Review of Meningococcal Group B Vaccines

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No broadly effective vaccines are available for prevention of group B meningococcal disease, which accounts for >50% of all cases. The group B capsule is an autoantigen and is not a suitable vaccine target. Outer-membrane vesicle vaccines appear to be safe and effective, but serum bactericidal responses in infants are specific for a porin protein, PorA, which is antigenically variable. To broaden protection, outer-membrane vesicle vaccines have been prepared from >1 strain, from mutants with >1 PorA, or from mutants with genetically detoxified endotoxin and overexpressed desirable antigens, such as factor H binding protein. Also, recombinant protein vaccines such as factor H binding protein, given alone or in combination with other antigens, are in late-stage clinical development and may be effective against the majority of group B strains. Thus, the prospects have never been better for developing vaccines for prevention of meningococcal disease, including that caused by group B strains.

Nearly one-half of all cases of meningococcal disease in the United States are caused by capsular group B strains, for which there is no broadly effective vaccine [1]. In many European countries, the proportion is even higher (90%) [2, 3], in part because of routine infant and/or toddler meningococcal group C polysaccharide-protein conjugate vaccination [4]. Group B strains cause a disproportionate number of cases in infants <1 year of age, the age group with the highest incidence of disease [5–7]. These strains also cause prolonged epidemics, such as those that occurred during the 1980s in Cuba and Norway and, more recently, in New Zealand [8]. A quadrivalent group A, C, W-135, and Y polysaccharide-protein conjugate vaccine was introduced in the United States and is recommended for routine use beginning at 11 years of age [9]. A more immunogenic quadrivalent conjugate vaccine [10, 11] and a Haemophilus influenzae type b--meningococcal group C and Y conjugate vaccine [12], both suitable for infants, are in late-stage clinical development. Control of meningococcal disease, however, will not be achieved until a broadly effective vaccine is available against group B strains, which is the subject of this review.

PROTECTION AGAINST MENINGOCOCCAL DISEASE

Considerable evidence indicates that complement-mediated serum bactericidal antibody (SBA) confers protection against meningococcal disease (reviewed in [13, 14]). An SBA titer of ≥1:4, when measured with human complement, is generally accepted as a surrogate of protection [13]. Recent seroepidemiologic and experimental evidence also indicates that protection may be conferred by bactericidal activity present at serum dilutions <1:4 and/or by opsonophagocytosis [15]. Nevertheless, because of high specificity, vaccine efficacy can be inferred from SBA titers ≥1:4, and the results can be used by national regulatory authorities for the licensure of new meningococcal vaccines.

CHALLENGES FOR GROUP B VACCINE DEVELOPMENT

When polysaccharides are conjugated to carrier proteins, the polysaccharide antigens become immunogenic in infants and prime for memory anticapsular antibody responses (reviewed in [16, 17]). The meningococcal group B polysaccharide, however, is a homoligomer of α(2→8)-N-acetyl neuraminic acid (polysialic acid) and is an autoantigen [18]. The poly-
Table 1. Group B Vaccines Investigated in Clinical Trials

