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Jazz musician with trumpet

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Small caps denote presenting author.
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Abstract 929

Adoptive Cell Therapy for Lymphoma: Use of CpG-Loaded Tumor Cells to Generate Potent Anti-Tumor CD4 T Cell Immunity. MATTHEW J GOLDSTEIN*, Bindu Varghese, PhD*, Ranjani Rajapaksa, PhD*, Joshua Brody, MD, Shoshana Levy, PhD* and Ronald Levy, MD, Division of Oncology, Stanford School of Medicine, Stanford, CA, USA

Background: Recently, we have investigated adoptive cell therapy for treating lymphoma. The efficacy of this maneuver has been demonstrated by curing large established tumors. Specifically, we use active immunization to generate anti-tumor T cells *in vivo* and transfer these T cells into lymphodepleted recipient mice (Brody J, Goldstein MJ, Czerwinski DK, and Levy R; Blood, 2009). A major challenge in adoptive therapy is the method of generating anti-tumor T cells. Traditionally, tumor-specific T cells are expanded to large numbers *ex vivo*. Herein, we describe a new, whole-cell vaccine that is effective in inducing anti-tumor T cells *in vivo*. This vaccine combines tumor antigens with an immune stimulant: irradiated-tumor cells (a source of tumor antigens) are loaded with the TLR agonist CpG (an immune stimulant). Our vaccine approach has several potential advantages: (1) anti-tumor immunity generated by our CpG-loaded, whole-cell vaccine is poly-antigenic and thus, not limited by the expression of a single antigen target on tumor cells; (2) *ex vivo* expansion may generate large numbers of effector T cells that can induce tumor regression in the short-term, but have a limited ability to maintain a persistent anti-tumor response. Our model avoids *ex vivo* manipulation of anti-tumor T cells and thus, may preserve and enhance a memory T cell population that sustains the anti-tumor response.

Methods: We derived a new pre-B cell lymphoma cell line in the C57BL/6 background. Primary bone marrow cells were isolated from C57BL/6 donor mice and transfected with a recombinant retrovirus containing the Bcr-Abl oncogene. The emerging transformed cell line was designated H11. This cell line expressed the B lineage marker CD19 but was negative for MHC II and surface Ig. Irradiated H11 tumor cells were pre-loaded with CpG for 24 hours and administered to donor mice by daily, sub-cutaneous injections for five days. Donor splenocytes were harvested seven days following vaccination and adoptively transferred into lethally irradiated recipient mice that were subsequently challenged with a lethal dose of H11 tumor cells.

Results: Vaccination with CpG-loaded H11 tumor cells (CpG-H11) generated anti-tumor T cells that are effective in adoptive cell therapy. 100% of mice receiving adoptive therapy with vaccine-induced T cells were protected from tumor challenge. In contrast, vaccination of donor mice with untreated H11 tumor was insufficient for generating anti-tumor T cells. Only 20% of mice treated with T cells from these donors were protected from tumor challenge. In spite of the H11 tumor being MHC Class II⁺, we observed that anti-tumor immunity generated by the CpG-H11 vaccine was CD4 T cell mediated. CD4 T cells were isolated from CpG-H11 vaccinated donors by flow cytometry. Fewer than 1.8×10^6 CD4 T cells were sufficient to protect 80% of recipient mice from tumor challenge. In contrast, equivalent numbers of donor CD8 T cells provided no benefit. These results strongly suggest that the CpG-H11 vaccine induced cross-presentation of tumor antigens by antigen-presenting cells (APCs). We have demonstrated that CpG-loaded H11 tumor cells can take up CpG into the immediate environment activating nearby APCs. These APCs have greater phagocytic potential and express higher levels of co-stimulatory molecules such as CD40. Ongoing studies will determine whether APCs which encounter the CpG-H11 vaccine but not untreated H11 tumor cells, can stimulate proliferation of anti-tumor T cells.

Conclusions: Here we describe a novel, whole-cell vaccine approach that induces anti-tumor T cells for adoptive therapy to treat lymphoma. This vaccine is superior to vaccination with tumor cells alone. We are currently developing this therapy for evaluation in a clinical trial to treat mantle cell lymphoma.

