Journal of Neuromuscular Diseases 2 (2015) S83–S87
DOI 10.3233/JND-150096
IOS Press

Perspective

Looking Forward to New Therapies: A Personal Perspective on the Translational Landscape for Muscular Dystrophies

Kate Bushby*

Every patient hopes for a cure. Medicine across the centuries has expanded the numbers of diseases for which this is a realistic prospect, including many infections, surgically treatable conditions and now many cancers. For many other chronic conditions management with disease altering therapy is possible but not curative. The vast majority of these advances in medical care have been based on knowledge of the underlying cause of the disease, rendering them amenable to the development of specific therapy. With so many diseases now amenable to treatment, the diagnosis of an "incurable" condition is arguably more difficult to bear than ever before.

THE CONTEXT FOR THERAPY DEVELOPMENT IN RARE DISEASES

In many rare diseases, defined as those affecting less than 1 in 2000 of the population and frequently genetic, curative therapies were a distant dream until the explosion of genetic information enabled by the new technologies first of positional cloning, then the transformative Human Genome Project and now the enabling technologies of so called "Next Generation Sequencing" whereby the approaches to the definition of the underlying disease have been able to make incremental leaps. Essentially, a new therapy development paradigm has emerged whereby the definition of the underlying genetic cause of disease enables the establishment of animal and cellular models within which disease pathways can be mapped. This allows for the testing of new therapeutic options, establishing the pathway for the follow on stages of drug development to establish proof of concept in human trials and ultimately therapy delivery. In the early days of gene discovery, every announcement of a new gene identification was heralded as the first step to therapy delivery, and indeed the rhetoric around the current Next Generation Sequencing technologies continues to emphasise the hope that these techniques bring to the development of new therapies for conditions which are currently without definitive treatment options [1].

The inherited neuromuscular diseases (NMD) have been amongst the forefront of the conditions for which such developments have been claimed. New genes for neuromuscular phentoypes have caused a major rethink of the categorization of the diseases within this complex group, with more than 400 genes likely to be involved in causing NMD. The identification of the dystrophin gene in 1986, responsible for Duchenne and Becker muscular dystrophies, was an early landmark in this process, and has been the most extensively studied in this group, with therapeutic approaches to modify the mutation such as stop codon suppression and antisense oligonucleotides, gene replacement, targeting of downstream technology, upregulation of alternative proteins, stem cell therapy and gene repair all showing promise in animal models and increasingly moving to human studies. A rich drug development pipeline is now in place for DMD with multiple therapeutic strategies under evaluation and major pharma involvement [2]. It is anticipated that other NMD will benefit from such strategies, and indeed developments are also

*Correspondence to: Kate Bushby; E-mail: kate.bushby@newcastle.ac.uk

ISSN 2214-3599/15/$35.00

advanced in other areas such as spinal muscular atrophy and myotonic dystrophy [3].

Over the 28 years though since the identification of the dystrophin gene the experience of families that a therapy may be "just around the corner" has not changed. In 1989, a mother of a young boy with DMD told me that as the dystrophin gene was now known, he would not need a wheelchair. This young man is still alive, thanks to developments in care standards, but has not had access to a single therapeutic strategy based on the underlying cause of the disease. For patients and families diagnosed in recent years, the pain of a therapy that is still not available can be even more acute. In 2014 Alex Johnson mother of a young boy with DMD and one of the founders of Joining Jack wrote in her blog "I don't think people actually appreciate the position that parents and adult members of the DMD community are now in. Treatments are actually dangling in front of us but we can't grasp hold. Please believe me when I say I am frantically trying to grab hold of these! I desperately want a lifeline for my son".

