The Antibody Society is pleased to invite you to attend its annual Meeting, Antibody Engineering & Therapeutics, which will be held December 12-15, 2017, in San Diego, CA. We will be celebrating the 10th anniversary of the Society at the Society's Special Session on Thursday December 14, 2017.

In the summaries below, the session chairs discuss the relevance of their topics to current and future antibody therapeutics development.

Antibody Engineering & Therapeutics, December 12-15, 2017

Tuesday December 12, 2017. Keynote presentations (morning)

The meeting will open at 8.15am with remarks by **James D. Marks**, M.D., Ph.D., San Francisco General Hospital, and 4 keynote addresses on the following topics:

- Deciphering the Human Immunome, presented by **James E. Crowe, Jr.**, M.D., Vanderbilt University Medical Center;
- Paracrine Delivery: Therapeutic Biomolecules Produced in situ, presented by **Andreas Plückthun**, Ph.D., University of Zürich;
- Biologic Drug Delivery Across the Blood-Brain Barrier with IgG Fusion Proteins, presented by **William M. Pardridge**, M.D., UCLA and ArmaGen, Inc.; and
- Ocrelizumab in Relapsing and Primary Progressive Multiple Sclerosis, presented by **Peter Chin**, M.D., Genentech.

Tuesday December 12, 2017. Track 1 (afternoon)
Overcoming Antibody Delivery Challenges Including Brain And Intracellular Targets

Paul J. Carter, Ph.D., Senior Director and Staff Scientist, Department of Antibody Engineering, Genentech, Inc., and **Andreas Plückthun**, Ph.D., Professor, Department of Biochemistry, University of Zürich, Switzerland will co-chair a session on overcoming antibody delivery challenges including brain and intracellular targets.

Antibody drug development is now a mature field with >60 marketed antibody therapeutics and hundreds more in clinical trials. Indeed, many of the more tractable and better understood targets for the treatment of human diseases have been extensively exploited for antibody drug development. This begs the question, where will new targets for future antibody drugs come from? One possible source of new targets for antibodies is in overcoming major delivery challenges that make some potential therapeutic targets challenging, if not impossible, to reach with conventional approaches. Presentations in this session will focus on three such delivery challenges highlighting basic research trying to understand the problems and translational studies attempting to overcome them.

The first delivery obstacle is to facilitate protein transport across the so-called blood-brain barrier (BBB) that prevents free diffusion of macromolecules from the blood into the interstitial fluid of the brain. This is an urgent and important problem to solve, given the tens of millions of individuals worldwide who are afflicted with neurodegenerative diseases and the lack of disease-modifying therapies. Incurable forms

of brain cancer also represent another major unmet medical need. The second delivery challenge is increasing the efficiency of delivery of protein drugs to the lung. Addressing this challenge may facilitate the treatment of a range of serious lung diseases including autoimmunity, inflammation and cancers. The third delivery challenge is the "holy grail" for protein therapeutics of enabling proteins to cross the plasma membrane for delivery in a functional form to the cytosol. More than half of the targets for current drugs are located inside cells and accessible only to small molecule drugs. Efficient targeted delivery of protein drugs to access intracellular targets may greatly expand therapeutic target space. For example, blocking of protein-protein interactions is often readily possible with proteins and usually much more difficult with small molecules.

In the opening talk of this session, **Jasi Atwal** (Genentech) will present on bispecific antibodies to increase antibody delivery across the BBB into the brain. One arm of the bispecific binds to a receptor enriched at the BBB, such as transferrin receptor or CD98 heavy chain. The other arm of the bispecific binds to the brain target of interest. **M. Jack Borrok** (MedImmune) will describe targeting of caveolae-associated proteins to improve the delivery and efficacy of therapeutics that act within the lungs. Concurrently unwanted interactions with non-target tissues can be reduced. An alternative approach to delivery of protein drugs to the lung is by inhalation. This local lung delivery may provide rapid onset of pharmacologic action, as well as reduced systemic exposure and lower dose. **Diane Van Hoorick** (Ablynx) will provide a case study on an inhalable anti-respiratory syncytial virus (RSV) Nanobody®, ALX-0171, that is currently undergoing clinical evaluation for infants with RSV infection.

The final three talks will all approach the formidable problem of protein delivery, across the plasma membrane into the cytosol of cells. **Wouter Verdurmen** (Radboud University Medical Center, Nijmegen, The Netherlands) and collaborators developed a biotin ligase assay to quantify the relative efficiencies of various transport systems. This assay has been used to optimize protein transport by bacterial toxins and objectively compare it to cell-penetrating peptides and super-charged proteins. Next, **Ernst Wagner** (Ludwig Maximilians University, Munich, Germany) will describe the identification of potent intracellular delivery carriers derived from chemical evolution processes. Briefly, sequence-defined carriers from automated solid phase-assisted synthesis combine natural and artificial amino acids are combined with other transport elements, providing receptor-targeting and endosomal release function. In the final presentation of the session, **Thomas Marlovits** (Institute of Molecular Biotechnology, Austria) will describe bacterial type III secretion systems. These syringe-like "injectisomes" are megadalton in size and transport bacterial toxins across membranes directly into a eukaroytic host cells. Investigation of the injectisome led to the design of substrates that can be translocated directly into eukaryotic cells.

