Lay Summary Myotubular Trust Grant to Dr James Dowling, Hospital for Sick Children, Toronto, Canada.

PI3 Kinase Inhibition as a Novel Treatment Strategy for MTM

Myotubular myopathy (MTM) is one of the most severe neurologic disorders of childhood. It is characterized by significant lifelong morbidity (including ventilator and wheelchair dependence), and early mortality. Currently, no treatments or disease modifying therapies exist for MTM. Much current research effort is focused on developing gene therapy for MTM. However, while gene therapy may represent the ultimate treatment for MTM, complementary and/or alternative therapeutic strategies have the potential for significantly improving quality and length of life for all MTM patients. The goal of our research program is to identify and develop small molecule based complementary therapies for this devastating disorder.

MTM is caused by mutations in the MTM1 gene. MTM1 (or myotubularin) is an enzyme responsible for removing phosphates from lipids called phosphoinositides. We have shown that loss of MTM1 results in the accumulation of a specific phosphoinositide called PI(3)P. Based on this, we hypothesize that (a) this accumulation of PI(3)P is responsible for many of the problems that affect the muscle in myotubular myopathy and (b) reducing (or "rebalancing") levels of PI(3)P may reverse or prevent these problems and thus result in clinical benefit. We tested these hypotheses using a genetic strategy, where we genetically inactivated in the mouse an enzyme that can make PI(3)P (a PI3 kinase). Inactivating this PI3 kinase in the mouse model of MTM resulted in mice that are completely healthy AND have no problems with their muscles. This exciting result suggests the possibility that inhibiting PI3 kinase in patients may be meaningful treatment strategy.

Currently, no drugs are known that specifically inhibit the specific PI3 kinase we have been studying. The goal of this proposal, therefore, is to develop a drug that can inhibit the PI3 kinase AND improve the disease process in animal models of MTM. We are using a unique "cross platform" approach for developing this new drug. It includes targeted and large scale screening of chemical "libraries" (collections of drugs with different properties) applied to three models of MTM- the nematode (great for very high throughput screening), the zebrafish (great for testing several compounds in a system with muscle that acts like human muscle), patient skin cells, and the mouse model of MTM. The expected outcome of these inter-connected screens is the development of new PI3 kinase inhibitor suitable as a potential therapy for MTM.

In conclusion, we have identified a novel potential treatment strategy (rebalancing PI(3)P levels) and will, using the support of the Myotubular Trust, develop a new potential drug based on this strategy. Successful completion of our proposal will identify a unique possible treatment option that may serve as an excellent complement therapy for MTM to gene and protein therapy.

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