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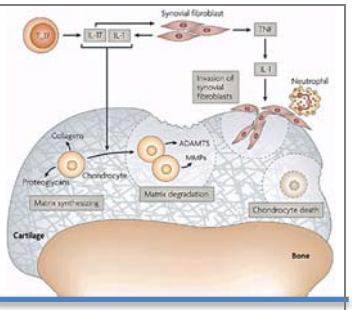


Tg197 transgenic mice:
a unique model of human arthritis pathology

Tg197 is a **transgenic mouse overexpressing human TNF** resulting in the spontaneous development of arthritis pathology closely resembling human rheumatoid arthritis. The mice develop arthritis with **100% penetrance** and provide a fast in-vivo model for the evaluation of human therapeutics targeting rheumatoid arthritis

The **Tg197 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 has since be used extensively for the FDA approval of many anti-rheumatoid candidate drugs.

Model Description

Tg197 mice develop spontaneous arthritis characterized by ankle swelling, hind limb distortion, impaired movement and progressive weight loss. With symptoms first becoming apparent at 3-4 weeks of age, the disease becomes established at 6-7 weeks of age and progressively worsens with age. Animals left untreated exhibit increased morbidity by 11-12 weeks of age.

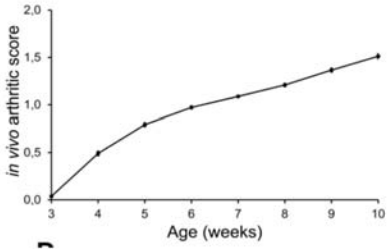
Tg197 mouse 3 weeks old

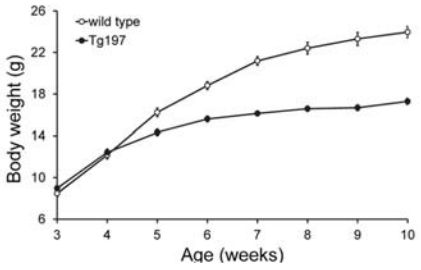
Tg197 mouse 6 weeks

Tg197 mouse 10 weeks old

Arthritic Score and Body Weight

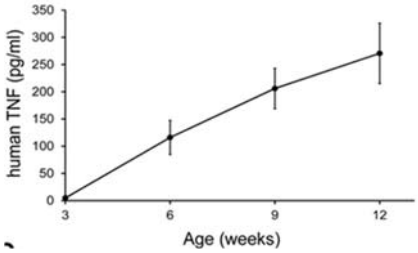
Tg197 mice exhibit progressive worsening arthritis and reduced body weight gain due to the human TNF overexpression that causes cachexia

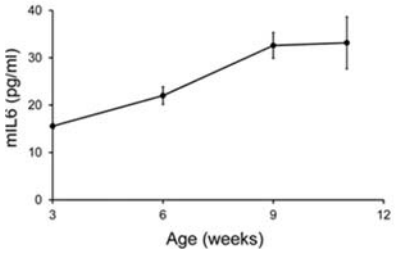




Circulating Cytokine Levels

Tg197 mice exhibit increased levels of serum circulating human TNF and mouse IL-6





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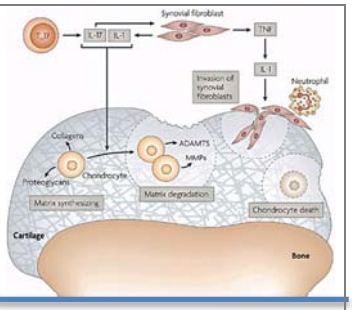

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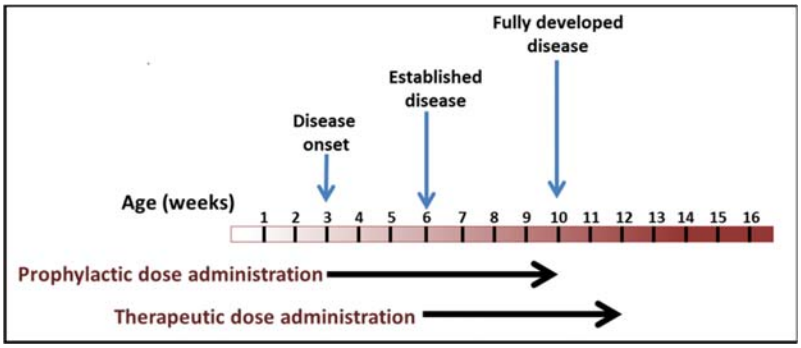
Preclinical Platform

Treatment can start either at 3 weeks of age, at the onset of pathology (prophylactic protocol), or at 6 weeks of age, at the stage of established pathology (therapeutic protocol)

Keffer et. al. 1991, "Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis", **EMBO J.**, 10, 4025-4031.

