

Rheumatoid Arthritis

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disorder characterized by chronic inflammation of the synovium, which over time results in damage to the joints, leading to pain and disability. It occurs in approximately 1% of adults, and approximately 2.5 times more women than men are affected. Immune factors involved in the progression of RA are mainly manufactured by CD4+ T cells, monocytes, macrophages, or fibroblasts. Cytokines produced by these cells such as tumor necrosis factor α (TNF- α) and interleukin-1 are the keys to the damaging cascade that ultimately triggers the production of matrix metalloproteinases and osteoclasts resulting in irreversible damage to soft tissues and bones.

Understanding of molecular pathogenesis of RA has enabled development of innovative agents to modulate specific components of the disease progress for early intervention or treatment. Various experimentally induced RA rodent models have been used extensively as the mainstay for evaluation of those therapeutic candidates.



PharmaLegacy Models and Research Tools

RA disease models:

- * Type II collagen induced arthritis (CIA) in DBA/1 mice
- * Type II collagen induced arthritis in Wistar / Lewis rats
- * Adjuvant arthritis in Wistar / Lewis rats
- * Streptococcal cell wall induced arthritis in Lewis rats)

Model characteristics:

- * Symmetrical joint involvement, peripheral joints affected, persistent joint inflammation
- * Synovial hyperplasia, inflammatory cell infiltration, marginal erosions
- * Genetically regulated by MHC and non-MHC genes, responsive to most therapies effective in RA
- * Female rats have greater disease susceptibility to streptococcal cell wall induced arthritis, while male mice are more susceptible to CIA
- * Unlike other models, mouse CIA model is not responsive to non-steroidal anti-inflammatory drugs
- * Different from human RA, anti-collagen responses are not present in many cases of rat CIA, and rheumatoid factor is not present in neither CIA nor streptococcal cell wall-induced arthritis in rats

Measurement of bone destruction, inflammatory responses, and molecular pharmacology:

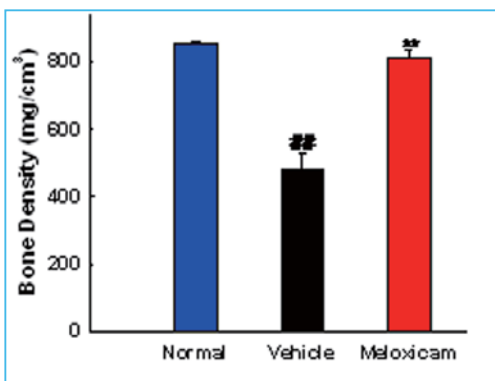
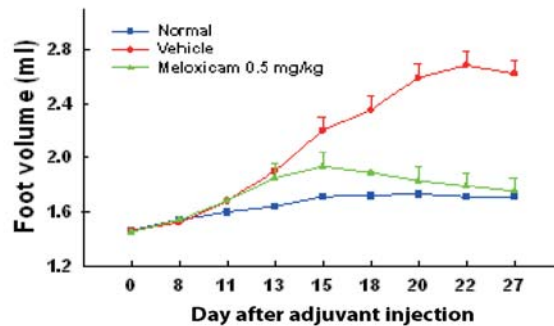
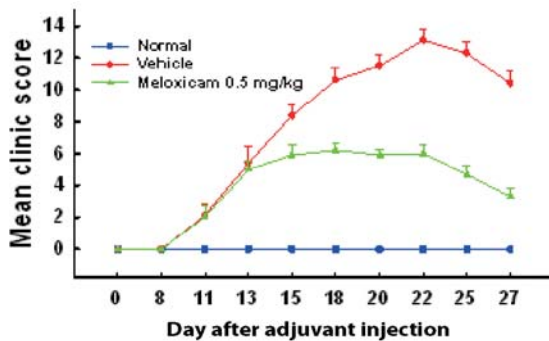
- * Bone mineral density (peripheral QCT), bone erosion, abnormal bone growth and joint space narrowing (X-rays, micro-CT)
- * Antigen-specific T-cell and B-cell responses, cytokine and signal transduction levels, and cell function analysis (ELISA, RT-PCR, Western blot, flow cytometry)

Histopathology:

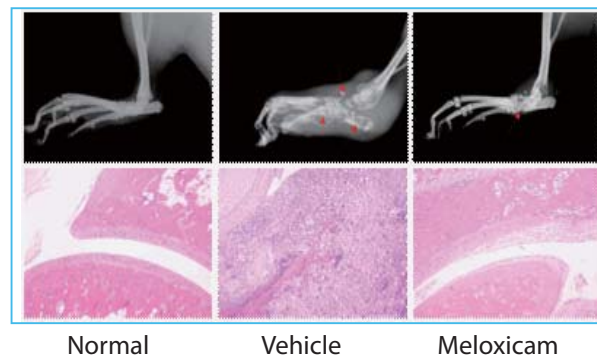
- * Histomorphometry (bone destruction)
- * Immunohistochemistry (cellular infiltration in joint tissue)

Case Study - RA Model and Endpoints Measurements

Effect of Meloxicam treatment (day 8-27) on adjuvant-induced arthritis in Lewis rats:



##P<0.01 vs. Normal. **P<0.01 vs. Vehicle



X-ray examination and HE stained sections of hind paw

With fully validated RA models and the state-of-art equipments, PharmaLegacy provides exceptional services for preclinical pharmacology studies of the drug candidates for RA treatment, including:

- Evaluation of therapeutic profile and potentials of the candidate compounds
- Proof of concept for early drug development
- Demonstration of differential regulation of disease progression and clinical symptoms
- Examination of anti-autoimmune disorder as well as anti-inflammatory effect such as T cell and B cell response, and cytokine/chemokine response
- Investigation of the mechanisms of immunological tolerance induction

About PharmaLegacy Services

- World-class quality with increased speed and output at competitive cost.
- International GLP and QA-based operation.
- Electronic data management system (BioBook) for quality execution and maximum IP protection.
- AAALAC accredited large capacity to house over 10,000 animals under SPF and conventional conditions.
- Availability of 4,000 non-human primates for research use.