

Session 7: Cancer Applications

Thursday 15th April 2010. Moderator: Mark C. Glassy

[14.00–14.30]

‘The normal IGHV1-69 derived B cell repertoire contains “stereotypic” patterns characteristic of unmutated CLL’

F. Forconi, K.N. Potter, I. Wheatley, N. Darzentas, E. Sozzi, K. Stamatopoulos, C.I. Mockridge, G. Packham and F.K. Stevenson

Southampton University, Southampton, UK

The cell of origin of chronic lymphocytic leukaemia (CLL) has long been sought, and immunoglobulin gene analysis provides new clues. In the unmutated subset (U-CLL), there is increased usage of the 51–p1-related alleles of the IGHV1-69 gene, often combined with selected IGHD and IGHJ genes. Stereotypic characteristics of the HCDR3 result and suggest antigen selection of the leukemic clones. We have now analyzed 51p1/IGHJ6 combination in normal blood B cells from 3 healthy persons for parallel sequence patterns. A high proportion (33.3% of sequences) revealed stereotypic patterns, with several (15.0%) being similar to those described in U-CLL. Previously unreported CLL-associated stereotypes were detected in 4.8%. Stereotypes (13.6%) not detected in CLL also were found. The HCDR2-IGHJ6 sequences were essentially unmutated. Junctional amino acids in normal B cells were heterogeneous, as in cases of stereotyped CLL. Phenotypically, normal B cells expressing 51p1-derived IgM were naïve. This snapshot of the naïve B-cell repertoire reveals subsets of B cells closely related to those characteristic of CLL. Conserved patterns in the 51p1-encoded IgM of normal B cells suggest a restricted sequence repertoire shaped by evolution to recognize common pathogens. Proliferative pressure on these cells is the likely route to U-CLL.

[14.30–14.50]

‘New cancer-specific targets defined by natural human monoclonal antibodies’

Nicole Schatz, Annette Huber, Tanja Grimmig, Rebecca Schenk, Stephanie Brandlein, Frank Hensel and H. Peter Vollmers

University of Würzburg, Germany

Abstract not provided.

[14.50–15.10]

‘Ab targeted nanoparticles for cancer therapy’

Chris Scott

The Queens University of Belfast, Northern Ireland

Abstract not provided.

[15.10–15.30]

‘Antibody-maytansinoid conjugates (AMCs) in the treatment of cancer: From promise to reality’

John M. Lambert

ImmunoGen Inc., Waltham, Massachusetts, USA

Early clinical development in the field of targeted delivery of cytotoxic drugs to tumors using antibodies failed to achieve effective, well tolerated anticancer products. In recent years, several new highly potent cell-killing agents such as derivatives of the potent anti-mitotic microtubule agent, maytansine, are being utilized. Several AMCs have shown encouraging efficacy in clinical trials, including T-DM1 which is being developed by Genentech using ImmunoGen’s maytansinoid technology, SAR3419 being developed by sanofi-aventis, and IMG901 being developed by ImmunoGen. The new payloads for ADCs are realizing the promise of antibody-mediated delivery in cancer patients.

[15.30–15.50]

'MAb216, a human IgM, in a phase I study for treatment of B-lineage acute lymphoblastic leukemia'

Neelima M. Bhat, Michaela Liedtke, Clare J. Twist, Marcia M. Bieber, Steven E. Coutre and Nelson N. H. Teng

Stanford University, California, CA, USA

MAB216 is a naturally occurring human IgM monoclonal antibody derived from the VH4-34 (variable heavy chain) gene. In vitro, mAb216 specifically binds and is cytotoxic to normal and malignant human B-lymphocytes and B-progenitor lymphoblasts from patients with ALL. Binding of mAb216 to its linear lactosamine ligand leads to formation of large membrane pores resulting in cell lysis. This non-classical apoptosis occurs in the absence of complement fixation but the cytotoxicity is enhanced by complement. Despite improvements in front-line therapy for adult ALL, most patients eventually relapse and do not tolerate or respond to reinduction therapy. Novel targeted therapies are needed that have both activity against adult ALL and a toxicity profile distinct from conventional chemotherapy.

The primary aim of the study was to determine the maximum-tolerated dose, and dose-limiting toxicity of mAb216 as a single agent and in combination with vincristine in patients with relapsed or refractory B-ALL. A secondary aim was to preliminarily assess clinical efficacy. Patients were treated with escalating doses of mAb216 beginning at 1.25mg/Kg on day 0 and day 4–7. The second dose of mAb216 was given in combination with vincristine. Of the 13 patients enrolled in this study, 12 were fully assessable for toxicity. MAb216 was well tolerated with no hemolysis or immune complex formation. The maximum tolerated dose has not reached through 5mg/kg of antibody. One episode of grade 3 epistaxis was the only dose-limiting toxicity observed. At 2.5 mg/kg one patient developed hives during the infusion that resolved with treatment. 10/12 patients experienced a reduction of their peripheral blast count between 8–65% after infusion of mAb216 alone. The second dose of mAb216 in combination with vincristine achieved a 93% reduction in

peripheral blast count in 6/11 patients. One patient had a hypocellular bone marrow with no residual blasts on day 21. In conclusion, treatment with mAb216 in combination with vincristine is feasible and well tolerated in patients with relapsed or refractory B-cell ALL. Targeting of mAb216 to the leukemic blasts was efficient, and favorable early responses were observed.

This clinical result will be discussed in context of the role of human IgM antibodies in innate immunity and cancer treatment.

[15.50–16.10]

'B cells on the road to reveal novel tumor associated antigens: Potential capacities of B lymphocytes in peripheral blood and the tumor tissue itself are compared'

Beatrix Kotlan, Mepur H. Ravindranath, Jozsef Timar and Mark C. Glassy

National Institute of Oncology, Budapest, Hungary

Abstract not provided.

[16.30–16.50]

'Treating melanoma with a novel monoclonal antibody'

John Haurum

ImClone Systems Inc., New York, USA

Abstract not provided.

[16.50–17.10]

'Fsn0503: A novel Cathepsin S specific antibody that blocks tumour invasion and angiogenesis'

Shane Olwill

Fusion Antibodies, Belfast, Northern Ireland

Abstract not provided