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Efficiency of Genetic Immunization for the Generation of Antibodies Against Membrane Proteins

Debra T. Hansen, Ph.D., Associate Research Professor, Center for Applied Structural Discovery, Arizona State University

Cambridge Healthtech Institute recently spoke with Debra Hansen, Associate Research Professor at Arizona State University's Center for Applied Structural Discovery, about her upcoming presentation **"Efficiency of Genetic Immunization for the Generation of Antibodies Against Membrane Proteins"** at the **Antibodies Against Membrane Protein Targets - Part 2** conference to be held September 21-22, 2016, as part of the **14th Annual Discovery on Target event in Boston.**

SPEAKER Q&A

Q: What is genetic immunization?

Genetic immunization, also called DNA immunization, delivers nucleic acids to the host in order to generate an immune response. Genetic immunization has applications in vaccine development and in antibody generation. The approaches include simple needle injection, electroporation-based methods, and biolistic (gene gun) delivery of DNA-coated particles. The different methods vary in efficiency of intracellular delivery and in the types of immune responses. We typically use biolistic delivery, which leads to direct DNA transfection of keratinocytes and dendritic cells, and results in *in vivo* expression of the antigen in both the dermal tissues and the lymph nodes.

Q: Can genetic immunization be used to raise antibodies against membrane protein antigens?

There are published reports in the past few years that used DNA alone to generate conformational monoclonal antibodies against proteins containing 6-12 transmembrane domains. We also recently published a study using a structurally diverse set of membrane proteins to show, for the first time, that the biolistic approach efficiently raises a polyclonal response against naturally immunogenic membrane proteins.

Q: What are the advantages of using genetic immunization for antibody production over other methods?

Because genetic immunization relies on the immunized host to express, fold, and modify the antigen, the resulting antibodies recognize native antigen conformations, post-translational modifications, and intermediate assembly states. The method is efficient in that it avoids the need to produce difficult antigens in stable form over the course of an immunization schedule. Specific to membrane proteins, genetic immunization allows for immune recognition of the myriad in-membrane interactions with native lipids_ENREF_74_ENREF_75, with varied membrane topologies, and with other endogenous membrane-embedded macromolecules. Therefore, we hypothesize that genetic immunization will yield a highly diverse antibody repertoire for membrane proteins compared to protein-based immunization and *in vitro* methods.

Q: What are the challenges of using genetic immunization to produce antibodies against membrane proteins?

As with any host-based immunization method, genetic immunization faces challenges overcoming immune tolerance. However, several reports have effectively begun to

address this issue. Another important challenge is to show that the various DNA-based methods lead to appropriate recognition of conformational epitopes on the membrane protein antigen. Only conformational antibodies are useful as co-crystallization ligands or as functional antibodies, such as agonists and antagonists. Also, with respect to membrane proteins, there is yet no comparison between the choice of DNA vector or delivery method, or even of antibody quality between genetic immunization, protein-based immunization, and in vitro approaches. These points should be addressed as clearly there is intense interest in membrane proteins and their ligands for the development of therapeutics.

Speaker Biography: **Debra (Debbie) T. Hansen, Ph.D.,** *Associate Research Professor, Biodesign Center for Applied Structural Discovery, Arizona State University*

Debbie Hansen is an Associate Research Professor in the ASU Biodesign Center for Applied Structural Discovery, directed by Dr. Petra Fromme. Debbie develops recombinant technologies to support the highly challenging atomic-resolution structure determination of integral membrane proteins that are central to disease processes. She also collaborates with Dr. Stephen Johnston, director of the ASU Biodesign Center for Innovations in Medicine, where she is developing genetic immunization for the production of antibodies targeting membrane proteins and for vaccine applications. Debbie previously developed a recombinant human telomerase bacterial expression system while she was a Research Assistant Professor at the Medical University of South Carolina. As a Post-doc and Scientist at Yale University, she characterized novel enzymes and pathways in protein translation. She earned her Ph.D. from the University of Georgia and her B.S. from Purdue University, where she developed genetics for diverse microbes and identified new pathways in amino acid biosynthesis.