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IBC's 23rd Antibody Engineering and 10th Antibody Therapeutics Conferences, and the Annual Meeting of The Antibody Society

December 2–6, 2012, San Diego, CA

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Now in its 23rd and 10th years, respectively, the Antibody Engineering and Antibody Therapeutics conferences are the Annual Meeting of The Antibody Society. The scientific program covers the full spectrum of challenges in antibody research and development from basic science through clinical development. In this preview of the conferences, the chairs provide their thoughts on sessions that will allow participants to track emerging trends in (1) the development of next-generation immunomodulatory antibodies; (2) the complexity of the environment in which antibodies must function; (3) antibody-targeted central nervous system (CNS) therapies that cross the blood brain barrier; (4) the extension of antibody half-life for improved efficacy and pharmacokinetics (PK)/pharmacodynamics (PD); and (5) the application of next generation DNA sequencing to accelerate antibody research. A pre-conference workshop on Sunday, December 2, 2012 will update participants on recent intellectual property (IP) law changes that affect antibody research, including biosimilar legislation, the America Invents Act and recent court cases.

Keynote presentations will be given by **Andreas Plückthun** (University of Zürich), who will speak on engineering receptor ligands with powerful cellular responses; **Gregory Friberg** (Amgen Inc.), who will provide clinical updates of bispecific antibodies; **James D. Marks** (University of California, San Francisco), who will discuss a systems approach to generating tumor targeting antibodies; **Dario Neri** (Swiss Federal Institute of Technology Zürich), who will speak about delivering immune modulators at the sites of disease; **William M. Pardridge** (University of California, Los Angeles), who will discuss delivery across the blood-brain barrier; and **Peter Senter** (Seattle Genetics, Inc.), who will present his vision for the future of antibody-drug conjugates.

For more information on these meetings or to register to attend, please visit www.IBCLifeSciences.com/AntibodyEng or call 800-390-4078. Members of The Antibody Society and *mAbs* journal subscribers receive a 20% discount for meeting registration. To obtain this discount, email kdostie@ibcusa.com. *mAbs* is the official therapeutics journal of The Antibody Society and offers a discounted subscription to Society members for $49.

December 2, 2012: Intellectual Property Issues that Impact Antibody Engineering

Session chair: John Marquardt, Marquardt Law. The increasing popularity of antibody therapeutics in conjunction with recent legal developments and court precedents push scientists and business leaders to better understand the intersection of intellectual property and the commercial development of antibody therapeutics. The upcoming IBC Antibody Engineering Conference session on "Intellectual Property Issues that Impact Antibody Engineering" aims to educate scientific and business leaders on these issues and provide them with strategies and tools to navigate the complex landscape.

Currently, ~30 monoclonal antibodies (mAbs) have received US marketing approval. The number of mAbs entering clinical studies increased dramatically in recent years, rising from fewer than 20 candidates per year in 1997 to more than 50 candidates per year in 2010. Candidate molecules submitted to the FDA employed a wide variety of formats including engineered, bi-specific, fragments, domains, and antibody-drug conjugate antibodies. Given the historical 17% FDA approval cumulative success

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ratio, and the typical 8.2 y combined clinical and FDA approval time, the number of mAbs receiving US marketing approval will likely continue to increase.

Scott Miller (Life Technologies Corporation) will present a talk titled "Breaking Down and Understanding Complex IP Landscapes." He will provide tips on how complex IP landscapes can be understood, tracked and navigated. He will discuss methods for identifying IP bottlenecks and practical tools for patent watching, litigation watching, and IP landscaping services. **Vicki** Norton (Duane Morris, LLP) will discuss Cabilly and other notable antibody patents in a presentation aimed at familiarizing participants with notable patents in the therapeutic antibody space. **Adrian Antler** (Jones Day) will present a talk titled "Written Description Requirement for Antibody Patents." This talk will guide listeners through changes in the requirements for obtaining United States Patents on antibody therapeutics.

