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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.

Keywords: animal model; man; vaccine

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 (McElhaney, 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.

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Mouse Models

Advantages

Most often, mice are the species of choice for the development of human vaccines, including those targeted at the elderly (Gerdts *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

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 β-amyloid peptide (Aβ) showed a significant reduction of cerebral Aβ deposition and an improvement of behavioural deficits (Schenk *et al*., 1999; Morgan *et al*., 2000), but did not develop any haemorrhagic or encephalitic complications that were clinically observed among 5% of vaccinated AD patients in a phase II clinical trial (Orgogozo *et al*., 2003).

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.

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.

Limitations

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

of the most appropriate model will be the prerequisite to transfer successfully the results of preclinical research into clinical applications. The available animal models are not perfect and do not fully replicate the complexity of the aged human situation: the pre-immune status of humans (due to multiple previous infectious episodes and/or vaccinations) may differ from that of animals, while confounding factors (e.g. health status, use of medication, personal habits) are difficult to reproduce at the preclinical level. However, the use of animals lacking this complexity may allow a better demonstration of the improved immunogenicity of a candidate vaccine. The most relevant animal model is not necessarily the least expensive or the most convenient one, and there is a need to acquire more data on the immune system of large animal species, in particular during ageing.

Conflict of Interest

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

References

Arora S, Sharma S, Goel SK, Singh US (2005) Effect of different adjuvants in equines for the production of equine rabies immunoglobulins. *National Medical Journal of India*, **18**, 289–292.

Asanuma H, Hirokawa K, Uchiyama M, Suzuki Y, Aizawa C *et al.* (2001) Immune responses and protection in different strains of aged mice immunized intranasally with an adjuvant-combined influenza vaccine. *Vaccine*, **19**, 3981–3989.

Aspinall R, Pido-Lopez J, Imami N, Henson SM, Ngom PT *et al.* (2007) Old rhesus macaques treated with interleukin-7 show increased TREC levels and respond well to influenza vaccination. *Rejuvenation Research*, **10**, 5–17.

Barbour AH, Rampling A, Hormaeche CE (1996) Comparison of the infectivity of isolates of *Listeria monocytogenes* following intragastric and intravenous inoculation in mice. *Microbial Pathogenesis*, **20**, 247–253.

De Donato S, Granoff D, Minutello M, Lecchi G, Faccini M *et al.* (1999) Safety and immunogenicity of MF59-adjuvanted influenza vaccine in the elderly. *Vaccine*, **17**, 3094–3101.

Deng Y, Jing Y, Campbell AE, Gravenstein S (2004) Age-related impaired type 1 T cell responses to influenza: reduced activation ex vivo, decreased expansion in CTL culture in vitro, and blunted response to influenza vaccination in vivo in the elderly. *Journal of Immunology*, **172**, 3437–3446.

Gandy S (2004) Toward modeling hemorrhagic and encephalitic complications of Alzheimer amyloid-beta vaccination in nonhuman primates. *Current Opinion in Immunology*, **16**, 607–615.

Gerdts V, Littel-van den Hurk SD, Griebel PJ, Babiuk LA (2007) Use of animal models in the development of human vaccines. *Future Microbiology*, **2**, 667–675.

Goodwin K, Viboud C, Simonsen L (2006) Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine*, **24**, 1159–1169.

Hein WR, Griebel PJ (2003) A road less travelled: large animal models in immunological research. *Nature Reviews Immunology*, **3**, 79–84.

Hein WR, Mackay CR (1991) Prominence of gamma delta T cells in the ruminant immune system. *Immunology Today*, **12**, 30–34.

Higgins DA, Carlson JR, Van Nest G (1996) MF59 adjuvant enhances the immunogenicity of influenza vaccine in both young and old mice. *Vaccine*, **14**, 478–484.

Holland D, Booy R, De Looze F, Eizenberg P, McDonald J *et al.* (2008) Intradermal influenza vaccine administered using a new microinjection system produces superior immunogenicity in elderly adults: a randomized controlled trial. *Journal of Infectious Diseases*, **198**, 650–658.

