On the **10th Year Anniversary of the launch of STAR** (Strategy to Accelerate Research), CMTA Chairman, Gilles Bouchard, gives a webinar explaining the current status and remarkable advances made in CMT research. Below is the transcription, or the recorded webinar can be heard here: https://www.cmtausa.org/resource-center/learn/cmta-webinars/

Webinar Transcription:
I'm the chairman of CMTA, and our family's been involved with CMT and CMTA for almost 15 years. Our son Yohan was diagnosed with CMT about 15 years ago. So it's been quite a journey for us, as for many of you, I'm sure. What I want to do today is give you an overview of the STAR program.

STAR Webinar – 11/13/2018

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As you can see from the logo, we are celebrating the **10-year anniversary of STAR.** STAR has been very successful, offering promise and hope for the 3 million people worldwide with CMT. Nevertheless, for people like you and for me, **10 years feels like an eternity when there are still no viable treatments for CMT.** On the other hand, 10 years is actually a short period of time when it comes to developing drugs.

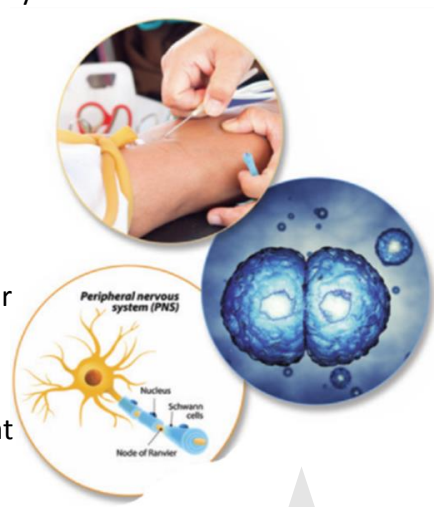
About 10 years ago, we had a CMTA board meeting to discuss our approach to research. We realized that while there was some good research and a few really brilliant researchers working on CMT, there wasn't really a lot going on in terms of research that would bring drugs to market. And we asked ourselves, how do you **accelerate** research?

It's extremely challenging to develop new drugs. On average, it takes **10.5 years from the time a drug is identified to get approval.** The clinical part of this 10-year process takes about 8 years. Even scarier, **90% of the drugs fail during the approval process.** And it costs hundreds of millions of dollars ……

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, but significant opportunities:

1. Well defined genetic causes. More discovered every year
2. There are ways to test potential CMT treatments using assays, CMT stem cells, and CMT animal models
3. Classified a rare disease (< 200k in USA) , yet a significant number of patients
4. Take advantage of advances in genetic and neurological therapies

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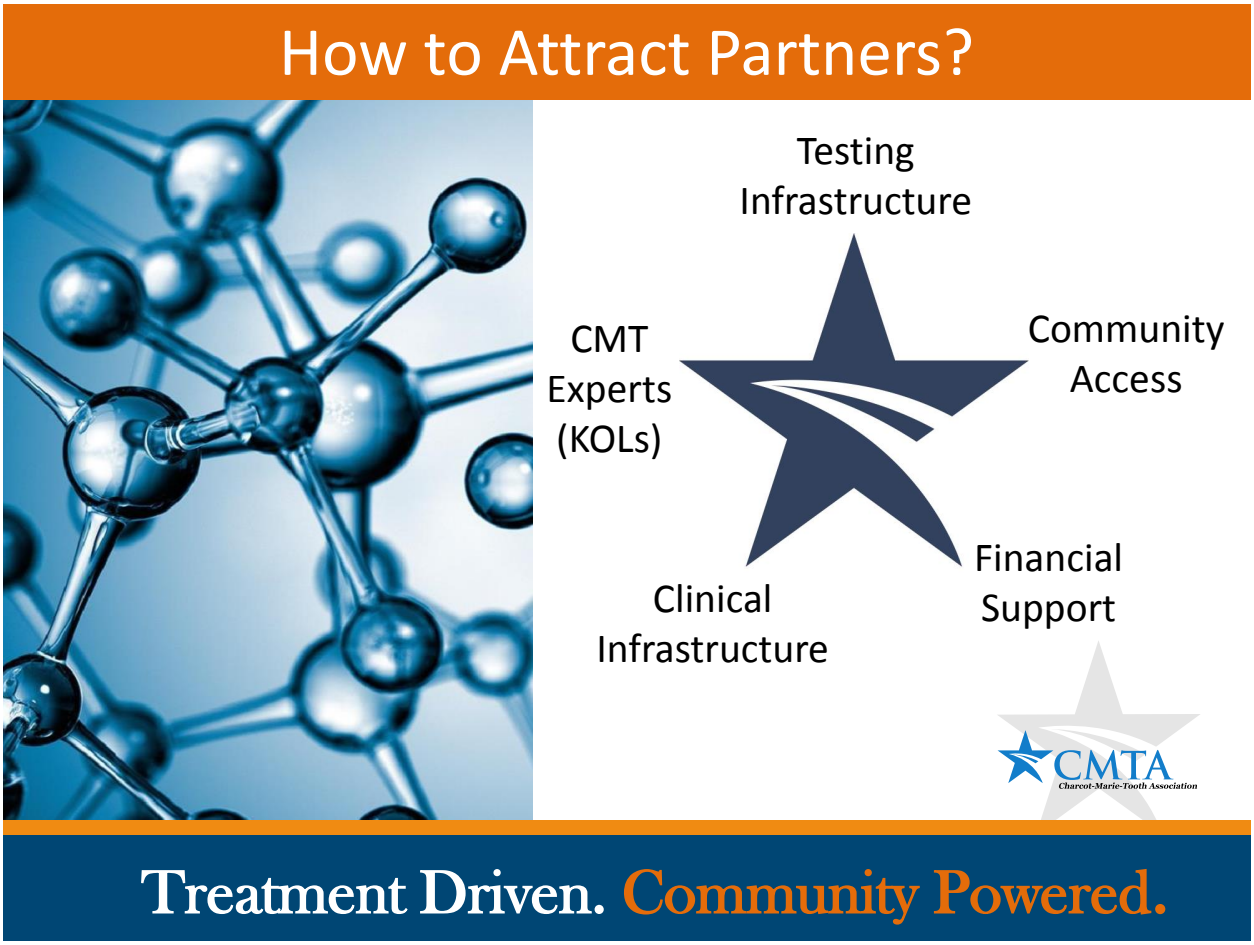
So we asked ourselves, from a business point of view, how to accelerate this process?
From a research point of view, let's look at the some of the positives about CMT:

- **The causes for the most common types of CMT are very well known,** and more types are discovered every year, which is not the case in many diseases, especially for the nervous system. We can create animal models. We can create assays or cells in Petri dishes so we can create stem cells. Now we can test and create models of CMT, which are very valuable to our partners.
- The other positive is that **CMT is classified as a rare disease,** which gives companies some advantages in the market. Although CMT is rare, it's still fairly common and there

are a large number of people with CMT, which is helpful for companies because obviously it's still a big market and it allows us to have enough patients for clinical trials..

- Since the CMTA has these **models, we can take advantage of the latest developments in genetic and neurological therapies.** As you know, since the genome was sequenced, there's just been an explosion of technologies and applications, and many of those actually apply very well to CMT. So that's very positive for us.



What makes it interesting for a pharmaceutical company to work on CMT?

- **Testing Infrastructure** – We have developed a very extensive testing infrastructure. We created animal models, assays (tests). We created stem cells when they were needed. We also work with companies who specialize in testing animal models and analyzing tests. It's what we call the **STAR testing infrastructure**, and it's a very powerful infrastructure. In fact, most companies approach us because they've heard about this testing infrastructure, and they want to work with us on testing their compounds or their drugs or their ideas. And you'll see, as I go through the details by each disease, I'll give you examples of the things we've done there.
- **Key Opinion Leaders (KOL):** Companies know their drugs and technology well, but they might not be experts in CMT, so they won't have access to key opinion leaders, who are **experts in CMT**. This is why we built such a strong scientific advisory board – they

collaborate with our partners and advise them on CMT. This creates strong teamwork and complementarity between their knowledge and the expertise of the companies.
- **Community Access.** I always say that the CMT community is our biggest asset. Companies want to talk to the community to better understand the disease. They want to understand what's called the *burden of disease*, how it affects people, how it affects people's lives.

Almost every company tends to have dedicated resources to engage the community. Our CMT Association is a huge asset for us as we reach many people worldwide. **And again, we thank you all for just being part of that.**

- **Clinical Infrastructure**: Once companies are done with the testing in animals or in assays, they want to test in humans and bring drugs to market. And this is where drug development becomes very expensive. Again, hundreds of millions of dollars are spent in clinical trials. And the more people you need, and the longer it takes, the more expensive it is, and that can often be an inhibitor for companies to work on the disease. It is especially challenging in CMT, b**ecause it's a slowly evolving disease.**

So how do you tell that a drug is working in a slowly evolving disease without spending years and years following a large number of people?
We work with the INC (Inherited Neuropathies Consortium), started by Dr. Mike Shy, who has involved many world-renowned clinicians and scientists. They had the vision to create this infrastructure like the Centers of Excellence (COE), where they see people with CMT. They do what's called **natural history**, where we see how the disease evolves over time with patients, and then we develop **biomarkers or ways to measure the progression of the disease.**

The whole idea behind biomarkers is that we want to run clinical trials in just a few months with a handful of people, and get a good quality read whether the drug is working. And we've made tremendous progress here. And that's a really attractive part for companies now.

Financial Support – We've learned that we have to be very flexible, and we have to provide the kind of support that fits their business models. So we work together on joint projects or even give them access to some funding through investors. We've learned to be very flexible on how we can help companies where needed.

Core Business Principles

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Basically, 10 years ago, we went out and laid out **five core business principles** by which we were going to drive the STAR program. And we still live by those five, and I want to go through them because I think they are the core reason why the STAR program is being successful. And they're very important to understand also how STAR works. By the way, you'll see a lot of things go by fives, like the five tips of our star!

The first one is **strategy**. What does this mean? Well, the way most organizations work is they collect money, and they fund the best proposals that people send to them. At the time, we talked to a few leading organizations that had turned this around. They realized that while this is nice, it's really not the most efficient. What you want to do is get some strong thinkers together, get the best researchers, and define what needs to be done to solve this problem. What are the gaps? What elements of the puzzle are missing to find a cure, to lead a path to a cure? And this is where we focus our investments, and we actually go to the **best researchers**, the best teams, and ask them to put proposals for us to fill those gaps.

Then the next thing we do, which might sound obvious, is we **hold people accountable**, which is not very common in the medical world, which means if they don't succeed, then we work with other people (which has actually happened). Or we don't pay them until they deliver, go through a milestone, et cetera.

And the other thing that's very important is we really require **collaboration**. A lot of scientists tend to work in silos and don't always want to share information. And we found that it was really important to get people to work together, and we've created some really strong teamwork across our advisors and teams here. And it's made a big difference.