Kevin McCabe (Sterne, Kessler, Goldstein and Fox P.L.L.C.) will guide participants through the provisions of the law in a session titled "Navigating the Biosimilars Provisions." He will guide listeners through the provisions of Biologics Price Competition and Innovation Act of 2009 (BCPIA). **Steve C. Carlson** (Fish and Richardson, LLC) will present a talk on the America Invents Act and the Mayo v. Prometheus case. He will summarize portions of the recently enacted America Invents Act and discuss recent developments in subject matter patentability as defined in the Supreme Court case May v. Prometheus. Finally, **Ulrich Storz** (Michalski Hüttermann and Partner) will discuss patentability and regulatory approvals of therapeutic antibodies from the European perspective.

This session of IBC's 23rd Annual Antibody Engineering Conference promises to provide practical advice to scientists and business leaders developing therapeutic antibodies.

December 3, 2012: Antibodies in a Complex Environment

Session co-chairs: Richard Begent, University College London; Kerry Chester, University College London. It is a splendid feature of antibodies that it is feasible to create almost any specificity and link to almost any biological or chemical entity; largely as a result of this, applications in biomedicine are already very encouraging. It is manifest, though, that many of the limitations of current uses and potential applications are because the environments in which the antibodies or immunoconjugates must operate are so complex. This session addresses a range of issues in this area and will demonstrate how progress can be made through moving toward more thorough analysis of the dominant issues.

Kerry Chester (University College London) will tackle the target heterogeneity of certain cancers that often render a single therapeutic strategy ineffective. She will show how direct antitumor effects can be combined with strategies to limit tumor cell interaction with specific elements of extracellular matrix preventing cell migration, infiltration and metastasis. Therapeutic agents resulting from these insights are based on antibodies engineered with multiple specificities to give enhanced therapeutic potential within a single entity.

While antibody engineers commonly focus on a small number of antibody specificities, successful natural humoral immunity routinely makes use of multiple specificities and targets. These have been complex to explore, but were unlikely to have evolved unless they were important for effective immunity. **Roberto Polakiewicz** (Cell Signaling Technology, Inc.) will describe a new method based on proteomic analysis and DNA sequencing that elucidates this issue, giving important pointers to routes for developing effective therapeutic and diagnostic reagents.

Cancers are not only dependent on internal hallmarks of neoplasia, such as uncontrolled proliferation, immortality and resistance to apoptosis, but also require a tumor supportive microenvironment. **John McCafferty** (Cambridge University) has investigated a series of cells and extracellular proteins that are important elements of this supportive environment. The range of antibodies that he has developed block these processes and it can be envisaged how they may be used in combination with direct anti-tumor therapies to enhance effectiveness.

Antibody-mediated immune responses are known to be dependent on antibody isotype and Fcγ receptor interaction. **Ann White** (University of Southampton) will show the particular importance of Fcγ RIIB-mediated cross linking in the in vivo function of immunostimulatory antibodies. She will also show the importance with some antibody isotypes of FcγR-independent mechanisms of immunostimulatory antibodies. These are likely to be important issues in design of the next generation of therapeutic antibodies.

Although antibodies have conventionally been thought to be incapable of entering cells and binding specifically and effectively to their targets, the last two annual IBC Antibody Engineering Conferences have seen convincing demonstrations that there are important exceptions. This year **Qi Zeng** (A*STAR) will present evidence that intracellular oncoproteins can be inhibited by exogenous antibodies. Those looking for a radical new approach to cancer therapy with antibodies or vaccines will find food for thought in this growing field.

Understanding of the intracellular environment is also critical for the effectiveness of antibody drug conjugates in which the role of the antibody is selective delivery of a cytotoxic payload rather than intracellular effect. **John Lambert** (ImmunoGen, Inc.) will show the effect of immunoconjugate design on intracellular penetration and retention and in particular of the importance of linker design in controlling effective delivery.

As well as addressing a series of linked examples of critical importance to design of therapeutics, it is intended that the session will inform and stimulate participants toward greater success in their own field of endeavor through exploring the complexity of systems in which they are engaged.

