**Behind the Genes Transcript**

**Can patient collaboration shape the future of therapies for rare conditions?**

**Ana Lisa:** **Welcome to Behind the Genes.**

[Music plays]

**Anne:** What we’ve understood is that the knowledge and experience of families and patients is even more vital than we’ve all been going on about for a long time. Because the issue of there being a liver complication in myotubular myopathy has been hiding in plain sight all this time, because if you asked any family, they would tell you, “Yes, my son has had the odd liver result.” There were some very serious liver complications but everybody thought that was a minor issue, but if we are able to engage the people who live with the disease and the people who observe the disease at a much more fundamental level we may be able to see more about what these rare genes are doing.

[Music plays]

**Ana Lisa: My name is Ana-Lisa Tavares, I’m Clinical Lead for Rare Disease research at Genomics England and your host for this episode of Behind the Genes. Today I’m joined by Anne Lennox, Founder and CEO of the Myotubular Trust, Dr Meriel McEntagart, an NHS consultant and Clinical Lead for Rare Disease Technologies at Genomics England, and Dr Carlo Rinaldi, Professor of Molecular and Translational Neuroscience at the University of Oxford.**

**Today we’ll be hearing about the importance of involving the patient community, particularly as new rare therapies are developed, and discussing the forward-facing work that’s happening that could have potential to unlock novel treatments for many rare conditions. If you enjoy today’s episode we’d love your support. Please like, share and rate us on wherever you listen to your podcasts. Thank you so much for joining me today. Please could you introduce yourselves.**

**Anne:** I’m Anne Lennox, I’m one of the founders of the Myotubular Trust, a charity that raises research funds for and supports families affected by the rare genetic neuromuscular disorder myotubular myopathy.

**Meriel:** I’m Meriel McEntagart, I’m a consultant in clinical genetics in the NHS and I have a special interest in neurogenic and neuromuscular conditions.

**Carlo:** Hi, I’m Carlo Rinaldi, I’m Professor of Molecular and Translational Neuroscience at the University of Oxford. I’m a clinician scientist juggling my time between the clinic and the lab where we try to understand mechanisms of diseases to develop treatments for these conditions. And I’m also here as a representative of the UK Platform for Nucleic Acid Therapies, UPNAT. Thanks for your invitation, I’m very pleased to be here.

**Ana Lisa: Thank you. Meriel, I’d love you to tell us a bit about your work and how you met Anne, how did this story start?**

**Meriel:** Thank you. Well prior to being a consultant in clinical genetics, I spent 2 years as a clinical research fellow in neuromuscular conditions, and as part of that training I worked on a project where the gene for myotubular myopathy had just been identified, and so there was a big international effort to try and come up with sort of a registry of all the genetic variants that had been found as well as all the clinical symptoms that the affected patients had, and then do kind of a correlation of the particular variant mutation with symptoms.

I worked when I was training to be a clinical geneticist because of my interest in neuromuscular conditions so when I eventually became a consultant at St George’s Hospital I was actually interviewed by the Professor of Paediatrics and he knew Anne and her son, when Anne was looking for more information about the condition he suggested that perhaps I might be a good person for Anne to talk to.

**Ana Lisa: Thank you. Interesting connections. Anne, can you tell us your story and how this led you to found the Myotubular Trust?**

**Anne:** Yes, thanks Ana-Lisa. Well, as many families will tell you when they’re newly diagnosed with a rare disease, you go from knowing nothing about a condition to being one of the few deep experts in that condition because there are so few deep experts. So this happened to us in 2003 when our son, Tom, was born, and when he was born he was floppy and his Apgar scores, the scores they do on new-born babies, were pretty poor, and before long we knew that it was more than just momentary issues at birth. And, cutting a very long story short, 5 weeks later he was diagnosed with this very rare neuromuscular genetic disorder that we didn’t know we had in the family. We were told that this was a very serious diagnosis.

