A Native-Like HIV-1 Envelope Trimer that Engages Multiple Germline Precursors of Broadly Neutralizing Antibodies

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I. Introduction

Inducing broadly neutralizing antibodies (bNAbs) against HIV-1 by envelope protein (Env) vaccines has been problematic. Since 2009 a wealth of new bNAbs have been identified that can be used as templates for vaccine design. However, there is accumulating evidence that HIV-1 Env vaccines generally do not bind to the unmutated germline versions of these bNAbs, which may be one reason why Env vaccines have not been able to induce bNAbs.Env subdomain immunogens have been engineered to interact with germline precursors of bNAbs, but these immunogens have the disadvantage that they do not impose constraints on the angles of approach to bNAb epitopes that are present on the native Env trimer. Furthermore, these subdomain approaches only target one specific epitope cluster. Recombinant native-like Env trimers have the advantage that they only germline Abs that approach their target with the right angle will be selectively activated. Furthermore, they allow the triggering of germline Abs against diverse epitopes on the trimer. We designed a BG505 SOSIP gp140 trimer containing 18 amino acid changes that collectively allowed efficient binding to the germline versions of several V1V2-apex bNAbs (PG16, PG9, CH01 and PGT145) as well as several CD4 binding site bNAbs (VRC01, PGV9, 12A12). Surface Plasmon Resonance (SPR) assays showed that several germline Abs bound with nanomolar affinity to this new BG505 SOSIP germline trimer. This rationally engineered germline trimer represents a suitable priming protein for vaccine regimens aimed at inducing bNAbs.

II. Kick-start of the evolutionary process that leads to bNAbs

Co-evolution

III. Native-like trimers (BG505 SOSIP.664) for the inductions of NAbs

IV. Design of the BG505 SOSIP.664 germline trimer

Focus 1: V1V2-apex

Focus 2: CD4bs

Native-like soluble Env trimer

1. Rational design
2. Antibody functional studies
3. Literature research

18 amino acid changes compared to BG505 SOSIP.664

V. BG505 SOSIP.664 germline trimer: DSC and EM

A) 46.7 °C

B) 47.7 °C

Closed/Open/Non-native: 57%/43%/0%

VI. Germline trimer binds germline version of several bNAbs on ELISA

VII. Germline trimer binds germline version of several bNAbs on SPR

VIII. Activation of a B cell line expressing germline VRC01 (BCR)

Conclusions

1. BG505 SOSIP.664 is a useful scaffold for germline antigen design.
2. 18 aa changes did not affect the native-like trimeric structure.
3. The germline trimer binds a variety of germline antibodies.
4. The germline trimer activates a B-cell line expressing germline VRC01.
5. This rationally engineered germline trimer represents a suitable priming immunogen.