

# Therapies to help the blind and visually impaired

Neil Lagali of The Institute for Clinical and Experimental Medicine at Linköping University, Sweden, is leading an international team of experts working to eradicate corneal blindness



**A**pproximately 30 million Europeans are currently blind or visually impaired, leading to a reduced quality of life and a tremendous increase in healthcare costs and lost productivity. The unemployment rate in this group is 75% for those of working age, leading to an annual loss of 290 million workdays in Europe, while the cost of blindness alone, both medical and non-medical (home adaptation, assistance) is estimated at €20bn per year. Corneal blindness is the second largest cause of blindness globally after cataract, and while most corneal blindness is preventable, millions remain unnecessarily blind due to problems of access to or lack of effective treatments.

The cornea can lose transparency due to several causative factors, leading to blinding conditions originating at the tissue, cellular, and molecular level. The current state-of-the-art is characterised by an acute shortage of donor tissue, non-standardised and inefficient use of donor cells, and a lack of targeted molecular therapies. The main goal of the Horizon2020 project ARREST BLINDNESS is

therefore to develop and validate more effective advanced regenerative and restorative therapies to treat the loss of corneal transparency so that it does not result in blindness.

## What advanced therapies are being developed?

This goal is being achieved through three main objectives, developing advanced therapeutic approaches at the tissue, cellular, and molecular levels. Within these objectives, new advanced therapies are being brought from the laboratory to a stage of readiness for first clinical testing, while other innovative therapies are being brought into the clinic for first-in-man studies.

At the tissue level, a scarce and unpredictable supply of donor tissue results in millions of preventable cases of blindness globally. Moreover, human donor tissue is of variable quality and contains donor cells which can cause rejection by the host. In ARREST BLINDNESS, vision-restorative corneal transplantation with donor tissue is being replaced with tissue-engineered corneas based on

natural materials. These are laboratory-made scaffolds engineered from purified natural collagen, and are free of cells that could cause tissue rejection. Two such scaffolds, aimed at the treatment of eye trauma and keratoconus, are being evaluated in two Phase I clinical studies as innovative medical devices manufactured by two European SMEs.

At the cellular level, new GMP-compliant cell-based therapies are being investigated within ARREST BLINDNESS, to address a lack of standardised, approved cell-based therapies for restoring the critical cell layers responsible for corneal transparency, the corneal epithelial and endothelial cell layers. Standardised and GMP-produced human corneal endothelial and epithelial stem cell sheets are being evaluated in pre-clinical and Phase II transplantation studies, respectively, to obtain regulatory approvals for further clinical studies and clinical applications.

## New approaches to the visually impaired

Finally, new molecular agents and drug delivery approaches are being evaluated for restoring the neural and immune environment within the cornea, to address the lack of approved therapies for high-risk situations where the cornea has a nerve deficiency or is immune compromised. Specifically, neural regenerative therapy combined with a new drug delivery technique is addressing the lack of neural support in current corneal transplants, to improve their success rate.

Moreover, the critical immune balance in the cornea is being restored by first imaging the immune status of the cornea using a newly-developed non-invasive imaging approach based on optical coherence tomography, then applying advanced methods to target aberrant blood and lymph vessel growth to maintain the cornea's immune-privileged status. Successful



ARREST BLINDNESS consortium partners, during the project kick-off meeting in Brussels, January 2016

preclinical studies are now leading to clinical implementation of these novel imaging and therapeutic methods.

The innovative approaches being developed and moved into clinical testing within the objectives of ARREST BLINDNESS are bridging the gap between advanced regenerative medicine, biomaterials, imaging, and drug delivery technologies and the millions of blind and visually impaired people who could most benefit from these.

### Clinical studies and training

A cornerstone of ARREST BLINDNESS is four clinical studies being undertaken by partners, each addressing a different corneal pathology leading to blindness, by using innovative, advanced new technologies promoting regeneration and restoration of tissue. By the end of the first reporting period, two clinical studies in Germany and Belgium are well underway with 30-50% of patients recruited. The initial indications are that a novel GMP-compliant medical device and GMP cell-based therapy are functioning well, maintaining vision in patients who would otherwise be blind. Two further clinical studies are planned with applications being submitted to ethical and regulatory authorities based on successful preclinical studies.

