All right, well, welcome everybody to the May NF2 meetup. My name is Connie Sorman. I am an individual giving officer at the Children's Tumor Foundation, and I am excited to be here with all of you tonight. So, welcome. Just wanted to let you know that there are captions available by a live captioner. You can press the CC button at the bottom of your screen. And, Emily, can you throw that into the chat as well please? Thank you. Your microphones should remain muted unless you are asking a question and asked to unmute just so that everybody can hear the presentation. We welcome everyone to introduce themselves in the chat, especially if you haven't been here before. We'd love to know who you are and why you joined us. Also, we're going to have Q and A at the end of the presentation, so please hold your questions or put them into the chat if you are afraid you'll lose them. And then I will also be sharing the link to the NF Conference abstract book in the chat for your reference, so that if you're interested in any of the things you hear about in tonight's presentation, you will be able to look into that a little bit further. We also have a slight change in our agenda this evening. Dr. Adunka will be moderating and welcoming and doing fielding questions from the chat. But Brigid Garelik, who will be introduced a little bit later, and Cristina Fernandez-Valle will be the speakers tonight. So I will introduce you to Dr. Adunka in case you haven't joined us before. He is the William H. Saunders endowed professor and the Vice Chair for Clinical Operations in the Department of Otolaryngology. I think I got it this time. Head and neck surgery at the Ohio State University. He also serves as the director of the division of otology, neurotology, and cranial based surgery within the department. Further, he's the Director of Pediatric Otology on the hearing program at Nationwide Children's Hospital, one of the largest institutions of its kind in the United States. Dr. Adunka has been the medical chair of the NF2 accelerators since 2021. We're really excited to have his participation, and he served as a member of the CTFCCAB since 2016. So welcome, Dr. Adunka.

- Yeah, thank you, Connie. Really appreciate you organizing, and welcome, everyone, to this exciting session. So today, we wanted to get a review of what was discussed at the recent NF Conference. So, and first, Dr. Brigid Garelik, who's our brand new Children's Tumor Foundation Chief Medical Officer, will talk about the clinical, you know, news, in a way, from the conference, and Dr. Cristina Fernandez-Valle will talk about the basic science news from the conference. So first, Dr. Garelik, again, is the brand new Chief Medical Officer at the CTF. She's an accomplished pediatric oncologist, scientist, and senior level pharma biotech executive with extensive experience in the healthcare landscape spanning basic research, patient care, and global drug development. She brings to the role a broad therapeutic expertise, leading teams in developing novel therapies in small molecules, biologics, and cell as well as gene therapy from the preclinical stage to successful approvals and product launches to market. Her prior experience includes 10 plus years a physician scientist at a large academic center followed by 15 plus years in oncology clinical development in both global pharmaceutical corporations and biotechnology organizations. I'd like to, you know, maybe introduce Dr. Cristina Fernandez-Valle as well, and maybe Brigid can get us started after that. So Dr. Fernandez-Valle is the Pegasus Professor at the University of Central Florida, and she received a PhD from the University of Miami School of Medicine, and has conducted, you know, NF-related and schwannomatosis-related research in the postdoctoral period. Over the past 25 years, her research has focused on Merlin tumor biology and more recently on identifying therapeutics for NF2 associated schwannomatosis and pain mechanisms in schwannomatosis. So thank you again all for being here. I'm excited to hear the updates. Unfortunately, I was unable to make it to the conference this past June, or this June, but I can't wait to hear the updates, so maybe Brigid, you can lead us off and followed by Cristina.

- Thank you. Let me just share my screen. Can everyone see that?

- [Dr. Adunka] Looks good.

