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Exploiting ovine immunology to improve the relevance of biomedical models☆

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ABSTRACT

Animal models of human disease are important tools in many areas of biomedicine; for example, in infectious disease research and in the development of novel drugs and medical devices. Most studies involving animals use rodents, in particular congenic mice, due to the availability of a wide number of strains and the ease with which they can be genetically manipulated. The use of mouse models has led to major advances in many fields of research, in particular in immunology but despite these advances, no animal model can exactly reproduce all the features of human disease. It is increasingly becoming recognised that in many circumstances mice do not provide the best model and that alternative species may be more appropriate. Here, we describe the relative merits of sheep as biomedical models for human physiology and disease in comparison to mice, with a particular focus on reproductive and respiratory pathogens.

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1. Introduction: Applications of animal models

The development of biomedical products (vaccines, chemotherapeutics, and devices) requires a deep functional understanding of how they exert their effects and perform over time, with safety being a primary criterion. *In vitro* cell culture systems provide a wealth of functional information on many aspects of cell activation, proliferation and controlled cell death. However, there is currently no *in vitro* substitute for *in vivo* experimentation that provides insight into the complex interactions of multiple cell types within organ structures. This is particularly true for the immune system that depends on cells migrating between and within anatomical compartments to reach defined areas of organised lymphoid tissues to become activated and then migrate back to the periphery to exert their effects. Consequently, it is likely that animal models will remain an essential component for the safe and effective translation of biological products and devices that interact with the immune system for applications in both human and animal medicine.

Rodents (mice, rats, guinea pigs) and lagomorphs (rabbits) have traditionally been the species of choice for biomedical models of human disease, the application of which has resulted in enormous advances in medicine. The validity of any animal model for determining biological effects in another species is always open to debate; hence the choice of model should mimic the biological effect in question as closely as possible for the target species. There are multiple criteria that influence this choice which often means that some features need to be balanced off against others, this will depend on the hypothesis being tested. The size, physiology, immunology and temperament of animals as well as the practical means to conduct the experiments (infrastructure facilities, tools and reagents) are all factors in the selection of animal models. Any one feature of a model that is desirable for one purpose may be a distinct disadvantage for another. In this review, we will discuss the pros and cons of sheep as biomedical models and discuss prospects for the future.

It is worth stating at the outset that although animal models are essential for understanding integrated biological systems, their use is tightly regulated and alternative methods to animal experimentation are employed wherever possible. There are a number of bodies globally that promote alternative means of conducting biological research that does not involve animals. These include the UK National Centre for the Replacement, Refinement and Reduction (NC3Rs) of Animals in Research (URL 1), the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) which aims to reduce, refine or replace the use of animals for safety and efficacy testing of chemicals, biologicals and vaccines (URL2) and in the United States there is the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) which establishes guidelines, recommendations, and regulations that promote the regulatory acceptance of valid tests

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while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness (URL3). A recent workshop recommended that international harmonization and collaboration between human and veterinary researchers would accelerate progress on the 3Rs. This is particularly important when considering the validation and application of animal models for human disease (Stokes et al., 2012).

Although the principles of the 3Rs are becoming more deeply embedded in research, the benefit of animal research for human health is (quite rightly) open to debate and challenge and *in vitro/in silico* alternatives should be sought wherever possible. There is no doubt, however, that there are many major medical advances that would not have been made without animal models (Matthews, 2008). Ten years ago, it was proposed that there should be more systematic reviews of animal studies as this would inform more robust experimental design and ensure that research outcomes are translated to clinical benefits more effectively (Pound and Bracken, 2014). Central to this debate is the predictive value of animal models and the available alternatives for human medicine. Interspecies differences in genetics, epigenetics and physiology can all potentially influence the performance of biomedical products and therefore studies in one species may not predict performance in another. The predictive value of certain models, particularly those relating to human drug development, is still questioned and regarded as sub-optimal by some (Pound and Bracken, 2014). However, considering the cellular and molecular interactions involved in immune activation, *in vitro* observations using cell and organ culture can only go so far and cannot replicate or predict parameters such as the magnitude, quality and duration of immunity induced by vaccines. The approach therefore should be the selection of the most appropriate model available. To date, laboratory mice have been the model of choice for most immunology studies as they can be easily produced, handled and genetically manipulated. They may not always be the most appropriate model but may be the best that is available. A wider range of models to choose from should therefore ultimately reduce animal usage as the most relevant would be used for any particular given purpose.

