

# STAR Webinar - December 2019



THE DRIVING FORCE BEHIND CMT RESEARCH



CMTA Board Chairman Gilles Bouchard will begin by giving an overview of STAR, followed by an in-depth review of our gene therapy program by Drs. John Svaren and Kleopas Kleopa, members of our Scientific Advisory Board. These world-renowned researchers will explain what gene therapy is, how it can be used to advance treatments for CMT, and cover the latest advances from the STAR program. This webinar will also explain how we are preparing for clinical trials for many types of CMT.



## Our Mission



We are driven to  
accelerate  
treatments for CMT

We are powered by  
the CMT community



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STAR stands for "Strategy to Accelerate Research," and it's really core to the CMTA's mission: our role is to accelerate treatments for CMT. In this work, we are driven by you and powered by you, the CMT community. **You provide more than 80 percent of our resources, so, in essence, STAR is really your program. STAR is for you, and by you.**



## The Challenge & The Opportunity

### Drug development takes a lot of time, money, and is very risky

Study of 106 drugs over last 18 years:

- 10.6 years in average. 8 years from clinic to approval
- 90% fail before approval
- Costs in the hundreds of millions

### No treatments for CMT today, but significant opportunities

- Well defined genetic causes make it possible to:
  1. Develop ways to test potential CMT treatments using assays, CMT stem cells, and CMT animal models
  2. Take advantage of advances in genetic therapies
- Biomarkers can make clinical trials shorter and more affordable
- Classified a rare disease (< 200k in USA) , yet a significant number of patients



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When we started STAR over 10 years ago, we really wanted to take a business approach. We wanted to bring the rigor, the focus, the accountability that you have in a business.

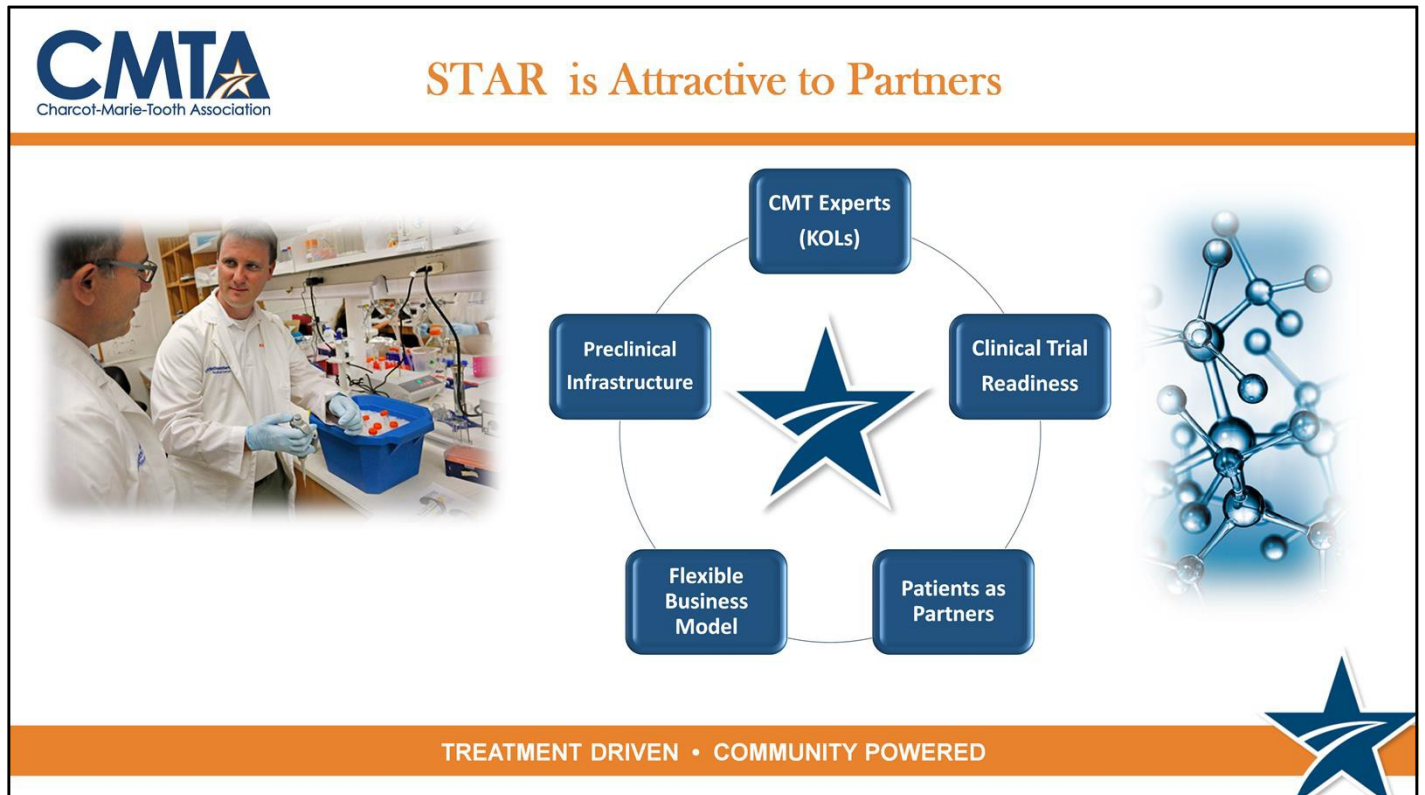
When you run a business, the first thing you do is try to figure out your strengths and your weaknesses, and the best strategy to be successful.

Taking drugs to market is a tough business, and **it takes well over 10 years on average to develop a drug**. Most new drugs fail in clinical trials. And it costs hundreds of millions of dollars. So how do we make this attractive to partners? How do we accelerate research?

- One of the most attractive things about CMT is that for most types we have very well-defined genetic causes. CMT is what the scientists call a monogenic disease, which means we can replicate and test this disease in the laboratory.
- There are also a lot of new therapies and technologies to address genetic issues. And those play right into what CMT is as a disease.
- Biotech companies once looked at CMT as a slowly evolving disease, which would therefore require very long and very expensive clinical trials. If anything, this has been the biggest inhibitor for pharmaceutical companies to get involved in developing drugs for CMT. So more than 10 years ago, in partnership with the Inherited Neuropathies Consortium (INC), we embarked on a major effort to develop what are called biomarkers, and also to develop an important clinical infrastructure so it would become much easier, faster and cheaper to run clinical trials on CMT. We have made

tremendous progress there. And this barrier is really starting to crumble.

- Finally, from a business point of view you may think being a rare disease is a disadvantage, but because of the laws in the US and in Europe, it is actually attractive for companies to work on rare diseases. There are some advantages for businesses on the tax side and the protection of intellectual property.




So, if attracting partners is the core of our strategy, how do we make CMT attractive to partners? We need them because even though we've raised a lot of money from this community, we don't have the billions of dollars it takes to develop drugs. In working with partners, we found that there are five key things they look for.

1. The first one is what they call KOLs or experts. In general, companies are experts in drug development, but they don't know CMT very well. So they want to engage with CMT experts. That's why we built our incredibly strong Scientific Advisory Board with over 30 great scientists.
2. The next thing they want is the ability to test in the lab, what we call preclinical tests. This is how drugs are developed, and we spent a lot of effort building a very broad, very powerful preclinical testing infrastructure. When they contact us and see what we've developed thanks to your support, they tell us that they feel like kids in a toy store!
3. The third one is clinical trial readiness. This was a major inhibitor for CMT research and for companies. But again, we've made tremendous progress, and we feel that we can run much shorter clinical trials.
4. That's great on the medical side, but companies also want a strong, reliable and trustworthy business partner. What we found is not all companies are the same; they want different things. So we have to be flexible and adapt how we work with them on the business side based on what they need. Some companies, for example, are early stage companies that need money so we do co-funding with them. But others are


loaded with money and they are looking more at licensing or buying technologies that we've developed with our partners. Other companies are looking at raising money, so we help them and engage with their potential investors. We have a lot of people with business experience on our board, and we really try to leverage this to help companies be successful on the business side as well.

