Antibodies and molecular recognition (Ramot)

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"M2", a novel cysteine constrained looped 14-amino acid peptide, has been developed and optimized to bind HIV gp120. M2 binding allosterically elicits conformational rearrangements in the structure of HIV gp120 revealing the "CD4 induced" co-receptor binding site yet without occluding the native CD4 binding site. Hence this gp120 modality benefits from "both worlds"; accentuating and exposing both receptor binding sites in a single candidate vaccine immunogen.

The Need and Potential Application

The need for a prophylactic AIDS vaccine is indisputable. Thus far, all attempts towards producing an immunogen that can elicit neutralizing immunity have failed. Two distinct targets for neutralizing antibodies have been defined: the CD4 binding site and the co-receptor binding site. One vaccine modality currently being developed is CD4 bound gp120 that exposes the CD4 induced co-receptor binding site at the expense of occluding the primary receptor-binding site with CD4 or its mimetics. Clearly, it would be advantageous to be able to produce in a single immunogen a stable gp120 that simultaneously exposes and accentuates both neutralization targets, i.e., the CD4 binding site itself and the CD4 induced co-receptor binding site. The current innovation accomplishes precisely this objective by M2-peptide modulation of gp120. The M2-peptide binds to a previously unrecognized surface of gp120 and locks gp120 into the CD4 induced conformation yet without occupying the native CD4 binding site. Moreover, we postulate that this novel conformation that has already undergone conformational rearrangements actually better exposes the CD4 binding site and enhances its immunogenicity.

Advantages

Most AIDS vaccine candidates attempt to elicit neutralizing antibodies towards the primary receptor binding site for CD4. The alternative candidate vaccine currently being developed by the IHV and previously by Chiron forfeited the primary target in favor of inducing the CD4 induced co-receptor binding site by using the CD4-gp120 complex as the vaccine immunogen. We propose a unique vaccine candidate that simultaneously presents both targets in a single vaccine immunogen. Moreover, it is postulated that this single modality will be qualitatively improved over a mixture of two immunogens, each presenting only one receptor target.

Stage of Development

The lead M2 peptide has been produced as a phage displayed peptide and proven to elicit the desired double targets efficiently. However, to be translated into a working vaccine it still needs to be optimized to function as an isolated synthetic peptide able to bind and lock gp120 into its desired conformation at body temperature. For this we have developed a comprehensive work-plan to screen and perfect the peptide of choice and in collaboration with leading peptide chemists generate the ultimate peptide modulator. This will be cross linked to gp120 and tested as an AIDS vaccine immunogen.

Patents

The concept of CD4 induced immunogens has been covered by a cluster of patents [5,925,741, 6,020,468, 6,143,876, 6,329,202, 6,410,318, 6,812,026].
The M2-peptide is covered by a recent US patent [8,715,684].
We are confident that the ultimate peptide modulator to be produced and its complex with gp120 will be sufficiently novel and unobvious such that it will provide ample new matter for future patent applications.

Supporting Publications

Roitburd-Berman et al [2013] Allosteric induction of the CD4-bound conformation of HIV-1 Gp120. Retrovirology 10:147

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