

21-Dec-2016

Dear Dr. Halford,

I am writing to you in regards to manuscript FVL-2016-0132 entitled "Genital herpes meets its match: a live HSV-2 ICP0⁻ virus vaccine that succeeds where subunit vaccines have failed", which you submitted to Future Virology.

Thank you so much for the work and time you put into this piece. Unfortunately in light of the comments received from the reviewer(s), found at the bottom of this letter, Future Virology can not proceed further with your submission in its current form. I appreciate this was an invited piece so I would like to give you the opportunity to take the peer reviewer comments on board, if you wish to, and then submit under a new submission. However it would be subject to another round of peer review at this stage and I unfortunately cannot guarantee publication.

Thank you for considering Future Virology for the publication of your work. I hope the outcome of this specific submission will not discourage you from the submission of future manuscripts. You will not be charged a fee for the accelerated review of this submission.

I hope you have a lovely Christmas and a happy new year!

Sincerely,

Commissioning Editor, Future Virology

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Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author

This manuscript is partly a vision, partly science, and partly wishful thinking. The author, has taken his construct of HSV-2 vaccine into human subjects, and believes, based on little data, that this vaccine will provide both a therapeutic and a prophylactic benefit.

Major problems:

1. There are numerous exaggerations throughout the manuscript; e.g., the manuscript states "... vaccines are safe and elicit complete protection against genital herpes..". However, neither safety nor efficacy has been demonstrated by the data presented.
2. The author makes an argument that live attenuated vaccines are always superior to subunit vaccines and that VZV is a good example of an attenuated vaccine for a related virus. Unfortunately, that is true only sometimes, and whether it holds for HSV is unknown at this time. The recent success of a subunit VZV vaccine for zoster clearly shows that a subunit vaccine can outperform a live attenuated product, as the subunit vaccine is ~95% effective, compared to ~50% for the attenuated.
3. The author claims that ~10% of HSV infections resolved within the first month of infection. I know of no data to show that HSV infection has ever resolved in a human host.
4. The author presents results of 2 experiments on humans, the first one a safety study that he conducted on himself. While self-experiments are generally permitted, these still require IRB review. Please provide assurance that this protocol was IRB reviewed and that the participant signed an informed consent. Unfortunately, data on 1 person does not prove safety of a product.
5. The subsequent Phase 1 study was conducted on a Caribbean island nation. Again, no information about IRB for this study is provided, and the trial does not seem to be listed on clinicaltrials.gov. The data for efficacy are based on self-report on participants who were questioned by the author and other staff before and after. As the author states "self-reported cessation of genital herpes... should be viewed with skepticism." Agreed.
6. On Figure 8, there is an impressively small p value. However, how it was derived is not shown. Given that there were only 17 persons in this study, it is unlikely that an appropriate statistical test for performed to obtain this result.

Reviewer: 2

Comments to the Author

This manuscript is part autobiography, part criticism of the herpes vaccine field, part description of autoinoculation studies with the author's herpes vaccine candidate vaccine, part advertisement for the author's vaccine company, and part description of preliminary results of a phase I trial. As such, it is not appropriate for publication as a Perspectives article. Each aspect has its flaws:

1. **Autobiography.** This is an article about genital herpes vaccines, not the author's scientific biography. This is not appropriate.
2. **Criticism of the herpes vaccine field.** This author has written similar critiques of the herpes vaccine before, including the claim that previous work has focused on glycoprotein subunit vaccines. The author is not the only one to propose virus-based vaccines, contrary to the way the manuscript reads. There have been tests of live-attenuated viruses and there are current tests of replication-defective vaccines. The author dismisses the safety issues of live attenuated HSV as vaccines. To say that the previous trials violate the Hippocratic Oath (p. 11, line 37) because there has not been more rapid testing is unwarranted criticism. To say that "the world has little to lose" (p. 19, line 35) by more rapid testing of live HSV viruses is reckless.
3. **Description of autoinoculation studies.** This describes primary data from a clinical trial, which are not appropriate for a Perspectives article. Second, the clinical protocol, the IRB approving the protocol, and statement of ethical conduct are not described.
4. **Advertisement for the author's company.** It is obvious why this is not appropriate for scholarly writing.
5. **Description of results of a phase I trial.** These are also primary data, which are not appropriate for a Perspectives article. More seriously, the clinical protocol, the IRB, and statement of ethical conduct are not described.
6. **Flying U.S. trial subjects to St. Kitt for the immunizations and then flying them back to the US is ethically questionable.** Who is giving the immunizations in St. Kitt and who is following them medically when they return to the US? Where is the clinical protocol based? Is this an end run around the FDA?
7. **Equally serious is the question about the safety of the virus as a vaccine candidate.** The author argues that the Δ NLS virus is "safe and well tolerated" (p. 19, lines 28-29 and other). In fact, the results presented argue the opposite. Patient CE-27 shows a "60 cm² area of inflamed epithelium". This "adverse reaction" is not acceptable and must be reported in any future clinical trial filings. The author cannot state this virus is "safe and well tolerated" (p. 19, lines 28-29).

