# Exploring protein glycation for cancer therapy

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Abstract: Protein glycation has emerged as a new post-translation modification (PTM) that changes protein function and serves as a new link between the metabolic state of the cell and its fate. While glycation occurs non-enzymatically, cells evolved enzymatic mechanisms to regulate its abundance. The proposed study builds on our discovery that glucose glycation can block the function of the oncogenic NRF2 transcription factor (Sanghvi, Cell, 2019). Importantly, we identified the enzyme Fructosamine-3-kinase (FN3K) deglycase as required for NRF2 function such that its genetic inactivation selectively impairs NRF2 driven lung and liver cancers. Here we propose to systematically study protein deglycation by FN3K as a potential drug target with expected utility in NRF2 driven lung, liver, and gastro-intestinal (GI) cancers. We have assembled an outstanding team to accomplish these synergistic goals: Yael David (MSKCC) will determine the full scope of FN3K deglycated proteins using a new chemical probe (Maksimovic et al., JACS, 2020) and characterize the functional activity of FN3K. Leemor Joshua-Tor (CSHL) will explore three-dimensional structures of the FN3K enzyme with relevant ligands to gain insight into its unique enzymatic function and aid in developing inhibitors. Hans-Guido Wendel (MSKCC) will perform a pharmacological targeting of FN3K leveraging a collaboration with the Tri-Institutional Therapeutics Discovery Institute, which already identified first-in-class FN3K inhibitors. In summary, we have uncovered a new and surprising role for protein glycation relevant to cancer and metabolic diseases, and we propose a comprehensive study of its key regulator, FN3K, by exploring its structure and function and pursuing its therapeutic targeting.