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REVIEW ARTICLE

An mRNA vaccine to prevent genital herpes

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The rapid development of two nucleoside-modified mRNA vaccines that are safe and highly effective against coronavirus disease 2019 has transformed the vaccine field. The mRNA technology has the advantage of accelerated immunogen discovery, induction of robust immune responses, and rapid scale up of manufacturing. Efforts to develop genital herpes vaccines have been ongoing for 8 decades without success. The advent of mRNA technology has the potential to change that narrative. Developing a genital herpes vaccine is a high public health priority. A prophylactic genital herpes vaccine should prevent HSV-1 and HSV-2 genital lesions and infection of dorsal root ganglia, the site of latency. Vaccine immunity should be durable for decades, perhaps with the assistance of booster doses. While these goals have been elusive, new efforts with nucleoside-modified mRNA-lipid nanoparticle vaccines show great promise. We review past approaches to vaccine development that were unsuccessful or partially successful in large phase 3 trials, and describe lessons learned from these trials. We discuss our trivalent mRNA-lipid nanoparticle approach for a prophylactic genital herpes vaccine and the ability of the vaccine to induce higher titers of neutralizing antibodies and more durable CD4$^+$ T follicular helper cell and memory B cell responses than protein-adjuvanted vaccines. (Translational Research 2022; 242:56–65)

Abbreviations: HSV-1 = Herpes Simplex Virus Type 1; HSV-2 = Herpes Simplex Virus Type 2; LNP = Lipid nano particles; gC2 = HSV-2 glycoprotein C; gD2 = HSV-2 glycoprotein D; gE2 = HSV-2 glycoprotein E; Tfh = T-follicular helper cells; ADCC = Antibody-dependent cellular cytotoxicity

GLOBAL BURDEN OF HERPES INFECTION AND THE NEED FOR A PROPHYLACTIC VACCINE

Herpes infections are ubiquitous.[1,2] The global HSV-1 seroprevalence for ages 0–49 years is 66.6%, while HSV-2 seroprevalence is 13.2% for ages 15–49.[1] HSV-1 and HSV-2 infections are persistent with frequent recurrences. Genital herpes infections are caused by either HSV-1 or HSV-2.[3] Genital HSV-1 infection is acquired from oral-genital or genital-genital transmission and is common, with up to 50% of new genital herpes cases caused by HSV-1.[4-6] However, HSV-1 reactivation infection is less frequent than HSV-2; therefore, the overall burden of disease is higher for HSV-2.[7] While HSV-1 seropositivity indicates either oral or genital infection, HSV-2 seropositivity is almost exclusively from genital infection.[8]

Genital herpes may be symptomatic or asymptomatic. Sexual transmission by asymptomatic individuals is a major contributor to the high prevalence of genital herpes.[9] Anxiety about transmitting infection to intimate partners can be debilitating for people with genital herpes. Some individuals with genital herpes have recurrent episodes of HSV-2 meningitis.[10] The most dreaded complication of genital herpes is neonatal herpes.[11] Neonates can acquire HSV-1 or HSV-2 infection at the time of labor and delivery because of reactivation

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Submitted for Publication October 30, 2021; revision submitted December 9, 2021; Accepted for Publication December 16, 2021.

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1931-5244/$ - see front matter

https://doi.org/10.1016/j.trsl.2021.12.006

infection, but neonatal infection is more common when a primary genital infection develops during the third trimester and the infant is delivered before antibodies are transferred transplacentally.[12-14] Newborns may also acquire HSV-1 infection postnatally from oral contact with caregivers.[11] Neonatal infections have a high fatality and long-term neurological complications despite antiviral treatment.[11] Genital HSV infections increase the risk of acquisition and transmission of HIV, and a large burden of HIV is likely attributable to genital HSV-2 infection.[15-18]

An effective prophylactic genital herpes vaccine needs to be effective against genital infection by HSV-1 and HSV-2. An ideal vaccine will prevent genital lesions and asymptomatic subclinical infection to reduce the risk of transmission. Population-based mathematical models indicate that even a modestly effective herpes vaccine will have a substantial impact on HSV-2 sexual transmission.[19-23]

PAST AND CURRENT GENITAL HERPES VACCINE CLINICAL TRIALS

No genital herpes vaccine is FDA-approved despite 75 years of effort. Only a small number of vaccine candidates have reached phase 3 trials. These vaccine candidates are discussed below.