The fifth one is **partnerships**, probably the most important. If you remember, it takes hundreds of millions of dollars to develop a drug, clearly not the kind of money we have. So we have to bring pharmaceutical companies to basically come and play in this CMT sandbox, as we say, and bring the resources they have to develop these drugs.

So our core strategy has been to fill the gaps, to attract pharmaceutical companies and make it interesting for them to work on CMT and develop drugs for CMT. We have made a lot of progress in 10 years, and we see this progress really accelerating recently, and I'll give you several examples of that.

Partnerships: We have announced five partnerships. The one thing we look at in terms of the measure of success is how many partners are we able to attract, how many phone calls we get a month about companies interested in working on CMT. And frankly, the last two years, it's just exploded. So, besides the five that we've announced, there are actually **eight more**

companies that we have not announced because want to wait until their results are more advanced or published to go public.

And we have a pipeline, meaning that we are in **early discussion with another 15 more companies.** Three or four years ago, there were only a handful of companies who were working on CMT. So this is probably the most exciting part as it shows that STAR's starting to work because there is a long list of companies actually doing some work on CMT, and an even longer list of companies interested in trying to figure out how to work on CMT.

For reference, we also have five wonderful partners who help us work with pharma companies through all the testing procedures.

Sanofi Genzyme – is a very big company, and we started by screening their whole library, and basically, we're down to one compound now, and we're in the process of testing it, and we should know very soon whether it works successfully, and then we'll decide what is the next step on this one.

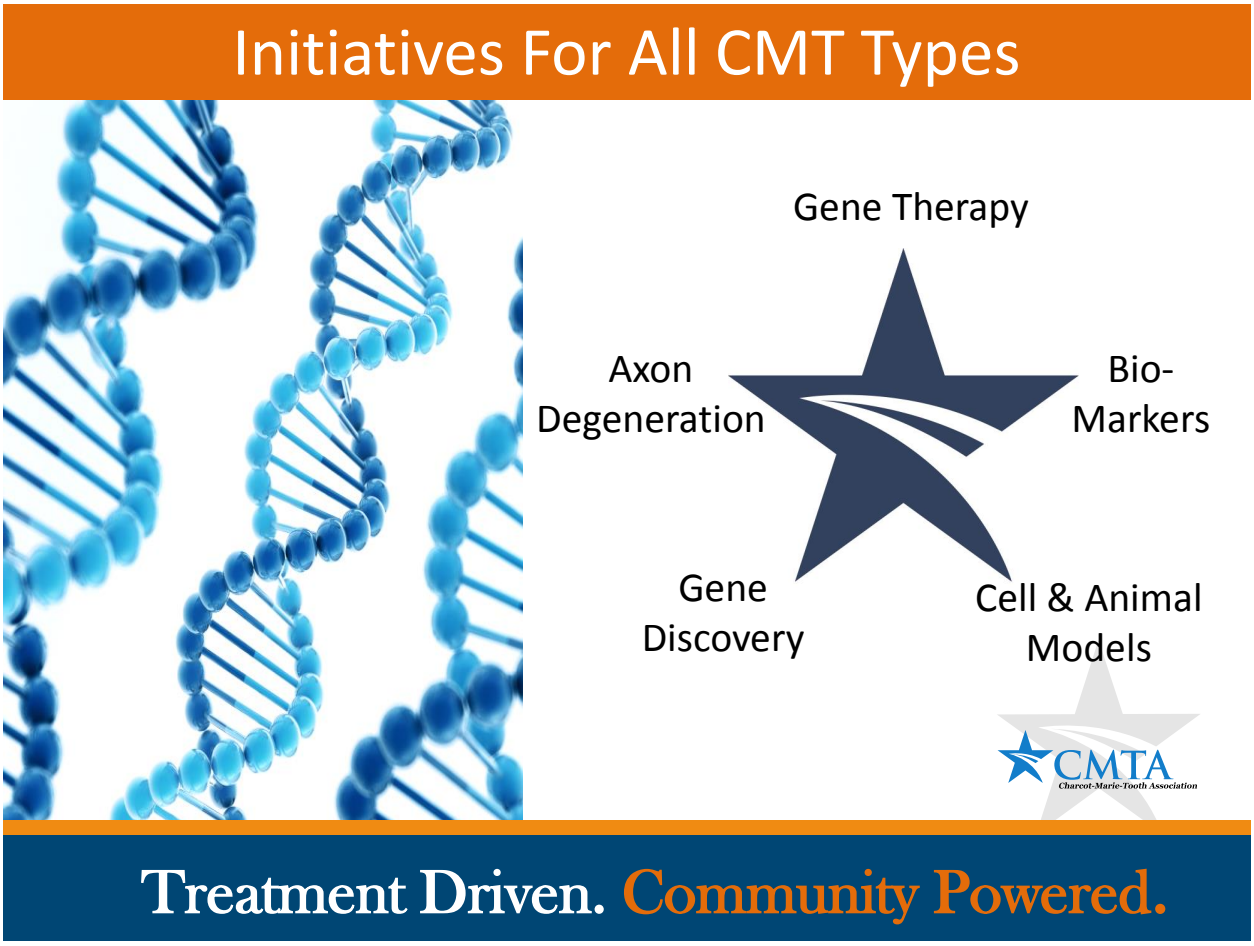
But even more exciting is that we've actually grown that relationship, and we have now **three other projects with Sanofi**. There's another family of compounds that they're very interested in, and we're actually testing those as well in CMT right now. They've also done some really good work with us on **biomarkers**, which hopefully will be published soon.
Lastly, we've done some work on what's called **target discovery** where we have worked together on **finding other potential drug discoveries or other compounds** that targets CMT, and this has led to additional projects.

