An interdisciplinary approach to find an efficient treatment for childhood-onset neurodegeneration with brain atrophy (CONDBA) disease

Background. Childhood-onset neurodegeneration with brain atrophy **(**CONDBA) is a life-threatening, progressive, and rare neurodegenerative disease that is caused by a non-inherited genetic mutation in the Upstream Binding Transcription Factor (UBTF) gene. The disease is usually identified during early childhood, as CONDBA patients begin development normally, but then they start to show regression in their cognitive and language skills, typically at 2-3 years of age, followed by the development of progressive motor deficits [1]. Unfortunately, there is currently no medical treatment to assist these young patients, and their condition continues to deteriorate over several years and may lead to their early death.

What do we know about CONDBA? The UBTF gene encodes a protein that is essential for the transcription of important genes. Transcription is the process where a part of the cellular DNA is copied to an RNA, which then proceeds to the ribosome to produce a protein. One mutation in the UBTF gene, E210K, causes the protein it encodes to become pathologically efficient, resulting in increased production of the RNA inside the cells [1]. Recent studies have shown that this excess RNA production is destructive to cells, as it results in accumulating damage to the DNA, damage to the ribosomes that produce the cellular proteins, and eventually, cellular death [2].

Only a few studies have explored the progression of CONDBA and attempted to unveil its mechanism(s) of action. These studies include investigating fibroblast cells collected from patients, magnetic resonance imaging (MRI) studies to identify the degeneration process and death of brain cells , and more recently, the generation of a mouse model that carries the human E210K mutation and shows a similar phenotype to the human disease [2].

Our team. Adi Goldenberg, whose daughter Elya has been fighting the CONDBA disease for 18 years, has brought together an interdisciplinary team of scientists to find and test new therapeutic treatments for different aspects of this disease. Our team includes experts from several universities and companies: Prof. Giuseppe Testa (University of Milan, Italy), Prof. Atan Gross, Prof. Maya Schuldiner, and Dr. Haim Barr (Weizmann Institute of Science, Israel), Prof. Shlomo Wagner and Dr. Shani Stern (University of Haifa, Israel), Prof. Hod Dana (Cleveland Clinic and Case Western Reserve University, USA), Dr. Deborah Toiber and Dr. Barak Rotblat (Ben Gurion University, Israel), Dr. Natalie Ivgy-Ohana (Minovia, Israel), and Dr. Omer Miller (Vivox, Israel). We are supported by the Jackson Laboratories, a world leader in mammalian genetics and human genomics research, and the Weizmann Institute of Science Unit of Drug Discovery. We are consulted by Dr. Yuval Landau (neurologist, Schneider Children's Medical Center, Israel). This team has the complementary expertise necessary to identify pathologies and test treatments at the cellular, behavioral and functional levels of the disease.

Goal 1: Translating and repurposing existing treatments to assist CONDBA patients

The recent development of a mouse model for CONDBA opens up new opportunities for pre-clinical testing of existing treatments for other diseases that may be translated and repurposed for CONDBA patients. The most promising treatment approach is to suppress the pathologic gain of function of the mutated UBTF gene. Several new drugs that are under clinical trials offer this desired effect [3, 4]. BMH-21, CX-3543, and CX-5461 are small molecules that inhibit RNA polymerase I, the main protein that becomes overactive due to the UBTF mutation in CONDBA patients. Potentially, these drugs can balance the fundamental pathology of CONDBA and

minimize some of the damage associated with the disease. BMH-21 can cross the blood-brain barrier [5], which means that it can be administered to either mice or human using a simple systemic injection, as opposed to more invasive techniques. With guidance by the Dana and Wagner labs, and the animal work expertise of the Jackson Laboratories, we will treat these mice with different drug combinations and test the effects on cellular mortality, and motor and behavioral deficits. If the treatment has a beneficial effect on the mice, then we will work with Drs. Landau and Testa to translate this treatment towards clinical testing in patients.

Goal 2: Developing novel therapeutic treatments to assist CONDBA patients

While BMH-21 treatment may balance some of the pathologies caused by the UBTF mutation and prevent some progressive degeneration in patients, the complex, multi-faceted nature of the CONDBA disease, and the accumulating damage that leads to severe motor deficits, necessitate the development of new therapeutic targets to ameliorate their condition fully. Current evidence suggests that CONDBA includes loss of mitochondria and damage to the ribosomes, which lead to metabolic stress, DNA damage, and cellular death [2]. Here, we suggest collecting blood and skin samples from the 20 CONDBA patients that we have contact with, and represent the majority of known patients worldwide. We will work with the labs of Prof. Gross, Dr. Toiber, Vivox, and Minovia to identify cellular disease markers, such as increased inflammatory response, upregulation of RNA, transcriptomic and metabolomic changes, and mitochondrial and ribosomal damage. In parallel, the Stern lab will generate from the samples induced pluripotent stem cells (iPSCs) that carry the specific mutations of the patients. These cells will be used by the Weizmann Institute Drug Discovery Unit for screening potential drugs to protect the mitochondria, ribosomes, and DNA of these cells. Patient-derived iPSCs offer an additional and complementary approach to the new mouse model, as they enable to study the disease effects on different cell types separately differentiated from them, as well as to examine the efficacy of potential treatments to alleviate CONDBA pathologies. Finally, we will test the new drugs capability to minimize DNA damage (Dr. Toiber), mitochondrial and ribosomal deficits (Prof. Gross), as wells as a novel mitochondrial enrichment treatment, which is currently tested in clinical trials (Minovia).

Summary

Currently, there is no medical treatment available for the CONDBA disease, and CONDBA patients slowly deteriorate until their early death. We believe that recent developments and cutting-edge collaborative multidisciplinary research may provide us with new and effective ways to treat this disease. The poor condition and prolonged suffering of CONDBA children led our team to offer our expertise to search for potential therapeutics and cures. We are seeking financial support that will allow us to collect the samples, test them, and to perform the suggested experimental work with mice and CONDBA patients.

References

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