Research 101

Learn About the Process of Basic Science and Clinical Research

You can view this presentation at: youtu.be/0ONRA6t75H4

[00:00:00] **Roberta Pesce:** We're moving on to our next talk now, and it is about understanding basic science and clinical research. I am joined by Dr. Benjamin Greenberg, professor at UT Southwestern UC from yesterday. He is also the director of the Transverse Myelitis and Neuromyelitis Optical Program, the director of the Pediatric CONQUER Program at Children's Health, and, of course, SRNA Board member. Dr. Greenberg, hello again. Welcome, and over to you.

[00:00:31] **Dr. Benjamin Greenberg:** Hi, Roberta. Thanks, and thanks to the group in the prior presentation. The topic of AFM is so important, and, actually, everything that was discussed in the last section directly relates to what we're going to talk about for the next 20, 25 minutes. I'm going to be giving two different talks. I'm going to start with something called an introduction to research, and I'm going to share my screen. And let's see if we can't get this looking correctly here. Just one moment. And when we talk about research, we talk about it in a lot of different ways. And you heard a lot of different types of research that's going on. And it's important to have an understanding of how these all relate to each other. And so, what I'd like to do is give everybody an introduction to what research is and how we do it.

[00:01:36] **Roberta Pesce:** Ben, I'll share them for you, I think. Or if you can stop sharing. And are you in reading view?

[00:01:44] **Dr. Benjamin Greenberg:** Yeah, it was just in presentation.

[00:01:47] **Roberta Pesce:** Okay. I can also, I'll share them for you.

[00:01:49] **Dr. Benjamin Greenberg:** Thank you.

[00:01:50] **Roberta Pesce:** Just give me one quick second. Yep. One second.

[00:01:53] **Dr. Benjamin Greenberg:** And so, one of the things that's important to understand is research takes a lot of different forms. And you heard about some of it with the AFM talk. We heard about the notion of doing observational outcome studies. We talked about the notion of biorepositories, and a lot of times it can be confusing. So, Roberta, if you advance one slide.

[00:02:17] The first thing to understand is what research is. And at its core, research is about asking and answering questions. That's all research is but doing it in a systematic way. So, on the next slide, we ask the question, "Why do we even do research?" And the main reason is proving cause and effect. Proving associations between two different things is extremely important for understanding a disease and identifying effective treatments. Without doing research to scientifically prove why things happen or how things happen, we are limited in terms of what we can offer our patients. And it's scary to think about a world where research is not undertaken in a systematic way.

[00:03:05] And on the next slide, I give examples of what can happen without well-conducted research. We could still be doing bloodletting. We could tell people that their conditions are a result of evil humors or spirits moving throughout the body, and if you just have a good bleeding, you'll feel better. That was an accepted practice in the days before research. There are some therapies that are dangerous but could be used. Cocaine was used medicinally for decades because there were advantages. It could be used as a topical anesthetic. It could be used as a supposed modifier of mood because you feel a lot better after cocaine. But it came with significant dangers.

[00:03:55] And then there are therapies that are neither effective or safe, and an example was mercury. These days we talk about screening for mercury poisoning, heavy metal poisoning as being related to all sorts of conditions, but for years, mercury was tried as a therapy for all sorts of conditions, including syphilis and including certain what turned out to be autoimmune conditions. And so, without research, people will propose and try all sorts of things with no evidence to support the efficacy or safety of the intervention.

[00:04:26] So on the next slide, I'd like to give an example from recent history on how research can save us from ourselves. Very well-meaning human beings, whether they're patients' families, physicians, clinicians, or scientists, we want to help people. But without research, we can do significant harm. So, I'm going to tell you the story of minocycline relative to amyotrophic lateral sclerosis, ALS, known as Lou Gehrig's disease. So, if we advance one, the slide will build.

[00:04:57] First, it's important to know that minocycline is a safe molecule currently used as an antibiotic. And, Roberta, if you could advance one. Oh, no, sorry. Go back. I guess it's not building on yours. So, on this slide it talks about minocycline being safe. We use it as an antibiotic. As everyone is probably aware, ALS is a uniformly fatal neurodegenerative condition. And what was interesting was in cell culture models, so in animal studies and in a dish, minocycline helped neurons survive. So, everyone looked at this and said, "Geez, we have a safe medication that's currently on the market. In a model system, it helps save neurons, and people with ALS are dying. We need to put everybody on minocycline."

