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Engineered antibodies take center stage

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Authors: [Huston, James S.^{a,*}](#) | [George, Andrew J.T.^b](#)

Affiliations: [a] Lexigen Pharmaceuticals Corp, 125 Hartwell Avenue, Lexington, MA 02421-3125, USA | [b] Department of Immunology, Division of Medicine, Faculty of Medicine, Imperial College of Science, Technology and Medicine, London, UK

Correspondence: [*] Author to whom correspondence should be addressed at: Lexigen Pharmaceuticals Corp., 125 Hartwell Avenue, Lexington, MA 02421-3125, USA. Tel.: +1 781 861 5300, ext. 232 (direct); Fax: +1 781 861 5301; E-mail: jhuston@lexigenpharm.com.

Abstract: The start of the post-genomic era provides a useful juncture for reflection on the state of antibody engineering, which will be a critical technology for relating function and pathology to genomic sequence in biology and medicine. The phenomenal progress in deciphering the human genome [1,2] has given significant impetus to the application of engineered antibodies in proteomics. Thus, advances in phage display antibody libraries can now help to define novel gene function and the measurement of abnormal protein expression in pathological states. Furthermore, intrabody and antibody engineering provide vehicles for the development of molecular medicines of the future. In addition to these new directions, antibody engineering has begun to show concrete success in its long-term efforts to develop targeted immunotherapies for cancer and other diseases. The cornerstones of clinical development are the detailed academic clinical trials that continue to push the boundaries of engineered antibodies into the real world [3]. The field displays a healthy impatience for practical results, as research

accelerates with concerted efforts to transfer preclinical insights into clinical trials. Growing private and governmental expenditures will lead to the rapid expansion of life-saving immunotherapeutic agents. The present review developed from our effort to report on the 11th Annual International Conference on Antibody Engineering (3–6 December 2000). This annual meeting is a forum for discussions on the latest advances in antibody engineering groups from around the world, and now includes the broader agenda of engineering in molecular immunology. In bringing scientists together to exchange ideas at this open forum, new collaborations and the threads of new discoveries are woven. For example, Professors Gerhard Wagner (Harvard Medical School), Dennis Burton (Scripps Research Institute), and Peter Hudson (CSIRO, Melbourne, Australia) gave exciting insights on structural immunobiology that had implications across many disciplines. The growth in antibody engineering was highlighted by the attendance of some 600 participants at the meeting, doubling that of the 1999 meeting. Dramatic clinical acceptance of monoclonal antibodies during the past two years has fostered this growth, with sales in 2000 of \$1.8 billion and projections for 2001 of \$3 billion. However, economic measures cannot begin to convey the medical revolution that is being effected by these first humanized and chimerized monoclonal antibodies. At this juncture, the 10 monoclonal antibody therapeutics in clinical use are of murine origin, of which 3 are entirely murine (OKT3, Mylotarg, 90Y-labeled Bexxar), 4 have been chimerized (human constant domains replacing murine) (ReoPro, Rituxan and its 131I-labeled analogue (Zevalin), Simulect, Remicade) and 3 were chimerized and humanized (human residues being substituted for at least some mouse-specific framework residues in VH and VL) (Zenapax, Herceptin, Synagis). Fully humanized anti-CD52 (CAMPATH-1H [5]) has also been approved by the FDA for the treatment of B-cell chronic lymphocytic leukemia and should become available in late 2001. Humanization was initially developed by Dr. Greg Winter at the MRC Laboratory of Molecular Biology (Cambridge, UK) [6], who presented the meeting's keynote address, "Antibodies as a Paradigm for Molecular Evolution". His pioneering work in antibody phage display libraries has been reformulated into a daring approach to develop truly novel proteins with genetically paired structural elements. He described studies in combinatorial protein engineering with enormous implications for both industrial and therapeutic applications of macromolecules [7].

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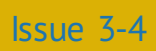
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