<table>
<thead>
<tr>
<th>Formulation, vaccine</th>
<th>Reference(s)</th>
<th>Clinical status</th>
<th>Immunogenicity results (humans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysaccharide-protein conjugate: n-propionylated group B polysaccharide derivative</td>
<td>[22]</td>
<td>Phase 1 (completed)</td>
<td>Did not elicit SBA</td>
</tr>
<tr>
<td>Detergent-treated OMVs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMV from 1 strain*</td>
<td>[28–33]</td>
<td>Phase 3 (completed)</td>
<td>Elicited SBA and opsonic activity</td>
</tr>
<tr>
<td>Mixture of OMV from 2 strains</td>
<td>[40, 41]</td>
<td>Phase 1 (completed)</td>
<td>Elicited SBA</td>
</tr>
<tr>
<td>Mixture of OMV from 2 mutants, each with 3 PorA proteins</td>
<td>[45–47, 128, 129]</td>
<td>Phase 2 (completed)</td>
<td>Elicited SBA</td>
</tr>
<tr>
<td>Mixture of OMV from 3 mutants, each with 3 PorA proteins</td>
<td>[44]</td>
<td>Phase 1</td>
<td>Not yet reported</td>
</tr>
<tr>
<td>OMV from Neisseria lactamica</td>
<td>[58]</td>
<td>Phase 1</td>
<td>Elicited minimal SBA responses</td>
</tr>
<tr>
<td>Native OMV (not treated with detergents): mutant with attenuated endotoxin, 2 PorA proteins, overexpressed fHbp, and other mutations</td>
<td>[75]</td>
<td>Phase 1</td>
<td>Not yet reported</td>
</tr>
<tr>
<td>Recombinant proteins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TbpB</td>
<td>[92]</td>
<td>Phase 1 (completed)</td>
<td>SBA responses not reported</td>
</tr>
<tr>
<td>NspA</td>
<td>[89]</td>
<td>Phase 1 (completed)</td>
<td>Did not elicit SBA</td>
</tr>
<tr>
<td>fHbp (2 antigenic variants)</td>
<td>[121–123]</td>
<td>Phase 2</td>
<td>Elicited SBA</td>
</tr>
<tr>
<td>2 Fusion proteins, GNA 2091–fHbp variant 1 and GNA 2132–GNA 1030, and NadA</td>
<td>[120]</td>
<td>Phase 1</td>
<td>Elicited SBA and opsonic activity</td>
</tr>
<tr>
<td>Recombinant proteins plus detergent-treated OMV: 2 fusion proteins, GNA 2091–fHbp variant 1, and GNA 2132–GNA 1030 plus NadA plus OMV</td>
<td>[124, 125]</td>
<td>Phase 2/3</td>
<td>Elicited SBA</td>
</tr>
</tbody>
</table>

**NOTE.** fHbp, factor H binding protein; GNA, genome-derived neisserial antigens; NadA, neisserial adhesin A; NspA, neisserial surface protein A; OMV, outer-membrane vesicles; SBA, serum bactericidal antibody; TbpB, transferring-binding protein B.

* The vaccine from Cuba was combined with group C polysaccharide (30, 31).

saccharide is expressed by a number of host tissues [19] and is a poor immunogen, even when conjugated to a protein carrier [20]. To increase immunogenicity, n-propionyl–derivatized group B polysaccharide-conjugate vaccines were prepared; these elicited SBA responses in mice [21] but not in humans [22]. Efforts to develop a group B vaccine, therefore, have focused on noncapsular antigens, such as proteins or lipopolysaccharide (in meningococcus, referred to as lipooligosaccharide [LOS], because of the presence of repeating short saccharides instead of long-chain saccharides). The principal challenge has been to identify surface-exposed noncapsular antigens that are safe and antigenically conserved and that elicit broad SBA responses. Promising noncapsular group B vaccine approaches are discussed below and include outer-membrane vesicles (OMVs), recombinant proteins, and a combination of an OMV and recombinant proteins (Table 1).

**STRATEGIES FOR GROUP B VACCINE DEVELOPMENT**

*Detergent-extracted OMV vaccines.* OMVs can be separated from meningococcal bacteria (Figure 1A) [23] or isolated as membrane blebs, which are released into media during bacterial growth. The OMVs are treated with detergents to extract LOS and decrease endotoxin activity [24]. By using sodium dodecyl sulfate–polyacrylamide gel electrophoresis, the detergent-treated vesicles were shown to contain 4 or 5 major outer-membrane proteins; SBA, serum bactericidal antibody; TbpB, transferring-binding protein B.
Figure 1. Detergent-extracted outer-membrane vesicle (OMV) vaccines. A, Electron micrograph of OMVs of Neisseria meningitidis. The scale bar is 100 nm, and the mean vesicle diameter was 80 nm (range, 50–200 nm). B, Major outer-membrane proteins (PorA, PorB, reduction modifiable protein [RmpM], and opacity protein A [OpcA]), as visualized by Coommassie-stained sodium dodecyl sulfate–polyacrylamide gel electrophoresis. Lane 1, Molecular mass standards; lane 2, strain NZ98/254; lane 3, strain H44/76. After vaccination, the serum bactericidal antibody responses in infants and children were directed predominantly against PorA. Adapted from published data [23]. Reprinted from Vaccine, 27(Suppl 2), Holst J, Martin D, Arnold R, et al. Properties and clinical performance of vaccines containing outer membrane vesicles from Neisseria meningitidis, B3–B12, Copyright 2009, with permission from Elsevier.