5. Last but not least, what's really interesting is that companies are very interested in engaging the CMT community, especially as they get closer to the clinical treatment of patients, because ultimately the CMT community is their market. So they want to know the impact the disease has on the patient community. Moreover, engaging patients is becoming very important as part of the approval process of drugs. In Europe right now you have to partner with a patient advocacy group to get a drug approved. And in the US the FDA is doing more and more of the same thing. So the fact that we can reach tens of thousands of CMT patients and that we have this really vibrant CMT community is a great asset for us and really attractive to our partners.




## STAR is Working

### Our Vision: A World Without CMT



- 30+ Expert Advisors
- 50 Active Projects - \$15M Invested in CMT Research
- Research Tools for CMT Types 1, 2, 4 & X
- 25 Industry Partners - 22 Joint Preclinical Studies in 2019
- 70 Branches – 35 Centers of Excellence

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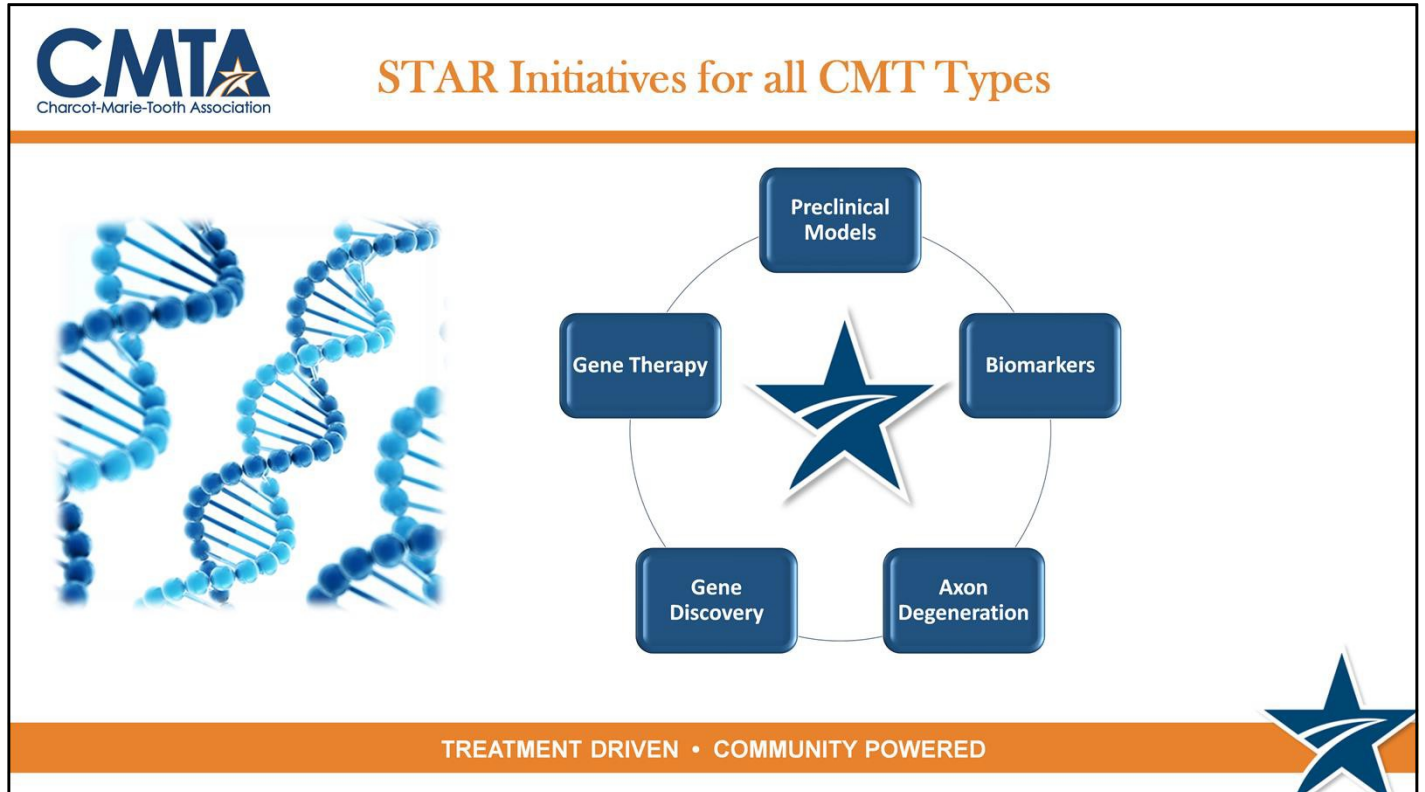
Now may ask, how is this working? We just put a few numbers together, and thanks to your support, we've made tremendous progress. We also realize that we have a lot of work left to do, but we feel like we're in a really strong position right now.

- We have a wonderful Scientific Advisory Board.
- We have about 50 active projects, by the end of the year, we'll have invested \$15 million in CMT research.
- We have developed really helpful testing tools for all major types of CMTs that our companies are using.
- As a result, we now have 25 industry partners. That's a really important metric—the one thing that makes us the most hopeful about the future. A few years ago we just had a handful of partners and it was hard to bring them in. Now people approach us all the time because they want to work on CMT with us. They want to use our tools and



infrastructure. And you can look at these numbers, these 22 joint preclinical studies. Those are 22 actual studies that people are running this year using our infrastructure. Now, last year, this was only a handful. So in business terms I think we are seeing a bit of an inflection point: you invest and you work hard for a few years, and all of a sudden your business starts taking off. That's what we're seeing right now in CMT research. A lot of things are starting to accelerate!

- And then we have this really wonderful, vibrant community—all the CMTA branches around the country and the CMTA Centers of Excellence. This has created a very powerful and helpful infrastructure, not just for us as a community, but also for our partners as well.



When we look at where to invest in STAR, we try to look at leverage points. So there are a lot of areas where we invest that cut across all CMT types or many CMT types.

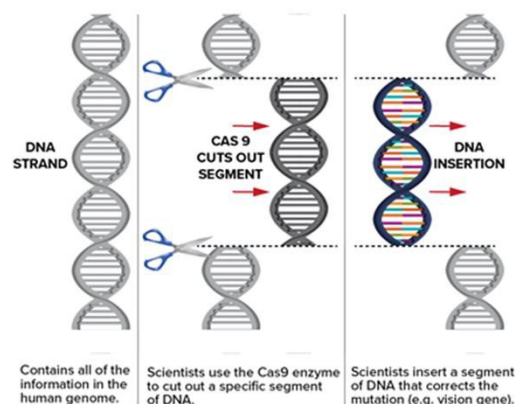
1. We already talked about the testing infrastructure that we've developed that cuts across most types of CMT.
2. We will cover and go in depth today into gene therapy.
3. We'll cover biomarkers as well.
4. Another area that's quite interesting but we're not going to cover as much is Axon Degeneration. It turns out that a lot of companies are working on ways to prevent nerves from degenerating for a broad set of neuropathies. And they want to use CMT as one of the rare disease indications for this. These companies are working with us now to try to find ways that to slow down or even stop the damage to nerves with some of their drugs.
5. Finally, you'll hear about all the great progress on gene therapy. Obviously to apply gene therapy you need to know which genes to fix. So we've really doubled down on trying to find more CMT genes.

This is an overview of what we do across all types of CMT. Dr. Kleopa and Dr. Svaren are going to focus on a couple of them today, but keep in mind that while we won't cover everything we do today, we have very thorough plans for each major CMT type and, in general, three or four key projects which are specific to each type.