2. Sheep as biomedical models

No animal model will exactly mimic human disease or precisely reproduce the effects of prophylactic/therapeutic agents or medical devices that are developed for human use. The choice of model depends on many factors and is dictated by the nature of the investigation/product and the relative advantages and disadvantages of each available model (Ducrot et al., 2011). Sheep are large and lend themselves to longitudinal analyses and repeat sampling from individual animals over time from a variety of anatomical compartments such as blood, lymph, and lung. Their size is a particular advantage for physiological models such as respiratory function, cardiovascular/ischemic disease, orthopaedics and reproductive/pregnancy-related disorders. They are also outbred and therefore representative of population diversity. All of these features are in contrast to the traditional small animal congenic mouse models. By comparison, mice have advantages in that they can be easily genetically manipulated and consequently have provided a wealth of mechanistic knowledge, particularly in relation to basic immunology.

There have been many published articles and reviews of sheep as models for a variety of human diseases/disorders and prophylactics/treatments. These include pregnancy disorders (Barry and Anthony, 2008), intrauterine inflammation (Melville et al., 2012; Collins et al., 2013), osteoporosis (Oheim et al., 2012), osteoarthritis (Gregory et al., 2012) respiratory syncytial virus (RSV) infection (Derscheid and Ackermann, 2012), asthma (Meeusen et al., 2009), vaccination (Scheerlinck et al., 2008), *in utero* gene therapy (Mehta et al., 2012), bacterial lung infection (Collie et al., 2013), acute lung injury and respiratory distress syndrome (Fernandez-Bustamante et al., 2012; Ballard-Croft et al., 2012), airway epithelial repair (Yahaya, 2012), preterm bronchopulmonary dysplasia (Albertine, 2013), aortic valve replacement (Martin and Sun, 2012) and stem cell therapy (Harding et al., 2013). In some cases sheep have been found to be a good model for humans (lung disease) but not for others (aortic valve replacement). It is not the purpose of this review to repeat the contents of these previously published reviews, particularly the physiological models, although we will refer to them. Here we will focus more on the immunological aspects of sheep in relation to models of disease and human disorders. To do that we firstly need to consider our capability to dissect and analyse the ovine immune system.

2.1. Identification of immunological parameters in sheep: cell subsets

Knowledge of the architecture of the immune system and the capability to measure the appropriate immunological parameters are prerequisites for validating *in vivo* models that involve immune activation and inflammation. This applies to models that investigate infectious diseases, models that evaluate vaccines and vaccine platforms and models that test orthopaedic medical devices.

Immune activation in mammals occurs through a complex series of molecular and cellular events that involves cell migration from blood and tissues to organised areas of lymph nodes where lymphoid and myeloid cells can interact in close proximity (Forster et al., 2012). Sheep have been a fundamental model for the elucidation of these processes. It is almost 30 years since a portfolio of monoclonal antibodies (Mabs) was produced to identify lymphoid cell subsets in sheep. These Mabs were fundamental to the ground-breaking studies that defined lymphoid cell subset distribution and recirculation between the blood and lymph (Mackay et al., 1985; Maddox et al., 1985; Hein and Griebel, 2003). The ability to perform lymphatic cannulation and collect cells from both efferent and pseudo-afferent lymph from peripheral sites in sheep has given major insights into immune activation and cell migration that could not be done physically in small laboratory rodents. Furthermore, cannulated sheep can be maintained for long periods (over a week) which allows for longitudinal analyses of the dynamics of immune activation in individual animals (Hein and Griebel, 2003).

One of the early discoveries using these Mabs to phenotype cell subsets in sheep was the proportion of cells expressing the T19 molecule (Mackay et al., 1989). This molecule is now known as WC1 and identifies γδT cells (Lund et al., 1993). It became clear that sheep (particularly lambs) have a very high proportion of circulating γδT cells compared to humans and mice (Mackay et al., 1989; Baldwin et al., 2014). The genes encoding γ and δ T cell receptor chains do not exhibit the high variability seen in the genes encoding α and β T cell receptor chains and γδT cells may therefore act as a bridge between innate and adaptive immunity (Hein and Griebel, 2003). The exact functional significance of this variance in γδT cells between species remains unknown but may reflect the requirement for ruminants to respond rapidly to certain pathogen challenges compared to humans and mice. Nevertheless, this difference should be considered when analysing immune activation and effector mechanisms in situations where sheep are being used for comparative immunological studies as biomedical models.

Those first studies on the compartmentalisation and activation status of cell subsets in the lymph and blood of sheep focussed predominantly on B cells and T cells as there were few Mabs at that time to reliably define myeloid cells. The studies were also conducted using single-colour flow cytometry. It is now possible to conduct

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