This Q & A article is from BDSRA’s “Ask An Expert” Facebook Chat in the BDSRA Closed Facebook group for parents and caregivers.

\*Please note: the information contained in this material is intended to provide basic information to Batten families and caregivers. It is not intended to be, nor is it, medical advice for individual children. Parents and caregivers should consult the patient’s physician prior to changing medication, medical treatment or daily activities.

“Gene Therapy Basics”

Featured Expert:

Steven Gray, Ph.D., Assistant Professor

University of North Carolina at Chapel Hill

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Q. What is gene therapy?

A. Gene therapy is a treatment approach where we try to treat a genetic disease by physically putting the missing gene back into cells within a patient's body. The way everyone is doing this will Batten disease, is we engineer a virus to do this. These are viruses that don't replicate. Rather, they are basically a shell carrying the missing gene into cells in the body, kind of like a molecular delivery truck. Viruses do this really well, so we hijack them to work for us. Since we are delivering the DNA itself, we are correcting things on a genetic level. This makes it a fairly permanent fix after one injection. With Gene Therapy, you aren't delivering the gene to every cell in the body. You are only delivering the gene to the cells that the virus goes to. We try to target the virus to what we can and what we think is most important, but that can still leave gaps. Thus, in the future we need to fill those gaps with another treatment or make our gene therapy technology better

Q. I'm interested to see if you think we could use different approaches on the same child. For example, ERT (Enzyme Replacement Therapy) with CLN2 kids and also gene therapy for possible treatment of the eye with them.

A. Yes, that should be possible

Q. Would it be possible to do this with all forms of Batten disease?

A. Some forms of Batten (CLN1, CLN2, CLN5, for example) have something called "cross correction". This means if we get the gene to one cell, it will sort of act like a factory to make the missing protein and spread it to other neighboring cells. These are the ones you can treat with ERT. This also makes them the "easiest" to treat with gene therapy

Q. What would happen if the virus was able to replicate? It might be able to go to more cells that way, but what is the downside?

A. We empty the virus of all its genes (which it needs to replicate). This makes room for us to package the therapeutic genes. Also, if the virus can replicate then usually the viral genes that enable that cause damage to cells. Further, it is a safety concern for the general population if it gets out of control

Q. Is there any possibility of negative outcome of gene therapy? Could it possibly make anything worse?

A. If we express too much of the gene, it can sometimes be toxic. Also, there can be immune responses that could cause damage. For other diseases (not Batten), we've given mice high doses where the overexpression of the gene killed the mice.

Q. Will it be able to reverse damage and will it also work with a typical forms of batten

A. Gene therapy can't replace stuff that is gone. At best, it can probably halt disease progression. If all the neurons are gone you can't survive. If an MRI shows clear shrinkage of the brain, that's pretty solid evidence that parts of the brain are dying off.

Q. What is the time frame from clinical trial to approval to treat all affected?

A. That's really hard to answer. We're in new territory with accelerated review of high impact therapies for rare diseases, but there are still a lot of unknowns.

Q. Dr. Gray could you comment on the risks associated to rejection of AAV9 upon delivery. I was told it was low, but would appreciate your opinion as well.

A. About 1/3 of people carry antibodies against AAV9. If you injected AAV9 intravenously in someone like that it would be completely blocked and wouldn't do anything (good or bad). Our approach has been to inject the AAV9 into the spinal fluid, where it avoids these antibodies. A bigger concern is that if your child doesn't express the gene at all, if you put the normal copy back in there is a chance their immune system would see it as "foreign" and reject it. This could make them worse

Q. Do a lot of people develop antibodies to AAV9 after a dose of gene therapy?

A. Great question which makes an important point. Once you have received the treatment once, you are effectively immunized and therefore can't get a second dose. This makes it really important for us to try and get it right the first time.

Q. Is the patient immune only to that specific vector? I understood that the vectors were continually being improved/modified.

A. Yes, the patient will be immune to just that virus. If you use a different virus shell, it could allow redosing. This is an active area of research for my lab, but that still requires you to go through the full drug approval process twice (since they would be 2 different "drugs")

Q. How long did it take you to do the mouse studies in CLN1?

A. About 3 years until we felt like we had a good treatment that we wanted to move into humans

Q. So it will or will not include atypical batten children

A. If you are sure of the gene that is disrupted, then even if it isn't a "typical" mutation then putting the fully correct form of the gene back should be therapeutic.  If the mutation is less severe and the disease progression is slower, for example, then putting the fully correct form of the gene back should work. It could even work better than in a typical patient.

Q. If the gene therapy is given in the spinal fluid and only goes to the brain cells, then would you expect to see progression of Batten disease in other organs, such as the heart? And would the virus get to retinal cells, or would the disease progress there, too?

A. For AAV9 at least, when we inject it in the spinal fluid about half gets out to peripheral organs. If you inject IV, about 99% goes to peripheral organs. There can still be gaps and things we aren't targeting well enough, inside or outside the nervous system. That's why I don't like to call gene therapy a cure. It is a treatment, and we're waiting to see how effective it will be. I should say that for forms like CLN3 where there isn't cross-correction, you will not be hitting all the cells in the brain. Maybe you'll hit 20% or so. I'm saying this so everyone understands it is a treatment (and possibly a very good one!) but it isn't perfect. Be realistic that this will be a treatment, and probably not a cure.

