SPEAKER SPOTLIGHT:

Gene Therapy for Severe Genetic Disorders and Pediatric Patients

Gene Therapies have become an opportune modality for targeting rare and severe diseases in children. However, working with young children with rare and difficult indications is fraught with complications. Dr.Gaspar talks us through his exciting research at UCL and Orchard, as well as the challenges and opportunities of working in this noveltherapeutic area.

Bobby Gaspar

President of Research and Chief Scientific Officer, Orchard Therapeutics

Bobby Gaspar is a physician/scientist working in paediatric immunology at the Institute of Child Health (ICH) and Great Ormond Street London, as well as co-founder and chief scientific officer at Orchard Therapeutics, a biotechnology company arising from his work at UCL/GOSH that is making gene therapy medicines for severe genetic diseases. He initially trained in paediatrics and then became interested in primary immunodeficiencies. His interests are in many different aspects of primary immunodeficiency including understanding the molecular and cellular defects and disease pathogenesis, bone marrow transplantation for severe immunodeficiencies and the development of gene and cell therapy for these conditions. Over the last decade, his team have conducted clinical trials that have shown that their approach to gene therapy can potentially permanently correct the immune defect in specific immunodeficiency conditions.

Could you describe your role at Orchard Therapeutics and UCL?

I am a Co-founder and currently serve as President of Research and Chief Scientific Officer of Orchard Therapeutics, a biotechnology company developing ex vivo autologous hematopoietic stem cell (HSC) gene therapies for rare, inherited diseases. In this role, I lead new research initiatives that explore the application of our ex vivo HSC approach in further neurodegenerative diseases and new therapeutics areas. Prior to the founding of Orchard, I was an Academic Physician for over 25 years at UCL and Great Ormond Street Hospital specializing in severe immunodeficiencies and the development of HSC gene therapy. In addition to my role at Orchard, I am a Professor of Pediatrics and Immunology at the UCL Great Ormond Street Institute of Child Health.

What are you currently working on?

My research from the very beginning has been focused on the treatment of severe primary immune deficiencies (SCIDs), including bone marrow transplantation and gene therapy. Bone marrow transplant can be a curative treatment option for certain patients with SCIDs. Because patients receive cells from a donor in this procedure, some can experience serious complications including graft-versus-host disease. The use of gene modified autologous HSCs offers a different therapeutic approach using the patient's own cells. We can insert a working copy of the missing or faulty gene into the patients own HSCs and then infuse the gene-corrected cells into the patient. Once these cells engraft, they are able to self-renew in a patient's bone marrow and can develop into many different cell types in the blood, with the potential to permanently correct the disorder in a single treatment. The use of the patient's own cells allows us to avoid certain complications associated with a bone marrow transplant.

At Orchard, we're working to apply this potentially curative treatment approach to a number of rare inherited disorders and have made significant progress in our clinical programs.

What are the biggest challenges in treating pediatric patients with these very severe rare genetic diseases?

In some conditions, the best outcomes are in children who are in the very early stages of the disease. So, one of the most pressing challenges in effectively treating pediatric patients is early diagnosis. Newborn screening (NBS) is widely recognized as an important tool for diagnosing serious conditions, including rare genetic disorders. In general, early detection allows for early intervention and improved treatment outcomes. However, NBS for many serious and potentially fatal rare diseases – including SCIDs – is not routine and varies depending on geography. If a child is diagnosed too late, treatment is limited to palliative care as the disease progresses. This is a critical issue if we are to bring the potential lifetime benefits of gene therapy to more patients globally. I'm proud to have led initiatives in the UK and Europe to expand NBS for SCIDs, and through Orchard we are working with leading scientists in this area and will soon be sponsoring a number of pilot programs in the EU and U.S.

When developing medicines for rare diseases, how do we keep the patient at the heart of the process?

The experiences of patients and their families have always been the motivating force behind my research. When I was a junior clinician more than two decades ago, I was seeing patients – babies and young children – who were dying of severe immune deficiencies, either from the disease itself or from complications resulting from a bone marrow transplant. The discovery that ex vivo autologous HSC gene therapy had the potential to permanently correct certain monogenic diseases was an exciting and powerful moment for me and my colleagues, and our research ultimately led to the founding of Orchard in 2015. It's thrilling for me to now see this technology moving from the clinical setting to potential product approvals, because I know what it means for patients and their families.

What are you anticipating as the most exciting developments in this space in the near future?

One of the most exciting developments in gene therapy today involves the treatment of central nervous system (CNS) disorders. In many of these disorders, there is simply no standard of care to halt or slow disease progression. One of the key challenges has been developing therapies that can be administered systemically and that are able to cross from the bloodstream into the brain. The use of gene-corrected HSCs represents a viable approach to overcoming this obstacle. We now understand that a subset of HSCs are able to naturally cross the blood-brain barrier and become microglia in the brain. Through gene modification of HSCs, we are seeking to use this mechanism to deliver therapeutic genes to the brain where they can have a therapeutic effect. While clinical development in this area is ongoing, I am hopeful that it will result in the development of innovative therapies for diseases that are often fatal and where no effective or approved treatment options currently exist.

What would you like to achieve at the Regenerative Medicine & Advanced Therapy Development Congress?

This is an exciting time in gene and cell therapy. We have the opportunity to potentially treat some of the most devastating and burdensome diseases in the world. At the Regenerative Medicine & Advanced Therapy Development Congress, I'm looking forward to hearing from colleagues in the scientific community about the latest advancements in gene and cell therapy with the greatest potential to transform the lives of patients and their families. I'm also looking forward to sharing my own research on the topic of hematopoietic stem cell gene therapy for certain monogenic disorders.