- Okay. So good evening, everyone. I'm excited to join this meeting and have the opportunity to present some of the clinical work that was presented at the Neurofibromatosis Conference this June. This is work presented by others that was selected to be highlighted that relates to NF2 clinical research at this point. Oh, it won't let me go further. Oh, there. Okay. So some of the clinical research that I'm gonna highlight tonight is one presentation that was done on the "Diagnostic Odyssey of Schwannomatosis" and how the updated criteria may affect this process moving forward. There was also work presented on the genetic findings of people with at least one non vestibular schwannoma and not meeting the criteria for NF2-related schwannomatosis. I'll highlight data presented and on the phase two study that was being done on Axitinib in patients with NF2 and progressive vestibular schwannomatosis. I'll briefly highlight the data presented on the INTUITT-NF2 study with Brigatinib. I will, however, remind everyone that there will be a formal presentation given by Dr. Plotkin, the PI running this trial next month, so this is really just showing that it was presented at the conference and a very brief introduction to that. And then I'll end my portion with talking about some work being done on how to image pain for schwannomas. So the first talk I wanted to present tonight was done by Dr. Vanessa Merker, and was titled "Diagnostic Odyssey and How to Improve the Diagnostic Delays and Communication to Patients with Neurofibromatosis". So some of the issues with neurofibromatosis with NF2-related and non NF2-related schwannomatosis that make the diagnosis difficult as we all know are that it is a rare disease, it has genetic complexity, and there's different clinical presentation across patients. A survey was done by Dr. Merker and her colleagues looking back retrospectively at one center's data from '95 to 2011, and this was, of course, before the new diagnostic criteria, and they found the median age to diagnosis was 6.9 years, and the median time that the diagnosis was communicated to the patients was 7.3 years. So not a large gap. However, 36.1% had at least one misdiagnosis when first presented. So the team is looking at really how to improve diagnosis, targeted interventions to increase awareness and consideration of schwannomatosis, the education of non-specialists in which hopefully CTF will also play a big role in assisting in that. Electronic triggers on medical records, now that we have electronic data systems, how to have those flagged so that if a patient shows up in another clinic or another center and the data's shared, it would flag that that patient was perhaps diagnosed with some manifestation back that would trigger and heighten the alert the physicians or specialists seeing them at the next time they're presenting to a doctor that they should think about neurofibromatosis two. And also more, and most importantly, work closely with all the specialties including pathologists and radiologists within your centers. They, she also highlighted to improve access to an awareness of the NF specialty clinics and improve diagnostic communication and, of course, make available more genetic counseling to these patients, to the patients. Sorry, I'm having trouble going forward with my... Oh, there. So she presented, Dr. Merker presented a conceptual model of how she and her team are envisioning an ideal diagnostic procedure for a patient with schwannomatosis. The patient experiences a health problem, they seek care, and then have a full diagnostic workup. At that time, any diagnostic uncertainty should be recognized and managed, and also, it is important to gather and integrate all information as I highlighted on the previous slide. Then establish and effectively communicate diagnosis. And this involves multiple functions across the healthcare system with medical management, patient education, psychosocial support, and developing a therapeutic alliance between the patient and all the subspecialists. And then this would lead to improved health decision making for the patient. They'll be more informed, better able to cope with the diagnosis and symptoms and ability to be proactive and engaged in their decision making. And at the same time, going back and forth, they're able to receive more appropriate treatment. And all of this will lead to better patient health outcomes. So it was a nice talk. There is, if anybody wants to go back, definitely more detail in her presentation on some of the interesting data that was gathered in the retrospective chart analysis, which is interesting and only an indication of how it can be utilized as a point to do better moving forward. The next talk was given by Dr. Smith on the, they did a study looking at the genetic findings in people with at