

Antibody Attacks

--- CABS Antibody Therapeutics Workshop

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The CABS Workshop on Antibody Therapeutics was materialized on Sunday, March 29 in Genentech Hall auditorium, UCSF Mission Bay. Organized by the Science and Technology Committee jointly with the Association of Chinese Students and Scholars (ACSS) at UCSF, this workshop attracted an audience of approximately 200. With six 35-minute talks, the workshop covered a broad range of topics in antibody drug development.

Dr. Zhiqiang An, CSO of Epitomics and recent textbook author on antibody therapeutics, gave an overview and introduction to antibody drugs. There are currently at least 24 monoclonal antibody products in clinical use, with another 158 in various stages of clinical development. Antibody drugs accounted for 4.6% of the total pharmaceutical revenue in 2006, but this class of therapeutics is predicted

by Datamonitor to account for 70% of growth between 2006 and 2012. Revenue from antibody therapeutics is expected to increase from USD 19.6 billion in 2006 to 43.4 billion in 2012. Antibody therapeutics are increasingly becoming more sophisticated, benefiting from technology advancements such as phage display technology, Xenomouse technology, and Fc engineering. We now see therapeutic antibodies that are exceedingly potent (Amgen's Denosumab has a Kd of 2 pM), bi-specific (Imclone's IGF1R/EGFR), smaller (Genentech's Lucentis and Enzon's PEGylated scFv), with extended half-life, less frequent dosing (Denosumab is twice yearly), and conjugated (Genentech's collaboration with Seattle Genetics to develop cytotoxin-conjugated oncology antibodies). While current antibodies are manufactured in mammalian expression systems, new production platforms using microbial systems, plants, and eggs have recently been developed.

A case study on Panitumumab was given by Dr. Xiaodong Yang, VP of Research and Preclinical Development at Intradigm Corporation. Developed by Abgenix/Amgen, Panitumumab (Vectibix™) is the first fully human anti-EGFR antibody approved by FDA for the treatment of cancer. As Senior Director of Oncology and project team leader of the Panitumumab program at Abgenix, Dr. Yang played a key role in discovery, development, and BLA submission of Panitumumab. In his talk, Dr. Yang reviewed both the Xenomouse platform and the discovery and development of Panitumumab. Transgenic Xenomice were created by inserting a single tYAC containing the human antibody locus and inactivating endogenous mouse antibody loci. Multiple lines of Xenomice were made with different versions of human heavy and light chains. For Panitumumab, the IgG2 version of Xenomice was used. Panitumumab has high affinity towards human EGFR (Kd of 50 pM), and is about seven times more potent than Cetuximab, a humanized anti-EGFR antibody from Imclone. A key discussion point was centered on the clinical performance comparison of Panitumumab and Cetuximab. The latter, being first-in-class, has more clinical data and enjoys a larger market share, whereas additional clinical trial data for Panitumumab are being generated. The jury is still out on comparison.

The subsequent four presentations focused on specific aspects of antibody technology. Dr. Cheng Liu of Eureka Therapeutics presented the clinical significance of Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) for oncology therapeutic antibodies, and discussed Eureka's ADCC enhancement technology platform. ADCC is thought to be the major mechanism for killing tumor cells by therapeutic antibodies. Thus, enhancing ADCC could substantially increase the potency for certain antibodies. A good example is Kyowa Hakko's anti-CCR4 antibody, which has an exceptionally low clinical dose, in the range of 0.003 mg/kg. Approaches to improving ADCC include Fc protein and glycosylation engineering, as well as inhibition of glycosidases during cell manufacturing.

Ms. Germaine Fuh, a scientist from the Department of Antibody and Protein Engineering at Genentech, introduced the concept of engineering antibodies with dual specificity, and provided specific examples of antibodies that potently target both VEGF and HER2. A wide range of antibodies can be developed to bind a specific target potently since antibodies have a large binding area and high structural diversity. It would thus be feasible to select a subset that can also potently bind a second target. Using synthetic antibody phage libraries, Ms. Fuh was able to identify dual specific antibodies that bind both VEGF and HER2. The initial hits have Kd of 0.3 and 0.03 uM against VEGF and HER2, respectively. Structural and Alanine scanning analyses revealed distinct subsets of residues interacting with the two antigens. After a series of antibody affinity maturation, the binding affinity was improved to 3 and 0.2 nM, respectively, while exquisite specificity was retained. These results challenge the dogma of "one antibody, one antigen" and offer a new option in antibody therapeutics.

Dr. Jian Long Lou, a faculty member of UCSF, showcased the yeast surface display technology platform. Combined with flow cytometry, yeast display technology has the advantage of convenience and speed. Dr. Lou further enlightened the audience with his successful endeavor in developing therapeutic antibodies against Botulinum neurotoxin (BoNT). Starting with phage and yeast libraries and armed with affinity maturation capabilities, his group was able to obtain highly potent anti-BoNT antibodies. These antibodies are useful in the development of BoNT detection assays and are being developed as protective agents against this dangerous neurotoxin and potential bio-weapon.

Dr. Jun Liu, a senior scientist in Genentech's Process Development group, reviewed the complexity and challenges related to protein drug degradation issues commonly encountered during the manufacturing and storage processes. Most protein drugs are only marginally stable and are subjected to many stressed conditions, which include long-term storage, high concentration, agitation, and rapid change in temperature. Further, after injection, protein drugs are in an environment that is very different from formulation conditions, and some proteins exhibit crystallization or precipitation in human serum. Protein aggregation is the most common problem and a major concern for safety and efficacy for large molecule drugs. Nevertheless, a well behaved protein drug can be developed by a careful consideration and balance of chemical and physical properties during discovery and process development.

All six talks were focused and extremely informative, and even the antibody specialists were impressed.