December 4, 2012: Antibody-Targeted CNS Therapy Beyond the Blood-Brain Barrier

Session chair: James S. Huston, The Antibody Society, Huston BioConsulting LLC, and the Boston Biomedical Research Institute. Over the past two decades, antibody engineering and associated development of therapeutic antibodies have made

revolutionary contributions to diverse areas of medicine. The emergence of chemo-immunotherapy for cancer treatment led to revolutionary advances in oncology, which continue to expand at a rapid pace. Antibody therapy has also contributed remarkable advances to the treatment of autoimmune disease, rheumatoid arthritis, and gastrointestinal disorders. However, antibody therapy of central nervous system (CNS) disease has seemed unusually quiescent. Progress has been slowed by the blood-brain barrier (BBB) that shelters the CNS from large molecules and cells in the circulatory system. This session has been organized to present the pioneering efforts that allow antibodies or antibody-based therapeutics to traverse or circumvent the BBB. Delivery of immunotherapy to CNS targets thus opens CNS neurodegenerative disease to potent new therapies. This progress is particularly timely, as the demographics of our large aging population are projected to create an avalanche of heretofore untreatable disease, especially Alzheimer and Parkinson diseases, as well as brain tumors and metastatic cancers that have invaded the brain.

William Pardridge (University of California, Los Angeles) opens this Session with a keynote address on his pioneering research that allows recombinant bispecific antibodies and therapeutic immunofusion proteins to traverse the BBB. These antibody-based approaches have also been used to deliver targeted nanoparticles across the BBB, which will be discussed by **Ruban Boado** (ArmaGen Technologies) for the non-viral gene therapy of brain disease. New approaches for transmigration across the BBB with single-domain antibodies selected from phage display libraries are discussed by **Danica Stanimirovic** (National Research Council of Canada). These targeting species have been engineered as immunoconjugates that provide for transcytosis across the BBB, receptor-mediated endocytosis into brain cells, and pharmacokinetic/pharmacodynamic relationships optimized for particular CNS diseases.

The formation of misfolded protein aggregates is the hallmark of many neurodegenerative diseases. Among these, Alzheimer and Parkinson diseases are especially tragic, and are detailed from the standpoint of immunotherapy in the final two research talks of this session. **Cynthia Lemere** (Brigham and Women's Hospital, Harvard Medical School) will focus on her investigations of passive immunotherapy directed against the amyloid-β protein (Aβ) aggregates of Alzheimer disease. She will discuss her studies with human mAbs to various forms of Aβ, addressing preclinical and clinical aspects of this important approach for the control of Aβ formation in Alzheimer disease. **Anne Messer** (New York State Department of Health) will discuss her research on the use of intracellular single-chain Fv antibodies (intrabodies) and bispecific intrabodies specific for different forms of α-synuclein, to reduce aggregate formation by intracellular α-synuclein, which causes Lewy body formation and severe neurodegeneration in the most severe forms of Parkinson disease.

Deep Sequencing in B Cell Biology and Antibody Libraries

Session co-chairs: Andrew Bradbury, Los Alamos National Laboratory; Jamie K. Scott, Simon Fraser University. Deep sequencing is transforming biology, allowing a far more detailed understanding of complex microbiomes, genomes and transcriptomes. More recently this technology has also been applied to the analysis and manipulation of molecules involved in the immune system, providing an unprecedented opportunity to analyze and quantify diversity and mutation among expressed antibody genes from B cells and plasma cells involved in naïve repertoires and in immune responses. However, before deep sequencing can be used to analyze diverse immune repertoires, tools are required to make sense of the tidal waves of data these new technologies can deliver. The challenges of sequence analysis, and new algorithms to overcome them are addressed in the talks by **Jacob Glanville** (Distributed Bio) and **Csaba Kiss** (Los Alamos National Laboratory).

