Perspective/Review

Immunology of bacterial polysaccharide antigens

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Abstract

Carbohydrates in the form of capsular polysaccharides and/or lipopolysaccharides are the major components on the surface of bacteria. These molecules are important virulence factors in many bacteria isolated from infected persons. Immunity against these components confers protection against the disease. However, developing vaccines based on polysaccharides is difficult and several problems have to be solved. First of all, most of the bacterial polysaccharides are T-lymphocyte independent antigens. Anti-polysaccharide immune response is characterised by lack of T-lymphocyte memory, isotype restriction and delayed ontogeny. Children below 2 years of age and elderly respond poorly to polysaccharide antigens. Secondly, the wide structural heterogeneity among the polysaccharides within and between species is also a problem. Thirdly, some bacterial polysaccharides are poor immunogens in humans due to their structural similarities with glycolipids and glycoproteins present in man. The T-lymphocyte independent nature of a polysaccharide may be overcome by conjugating the native or depolymerised polysaccharide to a protein carrier. Such neoglycoconjugates have been proven to be efficient in inducing T-lymphocyte dependent immunity and to protect both infants as well as elderly from disease. Another approach to circumvent the T-lymphocyte independent property of polysaccharides is to select peptides mimicking the immunodominant structures. Several examples of such peptides have been described.

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Keywords: Bacterial polysaccharides; Immunology; Present and future vaccines

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1. Introduction

The surface of many bacterial species is covered by polysaccharides. These can be in the form of capsules, glycoproteins or glycolipids. In Gram-negative bacteria, the lipopolysaccharide (LPS) also referred to as endotoxin, covers ca. 40% of the bacterial surface. The capsular polysaccharides (CPS) are made up of either monosaccharides making a homopolymer like α-(2 → 8)-linked sialic acid in *N. meningitidis* and *Escherichia coli* K1, or from repeating units normally consisting of two to six sugar residues. The CPS may be present in both Gram-negative bacteria such as *N. meningitidis, Haemophilus influenzae, E. coli* or *Salmonella typhi* and in Gram-positive such as *Streptococcus* and *Staphylococcus*. In most cases the bacterial CPSs are acidic. The glycolipid LPS is only present in Gram-negative bacteria and is part of the outer membrane. It is built of a lipid part and a polysaccharide part. The polysaccharide can be divided in a core oligosaccharide proximal to the lipid part and an O-polysaccharide. The O-polysaccharide is, like the CPS, either a homopolymer (*Vibrio cholerae* O1, *Brucella abortus, B. melitensis*) or made up from repeating units which may be di- to hexasaccharides.

It is well established that an immune response against the surface polysaccharides confers protection against the disease. The immunological properties of bacterial CPSs became the target of several investigators in the 1920s and 1930s. In the mid-1940s it was evident that: (i) CPS elicited type-specific protective immune responses;1–4 (ii) infants and young children did not respond with type-specific antibodies;5–8 (iii) type-specific antibodies conferred protection;6,9 (iv) vaccination with polysaccharides reduced the carrier rate of bacteria of the same types as in the vaccine10 and (v) neoglycoconjugates using oligosaccharides covalently linked to a carrier protein, could, in rabbits, induce high titred antibody responses which were, boostable and protective against challenge infection.10,11

However, the introduction of antibiotics put an effective stop for several decades to the development of vaccines based on either CPSs or neoglycoconjugates. In the 1970s, it was realized that treatment with antibiotics, although largely successful, was not the ultimate solution to handle infections. Advances in immunology with delineation of B and T lymphocyte responses, and the role of T lymphocytes for the immunological memory functions, as well as the structural elucidation of the surface polysaccharide made possible the development of new, polysaccharide-based vaccines. Today, several vaccines based on either purified CPSs or on neoglycoconjugates are available.

