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Wednesday 12th November 2008. Moderator: H. Peter Vollmers

[14.00–14.30]
Title to be confirmed
Zdenka K. Jonak
GSK, King-of-Prussia, Pennsylvania, USA

Abstracts not provided.

[14.30–14.50]
Natural human IgG antibodies as tools for cancer therapy
Stephanie Brandlein
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Abstracts not provided.

[14.50–15.10]
Antibody-maytansinoid conjugates: A new generation of linkers to provide enhanced potency against target cancers
Rajeeva Singh
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Antibody-maytansinoid conjugates are currently being tested clinically by ImmunoGen and collaborators against several cancers including hematological malignancies such as multiple myeloma, acute myeloid leukemia, and non-Hodgkin's lymphoma, and solid tumors including breast, gastric, and small-cell lung cancers. These conjugates consist of maytansinoids, which are cytotoxic, anti-microtubule agents, linked covalently to different antibodies against various cancer cell-surface targets including HER2, CanAg, CD19, CD33, and CD56.

In the antibody-maytansinoid conjugates presently undergoing clinical evaluation, the maytansinoid molecules are linked to the antibody molecule at lysine residues via a disulfide or a non-reducible thioether link. The disulfide linkers are designed with steric hindrance at carbon atoms adjacent to the disulfide bond to maximize plasma stability of the conjugate and to facilitate the intracellular release of the maytansinoid by disulfide-reduction. The non-cleavable thioether link is designed to be stable in plasma, and the conjugate upon binding and internalization in the target cancer cell is processed in the lysosome to release the thioether-linked maytansinoid attached to the lysine residue. The choice of the linker—sterically-hindered disulfides or thioether—in a conjugate is target dependent and is based on pre-clinical testing of several linkers.

In addition to the ongoing clinical programs in which some maytansinoid conjugates demonstrate very promising anti-tumor activity at well-tolerated doses, we are actively involved in understanding the role of linkers in the effective intracellular release of the cytotoxic maytansinoid metabolites and their mode of action at the microtubule target. In our investigation of new linkers we have created a new generation of highly promising linkers that are stable in plasma and yield even greater efficacy to the conjugates based on *in vitro* and *in vivo* pre-clinical studies. The presentation will highlight these new linkers and discuss their role in the creation of the next generation of antibody-maytansinoid conjugates.

[15.10–15.30]
Anti-ganglioside antibody-induced tumor cell death by membrane pore formation
Lourdes Roque, Joel de León, Adriana Carr, Cristina Mateo de Acosta and Rolando Pérez
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Gangliosides have been involved in multiple processes such as growth, differentiation, adhesion and more recently as regulators of cell death pathways. Some of these molecules can be considered as tumor-associated antigens, in particular, N-glycolyl sialic acid containing gangliosides are promising candidates for cancer targeted-therapy because of their low expression in normal human tissues. In this study, we provided a molecular and cellular characterization of a novel cell death

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mechanism induced by the anti-NGcGM3 14F7 mAb in murine tumor cell lines, but not in mouse normal cells (B and CD4+ T lymphocytes) that expressed the antigen. F(ab)'2 but not Fab fragments retained the cytotoxic capacity of the whole 14F7 mAb. P3 mAb which recognizes N-glycolylated gangliosides did not show any cytotoxic effect. Those mAbs showed quite different capacities to bind NGcGM3-positive cell lines measured by binding inhibition experiments. Impairment of ganglioside synthesis in tumor cells abrogated the 14F7 mAb cytotoxic effect; however exogenous reincorporation of the ganglioside did not restore tumor cell sensitivity to 14F7 mAb-induced cytotoxicity. Interestingly, this complement-independent cell death mechanism did not resemble apoptosis, since no DNA fragmentation, Fas mediation or caspase activation was observed. However NGcGM3 ganglioside-mediated 14F7 mAb-induced cell death was accompanied by membrane pore formation, suggesting an oncosis-like phenomenon. This novel mechanism of cell death let us to support further therapeutic approaches using NGcGM3 as a molecular target for antibody-based cancer immunotherapy.

[15.30–15.50]
IMC-1121B and IMC-A12: Preliminary clinical experience with anti-VEGFR2 and anti-IGF-1R antibodies

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IMC-1121B and IMC-A12 are human monoclonal IgG1 antibodies that target, respectively, the vascular endothelial growth factor receptor-2 (VEGFR2) and insulin-like growth factor receptor-1 (IGF-1R). Preclinical studies have demonstrated that these therapeutic antibodies confer growth inhibition in multiple in vitro and in vivo cancer models. Phase 1 studies have been conducted testing the safety, tolerability, pharmacokinetics and preliminary efficacy of these agents in patients with advanced, refractory solid tumors. Two phase 1 studies have assessed IMC-1121B at multiple weekly (2–16 mg/kg), q14 day (6–10 mg/kg) and q21 day (15–20 mg/kg) doses in 61 patients. Hypertension has been the most frequently observed side effect associated with IMC-1121B and has been considered a dose limiting toxicity (grade 3) in a small number of instances. MTD has been determined as 13mg/kg/week and has not been reached for q14/q21 day dosing. Pharmacokinetic analyses have indicated that serum trough levels observed with most doses exceed those associated with anti-tumor activity in pre-clinical tumor models. IMC-1121B has been associated with substantial tumor control including several partial responses and multiple instances of stable disease lasting at least 5 months in the weekly dosing ($n = 37$) study. Multiple instances of stable disease $>$6 months have been observed on the every 2 and 3 week dosing study. Phase 2–3 studies are underway or planned in multiple solid tumors. Two phase 1 studies have assessed IMC-A12 at multiple weekly (3–15 mg/kg) and q14 day (6–15 mg/kg) doses in 40 patients. Hyperglycemia has been the most frequently observed side effect associated with IMC-A12 and has been considered a dose limiting toxicity (grade 3) in a small number of instances. MTD has not been identified for weekly or q14 day dosing. Pharmacokinetic analyses indicates that serum trough levels observed with most doses exceed those associated with anti-tumor activity in pre-clinical tumor models. IMC-A12 has been associated with multiple instances of stable disease lasting at least 6 months in the weekly dosing ($n = 24$) and q14 day ($n = 16$) studies. Phase 2 studies are underway or planned in multiple solid tumors.