Identification and characterization of chaperone compounds for human beta-galactosidase deficiency

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Abstract. G_{M1}-gangliosidosis is an autosomal recessive lysosomal storage disease, caused by deficiency of lysosomal β-galactosidase (β-gal), encoded by the GLB1 gene. To date, more than 160 human GLB1 gene mutations has been identified in patients with this disease, and about 70% of them are missense mutations. Chemical (or pharmacological) chaperone therapy has been developed as a new therapeutic approach for the brain pathology of G_{M1}-gangliosidosis. This therapy employs small molecular compounds analogous to the substrate that can bind to and stabilize the mutant enzyme in affected cells. We have identified two potential chaperone compounds, *N*-octyl-4-epi-β-valienamine (NOEV) and 5*N*,6*S*-(*N'*-butyliminomethylidene)-6-thio-1-deoxygalactonojirimycin (6S-NBI-DGJ), both of which inhibit human β-gal. Both compounds could stabilize human β-gal *in vitro* and up-regulated residual activities of several beta-gal mutants in affected cells. Intriguingly, the profile of chaperone effects of 6S-NBI-DGJ on various mutants was different from that of NOEV, suggesting their effectiveness on different ranges of β-gal mutants. When administrated orally to the model mice, both compounds reached the brain by crossing the blood-brain barrier and attenuated brain pathology. These data indicate that both NOEV and 6S-NBI-DGJ are potential chaperone compounds with therapeutic values for the brain pathology of G_{M1}-gangliosidosis.

Keywords: Metagenomics; 16S; microbiome; microbial diversity; cloud computing; high performance; bio4j; distributed systems.