THE "TRANSLATIONAL GAP"

So, are there particular risks for translation of all of the exciting science in NMD or is this the embodiment of the well recognized translational gap, where risks to the process of transfer of knowledge from bench to bedside are known to extend from the science itself, through risks from lack of funding to regulatory, IP and market risks? There are well recognized additional challenges for rare diseases compared to the traditional pathway for common conditions [4, 5]. It can be more challenging to define the best molecule for development if model systems are not mature or well understood as is frequently the case in rare diseases. The animal models which are developed or identified following gene identification may be adequate to model some but not all aspects of disease and may fail to provide an adequate rationale for safety and/or efficacy [6, 7]. Expertise amongst the scientists in the field in taking a translational approach may be limited without a full understanding (for example) of the optimization of molecules for development, or the implications of bulk drug supply and the regulatory framework. Longer term, moving into human studies, it can be difficult to find the patients or the expert centres who can diagnose them properly and evaluate them effectively in the context of a trial. If no previous studies have been undertaken, then the culture and experience of performing trials will be lacking. Definition of outcome measures which satisfy regulatory requirements may be time consuming and difficult to correlate with long term clinical performance [8]. Demonstration of cost effectiveness and long term financial viability of such therapies may be difficult or impossible to establish.

INCENTIVES AND SUPPORT FOR TRANSLATIONAL EFFORTS IN RD

In recognition of the specific challenges for RD drug development there have been several initiatives internationally to promote research in the field. These include governmental strategies to promote a permissive regulatory environment (incentives for orphan drug development) and particular funding streams. In the European Union, all member states have been supported to produce a National Plan or Strategy for Rare Diseases which aim to promote the specific needs of RD patients from diagnosis to research capacity. Internationally, the European Union has had several initiatives from the funding perspective designed to support RD research and has recently joined forces with other funders as the International Rare Disease Research Consortium (IRDiRC) with the goal of promoting diagnosis for all rare diseases and 200 new therapies by the year 2020.

Supported by various of these funding streams, the NMD field has been able to develop strategies for clinical trial readiness, derisking the process of drug development and forging partnerships with all stakeholders including clinical and academic groups, patient organisations and industry. The TREAT-NMD network was initially supported as a Network of Excellence under the EU 6th Framework Programme and is now a global alliance with an elected executive committee and international representation [9]. The EU funding which allowed the establishment of the TREAT-NMD network has facilitated the development of various tools and resources which aim to advance translational research in NMD. At the preclinical level, standardized operating procedures for animal models and for the conduct of preclinical trials aim to reduce the risks of misinterpretation of animal studies and optimize the molecules heading for clinic [10, 11]. The TACT (TREAT-NMD advisory committee for therapeutics) extends this derisking strategy with the offer of thorough appraisals of molecules in development from a multidisciplinary perspective [12]. Registries of different kinds have formed a backbone of the work of TREAT-NMD, with a registry containing feasibility data on sites (the Care and Trial Site registry) [13] and

patient registries associated to TREAT-NMD in over 40 countries now available in core disease areas. These patient registries have proved to be very useful in identification of patients for trials, recruitment to studies, assessment of compliance to standards of care, contribution of definition of outcome measures and delivery of relevant data to regulators and payers [14–16]. Different models for registries exist across the network depending on the requirements of the different disease areas and registry owners. Definition of outcome measures for NMD, including key areas of regulatory interaction, have also been a priority for TREAT-NMD and continue to be a priority with increasing emphasis also on the development of biomarkers of disease with links to RD biobanks and MRI [17–20]. Collaboration with, support for and dissemination of care standards has been a core work of the Alliance with documents generated with international consensus and available in many different languages [21, 22]. All of these initiatives are supported by a communication platform, ethics council and website. National initiatives have also been very important alongside this international effort, with the MRC Centre in the UK linking the leading centres in Newcastle and University College London to advance translational research in the UK, and many well organized networks and centres across Europe and the rest of the world.

With all of these resources what have we learnt about the trial readiness of the community? There does now exist a robust mechanism to identify patients for studies and drug marketing, but gaps in the registries exist and linkage across the different registry, NH, biobanking and OM initiatives could be strengthened. This is being explored through a number of projects including the FP7 IRDiRC programme RD Connect [23] as well as through collaboration with the CINRG group and industry in a new platform envisaged for NMD to facilitate post marketing surveillance. Drugs are slowly moving through the various pipelines and lessons are being learnt on the performance of the selected outcome measures in the trial environment, their robustness, reliability and sensitivity to variable baseline levels of care. The first drug to be conditionally approved for DMD, ataluren, is now commercially available in several EU countries [24, 25].