At that time – more than 20 years ago – over 80% of those boys didn’t make it to their first birthday and the stark statistic we had in our head a lot was that only 1% made it past the age of 10. And that has changed due to better ventilator and breathing equipment, etc, but at the time we expected that he might not make it to his first birthday.

We were very lucky, we had Tom longer than one year, we had him for nearly 4 years, 4 very lovely years where it was tough, but he was a really lovely member of our family. Despite being really weak he managed to be incredibly cheeky and bossy, and he was a great little brother for his big sister. We were also very lucky that he was being looked after by Professor Francesco Muntoni, who is Head of the Paediatric Neuromuscular Service at Great Ormond Street. And, like Carlo, he is a clinical researcher and actually that I found to be amazing as a family member because you knew what was happening out there and Professor Muntoni, other than living with the reality day to day you want to know where things are going.

We began to realise that back then 20 years ago the more common rare neuromuscular diseases were finally beginning to get some fundamental research funds, like Duchenne, spinal muscular atrophy, and Professor Muntoni was very good at explaining to lay non-scientific parents like us that one day the technologies that would lead to a cure, that would re-engage proteins for other conditions and would translate down eventually into the possibility of replacing myotubularin, which is the protein not being produced or not being produced enough in myotubular myopathy. And then we began to understand actually what the barriers to that would be, that translating developments in more common, or let’s say more prevalent conditions, would be hard to do without some translation research being done; you could not just not lag years behind, you could lag decades behind if you haven’t done some other work.

So ,I met Wendy Hughes, another mother, of a boy called Zak who was a few years older than Tom, and these were the days before social media, and it was amazing to be in contact with another family going through something similar and we had great conversations. But then they were also looked after by Professor Muntoni and we particularly began to develop the idea as 2 families that we might be able to raise some research funds towards this concept of keeping pace with the scientific developments. And then we discovered there was no charity we could channel those funds through. Even the umbrella body for neuromuscular diseases who were covering 30 to 40 conditions, frankly, they just couldn’t trickle their funding down into investing in every neuromuscular disease, and slowly but surely it dawned on us that if we did want to make that difference we were going to have to set up our own charity.

So that’s what we eventually did and back in 2006, we founded what was actually the first charity in Europe dedicated to myotubular myopathy – luckily, more have come along since – and we were dedicated to raising research funding. In fact, it wasn’t our goal to set up another charity but around that time, about a year in, we happened to go to a meeting where the Head of the MRC, the Medical Research Council, was giving a talk and he said that in the last few years the MRC had begun to really realise that they couldn’t cure everything, that they couldn’t cure the diseases that would be cured in the next millennium from a top down perspective. There had to be a trick, there had to be a bottom up as well, because that was the only way this was going to happen. And I have to say that that was a really reassuring moment in time for us to realise that we weren’t just chasing pipe dreams and trying to do something impossible, that there was a role for us.

**Ana Lisa: I think it would be really interesting for people to hear your story and the amazing set-up and fundraising that you’ve done, and at the same time it would be really good for us to reflect on how this isn’t feasible for every patient and every family and how we’re going to need to work cooperatively to move forwards with rare therapies**.

**Anne:** When we explored the idea with Professor Muntoni and Meriel and others about setting up a charity one of the really reassuring things that Professor Muntoni got across to us was that this wasn’t about raising the millions and millions it would take to fund clinical trials but the issue in the rare disease space was funding the proof of principle work, the work where you take a scientist’s hypothesis and take it over the line, and the rarer the disease, the less places there are for a scientist to take those ideas. And the example he gave us was a piece of research like that might cost a hundred to a couple of hundred thousand, if you fund a piece of work like that and if it is successful, if the scientist’s principle gets proven, then behind you it’s much easier for the bigger muscle disease charities to also invest in it. It’s harder for them to spread their money across all the very rare diseases hypothesis out there, but if you’ve helped a scientist get over the line they’ll come in behind you and then they won’t be the ones who fund the tens of millions that it takes to run a clinical trial.