1. Phase 3 vaccine trials for genital herpes prevention. Glycoproteins essential for virus entry were the targets for 3 large phase 3 human trials to prevent genital herpes.[24-26] None of the trials achieved its primary endpoint, but each provided significant insights into the immune responses needed for success.

HSV-2 glycoproteins B and D (gB2/gD2) administered with adjuvant MF59 was used in randomized, placebo-controlled trials.[24] The primary endpoint was time to acquisition of genital herpes infection as determined by HSV-2 virus culture or seroconversion. The time to acquisition of infection was reduced by 50% in the vaccine recipients compared to placebo during the first 5 months, but no benefit was detected beyond that. The gB2/gD2 vaccine produced neutralizing antibody titers comparable to those in naturally infected subjects. The durability of neutralizing antibodies was not reported in this study; however, a prior phase 1/2 human trial using the same vaccine candidate showed a rapid decline in neutralizing antibody titers 6 months after the final (third) immunization.[27] Additionally, lower than expected antibody-dependent cellular cytotoxicity (ADCC) titers were reported in the trial suggesting that potent ADCC titers may be required for vaccine protection.[28] We postulate that immune evasion mediated by HSV-2 gE may explain the low ADCC titers. HSV-2 gE is an IgG Fc receptor and promotes virus evasion of IgG Fc-mediated functions, such as ADCC.[29,30]

In 2002, results of a phase 3 clinical trial were reported using gD2 with MPL and alum as adjuvants.[25] One study enrolled HSV-1 and HSV-2 double seronegative subjects while a second study enrolled subjects of any HSV serologic status. The primary endpoint was genital herpes disease. Based on the reduction in genital disease in the vaccine recipients, the efficacy of the gD2 vaccine was 38% in the first study (double seronegative men and women), and 42% in the second study (HSV-2 seronegative women that were either HSV-1 seropositive or seronegative). A subgroup analysis showed that vaccine efficacy in double seronegative women was 73% and 74% in studies 1 and 2, respectively. The vaccine was not efficacious in HSV-1 seropositive women or in men of any serostatus. The fact that the vaccine was not efficacious in HSV-1 seropositive women suggests that prior HSV-1 infection may interfere with vaccine protection. The vaccine failure in men raises concerns about possible sex differences in vaccine efficacy.[25]

To confirm the vaccine efficacy in double seronegative women, a follow up phase 3 clinical trial was conducted that enrolled only double seronegative women ages 18−45 years (Herpevac Trial for Women).[26] The primary endpoint was genital herpes lesions caused by HSV-1 or HSV-2 beginning one month after the second of 3 immunizations with a follow up period extending for 20 months. The overall vaccine efficacy was 20%; however, the efficacy against HSV-1 genital disease was 58% or 77% after 2 or 3 immunizations, respectively. The vaccine was not efficacious against HSV-2 genital disease. The average peak neutralizing antibody titer against HSV-2 was 1:29 1 month after the final (third) vaccine dose and was undetectable by 16 months.[26] The low peak HSV-2 neutralizing antibody titers and lack of durable response may explain the poor vaccine efficacy against HSV-2. ELISA gD2 antibody titers correlated with protection against HSV-1, while $CD4^+$ T cell responses did not, suggesting antibody responses were important for vaccine efficacy.[31] A substudy using serum from 30 vaccinated subjects showed 3.5-fold higher neutralizing antibody titers against HSV-1 than HSV-2, providing a possible explanation for protection against HSV-1 but not HSV-2.[32]

