AKU Research Strategy 2023-2028

Introduction

The ultimate aim of the AKU Society is to cure AKU. We are committed to researching potential treatments and cures for the condition. Our research strategy (2023-2028) outlines our plans to increase our understanding of the condition and drive research into developing treatments and cures.

What is AKU?

AKU is a rare autosomal recessive disorder caused by mutations in the HGD gene, resulting in the accumulation of homogentisic acid (HGA) and subsequent deposition of a black pigment in connective tissues, leading to severe joint and heart diseases.

Objectives

Objective 1: Development of Co-Therapies to Mitigate Elevated Tyrosine Levels

Objective 1 focuses on developing co-therapies to address the limitations of nitisinone treatment, particularly the elevated levels of tyrosine. The strategy aims to explore approaches to prevent tyrosine absorption in the gastrointestinal tract and enhance its elimination through the kidneys. By reducing the side effects of nitisinone, this objective aims to improve the safety and tolerability of AKU treatment.

Objective 2: Enzyme Replacement Therapy using Messenger RNA (mRNA) Administration

Objective 2 centres around the development of enzyme replacement therapy using mRNA administration. The strategy aims to restore the missing enzyme activity by introducing mRNA that encodes the functional enzyme. This approach directly targets the underlying genetic defect and provides a potential treatment option for AKU.

Objective 3: Development of Gene Therapy Strategies

Objective 3 focuses on the development of gene therapy strategies to correct the genetic defects causing AKU. This objective involves utilising advanced techniques such as CRISPR and novel DNA delivery methods to replace the missing enzyme and address the

root cause of the disease. The aim is to provide long-term solutions and potentially cure AKU by targeting the genetic mutations responsible for the disorder.

Collaborative Research Consortium

To achieve these objectives, the AKU Society works with a number of partners including the University of Liverpool, Liverpool University Hospitals, and several companies and institutions around the world. This multidisciplinary collaboration brings together expertise in genetics, molecular biology, and clinical research to accelerate our understanding and research into developing treatments and cures for AKU.

Research foundation and scientific achievements

The AKU Society has a proven track-record of conducting extensive scientific and clinical research. This includes studies utilising cell and tissue models, animal models, and clinical trials involving nitisinone. The knowledge gained from these studies provides a robust foundation for future research endeavours and informs the development of effective therapies for AKU.

Tyrosine reduction (Objective 1)

Co-therapies to combat post-nitisinone tyrosinaemia: The objectives will be achieved by tackling two main organs: the intestine and the kidney. In the renal approach, inhibitors of tyrosine reabsorption in the proximal convoluted tubules will be developed and validated. Preventing tyrosine renal tubular reabsorption should result in excretion of accumulating tyrosine in the body and thus lower circulating tyrosine. If successful, these new approaches would allow the highly effective HGA-lowering enzyme inhibitor nitisinone, proven to deliver highly desirable clinical outcomes, to continue to be used safely.

In the intestinal approach, alternative tyrosine catabolism bypassing HGA-formation, using plant enzymes including tyrosine ammonia lyase (TAL) will be developed to minimise gut tyrosine absorption. Further, the gut approach also envisages using substances such as molecularly imprinted polymers (MIPs) to bind tyrosine. Lastly, in the intestinal approach, which could have a commonality with the renal approach.

mRNA therapy (Objective 2)

Messenger ribonucleic acid (mRNA) therapy: A successful outcome of these studies may be translatable to the majority of AKU patients, particularly young patients, harbouring a range of different *HGD* mutations. mRNA and LNP technologies represent a groundbreaking approach for treating rare diseases. mRNA uses the body's cellular machinery to produce therapeutic proteins, while LNPs ensure their efficient delivery. This innovative combination offers new hope for individuals suffering from rare conditions, paving the way for tailored, effective treatments in the realm of precision medicine. Overall, this approach, in the era of COVID-19 research developments particularly in the field of nanoparticle delivery mechanisms, could allow repeatable administration of mRNA therapy to all AKU patients, regardless of age or type of *HGD* mutations.

Gene therapy (Objective 3)

Gene therapy: Successful gene therapy is the only intervention that will lead to complete restoration of metabolic function in an inborn error of disease. Currently, there is no gene therapy programme anywhere in the world to cure AKU to our knowledge. In contrast to other genetic diseases of the liver, AKU requires the insertion of the *HGD* gene into the nucleus of the hepatocytes, the main cells that synthesise this gene in the liver. There are over 211 mutations in exons of the *HGD* gene. Such diverse genetic alteration highlights the challenge of this form of corrective approach, therefore a complete replacement of the coding sequence (cDNA) of this gene is required. We have three different approaches: a) non-integrating viral delivery, b) CRISPR-Cas approach to replace the cDNA in the defective gene and c) non-viral naked cDNA delivery.

Conclusion

In conclusion, the AKU research strategy for 2023-2028 aims to advance approaches for the treatment of AKU. By focusing on co-therapies, enzyme replacement therapy, and gene therapy, the research consortium seeks to overcome the limitations of current treatment options and provide innovative solutions for AKU patients. Through collaboration, rigorous research, and strategic planning, the AKU Society and partners aim to develop effective therapies that address the genetic defects underlying AKU and significantly improve the lives of affected individuals.

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