NF2 Biosolutions /CereXis Webinar transcript : Understanding NF2 7.14.2020
With Dr Welling and Dr Evans

>> Mani: Good afternoon/evening to everyone in the US and on the other side of the Atlantic. My name is Mani Mohindru. I am the CEO of a young biotech company that was spun out of Recursion Pharma earlier this year. CereXis is working on rare tumors, and our lead clinical program is focused on Neurofibromatosis Type 2, or NF2 - the topic of today's webinar. Before I proceed with the introductions of the panelists, there are some housekeeping items that I would like to mention. We do have live captioning for the meeting. If you want to see captions, click the closed caption button at the bottom of your screen and select Show subtitles. You can adjust the settings to make them as small or as large as you would like. Also, you may find it helpful to click the 'view full transcript' option, which will allow you to see the full captioning.

The format of today's question will be questions and answers only. Moderated by my colleague Dr. Ajay Aggarwal, the Chief Medical Officer of CereXis and myself. All attendees will be in the unmute mode only during the session but can send in questions via the chat at any time we'll try our best to address them during the course of our discussion. Now, we're extremely pleased to have two very distinguished physician scientists today with us who have been involved in the understanding and management of NF2 for a long time nd really don't need much of an introduction. We have Dr. Gareth Evans with us today - he is a Professor of Medical Genetics and Cancer Epidemiology at the University of Manchester, UK. He is the author of the Manchester Criteria widely used to establish diagnosis of NF2 and has several landmark publications on the disease. Dr. Evans is a member of the CereXis's Scientific Advisory Board. We also have us with Dr. Brad Welling, an endowed Professor and Chair of Otology and Laryngology at the Harvard Medical School and Chief of Otolaryngology at Mass Ear and Eye. His clinical expertise focuses on hearing loss, facial paralysis and deafness related to NF2 and his research efforts are focused on NF2 associated vestibular schwannomas. Dr. Welling is also a Consultant for the company. Importantly, we are very thankful to NF2 BioSolutions for being our partners for this webinar and providing a lot of the logistical support. We have with us today Gilles Atlan, VP of NF2 BioSolutions. I would like to invite Gilles now to say a few words about the organization.

>> Gilles: Thank you very much, Dr. Welling and Dr. Evans, for your participation in this webinar. And thank you to Cerexis, Mani and Ajay for hosting this webinar and joining the fight. We are also happy to have Dr Welling joining our NF2 BioSolutions scientific advisory
And for your information as well, Dr. Evans is on the board of the Biosolutions branch in the UK. Interacting with Dr. Evans and Dr. Welling, I can tell you, that they are both very committed to the NF2 community , they are extremely collaborative and are helping so much in the process of finding a cure. A few words about myself and NF2 Biosolutions. My daughter Karen is 12 years old with NF2, she has had several surgeries already and she is the reason why I volunteer as the Vice President of NF2 Biosolutions. It's a nonprofit led by patients and families. The goal of NBS is to identify novel therapy platforms and approaches, check if it can be applied to NF2. And if yes, we jumpstart the research and fund it and do our best to accelerate it by removing the road blocks that these research labs are facing. Please check our website and continue to support, volunteer and donate to our nonprofit so we can have a long term therapy for NF2 as soon as possible. Thank you very much. And back to you, Mani.

>> Mani: Thank you, Gilles. Let’s get right on to the questions. Let's start with you, Dr. Welling, since you're on my extreme right starting from the beginning. Tell us how you got involved with NF2 and some of your work in the field, both from a research perspective, from understanding the molecular basis of NF2 to the amazing clinical work you've done over the past several years. Dr. Welling.

