DEPARTMENT for ENVIRONMENT, FOOD and RURAL AFFAIRS **CSG 15**

Research and Development

Final Project Report

(Not to be used for LINK projects)

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Project title	Development of badger vaccines
DEFRA project code	**SE3210**
Contractor organisation and location	VLA Weybridge Addlestone Surrey KT15 3NB
Total DEFRA project costs	£
Project start date	01/04/99
Project end date	31/03/02

Executive summary (maximum 2 sides A4)

One of the recommendations made by the Independent Scientific Review Group at the end of 1997 was that the option of a badger vaccine be retained as part of the strategy to combat bovine tuberculosis. This recommendation was based on a number of observations that suggested a vaccine for badger tuberculosis could be developed. Some badgers may remain uninfected, despite exposure to endemic *M. bovis* infection and some may survive for a number of years after natural or experimental infection. On-going pathological studies and the ability of the badger to survive *M. bovis* infection for prolonged periods indicate that the immune response is capable of containing infection for many years. In fact, early studies of the badger immune response to experimental infection led to the conclusion that badgers exhibit an immune spectrum during tuberculosis akin to other mammalian species. In a BCG vaccination study performed at VLA, cell-mediated immunity was apparently enhanced by BCG vaccination, and resulted in prolonged survival of *M. bovis*-infected badgers and delayed excretion of the organism.

However, the Krebs report highlighted a number of limitations associated with the development of a vaccine for badger tuberculosis. These included: 1) the lack of experimental systems available for the development and testing of a badger vaccine; 2) the lack of immunological assays for the badger; 3) restrictions on the use of captive badgers for experimental studies; and 4) the practical difficulties of delivering a badger vaccine.

Project SE3210 aimed to help retain the option of developing badger vaccines by addressing these issues through the following approaches:

- **Studies of the pathogenesis of natural TB infection in badgers**
  - To underpin the development of a relevant experimental infection model.
  - To increase understanding of the pathogenesis of disease to inform strategies for vaccination.
- **Development of vaccination/challenge models**
  - Including the mouse and (in collaboration with the Republic of Ireland) badgers.

- **Development of mucosal delivery systems**
  - Platform technology to protect BCG, DNA, and protein from acid hydrolysis.
  - Investigation of the mucosal delivery of live and subunit vaccines.
- **Development of improved vaccine candidates**
  - Determination of suitable adjuvants, subunit vaccines, and formulations using the mouse model.

Development of immunological assays for badgers is addressed in SE3213.

Main findings of the project:

- **Studies of the pathogenesis of natural TB infection in badgers**
  - A spectrum of pathology described – infected badgers have the potential to excrete *M. bovis* at early stages of disease, as well as late – *published in Vet Rec (2001)*.
  - A number of haematological and biochemical parameters found to correlate with tuberculosis - *published in Vet Rec (2000)*.
  - A panel of antibodies to nine different dog immunocyte surface markers were used for the immunohistochemical analysis of TB granulomas in fixed tissue from naturally infected badgers (in collaboration with University of Bristol) –*J Comp Pathol*, *in press*.
- **Development of vaccination/challenge models**
  - A vaccination/challenge model was established in mice and used to demonstrate the protective effect of a DNA vaccine – *published in Clin Infect Dis (2000)*.
  - Immune response detected in a population of wild badgers vaccinated with BCG (in collaboration with University College Dublin, Ireland) – *published in Vet Immunol Immunopathol (2001)*. The study proved principle that it possible to generate an immune response to vaccination with BCG in wild badgers, and highlighted the need to optimise the dose, route and regime of BCG vaccination in order to maximise the number of badgers responding.
  - Collaboration with the UCD was consolidated through a joint PhD project. VLA is now intimately involved in the experimental challenge studies that have recently been initiated in Ireland.
  - Primary badger cell cultures of epithelial and fibroblastic origin used to demonstrate the functionality of a DNA vaccine in badger cells – *published in Res Vet Sci (2001)*.
- **Development of mucosal delivery systems**
  - Dry tablet formulation developed that protects BCG, DNA and protein from acid hydrolysis but releases them at neutral pH (in collaboration with Aston Pharmacy School). A platform technology is now available for the oral delivery of live and subunit vaccines.
  - Vaccination of mice with BCG via the intranasal route induced an equivalent or higher degree of protection against systemic challenge with *M. bovis* compared with subcutaneous BCG vaccination. The protection afforded by i.n. BCG vaccination correlated with rapid production of IFNγ by lung T-cells following *M. bovis* challenge – *published in Clin Exp Immunol (2001)*.
  - Non-toxic versions of *E. coli* LT evaluated with *M. bovis* MPB70 protein look promising as adjuvants for the mucosal delivery of subunit vaccines.
- **Development of improved vaccine candidates**
  - Three mycobacterial proteins have been identified that confer promising protection to *M. bovis* challenge. These protein candidate vaccines can now be used to systematically evaluate adjuvants for their ability to improve protection, formulated either with single or combinations of proteins.

Scientific report (maximum 20 sides A4)

See Attached report.
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