comprehensive toolbox to successfully develop the right drug for the right patient at the right time

| Therapeutic Area | Patients |
|---|---|
| Chronic Kidney Diseases (CKD) | 12,000 |
| Immune Mediated Diseases | 3,000 |
| Metabolic Disease (Liver) | 2,000 |
| Healthy Controls | 1,500 |




**Evotec Opportunities**
- A.I./ML driven accurate patient stratification for better drug discovery with **pharma partners**
- Biomarker panels enabling partnerships with the **diagnostic industry and clinical laboratories**
- Companion diagnostics driving precision medicine in complex diseases e.g. kidney, cardiovascular and autoimmune diseases with **pharma and diagnostic partners**

**Legend:** Molecular patient database with immune-mediated diseases contains among others ~300 samples from Ulcerative colitis patients and ~300 Crohn's Disease patient samples.

## Efficacy models in IBD

- As many experimental models, also IBD models cannot fully recapitulate the disease features commonly seen in humans (genetic, environmental influences, gut microflora interactions..)
- Therefore, there is a need for multiple preclinical models that allow to reproduces some aspects of IBD: inflammation, leukocyte trafficking, breach of epithelial barrier integrity, T cell-mediated damages.

**Models routinely run at Evotec:**

| Colitis Models | MoA | Immune pathways involved |
|---|---|---|
| Acute and chronic **DSS** (UC) | Epithelial barrier defects | Innate immunity, M1 macrophages and neutrophils, Initially Th1, but later Th1/Th2 |
| Acute **TNBS** (CD) | Excessive effector cell responses and barrier defects | DTH-like response; Th1 (and possibly Th2) |
| **Anti-CD40** (UC) | Innate immunity defects | IL-12/IL-23-driven inflammation |
| **T cell transfer** or **IL10 KO mice T cell transfer** (CD) | Regulatory and effector T cell imbalance | Lack of CD45RBlow Tregs or lack of functional Tregs, IL-12/23-dependant Th1/Th17 |

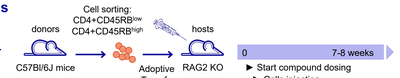
**Main readouts for intestinal inflammation:**
- Body weight loss
- Disease activity index
- Colon length, colon weight to length ratio
- Cytokines levels (plasma, colon, ileum)
- Histology scoring based on goblet cells loss, crypt structure, inflammation, hyperplasia. Several inflammatory and fibrosis markers in IHC (e.g., CD3+ cells)
- Flow cytometry: large panel (26 colors) in blood, spleen, colon, mesenteric lymph nodes, Peyer's patches.
- Microbiome analysis using shallow sequencing.

*Humanized mice for immune system or for microbiome can be used for different models.*

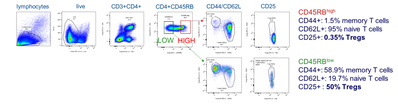
**Gold standard model: T cell transfer model of chronic colitis**

CD45RBlow and CD45RBhigh CD4+ T cells home to the intraepithelial and lamina propria compartments of both the small and large intestines.

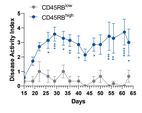
CD45RBhigh cells transfer induces colitis due to the absence of regulatory T-cell. CD45RBlow cells do not induce colitis.



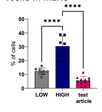

**Cell sorting gating strategy:**



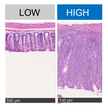

**Disease Activity Index**




**IL-17A among effector Tcells in MLNs**




**Colon – H&E staining**




## Conclusion

- We are advancing groundbreaking solutions for Inflammatory Bowel Disease (IBD), utilizing state-of-the-art technologies and platforms. Our primary focus lies in precision medicine and unique approaches. We aim to provide tailored, effective and minimally invasive treatments by considering each patient's unique characteristics.

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