Brad: Thank you very much. This is a great honor to speak to all of you today, and especially it's a great honor to share the platform with Dr. Gareth Evans, whose work I've greatly admired. I learn a great deal from him every time we get together. One of the brightest lights in the field. I really appreciate the chance to present with Dr. Evans today. And thank you for the opportunity. I have probably seen patients with NF2 for about 35 years, and -I'm hesitant to say that because you all know I'm only 40 years old, I've been working on this most of my life, but I will say that when I was in medical school, I was very impressed when we were able to do a surgery and restore a patient's hearing, how miraculous it was. When I was in medical school it was just when cochlear implants were coming on the scene and to be able to restore hearing to patients, it reminded me of what Helen Keller said; Blindness takes us out of contact with things. Deafness takes us out of contact with people. And so I've always had a great love for the ability that we have to try to preserve that thing that makes us so special as human beings, which is to be able to communicate with each other, to hear and speak. And to be involved in the medical specialty that deals in those has been a great influence on me. And it's been something I've really enjoyed. But NF2 is something I really hate. I mean, it takes away so many of these things. It makes it so difficult for patients that trying to find solutions has been fits and starts. I think when we discovered the gene, when I say we as a community, when Jim Gaselas's group in Boston and the group with you all up in Canada, it was discovered the gene in 1993, we all thought: This is a gene we can fix. This is something we can get our hands around. And here it is more than 25 years later and we're still trying to get the fix. I think that the research that has come out of our labs, I have to credit Lon, shen Cheng collaborators at Ohio State and my collaborators at Mass Eye and Ear have done outstanding work. I've enjoyed working with them. I want to tell I'm stepping down as the department head the beginning of August so I'll have more time to focus on important things like NF research. I'll turn it over to Gareth for his opening statement.

Gareth: Thank you, Brad. Thank you for your kind words. You've been at it a little longer than me. So my journey started in 1990. Actually, I left the Army. I was an Army doctor. And I went straight from doing pediatrics in the Army into doing genetics in Manchester. And I was given a two, two to three -year period to do research on tumor or cancer genetics and set up cancer genetic services. And I basically decided we had some good researchers in Manchester Thomas Trakin doing research and Richard Ransom – who is one of the foremost otolaryngologists who pioneered cochlear implants in the UK. And I decided that NF2 was just the right place to do my research. So I did a two-year research thesis on NF2. I went all around the UK, saw 100 patients in their homes, including Claire's husband, when he was quite a bit younger. And I learned about NF. And it was the perfect way. And of course having seen 100 patients in two years, I was able to sort of put it all in the air and say, look, what makes a diagnosis because you see lots of families and how it affects people in families. And they sort of stood the test of time. Although the criteria are now being changed. There are some flaws in the criteria that require tweaking. Not massive flaws, but there are a few flaws. So, really I've dedicated myself to NF2 ever since. And I'll talk later about how we develop services in the UK. But essentially I work with NF2 patients. I now do a clinic once a week where I see patients with

NF2, usually five or six. And I want to find the solution to how we can help NF2 patients not lose their hearing, not lose their function. Live a normal life, and I think we're on the road there. And I really hope we get there quickly.

Mani: This is great. And fortunately the work you've done is not just with the patients, it's with the families, because it's a community and you've looked at the genetics and also certainly -- I'm going to go back to you Dr. Evans maybe to expand a little bit further since you worked over the years on NF2, maybe talk about the various tumors associated with NF2 vestibular vestibular, meningiomas and others and what similarities do you see in the tumors.

Gareth: The hallmark is the development of bilateral tumors on the hearing, balance nerves we call a vestibular schwannoma. And these particular nerve sheath tumors that grow on the nerve sheath called schwannomas are the characteristic lesion, and the schwannomas can occur anywhere else in the body where there are schwann cells, cranial nerves, the spinal nerve roots and then on the major nerves around the body. And you can get these nodular swellings on the nerves under the skin and in the arms and legs. But you can also get them actually in the skin itself. So that's sometimes gets confusion with NF1 because you get tumors in the skin. But they're different. Most of them are what we call Clark lesions with hair on them. So the schwannomas occur all around the body. Meningiomas are the second most important tumors. And about 70% will get a meningioma in their lifetime. And these are tumors on the lining of the brain and less commonly on the lining of the meninges around the spinal cord. And those are really important in terms of morbidity now that we're better at treating the schwannomas. And then the final major tumor that occurs in about 20, 25% of people with NF2 are an intrinsic tumor in the spinal cord. Usually in the cervical spine but they can drop down further down in the spine. And occasionally into the brainstem itself. They usually are indolent and they can look terrible on the scan, but you have to judge when is the right time to do something about them. And usually you don't. But they can be a tricky one when you look at a scan and a patient has no symptoms, what do we do about this. And then suddenly patients have symptoms. So those are the three main tumor types you get in NF2 and then there's some additional features like in the eyes, particularly cataracts that don't usually create any visual problems; they're just what we call presema juvenile cataracts. And occasionally a congenital lesion on the retina, usually again doesn't cause any problems called a retinal hematoma. And then there are some other subtle features that we see but those are the main features.

