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# Cutaneous T-cell lymphoma, new insights

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of extranodal non-Hodgkin lymphomas characterized by homing of the tumoral T-cells into the skin.[1,2] The most frequent forms of CTCL are mycosis fungoides (MF) and its leukemic counterpart, the Sézary syndrome (SS). Currently, no curative treatment for CTCL is available, and the therapy aims to maintain a long-term complete remission and preserve quality of life. Patients with refractory or transformed MF and with SS have usually poor prognosis and the proposed treatment is mostly palliative.[3]

## Identification of genes associated with resistance to PUVA+IFNα treatment in mycosis fungoides

Interferon alpha (IFNα) is widely used in the treatment of mycosis fungoides (MF). The combination of IFNα with photochemotherapy (PUVA) showed both improved response and duration of complete remission. However, in spite of promising results of the initial studies, at present no information is available regarding specific prognostic factors that could enable prediction of patients' resistance to PUVA±IFNα treatment. In order to identify markers responsible for treatment resistance in MF patients, we performed gene expression profiling of pre-treatment samples from a series of MF patients enrolled in a randomized PUVA vs PUVA+IFNα clinical trial.[4] We used a Cox model (SAM) and Gene Set Enrichment Analysis (GSEA) to determine genes and biologically significant pathways associated with treatment resistance. Genes involved in NF-κB signalling, T-cell receptor (TCR) signalling, cytokine signalling and proliferation were differentially expressed between responders and non-responders. Interestingly, a study performed on paraffin-embedded tissues demonstrated that expression of markers representative of those pathways were present not only in the tumoural cells, but also in specific subpopulations of macrophages, dendritic cells and other non-neoplastic cell types constituting the tumour microenvironment, likely involved in the promotion of survival and proliferation of cutaneous T-cell lymphoma. Some pro-inflammatory factors such as NF-κB, inflammatory cytokines and their receptors in addition to TCR associated molecules could be promising targets for MF treatment.[5]

## Gene signatures in cutaneous T-cell lymphoma allow proposing new therapeutic targets and select targeted therapies

Gene signatures of these CTCL samples were analyzed using Connectivity Maps (cMap) which allowed us to combine the resistance gene expression signature with a database of bioactive small molecules expression profiles. Using this approach we identified several molecules as potential PUVA±IFNα resistance reversal agents. This includes SAHA – Vorinostat, ZolinzaTM – a histone deacetylase inhibitor (HDACi). Clinical trials in patients with refractory CTCL demonstrated an objective overall response of 30%[6] following SAHA treatment. Subsequently, SAHA has recently been approved by the U.S. Food and Drug Administration for the treatment of CTCL. Presently, SAHA is tested in clinical trials both as monotherapy and in combination with various anticancer drugs. In order to properly administer the drug and achieve the desired effect following treatment with combination therapies, the knowledge of the exact mechanism of action as well modulation and kinetics of particular gene expression altered is essential. We have investigated the alterations in gene expression profile, acetylation, proliferation and cell death in five CTCL cell lines after SAHA treatment over time. Our results demonstrate that SAHA induces cell death, growth arrest and acetylation of histones. The drug causes alterations in many pathways including downregulation of the TCR pathway members, inhibition of Th2 and promotion of Th1 cytokine profile. Furthermore, SAHA decreases phosphorylation of tyrosine kinase essential for TCR signaling (ZAP70) and other implicated downstream kinases (ERK, AKT) suggesting inhibition of TCR-mediated signal transduction as one of the mechanisms of SAHA action.

## Gene signatures in peripheral T-cell lymphoma allow identifying main deregulated pathways, proposing new therapies

A collection of gene expression data from T cell lymphomas (TCLs) has been analysed with the use of GSEA and cMap, in order to identify the most relevant pathways and propose new therapeutic approaches.

The pathways enriched in TCLs when compared to normal lymphoid tissues included ERK, STAT3, EGF, MET, CDK5, RACC, IL6, BCL2, IL3, IGF1, IL2, Proteasome and others. Furthermore, cMap analysis specified a collection of drugs which signature matched the profile of TCLs. These results emphasize mTOR inhibitors, histone deacetylase inhibitors (HDACi) and PI3K inhibitors as potential drugs for the treatment of TCLs.

## References


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