Synthetic oligosaccharide vaccines

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OBJECTIVE

Development of synthetic vaccines based on oligosaccharide conjugates against infections by Streptococcus pneumoniae.

INTRODUCTION

There exist 82 different serotypes of S. pneumoniae based on 82 different capsular polysaccharides. The capsular polysaccharide is responsible for the virulence of the bacterium. It prevents phagocytosis in the absence of specific antibodies. The defense mechanism to S. pneumoniae is based on humoral immunity: antibodies directed to the capsular polysaccharide will protect mice and humans to infection with viable pneumococci.

THE CURRENT VACCINE

A multivalent polysaccharide vaccine (Pneumovax^{R} 23) is available for persons older than 2 years believed to be at high risk for pneumococcal disease, including those aged 50 years and older and those with chronic systemic illness. A number of disadvantages still remain with this whole polysaccharide vaccine due to the inherent character of polysaccharide. Polysaccharides are non-immunogenic in newborns and do not induce an immunological memory, whereas tolerance induction is a severe problem.

A NEW APPROACH

Antigen presentation is possible via incorporation of antigenic determinants into liposomal membranes. Using naturally derived antigenic oligosaccharide determinants of polysaccharides from pathogenic bacteria, semisynthetic vaccines can be prepared.

GENERAL STRATEGY

- Preparation of oligosaccharides, being partial structures of capsular polysaccharides of different serotypes of S. pneumoniae:
  * via chemical and/or endoglycosidase degradation of isolated polysaccharides
  * via organic chemical and glycosyltransferase routes from monosaccharides

- Preparation of endoglycosidases and glycosyltransferases via recombinant-DNA techniques
- Inhibition assays with the different oligosaccharides prepared, aimed at the determination of the precise epitope
- Conjugation of the epitopes with lipid carriers as stearylamine and phosphatidylethanolamine
- Insertion of the oligosaccharide-lipid conjugates noncovalently within liposomes which are as such non-immunogenic
- Testing of the liposomes for their immunogenicity in mice
- Modulation of the immune response by adjuvants to optimize the effect
- Protective immunity in newborns

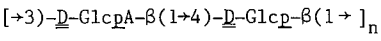
TESTING OF THE STRATEGY

This approach has already been worked out successfully for S. pneumoniae type 3. The hexasaccharide [→3)-D-GlcpA-β(1→4)-D-Glcp-β(1→]$_3$ was isolated from a partial acid hydrolysate of the capsular polysaccharide S3. It was coupled to stearylamine by reductamination with $NaCNBH_3$, and then incorporated into liposomes. These haptenated liposomes were tested for immunogenicity in mice. They induced protection to a lethal dose of S. pneumoniae.

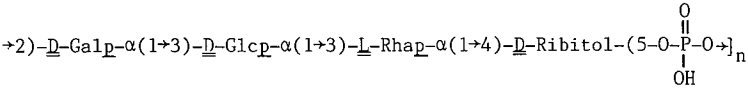
PRESENT INVESTIGATIONS

The present investigations are directed to S. pneumoniae serotypes 6B and 14. The results obtained for serotype 3 are subject of further optimalization.
Primary structures of the capsular polysaccharides:

S3



S6B



S14