Figure 2. Release of tumor necrosis factor (TNF)–α after incubation of human peripheral blood mononuclear cells for 4 h with outer-membrane vesicle (OMV) vaccines. The OMV concentrations that resulted in a 10-fold increased release of TNF–α concentrations, compared with release of background concentrations, are shown on the x intercepts. White circles represent native OMVs from wild-type (WT) strains, gray squares represent OMV vaccine prepared from LpxL1 KO mutants, and black triangles represent detergent-extracted OMV vaccines from corresponding WT strains. Adapted from published data [65], with permission from the American Society for Microbiology.
beginning in the second year of life, coincident with the acquisition of colonization by *Neisseria lactamica*, which is a common commensal of the nasopharynx in young children [52–54]. Exposure to cross-reacting *N. lactamica* antigens and, later, to colonization by *Neisseria meningitidis* has been thought to contribute to naturally acquired meningococcal immunity, although the specific antigenic targets and protective mechanisms are poorly understood [15]. To mimic naturally acquired immunity and to circumvent possible immunodominance of PorA, which has been hypothesized to impair serum antibody responses to non-PorA antigens [55], an OMV vaccine was prepared from *N. lactamica* [52, 54, 56, 57], which does not express an ortholog of meningococcal PorA. In a phase 1 study, adults who received the *N. lactamica* OMV vaccine developed minimal SBA responses, even though nearly all of the participants were naturally primed, based on the presence of bactericidal activity in serum samples obtained before vaccination [58]. The lack of SBA responses to the lactamica OMV vaccine is not surprising. Before 10 years of age, when *N. lactamica* colonization is common, the prevalence of SBA is low [7, 16]. In addition, although mice given an OMV vaccine prepared from *N. lactamica* were protected against a lethal *N. meningitidis* challenge [57], *N. lactamica* vaccines did not elicit SBA responses [57, 59]. The mechanism responsible for the mouse protection has not been defined.

Weynants et al [55] prepared detergent-treated OMV vaccines from mutant *N. meningitidis* strains in which the PorA gene had been inactivated to circumvent immunodominance. The mutants also were engineered to overproduce several “minor” outer-membrane proteins that are normally expressed in low copy number (transferrin-binding protein A, neisserial surface protein A [NspA], and outer membrane protein 85). The authors hypothesized that, in the absence of PorA immunodominance and with overexpression of these minor antigens, the breadth of the SBA responses to the mutant OMV vaccine would be increased. In vaccinated mice, only antibodies elicited by the OMV vaccine from the mutant in which all 3 minor antigens were overexpressed had serum bactericidal activity. The authors concluded that it was necessary to elicit antibodies directed against multiple “minor” antigens to achieve sufficient density of IgG on the surface of the bacteria to engage C1q and activate complement-mediated SBA. As described below (“Recombinant Protein Vaccines”), there may be exceptions to this model when the antibodies target a sparsely expressed antigen, such as factor H binding protein (fHbp), which regulates complement pathways [60].

**Native (non–detergent-treated) OMV vaccines.** Detergent treatment, which is used to lower endotoxin activity of OMV vaccines, also extracts desirable antigens, such as the lipoproteins fHbp and genome-derived neisserial antigen (GNA) 2132, which are 2 recently discovered vaccine targets (see “Recombinant Protein Vaccines”) [61, 62]. To avoid the detergent step...
Figure 4. A, Activation of the classical complement pathway by antibody. Binding of 2 optimally spaced IgG molecules to the bacterial surface engages C1q and activates the classical complement pathway, which results in increased deposition of C3b. Bound C3b can serve as an opsonin and can also lead to bacteriolysis by cleavage of C5 and assembly of the C5b-9 membrane attack complex. Not shown are the components of the alternative pathway, which can be activated by the classical pathway and serve as an amplification loop.

