Hyderabad Eye Research Foundation

Details of the excellence in research work for which nomination is being sent

INTRODUCTION TO THE FIELD OF WORK

The eyes are our window to the world and the tiny window within the eye that lets in light to allow for the miracle of vision to happen is called the cornea. The cornea is a unique biological tissue that is naturally transparent. The only other tissue that has this property is the human crystalline lens, but even that opacifies with advancing age, while the cornea remains crystal clear throughout an individual's lifetime. This is no easy feat because the cornea's exterior is constantly exposed to the outside environment, and this has been made possible by the special attributes of the ocular surface. The term "ocular surface" has acquired a special meaning over the last three decades and is used specifically to denote the delicate epithelial layers and their associated glandular elements that extends from the inner margins of one eyelid to the other, including the cornea and the conjunctiva. It is now known that the ocular surface behaves functionally as one unit, however, this knowledge is recent, and the field has undergone tremendous advancement in the last three decades. Another remarkable aspect of ocular surface disease is that although it affects vision by inducing chronic corneal damage, these cases are not amenable to corneal transplantation.[1]

The first major scientific disruption in the field of ocular surface was made by Kenneth Kenyon and Scheffer Tseng in 1989, who established the presence of functional corneal epithelial stem cells at the limbus.[2] By transplanting large pieces of healthy limbal tissue they reversed the blinding conjunctival overgrowth in burn-injured corneas, a clinical condition later termed as limbal stem cell deficiency. This squarely brought the limbus, the transition zone between the conjunctiva and cornea, at the centre-stage of ocular surface research. The second breakthrough came in the following decade when Graziella Pellegrini and her group in Italy, developed the technique of expanding the limbal cells as a multi-layered sheet in the laboratory from a tiny biopsy and achieving successful clinical results.[3] While ex vivo expansion emerged as an alternative, and began to be adopted across the globe, including at multiple centres in India, this technology was not without its drawbacks. Not only was a clinical grade laboratory prohibitively expensive to establish and maintain, but the technology also remained out of bounds for most surgeons and their patients. It seemed like limbal stem cell therapy would remain out of reach of the patients in the developing world who needed it most, until the development of simple limbal epithelial transplantation (SLET) in 2010 by Dr Virender Sangwan and Dr Sayan Basu.[4] The new innovative technique of SLET was disruptive in multiple ways, but most importantly it made limbal transplantation accessible and affordable to the patients who needed them most by obviating the need for expensive laboratories and specialized surgical skills. The other remarkable discovery was that of a different kind of stem cells, called the mesenchymal stem cells ,deeper down in the same limbal tissue. While this discovery was spearheaded by James Funderburgh and his team at Pittsburgh, Dr Basu joined the Funderburgh laboratory to perform the critical in vitro and preclinical validation of these limbal mesenchymal stem cells for the treatment of corneal scarring, the fourth most common cause of blindness and visual impairment worldwide.[5]

THE NOMINEE'S CONTRIBUTION TO THE FIELD OF OCULAR SURFACE

Dr. Sayan Basu is a fellowship trained corneal transplantation surgeon who has been working in the field of cornea and ocular surface since 2010. He has over 140 Medline-indexed peer reviewed publications, most of which are in frontline ophthalmology journals with a clear focus on ocular surface disease (https://orcid.org/0000-0001-5030-5003). He started his academic career working on the clinical outcomes of laboratory expanded limbal stem cell therapy, which is also known as cultivated limbal epithelial transplantation (CLET). He was instrumental in critically analysing the success rates of CLET and identifying the specific risk-factors of CLET failure in the Indian population.[6-10] Till date, his papers on CLET remain the largest clinical series and the most widely read and cited papers on CLET from India (https://scholar.google.com/citations?user=Y3hO_C0AAAAJ&hl=en).

He carried his learnings from the CLET projects to help co-develop the surgical technique of SLET, which intended to address the problem and limitations associated with the CLET technique of limbal stem cell transplantation, particularly in the Indian context.[4] Following the initial description of the technique and proof-of-concept clinical study, Dr. Basu devoted the next 4 years to validating the clinical outcomes in a larger cohort with a longer follow-up, which was published in 2016.[11] He is largely credited by his peers of standardizing every step of the surgical procedure and teaching the technique to other surgeons across India and internationally.[12] He has conducted surgical workshops regularly in Hyderabad ,Vadodara, New Delhi, Ambala, Kochi, Mexico City, Miami, Chicago, and Ho Chi Minh City, other than lecturing on the topic in numerous national and international meetings and conferences over the last 10 years. He has trained over 250 surgeons who now practice all over the globe.

