

We have created a herpes vaccine, called Δ gD-2, based on an HSV-2 virus genetically deleted for the gene that encodes glycoprotein D (gD-2). The result is a vaccine against both HSV-1 and HSV-2 that induces Fc receptor activating antibodies that mediate antibody-dependent cell-mediated killing (ADCK) as the primary mechanism of protection. The mode of action is unique; ADCK is induced to flag infected cells for destruction by natural immune cells.

What results have you seen that support the clinical development of Δ gD-2?

Extensive molecular and preclinical work has been completed for Δ gD-2, which induces unprecedented sterilizing immunity against both HSV-1 and HSV-2 challenge in multiple pre-clinical models. Not only did the vaccine prevent disease, but Δ gD-2 also prevented the virus from establishing latency, which no herpes vaccine has shown before. Latency refers to the ability of the herpes virus to remain dormant particularly in nerve tissue, often establishing lifelong infection with frequent subclinical or clinical reactivation.

Δ gD-2 acts via a novel mechanism of action that is mediated by non-neutralizing, Fc receptor activating antibodies to prevent both HSV-1 and HSV-2 infection with a wide range of clinical and laboratory isolates. The broad protection observed in a variety of pre-clinical models combined with the potential for sterilizing immunity, as evidenced by absence of latent virus, support the clinical development of Δ gD-2.

How is the mode of action of Δ gD-2 different than past failed attempts of other vaccine candidates?

We think that Δ gD-2 is more promising than other vaccines because it provokes a different type of immune response against HSV-1 and HSV-2 that is more effective at clearing virus and preventing the establishment of latency. Vaccination with Δ gD-2 elicits Fc receptor activating antibodies that facilitate the killing of infected cells, rapidly clearing the virus and thereby inducing sterilizing immunity. Other vaccine candidates have induced a response that elicits primarily neutralizing antibodies that attach to free floating virus. However, the herpes virus can still move and spread cell to cell, thereby evading neutralizing antibodies and allowing persistence of the virus and viral reactivation.

Why did previous attempts to develop a herpes vaccine focus on neutralizing antibodies?

Decades of research in herpes vaccine development have focused primarily on subunit vaccines designed to elicit neutralizing antibodies against one or two viral

proteins.⁶ When incubated with viral particles in vitro, neutralizing antibodies can prevent viral entry into cells. This strategy was effective as a vaccine for agents such as hepatitis B, however it had limited success with other pathogens such as herpes simplex viruses. The rationale for a subunit neutralizing antibody approach to HSV vaccine development emanated from observations that neutralizing antibodies that target viral glycoprotein D (gD) are elicited in response to natural human infection. While these antibodies do not prevent establishment of latency or prevent viral reactivation in pre-clinical models, they have been thought to limit the frequency and/or severity of clinical recurrences. Subunit vaccines comprised of recombinant gD alone or in combination with other viral proteins and with various adjuvants elicited high titer neutralizing antibodies and provided variable protection in pre-clinical models – but the clinical trial outcomes have been uniformly disappointing.

Why does the elimination of a surface protein lead to a different immune response?