Deep sequencing has been applied to two broad categories of problems involving the antibody response. The first is an examination of the natural world – responding to questions, such as: What is the true diversity of expressed antibodies among different subsets of B-cells? And what is the role of this diversity in disease processes? These question, as relate to the areas of lymphoid cancers, HIV infection and autoimmune disease, will be addressed in the talks by **Andrew Fire** (Stanford University), **Susan Moir** (National Institutes of Health) and **Ignacio Sanz** (Emory University), respectively. The second category is more applied, and relates to the diversity of antibody libraries and how one can use deep sequencing to analyze and improve the in vitro selection of antibodies using phage or yeast display. In parallel with the descriptions of the algorithms required to analyze antibody libraries, Csaba Kiss and Jacob Glanville will also describe the applications of these algorithms to antibody selections.

December 5, 2012: Development Status of Immunomodulatory Therapeutic Antibodies

Session chair: Philip E. Thorpe, University of Texas Southwestern Medical Center. The development of immunomodulatory antibodies is one of the most significant advances in cancer therapy in the ten years that IBC's Antibody Therapeutics Conference has been held. The best known antibodies of this category are anti-CTLA4 (e.g., ipilimumab), anti-PD1, and anti-PD1L mAbs, which have shown meaningful clinical activity in melanoma, renal cell cancer, and non-small cell lung carcinoma (NSCLC). These antibodies act by suppressing the downregulation of activated T cells, thereby maintaining and enhancing immune responses to tumor antigens. This session will focus on new and alternative approaches to creating immunomodulatory antibodies for the treatment of cancer and non-malignant diseases, including rheumatoid arthritis (RA) and multiple sclerosis (MS).

Dario Neri (Swiss Federal Institute of Technology) will deliver the keynote presentation in which he will discuss immunocytokines for the treatment of cancer and RA. Immunocytokines are fusions of antibody-binding domains with cytokines that activate or suppress immune activity. The strategy is to create fusion proteins that target fibronectin and

tenascin isoforms that are selectively present in the extracellular matrix surrounding angiogenic and remodeling blood vessels. For cancer, the immunocytokines deliver IL-2, TNF-α, or IL-12 to stimulate immune cell attack on the tumor vasculature. For RA, IL-10 is delivered to suppress immune reactivity around inflamed vessels.

Bruce Cree (University of California, San Francisco) will describe how B cell-depleting monoclonal antibodies can be used to deplete dysregulated B cells that contribute to MS pathogenesis. Clinical studies have shown promising efficacy with > 90% reductions in markers of disease and excellent tolerability; Phase 3 clinical trials are in progress.

Erik Fedyk (Millennium Pharmaceuticals, Inc.) will discuss vedolizumab, a humanized monoclonal antibody for treating inflammatory bowel disease. Vedolizumab binds to the guttropic $\alpha_4\beta_7$ integrin on vascular endothelium, thereby blocking the homing of MAdCAM-1 positive leukocytes into mucosal and inflamed tissues. Vedolizumab is in Phase 3 trials in patients with moderate to severe Crohn disease.

Gens Volkmer (Stanford University) will discuss pre-clinical evidence that CD47, which is overexpressed in numerous tumor types, transmits a "don't eat me" signal to macrophages and dendritic cells. Treatment with CD47-blocking antibodies enables immune cells to phagocytose tumor cells in vitro. This results in inhibition of tumor growth and prevention of metastases in xenograft tumor models.

Philip Thorpe (University of Texas Southwestern Medical Center) will give an update on the mechanism of anti-tumor action of bavituximab, an immunostimulatory chimeric monoclonal antibody that is showing promising activity in clinical trials in patients with various types of cancer. Bavituximab targets the immunosuppressive lipid phosphatidylserine (PS) that becomes exposed on tumor blood vessels and tumor cells. Tumors externalize PS and secrete PS-expressing exosomes that impose quiescence on immune cells, thereby creating a tumor microenvironment that supports tumor growth. Bavituximab causes myeloid-derived suppressor cells in tumors to differentiate into tumoricidal M1 macrophages that destroy tumor vasculature and tumor cells by antibody-dependent cell-mediated cytotoxicity. It also causes immature dendritic cells in tumors to mature and present tumor antigens that result in the generation of tumor-specific cytotoxic T cells. Thus, bavituximab reactivates innate and adaptive tumor immunity, and induces an immune cell-mediated shutdown of tumor vasculature.

