Yongxin Zhang et al., J Clin Cell Immunol 2015, 6:5
http://dx.doi.org/10.4172/2155-9899.C1.025

OMICS International
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4th International Conference and Exhibition on
Immunology
September 28-30, 2015 Crowne Plaza Houston River Oaks, Houston, TX, USA

Cancer-specific CTL Expansion with ZYX Bioreactor

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The use of therapeutic immune cell subsets (aka cell therapy) is becoming an increasingly cost-effective and attractive strategy for the treatment of cancer. Specialized cell subsets including dendritic cells (DC), cytotoxic T-lymphocytes (CTL), natural killer (NK) cells, cytokine-induced killer (CIK) cells, tumor infiltrating lymphocytes (TIL), and genetically engineered chimeric antigen receptor (CAR) T-cells have all shown efficacy, at times significant efficacy, in a variety of different clinical studies. Nonetheless, the field of cell therapy is hampered by the inability to consistently generate and expand sufficient numbers of high quality cells from a majority of patients. To address this critical issue, the investigators have developed a sophisticated bioreactor technology (Published patent information: PCT/US2012/000182) that maximizes metabolic support with minimized shear-stress forces, automatically monitors functional correlates to allow cell harvest at peak functional capacity, and permits cell sorting in situ to minimize cell loss and microbial contamination. This revolutionary technology has generated increased numbers of high quality hematopoietic stem cells for use in hematopoietic stem cell transplantation and has also demonstrated the capacity to generate enhanced numbers of functionally superior immune cell subsets. In current study, splenocytes from cancer cell-primed BALB/c mice were isolated and seeded in a ZYX Bioreactor (ZYX btr) cell culture chamber and 6-well plates at 10^6 /ml and cultured for 6 days with an RPMI containing mouse serum, IL-2, IL-7, and irradiated cancer cells (Renca cells, seeding density determined by surface area, 80% confluent). On day 6, suspension cells in the ZYX btr were processed for CD8+ cell isolation using a positive selection program and then cultured with the same medium for 3 more days. CD8+ cells in a static culture were isolated using a Miltenyi device and then placed back in plate to culture with the same medium for 3 more days. Following the expansion, 2x, 4x, or $8x10^5$/well effector cells were then added into 25,000/well target cells in triplicate and incubated for 4 hours. Supernatants were then harvested for LDH detection. CTL activity (% lysis) was calculated using the formula (Test cell mix-Effector control-spontaneous release)/(maximum release-spontaneous release). The data shows that when the effector cells were stimulated in the ZYX btr, the CTL expansion folds and overall lytic activity were significantly higher than those in the static culture ($p<0.05$). The ZYX btr significantly increased cancer-specific CTL production in the expansion, and the expanded CTLs in the ZYX bioreactor have higher killing activities in comparison with the static culture, which suggests that the ZYX bioreactor provides a better cell growth environment for antigen-specific CTL expansion than the static culture and will benefit cancer-immunotherapy.

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