Joshua D Brody, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.06

OMICS Group Conferences
Accelerating Scientific Discovery

International Conference & Exhibition on
Cell Science & Stem Cell Research

29 Nov - 1 Dec 2011 Philadelphia Airport Marriott, USA

Immunotransplant for mantle cell lymphoma: Phase I/II study preliminary results

Joshua D Brody[1], Debra Katherine Czerwinski[1], Victoria Carlton[2], Martin Moorhead[2], Jianbiao Zheng[2], Mark Klinger[2], Malek Faham[2], Ranjana Advani[1], Holbrook E Kohrt[1], Arash Alizadeh[1], Robert S Negrin[1], Kevin Sheehan[1] and Ronald Levy[1]

[1]Medicine, Stanford University, USA
[2]Sequenta Inc, USA

Mantle cell lymphoma (MCL) has a poor long-term prognosis. Though autologous transplant prolongs survival, novel and mechanistically distinct therapies are needed to target residual, myeloablation-resistant tumor cells that result in relapse.

Trials of CpG-based vaccines for *low-grade* lymphoma have shown induction of anti-tumor T cells and clinical responses. In a pre-clinical model, we developed the *immunotransplant* maneuver combining: 1) CpG-based vaccination, 2) harvest of vaccine-primed T cells, 3) myeloablation with stem cell rescue, and 4) T cell re-infusion. Immunotransplant amplifies the proportion of anti-tumor T cells by an order of magnitude and cures even bulky, systemic lymphoma burden

Methods: We initiated a phase I/II study of immunotransplant for newly diagnosed MCL patients to test the hypothesis that immunotransplant will amplify anti-tumor T cells as in the pre-clinical model. Anti-tumor T cells are assessed by co-culturing autologous tumor with peripheral blood T cells and measuring their production of: IFNg, TNF, IL2, CD137, perforin and granzyme by multiplex surface and intracellular flow cytometry. A secondary endpoint is measurement of molecular residual disease (MRD) using both standard allele-specific oligonucleotide (ASO) qPCR as well as high-throughput sequencing (HTS) of the entire IgH repertoire. The study is powered to detect a 50% improvement in sustained molecular remission rate compared to recent trials of standard transplant . Using the same HTS technology, we have also initiated studies of the entire TCRβ repertoire as an alternate approach of tracking the amplification of vaccine-induced T-cells.

Results: Accrual has been rapid with 25 patients enrolled in 22 months and 13 patients completing the complete protocol so far. Flow-cytometric immune response testing has demonstrated that immunotransplant amplifies the proportion of tumor-reactive T cells in 83% of patients thus far. Notably, we have observed some patients with primarily CD8 T cell responses, some with CD4 T cell responses, and some with a combination of the two. In some cases, tumor-reactive T cells have been tested for reactivity to autologous, non-malignant B cells and have demonstrated a significant proportion that are tumor-specific. TCRβ repertoire sequencing has also demonstrated instances of significant clonal amplification after immunotransplantation, some exceeding three orders of magnitude. In extreme cases, these have yielded dominant clones comprising as much as 50% of a patient's entire peripheral blood T cell repertoire post-transplant. HTS of the IgH repertoire has been an effective measurement of MRD bypassing the assay individualization of ASO qPCR and has been shown to be more sensitive than conventional flow cytometry.

Conclusions: Pre-clinically, amplification of anti-tumor T cells correlates with cure of even myeloablation-resistant disease. The reiteration of anti-tumor T cell amplification in our preliminary patient data raises the possibility that immunotransplant may improve clinical outcomes. Ongoing MRD testing should suggest whether certain patterns of T cell response –measured functionally per flow cytometry or clonally per HTS- correlate with clinical benefit and whether the cohort has a better-than-expected molecular remission rate.