The Rare Disease Gazette

Conversations with the world's experts about rare disease

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Editorial

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Rare Disease Detection: Rare But Not Alone

The plight of patients with rare diseases is a critical unmet need of patients in healthcare. The statistics are frightening; there are 7000 rare diseases in the world that affect 350,000,000 people. One in eleven Americans has a rare disease. Three-quarters of patients with rare diseases are children and only half of patients receive an accurate diagnosis. The average delay for a patient to receive a diagnosis with a rare disease is 1 1/2 years. It is deeply concerning that one in four patients with a rare disease waits four years for an accurate diagnosis. There is an urgent need to communicate knowledge and expertise in the field of rare disease detection.

The journal *Science*, (American Association for the Advancement of Science) in collaboration with Fondation Ipsen delivers international science webinars for the general public.

The Rare Disease Gazette is a magazine that broadcasts these discussions.

James Levine

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DON'T MISS!

The Conversation

Experts of the month: Erika Berg, Ph.D, hosts a conversation with world's experts about rare disease: Bridging silos: How scientists studying rare disease are building cross-disease communities to advance research and innovation.

The Conversation

Experts of the month

Julian Beach, M.B.A *(Medicines and Healthcare products Regulatory Agency (MHRA), London, England)*
Stephanie Cherqui, Ph.D. *(University of California San Diego, San Diego, California)*
Daria Julkowska, M.A. *(European Rare Disease Research Alliance (ERDERA), Paris, France)*
Kerry Jo Lee , M.D. *(U.S. Food & Drug Administration, Washington D.C.)*

Erika Gebel Berg, Ph.D.
(Science/AAAS, Washington, DC; moderator)

"Please work on a rare disease, because whatever we learn can be applied to so many other diseases. There are more than 400 million people out there with a rare disease, and so few have an effective treatment. We can learn so much and apply these findings to so many other diseases."

– Stephanie Cherqui

Erica Berg (*host*):
Today we will explore how collaboration across disciplines, organization types, and disease types is accelerating progress in rare disease research. By forming cross-disease communities, scientists can foster new ideas, discover shared mechanisms, and catalyze innovative treatments that might otherwise remain isolated within the boundaries of a single disease focus. This panel will dive into smart strategies in research and policy that are helping scientists studying rare disease become a collective force that drives more impactful research and quicker advancements toward new treatments. I would now like to take the opportunity to welcome a truly distinguished panel.

Kerry Jo Lee:
My name is Dr. Kerry Jo Lee. I am a pediatric gastroenterologist and hepatologist, and I serve as the Associate Director for Rare Diseases and the lead for the Accelerating Rare Disease Cures Program at the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

Daria Julkowska:
My name is Daria Julkowska and I am the Assistant Director of the Thematic Institute of Genetics, Genomics and Bioinformatics at INSERM in France. I am also the coordinator of the European Rare Diseases Research Alliance (ERDERA) which is the largest rare disease partnership in Europe.

Stephanie Cherqui:
I am Stephanie Cherqui and I am a professor at the University of California San Diego (USCD) in the pediatric department. My lab focuses on developing a new therapy for rare diseases using hematopoietic stem cell and gene therapy, and we take research from bench to bedside. I am also the director of a gene therapy initiative at UCSD.

Julian Beach:
I am Julian Beach and I am the Interim Executive Director for Healthcare Quality and Access at the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK. In my role, I lead medicines licensing within the UK for all medicine types, from innovative to established medicines. It is really great to have this conversation about rare disease therapies and how we can accelerate their use and take-up.

Erica Berg (*host*):
I am going to put the first question to Kerry Jo. We have been talking about cross-disease collaboration or taking rare diseases as a collective in order to try to make progress. What are the biggest benefits you have seen from cross-disease or interdisciplinary collaboration in rare disease research and can you share a concrete example?

"There are complex challenges in developing rare disease therapeutics that not only benefit from, but need, the multiple perspectives from all members of the community."

Kerry Jo Lee:
From the perspective of developing and delivering rare disease therapies to patients that are safe and effective, rare disease drug development really takes all members of the community in order to be successful. Patients, academics, clinicians, industry, and regulators all have to work together. There are complex challenges in developing rare disease therapeutics that not only benefit from, but need, the multiple perspectives from all members of the community. These insights help inform optimal clinical trial design, establish fit-for-purpose endpoints for rare disease clinical trials, and enhance our understanding of the therapeutic landscape of benefit-risk from diverse patient populations. Silos are simply not effective when you are trying to move the needle and avoid reinventing the wheel over 10,000 times for 10,000 various rare diseases. We have many examples at the FDA where research has aided therapeutic development, particularly in the pre-competitive space. This is where it really helps us inform novel approaches to innovative clinical trial design, looking at the use of Bayesian methods and smart designs to reduce the numbers of patients you would need to have in various arms of clinical trials. We have been characterizing fit-for-purpose endpoints, such as novel surrogate biomarkers or clinical outcome assessments, both of which are critical to incorporate into a clinical trial.