If it’s got potential, then that’s where the commercial world comes in, and that’s where the biotechs come in. So he’d given the example of if you spent £ten0,000 on a piece of research and it actually is proven, in behind you will come the bigger charities that would put in the million that takes it to the next phase, and in behind them will come the bio-checks that’ll provide biotechs that’ll provide the tens of millions.

And then, you know, a lot of what happens relies on serendipity as well, we know that, and you could easily run away with the idea that you made everything happen but you don’t, you stand on the shoulders of others. And our very first grant application in our first grant round, which received extraordinary peer review for how excellent the application was, was a £100,000 project for a 3-year project that had gene therapy at the core of it by a researcher called Dr Ana Buj Bello at Généthon in Paris. This piece of research was so promising that 18 months in she and another researcher were able to raise $780,000 and, as Professor Muntoni predicted, from the French muscle disease charity AFM and the American muscle diseases charity MDA. And 18 months into that 3 years it was so promising that a biotech company was started up with $30 million funding, literally just on her work.

So that doesn’t always happen but, as Professor Muntoni explained, our job was not that $30 million, our job was that first £100,000, and our job was also to make ourselves known to the people in the neuromuscular field. If you have lab time, if you have research time and you have a choice where you’re putting it there is a place you can go to for a myotubular myopathy related grant application, so it’s not just that this will come to us out of the blue, people will have done prior work, and our existence makes it worth their while, hopefully, to have done that prior work.

**Ana Lisa: That’s an amazing story how you’ve set up this charity and how successful that first application for gene therapy was. I’d love to hear more about that gene therapy and did it get to the clinic and to hear that story from you. Because I think there are a lot of learnings and it’s really important that the first patients who are treated, the first families that are involved, the researchers who start researching in this area, the first treatments lead the way and we learn for all the other treatments for all the other rare conditions that we hope and that together as a community we can share these learnings.**

**Anne:** Yeah. I sometimes describe it a bit like going out into space. When you see a rocket going off look at how many people are behind and the amount of work that’s been done, the degree of detail that’s managed, and then you go out into space and there are a whole load of unknowns, and you can’t account for all of them. Who knows what’s out there in this sphere. But the amount of preparation, it feels similar to me now, looking back. We were so idealistic at the beginning. Our grant to Dr Buj Bello was 2008 and actually it is a really fast time in, the first child was dosed in the gene therapy trial in September 2017.

**Ana Lisa: So, we’re talking less than 1 years.**

**Anne:** Yeah. And in the meantime obviously as a charity we’re also funding other proof of principle research. One of the founding principles of the charity was to have a really excellent peer review process and scientific advisory board so that we wouldn’t get carried away with excitement about one lab, one research team, that everything would always come back to peer review and would be looked at coldly, objectively. I don’t know how many times I’ve sat in a scientific advisory board meeting with my fingers crossed hoping that a certain application would get through because it looked wonderful to me, and then the peer review comes back and there are things you just don’t know as a patient organisation. So, yes, in those 9 years we were also funding other work.

**Ana Lisa: You’ve just given an interesting perspective on sharing the learnings between the scientists, clinicians, the experts in a particular condition, if you like, and the families, and I’d be really interested to hear your views on what’s been learnt about how families and the patient community can also teach the clinical and scientific community.**

**Anne:** So, the first child was dosed in September 2017 and by the World Muscle Society Conference 2 years later in October 2019 the biotech had some fantastic results to show. Children who had been 24-hour ventilated were now ventilator-free, which, unless you know what it’s like to have somebody in front of you who’s ventilator-dependent, the idea that they could become ventilator-free is just extraordinary.

