

Monday, April 12th
Usher Syndrome Coalition Conference Call

On the call:

Mark Dunning
Abby Wilkins
Christine and Gabe Corbin
Melissa Chaikof
Karmen Trzupsek
Amy Selinski
Angel Morrobel
Steve Browne
Marly Kenna
Amy Lovelett
Steve Rose
Heidi Rehm

First topic: Usher Syndrome Family Conference

Karmen: Hopefully everybody received – Mark I know you got the Eblast from FFB- it went out later than I thought, but at least out. There are several things were working on, namely the general layout of the weekend. Friday is a small reception, check in and mill-about and meet other people. Probably have light drinks and appetizers. Saturday we will have the conference at Children's. All Saturday morning will be whole group speakers, and in the afternoon we were planning on grouping into smaller sections. We're working on finalizing the agenda (including speakers). For sure know that one breakout session is with Dorothy Walt, the Northwestern regional representative for National Helen Keller Foundation. She herself is deaf-blind, very charismatic, and knows a lot of the deaf-blind community up here (Seattle). We are planning on having someone from their office set up a booth. We need to know who from this group (on the conference call) is planning to attend and if anyone wants a booth or to do smaller break-out session.

Mark: I'll be there to do anything you want for small session. Decibels will probably want a booth.

Marly: I'm not sure yet, it depends on what else is happening her, we'll see if I can make it.

Karmen: Steve Rose, are you planning to attend? July 9-10?

Steve: So far my calendar is free, so it's Seattle right? I'll put it on my schedule but can't say for sure, I will try to.

Karmen: Who from this on-going call is going? Would anyone want to set up booth for people to stop and chat. Maybe one for FFB?

Steve Rose: Not sure, but probably. We're currently going through budget process.

Mark: Karmen, I have been asked to do break-out session at a conference on Usher in the family, so if I could do that a second time that might be good. The first one is in Europe so it's not the same crowd, but it's the same subject matter.

Karmen: Yes. More on the schedule: in the morning it's all science directed at lay person level as an effort to get out current research and what's currently being done for families. But in the afternoon those who want more social/life issue sessions can do that and science people can stick to science. And we were thinking of providing some opportunity to have "Meet the Doc" coffee event for all physicians and researchers there.

Mark: Karmen, have you heard of Marilyn Kilsby? She has run similar conferences to this in Europe for quite a while and might know what good subjects are.

Karmen: Heidi and Marly, didn't you have speaker talk about going to/applying to college?

Marly: Yes, Melissa and her daughter. It was complementary but not the same thing and I thought it was a topic important to the audience.

Mark: We had quite a few professionals for the science-y aspects and everyone got a lot out of it. Level of knowledge is very different.

Marly: We had a skewed group of professionals because it was molecular biology focused in the morning. I would imagine if you sampled a general ORL group the level of knowledge would not be the same. I imagine that would be true for audiologists, ophthalmologist. I mean, I learned a lot at the conference and this is what I do. Even if amount of detail wasn't so "detailed" it would have been good.

Karmen: Here (the Northwest) we have no specialty clinic for USH so most families end up seeing a general genetics group.

Marly: Right, our general genetics group has uneven knowledge, because there is so much to know and it changes every day.

Karmen: I'm trying to make sure that I reach out to everyone I should be. Also, Saturday night were having a BBQ in a pretty Seattle park. It's a nice, easy way to wrap things up and have families spend time together.

Mark: Are there preferred hotels?

Karmen: Yes, and we have those locked down. In the next couple of weeks we need to nail down the agenda so we can send out the agenda/speakers so people can book their hotels. We have 2 hotels because the reasonably priced hotels near university are very small. So not everyone will fit in one. But we have rooms locked down in a block.

Mark: Good, I have interested families, but they want more details.

Karmen: We need to nail down details in order to send an Eblast and put more information on the Hear See Hope website.

Chris: How young can the kids be to bring them?

Karmen: As young as you want and we'll take care of childcare for the day based on who says they're coming. We'll have activities for ages 5 and up with board games, snacks, xbox, and friends of HearSeeHope volunteers will take care of the little ones. We have *so* many games and toys. The only thing we're trying to work out is: we want the small kids on site at Children's, but depending on how many kids are coming we may need to utilize the preschool down the road – they have stuff and space for the older kids. But not sure how many 5-6 year olds are comfortable not being in same building as mom/dad.

Marly: Insurance for watching the kids was concern last year. With kids at Children's (Boston) there was no issue, but off site it was.

Karmen: I think insurance is an issue if you pay someone, but not as much if volunteers are taking care of kids and the parents agree to it.

Marly: I don't remember what we ended up doing but you might want to check it out.

Mark: anything else on conference? If we can get that out to people that would be good, but I know we don't have a lot of general answers yet.

Karmen: Yup, well get that out in next couple of weeks so people can start to plan.

