A given tumor is usually dependent on the oncogene that is activated in the respective tumor entity. This phenomenon called oncogene addiction provides the rationale for attempts to target oncogene products in a therapeutic manner, be it by small molecules, by small interfering RNAs (siRNA) or by antigen-specific T cells. As the proto-oncogene product is required also for the function of normal cells, this raises the question whether there is a therapeutic window between the adverse effects of specific inhibitors or T cells to normal tissue that may limit their application, and their beneficial tumor-specific therapeutic action. To address this crucial question, suitable mouse strains need to be developed, that enable expression of the human proto-oncogene not only in tumor but also in normal cells. The aim of this work is to provide such a mouse strain for the human proto-oncogene product c-MYC. We generated C57BL/6-derived embryonic stem cells that are transgenic for a humanized c-Myc gene and established a mouse strain (hc-Myc) that expresses human c-MYC instead of the murine ortholog. These transgenic animals harbor the humanized c-Myc gene integrated into the endogenous murine c-Myc locus. Despite the lack of the endogenous murine c-Myc gene, homozygous mice show a normal phenotype indicating that human c-MYC can replace its murine ortholog. The newly established hc-Myc mouse strain provides a model system to study in detail the adverse
effects of therapies that target the human c-MYC protein. To mimic the clinical situation, hc-Myc mice may be cross-bred to mice that develop tumors due to overexpression of human c-MYC. With these double transgenic mice it will be possible to study simultaneously the therapeutic efficiency and adverse side effects of MYC-specific therapies in the same mouse.