## What is Gene Therapy?

- **Gene Therapy** is the use of genes or gene editing as treatment
- Involves introduction of genetic material (DNA or RNA) in the cells and tissues of an individual instead of drugs or surgery
- Several gene therapy approaches include:
  1. **Replacing** a faulty (missing or mutated) gene that causes a disease with a healthy copy of the gene
  2. **Inactivating or 'silencing'** a mutated gene that is functioning improperly (has toxic gain of function effects)
  3. **Editing** part of a mutated toxic gene through "cut and paste" approach



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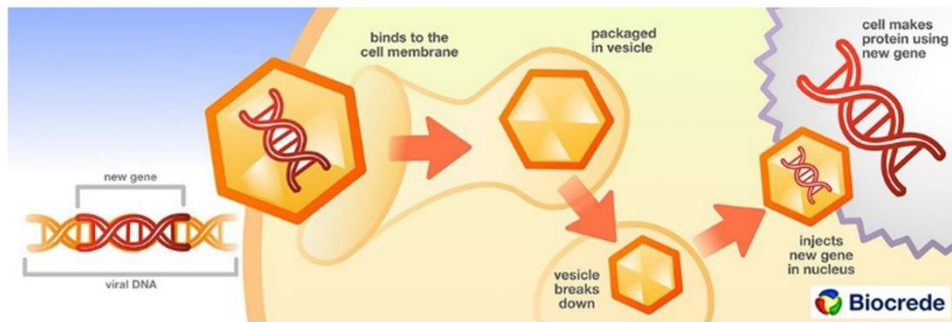


Gene therapy is the use of genes or gene editing as a treatment. This process involves the introduction of genetic material, for example DNA or RNA, into cells and tissues of an individual instead of other treatments such as drugs or surgery.

There are different types of gene therapy, including replacing a faulty gene that would be a missing or mutated gene that can be replaced by a healthy copy of the same gene, or inactivating or silencing a mutated gene that has taken a toxic gain of function—a harmful effect on the body that occurs because the gene is functioning improperly.

And finally, editing a part of a mutated toxic gene that has a harmful effect—essentially a cut and paste approach where you selectively cut out part of the gene and replace it with a healthy part of the gene. This is a technically more challenging approach than replacing or silencing a gene.

## How Does Gene Therapy Work?



- Vector (= virus) delivers the therapeutic gene into the target cell
- The vector's genetic material is inserted into the target cell
- Functional proteins are created from the therapeutic gene causing the cell to return to normal

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How does gene therapy actually work?

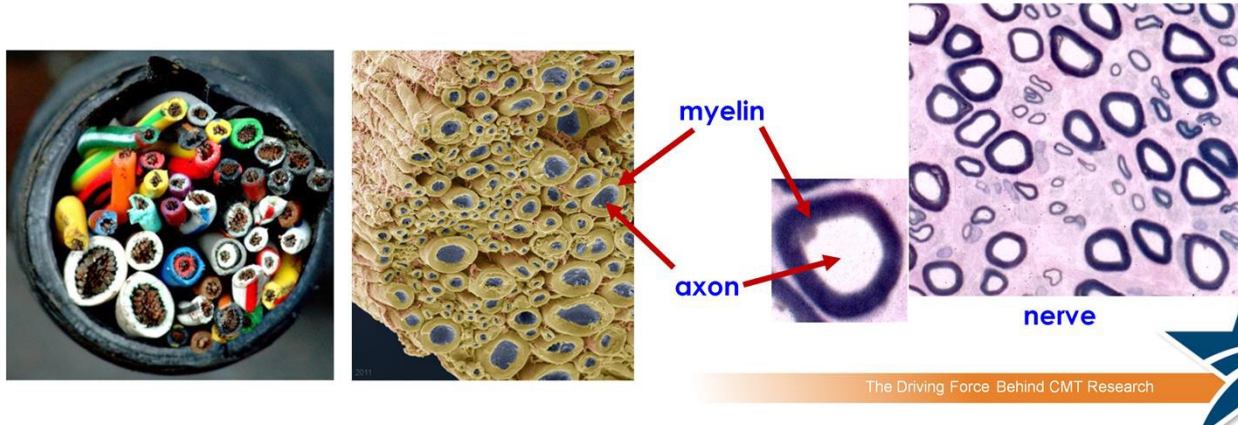
In most cases we use viral vectors (tools commonly used to introduce genetic material into cells) to deliver the therapeutic gene. These viruses are used as vehicles to package and deliver our therapeutic genetic material. They have been modified so that they're not infectious or contagious. They have the ability to enter the cell.

Once inside the cell they will release the genetic material and that will start the production of the protein, and this will correct the defect in the cell and be a treatment for the disease.

And here it's important to note that this will be a once-in-a-lifetime treatment, so once the virus is inside the cell and releases the genetic material, it will stay and keep producing the protein that the cell needs to function.

## The Types of CMT

- **Nerves** are bundles of many nerve fibers, most of them wrapped in myelin
- **Myelin** is an **insulating and protective coating**, formed by **Schwann cells**, which also makes nerve impulses much faster (from ½ to >50 meters/second ! *like 3G to 4G*)
- Myelin problems cause **demyelinating CMT** (CMT1, CMT4). Problems with nerve fibers (i.e. **axons** = long extensions of nerve cells transmitting signals) cause **axonal CMT** (CMT2)



The Driving Force Behind CMT Research

Now let's look at the types of CMT so that we can understand how we can apply gene therapy to CMT neuropathies.

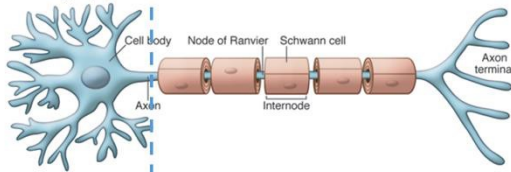
First of all, nerves are bundles of many nerve fibers, and most of them are wrapped in myelin. They are similar to electrical cables, as you can see in the picture on the lower left, that are made of many wires and these wires have a plastic coating.

And in nerves this coating is called myelin. It's an insulating and protective coating that is formed by specialized cells known as Schwann cells. Myelin is very important because it speeds up the conduction along the nerves by a hundred times, like going from 3G to 4G, but also supports and maintains the nerve fibers.

So depending on whether the damage is in the Schwann cells in the myelin or in the axons, we will have demyelinating types of CMT or axonal types of CMT.



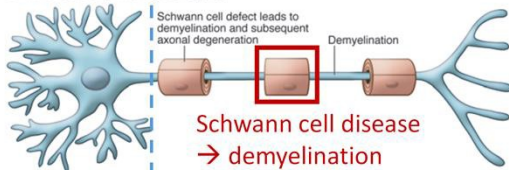
**A** Healthy peripheral neuron



- **Mutations in more than 100 different genes cause CMT neuropathies**

- They have **diverse cellular functions**, resulting in **many disease mechanisms**

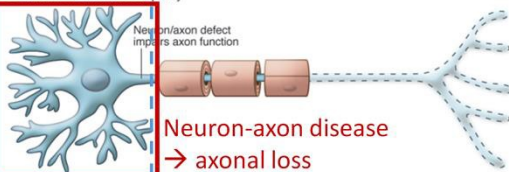
**B** Inherited demyelinating neuropathy



- Mutations in genes expressed by **Schwann cells** mostly cause **demyelinating CMT** – *but eventually this destroys the axons as well*

- Mutations in genes expressed in **nerve cells and their axons** mostly cause **axonal type of CMT**

**C** Inherited axonal neuropathy



- In some CMT types the mutation has a **toxic effect (gain-of-function)** and in other types the mutation results in **loss-of-function**

The Driving Force Behind CMT Research

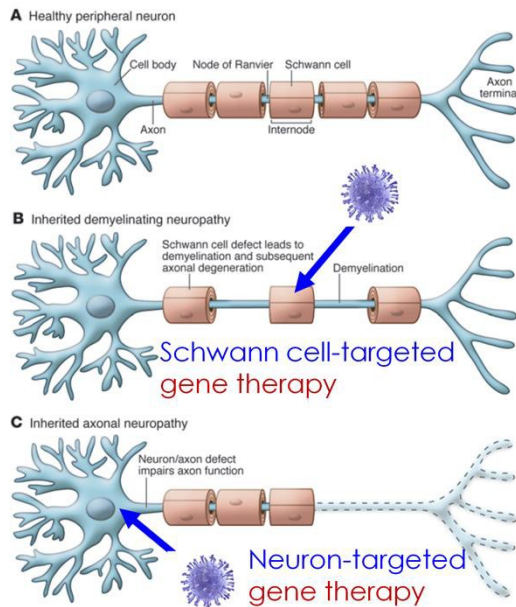


In the diagram of a healthy nerve that would for example be a motor neuron, you notice that it starts with the cell body which is located in the spinal cord, and that sends a long extension all the way to our muscles in the arms or legs. This is the peripheral nerve. All along this nerve you need to have myelin and this is formed by Schwann cells.

