STABILIZED HUMAN IMMUNODEFICIENCY VIRUS (HIV) ENVELOPE (ENV) TRIMER VACCINES AND METHODS OF USING THE SAME

Statement as to Federally Funded Research

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Background of the Invention

Vaccines that elicit cellular immune responses against viruses seek to reflect global viral diversity in order to effectively treat or prevent viral infection. For HIV vaccines, the initiation of robust and diverse human immunodeficiency virus (HIV)-specific T cell responses is desirable for an effective HIV vaccine. The highly variable Envelope protein (Env) is the primary target for neutralizing antibodies against HIV, and vaccine antigens may be tailored accordingly to elicit these antibody responses. To this end, immunogens mimicking the trimeric structure of Env on the native HIV virion are actively being pursued as antibody-based HIV vaccines. However, it has proven difficult to produce biochemically stable trimeric Env immunogens that elicit diverse neutralizing antibody responses.

Thus, there is an unmet need in the field for the development of vaccines that include novel, optimized trimeric Env immunogens, which can elicit broadly neutralizing antibody responses in order to allow for more successful HIV vaccination outcomes.

Summary of the Invention

In a first aspect, the invention features a stabilized trimer having three gp140 polypeptides in which at least one (e.g., two or each) of the gp140 polypeptides includes an amino acid sequence having at least 90% identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity) to, or the sequence of, SEQ ID NO: 2 (mEnv+).

In a related second aspect, the invention features a stabilized trimer having three gp140 polypeptides in which at least one (e.g., two or each) of the gp140 polypeptides includes an amino acid sequence having substantially the sequence of (e.g., 99% or more identity), or the sequence of, SEQ ID NO: 1 (mEnv) or SEQ ID NO: 3 (cEnv).

In some embodiments, the stabilized trimers are heterotrimers. The stabilized polypeptide heterotrimers may include two mosaic Env1 gp140 polypeptides (e.g., mEnv and/or mEnv+) each including an amino acid sequence having at least 90% identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity) to, or the sequence of, SEQ ID NO: 1 or 2, and one clade C Env gp140 polypeptide (e.g., "cEnv" having SEQ ID NO: 3) including an amino acid sequence having at least 90% identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity) to, or the sequence of, SEQ ID NO: 3 (cEnv) (e.g., two mEnv and one cEnv; two mEnv+ and one cEnv; or one mEnv, one mEnv+, and one cEnv). In other embodiments, the stabilized heterotrimers may include one mosaic Env1 gp140 polypeptide (e.g., mEnv and/or mEnv+) including an amino acid sequence having at least 90% identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity) to, or the sequence

bivalent mEnv and cEnv mixture elicited responses that were typically comparable to the better of the two individual trimers (Figure 16A – 16B). In addition, low tier 2 nAb activity was detected against clade B virus REJO.LucR with the combined regimen but not either trimer alone (*P<0.05; Mann Whitney test) (Figure 16B). These data demonstrate that the mixture of immunologically complementary mEnv and cEnv trimers were superior to either trimer alone.

We further developed an optimized version of the mEnv polypeptide, referred to herein as "Mosaic 1 Env gp140 version 2" or "mEnv+." As shown in Figure 2, mEnv+ (lane 4) is expressed at higher levels than cEnv (lane 1) or mEnv (lane 2). mEnv+ also demonstrates robust purity and stability, as shown by size exclusion chromatography (Figures 17A – 17B) and by SDS-PAGE profile (Figure 17C). The immunogenicity of mEnv+ was comparable to that of mEnv, regardless of adjuvant used (Figures 18A – B). Neutralization assays further demonstrated the comparable immunogenicity of mEnv+ as compared to mEnv (Figure 19).

Other Embodiments

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth.

US Provisional Application 61/749,737 is hereby incorporated by reference in its entirety. All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication or patent application was specifically and individually indicated to be incorporated by reference in their entirety.