Our therapeutic product centers engage in public-private partnerships, consortia, workshops, and work with researchers through grants that are administered to define, for example, the natural history of patient populations, in coordination with our Office of Orphan Products Development or through the FDA's Broad Agency Announcements. So there are many different ways in which we work with the community in order to foster the advancement of science.

Julian Beach:
I think it is the cross-disease registries. It is the patient registries. It is using the data, because one of the critical aspects for me is that rare diseases, by their definition, are rare. So it is how you can bring together enough information to make a common pathway or how you can make pools of data big enough to actually reach a critical mass. This then allows you to look at what is possible from a regulatory point of view or what makes sense from a scientific point of view. But ultimately, how do you then consider each patient's data individually and use it to treat them? I think there is a number of ways, but it is really about seeing how you can pool data to then look at how to treat that individual.

Stephanie Cherqui:
If I can add on that, pooling the disease data together and delivering the technology, as Kerry said, is very important. You asked for a concrete example. There is a nonprofit organization called n-Lorem that stands for Nano-Rare Patient Colloquium. It was created by an expert in antisense oligonucleotides (ASOs). They created this nonprofit organization to be able to use the same ASO technology for extremely rare diseases. Sometimes it is an N=1 patient population. But because the technology is shared across all these diseases that meet certain criteria, they can treat these patients for life. I think this is a beautiful example of how collaboration between experts and physicians, who are ready to give their time to deliver this new technology, can really impact patients with an ultra rare disease.

Daria Julkowska:
If I may add a final comment, from a different perspective. For me, this interdisciplinary and multi-stakeholder collaboration is something that led to the creation of the European Rare Disease Research Alliance, which we call ERDERA. We went from having only 20 different funding bodies in 2015 to more than 180 organizations today, which encompass funders, industry, patient organizations, research performing organizations, hospitals, and infrastructures that really work under one umbrella to accelerate the rare diseases ecosystem. So there are different dimensions and I think this kind of structural dimension is also very important.

Erica Berg (*host*):
I have a follow up question for you, Daria. ERDERA is bringing together stakeholders from many different countries. What has surprised you the most in terms of what makes these types of cross-border and cross-disease collaborations successful or challenging?

Daria Julkowska:
Today we have 37 different countries participating in ERDERA, so as you can imagine, it really goes beyond Europe. We also have Canada, Australia, and New Zealand, for example, on board. What surprises me is that we release a lot of funding opportunities and what we have noticed is that bringing the different consortia together is already sufficient to foster collaboration. First of all, many of them are being built from scratch. We often say that the rare disease community is small and we would think that everyone already interacts a lot and everybody knows each other. But in reality, when it comes to the research projects, there are a lot of consortia that are gathering new resources and complementarities together. And even if, in the end, those projects are not selected, it is already enough to sustain the collaboration. So I think this was one of the most surprising things, because it means that the collaboration is so important that even though they do not receive support from funding, they still continue to collaborate. When it comes to more difficult aspects, sometimes it may be the language barriers, but most of the time it is something outside of the research problematic.

We had this experience where we financed clinical trials in which we had groups from multiple countries and every time they needed to revise the protocol, it had to be translated into all the national languages, which led to additional delays or costs for the trial. So there are some things that are outside of the research scope or research parameters, but they may hamper or at least delay the collaboration.

Erica Berg (*host*):
Julian, I was wondering if you could share some common scientific or therapeutic themes that you have seen emerge across different rare diseases that make this type of cross-disease research so valuable?

Julian Beach:
I think there are a number, but it is all about identifying where there are underlying genetic mutations or where there are treatments that could target common pathways. Are there particular targeted therapies that could work across different disease areas or different condition types? I think it is really about looking at the different effective therapies, which can be based on very different technologies. These might involve delivering a payload, accessing mRNA, or using CRISPR, to apply targeted-type aspects based on genomic sequences. In the future we may potentially sequence a person's germline to help determine which therapy would be most effective, so the therapy is personalized to that individual. All of those things will then enable that research base to come up with those final therapies. I guess this is also where we use this kind of research to inform other research, which then can be applied to broader areas of medicine and larger populations of thousands or ten thousands of people. So there are translatable elements and the focus on rare diseases really drives that research. It drives thinking. It shifts the paradigm and challenges us to reconsider how we think about medical research. So with the human body, when you have the genomics to understand what tests can be put in place and what different diagnostic tools that you would then need to develop, all of those aspects can then be translatable across different disease types to give you that final outcome.

