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PJ Brooks PhD, program director in the Office of Rare Diseases Research at the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH) in the USA, highlights the importance of going beyond one disease at a time in clinical trials, some of the roadblocks that still remain and why gene therapy and gene editing have significant potential for the rare disease community.

What have been your core priorities since your appointment as Program Director of the Office of Rare Disease Research in August 2018?

My main focus is on accelerating clinical trials in rare disease by moving beyond “one disease at a time” approaches. This includes developing therapeutics that target shared molecular mechanisms underlying multiple rare diseases, and the implementation of platform vector gene therapy trials.

It is an approach we feel very strongly about at NCATS, given the current rate at which we are developing rare disease treatments. We have to do it better and faster – not just a little bit better and faster but we have to improve by an order of magnitude.

Many rare diseases are genetic diseases, with a limited number of underlying causes (etiologies). Therefore, gene therapy, gene editing, and focusing on shared molecular etiologies have tremendous potential for such diseases.

NCATS describes itself as a different breed of scientific organization with an unprecedented mission. What exactly makes the centre so unique and pioneering?

NCATS is unique because we focus on translation as a scientific discipline. Nearly every NIH Institute and Center supports translational research in their efforts to develop treatments for specific diseases. At NCATS however, our focus is the scientific study of the translational process. We are constantly looking to make this process better, faster and ultimately bring more treatments to more patients more quickly. In addition, we are disease agnostic and thus cut across all the different NIH Institutes and Centers. Our new approaches can potentially impact all of them, which is very exciting.

In addition, all our projects are very collaborative in nature. Translation is truly a team sport. The old model, where there is one researcher in his lab, developing a drug, is outdated. At NCATS, we embrace collaboration. In fact, within the NCATS Division of Preclinical Innovation, which houses the Therapeutics for Rare and Neglected Diseases (TRND) program, (https://ncats.nih.gov/trnd) every project is a collaboration with an outside group.

At NCATS, we think of the three D's: Develop, Demonstrate and Disseminate. We develop new programs, demonstrate that they work (or do not work), and if they do, we disseminate them widely. The goal is not to keep them with the original developers, but to disseminate our programs to have the widest possible impact on multiple disease areas.

What are the capabilities of NCATS as a catalyst to the improvement of translational effectiveness?

Using the analogy of an enzyme as a catalyst that brings together two reactants into physical continuity, NCATS collaborations bring together the right people at the right time to make things happen and catalyze t innovation.

Specifically, in the NCATS Office of Rare Diseases Research, we support the Rare Disease Clinical Research Network (RDCRN), in partnership with other NIH Institutes and Centers. The RDCRN is

designed to advance medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrollment and data sharing. Through the approximately 20 RDCRN consortia, physician scientists and their multidisciplinary teams work together with patient advocacy groups to study more than 200 rare diseases at sites across the nation. Each consortium focuses on at least three related diseases, and are also required to do natural history studies, which are essential for clinical trials. As one example of the impact of the RDCRN, natural history data documenting how several rare inherited disorders progress in patients over time led to clinical outcome measures in the first clinical trial of gene editing in a rare monogenic disease https://ncats.nih.gov/pubs/features/rdcrn-gene-editing .

Essentially, within the RDCRN we have clinical data, scientific expertise, access to patients, and connections to patient advocacy groups, which can allow pharmaceutical companies to come to us and work with those consortia to get their clinical trials started.

Given recent breakthroughs in biomedicine and an increased understanding of the dynamics behind rare diseases, is the classic clinical trials process still relevant and fit-for-purpose?

Clinical trials that are adequate, well designed and well controlled are essential to knowing if a drug works. Nonetheless, I believe that we could do them a lot more efficiently. We should pursue platform type approaches a lot more than they are currently implemented. Going beyond one disease at a time is probably one of the biggest opportunities in gene therapy and small molecules. Taking it one step further, the future could likely be genome editing, in both recessive and dominant diseases. Clinical researchers are slowly but surely catching up on this paradigm, but science is just waiting to be moved into clinical trials.

It can almost be a virtuous cycle: If we had people thinking more about shared molecular etiologies and doing clinical trials that way, we would have more research in therapeutics that work based on shared molecular etiologies. We are just at the beginning but I hope there will be a quick adaption of the platform approach moving forward.

