Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a devastating childhood disorder caused by mutations in the X-linked gene *DMD* coding for dystrophin. DMD is the most common muscular dystrophy affecting 1:3500 males and is characterised by the absence or severe reduction of dystrophin protein in muscle, a massive increase in serum creatine kinase levels, progressive and severe muscle wasting, inflammation and fibrosis. The onset is usually before 3 years of age, affected children are commonly wheelchair-bound by age 12, and many succumb to cardiac or respiratory failure in their twenties or thirties. There is currently no cure for DMD and no effective therapy to stop the disease progressing to early death. Corticosteroids, the only drugs routinely used for DMD, improve strength and can prolong ambulation by 2-4 years but come with side effects that need to be carefully managed and limit the use of these drugs. Current therapies under development aim to correct the dystrophin defect with viral vector-mediated gene replacement or stem cell therapy, or by upregulating the alternative protein utrophin; mutation specific therapies include exon skipping or stop codon read through. Another approach with wider appeal to multiple disorders is to identify pathways downstream of the primary dystrophin deficiency and target these. While this will not correct the genetic defect, drugs that maintain muscle mass and function, and prevent inflammation and fibrosis are likely to be an important part of the future therapeutic armoury. A feature of dystrophic skeletal muscle is invasion by inflammatory cells consisting primarily of discrete populations of macrophages but also including cytotoxic T cells, neutrophils, eosinophils and mast cells. This chronic presence of inflammatory cells ultimately leads to increased necrosis and fibrosis of the muscle resulting in a functional deficit. Dampening of this inflammatory response in dystrophic skeletal muscle results in a reduced pathology and a prolonging of ambulation. This is the basis for the frontline clinical use of corticosteroids in Duchenne muscular dystrophy. Corticosteroids such as Deflazacort have immunosuppressive effects, increase muscle strength and extend the time that patients remain ambulant. The down side is a number of un-wanted side effects including weight gain, susceptibility to infection and a cushinoid appearance. Thus there is a requirement to identify therapeutics with are better tolerated to reduce inflammation