"Natural history studies and understanding the natural course of a disease are very important to help plan and develop a trial that is going to demonstrate substantial evidence of effectiveness or characterize safety."

Kerry Jo Lee:
To build upon what Julian was talking about, translational science is a critically important area for rare disease drug development. The translational science, par-

ticularly within CDER for the therapies that we have, helps to support the selection of novel surrogate biomarkers, which is very important when it takes too long to see the effect of a clinical outcome. Translational science also supports what we call confirmatory evidence. Mechanistic and pharmacodynamic data can comprise the confirmatory evidence, which is the part of a marketing application that helps to demonstrate substantial evidence of effectiveness, in addition to the one adequate and well-controlled trial that is conducted. Those are really critical aspects of translational science that help to support how we think about putting together and reviewing marketing applications for rare disease therapies. There are two other components of research that are also very important. We support a lot of research on natural history studies. Natural history studies and understanding the natural course of a disease are very important to help plan and develop a trial that is going to demonstrate substantial evidence of effectiveness or characterize safety.

We have a lot of heterogeneous patient populations due to phenotypic and genotypic diversity. Understanding what those subsets are, even within a rare condition, can help you pick the right patient population for your therapy, the right trial duration so that you can demonstrate an effect, and can also help you pick the endpoints as well as the timing of those endpoints in order to demonstrate an effect. So natural history study is one component. Finally, we have support for statistical innovations and modeling that really help us find new approaches that might be successful, that lead to benchmarks for how we interpret the success of studies. So all of those are different ways in which I think we support research as well.

Erica Berg (*host*):

Stephanie, I want to talk about your research, which spans a spectrum of diseases, from cystinosis to Alzheimer's disease. What insights or techniques have translated unexpectedly well across these very different diseases?

Stephanie Cherqui:

Cystinosis is a very rare disease that affects perhaps 3,000 to 4,000 patients in the world. I was always passionate about gene therapy, and at the time I was involved in finding the gene responsible for cystinosis. When I had to develop the gene therapy approach, we realized that it was a very challenging disease because all of the organs are degenerating, so we have to bring a new protein to all of the organs. The protein involved is non-secreted, so it was very hard to provide this protein to all tissue cells. However, I was already involved with the families and the community, so I really wanted to make a difference. I decided to use bone marrow stem cells, and in particular hematopoietic stem cells, to try to deliver this protein to all the tissues as these cells can naturally migrate and engraft in all the tissues throughout the body. Very unexpectedly, the hematopoietic stem cells had a very dramatic positive impact on the disease in the mouse model. We were able to then go from the bench to the bedside. We have now completed the phase one and phase two clinical trials with positive outcomes. This program has now been acquired by Novartis and we are going to start the new phase of the trial.

Along the way, we asked ourselves, "How can hematopoietic stem cells, which give rise to blood cells, generate this tissue rescue throughout the body?" We determined the mechanism of action and realized that we could create macrophages or microglial cells in the brain, which then form tunneling nanotubes to deliver the organelles to diseased cells. This discovery led us to ask, "If this works for cystinosis, why can it not work for many other disorders that involve non-secreted proteins that are found in organelles?" From there, we have now been able to apply the same technology to Danon disease, which often requires patients to undergo a heart transplantation, Sanfilippo syndrome type C, which is a neurodegenerative disease, and also Friedreich ataxia, which is a mitochondrial disease. So this has opened a completely new way of treating these patients. We will also be starting a clinical trial next year on genetically modified hematopoietic stem cells. What we learned from each disease has revealed so much about the mechanisms of action and their potential for use in the central nervous system. We thought why not apply this approach to Alzheimer's disease? There were clues that suggested it might work, and, indeed, in the mouse model, we were able to rescue Alzheimer disease with the same technology. Now we are also working towards translating these findings into clinical applications.

"That is also the message I give to my students, each time I have the opportunity to do so: please work on a rare disease, because whatever we learn can be applied to so many other diseases. There are more than 400 million people out there with a rare disease, and so few have an effective treatment. We can learn so much and apply these findings to so many other diseases."

I remember during my PhD, one of my committee members saying, "You have done a great job finding the gene for cystinosis and making the mouse model, but why do you choose to work on such a rare disease?" I answered him by saying, "First of all, there is no rare disease when you are a parent and your child is affected by a rare disease." Thank God there are people who work on rare diseases. I also told him, "What you learn when studying a rare disease, you can apply to so many other disorders." I wish he could see me now, because this is exactly what happened. That is also the message I give to my students, each time I have the opportunity to do so: please work on a rare disease, because whatever we learn can be applied to so many other diseases. There are more than 400 million people out there with a rare disease, and so few have an effective treatment. We can learn so much and apply these findings to so many other diseases.

