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 phenotypes 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
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]. 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 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 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 of 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 Johnson: “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.

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 Johnson: “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 of 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 Johnson: “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.

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 Johnson: “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.
REFERENCES

[1] Boycott KM, Vansickle MR, Bulman DE, MacKenzie AE. Rare-disease genetics in the era of next-generation sequencing: Discovery to translation. Nat Rev Genet. 2013;14:484-91.

[2] Buddy K, Lochmuller H, Lynn S, Straub V. Interventions for muscular dystrophy. Molecular medicines entering the clinic. Lancet. 2009;374:1409-16.

[3] Brooks PL, Tague DA, Gross 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, Aarts-Rooijens NV, Hager L, Herczegfalvi A, Sloep E, Irwin J, Kirschner J, Mocanen P, Muntoni F, Ozcelik MC, Rabbett R, Belmann-Soeter C, Rosenfeld J, Siervogel T, Vissers E, Straub V, Buddy K, Petruzielo G. Guidance in social and ethical issues related to clinical trial design and novel therapies for hereditary neuromuscular rare diseases: “Translating” the translational. PLoS Currents. 2013;5.

[6] Landis SC, Amagai M, Asahidori K, Austen KF, Blumenstein R, Bradley EW, Crystal RG, Damell RB, Ferrante RJ, Filili H, Finkestein L, Fisher M, Gendelman HE, Golob RM, Grubbs JW, Gross RA, Habib A, Hesterlee SE, Hovell DW, Huguerand J, Kinner K, Kuroseki W, Krause D, Luria SE, Levine MS, MacDonald MI, McCall JM, Morley RT, et al. Naramsin K, Noble LJ, Porin S, Porter JD, Steward O, Unger E, Utsu T, Silberberg SD. A call for transparent reporting to optimize the predictive value of preclinical research. Nature. 2012;490:187-91.

[7] Scott S, Kraus BE, Cole J, Linehan JM, Thompson K, Kelly N, Bostrom A, Theodores J, Al-Nakha BM, Vieira FD, Ramsamujh 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 Neurological Research Group on Motor Neuron Diseases. 2008;9:4-13.

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

[9] Lynn S, Straub V, Lochmuller H, Aarsman R, Buddy 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;21:347-8.

[11] Nagaraja K, Willmann R, Network GN. The Wellstone Muscular Dystrophy Cooperative Research Network. 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, Nagaraja K, Wexler RR, Cairegaras D, Kotulinynberg R, Flanagan KM, Kaufmann P, McNeil E, Mendell J, Hesterle S, Wells DJ, Buddy 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, Tolusso A, Grambsch K, Kong K, Buddy K, Straub V, Kurnitthemberg K, Kroescher J. The TREAT-NMD care and trial site registry: An online registry to facilitate clinical research for neuromuscular disorders. Orphanet J Rare Dis. 2013;8:171.
[14] Bladen CL, Salgado D, Mongsu S, Foncuberta ME, Kekou K, Kosma K, Hawkins K, Lamont L, Roy AJ, Chamova T, Guergueltcheva V, Chan S, Komrat L, Campbell C, Dao Y, Wang J, Baraie N, Brabec P, Laidheh J, Walter MC, Schreiter-Katz O, Karagi V, Gavano M, Viovanathan V, Buiyat F, Bucicu F, Kimura E, Kekou Z, van den Bergen JC, Rodriguez M, Ronsburg R, Lasokowska A, Koster-Katz O, Zimowska J, Santos R, Nega E, Artemeva S, Basci VM, Viovanathan D, Posada M, Biloter C, Jeaniet PY, Juoncourt F, Diaz-Manero J, Gallardo E, Karaduman AA, Topaloglu H, Shrew C, Stringer A, Martin AS, Piyu H, Bellgard MI, Kerschner J, Flanigan KM, Strab V, Busby K, Verschuuren J, Arentsma-Rus A, Beroud C, Loichmiller 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, Nilsson P, Al-Khalili Szigyarto C. Affinity proteomics within registries, biobanks and clinical bioinformatics for rare diseases: A BIO-NMD study for blood biomarkers of rare diseases. J Gen Intern Med. 2014;29(Suppl 3):S780-7.