There are over a hundred different genes that can cause CMT neuropathies. They have various functions in the cell, and this results in many different mechanisms. If the mutated genes are mostly expressed in Schwann cells, then you have a demyelinating type of CMT because myelin suffers first. But this will eventually also destroy the axon. And if the mutations are found in neurons then we will have an axonal type of CMT.

In addition, we classify CMT neuropathies by the type of mutation and whether this is a toxic gain of function mechanism or a loss of function. And that will also determine the gene therapy approach.

## What are the Potential Gene Therapies?



Gene therapies have to address the **disease mechanism**:

- For CMT neuropathies caused by **loss of function** (mostly **CMT 4 and X**) mechanisms we can deliver the healthy gene to restore the function (**gene replacement**)
- For CMT neuropathies with **toxic gain of function** (mostly **CMT 1 and 2**) mechanism we can either **silence** (reduce) the toxic gene or try to **repair** (edit) the mutation

In most cases **gene therapies have to be delivered to the affected cell type**:

- Therapies for **demyelinating CMT** have to be **targeted to Schwann cells**
- Therapies for **axonal CMT neuropathies** need to be **delivered to neurons** and their axons

The Driving Force Behind CMT Research



So what are the potential gene therapies we can use for CMT neuropathies?

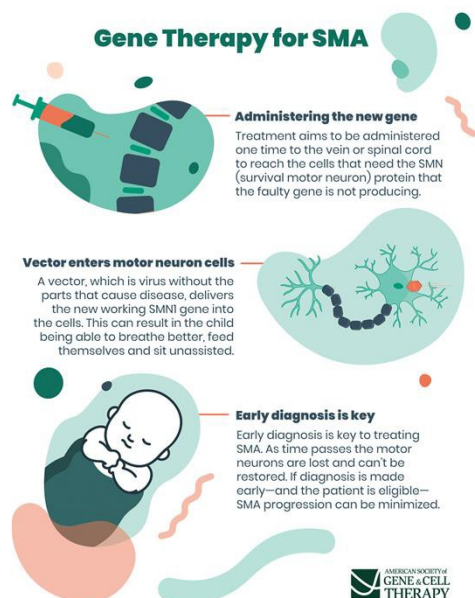
We have to address the disease mechanism described in the previous slide. For CMT neuropathies that are caused by a loss of function of the gene (this is the case with most CMT4 neuropathies and CMT1X), we have to introduce a healthy copy of the gene, so that's a gene replacement.

For CMT neuropathies with a toxic effect of the mutation (as is usually the case with CMT1 and CMT2 types), we have to either silence the toxic gene, repair it, or modify it so that we can prevent the toxic effect.

In addition, we have to deliver this treatment to the particular cell type that needs the treatment. So for the myelinating CMTs we have to target the Schwann cells and for the axonal CMTs we have to target the neurons, so that means a different approach because the cells are located in different parts of the body.

## Gene Therapy: the Future is Now!

### Gene Therapy for SMA



Spinal Muscular Atrophy is a devastating disease, which affects the same motor neurons that are affected in CMT

Until recently, there was no treatment

Two New Genetic Therapies recently **approved for SMA:**

- AAV Gene replacement Therapy (Avexis)
- ASO Therapy (Ionis)

**Dramatic Effects** observed with both therapies

Can we follow the same game plan for CMT?

**Yes!**

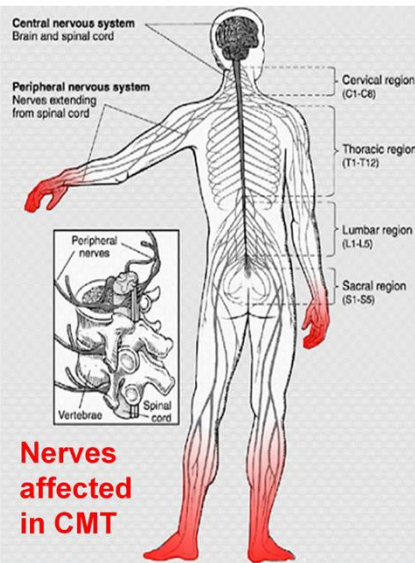
The Driving Force Behind CMT Research

Now that you're all experts on CMT genetics and gene therapy, let's outline the efforts that the CMTA has spearheaded to try to bring new treatments to the clinic!

The science of gene therapy has actually been around for a couple decades. But there were a number of safety issues that had to be addressed. What has generated a lot of excitement in the last couple of years are treatments that are FDA approved for different diseases. The specific example we want to discuss is a disease known as Spinal Muscular Atrophy (SMA). This is actually a motor neuron disease, and it actually affects the same neurons that are affected in CMT. But SMA is a devastating disease that affects infants, and until recently there was really no treatment. But there are now two new genetic therapies that have been recently approved for Spinal Muscular Atrophy.

This includes AAV gene replacement therapy using viral vectors, just as we just outlined, by a company called Avexis. The diagram on the left summarizes how this therapy works, again by delivering the correct gene to the motor neurons. And there's another genetic therapy involving antisense oligonucleotides (small pieces of DNA or RNA that can bind to specific molecules of RNA and block the ability of the RNA to make a protein or work in other ways) which we'll cover a little bit later. The good news for SMA is that there were dramatic effects with both therapies, as long as they're administered early enough in the disease.

We're not only grateful for these advances for SMA, but they also provide us with an avenue we can pursue with CMT because it affects many of the same cell types affected by CMT.



### The CMTA sponsored a Gene Therapy for CMT workshop, summer 2018:

- Invited Gene Therapy Experts: Leading Scientists and Clinicians
- Scientists involved ongoing efforts for SMA, MD, GAN, CMT2D and CMT4J

### Assets for Gene Therapy Development:

- Previously funded efforts for [Dr. Kleopa](#) and partnership with [Ionis](#)
- [Animal Models](#) of many types of CMT
- [Biomarkers](#) and Clinical Trial Planning Expertise
- Recruited Leading [Gene Therapy Experts](#) to Scientific Advisory Board

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To take advantage of this, we convened a gene therapy workshop for CMT in the summer of 2018 to get our plans together and take advantage of a number of different advances. We invited scientists and clinicians that were involved in SMA, Muscular Dystrophy, and different types of CMTs like CMT2D and CMT4J. There are also trials going on for Giant Axonal Neuropathy, or GAN.

We have number of assets that we outlined earlier. First of all, we had previously funded efforts of Dr. Kleopa to apply gene therapy and we'll cover these specific examples in a minute. We have also partnered with other companies using ASOs. The animal models that we have developed are very important testing systems for development of gene therapy for CMT.

Another aspect that's not to be neglected is the fact that we need to have good biomarkers (measurable indicators of the severity or presence of some disease state) and clinical trial planning expertise, which is critical for labs that want to invest in CMT.

And then ultimately we realized that we needed to recruit some leading gene therapy experts to our Scientific Advisory Board to lend their expertise and their advice as we move forward.