Jefferson T, Rivetti D, Rivetti A, Rudin M, Di Pietrantonj C *et al.* (2005) Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. *Lancet*, **366**, 1165–1174.

Kovaiou RD, Herndler-Brandstetter D, Grubeck-Loebenstein B (2007) Age-related changes in immunity: implications for vaccination in the elderly. *Expert Reviews in Molecular Medicine*, **9**, 1–17.

Kumar R, Burns EA (2008) Age-related decline in immunity: implications for vaccine responsiveness. *Expert Review of Vaccines*, **7**, 467–479.

Marco AJ, Prats N, Ramos JA, Briones V, Blanco M *et al.* (1992) A microbiological, histopathological and immunohistological study of the intragastric inoculation of *Listeria monocytogenes* in mice. *Journal of Comparative Pathology*, **107**, 1–9.

Mbawuike IN, Acuna C, Caballero D, Pham-Nguyen K, Gilbert B *et al.* (1996) Reversal of age-related deficient influenza virus-specific CTL responses and IFN-gamma production by monophosphoryl lipid A. *Cellular Immunology*, **173**, 64–78.

McElhaney JE (2005) The unmet need in the elderly: designing new influenza vaccines for older adults. *Vaccine*, **23**, S10–S25.

Morgan D, Diamond DM, Gottschall PE, Ugen KE, Dickey C *et al.* (2000) A beta peptide vaccination prevents memory loss in an animal model of Alzheimer's disease. *Nature*, **408**, 982–985.

Muirhead TL, McClure JT, Wichtel JJ, Stryhn H, Frederick Markham RJ *et al.* (2008) The effect of age in serum antibody titers after rabies and influenza vaccination in healthy horses. *Journal of Veterinary Internal Medicine*, **22**, 654–661.

Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M *et al.* (2003) Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. *Neurology*, **61**, 46–54.

Podda A (2001) The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine. *Vaccine*, **19**, 2673–2680.

Posnett DN, Engelhorn ME, Lin Y, Merghoub T, Duan F *et al*. (2009) Development of effective vaccines for old mice in a tumor model. *Vaccine*, **27**, 1093–1100.

Saalmüller A, Pauly T, Höhlich BJ, Pfaff E (1999) Characterization of porcine T lymphocytes and their immune response against viral antigens. *Journal of Biotechnology*, **73**, 223–233.

Sambhara S, Kurichh A, Miranda R, Tamane A, Arpino R *et al*. (1998) Enhanced immune responses and resistance against infection on aged mice conferred by Flu-ISCOMs vaccine correlate with up-regulation of costimulatory molecule CD86. *Vaccine*, **16**, 1698–1704.

Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H *et al*. (1999) Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature*, **400**, 173–177.

Subbarao K, Roberts A (2006) Is there an animal ideal model for SARS? *Trends in Microbiology*, **14**, 299–303.

Takamatsu HH, Denyer MS, Stirling C, Cox S, Aggarwal N *et al*. (2006) Porcine gamma delta T cells: possible roles on the innate and adaptive immune responses following virus infection. *Veterinary Immunology and Immunopathology*, **112**, 49–61.

Vila-Corcoles A (2007) Advances in pneumococcal vaccines: what are the advantages for the elderly? *Drugs and Aging*, **24**, 791–800.

Vogel LN, Roberts A, Paddock CD, Genrich GL, Lamirande EW *et al*. (2007) Utility of the aged BALB/c mouse model to demonstrate prevention and control strategies for Severe Acute Respiratory Syndrome coronavirus (SARS-CoV). *Vaccine*, **25**, 2173–2179.

Zhang Y, Wang Y, Gilmore X, Xu K, Wyde PR *et al*. (2002) An aged mouse model for RSV infection and diminished CD8 + CTL responses. *Experimental Biology and Medicine*, **227**, 133–140.