Disclosures: No relevant conflicts of interest to declare.

Abstract 930

CD8⁺ T Cells Engineered to Express a ROR1-Specific Chimeric Antigen Receptor Specifically Recognize ROR1 Positive B Cell Tumors. MICHAEL HUDECEK, MD*¹, Thomas M Schmitt, PhD*¹, Sivasubramanian Baskar, PhD*², Wen-Chung Chang*³, David G Maloney, MD, PhD¹, Michael C Jensen, M.D.*³, Christoph M. Rader, Ph.D.*² and Stanley Riddell, MD*¹, ¹Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, ²Experimental Transplantation and Immunology Branch, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD, USA, ³Division of Cancer Immunotherapeutics & Tumor Immunology, City of Hope National Cancer Center, Duarte, CA, USA

The orphan tyrosine kinase receptor ROR1 was previously identified as a highly expressed gene by expression profiling of B cell chronic lymphocytic leukemia (B-CLL), [Klein et al. *J Exp Med* 2001], and has subsequently been shown to be expressed on mantle cell lymphoma (MCL) and a subset of B cell acute lymphoblastic leukemias (B-ALL). ROR1 encodes a 105 kDa protein that contains Ig-like, cysteine rich, kinase, tyrosine kinase and proline rich domains and is expressed during embryonic development but is absent on normal adult tissues including non-malignant B cells. The function of ROR1 in normal and malignant cells is not known, although secreted Wnt proteins have been proposed as candidate ligands. Analysis of ROR1 protein expression using specific polyclonal antibodies revealed uniform, stable, and restricted cell surface expression on B-CLL, suggesting this molecule is a candidate for targeted immunotherapy of B cell malignancies [Baskar et al. *Clin Cancer Res* 2008]. We constructed a lentiviral vector that encodes a chimeric antigen receptor (CAR) consisting of single chain variable (scFV) fragments of the heavy and light chains of a murine monoclonal antibody specific for ROR1,

linked to an IgG4 Fc domain, the T cell receptor CD3 zeta chain and a CD28 costimulatory domain. The specificity and function of the ROR1 CAR was compared with a similarly designed CAR specific for the CD20 molecule, which is expressed on both malignant and normal B cells, and is being targeted with gene-modified T cells in clinical trials. Primary human CD8⁺ T cells were transduced with the ROR1 and CD20-specific CARs respectively, and T cells expressing high levels of the receptors were sort-purified using an anti-Fc antibody. T cells that expressed either the ROR1-specific CAR or the CD20-specific CAR efficiently lysed primary B-CLL samples (5/5) obtained from patients with advanced disease, and also lysed a MCL cell line (JeKo-1), and a ROR1⁺ B-ALL cell line (BALL-1). ROR1-specific T cells did not recognize the myeloid leukemia cell line K562, but efficiently lysed K562 cells that had been transfected to express ROR1, confirming the specific recognition of ROR1 on target cells. Consistent with the expression pattern of the target molecules, T cells that expressed the CD20-specific CAR also efficiently lysed normal primary and EBV-transformed B cells, but T cells that expressed the ROR1-specific CAR did not recognize nonmalignant or EBV-transformed B cells. Activation of normal B cells by engagement of the B cell receptor or activation through CD40 induced B cell proliferation and upregulation of the CD80 and CD86 costimulatory molecules, but did not result in ROR1 surface expression by flow cytometry or recognition by T cells that expressed the ROR1-specific CAR. These results suggest that targeting ROR1 with gene-modified T cells may have advantages over targeting B cell-lineage restricted molecules such as CD19 and CD20 that are expressed on normal mature B cells. Studies to determine whether ROR1 is expressed during a stage of normal B cell development are in progress. ROR1 is highly conserved in non-human primates and this model may be suitable to determine potential toxicities of adoptive immunotherapy with ROR1-specific CAR expressing T cells.

Disclosures: No relevant conflicts of interest to declare.

