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Interview with Dr. Florian Eichler

Florian Eichler, MD

Editor's note: Florian Eichler, MD, is the director of the Leukodystrophy Service at Massachusetts General Hospital and an associate professor of neurology at Harvard Medical School. This interview has been lightly edited for clarity and length.

Human Gene Therapy: **Could you tell me about your career path and how you came to be interested in gene therapy?**

Dr. Florian Eichler: I am a neurologist by training, I was at Johns Hopkins with Hugo Moser, who is a giant in the field of metabolism and leukodystrophies. At the time, gene therapy was in its infancy and disorders that we worked on were treated with either enzyme replacement or substrate reduction therapy, not through gene therapy. When I came to Harvard and did my training here, it was obvious that we were about to turn the page and enter a new era, which was particularly exciting in neurology. We are often very smart about diagnostics, but often without appropriate treatments to help our patients. So I was really eager to learn about how I could do something that would help move the field forward and help patients.

I owe my mentor at Johns Hopkins a great deal for his ability to see the patient perspective and plight as central to everything. For him, it was not about advancing a specific approach or certain type of treatment, he used to tell me: if something works, keep doing it; if it does not, try something new. That was what guided me into gene therapy. We knew that bone marrow transplantation to treat adrenoleukodystrophy worked if applied in the early stages of the brain disease. It did not work if it was applied too late when the disease was too advanced and the patient had suffered more effects.

We also knew that even if it was applied early, there were engraftment problems, graft versus host disease. That could be overcome by rather than using cells from a donor, using cells from the patient themselves. That became the nidus of our *ex vivo* gene therapy.

I was very lucky to build here on the work of Patrick Aubourg and Natalie Cartier in France, who treated the first two boys, and then we

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launched a large trial in the United States together with Christine Duncan and David Williams.[1] My role is really in making sure that those neurological disease parameters and the disease biology were appropriately imbedded into the gene therapy setting, recognizing that even the best treatment will not work if you get the window of intervention wrong. That led to the first Food and Drug Administration-approved treatment for childhood adrenoleukodystrophy in September of this year.

A few years ago, we observed that although there was this brain disease that can be treated by *ex vivo* gene therapy, most patients who reached adulthood had a debilitating spinal cord disease that was very different in nature called adrenomyeloneuropathy. This spinal cord disease is much better treated with an adeno-associated virus 9 (AAV9) approach delivered intrathecally. I was watching what was happening in the spinal muscular atrophy (SMA) field and we took a similar approach to deliver the corrected gene using an AAV9 vector into the spinal fluid, which resulted in a few publications,[2–4] and we are now about to launch a trial in humans early in 2023.

Human Gene Therapy: **You were able to adapt an approach from the SMA field to use in treating patients with leukodystrophies, do you think that can be a more widely used strategy or will most therapies need to be specifically tailored to the disease and require unique approaches?**

Dr. Eichler: I think that there is a lot of passing of the baton between different trials and therapeutic approaches, but we have to be well aware that there will be different contexts in another disease. What is optimal for one disease setting will not be so for another disease setting. Which is not to say that you should not be borrowing and stealing as you go along because it helps you accelerate progress. Having gained over decades so much knowledge about single gene-causing diseases in neurology, we are now at the point when we can act on it. That is tremendous, using that knowledge about a gene to transform a life is our aspiration, but the devil is in the details. What cells are affected by the disease? What is the target? What is the disease stage? What is early enough to treat and when is too late?

Can you intervene in a way that distributes enough corrected gene copies to the compartment so that the organ function recovers? The platforms of gene therapy have to be wed with the disease biology. The trials that do that well are those that are usually successful. If your platform is poor, inefficient, or toxic, or if your disease biology is not well understood, then you run into huge obstacles. However, if you can bring together the right gene therapy platform and understanding of the disease, you can find a sweet spot and really turn things on.

Human Gene Therapy: **Do you think that all of the tools are in place to move into the clinic or do new and better tools need to be developed, such as better vectors, more precise regulation of expression of the delivered gene, improved targeting of the correct cells, or screening and diagnosing patients early enough?**

Dr. Eichler: We have most of the tools that we need to get into the clinic. Is it going to be perfect when we start? No, we will need to be prepared to optimize over time, but the value of doing things in the clinic in the human species cannot be overestimated. There is only so much that you can learn from animal studies. Ultimately, the real experience comes from the human encounter. I would say that the largest deficiencies that we are still facing are understanding the acute versus chronic immune responses and possible long-term mutagenesis questions. These are things that we do not understand well enough and even the best predictive models are still not revealing these answers.

We have enough to get into the clinic and go into humans in the clinic, but we have to proceed with caution. It has to be done in a circumspect way where we recognize whether the risk/benefit is appropriate at every stage and cautiously extrapolate with each patient what the next step should be. I think that the principle that single genes cause devastating disorders is true, but the reverse is true as well: fixing one gene can cure these disorders.

We are learning now to what extent can one size fit all. And can we learn from each other to adapt and accommodate as we move into different disease realms, which I think will happen. It is extremely exciting in the field and I think that the next generation is going to look at biology in a completely different way to help transform lives. We already see that clinicians today look at SMA patients completely differently than past generations have. My pathology chair recently commented that we have not had many autopsies on leukodystrophy patients reported recently and I said that is because we have new treatments.

We are identifying patients early with newborn screening and treating them at appropriate stages, so they are not coming to autopsy. When I started, patients were arriving in wheelchairs at death's door. That was 15 years ago, and in that time, we have seen a complete turnaround. My patients are reporting back from summer camps and soccer fields, it is a real blessing.

Human Gene Therapy: **You mentioned that you are starting a new clinical trial soon. Is that what you are most excited about at the moment**

or is there anything else that you are most excited or optimistic about.

Dr. Eichler: There are several things that I am really excited about. I usually get excited about a new project that I have not started yet, so that is among them. Right now, we are undertaking a very exciting *in vivo* AAV gene therapy trial for Canavan disease trial based on Guangping Gao's work. The learning has been tremendous, I feel like we are revisiting biology that has not been looked at in 50 years. We are starting to re-examine how myelin develops in children and learning what happens when you put the gene back in, so it is exciting to see that growth.

In addition to the systemic administration of AAV9-mediated gene therapy for Canavan disease, we are planning clinical trials on how to reactivate inactivated X chromosomes in symptomatic heterozygous females with adrenoleukodystrophy. We are also thinking about regulatory aspects of gene editing and how to dose genes correctly with new gene editing tools. It is nice to see the life and learning cycles as they occur.

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