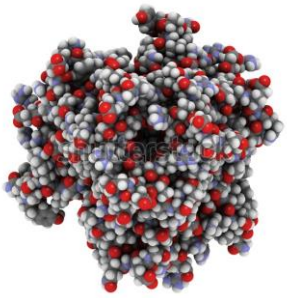
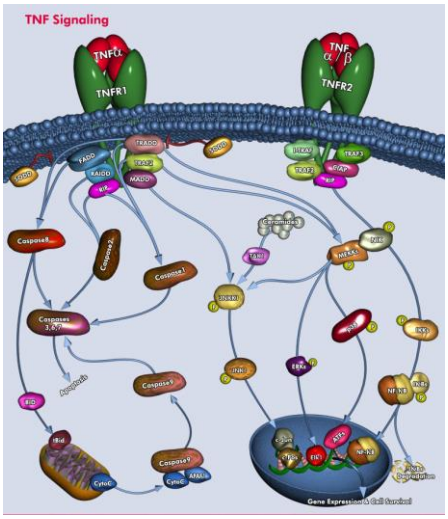
Biomedcode
Priming drugs for success

Tg5453: a mouse model of transmembrane TNF driven arthritis





Interesting fact:
Transmembrane TNF plays a central role in local inflammation and its blockade is considered necessary for the efficient treatment of disease indications such as Crohn's disease. The Tg5453 model is an ideal tool for the evaluation of the efficacy of test compounds to block transmembrane human TNF in vivo, thus offering support for indication extrapolation of the test compounds towards gut inflammatory conditions.

Model Description

Tg5453[1] is a transgenic mouse with transmembrane human TNF deregulated expression resulting in the spontaneous development of arthritis pathology that closely resembles human rheumatoid arthritis.

The mice develop arthritis with 100% penetrance and provide a fast in-vivo model for evaluating human therapeutics targeting rheumatoid arthritis**.**

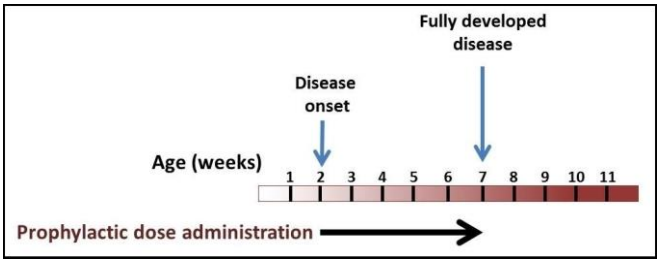
The Tg5453 mouse model was successfully used in establishing the therapeutic efficacy of **Remicade®,** the first anti-TNF therapeutic to be successfully applied in the clinic, and is currently used for screening anti-rheumatoid candidate drugs.

Preclinical efficacy evaluation

Tg5453 mice develop spontaneous arthritis characterized by swelling of the ankles, hind limb distortion, impaired movement and progressive weight loss, closely resembling the human pathology. Symptoms start to develop from 2 weeks of age and the disease rapidly develops to quite severe pathology.

Study design

Preclinical drug efficacy is evaluated in a prophylactic regimen starting dose administration at 2 weeks of age upon disease initiation and lasting for 5 weeks up to the 7th week of age of the animals.



[1] Georgopoulos S., Plows D., Kollias G., 1996, "Transmembrane TNF is sufficient to induce localized tissue toxicity andchronic inflammatory arthritis in transgenic mice", **J. Inflamm.,** 46, 86-97.

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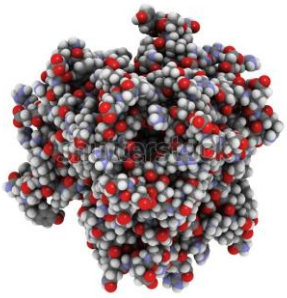


Read-out parameters

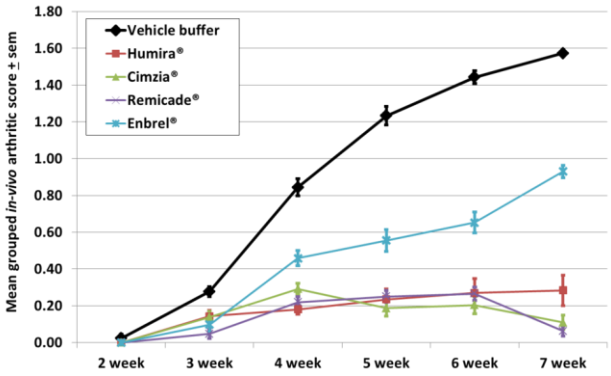
- *In vivo* body weight measurements for the whole duration of the study
- *In vivo* evaluation of ankle and paw joint swelling for the whole duration of the study
- *In vivo* evaluation of the progression of arthritis as depicted in the general well being of the animals & the development of cachexia
- Histopathological evaluation of the arthritis pathology in ankle joints

Arthritis clinical evaluation

In vivo scoring, performed blindly on a weekly basis, allows the accurate monitoring of the disease progress.