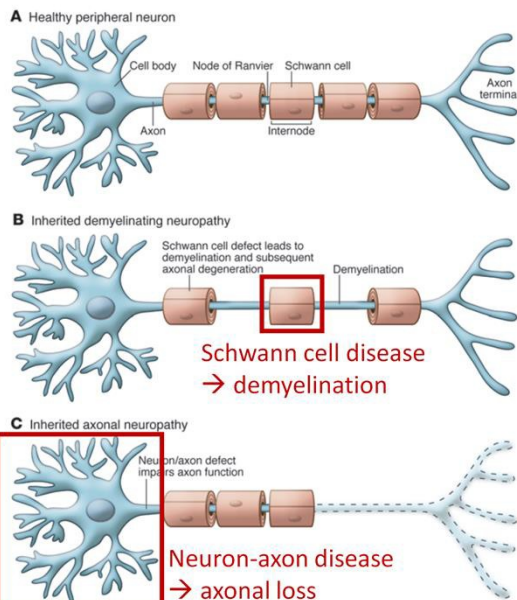
Following the Gene Therapy Workshop, we recruited leading Gene Therapy experts to join the CMTA Scientific Advisory Board to help define the CMTA plan:

1. **Steven Gray**, University of Texas Southwestern  
Involved in Gene Therapy Efforts for GAN and CMT4J
2. **Scott Harper**, Nationwide Children's Hospital, Columbus, Ohio  
Leader in developing Gene Silencing Therapy for Muscular Dystrophy, and CMT2D
3. **Kleopas Kleopa**, Cyprus Institute of Neurology and Genetics  
Neuromuscular Neurologist, and Pioneer in development of Gene Therapy for Demyelinating CMT

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These experts include, Dr. Kleopa, from whom you just heard, who's really pioneered a lot of the development of gene therapy for demyelinating CMTs. And then we have two additional experts: Steven Gray at University of Texas Southwestern, and Scott Harper at Nationwide Children's Hospital. They are really leaders in the field, Dr. Gray for example is already engaged in efforts for CMT4J and another type of CMT (GAN). Recruiting these experts has been instrumental in us being able to plan how we can best use CMTA investments to accelerate the development of new gene therapy treatments.



1. Develop a CMTA-sponsored Effort to target **CMT2** for AAV9-based gene therapy
  - Most common form of CMT2 is caused by mutations in the MFN2 gene (CMT2A)
2. Develop Gene Therapy for **CMT types 1 and 4**
  - Optimize Gene Therapy Approaches for CMT4C, CMT1X by improving Schwann cell delivery
  - Target CMT1A for gene therapy employing RNA interference
3. Develop **Company Partnerships** to help bring these therapies to clinic



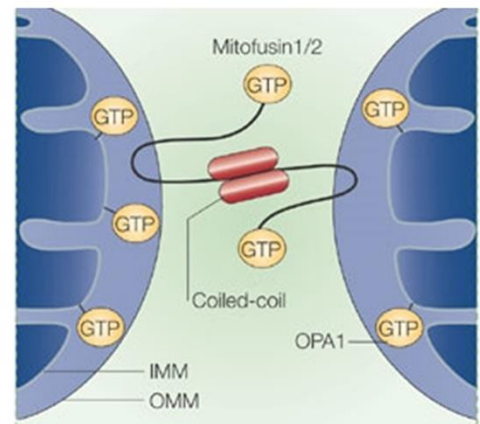
With their advice we have formed a plan essentially to:

1. Develop a CMTA sponsored effort to target CMT2 using AAV9-based gene therapy. AAV9 has been used in other FDA approved treatments, and we decided initially to focus on the most common form of CMT2 which effects roughly 10 percent of people with CMT. This is caused by mutations in the Mitofusin-2 gene and is classified as CMT2A.
2. Our second objective is to develop gene therapy for CMT types 1 and 4, the demyelinating forms of CMT. Dr. Kleopa's work in this area will be covered in the next several slides. Basically we need to optimize our approaches to improve delivery of the genes to Schwann cells. And we also definitely want to target the most common form of CMT which is CMT1A using another kind of technology called RNA interference.
3. And finally, we want to develop company partnerships that can help us actually bring these therapies to market.



## Collaboration with Passage Bio

- Based on pioneering studies of CMTA scientific advisory board member Dr. Robert Baloh
- Passage Bio will develop and test gene therapy using [CMTA-sponsored rat models](#) of CMT2A
- Will collaborate with the Inherited Neuropathy Consortium to sponsor [preparations for clinical trials](#) in CMT2A
- Clinical Trials can commence when preclinical studies are complete after undergoing [FDA approval process](#).
- [Other Collaborative Efforts](#) are in Discussion



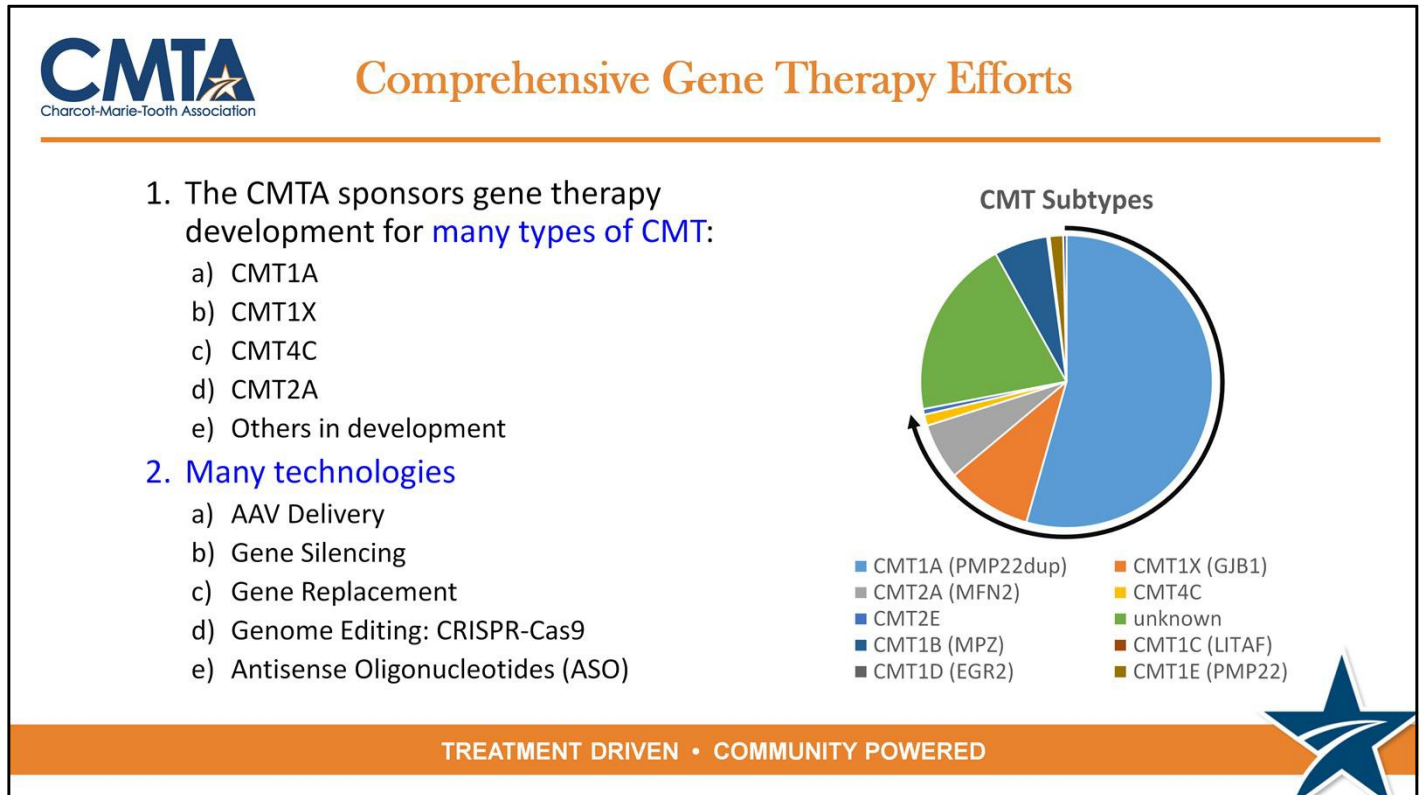
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On that last point, just one year after this workshop, we were pleased that our efforts met with some success particularly in our initiative to develop a new gene therapy for CMT2A. Based on studies by one of our board members, Dr. Robert Baloh, we found that there is a way to overcome the mutation in CMT2A.

