IDENTIFICATION OF NEW HDAC INHIBITORS FOR THE TREATMENT OF FTD-GRN

Lynch BA[1], Fuller N[1], Herz J[2], Tesla R[2], Nicholson AM[3], Ivarsson M[1]
[1] Rodin Therapeutics, 300 Technology Square, Cambridge MA 02139 USA
[2] Dept. of Molecular Genetics, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX 75390 USA
[3] The Bluefield Project to Cure Frontotemporal Dementia, 637 Carolina St. San Francisco, CA 94107 USA

Abstract

FTD-GRN is a familial form of progressive frontotemporal dementia (FTD), caused by haploinsufficiency in the progranulin gene (*GRN*). FTD-GRN is currently untreatable to any significant degree. Previous work has identified upregulation of expression from the remaining normal *GRN* allele in patients as a potential therapeutic strategy. Histone deacetylase inhibitors (HDACi) have emerged as a compound class with the ability to upregulate progranulin expression; the HDACi SAHA (vorinostat, an approved cancer drug) was first reported as upregulating *GRN* expression in *in vitro* models of FTD-GRN (Cenik *et al*. JBC 2011: 286 16101-16108). SAHA is a broad spectrum HDACi, which inhibits multiple members of the multi-class HDAC family. Non-selective HDACi such as SAHA generally have significant hematological and other toxicities, which is a major impediment to using HDACi as therapy for FTD-GRN treatment. We have been exploring the use of more selective HDACi as potential therapeutics in treating FTD-GRN. Recent reports have identified Class I selective HDACis as having the potential to upregulate progranulin, but not all Class I selective HDACis upregulate progranulin, and most known Class I selective HDACis still exhibit significant toxicity. We report that screening a set of unique Class I HDACis in a modified Neuro-2A reporter cell line identified a subset of the tested compounds that upregulate progranulin. Secondary screening in the human SH-SY5Y line confirmed that some of the positive compounds work in this human line. These novel lead compounds exhibit a much-improved safety profile relative to SAHA and known Class-I HDACis in an *in vitro* colony forming unit assay utilizing human bone marrow cells, and thus have the potential to be developed as therapeutics to treat FTD-GRN.