Session 2: Therapeutic Applications I

Wednesday 14th April 2010. Moderator: Mark C. Glassy

[10.00–10.30]
‘Monoclonal antibodies in the clinic, in the pipeline and in our dreams’
Don Capra
Oklahoma Medical Research Foundation, USA

Abstract not provided.

[10.30–11.00]
‘Summary analysis of the pre-clinical and clinical results of brain cancer patients treated with pritumumab’
Mark C. Glassy
Nascent Biologics Inc., San Diego, California, USA

Abstract not provided.

[11.30–12.00]
‘Combination therapies to enhance efficacy of cancer treatment’
Zdenka L. Jonak
GlaxoSmithKline, King-of-Prussia, Pennsylvania, USA

Abstract not provided.

[12.00–12.20]
‘The epitope space as defined by proteomic similarity’
Darja Kanduc
University of Bari, Bari, Italy

An epitope is defined as a specific restricted antigen region that is capable of eliciting an immune response and of combining with a specific site (or paratope) of immunoglobulins. The specificity of the epitope-paratope interaction is at the core of the immune response and represents the foundations of immunology. However, after more than one century from the Ehrlichian antibody theory, we remain ignorant of the molecular and mechanistic factors that shape epitope-paratope interactions, determine antibody-antigen binding, and dictate antigen immunogenicity. During the last decade, we offered a robust set of experimental data suggesting that low level of sequence similarity to the host proteome modulates the B cell epitope repertoire in the humoral immune response. In parallel, a structured meta-analysis of scientific literature further supported our low-similarity theory by documenting that a low level of sequence identity to the host proteome was a minimum common denominator unifying the heterogeneous assembly of epitopes experimentally validated, described and used all over the world. The low-similarity theory has important implications in science and medicine. Scientifically, proteomic similarity analyses give a solution to the self-nonself discrimination issue that still lies unsolved in immunology reports. Clinically, low-similarity peptides might have a strong impact on the rational development of effective peptide-based treatments in cancer, infection and autoimmunity. In addition and surely of no least importance, the low-similarity offers the possibility of hitting the target with highest specificity and lowest cross-reactivity. Effective, safe and theoretically infallible immuno-therapeutical tools appear at hand.

[12.20–12.40]
‘Tribody™: A platform for novel antibody-derived biopharmaceuticals’
Nico Mertens
Biotecnol SA, Oeiras, Portugal

Tribodies are multifunctional recombinant antibody derivatives, which utilise the natural in vivo heterodimerization of the heavy chain (Fd fragment) and light chain (L) of a Fabfragment, to form a scaffold,
upon which additional functions can be incorporated, such as additional binders—e.g., scFv binding domains. Each chain can be extended preferably at the C-terminus with an additional scFv binder. The chains are co-produced and produced in mammalian cells, where the host-cell BiP chaperone drives the formation of the heavy chain-light chain heterodimer (Fd:L)—this reaction does not appear to be inhibited by the chain extensions. This leads to a very specific heterodimerization, using molecules abundantly present in serum (non-immunogenic). These heterodimers are secreted into the media, where > 90% of the product were of the correct Fd:L heterodimeric form. These are stable, with each of the binders retaining their specific affinities, with the bivalent tribody having higher affinity, and higher activation of T-cell proliferation and cytotoxicity in vivo. This design allows easy engineering of multispecificity in a single molecule. Tribodies can be efficiently produced in mammalian cells and in the yeast Pichia pastoris. The main product is always the heterodimer, with some contamination of L-chain and L-chain dimer (Bence-Jones molecules), but these are easily removed by cation exchange chromatography. From cells adapted to serum-free medium, a simple combination of chromatography steps can yield pure product in a reproducible way. Although each molecule differs in yield and column behaviour, a general purification scheme could be developed. Tribodies developed as a bisppecific antibody either targeting two different tumor antigens (trispecific) or one tumor antigen bivalently, while monovalent targeting effector cell activators (e.g., CD3 on T-cells) were produced and demonstrated activity. Also immunocytokines with IL2 could be produced and were able to target the cytokineto the target cells. Cross-linking the CD3 at the tumor cell resulted in T-cell proliferation as well as active and specific killing of the tumor cells in a mouse lymphoma model. In this model, there was no need for additional CD28 or IL-2 stimulation. In a mouse B-cell lymphoma model, the Tribody behaved superior as compared to scFv2 (BiTe format) or the IgG1. 3 injections of 200 pmole (15 µg) was sufficient to obtain 100% cure. These mice did not relapse. Tribodies are excellent scaffolds for constructing trivalent, bivalent bispecific, trispecific antibody derivatives or antibody-drug conjugates.

[12.40–13.00]
‘BiTE antibodies in clinical trials – POC and a novel platform’
Tobias Raum
Micromet AG, Munich, Germany

BiTE antibody technology is based on single chain bispecific antibody molecules, binding to CD3 on cytotoxic T cells and a surface antigen on a target cell, such as a cancer cell. This close cell contact leads to the efficient killing of the target cell. The first BiTE antibody blinatumomab directed against CD19 on NHL cancer cells has proven efficacy in a clinical phase I trial. At a dose of 60 µg per square meter body surface per day administered for 4 weeks as continuous i.v. infusion the objective response rate was 100% in seven patients (2 CR, 5 PR). Preliminary results from 16 evaluable patients of a phase II clinical trial in an B-ALL setting with complete haematological remission but molecular relapse (MRD+) indicate that treatment with blinatumomab can lead to conversion of MRD positivity into a MRD negative status in 81% of the patients.

An advanced new BiTE platform was recently developed, which is designed to generate BiTE antibodies that are cross-reactive between human and monkey target antigens to allow for early risk reduction with the clinical candidates in monkey studies. Results of such monkey studies using new BiTE antibodies will be presented.