Erica Berg (*host*):

I think we have done a great job of making the case for why this type of cross-disease collaboration is so important in the rare disease space. I am now going to shift gears a little, to talk about how we build and sustain these collaborative communities of researchers, regulators, and all the other stakeholders, that make progress faster and better. Daria, how do you build trust and a shared language among researchers, clinicians, regulators, industry, and patient groups, who may come from very different backgrounds, in order to work toward a common goal?

"We soon realized that that a neutral mediator, who was able to facilitate the dialogue between the industry partners and the academics, was essential."

Daria Julkowska:
I would say it requires mediation, mentoring, and training. Why do I say that? Because we cannot expect every stakeholder to fully understand each other's perspective from the start. We have a lot of experience in building a full pipeline for these collaborations. For example, in our public-private partnerships, such as the Rare Disease Research Challenges, we have seen it play out. In these initiatives, industry partners, in collaboration with patients, have set challenges to which academics have responded with proposals. We soon realized that a neutral mediator, who was able to facilitate the dialogue between the industry partners and the academics, was essential. This is because there can often be a preconception or misinterpretation of what the other one is like. The industry might be seen as always wanting to make money, while academia may be perceived as not always delivering the high-quality or usable outputs, for example. So this is something that we have learned and we are applying. We also offer free mentoring services to research applicants. When the consortia apply with the research projects and are invited to submit their full proposal, they have the possibility to access a pool of mentoring experts that are specialized in quality assurance, statistics, innovative methodologies, regulatory affairs or business development. They can accompany the consortium in a way that helps them better conceptualize their project, ensure follow-up, and work towards concrete outputs. The final aspect involves the dialogue and understanding between patients and research communities. We have realized that setting up dedicated workshops or trainings where researchers and patients are sitting together, to better explain what they do and what their needs are, can be really successful. Currently, for our funded projects, these kinds of trainings are mandatory before they start the project. It is in this way that we can ensure that we apply different types of tools, without putting the burden on the research groups, patients or other stakeholders, so that they have all the knowledge from the start.

Julian Beach:
I think it begins with building a foundation of communication. One of the things that the MHRA does very well is having that open communication style, and I think that really goes a long way. As Daria was saying, the easier you can make communication, the more scientific conversations you can have and the more language is deconstructed so that you do not build artificial barriers. Something that I see quite regularly is that there is a fear factor. People think, "Should I have a conversation? Should I do this? Should I do that? Should I talk to a regulator? Should I talk to a funder?" We really need to ask how we can help and support people as they move through their careers and experiences so that they can focus on that patient outcome and bring the patient perspective into the conversation, and stay centered on what the ultimate aim is. So it comes back to a basic level of communication and trust. How do you generate human relationships? How do you have that overall discussion to reach the desired outcome?

"We also have very robust programs in patient-focused drug development as well as patient listening sessions where those communities can come and talk to us and share their lived experience so that we understand the risk-benefit considerations and what it is like to live with a certain condition."

Kerry Jo Lee:
I wanted to add just a few more things on this topic, because I think it is a really critical aspect of how we are going to succeed moving forward. I wholeheartedly agree that it is through engagement, but also through education. We often hear at the FDA that we are a black box and people do not understand how we work or the regulatory components of how to move from bench to bedside. So we definitely have been strong proponents of engagement through our public-private partnerships, consortia, symposia, and public workshops. We also have very robust programs in patient-focused drug development as well as patient listening sessions where those communities can come and talk to us and share their lived experience so that we understand the risk-benefit considerations and what it is like to live with a certain condition. This is very valuable to how we think about advising on the clinical trials that are submitted to us. Finally, the education component comes with an access aspect. We have a history of putting on these workshops at the FDA that were in situ: they happened in a moment of time, and if you were there, you got the lessons, but it is hard to find them afterwards. One of the things we have tried to do through the Accelerating Rare Disease Cures Program is list those that we think are really impactful for rare disease drug development on our website. That way stakeholders can simply use the dropdown menu to look at the components such as how we use real-world data, what the innovative statistical designs are, how to collaborate on natural history studies and registries and why they are so important, and have all that information available to access whenever they need it.

Erica Berg (*host*):
Stephanie, can you talk about your role in research consortia, such as the Cystinosis Stem Cell and Gene Therapy Consortium? From your perspective, what are the keys to maintaining these productive long-term collaborations?