least one non vestibular schwannoma and not meeting the criteria for NF2-related schwannomatosis. So there, as everyone knows on the call, I'm sure there's one in 500 people will develop a schwannoma in their life. Approximately 50% are vestibular, but another 50% are non vestibular and are either isolated or occur in otherwise healthy people, a proportion of those. The bilateral vestibular schwannomas are most often NF2-related schwannomas. But the non NF2-related schwannomas, 50% are related, 50% of those are related to the other known and identified genes, SMARCB1 and LZTR1. So, and then also another point is that the non NF2 schwannomas are less likely to be vestibular in nature. So this group tested blood and tissue of 154 people from 150 families who had been diagnosed with non vestibular tumors. There were 17 people from 14 families that had SMARCB1 mutation. The reason for the 14 families is that, as the numbers indicate, some patients tested were from the same family. 20 had the LZTR1 mutations, two had NF2 identified that was not picked up initially, and one of those patients was when they looked at tumor and blood, and one of those ended up being a mosaic patient. 17 patients when they tested tumors only had NF2 mutations in the schwannoma tumor only. And then 98 of the 154 patients tested had no pathologic variant identified. So overall, there was a 36% detection rate, and most mosaic NF2 was detected if they had only two or more tumors that were tested. And again, this is just a highlight of this talk. If anyone's interested in hearing more, it is available to be in more detail in the program book and online. A third study I wanted to talk about that was brought forward and presented at the conference was a update on a phase two study of Axitinib and patients with neurofibromatosis two and had progressive vestibular, so had neurofibromatosis, NF2-related schwannomatosis and had progressive vestibular schwannomas. They pre-clinically had validated their target. Oh, so basically, the way Axitinib works is that it is a multi, it's an oral drug, and it's a multikinase inhibitor. And it inhibits already validated targets for NF2. And those are VEGF, PDGFR receptors, and the C-KIT ligand receptor. And the FDA has approved this drug, and it is available as second-line treatment in renal cell carcinoma. And more details on Axitinib is available in the reference below that was published in 2012 by Dr. Carmichael. The baseline schema for the study that was carried out was patients had an MRI and an audiogram to document their vestibular schwannoma and that it had progressed and also had baseline hearing. They entered the study, and they received 12 weeks of Axitinib, and then a response evaluation involving a follow-up MRI and audiogram were done. If patients demonstrated progressive disease, which was increase in the size of the tumor or unacceptable toxicity, they were taken off study, and if patients showed stable disease or better, they were to continue on study. And the objective response was to be greater than or equal to 20% decrease in the tumor volume. And the progressive disease was defined as an increase in that amount. So here are the results highlighted by Dr. Garcia at the meeting. They enrolled 12 patients, and eight of the patients were able to complete 12 cycles. The other patients were taken off for toxicity or progressed prior to the 12 cycles. They saw a response in two patients and a hearing response in three patients. However, the drug toxicity they presented, there were 100% of the patients reported drug related toxicity. Nine out of 12 had diarrhea, two of the nine had grade two, and nine of the 12 had hypertension, then there were a number of patients, seven that had hematuria and five had skin toxicity with two of those at grade two. So the conclusion at this point was that the drug was more toxic, with the data that was gathered, the drug is more toxic and less effective than that already available for the Bevacizumab, the VEGFR inhibitor, and further development in this indication is therefore not warranted. So while this is a negative result, I feel it's important to point out that research is ongoing and drugs are being tested, and also at, in an adaptive form that data is being aggregated and analyzed at an early point, and decisions are clearly being made on the value of moving an agent forward versus stopping further development based on the benefit risk. As I said, I am gonna highlight 'cause for the NF2 community, this is a highlight that was presented at the meeting is the INTUITT-NF2 study that was presented by Dr. Plotkin on the first drug being carried through the INTUITT trial Brigatinib. And what I wanna highlight today, and he'll get more into the detail, is that he started the presentation by showing that studies, there are