Tuesday December 12, 2017. Track 2 (afternoon)
Novel Antibody Display, Selection And Screening Technologies

The session on "Novel antibody display, selection and screening technologies", chaired by **Andrew Bradbury**, M.D., Ph.D. Research Scientist and Group Leader, Los Alamos National Laboratories; Chief Scientific Officer, Specifica, focusses on the new technologies expected to advance antibody library generation and selection in the future. Many of these reflect the rapidly growing role of next generation sequencing (NGS) in all aspects of in vitro antibody generation. Dr. Bradbury will discuss how NGS has enabled more informed discussions on antibody library sizes, and how traditional selection from antibody libraries does not address the full depth of possible positive antibodies. **Tim Whitehead** (Michigan State University) will discuss the power of NGS in protein engineering to analyze the outcomes of different selective pressures on antibody stability, affinity and function, and to use this

information in antibody discovery programs, while **Brandon DeKosky** (The University of Kansas) will describe how the combination of cloning natural paired antibody responses to viruses with yeast display vectors provides insights into neutralizing HIV and Ebola responses. In addition to NGS, **Benjamin Hackel** (University of Minnesota) will describe the engineering of novel alternative novel yeast display vectors as applied to the development of novel small non-antibody scaffolds. **James Wells** (UCSF) will describe an innovative use of novel proteomic technologies involving phage display to both understand how cancer cells remodel their membrane proteomes, as well as to generate recombinant antibodies against them. Once potential therapeutic antibody leads have been identified, they need to be further developed before they can be used in the clinic. This involves understanding and overcoming fundamental challenges related to the design and selection of antibodies with high affinity, specificity, stability and solubility, a topic that will addressed by **Peter Tessier** (University of Michigan).

Wednesday December 13, 2017. Track 1 (morning)
Engineering and Application of Therapeutic Antibodies for Neurodegenerative Diseases

The nervous system is especially vulnerable to the disrupted proteostasis and accumulations of toxic forms of proteins that occur naturally with aging, and/or as a result of genetic and environmental risk factors. As our overall populations age, these disorders loom as a massive public health problem due to the level of care required for affected individuals. Antibodies, with their inherent specificity for protein isoforms, will become increasingly critical as therapeutics and diagnostics. The session on the engineering and application of therapeutic antibodies for neurodegenerative diseases has been organized by **Anne Messer** (Neural Stem Cell Institute/ Univ. Albany), **Cynthia Lemere** (Brigham & Women's Hospital/Harvard Medical School) and **James Huston** (Huston BioConsulting, LLC). The speakers in this session will present a range of approaches for Alzheimer's and related dementias, Parkinson's, and ALS/motor neuron disease, including notes on the extent to which there can be overlaps among these and other protein misfolding diseases.

The talks in the first half of the session will focus on an important target in Alzheimer's, amyloid beta (Aβ). **Isabelle Aubert** (University of Toronto) will present the opening talk, "Delivery of Antibodies across the Blood-brain Barrier Using MRI-guided Focused Ultrasound," including promising data on functional improvement after treatments with anti- Aβ antibodies. [This talk also represents a continuation of the theme of approaches to blood brain barrier permeability in the keynote talk by William Pardridge (UCLA), and a session talk by Jasi Atwal (Genentech), on Tuesday, Dec. 13.] Next in our session, **Paul Weinreb** (Biogen) will present "Structural Basis for The Unique Selectivity of Aducanumab for Amyloid-b Aggregates." This human-derived antibody targeting Aβ, in phase 3 clinical trials, differs from other Aβ antibodies due to its high selectivity for both soluble oligomeric and insoluble fibrillar Aβ aggregates. The crystal structure of the antibody-peptide interface provides insights into the structural basis for its unique binding profile. **Michael Sierks** (Arizona State University) will present his cutting-edge engineering and catalytic antibody approaches to preventing formation of the toxic species in "Altering APP Processing with a Proteolytic Diabody."

The second half of the session covers immunotherapies for multi-faceted neurodegenerations. **Laura Ranum** (University of Florida) uses a mouse model of a human mutation that can lead to motor, cognitive, and/or anxiety symptoms due to accumulation of novel mutant proteins. These may be less rare than we currently appreciate. In the talk "Towards Development of Antibody Therapy for C9orf72 ALS/FTD", Dr. Ranum will present preclinical studies of peripheral delivery of human antibodies. **Peter Davies** (Feinstein Institute for Medical Research, NY) has developed very critical monoclonal antibodies

to Tau, which is a major player in neurofibrillary tangles of Alzheimer's disease, and the accumulating protein in hereditary and injury-induced dementias. "Treatment of Neuronal Pathology with Monoclonal Antibodies" discusses moving these valuable diagnostic and research tools into the therapeutic realm. The final talk, by **Eliezer Masliah** (National Institutes of Aging, NIH), is "Combinatorial Immunotherapeutic Approaches for Synucleinopathies of the Aging Population." This innovative approach harnesses both adaptive and innate immune processes that will be critical for dealing with Parkinsons and several other aging diseases that accumulate alpha-synuclein.