B, Regulation of complement activation by binding of human fH to the bacterial surface. Decreased classical pathway killing inhibits alternative pathway amplification. Human fH binds to surface-exposed factor H binding protein (fHbp). fH accelerates the decay of alternative pathway C3/C5 convertases, which down-regulates the positive feedback amplification loop of the alternative pathway. Binding of fH also leads to degradation of C3b by factor I (not shown), which decreases classical pathway activation and amplification by the alternative pathway. C, Binding of antibodies (Ab) to fHbp activates classical complement pathway bacteriolysis and also inhibits binding of fH to the bacterial surface. With decreased amounts of fH bound to the bacterial surface, there is less down-regulation of complement activation, and the organism becomes more susceptible to complement-mediated bacteriolysis.

and preserve desirable detergent-soluble antigens, it may be possible to prepare native OMV vaccines from strains selected to have naturally low endotoxin activity [63] or to use genetic approaches to attenuate endotoxin activity [64–66].

The lipid A portion of the LOS molecule is responsible for its endotoxin activity. One promising mutant with attenuated endotoxin activity contains a deletion in the LpxL1 gene (also referred to as the msbB gene) [67]. This mutation results in penta-acylated lipid A, which is poorly recognized by human Toll-like receptor 4 [68], instead of the more toxic hexa-acylated lipid A, which is present in most wild-type strains [63, 69, 70]. When incubated with human peripheral blood mononuclear cells, a native OMV vaccine from a penta-acylated mutant had >100-fold less endotoxin activity, based on lower stimulation of multiple proinflammatory cytokines, compared with a control native OMV from the wild-type strain [65, 66]. The native mutant OMV vaccine showed similar stimulatory activity as control, detergent-treated wild-type OMV vaccines that had been administered safely to humans. Representative tumor necrosis factor–α responses to the different wild-type and mutant OMV vaccines are shown in Figure 2.

Many of the newly discovered vaccine targets identified by genome mining (an approach referred to as “reverse vaccinology” [71]) are naturally expressed in relatively low copy number by N. meningitidis strains (which is one reason why these antigens remained unrecognized before genome research). With a few exceptions, humans recovering from meningococcal disease showed low antibody responses to these antigens [72], and the antigens were poorly immunogenic in mice administered native OMV vaccines prepared from wild-type strains [66, 73]. To enhance immunogenicity, native (ie, non–detergent-extracted) OMV vaccines were prepared from mutants engineered to overexpress desirable antigens such as fHbp [65, 66, 74]. In mice, a native OMV vaccine with genetically detoxified endotoxin and overexpressed fHbp elicited high titers of serum anti-fHbp antibodies with broad serum bactericidal activity (Figure 3). In adsorption studies, the majority of the bactericidal antibodies were directed at fHbp [65, 66]. The native OMV vaccine, which expressed PorA, also elicited strain-specific bactericidal anti-PorA antibodies [65]. The safety and immunogenicity of a prototype native OMV vaccine from a mutant N. meningitidis strain with genetically attenuated endotoxin activity, overexpressed fHbp, >1 PorA VR type, and other mutations is being investigated in a phase 1 clinical trial involving adults [75].

LOS has become another potential meningococcal vaccine target, because anti-LOS antibodies were reported to have serum bactericidal activity and/or opsonic activity [76–78]. However, the lacto-N-neotetraose (Gal-GlcNAc-Gal-Glc tetrasaccharide) on meningococcal LOS is shared by antigens on human red blood cells, which raises safety concerns. In addi-
A Phylogram of 70 unique factor H binding protein (fHbp) amino acid sequences, showing division of the proteins into 2 subfamilies, designated as A and B by Fletcher et al [100]. Subfamily B contains the proteins in the variant 1 group described by Masignani et al [61]. Subfamily A is subdivided into 2 branches, designated by Masignani and colleagues as variants 2 and 3. Each branch represents a distinctive protein sequence. The scale bar represents 5 amino acid differences per 100 amino acids.

B Modular structure. The architecture of fHbp consists of different combinations of 5 variable segments, designated VA to VD [116]. Each segment is derived from 1 of 2 genetic lineages, designated α (gray segments) or β (white segments). All of the distinctive fHbp protein amino acid sequences referred to in panel A could be assigned to 1 of 6 “modular groups,” designated I–VI. Panel B is reprinted from Microbiology 2009; 155:2873–83. Copyright ©2009 by the Society for General Microbiology.

