New and Emerging Therapeutics

You can view this presentation at: youtu.be/tIygNblJda8

[00:00:00] **Dr. Stacey Clardy:** Thanks for having me. It's always, honestly, an honor to speak to the group and with SRNA. It's an incredible organization and has been integral to everything we do at so many places, including the University of Utah.

[00:00:20] And so I have been asked to speak on new and emerging therapeutics and to do it in 20 minutes. And so originally, I started making a slide that was just packed with everything that's recently been approved and all the ongoing clinical trials. And I was plowing through that and then I realized it's a struggle for me to do, but it would be also impossible to memorize all of them.

[00:00:45] So, I want to talk to you a little bit today more about how do we find out what's going on, how do we stay up to date always, and we'll still go through some of the currently enrolling or just about ready for primetime sort of trials. These are my disclosures. I think you've probably noticed with many of the physician scientist researchers.

[00:01:07] We have several disclosures because really the only way to get things done in a timely fashion these days is to collaborate. So, for example, many of us will have grants with the federal government and then also our pharmaceutical partners may help supplement those. And we're trying to really bring everybody to the table because what we've realized over the past couple of decades is everyone doing this in a silo is certainly a disservice to the patients.

[00:01:32] And so if we can all get together at the table, including the patients, it goes faster and we make fewer mistakes. So, these are some of my disclosures. Many of you know SRNA has a fantastic podcast series and that it is designed for you. I also have a side gig doing the neurology podcast, the neurology minute daily briefing.

[00:01:51] Those are for neurologists, so they're full of jargon because this is how your neurologists are getting their education, but they're also free to you. So just be aware of that as another resource. And that's about it for my disclosures. So, let's talk about emerging treatments and let's talk about why it matters, why data matters, why evidence matters, right?

[00:02:12] So this picture is of a pyramid, and at the bottom are what we would consider your docs sitting around at these meetings, we try to get to where we can all brainstorm together ideas, opinions. Or, when we sit down and put pen to paper and write an editorial and say this really needs to change for our patients.

[00:02:33] And at the top, really, right near the top, are randomized controlled trials, right? So, the bottom is really the lowest level of evidence. The top is what we always strive for with randomized controlled trials. You all know and, it was gone over again today that for aquaporin-4 NMOSD, there are now four FDA-approved treatments.

[00:02:54] And that's fantastic and we keep talking about it because for many of us who have more gray hairs, we remember a time when there were no treatments for any of these. And so that's something to really be celebrated. Celebrate it quickly and then move on, right? Because we have to get treatments for the rest of these conditions.

[00:03:10] And so we'll talk a little bit about where we are for the rest of these rare neurological diseases. I think it is really important though, to realize and I think many of you probably do if you go out on social media, the power to change this is, is with the patients, right? You have probably seen this for some of the ultra-rare diseases, where the family or the patient is raising funds where the family or the patient is going to Congress, right?

[00:03:38] I just don't want you to ever forget that – that is far more powerful than physicians doing the same thing. Remember that you have that ability and that power and always keep that in mind when you're discussing things, when you're frustrated about what's going on. A quick overview, let's demystify this a little bit, right?

[00:04:01] Why does it take so long to get an approved treatment, right? So, it's this drug discovery process, right? If we're going to be rational about it, which we are now in, in modern times. Back in the day, it was pure trial and error, and somebody thought, oh, maybe and would try something but now we try to be rational.

[00:04:21] So this requires the basic science research to understand. So, you take a condition like transverse myelitis. So, you, take samples from patients or you take images from patients, and you look and you say, what went wrong? Wait, why did this happen? And then you look for a biomarker, right?

[00:04:39] So sometimes that biomarker is a signal like an antibody in aquaporin-4 and MOGAD that an autoantibody that's up and that shouldn't be there. Other times, we can use changes on imaging or other just things we can follow, things that give us a clue as to where the biological process went awry to cause the condition, right?

[00:05:00] And there are actually now companies that focus solely on speeding up this process. Because this could take decades. So, now leveraging the available AI and technologies, there are companies that will do high throughput screens of thousands of things to get us closer to a target. And speed up the left side of that figure.

[00:05:17] Then of course, once we've identified a target, we have to hope that there's a drug out there that can target it. That kind of either needs to be developed or the drug needs to be borrowed because it was developed for something else and we need to see if it's a fit, will it affect that, where the process went awry.

[00:05:35] And then it goes into clinical trials. And really the fastest in many cases we can do clinical trials is about five years in the rare neurologic diseases. We still always aim for five years, but recruitment slows everything down exponentially because they're rare and because we need to find the patients.