BEYOND TRIALS: THE CHALLENGE OF THERAPY DELIVERY

A new challenge is the pricing model for RD drugs and the appreciation of cost benefit from the perspective of patients and their families, health services and society as a whole [15]. The regulatory systems whereby trials are set in place and by which drugs are approved are risk averse, manifestly slow and a source of huge frustration at all levels but particularly amongst the patients and families who argue that with a life limiting and incurable disease, the greatest risk is of doing nothing. The time pressure felt by patients and families is also eloquently expressed by Alex Johson: “I have come to the conclusion that my clock ticks faster and with more urgency than that of researchers, clinicians, pharmaceutical companies and regulators”. So while increasingly robust mechanisms exist for incentivizing drug development these are not yet matched with mechanisms to ensure rapid mechanisms for approval, reimbursement and equitable availability.

It has been an immensely rewarding period to be working in Genetics and NMD in particular and the group in Newcastle now constituted as the Newcastle University John Walton Muscular Dystrophy Research Centre has actively contributed in this regard, alongside international partners representing all stakeholders. Over the last 25 years we have seen the context for NMD treatment move from an overwhelmingly nihilistic approach to a proactive strategy based on anticipatory management [21, 22]. Over the same period, the RD field has come of age and the possibilities to be able to realize diagnosis and therapies for patients where this was previously unimaginable are in place. The neuromuscular field has put building blocks in place to arrive at a stage where many of the areas of trial readiness achievable and multinational trials have successfully been established and delivered, though these remain very bureaucratic and timeconsuming to establish, especially within the academic setting. There is no doubt that keeping up to date on trial readiness will require ongoing amendment in the light of new knowledge and requirement for increased capacity but much of the armory is in place to be able to address these challenges.

There are however new challenges as we address the move from trials to therapy delivery. Regulators and healthcare providers are key players in this process. The promises embodied in RD plans and strategies and in the IRDiRC aspirations need to be fully realized and funded so that patients can at a minimum access the levels of diagnosis and management which have already (for example in DMD) enhanced life expectancy and quality of life and eventually to face the challenges of expensive new therapies. Regulators have a new set of diseases to understand and in particular to address the perception

of risk/benefit, especially from the perspective of the patients and their families. As and when new therapies come through the pipeline and need to be funded via healthcare systems there will be a huge challenge of large scale expensive therapy delivery with all the societal contexts and choices within which this will need to take place. New options for interventions may even require legislative change and extensive public debate, such as the recent adoption of prenatal mitochondrial transfer techniques in the UK. It is also clear that as increasing numbers of new diseases come through this pipeline more streamlined approaches will be required in order to envisage sustainable funding mechanisms. The framework that we have developed for NMD should provide some structure whereby these new challenges can be addressed and is evolving to try and address some of them. New therapies are closer than ever: nonetheless the balance of hope and reality is likely to continue to be a delicate one for years to come.

DISCLOSURES AND FUNDING

KB was with Volker Straub joint co-ordinator of the TREAT-NMD network from 2007–2011 and remains involved in its secretariat. TREAT-NMD was funded by the EU (LSHM-CT-2006-036825). The John Walton Muscular Dystrophy Research Centre is part of the MRC Centre for Neuromuscular Diseases and leads the RD Connect project (305444). KB leads the EUCERD Joint Action on Rare Diseases (20112201).