[00:05:47] And there was a big fight on whether or not it would be ethical to do a placebo-controlled trial of minocycline where some people would get minocycline with ALS and some people would get placebo. And there was a large fight saying that that's unethical because these people are dying, and we know minocycline is safe. We don't need to prove the safety. And, yet, after long debates, the placebo-controlled trial went forward. And if we now advance the slide, what's listed here from the publication are very technical terms, but I'll draw your attention to the bottom.

[00:06:20] The individuals on minocycline died faster than ALS patients on placebo. I'm going to say it again. The ALS patients on minocycline died faster. They declined faster and died faster. This was a safe drug as an antibiotic, but it turned out to be an unsafe drug in the setting of Lou Gehrig's disease because it didn't do what we saw in animals or in the dish. It didn't protect the individuals. It actually led to a more rapid decline and faster death. And so, what we see is the purpose of doing placebo-controlled trials is to protect us from ourselves. Even the most well-intentioned studies can lead to unintended consequences.

[00:07:03] So if we advance the slide, we can talk about how do we do research. So, I gave you an example of an interventional trial, so a placebo-controlled trial, but there are lots of different studies: retrospective studies, epidemiologic studies, observational studies. And it's important to put these in perspective in terms of how we do research. So, on the next slide, what you'll see is, stepwise, I think it will build. Roberta, if you advance, we'll see if we get it.

[00:07:32] **Roberta Pesce:** Yes. Let me stop sharing and restart for a quick second because I don't think it's building. But yeah, I'm working on it.

[00:07:38] **Dr. Benjamin Greenberg:** No problem. So, what's on the next slide is a discussion of how we go from hypothesis-generating research. So, you heard from Amy and from Nisha in the last talk about AFM on how we do animal models and cell culture models, and Nisha with these very fancy and complicated chips with little proteins on it that we can test blood and we can see whether or not your blood is sticking to a chip. And that's hypothesis-generating, or maybe preclinical testing. It's all in a lab, in general.

[00:08:11] But then we move into the interventional studies, phase one, and then phase two, and then phase three studies. And this is just the general idea of how we do research. We may find ourselves in any part of the spectrum, but this isn't our only pathway. On the next slide, what we see is there are lots of opportunities to assist in research, to take part in these hypothesis-generating or preclinical studies or even observational studies. So, for example, there are registries that you can take part of where you share your data. You fill out information about your history, and you as an individual are incredibly important. But when we have 1,000 of you and can compare and contrast data, it becomes extremely valuable. There are survey studies where we ask very specific questions: How are you feeling? How are you doing? And we can validate outcome measures.

[00:09:04] And then you heard a lot in the last session on AFM about the incredible value of sharing samples. Now, nobody likes to get their blood drawn, particularly the kiddos I treat do not like to get their blood drawn. And so, we do want to be sensitive to the fact that it is a sacrifice. There's a little bit of pain with the blood draw. If there are the opportunities to give a sample, I cannot stress enough how valuable it is for the research that happens.

[00:09:36] And then there are both observational and interventional trials. Observational where you agree to have assessments on a regular basis, or check-ins on a regular basis to collect the data, whereas interventional, where we're actually going to do something to you. And it's extremely important to recognize there are different types of interventional trials. There's what's called open label interventional trials where everybody knows what they're on. There are randomized trials where you can be randomized to one of two therapies. One is a known effective therapy. The other is a new experimental therapy.

[00:10:07] And then there are the placebo-controlled trials where people get randomized either a drug or nothing, similar to that minocycline trial. And the reason we do those is sometimes our hypothesis of a drug that's going to work turns out to be incorrect. And it turns out that taking nothing is better than taking the drug we recommend. So, lots of different ways to get involved.

[00:10:28] And as we near the end of this, I want to point out some specific places you can go and participate in studies. So, on the next slide, it's important to note that the SRNA is very involved in not just talking about research or reporting the results of research, but in promoting research and in trying to understand the conditions that all of you in our community face. And if you go to the wearesrna.org website and you go to the top right where it says Get Involved, you are given the opportunity, if you haven't already, to join the registry or to answer surveys, or to give your information so you can be contacted for research in the future. And as somebody who has used data that has come out of the registry in part of our publications, I cannot

stress enough how valuable it is. And so, if you can take the time to fill out these questionnaires, sometimes there are new ones that pop up, it is greatly appreciated.

