ArthritoMab™ Antibody Cocktail: a cocktail of anti-collagen type II antibodies induce a synchronized model of Arthritis in just 12 days.

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Abstract

The CIA model is mediated by autoantibodies, which bind to a particular region of type II collagen (CII) and complement. Research by Nutty Nandakumar and Rikard Holmdahl[1] has shown an antibody cocktail of collagen type II antibodies selected for their epitope specificity can induce arthritis. Evidence suggests that an antibody response to certain epitopes is better associated with arthritis than other epitopes. In the CIA mouse model, the antibody response that correlated with arthritis was mainly associated with the binding to the epitopes C1, J1 and U1.

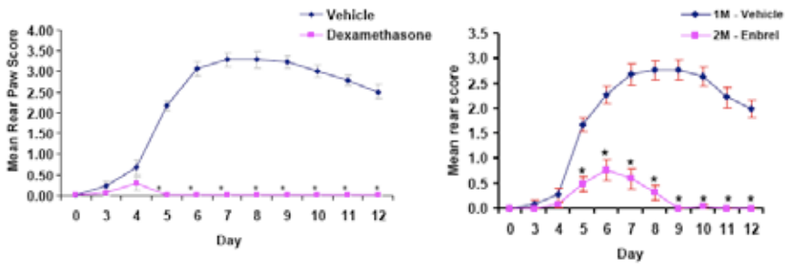
MD Biosciences ArthritoMab™ Antibody cocktail consists of four monoclonal antibodies to CII, 3 of which are IgG2b isotypes which induce stronger arthritis. These antibodies bind to the well-defined epitopes C11b, J1, D3 and U1, which are all major epitopes in mice immunized with CII and developing arthritis. These epitopes are also spread across the entire CII region (CB8, CB10, and CB11 fragments) possibly encouraging better immune complex formation on the cartilage surface or in the synovium. These complexes can then activate complement and induce inflammation by both the classical and alternative pathways. Monocytes in the joint are also activated by these complexes via Fc receptors releasing pro-inflammatory cytokines (i.e. TNF-α, IL-1β) that recruit neutrophils and macrophages.

The ability to induce arthritis using an antibody cocktail to CII provides an efficient protocol as an alternative to the lengthy CIA protocol. Disease is synchronized between the animals and the incidence is nearly 100%.

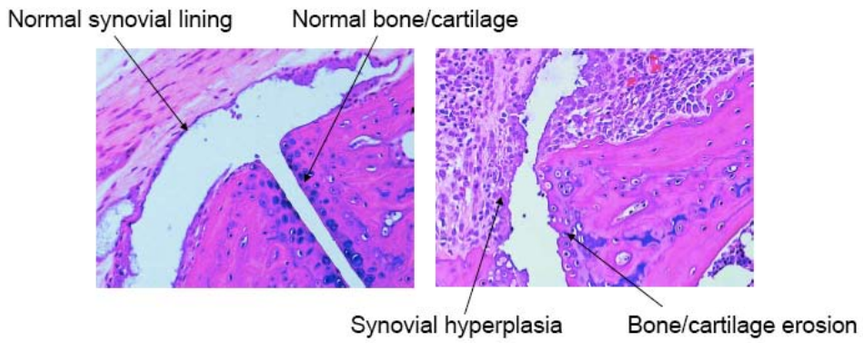
Methods: Induction of Arthritis

Mice were injected with ArthritoMab Antibody Cocktail on day 0 (either IP or IV). LPS boost is administered on day 3. Inflammation develops within 24 hours and the model is terminated on day 12. Note: The protocol can be modified to allow for a 6 day recovery phase, which can reveal the ability of a compound to promote arthritis resolution.

