

A181 **SUCCESSFUL THERAPY WITH ANTI-HMGB1 MONOCLONAL ANTIBODIES IN TWO SEPARATE EXPERIMENTAL ARTHRITIS MODELS**

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Background and objectives The nuclear protein HMGB1 (high mobility group chromosomal protein 1) is secreted by activated macrophages/monocytes and promotes inflammation. Extracellular HMGB1 is present in the synovitis of rheumatoid arthritis (RA) patients and intra-articular injections of recombinant HMGB1 induce arthritis in mice. Thus, the authors hypothesise that HMGB1 represents an endogenous mediator of arthritis as well as a target molecule for successful therapeutic intervention in RA. Polyclonal anti-HMGB1 therapy or recombinant boxA protein works in experimental arthritis models. However, no monoclonal anti-HMGB1 therapy has proven efficient in arthritis models. The aim was to evaluate the antiarthritic potential of a monoclonal anti-HMGB1 antibody (2G7) in two different models of arthritis; collagen-induced arthritis (CIA) in DBA/1 mice and *DNase II*^{-/-} x *IFN-IR*^{-/-} mice which spontaneously develop chronic polyarthritis resembling RA. DNase II is specifically needed for macrophage degradation of engulfed DNA. This model is associated with abundant extracellular HMGB1 expression including serum levels of several 100 ng/ml before and during onset of disease.

Materials and methods Female and male *DNase II*^{-/-} x *IFN-IR*^{-/-} mice, initially 5 weeks old, were treated in 5 weeks every second day with intraperitoneally injections with 100 µg of a mouse monoclonal anti-HMGB1 antibody 2G7 (IgG2b, non-commercial antibody, available upon request) or buffer control. Nine animals were included in each group with an equal sex distribution. Treatment of CIA in female DBA/one mice with anti-HMGB1 antibody 2G7 was initiated when the animal reached an arthritis score of ≥2. The animals were treated for 7 days with daily intraperitoneal injections of 70 µg 2G7 (12 animals) or 70 µg of irrelevant antibody (MOPC-195, mouse IgG2b, 7 animals). The outcome was evaluated by daily clinical scoring. Statistical evaluation was performed using Student's t test calculated on area under the curve values. Serial joint sections were stained with H&E to evaluate inflammatory cell infiltration or using staining with Safranin O to visualise cartilage damage and bone erosions.

Results Systemic HMGB1-specific blockade significantly ameliorated the clinical course in CIA as well as in *DNase II*^{-/-} x *IFN-IR*^{-/-} mice, and a protective effect on joint destruction was observed by histological evaluation.

Conclusion This study identifies beneficial effect of the HMGB1-specific mAb 2G7 in two different experimental arthritis models. The conserved structure of HMGB1 and the strong cross-reactivity between species of the investigated mAb, has thus enabled them to define a potential mAb candidate for further genetic engineering and clinical testing.