[00:11:28] On the next slide, I'll give the shameless plug for UT Southwestern. For our clinical trials, we do have a search for study opportunities on our website where you can put in your diagnosis and see if we're actively recruiting for, these are usually interventional studies if we have a drug study going on. But very importantly, in terms of drug studies, I'll end with the last slide, which is the website ClinicalTrials.gov. Every interventional clinical trial in the United States is required to register on ClinicalTrials.gov, meaning if you want to know if there's a new therapy study, stem cell study, medication study, rehabilitation study, drug study, it will be on this site.

[00:12:14] And it was phenomenally well done where you can put the condition or disease that you're most interested in. You can put your zip code and ask for studies in your region, and you can limit it to studies that are open for enrollment because this will list every study that has gone, even ones that are closed to enrollment. And so, it's a great tool to really go through and find where are opportunities for you to take part in research. And so, some people when they hear about research assume that in order to take part, they have to be part of a drug study, and the reality is you don't. Giving your data and giving your blood is so valuable and so appreciated by everybody. There are lots of opportunities to take part.

[00:12:58] So be on the lookout. Be engaged with the SRNA. They keep updated files of studies that are recruiting for our patient population. And if you ever have the chance and are willing and are able, we welcome your involvement in any of these studies. So hopefully that's helped to give you an introduction to research. And I'll defer to Roberta whether or not we should take a short break and return, or if we should just go through to the next talk. I know people have been online for a while at this point.

[00:13:26] **Roberta Pesce:** Yes. I would say, if possible, let's take a question or two, Ben, and then we move on real quick. And then we'll move on to the next talk if that works for you.

[00:13:35] **Dr. Benjamin Greenberg:** Absolutely fine.

[00:13:36] **Roberta Pesce:** Great. So, here's the question: "How do I weigh the risks and benefits of participating in a trial?" That's a good question.

[00:13:46] **Dr. Benjamin Greenberg:** It's an outstanding question. So, three types of studies to consider. First, an observation study with no sampling, a blood sampling or anything else, where really the only risk is to your confidentiality. So, if you're filling out surveys that are of a sensitive nature. Maybe we're surveying people about sexual function or we're surveying people about personal finances. Your risk is really around breach of confidentiality. And I'd love to say breaches and hacks never occur. I'll say clinical trials have not been a big target for hacking in the world. And so, we take a lot of steps to protect your data. So, I would say the risks are low.

[00:14:25] The benefits to the community are huge. The benefits to you as an individual are very small. So, you're doing it altruistically. It is low risk. Benefit to the community, low benefit directly to you. Secondly, if we have a study where we're taking samples, the risk to you is not just the confidentiality. Now we're adding the risk, for example, of a blood draw. Blood draws are safe, but it's the discomfort. And, in those situations, the value to the studies go up. We're getting biologic material, and the potential benefit to the community goes up. The direct benefit to you is still usually low. You're waiting for the whole community to benefit.

[00:15:02] And then we get to drug trials, and this is where it gets hard. The risk depends on what drug or intervention's being tested, whether it is a brand-new unapproved drug or whether it is something that's been approved in the past and we're now using it in a new situation. In that scenario, we know the risks because it's already been studied, and we can tell you. In a new drug scenario, that's where the risks are very difficult to quantify. You want to spend a lot of time talking to the investigator on what is known and unknown about that intervention. What animal models were done, what safety studies have been done before it came to a human.

[00:15:41] **Roberta Pesce:** Yep. Perfect. That's great. And maybe an additional one that is linked, and then I promise we'll go to the next presentation. "Are there any risks to providing my blood sample for research?"

[00:15:53] **Dr. Benjamin Greenberg:** Yeah. Two risks: breach of confidentiality and then just the actual procedure itself. The blood draw, technically some people faint during a blood draw, so I guess there's a risk of fainting. You might get a bruise at the site of the blood draw. But I've never seen anything more significant than that.

[00:16:10] **Roberta Pesce:** Okay. Perfect. Alright. Thank you so much, Dr. Greenberg. And I accidentally already gave a little bit of a giveaway...

[00:16:18] **Dr. Benjamin Greenberg:** No, it's all good.

[00:16:18] **Roberta Pesce:** ...on the next talk that is happening. Okay. Perfect.

[00:16:30] **Dr. Benjamin Greenberg:** It's a preview.