

Questions and Answers

Advancing the hope for Duchenne and Becker muscular dystrophy

Q1 – What is Duchenne / Becker muscular dystrophy?

Duchenne (DMD) and the milder form, Becker (BMD) muscular dystrophy are common and relentlessly progressive neuromuscular disorders causing progressive muscle weakness in skeletal, cardiac and smooth muscle.

Duchenne(DMD) and Becker(BMD) muscular dystrophy are **X linked recessive** disorders. Although many cases are inherited, the latest research suggests that approximately 35 per cent of all DMD cases are the result of random, spontaneous genetic mutations. This means that it is possible for any parents to have a boy affected by Duchenne or Becker muscular dystrophy. The two conditions are closely related. Both are caused by mutations or changes in the gene for dystrophin, a protein vital for muscle contraction and health. BMD is caused by mutations decreasing the amount of healthy dystrophin in muscle, while DMD is caused by mutations causing loss of most, if not all dystrophin from muscle.

Q2 – What does DMD do?

DMD is characterised by loss of muscle strength and function, which is **caused by the absence of "dystrophin"**, a stabilising protein found in many parts of the body including all muscles, the nerves and the brain. Loss of dystrophin results in progressive muscle weakness. Most boys with DMD lose the ability to walk by 10 years of age, and develop respiratory insufficiency by their teenage years. Most have cardiac involvement from an early age to varying degrees. Their lifespan is shortened to late teens to early twenties without specialist quality care. There is currently no cure for DMD.

Q3 – Why are DMD and BMD different from other muscular dystrophies?

Duchenne muscular dystrophy is the most common inherited muscle disease. Only Duchenne and Becker are termed “dystrophinopathies” because they are caused by the absence or reduction of the dystrophin protein. The muscular dystrophies are a collection of muscle disorders with three common features: they can be hereditary; they are progressive; and each causes a characteristic, selective pattern of muscle weakness. There are a large number of muscular dystrophies, which can be present at any point from early childhood to late adulthood, with a wide variation of muscle weakness and involvement of the breathing and heart muscles.

Q4 – Why would DMD and BMD be considered apart from other muscular dystrophies?

Each of the dystrophies has a specific genetic basis and pattern of muscle weakness and disease progression. Duchenne muscular dystrophy is the most common of these conditions. The genetic basis of DMD/BMD is loss or absence of functional dystrophin from muscle. This is very different from the genetic basis of other muscular dystrophies. Prior to the 1980's, the genetic defect that causes Duchenne was unknown. Today we know that it is no longer possible to investigate all muscular dystrophies as a collective - a cure or treatment for one type will be unlikely to be effective in other forms of muscular dystrophy. Treatments effective for DMD, such as corticosteroids, are ineffective for other forms of muscular dystrophy.

Q5 – Why is Duchenne muscular dystrophy important?

DMD is the most common genetic cause of early death in childhood. Yet most Australians have never heard of this disease. DMD is often confused with rare muscle disorders and even with the brain diseases like MS.

It has been estimated that the medical and social cost of rearing a child with Duchenne to the age of 20 years is 3 million dollars.

Australia's projected resident population in mid-2007 is 20,900,000, implying that there are approximately 1263 families with DMD and 267 families with BMD, or approximately 1530 families affected by dystrophinopathies in this country. The medical care of this generation of boys and young men with DMD and BMD will cost this country \$4,590,000,000.

Q6 – How common is DMD?

DMD affects approximately 1 in every 3,500 boys. Every year 20,000 children are born into the world with DMD. Early diagnosis of DMD is crucial as progression is delayed with early intervention.

Q7 – How likely is a cure for DMD?

Scientists in centres around the world are focussing on a cure for DMD. Trials of new medications and of novel gene therapies are underway or in planning in Australia, Europe and the USA. Several of these studies show potential to immediately slow progression of DMD, but we hope that a cure will soon be identified.

Amongst the most popular approaches are: drug therapy (PTC124, which will be suitable only for boys with stop mutations in their dystrophin gene), exon skipping or genetic manipulation (a series of molecular 'patches' designed to restore some production of dystrophin for each type of mutation), viral vectors to deliver a mini dystrophin gene, utrophin upregulation (a dystrophin substitute) and myostatin inhibition (known to build 'double muscles' in animal models where myostatin is knocked out).