In spite of the increased knowledge in immunology, there are several problems that remain to be solved:

i) Carbohydrate antigens exhibit a large degree of antigenic variation. This is evident from structural differences in the surface polysaccharides within the same species and is the basis of serogrouping or serotyping systems. For example, to date over 10 different serogroups of *N. meningitidis* and over 90 different serotypes of *Streptococcus pneumoniae* based on the CPSs have been identified. The number of LPS O-antigens for several species is exceeding well over 100. In addition, anti-polysaccharide antibodies are usually, serotype/serogroup-specific.

ii) Homology between carbohydrate structures present on bacterial surface and those of host cell membranes have been reported. For example, the *N. meningitidis* serogroup B CPS as well as the *E. coli* K1 antigen are antigenically similar to structures expressed on human foetal neuronal cells12 and consequently, poor immunogens in humans. Therefore, the use of *N. meningitidis* serogroup B CPS in a vaccine has the potential risk of inducing autoantibodies.12 The mimicry of host associated carbohydrate structures by bacterial polysaccharides could be a potential virulence and evasion factor.

iii) Polysaccharide antigens are mostly poor immunogens due to their T-lymphocyte independent (TI) nature. Often, anti-polysaccharide immune response is characterised by lack of T-lymphocyte memory, isotype restriction and delayed ontogeny.13 Children below 2 years of age and elderly respond poorly to polysaccharide antigens.14

The purpose of this review is to shed some light on the advantages and disadvantages of the use of bacterial polysaccharides in vaccines and on recently described alternative ways to induce immunity against polysaccharide structures.

2. Clinically important bacteria and their polysaccharides

2.1. Diversity of bacterial surface carbohydrates

A list of some examples of clinically important bacterial species and the approximate numbers of now known serogroups and/or serotypes is shown in Table 1. The serogrouping/serotyping is based on the reactivity of specific antibodies, often generated in animals, using reference strains of particular species, with the microorganism. The specific antibodies are usually directed against the surface polysaccharide antigens, either the CPS or against the polysaccharide part of the LPS. The reactivity of the antibodies reflects the structural diversity of the polysaccharides. As seen in Table 1, several species are highly heterogeneous in terms of the numbers of CPS and/or LPS structures. Serotyping of micro-
organisms is of great importance mainly from the epidemiological point of view. In epidemics or local outbreaks of a certain disease, it is important to monitor the spread of the causing agent and serotyping, if possible, is the simplest tool. In addition, certain diseases caused by some bacterial species may be limited to a few serotypes or serogroups. There are several examples of this phenomenon, *Vibrio cholerae* being one. Although more than 200 serotypes of *V. cholerae* are now recognised, until a decade ago, only *V. cholerae* serotype O1 was isolated from patients with the cholera disease. In 1992, a new serotype causing epidemic cholera emerged and was designated *V. cholerae* O139. The major differences between the *V. cholerae* O1 and O139 are the structures of the cell wall associated polysaccharides.

Another example is the species *E. coli*. This species, at present comprises more than 70 CPS antigens i.e., K-antigens and more than 170 O-antigens. *E. coli* may cause different types of disease like urinary tract infections, diarrhoea, septicemia and meningitis. The diarrhoeagenic *E. coli* strains can be further divided into different categories, based on the type of illness it causes. This is due to the fact that the different *E. coli* strains produce different virulence factors in the form of toxins, colonization factors or others. Many of these virulence factors are encoded by plasmids, yet they are associated with certain serotypes. For example, the enterohaemorrhagic *E. coli* strains are restricted to O26, O55, O111ab, O113, O117 and O157 serogroups, while among the enterotoxigenic *E. coli* more than 13 different serogroups are prevalent.

The species *S. pneumoniae* is divided into more than 90 serotypes based on the CPS structure. However, the present 23-valent vaccine covers more than 90% of the *S. pneumoniae* serotypes isolated from infections.

### 2.2. Polysaccharides as T lymphocyte independent antigens

Immunologically, an antigen can be classified either as T lymphocyte dependent (TD) or T lymphocyte independent (TI). Proteins and peptides are usually TD antigens since they require stimulation from helper T lymphocytes in order to elicit an immune response. The TD antigen is presented to T lymphocytes by the Major Histocompatibility Complex (MHC) molecules present on macrophages, B lymphocytes or dendritic cells. TD antigens induce an immune response that is long lasting due to formation of memory B and T lymphocytes. The antibodies against TD antigens are of high affinity and of multiple isotypes (IgA, IgM, IgG1, IgG2a, IgG2b, IgG3). The affinity of an antibody is a thermodynamic parameter that quantifies the strength of the association between the antibody and the antigen and depends on the structural complementarity of the binding site on the antibody and the binding site on the antigen.

