

P001 Screening for therapeutic compounds to treat eIF2B-related disorders

Rogério Alves de Almeida and Graham Pavitt

*The University of Manchester - Faculty of Life Sciences.
Manchester, UK.*

eIF2B-related disorders (eRD) are a group of inherited autosomal-recessive brain diseases caused by mutations in eukaryotic initiation factor 2B (eIF2B). Because of the structural and functional homology between human and yeast eIF2B, we previously used yeast to study this disorder and introduced changes equivalent to human eIF2B mutations to subunits of eIF2B.

Our aim is to find a compound that could be used as a therapeutic agent to treat eRD patients. In order to perform a drug screen, we are using two assays. The primary assay monitors yeast *GCN4* expression. In the yeast cells used in our study, *GCN4* was fused with beta-galactosidase. In eIF2B mutated yeast cells the translation of *GCN4* is enhanced compared to the wild type (wt), so any compound that reduces the *GCN4* levels close to the wt is selected for further analysis. The secondary assay monitors cell growth and is aimed to check compounds cytotoxicity.

We also wanted to generate a useful source of purified human eIF2 for eIF2B assays for clinical and research use. At this end, we have expressed human eIF2 subunits in yeast and chromatography purification is planned to have a pure source of human eIF2.