Ajay: Next question is for both you Dr. Evans and Dr. Welling. Can you help us understand the challenges associated with this disease both from the perspective of the patients as well as the patient's families, what kind of symptoms and what kind of other challenges they face in their day-to-day lives. So let's start with you, Dr. Evans.

Gareth: The main thing that affects pretty much everyone with NF2, even the mildest, mildest family is that they nearly always get tumors on both sides, both hearing and balance nerves. And it's very rare that those do not require treatment at some stage. So nearly always you will get hearing loss, unless you have a brilliant surgeon who takes the tumor out, preserves hearing. But then they can come back and you've got to deal with it again. And that's a tricky thing to do. You've got radiation as another thing. We're not that keen on using radiation in NF2 because a small malignant potential, and also it doesn't work anything like as well in NF2 as it does in the sporadic situation. So surgery is still by far the most important thing. But the problem in NF2 you can just get a proliferation of tumors. And people can end up having two or three spinal surgeries, three or four meningioma surgeries, and there comes a time

when someone throws in the towel; either the surgeon, or the patient says “I don't want anymore”. And that is why it's critical to come up with a treatment that means that we put Brad out to grass before he needs to go out to grass so that we still need you Brad. But I think nearly every surgeon will say they would rather we could cure NF2 than have to operate so many times on NF2. And the problem is the loss of hearing. They can often be problems with vision. So although the cataracts then cause blindness, treating the tumors can cause problems with vision because you get the facial nerve palsy means that the windscreen wipers don't work very well on your eyes and you get corneal caretopathy and ambliopia, dependent on one side. And multiple meningiomas it can mean raising cranial pressure and trying to deal with that side of things and then obviously the trickiness of operating on the spine.
And in the families, it's obviously coming up with a test so that you can preempt and diagnose the condition earlier in the children. It's a 50/50 risk normally, but actually nearly 50% of new onset NF2. So what we call mosaics. So the genetic fault was not inherited from their parents; it actually developed as they developed as an embryo and it only affects some of their cells, not all of their cells. Enough to cause them multiple tumors. And in those individuals it depends on how many cells are around in other cell types like in their gonads, in their ovaries or sperm cells, that will determine the risk to their children. But if they do pass it on, they have mild NF2, because it's only in some of the cells. They will pass on a severe form of NF2 to their children because it will be in all the cells.

Brad: Gareth, someone asked how do you tell if you're a mosaic or not. Maybe you answered it.
Gareth: Main way is we initially do test on blood. You have two copies of the gene. When you see a spelling mistake it should be at 50% alio frequency, because only 50% of the normal cells carry the genetic fault. So often we see mosaicism when we see it in only 10% of cells. Or sometimes 5% or even lower now. We can detect it down to about 2% now with next-generation sequencing. But often we don't see it at all in the blood, and we actually have to test two tumors to find an identical mutation in two tumors, and then we can go back to the blood and check it in the blood. And we can check it in sperm cells, actually, to check whether there's any likelihood of passing it on, if you already know what the genetic fault is by testing two tumors.