However, one of the things we’ve learnt about gene therapy is that we are going out into space so there are extraordinary things to be found, and extraordinary results are possible, as is evidenced here, but there is so much that we don’t know once we are dealing with gene therapy. So unfortunately, in May, June and August of 2020, 3 little boys died on the clinical trial. So we have a clinical trial where the most extraordinary results are possible, and the worst results are possible, and both of those things are down to the gene… What we discovered and what is still being uncovered and discovered is that myotubular myopathy is not just a neuromuscular disorder, it is a disorder of the liver too, and these children didn’t die of an immune response, which is what everybody assumes is going to happen in these trials, they died of liver complications.

And one of the things that has come out of that, well, 2 sides to that. Number one is that it is extraordinary that we have found a treatment that makes every single muscle cell in the body pick up the protein that was missing and produce that protein, but also what we’ve understood is that the knowledge and experience of families and patients is even more vital than we’ve all been going on about for a long time. Because the issue of there being a liver complication in myotubular myopathy has been hiding in plain sight all this time, because if you asked any family they would tell you, “Yes, my son has had the odd liver result, yes.”

We could see something that looked like it was not that relevant because it was outside the big picture of the disease, which was about breathing and walking and muscles, but actually there was this thing going on at the same time where the children had liver complications. There were some very serious liver complications but everybody thought that was a minor issue but if we are able to engage the people who live with the disease and the people who observe the disease at a much more fundamental level we may be able to see more about what these rare genes are doing.

**Ana Lisa: Yeah, thank you very much for sharing such a moving story and with such powerful lessons for the whole community about how we listen to the expertise that families have about their condition, and also I think the really important point about how we tackle the research funding so that we’re including and sharing learnings from the conditions that are initially studied in greater depth, and we hope that many more conditions will be better understood and more treatments found and that actually the learnings from these first gene therapy trials will really help inform future trials, not just for gene therapies but also for many other novel therapies that are being developed.**

[Recorded message. Music plays.]

**Ana Lisa: Carlo, I would really like to come to you about some of the initiatives that are happening in the UK, and particularly it would be really interesting to hear about the UK Platform for Nucleic Acid Therapies as a sort of shining example of trying to do something at a national scale across potentially many different rare conditions.**

**Carlo:** Thanks, Ana-Lisa. Thanks very much, Anne, for sharing your fantastic story. I mean, I just want to iterate that as clinician scientists we do constantly learn from experiences and constantly learn from you, from the patient community, and this is absolutely valuable to push the boundary. And I really liked your vision of a rocket being launched in space and I would imagine that this is a similar situation here. So, we are facing a major challenge. So, there is over 7,000 rare diseases in the world and with improvements of genetic diagnosis this is only increasing. So, in a way rare diseases is the ultimate frontier of personalised medicine and this poses incredible challenges.

So, you mentioned the bottom-up approach and the top-down approach and in a way, both are absolutely necessary. So your story is a fantastic story but also makes me think of all the other families where they don’t share perhaps the same spirit, you know, they are in areas of the world that are not as well connected or informed, where patient community simply cannot be ‘nucleated’, let’s say, around the family. So, there is definitely an issue of inclusivity and fair access.

So, what we’re trying to do at UPNAT, which is the UK Platform for Nucleic Acid Therapy, is to try to streamline the development both at preclinical and clinical level of nucleic acid therapies. So, we’ll start with antisense oligonucleotides just because those are the molecules of the class of drugs that are most ‘mature’, let’s say, in clinic. So, there are several antisense oligonucleotides already approved in the clinic, we know that they are reasonably safe, we understand them quite well, but of course the aspiration is to then progress into other forms of gene therapy, including gene editing approaches, for example.

And one of the activities that I’m involved, together with Professor Muntoni, is to try to streamline the regulatory process of such therapies and in particular curate a registry of, for example, side effects associated with nucleic acid therapy in the real world, and you would be surprised that this is something that is not yet available. And the point is exactly that, it’s trying to understand and learn from previous mistakes perhaps or previous experiences more in general.