2. Phase 1/2 human trials for prevention of genital herpes. A recent phase 1 study used a live attenuated replication-defective HSV-2 vaccine candidate, HSV529 that has a deletion in 2 genes essential for virus replication, UL5 and UL29. The vaccine was safe and well tolerated; however, immune responses were suboptimal.[33] The average peak titer for neutralizing antibodies in HSV double

seronegative subjects was 1:16, which was lower than the titers noted in HSV seropositive (previously infected) subjects. $CD4^+$ and $CD8^+$ T cell responses were induced in only 36% and 14% of seronegative subjects, respectively. In HSV-1 or HSV-2 seropositive volunteers, HSV529 did not boost neutralizing antibody titers. $CD4^+$ T cells responses were boosted in 27%−46%, and $CD8^+$ T cell responses in 8%−18%. Based on these results, the HSV529 vaccine candidate is not being pursued for prevention of genital herpes; however, further trials are planned to develop a therapeutic vaccine as treatment for subjects with recurrent genital herpes. The therapeutic vaccine combines HSV529 with glycoprotein antigen gD2 and capsid antigens UL19 and UL25 administered with glucopyranosyl lipid A in a stable emulsion (GLA-SE) as adjuvant (https://clinicaltrials.gov/ct2/show/NCT04222985). Other phase 1 trials using replication defective virus may be in the planning phase, including one that uses HSV-2 gD deletion virus as a candidate vaccine.[34,35]

LESSONS LEARNED FROM PAST CLINICAL TRIALS AND NATURAL INFECTION

First lesson: Three genital herpes vaccine candidates that targeted entry molecules were only partially successful. Neutralizing antibody titers were either low, not durable or both.[24-26] These results suggest that prophylactic vaccines directed at entry molecules should induce high and durable titers of neutralizing antibodies.

Second lesson: Additional support for the importance of antibodies in preventing infection comes from studies of neonatal herpes. Passive transfer of antibodies from mother to fetus protects newborns primarily because of neutralizing antibodies and ADCC.[36,37]

Third lesson: HSV is highly adapted to evade host immunity, making it difficult for a vaccine to prevent the virus from reaching the ganglia, which is the site of latency.[38-40] A vaccine that targets immune evasion strategies of the virus may help the host clear the virus before it establishes latency.

Fourth lesson: Many individuals acquire HSV-1 infection (orolabial) during childhood before sexual debut.[2] For example, in the US, HSV-1 seroprevalence among 14−19-year-olds is 30%.[41] The gD2 MPL/alum vaccine candidate did not induce protective immunity in HSV-1 seropositive subjects.[25] Future vaccines aimed at preventing HSV-2 infection must be effective in people who are HSV-1 seropositive.

Fifth lesson: In resource-rich countries, 50% of new genital herpes cases are caused by HSV-1. Therefore, a vaccine must be effective against both HSV-1 and HSV-2 genital infection.[4-6]

ADVANTAGES OF USING MRNA TECHNOLOGY FOR A GENITAL HERPES VACCINE

Modifications in mRNA constructs and lipid nanoparticle (LNP) formulation contributed to the success of the coronavirus disease 2019 (COVID-19) vaccines and will improve chances for success of a genital herpes vaccine.[42,43] The knowledge gained from COVID-19 mRNA vaccines will help streamline mRNA-LNP vaccine development for herpes and other next generation vaccines because of expertise gained in scaling up manufacturing, developing cold chain distribution, obtaining regulatory approval, and proceeding rapidly from small safety trials to large efficacy trials. We have learned that mRNA vaccines are safe and effective in young and old of both sexes and multiple races.[44-46] Safety in adolescents and young adults is important for the future development of a prophylactic genital herpes vaccine because these individuals are the intended recipients of the vaccine.

The mRNA vaccines induce high levels of humoral and cellular immune responses.[47-50] COVID-19 mRNA and influenza mRNA vaccines in clinical trials and our genital herpes mRNA vaccine in preclinical studies stimulated long-term memory B-cells, suggesting durable immunity.[51,52] The lack of durable immunity was a deficiency of prior genital herpes vaccine candidates.[24,26] Our genital herpes vaccine targets surface glycoproteins. An advantage of mRNA vaccines for expressing glycoprotein antigens is that when the mRNA is translated, glycosylation and other post-translational modifications are identical to proteins produced during natural infection, unlike subunit protein antigens produced in yeast or insect cells.

