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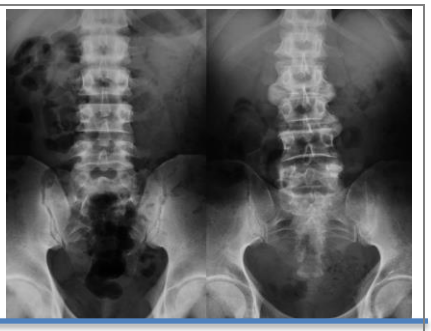
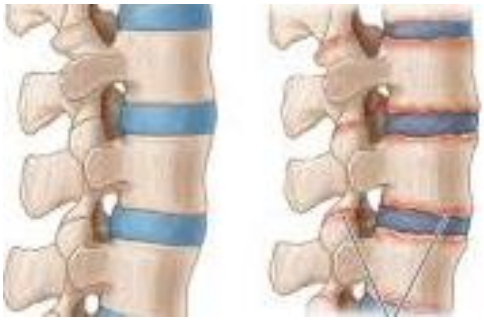
TgA86 a mouse model of human spondyloarthritis

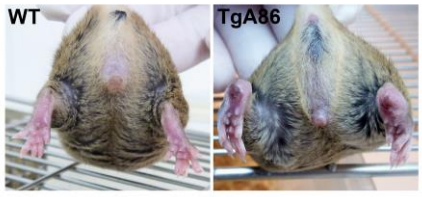




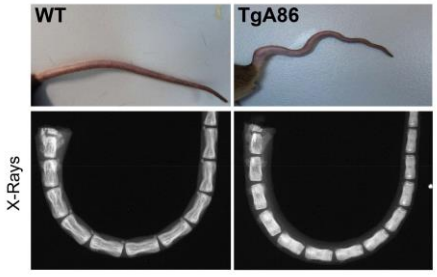
Spondyloarthritis (SpA) is a category of chronic inflammatory arthritides characterized by inflammation and structural damage accompanied by new bone formation. Its subforms are characterized by both axial and peripheral joint damage distinct in nature from that observed in Rheumatoid Arthritis as, apart from bone and cartilage damage, pathology includes the formation of pathological new bone that gradually leads to joint ankylosis. Therapeutic blockade of TNF has beneficial impact on the pathology of the different SpA subforms.

Model Description

TgA86 mice overexpress mouse **transmembrane TNF** from a Δ1-12 mTNF-globin transgene. They develop with 100% incidence peripheral and axial joint pathology accompanied by new bone formation features, all characteristic of human SpA pathology**.**



Peripheral pathology manifests as inflammatory polyarthritis with joint swelling and digit/limb deformation in all four limbs. Standardized assessment of in vivo signs of the peripheral pathology is performed using a scoring system that evaluates on a scale from 0-2 the severity of the pathology ranging from no disease to mild, moderate or severe pathology by assessing joint swelling, finger and limb deformation and grip strength. Pathology signs start appearing as early as 3-4 weeks of age and gradually become more severe reaching a maximum score around week 10 while after that score reaches plateau.



X-ray imaging of **tail**s reveals soft tissue swelling, brighter appearance of denser bones and vertebrae shape change.

Axial pathology is clinically characterized by bend tails and ankylosis (axial spondylitis). To assess severity and progression of in vivo signs of the axial pathology we have developed a scoring system that evaluates on a scale from 0-3 the severity of the pathology ranging from no disease to mild, moderate or severe by assessing tail bending and ankylosis. Single bends start appearing as early as 4 weeks of age and gradually their number increases and become tighter reaching a maximum score around week 10 while after that score reaches plateau.