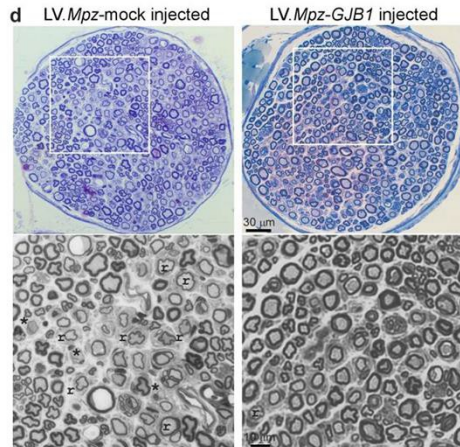
We formed a partnership with one of the leading companies in the gene therapy space, Passage Bio. You may be aware of the announcement that came out a while back where we formed an alliance that will develop and test gene therapy using some of the rat models of CMT2A that were originally sponsored through the CMTA. This will be a broad collaboration, including the Inherited Neuropathy Consortium (INC), to sponsor preparations for clinical trials in CMT2A.

We should mention that we have other efforts on other types of CMT in discussion with not only Passage Bio, but with other companies as well.

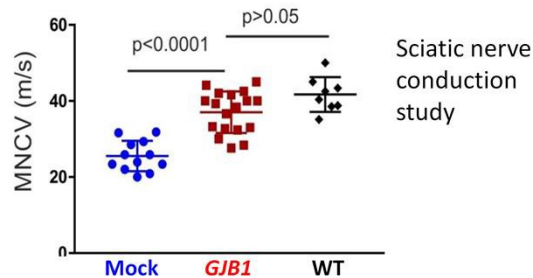


We wanted to have a comprehensive approach for different types of CMT. The pie chart represents the different types of CMT ranging from the most common—CMT1A—to some that are much rarer. And the arrow around the pie chart shows the number of types of CMT that are covered under existing plans or projects, or ones that are under discussion.

We are well on our way to covering almost 75 percent of people affected by CMT with our ongoing projects, and we're hoping that we can expand that in the future. This includes AAV delivery and many different technologies, and we'll mention more about gene silencing and Antisense Oligonucleotides in a minute. We are trying to leverage success in one type of CMT to achieve success in other types as well.



- A virus with ability to enter Schwann cells was chosen to deliver the gene
- **Improvement** of the nerve pathology and function in the CMT1X model **before and after onset** of neuropathy



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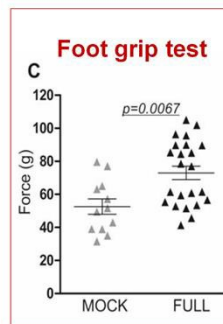
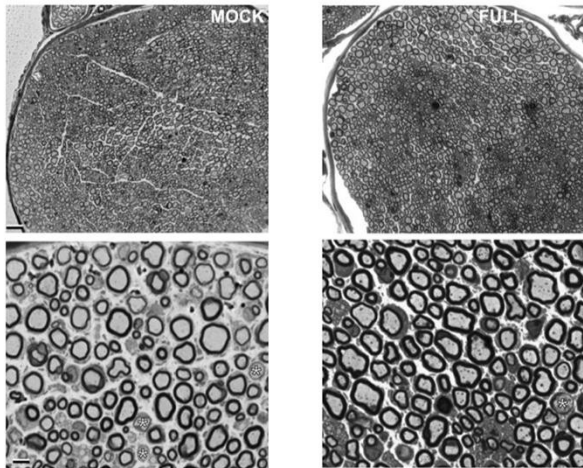
Let's look at two examples of gene replacement that we have developed for two representative types of demyelinating CMT neuropathies. The first one is the X-linked CMT which is one of the most common types. It's about 10 percent of all patients, and this results from a loss of function of a gene that is important for Schwann cells.

Our strategy was to design a viral vector to deliver the healthy copy of the Connexin gene to Schwann cells. With several years of work we have shown that we can achieve a replacement of this gene in Schwann cells and, in the picture on the left, there are examples of an untreated and a treated nerve and you can see that the myelin structure has improved in the treated nerve. This translates also into improved function with better muscle power and improvement of the nerve conduction velocity.

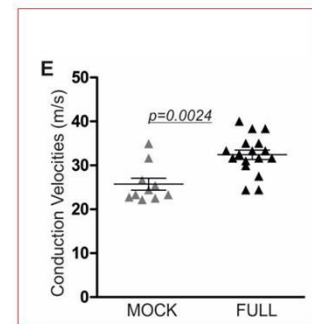
This is an initial proof of principle that we can actually achieve a treatment for this type of CMT with gene replacement.



→ Improved **nerve pathology**



→ Improved **motor performance**



→ Improved sciatic nerve motor **conduction velocities**

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The second example is about CMT4C. It's a rarer type of CMT but very important because it's representative for all the recessive CMT4 demyelinating neuropathies. Like for CMT1X, we designed a vector to replace the mutated gene in Schwann cells. We showed that we can achieve the expression of the gene using this viral vector. The slide shows pictures of an untreated nerve on the left and a treated nerve on the right, and you can appreciate the improvement of the myelin structure and better preservation of the nerve fibers. This translates into improved motor performance. The muscle power is improved and the nerve conduction velocities are faster, again providing proof of principle for this technology.

1. Evaluation of different vectors for **targeting Schwann cells**
2. Evaluation of different **delivery routes**
3. Evaluation of possible **toxicity**
4. Evaluation of **bio-distribution**
5. Provide the proof-of principle for treating **all CMT1X** mutations
6. Test treatment **before and after the onset** of the neuropathy in CMT1X
7. Test AAV-mediated **gene replacement** in CMT4C model

Relevant for  
**all CMT types  
1 and 4**

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Still we have a long way to go before we can reach the stage of clinical testing. We have now several lines of activities trying to optimize the tools in order to reach that stage.

Four major issues that we are trying to address include first of all the finding of the optimal viral vector. We're focusing on vectors that have been already used in clinical trials, and selecting the best one to target Schwann cells. We also evaluate the best way of injecting these vectors that will be safe and easy to apply to patients. We want to make sure that these vectors have no toxicity—that they're safe—and we also want to make sure they can get to the whole nerves around the body because this is what we need to correct in the demyelinating CMTs.

These issues are really crucial not only for the two types that we described before but for all demyelinating CMT neuropathies. So results from this work will be relevant for moving ahead with other types of demyelinating CMT.

We're also focusing on optimizing the treatment for CMT1X using new and safer vectors, and we want to show that the treatment can benefit various CMT1X mutations both before and after the beginning of the neuropathy, which is a very relevant question for patients.

And for CMT4C we also developed a new vector that is safer to deliver the mutated gene and demonstrate that we can benefit the model. So we hope that this work will get us closer to clinical testing with the proof of principle that these treatments can work.

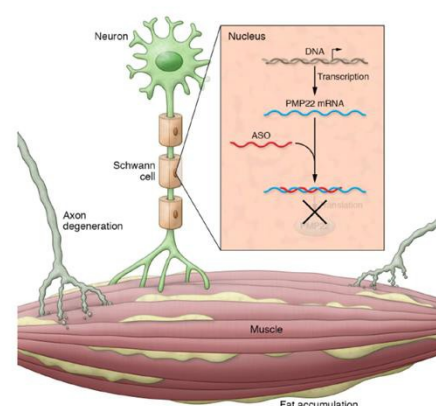
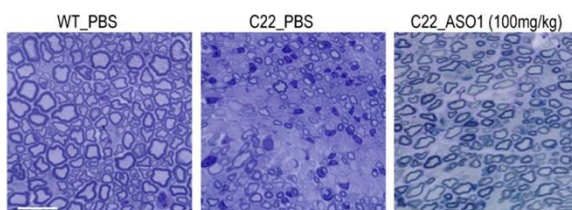
And we are very excited also to mention that this work has attracted interest from several biotechnology and pharmaceutical companies.