Joseph Shan (Peregrine Pharmaceuticals, Inc.) will then give an update on the performance of bavituximab in clinical trials in patients with cancer. Bavituximab has been shown to be well-tolerated both as a single agent and in combination with approved therapies. Bavituximab has demonstrated promising anti-tumor activity as an adjunct to standard chemotherapy, and is advancing to late stage clinical development in NSCLC.

Given that several of the new agents being described in this session have already been established as safe and effective in clinical trials, there is a high likelihood that some will become approved drugs. This is therefore a timely session that will give a glimpse of what is around the corner.

Modulating the Half-Life of Antibody Therapeutics

Session chair: Trudi Veldman, Abbott Bioresearch Center. Tailoring pharmacokinetics, efficacy and mechanism of action is critical for biologics differentiation. Whether one aims to target tumors with antibody fragments or small protein scaffolds and is looking for ways to improve the serum half-life of these molecules, or whether one is dealing with significant target-mediated clearance, this session provides insights into different approaches to extend the serum half-life of antibodies and protein therapeutics.

Roland Kontermann (University of Stuttgart) will review the various strategies and results of a comparative study of different approaches to extend the half-life of recombinant antibodies. **Javier Chaparro-Riggers** (Rinat/Pfizer) will present an interesting case study in which altered pH dependent antigen binding alters target-mediated disposition and circulating serum half-life of an antibody.

Several scientists will share their experience with small protein scaffolds and the strategies that they have developed to modulate the pharmacokinetic properties. **Ray Camphausen** (Adnexus/Bristol-Myers Squibb) will present Adnexus' approach and pre-clinical experience in modulating the pharmacokinetics of Adnectins by focusing on either increasing hydrodynamic volume or improving recycling through the neonatal Fc receptor (FcRn) pathway. **Syd Johnson** (MacroGenics) will describe pharmacokinetic studies in cynomolgus monkey and human FcRn-transgenic mice of bispecific DART molecules formatted as Ig-like or albumin domain fusion proteins. Lastly, **Kaspar Binz** (Molecular Partners) will present pharmacokinetic engineering methods to generated well-differentiated DARPin drugs.

Of general interest will be a presentation by **Gabriele Proetzel** (Jackson Laboratory) describing the humanized FcRn mouse for modeling antibody pharmacokinetics. The neonatal Fc receptor (FcRn) is the salvage receptor for antibodies, responsible for the extended serum half-lives of IgG and albumin. Significant species differences in FcRn make standard rodents a poor model for studying antibody half-life. The key features of a mouse model humanized for FcRn will be presented and benefits of using this model for preclinical pharmacokinetic assessment of antibodies will be discussed.

The success of a therapeutic protein drug depends on multiple features including target affinity, specificity, mechanism of action and, as has become more the focus recently, good drug-like properties and in vivo behavior. Understanding what features contribute to the pharmacokinetic properties of a protein drug and learning ways to modulate these properties through engineering is the topic of this relevant session.

The Antibody Society: Update on Current Initiatives

Session chair: Janice M. Reichert, Reichert Biotechnology Consulting LLC; Editor-in-Chief, *mAbs*. This session is designed to update participants on current and future activities of The Antibody Society (www.antibodysociety.org), which seeks to create common ground for the antibody engineering, novel binder, and antibody-based therapeutics community, in its

broadest sense. We organize our premier meeting each December and encourage others during the year, pursue antibody-related initiatives that will establish standards for data collection and organization, and support the development of our future generations of scientists.

