A yeast model for ALS and Distal Myopathy-2 Therapeutics

Published date: March 29, 2019

Technology description

Summary:
A yeast model for high throughput drug and small molecule screening for ALS and Distal Myopathy-2
Background:
Amyotrophic lateral sclerosis (ALS) is a heterogeneous neurodegenerative disease caused by loss of the upper motor neurons, i.e. neurons that extend from the cortex to the brain stem and the spinal cord, and lower motor neurons, i.e. neurons that connect the brainstem or spinal cord to muscle (Hardiman et al. 2017). Progressive loss of these neuron populations precede into two distinct early presentation of ALS symptoms: patients diagnosed with spinal-onset display a significant weakness of the limbs whereas bulbar-onset leads to difficulty swallowing (dysphagia) and difficulty speaking (dysarthria) (Hardiman et al. 2017). As the disease progresses, symptoms converge and death due to respiratory failure usually occurs within 3-5 years. ALS can also be grouped as either sporadic ALS (sALS), i.e. with no family history, which account for ~90% of all ALS cases, or familial ALS (fALS), i.e. with a family history of ALS, which accounts for ~10% of all ALS cases (Chen et al. 2013).
Distal Myopathy -2 (DM-2) is a relatively rare adult onset muscle disease characterized by muscular dystrophy affected mainly muscle in the throat and vocal chords leading to impaired speaking and swallowing (Kraya and Zierz 2013)
Despite considerable research efforts, the molecular mechanisms underpinning the disease remain unknown and there is no cure.
Technology Overview:
Researchers at Western University have developed a novel system allowing for cost-effective high-throughput drug and small molecule screening in yeast. In the current technology, expression of human MATRIN3 gene both WT and various identified ALS-associated and identified mutants in yeast results in formation of a toxic aggregate in the cytosol. This expression of human MATRIN3 (wild-type or mutant) also results in toxic phenotype resulting in slow to no growth for the yeast model. The current invention provides the tools to easily modulate expression of human MATRIN3.
Additionally, researchers have created MATRIN3 constructs that are sequentially deleted for the RNA recognition motifs as well as the Zinc-finger binding domains. These tools allow for toxicity and aggregation to be mapped to specific regions of MATRIN3 that are required for these phenotypes.

In summary, the current invention provides a robust platform for high-throughput cost-effective drug or compound screening and small molecule screening to target human MATRIN3 or mutant variants that have been associated with ALS and DM-2.

Advantages

• MATRIN3 dosage-dependent toxicity in yeast cells allowing for controlled expression in identification of target molecule
• MATRIN3 specificity and relevance to ALS
• Yeast cells in current model undergo oxidative phosphorylation making the model more comparable and similar to neurons (which are affected in ALS and DM-2)
• Current model works with different expression systems (different promoters/plasmids)
• Cost-effective high-throughput screen assays to identify target small molecule or drug to target human MATRIN3 toxic aggregate in yeast cell.
• Yeast system perfectly mimics and complements an ALS and DM-2 disease state neuron

Institution

WORLDiscoveries

联系我们

叶先生

电 话：021-65679356
手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com