Name of Principal Investigator(s)
Peter Wolf

Department
Dermatology

Title
Mechanisms of photo(chemo)therapy in cutaneous T cell lymphoma

Background
Phototherapy with UVB and photochemotherapy with psoralen plus UVA (PUVA) photochemotherapy is highly effective in the treatment cutaneous T cell lymphoma (CTCL) such as mycosis fungoides and other lymphoproliferative disorders. In most cases photochemotherapy leads to complete remission in CTCL but after variable times the disease frequently relapses. Although CTCL is generally a slowly progressing disease, it ultimately can spread to lymphoid tissues, peripheral blood, and other organs, leading to death. In a randomized clinical trial and mouse models, we will investigate whether maintenance treatment with PUVA does prolong the disease-free status in CTCL and study its mechanisms of action. CTLC is a disease of CD4+ or CD8+ T cells with expression of the regulatory transcription factor FoxP3 and memory function. PUVA has strong pro-apoptotic and immunomodulating properties, but the exact mechanisms by which PUVA leads to clearance of CTCL are not well understood. We hypothesize that PUVA may act by modulating the inflammatory and immune permissive environment in the skin, thereby suppressing the disease.

Objectives
To investigate in patients and mouse models how photo(chemo)therapy leads to clearance and maintenance of remission of skin alterations in CTCL (compared to psoriasis as a reference disease). A better understanding of the therapeutic mechanisms of photo(chemo)therapy in CTCL should help improve treatment strategies for this life-threatening disease.

Methodology
The PhD candidate will learn how to perform the assays and methods necessary to study the objectives above. She/He will learn how to use mouse models, including a humanized xenotransplantation SCID model to investigate CTCL. Blood and skin samples will be provided by an ongoing clinical study. The techniques include photobiologic methods such as UV light treatment and dosimetry, flow cytometry, PCR, western blot, multiplex ELISA, immunobead technology, apoptosis assays, immunohistochemistry, and immunofluorescence microscopy. The student will also isolate and expand Tregs, and apply T cell transplantation and cellular assays of immune function, and use microRNA profiling and microarray technology.

References

1. Wackernagel, A., Hofer, A., Legat, F., Kerl, H., and Wolf, P. 2006. Efficacy of 8-methoxypsoralen vs. 5-methoxypsoralen plus ultraviolet A therapy in patients with mycosis fungoides. *Br J Dermatol* 154:519-523.
2. Singh, T.P., Schon, M.P., Wallbrecht, K., Michaelis, K., Rinner, B., Mayer, G., Schmidbauer, U., Strohmaier, H., Wang, X.J., and Wolf, P. 2010. 8-methoxypsoralen plus ultraviolet A therapy acts via inhibition of the IL-23/Th17 axis and induction of Foxp3+ regulatory T cells involving CTLA4 signaling in a psoriasis-like skin disorder. *J Immunol* 184:7257-7267.

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