Cross-collaborations between industry and academia are taking place within the project, with industry partners providing new devices and technologies directly into academic research centres for validation and testing under appropriate conditions (i.e., in cells, in animal models, and with human subjects). This work is providing a direct path for these SMEs to develop new medical devices and pharmaceutical formulations for new applications and markets. As evidence for this, academia-industry partnership agreements have been signed, one patent has been granted and another application has been filed, and SME partners have included the new technologies into their business plans.

Training the next generation of corneal specialists and corneal researchers is also an important goal of ARREST BLINDNESS. Besides providing direct salary support for PhD trainees, postdoctoral fellows, researchers, residents and corneal fellows, the project meetings and work package tasks facilitate collaboration of young researchers across institutions and countries. Network building for young researchers was promoted by holding an EU Summer Training School on Corneal Regeneration, which was held by the co-ordinator at Linköping University in June 2017. The training school provided the opportunity for 19 young EU trainees and many supervisors, researchers and corneal practitioners from across Europe to interact, hear about the latest research and learn about clinical and scientific aspects of the cornea.

### How are devices making an impact?

The ARREST BLINDNESS consortium is on track for achieving a number of ambitious project goals.

As an example of this, a new collagen-based biomaterial and implantation technique has been developed to overcome the deficiencies of the previous attempts at tissue-engineering the cornea. During the first reporting period, this new medical device has been proven effective in a preclinical study and ethical and a regulatory application was filed for a first-in-man clinical study. In addition, another collagen-based device designed for a different application as a temporary emergency corneal replacement, has been implanted in the first patients in a first-in-man trial.

Both these devices are defining the state-of-the-art in the field of corneal replacements, where no similar technologies exist. These have the potential to alleviate the high demand and long waiting times for human donor corneas, which today keeps millions of cornea-blind people from being productive members of society. The two technologies are being developed by two European SMEs within ARREST BLINDNESS, who are poised to become early leaders in these new niche markets.

### The development of optical diagnostic equipment

While limbal stem cell transplantation to treat corneal blindness has achieved widespread adoption over the past decade, the procedure still carries high risks of allograft rejection and transplant failure, necessitating costly repeat procedures which have a poor prognosis. During the current reporting period of ARREST BLINDNESS, a multi-centre clinical trial of limbal stem cell transplantation recruited a number of patients where new advanced stem cell imaging and real-time surgical imaging tools were implemented to optimise the donor-to-recipient tissue harvesting and transplantation process, in order to improve patient outcomes.

These new procedures have the potential to set the standard for this stem cell surgery, to maximise the chances of alleviating patient blindness and thereby avoid the suffering and added cost of multiple risky procedures. By the end of the project, the impact of the new imaging and monitoring techniques will be assessed in terms of success rate of the transplantation procedure and other secondary outcomes.

Finally, during the current reporting period, new non-invasive optical diagnostic equipment has been developed to demonstrate state-of-the-art immune imaging of the ocular surface, which is a technology that had not previously existed. The imaging technique has been tested in preclinical models and in the first human subjects with

positive results. The technology has been miniaturised for compatibility with current slit-lamp imaging systems, making its reach potentially as widespread as every cornea clinic.

### Treating corneal blindness today

In combination with this innovation, preclinical testing is underway to develop new targeted molecular therapies targeting the immune response of the cornea and the lack of sensory nerve fibres, conditions that can lead to corneal tissue transplant rejection, corneal melting, ocular surface dryness, and blindness.

By the end of the project, new imaging, surgical techniques, and new molecular therapies will have been tested clinically, thereby presenting an end-to-end solution for treating the most difficult cases of corneal blindness today.

These innovations have the potential to change the manner in which high-risk cases of potential corneal blindness are assessed and treated. Safety and efficacy of corneal transplants are paramount, as each corneal transplant saves €170,000 in long-term healthcare costs, for total savings of €6.8bn if the current European transplantation rate of 2% could be doubled. Such a doubling is being additionally addressed by the advanced tissue-engineered corneas being developed within ARREST BLINDNESS.



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