Shealy et al. 2002, "Anti-TNF-alpha antibody allows healing of joint damage in polyarthritic transgenic mice". **Arthritis Res**. 4(5):R7.

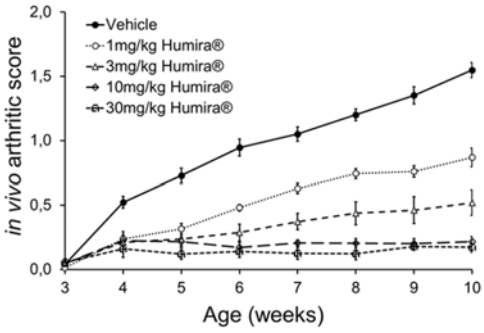
Brenner et al. 2015, "Regulation of tumour necrosis factor signalling: live or let die". **Nat. Rev. Immunol.,** 15(6):362



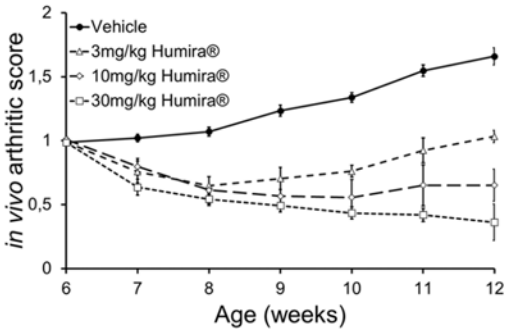
In vivo pathology evaluation criteria

- Body weight measurements
- Clinical evaluation of the progression of arthritis as depicted in ankle and paw joint swelling, finger deformation, loss of grip strength
- Clinical evaluation of the general well-being of the animals with the development of cachexia

Prophylactic Treatment



Therapeutic Treatment



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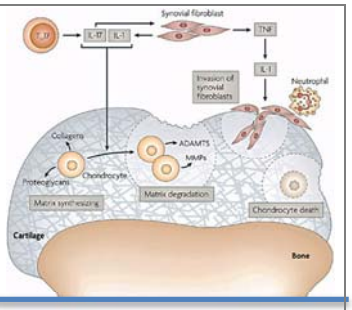


Tg197 transgenic mice: a unique model of human arthritis pathology

Arthritis clinical evaluation

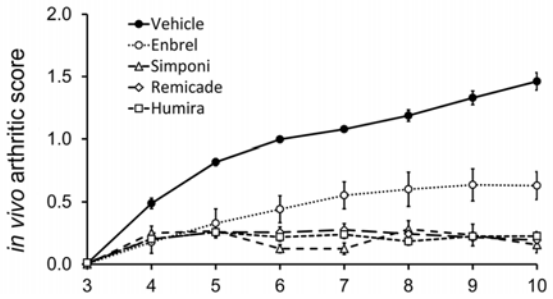
CLINICAL ARTHRITIS SCORE	
0-No disease	no arthritis (normal appearance, mouse can support its weight clinging to an inverted or tilted surface such as a wire grid or a cage lid for a period of time, whole body flexibility/evasiveness normal, grip strength maximum)
1.0-Mild-Moderate disease	mild arthritis (joint distortion by swelling, inflamed paw, all other parameters as above)
2.0-Moderate-Severe disease	moderate arthritis (severe joint, paw and finger swelling, joint –leg deformation, no support clinging to an inverted or tilted surface such as a wire grid or a cage lid, no whole body flexibility, no grip strength, climbing/feeding affected, starts shaking when trying to move, but manages to move forward)
3.0-Terminal disease	severe arthritis (ankylosis detected on flexion and severely impaired movement, mouse moribund, not shaking anymore, cannot turn/flip around readily when tilted to the side).

Keffer et. al. 1991, "Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis", **EMBO J.**, 10, 4025-4031.