Ionis – You may have heard about the breakthrough with Ionis last year. They used components called ASOs, which go straight to the gene and really counteract the negative effect of having a duplicated PMP22 gene. That was a **major breakthrough** because they were able to stop and sometimes even improve the situation in **two different animal models.** This was probably the best example of showing that when you reduce PMP22, it actually helps the behavior of the animals – a breakthrough!
Now, they are basically working very hard in trying to **design a drug for humans.** Even though they have the drugs for animals, it's obviously a lot more complex and challenging to develop the drugs for humans. They want a drug that's very efficient, so that it can get to the nerves, while remaining safe. We're also in discussion with them about clinical planning.

InFlectis – We'll talk in the context of 1B and 1A. Inflectis is a company in France that has developed a very interesting compound that has shown some exciting results in 1B and also in 1A.

Acceleron – You might have heard of Acceleron because we're actually **recruiting for clinical trials** right now. They have a **drug that helps rebuild muscles,** so while it's not a direct cure for CMT, it could really help people with muscle wasting caused by CMT.

Regenacy – one of several companies that's working on what's called **axon degeneration**. It's a field that's seen a lot of development the last couple years, where people try to find out ways to stop the degeneration of nerves.



To be the most effective with our resources, with our money, we find initiatives that cut across all diseases. Personally, I think it's strategically something that is very important, and guess what? There are five of them.

Gene Therapy – It's a field that's been around for quite a while, but it's completely exploded over the last two or three years. There are close to 1,000 clinical trials in gene therapy around the world.
Currently, these efforts have only produced 2 new drugs; one of which was approved in the U.S. less than a year ago for Spinal Muscular Atrophy (SMA). As we continue gene therapy research inside the lab, our ultimate goal is to transform it into effective treatments for people living with CMT. I encourage you to watch the PBS documentary: "The Gene Doctors" to understand my excitement, as it is clearly going to be a big part of our future.

Gene Replacement therapy also will be applicable to CMT. **With gene therapy, scientists take genetic material, put it in a virus, and the virus goes in the nerves, and this genetic material**

compensates for the gene that's either missing or deficient. This suits CMT very well because we know the genes that are deficient, and we have models where we can test it. So people are very excited about applying gene therapy to CMT.

Now, a new branch of gene therapy that's exploding and is relevant to CMT is **CRISPR,** also known as gene editing. Here you don't just put an additional gene material in the cell, **but you actually go in there and change it – change the genome.**

Axon degeneration – it turns out that there are a couple of really big markets that are driving this. One is chemotherapy, which creates a lot of neuropathies for people, and the other one is Diabetes. So a lot of companies are working on these diseases, and they are very interested in applying it to CMT.

And remember, from a business point of view, it's always very interesting for a company to have a rare disease indication for a medication because they get the advantages of the rare disease indication while having access to bigger markets. So there are at least **five companies** we're working with right now on different approaches to axon degeneration, and we've also launched several specific studies that we'll talk about per the various diseases. And one of the beauties of axon degeneration is it **could apply across CMT types, even the ones they are not diagnosed.**

Models: It's incredibly important to have quality animal models, usually mice, sometimes rats, and cell models or assays and stem cells. We can take people's skin samples and make stem cells, and then we can make neurons or Schwann cells (Schwann cells make myelin) out of them.

Gene discovery: As you know, we've discovered a lot of CMT-causing genes. I think we're up to 120, but there are still many types of CMT which have not been discovered, especially Type 2's. It's very important to continue that, especially in the context I mentioned earlier, that more and more of the new therapies are very gene-specific. So we need to continue to discover more genes.

Biomarkers

1. Blood sample as measures of Neuropathy:
   - Neurofilament L levels (Reilly lab). Other proteins on-going
   - Profiling of CMT1A microRNA's in blood samples (Svaren, Shy, Partner A)
2. Measurement of Skin Biopsies:
   - PMP22 mRNA levels for CMT1A (Svaren, Shy)
3. MRI of calf muscle to measure progression (Reilly, Shy)
4. Extension to other CMT subtypes (samples being collected)

Functional Outcome Measures:

- INC collaboration (NIH, MDA, CMTA) on outcome measures
- Biosensor/wearables (Proposal A)

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Biomarkers – We are collaborating with the INC, which CMTA supports directly. Most of the funding for the INC comes through the NIH, but both the MDA and the CMTA provide additional funding, and then we have also funded several specific projects on top of it.

Biomarkers are important to track disease progression over time. Scientists are looking at elements in your blood. For example, Dr. Mary Reilly's lab is looking at **neurofilaments** and her promising work is being published.

And then another project, again, in the blood, looking at what's called **microRNAs.** This was funded by CMTA with Drs. Svaren and Shy together with a partner company.

We are also looking at **skin biopsies** because you can actually detect levels of PMP22 in the skin. The CMTA is funding this encouraging project, spearheaded by Drs. Svaren and Shy.
We are also looking at **MRIs** of the calf muscle and looking at the fat content in the calf muscle, which correlates to disease progression. So, when you put all the three approaches together, we now think that we can run clinical trials over a shorter period, six months, with maybe as few as 50 people, which is a huge progress from the past when we needed hundreds and hundreds of people.