TRIVALENT MRNA VACCINE TO PREVENT GENITAL HERPES

In vivo transcribed mRNA was evaluated in the 1990s in preclinical models as a possible delivery mechanism for curing medical illnesses.[53,54] However, problems emerged because of mRNA instability, undesirable inflammatory immune responses, and inefficient delivery. Years of innovative work by Kariko and Weissman yielded the technology to overcome these setbacks. These investigators and their colleagues substituted uridine residues with 1-methyl-pseudouridine to reduce triggering innate immune sensors; they optimized 5′ cap, 5′ and 3′ UTRs, and polyA tail-length to improve mRNA stability; they removed double-stranded mRNA by purification to avoid triggering innate toll-like receptor sensors; and they used lipid LNP to deliver the mRNA to antigen presenting cells.[42,55-59] Based on these modifications, the mRNA

induced potent CD4$^+$ T-follicular helper cell and germinal center B cell responses.[48,59,60] T-follicular helper cells are critical for germinal center formation, somatic hypermutation, development of high-affinity antibodies, and effective long-term B cell memory.[61-64] In preclinical studies, modified mRNA vaccines provide extraordinary protection in animal models for Zika, influenza, HSV-1, and HSV-2.[47,49,58,64]

Trivalent nucleoside-modified mRNA-LNP vaccine to prevent HSV-2 genital herpes: The vaccine candidates that progress to phase 3 trials targeted viral glycoproteins that are essential for entry, either gD2 alone or gD2 and gB2.[24-26] Antibodies to gD2 are highly neutralizing and block its interaction with cell receptors nectin-1 and HVEM (herpesvirus entry mediator).[65,66] We hypothesized that vaccines directed only at entry molecules were not successful because the virus was able to evade antibody responses. HSV-2 glycoprotein C (gC2) and glycoprotein E (gE2) are immune evasion molecules. HSV gC2 binds complement component C3b to inhibit complement activation while gE2 binds the Fc domain of IgG to inhibit Fc-mediated ADCC and complement activation.[39,67-70] By adding gC2 and gE2 immunogens to gD2, the trivalent vaccine can block gD2 entry, gC2 evasion of complement, and gE2 evasion of activities mediated by the IgG Fc domain (Fig 1).

Our earlier studies evaluated a trivalent protein-adjuvanted vaccine for preventing genital herpes.[30,71] More recently, we pursued a trivalent nucleoside-modified mRNA-LNP vaccine (referred to as mRNA vaccine). The mRNA vaccine was designed using identical amino acid sequences as the protein vaccine to encode the ectodomains of gC2 amino acids 27-426, gD2 amino acids 26-331, and gE2 amino acids 24-405.[47,71] Uridine nucleosides in the mRNA were replaced by 1-methylpseudouridine (Fig 2). Each mRNA was purified by high-performance liquid chromatography and all 3 mRNAs were encapsulated into LNPs prior to immunization. The trivalent mRNA vaccine was administered intradermal or intramuscular. Our model of immunogen uptake into antigen presenting cells is shown in Fig 3.

Preclinical studies were conducted in mice and guinea pigs. We compared the trivalent protein vaccine adjuvated with CpG/alum to trivalent mRNA vaccine and showed that the mRNA vaccine induced superior immune responses, including ELISA IgG antibodies, neutralizing antibodies, antibodies that bind to crucial gD2 epitopes involved in virus entry and cell-to-cell spread, CD4$^+$ T cell responses, and T-follicular helper and germinal center B cell responses.[47] The trivalent immunogens, whether administered as mRNA or proteins, completely prevented genital lesions in mice and guinea pigs; however, differences in efficacy were notable for subclinical infection. Twenty-three percent of trivalent protein vaccinated mice had subclinical infection, defined as positive virus cultures on days 2 or 4 postinfection or HSV-2 DNA detected in DRG. In

