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Research for a Life without Cancer

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Preclinical investigation of new targeted combination therapies in cutaneous T-cell lymphoma

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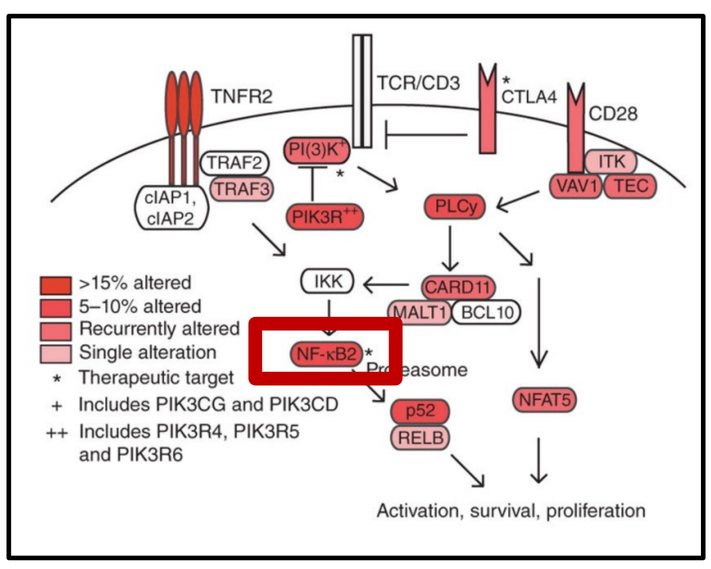
I. Introduction

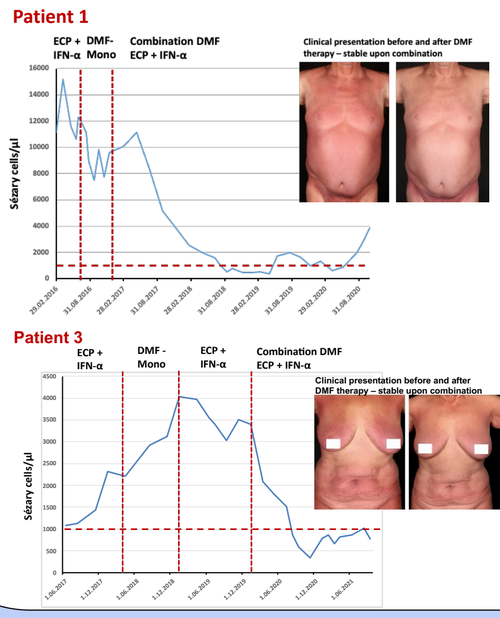
Sézary syndrome (SS), the leukemic variant of cutaneous T cell lymphoma (CTCL), shows high relapse rates and poor prognosis, which complicates the clinical course as well as the treatment. The circulating atypical T cells known as Sézary cells (SC) display a CD4+/CD8- T helper cell phenotype.

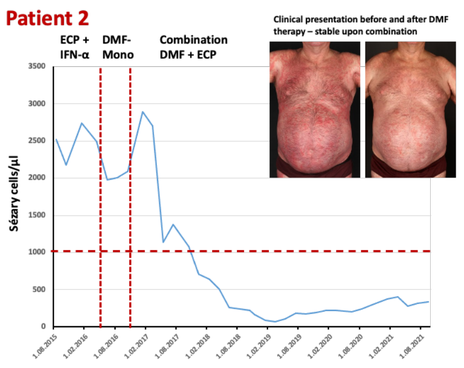
Due to frequent relapses and treatment-related side effects of current therapies as well as progressive therapy resistance of SS, there is an urgent need for the development of effective and well-tolerated therapeutic options. The malignant T cell population in CTCL is characterized by acquired resistance towards cell death rather than an increased proliferation rate. Therefore, nuclear factor κB (NF-κB) represents one important trigger structure that can render a cell resistant to cell death stimuli.



(Ungewickell et al., 2015)

II. Clinical findings



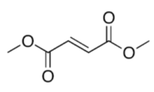


- All Sézary syndromes were in stage IV
- Monotherapies were not able to reduce Sézary cell counts in the blood, however, combination therapy consisting of DMF and ECP led to complete remission.