a number of studies that have been done to date for patients with neurofibromatosis two related schwannomatosis, and most of them have been one drug on one tumor type in these patients, and most of them also have been of the vestibular schwannomas. They've reported variable outcomes in terms of data information, and it's been a slow process in this standard drug development approach. So as many of you may have heard, Dr. Plotkin and his colleagues have developed and implemented the INTUITT trial, which is an adaptive platform basket trial and currently is open in six centers. And it enrolls patients with neurofibromatosis-related schwannomatosis who and have progressive, have progression of four tumor types identified and highlighted in this slide. Patients are entered into a master protocol, and then when a drug becomes available, there's further eligibility for them to meet, and they are randomized if there's multiple drugs being developed. But in this case, patients that met the criteria for Brigatinib were enrolled and initiated on the treatment for Brigatinib. And the six sites that are currently involved in the trial are highlighted here. And University of Indiana has most recently joined the group. And what I wanna highlight here is that data from the Brigatinib substudy was able to show that it met accrual goals and timelines. Within 36 months, they had all patients enrolled and a primary endpoint, which is exciting in a rare disease such as this, and also gathering data that is currently being analyzed further, and you'll hear more about it next month. This is just showing it, and that's... The last talk I'd like to talk about from the clinical realm that was presented in neurofibromatosis-related schwannomatosis was given by Dr. Thomas Wilson from Stanford University, and the work he's doing looking at visualizing pain in MRI, MRE radiology. So the Sigma-1 receptor has been identified as, as being upregulated at sites of pain generation and was thought to be a potential target to bind a radioligand for imaging. And that's the first paper highlighted here. The group was able to bind, find a radioligand that was very specific to bind to the S1R receptor, the S1 receptor, and that is 18F-FTC-146. And he presented the data on this that they're able now to visualize nerve injury in a neuropathic pain model, and the work is being taken further to look at schwannomas in patients with NF2. There is further data that he presented on the talk, preliminary data looking at the distribution of the radioligand in patients and identifying positive uptake versus baseline that I'm not presenting for the sake of the talk today, but it is interesting for anybody that wants to dig deeper into this. But it is moving forward, and right now, future goals are to complete a multi tumor cohort and enroll up to 18 patients. The team would like to evaluate motor nerve tumors if there's a different threshold from the threshold they've already identified for the sensory and pain tumors. And they wanna evaluate patients with NF1 and NF2-related schwannomatosis. They'll evaluate non-tumor sources of pain as well. The study of the antagonists in patients with increased uptake, they will study this antagonist with increased uptake and S1 receptor expression. And so in conclusion of his talk, he identified that there, and it's already I'm sure well recognized by this audience, there is a need for improved diagnostics to identify sources of pain. The S1 receptor is a chaperone protein that's upregulated at sites of pain, and the 18F-FTC radioligand is a very specific binding affinity for that receptor and has allowed them to now image its expression. So painful benign nerve sheath tumors do show an increased expression and correspondingly increased. What they look at when they have the radioligand is called the SUV max, and it's higher than background imaging that they see, and that is what's in more detail in the talk. I felt it just got a little bit too complex for the purpose of this talk, but again, if you're interested please go back. The data's pretty clear and very helpful. And this radioligand allows identification of painful nerve sheath tumors and may be useful in identifying non-tumor sources of pain. And just to go beyond this talk, and there was a lot of background, which I did not put in for for this audience, but that as everyone knows, being able to image and identify the schwannoma or the peripheral nerve sheath tumor that is causing pain is very important and can save patients from undergoing surgery on the wrong schwannoma and still come out with more pain, and then on top of that, morbidities that are not, that are not needed or wanted. So that is the end of my talk today. I'm going to hand it over to Dr. Fernandez-Valle to do the preclinical presentations. I'll stop sharing.