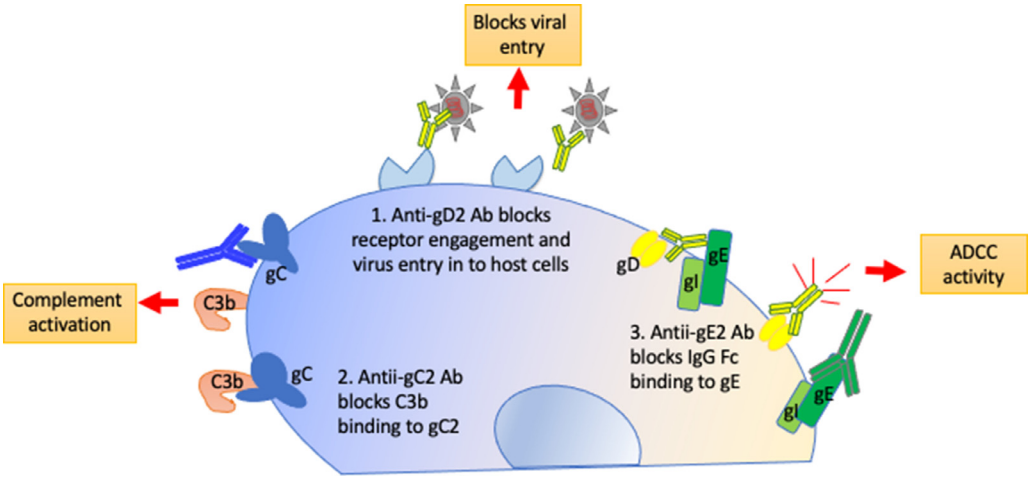

Fig 1. Model of antibody responses produced by the trivalent mRNA vaccine. The goal of the trivalent mRNA vaccine is: **1**, To block gD2 binding to receptor. Antibody to gD2 (yellow) binds to gD2 on the virus and prevents entry into the cell. **2**, To block gC2 on virus or infected cells from binding complement component C3b. Antibody to gC2 (blue) blocks the binding of C3b to gC2 allowing complement activation to proceed. **3**, To block binding of IgG Fc to the virus IgG Fc receptor, gE2/gI2. Antibody to gE2 (green) binds to gE2 and blocks the ability of gE2/gI2 to bind the Fc domain of IgG. In the absence of gE2 antibody, antibody to gD2 (yellow) binds to gD2 by its F(ab')$_2$ domain and the Fc domain of the same antibody binds to gE2/gI2 (green) to block activities mediated by the IgG Fc domain such as ADCC and complement activation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

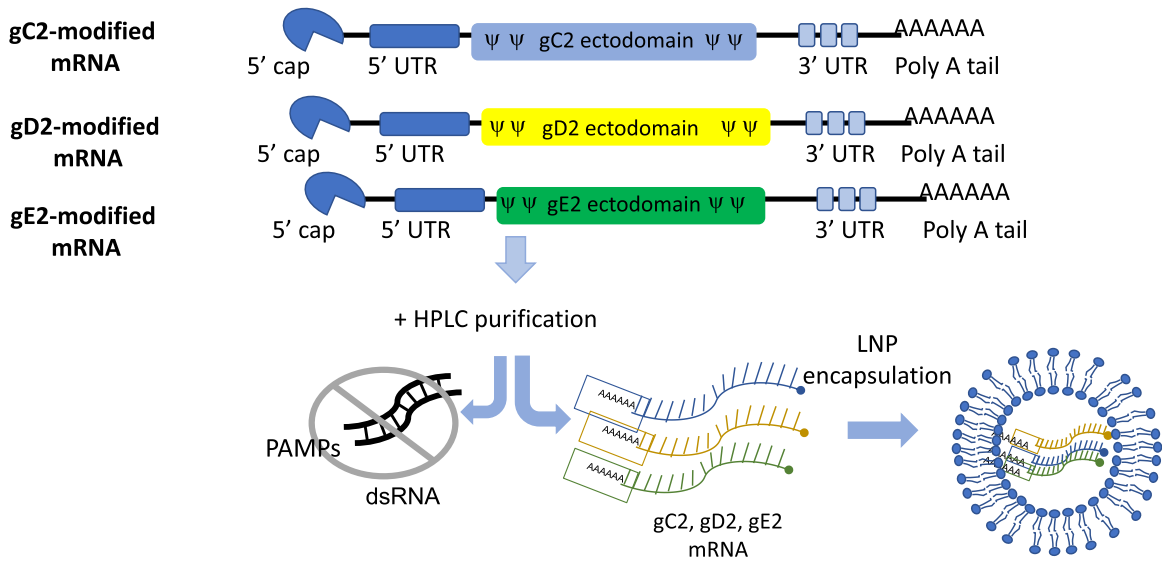

Fig 2. Nucleoside-modified trivalent mRNA-LNP vaccine. The trivalent nucleoside-modified mRNA-LNP encodes the ectodomain of gC2, gD2, and gE2. Uridine residues are replaced by 1-methyl-pseudouridine (ψ), and 5′ cap, 5′, and 3′ UTRs and poly(A) tails are modified to improve mRNA stability and translation efficiency. The mRNA is purified to remove double stranded RNA using high-performance liquid chromatography followed by encapsulation into LNPs. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

