Regulatory T cells to be tested in liver transplants

To lose a liver from cancer or an infection is a serious incident, for which transplantation of a donor organ may be a patient's only way of staying alive. Donor organs are available but they come with their own risks including the risk that the recipient's immune system will see the transplanted organ as foreign. Human leukocyte antigen (HLA) mismatches can lead to organ rejection which is why many patients take immunosuppressants to protect the transplants – often for the rest of their lives.

UK-based Quell Therapeutics Ltd hopes to change this paradigm by developing a cell therapy that will suppress the immune response and drive long-term tolerance of a transplanted organ. The company's technology is based on engineered regulatory T cells, otherwise known as Tregs.

Leading the company is Iain McGill, a seasoned pharma executive who was appointed Quell's founding chief executive in 2019. In an interview, Mr McGill spoke about the company's technology and what it hopes to accomplish for patients with transplants that currently require lifelong immunosuppression.

Quell was co-founded by the investment group Syncona Ltd and experts from King's College London and University College London, UK and Hannover Medical School in Germany. In November, it completed an oversubscribed $156 million Series B financing round to bring its lead product QEL-001 into clinical development and support other projects in its pipeline for neuroinflammatory and autoimmune disorders.

The Phase 1/2 study recently began recruitment in the UK and will investigate the safety and efficacy of QEL-001 in approximately 18 liver transplant patients. The patients will have received a transplant one to five years earlier from a mismatched donor. The recipients are HLA A2 negative while the transplanted organ is HLA A2 positive. The therapy will target HLA A2.

"Here you have a situation where you have a foreign body that's been transplanted inside an individual…The only cells in that body where the HLA A2 molecule is found [are those] on the transplanted organ. So we have a very unique way of targeting every single cell within that transplanted liver," the executive commented.

The targeting will be done by engineering the Treg with a chimeric antigen receptor (CAR). But the CAR modified Treg will perform differently than CAR T therapies used in a cancer setting. Instead of attaching to a disease-specific antigen, the CAR on the Tregs will target location specific antigens. "These are antigens that are located at the site of disease [the immune reaction] where their expression is maintained through the course of disease so you've got a constant way of activating your Tregs and getting them to control the environment," he added.

This speaks to the unique characteristics of the Tregs which prevent an over stimulation of the immune system as well as moderate the immune response. "Tregs are kind of the educators of the immune system. Quite often, when you have a number of T effectors that are recruited to either fight disease, or to attack a foreign organ, you also have a recruitment of Tregs to moderate and close down that reaction – to prevent it from overreacting," Mr McGill said. "Tregs patrol the body and help ensure that you don't have reactions against self. And therefore when you have a disease where, and there are a number of reasons why, the balance gets disturbed, Tregs normally would be the ones to come and help create that balance. When that balance is not there, there is an opportunity to engineer those cells to restore that balance," he added.

QEL-001 is an autologous therapy, which besides having a CAR, has been built with a phenotype lock for Treg stability and a safety switch that can be activated if needed. These features reportedly attracted the company's recent funders. The CAR and the safety switch are proven technologies in oncology. The phenotype lock is tailor-made to address a unique characteristic of the Tregs – their plasticity.

"Tregs are fairly plastic in their phenotype. They can flip between being a suppressive cell and being an attacking cell," Mr McGill commented. In order to stabilise the therapy, the company has developed phenotype locking technology which involves transducing the Tregs with multiple copies of the FOXP3 gene. This gene provides instructions for the FOXP3 protein which is the master transcription factor for Tregs. The transduction locks the Treg into position as a suppressor cell, with an added benefit. "You prevent that unwanted flip to becoming a T effector, number one, but also interestingly we found that doing that increased the cell's suppressive potency," Mr McGill commented.

Thus far, only one other trial has tested Tregs as a therapy in a liver transplantation setting. This was a study in Japan involving 10 patients with end-stage liver disease who received transplants. Seven of the patients achieved operational tolerance after administration of a Treg cell therapy and were able to discontinue immunosuppressive medicines. The results were published in the journal *Hepatology* in 2016.

More recently, a project funded by the European Union investigated multiple cell-based medicines for use in kidney transplantation. The international study compared regulatory T cell and macrophage therapies, as well as products made of dendritic cells, with standard-of-care immunosuppression. The therapies were administered to transplant recipients before or after their surgery. The results were pooled and showed that the cell therapies were able to reduce the need for immunosuppression in about 40% of the patients.

Mr McGill has high expectations for Quell's Treg project in the liver, noting that if immunosuppressants can be removed from the picture, the outlook for patients improves immeasurably. "If you can put them in a situation where they've no longer got the chronic problems associated with immunosuppression use, you can get a little bit further towards making liver transplant the cure that it was always intended to be," he said.

This article was prepared by the *MedNous* editor on the basis of an interview and literature search.

