Haynes: MPER-Peptide Liposome Immunogen Testing

OVERVIEW

One key strategy of immunogen design for HIV vaccine development is to identify immunogens that selectively bind neutralizing versus non-neutralizing antibodies. This approach circumvents the induction of dominant non-neutralizing responses frequently observed during natural infection and with current vaccine protein immunogens. We previously demonstrated that the virion lipid is an important component of the binding immunogen for the gp41 membrane proximal external region (MPER) neutralizing epitope. Moreover, we have shown that antibodies that target this MPER neutralizing site are frequently polyreactive and negatively controlled by immune tolerance mechanisms. To overcome the disfavored status of MPER neutralizing antibodies, the Haynes team designed an immunogen to recreate this neutralizing epitope that includes the gp41 MPER associated with lipid. It retains the same binding properties for the MPER neutralizing antibodies as seen with virions. Specifically, MPER-peptide liposomes selectively bind the 2F5 and 4E10 mAbs and their unmutated ancestor antibodies (the putative naïve B cell receptors), but do not bind non-neutralizing gp41 MPER antibodies. Additionally, in a 2F5 MPER bnAb variable Heavy and variable light chain (VHVL) mature knock-in mouse model, the team has demonstrated that the MPER-peptide liposome immunogen induces 2F5 bnAbs when formulated with the TLR4 agonist monophosphoryl lipid A.

The overall goal of this project is to develop a GMP manufacturing process for production of MPER peptide-liposomes (a.k.a MPER-656 Liposomes) at the appropriate quality and scale for use in a first-in-human phase I clinical trial to evaluate safety and immunogenicity. Specifically, we will determine if the MPER peptide-liposomes can expand gp41 proximal MPER broadly neutralizing precursors after vaccination.

RESEARCH OBJECTIVES

1.) Formulation of research grade MPER peptide-liposomes and immunological evaluation in murine and NHP animal models.

2.) GMP vaccine production of MPER peptide-liposomes by IDRI in Seattle, WA in collaboration with the IAVI VxPDC team.

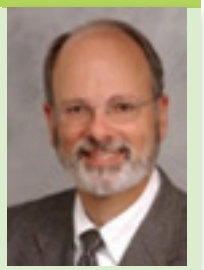
3.) Carry out a Phase I safety and immunogenicity trial with the HVTN.

PROGRESS

- An adjuvant selection trial was performed in non-human primates (NHPs), and Alum was selected as the adjuvant for the GMP MPER-peptide liposome formulation.
- A preclinical study in 2F5 mature knock-in mice confirmed the immunogenicity of MPER-656 Liposomes after several months of frozen storage. Additionally, continuous stability testing of early R&D lots has demonstrated that MPER-656 Liposomes are stable for at least 24 months when stored at -20°C.
- Process development for the GMP manufacturing process was completed at IDRI in 2017 with the support of the IAVI VxPDC team, and material was produced for use in the toxicology study.
- An ID50/ potency study was performed in mice using the toxicology study batch (engineering run) of MPER-peptide liposomes. These data will provide a baseline by which to compare potency of subsequent MPER-peptide liposome lots. An identical study will be done with the GMP clinical trial material (CTM) after production.
- A preclinical GLP toxicology study in rabbits was conducted by Charles River Laboratories (CRL) this year (2018) to verify safety of vaccination with MPER-peptide liposomes plus Alum adjuvant. There were no unscheduled deaths, no evidence of systemic toxicity, and no local irritation at the administration sites that were related to treatment with MPER-656 Liposomes. The in-life phase of the study ran from April to July 2018, and the full final report is almost complete.
- The HVTN face-to-face meeting for clinical protocol development was held in October 2018, and the protocol is entering into the regulatory review phase. The team is targeting late 1Q/ early 2Q 2019 for IND submission.
- Manufacture of the GMP grade clinical trial material (CTM) will be completed by the end of this year (2018).

On the current track, start of enrollment for the Phase I clinical study is expected to begin in summer 2019.

Grant at a Glance



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Grantee Institution
Duke University, Durham, USA

Project Title
MPER-Peptide Liposome Immunogen Testing

OPPID
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Grant Award
Up to $3.5 Million, awarded November, 2013

Collaborating Institutions
- ◊ Infectious Diseases Research Institute (IDRI), Seattle, USA
- ◊ International AIDS Vaccine Initiative VxPDC, New York City, USA
- ◊ Human Vaccine Trials Network, Seattle, USA
- ◊ NIAID/ Division of AIDS, Washington D.C., USA