

Session 2: Cancer I

Wednesday 12th November 2008. Moderator: Mark Glassy

[11.45–12.15]

Natural immunity, the one and only source for cancer-specific therapeutics?

H. Peter Vollmers

University of Wurzburg, Germany

Abstracts not provided.

[12.15–12.35]

Targeting the insulin-like growth factor type I receptor (IGF-IR) in cancer: The next EGFR?

Dale L. Ludwig

ImClone Systems Inc., New York, USA

Growth factor receptor-mediated signaling cascades contribute to human carcinogenesis, tumor pathogenesis and have also been implicated in cancer resistance to cytotoxic therapy. Monoclonal antibodies that target and inhibit growth factor receptors have become an important therapeutic class in oncology. Antibody blockade of ligand-dependent receptor tyrosine kinases such as epidermal growth factor receptor (EGFR) on the surface of tumor cells has shown to be effective, both as monotherapy and in combination with cytotoxic agents. Because of its role in tumor growth promotion and maintenance, therapeutic the EGFR has been demonstrated as a meaningful clinical target in multiple tumor types. Cetuximab, a chimeric IgG1 anti-EGFR blocking antibody, has been approved for treatment of colon cancer, head and neck cancer, demonstrated efficacy in lung cancer, and is being investigated in many other types of solid tumor. Similar to EGFR, the insulin-like growth factor-I receptor (IGF-IR) is frequently over-expressed in diverse tumor types, both solid and hematologic. It has been implicated in tumor cell proliferation and survival, and as a potential mechanism of resistance to cytotoxic therapy. Crosstalk between the IGF-IR and EGFR in tumors has also recently been reported. There are now more than a half dozen anti-IGF-IR therapeutic antibodies and several small molecule inhibitors being tested in

the clinic. Because of the close homology of the IGF-IR to insulin receptor, particularly in the intracellular kinase domain, small molecule development has been hindered by limitations to target selectivity. Antibody-directed therapy against IGF-IR may therefore be more advantageous. We have developed IMC-A12, a fully human IgG1 antibody that specifically binds to the IGF-IR with high affinity and blocks ligand-induced IGF-IR activation and signal transduction. It exerts its effects via direct receptor blockade and by mediating efficient receptor internalization and degradation. In xenograft tumor models in vivo, IGF-IR blockade by single agent A12 was shown to occur rapidly, resulting in significant growth inhibition of models of many types of solid tumor including breast, lung, colon, prostate, head and neck, sarcoma, and pancreas as well as multiple myeloma. Early results in Phase I clinical trials appear consistent with the preclinical results, providing preliminary evidence of biologic activity in many different tumor types and a manageable toxicity profile. These results demonstrate that targeting the IGF-IR with drugs such as IMC-A12 may be an effective anti-cancer therapeutic strategy and early promise has already accelerated development of these agents into late stage clinical testing in a diverse array of tumor indications and treatment strategies.

[12.35–12.55]

The power and promise of immunoglobulin repertoire analysis for cancer therapy

Beatrix Kotlan

National Institute of Oncology, Budapest, Hungary

E-mail: kotlanB@netscape.net

Background and Objectives: There are a great many questions in the field of tumor immunology, especially regarding anti-tumor humoral immune response. The studies on peripheral blood B lymphocytes in this respect have to be enlarged with other sources, for example lymph nodes and the tumor tissue itself. The nature and role of tumor infiltrating B cell trafficking into

solid tumors is an open question. It might influence tumor progression or have potential capacity for primary and metastatic tumor cell searching. There are a great many questions to be answered first in terms of clonality, immunoglobulin repertoire, antigen specificity and potential capacities of these B cells.

Methods and Results: A comparative DNA sequence analysis was performed after defining the nucleotide sequences of rearranged immunoglobulin heavy (VH) and kappa light chain (V κ) genes being PCR amplified and cloned by a suitable bacterial vector system. The VH-JH and V κ -J κ sequences were processed by BIOEDIT sequence editor, and the international ImMunoGeneTics (IMGT) database was used to define the closest germline homology at the variable (V), diversity (D) and join (J) regions. About a hundred new

sequences were ranked into families and clusters. In the course of multiple sequence alignments, these data could be compared with that of previous Ig variable regions of other sources. ClustalW, TreeView and VectorNTI 10 application programs were performed to define the homology rates regarding different sources and make comparison to the BLASTn database.

Conclusion: The detailed immunoglobulin repertoire analysis revealed characteristics for tumor associated antigen binding potential, the importance of which is high enough for further diagnostic and therapeutic use.

Acknowledgements: The work was supported by the Fulbright research grant No: 120610, the Hungarian OTKA T048933 grant and the Integrated Medical Sciences Association Foundation.