In contrast to TD antigens, the TI antigens do not give rise to immunological memory neither do they require T lymphocytes to induce an immune response. Memory responses are characterized by the production of high-avidity antibody, i.e., antibodies strongly binding to the antigen. A majority of carbohydrates are categorized as TI antigens in nature.

The TI antigens are further divided into TI type 1 and TI type 2 based on their interaction with B lymphocytes. 14,19 TI type 1 antigens are defined as antigens capable of inducing proliferation and differentiation of both naïve and mature B lymphocytes. 20 These antigens activate B lymphocytes and may induce immune responses in neonates, adults and in mice with an X-linked B lymphocyte defect (*xid*). 14 19–21 Common examples of the TI type 1 antigens are the bacterial LPS.

Conversely, TI type 2 antigens are of high molecular mass repetitive polysaccharide structures that exhibit no intrinsic B lymphocyte stimulating activity. 20 These antigens are also characterized by their poor in vivo degradability and inability to stimulate MHC class II restricted T lymphocyte help. 22,23 TI type 2 antigens will activate only mature B lymphocytes and most likely act by cross-linking the cell surface immunoglobulin (Ig) of specific, mature B lymphocytes. 20 This results in the production of antigen-specific antibodies. However, the TI-type 2 antigens are not suitable as vaccines for children below 2 years of age and for adults above 65 years of age since these populations do not respond.

<table>
<thead>
<tr>
<th>Species</th>
<th>Capsular polysaccharide</th>
<th>O-antigen/immunotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>1 (Vi antigen)</td>
<td>&gt;40 major serogroups</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>&gt;70</td>
<td>&gt;170</td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td></td>
<td>&gt;40</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>1 (O139)</td>
<td>&gt;200</td>
</tr>
<tr>
<td><em>N. meningitidis</em></td>
<td>&gt;10</td>
<td>&gt;10 (immunotypes)</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>&gt;80</td>
<td>&gt;10</td>
</tr>
<tr>
<td><em>Citrobacter</em></td>
<td>None</td>
<td>&gt;40</td>
</tr>
<tr>
<td><em>Hafnia</em></td>
<td>?</td>
<td>&gt;60</td>
</tr>
<tr>
<td><em>Proteus</em></td>
<td>?</td>
<td>&gt;60</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>6 (a–f)</td>
<td></td>
</tr>
<tr>
<td><strong>Gram-positive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus</em></td>
<td>&gt;90</td>
<td></td>
</tr>
<tr>
<td><em>pneumoniae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus</em></td>
<td>&gt;10</td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td>&gt;6</td>
<td></td>
</tr>
</tbody>
</table>

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Table 1: Number of serogroups/serotypes in some clinically important bacterial species

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2.3. Encapsulated bacteria, disease and vaccine

2.3.1. Haemophilus influenzae type b (Hib). Haemophilus influenzae is a Gram-negative microorganism that is often found in the oropharynx of man. The majority of H. influenzae strains are non-encapsulated, generally called non-typable H. influenzae—NTHi. However, some strains may be encapsulated. Six structurally different CPS types, a to f, have been recognized with type b being the most common type isolated from infections. H. influenzae type b, Hib, causes meningitis, epiglottitis, septicaemia and pneumonia. Before the availability of a vaccine, most Hib infections occurred in children, below 5 years of age. In this age group, the incidence of invasive Hib infection ranged from 30 to 100 cases per 100,000 in Europe and the USA. Adults rarely get invasive Hib infections unless there is a predisposing underlying disease. An annual incidence of 0.22 per 100,000 has been reported. The peak incidence of Hib disease in the pre-vaccine era was in children between 5 and 12 months of age, coinciding with the disappearance of maternal antibodies and prior to appearance of anti-capsular antibodies. A large scale double-blind study in Finland 30 years ago of some 100,000 children between 3 months and 5 years of age showed that (i) children above 18 months were protected with an efficacy >90%, (ii) children between 12 and 18 months had little protection, and (iii) no protection was seen in the age group of 3–12 months.

2.3.2. Hib capsular polysaccharide vaccine. The protective role of antibodies to the Hib CPS was known already in 1933. The Finnish study with purified Hib CPS as vaccine demonstrated the relationship of bactericidal anti type b specific antibodies and protection against the disease. Adults regularly have antibodies to the Hib CPS. The vaccinations with purified Hib CPS resulted in low levels of specific antibodies. It is, however, important to note that these antibody concentrations are the result of immunization with the TI-type 2 antigen lacking the ability to induce immunological memory response. It has recently been shown that antibody avidity was relatively low following primary immunization, and significantly higher following boosting. Most of the increase in avidity was observed for a few months after the primary immunization.