And this is very much in synergy with other activities in the UK in the rare disease domain. I’m thinking of the Rare Disease Therapy Launchpad, I’m thinking of the Oxford Harrington Centre, I am thinking of the recently funded MRC CoRE in Therapeutic Genomics. These are all very synergistic. Our point is we want to try to amplify the voice of the patient, the voice of the clinicians working on rare disease, and we want to systematise. Because of course one of the risks of rare disease therapies is the fragmentation that we do all these things in isolation. And I would argue that the UK at the moment leveraging on the relatively flexible and independent regulatory agencies, such as the MHRA, on the enormous amount of genetics data available through Genomics England, and of course the centralised healthcare system, such as the NHS, is really probably the best place in the world to do research in the rare disease area, and probably I’m allowed to say it because I’m a non-UK native.

**Ana Lisa: Thank you, that’s a brilliant perspective, Carlo, and across all the different therapeutic initiatives that you’re involved with. And, Carlo, presumably - we’re all hoping - these different initiatives will actually lead to ultimately a bigger scaling as more and more novel therapies that target both our RNA and DNA and actually are working, I guess further upstream in the pathway.**

**So classically in the past it’s been necessary to work out all the underlying biology, find a druggable target somewhere in that pathway and then get a larger enough clinical trial, which can be nearly impossible with many of the rare and ultra-rare conditions or even, as you’ve said, the sub-setting down of more common condition into rarer subtypes that perhaps can be treated in different ways. And with the many new different treatments on the horizon, ASO therapies, as you’ve said, is a place that’s rapidly expanding,** **and also crisper gene editing. I’d be really interested to hear your reflections on how this might scale and also how it might extend to other new treatments.**

**Carlo:** Yeah, that’s exactly the right word, ‘scaling up’. I mean, there will be of course very unique challenges to every single rare disease but I would argue that with genetic therapies, such as ASOs or crisper gene editing, the amount of functional work that you need to do in a lab to prove yourself and the scientific community that this is the right approach to go for can be certainly very important but can be less just because you’re addressing very directly because of the disease.

And then there are commonalities to all these approaches and possibly, you know, a platform approach type of regulatory approval might serve in that regard. You know, if you are using the same chemistry of these antisense oligonucleotides and, you know, similar doses, in a way the amount of work that you need to produce to again make sure that the approach is indeed a safe approach and an effective approach might be also reduced.

I would say that there are also challenges on other aspects of course, as you were saying, Ana-Lisa. Certainly the typical or standard randomised placebo control trial that is the standard and ultimate trial that we use in a clinical setting to prove that a molecule is better than a placebo is many times in the context of rare diseases simply not possible, so we need to think of other ways to prove that a drug is safe and is effective.

This is something that we all collectively as a scientific community are trying to address, and the alliance with the regulatory agencies, such as the MHRA, and you said that you have found your interaction with the MHRA very positive, and I can tell you exactly the same. So we are all trying to go for the same goal, effectively, so trying to find a way to systematise, platformise these sort of approaches. And I guess starting with antisense oligonucleotides is really the right place to go because it’s a class of drugs that we have known for a long time, and we know it can work.

**Ana Lisa: Meriel, can you tell us a little about the National Genomic Research Library at Genomics England and how this could link with initiatives to find many more patients as new treatments become available for rare and ultra-rare conditions?**

**Meriel:** Yes, I think what’s wonderful now is actually that what we’re really trying to do is give everybody the opportunity to have their rare condition specifically diagnosed at the molecular level, and the way in which that is being done is by offering whole genome sequencing in the NHS currently in England but to all patients with rare diseases.

And so, it’s about trying to establish their diagnosis. And as well as that, even if the diagnosis isn’t definitely made at the first pass when the clinical scientists look at the data, because the whole genome has been sequenced, actually all that information about their genome, if they consent, can then be put into the National Genomics Research Library. And that is a fantastic resource for national and international researchers who get approved to work in this trusted research environment to make new disease gene discoveries and identify these diagnoses for patients.

What’s also offered by Genomics England as well is when the National Genomics Library data results in a new publication, the discovery of a new gene or perhaps a new molecular mechanism that causes a disease we already know about, that feeds back into the diagnostic discovery pathway within Genomics England back onto the diagnostic side of all the data.