Wednesday December 13, 2017. Track 2 (morning)
Antibody-Drug Conjugates & Fusion Proteins

Gregory Adams, Ph.D., Chief Scientific Officer, Eleven Biotherapeutics will chair this session on antibody-drug conjugates (ADCs) and fusion proteins, which will feature the following speakers:

- **Julian Spallholz** (Texas Tech University) will discuss how redox selenium ADCs improve cancer cell monoclonal antibody cytotoxicity;
- **Masahiro Yasunaga** (National Cancer Center, Japan) will discuss ADCs for treating steroid-resistant malignancies and autoimmune disease;
- **Dimiter Dimitrov** (NCI-Frederick) will discuss targeting tumors and their vasculature with ADCs;
- **Julia Gavrilyuk** (Abbvie Stemcentrx) will discuss novel calicheamicin ADCs; and
- **Thomas Sandal** (Crescendo Biologics Ltd.) will discuss Humabody® Drug Conjugates as alternatives to ADCs.

Wednesday December 13, 2017. Track 1 (afternoon)
Post-translational Modification in Antibody Function

Dennis R. Burton (The Scripps Research Institute) and **Paul W.H.I. Parren** (Leiden University Medical Center) will chair this session focused on post-translational modification in antibody function.

The critical importance of sequence variation in antibodies is well recognized. Sequence diversity in antibody variable domains is essential for specific antigen recognition while linkage to different constant domains leads to distinct Fc-mediated effector activities. Post-translational modifications (PTMs) of these domains provide an additional immune mechanism by which the binding and activity of antibodies can be modulated. PTMs vary from chain additions, such as N- and O-linked glycosylation, glycation, cysteinylation and sulfation; chain trimming, such as C-terminal lysine clipping; amino acid modifications such as cyclization (into a N-terminal pyroglutamic acid), deamidation, oxidation, isomerization and carbamylation; to disulfide scrambling of hinge region interchain disulfide bonds. Each antibody can therefore give rise to a myriad of distinct antibody molecules with large activity and potency differences. Although post-translational modifications of antibodies have been observed and studied for decades, we only now start to understand the full impact of this incredible microheterogeneity. PTMs have moved from being viewed as a mere nuisance to antibody manufacturing that requires controlling to a potential handle to modify and improve specific antibody functions.

In this session, we will hear about current state-of-the-art in PTM detection and novel insights into the role and modulation of PTMs in our immune system as well as the way in which we can exploit PTMs to make better (therapeutic) antibodies. The first and the second (after the break) part of our session will

be initiated with lectures by renowned experts in their fields. Professor **Albert Heck** (Utrecht University) is a world-expert on the structural analysis of proteins by mass spectrometry. He received the Frank H. Field and Joe L. Franklin Award for outstanding achievement in mass spectrometry from the American Chemical Society and in 2017 he was received the NWO Spinoza Prize, which is the highest award in Dutch Science. Prof Heck will discuss how innovative and advanced mass spectrometry methods can be used to map antibody heterogeneity due to PTMs. **Leendert Trouw** (Leiden University Medical Center) will discuss the role of two amino acid modifications (citrullination and carbamylation) in the autoimmune disease rheumatoid arthritis (RA). On the one hand, the presence of antibodies against citrullinated or carbamylated proteins represents a prognostic marker for the disease. How antibodies recognize diverse antigens carrying these modifications is therefore an important area of study. Carbamylation of antibodies furthermore may also have functional consequences for antibody effector functions which will be highlighted. Professor **Gerhard Krönke** (University of Erlangen) will discuss how the PTM profile and inflammatory activity of autoantibodies in RA is regulated by TH17 helper T cells. His work gives us a novel insight into a mechanism by which the cellular immune system regulates the activity of antibodies and how its derailment may lead to the initiation of (autoimmune) disease.

After the break, **Taia Wang** (Stanford University School of Medicine) will discuss the diverse downstream proinflammatory, anti-inflammatory and immunomodulatory consequences of the engagement of type I and type II Fc receptors, which are influenced by the Fc's amino acid sequence and the complex, biantennary Fc-associated N-linked glycan, in the context of infectious, autoimmune, and neoplastic disorders. **Yingda Xu** (Adimab) will bring us back to the importance of PTMS in manufacturing and control of therapeutic antibody production. He will show novel data on the identification of chemically labile sites in antibodies and how this information may be used in therapeutic antibody lead selection. Finally, **Raiees Andrabi** (The Scripps Research Institute) will discuss how sulfation of residues in the antibody binding site is critical for certain broadly neutralizing anti-HIV-1 antibodies targeting the envelope glycoprotein.