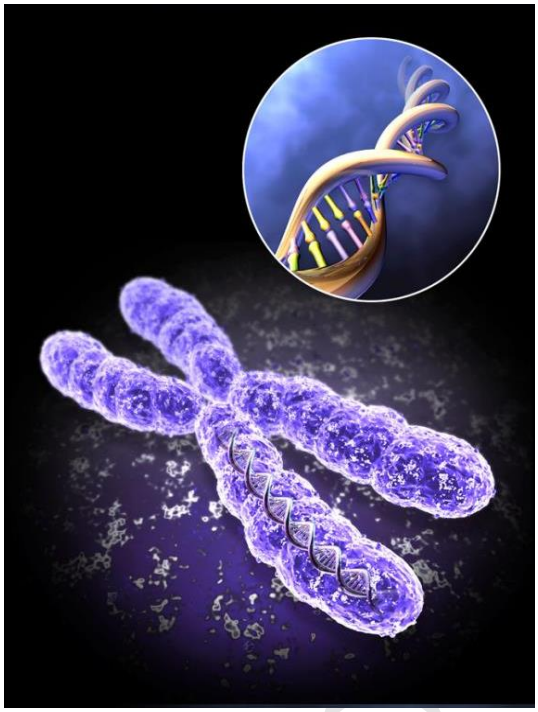
We've done a lot of work in CMT1A, and now we are funding efforts to address the other most common types, so you'll see a lot of this for 1B, 1X, 2A, and other types. Now those biomarkers are again, elements that we look at in the blood or in the skin, but also, the FDA wants to see what's called **functional outcome measures**. They really want to see the patients getting better. For example, with treatment, are people walking better, getting better use of their hands, etc. So the team has been really busy coming up with scores which are functional in nature and which try to capture how much better people are (or worse people are) as their disease evolves, and try to do it in a way where we can see small changes, and also in a way that correlates with those biomarkers. The good news is there's a major grant that was just approved by the NIH for the next two or three years to continue this work, so I think we're going to be in very good shape.

We are also interested in measuring activity in people's homes with **wearables**. We're looking at a proposal right now where we could measure people's gait, et cetera, when they're home. This would give us an indication about diseases progression while at home which would give us a longer timeline and more information.

Disease by Disease:

CMT1A

- Decrease level of Pmp22:
  - Small molecule screening (NIH and Sanofi)
  - ASO: Antisense Oligonucleotides (Ionis)
  - Genome editing: CRISPR (Company A)
  - Lentivirus approaches with shRNA (Proposal A)
- Additional targets:
  - P2X7 (Companies B & C)
  - Novel target identification (Svaren, Garippa, Company D)
  - Inhibition of axon degeneration
  - Stimulate muscle regeneration (Acceleron)
- Biomarkers
- Pharnext Announcement



CMT 1A – As you know, CMT1A is created by the duplication of the PMP22 gene, so the most obvious thing to do is to try to decrease the level of PMP22 in the body. We have the **small molecule screen going on with Sanof**i. We have the **ASO approach with Ionis.** We are now working with another company who actually wants to use **CRISPR to decrease PMP22,** so that's very exciting, and actually, those tests are just about to start. And then also we're looking at a very interesting proposal to combine a **gene therapy approach with an ASO approach where you would use a virus to send a little piece of RNA into the cells to try to interfere with the PMP22.**

Now, besides the pure focus on PMP22, there's been a lot of work done over the years to find other targets in the body that the new drugs could go after to help with CMT1A. One in particular that's shown some promising results is called **P2X7,** and we are working with two companies right now with drugs that target this. And they actually both are in testing right now.

We've done work to identify new targets, and we are actually funding a project that's in full speed right now to look and see if there are other elements that we can identify that could help decrease PMP22. And then we've mentioned **axon degeneration**. This applies to all CMT types. If the work progresses well with other types of CMT, it could be very applicable to CMT1A. We are doing the **muscle regeneration** work with Acceleron.

Recently, a company called **Pharnext** announced preliminary results from a Phase 3 clinical trial for CMT, which were encouraging. They showed that in some patients the disease improved, in others it was stable, and, sure, in others it got worse. But it was clearly better than the control group using the placebo. I think the general consensus around scientists is that this is interesting, and we want to see a lot more of the data as it becomes available throughout next year.

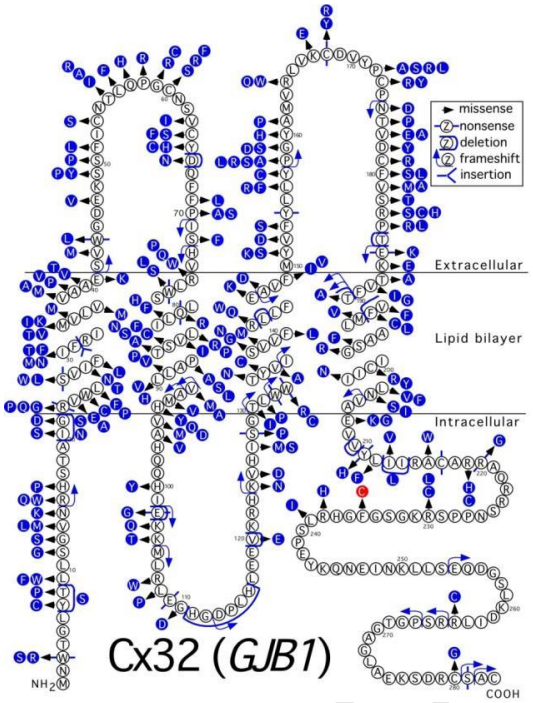
They will have to do this, obviously, as they engage the FDA, so it will be very interesting also to see how the FDA engagement happens. And we think all this will happen through 2019, so again, very interesting announcement.

We all have to really help them because they are defining how the FDA and the agencies think about CMT. Again, nobody's been there before, so we're working very closely with them, and all the patient advocacy groups are really involved.

It's our first chance in a way to make the voice of the CMT patients heard to the FDA and to the European agencies, so it's very important for us to all work together and basically make the voice of the patient heard.