So, patients who may have had genetic testing previously using whole genome sequencing where they’ve, if you like, had their sequencing done before the diagnosis was sort of known about, will also be picked up. And so, what this is really doing is trying to kind of give this really equal platform for everybody having testing to all have the same opportunity to have their diagnosis made, either on the diagnostic side or with research.

**Ana Lisa: So, sort of on a cohort-wide scale as new discoveries are made and published you can go back and find those patients that may actually have that diagnosis and get it back to them, which is brilliant.**

**Meriel:** Exactly. And this speeds up the whole process of getting these diagnoses back to people. So on a regular basis in the NHS, we will get feedback from the Diagnostic Discovery Pathway about “Here’s some patients who you requested whole genome sequencing from a number of years ago and actually now we think we know what the particular molecular condition is.” And so, it’s key of course for our patients with rare conditions to make that molecular diagnosis because then we’re able to have them identified for our colleagues who are doing this ground-breaking research trying to bring therapies for these rare conditions.

**Ana Lisa: Thank you. And I hope that, as currently, if a novel genetic mechanism, as you’ve just described, is identified that could explain a rare condition that those patients can be found and they can receive that diagnosis, even many years later, and hopefully as novel treatments become available and say there’s a chance to individualise ASO therapies, for example, to start with, that one could also go and look for patients with particular variants that could be amenable potentially to that treatment. And that’s really sort of exciting that one could look for those patients across England, irrespective of which clinic they’re under, which specialist they’re under, and I think that could be really powerful as new treatments develop. I suppose, Meriel, if somebody comes to see you now in clinic are things different?**

**Meriel:** Well, I think one of the things for me when patients come to clinic now is we might have an idea about what we think their condition is, maybe even we think it’s a specific gene. And we can offer whole genome sequencing and so it’s not just the way we used to do things before by looking just at the coding regions of the gene, we can find more unusual ways in which the gene can be perturbed using whole genome sequencing. But let’s say we don’t make the diagnosis. I encourage my patients, if they’re comfortable with it, to join the National Genomics Research Library, because really it’s been incredibly productive seeing the new genetic discoveries that are coming out of that, but as well I say to them, even if we don’t get the diagnosis the first time round when we look at the data, actually this is a constant cycle of relooking at their data, either if they’re in the NGRL or as well on the Diagnostic Discovery Pathway side of the service that’s run by Genomics England. So yeah, I feel like it’s a very big difference; they don’t have to keep coming every year and saying, “Is there a new test?” because actually they’ve had an excellent test, it’s just developing our skills to really analyse it well.

**Ana Lisa: Yes, and our knowledge, the technology and the skills keep evolving, certainly. And I think one of the things that I’m sort of hearing from this conversation is that balance of hope and realism, Carlo we were talking about earlier how you need all the pieces of the puzzle to be lined up - so the regulatory agency, the clinicians, all the preclinical work has to have been done, monitoring afterwards for side effects - every piece of the puzzle has to be lined up for a new treatment to make it to a patient.**

**And, Anne, I’d like to come back to you because we’ve talked about this before, how one balances these messages of optimism and hope which are needed for bringing everybody together as a community to crack some of these very difficult challenges highlighted by treatments for rare and ultra-rare conditions and at the same time the need for realism, a balance conversation.**

**Anne:** Yeah, that was one of our big learnings through the gene therapy trial and other trials we’ve had in the condition. As a rare disease charity, you do everything. You know, my title is CEO, but I tell people that’s Chief Everything Officer because there’s only a few of you and you do everything. So, you go and you lead the London Hope Walk and you also are a layperson on the Scientific Advisory Board and you also send out the emails about grants... And so, you could easily as a small rare disease charity conflate different communication messages because you’re in a certain mode. And so we have been from the early days in the mode of raising hope for people to say, “Look, we can make a difference as a patient community, we could raise funds, we might be able to move things forward, you’ve got the power to make a difference if you want to.” That’s one set of hope. And it’s not dreamlike hope, we’re linked to the reality of there are great breakthroughs. So, you know, in the world of spinal muscular atrophy these clinical trials have led somewhere very quickly, so we’re not selling false hope, we’re talking about the difference we can make.