- Thanks, Brigid. Perfectly on time, have to.

- Oh, sorry.

- Oh no, it's great. Thank you.

- Okay, can you hear me?

- [Dr. Adunka] Yep.

- Okay, I just got a warning saying I had to put a password for office. Thank you so much, Brigid, for summarizing that. I was one of the organizers for this year's NF meeting, and I'm happy to say that we dedicated a full day, that Monday, to discuss NF2-related and non NF2-related schwannomatosis for the first time. So you will find many presentations that, for the sake of time, I'm not able to review for you. So we just selected together with CTF3 presentations to talk about. And first one comes out of my lab, and I'll discuss the drug screens we're doing with patient schwannomas that are donated if there's sufficient tumor tissue that's not needed by pathology. I'll talk about the work from Larry Sherman's lab at Oregon Health Sciences University of which I'm also involved in that looks at pain mechanisms in non NF2-related schwannomatosis. And then I'll end by talking about an industry talk that was presented, which involves the company Vivace and a compound that's now in phase one clinical trials or phase one two clinical trials, and the preclinical work has been done by David Parkinson's lab at the University of Plymouth in the United Kingdom. So I'll get to my lab's work. So I've been working on NF2 for over 20 years. And for the last 10 years, we've been refining in the laboratory a drug screening strategy for NF2 schwannomas. And we started this work back in 2010 when we were working with Sanford Burnham Institute that happened to be in Orlando for 10 or so years. Their main site is in La Jolla in southern California. So together we developed high throughput screening assays, and we screened over 350,000 compound library and sent our cell lines to be studied by NIH as part of the Citidus Consortium, and one of the druggable targets that we identified with Sanford Burnham that was published in 2016 was the PI3 kinase pathway. So over the last 10 years, how we've been refining our drug screening strategy is showing you this as an example. So once we knew that the work of the screens that we have done and work of others in the field that showed that Merlin regulates PI3 kinase pathway, we obtained a 275 compound library from a company, and some of the novelties that we incorporated this last two or three years was we conducted our screens on human model schwannoma cell lines that we created in the lab. And we created them so they'd be isogenic, you'd have a wild type parental schwann cell and the identical cell that just had a deletion of the Merlin gene, so it would be Merlin deficient. So with a viability assay, we were able to identify from these 275 compounds, 25 that had concentrations that were very low in efficacy, like less than five micromolar. So from 275 we go to 25, and then we did cell activity assays, and we identified the top 10 here that had at least twofold more selectivity for the Merlin deficient over the wild type. And then another novelty we added were the cell death assays. So in the example I'm showing today, or discussing now, we looked at a, we used an apoptosis assay, and then we found that four of these 10 compounds promoted cell death in a time and dose dependent manner. And when we examined these four compounds, we found that only one of them, CUDC907, was actually in clinical trials for children and young adults with brain tumors, had also been studied in adults with breast cancer, and the company, Purist, is studying it, and had renamed it fimepinostat. So we studied CUDC907, and a year ago, we were able to get the investigational compound from the company. And I won't show you that data 'cause we're still working on that data, but we found that actually both of these compounds, the generic form and the compound created by the company that's in clinical use, promotes the slowing of the schwannomas in a rapid mouse allograft model. So some genetic mouse models can take over a year to analyze, but there is an allograft model that's been used by multiple labs, and it's a very rapid model that takes three to four weeks to get an answer. The last novelty we did was working with Christine Dinh, a neurotologist at the University of Miami, we've incorporated testing in human vestibular schwannoma primary cells. For this paper that was published in Oncotarget last year, she was able to test seven vestibular schwannomas with CUDC907 and show that it slowed proliferation, and it induced apoptosis. And this was the paper published last year, and Christine Dinh is the neurotologist that leads the work at the University of Miami, and we now have tested with her 17 vestibular schwannoma cells, and the last six have been studied with, or the last 11 have been studied using the investigational compound. And I've studied one non vestibular schwannoma, and we found that all of them respond to fimepinostat with cell death. And working with at Memorial Sloan Kettering, we've been talking, he's been talking to the DOD clinical trial consortium as to whether this would be a good compound to go into clinic. It's not yet known how tolerable the drug is. We're waiting for the results of the clinical trial in children and adults with brain tumors. So that's where that is. So now, I wanna switch topics and tell you what I'm doing with both model schwannoma cells and primary schwannoma cells that are donated to my lab by patients who have elective surgery and are deemed to have