We hope that this session will convey the current interest and high excitement in antibody PTMs and will serve to promote further research into the importance and impact of PTM microheterogeneity for polyclonal antibody responses as well as for monoclonal antibody therapeutics.

Wednesday December 13, 2017. Track 2 (afternoon)
Anti-Tumor Antigen Antibodies In Cancer Immunotherapy

K. Dane Wittrup, Ph.D., C.P. Dubbs Professor of Chemical Engineering and Biological Engineering, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, will chair this session on the use of anti-tumor antigen antibodies in cancer immunotherapy, which will feature the following speakers:

- **Yang-Xin Fu** (UT Southwestern) will discuss tumor targeting antibodies in the context of distinct innate and adaptive immune sensing;
- **Jennifer R. Cochran** (Nodus Therapeutics) will discuss innate and adaptive integrin-targeted combination immunotherapy;
- **Robert L. Ferris** (UPMC Hillman Cancer Center) will discuss cetuximab and therapeutic T-cell response;
- **Ann Cheung** (Dragonfly Therapeutics), will discuss NK cell engagement with TriNKETs™;

- **Amy S. Lee** (Keck School of Medicine, University of Southern California) will discuss targeting cell surface chaperone in cancer therapy; and
- **Edgar G. Engleman** (Stanford University School of Medicine, Stanford Blood Center) will discuss investigation of the basis for efficacy and resistance to tumor immunotherapy.

Thursday December 14, 2017. Track 1 (morning)
Biological Impact of Fc Receptor Engagement

Trudi Veldman (Senior Director Biologics, AbbVie Bioresearch Center) and **Chung-Ming Hsieh** (Executive Director, Biologics Discovery Boston, Merck & Co.) co-organized the session on 'Biological Impact of Fc Receptor Engagement', which will be chaired by Chung-Ming Hsieh.

Antibodies are both binding proteins to their cognate targets and bridging molecules to downstream biological pathways via interaction with the various Fc receptors (e.g., FcγR and FcRn), complement, and lectins. While our efforts in understanding the biology of therapeutic antibodies are often initially focused on the variable domain and target engagement, e.g., binding kinetics, potency, epitopes, it is crucial that we also gain understanding of the biology of the constant region of a therapeutic antibody and its impact on efficacy and safety.

This session aims to strengthen our current understandings on the biological impact of Fc receptor engagement. The first presentation by **Kenta Haraya** (Chugai) will discuss the generation and characterization of a novel IgG1 Fc variant with optimized binding to FcRn that does not have increased binding by rheumatoid factors. This Fc variant has been incorporated into a recycling antibody being developed for complement-mediated diseases.

The next three presentations will focus on the impact of FcγR engagement on antitumor activities of protein therapeutics. **Rony Dahan** (Rockefeller) will present the finding that the antitumor activity of a human CD40 agonistic antibody is dependent on FcγRIIb engagement and is inhibited by FcγRIIa engagement, highlighting the importance of Fc domain optimization for improved efficacy. Moving beyond antibodies, **Daniel Christ** (Garvan Institute of Medical Research) will present data indicating that the potent antitumor activity of interleukin-2-Fc fusion protein requires Fc-mediated depletion of regulatory T-cells. Lastly, **Frederick Arce Vargas** (University College London Cancer Institute) will present the depletion of tumor-infiltrating regulatory T cells by an Fc-optimized anti-CD25 in synergy with PD-1 blockade to eradicate established tumors.

The field also continues to make progress in engineering Fc for modulating antibody effector functions, FcγR or complement engagement, and circulating half-life. To this end, **James Ernst** (Genentech) will present effector function-attenuating mutations that maintain antibody stability and reduce toxicity. **George Georgiou** (University of Texas at Austin) will present a set of novel engineered Fcs for half-life extension and for highly selective engagement of a single FcγR or C1q.

Thursday December 14, 2017. Track 2 (morning)
Antibody-based innovations in the tumor microenvironment (Part 1)

Clinical successes of the checkpoint modulators have revived the ambition to cure cancer by manipulation of the tumor microenvironment, or by unleashing or even priming (novel) adaptive immune responses.

Hence, understanding the tumor microenvironment is an increasingly vital theme in the field of antibody-based therapeutics. This theme is excitingly addressed during two sessions "Antibody-based innovations in the tumor microenvironment 1 & 2", jointly chaired by **Kerry Chester**, Professor of Molecular Medicine, UCL Cancer Institute, University College London, United Kingdom, and **Janine Schuurman**, Vice President Research, Genmab, Utrecht, The Netherlands to be held in the morning (Part 1) and afternoon (Part 2) of Thursday December 14, 2017. The sessions' antibody-focused complementary topics are intended to expand knowledge at the cutting edge of the tumor microenvironment field, and are anticipated to boost lively discussions and stimulate new lines of thinking.