CLINICAL ARTHRITIS SCORE	
0 No disease	no arthritis
1.0 Mild-Moderate disease	mild arthritis
2.0 Moderate-Severe disease	moderate arthritis (severe joint, paw and finger swelling, joint –leg deformation, no whole body flexibility, no grip strength, climbing/feeding affected, impaired movement)
3.0 Terminal disease	severe arthritis (ankylosis detected on flexion and severely impaired movement, mouse moribund, cannot turn/flip around readily when tilted to the side).

Treatment with a variety of commercially available anti-hTNF therapeutics prevents the development of disease symptoms.



Representative graph of the progression of the in vivo arthritic score in Tg5453 animals untreated or treated with commercially available anti-hTNF therapeutics.

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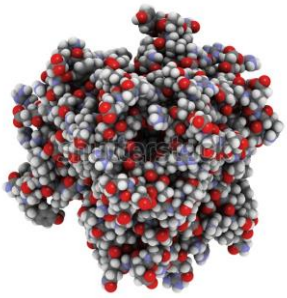


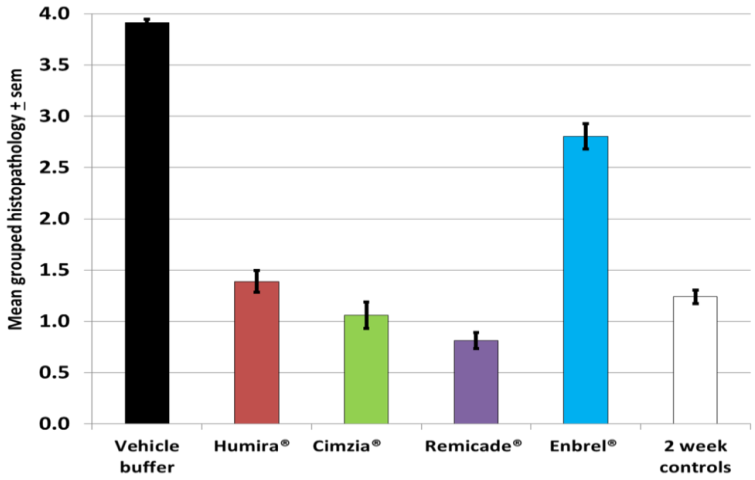
Histopathological evaluation

Histopathological scoring, performed blindly, allows the accurate evaluation of the disease status.

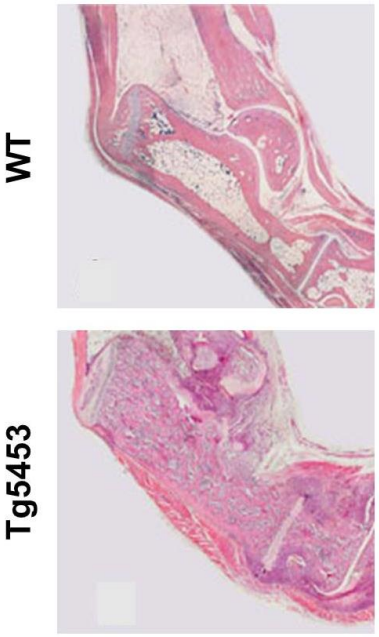
Histology

Histopathology in the **Tg5453** mice is characterized by infiltration of inflammatory cells, synovial hyperplasia, articular cartilage destruction and bone erosion, closely resembling that of human rheumatoid arthritis.

CUMULATIVE HISTOPATHOLOGICAL SCORE	
0 No disease	no detectable pathology
1.0 Mild disease	hyperplasia of the synovial membrane and presence of polymorphonuclear infiltrates. Mild tendonitis may be present.
2.0 Moderate disease	pannus and fibrous tissue formation and focal subchondrial bone erosion
3.0 Moderate-Severe disease	cartilage destruction and bone erosion
4.0 Severe disease	extensive cartilage destruction and bone erosion. Bone outline structure is lost



Representative graphs of the progression of the in vivo arthritic score in Tg5453 animals (left panel) and the histopathological arthritic score (right panel) observed at 7 weeks of age. Prophylactic treatment with commercially available anti-hTNF therapeutics prevents the development of disease symptoms.



Representative histology images of H&E-stained ankle joints of WT and Tg5453