Stephanie Cherqui:
I am not an MD myself, but when you go from bench to bedside, you have to be surrounded by a strong team. It takes a village. It is for this reason that I created the Cystinosis Stem Cell and Gene Therapy Consortium. I chose really amazing people who were willing to give their time, because they give a lot of it, to advise and support us at every step of the way. They helped us navigate the regulatory processes to develop a new clinical trial, which can be complicated when it involves stem cells and gene therapy. It was the first of its kind at the University of California San Diego. It was also important to involve the patient advocacy group. Nancy Stack, the president of the Cystinosis Research Foundation, is also part of this consortium. They are an essential part of it because you need to have someone who speaks all the "languages". They are the best people to help us navigate the disease landscape and guide us on the appropriate end points, and really explain what the families are truly struggling with. I am lucky with this consortium as we keep the dialogue open. We held meetings and brainstorming sessions to determine the

best clinical trial design and most meaningful end points. Now that it is completed, I can say it was a challenge, but it always moved forward thanks to a group of expert and kind people. Consortia like this are really key for these kinds of clinical translational projects.

Erica Berg (*host*):
Kerry Jo, I wanted to talk a little about FDA's Rare Disease Innovation Hub. How does that help facilitate these types of cross-disease collaborations and what sort of outcomes are you hoping for with the program?

> ***"The Hub, in terms of outcomes, is hoping to foster a number of public workshops called the Rare Disease Innovation Science and Exploration Public Workshop Series, also known as the RISE Public Workshop Series. These workshops are really intended to address challenges that are common to multiple diseases or across classes of diseases to think about how we can apply evolving science into innovative solutions that will accelerate rare disease therapies."***

Kerry Jo Lee:
The Rare Disease Innovation Hub is really an important advancement in how the FDA looks at cross-sectional issues in rare diseases. I will start with a little bit of history, as it may be confusing to people, and then talk about how the Hub builds and enhances upon what we have. Since about 2013, the centers have had staff dedicated to working across rare diseases: the Rare Diseases Team in CDER and the Rare Disease Program Staff in the Center for Biologics Evaluation and Research (CBER). We have collaborated and still do on many programs, such as the Rare Disease Endpoint Advancement Pilot Program, to develop endpoints, the Support for Clinical Trials Advancing Rare Disease Therapeutics (START) Program, which is very important, and even within CDER, there is the Accelerating Rare Disease Cures (ARC) Program, which is led by cross-disciplinary leadership across our clinical pharmacology and statistical offices. The enhancements through the Hub really reflect a much-needed focal point for the broader rare disease community where they can engage, access, and provide input and have bi-directional engagement with the FDA on matters that span the centers that are of importance to rare disease drug development at large.

The Hub, in terms of outcomes, is hoping to foster a number of public workshops called the Rare Disease Innovation Science and Exploration Public Workshop Series, also known as the RISE Public Workshop Series. These workshops are really intended to address challenges that are common to multiple diseases or across classes of diseases to think about how we can apply evolving science into innovative solutions that will accelerate rare disease therapies. As part of that bi-directional engagement that is so critical for the Hub, the public will be able to submit topics for consideration for these workshops. So we are listening. The Hub is really here to help facilitate dialogue and move the field forward, beyond just one center.

Erica Berg (*host*):
So, switching gears again, we are going to talk about the underlying structures that make all these types of collaborations possible. Daria, could you share how we can better leverage data sharing platforms, registries, biobanks, and all of these resources to support research across rare disease boundaries?

> ***"The goal is that every resource that is being added onto this platform becomes interoperable and what we call FAIR, which means findable, accessible, interoperable, and reusable. This is the only way to make the different resources visible and reusable, because if they are siloed or constructed in a way that does not follow the FAIR principles, we lose a lot of valuable data."***

Daria Julkowska:
In my opinion, in order to truly leverage those different types of data, there are three main elements to consider: interoperability, common standards, and ontology. The idea is, and this is something that we also implemented through the development of the Virtual Platform of Data Tools and Resources, that there is a place where you can easily find the different types of data. For example, there are catalogs that contain information on rare diseases, but there is also genetic data, biobanks and registries that are being connected. The goal is that every resource that is being added onto this platform becomes interoperable and what we call FAIR, which means findable, accessible, interoperable, and reusable. This is the only way to make the different resources visible and reusable, because if they are siloed or constructed in a way that does not follow the FAIR principles, we lose a lot of valuable data. We have also extended and created what we call the WikiPathways, and this is where interdisciplinarity is essential as you need biologists, chemists, but also clinicians and bioinformaticians, working together to create the rare disease pathways. These pathways can help accelerate the identification of the drug targets and improve the understanding of the disease mechanisms, but can also support efforts like drug repositioning. It really requires interdisciplinary collaboration, but also, and this is very important, the standardization and interoperability of different types of data.