Dr Basu also worked on the limbal mesenchymal/stromal stem cells (LMSCs) and standardized the technique of isolating them from tiny tissue biopsies. He worked with Prof. Funderburgh at The University of Pittsburgh Medical School, during 2012-13, on the *in vitro* characterization of the cells and demonstrated their wound healing and tissue regenerative properties.[5] After returning to India in 2013, Dr Basu established the current good manufacturing practice (cGMP) laboratory and started working on regulatory approvals for using the hLMSCs for the treatment of corneal ulcers, scars and burns. Dr Basu through his collaborators also developed a safe way of preserving these cells at room temperature, so that they can be transported across the length and breadth of the country without requiring expensive cold chain.[13] The Indian regulatory authorities have recently given the approval for the first human clinical trials for the use of hLMSCs (CTRI/2020/07/026891 and CTRI/2021/07/035034). This is one of the rare examples of successful bench to bedside research in Indian ophthalmology, and regenerative medicine in general and particularly in the field of ocular surface.

In addition to tissue and cell-based therapy, Dr Basu has also made remarkable strides in development of artificial corneal substitutes, in the form of implants and biomaterials. Keratoprosthesis are artificial corneal implants that are indicated in severe cases of corneal blindness that are neither amenable to corneal transplantation nor cell-based therapy. He was the first to adopt an Indian variant of the Boston keratoprosthesis and showed its clinical safety and efficacy in a large comparative series. [14,15] Again, this clinical series remains the largest study on keratoprosthesis from India and the world outside the United States.[14] He was also instrumental in working with AuroLabs, Madurai, Tamil Nadu, to develop a novel corneal implant called the LVP keratoprosthesis or LVPKpro, which has also been clinically validated.[16] He also continues to collaborate with international experts on refining and improving the designs of keratoprosthesis.[17] Dr Basu's group is now working on testing several innovative biomaterials for the treatment of corneal opacities.[18-20] These are in preclinical stages of development and are being tested in animal models of corneal disease, which he himself has been instrumental in developing.[21]

THE IMPACT OF THE NOMINEE'S CONTRIBUTIONS TO THE FIELD

Impact of SLET: While surgical innovations do keep happening, not all succeed in the way they were originally envisaged and rarely still do they exceed expectations. Modern medicine is replete with examples of well-intentioned ideas failing at the anvil of evidence-based evaluation. Novelty aside, new innovations must satisfy the clinical criteria for efficacy, safety, reliability, and replicability.[22] Dr. Sayan Basu was part of the clinical team led by Dr Virender Sangwan at the LV Prasad Eye Institute (Hyderabad, Telangana, India) that developed the required surgical technique.[4] He was also the architect responsible for validating the technique in the first cohort of 125 cases with a year-long clinical follow-up. Using his trade-mark methodological rigor, Dr Basu showed in the seminal paper published in the official journal of the prestigious American Academy of Ophthalmology, that the outcomes of SLET were reliable irrespective of the patient's age or the surgeon's experience.[11] Multiple subsequent peer-reviewed studies from several disparate groups have shown that SLET has comparable clinical efficacy to the more complicated cultivated technique for adults and is slightly better for children. While the anatomical success with SLET in adults is 72.6% (range 62%–80%) and in children is 77.8% (range 73%–83%), the comparative numbers for the laboratory cultivated technique are 70.4% (range 68%–80.9%) in adults and 44.5% (range 43%–45%) in children.[23]

A recent review analysing the socio-economic impact of SLET found that it has rapidly gained popularity and there were as many patients in the last decade that have been treated with SLET, as in the previous two decades by laboratory expansion (CLET).[24] The review included a survey that suggested that the number of SLET surgeries had already crossed the 1000 mark globally.