KB has been an investigator on trials in NMD run by Wyeth, PTC, AVI, Prosensa, Trophos and Pfizer and is the PI on the FOR DMD study funded by the NIH. She has acted without personal renumeration in an advisory capacity to Solid Ventures, LLC, PTC Therapeutics, Inc., BioMarin Pharmaceutical Inc., NB Capital Research GmbH, ScriptSwitch Ltd, Eli Lilly and Co (USA), Pfizer Inc. USA, ClearView Healthcare Partners, Lazard Capital Markets, Summit Corporation plc, Prosensa Therapeutics BV, Fentons Solicitors LLP, Insight Research Group, Galapagos SASU, Shire Human Genetic Therapies Inc., Amsterdam Molecular Therapeutics (AMT) B.V., Genzyme Europe B.V., Acceleron Pharma, Inc., AVI BioPharma, Inc., Debiopharm S.A.

REFERENCES

[1] Boycott KM, Vanstone MR, Bulman DE, MacKenzie AE. Rare-disease genetics in the era of next-generation sequencing: Discovery to translation. Nat Rev Genet. 2013;14:681-91.

[2] Bushby K, Lochmuller H, Lynn S, Straub V. Interventions for muscular dystrophy: Molecular medicines entering the clinic. Lancet. 2009;374:1849-56.

[3] Brooks PJ, Tagle DA, Groft S. Expanding rare disease drug trials based on shared molecular etiology. Nat Biotechnol. 2014;32:515-8.

[4] Rohn J. Billions spent on rare diseases. Nat Biotechnol. 2013;31:368.

[5] McCormack P, Woods S, Aartsma-Rus A, Hagger L, Herczegfalvi A, Heslop E, Irwin J, Kirschner J, Moeschen P, Muntoni F, Ouillade MC, Rahbek J, Rehmann-Sutter C, Rouault F, Sejersen T, Vroom E, Straub V, Bushby K, Ferlini A. Guidance in social and ethical issues related to clinical, diagnostic care and novel therapies for hereditary neuromuscular rare diseases: "Translating" the translational. PLoS Currents. 2013;5.

[6] Landis SC, Amara SG, Asadullah K, Austin CP, Blumenstein R, Bradley EW, Crystal RG, Darnell RB, Ferrante RJ, Fillit H, Finkelstein R, Fisher M, Gendelman HE, Golub RM, Goudreau JL, Gross RA, Gubitz AK, Hesterlee SE, Howells DW, Huguenard J, Kelner K, Koroshetz W, Krainc D, Lazic SE, Levine MS, Macleod MR, McCall JM, Moxley RT, 3rd, Narasimhan K, Noble LJ, Perrin S, Porter JD, Steward O, Unger E, Utz U, Silberberg SD. A call for transparent reporting to optimize the predictive value of preclinical research. Nature. 2012;490:187-91.

[7] Scott S, Kranz JE, Cole J, Lincecum JM, Thompson K, Kelly N, Bostrom A, Theodoss J, Al-Nakhala BM, Vieira FG, Ramasubbu J, Heywood JA. Design, power, and interpretation of studies in the standard murine model of ALS. Amyotrophic Lateral Sclerosis: Official Publication of the World Federation of Neurology Research Group on Motor Neuron Diseases. 2008;9:4-15.

[8] Mercuri E, Mazzone E. Choosing the right clinical outcome measure: From the patient to the statistician and back. Neuromuscular Disorders: NMD. 2011;21:16-9.

[9] Lynn S, Straub V, Lochmuller H, Aarstma Rus A, Bushby K. How to build an international research consortium for collaborative drug development - How TREAT-NMD has done this for neuromuscular diseases (in press).

[10] Willmann R, Dubach J, Chen K, Network T-NN. Developing standard procedures for pre-clinical efficacy studies in mouse models of spinal muscular atrophy: Report of the expert workshop "Pre-clinical testing for SMA", Zurich, March 29-30th 2010. Neuromuscular Disorders: NMD 2011;21: 74-7.

[11] Nagaraju K, Willmann R, Network T-N, The Wellstone Muscular Dystrophy Cooperative Research N. Developing standard procedures for murine and canine efficacy studies of DMD therapeutics: Report of two expert workshops on "Pre-clinical testing for Duchenne dystrophy". Washington DC, October 27th-28th 2007 and Zurich, June 30th-July 1st 2008. Neuromuscular Disorders: NMD. 2009;19:502-6.