sufficient tumor tissue that they can donate. So we can grow these tumor cells, schwannoma cells, in the laboratory either on a regular tissue culture plate or as spheroids. So basically, the tumor cells are dissociated. They're seeded into these wells where the cells don't attach, and after three days, they form these spheres, and then we're able to add whatever drug treatment we want after three days and then monitor their growth or shrinkage over the next seven days. So it's a 10 day assay. And here, you'll see some movies of the cleaved caspase assay, which is a cell death marker. And this is a non vestibular schwannoma cell, a paraspinal schwannoma that was donated from a patient in Miami at Nicholas Children's Hospital. And you can see that the tumor, the spheroids grown with the control vehicle do not really turn green. Those grown with the HDAC inhibitor, fimepinostat, have an explosion of green, which is indicating cell death is occurring. And then this is lapatinib, a receptor tyrosine kinase inhibitor, that's been tested in patients many years ago as well. And you can see that only the cells with the fimepinostat, the HDAC inhibitor, undergo apoptosis while the lapatinib treated and the DMSO treated after 10 days, the cells continue to grow and actually begin to spread out in this well. So what we've done, let me move forward, is here is an example of the cells growing in the dish. So when we obtain tumor cells, if the patient mutation is known, we annotated this is a point mutation in the NF2 gene. The cells grow beautifully without any kind of immortalization. We do western blots when we look for the expression of Merlin, LZTR, and SMARCB1. So this is the patient sample that's missing Merlin, but expresses LZTR and SMARC, and these are just positive controls, and this is a loading control. And what you see here is we've started doing high throughput spheroid assays where we can test a number of different compounds either alone or in combination, and we test them in duplicate wells at four different concentrations. And what you're seeing in each one of these little squares is the induction of cell death by the first three to five days, And then, since the cells have died, the peak cell death goes away. So that's at one micromolar, 0.1 micromolar, and then the lower doses you get, you no longer see that effect. And what you see is that only these two HDAC inhibitors, fimepinostat and panobinostat, actually induce cell death. And it could be that a cytotoxic drug can eliminate or shrink the tumor, whereas some of these other compounds that have been used in patients, and they've been shown to be cytostatic, which means they keep the tumors from growing for a certain amount of time, but they do not actually shrink the tumor. So my lab has started to focus on different cell death mechanisms trying to find a compound or a drug that would shrink the tumor selectively. So now, I wanna move on and talk about the work that Larry Sherman presented. He's been studying pain in schwannomatosis for several years now. And just to summarize his work, let me move this out of the way. He's found as well as others in the field that individuals that have pathogenic variants in the SMARCB1 gene experience increased pain because the neurons that sense painful stimuli have high levels of ion channels, and they've identified TRPV1 and TRPA1 channels, and they also have high levels of cytokines and chemokines such as IL6 that promote the painful stimuli that reaches the brain and allows you to express, feel pain. So several groups have found that interleukin-6, IL-6, is a chemokine that is expressed in schwannomas that cause pain. So schwannomas that I obtained from patients that donate and also work from Dr. Ostro at Johns Hopkins has found that these schwannomas secrete IL6, which is an inflammatory cytokine with wide ranging biological effects. And both the IL6 protein itself, the cytokine, as well as the receptor for that cytokine, are elevated in spinal cord and dorsal root ganglia models per pain. So Larry Sherman's reported that a neutralizing antibody of IL6 lowered the sensitivity to painful stimuli in mice models that have SMARCB1 pathogenic mutations or loss of SMARCB1. So the question is, is this now a good target? Would blocking the ability of IL6 to bind to its receptor reduce pain in patients? So there, and so this is a pictorial depiction of what is believed to be happening right now is that you have a schwannoma cell in your body that is SMARCB1 Deficient, and it increases the amounts of cytokines and different factors that can activate the dorsal root ganglion neurons. These are the sensory neurons that are just outside your spine to express high levels of these ion channels that allow the stimulus of pain to occur. So the idea would be is would a, if you, and I'm not sure why this is writing. I'm so sorry. Let me go back. If you can reduce the amount of TRPB1 ion channels or have an ion channel blocker or an antibody that blocks IL6, you might be able to decrease the pain sensitivity. So there is a STARFISH clinical trial being organized. There is an antibody against IL6 called Siltuximab with another name called Sylvant, easier to pronounce, that can be delivered by intravenous infusion. And so there are studies being, clinical trials being planned, and I'm not the right person to answer questions about this, but I believe it's Scott Plotkin who is leading the STARFISH trial. And Brigid, if I'm mistaken, you can let me know.