The morning session will open with a presentation by **John Anderson** (UCL) who will examine current thinking on immune evasion as a hallmark of cancer and why the solid tumor microenvironment is particularly hostile to immunotherapeutic function of effector cells. He will explain that, unlike adult cancers, pediatric cancers generally arise with few mutations and tend to be insensitive to existing immune modulators. Treatment approaches designed to target cell surface antigens in combination with agents to reverse immune evasion are likely to be required for this special group of patients. New data will be presented in support of this hypothesis.

Syd Johnson (MacroGenics) will then share data on how to achieve co-stimulation of immune cells specifically within the tumor microenvironment using bispecific Dual-Affinity Re-Targeting (DART) and TRIDENT antibodies that bind both tumor-specific antigens and T-cell costimulatory molecules. Importantly, tumor binding is required to trigger costimulation. The talk will be illustrated with a case study showing how to achieve optimal tumor dependent T cell engagement by varying the relative position and valence of each antibody binding site in the molecule; manufacturability, stability and PK will also be addressed.

Natalia Arenas Ramirez (University Hospital Zurich) will then present an elegant antibody-based solution to problems associated with IL-2 immunotherapy. IL2 binding to the IL-2 receptor α (CD25) subunit leads to unwanted side effects, including stimulation of immunosuppressive Tregs. The talk will describe development of NARA1, an anti-IL-2 monoclonal antibody that acts as a high-affinity CD25 mimic, preferentially stimulating CD8+ cells while keeping the Tregs low. Potent antitumor responses are achieved.

After the Networking Break, **Volker Schellenberger** (Amunix) will present an interesting approach to achieving activation in the tumor environment using bispecific T-cell engagers based on the ProTIA (Protease Triggered Immune Activator) platform. ProTIA combines tumor binding, proteolytic activation and polymer targeting due to an attached XTEN. Amunix' lead molecule, AMX-168, is expected to enter clinical development in 2018.

Next, **Shautong Song** (Icell Kealex Therapeutics) will showcase an innovative way to focus treatment within the tumor microenvironment via bi-specific T-cell engager-armed oncolytic vaccinia virus. The treatment has several modes of action: vaccinia virus can directly lyse tumor cells and bi-specific T-cell engagement directs T-cells to kill both tumor and by-stander cells. In addition, T-cell engagement promotes T-cell infiltration into tumors and the cytokines released upon activation create a pro-inflammatory microenvironment that inhibits tumor growth. The strategy provides a sophisticated means of reducing systemic side effects associated with bi-specific T-cell engagers.

To complete the morning session, **Dane Wittrup** (Massachusetts Institute of Technology) will explore how classical monoclonal anti-tumor antibodies, such as anti-HER2 or anti-CD20, synergize with immune

oncology antibodies, such as anti-PD-1. This is achieved not only by delivery of tumor debris to antigen presenting cells for cross presentation, but also by creating a more inflammatory state and a localized cytokine storm in the tumor microenvironment.

Thursday December 14, 2017. Track 1 (afternoon)
Novel Therapeutic Indications For Antibodies

James Larrick, M.D., Ph.D., Managing Director and Chief Medical Officer, Panorama Research Institute and Velocity Pharmaceutical Development, will chair the session on novel therapeutic indications for antibodies.

Intense efforts are underway in both academic and industrial labs to identify novel therapeutic targets using antibody technology. Much progress has been made, with many therapeutic antibodies populating the preclinical pipeline. Promising therapeutic antibody targets will be presented in this session. First, **John Cambier** (University of Colorado Medical Center) will describe therapeutic antibodies that silence B cells by emulating peripheral immune tolerance. Targeting CD20 by rituximab and similar cell-targeted therapies whose effects are mediated by B cell depletion has proven efficacious in a variety of autoimmune settings, but this approach has substantial risks due to long-term compromise of adaptive immunity. Dr. Cambier's lab has pioneered an alternative, non-B cell depleting approach, which employs emasculated antibodies directed against antigen receptor components to induce a reversible state of anergy. This approach has proven effective in treatment of mouse models of type 1 diabetes, lupus and rheumatoid arthritis.

Uncontrolled fibrosis contributes to the pathogenesis of disease affecting many tissues, among these congestive heart failure, chronic kidney disease and cirrhosis. Idiopathic pulmonary fibrosis (IPF) is a chronic fatal lung disease with rapid, progressive loss of pulmonary function. TGF-β can induce fibroblast differentiation and is fundamental to the pathogenesis of pulmonary fibrosis. Protein tyrosine phosphatase α (PTP-α) has been shown to be a key regulator of the TGF-β-mediated fibrotic process in animal models of IPF. **Bo Yu** (Larix Bioscience) will describe development of an inhibitory PTPα antibody for fibrotic diseases.

Despite aggressive LDL cholesterol reduction, substantial residual risk of coronary heart disease remains. APOC3 is a highly genetically validated therapeutic target for hypertriglyceridemia and cardiovascular disease. **Daniel Rader (**Perelman School of Medicine, University of Pennsylvania) will describe a series of anti-APOC3 monoclonal antibodies that markedly reduce triglycerides in a humanized mouse model. Targeting APOC3 with an antibody may be the next-generation therapy to reduce triglycerides and risk of coronary artery disease.

