



ORAL, NASAL & PULMONARY DELIVERY OF DRUGS AND VACCINES

IMMUNE STIMULATION AND ADJUVANTS

Dstl (Defence science and technology laboratory) is an agency of the UK Ministry of Defence with a research budget of some £180 million per annum. For the past decade, Dstl has been developing novel vaccines to protect against agents of biological warfare. This work has resulted in a series of patents relating to vaccine and drug delivery. Dstl is making these available for non-military use through exclusive and non-exclusive licenses via its technology transfer company, Ploughshare Innovations Ltd.

APPLICATIONS

- Single dose intranasal vaccine formulation
- Novel adjuvants based on ssRNA, Bacillus protein and chitosan
- Enhanced vaccine stabilisation
- Antiviral/anticancer formulations
- Pulmonary delivery

PATENTS

WO 2006/092607 (PIL case: P1410) describes microparticle compositions including single-stranded RNA, a stabilising agent and a biologically active macromolecule. Uses described include cancer treatment, treatment of infections and other applications based on stimulation of toll-like receptors. In this application it is demonstrated that ssRNA can be used to modulate the adaptive immunological response to a co-administered protein antigen *in vivo*. The data suggests that coencapsulation of ssRNA with protein enhances the immunogenicity of the encapsulated protein.

Examples include delivery of ovalbumin to dendritic cell culture and *in vivo* studies in mice, demonstrating potent adjuvant activity and modulation of adaptive immunological responses.

Patent status: enters national phase in September 2007.

WO 2001/70200 (P1264) describes a microparticle formulation for administration to mucosal surfaces which provides two doses of the active ingredient, allowing for single-dose vaccines. The invention focuses on a composition comprising a biologically active agent that is both encapsulated within microspheres and also either free in the composition or partially adsorbed onto, or weakly associated with, the surface of the microsphere. The higher bioavailability of the latter means that when administered it is swiftly incorporated into the system of the recipient resulting in an immediate high immune response. This initial response is then reinforced via the slow release of the agent from the microspheres. The microparticle promotes vaccine uptake into antigen presenting cells.

Licensing Opportunities

The patent has been exemplified in mice using nasal delivery of *Yersinia pestis*.

A further commercial demonstration was carried out in a murine model with pulmonary delivery of microencapsulated mycobacterial antigenic target (ESAT-6) which was shown to engender robust cell mediated response (Carpenter *et al.*)

Patent status: granted in Europe and Australia and pending in the USA, Canada and Japan.

WO 2000/56362(P1221) describes compositions including polycationic carbohydrates such as chitosan and cationic pluronics as immunostimulants for oral and nasal administration. This invention shows that when these compounds are used in the context of vaccines they act as adjuvants producing an increase in the immune response to the antigenic agent being delivered. Examples include microencapsulation of diphtheria toxoid and *Yersinia pestis* in mice.

Patent status: granted in Australia, New Zealand and Europe; pending in US, Canada and Japan.

WO2004/062651(P1349) describes biodegradable microspheres (diameter 0.5 to 5µm), containing antigen, that engender an immunological response following delivery via an aerosol, provided the microspheres are of a type which are delivered most efficiently to the lung. The inventors have found that nebulisation of PLA microspheres generates a respirable 'plume' of aerosolized particles which can be used to deliver immunogens to the respiratory tracts. This approach can also be expanded to include dry powder inhalers where such powders are stable at ambient temperatures. This would allow for the option to self-administer vaccines by inhalation, using devices such as nebulisers.

Examples include delivery of *Yersinia pestis* rV antigen in mouse models using a commercially available nebuliser.

Patent status: currently in national phase in Australia, Canada, Europe, Japan and US

WO 2006/095176 (P1413) describes a vaccine formulation comprising spore coat-associated proteins from a member of *Bacillus* genera as adjuvants. To elicit a strong mucosal immune response, particularly for intranasally administered antigens, an adjuvant is required. However, there is a requirement for effective mucosal adjuvants that are not based on toxins which, although they elicit good responses are unlikely to be licensed for use in human vaccines.

The patent has been exemplified in mice using Spore-coat associated protein N (CotN) from *Bacillus anthracis* but CotN from other Bacilli may be used, e.g. *Bacillus cereus*.

Patent status: enters national phase September 07.

Licensing Opportunities

The patents relevant to each commercial application are shown below:

Application	Patent
One shot vaccine (no booster)	P1264
Novel adjuvants	P1221,P1410 & P1413
Enhanced vaccine stabilisation	P1410 & P1349
Antiviral/anticancer formulations	P1410
Pulmonary delivery	P1264 & P1349

Relevant scientific papers:

- WILLIAMSON E.D., SHARPE G.E.J., ELEY S.M., VESEY P.M., PEPPER T., TITBALL R.W. and ALPAR H.O.
Local and systemic immune response to a microencapsulated sub-unit vaccine for plague. *Vaccine* 1996, 14: 1613-1619.
- EYLES J., SHARPE G.E.J., WILLIAMSON E.D., SPIERS I.D. and ALPAR H.O.
Intra-nasal administration of poly lactic acid microsphere co-encapsulated *Yersinia pestis* sub-units confers protection from pneumonic plague in the mouse. *Vaccine* 1998, 16: 698-707.
- ALPAR H.O., EYLES J.E. and WILLIAMSON E.D.
Oral and nasal immunisation with microencapsulated clinically relevant proteins. *STP Pharma Sciences* 1998, 8 (1): 31-39.
- FLICK-SMITH H.C., EYLES J.E., HEBDON R., WATERS.E.L., BEEDHAM R.J., STAGG AJ, MILLER J., ALPAR H.O., BAILLIE L.W.J. and WILLIAMSON E.D.
Mucosal or parenteral administration of microsphere associated *Bacillus anthracis* Protective antigen protects against anthrax infection in mice. *Infect.Immun.*2002, 70 (4): 2022-2028.
- WESTWOOD A., ELVIN S.J., HEALEY G.D.,WILLIAMSON E.D. and EYLES J.E.
Immunological responses after immunisation of mice with microparticles containing antigen and single stranded RNA (polyuridylic acid). *Vaccine* 2006, 24: 1736-1743.
- CARPENTER Z. K.,WILLIAMSON E.D. and EYLES J.E.
Mucosal delivery of microparticles encapsulated ESAT-6 induces robust cell-mediated responses in the lung milieu.

Licensing Opportunities

Licensing

Ploughshare is able to license the above patents and related know how for single or multiple applications. Support from within the Dstl organisation in technology transfer and further development may be available.

For further details please contact:

Dr. James Hamilton

T: 01980 590073

E: Jameshamilton@ploughshareinnovations.com