[12] Heslop E, Csimma C, Straub V, McCall J, Nagaraju K, Wagner KR, Caizergues D, Korinthenberg R, Flanigan KM, Kaufmann P, McNeil E, Mendell J, Hesterlee S, Wells DJ, Bushby K. The TREAT-NMD advisory committee for therapeutics (TACT): An innovative de-risking model to foster orphan drug development. Orphanet J Rare Dis (in press).

[13] Rodger S, Lochmuller H, Tassoni A, Gramsch K, Konig K, Bushby K, Straub V, Korinthenberg R, Kirschner J. The TREAT-NMD care and trial site registry: An online registry to facilitate clinical research for neuromuscular diseases. Orphanet J Rare Dis. 2013;8:171.

[14] Bladen CL, Salgado D, Monges S, Foncuberta ME, Kekou K, Kosma K, Dawkins H, Lamont L, Roy AJ, Chamova T, Guergueltcheva V, Chan S, Korngut L, Campbell C, Dai Y, Wang J, Barisic N, Brabec P, Lahdetie J, Walter MC, Schreiber-Katz O, Karcagi V, Garami M, Viswanathan V, Bayat F, Buccella F, Kimura E, Koeks Z, van den Bergen JC, Rodrigues M, Roxburgh R, Lusakowska A, Kostera-Pruszczyk A, Zimowski J, Santos R, Neagu E, Artemieva S, Rasic VM, Vojinovic D, Posada M, Bloetzer C, Jeannet PY, Joncourt F, Diaz-Manera J, Gallardo E, Karaduman AA, Topaloglu H, Sherif RE, Stringer A, Shatillo AV, Martin AS, Peay HL, Bellgard MI, Kirschner J, Flanigan KM, Straub V, Bushby K, Verschuuren J, Aartsma-Rus A, Beroud C, Lochmuller H. The TREAT-NMD DMD Global database: Analysis of More Than 7000 Duchenne Muscular Dystrophy Mutations. Hum Mut. 2015.

[15] Landfeldt E, Lindgren P, Bell CF, Schmitt C, Guglieri M, Straub V, Lochmuller H, Bushby K. The burden of Duchenne muscular dystrophy: An international, cross-sectional study. Neurology. 2014.

[16] Bladen CL, Rafferty K, Straub V, Monges S, Moresco A, Dawkins H, Roy A, Chamova T, Guergueltcheva V, Korngut L, Campbell C, Dai Y, Barisic N, Kos T, Brabec P, Rahbek J, Lahdetie J, Tuffery-Giraud S, Claustres M, Leturcq F, Ben Yaou R, Walter MC, Schreiber O, Karcagi V, Herczegfalvi A, Viswanathan V, Bayat F, de la Caridad Guerrero Sarmiento I, Ambrosini A, Ceradini F, Kimura E, van den Bergen JC, Rodrigues M, Roxburgh R, Lusakowska A, Oliveira J, Santos R, Neagu E, Butoianu N, Artemieva S, Rasic VM, Posada M, Palau F, Lindvall B, Bloetzer C, Karaduman A, Topaloglu H, Inal S, Oflazer P, Stringer A, Shatillo AV, Martin AS, Peay H, Flanigan KM, Salgado D, von Rekowski B, Lynn S, Heslop E, Gainotti S, Taruscio D, Kirschner J, Verschuuren J, Bushby K, Beroud C, Lochmuller H. The TREAT-NMD Duchenne muscular dystrophy registries: Conception, design, and utilization by industry and academia. Hum Mut. 2013;34:1449-57.