contrast, only 2.6% of mice immunized with the mRNA vaccine had subclinical infection based on a single mouse that had HSV-2 DNA detected in DRG on day 4 postinfection.[47] In the guinea pig model, 50% protein-vaccinated animals had recurrent vaginal shedding of HSV-2 DNA on 9% of days compared to 20% of mRNA-vaccinated animals with recurrent vaginal shedding on 2% of days.[47] These results describe the potency of the mRNA vaccine in preventing genital lesions and subclinical infection in preclinical models.

We recently addressed the durability of immune responses and protection by the mRNA vaccine.[52] We immunized guinea pigs with the trivalent protein or mRNA vaccine and challenged them 8 months after the final immunization. Neutralizing antibody titers and ELISA IgG titers declined markedly (6.2-fold) in the protein but less (2.2-fold) in the mRNA vaccine group. Eighty-five percent of guinea pigs immunized with the mRNA vaccine remained protected against genital disease at 8 months and none died, while the protein vaccine protection declined dramatically resulting in death in 30% and genital lesions in 80%.[52]

We used BALB/c mice to evaluate memory B cell responses as a possible mechanism to explain differences in durable immunity. The mRNA vaccine stimulated more robust $CD4^+$ T follicular helper cell and germinal center B cell responses than the protein vaccine.[47,52] These responses led to potent antigen-specific memory B cell responses that lasted at least one year after the second immunization. Responses to the mRNA vaccine were far superior to the protein vaccine.[52] We evaluated bone marrow cells by ELISpot for vaccine-specific antibody secreting cells. We detected more antibody secreting cells producing antigen-specific IgG1, IgG2a, and IgG2b in the mRNA than protein group.[52] High and durable antibody titers likely explain the outstanding protection provided by the mRNA vaccine.

Trivalent mRNA vaccine for preventing HSV-1 genital infection: HSV-1 accounts for 50% of first episodes of genital herpes.[72,73] Therefore, a prevention vaccine for genital herpes must be effective against both HSV-1 and HSV-2. The Herpevac Trial for Women reported that the HSV-2 gD2 vaccine provided better protection against HSV-1 than HSV-2.[26] We evaluated the HSV-2 trivalent mRNA vaccine for cross-protection against genital HSV-1 infection in mice. Mice were immunized twice with the mRNA vaccine and challenged intravaginally with a high dose (2 million PFU) of HSV-1. Mice were totally protected from weight loss and genital disease. Fifty-five percent of animals developed subclinical infection defined by vaginal HSV-1 virus titers on days 2 or 4 postinfection; however, no HSV-1 DNA was detected in DRG indicating that the vaccine successfully prevented both disease and latency.[49]

Table 1 summarizes the mRNA vaccine results for preventing HSV-1 or HSV-2 genital disease and

