

# A Revolution in the Retina

On 4<sup>th</sup> July, Dr Raja Narayanan, the head of LVPEI's Anant Bajaj Retina Institute, performed a 25-minute procedure on a patient with a form of macular degeneration which has no known cure. This procedure is part of a safety trial for an investigational new drug (IND) in collaboration with Eyestem, a cell therapy company from Bengaluru. We are looking to find a cure for 'Dry' Age-related Macular Degeneration (AMD), a blinding condition associated with aging.

Dr Narayanan, with carefully calibrated movements, injected the drug into the patient's sub-retinal tissue, a procedure few in India have the experience to execute. This was part of a multi-centre phase 1 trial, and we await the full roll-out and results. Irrespective of its outcomes, LVPEI is now firmly among those research institutions that are pushing the human frontiers of sight restoration.

## Full-feature translational research

If successful, the LVPEI ecosystem will be critical to this product's success. This cutting-edge biological product is the only one in Asia and is produced at LVPEI's GMP facility for the entire trial. After approval from CDSCO, LVPEI was one of the three trial centres for the phase 1 safety trial. The LVPEI Image Laboratory and Analysis Centre (LILAC) is the sole image reading centre that scans patients' images and helps pick patients for the trial.

The LVPEI research pipeline is now feature-rich and offers a full pipeline from the bench to the bedside. Apart from our traditional research expertise, we have now added biomaterials and pharmacology to our research process. Research ideas that have matured in laboratories and have achieved in silico/in vitro proof-of-concept, will progress to the GMP facility for production to commercially acceptable standards. Today, LVPEI's GMP facility makes six approved products (and this new Dry AMD treatment is the third to reach clinical application).

Those products can then be tested at our Zebra fish facility or in animal models for safety and toxicity testing. Once they pass that stage, LVPEI is fully equipped to undertake clinical trials. LVPEI has its own homegrown research products and is also open to collaboration with others who share our vision and ambition—pushing the final frontiers of sight loss.

This complementary approach showcases the depth of translational research of our organization and may prove critical for finding a cure for AMD and other such retinal impairments that have fewer chances of sight recovery. Over 8 million people worldwide live with vision loss due to AMD. Blindness due to the 'wet' form of AMD has decreased by 30% between 1990-2020 because of the availability of a treatment called anti-VEGF injections. However, 'Dry' AMD has no such cure today which improves the vision. AMD is one of many conditions that are hard to catch and is irrecoverably blinding, as they destroy the retina.

## Gene Editing – a new approach to management of diseases

A few months ago, news reports streamed in about the relative success of a revolutionary technique that edited genes inside the retina after an injection of a new drug, EDIT-101. The BRILLIANCE trial, run in USA, showcases the safety and efficacy of this new drug in improving some vision.

This is a new era of research, made possible by a gene editing tool called the CRISPR-Cas9 system. This system comes as a 'package' with a molecular 'scissor' to snip open the DNA at precise locations and activates the cell's own repair machinery to make changes and patch up the damage. This allows gene modifications and gene augmentation inside living cells to restore normal functions. However, this approach is best suited for very young individuals with surviving but nonfunctional cells. At LVPEI, we are pursuing 'cell replacement' therapy, where we aim to replace the lost or defective cells with normal cells to restore tissue function. This approach can benefit both young and older individuals at different stages of disease.

### CRISPR at LVPEI

Dr Indumathi Mariappan and her research team are leading basic and translational research efforts towards addressing the problem of retinal diseases. They use induced pluripotent stem cells (iPSCs) that can make any type of cells, including those in many eye tissues such as the retina and cornea. In early July, the team published a key paper along with scientists from the Council of Scientific and Industrial Research - Institute of Genomics and Integrative Biology (CSIR-IGIB) that presented results of a new CRISPR-Cas9 tool that is more precise and efficient than existing technologies ([The Hindu Science has published a detailed story on this exciting development](#)). While the IGIB team developed this precise CRISPR-Cas9 tool, Indumathi and her team evaluated them in patient-specific iPSC lines that carried rare, genetic retinal mutations. They observed a successful mutation correction and without any unwanted 'bystander' changes elsewhere in the genome. Their edits had restored normal protein expression in those iPSC-derived retinal cells. As the correction was in a patient's own cells, this opens up whole new opportunities in cell replacement therapies.

Will a similar cell replacement therapy work for Dry AMD too? Eyestem recently received approval for human trials on their drug to treat Dry AMD. The condition occurs due to age-related loss of the retinal pigment epithelial (RPE) cells in the retina. Eyestem's solution is to replace the lost RPE cells with iPSC-derived RPE cells of a healthy individual. Their product is ready for phase 1 trials after successfully clearing animal model studies. The LVPEI ecosystem has the research experience, expertise, and systems in place to take this approach closer to fruition. As a tertiary care facility, we have the wherewithal to offer clear consent and awareness information to our patients who are interested in participating in such drug trials.

On 4<sup>th</sup> July, along with Eyestem, LVPEI leapt into the future. While our first patient is doing well, it will take a few more years for all the results to roll in and, if satisfactory, for full-scale treatments to begin. We, along with our patients, have pushed the frontiers of care and lived up to the excellence that is at the core of the LVPEI promise. These are exciting times.

- Prashant Garg