Small Molecule Screens for Selective Growth Inhibitors in a Yeast Model of Familial Paraganglioma

[1]Irina Bancos, MD, [1]John Paul Bida , Ph.D, [1]Mary Bundrick, Defeng Tian, Ph.D, [2]Derek Hook, Ph.D, [2]Gunda I. Georg, Ph.D, [2]Vadim J. Gurvich, Ph.D., M.B.A, [1]Jim Maher, Ph.D

[1]Mayo Clinic College of Medicine, Rochester, MN;
[2]University of Minnesota, Minneapolis, MN

Objective: To utilize a cell-based assay in a high-throughput screen (HTS) of 200,000 small molecules to identify compounds that are differentially toxic to a yeast model of familial paraganglioma (PGL).

Design and methods: Mutations identified in familial PGL suggest a loss of function of SDH subunits B, C, or D is the common cause of tumorigenesis. The highly conserved nature of the SDH complex allows a yeast model of PGL developed by deleting the sdh2 gene (homolog of human SDHB) to reflect similar biochemical and growth phenotypes as human PGL cells. The yeast model demonstrated increased levels of ROS, succinate accumulation, and a broken TCA cycle.

With this yeast model a high-throughput growth assay was developed to identify small molecules that selectively inhibited the growth of the sdh2Δ strain when compared to the "wild-type" WT strain. The growth assay was utilized by the University of Minnesota Institute for Therapeutics Discovery and Development (ITDD) to screen compounds from the Library of Pharmacologically Active Compounds (LOPAC 1280), and an additional 200,000 randomly synthesized compounds from the ITDD library. The differential effects of the compounds were quantified by fitting the resulting growth curves to a mathematical model and identifying changes in maximum growth rates, saturation, and lag time.

Results: HTS screening identified 162 compounds as being toxic to sdh2Δ mutant strain. Upon retesting differences >20% for maximum saturation, lag time, or maximum growth rate were observed for 6, 2, and 5 compounds respectively.

Conclusions: With no effective cure for the ~20-40% of metastatic PGLs small molecules that selectively inhibit the growth of PGL-like cells will have immediate therapeutic value. We have identified several candidate molecules that show promise in a yeast model of PGL and are actively working toward testing these compounds in human PGL cell lines currently under development in the lab.