- [Dr. Brigid] Yeah, you're correct. That's correct.

- I'm correct. All right, thanks. So the last part is really exciting. This is a novel target that has not been studied before in NF2, and it's not because it's not an enzyme, it's not a kinase. A lot of the drugs that have been tested in patients are antikinase or kinase inhibitors. So there's a new target that's been known for a while. It's part of what they call the Hippo-YAP-TEAD pathway. So these are transcriptional factors that regulate gene expression. And we know that when there's loss of Merlin in a schwann cell, this pathway is active and leads to promotion of tumor cell proliferation, inhibition of tumor cell death. And the work that was presented was presented by Liam Larrabee who is in Dave Parkinson's lab at the University of Plymouth in the UK working together with the Vivace compound. And I'm sorry for all those green lines that I mistakenly drew. Please ignore them. So what's been known is that in a schwann cell, you have all of these receptors that bind to different ligands and different chemokines, growth factors in the extracellular space that transmit growth signals and, to the cells. And when Merlin is not there, these, well, it's more complicated than what's shown here, but when a cell is low density, you want proliferation. When a cell is at high density, you don't want proliferation. So Merlin is actually a molecule that balances the signals so that it allows growth to happen and proliferation to happen when it's needed, but when it's not needed, it then becomes the tumor suppressor and stops the signaling to go into overdrive. And then so Merlin is what we call upstream of this Hippo. So Hippo is the drosophila name, the fruit fly name, for the MST1/2 gene. So it's the same gene, it's just Hippo is a easier name to remember than MST. So there's this pathway by which YAP and TAZ, these are two isoforms of the same protein, they then combine two T, which is a transcription factor. And this factor allows genes that control cell proliferation or tie cell death to be transcribed, and then they form proteins that carry out the function. So many scientists over the years have created numerous mouse models where they've inactivated the NF2 Hippo pathway to create mouse genetic models for both schwannomas, meningiomas, and appendamomas. And what Liam Larrabee and Dave Parkinson showed at the meeting was that Vivace has been creating TEAD inhibitors, so this would be a drug that prevents the YAP from binding TEAD so that TEAD can no longer transcribe the genes. So they have this compound 3989 that's in clinical trial for various types of tumors such as mesothelioma that are known to have activation or loss of Merlin function. And they worked with the UK Plymouth group to test it in a meningioma xenograft model. And this is very similar to the xenograft model created by Long Xang Chang at Nationwide Children's Hospital that was used to identify Brigatinib, the drug that's in the Intuit trial. So cells are injected into the skull, and they can be treated with the vehicle or treated with the Vivace compound. And then over time, with imaging of photons of light from these cells, you could see that the normal growth rate of a vehicle treated to grow much faster than if the receiving the Vivace compound. So these are the first data that provide early preclinical proof of concept for effectively drugging this Hippo-YAP-TEAD pathway. So VT3989 is undergoing dose optimization studies in clinical trials to identify which are the dosing schedule and the amount of drug that is safe to give to a patient. So further evaluation of VT3989 in patients with meningiomas and other tumors that have germline NF2 mutations are required to see if there's any efficacy. So they were able to study I think four or five patients in the phase one clinical trial, and I think they're waiting for more information. So that's highlight of some of the NF2 and schwannomatosis that were presented. As I said, there are many, many more, and they will be available to you on abstract book. And I'm happy now with Brigid to take any questions as necessary. Thank you.

- [Dr. Adunka] Thank you very much. Yeah, I wanted to see, do we have any questions in the chat?

- [Connie] So we did have one from Brigid's talk earlier, and it was from Adam Goodkind. "What was the takeaway from Smith's study?"

- Yeah, and I had answered in the chat, but I'm happy to address it here to the group. The preliminary work has shown that the radioligand is able to image the schwannomas and shows increased uptake in what they've identified and potentially painful compared to background, but now, it's more works to be done. So future work will test more patients in both tumor and non-tumor pain. See, and that's next step too, is it only the tumors or can they identify pain elsewhere? So it's still under study. It's not ready for patients yet, unless you're in this study.

- Great. And there is another question from Adam in the chat. "Is there any use of AI to do a study of tumors and drug efficacy?" Does anybody wanna take that one?

- I know that Recursion is a company in Utah that is really leveraging AI in their studies, and I'm certain there are other investigators that have started looking at AI. I do not know of any right now that I could offer you, Adam. Brigid?

- Yeah, some companies are starting to utilize it too, more at the drug screening level where they're identifying new targets and new drugs through screening process. I'm not aware of it being utilized in the clinical setting for efficacy. The closest probably is some people starting to use technology as readouts, but it's not necessarily AI for pain and other related symptoms that, and they have devices that they wear or take home. And then also cross cardiology and things like that. But yeah, I, in my experience, and it's all new and evolving rapidly, so I may give a different answer a couple weeks from now, but so far, I'm not aware of any in the clinical setting looking at efficacy.

- Great, does anyone else have a question they'd like to ask? And I did drop the link to the NF Conference abstract book in the chat, but I'll also include it in the follow-up email to this meeting with the recording.

- Oh, Brigid, do you wanna talk?

