

## Summaries of the chapters

### Summary

**Lisa R. Schopf, Karen Anderson and Bruce D. Jaffee**

#### **Rat models of arthritis: Similarities, differences, advantages, and disadvantages in the identification of novel therapeutics**

Rat adjuvant (AA) and collagen-induced (CIA) polyarthritis models, and more recently the monoarticular streptococcal cell wall (SCW) model have been used to evaluate novel therapeutic approaches to treat Rheumatoid Arthritis. All three models share mechanistic and pathologic features with each other, as well as with human RA. Most notably, they are all T cell and macrophage mediated. All have been linked to pro-inflammatory molecules, and exhibit elevations in serum acute phase proteins. Differences in joint destruction, cytokine and inflammatory mediator production and paw edema between the animal models are mostly quantitative, not qualitative. As a general rule, the AA model is the most robust, followed by CIA and then SCW. However, the aggressive nature of all of these animal models needs to be considered when comparing to human RA. The AA model has been the most extensively used, thereby having the largest database, which aids in predicting potential human efficacy, and its robust nature allows for ease in compound evaluation and ranking. CIA has an advantage due to the auto-antibody component and the directed nature of the cartilage destruction. The SCW model most closely resembles an arthritic flare, has fewer systemic complications, and requires much less compound when given therapeutically. In this review, we will compare these three animal models by discussing paw swelling and its associated joint histopathology, gene expression in joints, as well as acute phase proteins and biomarkers of cartilage and bone integrity, in addition to imaging technologies to quantify bone destruction.

**Key words:** rheumatoid arthritis, rat, inflammation, cartilage, bone, acute phase proteins, micro-computed tomography, joint pathology, mRNA

### Summary

**Leo AB Joosten and Wim B van den Berg**

#### **Murine collagen induced arthritis**

Rheumatoid arthritis is characterized by chronic inflammation in the joints and progressive destruction of cartilage and bone. The disease is often considered as an autoimmune process, the articular cartilage being an intriguing component, since it is the victim but also a likely trigger of the disease. Models have been developed which have proved the arthritogenic potential of cartilage autoantigens such as collagen type II, proteoglycan, COMP and HC-gp39. Collagen type II induced arthritis (CIA) is a widely accepted arthritis model, based on T cell and antibody mediated autoimmune reactivity against cartilage collagen. The model is characterized by severe cartilage and bone erosions. Induction has been demonstrated in various strains of rats and mice, susceptibility showing tight genetic restriction. The model of collagen arthritis is highly suited to analyze principles of autoimmune disease expression as well as antigen-specific immunosuppression. Moreover, it can be used to study mechanism and mediators involved in autoimmune cartilage and bone destruction. This chapter will mainly deal with features of collagen-induced arthritis in the mouse.

**Keywords:** rheumatoid arthritis, animal model, collagen induced arthritis, cartilage destruction, bone erosion, cytokines, interleukin-1, tumor necrosis factor alpha, autoimmune, type II collagen

#### **Summary**

**Stephen A. Stimpson, Virginia B. Kraus and Bajin Han**

#### **Use of animal models of osteoarthritis in the evaluation of potential new therapeutic agents**

This chapter introduces the investigator to the options for osteoarthritis (OA) animal models and provides examples of their use to aid in the development of a strategy for evaluating potential new therapeutic agents for OA. Both spontaneous and induced OA animal models in several animal species are described. In addition, this chapter provides a comprehensive summary of the last decade of research utilizing OA animal models in the evaluation of potential new therapeutic agents for OA, including symptom modifying and disease modifying osteoarthritic drugs (DMOADs).

**Key words:** osteoarthritis, animal models, drugs, DMOAD, pain, cartilage, biomarker, bone, muscle, joint, synovium, collagen, clinical trial, matrix metalloproteinase

#### **Summary**

**Roberto Benelli, Guido Frumento, Adriana Albini and Douglas M. Noonan**

#### **Models of Inflammatory Processes in Cancer**

Largely set aside for over a century, it is now clear that inflammation often plays a critical role in cancer insurgence and progression. Inflammation can act at most steps along the road to cancer, including initiation, promotion, angiogenesis and immune suppression. Here we rapidly review the concepts behind the links between cancer and inflammation. We then describe the advantages and downfalls of principal models applicable to analysis of tumor-associated inflammation, including genetic manipulation, angiogenesis, cytokine and chemokines, and immune suppression.