But then as soon as you flip into “There’s a clinical trial being run” that’s a completely different type of communication and you cannot conflate that message with the previous message. And we always say to everybody, “We’re your team, we’re a family, we’re a team, we all help each other. When you are considering joining a clinical trial your team is the clinical trial team.

The other team does other things for you but the people you need to work with and ask hard questions of and listen hard to, that’s your clinical trial team led by the principal investigator because then you’re in that with them. And, you know, the reality of the fact that many, many clinical trials don’t work as we wish they would be and the decision you make for your child, your baby, your little one, to join a clinical trial… because that’s what it comes down to in our disease, has to be made with that team, not the team that’s selling you a fundraising event. It’s worth reminding rare disease patient organisations we’re wearing different hats and the hope and the realism are different tracks you have to go down.

But at the same time as being realistic you also have to keep remembering that there is still grounds for hope, we are moving forward. And 21 years ago, when Tom was born the idea that you would be able to get all of the muscles in the body to switch back on – putting it in lay terms – seemed like a bit dream. Well, that is what has happened in the gene therapy clinical trial, we just have to now make it safer and understand more about what we’re dealing with. So, the 2 things, the hope and the realism, do exist side by side.

**Ana Lisa:** **I think that perfectly encapsulates a lot of the messages around rare disease therapies where there’s such hope that novel treatments will really target directly the DNA or RNA to potentially correct the problem across many different rare conditions and therefore actually making treatments one day suddenly available to a much, much bigger population of people with rare conditions than we could’ve dreamt of 20 years ago or perhaps now, and at the same time this massive need to work cooperatively to all make this as fair, as equitable. Not everybody is going to have the opportunity to fundraise massively to be an expert about their condition, and the importance of sharing these learnings and also really, really listening to the patient community and really, as Carlo was saying, keeping track of side effects, having registries/databases to share these is going to be incredibly important.**

[Music plays]

**Ana Lisa: Anne, can you tell us a little about your reflections on equity from the patient community perspective?**

**Anne:** Well I mentioned serendipity early and one of the aspects of serendipity that played into our favour for setting up the Myotubular Trust was that by hook or by crook Wendy Hughes, who set up the charity with me, and I were both able to devote time at that period of our lives to setting up a charity. When my husband, Andrew, and I were told that Tom would more than likely die before his first birthday, one of the decisions we made as a family was that he would never not be with a parent, we would always have someone around, and that kind of meant someone had to give up a full-time job and that was me. We thought, “If Tom has a few scarce months on the planet, we’ll be with him.” And then when Tom lived to be nearly 4, as a family we got used to living on one salary and we were very lucky that we could pay the mortgage that way and run our family that way and eventually that meant I had the time to run the charity.

That doesn’t happen that easily, that’s a tall order, particularly when you have somebody in the family who has such high needs. And one of the things that I have often thought about is that in the rare disease space we could do with a different funding model for rare disease charities, we could, in an ideal world I have this nirvana that I imagine where there’s a fund that you can apply to that is contributed to by the people who make profits out of finding rare disease cures - so the pharmaceutical companies and the biotechs - and there’s a fund that they contribute to and that if you have a rare disease and you are willing to set up an organisation that supports families, that raises research funds, that provides a way of hearing the patient voice, then you could apply to that for running cost funds and then you’d be able to run this charity. And then you wouldn’t have to rely on whether you live in an area where people will raise money for you or… We were very lucky that we came across a few great benefactors who would give us money for running the charity, which is actually how we fund it.