LYMPHOMA: THERAPY WITH BIOLOGIC AGENTS, EXCLUDING PRE-CLINICAL MODELS: TREATMENT OF B-CELL LYMPHOMAS WITH ANTI-CD20 ANTIBODIES

Abstract 931

"Hiper CVAD Followed by Rituximab Purging Previous to Autologous Stem-Cell Transplantation as Therapy of Mantle Cell Lymphoma. Results of Manto 2000 study". F.J. Capote*¹, Eva Gonzalez-Barca*², Albert Oriol, MD*³, Antonio Romero-Aguilar*⁴, Angel Leon*⁵, F.J. Fernandez-Calvo*⁶, Elena Pérez-Ceballos*⁷, Eva Donato*⁸, Dolores Caballero*⁹, Jose Antonio Queizán*¹⁰, María Jesus Peñarrubia, MD*¹¹, Luis Palomera*¹², Julio Prieto*¹³, Pilar Giraldo, MD*¹⁴ and JUAN BERGUA, MD*¹³, ¹Hospital Puerta del Mar. Cadiz, Cadiz, ²Hematology, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain, ³Hospital Universitari Germans Trias i Pujol, Badalona, Spain, ⁴Hematology, Hospital Virgen de las Nieves. Granada, Granada, Spain, ⁵Hospital Univ. La Fe. Servicio de Hematología, PETHEMA cooperative group, Valencia, Spain, ⁶Hematology, Clínico. Valladolid, Valladolid, Spain, ⁷BM Failure Spanish Study Group (PetHEMA-GETH), Murcia, Spain, ⁸Hospital General de Castellón, Castellón, ⁹Hematology-BMT Unit, Hospital Clínico Salamanca, Salamanca, Spain, ¹⁰Hospital General de Segovia, Segovia, ¹¹HOSPITAL RÍO HORTGA, Valladolid, Spain, ¹²Hospital Lozano Blesa, Zaragoza, Spain, ¹³Hematology. Hospital San Pedro de Alcántara. Cáceres, PETHEMA cooperative group, Cáceres, Spain, ¹⁴Hospital Miguel Servet, Zaragoza, Spain

Purpose: Multicentre phase II study in newly diagnosed Mantle cell lymphoma patients to determine the feasibility, overall response (OR) and failure free survival (FFS) of intensive chemotherapy type Hyper-CVAD followed by *in vivo* purging with Rituximab previous peripheral stem-cell transplantation.

Treatment scheme consisted in four cycles of Hyper-CVAD chemotherapy as is described by Romaguera et al. After chemotherapy four weekly Rituximab courses (375mg/m²) were administered previously to peripheral stem-cell collection. Rituximab was not added at the same time as chemotherapy cycles; its role consisted in working as a purging agent previous stem-cell mobilization. After Rituximab administration peripheral blood progenitors were collected. Mobilization was performed using Cyclophosphamide plus G-CSF at dose of 10 µg/Kg/day. If the first mobilization was unsuccessful, a second scheme was used, using Ifosfamide (10 g/m² in 72 hours infusion on day 1), Mesna (10 g/m² days 1 and 2), VP16 (150 mg/m² days 1 to 3) plus G-CSF at dose of 5 µg/Kg each 12 hours. The aim was obtain 2×10^6 CD34 cells/Kg. After mobilization peripheral autologous stem-cell transplantation (PASCCT) was performed using BEAM (BCNU, Ethoposide, Ara-C and Melphalan) as conditioning regimen. A week after platelet recovery ($>50 \times 10^9/L$) another four weekly Rituximab courses (375mg/m²) were added. Patients were followed after treatment in each centre.

Forty-four patients diagnosed of mantle cell lymphoma and previously not treated were enrolled from fifteen Spanish Institutions from 2000 to 2006. The median age of the patients were 55.77 year old. Male/female rate was 3:1. Forty patients had an Ann-Arbor stage IV, and gastrointestinal involvement was present in twenty-nine. Marrow was infiltrated in 83.3% of the cases. Age IPI adjusted were ≥ 2 in 45% of the cases respectively (table 2). Blastic mantle cell lymphoma was diagnosed in 5 patients (11.9%). The median follow-up of the patients was 75.07 months. In the intention to treat, of the forty-four patients only 26 patients receive all the treatment (59%). Autologous peripheral stem-cell transplantation was not performed in 16 patients. The causes of not complete the treatment schedule was: three patients refuse to be transplanted; mobilization failure in four; death