

FOURTH • EDITION *Vaccines*

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successfully for glatiramer acetate,⁹⁵ a peptide copolymer of alanine, lysine, glutamic acid, and tyrosine that is licensed for the immunotherapy of multiple sclerosis (MS). It may function by inducing a shift from Th1 responses to glatiramer acetate-specific Th2 cells, which can mediate bystander suppression and thus ameliorate autoimmune antemyelin responses.

Carbohydrate- and Polysaccharide-Based Vaccines

Many bacteria have an outer polysaccharide capsule. Antibodies directed against capsular polysaccharides are protective for most encapsulated bacteria, thus establishing capsular polysaccharides as vaccine antigens. Components of lipopolysaccharide, another abundant surface molecule on Gram-negative bacteria, are used as vaccine antigens. Carbohydrates specific to the surface of certain types of cancer also have been used as vaccine antigens.

PLAIN POLYSACCHARIDES

The natural capsular polysaccharide contains up to hundreds of defined repeat units distinct for each bacterial species and antigenic subtype; each monomer consists of monosaccharides, phosphate groups, and other small organic moieties. The polysaccharide is shed by the organism during its growth and is harvested and enriched from the culture medium. These polysaccharide preparations are usually immunogenic in adults and children over 2 years of age. The polysaccharide elicits antibodies that may mediate bacteriolysis or opsonization of the organism, thereby protecting against infection. Polysaccharide vaccines have been licensed for Hib⁹⁶ (monovalent), *N. meningitidis*⁹⁷ (quadrivalent), and *Streptococcus pneumoniae*⁹⁸ (tridodecavalent). The shortcomings of these vaccines is that the polysaccharides, being T-cell-independent immunogens, are poorly immunogenic in children younger than 2 years owing to the immature status of their immune systems, and polysaccharides do not elicit immunologic memory in older children and adults.

CONJUGATED POLYSACCHARIDES

Infants and children younger than 2 years old do respond immunologically to T-cell-dependent immunogens (e.g., proteins). Conjugation of polysaccharide to a carrier protein converts the polysaccharide from a T-cell-independent to a T-cell-dependent immunogen. Consequently, polysaccharide conjugate vaccines can elicit protective immunoglobulin G (IgG) and immunologic memory in infants and young children. This strategy is important particularly for encapsulated bacteria such as Hib and *S. pneumoniae* (pneumococcal) owing to the preponderance of invasive diseases caused by these bacteria in children younger than 2 years old. The Hib bacteria are a single serotype ("b"). There are four licensed Hib conjugate vaccines,⁹⁹ all with different carrier proteins (TT, diphtheria toxoid, CRM₁₉₇, and an outer membrane protein complex from *N. meningitidis*) of different sizes and immunologic character, distinct polysaccharide chain lengths, and distinct conjugation chemistries. Thus these conjugate vaccines display one or more differences in the following properties: response of 2-month-old infants to the first dose of vaccine, responses of 4- and 6-month-old infants to the second and third doses, response of children older than 1 year to a booster dose, kinetics of

decay of antibody levels, peak antibody titer, and age at which protection first can be shown.

Pneumococcal bacteria consist of approximately 90 serotypes, as reflected in distinct capsular polysaccharide structures. For designing a pediatric pneumococcal conjugate vaccine, seven serotypes have been recognized as responsible for approximately 60% to 75% of the major pediatric pneumococcal diseases (acute otitis media, pneumonia, meningitis); a heptavalent pneumococcal conjugate vaccine has been licensed for pediatric use.¹⁰⁰ Other vaccines being tested in advanced clinical trials consist of mixtures of up to 11 individual pneumococcal polysaccharide conjugates.¹⁰¹

A conjugate of group B streptococcal polysaccharides can be used to immunize pregnant women¹⁰² for the prevention of neonatal group B streptococcal meningitis (in contrast to Hib and pneumococcal invasive diseases, which are virtually absent from children younger than 1 to 2 months old). In this case, the polysaccharide conjugate vaccine would be advantageous over a polysaccharide vaccine in terms of eliciting high enough anti-polysaccharide antibody titers to enable sufficient protective IgG to cross the placenta to the fetus.

OTHER CARBOHYDRATES

Tumor cells have been shown to have specific carbohydrate structures either lacking or deficient in other cell types. Such carbohydrates may have utility as cancer vaccines. Examples include the use of sialyl-Tn carbohydrate for ovarian and breast cancer¹⁰³ and G_{M2} ganglioside for melanoma.¹⁰⁴ Such carbohydrates are rendered more immunogenic by conjugation to carrier proteins, as is done for capsular polysaccharides.

Anti-idiotypic Antibody Vaccines

The *idiotypic* (Id; i.e., idiotypic determinant) is associated with the hypervariable region of the antibody (Ab) molecule and represents the unique antigenic determinants of that Ab. An antibody-1 (Ab-1) is defined as an antibody that recognizes a particular antigen (e.g., a vaccine candidate). The Id on Ab-1 itself can act as an immunogen that can elicit an immune response; the Abs that bind to the Id on Ab-1 are referred to as *anti-idiotypic antibodies* (anti-Id) or Ab-2. The *paratope* is the site on Ab-1 that binds to the particular antigen; thus the binding site of an anti-paratope antibody is a molecular mimic or mimetope of the antigen. If the Id and paratope represent the same or overlapping sites, then the particular antigen and anti-Id both bind at that site and have similar conformations and thus are mimics (Ab-1 is the image of the antigen and anti-Id). By virtue of the antibody-binding site of the anti-Id mimicking the conformation of the particular antigen (which may be a vaccine candidate), anti-Id molecules themselves can be used as vaccine candidates in which an epitope (mimicked by the Id) is presented on Ab-2, the carrier molecule. An excellent proof-of-principle that anti-Id represents an effective vaccine strategy comes from the demonstration that immunization of chimpanzees with anti-Id that mimicked HBsAg protected the animals from HBV infection.¹⁰⁵

Numerous technologies exist for using an antigen as a vaccine candidate. Moreover, antibody molecules (Ab-2) are not necessarily a desirable carrier for an antigen (anti-Id).