All the research money we raise goes 100% into research, not a penny of it goes towards running costs because we have serendipitously found people who will be benefactors for the charity, but we’re relying on a lot of good luck for that kind of model to work. And when you look at how much profit is made from developing rare disease treatments and cures – which is fine because that’s what puts the passion and that gets people working on it – then why not have an advance fund to run rare disease charities? One of my nirvana dreams.

**Ana Lisa: It’s good to dream. Indeed, my hope is that there will be some amazing shining examples that lead the way that open doors, make things possible, prove that something can work and how and that then that will enable many other treatments for many additional rare conditions to be added in so that if you’ve learnt how this particular treatment modality works for this rare condition and there was funding behind it and everything else that’s needed that then you can, the learning from that, I’m going to use the word ‘tweak’, which sounds minor and could be very major but actually the concept that you can then tweak all those learnings and findings so that that same type of treatment modality could be adapted to treat somebody else with a different rare condition in a different location would be absolutely incredible and really powerful, given that if something like 85% of rare conditions affect less than one in a million people it’s not going to be feasible to use the same strategies that have been used in the past for very common conditions.**

**One of the other big barriers is the cost of developing treatment for ultra-rare conditions. Where it’s a small number of patients that you have and therefore all the challenges that come with monitoring, checking for efficacy, monitoring safety and ultimately funding the challenges are much greater, however if some of these treatment modalities are also going to be used to treat common conditions it might be that actually there’s a lot more cross-talk between the nano-rare, ultra-rare, rare and common conditions and that we can share a lot of that learning. I’d love to hear from each of you where you hope we will be for rare disease and rare therapies.**

**Carlo:** Well my dream is that in 5-10 years’ time an individual with a rare disease is identified in the clinic, perhaps even before symptoms have manifested, and at that exact time the day of the diagnosis becomes also a day of hope in a way where immediately the researcher, the centre, genetics lab, flags that there are the specific mutations, we know exactly which is the best genetic therapy to go after, antisense oligonucleotides as opposed to CRISPR editing, and a path forward, both at the preclinical and clinical level, to demonstrate and to cure these patients eventually is already laid out in front of the patient. So, transforming the day of their diagnosis as a day of hope, this is my dream with the next ten years.

**Ana Lisa: Thank you, that’s a wonderful dream. Meriel, can I come to you?**

**Meriel:** Yes, I think I just want to echo Carlo. We’ve had great developments and progress with getting whole genome sequencing into the NHS for testing but what we really need is for it to be fast and efficient and getting those diagnoses established quickly. And we have had that set up now and we’re really getting there in terms of speed, but then what we need is exactly what’s the next step and actually structure like UPNAT that are developing these processes that we can then say to the patient, “And from there, now that we’ve established your diagnosis, this is what we have options to offer.”

**Ana Lisa: Brilliant. And presumably that if the diagnosis isn’t achieved now there is a hope that it will be achieved in the future as well. Anne...**

**Anne:** Well, stepping 100% into the patient’s shoes rather than the scientific side that we don’t so much influence.... stepping in the patient’s shoes, in 5 years’ time I would absolutely love it if we were in a situation where all the parties that have come to the table looking at a therapy or in the earlier research genuinely want to bring the patient voice into the room. As Carlo talked about, there’s even going to be more and more and more of these rare diseases, then those voices, those few people who have experience of it, they may be able to shed light on something. Maybe even sometimes don’t even know it’s a fact that they know but that were brought to the table as passionately as everything else is brought to the table.

[Music plays]

**Ana Lisa: We’ll wrap up there. Thank you so much to our guests, Anne Lennox, Carlo Rinaldi and Meriel McEntagart, for joining me today as we discuss the collaborative power of working together and look to the future of rare therapies that could have the potential to unlock treatments for many rare conditions. If you’d like to hear more like this, please subscribe to Behind the Genes on your favourite podcast app. Thank you for listening. I’ve been your host, Ana-Lisa Tavares. This podcast was edited by Bill Griffin at Ventoux Digital and produced by Naimah Callachand.**