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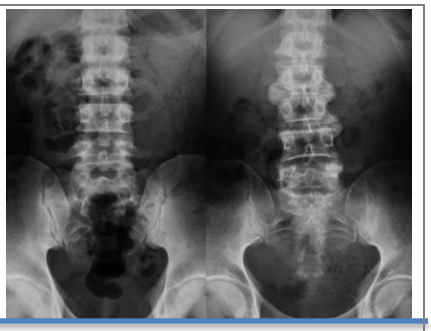
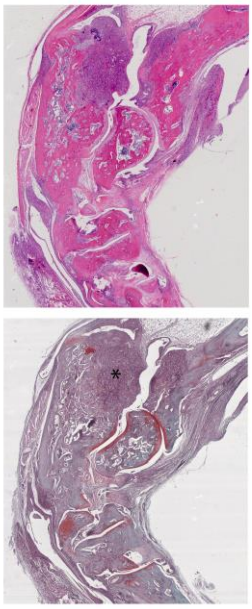
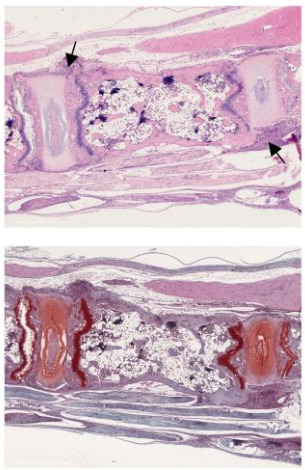


TgA86 20wks



H&E (up) and Safranin O staining of hind limb joints

TgA86 20wks



H&E (up) and Safranin O staining of a tail vertebra

Histopathology

Peripheral pathology includes hallmarks closely resembling those of human SpA pathology, including enthesitis, synovitis and bone erosion while cartilage destruction is also obvious all over the joint. Safranin O staining of proteoglycans further reveals hypertrophic chondrocytes in the site of new (ectopic) bone formation.

Pathology features for **axial spondylitis** include enthesitis localized at the border of the intervertebral discs together with intervertebral disk degeneration evident as decrease of nucleus pulposus and thinning of annulus fibrosus, red bone marrow and occasionally new bone formation. Bone marrow consistency is altered with decreased marrow adipose tissue extent and conversion to cartilage-like matrix.

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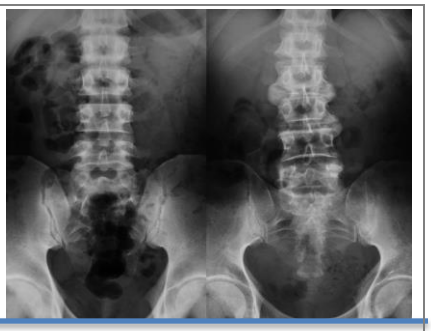
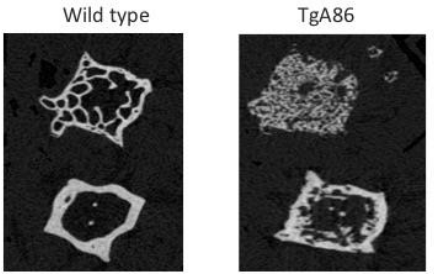
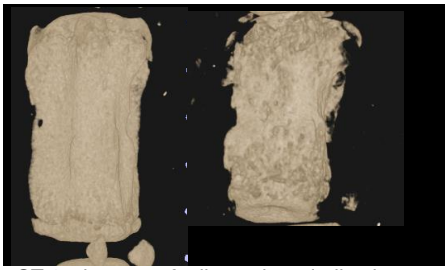
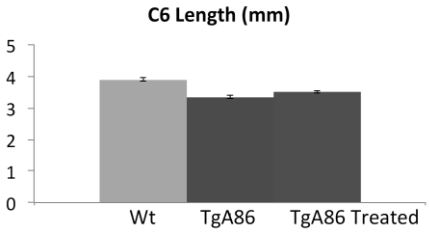




µCT 2D images of transverse sections of tail vertebrae indicating structural changes in bone architecture.

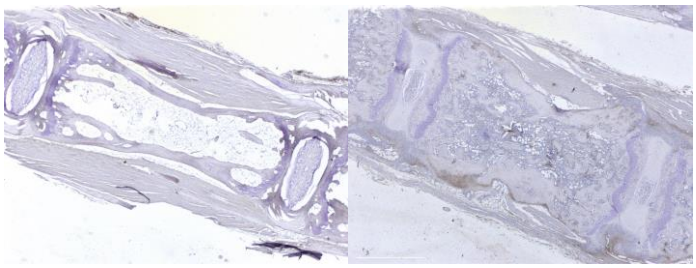

µCT 3D images of tail vertebrae indicating shortening and active bone loss and formation resulting in changes of bone shape.