## Gene Silencing for CMT

- **ASOs decrease levels of PMP22 RNA for CMT1A**

- Direct injection of ASOs
- Addition of homing mechanism in progress



- **A related technology, RNA interference (RNAi), can be used to accomplish the same goal**

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Although there are remaining challenges, we have confidence we can overcome them. The

success achieved in CMT1X and 4C by Dr. Kleopa is actually encouraging for CMT1A, so we're focusing our efforts to apply this technology to CMT1A, which is the most common form of CMT.

One of the reasons we have confidence in that success is due to another company collaboration with Ionis Pharmaceuticals, which uses antisense oligonucleotides (ASOs). CMT1A is a little bit different than the other types of CMT since there's not actually a mutation of a single base but rather a duplication of the gene, so that you have excessive levels of PMP22.

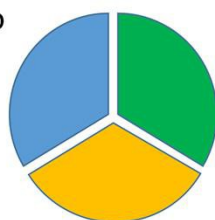
The work published with Ionis showed that if you use antisense oligonucleotides to suppress PMP22, you see in two different models of CMT1A a fairly dramatic improvement in the myelination. We are continuing to work with Ionis to try to perfect and refine and make more potent antisense oligonucleotides.



## Gene Therapy: Targeting PMP22 (CMT1A)

- ASO studies show that targeting of PMP22 improves Neuropathy in CMT1A model. Can we use Gene Therapy for the same goal?
- Three Way Collaboration between Drs. Kleopa, Svaren and Gray

Optimizing **delivery** to Schwann cells



Developing **RNAi** for PMP22

Making the system **specific to Schwann cells**

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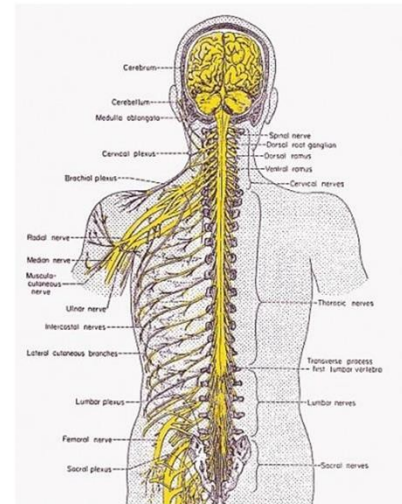


This success also made us realize that you can use a related technology known as RNA interference, or RNAi, to accomplish the same goal, that is, to reduce PMP22. In collaboration with Drs. Kleopa and Svaren and with Dr. Gray at UT Southwestern, we've just initiated a project that's targeting the same technology used for CMT1X and 4C but that's now targeting a model of CMT1A.

This is a three-part project where we continue to try to address the challenges that Dr. Kleopa mentioned, which is to optimize the delivery to Schwann cells, while developing and optimizing the RNA interference for PMP22, and then also trying to make this system as safe as possible by targeting this suppression to Schwann cells rather than other cell types.

### Genome Editing: Using CRISPR-Cas9 to fix the causative mutation or remove the mutation:

- Motor Neuron Disease:  
Partnering with a leading genome editing group: CMT2A, CMT2E, CMT2F
- CMT1A (in this case to reduce levels):  
Toolgen



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Our efforts also include an exciting extension to the relatively new technology that many people have read about, which is sometimes referred to as genome editing, or CRISPR-Cas9. Many people have read articles about this and it has generated a lot of excitement in the field because this is actually a way to take mutations and actually fix them, so you really can fix the source of the disease.

This new technology is being applied and has entered clinical trials for some types of diseases, particularly for those in the blood stream where you can replace blood-generating cells relatively easily.

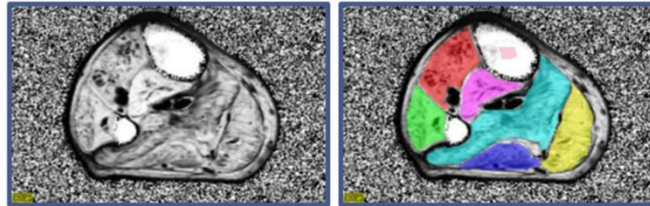
The extension of CRISPR-Cas9 to diseases affecting the nervous system will probably take some more time to do all the safety studies and refine the system. But we are really pleased to announce that we are partnering with one of the leading genome editing groups that has focused on axonal forms of CMT, 2A, 2E, and 2F. And we are also collaborating with a company called Toolgen which has developed an approach for CMT1A and has published some positive results.

While this technology may be a few years behind gene replacement therapy, there is a lot of excitement in this area and ultimately this will become a technology that will really spur development of novel therapies for CMT.



Direct  
Funding  
+  
INC  
Support

- Muscle **MRI** (one of the most sensitive measures of progression)
- **Blood samples** of proteins to measure Neuropathy
- **Skin Biopsies**
- CMT **Evaluation Scores**
- **Wearable** devices



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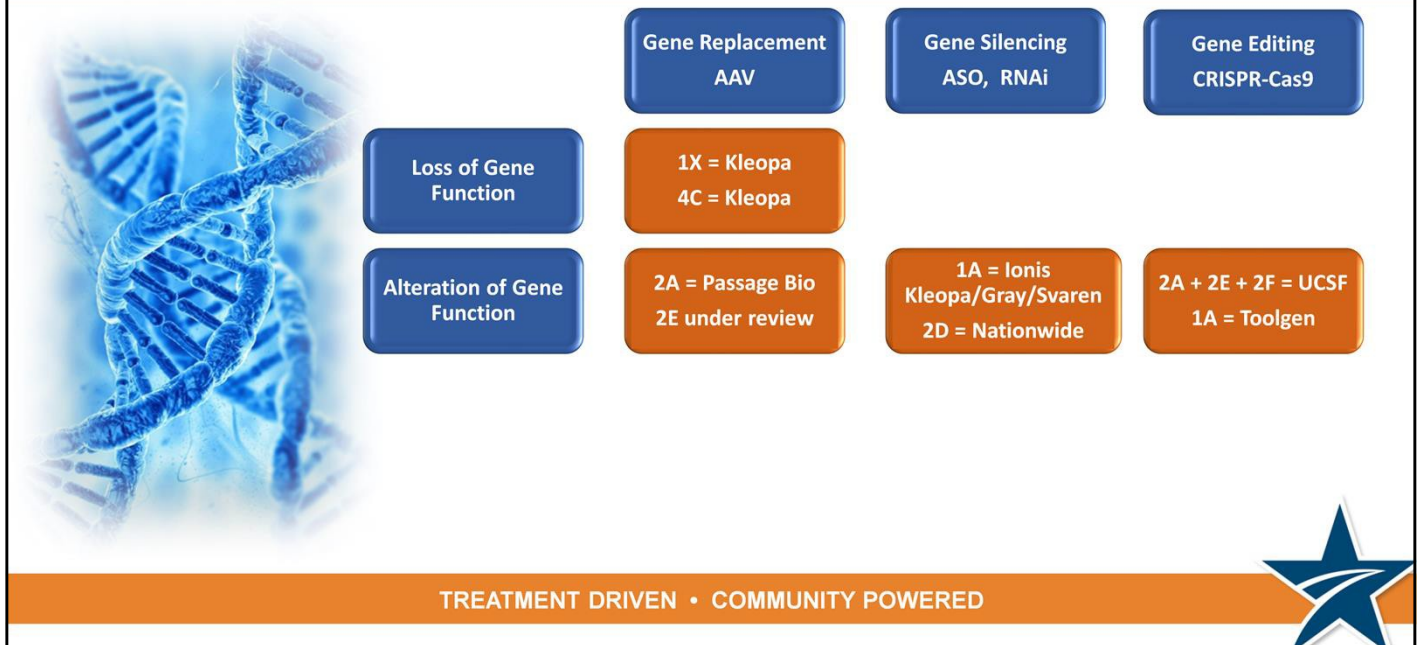


All these approaches depend on having good measures that can be used in clinical trials. When we talk to companies, they want to know how they can plan a clinical trial in a way that they'll get a definitive answer relatively soon. And this has been a challenge for a slowly progressive disease like CMT. But we took this challenge seriously and we supported a number of initiatives.