**Keywords:** chronic inflammation, angiogenesis, immune suppression, gene-targeted animals/transgenic animals, cytokines, chemokines, innate immunity, cancer

#### **Summary**

**Antonio Musarò and Nadia Rosenthal**

#### **Advances in stem cell research: use of stem cells in animal models of muscular dystrophy**

The maintenance of a working skeletal musculature is conferred by its remarkable ability to regenerate after injury. However, the reconstruction of skeletal muscle tissue in several muscle diseases, including muscular dystrophy, is hampered by the lack of availability of functional substitution of the injured myofibers. Recently, a wide range of stem/progenitor

cell types have been proposed for muscle cell therapy, including embryonic stem cells, myoblasts, and bone marrow stem cells.

Although stem cell therapy has not yet solved the major problem related to cell transplantation, namely the capacity to survive and to improve muscle regeneration, recent studies are beginning to elucidate the signals and mechanisms whereby regenerating muscle recruits circulating cells to sites of injury or degeneration.

In this chapter we will discuss the potential contribution of stem cells in the treatment of muscular dystrophies, in which a chronic inflammatory response exacerbate the muscle disease.

**Key words:** muscle diseases, inflammation, myonecrosis, animal models, dystrophin-glycoprotein complex, muscle regeneration, stem cells, satellite cells, cell therapy, growth factors

### **Summary**

**Karen F. Kozarsky**

#### **Gene transfer technology**

In this chapter, gene transfer vectors are described, as well as their use in generating animal models of inflammation and in dissecting out the pathways involved. Non-viral and viral gene transfer systems are described, and examples of their use in animal models of arthritis and asthma are included.

**Key words:** gene transfer, retrovirus, lentivirus, adenovirus, adeno-associated virus, arthritis

### **Summary**

**Matthias Müller and Nicole Avitahl-Curtis**

#### **Transgenics**

Transgenic and knockout technologies, developed during the past two decades, allow gene function studies in the mouse that are mostly not possible in other organisms. Null mutations, as well as subtle missense or gain-of-function mutations, can be introduced into virtually any gene in the mouse germ line using gene-targeting technology. In addition, the conditional or even inducible inactivation of gene expression in vivo can be used to inactivate a gene in only a subset of cells and/or at well defined stages of development.

Phenotypes of these mice not only unmask the role of individual genes in the pathophysiology of disease, but also provide further insights into the critical nature of a given gene in normal homeostasis. Decades of intense effort to replicate human inflammatory diseases in mice have led to standardized immune manipulation methodologies. Application of these techniques in genetically altered mice is providing important clues to the biology of inflammation.

This chapter focuses on new transgenic mouse technologies developed during the past years, which will help to understand the roles of specific genes in the pathophysiology of major inflammatory diseases.

**Key words:** transgenic mice, RNA interference, reporter lines, RMCE, bioluminescence imaging, luciferase, FTY720

**Sreekant Murthy, Elisabeth Papazoglou, Nandhakumar Kanagarajan and Narasim S. Murthy**

**Nanotechnology: Towards the detection and treatment of inflammatory diseases**

**Summary**

**Susan Brain**

**UK legislation of in vivo aspects in inflammation research**

Studies involving animals have identified novel therapeutic anti-inflammatory targets. Furthermore, appropriate animal models, with bio-markers that also correlate to human disease, play central roles in the early screening of promising novel treatments. This chapter discusses the legislation that is required to carry out inflammation research experiments involving animal species, examining the process from a UK perspective. Opportunities for reduction, replacement and refinement are also evaluated and problems related to skills shortages discussed.

**Key words:** Legislation, Use of animals, Animal models, Law, certificate of designation, project licence, personal licence, reduction, refinement, skills shortages

**Summary**

**Naoko Kagiya, Takuya Ikeda and Tatsuji Nomura**

**Japanese guidelines and regulations for ethical animal experimentation**

The Law for the Humane Treatment and Management of Animals was amended in 2005 and the 3R-principle was specified. Based on the amendment, the Standards Relating to the Care and Management of Laboratory Animals and Relief of Pain were revised. The Japanese Diet concluded that bioscience should not be regulated only from the aspect of humane treatment of animals. Following the decision, regulatory agencies promoting science and technology established national guidelines in 2006 describing policies and institutional responsibilities for conducting animal experimentation. Based on these policies, the Science Council of Japan formulated detailed guidelines as a vital reference when institutions establish their local regulations. The detailed guidelines cover both aspects of scientific rationality of *in vivo* research and humane treatment of animals. Thus, self-regulation of animal experimentation is enforced with two types of guidelines.

**Keywords:** legal standing of the 3R principle, institutional responsibilities for conducting, animal experiments, detailed guideline as a vital reference, enforced self-regulation

**Joanne B. Morris, Jeffrey Everitt and Margaret S. Landi**

**United States guidelines and regulations in animal experimentation**

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