Another approach to reverse acute type 1 diabetes (T1D) with an anti-TLR4/MD-2 monoclonal antibody will be described by **William Ridgway** (University of Cincinnati College of Medicine). New onset T1D (hyperglycemia, polyuria and weight loss) in non-obese diabetic (NOD) mice was attenuated by treatment with antagonistic TLR4/MD-2 specific monoclonal antibody ("TLR4-Ab"). 90% of NOD mice treated with TLR4-Ab showed a clinical response (delay in progression to end stage T1D), and 70% have permanent reversal of T1D. Successfully treated mice demonstrate decreased islet inflammation and preserved insulin staining of islet beta cells. Although TLR4-Ab does not stimulate T cells directly, immune tolerance can be restored to the adaptive immune system by this treatment. The TLR4/MD-2 pathway is a promising new therapeutic approach for treating autoimmunity.

FGF21 analogs belong to an emerging class of therapeutic candidates for type 2 diabetes and fatty liver disease. An engineered bispecific anti-FGFR1/β-Klotho agonist antibody that acts as a long-acting FGF21-mimetic will be described by **Junichiro Sonoda** (Genentech, Inc.). In addition, the mechanism of antibody action, together with the results from the first-in-human study performed with obese human subjects will be presented.

Preclinical studies showed the feasibility of targeting mural cell survival by using modulating antibodies capable of activating Notch 3 signaling. **Joseph F. Arboleda-Velasquez,** (Harvard Medical School, Massachusetts Eye and Ear) will discuss implications of this work for prevalent causes of mural cell degeneration, including diabetic retinopathy and cerebral small vessel disease.

Thursday December 14, 2017. Track 2 (afternoon)
Antibody-Based Innovations In The Tumor Microenvironment (Part 2)

The discussion on antibody-based innovations in the tumor microenvironment continues in the afternoon in this session chaired by Janine Schuurman, Vice President Research, Genmab, Utrecht, The Netherlands and Kerry Chester, Professor of Molecular Medicine, UCL Cancer Institute, University College London, United Kingdom.

The session opens with a presentation centering on adaptive immune responses boosted by therapeutic cancer vaccines using RNA. **Sebastian Kreiter** (BioNTech) will focus on preclinical and clinical efforts to use personalized neoepitope vaccines in combination with immunomodulatory antibodies.

Edward Roberts (UCSF) will follow with a complementary line of thinking harnessing long term anti-tumor therapeutic effects. He will share data, including imaging data, to give us insights in the requirements for effective tumor antigen trafficking to the lymph nodes by the dendritic cells. These understandings may stimulate ideas for effective T cell priming approaches.

The TNFR super family (TNFR-SF) is a highly represented target class in the immunomodulatory targets space. Clustering is an important prerequisite for agonistic effects of antibodies against these targets. **Nick Wilson** (Agenus) will share emerging data on the role of antibody Fc and Fc-receptor biology to optimize the agonistic properties of antibodies against this target class.

Daratumumab, an anti-CD38 antibody that is approved for the treatment of relapsed / refractory myeloma, has multiple mechanisms of actions. Apart from rapid tumor cell reduction and direct anti-tumor effects, daratumumab significantly reduces CD38+ immune suppressive cells in the tumor microenvironment. **Kate Sasser** (Genmab) will focus on the immune modulatory activity of this antibody substantiated with data from in vitro evaluations and clinical studies.

Bispecific antibodies directed against both CD3and a tumor target can engage non-tumor-specific T cells, resulting in effective tumor-specific cell killing. **Dirk Hose** (Heidelberg University) will share data on a bispecific IgG-based molecule that targets CD3 and the B-cell maturation antigen (BCMA), which has been implicated in multiple myeloma. This presentation will cover the generation of this molecule and include early stage clinical learnings.

Anti-CD3 bispecifics can have severe toxicity profiles related to the expression profile of the tumor antigen. The last speaker of this full-day session on the tumor microenvironment will share data on the

improvement of the therapeutic index of an anti-CD3 bispecific antibody also directed against a widely expressed antigen, epidermal growth factor receptor (EGFR). In this case study, **Leila Boustany**, (CytomX) will present the localization of the activity to the tumor microenvironment, which is accomplished by an engineering approach, i.e., a protease activatable EGFRxCD3 bispecific exploiting the protease activity present in the tumor microenvironment.

We anticipate that these complementary scientific insights focusing around antibody-based innovations in the tumor microenvironment will excite us all and inspire our forward-looking capabilities.

Thursday December 14, 2017.
The Antibody Society's Special Session

Founded in 2007, the Society will celebrate its 10th anniversary at a Special Session on Thursday afternoon. **Paul W.H.I. Parren**, President of the Society, will provide an overview of the Society's 2017 initiatives, including antibody international non-proprietary naming, problems with reagent antibodies, standards for adaptive immune receptor repertoire data, and establishment of antibody therapeutics development metrics, and achievements. He will also discuss he Society's plans for the future.

