OR.28. Immunotherapy of Chronic Lymphocytic Leukemia Patients with Gc Protein-derived Macrophage Activating Factor, GcMAF or its Cloned Derivative, GcMAFc

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Serum Gc protein (known as vitamin D-binding protein) is the precursor for the macrophage activating factor (MAF). The MAF precursor activity of serum Gc protein of cancer patients was lost or reduced because Gc protein is deglycosylated by serum α-N-acetylgalactosaminidase (Nagalase) secreted from cancerous cells but not from healthy cells. Thus, serum Nagalase activity is proportional to tumor burden and serves as a prognostic index. Deglycosylated serum Gc protein cannot be converted to MAF. Since macrophage activation for phagocytosis and antigen-presentation to B cells and T cells is the first indispensable step for development of both humoral and cellular immunity, lack of macrophage activation leads to immunosuppression. Lack of macrophage activation and severe immunosuppression explain why advanced cancer patients die with overwhelming infection (e.g., pneumonia). Stepwise treatment of purified serum Gc protein or cloned Gc protein with immobilized β-galactosidase and sialidase generates the most potent MAF (termed GcMAF or GcMAFc, respectively) that produces no side effect in humans. Intramuscular administration of 100 ng GcMAF, or GcMAFc, activated systemic macrophages to develop an enormous variation of receptors that recognize cell surface abnormality of a variety of cancer cells and to become tumoricidal. GcMAF also has a potent mitogenic activity on myeloid progenitor cells that generate systemically a 40-fold increase in the activated macrophages in 4 days. When Chronic Lymphocytic Leukemia (CLL) Patients were intramuscularly administered with 100 ng GcMAF or GcMAFc/week, their leukemic cells were eradicated in 20-32 weeks. These patients were leukemic cell-free for more than nine years after the therapy.

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OR.29. Sentinel Node-based Immunotherapy of Colon Cancer

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The first tumor-draining lymph node; the sentinel node can be identified by peritumoural injection of a tracer. This is the hypothesised location for the activation of tumor-reactive lymphocytes. Accordingly, proliferation and IFN-gamma production in response to the autologous tumor has been identified by our group in sentinel node-acquired lymphocytes from patients with colon and bladder cancer. The possibility of an adoptive immunotherapy approach based on this cell population was addressed in a proof-of-principle clinical trial. Lymphocytes were isolated from 16 patients with advanced or high-risk colon cancer. *In vitro* expansion with addition of autologous tumor extract and IL-2 mainly promoted the outgrowth of CD4+ Th1 lymphocytes, which were safely re-transfused to the patients. No side effects were observed. Four patients with stage IV tumors responded with complete tumor regressions. Some of the patients also received chemotherapy and this may have contributed to the favorable outcome in these cases. In conclusion, adoptive immunotherapy with sentinel node-acquired lymphocytes is feasible and appears to convey anti-tumor effects in humans without apparent side effects.

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OR.30. Activation Induced Cell Death (AICD) of Human Melanoma Antigen Specific MHC Class I TCR Engineered CD8 T Cells is an Intrinsic Process That Involves JNK and p53

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The lack of sufficient tumor antigen specific T cell precursors in most cancer patients and the potential premature elimination of a significant fraction of tumor reactive T cells through epitope specific activation induced cell death (AICD) represent key limiting factors hindering the development of an effective T cell based cancer immunotherapy. We here show that with TCR engineering approach we can generate sufficiently large numbers of customized tumor reactive T cells, and that these engineered CTL exhibit all the properties of the natural anti-tumor CTL, i.e. epitope specific effector cytokine production, degranulation, epitope specific cytolytic effector function, and AICD. In our efforts to generate customized anti-tumor CTL that are less susceptible to undergo AICD, we show that the AICD in TCR engineered CD8+ CTL is a death receptor-independent, caspase-independent, intrinsic process that involves the activation of JNK and blocking JNK could rescue a substantial fraction of these CTL from undergoing AICD, similar to our findings with the natural CTL (Chhabra et al. EJI, 2006 and Mehrotra et al., JI, 2004). Furthermore, we also show that p53 plays a critical role in the mitochondria-centric AICD of the tumor antigen specific human CTL. These findings have implications for T cell based cancer immunotherapy protocols.

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OR.31. Optimizing the iNKT Cell Dependent Antitumor Effect Using an Altered Glycolipid

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Invariant Natural Killer T (iNKT) cells form a separate lymphocyte lineage with features of both innate and adaptive immunity. Unlike conventional T lymphocytes, iNKT cells respond to glycolipid antigens presented by CD1d. Activation of iNKT cells with alpha galactosyl ceramide (α-GalCer), the prototype ligand, engages iNKT cells to secrete large quantities of T helper (Th)1, Th2 and Th17 cytokines and increases the cellular cytotoxicity of both iNKT and NK cells. In the context of