CMT1X

- Biomarker studies in progress
- Natural history studies just published (Scherer)
- New mouse models of CMT1X in process (Partners A & B)
- Gene therapy, CMTA/MDA Collaboration (Kleopa)
- Inflammation (Martini): Conversations with several companies
- Axon degeneration: (Proposal A)



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CMT1X
By the way, on the right is the CMT1X gene, and I think there are over 400 different mutations of the CMT1X gene.

There was a study on natural history that was just published. **I encourage everybody to go to the Centers of Excellence and to go back because then our scientists can not only study your CMT, but see how it evolves over time, and that's what's called natural history.** And this is one of the most important things that pharmaceutical companies want to see, to really help them figure out how the disease evolves after the drugs get administered to people. So, there's good data on 1X, and I think we'll continue to see it happen in also in other diseases, but we need more and more patients to do that.

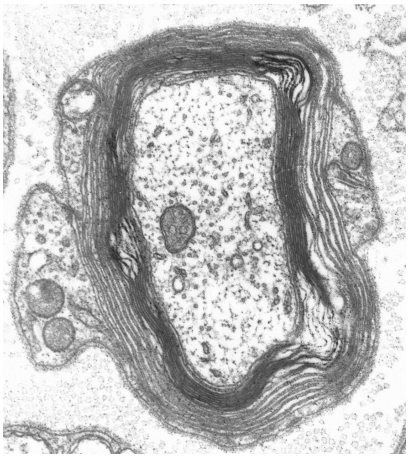
We just approved this year the funding to develop **new mouse models** of CMT1X. Pretty much all the work on 1X has been done with a mouse where the whole gene was removed, and it's actually a very good model. But we feel it's time to get more precise models with specific mutations, especially as new genetic technologies are coming into play. So we'll need better models that we can just look at the specific gene mutations. This is being funded, and it's in progress.

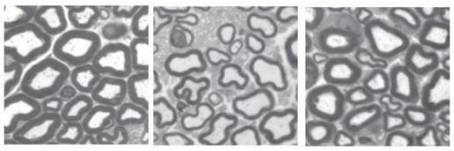
We are also co-funding a Dr. Kleopa's **gene therapy project** with the MDA . He has shown some really good results in mice, where he was able to get the gene material to the Schwann cells, and it did have an effect. So we continue to push on this project, and we try to find ways to make it more translational, meaning – how do we bring this to humans as quickly as possible.

The role of inflammation for CMT1X was highlighted by Dr. Martini in Germany. And there are several companies that we've talked to that have drugs that target the element that he identified as being part of the inflammation. The challenge there is that it's hard to find a drug that doesn't also affect your immune system, so we are in discussions with drug companies to see if we can find a drug that does go after this inflammation factor but doesn't also wreak havoc in your immune system.

And last but not least, **axon degeneration,** is very important for 1X, as it is one of the types of CMT where we see fairly severe axon degeneration, so we are evaluating right now a proposal to actually do a specific experiment to try to **highlight the role created by axon degeneration with a specific target.**

CMT1B





- Three mouse models available for the three main clinical presentations of CMT1B
- Inflectis / Sephin:
  - Collaboration with Inflectis on genetic tests, animal test and clinical planning
  - Phase 1 (safety) clinical trial approved
  - Unfolded Protein Response (UPR) types published (Shy)
  - Possibly applicable to CMT1A
- Assess role of axon degeneration in CMT1B (Wrabetz)
- Biomarkers

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Now let's move to 1B which has about 200 mutations which fall into 3 categories, and we have **good mouse models for each one of the categories of CMT1B** – early onset, mid onset, and late onset. We are continuing to do some testing with InFlectis at the animal level, and we are in the early stages of clinical planning.

By the way, if you look at the picture on the bottom left, you see three little pictures. The left one shows the myelin around the axons for a normal mouse. The middle one is a 1B mouse, so you see it's really degraded. And on the right side is a 1B mouse treated with **Sephin**, so that's why people got really excited about Sephin because it showed some really good results in the mice. And the other good news is **InFlectis with their drug Sephin were recently approved for the Phase 1 trial in Europe.** Phase 1 is when you actually go to healthy patients and just test the drug for safety, so if you combine this with the animal model trial we're doing with them, pretty soon after that, it'll be late next year, if it's all positive, they might be able then to move to clinical trials in humans, which would be very exciting.

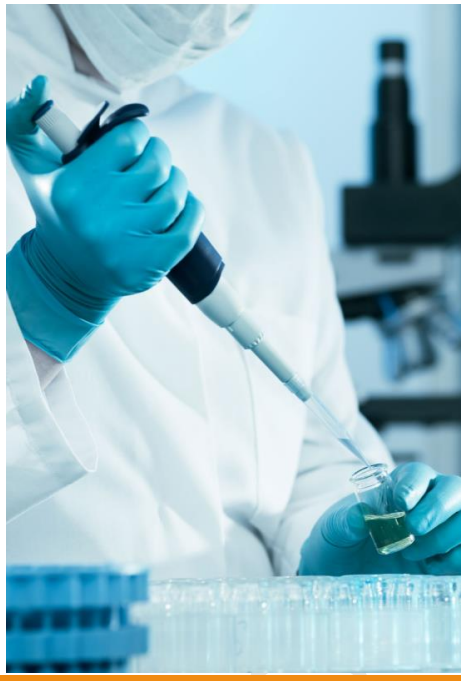
The other part of the puzzle is called **UPR,** the unfolded protein response, and because Sephin seems to be acting on this UPR, (gene makes the protein form in a different way). Dr. Shy analyzed many of the CMT1B mutations and figured out the ones that were affected by UPR. So those were the ones that would be most likely candidates to work with Sephin.