Raffaella Ballocco (World Health Organization) will address the topic of international non-proprietary names (INNs) for monoclonal antibodies. Dr. Ballocco is Secretary of the WHO Expert Group on INN.

Janice M. Reichert (Executive Director, The Antibody Society) will report on the biopharmaceutical industry's progress in developing antibody therapeutics. She will discuss the 8 antibody therapeutics approved in either the US or EU in 2017 and the 'Antibodies to watch in 2018', which include 10 antibody therapeutics in regulatory review, 14 antibody therapeutics in late-stage clinical studies that are likely to move to regulatory review in 2018, and 19 antibody therapeutics in late-stage clinical studies with primary completion dates in 2018. Dr. Reichert will also reveal new data on antibody therapeutics development metrics, including clinical phase transition and approval success rates.

Friday December 15, 2017. Track 1 (morning)
Novel engineering strategies to enhance antibody functions

Paul J. Carter, Ph.D., Senior Director and Staff Scientist, Antibody Engineering, Genentech, will chair the session on novel engineering strategies to enhance antibody functions.

A recurring theme with this conference since it began in the early 1990s has been the presentation of new antibody engineering technologies and their application to the design of antibodies for specific clinical applications. True to this tradition, this session will showcase a broad range of different antibody platform technologies for improving existing antibody properties or engineering antibodies with brand new capabilities. Antibody technologies to be highlighted include bispecific antibodies in many different formats, PEGylation, glyco-engineering and engineering of isoelectric point (pI).

Greg Lazar (Genentech) will present on agonizing the TNFR superfamily independent of FcγR-mediated cross-linking using multiple antibody technology platforms. This talk will highlight *in vitro* and *in vivo* proof-of-concept data. **Taichi Kuramochi** (Chugai Pharmabody Research) will provide a case study on pI engineering of an antibody variable domains and constant regions to enhance the potency of pH-

dependent antigen binding antibody. **Gestur Vidarsson (**Sanquin Research) will describe how the natural glycans of antibodies can be tailored to increase ADCC and/or CDC activities. For example, combining hypergalactosylation with afucosylation increases the potency of ADCC activity beyond that achieved by afucosylation alone.

After the networking break, **Martin Steegmaier** (Roche Innovation Center Munich) will discuss applications of CrossMAbs in bivalent (1+1), trivalent (2+1) and tetravalent (2+2) formats for cancer immunotherapy and the use of novel targeting approaches for neurological diseases. Additionally, bispecific antibodies in DutaFab format for ophthalmologic diseases will be described. **Qing Li** (Medimmune) will demonstrate tumor uptake of a PEGylated antibody fragment. Specifically, this presentation will focus on investigation of the correlation between hydrodynamic size, pharmacokinetic parameters and tumor uptake of a PEGylated diabody. **Kartik Chandran** (Albert Einstein College of Medicine) will close the session by presenting a bispecific antibody "Trojan horse" approach for broad protection against ebolaviruses. One arm of the bispecific antibody binds a conserved epitope on ebolavirus glycoprotein. After internalization of the virus/antibody complex into cells and trafficking to late endosomes, the second arm of the bispecific blocks infection by binding to the viral entry receptor, NPC1.

Friday December 15, 2017. Track 2 (morning)
Immune-oncology Checkpoints

James Larrick, M.D., Ph.D., Managing Director and Chief Medical Officer, Panorama Research Institute and Velocity Pharmaceutical Development, will chair the session on immune-oncology checkpoints. The management of cancer has dramatically changed over the past decade with the introduction of novel immunotherapies, chief among them inhibitors of checkpoint receptors — molecules whose function is to restrain the host immune response. Antibodies inhibiting CTLA4 and PD1-PD-L1 have shown remarkable clinical benefit. The field is evolving rapidly, with many clinical trials testing novel checkpoint inhibitors (e.g., anti-LAG3, anti-TIM3), alone, in combination, or with other targeted therapies. A sampling of novel approaches will be covered in this symposium.

This Friday morning (December 15, 2017) session will be led off by **Mickey Hu** (Panorama Institute of Molecular Medicine) who has developed a series of novel immunomodulatory drugs that suppress PD-L1 expression in tumor cells and inhibit the PD-L1/PD-1 checkpoint, resulting in the recruitment of natural killer (NK) cells into the tumor microenvironment that leads to tumor suppression. Efforts to combine immunomodulatory drugs with checkpoint blockades to overcome difficult-to-treat cancers with tolerable side effects will be described.

Clinical lead candidate antibodies often lack species cross-reactivity, necessitating the development of substitute antibodies for pre-clinical development in mice or monkeys. Next, **Erik Hofman**, (Argenx) will describe the use of the SIMPLE Antibody platform to generate functional human-mouse cross-reactive antibodies against several validated immune checkpoint proteins, including PD-1, VISTA and LAG-3.