Recombinant protein vaccines. New vaccine discovery approaches, including genome mining [62, 71, 82–84], proteomics [85, 86], and immunological approaches [87], have identified a large number of novel vaccine targets for prevention of group B meningococcal disease. These include NspA [87–89], transferrin-binding proteins [90–92], opacity proteins (Opc) [93–95], GNA 2132 [96–99], fHbp (previously referred to as GNA 1870 or LP2086 [61, 100]), FetA (an iron-regulated outer membrane protein) [101], neisserial adhesin A (NadA, also referred to as GNA 1994) [102–105], and others [62, 106]. To date, the vaccine potential of nearly all of these candidates has been limited by either antigenic variability (eg, FetA and Opc), lack of the gene in strains from some hypervirulent lineages (eg, NadA), phase variability (Opc), or low constitutive expression of the antigen by some strains (fHbp, GNA 2132, and NspA). There also may be poor expression of important conformational epitopes by the recombinant protein (NspA) [89, 107]. Thus, a vaccine containing only 1 recombinant antigen is unlikely to be sufficient for broad protective meningococcal immunity.

One of the most promising of the new protein antigens is...
As described above, binding of fH to *N. meningitidis* was reported to be specific for human fH [81]. This human specificity adds another mechanism to explain why *N. meningitidis* is strictly a human pathogen. A crystal structure of a portion of fH in complex with fHbp that provided a structural basis for specificity of binding human fH has been reported [113]. As a vaccine antigen, fHbp is unique in that antibodies to fHbp both activate classical complement pathway bacteriolysis directly and block binding of fH to the bacterial surface [60, 114]. Inhibition of fH binding would be expected to enhance susceptibility of the organism to classical and alternative pathway bacteriolysis (Figure 4C).

Meningococcal fHbp can be subclassified into 3 antigenic variant groups on the basis of antigenic cross-reactivity and sequence similarity of the entire protein (Figure 5A) [61]. In general, antibodies prepared against fHbp in the variant 1 group (also referred to as subfamily B by Fletcher et al [100]) were bactericidal against strains expressing fHbp from the variant 1 group but not against strains expressing fHbp from the variant 2 or 3 groups (together, referred to as subfamily A) and vice versa [61, 100, 103]. There are also subvariants of fHbp in each of the variant groups (proteins that differ by <10% of amino acids from those of the canonical protein of the respective antigenic variant group) [103, 115]. Recently, the molecular architecture of fHbp was shown to be modular (each fHbp variant contains different combinations of 5 variable segments, each of which is derived from 1 of 2 genetic lineages [116]) (Figure 5B). The breadth of protection conferred by anti-fHbp antibodies against strains expressing fHbps from different modular groups was recently described [117].

fHbps are part of 2 promising meningococcal vaccines being investigated in humans. One vaccine, referred to as LP2086, contains 2 recombinant lipitated proteins from the fHbp subfamilies A and B. The second vaccine contains fHbp in the variant 1 group (subfamily B) as part of a multicomponent vaccine (Figure 6) [96]. Two of the components are fusion proteins (GNA 2091 fused with fHbp and GNA 2132 fused with GNA 1030), and the third component is recombinant NadA. Of these 5 antigens, fHbp, GNA 2132, and NadA were reported to be responsible for most of the SBA responses in mice [96].

GNA 2132 antigen is a surface-accessible lipoprotein of unknown function. The gene was detected in all *N. meningitidis* strains tested to date and was also present in strains of *N. lactamica* and *Neisseria gonorrhoeae* [62]. On the basis of sequence alignments, portions of GNA 2132 were highly conserved. In mice, recombinant GNA 2132 elicited SBA responses, although only a subset of strains was susceptible with human complement [99]. Human adults administered OMV vaccine combined with recombinant GNA 2132 had higher SBA responses measured with human complement than did adults.
who were given a control OMV vaccine without the recombinant protein [97].

NadA is an adhesin or invasin that binds to epithelial cells in vitro [102]. In mice, recombinant NadA elicited SBA responses [105]. The antigen is conserved (>96% amino acid identity) among group B strains, but the gene is absent from strains from certain genetic lineages that are responsible for ~40% of group B disease [103, 105, 118, 119].

