CTSF
Cure Tay-Sachs Foundation

12730 Triskett Road
Cleveland, Ohio 44111
(216) 812 - 5855
Fax (216) 251-6728
ken.bihn@curetay-sachs.org

Research Update – September 2013

We have been on a roller coaster ride with the Tay-Sachs Gene Therapy Consortium (TSGT) and our gene therapy research. While I live it on a daily basis, most of you don't have access to all the research developments and I have been lax with my research updates – let me fix that now. I am going to give you a layman's update about what has happened and what our plan is going forward.

WHAT HAPPENED:

When I last did a formal update our hope was to start clinical trials in March 2013 – that did not happen. The gene therapy project was going great – it worked in small animal models, it worked in large animal models, and it worked in Tay-Sachs sheep. We had the viral vectors in production and the Toxicity Study was underway at Univ. of FL and going great. As a final safeguard the research team wanted to test new state of the art equipment for pinpointing brain injections – so we did some vector injections into monkey brains. The new equipment worked great and everything looked fabulous – until the monkeys started to show neurological impairment. They were having a negative reaction to the vectors. This was completely unexpected. The best theory was that the vector dose was too high and the brain could not handle it. We tried 1/30th of the original dose – but yet again the animals showed neurological impairment, although at a much later time after injection. The gene therapy field has always believed that there is no toxicity associated with making large amounts of lysosomal enzymes. Our notion has always been that the more Hex A we could generate the more effective our treatment would be. Maybe that is not true? Maybe the vectors are flawed? Maybe the enzymes (Hex A and Hex B) are special in that cells in the brain can't tolerate making too much of these enzymes? Maybe it is a problem specific to primate brains? Our thinking after these experiments is that there is a limit to how much we can ask neurons to make of normal Hex A and Hex B, and unfortunately we seem to have crossed that unknown limit. With all the questions – we cannot put these vectors into a human brain until we have answers. The clinical trials were put on hold and another research plan was created. It is frustrating and disappointing – but far better than losing a child in the trial.

THE NEW PLAN:

We could not look for answers by injecting more primates – we needed to replicate our results in a more readily available model. The TSGT came up with a well thought out four step research plan. Step one was to replicate the results we saw in the monkeys in Nude Mice. These are a special type of research mice with a defective immune system. Step 2 was to develop multiple vectors variations

CTSF
Cure Tay-Sachs Foundation

12730 Triskett Road
Cleveland, Ohio 44111
(216) 812 - 5855
Fax (216) 251-6728
ken.bihn@curetay-sachs.org

to test on the Nude Mice - see if a combination can be found that does not create the negative reaction. We never saw this reaction in our other animal studies – why now? Step three will take what we learn from the Nude Mice and the various vector combinations and use the safest ones in primates. We have to be able to explain why we got the reaction we got in primate testing and why we believe the new vectors will be safe. Basically we are testing the vector we would use in the kids. Step three is a short term test – to be sure we fixed the problem we had seen the first two times we injected monkeys. And finally Step four will be to study the successfully injected monkeys for a longer time period (180 days) – to make sure no other unknown variables present. The entire study is budgeted to cost $545,000 and is scheduled to be completed by end of 2014. The CTSF and the NTSAD have agreed to co-fund the study with a 50/50 split. One unique feature of this plan is we don't move forward if we cannot complete a step. That limits our financial commitment should the team be unable to find a safe, useable vector. But we have every confidence we'll find a vector and move this research to clinical trials.

WHERE ARE WE NOW?

The research team was able to replicate the reaction we got in the monkeys using Nude Mice. Next the research team has created over 20 different vector combinations and hopes to settle on 14 variations to test – looking for the safest, most effective vector to validate on monkeys and ultimately select one version to use on our Tay-Sachs kids. The team is paring to 14 now and testing. The CTSF has grant funding agreement in place with UMass and the New England Primate Research Center. All the pieces are in place – now we need to find the vector that works!!

OTHER RESEARCH NEWS

The UK wing on the TSGT got some very exciting news recently. The UK's equivalent of our NIH has agreed to fund two years of the TSGT's research at the University of Cambridge under the direction of our favorite researcher from across the pond – Professor Tim Cox. Additionally the funding will be extended to cover the clinical trials over in England if the research produces safe and effective vectors. They have the same challenges we have here in the states – expect they have the needed funding in place. It is a wonderful accomplishment for Prof. Cox, his brilliant team and the CATS Foundation that has been raising funds to support the TSGT work. Even the CTSF was lending financial support to Prof. Cox back in 2007 and 2008. This is a nice win for all of us.

There is a research group in Italy doing work with a combination of bone marrow stem cells and gene therapy. The study is working with kids with metachromatic leukodystrophy. Babies born with

CTSF
Cure Tay-Sachs Foundation

12730 Triskett Road
Cleveland, Ohio 44111
(216) 812 - 5855
Fax (216) 251-6728
ken.bihn@curetay-sachs.org

metachromatic leukodystrophy appear healthy, but their development starts to reverse between the ages of one and two as part of their brain is destroyed. Sound like any disease we know of? Bone marrow stem cells are taken from the patient then the viral vectors carrying the normal gene for the missing enzyme are used to 'infect' the cells and make them produce large amounts of the normal enzyme. These are then put back into the patient and some of the cells migrate into the brain where they supply all other cells with normal enzyme. The best part is this is done through IV – not brain injections. The downside is they are working with kids before they show symptoms, or very early symptoms – how often do we catch a Tay-Sachs kid before they show symptoms? But the research is showing promise in a neurological disease and that interests us. Additionally our friends at UC Davis have some experience with this type of research and they are interested in doing a Tay-Sachs project. Our gene therapy experts have looked at it and think it worth exploring. UC Davis is working up a budget and timeline – best guess is at least $350,000 with a timeline into late 2014. I expect some numbers in the next week or two – then we can decide what makes sense. The more viable treatment options we have the better our chances of true success. That is why we keep on raising money!!

It is not beyond the realm of possibilities that we could have three clinical trials underway by 2015 – our US branch of the TSGT, our UK branch of the TSGT and this new possibility of bone marrow stem cells and gene therapy. We won't know if any of them actually work unless we try. In the research world tries cost money – so we'll work on fund raising while the genius researchers do the testing.

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

Kenneth Bihn
President
Cure Tay-Sachs Foundation