STATEMENT OF PROPOSED STUDY OR RESEARCH
Paul Phelps, India, Medicine

Characterization of Human Corneal Epithelial Stem Cells

Discovery of and implementation of effective treatments for eye disease is both my personal goal and the mission of Aravind Eye Hospital. The cornea service at Aravind treats thousands of patients each year, with more surgeries performed and more patients seen than any other eye care facility in the world. While the economically impoverished of India are especially affected by preventable vision loss – up to three times more than patients in the United States,[1] Aravind provides the best available treatments to their patients. Their Ophthalmologists have learned to increase efficiency with assembly-line operating room design. This has increased the number of surgeries that one surgeon can complete in a day, and therefore has cured many more blind patients in India.

Various solutions are needed to cure cornea disease which occurs across the globe, and the Aravind Medical Research Foundation is promoting discovery in the area of stem cell research. Stem cell (SC) research is an active area of innovation for cures to intractable diseases across the medical spectrum; but there are two fundamental types of SCs, embryonic and adult. Embryonic SCs are harvested from aborted fetuses and may have the capacity to produce a whole organism, which makes them a controversial source of SCs. Alternatively, adult SCs function to replace various tissues lost during normal or pathological processes, such as skin exfoliation or wound healing, and can be extracted from adult tissue with relative ease.

Deceased-donor transplant is ineffective in some cases of corneal disease (i.e. chemical or thermal injury, Stevens-Johnson syndrome, cicatricial pemphigoid, etc.), but a method known as autologous grafting is an alternative for otherwise intractable cases. Tissue harvested from the patient may be grown outside the body for the purpose of eventually transplanting the tissue back into the patient. Success of this technique necessitates further characterization of the corneal epithelial SC population. Previous research has shown that the human eye harbors SCs in the limbus, the circumferential area where the cornea meets the sclera. However, this population of cells is not made up purely of SCs: it contains differentiated cells in addition to corneal epithelial SCs.

A distinct advantage of conducting my research in India is that I will learn more about eye disease from the diverse patient population. Many of Aravind's patients have eye pathology – often due to infectious disease – which has progressed beyond anything that I would encounter in United States or Europe. The opportunity for me to both conduct adult SC research and work with such a diverse patient population is impossible to match anywhere else in the world, so it is essential that my research project be conducted in India.

The Aravind laboratory of Dr. VR.Muthukkaruppan has successfully identified corneal epithelial SCs based on special characteristics of SCs. These properties include a high nucleus-to-cytoplasm ratio and specific protein expression patterns.[2] The adult human

[1] World Health Organization Statistics (http://www.who.int/mediacentre/factsheets/fs282/en/)
[2] Arpitha P, Prajna NV, Srinivasan M, and Muthukkaruppan V. (2005) High Expression of p63 Combined with a Large N/C Ratio Defines a Subset of Human Limbal Epithelial Cells: Implications on Epithelial Stem Cells. **Investigative Ophthalmology & Visual Science** 46:3631-3636

SCs used in the laboratory at Aravind are the same type that could be cultivated for future autologous transplants. I hope to help advance current understanding of these cells through basic science research.

The proliferative potential of adult SCs is essential for their therapeutic use. Past research has shown that cellular production of specific proteins, such as transcription factor p63, is necessary for SC proliferation. I intend to determine where and when p63 is expressed in corneal epithelial SCs using techniques such as laser confocal microscopy, which makes use of a computer to reconstruct a three dimensional image of cells, and a special form of mRNA labeling referred to as in situ hybridization. The ultimate goal of my project will be to facilitate cost-effective treatment for corneal damage by learning if p63 can be use as a marker to rapidly identify corneal epithelial SCs.

I have worked with Dr. V.R. Muthukkaruppan on this proposal to characterize corneal epithelial SCs. Based on my previous research experience I am confident that I can accomplish my research goals during my tenure at Aravind. I have expertise in the research techniques required to complete this project, skills which were honed while I worked as a research assistant at MIT and an Alpha Omega Alpha (Medical Honor Society) summer scholar at the University of Minnesota. Some of the data I produced at MIT was published in the top, peer-reviewed journal.[3] I hope to surpass previous achievements with my work at Aravind.

Although I am primarily interested in conducting scientific research on this unique stem cell project, I also intend to immerse myself in the community of Madurai. Volunteer work with eye camps that screen patients in rural areas surrounding Madurai will extend my cultural interaction beyond the laboratory. In regards to learning the local dialect of Tamil, I have taken the first steps to learning the language, and plan to continue these efforts when I arrive in India.

The final advantage of having my research project at Aravind is that I will get a hands-on look at how their uniquely efficient surgical methods can take care of so many patients while keeping costs low. Many patients in both India and the United States are unable to afford health care, and I hope to see how doctors in India navigate this problem. This would be an important insight as a future doctor in the U.S., where payment for health care is a growing issue. Beyond science and medical outreach interactions, I'm eager to learn about the many customs and traditions of India.

My long-standing interest in international education resulted in a successful nine-month study abroad in the United Kingdom during my undergraduate years, and will act as a springboard for achievement in the Fulbright Program in India. My passion for cultural understanding will facilitate positive connections with my Indian colleagues and neighbors. I hope that through promotion of scientific advancement, concern for treating preventable disease, and a willingness to embrace new cultures, I will promote the mission of the Fulbright Program in India.

[3] Rosenzweig M, Brennan KM, Tayler TD, Phelps PO, Patapoutian A, Garrity PA. (2005) The Drosophila ortholog of vertebrate TRPA1 regulates thermotaxis. **Genes & Development**. 19:419-24