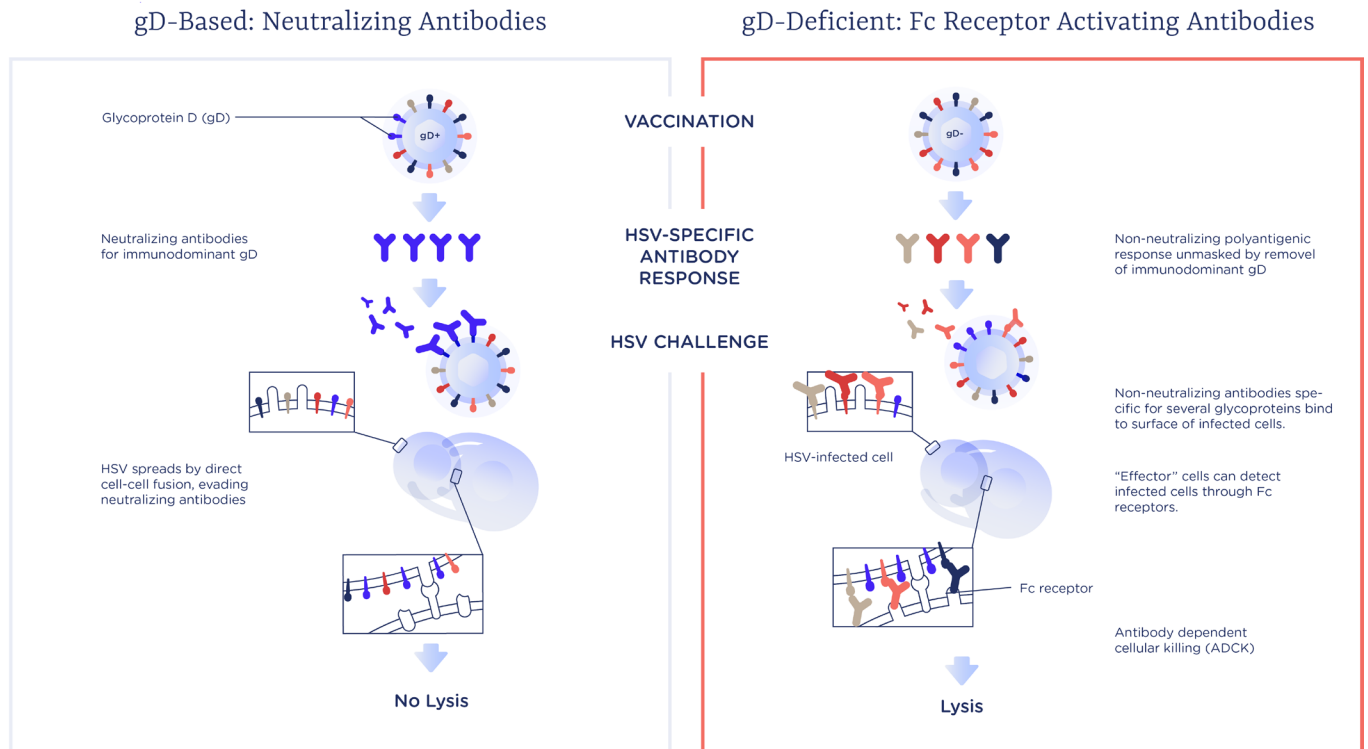
The precise mechanisms by which the deletion of an immunodominant viral antigen results in the formation of non-neutralizing antibodies is under investigation. One hypothesis is that glycoprotein D (gD) competitively binds to a receptor called HVEM (herpesvirus entry mediator, a TNF receptor), and this interaction may promote the induction of neutralizing or inhibit the generation of non-neutralizing, Fc receptor activating antibodies. In the absence of glycoprotein D, the balance may be shifted, and the immune system appears to react effectively to the other viral proteins expressed by the infected cell, and rapidly clears the virus before it has time to infect cells, spread between them, or establish latency in nerve cells.

If glycoprotein D (gD) is needed for viral cell entry, how does a gD-deleted vaccine replicate and stimulate an immune response?

HSV-2 contains a protein on its surface known as glycoprotein D (gD) which it needs to enter host cells. It is also essential for cell-to-cell spread of the virus. If the gD gene is deleted from HSV-2 and the virus is grown using a cell line that provides the HSV-1 gD protein to complement the missing surface protein, a hybrid virus is produced that is safe and restricted to a single cycle of growth. When vaccinated, the gD-1 complemented HSV-2 virus replicates once, however the non-infectious progeny cannot spread from cell to cell as it lacks the gene that codes for glycoprotein D.

Mode of Action

Vaccination with a gD-deficient HSV induces sterilizing immunity through Fc receptor activating antibodies, unlike gD-based candidate vaccines that induce predominantly neutralizing antibodies.



Adapted from Bolland & Pierce (2015).⁶

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