[00:05:52] That's where SRNA and the other organizations, and you come in, as well. So again, like target identification, very important. We've got to be rational about this because there are risks to everything, right, as you know. And then optimizing that target once we figure it out. And then down here at regulatory approval is the other step.

[00:06:11] So, even after you finish the clinical trial, there's that extra layer of safety where experts get in a room, they may not know about your condition, but they know about safety and drug safety and what's required there. And, so once a trial's done, it has to go to regulatory. This is really what we, in the US, think of as the FDA. And in Europe, we think of as the EMA.

[00:06:31] And each set of countries or country has a different board where they say, okay, we'll look over what you found with your clinical trial, but we're going to put an extra sort of critical lens to make sure that the risks of what you're proposing are outweighed by the benefits to a patient.

[00:06:48] So, I went through and I was doing this. I went on clinicaltrials.gov and I was making the list for you, and I realized it's going to be immediately outdated. So, let's just make sure you have the tools. Clinicaltrials.gov is freely available to all of us, right? This actually collects not just US clinical trials, right?

[00:07:06] It's a .gov website. So, you might think US clinical trials. Essentially, really any clinical trial of any credibility, anywhere in the world is logged on this website. So, you can see there's search boxes. So, under conditioned disease, you could type in transverse myelitis, you could type in optic neuritis, or you can put in some other modifiers, right?

[00:07:24] Maybe sort of nicknames or colloquial names for what you're looking at. And, you will then have a list generated as soon as you hit search that tells you any trials going on. And it'll tell you the ones that are enrolling, the ones that are closed, the ones that might be coming up in the next couple of years.

[00:07:41] Some of them are small trials that just one site and maybe they're not an in intervention necessarily. Just like, you can donate blood or images and all the way up through the full scale, really large enrolling interventional clinical trials. So, if you remember anything from my talk, just remember this.

[00:07:59] This is how you always have your finger on the pulse of what's going on, what's coming down the road, and who's doing it and where, and is it right for you. Do you even want to be involved, right? Because they're required to follow the same format and list exactly what they're doing in a non-jargony summary.

[00:08:15] And this is just what you need. So, if you remember this, you'll always be up to date. You check this before any upcoming doctor visit, right? Just type in the condition, see if something new popped up. In the US especially, anyone doing a trial is mandated to keep this up to date. So, it's a powerful resource.

[00:08:33] This is what I go to when I'm walking in the room with one of my ultra rare patients. Maybe it's a genetic diagnosis. I type it in here, and then I can walk in the room and say, "Hey, here's what we have coming up." Or "I don't see anything right now," and then it's immediately to the minute up to date information.

[00:08:51] So this is powerful for you. Now let's do what I told you I wasn't going to do too, much of it, but let's fly through it. You already heard today we have four approved therapies for NMOSD. I do want to show you for those, three of those four, because Eculizumab and Ravulizumab, I'm combining here, right?

[00:09:06] Because they're both complement inhibitors. And as Dr. Flanigan was telling you, it's just how frequently do you need to be dosed? Most of our patients who are on Eculizumab are now switched over to

Ravulizumab because it's easier on their body. It's every eight weeks instead of every two. But I want you to look at these figures and for the next three slides I have these figures.

[00:09:23] This is what has to happen in a clinical trial, right? That top line is the people who received placebo, right? And that bottom line is the people who received drug in the trial. And this is how, long till a relapse, right? So, that's a nice sizable difference, right? And so, what I wrote here in text at 48 weeks, we have to follow for a long time.

[00:09:45] And these trials, that's another reason they take so long. 97% of the patients for this drug were free of relapse compared to 63% who were on placebo. Now keep that, take a picture of that in your mind. We're going to do it for the other drugs also. Fantastic Inebilizumab. So, you can see a similar graph. These are all generated by different people.

[00:10:02] But boy, look at that same thing. Top line. They didn't get drug. Bottom line, they did get drug right? And those differences are all statistically significant. Same thing for Satralizumab, right? So, the top line is, who got drug, bottom line is who didn't, and time to a relapse, right? So, these are the kind of things we're looking at.

[00:10:20] We all have to be convinced before we suppress someone's immune system or muck with it in any way, shape or form, that there's a rationale for the target. Those all targeted different parts of the immune system that we know by looking at blood and biomarkers and spinal fluid are out of whack and make plausible sense for how that bad auto antibody could be causing the damage, right?

