**Intestinal Bowel disease (IBD)**

IBD is a group of inflammatory conditions of the small intestine and the colon. Crohn’s disease and ulcerative colitis are the principle types of IBD (Fig1 and 2).

![Fig.1 Inflammatory Bowel Disease subsets](http://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/small_large_intestine/crohns_disease.pdf)

![Fig.2 Anatomical distribution of Crohn's disease and ulcerative colitis (left panel). Anatomical distribution of Crohn's pathology in human patients (right panel).](http://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/small_large_intestine/crohns_disease.pdf)

**Fig.2** Anatomical distribution of Crohn’s disease and ulcerative colitis (left panel). Anatomical distribution of Crohn’s pathology in human patients (right panel). In **one-third of patients** with Crohn’s disease, the gross pathologic changes are limited to the **terminal part of the ileum** while about **40% of patients** have ileocolitis involving the **distal ileum and proximal colon**.

**TNFΔARE: a dual genetic model of spontaneous chronic arthritis and inflammatory bowel disease (IBD)**

**Model Description in Brief:**

The TNFΔARE model is a unique dual disease model closely resembling human arthritis and IBD pathologies. It offers an ideal preclinical evaluation platform of therapeutics in a complex disease setup that involves multiple cellular and molecular pathways that could be potential therapeutic targets.

- TNFΔARE mice develop spontaneous chronic arthritis and inflammatory bowel disease (IBD) with high reproducibility and 100% penetrance.
**Model Description in Detail:**

Deregulated mouse TNF expression in the \text{TNF}^{\Delta\text{ARE}} mice leads to the gradual development of spontaneous inflammatory polyarthritis and inflammatory bowel disease (1, 2).

The co-incidence of arthritis and IBD pathologies in the \text{TNF}^{\Delta\text{ARE}} mouse closely resembles the phenotype manifested in human spondyloarthropathies (3). The overall similarities with the human pathology as well as the high reproducibility and full penetrance of disease make the \text{TNF}^{\Delta\text{ARE}} model an attractive platform for the simultaneous evaluation of the efficacy of therapeutics in two different pathologies.

**Spontaneous Chronic Arthritis** in the joints of the \text{TNF}^{\Delta\text{ARE}} mice starts at 4-6 weeks of age and histological analysis of the ankle joints reveals inflammatory changes consistent with those observed in the human RA.

More specifically, histological features of the disease include synovial hyperplasia, polymorphonuclear infiltrates, pannus and fibrous tissue formation, subchondrial bone erosion and articular cartilage destruction.

As disease progresses, arthritis symptoms evolve from mild inflammation in the periarticular tissue and/or mild oedema to moderate and severe inflammation and pannus formation with superficial to in-depth cartilage and bone destruction (Fig.3).

![Fig.3 TNF^{\Delta\text{ARE}} arthritis progression with age](image-url)
Inflammatory Bowel Disease (IBD) pathology in the TNF$^{\Delta\text{ARE}}$ mice becomes evident at 6 weeks of age. Unlike any other mouse model of intestinal inflammation, and similar to Crohn’s disease patients, pathology in the TNF$^{\Delta\text{ARE}}$ mice manifests in the terminal ileum by the 6th week of age of the animals and pathology appears at the proximal colon at advanced ages of the animals. Moreover, histological analysis of the ilea reveals inflammatory changes similar to those observed in Crohn’s disease patients.

**Fig. 4** TNF$^{\Delta\text{ARE}}$ gut pathology closely resembles human IBD pathology.

More specifically, basic histopathological characteristics include villus blunting and submucosal inflammation with prevailing PMN/macrophage and lymphocyte aggregates and rudimentary granulomata.

Progressively, mucosal and submucosal infiltration takes place involving chronic as well as acute inflammatory cells including lymphocytes, plasma cells and polymorphonuclear cells. The inflammatory infiltrate eventually extends deep into the muscular layers of the bowel wall, with the typical characteristic of transmural inflammation (Fig.5).

**Fig. 5** TNF$^{\Delta\text{ARE}}$ Intestinal inflammation progression with age
Cellular pathways involved in the TNFΔARE arthritis and IBD pathology

- Key cellular and molecular pathways involved in the TNFΔARE pathology have been identified by crossing TNFΔARE mice to various knock-out mice as indicated in Table 1.

![Table 1](image)

*Table 1.* Genetic studies shed light on the role of specific cellular and molecular players in TNFΔARE pathology.

- A key player in the TNFΔARE pathology is the synovial fibroblast, a stroma cell with multiple roles in arthritis (Fig. 6).

![Fig. 6](image)

*Fig. 6* Critical roles of synovial fibroblasts in Arthritic Synovium
A cellular and molecular mechanism involved in TNF$^{ΔARE}$ Arthritis pathology is described in Fig. 7.

- TNFR1-mediated signaling in Synovial Fibroblast plays a leading role in the TNF$^{ΔARE}$ arthropathy

**Fig. 7** Cellular and molecular players in TNF$^{ΔARE}$ arthritis pathology.

A cellular and molecular mechanism involved in TNF$^{ΔARE}$ IBD pathology is described in Fig. 8.

- Myeloid-origin cells are crucial for the development of pathology

**Epithelium**
- Preferential accumulation and predominance of TNF and IFNγ-producing CD8αβ T-cells
- Early decrease of TCRγδCD8αα and TCRαβCD8αα T cells

**Lamina Propria**
- Increased Th17 responses
- IFNγ-producing CD8αβ T-cells

**Fig. 8** Cellular and molecular players in TNF$^{ΔARE}$ IBD pathology.

**References**

3. Armaka et al. JEM 2008 205:331
TNF\textsuperscript{ΔARE} used for the evaluation of therapeutics targeting IBD

\textbf{Fig.9} Representative TNF\textsuperscript{ΔARE} weight curve, joint and ilea histopathology data acquired with the negative and positive control treatments