Alt: Physiologically Relevant and Rapidly Generated HIV-1 Vaccine Mouse Models

OVERVIEW

Mouse models expressing bNAbs or their precursors are commonly used as assay systems to test and optimize immunogens at the preclinical stage. The Alt laboratory developed a new mouse model that allows the precursor human immunoglobulin heavy (IgH) chain variable region exon (VH) for a bNAb to be developmentally assembled by V(D)J recombination and to dominate the IgH repertoire of the mice, and demonstrated the technique for the potent VRC01 class of HIV-1 bNAbs. In this VRC01-rearranging model, most individual B cells express one of a multitude of different variations of the potential VRC01 precursor IgH chain, providing a much more human-like precursor VRC01 repertoire. Indeed, sequential immunization in this model induced affinity maturation of VRC01-type HIV-1 neutralizing antibodies, although it did not achieve fully mature VRC01-class bNAbs. The diverse repertoire of naïve B cells in this VRC01-rearranging model stands in contrast to models that "knock-in" the pre-rearranged variable region exons of the bNAb unmutated common ancestor (UCA). This latter case results in an essentially monoclonal naïve B cell population that expresses the installed elements of the UCA, and may be poorly reflective of the true physiological circumstances of priming very rare precursors in a diverse repertoire. At the other extreme are mouse models with fully human Ig variable region loci; while these models can generate more complex antibody repertoires, mice have far fewer B cells than humans, which substantially diminishes the probability that such an engineered mouse will harbor the rare, specific precursor that must be engaged to prime the bNAb lineage. Here again, the VH rearranging mouse model from the Alt group offers the advantage of higher frequency for such precursors while maintaining B cell receptor diversity.

Under this award, the investigator's laboratory is making significant progress in the development of even more physiologically relevant mouse models for testing candidate HIV-1 vaccine strategies. The first aim is engineering a mouse model that generates highly diverse IgL chain repertoires of potential VRC01 precursors. Combining this IgL rearranging capacity with the VRC01 IgH rearranging model will generate an extremely diverse primary BCR repertoire of VRC01 precursors in mice for testing immunization strategies to elicit VRC01-class bNAbs. Other refinements of IgL rearranging strategy seek to generate a more "human-like" IgL repertoire in mice by enhancing the junctional diversity during V(D)J recombination. The second aim is to make a model in which expression of bNAb affinity maturation intermediates is targeted specifically to mouse germinal center B cells. Expressing such bNAb intermediates at this physiologically relevant stage can avoid potential central or peripheral tolerance checkpoints and will be especially important for testing boost immunogens in sequential vaccination strategies. Notably, the bNAb intermediates evaluated in the model can include those identified from human subjects in clinical trials of immunogens designed to elicit bNAbs. A third aim involves making these models readily available on an ongoing basis to major colleagues in the field for vaccination experiments. The Alt lab has provided different versions of the existing VRC01 models to Dr. Facundo Batista's lab to test immunogens developed by Dr. Rogier Sanders and John Moore's groups. Newly developed mouse models, once established, will continue to be made available to collaborators.

The grant is led by Frederick W. Alt, at the Boston Children's Hospital.

RESEARCH OBJECTIVES

1.) Generation of VCR01 mouse models with diverse bNAb IgH and IgL precursor repertoires.

2.) Evaluate mouse models that express bNAb intermediates directly in germinal center B cells.

3.) Provide of cohorts of pertinent mouse models to CAVD collaborators.

Grant at a Glance

Principal Investigator
Frederick W. Alt, PhD

Grantee Institution
Boston Children's Hospital; Boston, USA

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Physiologically Relevant and Rapidly Generated HIV-1 Vaccine Mouse Models

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Grant Award
Up to $2.5 Million, awarded in August 2017