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More on Vical's Herpes Vaccine: An Interview with Larry Smith, Ph.D.

By Josh Bloom — May 13, 2018

Larry Smith, Ph.D. Senior Vice President of Research at Vical Photo; Company Website [1]

Recently I gave a brief update [2] on the progress of VCL-HB01, an experimental therapeutic vaccine for genital herpes, which is being developed by Vical, a San Diego-based biopharmaceutical company. The update was brief because there was little new information on the progress of the vaccine as it made its way through human clinical trials.

But Larry R. Smith, Ph.D., who is Vical's Senior Vice President of Research agreed to answer some questions about the progress of the vaccine.

JB: *There has been considerable controversy about the utility of synthetic vs live attenuated vaccines for either treatment or prevention of genital herpes. This issue has been greatly amplified because (to be kind) there is a cloud over both the Theravax and Genocea protocols and results. Can you briefly comment on the science behind the two vaccines?*

LS: From what we have read in the press, our understanding of the controversy surrounding the Theravax vaccine is the manner in which a Phase 1 trial was conducted, i.e., outside of the appropriate regulatory oversight by FDA. We also believe Theravax is a live-attenuated virus vaccine which appears to have a single HSV-2 gene deleted to weaken (attenuate) it to enhance its safety profile. In general, live-attenuated virus vaccines, such as Merck's widely-used M-M-R®II vaccine, can have certain positive attributes: 1) a broader array of viral antigens, theoretically increasing the likelihood of protection; 2) production of viral antigens in a natural fashion (endogenously from within an infected cell); and 3) ability to function without the need for an

adjuvant **(1)**. However, these types of vaccines may also engender more potential safety concerns since they are live viruses.

By comparison, GEN-003, as described in Genocea's publications, is a recombinant protein-based vaccine formulated with a novel adjuvant called Matrix M2 to enhance its immunogenicity and efficacy. It contains two truncated HSV-2 proteins produced in insect cells that are provided in a non-natural fashion. Genocea went through several Phase 2 clinical trials where they were optimizing antigen and adjuvant concentrations to maximize immune responses and corresponding efficacy.

JB: *How does Vical's strategy differ from that of other vaccine approaches?*

LS: VCL-HB01 is a plasmid **(3)** DNA-based vaccine formulated with our proprietary adjuvant, Vaxfectin®. There are several advantages of using DNA vaccines, including 1) no live virus is used which reduces risk of safety issues inherent to live virus vaccines; 2) production of viral antigens in a natural fashion (endogenously from within a cell) similar to a live virus vaccine; 3) simple and cost-effective *E. coli*-based fermentation; 4) ability to induce T-cells and antibodies; and 5) no immunologic response to the plasmid DNA itself, which allows for repeated doses.

JB: *The Vical website gives very sparse detail about the efficacy of VCL-HB01. As I mentioned in my article, the language is reminiscent of that used by Genocea. Can you tell us why your Phase 1/2 trial results are materially different from those reported by Genocea?*

LS: On our website, we have a comprehensive presentation of our Phase 1/2 data that was presented at the 2016 ICAAC conference. The results of our Phase 1/2 trial compared with the results of other HSV-2 vaccine trials differ due to a number of variables in trial designs, including:

- Vaccine technology platform (plasmid DNA vs. protein subunit vs. live attenuated virus)
- Vaccine compositions: antigens selected (full-length vs. truncated) and adjuvant
- Background yearly HSV-2 lesion recurrence rates
- Swabbing periods to measure viral shedding and lesion rates
- PCR methodologies used to measure virus shedding

JB: *It would seem that Vical's protocol resulted in compliance rates and accuracy in reporting that is extremely high compared to that of other clinical trials. Can you comment on the protocol and how it resulted in better reporting by patients?*

LS: We can't comment as to what degree the compliance rates and reporting accuracy of our Phase 2 trial differed from other clinical trials. But in an effort to maximize compliance rates, we implemented institutional review board (IRB)-approved incentives to facilitate participant compliance with daily monitoring using an eDiary and clinical follow up visits. We believe this had a positive effect on keeping patients invested in the study and accountable for visiting the clinic for evaluation.