Xin Lu (University of Notre Dame) will present data indicating that targeted therapy against myeloid-derived suppressor cells, using multikinase inhibitors such as cabozantinib and dactolisib, can synergize with immune checkpoint blockade antibodies (e.g., anti-CTLA4, anti-PD1) to eradicate metastatic castration-resistant prostate cancer.

A key feature of effective cancer immunotherapy relies on enhanced anti-tumor immune response and reduced suppressive effects. As natural cytokines are made to maintain a balance between activation and suppression, they are often unable to achieve desired therapeutic efficacy. **Cheng-I Wang** (Biomedical Sciences Institutes, ASTAR, Singapore) will describe a cytokine receptor agonist antibody that mimics IL-2's immune stimulatory effects on CD8 T cells with minimal Treg activation.

Cow antibodies have unusually long CDR3 regions. **Vaughn Smider** (The Scripps Research Institute) has characterized the genetic and structural properties of these antibodies, and has identified novel antibodies against HIV and exhausted T-cell targets utilizing this approach.

The final speaker, **Sarah Crome**, (Princess Margaret Cancer Centre, University Health Network, Canada) will describe efforts to characterize a unique innate lymphoid cell (ILC) population that suppresses the expansion and function of tumor-associated T cells, and is associated with early recurrence in high-grade cancer. This regulatory ILC population has properties that overlap with NK cells and other defined ILCs, yet can be differentiated by a distinct gene expression signature. Studies defining molecular interactions that control regulatory ILC function and ways to target this population to enhance immunotherapy will be presented.

Friday December 15, 2017. Track 1 (afternoon)
Role of the T-Cell Repertoire in Cancer, Infectious Diseases and Autoimmunity

Jamie K. Scott, M.D., Ph.D., Professor and Canada Research Chair in Molecular Immunity, Department of Molecular Biology & Biochemistry and Faculty of Health Sciences, Simon Fraser University, will chair this session on the role of the T-cell repertoire in cancer, infectious diseases and autoimmunity, which will feature the following speakers:

- **Mark Cobbold** (MGH Cancer Center) will discuss mining shared neoantigen-specific TCRs from healthy donors for tailored cancer immunotherapy;
- **Pia Kvistborg** (The Netherlands Cancer Institute) will discuss dissecting the tumor-specific T cell response;
- **Thomas Duhen** (AgonOx) will discuss how CD39 and CD103 identify tumor-reactive CD8 T cells in human solid tumors;
- **Ryan Emerson** (Adaptive Biotechnologies) will discuss how to use high-throughput TCR sequencing to read immune memory;
- **Eilon Sharon** (Howard Hughes Medical Institute, Stanford University) will discuss how genetic variation in MHC proteins is associated with T-cell receptor expression biases;
- **Naglaa H. Shoukry**, (University of Montreal, CHUM Research Centre) will discuss the dynamics of the T cell repertoire during multiple episodes of hepatitis c virus infection.

Friday December 15, 2017. Track 2 (afternoon)
Innovating Antibody Therapeutics

Paul W.H.I. Parren, Ph.D., Professor, Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, and **William R. Strohl, Ph.D.,** President of BiStro Biotech Consulting, LLC, will co-chair a session on innovating antibody therapeutics.

In today's highly competitive therapeutic antibody environment, continued innovation is key to success. This session highlights a number of innovative approaches to antibody discovery, engineering, and analysis. The first presentation, given by **Chris Bailey-Kellogg, Ph.D**., Professor of Computer Science, Dartmouth University, explores the use of a method called EpiScope which combines a sophisticated computer algorithm with experimental binding assays on a limited number of antigenic variants to determine the epitopes to which antibodies bind. Using both prospective and retrospective analyses, EpiScope was able to determine the epitopes in the majority of examples tested. The second presentation, given by **Mats Ohlin, Ph.D.** and Professor, Department of Immunotechnology & SciLifeLab at Lund University, will demonstrate how antibodies from different germlines may evolve through divergent pathways based on preferred evolution patterns. **Kevin Hollevoet, Ph.D**., Group Leader and Postdoctoral Fellow, Therapeutic and Diagnostic Antibodies, University of Leuven, Belgium, will describe the highly innovative and forward-thinking use of gene therapy approaches for the delivery of antibodies. This is a new area that is now being pursued by several groups and offers novel approaches to solving antibody delivery issues, especially in cases where multiple antibodies or chronic high dosing schedules are required. **Karthik Viswanathan, Ph.D**., Director of Research at Visterra, Inc., then will show how the use of a novel approach to modulating the interaction of IgGs with FcRn can result in increasing half-life while retaining robust structural stability and Fc receptor interactions. **Natalie Castellana, Ph.D.,** Chief Executive Officer of Digital Proteomics LLC, will show how a proteogenomic approach using deep sequencing and mass spectrometry can yield a unique picture of the serum immune repertoire. Finally, **William R. (Bill) Strohl** will give an overview of current technologies being used in clinical stage antibodies and will tie those data together with highlights of the meeting to present a picture of the current and future state of innovative antibody therapeutics.