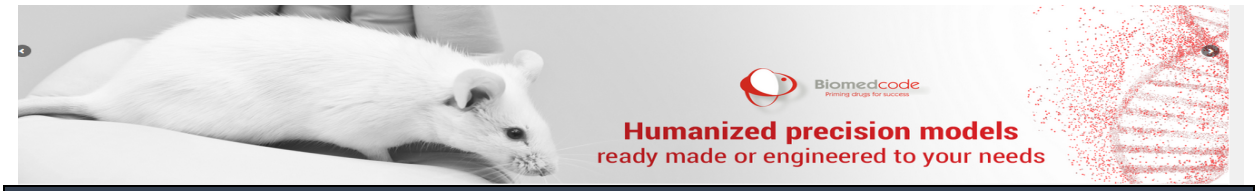

TNF$^{\Delta ARE}$ Dual Disease mouse model

White Paper

The Human Pathologies

Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) describes a group of disorders that involve chronic inflammation of the digestive tract with Chron's disease and Ulcerative Colitis being the most common pathologies. IBD usually involves severe diarrhoea, abdominal pain, fatigue and weight loss and pathological findings include mucosal, submucosal and transmural inflammation and tissue destruction.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a disease characterized by chronic inflammation of the joints associated with bone and cartilage destruction. RA is a severe burden to patients leading to disability, pain, severe impairment of quality of life, and even life threatening conditions resulting in significantly enhanced mortality.

The TNF-DARE dual disease mouse model

TNFΔARE mice develop spontaneous chronic arthritis and inflammatory bowel disease (IBD) with 100% penetrance

TNF$^{\Delta ARE}$ Model description

TNF$^{\Delta ARE}$ mice express deregulated mouse TNF that leads to the gradual development of spontaneous inflammatory polyarthritis and inflammatory bowel disease. The co-incidence of arthritis and IBD in the TNF$^{\Delta ARE}$ mouse closely resembles the phenotype manifested in human spondyloarthropathies.

TNF$^{\Delta ARE}$ Spontaneous Chronic Arthritis first becomes apparent at 3-4 weeks of age. Histopathological findings in the ankle joints include synovial hyperplasia, polymorphonuclear infiltrates, pannus and fibrous tissue formation, subchondrial bone erosion and articular cartilage destruction similar to those observed in the human RA.

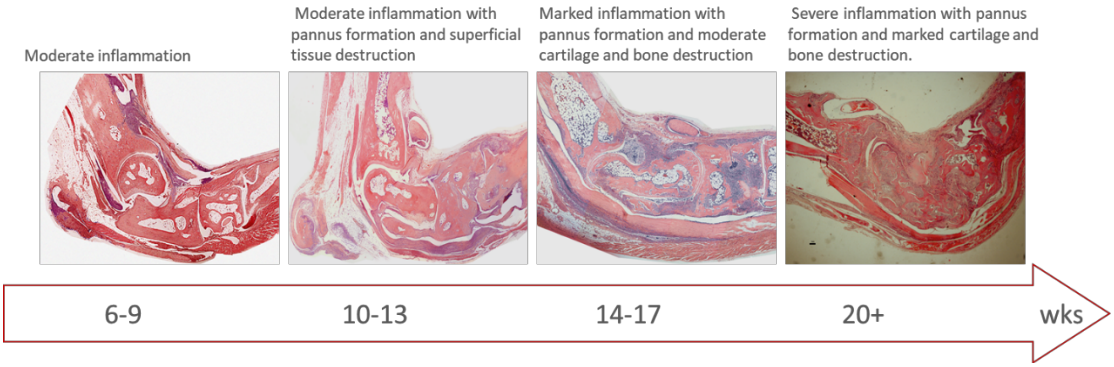

Fig.1 *TNF$_{\Delta ARE}$ arthritis progression evolves from mild inflammation in the periarticular tissue and/or mild oedema to moderate and severe inflammation and pannus formation with superficial to in-depth cartilage and bone destruction.*

34 Al. Fleming Str. | 16772 Vari (Athens) | T: +302109655366 | F: +302109654621
info@biomedcode.com | www.biomedcode.com

TNF$^{\Delta ARE}$ Inflammatory Bowel Disease becomes apparent at 6 weeks of age and, similar to human Crohn's disease, the pathology first manifests in the terminal ileum while in advanced stages pathology also appears at the proximal colon. Histopathological findings include villus blunting and submucosal inflammation progressing to mucosal and submucosal infiltration, eventually leading to transmural inflammation (Fig.2).