Erica Berg (*host*):
Does anyone else have any experience with these types of registries that they would like to share?

Kerry Jo Lee:
FDA supports the Rare Disease Cures Accelerator Data Analytics Platform, which is a repository where all types of data can be submitted and curated for querying, to understand many of the things that were just discussed. I cannot underscore enough the point that was made about interoperability. As Julian mentioned, capturing the rare disease patient experience is critical. You could be missing a couple of data points and have an entirely different picture of what you need in order to bring a therapy successfully to market. The other thing that I would underscore is when you are building these databases, you must first think about what question you are trying to answer, and ensure that those elements are built in, and that you

are collecting those elements into your program. From a regulatory context, are you collecting the endpoints that are relevant? Are you collecting correlation between biomarkers and clinical outcomes? Are you capturing clinical characteristics of these heterogeneous populations that will be important to defining the patient populations? All of those elements become really important. You have to start off with a plan in mind and ensure you are building to answer those questions you have previously defined.

"Standardization and collaboration are crucial. As we have been saying, the challenge is how to get enough data, how to understand that data, and then how to extrapolate information from it. There is still a long way to go in terms of how we can increase that standardization."

Julian Beach:
I think one of the things that you do have to look at is simplicity as well and how effective it is to use the data. The more data that you collect and want to analyze, the less useful it can become. So it is really about looking at key survival outcomes. When you start looking across national boundaries and pooling that data, you need to consider the ethical and legal standards that go along with this information as well. In the global context of rare disease numbers, you may have N=10 patients for a particular rare disease in each country and pooling the data gives you a total global population. However you need to be looking at things from a different perspective than we have in the past. Standardization and collaboration are crucial. As we have been saying, the challenge is how to get enough data, how to understand that data, and then how to extrapolate information from it. There is still a long way to go in terms of how we can increase that standardization. Even when you look at an ecosystem like the UK, where you have a common health standard, a unified health system, and the Clinical Practice Research Datalink (CPRD) service, which brings together all of the information within the UK, there are still things which can be added. Registries and other tools continue to be layered on top. So the question is: how can we ensure that simplicity is built into the system as well?

Erica Berg (*host*):
Julian, from a regulatory standpoint, is there ways that agencies can better support or even incentivize the development of therapies and treatments that have cross-disease potential?

Julian Beach:
I think if I start with the original approach, there are definitely ways that people can see how ecosystems can align. Within the UK, we have something called the Innovative Licensing and Access Pathway (ILAP). That brings together key elements like regulatory approval, funding approval, and then the actual use of the medicine. It essentially streamlines access so that patients can receive these products much more quickly. It is about aligning those processes. Then, if you are looking at how to build on the original filing, to repurpose that medicine for a different use, for example, there are opportunities to draw on prior knowledge. This could include clinical or quality data, how you make the medicine, endpoints, or non-clinical effects. The key is determining the translatability. From a regulatory standpoint, we can be clearer when using generic wording such as "pathway designations", because I do not believe that they provide a panacea without having some definition around what that platform actually entails.

Erica Berg (*host*):
Stephanie, I was wondering if you could share from your perspective what you think are the key barriers that prevent more widespread cross-disease collaboration and have you seen any creative solutions that have worked to bridge those silos?

"People who are creating or organizing these biobanks are sometimes not very willing to share. Sometimes it can be complicated as there is a sort of competitiveness. We all want to collaborate and share, but you also want to be the first. So that exists and we have to be honest about it, as it could be a barrier in cross-collaboration in the rare disease field."

Stephanie Cherqui:
One example is biobanks or repositories of tissues and blood. These are crucial in rare disease research, but they are costly. There are some national biobanks that are supported by federal funding, but as we said, rare diseases involve very few patients here and there, and we cannot have tissues or blood for all the disorders. Most of the time, they are created by a specific research group at a specific location and are supposed to be available to the public, but this is not always the case. For Friedreich ataxia, for example, it has been more than a year that I have been trying to acquire some tissue that is supposedly available, but going through the MTA (Material Transfer Agreement) process and accessing it is very complicated. People who are creating or organizing these biobanks are sometimes not very willing to share. Sometimes it can be complicated as there is a sort of competitiveness. We all want to collaborate and share, but you also want to be the first. So that exists and we have to be honest about it, as it could be a barrier in cross-collaboration in the rare disease field. I think the key people in that landscape are the advocacy groups, because they have the opportunity to bring together the researchers, scientists, and physicians working on a specific disease through symposium or workshop events, and then we are all together in a room and we have to discuss and share our data. Usually, that is a key component needed for collaboration. I think there is definitely much more to be done in that field.

