Pecha Kucha: Articulation between an Argentine patient organization, the Argentinian state and researchers from the University of Huazhong (China) for inclusion of 10 Argentine patients in ND4 gene therapy trial for Leber hereditary optic neuropathy (LHON)

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Stargardt APNES-Retina Argentina is a non-profit association that includes patients and family members with inherited retinal and optic nerve dystrophies (IRDs). They are diseases of genetic origin, which lead to low vision or blindness and that recur in families. They affect children, youth and adults and hinder effective school and work inclusion and often cause exclusion and poverty as well as isolation and depression in patients. Stargardt APNES-Retina Argentina is a member of the Argentine Network of Patients for Advanced Therapies (RedAPTA), which is a network developed by the Ministry of Science and Technology that brings together associations of patients whose pathologies will require advanced therapies such as gene therapy and gene editing to reach a cure.

Today there is just one treatment approved for this condition but it is very expensive. Similarly, appropriate molecular (genetic) diagnosis of these conditions is exceedingly expensive. In Argentina, public and private health systems do not cover genetic diagnosis, generating great inequality between patients who can and cannot afford them. There is an expectation that advanced therapies including gene therapies and gene editing applications could effectively cure these diseases, but currently there is no such research happening in Argentina. Stargardt APNES-Retina Argentina sought to impact on this domain in a few ways. First, it started by capturing clinical and genetic data of OND patients in a database registered with the Ministry of Justice of Argentina, with full support of and consent by the patient community. Second, we signed an agreement with the Ministry of Science and Technology (MINCYT) who sponsored the molecular diagnostic test for one specific IRD for patients without resources, thus equalizing access to genetic testing for the poor. We also signed an agreement with the University of Barcelona, Spain, to do adequate genetic tests to identify the genetic variants which cause IRDs at a cost lower than market cost.

Third, and most relevant to the topic of the 2019 GFBR, we actively sought out an ongoing gene therapy clinical trial and negotiated access for our patients to this trial. At the end of 2017, we identified a phase 3 clinical trial from the University of Huazhong, Wuhan, China for Leber Hereditary Optic Neuropathy (LHON) that was recruiting patients. We then searched our database for patients already sequenced whose profile matched the trial criteria and searched for all the information published in renowned scientific journals relating to the previous phases of the trial and its follow-up of the cohorts. Once we were satisfied that this was a legitimate clinical trial that could be of benefit to our patients, we then requested expert evaluation of the Advisory Commission of Regenerative Medicine and Cellular Therapies of the MINCYT. This Commission is constituted by an interdisciplinary mix of researchers in advanced therapies, biologists, bioethicists, lawyers, philosophers and other pertinent disciplines. The Advisory Commission confirmed that since it was in phase 3 clinical trial, regulated in China and contained in clinicaltrials.gov, and supported by published evidence, a logical mechanism and pathophysiological understanding and free inclusion, it was acceptable to try to include Argentinian

patients in it. We then contacted patients in our database with the relevant profiles to gauge interest.

We contacted the clinical trial researchers at the University of Huazhong to ask them to evaluate the medical records of our patients (between 9 and 33 years old). The informed consent approved by the Ethics Committee of the hospital in China was evaluated by the Ethics Committee in the MINCYT and explained in detail to patients and their families. We actively mediated between the Chinese researchers and the Argentinian patients, because we were concerned that in their desire for a cure, patients and their families could be vulnerable to inappropriate offers of unapproved treatments. Shiyan Hospital authorities, doctors and researchers explained through the interpreter who accompanied the patients and families of the procedure they would perform and the signing of the informed consent was done in front of TV cameras and transmitted through the Chinese TV, performing a teaching task also with the population that was not directly involved with the application of therapy.

The therapy was extremely successful mainly for patients who traveled blind or with very low vision and who improved their vision and returned to their normal life including school, university and work.

But the best result was the correct and fluid articulation between all the actors involved: association of patients, local and foreign researchers, and the Argentinian national state that through the commissions implemented in the MINCYT supported and accompanied all the instances of this project allowed patients with low resources to have equal opportunities to access advanced therapy, preserving their safety at all times. The collaboration established with local researchers and from HIC countries allowed us to have the precise diagnosis in time, and then they could participate in the clinical trial and move towards a cure.

Genetic sequencing and advanced therapies as a whole are invaluable tools to better understand genetic diseases and address the solutions for IRDs. Patients are the origin and destination of these scientific developments. The researchers' job must be to find the cure, patient organizations must provide information, act as a link, instruct patients and disseminate the correct operations, avoiding unnecessary risks that may worsen their condition. The role of the state is to safeguard the safety of citizens, encouraging research, supporting organizations by providing expert evaluation and equalizing opportunities, saving the inequity that prevents access to diagnosis and therapies to many of the citizens living in LMIC countries.