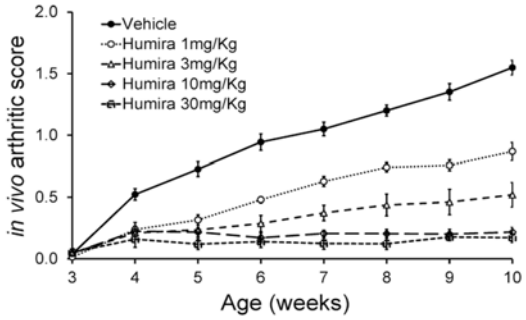
Shealy et al. 2002, "Anti-TNF-alpha antibody allows healing of joint damage in polyarthritic transgenic mice". **Arthritis Res**. 4(5):R7.

Brenner et al. 2015, "Regulation of tumour necrosis factor signalling: live or let die". **Nat. Rev. Immunol.,** 15(6):362

Cinical scores are significantly reduced upon treatment with all commercially available anti-hTNF biologics.



Clinical scores are modified in an anti-hTNF dose dependent manner.



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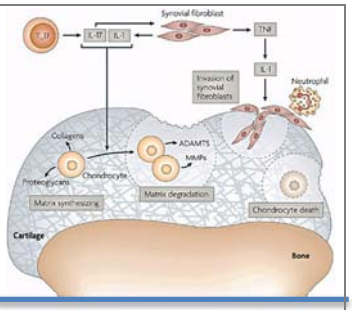


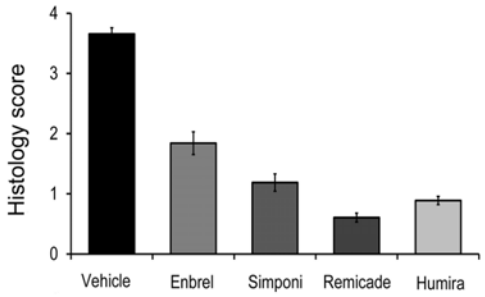
Tg197 transgenic mice: a unique model of human arthritis pathology

Tg197 Histopathology features
- Synovitis
- Cartilage destruction
- Bone erosion

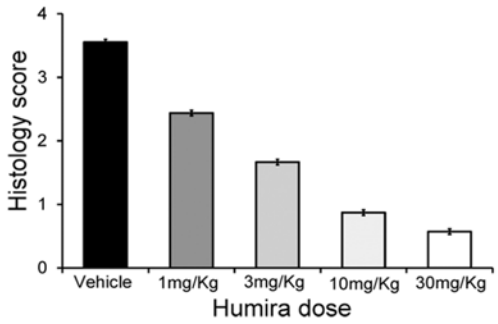
Arthritis histopathological evaluation

CUMULATIVE HISTOPATHOLOGICAL SCORE	
0-Normal	no detectable pathology
1-Mild	hyperplasia of the synovial membrane and presence of polymorphonuclear infiltrates. Mild tendonitis may be present.
2-Moderate	pannus and fibrous tissue formation and focal subchondrial bone erosion
3-Moderate-Severe	cartilage destruction and bone erosion
4-Severe	extensive cartilage destruction and bone erosion. Bone outline structure is lost

Histopathological scores are reduced upon treatment with anti-hTNF biologics.

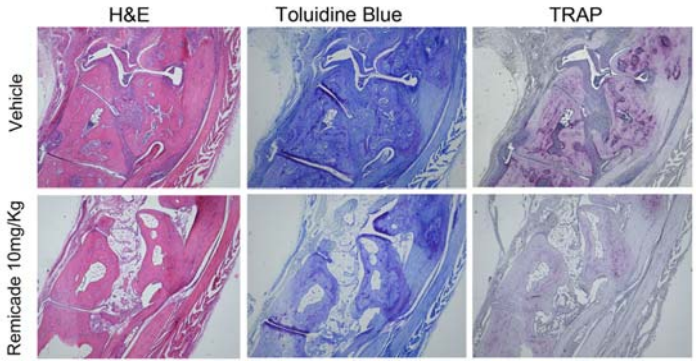


Histopathological scores are modified in an anti-hTNF dose dependent manner.



Tg197 Detailed Histopathology
- **H&E**: Synovitis
- **Toluidine Blue**: Cartilage destruction
- **TRAPS**: Bone erosion

When treatment affects the different components of the arthritic pathology in a differential manner, detailed histopathological evaluation to assess each pathology feature separately is performed.



