Griscelli Syndrome Type II (GS) is a genetic disorder where the affected have silvery skin and hair and immunodeficiency.[1,2] The disease has an autosomal recessive inheritance pattern. Type II is the most common form of GS and the immunodeficiency is unique to it as neurological disease is unique to type I.[3] Characteristic of GS are hair follicles with clumps of trapped pigment explaining the partial albinism. Similarly, in melanin producing cells the pigment gets trapped and is never exported. Type II is caused by mutations in the gene *RAB27A*. The protein encoded by this gene is a GTPase and is involved with the export of cellular products to the outside of the cell.[3] Failure to export pigment explains the observed abnormalities in pigment. GS patients have normal lymphocyte counts and yet are unable to fight off infections.[1,2] The thought behind the link between *RAB27A* and immunodeficiency is that when the lymphocytes are unable to export components of the lysosome they are unable to fight off infections.[3] GS patients require bone marrow transplants to extend lifespan beyond a few years. Still unknown are the details of the larger network of proteins that *RAB27A* interacts with to export cellular products and why failure of part of that network leads to specific phenotypes rather than early embryo lethality.

My **objective** is to clarify the specific role of *RAB27A* including how it functions tissue specifically and is distinct from other closely related RAB GTPases. I **hypothesize** that healthy tissues in individuals with *RAB27A* mutations are utilizing other transport proteins to bypass the non-functioning *RAB27A* protein. Mice will be used as a model organism for experiments because the ashen phenotype in mice models is already well characterized, easy to observe, and associated with the mouse copy of *RAB27A*.[5] Cell cultures of melanocytes will also be used because they allow the visualization of exocytosis on the cellular level.[5] The **long term goal** is to uncover mechanisms for successful exocytosis in the absence of functioning *RAB27A*.

Aim Number 1 – Perform mosaic analysis on ashen individuals with CRISPR generated inducible knockouts of other transport proteins. In this method CRISPR will be used to create UV inducible knockouts in other proteins related to *RAB27A* in mice that already lack functioning *RAB27A.* The results will be assessed by observing patches in the mouse that display albinism only after the inducible knockout is turned on. By inducing the mutation only in small patches of tissue and then performing mosaic analysis, lethal mutations can be observed without killing the entire mouse. The goal of this aim is to identify other transport proteins that when lost in combination with *RAB27A* stop exocytosis in cells that were still able to transport pigment when lacking *RAB27A* alone. Genes that fit such a description will offer likely candidates for transport pathways that are being used to bypass a malfunctioning *RAB27A* pathway in healthy tissue.

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