Congenital Muscular Dystrophy by Collagen VI defects:

Research Fund to Find a Cure

What is Collagen VI-Congenital Muscular Dystrophy (Ullrich type)?

While the phenotype of Ullrich Congenital Muscular Dystrophy (U-CMD) was first reported by Otto Ullrich in 1930,[1] culprit mutations in genes encoding the three α-chains of collagen VI protein (COL6A1, COL6A2, and COL6A3) were only identified in 2001.[2] Collagen VI forms a micro fibrillar extracellular network that, among other possible functions, may link extracellular proteins with basement membrane around muscle cells. The extracellular matrix forms the outside environment around the muscle cell. It performs critical functions by supporting muscle cell stability and regeneration. Mutations in the same genes also cause the milder phenotype of Bethlem myopathy and some intermediate presentations. The distinct phenotype of U-CMD is characterized by congenital generalized muscular weakness and typical hypermobility of distal joints in association with proximal joint contractures. Additional features may include a prominent calcaneus, kyphoscoliosis, congenital dislocated hips, and follicular hyperkeratosis. Affected children show significant delay in motor development, although ambulation may be achieved in milder forms. The natural course often shows progression of contractures, muscle weakness, and scoliosis with concomitant decline of respiratory function,[3] a primary driver of mortality and quality of life deterioration. Problems breathing will likely lead to the need for breathing support in the first or second decade of life. Apart from palliative care there is currently no effective treatment for children and adults carrying Collagen VI defects.

A newly discovered intronic mutation is responsible for a large proportion of ColVI affected individuals: Potential Correction by a Gene Therapy Approach

A large collaborative group including 3 continents, America, Europe and Oceania, published a very important discovery earlier this year in the prestigious journal Science Translational Medicine.[4]

They selected patients with typical clinical symptoms and typical biopsies, suggestive of collagen VI deficiency but they were negative for known ColVI mutations

even when using the powerful tool of whole-genome sequencing. So they used a different tool called transcriptome sequencing where you analyze the transcribed message, no the original DNA gene, and you can detect transcript-level changes that are unique to the patient compared to 180 control muscle samples. With this technique they found a deep-intronic mutation which causes a severe form of CollagenVI muscular dystrophy which presents with subtle symptoms at birth, delayed walking, then rapid progression to Ullrich-CMD. This newly discovered intronic mutation is now thought to be one of the most common causes of UCMD.

An intron in a gene is any nucleotide sequence within a gene that is removed by RNA splicing during maturation of the final RNA product. Introns do not encode protein products but they are integral to gene expression regulation. The novel intronic mutation found in the ColVIA1 gene creates a splice site that activates the insertion of a pseudoexon which translates in the inclusion of 24 extra amino acids to the ColVIa1 protein chain. This extra segment of the protein interferes negatively with its correct function leading to the pathogenic effects observed.

The encouraging news about this particular class of mutations is that these are amenable of correction by a gene therapy approach known as “exon skipping”.[5] The best and closer antecedent of the therapeutic potential of an exon skipping approach is the approval by the US Food & Drug Administration (FDA) of the first-ever treatment for a pediatric muscular dystrophy, Duchenne (DMD).[6] It is an injectable product called Exondys 51 (eteplirsen), sponsored by Sarepta Therapeutics consisting in an antisense oligonucleotide which can correct the dystrophin gene by exon skipping in ~13% of the Duchenne patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping.

Going back to the intronic mutation on the ColVIA1 gene, an international research team from the National Institute of Health (NIH) of the United States and the University College London has already obtained positive results using a similar “exon skipping” approach in isolated cells originating from people with U-CMD. By targeting this mutation, these researchers were able to suppress the incorporation of the pseudoexon in the transcript correcting the gene and its protein product back to its original form and function. This is a proof-of-principle study that demonstrates that “exon skipping” could be developed for therapies for this type of Ullrich-CMD.

Fundraising to Accelerate a Treatment Development for this Ullrich Type of Collagen VI-CMD

As is the case for most rare diseases, research funding is often scarce, especially lack of drug discovery initiatives funded by pharmaceutical companies, due to the small patient market, and in consequence, is not easy to get researchers interested in rare disorders.

For common diseases there are different schemes and models of progressive and concatenated funding from federal grants to seed funding/venture capital and then licensing/merge/acquisition by established pharma/biotech companies. Instead, for rare diseases, there is not a clear path or model and it often relies on patient/family oriented foundations who carries the toll of advocating, create awareness, localize patients, clinicians and researchers and constantly promote fundraising campaigns to fund basic and translational research hoping that a solid pre-clinical set of data on a potential therapy will be finally taken by private companies to develop and market a therapeutic product or intervention.

For our specific case, ColVI-CMD, we luckily have already in place a few well-established local and international patient foundations (e.g., Cure CMD,[7] Noelia Foundation,[8] MDUK[9]) and international consortiums[10] who have made a good progress in consolidating a solid base over where to build a therapeutic pipeline to cure this type of pathology.

We are at a crucial moment where a gene therapy approach is cooking in research labs with high rationale and potential to be translated into a cure for this type of disease. The specific gene therapy approach is working for other diseases, we know the scientists and research teams able to tune up this methods for Collagen VI defects, and we know enough number of patients with this particular mutation who could be recruited for a clinical trial. But we need a fundamental element, MONEY, to articulate those key pieces and start collecting compelling data to demonstrate the feasibility of this treatment to cure this Ullrich Type of Collagen VI-CMD. A first step in funding this research project was just announced by MDUK on 08/31/17 (see MDUK press release here: http://www.musculardystrophyuk.org/news/news/over-290k-invested-into-ullrich-muscular-dystrophy-research/).

Although in experimental medicine is difficult to predict how much funds would be necessary to obtain the kind of deliverable originally planned the most effective type of grant that has obtained the biggest impact for health-related research is the original and historically oldest grant mechanism used by NIH, known as RO1.[11] As such our recommendation to a set goal for a fundraising focused in this particular case of Ulrich-type-CMD by intronic mutation in the Collagen VI A1 gene is an RO1-simil funding level. A 3 years grant of $250,000 US Dollars/per year (direct + indirect costs) totalizing $750,000 in 3 years will have a tremendous impact to attract the next link of the chain which would be obtaining venture capital for the translational step of this pre-clinical approach into a real therapy for patients. Developing this therapy would help an estimated (actually, underestimated) 2,100 children and adults with this specific type of ColVI defect.

However, Muscular Dystrophy by Collagen VI deficiency is a progressive disease which needs more and more interventions as time goes by since secondary pathologies appear and evolve as individuals age. Two incapacitating symptoms that inevitably progresses in all Collagen VI cases, an underestimated number of 80,000 patients worldwide, are fibrosis and joint contractures. There is a unanimous consensus in the field that a treatment to improve this conditions is absolutely necessary. The research on these complications is scandalously scarce because of lack of funding. Thus there is necessary to facilitate programs to study this incapacitating symptoms and our goal is to open a call for proposals from the experts in the field. Towards that end we will set an initial fundraising goal of $300,000 US Dollars for a two years project to study each of these ailments.

Your generous contribution will bring the cure of this devastating disease closer to reality for thousands of patients worldwide. Please make your donation by visiting the "Donate Now" link at the Cure CMD website: https://www.curecmd.org/donate

There are not enough words to express our appreciation.

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