International Congress Series 1289 (2006) 307–310

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The lipid core peptide system in vaccine delivery

Istvan Toth [a,*], Peter Moyle [a], Levente Karpati [a], Aniko Horvath [a], Colleen Olive [b], Michael Good [b]

[a] *School of Molecular and Microbial Biosciences, The University of Queensland, Australia*
[b] *Queensland Institute of Medical Research, Queensland, Australia*

Abstract. Lipid core peptide (LCP)-based group A streptococcal (GAS) vaccines incorporating numerous GAS M-protein epitopes have been synthesized in high purity. The LCP system incorporates adjuvant, carrier, and antigens into a single well-characterized construct. A tetra-epitopic vaccine, incorporating a highly conserved GAS M-protein C-terminal epitope and three strain-specific epitopes from the variable GAS M-protein N-terminal region, was synthesized using stepwise solid-phase peptide synthesis. Immunization of mice with this construct yielded high IgG antibody responses without the use of traditional adjuvants.

Keywords: Immunoadjuvants; Vaccine delivery; Vaccine design; Streptococcal infection; LCP system

1. Introduction

In general, short synthetic peptides do not elicit effective antibody responses when administered alone. These peptides are normally coupled to larger proteins such as keyhole limpet haemocyanin (KLH) or bovine serum albumin (BSA) in order to provide the necessary T-cell help required to elicit strong antibody responses to the peptides of interest. As an alternative, several approaches have been investigated to enhance the antigenicity of synthetic peptides for human use. The multiple antigen peptide (MAP) system [1] is based upon a polylysine core onto which multiple copies of immunogenic peptides are synthesized. Another example uses synthetic analogues of the bacterial lipoprotein N-terminus (Pam_3Cys), which effectively activates macrophages, neutrophils and lymphocytes [2]. In the LCP system [3], the carrier, adjuvant and antigen are contained in the same molecular entity (see Fig. 1). A further approach is epitope polymerization [4,5];

* Corresponding author. Tel.: +61 7 3346 9892; fax: +61 7 3365 4273.
E-mail address: i.toth@uq.edu.au (I. Toth).

0531-5131/
doi:10.1016/j.ics.2005.11.057

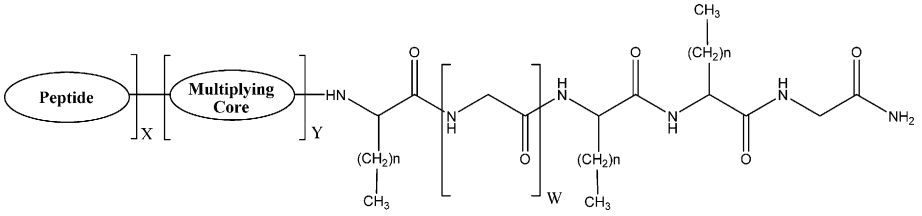

Fig. 1. The lipid core peptide (LCP) system.

however, this technique results in a chemically ambiguous product, resulting in purification and characterization difficulties. In the case of MAP and LCP systems, the number of different peptide epitopes that can be incorporated into the construct is limited. This may be problematic when developing vaccines intended to provide broad strain coverage, however, this may be overcome by mixing different LCP constructs together.

2. Material and methods

We have designed and synthesized a vaccine candidate which contained three [P2: 8830 DNGKAIYERARERALQELGP; P3: NS1 RVTTRSQAQDAAGLKEKAD; and P4: PL1 EVLTRRQSQDPKYVTQRIS] of seven common amino terminal serotype epitopes, the sequence of which were derived from group A streptococcal (GAS) isolates obtained from the Northern Territory of Australia – a region highly endemic for GAS [5]. We also included a conserved epitope (P1: J8: QAEDKVKQSREAKKQVEKALKQLEDKVQ) in order to generate a vaccine with broader strain coverage (see Fig. 2).

2.1. Synthesis of the LCP systems [LCP-J8-8830-NS1-PL1 (see Fig. 2) and LCP-J8-8830-PL1]

LCP constructs containing three 2-aminododecanoic acid residues, two glycine spacers, and two copies of the J8, 8830, and PL1 epitopes were synthesized on MBHA resin using Boc chemistry. LCP-J8-8830-NS1-PL1 also included two copies of the NS1 epitope. A glycine spacer was employed between the MBHA resin and the first C12-LAA. Previous experiments indicated that higher antibody responses were achieved by incorporating glycine as a spacer between the second and third C12-LAA residues [6]. To introduce different peptide epitopes into the LCP system, orthogonally protected Boc-Lys(Fmoc)-OH was employed. The LCP construct was removed from the resin using hydrogen fluoride, and characterized by SDS–PAGE and/or electrospray ionization mass spectrometry.

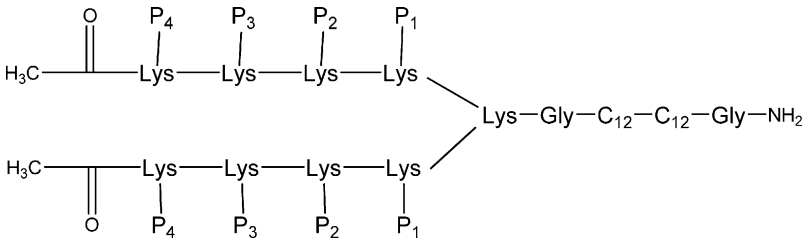

Fig. 2. The LCP-J8-8830-NS1-PL1 construct.