Novel dystonia treatment drugs

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Value Proposition

Dystonia is a movement disorder characterized by sustained, often painful involuntary postures, causing motor disabilities and a marked decrease in quality of life. Dystonia is the third most common movement disorder behind Parkinson's and essential tremor, and is a symptom in a broad range of clinical contexts (e.g. neurodegeneration, trauma, medication side effects.) Once symptoms of dystonia appear, they are typically unremitting, and most importantly, therapeutic treatments for dystonia are severely limited. Current drug treatments which include anticholinergics (drugs that block the neurotransmitter acetylcholine) benzodiazapines, dopaminergic agents, and botulinum neurotoxin injections (to prevent constant spasms), only treat symptoms instead of the underlying molecular culprits of dystonia and are poorly tolerated because of side effects.

Technology

- Whole genome sequencing and high throughput si-RNA sequencing on inherited forms of dystonia have identified a stress response pathway causative in dystonia - constitutively active phosphatase (CreP) causes phosphorylation and subsequent instability of the eIF2a protein, which then causes sporadic dystonia.
- Researchers have identified a class of drugs, **HIV aspartyl protease inhibitors, that target specific parts of this pathway**, either by inhibiting the phosphatase, stabilizing the eIF2a protein, or by reducing gene expression of genes involved.
    - These targets were identified in a high-throughput drug screening assay developed for a rare inherited form of dystonia.
    - Inventors verified targets identified in the screen using siRNA knockdowns in human cell lines.
    - Inventors showed eIF2a is relevant to dystonia by showing that the addition of salubrinal (a chemical that inhibits eIF2a phosphatase) *in utero* for a genetic mouse model of dystonia improves perinatal survival.
    - Inventors then showed that HIV aspartyl protease inhibitors, such as ritonavir, liponavir, saquinavir, nelfinavir, and indinavir, could attenuate these target signaling pathways in human cell lines.
    - Inventors further showed that addition of these HIV aspartyl protease inhibitors in cell lines could rescue TorsinA mis-localization (the cellular phenotype of dystonia) in cells.
- HIV aspartyl protease inhibitors, such as ritonavir, liponavir, saquinavir, nelfinavir, and indinavir, are currently marketed clinically approved drugs for HIV positive patients.
- By attempting to address the molecular cause of dystonia, the inventors have thus presented the excited possibility of a direct treatment for dystonia that would have long-term effects.

Other Applications

- Identification of this pathway could lead to other biomarkers for dystonia, leading to rapid diagnoses, improved treatment plans, and reduced healthcare burden.