2.3.3. Streptococcus pneumoniae. Streptococcus pneumoniae is still a major cause of morbidity and mortality in adults and children despite the availability of effective antimicrobial therapy, although resistance against several of the common antimicrobial agents is an emerging problem worldwide. The virulence is caused by the CPS, and there are now >90 different capsular types described. The clearance of the infecting bacteria depends on the presence of type-specific antibodies against the CPS. Due to interaction of the antibodies with complement, the bacteria are opsonised and phagocytised.

Pneumococci are responsible for a variety of infections ranging from mild mucosal infections like otitis media, to serious bronchopneumonia and potentially life threatening meningitis. Pneumococci colonize the respiratory mucosa of both healthy and sick individuals. Healthy adults and children may carry pneumococci, however, the carrier rate is higher in children especially those attending day care centres, and still higher in those with respiratory infections compared with healthy children. The illness is a result of the spread of the pneumococci to tissues from the oropharynx. Epidemiological studies in the 1980s have found an annual incidence of pneumococcal bacteraemia to be between 9 and 18 cases per 100,000 persons of all ages. In children, the rate varied from 105 to 234 cases per 100,000 individuals.

It has been estimated that in the USA there is on an annual basis 3000 cases of meningitis, 50,000 of bacteraemia, 500,000 of pneumonia, and 7,000,000 cases of acute otitis media. Approximately 40,000 deaths caused by pneumococci occur each year in the USA. In developing countries it has been estimated that acute lower respiratory infections caused by pneumococci account for more than 4 million deaths annually, most of them in children being below 5 years of age.

2.3.4. Streptococcus pneumoniae capsular types. The immunogenicity and immunochemistry of pneumococcal CPSs has been reviewed recently. Of the >90 capsular types identified, only a few are common causes of pneumococcal disease. The seven most commonly isolated serotypes cover up to 85% of all pneumococcal strains causing invasive infections in children. Some of the available pneumococcal polysaccharide vaccines are composed of 23 of the most common pneumococcal serotypes. They represent 85–90% of the serotypes that cause invasive infections in adults in industrialized countries. As mentioned before, children do respond poorly to CPSs up to the age of 2 years, and the least immunogenic pneumococcal serotypes (6B, 14, 19F, 23F) up to the age of 5–10. In addition, the pneumococcal polysaccharides are TI type 2 antigens and fail to induce a memory function.

2.3.5. Neisseria meningitides. Meningitis caused by N. meningitidis is a serious disease with high mortality. The major virulence factor in meningitis caused by N. meningitidis is a CPS. N. meningitidis is an exclusively human pathogen, and transmission is accomplished by droplets from colonized upper respiratory mucosal
membranes. There are more than 10 serogroups based on the structure of the CPS, however, > 90% of cases of meningitis are caused by strains belonging to serotypes A, B, C, W135 and Y. All five serotypes can cause epidemics. However, the group A strains are the causative agent in repeating epidemics in sub-Saharan Africa. In Europe and Latin America serogroup B is most prevalent, causing more than 50% of the cases, whereas serogroup C is most prevalent in North America. Meningococcal meningitis is spread all over the world and affects all age groups. Therefore there is a need to vaccinate the whole population. Already in 1913, Flexner showed that serum containing specific anti-CPS antibodies, when used therapeutically, decreased the fatality rate of meningococcal meningitis.

3. Neoglycoconjugate vaccines

3.1. Haemophilus influenzae b (Hib) neoglycoconjugate vaccine

In the early 1990s, different Hib conjugate vaccines were introduced and resulted in a dramatic reduction of meningitis in children in Finland, the UK and the USA. The reported efficacy for infants below 1 year was 99%, for 1–2 year old infants, 97% and for 2–3 year old children it was 94%. Another benefit of the Hib conjugate vaccines was a reduction of carriage of Hib, that probably led to lower transmission rates to children who lacked protective antibodies.