In a phase 1 study [120], adults were administered the multicomponent recombinant protein vaccine described in Figure 6. Their serum samples were assayed for bactericidal activity against 3 representative test strains (H44/76, NZ98254, and S3032), each of which are from different genetic clonal complexes. Two of the strains were responsible for large group B epidemics in Norway (H44/76) and New Zealand (NZ98254), and S3032 was from a patient in the United States. High SBA responses were observed against strain H44/76, which expressed a homologous fHbp to the recombinant protein antigen in the vaccine (the GMT was 1:4 in serum samples obtained before vaccination and increased to 1:64 in serum samples obtained 4 weeks after a third dose of vaccine); 97% of participants developed protective titers of ≥1:4 when measured with human complement (Figure 7). SBA responses were much lower against the 2 other test strains, which were selected because neither had the gene for NadA and both expressed fHbp antigens mismatched for the vaccine antigen (Figure 7). The majority of the postvaccination serum samples, however, conferred passive protection against these strains in an ex vivo human bacteremia model (Figure 7) [120]. The greater sensitivity of the passive protection ex vivo bacteremia assay may reflect higher complement concentrations in the whole human blood assay (90%) than in the SBA assay (20%–25%) and/or the presence of phagocytic cells in the blood assay.

In the multicomponent vaccine formulation that has advanced to phase 3 testing, the 3 recombinant proteins (5 antigens) were combined with a detergent-treated OMV vaccine that had been used to control a group B epidemic in New Zealand [34]. As of fall 2009, there are no published reports of the results of clinical trials using this vaccine or a bivalent fHbp vaccine. Early clinical data from testing these vaccines have been reported at conferences [121–125]. Both vaccines were well tolerated and elicited SBA responses in children and adults. Although the data were promising, detailed information is needed for critical assessment of the safety and efficacy of these vaccines.

CHALLENGES IN ASSESSING VACCINE EFFICACY

Because of the low incidence of meningococcal group B disease, it is not feasible to perform prospective, randomized, controlled clinical trials to assess the efficacy of new group B vaccines. For vaccine licensure, the breadth of protection will be estimated from immunogenicity studies conducted among different age groups and in different geographic locations and by testing SBA against genetically diverse strains. This approach presents several challenges. First, the number of serum samples available from the infant trials will be limited, which precludes performing assays against a large number of genetically diverse test strains. Because of variability in antigen sequence and expression, it will be necessary to select a representative strain panel that ensures that the resulting SBA data can be extrapolated to estimate protection against disease-causing strains in the population. Second, as discussed above, by relying only on SBA titers ≥1:4 as a measure of protection, the immunogenicity data will likely underestimate protection induced by vaccination [15, 97, 120]. A more sensitive assay is needed. Determination of whether protection is conferred by antibodies that only have opsonic activity or have SBA titers <1:4 would permit use of expanded serologic assays and advance vaccine development, as well as help formulate optimal public health strategies for introduction of the new vaccines. Third, up to a third of the effect of group C conjugate vaccines on control of meningococcal disease in a population has been attributed to decreased colonization and transmission of group C organisms (herd immunity) [126]. No information is available on whether protein-based meningococcal vaccines affect transmission of the organism, and no clinical information is available on protection against non–group B strains. The protein antigens used for group B vaccines are shared across strains with other capsular groups [127], and mice administered OMV vaccines from group B mutants developed broad SBA responses against epidemic group A, W-135, and X isolates from Africa [127]. Referring to the new protein vaccines as “group B” vaccines is therefore a misnomer, because the vaccines likely also will protect against capsular group A, C, W-135, and Y strains, which will be an added bonus to vaccination.

Acknowledgments

Financial support. National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH; Public Health Service grant R01 AI046464); the work at Children’s Hospital Oakland Research Institute was performed in a facility funded by Research Facilities Improvement Program, National Center for Research Resources, NIH (C06 RR-16226).

Potential conflicts of interest. D.M.G. is principal investigator of laboratory research conducted on behalf of Children’s Hospital Oakland Research Institute that is funded by grants from Novartis Vaccines and Diagnostics and Sanofi Pasteur; holds a paid consultancy from Novartis; and is an inventor on patents or patent applications in the area of meningococcal B vaccines.

Supplement sponsorship. This article was published as part of a supplement entitled “Immunization to Prevent Meningococcal Disease: Yesterday, Today, and Tomorrow,” which was sponsored by DIME and funded through an educational grant from Novartis Vaccines.
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