TREATRUSH Report Summary

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Final Report Summary - TREATRUSH (Fighting blindness of Usher syndrome: diagnosis, pathogenesis and retinal treatment (TreatRetUsher))

Executive Summary:

Usher syndrome (USH) is the most frequent cause of monogenic inherited sensory disorder associating deafness and profound visual impairment due to retinitis pigmentosa (RP) underlying retinal degeneration. The lack of an early diagnosis of Usher syndrome, and especially Usher syndrome type 1, is devastating. The result can be a loss of the opportunity for an early cochlear implantation. As the disease progresses, sign language will become a less and less efficient mode of communication. Based on the results of recent clinical trials, therapy for retinal degenerations is now a reachable goal. Therapeutic approaches however imply the understanding of the retinal pathogenesis, yet almost entirely unknown, and the development of suitable tissue/animal models.

Therefore the main objectives of the scientists of the TREATRUSH consortium are:
1. The generation of suitable animal and tissue models for studying USH retinal dysfunction and monitoring gene therapy efficiency.
2. The uncovering of USH retinal pathogenesis and its underlying cellular and molecular mechanisms for all USH1 and USH2 forms. To this purpose, development of multidisciplinary innovative physiological, biochemical, cell biology, and cell imaging approaches is planned.
3. The development of novel protocols and guidelines for early diagnosis of USH whatever the clinical subtype, as well as evaluation and dissemination of the results.
4. The development of retinal gene therapy strategies up to a clinical trial.

Project Context and Objectives:

Usher syndrome (USH) is the most frequent cause of monogenic inherited sensory disorder associating deafness and profound visual impairment due to retinitis pigmentosa (RP) underlying retinal degeneration. This dual sensory deficit that affects young individuals can lead to an extreme disability. Its prevalence is estimated to 1 out of 25,000 to 10,000 individuals. Its mode of transmission is autosomal recessive. Patients affected by the USH1 form, the most severe form, suffer from severe to profound congenital deafness and balance defects. Young children ability to maintain a sitting posture is delayed, as well as their further developing of the ability to walk. Night blindness is the first symptom of RP, which is characterized by a juvenile age of onset reported on average at 10 years of age. It is closely followed by the narrowing of the visual field. The diagnosis of USH1 is established on average only at 17 years of age.

In patients affected by USH2, deafness, also congenital, is moderate to severe with no sign of balance defect. Night blindness appears at about 15 years of age and the syndrome is diagnosed on average at 24 years of age.

USH3 is not as strictly defined. Hearing impairment is progressive. Balance problems are present in about half of the cases. Night blindness appears at about 15 years of age and the syndrome is diagnosed on average at 24 years of age.

The main goal of the TREATRUSH project is to develop tools for early diagnosis of Usher syndrome, and especially Usher syndrome type 1, to understand the underlying pathogenesis of RP in the objective of preventing and treating the retinal degeneration of this disease.

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loss of the opportunity for an early cochlear implantation. As the disease progresses, sign language will become a less and less efficient mode of communication. Based on the results of recent clinical trials, therapy for retinal degenerations is now a reachable goal. Therapeutic approaches however imply the understanding of the retinal pathogenesis, yet almost entirely unknown, and the development of suitable tissue/animal models.

Identified soon after the invention of the ophthalmoscope, Usher syndrome has been subdivided into three clinical subtypes (USH1, USH2 and USH3) by the British ophthalmologist Charles Usher (1865-1942) (Usher, 1914). USH1 and USH2 are the most frequent subtypes in Europe. However, due to a founder effect, in the Finnish population USH3 accounts for 42% of the USH cases, whilst only for 2% in most of the other countries.

Nine of the USH genes have been identified (USH1B/MYO7a (myosin VIIa gene), USH1C/USH1C (harmonin gene), USH1D/CDH23 (cadherin-23 gene), USH1F/PCDH15 (protocadherin-15 gene), USH1G/SANS (sans gene), USH2A/USH2A (usherin gene), USH2C/VLGR1 (VLGR1 gene), USH2D/WHRN (whirlin gene), and USH3A/USH3A (clarin-1 gene). Four of these genes have been found by members of the TREATRUSH consortium. Recently scientists of the consortium found five novel genes which are candidate genes for the Usher syndrome.

The consortium
1) developed a highly robust and informative molecular diagnosis for Usher syndrome;
2) explored in depth genotype/phenotype correlations;
3) brought major insights into the pathogenesis of the RP of the syndrome;
4) developed gene therapy strategies to cure the RP of the syndrome.