Q8 – What is Parent Project Australia?

Parent Project Australia (PPA) is a non-profit charity incorporated in Queensland and authorized to raise funds Australia-wide. Professionals and family members from around Australia comprise the membership. PPA is a member of the supervisory board of the global association of Parent Projects – UPPMD.

Parent Project Australia's mission: Using national and international collaboration, to improve the treatment, quality of life and long-term outlook for families affected by DMD and BMD through research, education and advocacy.

Q9 – What are PPA's Objectives?

To work together to improve the lives of Australian persons and families affected by Duchenne and Becker muscular dystrophy.

To focus on the most life-threatening forms of muscular dystrophy, Duchenne & Becker.

To support and promote Australian muscular dystrophy research.

To apply for funding from government, semi-government and private organizations for the purpose of pursuing the Association's objectives.

To promote public awareness of Duchenne & Becker muscular dystrophy through media, educational and fund raising campaigns.

To lobby the government, semi-government and the private sector for equitable representation for Duchenne and Becker muscular dystrophy in social, financial and institutional policy making.

To lobby the government, medical community and the commercial sector to introduce proactive treatments and procedures which will detect, monitor, treat and improve the lives of persons affected by Duchenne and Becker muscular dystrophy

To network globally to identify viable research, treatments and quality care standards, which will enhance the lives of persons everywhere affected by Duchenne and Becker muscular dystrophy.

To cooperate with like-minded organizations in order to advance research, treatments, equity and quality of life for persons affected by Duchenne and Becker muscular dystrophy.

Q10 – What can be done now?

We need to convey to the wider community and government the significant achievements research has achieved both in Australia and in the global community.

We believe that our national government, in all conscience, should be keeping pace with other developed countries, given:

- the incidence of the dystrophinopathies (Duchenne and Becker muscular dystrophy) in Australia
- the ability of early treatment to slow progression and prolong life expectancy in these conditions
- the fact that we have world-class researchers focussing on DMD in this country
- the fact that curative therapies for DMD may be identified by research studies soon to commence in other parts of the world

This can be achieved by focussing on the following areas:-

National Database

The establishment of a national database of boys and young men to enable scientists to identify candidates for specific clinical trials and to collect information about the Australian DMD/BMD population. This database will form the groundwork necessary to facilitate immediate access of Australians with dystrophinopathies to new treatments, as soon as they become available.

Diagnostics

A vital piece of information in the national database will be details of the exact mutation present in each Australian with DMD or BMD. Without this information, doctors will not be able to identify candidates for new treatments for these conditions.

The cost of **DNA sequence analysis** of the dystrophin gene (factoring in estimates of sample collection costs, sample courier costs and laboratory analysis costs) to collect and to screen every remaining affected family in Australia is calculated to be in the range of \$620,000.

The annual cost of staying caught up as new cases are diagnosed, is in the range \$13,600 to \$20,400.

The cost of establishment and maintenance of a national clinical trial database for boys and men with DMD and BMD will be between \$75,000 to \$100,000 per annum.

Over a 1-3 year period, establishment of a national database and identification of the mutation present in all patients with DMD/BMD will cost approximately one million dollars. This seems a lot of money, but this cost is small compared with the cost to the community of a single child with Duchenne muscular dystrophy.

NB. Detailed formulae based on present costs and the incidence of the dystrophinopathies in Australia, were used to compile this summary information.

Clinical Trial Infrastructure

Investment in infrastructure for clinical trials will ensure that in the future new therapies can be made immediately available for all patients as soon as they are proven to be safe and effective. This will require dedicated and trained personnel experienced in assessment and management of people with DMD and BMD, and experienced in running large clinical trials. Each large state centre will need such personnel, in order to ensure that all patients can have equal access to the best and most up-to-date treatments.

Having someone dedicated and affiliated with the major clinics/teaching hospitals in each state would be a very good start. These positions could begin as half-time positions initially. Clinical Trials coordinator (Full-time)@ \$70,000 + Administrative person (Part-Time)@ \$20-25,000.

As much as \$400,000/year will be needed in order to establish an effective clinical trials network in Australia.