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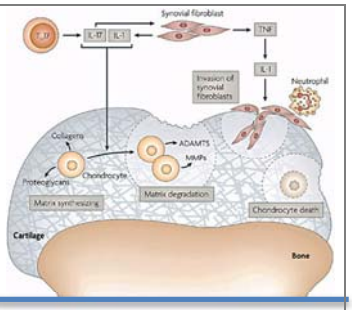
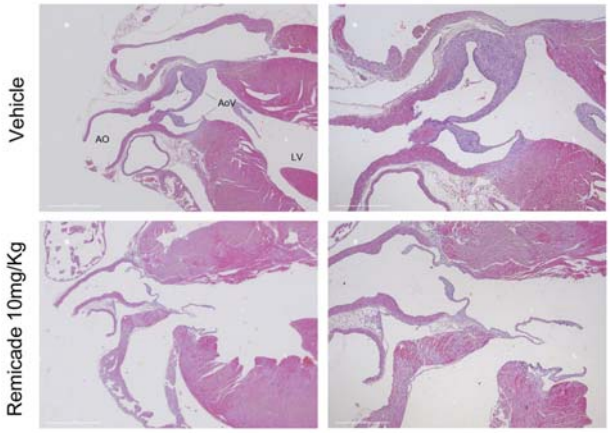


Tg197 Comorbidities

Heart Valve Pathology

Tg197 mice present a comorbid condition involving aortic valve thickening with functional implications, pathology that is also found in human arthritis patients. The pathology is ameliorated upon treatment with anti-hTNF antibodies

Ntari et al. 2018, “Comorbid TNF-mediated heart valve disease and chronic polyarthritis share common mesenchymal cell-mediated aetiopathogenesis”.
Ann Rheum Dis. 77:926-934.



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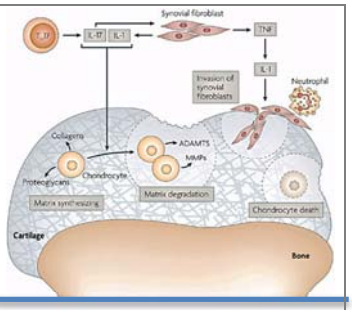

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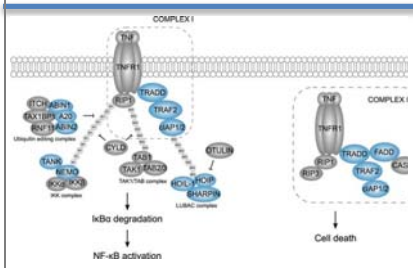


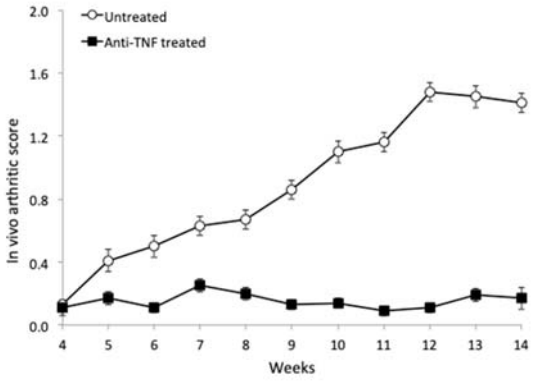
Van Hauwermeiren et al. 2013, "Safe TNF-based antitumor therapy following p55TNFR reduction in intestinal epithelium". JCI, 123, 2590-603.
The article includes description of the generation and use of hTNFR1KI mice.

Tg197hTNFR1KI mice

Tg197 transgenic mice, crossed to hTNFR1KI mice result in a new arthritis model with fully humanized TNF-TNFR1 interactions allowing the simultaneous efficacy testing of anti-hTNF and anti-hTNFR1 therapeutics.

Model Description

Tg197hTNFR1KI 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 such as joint swelling start to develop from 6 weeks of age and disease gradually develops to fully established pathology including ankylosis and severely impaired movement by 12-15 weeks of age.
Preclinical drug efficacy is evaluated starting dosing at 4-6 weeks up to 15 weeks of age.



Representative graph of the progression of the in vivo arthritic score in Tg197hTNFR1KI mice treated or not with commercially available anti-hTNF therapeutic.