Altogether these results represent an important step and the achievement of the main objectives of the TREATRUSH project:
1. The generation of suitable animal and tissue models for studying USH retinal dysfunction and monitoring gene therapy efficiency.
2. The uncovering of USH retinal pathogenesis and its underlying cellular and molecular mechanisms for all USH1 and USH2 forms. To this purpose, development of multidisciplinary innovative physiological, biochemical, cell biology, and cell imaging approaches is planned.
3. The development of novel protocols and guidelines for early diagnosis of USH whatever the clinical subtype, as well as evaluation and dissemination of the results.
4. The development of retinal gene therapy strategies up to a clinical trial.

Project Results:
All the objectives set by the TREATRUSH consortium at the beginning of the project have been achieved. A total of 436 Usher patients were recruited throughout Europe (France, Germany, Italy, and more recently also Slovenia and Spain) and have been included in the TREATRUSH database, containing general patient data, ophthalmological and otological data and the results of the genetic analysis. On the basis of this precious network and patient data collection, the consortium could not only enormously improve the clinical and molecular diagnosis of Usher syndrome but also develop and make accessible guidance for Usher patients’ clinical and molecular diagnosis, providing to the public general recommendations for assessment, counseling and possible prevention and development of therapeutic strategies. A new molecular diagnosis strategy was developed which now allows 95% of the mutations present in the patients to be detected. A prospective testing of 234 patients with IRDs or USH1 indicated that the clinical sensitivity of the developed test is high and preferable to a whole exome sequencing (WES) testing, therefore this new developed test can be considered time-saving, more efficient and especially more economical. This represents a major improvement in the quality of the molecular diagnosis. Concerning the phenotyping of patients, light sensitivity of the dark-adapted eye is a valuable indicator of retinal function, but this test is time-consuming and uncomfortable, especially for children. Therefore within the EU-project TREATRUSH, a test for assessing the scotopic threshold for early detection of Usher’s syndrome was developed: the Tübingen Scotopic Threshold Test (TSTT), a device to measure dark adaptation in children.

A major step forward in the understanding of the cellular and molecular mechanisms of the retinopathy of the Usher syndrome type 1 has also been realized by the scientists of the TREATRUSH consortium by using other models than the mutant mice,
since they do not display retinopathy. The results led to the finding that, in both rods and cones in macaques and humans, the Usher 1 proteins were mainly associated to the calyceal processes and at the interface between these processes and the outer segment of the photoreceptors. They were also present at the interface between the outer and the inner segment. The absence of calyceal processes in the rodent retina as well as the absence of the Usher 1 proteins at the interface between the inner and the outer segments may thus underlie the absence of retinal defects in Usher 1 mouse models. Consequently, given that mice are of little use as a model of the retinopathy of the syndrome, the consortium scientists decided to set up cell cultures of macaque retina as a replacement approach. They also studied the key mechanism that maintains outer segments in adult mouse cones. The outer segments of cones serve as light detectors for daylight colour vision, and their dysfunction leads to human blindness conditions. They found that the cone-specific disruption of DGCR8 in adult mice led to loss of outer segments. However the number of cones remains unchanged. These observations suggest that a re-expression of the involved sensory-cell-specific miRNAs could be a potential strategy to regenerate the lost outer segments. Despite the impossibility to generate a retinal phenotype in Usher mouse models, probably due to the lack of calyceal processes in mouse retinal photoreceptors, the TREATRUSH scientists have investigated whether increasing further the photoreceptor cell stress could reveal a phenotype. Following a given experimental paradigm, increasing photoreceptors stress in two Usher 1 mouse models a clear functional defect was observed by means of ERG in both models. The reduction was greater in homozygote animals than in wild type (WT) mice and the differences among groups were statistically significant. This last result could revalue a consideration of the mouse, in despite of the former negative results, as adequate animal model for USHER 1 studies.

In parallel a new recording technique, able to record light responses at different light levels, in the scotopic, mesopic and photopic range, from single rods for a variety of visual stimuli was developed. This technique makes it possible in the future to characterize the response of rods in different mouse models of disease. Treatrush scientists worked to develop gene therapy via viral vectors associated with the adenovirus (AAV) enabling the efficient transfer of therapeutic genes into retinal photoreceptors with the aim of preventing their degeneration. Due to the difficulty to transfer large genes such as MYO7A in one regular sized AAV vector, they decided to use a dual AAV vector system, reporting successful rescue in the shaker 1 mouse retina. These results bode well for the development of dual AAV-MYO7A vectors for retinal gene therapy of USH1B.

The detailed description of the results achieved with dual AAV-MYO7A vectors are included in a recent publication (Trapani&Colella et. al, EMBO Mol Med. 2014 Feb 1;6(2):194-211).

