Optimizing the conditions for GGDPS crystal growth

Andrew Pham[1], Lucas Struble[2], Sarah Holstein[3], Gloria Borgstahl[4]

[1]No affiliation given [2]The Eppley Inst For Cancer Res, [3]Department of Internal Medicine, [4]The Eppley Inst For Cancer Res

andrew.pham@unmc.edu

Several incurable cancers are characterized by abnormal protein production and secretion. This includes excessive monoclonal protein (MP) secretion in multiple myeloma (MM) and excessive glycosylated mucin production in pancreatic ductal adenocarcinoma (PDAC). Aberrant production and secretion of these cancer-related proteins lead to increased disease progression indicated by enhanced metastasis, tumor growth, and drug resistance. As both cancers are incurable and have a high chance of developing drug resistance as the diseases progress, new treatments are highly desirable. Research has shown that inhibition of geranylgeranyl diphosphate synthase (GGDPS) disrupts the function of the intracellular trafficking Rab family of proteins. GGDPS is responsible for synthesizing the 20-carbon isoprenoid group (geranylgeranyl diphosphate or GGDP) that is added to the carboxy terminus of Rab. This addition is essential for Rab's function in intracellular trafficking. Disrupting Rab geranylgeranylation leads to disruption of monoclonal proteins and mucin trafficking resulting in the activation of the unfolded protein response and apoptosis.

Our collaborators have synthesized new potent inhibitors with high specificity for GGDPS. The goal of this study is to obtain the crystal structure of these inhibitors bound to GGDPS to understand the mechanisms behind GGDPS binding and to better rationalize the design of future GGDPS inhibitors. Currently, we have obtained initial GGDPS protein crystals that require further optimization. These crystals were seen a month after the initial screening and exhibited either a needle or a feather-like structure. We are working on growing diffraction quality GGDPS protein crystals for drug development.