Next: Steve Rose

Steve Rose: FFB has been working with Oxford Biomedica to bring genetic therapy together to both Stargardt's (StarGen™) and Usher Syndrome (UshStat™). USH1b is what the FFB is working with on Oxford. We're looking at a Lentiviral base gene therapy using MYO7A for Usher 1b. We expect to be enrolling in late 2010 for the Stargardt's clinical trial and in Q2 or Q3 2011 for the UshStat™ gene therapy for Usher 1b. The studies will start in France at our Paris center under the direction of Dr. Jose Sahel and then move to USA as part of a FFB National Eye Evaluation Research (NEER) clinical trial network. So we have that project going. We also have independent USH1B gene therapy project ongoing with David Williams, Sam Jacobson, and Bill Hauswirth using AAV. You can't "overstuff" AAV, as was originally reported and instead the DNA is in pieces and it has to be reassembled correctly inside the cell. The other thing we've been up to is talking with Copernicus in Cleveland about using a nanoparticle delivery system that can accommodate DNA up to 20KB in size. We're looking at USH2A using this delivery system. And same for USH3 as well, but we're still in discussion with nanoparticle delivery and have conference call with investigators and the company to

discuss how to proceed with this. There are a lot of questions involved (e.g. - efficiency of gene delivery and long-term expression), and some publications are already out from Dr. Muna Naash's laboratory in Oklahoma (working with Copernicus). We're talking with Ray Lund in Oregon about USH2A as well as he just published a paper on cell therapy in Dr. Tiansen Li's Usher 2A mouse model. And with Boystown we're collaborating on USH mouse models that appears to be retinal degeneration. You can "see" the RP within a couple months.

Marly: Do the animal models have hearing loss as well?

Steve Rose: the MYO7A model had the hearing defect.

Marly: Most have hearing loss and not RP.

Steve Rose: We're focusing on the eye. The models are no different from standard model plus a tweak to allow us to get retinal degeneration. So there are a lot of irons in fire on the Usher front. I know that Neurotech is thinking about where they want to go with the ECT-CNTF device. This may have applicability to USH, we need to see where goes. Bottom line: we are looking at many fronts in USH.

Marly: Being able to diagnose genetically is more important than ever. When we started this a couple of years ago we said that, but now in the next few years, gene therapy is a real possibility. So we need to redouble our efforts to make timely and accurate diagnosis in these patients so they are ready for the trials/treatment.

Steve Rose: Yes, genotyping for gene therapy trials, a paper just came out on this. We're finding that different genetic phenotypes respond to non-gene therapy as well (i.e. vitamin A).

Marly: It was certainly true in the cancer world, so makes sense in RP/USH world too.

Steve Rose: that enough of a background? We're excited. Things never move as fast as we want them to but it is moving forward.

Steve Browne: I'm curious about the end points. What is the thinking on what the end points are going to be?

Steve Rose: Part of that (for USH1b) depends on CNTF trials and results (the response of visual field using both dynamic/static testing). So the direct answer is I can't tell you what the primary endpoint (e.g.- what is success) at this moment, but we have a number of ideas in mind that would be measurable quantitatively. Phase 1 clinical trials are about safely, and that's what we're looking for first. But we're funding studies to find what primary end points are.

Steve Browne: I know there are OCT/ERG/Infrared for measurements— are their different measurements being talked about?

Steve Rose: I think a number of people are thinking about using ERG (it's sophisticated) but nobody has used ERG as primary endpoint yet. We're looking at non-invasive imaging as a potential endpoint with respect to visual field (i.e.- perimetry) and Jacques Duncan's work using AO-SLO (adaptive optics-scanning laser ophthalmoscopy) and Dr. Richard Weleber's work using his "Hill of Vision" algorithm in perimetry.. The Hill of Vision is like a topographic mapping of the perimetry responses, so mountains and valleys against sea level and the mountains/valleys tell you which part of retina can or has the potential to "see" and which can't. We're going to be implementing that for an upcoming phase I clinical trial for RP. It's not FDA validated yet but we're hoping to validate it for future clinical trials.

Mark: One other issue I wanted to talk about is around the fact that USH is under diagnosed historically and what does that mean for use in terms of these trials and in terms of what we communicate to the families. Heidi, can you talk about what you've found?

Heidi: Sure. So we're still in the early stages. But in first 46 OtoChip, 13% of apparently non-syndromic cases turn out to be clearly positive for USH mutation. That was our suspicion all along, somewhere in 10% range. We need more cases to support it further. Of four of these cases, 3 are MYO7A or USH2a and the fourth is CDH23 (so we don't know if it's a true USH case, but they are still at risk). That's the stats right now.

Mark: That correlates what Bill Kimberling has as well. He has done a couple of studies which are still under review. One of the groups was a group of deaf students and the other a group of CI patients. He is finding somewhere between 8-12%. The question is, why are we missing so many people? Historically we're talking between 3-12%, so we're missing a lot of people. Does that change what we should be telling parents about outcomes for kids who test positive for USH?