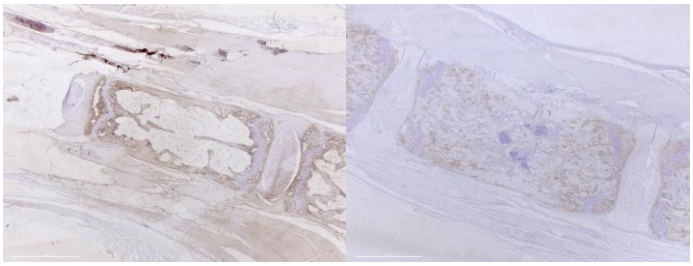
µCT analysis

CT scanning of tail vertebrae revealed changes in bone structure with reduced density of cortical bone and increased formation of bony structures in the vertebral lumen. 3D modeling of healthy and diseased vertebrae revealed shortening of the vertebrae and change of their shape.
Pathology features were ameliorated with early but not with late treatment.

Immunohistochemistry



Staining with anti-periostin antiboy reveals increased osteoblast activity on the vertebral surface of TgA86 (right) in comparison to wt mice (left).



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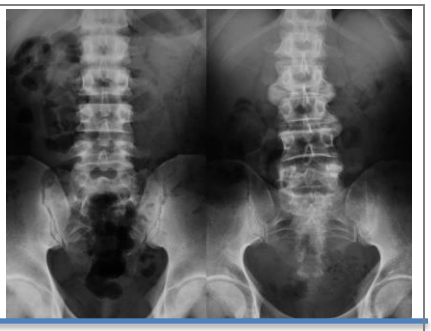
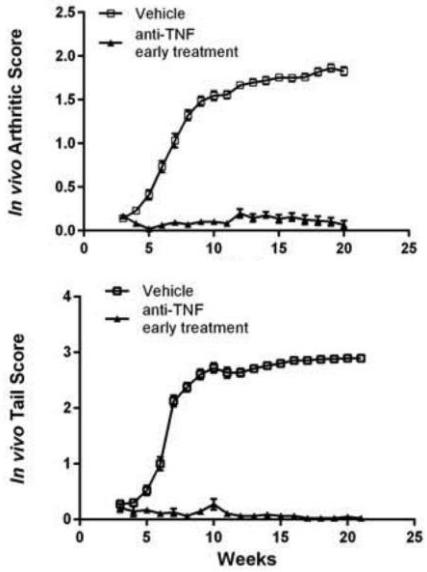


Preclinical drug evaluation platform

Using in vivo and histopathological evaluation criteria we have evolved and standardized a preclinical platform that allows the assessment of the efficacy of spondylitis therapeutics.

In vivo evaluation

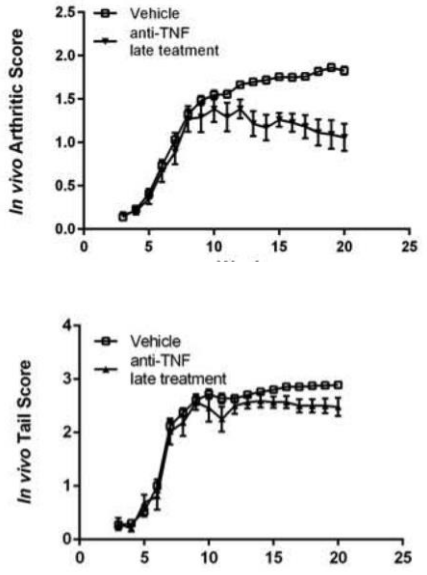
Groups of age and sex matched mice are treated or not from week 2.5 (early treatment) or 9 (late treatment) to week 20 with a dosing scheme of etanercept that has previously proved efficacious in the treatment of arthritis. Disease progression is monitored on weekly basis.



