Session 4: Cancer – III

Wednesday 6 October 2004. Moderator: H. Peter Vollmers

[14.00–14.20]
Phase I Pretarget® Radioimmunotherapy (RIT) trial with a novel anti-TAG-72 Fusion protein
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Introduction: Pretarget® RIT is a 3-step therapeutic regimen that can increase the dose of radionuclide delivered to tumor sites while limiting radiation exposure to normal tissues. The 3 components include a streptavidin-containing targeting molecule, a clearing agent, and DOTA-Biotin, to which 90Y and 111In are chelated. This phase I trial was carried out to determine the feasibility and safety of using a new genetically engineered fusion protein (CC49) as the targeting moiety in Pretarget® RIT.

Methods: 9 patients with therapy resistant metastatic colorectal cancer (TAG-72 positive) received 160 mg/m\(^2\) of CC49Fusion protein intravenously (IV), followed by the synthetic clearing agent (sCA) at a dose of 45 mg/m\(^2\). 90Y/111In-DOTA-Biotin, was administered IV 24 hours after the sCA at a DOTA-Biotin dose of either 0.65 or 1.3 mg/m\(^2\). All patients received 5 mCi of 111In-DOTA-Biotin for imaging/dosimetry purposes and patients # 4–9 received 10 mCi/m\(^2\) of 90Y-DOTA-Biotin as well.

Results: The mean plasma T1/2 of CC49-fusion protein was 23 ± 6 hours. Greater than 95% of the circulating CC49-fusion protein was eliminated from the circulation within 6 hours of sCA administration. The radiolabeled DOTA-Biotin rapidly localized to tumor sites while the unbound fraction was rapidly excreted via the urinary tract. The tumor to marrow radiation dose ratio was 139:1 and tumor: whole body was 56:1; much higher than that observed with radiolabeled antibodies. No infusion-related toxicities or hematological toxicities were noted. Because this study utilized a low dose of 90Y (10 mCi/m\(^2\)), objective tumor responses were not observed (one patient had stable disease for 6 months).

Conclusion: CC49Fusion protein performs well in Pretarget® RIT and further study with escalating doses of 90Y-DOTA-Biotin should be pursued. This strategy has the potential to deliver therapeutically effective radiation tumor doses to TAG-72 positive solid tumors.

[14.20–14.40]
Study the Fc effectors function and therapeutic phage antibodies generated in Genentech
Yan Wu
Genentech Inc, USA

Fc receptor play an important role in immune regulation, they link antibody-mediated response with cellular effectors function. All therapeutic antibodies in Genentech use human IgG1, but we want to use murine IgGs for animal study because of the immunogenicity by human IgG. Three distinct classes murine FcRs have different IgG binding affinities and IgG subclass specificities. We have performed detail study to compare the bindings of three murine IgGs and human IgG1 to murine and human FcgRI, RII, and RIII. Our study has helped us to determine which murine IgG functions most similar to human IgG1 in both murine and human system. We have also identified mutants in murine IgG that totally abolish its effectors function, and this function has been demonstrated in mice model.

My lab is also responsible to screen and characterize monoclonal antibodies using a human synthetic phage library that is developed in Genentech. We have identified many functional antibodies. I will talk about one group of antibodies that could complete inhibit the activity of human HGFA and another potential therapeutic antibody against a tumor antigen target.
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[14.40–15.00]  
**Agensys – Development of a rich antibody product pipeline to novel targets**  
Aya Jakobovits  
*Senior Vice President, Technology and Corporate Development, Chief Scientific Officer*  

Agensys, Inc. exploits multiple product opportunities to develop fully human monoclonal antibodies (MAbs) to treat solid tumors based on its own proprietary targets. The company has discovered and validated a rich portfolio of novel, clinically relevant cancer targets that have been carefully selected to facilitate the development of new efficacious therapeutics with fewer and less severe side effects. Agensys has selected novel targets with expression in a significant percentage of patients’ specimens, with limited expression in normal vital tissues and with structural and functional features suitable for therapeutic intervention. Agensys’ discoveries represent cell surface targets which are expressed across 14 solid tumors, including cancers of the prostate, kidney, bladder, lung, colon, pancreas and ovary. Among these novel targets are PSCA1 (expressed in the majority of prostate, pancreatic and bladder cancers), AGS-16 (expressed in the majority of kidney cancers) and STEAP-12 (expressed in the majority of prostate, lung and bladder cancers). Agensys has assembled internal capabilities to both develop and manufacture therapeutic human MAbs. Using XenoMouse® technology, the company is generating fully human antibodies to multiple targets from its portfolio and validating their potential therapeutic efficacy using its proprietary patient-derived xenograft mouse models. The generation and selection of antibody product candidates to targets such as PSCA, STEAP-1 and AGS-16 will be presented.

**References**  

[15.00–15.20]  
**Promising tumor recognizing capacity of B cells in breast carcinomas. The “Proof of Principle”**  
Beatrix Kotlan, Jean-Luc Teillaud, Jozsef Toth, Peter Simsa, Wolf-Herman Fridman, Michael McKnight and Mark C. Glassy  
*National Medical Center, Budapest, Hungary*  

Abstract not received.

[15.20–15.40]  
**Comparison of rituximab-mediated interferon-γ production and cytotoxicity by human NK cells**  
Sébastien Dall’Ozzo, Pierre Bardos, Hervé Watier and Gilles Thibault  
*EA “Immuno-Pharmaco-Genetics of therapeutic Antibodies”, Université François Rabelais de Tours, France*  

Rituximab (Mabthera®, Rituxan®) is a chimeric anti-CD20 IgG1 monoclonal antibody (MoAb) widely used in the treatment of B cell malignancies. In vitro studies suggest that it induces lymphoma cells lysis through antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity, FcγRII-dependent phagocytosis or direct signalling leading to apoptosis. A recent *in vitro* study has reported that anti-tumor activity of trastuzumab in association with IL-12, used in the treatment of HER2-overexpressing malignancies, might result from cytokine secretion by NK cells. In the current study, IFNγ production by resting human NK cells in response to rituximab-coated Daudi cells was investigated by flow cytometry. Results show that significant percentage (15–25%) of CD16+(FcγRIIIa)/CD56dim NK cells produce intracellular IFNγ after FcγRIIIa engagement by rituximab- or mouse anti-CD16 mAb 3G8-coated Daudi cells in the absence of cytokines. Moreover, conversely to rituximab-mediated ADCC against Daudi cells, the percentage of the IFNγ+ NK cells increases when the NK: Daudi ratio decreases (from 10:1 to 0.5:1). Finally, we show that rituximab-mediated IFNγ production by NK cells is inhibited in the presence of GF109203X PKC inhibitor concentrations that do not block rituximab-mediated ADCC. Taken together, these results suggest a) that IFNγ production by NK cells could be involved in the anti-tumor activity of rituximab *in vivo*; and b) that cytokine production and cytotoxicity by NK cells require at least partially different signaling pathways upon FcγRIIIa engagement.

[16.00–16.30]  
**Cancer immunotherapy**  
Zdenka K. Jonak  
*GlaxoSmithKline, USA*  

Abstract not received.
Antibody and TA90 immune complex: A new tumour marker for early detection of subclinical metastatic melanoma
Rishab Gupta and Donald Morten
John Wayne Cancer Institute, Santa Monica, CA, USA

Abstract not received.