

TITLE: EFFECT OF METFORMIN ON THE HUMAN IMMUNE SYSTEM

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RESEARCH PROJECT DESCRIPTION

The dysregulated distribution and functions of CD4⁺ T cells are major contributors to systemic lupus erythematosus (SLE) pathogenesis, and their targeting represents a focus for therapeutic intervention (1). Cellular metabolism has been identified as a major regulatory mechanism of T cell functions (2). A number of drugs affecting cell metabolism are currently screened for cancer and/or metabolic syndrome diseases. Based on this evidence, we hypothesize that metabolic inhibitors represent promising candidates to repurpose for lupus therapeutics. We have recently published a proof-of-principle of this hypothesis in mouse models of lupus (3). We have shown that a combination of metformin, a glucose-lowering drug, and a glucose inhibitor, eliminated all signs of disease in lupus mice. To translate these findings to the clinic, we need to directly assess the impact of *in vivo* treatments with metabolic inhibitors on human CD4⁺ T cells. To accomplish this, we propose to test the hypothesis that the standard therapeutic treatment with metformin changes the phenotypes and metabolism of human CD4⁺ T cells as compared to the T cells from untreated controls. Specifically, we will compare effector T cell subset distribution, inflammatory cytokine production, cellular metabolism parameters and glucose metabolites in CD4⁺ T cells collected from endocrine patients (type 2 diabetes [T2D], polycystic ovary syndrome [PCOS]) treated with metformin, and matched controls that were not treated with the drug.

The role of the medical student will be:

- 1: To coordinate blood sample collection from the endocrine clinic, including matching treated patients with appropriate untreated controls, as well as record keeping.
2. To participate in the bench work to purify CD4⁺ T cells and analyze their phenotype (flow cytometry, metabolic measurements, gene expression studies).

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References:

1. Crispin JC, Kyttaris VC, Terhorst C, Tsokos GC. T cells as therapeutic targets in SLE. *Nat Rev Rheumatol.* 2010;6(6):317-25.
2. Pearce EL, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. *Immunity.* 2013;38(4):633-43. PubMed PMID: 23601682; PMCID: 3654249.
3. Yin Y, Choi SC, Xu Z, Perry DJ, Seay H, Croker BP, Sobel ES, Brusko TM, Morel L. Normalization of CD4⁺ T cell metabolism reverses lupus. *Sci Transl Med.* 2015;7(274):274ra18. doi: 10.1126/scitranslmed.aaa0835. PubMed PMID: 25673763.