[00:10:43] And so all three of them, different targets along that very complex immune pathway, they all worked, right? So that's how it's done in a way. It's not rocket surgery when you think of it that way, right? Look at the final common denominator. Look at the pathway, find a biomarker targeted. So, what's going on?

[00:10:59] Now you again heard about this MOGAD. So right? Literally as soon as, and frankly before those NMO treatments were approved, everyone was already going, okay we're on the right pathway. We know we can do this in rare neurologic disease. Let's go. And so already the discussions were on MOGAD before those NMO top line results were even released.

[00:11:20] So, the two trials widely currently enrolling for MOG right now, especially in the US and as was mentioned before, are the cosMOG trial and the METEOROID trial, right? UCB is sponsoring the cosMOG trial. Roche/Genentech, the METEOROID trial. You'll recognize the name at least in this Roche/Genentech trial of Satralizumab because that's approved for aquaporin-4 positive NMOSD, right?

[00:11:43] And so they were looking at that, could that be a mechanism in MOG? Seemed plausible. So, the trial's ongoing, the cosMOG trial of course is a different mechanism, right? And looking at also clearing out and getting rid of those pathogenic MOG autoantibodies. Both of these are enrolling. If you have MOG, if you know someone who has MOG who may want to be involved in these trials let them know, right?

[00:12:10] They're ongoing. This is how it gets done. Transverse myelitis and optic neuritis, right? These are harder because as many of you know you get one of these labels, this means we didn't find an antibody. We didn't say, oh, this developed into multiple sclerosis, or, oh, we had a clear infection that caused it and it was a monophasic event.

[00:12:32] When you carry these labels, they're not associated with one pathogenic mechanism like an aquaporin-4 antibody or something. So, it's harder to study in that sense, right? A more heterogeneous group

has to be more careful when designing trials. Nonetheless, there is a trial coming up. This is going to start enrolling almost imminently, right?

[00:12:52] So either before the end of 2025, or right at the start of 2026, many sites scattered across the US and this is looking at, for a new optic neuritis or a new transverse myelitis, right? Now, I know that's tough, right? You go what about an old one? This is not targeting that because once you move into the chronic phase, it's different.

[00:13:15] The process is different at the level of the immune system. And the changes that we make in the recovery go for is different, right? So Timely-Plex is the new acute people. So, if you're involved in the community and you suddenly hear about a neighbor or someone in the community going, I've had my first time ever optic neuritis, or my first time ever, transverse myelitis, let them know about this trial.

[00:13:34] So what they're doing overall, these always have complex figures, and you can have access to this later if you want to know, but they are trying to see should we be even more aggressive upfront than most centers are? So, most of the time, and I realize many of you will know this, if you have optic neuritis or transverse myelitis, you'll get steroids.

[00:13:53] And then we'll stop and see, did you get any better? And if not, we may consider something called plasma exchange. And, what the big question being asked here is, what if you combine both of them from the outset immediately and compare that to people where you do just the steroids followed by the plasma exchange? Does it make a difference in their recovery in the longer term?

[00:14:15] It's a good question to ask because you might say, why don't we just do it all upfront for everybody? But you get risks with all of this stuff. And for most people, plasma exchange, that's going to require hospitalization, right? Risks come with that. Now are you getting hospital acquired complications, things like that.

[00:14:31] So that's why this is a very good question to know, because it could be that we find out, no, when you follow longitudinally the way most centers are doing it one treatment at a time, assess next treatment at a time, assess may be the safer way or maybe the right way, or maybe not.

[00:14:47] So that's what this trial is trying to get at. Very excited that this will start enrolling soon, and that so many centers in the US are involved. I'm going to talk briefly about autoimmune encephalitis. I don't know how many people here are familiar with that, but I'm going to talk to you about this as an example that I am very familiar with, right?

[00:15:03] I'm the primary investigator, principal investigator on this Extinguish trial. This is currently enrolling. It's for something called NMDA receptor encephalitis, right? And there's another one as well, I want to tell you about two again, Roche/Genentech. You'll recognize the name of the drug again Satralizumab, also enrolling for NMDA receptor encephalitis.

[00:15:21] Two trials for that condition. If you hear about it, especially acutely, please let those folks know because this is harder to enroll in trials than NMO or MOG or transverse myelitis because when it strikes acutely, people have often delayed diagnosis don't know what's going on, and they're severely sick often in the ICU.

[00:15:40] And so it's very hard to raise awareness to a community that doesn't know that they have the disease until they're in the ICU, right? These trials are ongoing. But why do I bring that up? Beyond raising awareness to those of you who are involved in the community, this is hard stuff. And so, I think autoimmune encephalitis is a cautionary tale here.

