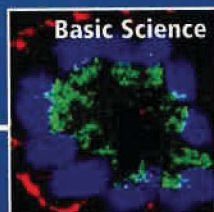


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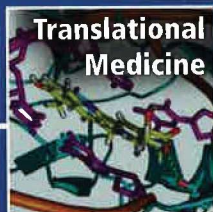
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Proceedings

Volume 49 • April 2008



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Advances in technology, progress in prevention, and rapid developments in the field of translational cancer medicine have led to the increasing importance of fostering dynamic collaborations among physicians and clinician-scientists. These collaborations will assist in gaining greater understanding and insight into the significant contributions of laboratory research to drug development and patient care; to the design and conduct of clinical research protocols; to the epidemiological implications of cancer incidence; and to the immediate translation of the findings of laboratory research for the benefit of improving care and quality of life of the cancer patient.

This Annual Meeting is directed towards scientists and clinicians engaged in all aspects of clinical investigations pertaining to human cancer as well as the scientific disciplines of cellular, molecular, and tumor biology; carcinogenesis; chemistry; developmental biology and stem cells; endocrinology; epidemiology and biostatistics; experimental/molecular therapeutics; immunology; radiobiology/radiation oncology; imaging; and prevention and survivorship research.

After participating in this CME activity, physicians should be able to:

- Demonstrate a clear understanding of the latest research findings in all areas of cancer research and how these findings will impact future decision making in the detection, diagnosis, prognosis, treatment, and prevention of cancer;
- Translate how the integration of information from the basic, translational, and clinical sciences applies to the development of new drugs, and clinical research trials;
- Employ technological advances to accelerate the research progress, improve early detection and screening options, which will ultimately extend patients' lives and improve their quality of life;
- Formulate new strategies and forge collaborations that will further scientific and clinical research efforts towards the prevention, diagnosis, early detection, and treatment of cancer
- Evaluate the use of biomarkers and other indicators to better treat patients in this era of personalized medicine, and to make recommendations for clinical trials;
- Interpret scientific advances that increase understanding of cancer biology and pathogenesis.

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glioblastomas. Finally, recent studies have proposed the existence of CD133-positive GBM stem cells. In this study, a panel of high grade human glioma cell cultures were analyzed first for gene expression profile and further for the expression of stem cell markers and different lineage markers recognizing astrocytes, oligodendrocytes, neurons and microglial cells by real-time RT-PCR. In parallel, the sensitivity to imatinib mesylate/STI571/Glivec and AEW541, two small molecular inhibitors targeting PDGFR- and IGF1-receptors respectively, were also investigated. 11 out of 20 cultures displayed CD133 expression measured by real-time RT-PCR. These could be further divided into two subsets both by gene-expression signatures and different stem cell and lineage markers. Type I cultures displayed high expression of CXCR4, Sox2, EAAT1 and GFAP, and low level of CNP, PDGFR β , CXCL12 and extracellular matrix proteins as compared to Type II. Further functional analysis by neurosphere assay revealed that Type I cells were better at neurosphere formation than Type II cells. Interestingly, these two subsets of CD133+ cultures displayed different sensitivities to PDGFR and IGF1R inhibitors. Type II cells were sensitive to either imatinib, AEW541 or both, while Type I cells were insensitive to both. However, when a combination treatment with imatinib and AEW541 was tested on Type I cells, a prominent growth inhibition was observed. Clinical significance of these subsets was indicated by the coordinated expression of Type I and Type II "markers" in human glioblastoma samples. In summary, two novel subsets of CD133-positive human glioma cultures could be identified and distinct differences between the two subsets with regard to sensitivity to AEW541 and imatinib were demonstrated. One of these subsets, which displayed high level of CXCR4, Sox2, EAAT1 and GFAP expression, was more prone to form neurospheres, was resistant to treatment with PDGFR and IGF1R inhibitors individually but showed sensitivity to combination treatment. The findings suggest continued studies to evaluate these novel potential treatment options for GBM based on targeting of CD133-positive cancer stem cells.