As for accuracy in reporting endpoints, we implemented a very important definition for our primary endpoint –both clinically and virologically-confirmed lesion recurrences. By having each lesion outbreak clinically confirmed by the investigator at each clinical site, in addition to having each lesion virologically confirmed by PCR verification of HSV infected swabs, very good assurance

was established that an actual lesion recurrence had occurred. This method has advantages over measuring virological confirmation alone or subject self-reported lesions using a diary only.

JB: *VCL-HB01 is a bivalent vaccine, which means that the selection of the components is critical in eliciting a robust immune response. Can you explain your choice of full-length HSV-2 UL-46 and gD antigens? How are these antigens different from others that have failed?*

LS: The selection of which HSV-2 antigens to incorporate in a vaccine has always been a key decision. That's why we sought guidance from global HSV-2 experts Drs. Larry Corey and David Koelle at the University of Washington (UW) and leveraged their extensive immunological experience with antigen identification. Under an NIH-funded grant, we collaborated with UW investigators to create plasmid **(3)** DNA vaccines for several of their lead antigen candidates and tested these vaccines in mice for immunogenicity and efficacy. We constructed plasmids expressing full-length HSV-2 proteins to maximize antigenic epitopes **(4)** and subsequently the immunogenicity of the vaccines. Then we selected vaccine candidates that were tested in a therapeutic model in guinea pigs in collaboration with Dr. Nigel Bourne at the University of Texas Medical Branch. This model provided **proof of concept** that our vaccine candidates possessed therapeutic efficacy because guinea pigs (in contrast to mice) are prone to lesion recurrences due to previous-infection with HSV-2. Based on the preclinical data, we selected UL-46 and gD for clinical development. To our knowledge UL-46 has not been previously tested in a clinical trial for therapeutic efficacy; in contrast, gD was tested as a single-antigen protein vaccine and appeared to demonstrate therapeutic efficacy [3] against lesion recurrences.

JB: *Vical has added an adjuvant called Vaxfectin to VCL-HB01. Can you explain its function?*

The name Vaxfectin® is a portmanteau of "vaccine" and "transfection". Vaxfectin® is Vical's proprietary cationic lipid-based formulation that has been shown [4] to effectively enhance plasmid DNA-based vaccines in a variety of animal models. It does this, like a number of other adjuvants, by augmenting a proinflammatory response that is conducive for enhancing both antibody and T-cell responses. It is important to note that Vical has investigated Vaxfectin® as a DNA vaccine adjuvant in over 400 human subjects.

JB: *It would seem that the historical PCR assays (PCR assays measure viral genetic material very accurately) and your assay are different. Can you comment?*

LS: We consider the assay performed at UW to be a widely used gold-standard. It goes without saying that optimizing all of the critical PCR parameters are required for creating a robust assay. From our understanding, the UW group developed the PCR assay and refined it over time with various improvements that resulted in their current assay. For instance, they have reduced the lower limit of HSV DNA detection to 150 copies/mL and optimized the solution for storing viral swabs for long periods of time.

JB: *Can you compare the trials of VCL-HB01 with those of Valtrex? Which trial paints a more accurate picture of anti-herpes efficacy.*

LS: There are major differences in general between how antiviral drugs and vaccines exert their antiviral effects. Drugs such as Valtrex are direct-acting small molecules that inhibit a key

enzymatic step in the HSV-2 replication cycle. The drugs must be administered daily to maximize efficacy.

In contrast, a vaccine is a biologic that is given in a series (four injections in the case of our Phase 2) and indirectly influences antiviral responses by mobilizing immunological effectors to curtail viral replication. Since vaccines can stimulate antiviral memory cells, they do not need to be administered as frequently as drugs and theoretically may reach peak function over time after all doses have been administered.