- About the gene, I thought I saw a question I think about gene replacement, yes. It's continuing to be investigated. There's a lot of work going on in both NF1 and NF2. It's still at very early stages. There are obstacles to overcome with how much gene to be, how much gene is needed when the delivery should be given, the delivery system, and can it be systemic versus local. CTF is continuing to fund and support as well as the Gilbert Foundation, a number of initiatives. Of course, per NF2 specific presentations at the conference, I didn't include anything here. There was some presentations on gene therapy this year in rare disease and some of the success stories with that. And that, again, too can probably be available in the abstract book or if anybody wants more information, I'm happy, just reach out to me, and I'm happy to send it to you. And we, as I said, have a gene therapy group. We're working with investigators in the labs that are continuing to look at this initiative.

- There are some efforts of, you know, getting the gene products into acoustic tumors, sporadic ones, but ultimately also NF2 with one of the gene therapy companies out of Boston, Akouos, and they will likely get an IDE with, IND, sorry, with the FDA to treat acoustic tumors via a trans canal injection of the gene product. And it's the same product that's actually used in Avastin, so it's anti VEGF. And there's some promising data on that, you know, so hopefully that can be expanded to NF2. But again, it's definitely going to come, and hopefully, something that can be meaningfully implemented for NF2. Yeah.

- And did we answer Paul Verona's question about the study? The IL6?

- So is the question about whether IL6 might be useful for those with plexiform neurofibromas? Is that the question, Paul?

- Yes, if it was transferable to patients with NF1, like targeting a similar aspect.

- If there's pain, so plexiform neurofibroma that's causing pain?

- Yes.

- I would think that if it's, so the STARFISH protocol doesn't have NF1 in it, does it, Brigid? But I'm thinking if it works and is safe, should, or shouldn't it be a big barrier?

- Yeah, I don't know enough about the eligibility. I have to go back and look. It's on clinicaltrials.gov, Paul. I know you know how to get in there.

- Okay, great. Let's see.

- And I think there was a question also. Where did I see this?

- Something about IVF.

- That NF2 tumors and sporadic tumors are reasonably similar. Sometimes. Not always, and, but in terms of gene therapy, that may apply depending on what you want that gene therapy to do, right? So gene therapy's sort of this catchall kind of term, but there are quite substantial differences in what gene therapy is meant to accomplish, so it gets pretty esoteric, but generally, yes.

- And then there was a question about IVF from Michael Skyer.

- Yeah, I don't know of any. Maybe Oliver, Cristina, you do? Gene editing?

- I'm not, that's really outside of my expertise, gene editing of embryos, but it's a interesting question. I just don't know the answer to it.

- Yeah.

- I know that's an area of active research, not only for NF2, but other germline inheritable mutations. Again, that's not, as a basic scientist, that's not an area of expertise. Those are good questions to, you know, ask the clinicians and the geneticists involved in IVF.

- And it may be reasonable to, I think we had some reproductive questions in the chat on previous sessions, so it may make sense to consider bringing on someone with expertise to this forum down the road, you know, who can really educate all of us on these kind of topics. Yeah, but I wish I could help, Michael, on this question.

- Okay, well, thank you all for your presentations and for enlightening us about all the exciting research from the conference tonight. To all of our attendees, thank you for joining us, and if you indicated an interest in becoming an NF2 accelerator when you registered, someone from the CTF staff will be in touch with you soon. The next meetup will be a webinar on September 6th at 2:00 PM announcing the exciting research about the INTUITT trial from the NF Conference by Dr. Scott Plotkin, so make sure to mark that on your calendar. You'll get an invitation to that very soon. And if you have any other topic suggestions for upcoming events, please email us at NF2@ctf.org. Have a great night everybody.

- And Michael, if you wanna follow up with me, Connie, it seems his question hasn't been addressed. I could talk to him one-on-one maybe with a little bit more of the challenges. I think that there's, Aaron maybe do a little bit background for him before we meet.

- Okay, sounds great.

- That's great, Brigid.

- I can appreciate what you're facing, Michael, so I'm happy to help in any way I can. Or email. Okay, great.

- Thank you.

- Thank you all for your attendance to share this information with you. Bye.