[17] Mora M, Angelini C, Bignami F, Bodin AM, Crimi M, Di Donato JH, Felice A, Jaeger C, Karcagi V, LeCam Y, Lynn S, Meznaric M, Moggio M, Monaco L, Politano L, de la Paz MP, Saker S, Schneiderat P, Ensini M, Garavaglia B, Gurwitz D, Johnson D, Muntoni F, Puymirat J, Reza M, Voit T, Baldo C, Bricarelli FD, Goldwurm S, Merla G, Pegoraro E, Renieri A, Zatloukal K, Filocamo M, Lochmuller H. The EuroBioBank Network: 10 years of hands-on experience of collaborative, transnational biobanking for rare diseases. European Journal of Human Genetics: EJHG. 2014.

[18] Ayoglu B, Chaouch A, Lochmuller H, Politano L, Bertini E, Spitali P, Hiller M, Niks EH, Gualandi F, Ponten F, Bushby K, Aartsma-Rus A, Schwartz E, Le Priol Y, Straub V, Uhlen M, Cirak S, t Hoen PA, Muntoni F, Ferlini A, Schwenk JM, Nilsson P, Al-Khalili Szigyarto C. Affinity proteomics within rare diseases: A BIO-NMD study for blood biomarkers of muscular dystrophies. EMBO Mol Med. 2014;6:918-36.

[19] Bushby K, Connor E. Clinical outcome measures for trials in Duchenne muscular dystrophy: Report from International Working Group meetings. J Clin Invest. 2011;1:1217-35.

[20] Mercuri E, Mayhew A, Muntoni F, Messina S, Straub V, Van Ommen GJ, Voit T, Bertini E, Bushby K. Towards harmonisation of outcome measures for DMD and SMA within TREAT-NMD; report of three expert workshops: TREAT-NMD/ENMC workshop on outcome measures, 12th–13th May 2007, Naarden, The Netherlands; TREAT-NMD workshop on outcome measures in experimental trials for DMD, 30th June–1st July 2007, Naarden, The Netherlands; conjoint Institute of Myology TREAT-NMD meeting on physical activity monitoring in neuromuscular disorders, 11th July 2007, Paris, France. Neuromuscular Disorders: NMD. 2008;18:894-903.

[21] Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, Kaul A, Kinnett K, McDonald C, Pandya S, Poysky J, Shapiro F, Tomezsko J, Constantin C. Diagnosis and management of Duchenne muscular dystrophy, part 2: Implementation of multidisciplinary care. Lancet Neurol. 2010;9:177-89.

[22] Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, Kaul A, Kinnett K, McDonald C, Pandya S, Poysky J, Shapiro F, Tomezsko J, Constantin C. Diagnosis and management of Duchenne muscular dystrophy, part 1: Diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010;9:77-93.

[23] Thompson R, Johnston L, Taruscio D, Monaco L, Beroud C, Gut IG, Hansson MG, t Hoen PB, Patrinos GP, Dawkins H, Ensini M, Zatloukal K, Koubi D, Heslop E, Paschall JE, Posada M, Robinson PN, Bushby K, Lochmuller H. RD-Connect: An integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. J Gen Intern Med. 2014;29(Suppl 3):S780-7.

[24] Haas M, Vlcek V, Balabanov P, Salmonson T, Bakchine S, Markey G, Weise M, Schlosser-Weber G, Brohmann H, Yerro CP, Mendizabal MR, Stoyanova-Beninska V, Hillege HL. European Medicines Agency review of ataluren for the treatment of ambulant patients aged 5 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene. Neuromuscular Disord. 2015;25(1):5-13.

[25] Bushby K, Finkel R, Wong B, Barohn R, Campbell C, Comi GP, Connolly AM, Day JW, Flanigan KM, Goemans N, Jones KJ, Mercuri E, Quinlivan R, Renfroe JB, Russman B, Ryan MM, Tulinius M, Voit T, Moore SA, Lee Sweeney H, Abresch RT, Coleman KL, Eagle M, Florence J, Gappmaier E, Glanzman AM, Henricson E, Barth J, Elfring GL, Reha A, Spiegel RJ, O'donnell MW, Peltz SW, Mcdonald CM, PTC124-GD-007-DMD STUDY GROUP. Ataluren treatment of patients with nonsense mutation dystrophinopathy. Muscle Nerve. 2014;50(4):477-87.