Some of them have developed within the context of Inherited Neuropathy Consortium, which is partially supported by the CMTA. And there's also been direct funding of CMTA of some of these efforts as well.

Looking at muscle MRI has turned out to be one of the most sensitive measures of progression in CMT. We are also looking at proteins in blood samples that can be used to measure neuropathy. We've used skin biopsies to develop other methods. There's been a lot of work in CMT evaluation score development. And we're also investing in wearable devices that can be used in the clinic or even at home to assess balance and movement.

The coordinated use of all of these biomarkers and outcome measures is such that we can hopefully provide companies and investors with relatively quick assessments of whether a clinical trial will be effective. And this is really crucial for those entities to be able to actually provide investment in these new technologies. Progress in this area is just as important as development of the gene therapy itself.

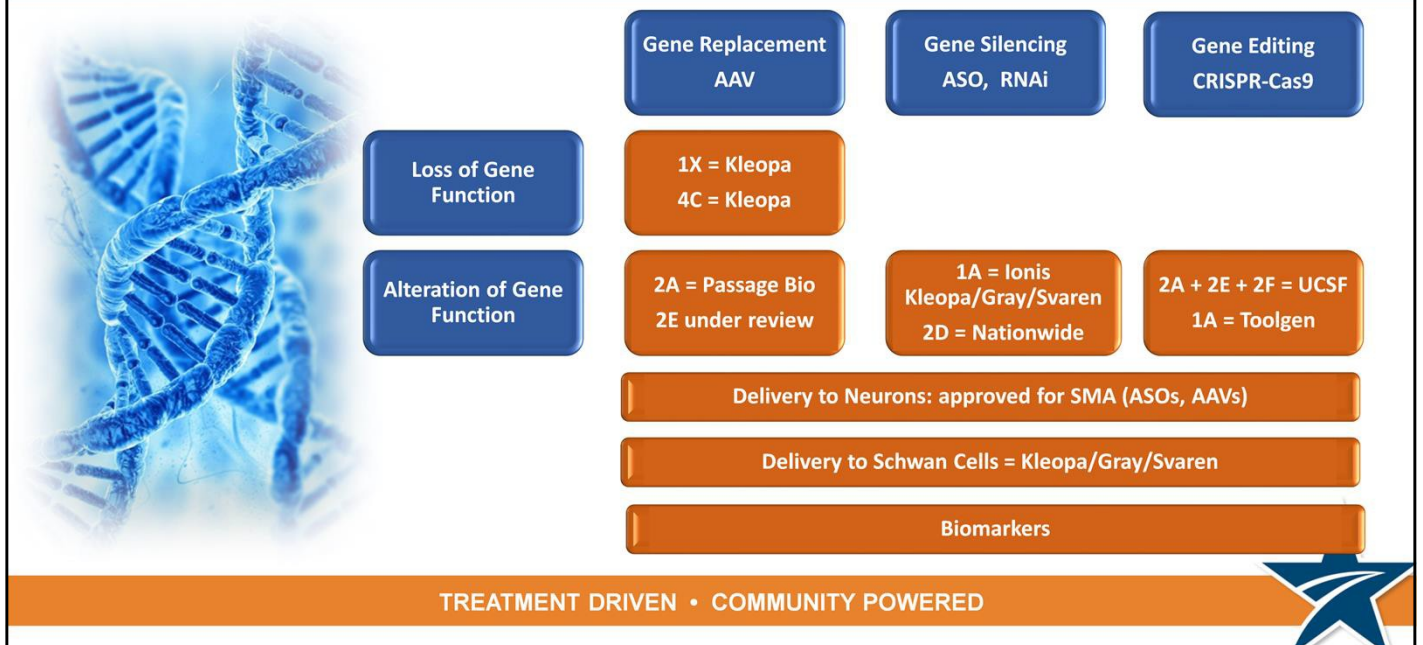


We covered a lot of ground in a few minutes here so let's just take a minute to share with you how all the pieces of this puzzle fit together.

First, we learned there are two major types of gene defect: what we call "loss of function" where the gene stops working, or what is called a "toxic gain of function" where the gene starts doing something toxic to the body.

And there are three major technologies in gene therapy. Gene replacement, where you take a virus (AAV) and send a replacement gene; gene silencing, where you use technologies like RNA interference (RNAi) to interfere with the protein production; and gene editing, also known as CRISPR-Cas9.

What you see on this chart is how all the CMTA-funded projects and CMTA partners we discussed today map onto this matrix, and how the strategy we launched last year has already brought in great partners and projects across this spectrum, with more to come in the near future.



It's also very important to be able to deliver the therapy to the right cell. For neurons (CMT type 2s), there is general optimism there because it's been done before in SMA, for example.

But for Schwann cells (CMT types 1, X and 4), it's a whole different challenge because you have to deliver therapy to the millions of Schwann cells which are along your nerves. So that's why we launched this very important collaboration with Drs. Kleopa, Gray and Svaren to optimize delivery to the Schwann cells.

And finally, you have to deliver this to humans and run efficient clinical trials. This is why biomarkers are so important, and thanks to recent advances the scientists think that we can run clinical trials with fewer than a hundred patients in less than a year.

We've covered a lot of ground but this is not random, we are very strategic and thoughtful about where we invest and where we spend your investment.

## Why Support STAR?



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We're not done—there is a lot of work to left to do. And that's why it's important to continue support the STAR program. There are five key reasons that we ourselves support STAR.

The first one is that it is an incredibly strong program. It is recognized as the leading CMT research program. Top researchers and top companies are now calling us to work with us, and nothing could be more exciting.

We take very good care of our financials. We keep our overhead very low; 15 percent or less is our goal, and we've achieved that in the past two years. Most nonprofits tend to spend twice as much in overhead. Part of the reason for that, by the way, is thanks to you: because most of our resources come from the community, we don't spend time chasing government money, big foundation grants, or running fancy fundraising events. That keeps us very efficient and very focused.

And we are recognized for this. If you look at all the independent evaluation agencies like Charity Navigator, we get very high ratings.

The other point, which is very unique to the CMTA, is that the board members—the people who actually make decisions—are also very invested themselves Over 20 percent of our resources and funding comes directly from board members, which means that the people in charge are voting with their own dollars. They put their money where their mouth is.

Finally, our strategy is based on partnerships, and our partners spend at least 10 times more money than we do. So, when you support STAR, your money gets multiplied by a big factor through the involvement of our partners.



All those things together make CMTA STAR research very compelling and very attractive, and that's why we continue to work very hard on your behalf.



## Everybody Has a Role to Play!



- Join / help an **Event** or a **Fundraiser**
- Join the **INC Patient Registry**
- Visit a CMTA **Center of Excellence**. Then Visit Again!
- Join "**Patients as Partners**"
- Sign-up for **eNews**
- Remember the 3 W's: **Work, Wealth, Wisdom**

# THANK YOU!

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We have all come into this for our own reasons and our involvement is very personal, but at the end we all have a role to play. Please get involved and be part of this incredible movement. At the end, this is your program, for you, and by you.

- We have wonderful branch events and patient/family conferences around the country.
- It's really important to be part of the CMTA Center of Excellence network and to register with the INC. It will help our research and it will help you.
- Because we have more partners, we have launched the Patients as Partners initiative, so you can be involved with companies.
- There's a lot going on, so please sign up for eNews and stay informed!
- And remember the three Ws: you can help with work, with wealth and or with wisdom.

A big thank you to everybody. Remember: STAR is all because of you and everybody in the whole CMT community. We're very proud of where we're at today, but there's a lot left to do and we need your involvement and support now more than ever before.

INC Patient Registry

<https://www.rarediseasesnetwork.org/registry>

CMTA

<https://www.cmtausa.org>

Annual Appeal – \$1.85M in matching funds!!

<https://www.cmtausa.org/we-are-family/>

Sign-up for e-news

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