

DESCRIPTION FOR THE GENERAL PUBLIC

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of lymphomas characterized by accumulation of malignant T cells in the skin. Mycosis fungoides (MF) and Sézary syndrome (SS) are the most frequent forms of CTCL. MF is more indolent in behaviour and presents with patches and plaques that may evolve into tumors. SS is an aggressive and leukemic variant of CTCL, characterized by severe erythroderma, with lower occurrence than MF. Both affects older people and are not curable. The treatment is aimed at the reduction of symptoms, clearance of skin disease in particular, prevention of disease progression and minimizing the recurrence. In our aging society the incidence rate of CTCLs have risen over the past years so there is a challenge here to find more effective diagnostic tools and targeted treatment options. Recently HDAC inhibitors (HDACi), such as Vorinostat (SAHA), Romidepsin and Belinostat, have been introduced to CTCL treatment. They regulate activity of histone deacetylases (HDAC) involved in the epigenetic regulation of gene expression. However, HDACi, that are already used in clinic, have a broad spectrum of action, interfere with multiple HDACs and as a result regulate many biological events, thereby causing serious side effects. We are in need now to develop more potent and tumor-specific HDACi. In order to achieve that it is necessary to understand the mode of action of each HDAC, which of them are deregulated in particular tumors and what the consequences are, so that HDACi could be used more specifically, with other agents and thus increased effectiveness of therapy in patients. The purpose of this project is to analyze the impact of a selected HDAC on cancer cells in CTCL. There are four groups of HDACs, HDAC inhibitors affect class I, II, and IV HDACs (11 HDACs). Class II HDACs are particularly interesting as based on literature their expression could be cancer specific and associated with the type and aggressiveness of the disease. Our studies will be focused on chosen class II histone deacetylases: HDAC9 and HDAC10, as our preliminary studies have shown significant over-expression of this genes in patients with Sézary syndrome. In this project we aim to investigate the significance of HDAC9 and HDAC10 in Sézary syndrome, its influence on cell biology, global gene expression and particular cellular pathways. The results will contribute not only to a better understanding of the pathogenesis of Sézary syndrome and perhaps to the improvement of therapy, but also will increase the general knowledge of this histone deacetylase and its mode of action.