There is also encouraging results using Sephin on CMT1A. **We could potentially have clinical trials with both diseases if all goes well.**

Axon degeneration is also very applicable for 1B. In fact, we funded a project which is active right now, just like in 1X, to see basically if the specific target has an effect with CMT1B. We should have the results on this next year.

CMT2

- CMT2A and CMT2E stem cells, rats and mouse models in high demand from partners
- Gene therapy:
  - Baltimore summit to define strategy
  - Support CMT2D single-patient initiative
- Axon Degeneration:
  - Proof of principle experiment on-going (Partner A)
  - Several companies with relevant compounds
- CRISPR project with partner UCSF
- Gene Discovery (Züchner)
- CMT2A: Increasing activity of Mfn1/Mfn2 genes:
  - Screen of approved drugs for Mfn 1 reporter completed
  - New drugs to enhance mitofusin activity (Partner B)
- CMT2E: Drug screening initiated on stem cells



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CMT 2

I put all the CMT2's together because we find that a lot of technologies now apply across CMT2s. So why is this so exciting? Basically, a few years ago there wasn't much going on in CMT2, and all of a sudden we see a lot of activity. And this is because two interesting things are happening. First, all these new genetic technologies tend to apply really well for CMT2 because, if you recall, **CMT2 affects neurons,** and the genetic material of neurons is actually located in the spine. 90% of your neurons are in your central nervous system, so the people who are working on those technologies for the brain or the spine are very familiar with neurons, and also they're very easy to get to and to deliver a drug to. So they really want to start to try that on CMT2s.

And the other part, based on our strategy, is that we have developed some really good models of CMT2. We have two excellent 2A rat models which our partners really love. There's a good mouse model of CMT2E, and we also have some good stem cells. So all this coming together is creating a lot of interest in CMT Type 2. A lot of these technologies apply across CMT2 and will carry over to CMT1, but it's a good place to start with a lot of these new technologies, so let's go through it.

Gene therapy. There is a lot of focus on gene therapy, especially for CMT2. What we did is we put together a **summit in Baltimore** this summer, and it was really incredible because we asked the world experts in gene therapy to join us to help us basically not only educate ourselves but to also build our strategy. In the room, we had a dozen of the world's leading **experts in gene therapy.** It was really amazing to see the quality of the people, their willingness to come work with us, and also the openness. They were sharing very openly, and it was incredibly productive. And basically, what we've been doing since then is we've been working with them to define a very specific gene therapy strategy, with a lot of activities, a lot of partners involved. It's something that's really, really exciting to us because it will probably start in a couple of CMT2 types and may have broad applications over time across all CMT types.

And also I want to mention that there's a family that's done some really amazing work on **CMT2D**, and they are pushing a single-patient initiative. And they've approached us to work together with them, and we'll support them wholeheartedly, because they're also helping push the envelope.

Axon degeneration – we have an experiment going on with a partner on **CMT2A** that holds promise and we also have other companies that are willing to work with us on this, so very exciting.

Now, **CRISPR,** that's another really interesting area. And I'm sure you've seen it on TV, you've heard a lot of the discussions about it. We've been approached by UCSF, and you might have seen their video about CMT, they are really interested in working on CMT, and they really want to work with us. They were part of our last STAR meeting. We have STAR meetings twice a year, the last one was in San Diego in October, 2018 and it was just an incredible meeting. I think all the scientists there were just glowing about how this was the best meeting ever and the quality of the new people coming in, and the CRISPR folks were there, and they really lit up the room with their ideas.

Still a bit exploratory, but fast-moving, is a technology called **CRISPR surgery** where you take blood samples from a given patient and then from those blood samples they make stem cells. Then these stem cells are grown into neurons, and then they edit those neurons with CRISPR to fix the defective gene. And then they reintroduce this into the body.

We also talked about the **need to continue to discover new genes,** especially for **CMT2s,** so we actually increased our funding for Dr. Zuchner in Miami, who's doing an incredible job with his database, and he's discovering genes almost on a regular basis.

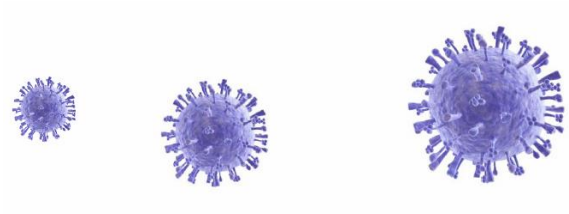
And then a couple of disease-specific initiatives. We actually did a screen of approved drugs for CMT2A. Unfortunately, the hits were not that convincing, so I'm not sure we're going to follow up with that, but it was important to do it, and we have a good assay to do that. And then there was a paper that came out last year about some specific drugs that could really help with the activity of **mitofusin,** and we are basically doing a pilot program with them to try to dig into this further, so this could be very exciting for **CMT2A.** And in **CMT2E**, thanks to the work that was

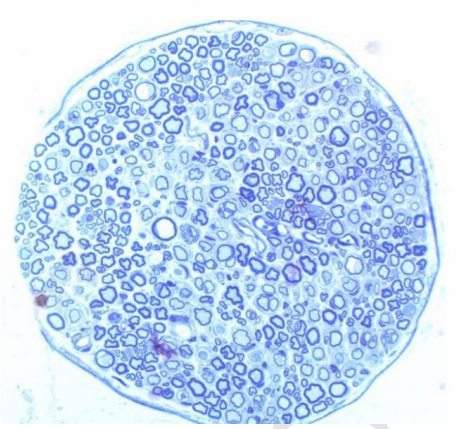
done on creating the stem cells, we are just starting to do some drug screening using those stem cells, which is very exciting.