[16] Bushby K, Connor E. Clinical outcome measures for trials in Duchenne muscular dystrophy: Report from International Working Group meetings. J Clin Invest. 2011;1:1277-35.

[17] Mercure E, Mayhew A, Muntont F, Messina S, Straub V, Van Onsman GI, Vito T, Bernstein E, Bushby K. Towards harmonization of outcome measures for DMD and SMA within TREAT-NMD: report of three expert workshops: TREAT-NMDENMC 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.

[18] Bushby K, Finkel R, Birnkrant DJ, Carr LE, Clemens PR, Cripe L, Kauf A, Kiemert K, McDonald C, Pandya S, Poyorky J, Shapiro F, Tomezcko J, Constantin C, Diagnosis and management of Duchenne muscular dystrophy, part 1: Diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010;9:77-93.

[19] Thompson R, Johnston L, Tarascio D, Monaco L, Beroud C, Gui GI, Hansson MG, I, Hoen PB, Patrinos GP, Dawkins H, Etno M, Zatalkoulk K, Kouti D, Heslop E, Piusckhl JE, Posada M, Robinson PN, Busby K, Loichmiller H. RD-Connect: An integrative platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. J Gene Med. 2014;29(Suppl 3):6780-7.

[20] Haas M, Vick L, Balabanov P, Heslop E, Parents GP, Dawkins H, Etno M, Zatalkoulk K, Kouti D, Heslop E, Poysckhl JE, Posada M, Robinson PN, Busby K, Loichmiller H. The burden of Duchenne muscular dystrophy, part 2: Implementation of multidisciplinary care. Lancet Neurol. 2010;9:177-89.

[21] Busby K, Finkel R, Birnkrant DJ, Carr LE, Clemens PR, Cripe L, Kauf A, Kiemert K, McDonald C, Pandya S, Poyorky J, Shapiro F, Tomezcko J, Constantin C, Diagnosis and management of Duchenne muscular dystrophy, part 1: Diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2014.

[22] Bushby K, Finkel R, Birnkrant DJ, Carr LE, Clemens PR, Cripe L, Kauf A, Kiemert K, McDonald C, Pandya S, Poyorky J, Shapiro F, Tomezcko J, Constantin C, Diagnosis and management of Duchenne muscular dystrophy, part 2: Implementation of multidisciplinary care. Lancet Neurol. 2014;34:1449-57.

[23] Thompson R, Johnston L, Tarascio D, Monaco L, Beroud C, Gui GI, Hansson MG, I, Hoen PB, Patrinos GP, Dawkins H, Etno M, Zatalkoulk K, Kouti D, Heslop E, Poysckhl JE, Posada M, Robinson PN, Busby K, Loichmiller H. RD-Connect: An integrative platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. J Gene Med. 2014;29(Suppl 3):6780-7.

[24] Haas M, Vick L, Balabanov P, Heslop E, Parents GP, Dawkins H, Etno M, Zatalkoulk K, Kouti D, Heslop E, Poysckhl JE, Posada M, Robinson PN, Busby K, Loichmiller H. The burden of Duchenne muscular dystrophy, part 2: Implementation of multidisciplinary care. Lancet Neurol. 2014.

[25] Bushby K, Finkel R, Birnkrant DJ, Carr LE, Clemens PR, Cripe L, Kauf A, Kiemert K, McDonald C, Pandya S, Poyorky J, Shapiro F, Tomezcko J, Constantin C, Diagnosis and management of Duchenne muscular dystrophy, part 1: Diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2014;34:1449-57.

K. Bushby / Looking Forward to New Therapies S87