Heidi: The difference in diagnosis is that we used to diagnose when RP became apparent. So it was a disconnect from when you were looking for hearing loss etiology. It could be a tracking/associating issue during the time where you're looking for an etiology.

Marly: Heidi, those four patients have 2 mutations? (HEIDI: Yes). So the inconclusive groups are single carriers?

Heidi: Yes, it's a combination of not knowing if the second mutation has anything to do with it and don't know if first mutation is pathogenic.

Christine Corbin: I have an USH2A gene with mutations question: My son has two mutations. My husband and I both have 1 mutations, but not sure if mine causes it. Does this happen a lot?

Heidi: Yes, it happens. In many cases you find 1 truncating mutation (pathogenic) that predicts that the protein will be shortened or absent so you can reasonably assume the

etiology is related to that one gene even when you didn't find a 2nd mutation or the 2nd mutation is not clear. So if you have at least 1 clear mutations, you say its positive case. What worries me is when the only mutation found is inconclusive.

Mark: So, my question is that as we're finding this (talking to other families who demonstrate vision phenotype earlier or later that expect)

--- MARLY: are we talking regular eye appointment or ERG studies?---

hard to know but there are some with clinical showings in early teens, others are in their 60s with pretty good vision. Traditionally we tell families that USH1 is the most severe with RP setting in around puberty, etc...but this doesn't always hold true. So how do we communicate hope to the families? I think we scare the hell out of families when we tell parents of 18 month old that their baby has USH 1, but in reality, the traditional timeframe might not hold true in their case.

Marly: I tell them the historical types were created based on clinical findings. So USH1 kids met a clinical type of USH. But we're finding with genetics that even within those clinical groups there is a huge diversity with how it can be displayed. So, for example, we have a MYO7A patient who was a very late walker, had early weird ERG data, but they have hearing aids and normal language. It's much more heterogeneous than we thought (like Cx26). That's what we've been telling them along, with the fact that if they have a genetic diagnosis they might be able to get in on these clinical trials that are starting up.

Mark: What do you families on the call think? What would not be overly negative but get the point across?

Melissa: Well, Rachel wasn't diagnosed until she was 19. But I think that if I got that diagnosis earlier I would want to be told more of a range rather than absolutes. I remember sitting in the doctor's office when Rachel was 15 and the doctor pronounced her eyes "clean as a whistle" – direct quote. So if I had been told earlier don't think it would have been good.

Angel: I think there is, even within professionals, the lack of in-depth knowledge about it. Everything goes back to numbers. But lets say my kids don't fit the profile because they were implanted early, perform well in balance, and so had a late diagnosis. To them it's not as important to do training in the hospital to make others aware, because you may not get a case for a long time-- so it reduces motivation for it. You hear "Oh there's not much we can do" but with information that you [on the call] are sharing it gives a different perspective. So for me, getting people more involved will lessen the shock value. You need to perceive someone who is well informed, no matter who it is. The support people (social workers) especially. And just get everybody more aware of USH.

Mark: I find families so traumatized by the diagnosis and the surprising expectation that they're going to wake up some morning and their child won't see again. Especially with USH1 ("it will happen soon") is terrifying for families. On flip side, USH2 families, seem to have more time than they thought. I can't seem to find that line of telling them the truth but also giving them hope that it might be better than expected.

Steve Browe: It's a double edge sword because normally a doctor who gives diagnosis knows very little about disease and there is a lot of misinformation on internet. But the flip side is that there is great variability that creates a lot of uncertainty. I don't know that that gives a lot of solace, but getting accurate info on genotyping and gene therapy gives hope to people. Because if doctor says "nothing we can do," there is no reason to go back.

Mark: I think that what Steve Rose said earlier is enough to give you hope. There is variability in all areas, and there are other treatments going on. That gives people enough hope without giving false sense of reality. We don't know what the real outcome is for USH of a particular genetic type. But if we've only been diagnosing 3%, there are a lot of people out there undiagnosed—maybe these people haven't been diagnosed because they are the less severe end of the spectrum. Why not give out this hope to families? Just giving the straight up and down "USH1 is the most severe...you lose vision by adolescence" is inaccurate.

Steve Brown: When first diagnosed, Kimberling told me RP is a slow moving disease. For the majority of people, it doesn't move quickly.

Mark: And they don't get enough info and then go the internet.

Christine: We need to tell parents what to do next. My son- his eyes are fine now, but when should we get them checked?

Marly: We're struggling with that here at Children's...how not torture families with unnecessary visit but to still track them appropriately. We're studying babies trying to get the answer to that question of when their eyes start to be affected. I think that about once a year was the recommendation we came up for this morning for babies. But once you know what's going on, you might not need to do that. And maybe ERG every year is not necessary. ERG remains gold standard, but we don't know what's best yet as far as follow up goes.

Mark: I appreciate everyone taking the time to chime in. It's a topic to be discussed further.