Some people asked questions about **CMT2C** because the gene is the same as on some version of SMA. They were asking about the SMA drug that has been marketed. But, again, and I'm not a specialist here, but this drug is for a type of SMA that affect a different gene than the one for CMT2C. There's some good work going on in CMT2C in a couple of centers in the U.S., and some of those things we're talking about would apply across all of the CMT2s.

CMT4

- Gene therapy:
  - CMT4C project (Kleopa) with MDA
  - Baltimore summit to define strategy
  - Support CMT4J initiative
- Axon Degeneration
- Gene Discovery (Züchner)





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CMT4. Now, **CMT4** is very well suited for **gene therapy** because it's monogenic, but also because, remember, CMT4 is recessive, so both genes are affected, so there is what's called *loss of function*, and this should be very attractive for people working on gene therapy because they can replace all the defective genes.

We've had this project with Dr. Kleopa co-funded with the MDA that has actually showed some promising results in CMT4C and was included, obviously, in our Baltimore discussion. And then, again, there's a family doing a wonderful job on CMT4J pushing also a gene therapy approach, and we are in discussion with them how we can work together and support them. So a lot of

exciting things for CMT4 on gene therapy, and of course, axon degeneration would apply there as well, and gene discovery as well.

We're not done yet. We have a lot more work ahead of us than what we've done, so it's really important to support STAR. And I just want to explain to you, from our perspective, **why it's so important, and more important than ever, to support STAR.**

Why Support STAR?

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Leading Program – It's a really exciting program, and a lot of partners are coming to it. Again, people speak by joining us, and the list of companies keeps growing, and there's no better measure of success and credibility for me than this. But besides this, we're also very careful about our resources. If you look at our financials, they're really best in class, and we continue to improve them.

Best-In-Class Financials – If you look at most organizations, they tend to have overhead levels in the upper 20's. CMTA historically was around 20%, which is really good, if you look on Charity Navigator, it's actually quite good. But we've actually improved it. We made a lot of tough decisions the last two years because we want to continue to improve that. And if you look at last year's financial, we were down to 12% as overhead, which is absolutely world-class, and I'm

really proud of the team. And we actually think we can sustain kind of this low-teens level looking forward, so a very, very world-class performance here.

Decision Makers – And the other thing that is very special, and I really am proud of about the organization, is that the people who are making decisions (the board members) are also major donors. So in a way, people put their money where their mouth is. About 20% of our revenue comes from the board itself, so the point there is we're going to take care of your donations very well because ours is there as well. We are all major stakeholders here. We're all in. We believe in it, and again, we speak with our own money and own fundraisers, and this, I think, is very unique about this organization. And I can't say enough about my colleagues on the board and their dedication and the amazing work they do. And it's recognized, and we work very hard for this.

Recognized: We just got upgraded to platinum by GuideStar. With Charity Navigator we've been in a three-to-four star range for the last few years, even though they keep raising the bar. And last year, for the first time, they gave us a perfect 100% rating on transparency and governance. We're very proud of that, so it's very important to look at those third-party evaluations.

Multiplier Effect – Because we work with partners, the heart of our strategy is that when we spend one dollar, we incite partners to come in and spend 10 times more at least. **So when you give a dollar to STAR, obviously, we take good care of it, it's spent very wisely, but also it brings in partners that spend the big money, and our partners spend tens of millions of dollars on CMT, and this multiplier effect is really important**.

Remember, we don't have the hundreds of millions of dollars that it takes to develop the drugs.

Everybody Has a Role to Play

- Get Involved! Join / help an event or a fundraiser. Make CMT your cause!
- Join the INC Patient Registry
- Visit a CMTA Center of Excellence. Then Visit Again!
- Remember the 3 W's:

  Work, Wealth, Wisdom

THANK YOU!

CMTA
Charcot-Marie-Tooth Association

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This is a very challenging but also very personal journey to me. **That's why I wanted to show a picture of Yohan here, my little hero.** He didn't choose to have CMT, but he's the reason why we are involved, and why we have a passion around this. And I think for all of you on the phone, I'm sure it's the same thing. You all have a personal journey, so the point I want to make is, 10 years ago when we looked at the situation, it was bleak. It was like staring into the abyss. There wasn't much to do. It's not the case anymore. There's a lot everybody can do.

Everyone can join the movement. Please get involved. Everybody has a role to play. These are exciting times, but there's a lot of work left to do, and we need everybody on board to help us.

The CMTA has branches, we have fundraisers, we have walks. Just please make CMT your cause and help us. And also, help yourself. Make sure to join the INC Patient Registry so you'll be there when clinical trials come along. Go visit a Center of Excellence, and go again. This is how we get a natural history. It's really important, especially for the less common types of CMT. We need more and more patients so we'll be ready for clinical trials.

And then when I started working on nonprofits, people told me about the three W's, and I think that applies to everybody. So we can all help through Work, through Wealth, and through

Wisdom, and hopefully all three or a combination thereof. And then all together, we'll move this forward.

CMTA RESOURCES

Questions?

Patient Registry
https://www.rarediseasesnetwork.org/registry

Clinical Trials
https://clinicaltrials.gov

CMTA
https://www.cmtausa.org

Annual Appeal - $150k match!
www.cmtausa.org/35years

Sign-up for e-news
www.cmtausa.org/enews

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The work the CMTA is doing right now on all fronts is nothing short of impressive. Please get involved!
http://www.cmtausa.org