3.2. Meningococcal neoglycoconjugates

Purified CPSs from serogroups A, C, W135 and Y are marketed vaccine products, and as TI type 2 antigens elicit antibody responses with no memory function, with the possible exception of serogroup A polysaccharide which induces an antibody response also in infants. The serogroup C polysaccharide is not immunogenic in children below 2 years of age, and development of antibody titers is slow. Neoglycoconjugates are being developed using the same principles as for Hib. The type A and C neoglycoconjugate vaccines are safe and well tolerated in infants and young children. A three-dose regime for primary immunisation resulted in specific anti-A and anti-C polysaccharide antibody titers. All vaccinated children had elevated titres of bactericidal antibodies. So far, all data indicate that meningococcal neoglycoconjugate vaccines will have as great a chance to be successful as the Hib. Most likely, meningococcal A+C and meningococcal A+C+W135+Y neoglycoconjugates will be soon available on the market.

3.2.1. Meningitidis serogroup B. The meningococcal serogroup B polysaccharide, a homopolymer of (2→8)-linked sialic acid residues, is poorly immunogenic in man. The development of an effective vaccine against N. meningitidis serogroup B is complicated by the inability of this polysaccharide to induce a significant antibody response even when conjugated to a carrier protein. The poor immunogenicity of the serogroup B polysaccharide is due to immunologic tolerance induced by foetal exposure to cross-reactive polysialylated glycoproteins expressed in a variety of host tissues, such as neuronal cell adhesion molecules.

3.3. Other neoglycoconjugates

The success of the Hib conjugates resulted in a focused interest on converting other CPS antigens from TI to TD antigens. Group B streptococci (GBS) are the major cause of meningitis and sepsis in neonates. At least six capsular types have been associated with human disease, and type-specific antibodies are responsible for protection via opsonisation of the bacteria and interaction with the complement cascade. Immunogenic neoglycoconjugates have been developed able to induce protective antibodies in animals. Similar attempts have been made to develop immunogenic and safe vaccines against the Vi polysaccharide of S. typhi and CPS and LPS of E. coli, S. sonnei, and S. flexneri.

4. Alternative vaccine strategies

4.1. Polysaccharide peptide mimics

Another vaccine strategy is the development of peptides that mimic polysaccharide antigens. These peptides can be identified using anti-idiotypic antibodies or phage display libraries, and can mimic the immunological function of polysaccharides. The exact mechanisms responsible for this mimicry are yet unknown. Peptide mimics commonly contain a large number of hydrophobic amino acid residues, often with aromatic side chains. Based on these similarities, it is hypothesised that aromatic–aromatic and hydrophobic interactions are critical forces that modulate binding and that the basis of cross-reactivity is structural mimicry. This has been challenged by others who showed data indicating that the mechanism of peptide binding differs from that of carbohydrate binding. The specific interactions involved in molecular mimicry are complex, however, this concept may be of use in developing novel vaccine strategies against polysaccharide antigens. The primary advantage of using peptides as antigens rather than carbohydrates is their potential to stimulate
TD immunity. Peptides can be processed by antigen presenting cells (APC) and presented to T lymphocytes by MHC molecules. Since peptides are simpler molecules, they also have the potential to focus the immune response on protective epitopes. However, several problems associated with peptide antigens need to be solved. The major issue is their poor chemical stability and subsequent lower antigenicity in vivo. Small peptides are often degraded rapidly and consequently are weak immunogens. Different delivery systems, like liposomes, immune stimulating complexes (ISCOMs), proteosomes and biodegradable particles have been shown to successfully induce peptide- and pathogen-specific immune responses.

Several methods for identification of peptides mimicking polysaccharides have been used. One is the anti-idiotypic antibody technology. During the generation of an antibody-mediated immune response, either after infection or vaccination, an individual will develop antibodies to an antigen as well as anti-idiotypic antibodies, whose immunogenic binding site (idiotype) mimics the antigen. In this context, anti-idiotypic antibodies directed at the variable domains of anti-carbohydrate binding antibodies can act as immunogens and induce an anti-polysaccharide immune response.

A monoclonal anti-idiotypic antibody that mimics meningococcal serogroup C polysaccharide has been described. The anti-idiotypic monoclonal antibody could inhibit the binding of human anti-C polysaccharide sera to C-polysaccharide. The same authors showed that this monoclonal anti-idiotypic antibody could induce protective anti-meningococcal serogroup C polysaccharide antibodies in mice.