Brad: I'm going to jump back say a word about how this affects patients and their families from my perspective. I think that -- I completely agree with what Dr. Evans just said. I think there's a challenge because people call this a benign disease. But really it doesn't act benign. It can cause such devastating problems and yet people, other people may not understand the difference between an aggressive disease like this that can take away function and take away life. And the cancer that's going to spread to other places quickly and cause death. And I think it leaves families in the lurch a little bit. I think that it's difficult to get the attention of the national cancer institute when we talk to them about a disease that is not typically malignant. We can't get the funding that they get for colon cancer or breast cancer. I feel like there are challenges in communication not only because of deafness and the blindness, as Dr. Evans stated. Patients who have a facial paralysis that don't cover their cornea can have an anesthetic effect from one of the tumors so they don't feel that their eye is irritated. Then they're much more likely to cause this corneal calcification that can cause blindness. I think one of the frustrating things I see for families is that we don't have a straight course forward. We don't say to you here's what you do: A, B, C, D. And this is the end of it. It's a very unknown course and there's a lot of decision trees all along the way, where each case is different. And you have to weigh so many different things. Now, I think the tool set we have is much better now than it was 10 years ago or 20 years ago. One of the things I credit Dr. Evans and his group with is the genotype/phenotype correlation, the specifity knowing where the mutation

is and to be able to predict how severe the patient's going to be with their disease, knowing where the mutation is and what type of mutation it is. And that's been -- that database took a long time to accumulate over many years, decades, a couple of decades really. But that's an important tool. We're getting better at our imaging. We're getting better at detection of mutations and I think that in some situations when we know that a patient, a young patient inherits the disease from a parent, to intervene early on can save a lot of problems. But we still don't cure this disease with a knife. It's a genetic disease, and we need to find other, better solutions. I think another challenge is we've struggled to get good mouse models or animal models for this disease. Mice and humans are not the same. And as much as we like to think that we can target mice and have it translate into men, that doesn't always work. It's not just in this disease process but in a number of processes. So getting good models is difficult. I think another big challenge that we all face in the field who are trying to get to better treatments, is it's not only got to be safe and effective, it's got to be really tolerated for a long period of time until we get to a cure. So if you've got a disease that's going to take your life within a year you can tolerate being miserable and sick on the chemotherapy, but that's not something we want to do for NF2 patients. It limits a little bit the pathways we can go down.
I think the fear of the unknown and just not really having great answers. There are always nuances about how we're going to treat patients makes it difficult for patients and for families. And for us too. We always want to choose the best treatment. And sometimes we don't know exactly what that is.

Mani: Maybe expanding on some of the things that you've talked about, you certainly are a surgeon. So that's sort of how you manage a lot of these patients even though it's not ideal. But I just wanted to drill down a little bit further from your perspective as a healthcare and as you work with patients and the families and the testing of surgery and the setting of NF2, or rather multiple surgeries in the setting of NF2. How do you deal with it and all the risks associated with it in consultation with the families? It's something, as you both have said, Dr. Evans has said as well, it's not just one surgery and that's the end of it. How do you get to the decision-making and the course of action.

Brad: I think we try to prioritize the various aspects of the disease and one of the top of the list is always is this a life threatening tumor; is that something that's going to cause the patient to die if we don't take care of it? If that's the case, that's usually an easier decision to say we need to take this tumor out. If it's compressing the brainstem that it's going to block the flow of spinal fluid and cause a massive pressure in the head, then that's an easier decision. Not that it's a pleasant decision. But it's not that there's a lot of option with that type of a tumor. . But the difficulty comes with smaller tumors that particularly, for example, let's say a tumor that's on the balance nerve that's compressing the hearing nerve but hearing is functional there's one on the other side and that's also knocked out the function yet. The hearing is still reasonably good. But as the tumors grow, they're going to compress the brainstem, if something is not done. And when do you decide to operate as opposed to preserve function? Those are difficult decisions and another unknown that comes in is when are we going to have a drug that will stop or shrink these tumors. And so it may be that 10 years ago or five years ago I would have said this tumor has got to come out; we're not that close to finding something that may work. But we hope, we think as we get closer we think we're more likely to have treatments, it's still a very difficult decision to make. And one of the things that I would say is maybe unique to my perspective, and I think there are others who would agree with me but many who may not when it comes to surgery, is that when tumors are small enough, you might save the hearing. Usually in my book that means less than a centimeter in diameter and not really impacted into the inner ear. They have a little bit of space there where we can work safely. And then taking