Results



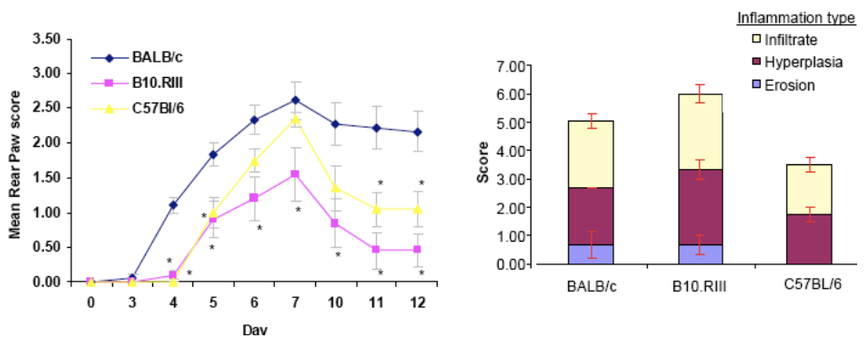
Balb/c mice were administered ArthritoMab™ antibody cocktail on day 0 and boosted with LPS on day 3. Data shows clinical score using Dexamethasone (left) and Enbrel (right).



Above: Histological analysis shows significant changes in the joints of the arthritis group compare to the normal control.

Susceptibility to a variety of mouse strains

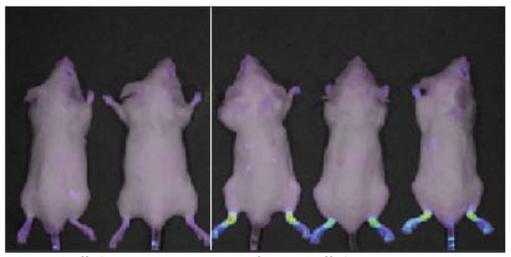
The Collagen Antibody-Induced Arthritis model can be carried out in arthritis susceptible strains such as DBA/1 as well as Balb/c, B10R.III, and C57Bl/6 which is an advantage when using transgenic strains.



Clinical scores (left) and Histological scores (right) of varying strains in the collagen antibody-induced arthritis model. ArthritoMab was administered on day 0 with an LPS boost on day 3. Data shows that while clinical scores appear lower in some strains, histology shows that there is inflammation present.

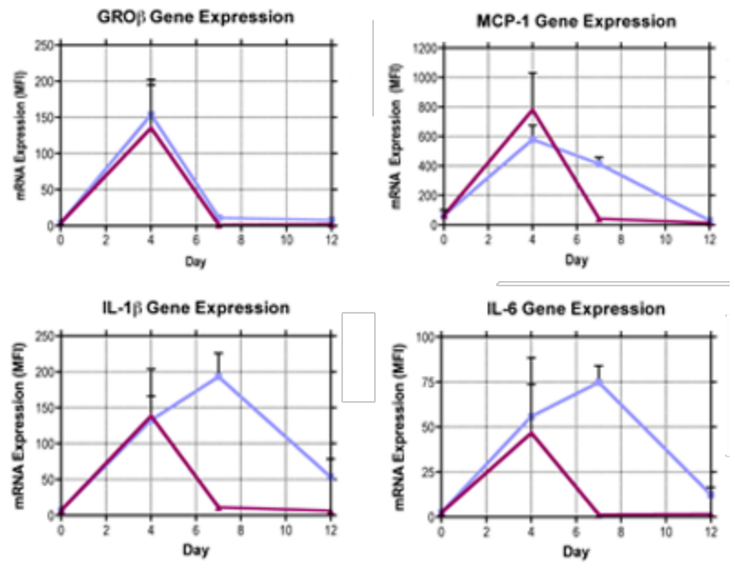
Imaging

At 24 hours, all animals were given a probe which is activated by proteases. Images were captured using Xenogen Prosense™ at 680 nm.



Naive Balb/c *Arthritic Balb/c*

Gene Expression



Joints were isolated on days 0, 4, 7, and 12 from both a vehicle and dexamethasone (1 mg/kg) treated groups. Homogenized joints were assayed for mRNA levels expressed as median fluorescent units (MFI). Mean values are show with error bars representing SEM.

Conclusion

The Collagen Antibody-Induced Arthritis Model using ArthritoMab™ Antibody Cocktail is ideal for rapidly screening anti-inflammatory therapeutic agents. The rapid and synchronized protocol is an excellent alternative for researchers to be able to run rapid and successive studies with the following benefits:

- Shortened study length (12 days vs >42 days)
- Synchronized disease onset
- Nearly 100% disease incidence
- Susceptibility in multiple strains
- Flexible protocol design

References

1. J. Immunol. Methods (2005) 304:126