**PROTEOTOXICITY AND CARDIAC DISEASE**

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**Objective:** Many factors can affect protein folding and misfolding, but the cellular pathogenic aspects of protein misfolding and aggregation are collectively termed “proteotoxicity.” Proteotoxicity, the cellular pathology that occurs when a protein misfolds and/or aggregates, can cause heart disease and eventually cardiac failure. We have been studying the proteotoxic processes that take place in the cardiomyocyte, using the disease known as desmin related myopathy, which can be caused by mutations in various chaperone, chaperone-like and chaperone interacting proteins. Specifically, mutations in the small heat shock-like protein alpha B crystallin results in misfolded protein aggregates, leading to cardiac disease and, eventually death in a transgenic mouse model of the human disease. Here we undertake an unbiased, total genome screen for RNA transcripts and their protein products that impact on aggregate accumulations in the cardiomyocytes.

**Method:** Primary mouse cardiomyocytes that accumulate aggregates as a result of a mutant alphaB crystallin causative for human Desmin Related Cardiomyopathy were used for a total genome-wide screen to identify gene products that impacted on aggregate formation. We infected cardiomyocytes using a short hairpin RNA lentivirus library in which the mouse genome was represented.

**Results:**The screen identified multiple candidates in a number of cell signaling pathways that were able to mediate significant decreases in aggregate levels.

**Conclusion:** The screen also identified unexpected candidates that impact aggregation and improve cell viability and function. A candidate, Janus Activating Kinase 1 (JAK1), will be discussed in detail.