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Session 11: Therapeutic Antibodies

Wednesday 9th November 2011. Moderator: Sachdev Sidhu

[14.00–14.20]
'The landscape and future trends of antibody-based therapeutics'
Yan Wu
Kadmon Corporation, New York, NY, USA

Abstract not provided.

[14.20–14.40]
'Engineering therapeutic antibodies for subcutaneous delivery'
Robert Kelley
Genentech Inc., South San Francisco, CA, USA

Abstract not provided.

[14.40–15.00]
'Turning murine research MAbs into humanized drug candidates: case studies'
Richard Buick
Fusion Antibodies Ltd, Belfast, North Ireland, UK

Abstract not provided.

[15.00–15.20]
'Anti-citrulline antibody as novel therapeutic drug in early rheumatoid arthritis'
Jos Raats
ModiQuest Research, Nijmegen, The Netherlands

We have developed a novel treatment for Rheumatoid Arthritis (RA), which prevents the onset or exacerbation of the disease.

For the development of this novel therapy, we focussed on more RA specific targets like Deiminated Peptide-Epitopes (DPE). Deimination is the posttranslational modification of arginine into citrulline residues induced by peptidyl-arginine deiminases that are released in the inflamed joints from dying cells. A growing number of studies indicated that these modifications could be responsible for the initial triggering of autoimmunity and the breaking of tolerance.

We identified a subset of rCit-hMabs that were capable of preventing the onset of inflammation in both CIA and CAIA animal models. When mild inflammation was present, administering the rCit-hMabs resulted in stabilization of the inflammation and prevented further increase of the inflammatory response. Histological analysis of the inflamed joints revealed, that bone damage was strongly prevented, as compared to control animals. To identify the epitopes recognized by the rCit-hMabs, we performed IP, followed by MS-analysis on post-lytically huPAD4 deiminated human 293F cells. The main DPE recognized by the rCit-hMabs was used to generate new therapeutic Mabs. Introduction of these novel rCit-hMabs in the CAIA model proved them to be potent inhibitors of the inflammatory response.

ModiQuest has developed a family of novel rCit-hMabs which have strong therapeutic potential in regard to preventing: 1) the onset of the inflammation, 2) joint damage during inflammation, 3) further increase of inflammation and swelling, 4) inflammation relapse and tissue/joint damage to occur.

The availability of the previously developed diagnostic test for RA, detecting RA up to 10 years before onset of the disease, makes this novel therapeutic approach of special interest for early stage RA. In a more progressive form of RA a combination therapy might be possible with existing biologicals that have different mechanisms of action.

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[15.20–15.40]
'Therapeutic antibodies for the treatment of chronic kidney disease'
Sarah Barker
University of Toronto, Ontario, Canada

Disturbances in mineral metabolism underlie many diseases, and in particular, play a central role in chronic kidney disease (CKD), which is approaching epidemic proportions worldwide. Fibroblast growth factor 23 (FGF23), a secreted signaling protein, plays a key role in maintaining phosphate balance by interacting with specific cell-surface receptors. FGF23 levels are dramatically increased in patients with CKD and strongly correlate with disease outcome. The current thinking is that FGF23 is not just a mere biomarker but is in fact pathogenic for morbidity and mortality in CKD. Thus, FGF23 is an excellent candidate target for therapeutic strategies for the alleviation of CKD. We are developing state-of-the-art synthetic human antibodies as selective inhibitors of the signal transduction pathways mediated by FGF23 and its receptors using a phage-display platform. Over the past decade, human antibodies have emerged as a powerful new class of drugs for cancer and immunological diseases. Our research is extending this powerful approach to kidney disease, as the antibodies we develop can be directly translated into novel therapeutics for the treatment of CKD and other diseases associated with FGF23 and its receptors.

[15.40–16.00]
'Engineering next generation therapeutic antibody technologies'
Bjorn Hock
Merck Serono, Darmstadt, Germany

Abstract not provided.

[16.00–16.20]
'RECRUIT-TandAbs – Engaging immune cells to kill cancer cells AFM13 – a bispecific tetravalent TandAb for treating Hodgkin lymphoma'
Erich Rajkovic, C. Hucke, S. Knackmuss, V. Molkenthin, U. Reusch and M. Little
Affimed Therapeutics AG, Heidelberg, Germany

RECRUIT-TandAb® antibodies are immunotherapeutics being developed as novel and better treatments for haematological and solid tumors. RECRUIT-TandAb® are bispecific and tetravalent, comprising solely variable domains. They address key issues of monoclonal antibodies (both normal and ADCC enhanced), such as (i) the V/F polymorphism and (ii) the non-selective binding to immune effector cells versus granulocytes. RECRUIT-TandAb® bind to NK-cells and macrophages (via CD16A) or T-cells (via CD 3) cells with high affinity right after infusion thereby targeting these cells to the tumor by binding to a tumor-associated antigen. Furthermore, TandAbs have significant advantages over other fragment technologies like (i) bivalent binding to the target antigens and, (ii) longer half-life.