Erica Berg (*host*):
Kerry Jo, I wanted to talk a little about regulatory pathways. Given the Hub's cross-center role, how do you approach aligning priorities and regulatory pathways between CDER and CBER, to support the cross-disease initiatives?

Kerry Jo Lee:
I think the Hub is a fantastic addition in terms of enhancing and strengthening our communication. It provides a visible and tangible connection point, not only for the

external community, but for us within the agency as well, for dialogue, information sharing, and harmonization between the two centers. I would say that our priorities are already aligned. We want to speed up and increase the availability of safe and effective therapies for the rare disease patient population. What the Hub does is provide those vital connections and structures, internally. For example, there is the Rare Disease Policy and Portfolio Council now under the Hub, which I co-chair with another colleague from CBER. That is a designated forum where we can connect, collaborate, and discuss our portfolios and how we can evolve our shared initiatives in lockstep towards our common goal.

Erica Berg (*host*):
I wanted to spend a little time now talking about funding issues. Daria, given your experience with European funding schemes, what structural changes do you think would best incentivize or reward interdisciplinary research in rare disease?

Daria Julkowska:
Honestly, for the interdisciplinary research, we already have a lot of different types of collaboration. For example, in our case, having complementary disciplines or partners is something that is mandatory when you are applying for every funding opportunity. There is perhaps one field which I believe is really lagging behind, and that is the field of social sciences and humanities, including socioeconomic aspects. This is where the rare disease community, particularly on the medical side, is not yet used to collaborating with sociologists, economists, and so on. I believe that this is where we need to make a stronger effort when talking about interdisciplinarity.

"If we want to accelerate the development of treatments for rare diseases, knowing that 95% of them still lack an effective treatment, we must acknowledge that we will not be able to develop one treatment per disease. I think it is important to focus efforts on building more knowledge and gathering communities together. This can be done through the specific funding opportunities and also by stimulating innovation through public-private partnerships."

Another important aspect is to talk about cross-disease research, because in my opinion, this is not yet something that is fully anchored in our way of thinking. We still think about rare diseases by focusing on individual diseases or groups of rare diseases. We need to come from a different perspective, so that we are reducing the number of rare disease categories and finding the commonalities. This is something which is not yet sufficiently put forward. If we want to accelerate the development of treatments for rare diseases, knowing that 95% of them still lack an effective treatment, we must acknowledge that we will not be able to develop one treatment per disease. I think it is important to focus efforts on building more knowledge and gathering communities together. This can be done through the specific funding opportunities and also by stimulating innovation through public-private partnerships. The collaboration with industry, in this area, is extremely important. We must not forget the third side of the triangle where we include the regulatory agencies or health technology assessment bodies from the very start when thinking about this type of research. I am sure that Kerry Jo and Julian would agree on this point. Because if we continue thinking in terms of one treatment equals one condition, then we will face serious bottlenecks when trying to implement cross-disease approaches. So, I think what is really important is sharing knowledge, driving systemic change in how we think about rare diseases, and then supporting innovation and funding in this respect.

Kerry Jo Lee:
I wholeheartedly agree about thinking about the regulatory component early on.

Julian Beach:
Agreed. I think Daria's comment about the HTA involvement occurring early on and approaching it collaboratively is key. It has to be seen as a whole, and I think this is very much an evolving space for rare therapies in terms of how we can then distribute them into the health systems.

Erica Berg (*host*):
We were saying that there needs to be a systemic change in how people view these cross-disease approaches more generally. Any thoughts on how that could be achieved? Is it a regulatory issue, a policy change, a shift in how researchers think, or a little bit of everything?

Julian Beach:
I think it is a bit of everything. I think it involves really looking at the risk paradigm that needs to be considered to make informed decisions involving patients. At what point can a medicine be used? At what point is a product safe? Equally important is having that does-it-work comparison, and for how long? Those are the types of things that you can do in the short term, but having some really clear systems for post-market surveillance and follow-up is also important. Once you have had that treatment, when does it come back into that pharmacovigilance space? All of these factors are really critical to enabling earlier access to treatments and therapies.

