of drug targeting technology. The problem is that drug targeting science in the year 2001 is at an embryonic stage and is rarely mentioned in the context of modern pharmaceutical development. Certainly, drug delivery is part of the pharmaceutical fabric, but drug delivery relates to controlled release of drugs and emanates from the material sciences. Drug targeting involves the movement of drugs through biological membranes, generally via endogenous transport systems, and originates in transport biology. The future application of genomics will lead to the discovery of thousands of new protein drug candidates[3]. However, future development of protein drugs will be limited, in many cases, by the ability to target these large molecule drugs to spaces deep within target cells. The use of antisense radiopharmaceuticals for the imaging of gene expression in humans *in vivo* is just one of many examples of future development of large molecule pharmaceuticals that will not be possible without the availability of effective drug targeting technology.

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Drug delivery

Adjuvancy enhancement by modulated release from microspheres

Compared with traditional vaccines based on heat-killed viruses, vaccines based on subunits, recombinant proteins or synthetic peptides are less immunogenic. The latter types of vaccines will require better adjuvants and/or delivery systems to induce an optimal response. Muramyl dipeptide (MDP) is an important immunostimulating compound under investigation as an adjuvant in human vaccines. It is the immunostimulating compound present in Complete Freund's Adjuvant (CFA), and maintains the adjuvant activity without the severe adverse effects of CFA. Unfortunately, when MDP is administered as a bolus, it is pyrogenic. There have been efforts to develop sustained release dosage forms of MDP to lower the dosage and reduce the adverse effects but the effect of these continuous release dosage forms on the immune response of adjuvants has not yet been assessed in animal models. Threonyl-MDP, which is an analog of MDP synthesized by replacing the alanine amino acid in MDP with threonine, is also under investigation as a possible adjuvant. Threonyl-MDP is more potent and less pyrogenic compared with MDP itself.

Puri *et al.* have recently reported an *in vivo* investigation of sustained release dosage forms of MDP and threonyl-MDP, and the resulting impact on adjuvant effect[1]. Ovalbumin microspheres (OVA-MSs) loaded with MDP were prepared from ovalbumin (OVA), glutaraldehyde and MDP by an emulsion technique. OVA-MSs possessing various degrees of crosslinking and matrix densities were prepared in order to study the effects of these properties on the resulting *in vitro* release rates of MDP. The *in vitro* MDP release rate exhibited a triphasic profile consisting of an initial burst, a sustained release phase and a terminal rapid release phase. The total amount of MDP released was inversely proportional to the degree of crosslinking and the matrix density of the OVA-MSs.

The *in vivo* effects of MDP- (and threonyl-MDP) loaded OVA-MSs were then studied. Mice were immunized intradermally in various treatment groups to investigate the factors affecting an antibody response to OVA. The factors investigated included the crosslinking and matrix density of OVA-MSs. Mice given a single immunization of MDP-loaded OVA-MSs exhibited an enhanced OVA antibody response for three months. An inverse relationship between the *in vitro* release rate of MDP from OVA-MSs and an *in vivo* antibody response was observed. Threonyl-MDP-loaded OVA-MSs produced better results than those loaded with MDP. Immunization with threonyl-MDP-loaded OVA-MSs led to a significantly increased induction of antibody response compared with MDP-loaded OVA-MSs. The sustained release of MDP also enabled a reduction in its dosage. The MDP dose in this study was 25% of that of previous studies and still resulted in a high antibody response for three months after a single immunization. This is the first reported observation of enhanced *in vivo* antibody response in the presence of continuous, controlled release of an adjuvant. Microsphere-modulated delivery of adjuvants might have applications in future vaccines.

Controlled release of nerve growth factor

The neurotrophin family is a group of growth factors that stimulate nerve growth and regeneration. Included in the family are β-nerve growth factor (β-NGF), brain-derived neurotrophic factor, and neurotrophin-3. *In vivo* experiments, in which β-NGF was added to nerve guide tubes, have resulted in increased nerve regeneration but it has proven difficult in these experiments to maintain growth factor release over the rather long duration of nerve regeneration. A delivery system that would provide prolonged release of active growth factor over the entire duration of wound healing would be very desirable. Heparin-containing delivery systems have been used to immobilize high affinity heparin-binding growth factors and protect them from degradation. However, the

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delivery of growth factors with low heparin-binding affinities using heparin-containing delivery systems has not been previously reported. β-NGF possesses a low binding affinity for heparin and has even been used as a negative control in experiments involving heparin-binding proteins[2].

Sakiyama *et al.* have recently reported the potential for a neurotrophin delivery system which utilizes a fibrin matrix. Within the matrix, heparin-binding peptides were covalently immobilized to fibrin, heparin was bound to these immobilized peptides, and β-NGF was non-covalently associated with the heparin (Ref. 3). Heparin binding peptides were cross-linked into fibrin matrices during polymerization and these covalently immobilized heparin-binding peptides were then used to sequester heparin within the fibrin matrix. The polymerization was performed in the presence of β-NGF. The resulting delivery system matrix possessed a high excess of heparin sites to β-NGF. Thus, despite the low affinity of β-NGF for heparin, a sustained release of the growth factor is exhibited from the heparin-containing fibrin matrices. Without the heparin delivery system, almost all of the β-NGF within an unmodified fibrin matrix was released within the first day. A fibrin matrix containing the heparin delivery system released approximately 50% of the initial total β-NGF the first day, and after 15 days 30% of the initial β-NGF remained in the matrix. The modified fibrin matrix containing heparin-binding peptide, heparin, and β-NGF also enhanced neurite extension in a cell culture study. When chick dorsal root ganglias (DRGs) were incubated in the presence of an unmodified fibrin matrix containing β-NGF but with no heparin or heparin-binding peptide, no enhancement of neurite extension was observed. When DRGs were incubated in the presence of the fibrin matrix containing delivery system, a 75% enhancement of neurite extension was observed. The prolonged release of nerve growth factor from an implantable matrix could be beneficial for applications in nerve regeneration, when the regeneration process could take up to weeks or months.

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