out the tumor, although it does present a risk to the hearing, does also present the opportunity to potentially save the cochlear nerve, the one that carries the hearing fibers. And intervening early in that case may save the hearing, or if you don't, you may save the cochlear fibers. In a small series that we did that's really not scientifically very sound because we only had seven patients and retrospective group of patients, I would say we were much more successful in those patients giving them a cochlear implant and have them be able to hear reasonably well and we have with our patients who have no cochlear nerve preserved and we have to do an auditory brainstem implant. The auditory brainstem implant most often gives people sound awareness but only in about 12% do they get any open set speech recognition so that they can understand words without lip reading. And people find that it's helpful and they find that sound awareness is very beneficial but being able to understand words without lip reading is much better. So sometimes we make a decision to intervene early with the knowledge that even if we lose the hearing in the surgery that we could use cochlear implant later on and preserve that important communication ability. So I think I've had patients who have said to me no mas, I don't want any more surgery. We said if you don't operate on this tumor it's going to cause serious problems, they said I don't care I have had enough I'm not willing to do it. And that's a sad state to get to but I can understand that people can get tired of having surgeries. And most of the surgeries it's try to preserve the function where they are and it's rare that they actually get better from surgery. And I understand their point, but I hate to see people throw in the towel. And I think that we'd love to have better treatment options.

Mani: No, that's a good perspective. And Dr. Evans, you're obviously based in the UK, you probably ...

Gareth: I did once go to a CTF meeting and they bought me a ticket from Manchester to Aspen. The only problem it was Manchester, New Hampshire. And the ticket wasn't any use to me when I got to the airport.

[LAUGHTER]

Mani: Maybe coming back here. So how is the practice different or similar in your side of the world versus here in terms of management, maybe specifically?

Gareth: I think it will be very similar in the sense that Brad is part of a team and multidisciplinary team. And they make decisions as a team rather than an individual surgeon. With the patient. And obviously advising the patient what the best course of action is that there's an element of choice. But what we built up very early on in Manchester was a multidisciplinary team clinic, where we had a neurosurgeon and ENT surgeon, a neuro radiologist, spent hours looking at the scans before the meeting. Myself as sort of a physician who would look at the patient in the morning and check any new problems doing neurological examination. We now have neurologists in addition to me to do that. And that eventually led to we applied for something called highly specialized services, which meant we actually located only four clinics that looked after all NF2 patients in England. So 55 million people are looked after by only four centers. Now, some of those centers do outreach clinics so that they can be seen nearer to their home by a local team with a member of the core center there. But essentially virtually all those patients are managed by four centers. So that's at the moment about 920 patients in England. We know all the patients. We've got all their data. And it enables us to have totally coordinated care where they're seen at least once a year by the full team. And they have -- we have audiologists and ophthalmologists, physios, nurses, all of those people involved in the clinic and involved

with helping them. So it's a one-stop shop for them. They don't have to go to pillar to post to see different specialists. And we're extremely lucky in the UK with socialized healthcare that that is one of the great things that is able to supply is this highly specialized care. And we're sure that this has had a major effect on survival. It meant that we had access in 2010 with very specific circumstances to the use of bevacizumab, Avastin treatment, because of the fantastic work that has been done in Boston by Scott Plotkin, to find that it was effective in treating growing schwannomas. It doesn't work for meningiomas, which is a problem. And that's why we need another drug. It also long term causes problems with the kidney. And with blood pressure. And that's why we need another drug because if you take people off Avastin, the tumors usually come back. It only keeps them at bay. It doesn't kill them. It just stops them, shrinks them a bit and they start coming back again. So we need a more permanent solution, or at least a solution that has less long-term side effects in terms of the effects on the kidneys.