#4619 Cord blood and adult endothelial stem/progenitor cells are highly X-ray sensitive but their mode of cell death is both dose and age dependent. Marc S. Mendonca, Helen Chin-Sinex, Ryan Dhaemers, Laura Mead, Merv C. Yoder, David A. Ingram. *Indiana University School of Medicine, Indianapolis, IN.*

The ability to isolate and characterize endothelial stem/progenitors should lead to a better understanding of their role in radiation-induced tumor response and normal tissue injury. We have characterized the X-ray sensitivity of four high proliferative potential endothelial stem/progenitor cell isolates from cord blood (CBM4, CBF10) and from adult peripheral blood (EPC060805 and LM2). Irradiation with 160 kVp X-rays revealed these cells to be all equally and highly radiation sensitive with 3 Gy killing > 90% of the cells, without the induction of apoptosis. However, at high radiation doses (10Gy or greater) despite extensive and equal cell killing, the cord blood endothelial progenitors underwent substantial apoptosis but the adult endothelial progenitors did not. In addition, after 10 Gy, a stabilization of DNA damage response p53 protein and an increase in the proapoptotic Bax protein were observed only in the cord blood endothelial progenitors. Furthermore, recent studies reveal that after 10 Gy instead of apoptosis the adult endothelial progenitors undergo radiation-induced senescence. Cell cycle and Western analysis revealed evidence of cell cycle checkpoints induction in both the cord blood and adult endothelial progenitors. The data indicate that while these endothelial progenitor cells are equally radiation sensitive their mode of cell death is dose and age dependent, and appears independent of cell cycle checkpoint function.

IMMUNOLOGY 7: Adoptive Cell Therapy

#4620 CE7 epitope of L1CAM is a potential target for tumor specific T cell therapy in lung cancer. Karen L. Reckamp, Michael Statsny, Christine Brown, Michael C. Jensen. *City of Hope and Beckman Research Institute, Duarte, CA.*

Lung cancer is the leading cause of cancer death in the United States with an overall 5-year survival of 15%. New strategies for the treatment of lung cancer are clearly needed. Genetically engineering effector T-cells with functional capabilities to overcome the obstacles of immunosuppression and specific T cell anergy is a conceptually attractive strategy for treating lung cancer. L1CAM has been shown to be overexpressed in multiple tumors and associated with invasive/metastatic tumor biology. Published reports, as well as our own preliminary data, have demonstrated L1-CAM expression on a panel of SCLC and NSCLC lines. The L1-CAM specific monoclonal antibody CE7 from which the CE7R CAR was derived binds to an epitope on the L1 adhesion molecule with high affinity ($K_d=10^{-11}$). L1 is an immunoglobulin superfamily high-molecular-mass glycoprotein of approximately 200kDa that mediates homophilic cell-cell adhesion. CE7 appears to bind to a tumor-specific epitope on L1-CAM based on aberrant splice variants expressed by

tumor cells. We evaluated the CE7 epitope on small cell (SCLC) and non-small cell lung cancer (NSCLC) cell lines by FACS and western blot. Cytotoxic T lymphocyte (CTL) killing was assessed by 4-hour chromium release assays. We also evaluated the targeting of L1-CAM expressing lung cancer cell lines with cytolytic T cells genetically modified using SIN lentiviral vectors to express a L1-CAM specific chimeric antigen receptor composed of an scFv derived from the CE7 hybridoma that is in turn fused to IgG4:CD4Tm:CD3- ζ cyto (CE7R). We found that CE7 monoclonal antibody (mAb) binds to tumor L1-CAM on lung cancer lines, especially small cell lung cancer lines. CE7R expressing CTL can kill L1-CAM-expressing lung cancer cells via CE7R mediated recognition and CTL activation as evidenced by dose-dependent blocking with CE7 monoclonal antibody. Pre-clinical orthotopic and metastatic murine models of lung cancer adoptive therapy have been established using biophotonic reporters and *in vivo* Xenogen and micro-computed tomography imaging. These data and future murine modeling will further validate L1-CAM as a target on human lung cancer and potential target for novel T cell therapies. Supported by K12 CA 01727 and the Phase One Foundation.

