Ataxia-telangiectasia (A-T) is a devastating genetic disease caused by loss of the ATM gene. This disease currently lacks effective treatment options and the affected individuals suffer devastating effects, including neurodegeneration, cancer predisposition, insulin resistance, recurring and frequent lung infections, immune system dysfunction, and sterility. Previously, the ATM protein was known to have well-described functions in DNA damage repair signaling; however, our lab has recently uncovered additional and potentially important functions of the ATM protein in regulating mitochondrial function and cellular metabolism. Specifically, we have found that ATM appears to be required for optimal cell metabolism and metabolic stress responses and that cells lacking ATM protein function become profoundly sensitive to particular types of metabolic stress. Importantly, we have also noted that certain cellular treatments are able to mitigate this metabolic stress sensitivity, suggesting the possibility of development of practical treatments to slow down the development of problems in A-T patients.

We have used these observations to design an approach to screen for ways to slow down or prevent the metabolic sensitivities in ATM-null cells. We will screen using both genetic modifications as well as various bioavailable compounds to identify biological pathways of importance in this sensitivity and potential compounds that could modify this metabolic sensitivity. We believe that this project has the capacity to generate novel therapeutic approaches to modify the devastating challenges in A-T.