Affimed's lead program AFM13 is a RECRUIT-TandAb® for the treatment of Hodgkin Lymphoma (HL) recruiting natural killer (NK) cells and macrophages to the specific CD30 surface antigen on HL cells. AFM13 is in clinical trials in Hodgkin Lymphoma patients and, in the first dosing levels, appeared to be safe and well tolerated.

A second product, AFM11 (CD19xCD3), is being developed for treating NHL; it recruits T-cells (via CD3) to the CD19 surface antigen on malignant B-cells. AFM11 is currently in GMP production.

The anti-CD30 moiety of AFM13 was derived from a mAb that had already shown preliminary promising results in clinical trials. The human antibody specific for the CD16A receptor on NK cells was derived from Affimed's human phage display antibody libraries. The heavy and light chain variable domains of both antibodies were engineered into a four-domain TandAb® gene-product. The linkers between the domains were designed to prevent intra-domain pairing and to force dimerization resulting in the formation of the functional homodimeric TandAb® molecule. AFM13 is able to rapidly induce the lysis of CD30+ cells at picomolar concentrations in presence of PBMCs. Intensive *in vitro* characterization of AFM13 has demonstrated its remarkable specificity for just the CD16A receptor on NK-cells, which, however, only becomes activated in the presence of tumor cells: There is no systemic activation of NK-cells. A robust and scalable GMP production in mammalian cells, a down-stream process and a lyophilized formulation with excellent stability have been established. AFM13 was well tolerated in toxicology studies in Cynomolgus monkeys.

Affimed's lead product AFM13 is a RECRUIT-TandAb® (CD30xCD16A) for treating Hodgkin Lymphoma by recruiting natural killer cells (via CD16A) to the specific CD30 surface antigen on Reed-Sternberg cells. In 2010, AFM13 entered a phase I clinical trial

and after treating several patients the drug appears to be safe and well tolerated.

[16.20–16.40]
'Targeting the MUC1-SEA module with antibodies for ablating human MUC1 positive cancer cells'
Edward Pichinuk and Daniel H. Wreschner
Tel-Aviiv University, Ramat Aviv, Israel

MUC1 is a mucin-like glycoprotein preferentially over-expressed on the cell-surface of a variety of human cancer cells and has long been a subject of interest in targeted tumor therapy. Cleavage of MUC1 yields two unequal chains, a large extracellular subunit non-covalently bound to a smaller subunit comprising transmembrane and cytoplasmic domains. The MUC1 subunit is released into the peripheral circulation where it readily sequesters antibodies soley directed against the chain. In order to avoid peripheral sequestration, Abs directed against MUC1 must be engineered as to target the cell-bound moiety of MUC1. Here we report generation of a group of IgG1 anti-MUC1 monoclonal Abs denominated DMB4B4, DMB4F4, and DMB5F3 directed against the junction forming the SEA domain, a well conserved moiety which is tethered to the cell surface at all times. A series of binding studies using a set of well-defined MUC1 isoform constructs demonstrated that the SEA domain epitopes bound by the antibodies are largely conformational and involve elements contributed by both the and the subunits. In addition to their binding differentiated breast cancer cells at picoM concentrations with outstanding Kd of 5.89 $\times$ 10^{-12} M, the IgG anti-MUC1 Abs strongly bind breast cancer stem cells, suggesting an ability to target both 'mature' differentiated tumor as well as the self-reproducing cells giving rise to new malignant growth. In order to demonstrate that that the DMB anti-MUC1 Abs can be used in cell killing, DMB5F3 was linked to the pseudomonas bacterial exotoxin ZZ-PE38. The anti-MUC1 Ab not only internalized the toxin, it resulted in strong cytotoxicity of MUC1+ breast cancer at Ab concentrations as low as 20pM. With a view for clinical application, antibody DMB5F3 was partially humanized by production of chimeric IgG combining the H and L variable regions of DMB5F3 with the human constant region. Recombinant chimeric DMB5F3 (chDMB5F3) generated in CHO cells bound specifically to a variety of MUC1 expressing cancer cells with a very high affinity, exceeding that seen with Cetuximab (anti-EGFR1) and Tratuzumab (anti-erbB2). Immunotoxin formed by linkage of chDMB5F3 with the pseudomonas bacterial exotoxin ZZ-PE38 resulted in marked cytotoxicity of MUC1+ cancer cells. Potency of the chDMB5F3 immunotoxin was comparable to, and at times exceeded, that seen with Cetuximab and Tratuzumab immunotoxins. Taken together, these findings indicate that targeting conformationally-determined epitopes on the cell-bound MUC junction on MUC1+ malignancies results in specific cytotoxicity against both established tumor as well as against the self-reproducing tumor stem cells.