Mani: Thank you.

Ajay: Next question, building on your answer, do you think that agility are stable is meaningful treatment both for your patients and you as a physician were unique as far as it will go and just from your perspective, Dr. Evans?

Gareth: So stable disease in NF2, if you can find someone who is asymptomatic and just stop everything, then that's as good as a cure, because it's a benign disease. The tumors aren't going to spread. If you just stop them all, then that's fantastic. Because they can live a normal life with a few internal tumors stopped at that stage, frozen at that stage. Now, I guess reality won't necessarily be as easy as that, but you do not need to shrink the tumors to make a difference. If you get in there early enough, you can just stop it before people lose hearing, before people lose balance. Before people lose other functions in terms of their ability to ambulate and live a normal life. So absolutely maintaining stable disease or making it stable is extremely good. You can't do that with cancer because a cancer might be stable but it can metastasize. So it's a very different scenario to treating a cancer, where you need to do more than just keep the tumor stable.

Brad: I completely agree. And one of the tricky things about it as we discussed before most of the funding agencies in the United States -- I don't know how it is in the UK -- but most of the funding agencies in the United States do not look at that as a reasonable endpoint. They want to see the tumors shrink and go away because they're used to funding cancer treatments, not benign, quote/unquote, benign disease. I look the terminology tumor predisposing syndrome more than I like benign because it does predispose to tumors. So I think that stabilization is an ideal endpoint if we can know how to turn off the tumors from growing that would be sufficient. We're getting a lot of good questions coming in. I know we have other questions to answer. Do you want to go to some from the audience?

Mani: Since we have you talking, Dr. Welling, maybe you can talk about why are the vestibular schwannoma in NF2 usually the first ones to develop as opposed to other schwannomas; is that the case and maybe why.

Brad: I can tell you exactly. I don't know. I wish I did. You know, that's my life goal actually to figure out why vestibular schwannomas are more likely to occur than any of the other cranial nerve schwannomas, they're nine or ten times more likely than any of the others. I honestly.don't know. I've hypothesized certain things it's like certain types

of nerves and the balance nerves are some that seem to attract viruses is there a viral etiology that turns off one of the virus suppressor genes, I don't know, maybe. We know patients who are have radiation are more likely. Survivors of hire row shim ma and more apt. And particularly patients who inherit it as NF2 why is it that the vestibular nerves get them before others. I don't know. Dr. Evans can probably tell us.

Gareth: No, all I will say it's not peculiar to NF2 because NF2 just mirrors what happens in sporadic tumors, because of all schwannomas occur on the vestibular nerve. And that means that clearly they are going to be the primary site because the other sites are much less common individually. So what we see, which is quite astonishing, with the fantastic MRIs we have now, when we scan people who have inherited NF2, before they get symptoms, is we see dotted along both the vestibular nerves, sometimes three, four, five separate starting points for tumors. And you don't really see that anywhere else. It's just the vestibular nerves where that occurs. And it used to be thought that there was something special about the glial Schwan cell junction that it was important on the nerve that's nonsense because they occur all away along the nerve. And we don't know. We don't know why that nerve I think Brad's got some good points. Maybe it's a nerve that we're using all the time or we're using our balance all the time. But that still doesn't really explain it. But there is something about the vestibular nerve, not just in NF2, but in people in general, that is much more susceptible to developing tumors. And NF2 is just a reflection of that except that you get many, many more schwannomas. And in NF2, instead of getting one schwannoma on the vestibular nerve, you get a bunch of grapes that wrap around all the other nerves and that's why it's very hard to treat the vestibular schwannomas in NF2 and why facial nerve weakness afterwards is more common. And why also radiotherapy doesn't work as well, because you'll treat what you think is the middle of the tumor to try and treat the rest of it, and the few grapes on the outside won't get a lethal dose of radiotherapy and will regrow. So that is why the treatments are much harder and there's something really odd about the nerve we don't really understand. The Nobel Prize will have to go to someone in the next generation, Brad.

