6-thioguanine in vivo selection for hematopoietic stem cell transplantation (HSCT)

Hematopoietic stem cell transplantation (HSCT) is often the only/last treatment option of some malignancies, congenital diseases and bone marrow failure. For efficient engraftment of donor HSC's stem cell niches have to be provided. Here we developed an in vivo selection scheme for HSCT based on the fact that 6-thioguanine (6TG) toxicity is essentially predicated on its HPRT mediated conversion to thioguanine nucleotide and strongly myelosuppressive. At appropriate concentrations 6TG is strongly myeloablative with little toxicity to other tissues. Therefore it is possible to eliminate diseased bone marrow and replace it with healthy donor bone marrow that lacks HPRT. We have shown that only Hprt proficient cells are susceptible to 6-TG allowing selection in favor of Hprt deficient donor HSC's in vivo and that a 4 week selection regimen results in a 95% replacement of the host's marrow. Engraftment is more robust with 6-TG selection than with radiation. The proposed method offers selection through a less toxic compound (compared to other schemes) hence less side effects, use of smaller, siRNA-producing vectors (therefore potentially more efficient), possible use of non-integrating vectors and less patient discomfort. The general aim of this project is to show that HSC’s deficient for HPRT can be selected for in vivo through 6TG administration, that this procedure would be applicable for conditions like hematological malignancies, congenital diseases and bone marrow failure i.e., where HSCT is indicated and to test all aspects of this procedure to eventually allow for phase-I clinical trials.

Biography

Robert H Schiestl has obtained his PhD from the University of Vienna. He was a Postdoctoral Fellow at Edmonton, Alberta, Rochester, NY and Chapel Hill, NC before being Professor at Harvard where he stayed for 10 years. Since 15 years he is a Professor at UCLA with 187 publications, 10 patents and 2 startup companies.

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