Potential Impact:

Treatment of retinitis pigmentosa in Usher patients will be particularly valuable because of their dual sensory disability. At present, there is no way to alleviate their progressive visual impairment. However, major breakthroughs have been recently achieved in the treatment of retinal disorders by gene therapy. We think that the development of a gene therapy approach for USH retinal degeneration has to be based on the present cutting-edge retinal gene therapy strategies The driving force of the project was to bring together the best of the expertise in the auditory and vision fields (cochlea and retina) and in both medicine and basic biology, to tackle the objective of alleviating and even treating the devastating sensory disability of Usher syndrome-affected patients. For this purpose, the TREATRUSH consortium has gathered the best experts in the field, the USA leader group who pioneered it and who is currently reporting the most efficient viral-mediated gene transfer in the retina, together with a European collaborating group. They have already set up a gene delivery platform extensively validated for retinal disorders in animal models which is under testing in humans. In addition, a leading European industrial pattern is dedicated to the development of a GMP-compliant procedure for large scale production of AAV vectors to be used for clinical trials. The concerted work of ENTs and ophthalmologists, from the very beginning of the project guaranteed an improvement of the patient management. The need for an early diagnosis have been fulfilled thanks to the implementation of a set of clinical tests providing novel clinical tests and the development of novel mutation screening and molecular diagnosis.

Parents of USH1 children will get the necessary information for taking medical and educational decisions (cochlear...
implantation for oral language versus sign language), and USH2 patients for adequate choices regarding their professional and personal life.

The future clinical trials will benefit from the development of accurate measurements for photoreceptor defects. The developed clinical and molecular diagnostic tests will facilitate the selection of adequate patients for the clinical trial. The follow-up of their visual function will also fully benefit from these tests as well as from a focus of the observations of their photoreceptors dictated by the results gathered on the pathogenic processes.

Innovation has been achieved such as:
- improvement of the molecular diagnosis of Usher syndrome
- highly promising discoveries on key elements affecting the formation and the maintenance of the photoreceptor outer segments in normal and pathological conditions
- improvement of the AAV vector for delivery in the photoreceptor cell
- vectorisation of large DNA sequences for retinal gene therapy.

The multidisciplinary dimension of the project was given since all the objectives of the project rely on multidisciplinary approaches.

The study of the natural course of the disease, from its earliest onset up to the degeneration of the photoreceptors in patients involves clinical investigation of the balance system, the auditory system and the visual system, with the implementation of biophysical investigation tools for each of them.

Diagnosis improvement also relies on a multidisciplinary approach as association of clinical tests, novel approaches for mutation detection and search for new USH genes based on the cutting edge technology of DNA sequencing.

The deciphering of the retinal pathogenesis undertaken during the project was a paradigm of multidisciplinary and integrated studies. It included a search for molecular pathways by transcriptomic and proteomic analyses in vivo and in vitro investigations of the electrophysiological properties of the photoreceptors, real-time in vitro imaging by confocal and multiphoton microscopy and the use of a panel of different genetic approaches.

The therapeutic approach was also multidisciplinary as it is based on an expertise in virology, and uses animal models.

Translation was the Ariane’s thread of the entire project. By gathering leading European scientists and physicians in the auditory (cochlear) and visual (retinal) fields, and in future clinical trials as well, and the American leading group in retinal gene therapy that has obtained the most robust delivery of AAV virus to human retina together with its European collaborative group, translational applications of the basic research have been handled at the best level. As in most RPs, the photoreceptor is the primary target cell of the deficit in USH1 and USH2 syndromes. Optimization of these vectors has to be carried out for an improvement of gene transfer in the photoreceptor cells. Proof of AAV vector efficiency for phenotype rescuing will be based on the use of animal and tissue models. However, because mouse and human retina may differ in their sensitivity to AAV serotype, these experiments will be conducted in vivo, not only in the mouse but also in macaque.

The results obtained during the last 12 months of the project with the generation of dual AAV vectors encoding for MYO7A and their testing in the retina of shaker1-/- mice are very encouraging for the development of dual AAV-MYO7A vectors for retinal gene therapy in USH1B affected patients. Efforts developed to increase the efficiency of the gene transfer to photoreceptors will have a huge impact on retinal therapy since most forms of retinitis pigmentosa are due to photoreceptor cell defects. It will find application in both affected children and ageing individuals. Preparation of the clinical trials, by toxicity studies and analysis of the in situ distribution of the vector in at least two species, will lead to the trial.

The European added value of the project relies on the following points.
• The confidential patient database has and still will force the development of European standards for patient evaluation and a better management of the patients. In particular, the concept of a sensory evaluation, namely of both vision and audition, in any patient visually or hearing impaired should irradiate from this project.

• The parallel medical research effort initiative in different European countries, will guarantee a more critical evaluation of the strategic choices, the clinical practices and their results.

• Progress and results will still be efficiently disseminated throughout the various European countries and will encourage similar initiatives with information about the possible difficulties encountered.

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