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Lipopeptide-Based Vaccines

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INTRODUCTION

The move to rational design of vaccines can, at least in part, be attributed to the demands of authorities for compliance with a host of regulatory requirements. The ability to *rationally* design the next generation of vaccines can be attributed to our increasing understanding of how the immune system recognizes antigen and how it then responds to it. The most relevant fields of discovery that have enabled this are (*i*) an awareness of the role that short peptide sequences, the *epitopes*, play in immune recognition; (*ii*) an appreciation that among the first cells to encounter pathogens are cells of the *innate* immune system of which the dendritic cell (DC) is of particular importance; and (*iii*) an understanding of the different types of immune responses that are associated with recovery from infection. Information from all of these areas provides us with insights as to the form of antigen and its method of delivery that will lead to an appropriate immune response.

As details of the rules governing antigen recognition and stimulation of the immune system have emerged, a rapidly increasing literature and an escalation in the inventory of vaccine technologies have followed, promising new and improved approaches to immunization. Among these technologies is the utilization of synthetic peptides, which have been the tools of immunologists for many years. Although the use of peptides has been largely restricted to their application in basic research, the prospect of making totally synthetic vaccines has been a recurring theme. The concept of using synthetic peptides as a basis for vaccine design is simple; if the epitope that is recognized by an antibody or a T cell or some other effector of the immune system is known, then a vaccine can be designed around that epitope. A simple idea perhaps but the method of delivery of the epitope(s) is of paramount importance and our ignorance of that has delayed the realization of totally synthetic vaccines.

Once the basis of recognition of short peptides by receptors on T lymphocytes was understood, peptide epitopes became an obvious choice for inducing T-cell immunity (1–3). Furthermore, because some antigens possess B-cell epitopes that can be mimicked by synthetic peptides, epitope-based vaccine candidates were also investigated for their ability to induce antibody-based immunity (4–6). Short peptides, however, induce T- and B-cell responses only when administered with potent adjuvants (7,8). We now understand that this is because simple peptides lack features that are an inherent property of many proteins or other components of invading pathogens that the immune system has evolved to recognize as foreign and dangerous. With this knowledge we are now in a position to apply some of what we know about the ligands that provide these ''danger signals'' that are relayed by receptors, such as the Toll-like receptors (TLRs) present on antigen-presenting cells (APCs), and incorporate these ligands into new candidate vaccines. We are also beginning to apply what we know about the transport mechanisms operating in cells to transport vaccine cargos into the correct compartments for appropriate antigen processing.

Apart from an appreciation of the importance that short peptide sequences play in the induction of immunity, a number of technical advances have contributed to the feasibility of designing totally synthetic vaccines. Long sequences of amino acids can now be synthesized with confidence using modern synthesizers, including those that make use of microwave technology to facilitate coupling reactions (9). These instruments now make the synthesis of small proteins ($\geq$60 amino acids) feasible. Chemoselective ligation procedures (10–21) allow synthetic peptide *modules* to be ligated, producing multimeric immunogens. The ability to assemble multivalent antigens allows us to incorporate different epitopes from multiple serotypes of pathogens as well as series of epitopes that cover the polymorphic class I and class II molecules of the major histocompatibility complexes (MHCs) within the target species.

Advocates of peptide or epitope-based vaccines have been pursuing their trade for three decades, starting perhaps with the encouraging and seminal study of Langbeheim et al. (22) in 1976, where antibodies raised against MS-2 coliphage synthetic fragments were able to neutralize the virus. Since then, however, the poor immunogenicity of peptides, the difficulty in raising antibody against native antigens using epitope approaches and the problems of multivalency, have produced a general air of disenchantment in the minds of many vaccinologists and also of those in control of strategic policy within pharmaceutical companies when it came to considering totally synthetic vaccine strategies. Now, with these new technical advances and insights into immune mechanisms, there has been a paradigm shift, resulting in a major revision in the way in which epitope-based vaccines are viewed. The recent design of successful peptide-based vaccine candidates against infectious diseases including viruses (23–27), bacteria (27–30), parasites (31–34), as well as tumors (35–38) and self-hormones,