The endpoints used in the published antiviral drug trials for Valtrex and others measured a single event, including time to first recurrence and the percentage of subjects who were recurrence free. We believe that the primary endpoint of our Phase 2 trial, which measures annualized lesion recurrence rates, is more clinically meaningful because it captures more than just the first recurrence in the context of a chronically-recurring viral infection. Additionally, it may more faithfully represent the long-term effects of a vaccine. Statistically, it is a more powerful endpoint because more data is captured during the trial than just a single event. Furthermore, we worked closely with the FDA in developing the endpoint for the Phase 2, and we believe that it is more representative of the efficacy expected by symptomatic HSV-2 positive subjects who have multiple lesion recurrences each year.

JB: *There is a clear dividing line between prophylactic and therapeutic strategies for preventing/treating genital herpes. Vical has gone the therapeutic route despite that fact that the candidate from Penn is being evaluated for prophylactic rather than therapeutic use because Dr. Friedman does not believe that the vaccine would work well enough to be therapeutic. Can you comment?*

LS: We believe that there are considerable challenges with conducting prophylactic trials; importantly, very large numbers are required to show efficacy and the studies are very expensive. Based on available literature, we note that a previous prophylactic HSV vaccine approach failed a Phase 3 trial after enrolling more than 8,000 women and taking eight years to complete. Our long-term clinical development strategy is to first demonstrate therapeutic efficacy to validate the selected antigens and then potentially consider testing the prophylactic efficacy of our vaccine, which would necessitate partnership with a large biopharmaceutical company.

JB: *Most importantly, millions of HSV infected people are desperately awaiting any sign of hope for a successful HSV vaccine. What can we tell them now that is not published or widely known? When do you expect to issue a press release providing more detail?*

LS: As you know, no new therapy has been approved for HSV-2 in over 20 years and physicians remain frustrated at the limited options for treating their patients with genital herpes. A licensed HSV-2 therapeutic vaccine could represent a paradigm shift in the treatment of genital herpes.

We expect to announce the primary efficacy results and safety findings from the Phase 2 trial in June. As a reminder, the primary endpoint compares the annualized number of recurrences in participants receiving four monthly doses of VCL-HB01 compared to placebo. Additional endpoints from the trial will be evaluated at a later stage of the trial and we plan to submit detailed study results for presentation at an upcoming scientific conference.

If the primary endpoint of the trial is achieved, we intend to commence partnering outreach with biopharmaceutical companies to conduct a pivotal Phase 3 trial and move towards commercialization of this product candidate.

JB: *What do you tell people who call and try to get into a trial?*

LS: We are no longer recruiting patients into our Phase 2 study; we expect the last patient visit will occur in July. For those that call Vical expressing interest in the vaccine and in participating in the Phase 2 trial, we encourage them to monitor our website for updates on the program and for links to useful sources of information such as the CDC and NIH.

NOTES:

(1) Adjuvant are additives that help boost the immune response of vaccines. One class, aluminum salts, have been used for nearly a century for this purpose. Not all vaccines contain adjuvants.(

2) Plasmids are small pieces of DNA, usually round, which are capable of replicating themselves when in a suitable organism (often bacteria). They exist as separate entities and are not part of chromosomes. Plasmids are a primary tool in the production of DNA vaccines. They are the source of the antigens that will be incorporated into the vaccine.

(3) An epitope is the portion of an antigen where the antibody binds.

Source URL: https://www.acsh.org/news/2018/05/13/more-vicals-herpes-vaccine-interview-larry-smith-phd-12953

Links

[1] http://www.vical.com/About-Us/overview/default.aspx

[2] https://www.acsh.org/news/2018/05/01/vical%E2%80%99s-vcl-hb01-genital-herpes-vaccine-ready-big-time-12908

[3] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(94)92581-X/fulltext

[4] https://www.tandfonline.com/doi/full/10.1517/17425247.2010.538047