Q. What is the next step if gene therapy stops progression? Intensive rehab to try to regain lost skills?

A. My opinion is that PT will be extremely important after a treatment like this to maximize the benefits, but no one really knows for sure what this will look like. It's still an experiment... mice will only tell us so much. For INCL though, the hard news is that the treatment isn't working as well after symptoms have started. Too much damage is done at that point already. To see the really good benefits we have to dose pretty early. This could be different for all the NCLs though. INCL is the most severe

Q. Dr. Gray thank you for all of your work. Our daughter has progressed too far for this to be of use to her but is there anything we can do as parents of a CLN1 baby to help you with your progression?

A. I'm really sorry to hear this and it is inspiring that you are still actively working to help other families. Start advocating for newborn screening for CLN1. The sooner this happens it will save more CLN1 babies than anything else.

Q. In the broader Gene Therapy medical community, can you point to other treatments of other diseases where there was significant benefit? I'm curious how advanced the work being for NCL Gene Therapy is versus other disease types. Or is it all still too early to tell?

A. There is really amazing results for hemophilia, and also some eye diseases such as Leber's Congenital Amaurosis. For nervous system diseases, the trial for Spinal Muscular Atrophy is looking very good from what I've seen. CLN3 and CLN1 are at the front of the pack of the gene therapy community, so to speak. CLN2 was one of the very first brain-directed trials, but the technology wasn't really advanced then as well as it is now.

Q. Hi! thank you for doing this! I know you mentioned about pushing for newborn screenings, but if Batten is diagnosed and early on, with little symptoms showing, would there still be the possibility of receiving the gene therapy? Or does the effectiveness of when the treatment is given play more of a factor?

A. That makes total sense and it is something we are wrestling with. It depends on a lot of this, like how proven and safe the treatment actually is. For a while at least, it might be a situation where you are just hypervigilent about watching for early signs and then give the treatment when they start showing up.

Q. Even though your research has shown most benefit when applied early in the disease development, wouldn't it be courageous to attempt treatment on an advanced sufferer? Although expectations of benefit would not be expected to be major, the possibility of some relief from the rapidly progressing disease might deserve a test? Perhaps a child at an advanced stage of the disease could have some improvement to the quality of their short life?

A. This is a difficult question that the clinical team will be considering very carefully as we move closer to getting a trial started. There will also be guidance from external regulatory agencies and review boards that may dictate what types of patients can or can’t be in the trial. I’m going to write a few things that apply to this, and please don’t take them as being insensitive. At the start of the trial, it is a very delicate time. On one hand, we would like to give everyone a chance however small it might be. On the other hand, if something bad happens at the start then this can halt the entire trial and make it inaccessible to everyone. To be blunt, this is the danger of enrolling a child that is already very sick. They could have complications or even die from the natural course of the disease, but it would be impossible for the trial investigators to say whether it was the disease or if it was something bad the treatment was doing. Going forward, what will be in the best interest of the whole INCL community is that this treatment gets made available to everyone as quickly as possible. The way that will happen is if it gets tested carefully within a clinical trial: If it is safe and if it looks good then this will lead to full FDA approval as fast as possible. Once (if) a trial starts, the clinical team would only be able to enroll one child at a time and ultimately this order will be decided by them.

Q. Thank you for all your all doing is how I want to start this. I truly mean that. Our team has been pounding the streets for kids suffering from battens and raised quite a bit of funds in the past 6 months unfortunately it's NOT the 2 million dollars required for the treatments like this for these kids and we all know time is against us with this disease. When is it gonna be affordable for a family to Provide for their child? We don't have high profile contacts nor do we even know the first thing thing about fundraising. But I know this, last year I meet families like mine. Families who you can see want a cure or a shred of hope. It's why we've started doing it. We as a community have to change this. My son hasn't had a seizure in a year and a half and I thank god every day for that. I'm going nuts looking at our goal and seeing our actual balance. This disease is cruel and brings out the worst and best in some people. But 2 million dollars??? I'd give my life to help him.

A. This is one of the things that is most difficult for me also on the research side. It absolutely is NOT fair for families to have to advocate and fundraise and fight with insurance, all while you’re trying to take care of a very sick child. It also wasn’t fair for your child to be born with this in the first place. I have 3 kids and I don’t know what I would do… I don’t know if I could handle it. For that I have so much admiration for the families that find a way to fight and fundraise and still show love for their children in the most amazing ways. I agree that we’re talking about insurmountable amounts of money, but it has to come from somewhere. The government is getting better about this, but it is still very slow and there are 7,000 rare diseases all trying to access the same small pot of funds. As a researcher, I don’t like using foundation dollars but if I didn’t then the research wouldn’t move nearly as fast (or at all). Our work for INCL was basically done on shoestring (which amounts to a few hundred thousand dollars). The truth is, when you are trying to create something that has never been done before and all of it is cutting edge technology, things are expensive. The most expensive stuff comes when you are trying to do final safety studies, and when you are making the “drug” for the first time to go into kids. These are things that have to be done right, they require lots of oversight and documentation. That is where most of the cost comes from. I should be absolutely clear that these are research costs, not treatment costs. In a clinical trial, patients should be able to participate without paying for any direct hospital or drug costs.