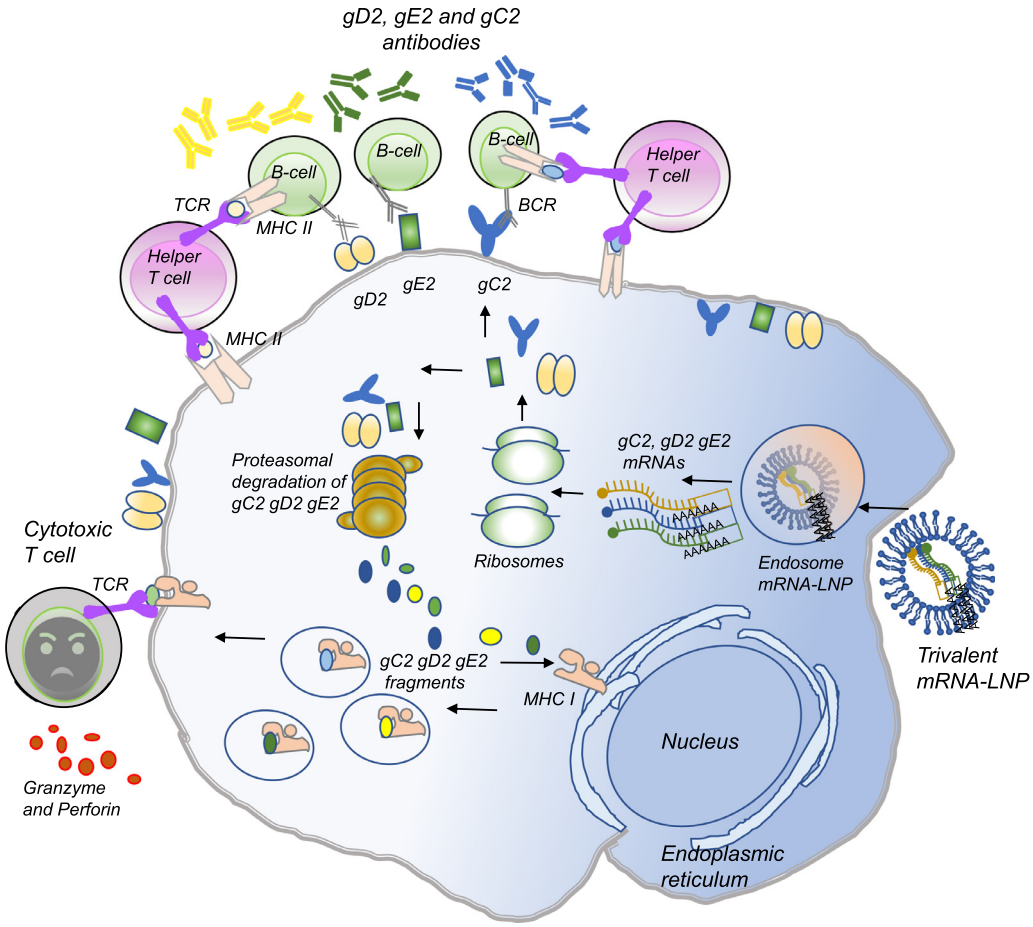

Fig 3. Stimulating immune responses by immunization. The trivalent nucleoside-modified mRNA-LNP vaccine is delivered to antigen presenting cells (APC) and endocytosed. The mRNA is released in the cytosol and translated into gC2, gD2, and gE2 proteins by ribosomes. The proteins are degraded in endosomes and presented on the cell surface to helper T cells by major histocompatibility complex (MHC) class II proteins. The helper T cells stimulate B cells to produce antibodies. The intracellular antigens are also broken down into smaller fragments by the proteasomal complex, and the fragments are then presented on the cell surface to cytotoxic T cells by major MHC class I proteins. The activated cytotoxic T cells kill HSV-2 infected cells by secreting cytolytic molecules, such as perforin and granzymes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

subclinical infection in mice infected one month after the final immunization, and preventing HSV-2 genital disease and subclinical infection in guinea pigs challenged one or 8 months after the final immunization.

Trivalent mRNA vaccine for preventing neonatal herpes: A goal of a genital herpes vaccine is to prevent disseminated infection in newborns, including infection of the developing brain.[14,74] The global incidence of neonatal herpes is 1 case per 10,000 births.[15] Although uncommon, neonatal herpes is a dreaded consequence of genital herpes. Antiviral treatment is recommended for infected infants, yet long-term neurological complications are reported in two-thirds of surviving children.[75,76] Several vaccine candidates have been evaluated in the mouse neonatal herpes model, including replication-defective live virus, single-cycle live attenuated virus, and trivalent protein. Each provided excellent protection.[77-79] Below we summarize our results using the trivalent mRNA vaccine that also was highly protective.