Research

It is very difficult to give a salary value for future research projects that will make a difference. Nearly every project contributes another piece to the puzzle. The **cost of research** through PhD fellowships can be estimated at AU\$80-100,000 over a three year period. This covers the cost of scientist's wages. Materials and equipment add to the cost.

To date the PPA's aim has been to fund research fellowships because it is a win/win - Two things are advanced, both our knowledge of Duchenne and the career of a young Australian scientist.

The average PhD Scholarship is around AU\$18-20K/year (Min. 12K/year Max. 25K/year as students apply for various supplementary sources of funding) This is usually for 3 years = AU\$75K.

A research grant package costs between AU\$80K - \$100K/YEAR. This is a modest but workable amount as one of the main expenses is the salary for someone to do the work. A typical salary for a Researcher is around \$56K (this includes all on-costs for the University) thus \$80K pays for Research Assistant + \$20K maintenance. Technicians and junior graduate researchers can be employed for between \$45,000 - \$60,000.

For postdoctoral studies the salary may be approx. AU\$75,000 - \$100,000 - thus requiring a grant of AU\$100K. Ideally most grants are awarded for 2 years min but a three-year project would be approximately \$300,000.

Short-term travel packages may cost AU\$8K (travel and living costs) but could facilitate international exchanges of 2 months or more and be a catalyst to expand research. A useful guide is the [NHRMC guidelines](#) for salaries.

The Genetic Revolution

At a recent FDA/DIA workshop in Washington, Perth scientist and exon skipping expert Prof Steve Wilton presented very convincing arguments about the new field of personalized genetic medicine and the action of his morpholinos. He argued that they should not be considered pharmaceuticals but customized molecular treatments designed for one individual thus making extensive testing protocols largely irrelevant.

Respiratory Care

Increase the accessibility and availability of Cough assist machines to increase quality of care to youth affected by DMD. The cost per machine is approx. \$9,000 each (reducing to \$8,000 when purchased in bulk) The PPA has contributed several machines to the equipment pool of MontroseAccess in order to ensure proper clinical use and training for families.

These machines are utilised for treating chest infections and pneumonia. The machine assists to fully inflate the lungs (lung inflation is restricted in DMD as weakness of the breathing muscles limits the ability to inspire fully) by pushing a preset volume of air into the chest. This is followed immediately by the reverse cycle, which draws out the air, along with retained secretions. Cough assist machines are invaluable in rapidly clearing secretions, which can cause chest infections to transform into pneumonia, which can be life threatening in boys and young men with DMD and BMD. Even between chest infections, cough assist devices aid in maintaining respiratory function and well-being.

Q11 – How does the PPA participate in the complicated field of medical research and genetic technology?

In 2005, four of Australia's premier biomedical and clinical scientists agreed to form a scientific advisory committee to consider research proposals and provide advice to Parent Project Australia. Research grants for young Australian scientists are awarded based on the advice of this expert panel. Through this program, our knowledge of Duchenne and Becker muscular dystrophies is increased and the careers of clever Australian scientists are advanced.

Parent Project Australia's scientific advisory committee includes:

- **Professor Andrew Hoey**, Head of Department (Biological & Physical Sciences) Faculty of Sciences, USQ.
- **Professor Steve Wilton**, Head, Experimental Molecular Medicine Group, Australian Neuromuscular Research Institute at the University of Western Australia.
- **Professor Kathryn North**, Head of the Discipline of Paediatrics and Child Health, University of Sydney. Head, Neurogenetics Research Unit and Deputy Head, Institute for Neuromuscular Research, Childrens' Hospital at Westmead, Sydney.
- Assoc. **Professor Andrew Kornberg**, Scientific Director at the National Muscular Dystrophy Research Centre, Melbourne.

Parent Project Australia holds biennial conferences. In October 2006, PPA partnered with MontroseAccess to stage "Turning the Tide", at the Royal Brisbane Hospital Conference Centre in Brisbane for the benefit of families and the medical profession. This was a national conference supported by the federal government (FACS) and many generous sponsors. Our international program of speakers drew a crowd of 300 delegates enabling all stakeholders to update their knowledge of all aspects of care, treatment and research. A series of DVDs from that meeting are available for those families who were unable to attend the conference.

We thank you for your time in reviewing the information presented.

If you would like additional information please contact:-

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