Kerry Jo Lee:
I think a part of your question was asking how we take these experiences and translate them more broadly to the community. We think about that a lot and it takes all of us buying into that. I think the rare disease community, external to regulators, needs to come together as a broader community and understand that the individual condition and the therapies designed to help are unique, but the challenges that you are going to face are common. "How do I adapt a clinical outcome assessment for my disease?" "What is the level and degree of translational science that I need to support my biomarker?" "What types of innovative statistical designs can I employ?" "How do I incorporate real-world data to augment my applications?" Those are issues that go beyond the individual diseases. I think the more we do to share those approaches, the more helpful those approaches will hopefully be to others.

Erica Berg (*host*):
Looking ahead 5 to 10 years, what does a mature, thriving, and cross-disease research ecosystem for rare disease look like? How do we get from here to there? Stephanie, let us start with you.

"When you prove the safety of a technology for one rare disease, the goal would be to streamline the process so that it could then be applied to more diseases, with only minimal safety studies needed to bridge the gap from one disease to another. If this kind of platform was widely accessible to many, I think it would really accelerate the process and change the landscape of how we use gene therapy for many disorders."

Stephanie Cherqui:
So in regards to gene therapy, the main challenge is the manufacturing and the technology needed to optimize safety. They are the most costly and long studies to carry out. One of the best ways to really use the resources in a way that we can apply to many disorders is through the platforms. I know that the FDA is really supporting that now. We want to be able to apply a technology to many of our disorders. When you prove the safety of a technology for one rare disease, the goal would be to streamline the process so that it could then be applied to more diseases, with only minimal safety studies needed to bridge the gap from one disease to another. If this kind of platform was widely accessible to many, I think it would really accelerate the process and change the landscape of how we use gene therapy for many disorders. I am sure this is true not only for gene therapy, but I think the platform and streamlining the regulatory process would be the key.

"I would say that the ideal kind of ecosystem is, first of all, focused on the needs of patients. They are really the drivers of this ecosystem and it encompasses all the elements of the pipeline: from the fundamental research until the end of the process. And when I say the end of the process, it is not when the drug or therapy is approved, but when it is actually accessible to patients."

Daria Julkowska:
A few weeks ago when I was in a meeting, somebody said that rare disease patients do not see the timeline in the same way. So for them, especially when it comes to the diagnosis, even a short delay, like a weekend, is too long. It is too long because it hampers the time to receive the diagnosis. I would say that the ideal kind of ecosystem is, first of all, focused on the needs of patients. They are really the drivers of this ecosystem and it encompasses all the elements of the pipeline: from the fundamental research until the end of the process. And when I say the end of the process, it is not when the drug or therapy is approved, but when it is actually accessible to patients. So for me, in this ideal ecosystem, there is also more of a focus on innovation that allows for the acceleration of this access. And for that to occur, we really need to collaborate with all stakeholders. I believe that we are on the right path, especially when it comes to this inclusion of the regulators, the industry, and the HTA. There is currently more and more dialogue about this, so I believe that in five to 10 years, we will get there.

Julian Beach:
It is a really exciting question because I think innovation is growing at such a pace that when we think about the 5- or 10-year outlook we have got to ask: how do we ensure that the right structures and funding are in place to enable regulators, innovators, and industry to reduce the time from discovery to patient? And how can we make sure that prior knowledge and information sharing across different disease types is clearer and less ambiguous? From a UK and European standpoint, there are a large number of regulations that were written 25 or more years ago. We need to think about how we can update them to make them have a more patient-centric approach, as Daria has clearly articulated. For me, the key is looking at how do we maintain patient safety, while making sure that the risk assessment is proportionate, and most importantly that patients are involved in the definition of risks. I think those are the biggest changes I see, which will enable innovation to move forward.

Obviously, there are the technological things and the other parts that will enable it, like AI, machine learning, and data sets, as we have been discussing. But those kinds of advances are built on a strong regulatory foundation, the involvement of all stakeholders and a supportive ecosystem.

"Rare disease drug development is complex. There are challenges that always arise and in this space, there are a lot of firsts. I really think that we can use the experience of others to help navigate the community. That way, when you hit those roadblocks and those complexities you are able to navigate them more nimbly and effectively, because the end goal is ensuring we can get safe and effective therapies to patients as quickly as possible."

Kerry Jo Lee:
I would love to see increased cross-sectional and robust collaboration in the pre-competitive space. To build that prior knowledge before we get into development. I would also love to see a stronger partnership and increased collaboration within the rare disease community, which includes patients, academics, clinicians, sponsors, and regulators, both within individual conditions as well as across different conditions. Rare disease drug development is complex. There are challenges that always arise and in this space, there are a lot of firsts. I really think that we can use the experience of others to help navigate the community. That way, when you hit those roadblocks and those complexities you are able to navigate them more nimbly and effectively, because the end goal is ensuring we can get safe and effective therapies to patients as quickly as possible.

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