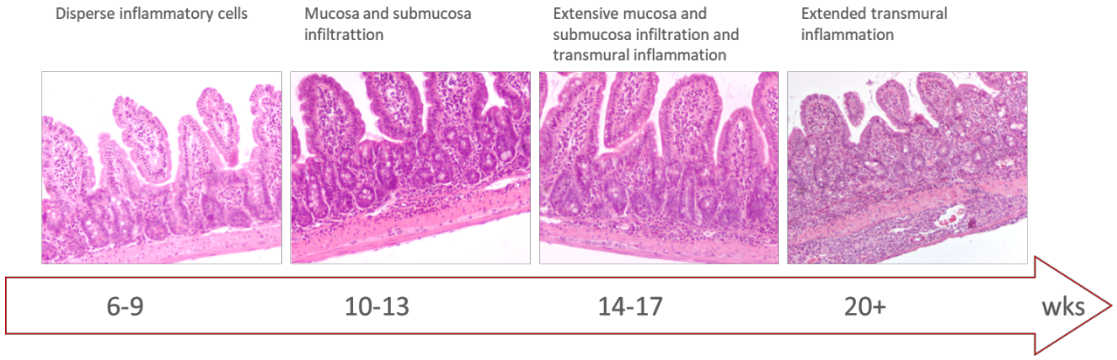

Fig.2 *TNF$_{\Delta ARE}$ Intestinal inflammation progression with age*

TNF$^{\Delta ARE}$ Pathological Cellular Pathways

Key cellular and molecular pathways involved in the TNF$^{\Delta ARE}$ pathology have been identified by crossing TNF$^{\Delta ARE}$ mice to various knock-out mice as indicated in Table 1.

Tnf$^{\Delta ARE/+}$

Crossed to the following knock-outs		***IBD***
RAG-1	Absence of mature T- and B-cells	Neutralized
CD4	Absence of CD4 cells	Exacerbated
β2M	Absence of CD8 T cells	Attenuated
TCRδ	Absence of TCRγ δ	Similar
μMT	Absence of B-cells	Similar
p40	Absence of IL12 and IL23	Attenuated
IFNγ		Attenuated
β7-integrin		Neutralized
CCR9		Similar
TNFRI		Neutralized
TNFRII		Attenuated
IL4		Similar
MK2		Exacerbated
JNK2		Delayed onset
Tpl2		Delayed onset

References

- Kontoyiannis D. et al. (1999) Immunity, 10, 387-398
- Kontoyiannis D. et al. , (2002) JEM, 196, 1563-74.

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Priming drugs for success

The TNF$^{\Delta ARE}$ Preclinical Platform

The TNF$^{\Delta ARE}$ mouse 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.

Study design

Preclinical drug efficacy is evaluated in a prophylactic regimen starting at 4 weeks of age upon disease initiation and typically lasts for 8 weeks.

Modes of andministration

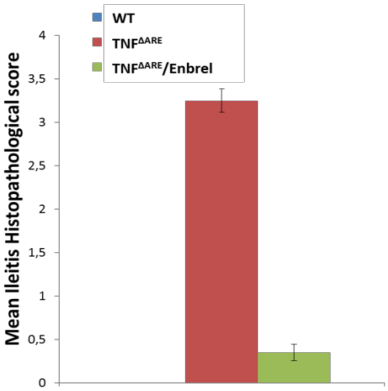
- intraperitoneal
- subcutaneous
- intraarticular

Read-out parameters

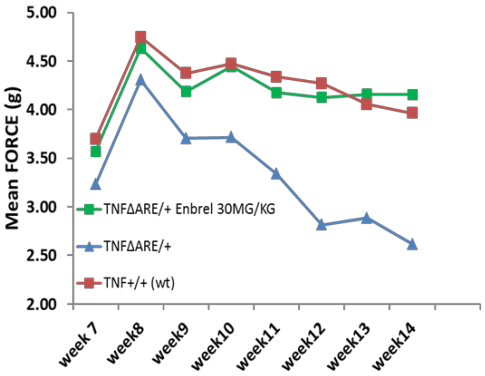
- body weight measurements
- grip strength measurements
- histolopathological arthritis evaluation of the joints
- histopathological intestine evaluation

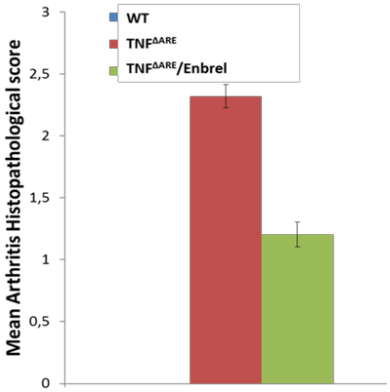
The TNF$^{\Delta ARE}$ Model Validation with anti-hTNF therapeutics

Inflammatory Bowel Disease



Arthritis





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