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Hematopoetic-stem-cell based therapy for HIV disease

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Our goals are to develop insight and understanding of the effect of deleting the chemokine receptor CCR5 in T cells important for HIV entry and its interplay with immune regulation in HIV, forming basis for a novel technology platform to cure HIV disease. A major innovation is the use of hematopoetic stem cell (HSC) transplantation of the cells resistant to HIV such as CCR5Δ32 cells, which do not express CCR5 due to a deletion in the promoter. The mutation spontaneously occur in 4-15% of the European population (with frequency remarkably increased in North), confer resistance to HIV in homozygous individuals and could cure HIV disease based on the outcome of bone marrow engraftment in HIV patients with leukemia using a CCR5Δ32 homozygous donor. However, patients receiving a bone marrow allotransplantation often suffer from graft-versus-host disease (GvHD), and for that reason HIV infection is not considered an indication, unless leukemia warrants transplantation. To advance this field, it is, however, vital with i) mapping of donors in bone marrow registries to identify CCR5Δ32 donors for world-wide matching to HIV+ leukemic recipients; ii) to advance strategies to understand immune dysfunction and immune regulation in HIV and be able to offer suppression of GvHD and iii) to explore function of CCR5Δ32 T cells and the possibility to manipulate CCR5 in stem cells moving towards future autotransplantion of CCR5 deleted hematopoetic stem cells. Our approach is to first screen Registries of Bone Marrow Donors in Norway and the Czech Republic and identify donors homozygous for Δ32 mutation. Secondly, in order to ameliorate GvHD, we intend to exploit mechanism of inhibition of interleukin-2 (IL-2) gene expression, which plays a crucial role in repression of CD4+T conventional cells (Tcons) by naturally occurring CD4+CD25+ T regulatory cells (nTregs). Transfer of cyclic AMP (cAMP) from nTregs to Tcons and/or its receptor-mediated induction in adaptive Tregs underpins function of potent transcriptional repressor termed Inducible cAMP Early Repressor (ICER) leading to suppression of IL-2 synthesis thus reflecting potential suppressive function of T cells during GvHD. Further understanding of the mechanisms of immunological self-tolerance will also provide insights into how strong immune responses such as graft rejection could be restrained and engraftment of HIV resistant cells in HIV+ leukemic patients could be augmented.

Biography

Josef Bodor received his PhD (1990) with honors from Institute of Molecular Genetics in Prague, Czech Republic. As of 2013, he is a Senior Investigator working at the Institute of Experimental Medicine in Prague, Czech Republic. He is a senior scientist with faculty experience from Ivy League Institutions in US hosting on sabbatical leaves around the world (Harvard University Boston, MA, Columbia University; New York, NY, Kyoto University, Kyoto, Japan, Würzburg University, Würzburg, Germany, and Johannes Gutenberg University in Mainz, Germany).

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