GOLD STANDARD ANIMAL MODELS

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1 INTRODUCTION: IMPORTANCE OF AND DANGERS IN USING ANIMAL MODELS FOR DRUG DEVELOPMENT

Using data from animal models for designing and approving human trials is necessary but must be done cautiously. Animal models should be characterized carefully and compared to similar human systems including in vitro studies using human cells. For example, CD4 is expressed on human macrophages but not on murine macrophages. Using multiple animal models is important and no data from any of these systems should be ignored. When animal models are used to examine the efficacy of treatment, it is very important that treatment in animal models start after clinical symptoms become evident. Moreover, drugs should also be tested using in vitro human systems when available. Well-characterized animal models can also be used to examine the ability of certain prophylactic treatments to prevent the onset of disease or pathologic symptoms. Finally, human trials should be based on sound scientific evidence using animal models and other appropriate model systems. Even when human trials go awry, we must investigate the results openly and carefully in order to determine why there were differences between the human trials and the animal models. This will lead to the development of better models and thus faster and more effective treatments in the future.

Testing of biologics has dramatically expanded the horizon of possible treatments; a successful example being infliximab, a tumor necrosis factor-alpha (TNF-α) inhibitor used to treat rheumatoid arthritis. Caution must be taken when using antibody reagents. These reagents may be fully or partial agonistic or antagonistic, leading to very different treatment results. Often these antibodies are thought to block or activate the function of cytokines or specific cellular receptors. It is important, therefore, to rigorously test the effects of these reagents in several animal models due to the complex intricacy and redundancy of all living systems and therefore the many possible dangers.

Monoclonal antibody reagents have often been used to block a specific signaling receptor. However, it has been shown in animal models that a monoclonal antibody (mAb) can cross-link the receptor it binds and thus result in signaling rather than blocking the signal [1, 2]. This cross-linking is especially powerful if the fragment crystallizable (Fc) region of the treatment antibody binds to Fc receptors on the patient's own cells, resulting in extensive cross-linking. Complement activation and other inflammatory responses are, therefore, very real possibilities as a result of monoclonal antibody treatment. Although there are dangers in using these treatments, there is also the exciting potential in transplantation, cancer, and autoimmune disease. Some evidence suggests that short-term treatment with the antibodies that block T-cell activation may result in long-term autoantigen-specific tolerance and remission from clinical disease.

2 IMMUNOMODULATION

For activation, T lymphocytes require antigen-specific signals through the binding of their T-cell receptor (TCR) complex and co-stimulatory signals including

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