#4621 In vitro priming of umbilical cord blood derived T cells using HER-2 peptide pulsed dendritic cells. Hae-Kyeong Yoon, Ha-Young Lee, Jin-Hee Ahn, Cheolwon Suh, Shin Kim, Jong-Lyel Roh, Sung-Bae Kim. *Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea.*

Introduction: HER-2 is an established target for antibody therapy. *In vitro* priming of T cells with dendritic cells (DCs) pulsed with clinically relevant peptide is an attractive strategy to generate tumor-specific T lymphocyte to activate the host's own immune system to raise an anti-tumor response. We investigated whether tumor specific T cells from umbilical cord blood (UCBs) using autologous DCs pulsed with HER2/neu derived peptide (KIFGSLAFL, E75) could be induced. Methods: UCBs in this experiment were examined with serologic HLA-typing. Only UCBs samples with HLA-A2 and confirmed with HER-2 expression by RT-PCR were used. Immature DCs generated in the presence of interleukin-4 and granulocyte/macrophage colony-stimulating factor from UCBs for 5 days, and then matured with lipopolysaccharide (LPS) and interferon-gamma (IFN- γ). For induction of T cells, DCs were cultured with autologous non-adherent cells and peptide (50 μ g/ml) was pulsed 3 times, every 2 days. Results: The phenotypes of DCs (CD 80+, CD83, CD 86, and HLA-DR) derived from CD14+ and CD 34+ showed comparable. *In vitro* primed T cells showed significant peptide-specific IFN- γ cytokine response. Higher expression of CD45RO+ and CD25+ were observed in HER-2/neu specific cytotoxic T lymphocytes when compared with non-activated T cells (20.7%, 36.3% vs. 0.3%, 13.2%). Conclusion: These data suggest that *in vitro* immunization using DCs could be beneficial in generating tumor specific T cells from Umbilical cord blood, which may be used for adoptive immunotherapy of HER-2 positive breast cancer.

#4622 Adoptive immunotherapy and therapeutic concurrent chemoradiation have synergistic antitumor effects in a mouse model of squamous cell carcinoma. Jeffrey S. Moyer, Ji Li, Alfred E. Chang. *Univ. of Michigan, Ann Arbor, MI.*

Concurrent chemotherapy and fractionated radiation are being increasingly used as the initial treatment for many patients with squamous cell carcinomas of the head and neck (SCCHN) in an effort to preserve function at the primary site as well as to possibly improve survival. Despite this treatment approach, many patients die from locoregional and distant disease. Adoptive immunotherapy with tumor-draining lymphocytes has been used by some investigators to try and improve survival in patients at high risk for recurrence or regional and distant metastases. In an effort to improve outcomes in this patient population, we undertook experiments to determine the feasibility of adoptive transfer of tumor-draining lymphocytes in mice treated with chemotherapy and fractionated radiation. Mice with 7-day subcutaneous SCCVII tumors were treated with 2 days of systemic cisplatin (4 mg/kg) and 5-fluorouracil (50 mg/kg) and 5 days of fractionated radiation to the flank tumor site (3 Gy/day; 15 Gy total). Tumor-draining lymph nodes (TDLN) from untreated mice with 9-day SCCVII tumors were harvested and activated for two days with anti-CD3 and anti-CD28 mAbs and subsequently expanded with IL-2 (60 IU/mL) for 3 more days. Mice were given a single intravenous injection of TDLN (30×10^6) three days after the completion of chemoradiation treatment (Day 14). Mice treated with chemoradiation or chemoradiation and TDLN had significantly slower tumor growth and better survival when compared to no treatment or TDLN alone-treated groups ($p < 0.05$). In addition, 2/20 (10%) of chemoradiation-treated animals and 3/20 (15%) of TDLN/chemoradiation-treated animals had a complete tumor response as compared to 0/20 (0%) in both untreated and TDLN alone-treated animals. Importantly, TDLN/chemoradiation-treated mice with a complete tumor response were completely resistant to multiple, repeat tumor challenges while chemoradiation-treated mice developed tumor with the initial rechallenge of relevant tumor. Consistent with these findings, splenocytes from TDLN/

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