Anti-idiotypic antibody technology has also been useful to develop immunogens mimicking disialo-alpha-gal epitopes present on the surface of S. flexneri, Cryptococcus neoformans, N. meningitidis serogroup A, B. abortus and group B streptococci. The advantage of phage display libraries is that they allow rapid screening and identification of reactive peptides. Thus, the use of phage display libraries is an efficient and effective way to identify potential vaccine candidates capable of inducing functional, anti-polysaccharide antibodies. A list of peptides mimicking carbohydrate structures is shown in Table 2.

### 4.2. DNA vaccines

DNA vaccines represent a novel vaccine approach, which employs genes encoding proteins of pathogens, rather than the proteins or pathogens themselves as in more conventional approaches. The vaccines consist of bacterial plasmids containing a strong promoter, which will function in mammalian cells and a gene encoding the protein antigen. After injection, the protein antigen is produced in situ and can elicit immune responses. From an immunological standpoint, the advantage of this technology is that both humoral and cellular immune responses are generated, with the production of antibodies, and T cell responses.

However, DNA-based vaccines were not considered as an option for development of vaccines against diseases caused by bacteria possessing polysaccharides as protective antigens, since the carbohydrate antigens are secondary gene products. However, the field of peptides mimicking carbohydrate structures opened the possibility to use this technology to induce anti-polysaccharide immunity. The DNA vaccines may have several advantages compared to conventional vaccines: (i) DNA vaccines are easily constructed by standard molecular cloning techniques; (ii) the vaccines are stable and heat resistant, which make them especially suitable for vaccine delivery in developing countries; (iii) they

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Method</th>
<th>Reference</th>
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<tbody>
<tr>
<td>B. abortus LPS</td>
<td>Phage display library</td>
<td>79, 83</td>
</tr>
<tr>
<td>S. flexneri 5a LPS</td>
<td>Phage display library</td>
<td>61</td>
</tr>
<tr>
<td>C. neoformans polysaccharide</td>
<td>Phage display library</td>
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<tr>
<td>C. neoformans polysaccharide</td>
<td>Phage display library</td>
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<tr>
<td>Meningococcal polysaccharide</td>
<td>Anti idiotype</td>
<td>62</td>
</tr>
<tr>
<td>Meningococcal polysaccharide</td>
<td>Carbohydrates on adeno-carcinoma cells</td>
<td>Phage display library</td>
</tr>
<tr>
<td>Streptococcal polysaccharide</td>
<td>Phage display library</td>
<td>65</td>
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<tr>
<td>Blood-group antigen</td>
<td>Phage display library</td>
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</tr>
<tr>
<td>Tumour associated carbohydrate</td>
<td>Phage display library</td>
<td>84</td>
</tr>
</tbody>
</table>
should be cheaper in production and purification compared to polysaccharide or neoglycoconjugate vaccines; (iv) they have the capacity of inducing an immune response with a predominance of IgG2a isotype. The IgG2a isotypes have been reported to be particularly effective in conferring protection against encapsulated organisms because of their ability to opsonise and fix complement. Finally, DNA vaccines allow administration of multiple DNA-encoded antigens. This technology has recently been demonstrated by Kieber-Emmons who constructed a DNA vaccine encoding a peptide mimic of the blood group related antigen Lewis Y (LeY). DNA immunization of mice resulted in an anti-LeY antibody response of the IgG2a isotype. The studies showed that DNA vaccination primes for a carbohydrate inducible IgG antibody response, and that induced anti-LeY IgG2a antibody mediates cell killing. This is the first report of DNA vaccination inducing TD immunity against a carbohydrate antigen and opens a completely new field for the development of a new generation of vaccines against polysaccharides present on the surface of pathogenic microorganisms.

5. Concluding remarks

Bacterial polysaccharides are the major surface components and the immunity confers protection. The use of polysaccharides in vaccines has been partially successful, however, several problems remain to be solved. Pure polysaccharides are poor immunogens and most of them are TI antigens. Polysaccharide neoglycoconjugates as vaccines could be a way to convert a TI to TD antigen. Several examples are described with the Hib conjugate vaccine as the best example. Peptide mimics of carbohydrate structures is a new approach that may have good potential in the development of new vaccines. The advantages and disadvantages of these three approaches for anti-polysaccharide vaccines are listed in Table 3.

References