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Research summary

Previous AAV vectors encoding Hexosaminidase (Hex) showed toxicity in monkeys without showing toxicity in other animal models. Our hypothesis is that exceptionally high expression levels were the direct cause of the unexpected toxicity. Therefore our goal was to find an optimal design that would be both non-toxic and effective.

Multiple new vectors were constructed and tested in mice. Three new vector designs based on safety parameters and level of enzyme overexpression were selected to test in monkeys.

The behavior of all six AAV-injected monkeys remained normal throughout the 90-day study. Brain MRIs were carried out monthly. Detailed analysis of brain tissue revealed that group 1 monkeys expressed the highest enzyme activity at the injection site (87-fold above normal). In addition these animals had some evidence of toxicity, and in one injection site it resembled in the original observations with significant loss of neurons. The brain of monkeys in groups 2 and 3 displayed only minimal to mild changes and total Hex activity was 9 times normal. The neuropathology findings in all groups agree with brain MRIs data as an abnormal signal in one injection site corresponded to a region with significant loss of neurons.

The formulation tested in group 1 was compared to the original AAV vector for its ability to reduce GM2 ganglioside content in the brain of Sandhoff (GM2) mice. We showed that the two formulations are equally potent in reducing GM2 content in brain. However because of the considerable neuropathology documented at one injection site with formulation 1, we decided to test the efficacy of a second vector design (tested in group 2 monkeys) in reducing GM2 content in the brain of GM2 mice. The brain of these AAV-injected GM2 mice is being analyzed currently.

The outcome of the biochemical efficacy experiment in SD mice will determine the last stage of the studies in monkeys, which will include toxicity and analysis of vector distribution in different organs. The final design of this study in monkeys will be discussed with the FDA to ensure its suitability before proceeding with the final phase of vector selection.

This update will be posted on the Cure Tay-Sachs website under Quarterly Updates. You can also learn more about the TSGT at www.tsgtconsortium.com. If you have any questions or comments about this update I can be reached at ken.bihn@curetay-sachs.org or you can call the foundation offices at (216) 812-5855

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