To this end, the FDA has also been very supportive in embracing this sort of alternative approach in the oncology space. I don’t work for FDA, so I can’t speak for them, but in my experience, they are always eager to listen, as they naturally want drugs developed in a smarter and more efficient way. It is not their job to tell us how to design clinical trials, but to react to what people bring to them. I believe it is a matter of approaching them with clinical trial approaches based on good science and

they will respond positively.

The number of human conditions with a known molecular basis is increasing rapidly, but the development of corresponding therapies is lagging far behind (approximately 500 therapies for 6,000 disease phenotypes). Why is this?

Part of it is that with DNA sequencing we are discovering a lot more diseases, and a lot of them are rare cancers. Fundamentally, it comes down to the way we think about disease. We have always thought and talked about developing therapies one disease at a time. That made sense in the beginning – diseases were defined based on symptoms, and we did not know anything about etiologies. But being able to develop drugs which address disease etiologies is what really matters. So, for rare genetic diseases, rather than thinking about thousands of rare diseases we should reverse our thinking and look at it from a standpoint of etiologies: There must be far less than 7000 of them. For monogenic disorders; splicing mutations, premature stop codons and misfolded proteins is the basis for most of them, and all three are “druggable”. This raises the question: What if we think about three diseases with thousands of different clinical manifestations? This would mean that we could develop drugs faster and get a lot more people into rationally designed clinical trials based on their actual mutations. Again, its analogous in principle to classifying cancers based on the underlying druggable molecular target rather than the location in the body, which is becoming the standard approach in oncology. Admittedly, it’s a different way of thinking about rare diseases, but the science is there, and I think it’s a faster way to bring more treatments to more patients more quickly.

What would you identify as the main roadblocks along the path to translation when it comes to developing rare disease therapies?

Some of the standard roadblocks remain. Oftentimes there is a lack of natural history and information. People are now realizing the importance of having a rational basis for an outcome measure in a clinical trial. The best information still comes from properly conducted natural history studies. As I noted above, we support a lot of these studies through the RDCRN, but there are more rare diseases than we can support through this mechanism.

Another roadblock we face is access to funding, both public and private. In the drug development area, in the past, pharma companies saw the rare disease space as less attractive than more

common diseases. However, we have seen a lot of progress in this regard, as there is clearly increased interest in rare diseases from small, medium and big pharma the like. It’s an exciting time

Another issue is that with gene therapy in a rare disease with a very small patient population, you may actually end up treating most of your patients in the clinical trial. If so, because gene therapy is a one-time treatment, there will not be any market for your drug. This is fundamentally different than most treatments that must be taken continuously. This is not an issue of price; there simply is not even a market. Given the recent success stories in gene therapy, and the rapid pace of gene editing, its important to think about creative ways to address those issues, so that no diseases are left behind. With the potential implications of gene therapy, we have to think creatively about platform approaches to address some of those issues.

How can digital technologies (and the embracement of digital disruption & big data) overcome some of the operational and scientific obstacles to rare disease trials?

There are many ways in which digital technologies can overcome certain obstacles to rare disease trials. One example is wearables that are able to collect objective data and then store and analyze it. This type of data is excellent natural history data without a lot of effort. The burden for patients to travel is removed, which is especially relevant for very sick patients that are often physically not in a condition to travel across the country.

For diseases that affect people’s behavior, you could also record people via remote video, optimally in their own home, behaving how they do on a day-to-day. This seems potentially very impactful, especially as the US is a big country with only a few specialists in certain rare diseases. Rather than having patients travel to those experts, you could imagine clinical trial evaluations being done remotely.

What pertinent initiatives at NCATS would you like to highlight?

In addition to those mentioned above, NCATS also supports the Clinical and Translational Science Awards (CTSA) program, which is designed to develop innovative solutions that will improve translational science. Under the CTSA Collaborative Innovation Awards program, there are a couple of rare disease related efforts.

One is the Growing Gene and Cellular Therapies project (www.ggact.org/) which is designed to support new investigators to initiate clinical gene therapy trials. Another is Early Check (https://earlycheck.org/), which is testing a new approach to newborn screening for genetic diseases. Treating degenerative disease will be most effective if started before the disease has progressed, but without newborn screening, patients will be identified based on symptoms, which result from disease progression. In Early Check, the goal is to offer “opt in” newborn screening for SMA (spinal muscular atrophy) and Fragile X syndrome to the parents of every baby born in the state of North Carolina. It’s a really exciting translational science experiment.

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