Brad: I don't know, I've got some smart people here, won't be me but maybe some of our people.

Mani: I know we're running short of time here but I want to cover two topics since I have the two of you here. One, you know, maybe Dr. Evans since you've been talking, expand on your work on the epidemiology of the disease you've obviously spent a lot of years studying the rare disease and going to patients' houses things you've mentioned already. But give us your firsthand perspective what's the numbers, the epidemiology, the prevalence of this disease. And everybody comes back to you.

Gareth: Well, there's only been one other epidemiological study in the world and that was in Finland where they did a very small study and we've now got effectively a whole epidemiological study in the UK, because we cover the whole of the UK. And we've now remapped what I did before and essentially it's all the same around UK and also the world because the new mutation rate is so high, the literary says 50 percent of NF2, 50% de novo. There's much more than that that are de novo, that's 70%, if you count the mosaics. And so what you have is about one in 27,000 people are born with NF2, that they have that susceptibility. They're not born with the tumors; they're born with an NF2 mutation in all of their cells or quite a lot of their cells at birth. So they are programmed, unfortunately, at some point, to develop tumors. Now, the next thing that people talk about is prevalence. So that is the number of people diagnosed

with the condition the any one point in time. And that is lower than 1 in 27,000, because often the mosaics don't present until they're 40 or 50. So they spend more than half of their life not diagnosed. Therefore, that comes off your incidence, and unfortunately the severe NF2s don't live a normal life expectancy. So that comes off as well. So in the end your prevalence is about twice your, half as common as your incidence, about 1 in 50 to 1 in 55,000. And that's in our very, very highly ascertained UK population.

Mani: Thank you. That's good -- that's always a question that comes up everywhere. What is it, it's not talked about. And I know Dr. Welling has obviously discussed this. It's not considered malignant and there's not enough funding. So I'm going to go to you again now, Dr. Welling, to expand a little further. Tell us what the landscape looks like from what you are reading and seeing and what's been published, tell us some of the promising drug targets or drug candidates or even the pathways that are being used? And I do want to say there was a question on the chat where they talked about even high FGFR or TNF alpha expressions being associated with prior risk for the disease. So all these things, give us some sense of what's going on from a research perspective we talked about.

Brad: Sure. Let me answer Tony's question first in terms of expression of factor from the tumors. This is true probably both in NF2--related schwannomas and in sporadic schwannomas, where certain tumors, even though they're small, will knock out the hearing. And we think that may have to do with excretion of certain factors from the tumors like the TNF alpha. And others seem to be more protective. Like with fibroblast vector Type 2. And yes, that research came out of Dr. Steglich's lab and that's ongoing we put in a proposal to look at that in addition to other findings with NF2 and the genetics and the vestibular findings and hearing and that work is very interesting. When it comes to the different pathways, one of the things that seems to me has happened since the gene was discovered, everybody's been working on trying to figure out what is it that Merlin does.

When Merlin gets mutated, what pathways go into action to let these cells run up against each other and then instead of stopping with contact inhibition, why they continue to mound up and the schwan cells continue to proliferate. So many pathways we don't have time to talk about them. I'm not an expert in all of them. But I would say many of them have drugs that we can target to them. And one of the efforts that we just were involved in with a consortium called the Sonodus group sponsored by the children's tumor foundation, was to try to find a large panel of drugs that had already been FDA-approved or had gone down the procedure through Phase 2 testing at least so we thought they were accessible to us. And we screened a large number of drugs.

We initially started with almost 2,000 drugs, and we narrowed that down to 45 that we thought targeted specific pathways. And we looked at that in cell cultures and mouse models tried to funnel it down to drugs we can bring forward to clinical treatment. So it's been tricky. And I would say that unfortunately the drugs that seem to target schwannomas don't always target meningiomas.

