NIAID Monoclonal Antibody Therapeutics for Biodefense and Emerging Infectious Diseases Workshop

Executive Summary

The first Monoclonal Antibody (mAb) Therapeutics for Biodefense and Emerging Infectious Diseases (BEID) Workshop, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), through the Division of Microbiology and Infectious Diseases (DMID) and organized by the Office of Biodefense Research Affairs (OBRA) of DMID, was held on March 29, 2006 at the Bethesda Pooks Hill Marriott. More than 95 leading scientists from academic institutions, biotech and pharmaceutical companies, as well as program staff from the NIAID, the Department of Health and Human Services (DHHS), the Department of Defense (DoD), and the Food and Drug Administration (FDA), participated.

This one day workshop focused on four areas critical to the success of developing mAb therapies for BEID, as outlined in the agenda below. The first session covered the complex and diverse mechanisms of action of mAb-based therapies for three different pathogens/toxins: botulinum neurotoxins, West Nile Virus, and enveloped viruses (e.g. Lassa Fever Virus and Pichinde Virus). These most recent scientific discoveries presented and associated discussions widened our knowledge and demonstrated that basic research to understand the mechanisms of mAb-mediated protection is essential for mAb drug development. The second session focused on new technologies for mAbs engineering for better safety, potency and stability. These presentations demonstrated that knowledge-based mAb engineering, stemming from comprehensive structure-function studies of the mAb molecules, provides direct approaches to engineer, select and improve mAb drug candidates for their intended applications. The third session consisted of presentations on the preclinical development path for mAb therapeutics and included talks on mAb immunogenicity, a case study for a mAb under development for the treatment of inhalational anthrax, and a talk from the FDA covering the basics of preclinical development. The fourth session focused on clinical evaluation of mAb therapeutics. Following a talk from the FDA on regulatory requirements, including when the “Animal Efficacy Rule” (21 CFR 314 Subpart I (314.600-314.650) would be used, a case study of the Phase 1 clinical evaluation of a mAb for the treatment of anthrax was presented. The presentation also included the discussion of the the development of appropriate anthrax treatment animal models for the

evaluation of this drug under the “Animal Efficacy Rule”. These successful case studies and other collaborative efforts on the mAb drugs presented at the workshop exemplified as well as emphasized the importance of good partnerships between government agencies, academics, and industry for the continued success of BEID mAb therapeutics development.

Furthermore, key issues and gaps for the development of mAb therapies for BEID were identified and discussed by the participants, and included:

1) The absence of appropriate therapeutic animal models for many of the BEID limits the advancement of mAb therapeutics through the licensure path in cases where the “Animal Efficacy Rule” will apply. The lack of appropriate animal models is due to, for example, limited knowledge, funding, infrastructure, and the lengthy time that is required for the development and validation of animal models.

2) There is no publicly accessible and centralized database available as a resource to the research community for mAb engineering efforts that relates structure-function findings relevant to improving mAb safety, potency, and stability. A wealth of information and relevant databases, if exist, mainly reside within industry as their own proprietary and intellectual properties; published literatures are quite scattered and incomplete.

3) There are still limited *in vitro* platform technologies available for early screening of mAbs candidates during preclinical evaluation phase. Early assessment of the safety profile and efficacy could significantly cut cost and shorten the development cycle for mAb therapeutics.

4) Workshop participants sought FDA regulatory guidance specific to the licensure path for mAb therapeutics for BEID under the “Animal Efficacy Rule” and/or for emergence use. Some pointed out that BEID mAbs are intended for emergence use only one time and the requirements for immunogenicity assessment could be different from those of mAbs for anti-cancer treatment that most of the regulatory requirements for mAb drugs are currently based on; others voiced their concerns about the regulatory challenges for emergency use of mAb drugs that are investigational new drug (IND) and targeting emerging infections.

Time	Sessions	Speaker	Title and Slides
8:00	Registration opens		
8:30	Introduction	Dr. Helen Schiltz OBRA	Welcome remarks
8:45		Dr. Michael Kurilla OBRA	NIAID BEID programs overview
9:00	I: Mechanism of action for mAb-based therapies for BEID	Dr. James Marks U. California, San Francisco	Mechanism of antibody neutralization of botulinum neurotoxins
9:30		Dr. Daved Fremont Washington. U, St. Louis	Monoclonal antibody as the post exposure therapy for West Nile Virus infection
10:00		Dr. Melina Soares U. Texas Southwestern Medical Center, Dallas	Tarvacin ™-Antiviral: a novel monoclonal antibody based therapy for enveloped viruses
10:30	Morning Break		
10:45	II: Engineering of mAb for better safety, potency, and stability	Dr. Kris Briggs Diversa Inc.	Comprehensive optimization of antibody therapeutics by directed evolution
11:15		Dr. Stephen Demarest Biogen Idec	The intrinsic stability an antibodies based on experiment, design, and prediction
11:45		Dr. Brent Iverson U. Texas, Austin	Engineered antibodies for the treatment of anthrax
12:15	Lunch Break		
1:20	III: Preclinical development of monoclonal antibody therapeutics for BIEID	Dr. Kathryn Stein Macrogenics, Inc.	Immunogenicity of monoclonal antibodies

1:50		Dr. Israel Lowy Medarex Inc.	Properties and development of Valotin: A potent, fully human monoclonal mAb to PA for the treatment of inhalational anthrax
2:20		Dr. Hanan Ghantous CDER, FDA	Preclinical Safety assessment for monoclonal antibodies for BEID
2:50	Afternoon Break		
3:10	IV: Clinical development of monoclonal antibody therapies for BEID	Dr. Renata Albrecht CDER, FDA	Regulatory requirements for clinical development of mAb therapeutics for BEID
3:40		Dr. G. Mani Subramanian Human Genome Sciences, Inc	Development of ABthrax, a fully human monoclonal antibody directed against Bacillus anthracis protective antigen (PA), for the treatment of inhalational anthrax
4:10	General Discussion		
4:50	Close of Workshop		