[00:15:59] Already two trials in this field had to be terminated, right? And the reason is it's hard to enroll. One of the main reasons, not the only reason, but sometimes they just don't work. But one of the main struggles is that they are very hard to enroll. So, if anybody here has expertise on how to raise awareness acutely let us know for sure.

[00:16:18] But the point is, development of new treatments in any of the rare conditions cannot happen without participation, without the patients who, in the midst of working through the diagnosis and everything that comes with that, are also interested in finding out more and being involved in the better treatments.

[00:16:40] Not always necessarily for you, but for the next person, right? And so, this is really, I think, the imperative to all of us. When I talk to physicians, I have a version of this slide as well, because sometimes we fall down here, sometimes we are just so busy going through the day from one patient, maybe to the next patient.

[00:16:59] We don't look at clinicaltrials.gov and we don't discuss what are those opportunities, what is the future? What is enrolling now, what might be enrolling in the future? And if we don't tell our patients that, we're not really giving you the information that you need to make informed decisions, right?

[00:17:16] We can tell you about the treatments that are approved, but if we don't tell you what might be coming up, what opportunities you have to be part of the better solutions, then we're not really doing our job. But I get it. It's busy. It's hard. We have so many other things like symptom management to discuss, all the things that come up as you know during a clinic visit; costs of things, access, getting disability placards, all that kind of stuff.

[00:17:43] But this is crucial. And so, this is where you can also help to keep us on track, to help to train us, right? So, at the end of the visit I encourage my patients to do this. Okay, what's new? What's in the pipeline? What's coming up, right? This is very important. And, on the couple times when I haven't done it, patients bringing this up, again, it helps me to shift. It helps us to get into that mind frame of, here's your current treatment plan, but what's plan B and what's plan C, right?

[00:18:11] You and I, you, your doc, the patient. We both need to know that, we need to have our backup plans and, asking this question always brings that up, as well. So, I didn't want to do too much. I hope that we got some useful kind of framework, a way for you to have the control. Clinicaltrials.gov, being aware of the conversation and leading the conversation for your docs, right?

[00:18:36] The best thing you can do in every visit is discuss the challenges you've had, things you need immediately, symptoms that need to be addressed. But then at the end, I would say always don't forget what's new, what's coming down the pipeline, how can I be involved if you want to, right?

[00:18:55] But at least to know about it. And that is where increasingly we count on you as part, as a partner in all of this. So, I am a little bit off the hook, right? Because I looked at the agenda and so I had slides on both of these things and I was super happy to see that you're going to hear about immune tolerance next, which deserves its whole own talk as a new and emerging therapy.

[00:19:19] And same thing for stem cell therapies, including the Q cell trial updates. So, those are two big things that warrant their own talk. So that's why I didn't get into them. And you're going to hear it straight from the experts. That's what I have. I'll leave it to the SRNA folks if we have any time for what's next.

[00:19:37] **Dr. GG deFiebre:** Thank you so much. Thank you so much, Dr. Clardy. We did have one question where someone asked if AI is being used to find other treatments.

[00:19:47] **Dr. Stacey Clardy:** It is actually. And I know there's, for example, in Utah, there's one company called Regeneron, for example. There are a few companies now internationally that are using proprietary largely, but AI to do that.

[00:20:02] Remember back to the slide about, going from disease identification all the way through clinical trial and regulatory. The piece we were talking about with what are good candidate targets and good candidate molecules. So, some of the companies focus on existing off the shelf compounds already approved, and can they be repurposed for some of the new discoveries in terms of pathophysiology, what's causing these diseases?

[00:20:27] Some of the other companies take the opposite attack and they look at what we know about disease pathophysiology, pathology, and they're identifying potential targets to intervene, right? So just like we use very often NMO aquaporin-4 positive as our model, and those three big, approved drugs target different parts of the immune cascade that go wrong.

[00:20:50] There are companies out there that will take that basic science data, look at every piece of that pathway and say, do we have a drug for it? Is it a good target? And do that rapidly, right? In like thousands of fold on a daily basis. They're still young. Some of them have just after 10 years of development, gotten their platforms perfected and they're now cranking out their first targets and their first trials.

[00:21:16] But it is one of those things where we have the benefit of the fact that they've been perfecting that now for years and now we get to see the returns just sort of in the past year. And so, I'm watching that space too because they're starting to crank out, right? That's exciting because if we can eliminate years, right. That's what we need to do.