The analyses also suggested that the SLET procedure is a significantly cost- saving strategy saving each treatment centre around INR 40 million per annum. The economic derivates for SLET include reducing the number of surgeries, because of its higher success rates, which may also alleviate pressure on beds and associated costs. Indeed, SLET has replaced the laboratory expansion technique as the preferred surgery option for patients with limbal stem cell deficiency. It can be done in institutes that do not have access to facilities for cell culture and surgeons can be trained to undertake the SLET procedure in less than a week (and then in turn to pass on the training). From the patient's perspective, there is one rather than two surgeries, so less time to be spent in hospital, and a factor of 8-fold/10-fold savings in the costs of undertaking SLET versus CLET. [24] The published clinical data suggest that SLET is advantageous over CLET.[23] The economic argument for using SLET rather than CLET is demonstrated in this study in a way that other centres can access it and run their analysis. In summary, simplification of SLET technique so that cells slowly grow out of the small tissue explants to form a new cornea offers a viable, financially attractive and much more accessible approach to treat loss of vision. [24]

It is indeed heartening to note that SLET, a true made-in-India therapeutic innovation has been put through intense scientific scrutiny world-wide and has emerged as an effective, safe, reliable, and replicable surgical technique of treating ocular surface diseases due to limbal stem cell deficiency.[22] The most impressive aspect of SLET, however, has been the ease with which it has crossed the boundaries of specialty practice and has been adopted and adapted in the management of ocular surface tumors and degenerations. This is largely because SLET is analogous to an open-source software platform which allows the users to customize it based on their individual preferences. More importantly, SLET does not require any additional surgical paraphernalia, logistical support, or extensive training.

Impact of Limbal Mesenchymal/Stromal Cells and Biomaterials: In India, according to the National Programme for Control of Blindness, close to 6 million people suffer from bilateral corneal blindness and 25,000 to 30,000 cases get added to this list annually (https://npcbvi.gov.in/writeReadData/mainlinkFile/File341.pdf). Hospital-based studies in India have also reported that corneal diseases account for 26-37% of all blindness in children, a demographic which also carries a relatively poorer prognosis for corneal transplantation.[25] While corneal opacification due to wounding remains the most common cause, corneal ectasias are the second most common cause in bilateral cases. Moreover, the rate of progression of ectatic disorders like keratoconus is generally more severe in Asian patients. A recent study of 28,824 patients presenting to the LVPEI from 2016 to 2018, found that 60% of the eyes affected by corneal visual impairment or blindness, carried an unfavourable prognosis for corneal transplantation. [25] While our work promises a simpler alternative to corneal transplantation in all patients with corneal blindness, it also specifically targets this large proportion of patients who otherwise carry an unfavourable prognosis for corneal transplantation.

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Impaired vision or blindness can affect a person's independence, education, employment, socio economic status, and most importantly the quality of life. In India most people affected by corneal blindness are relatively young and it affects the most productive years of their lives. The overarching goal of our proposal is to provide a solution that can not only improve the patient's vision but also positively impact their lives, including their physical and emotional well-being.

SUMMARY

Corneal opacification is the 4th most common cause of blindness affecting about 5 million people globally every year.[26] The major causes of corneal opacification are infectious keratitis, corneal surface damage, keratoconus, and nutritional deficiency.[27] The world health organization (WHO) has estimated that of the 45 million people who are suffering from blindness globally, 6 to 8 million of them are blind due to corneal disorders. [26] Corneal opacification is not medically reversible and corneal transplantation is the current standard of care for those with severe disease and vision loss. However, corneal transplantation has its limitations with respect to long-term graft survival, prolonged use of topical or oral immunosuppressive medications and life-long clinical follow-up. There is also, unfortunately, a huge gap between the demand and supply of donor corneal tissue worldwide, which is further complicated by the lack of adequate eye-banking networks, especially in the developing world.[28] With advancements in regenerative medicine and tissue engineering, many possible alternative approaches to corneal transplantation have emerged in the recent past. These include biomimetic hydrogels, stem cells and gene/molecular therapy. Of these, biomimetic hydrogels have shown the greatest promise and various groups have explored the use of different hydrogels with or without cells as an alternative to corneal transplantation for restoring corneal transparency.

Dr Sayan Basu has worked towards finding therapeutic alternatives to corneal transplantation, because being primarily a corneal transplantation surgeon himself he understands the limitations of the approach. The global shortage of donor corneal tissue notwithstanding, a large proportion of the cornea blind individuals in developing countries like India have pathologies that carry a poor prognosis for corneal transplantation. He has through his research over the last decade focused on three approaches: cell-based therapy, therapeutic biological hydrogels and synthetic corneal implants. He has had a tremendous clinical and social impact with SLET and is similarly focused on prioritising accessibility and affordability with the hLMSCs, biomaterials and implants.

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