It would be ideal, of course, to have one drug that would hit both because those are the two primary tumors as Dr. Evans explained that are important. I would say that we also have struggled a little bit with mouse models and not reacting, the mouse cell lines don't react exactly as human cell lines would. And human cell lines that have human mutations don't grow very well so they're hard to use for tests. Yet I would say that there are still a number of drugs in the pipeline that are to be tested and the first one that's coming out of that particular pipeline for a clinical trial is Bergatinib more small cell lung cancers. It's been approved buy the FDA for that use. We know its profile what it looks like and we know it targets meningioma cells and schwannoma cells. And that clinical trial is about to get

started. We also have, as you're very well aware CereXis knows, we've worked many years on a drug that's been called AR42, or now Rec 282 a drug that targets the other pathways that regulates cell growth. And we have some preliminary data, both from a Phase 1 study where we looked at the safety of the drug and Phase 0 study we looked at the drug getting into tumors. And this is another study that we hope will get kicked off soon for Phase 2 trial so we can really look and see how efficacious is this against these tumors. It's possible that we may need combination therapy. That it might be that it's not one drug, it may be two drugs that we have to use to try to tamp down these multiple different pathways that can occur to release the cells from contact inhibition when they should stop growing. And I think that one of the drugs, the only drug really that we have seen a lot of benefit from is one that Dr. Evans has referred to which is bevacizumab, or Avastin.

One of the questions that was asked was has that been applied directly to the tumor. I don't know if it has, but I do know there's a group that's proposed that. And I know that's a mechanism that is going to be looked at if it hasn't already.

But I have been amazed, it's taught us interesting things about the pathology of the tumors that some of the patients do get improvement in their hearing. I never would have believed that. I thought Scott Plotkin was lying to us when he told us that the first time. But it's true. About 35 or 40% of the patient get an actual improvement in their hearing. Mostly in the clarity of their hearing; not as much in the pure tone averages. But so it doesn't get a lot louder, but the clarity improves a lot in some of these patients. And that's encouraging. It's a little clue about what's going on with the hearing loss. It may be that the bevacizumab or Avastin is blocking the excretion of one of these exosomes in the internal ear and removing that toxicity will allow the mechanisms to start working again.

I'm always the optimist. And I always tell people, oh, in five years we'll have something. And every five years I say that. So I think that at some point we're going to have something that's going to work about either than what we have now. And I hope it's sooner rather than later. Lapatanib is another drug we were involved in a study with. And I'd say even though it didn't hit the shrinkage target that was the goal, Metias Caranos showed that a large number of patients didn't have their tumors advance while they were on Lapatanib. It's not without its side effects but it's encouraging to see other drug studies that are coming forward that seem to have some benefit.

And so I think there are a number in the pipeline but getting them executed and carrying them out is challenging, and I'm hopeful that with the combined efforts of the whole NF2 research community and the support of the NF2 patients, really, you all do a great job of driving these things forward and supporting the efforts. I'm optimistic that we will get something that will be useful and helpful to stop these things.

Mani: Absolutely. We hope so too. We'd love to keep talking to you and I'm sure the audience, too, with wonderful questions coming but I know we promised you a certain time and you're busy.

Gareth: I typed three answers.

Mani: I grant you that. So thank you so much, Dr. Evans and Dr. Welling. You have been picking up the questions and addressing some of those as well. Thank you I know the people on the line really appreciate that. We should wrap it up. We're five minutes over our time, which is good considering the wonderful discussion we've had I would like to thank both of you Dr. Welling and Dr. Evans again for taking time out of your busy schedules and providing this wonderful discussion. I hope others benefited from it as much as we did.

I also want to thank NF2 Biosolutions as well as all the patients, family members and others who are here on line with us. This is our first attempt at this webinar. So we appreciate if you had any glitches or if you couldn't get to the questions. But as we all continue to work to improve lives affected by NF2 please continue to send us suggestions, questions. You have my e-mail address in your registration confirmation. Thank you everyone here who have joined here today and have a great day. Thank you again.

>> Thank you all.
>> Thanks everyone. Good luck. We need a solution.
Mani: Right. Thanks.