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Accumulating clinical evidences over recent years support the notion that the immune system has the potential to cure cancer. The first convincing example of an adoptive cellular therapy is the graft versus leukaemia effect observed after allogeneic haematopoietic stem cell transplantation. The recent advances in gene-transfer technologies developed over the last decade have offered new tools to reduce the toxicity and increase the specificity of this approach. T-cell can now be engineered to express new high avidity T cell receptors (TCR) or Chimeric Antigen Receptors (CAR) that recognize specific tumor associated antigens, thus redirecting the principal firing power of immunity against cancer cells. In particular, clinical testing of CAR-T cell therapy has shown to significantly increase the survival of several patients with B cell acute lymphoblastic leukemia and aggressive B cell lymphoma, for which this powerful new class of therapeutics was recently been approved for commercialization. Although these successes poised to revolutionize the whole oncology field, successful T cell therapy for other hematologic tumors is still hampered by the absence of cancer-restricted antigenic markers. The most potential tumor-associated antigens are often self-antigens shared with normal hematopoietic stem cells (HSCs), thus are not amenable for an immunotherapy approach because this treatment will result in sustained and severe hematopoietic toxicity. We recently developed and optimized a strategy based on CRISPR/Cas9 technology that enables efficient and specific gene editing of endogenous genes in human primary HSC, thus allowing site-specific transgene integration or permanent gene inactivation. Here, the Ph.D. candidate will exploit this technology to genetically engineer the host HSC to avoid on-target, off-tumor toxicity. In particular, HSC will be edited in order to avoid the presentation of specific antigens, thus generating stealth HSCs that are resistant to the attack of T cells armed with a TCR/CAR specific for that target. This strategy will allow develop new adoptive T cell therapy approaches that could targets also genes shared on both leukemic and healthy HSC while sparing the toxicity on the healthy donor cells.