Effect of early treatment on the progression of joint (arthritis) and axial (tail) pathology

Early Treatment

Anti-TNF treatment starting at 2.5 weeks of age (prophylactic scheme) results in complete abolishment of both peripheral and axial pathology at clinical level.



Effect of late treatment on the progression of joint (arthritis) and axial (tail) pathology

Late treatment

Therapeutic treatment starting at 9 weeks of age, when pathology is already established, results in limited amelioration of the clinical signs of both peripheral and axial pathology

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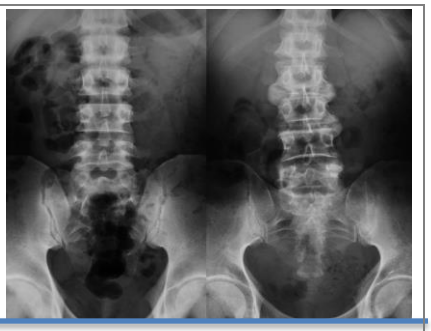
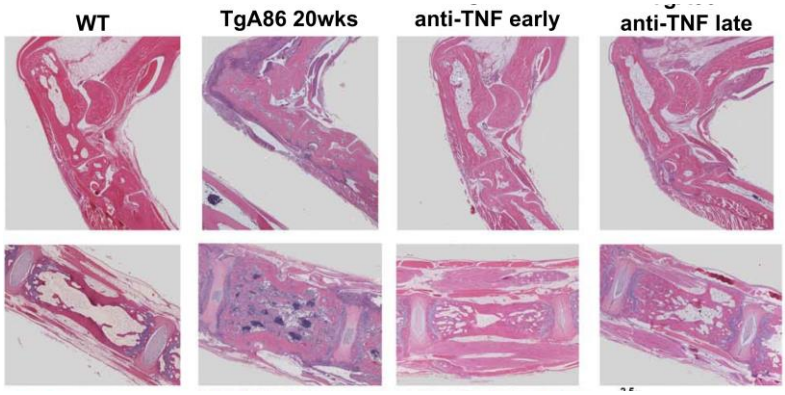
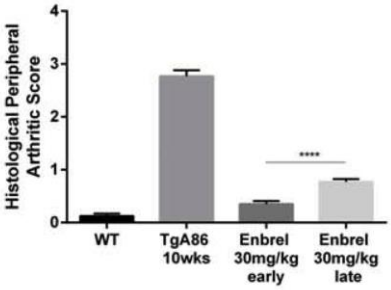
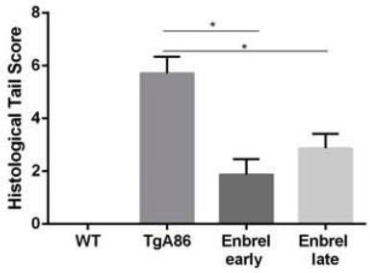


Histopathological evaluation







Histopathological scoring of hind limb joints (arthritis, up) and tails (axial spondylitis, down) from diseased and treated TgA86 mice.

Joints treated with prophylactic anti-TNF treatment do not present any signs of enthesal cell proliferation and infiltration, leading to new bone formation or signs of synovial inflammation.

The same for **tail** vertebras where enthesitis is not developed and intervertebral disc remains intact. Moreover, in tail bone marrow, B cell aggregates are decreased after anti-TNF therapeutic treatment, while the prophylactic scheme results in complete abrogation of immune cells infiltration.

Literature

1. Alexopoulou L, Pasparakis M, Kollias G., 1997, "A murine transmembrane tumor necrosis factor (TNF) transgene induces arthritis by cooperative p55/p75 TNF receptor signaling", Eur J Immunol, 27(10):2588-92.

2. Baeten D., Breban M., Lories R., Schett G. and Sieper J. 2013 “Are Spondylarthritides Related but Distinct Conditions or a Single Disease With a Heterogeneous Phenotype?” Arthritis Rheum. 65, 12–20.

3. Vieira-Sousa E, van Duivenvoorde LM, Fonseca JE, Lories RJ, Baeten DL. 2015 “Review: animal models as a tool to dissect pivotal pathways driving spondyloarthritis” , Arthritis Rheumatol. 67, 2813-27.