The session includes updates on (1) the Society's website and LinkedIn group; (2) Society-affiliated journals; (3) publications of the Society; and (4) benefits of membership in the Society. The Society's website (www.antibodysociety.org) serves as a valuable resource for our community. Summaries of the latest advances in making antibody therapeutics into clinical products (Antibody News), are posted on a regular basis by **Janice Reichert** (Reichert Biotechnology Consulting LLC; Editor-in-Chief, *mAbs*), who will provide updates on communications from the Society. The Society maintains a comprehensive list of antibody therapeutics approved for marketing in the US and European Union. In addition, links to informatics resources and "Guidelines on Information About Therapy Experiments," which include online GIATE computer resources from Prof. Richard Begent and colleagues.

The Society administers lively discussions on "The Antibody Society" LinkedIn group, reached via our website. Members are encouraged to post questions and comments relevant to antibody research and development. This forum allows free exchange of information and expertise between Society members, including the Board of Distinguished Advisors and Board of Directors. The Society is pleased to be affiliated with two distinguished PubMed-indexed journals, its Official Journal, *Protein Engineering Design and Selection* (*PEDS*), and its therapeutic antibody research journal, *mAbs*.

The Society organized an Antibody Special Issue (October 2012) for *PEDS* (http://peds.oxfordjournals.org). In cooperation with the Society, *mAbs* (landesbioscience.com/journals/mabs) published a comprehensive report on IBC's 22nd Annual Antibody Engineering and 9th Annual Antibody Therapeutics International and the 2011 Annual Meeting of The Antibody Society held December 5–8, 2011 in San Diego, CA USA. The report appeared in the March/April 2012 issue of *mAbs* and can be freely downloaded at landesbioscience.com/journals/mabs/article/19495/. Reports on the 2012 meetings will be published in the March/April 2013 issue of *mAbs*.

Society membership is free for graduate and undergraduate students and only $50 for post-doctoral research fellows. The standard membership fee for The Antibody Society is $100. Benefits of membership include a 20% discount to the Society's Annual Meeting and markedly reduced subscriptions for Society-affiliated journals.

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December 6, 2012: Immunomodulatory Antibodies for Cancer Therapy

Session chair: Louis M. Weiner, Georgetown University Medical Center. Antibodies have emerged as critically important platforms for cancer therapy. Initial successes with reagents such as trastuzumab, rituximab, cetuximab, panitumumab and bevacizumab laid the groundwork for a number of exciting new antibodies that are the subject of this session. These molecules can either manipulate signaling or deliver cytotoxic agents. One of the most exciting new developments in the field is the emergence of immunomodulatory antibodies that directly manipulate T cell directed immune responses, or stimulate the induction of adaptive immunity through the process of antibody-facilitated antigen presentation.

Her2 is an important target in breast cancer and is being exploited by a new generation of antibody-based therapeutics. Some of these molecules are unconjugated, and seem to act by perturbing Her2 related signaling. Others exploit Her2 as a target for the delivery of cytotoxic agents. **Mark Sliwkowski** (Genentech) will describe advances in developing new Her2 targeted therapies.

Antibodies directed against immune checkpoints such as CTLA4 have demonstrated significant anti-tumor activity in patients with melanoma. Many other candidate checkpoints have been identified and targeted by antibodies, and one such antibody directed against PD-1 has exhibited remarkable promise in a recently reported clinical trial. These and related results will be presented by **Charles Drake** (Johns Hopkins University). Seattle Genetics has pioneered the use of antibody-drug conjugates, including a clinically-approved agent targeting CD30 in lymphoma. **Megan O'Meara** (Seattle Genetics) will present recent results of combination studies employing brentuximab vedotin.

Returning to the concept of immunomodulation, **Tibor Keler** (Celldex Therapeutics) will describe results using an agonist anti-CD27 antibody that induces T cell activation in combination with stimulation of the T Cell Receptor. Finally, **Jon Wigginton** (Bristol-Myers Squibb) will describe components of that company's extensive portfolio of immunomodulatory antibodies with promise in cancer.