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Vaccines for the Elderly: The Quest for the Ideal Animal Model

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Summary
A decline in protective immune responses following vaccination is one of the main features of immunosenescence. Improved vaccine candidates for elderly adults are thus urgently needed. For scientific and regulatory requirements, such new vaccines must first be evaluated at the preclinical level, and there is a continuing quest for the ideal animal model with which to perform such studies. The main advantages and limitations of murine models, those most commonly used for human vaccine research, and of large animal models are reviewed and discussed.

Introduction
Ageing is associated with profound alterations of the immune system that are collectively termed ‘immunosenescence’. These changes contribute to the increased susceptibility to infectious diseases, the reactivation of latent infections and to the decline of protective immune responses to vaccination observed in many adults above 60–65 years of age (Jefferson et al., 2005; Goodwin et al., 2006; Kovaiou et al., 2007; Kumar and Burns, 2008). Although existing vaccines can significantly reduce the risk of complications and death from infections in the elderly compared with younger individuals (McEllhaney, 2005; Vila-Corcoles, 2007), the development of new vaccines capable of overcoming the defects of ageing is still urgently needed. For both scientific and regulatory requirements, including safety concerns, improved vaccine candidates for older adults first have to be evaluated in appropriate animal models. The relevance of the results obtained with such models is influenced by the selected animal species.

Mouse Models

Advantages
Most often, mice are the species of choice for the development of human vaccines, including those targeted at the elderly (Gerds et al., 2007). Among the major advantages of aged murine models are the commercial availability of aged mice or the possibility to raise them relatively easily in animal facilities, their well-defined genetic background and health status, their ease of handling and relative cost-effectiveness, the possibility of genetic manipulation and the availability of a wide range of specific immunological tools. Most importantly, senescent mice have been shown to display altered immune responses to vaccination (e.g. against influenza; Mbawuike et al., 1996; Asanuma et al., 2001) that reproduce some features of immune defects in the elderly (Deng et al., 2004; Goodwin et al., 2006). The utility of aged mouse models for evaluation of the immunogenicity and efficacy of novel vaccines for older individuals has been reported for several infectious diseases and pathologies, such as influenza, respiratory syncytial virus, severe acute respiratory syndrome coronavirus (SARS-CoV) or cancer (Mbawuike et al., 1996; Sambhara et al., 1998; Zhang...
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et al., 2002; Vogel et al., 2007; Posnett et al., 2009). Furthermore, the capacity of some vaccine candidates to efficiently restore the deficient immunity in senescent mice was subsequently confirmed in ageing humans (Higgins et al., 1996; De Donato et al., 1999; Podda, 2001; Holland et al., 2008).

Limitations

Despite their multiple advantages, rodent models are associated with a number of limitations. With regard to vaccination practices, the injected vaccine volume in the mouse is generally not proportional to that in man (e.g. for the intramuscular route a volume of 50 µl is injected into the mouse quadriceps muscle versus 500 µl into the human deltoid muscle). Furthermore, the injection sites, and therefore the lymph nodes targeted by immunization, often differ between mice and man. This may lead to possible differences in immune response. Strict intranasal immunization is difficult to carry out in mice, where there is a potential risk of inhalation (intrapulmonary route) or ingestion (oral route) of vaccine antigens. As for the intradermal route, the skin structure and composition differs greatly between mice and man.

With respect to vaccine efficacy studies, many mouse models extensively use inbred populations and require artificial challenge routes or excessive infection doses due to the host-specificity of most pathogens (Marco et al., 1992; Barbour et al., 1996). This can impact on the relevance of disease pathogenesis and immune correlates of protection observed in these models compared with man (Subbarao and Roberts, 2006; Gerdts et al., 2007). Regarding safety concerns, the murine models may also be unable to predict certain side-effects potentially occurring in vaccinated people. For instance, transgenic mice created to model Alzheimer’s disease (AD) immunized with fibrillar transgenic mice created to model Alzheimer’s disease (Holland et al., 2007). However, studies involving larger numbers of macaques are required to see whether a significant proportion develops allergic encephalitis as observed in Aβ-vaccinated people.

Geriatric horses might also be a promising model for testing new vaccines for ageing people (Arora et al., 2005; Muirhead et al., 2008), but further investigation is needed.

Large Animal Models

Advantages

Investigations of vaccine responses in geriatric animals other than mice have been very limited, but the use of large, aged animal models might be of great interest (Hein and Griebel, 2003; Gerdts et al., 2007). In particular, large outbred animals often permit use of a comparable route and volume of vaccination and a similar route and dose of challenge as used in man, thereby allowing collection of more relevant correlates of immune-mediated protection for people. Some of these larger species, such as pigs, are also considered more appropriate models for either mucosal or cutaneous immunization.

Recently, the effectiveness of interleukin (IL)-7 treatment to improve immunity to influenza vaccination was reported in aged rhesus macaques (Aspinall et al., 2007). Likewise, in the field of therapeutic vaccines to AD, studies have been initiated in a limited number of old rhesus monkeys to assess the efficacy and safety of Aβ immunization, considering that non-human primates have a more human-like immune system than rodents and that they naturally develop Aβ pathology with age (Gandy, 2004). However, studies involving larger numbers of macaques are required to see whether a significant proportion develops allergic encephalitis as observed in Aβ-vaccinated people.

The main disadvantages associated with such large animal models reside in their high cost, the need for specific handling skills and dedicated housing facilities and their availability in relatively low numbers, which may impact on the statistical relevance of studies conducted in these species. Moreover, there is a limited knowledge of the immune system of such models, in particular of geriatric large animals, and few specific immunological tools are available. Data have shown that the immune system of ruminants, especially of sheep and cattle, as well as that of pigs, contains many more T cells expressing the γδ T-cell receptor (TCR) than that of man (Hein and Mackay, 1991; Takamatsu et al., 2006). Furthermore, a substantial proportion of extra-thymic CD4+ CD8+ double positive T cells is described in pigs (Saalmüller et al., 1999) and these cells are rarely present in human peripheral blood. Such particularities are likely to generate differences in the immune response to vaccines between large animals and people.

Conclusions

The use of relevant animal models for developing and testing novel vaccines for the elderly is crucial, as it is for human vaccine research in general. The selection
Conflict of Interest

The author was an invited speaker at the Merial European Comparative Vaccinology Symposium and received travel expenses for this presentation.

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