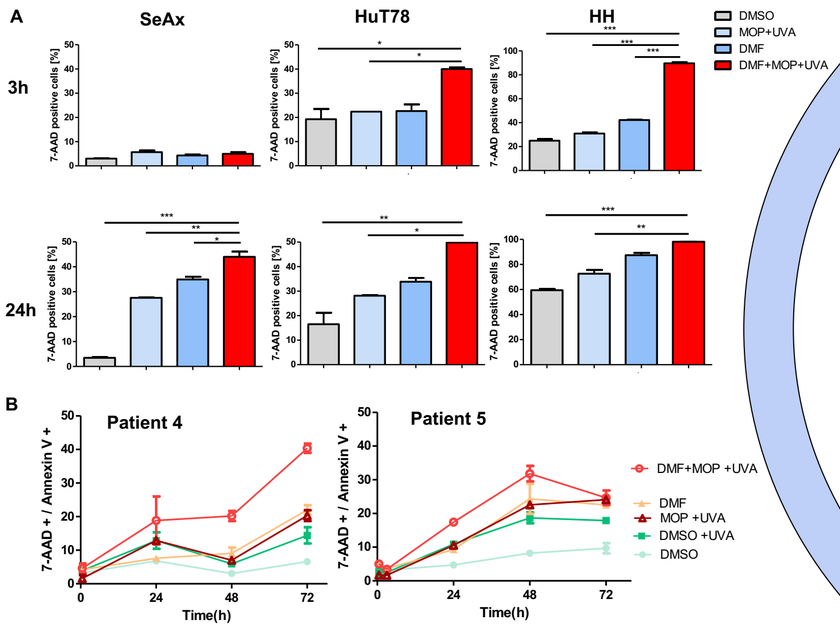
III. Aim

- Investigate ECP and DMF as a novel combined therapy in CTCL cell lines and understand their synergistic effects based on immunomodulation and cell death.
- Identify underlying molecular mechanisms of this new therapeutic approach.

Mimicking combination therapy *in vitro* and *ex vivo*

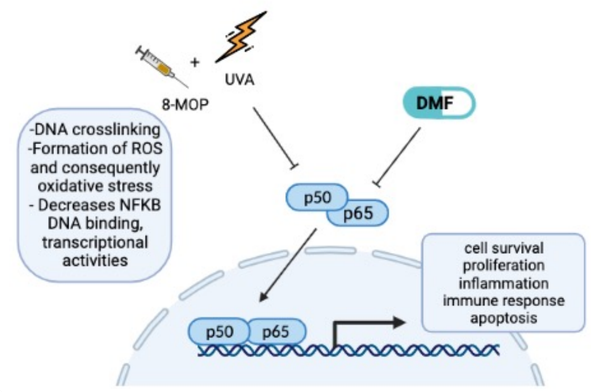


IV. Combination therapy induces higher cell death than monotherapies

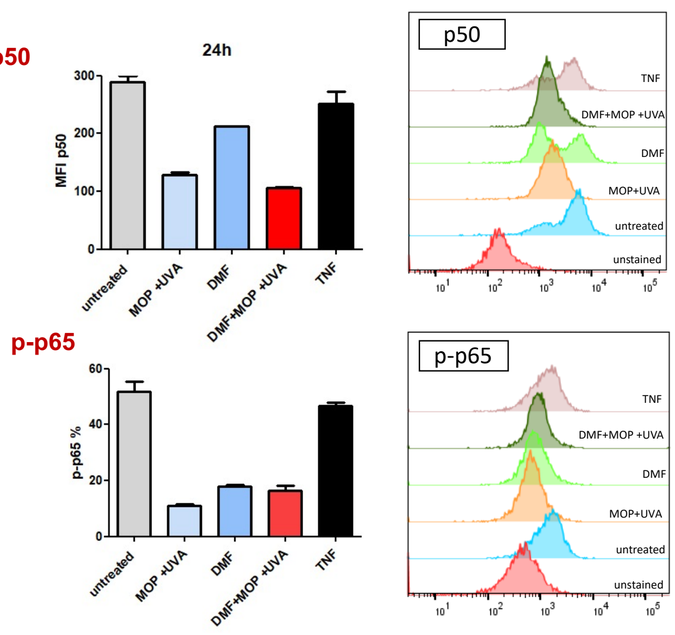


DMF and UVA synergistically induce cell death in CTCL cell lines and primary patient SS cell. A Cell death assay in SeAx, Hut78 and HH cells 3h and 24h after DMF, UVA, or combination treatment. Significance is indicated by the p value scale (n=1) (*p < 0.05; **p < 0.01, one-way Anova) **B** FACS analysis of apoptosis in SS patient-derived cells after 24, 48 or 72 h of indicated treatments.

Restoration of cell death via combination therapy



V. p50 and phosho-p65 activity in CTCL cell lines



Combination treatment reduced the expression of both p50 and phosphorylated p65. HH cells were analyzed for p50 and p-p65 expression using flow cytometry. Cells were treated with 30µM DMF and 2J UVA alone and in combination, as well as with TNFα as a positive control. (n=1). After 24h, combination treatment reduced p50 activity, however, phospho p65 activity was also reduced by UVA monotreatment.

VI. Conclusion

- **CTCL cell lines show unique cell death patterns in response to combination therapy consisting of DMF and UVA irradiation**
- **SS patient cells show different responses to the combination treatment depending on the previous therapies the patients received**
- **Further analysis regarding the effect of the combination therapy on the Thioredoxin-1 induced NFKB inhibition will be conducted**
- **Single cell RNA sequencing analysis in patient samples will unveil the involved pathways**