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THE PROMISING POTENTIAL OF THE SMALL MOLECULES S-ADENOSYLMETHIONINE AND MG132 IN THE THERAPEUTIC MANAGEMENT OF THE MOST LETHAL RIBOSOMOPATHY, BOWEN-CONRADI SYNDROME

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Background:
Bowen-Conradi Syndrome (BCS) is a rare genetic disease exclusively in the Hutterite population at an incidence of 1/355 live births. BCS individuals display major developmental delays, with pre- and postnatal growth retardation, and an average life expectancy of 13 months. The cause of BCS is a mutation in the ribosome assembly factor/SSU Processome component Emg1, where an aspartic acid is converted to a glycine. Currently there is no treatment for BCS.

Objective:
This research evaluates the small molecules *S*-adenosylmethionine (SAM; the methyl group donor of the Emg1 methyltransferase) and the proteasome inhibitor MG132 as the first potential therapeutic interventions for BCS. It is anticipated that therapeutic concentrations of these small molecules will lead to a reduction in the growth defects associated with BCS.

Methods:
The BCS growth defect under various concentrations of SAM and MG132 was investigated using a yeast model system and biochemical methods, such as dot plates and growth curves (for rescue of the growth defects), westerns (for stabilization of the BCS Emg1), and northern blots (for restoring the pre-rRNA processing pathway).

Results:
A preliminary screen using dot plates indicates an increase in growth for Emg1-BCS cells with increasing amounts of SAM. Growth curves reveal an increase of 61.34% and 10.98% in BCS cell growth for SAM and MG132, respectively. Western blot validation demonstrates a 43.77% increase in protein levels with the use of SAM compared to the control. The results of the northern blot suggest a possible restoration of pre-rRNA processing through the use of SAM. The results for protein expression after treatment with MG132 are inconclusive and require further analysis. Furthermore, northern blot validation following MG132 treatment is needed to determine the mechanism of effect.

Conclusion:
Based on our preliminary results, it is likely that SAM and MG132 are the first promising treatment options for BCS-affected individuals.