Specific points:

1. **Was this study supported by the author's company? If so, this must be stated.**

Reviewer: 3

Comments to the Author

The MS FVL-2016-0132, entitled “Genital herpes meets its match: a live HSV-2 ICPO - virus vaccine that succeeds where subunit vaccines have failed” describes the author’s experience with a HSV-2 ICPO-mutant, which he argues is the “solution to the world’s herpes problem”. He states that he was the first to propose a live HSV-2 vaccine in 2007, which he now follows by demonstrating that his virus mutant is “safe and elicits complete protection against genital herpes”. The MS is a very impassioned plea designed to further stimulate patient interest in the authors company which offers the vaccine service and has already raised > \$50,000, likely from the study participants. It provides a very selective interpretation of the facts and lacks impartial analysis of current knowledge.

1. The MS would greatly benefit from a better discussion of the vaccine goals: preventative or therapeutic? What is the targeted population, what are the clinical endpoints and what is the role in immune modulation? What criteria were used to select the studied patients (Fig. 8) and why? What was their HSV immune status at the time of the first vaccine administration and how did it change?
2. The author claims that he was the first to suggest the use of live mutant vaccines in 2007. Unfortunately, this is not true. Live attenuated vaccines were already described in the late 90s (reviewed in Aurelian, 2004).
3. The author also states that his data document the ability of the ICPO- mutant to prevent infection of vulnerable partners and reduce disease symptoms. Unfortunately, this is also not true. The presented data indicate that the ICPO- mutant is protective in the mouse ocular model and it reduces virus shedding in the guinea pig vaginal model. However, the ocular model is rather unique and it does not fully reflect the human epithelial (genital) disease. Also, it is unclear whether reduced shedding decreases the virus titers levels that prevent infection of susceptible partners. In fact, one of the arguments, also made by the author, is that asymptomatic shedding (low virus titers) is the reservoir that sustains the high numbers of infected subjects, thereby justifying vaccine development.
4. Antibody production is used as the sine qua non criterion of vaccine efficacy. The author documents the relatively wide antigenic spectrum of the antibody, but makes no effort to identify the recognized proteins and how they contribute to protection from infection or disease therapy. In this context he continues his partially correct statements about infected cell proteins, including the absence of regulatory proteins in the virions. In fact, virions are known to contain regulatory proteins in the tegument and their potential role in immune modulation are totally ignored.
5. The author recognizes the importance of periodic latency reactivation to the generation of virus-specific antibody and periodically talks about non-optimal, i.e. not protective antibody response. However, he never bothers to discuss what is a non-protective immune response, does not examine its generation and argues that virus neutralization, which obviously measures antibody capable of inhibiting virus growth, is not the best assay to define the efficacy of vaccination.
6. Most people are infected with HSV-1 early in life and are HSV-1 seropositive. This serum antibody neutralizes both HSV-1 and HSV-2, yet it does not protect from infection with HSV-2 or other HSV-1 strains and these can also establish latency and reactivate. Antibody also does not prevent the development of symptomatic recurrent disease. Clearly, therefore, immune modulation plays a crucial role in the potential efficacy of a putative vaccine. Extensive studies have looked at this question in the

past and have shown that the virus modulates T cell mediated immunity and this plays a significant role in recurrent disease. This ought to be discussed.

7. The statement that young adults are HSV-1 seronegative and therefore 50% of them acquire genital HSV-1, is unsupported. The more likely interpretation of the increased proportion of genital HSV-1, which is primarily seen in college students, is different sexual behavior. In any case this does not deal with antibody-mediated protection from infection and recurrent disease symptoms.

8. The author dismisses all previous studies as phenomenological and not worth considering, although they are equivalent or actually superior to those presented in this MS. Skinner used a wild type vaccine in a relatively large study cohort and showed antibody development. Casanova used a HSV-2 mutant deleted in the protein kinase activity of RR1, which has virtually absolute protection from fatal and cutaneous HSV-2 disease in the mouse model and significantly reduces HSV-2 cutaneous and vaginal disease in the guinea pig model of recurrent disease. Vaccination of guinea pigs previously infected with HSV-2 caused a 75-90% reduction in the number of animals with recurrent disease and reduced the frequency and duration of the recurrent episodes experienced by the animals that were not fully protected (Wachsman et al., 2001). Protection was through modulation of T cell-mediated responses, shifting the balance from the down regulatory Th2 to the stimulatory Th1 responses/cytokines (reviewed in Aurelian, 2004).

9. In the absence of an M&M section, it is difficult to fully evaluate what was done including vaccine construction and the selection of the patients in Fig. 8. However, neuralgia is likely related to neuronal inflammatory cytokines and menstrual OB is likely related to hormonal regulation and how these are affected by vaccine-induced antibody production is a real stretch of the imagination. Also the data in Fig. 8 include 3 HSV-2 and 2 HSV-1 GH patients with minimal disease duration (3-4 days) reduced to 1-2 days. Finally, the validity of a self-reported data without physician confirmation, are questionable despite the authors' arguments.