We used a mouse model for neonatal herpes where female mice were immunized with the trivalent mRNA vaccine months prior to mating and the pups born to immunized dams were infected intranasally with HSV-2 on postnatal day 2. The mRNA vaccine was highly efficacious in preventing neonatal herpes for first- and second-generation pups.[80] The trivalent mRNA vaccine induced high titers of IgG ELISA and neutralizing antibodies in the mothers that protected their newborns against HSV-2. We did not evaluate ADCC titers, but others have reported that ADCC contributes to protection.[14,36,79,81,82] We are currently performing

Table 1. Short- and long-term protection against genital HSV-1 and HSV-2 by trivalent mRNA vaccine

Condition	Mice*,47,49		Guinea pigs*,47,52	
	HSV-1‡ short-term†	HSV-2‡ short-term†	HSV-2 short-term†	HSV-2 long-term†
Serum neutralizing titer prior to infection	1:6480	1:4480	1:5888	1:2624
Survival	24/24 (100%)	44/44 (100%)	30/30 (100%)	20/20 (100%)
Genital disease	0/24 (0%)	0/44 (0%)	0/30 (0%)	3/20 (15%)
Subclinical infection				
Day 2 vaginal titers	16/29 (55%)	0/64 (0%)	15/30 (50%)	15/20 (75%)
Day 4 vaginal titers	4/29 (14%)	0/64 (0%)	3/30 (10%)	8/20 (40%)
HSV-2 DNA in DRG after day 28	0/25 (05)	0/15 (0%)	4/30 (13%)	6/20 (30%)
Vaginal shedding of HSV-2 DNA after 28 days	NA	NA	6/30 (20%)	11/20 (55%)
Vaginal shedding of virus after day 28	na	NA	0/30(0%)	0/20(0%)

Abbreviation: NA, not applicable.
*Mice were immunized with 10 μg while guinea pigs were immunized with 20 μg each mRNA.
†Short-term refers to mice or guinea pigs infected one month after the final immunization. Long-term refers to guinea pigs infected 8 months after the final immunization.
‡Vaginal infection doses in mice for HSV-1 and HSV-2 were 2×10^6 PFU and 5×10^3 PFU respectively because the LD_{50} of HSV-1 for vaginal infection in mice is 2000-fold higher than HSV-2.[49]

similar studies to assess mRNA vaccine protection against HSV-1 neonatal herpes.

FUTURE CONSIDERATIONS: MRNA-BASED THERAPIES FOR GENITAL HERPES

mRNA vaccines may also be administered as treatment for individuals already infected with HSV-1 or HSV-2. The immune responses needed to control infection may differ from those required to prevent infection. $CD8^+$ T cells may be crucial for controlling recurrent herpes.[83-88] Therefore, antigens used for treatment of recurrent genital herpes may differ from prevention. Another future consideration is to administer mRNA that encodes monoclonal antibody to a recently infected pregnant individual near term to prevent virus transmission to the newborn.

SUMMARY

The mRNA technology had made steady progress in the laboratory and preclinical studies for several decades; however, the true potential of the technology has only been recognized with the impressive success of mRNA COVID-19 vaccines.[44,45] Efforts to develop an effective vaccine for genital herpes have proven difficult. For the past 5 years, our efforts have focused on an mRNA vaccine.[47,52] Our strategy is to block virus entry and immune evasion from antibody and complement. Our candidate, the trivalent mRNA vaccine shows great promise in mice and guinea pigs in preventing HSV-1 and HSV-2 genital infection. The mRNA vaccine induces robust T-follicular helper cell and antigen-specific memory B cell responses. We are optimistic about success for the prophylactic mRNA vaccine in future clinical trials. Ultimately, our goal is to develop vaccines for both prevention and treatment to address the needs of those with no prior history of genital infection and the half-billion people already infected.

ACKNOWLEDGMENTS

Conflict of interest: Both authors have read the journal's policy on disclosure of potential conflicts of interest and the journal's authorship statement. The manuscript has been reviewed and approved by both authors. SA and HMF are inventors on patents awarded to the University of Pennsylvania on the use of HSV-1 or HSV-2 subunit proteins or nucleoside-modified mRNA for prevention or treatment of genital herpes. We have disclosed those interests fully to the University of Pennsylvania, and we have in place an approved plan for managing any potential conflicts arising from licensing of our patents.

Data availability statement: All data are available within the article or will be made available upon request.

Authors acknowledge NIH RO1 AI139618 and unrestricted research funding from BioNTech.

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