A comprehensive report on the research activities of C-TRACER at the L V Prasad Eye Institute, Hyderabad, India


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Champalimaud
Translational Centre
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Inauguration
January 30 2008
LVPEI
Champalimaud
Foundation
L V Prasad Eye Institute

The Champalimaud Translational Centre for Eye Research has been set up at LVPEI in January 2008. The Foundation has a long-term commitment to support medical research, in particular neurology, oncology and vision sciences. The Champalimaud Foundation and L V Prasad Eye Institute have agreed on the development of a vast program of translational research through the establishment of the Champalimaud Translational Centre for Eye Research or C-TRACER. Research at C-TRACER will focus on the following areas:

Mission of C-TRACER

- Translational research utilising existing and novel clinical methodologies with the objective of furthering the knowledge of vision in ways that can be readily applied to patients;
- Research and therapy through the utilisation of stem cells in vision-related illnesses;
- Molecular and functional genetics of inherited eye diseases;
- Gene therapy and cell-based therapy of monogenic disorders of the eye;
- Exchange programs involving scientists chosen by LVPEI and the Champalimaud Foundation;
- Introduction of capacity building programs for developing Lusophone countries such as Mozambique, Angola, Timor and others;
- Organize the Antonio Champalimaud Symposium on January 30th of every year, during which leaders in the area of ophthalmology from the world, as well as distinguished scientists from India, are invited to lecture.

With the creation of C-TRACER, the Champalimaud Foundation will try to work towards the prevention, treatment and eradication of vision-related illness in India and some other parts of the world.

Short summary of performance statistics

- Over 700 limbal stem cell surgeries done; over 60% successful – a world record.
- Over 20 oral mucosal cell-based surgeries done: success rate being assessed
- Risk alleles for age -related macular degeneration identified
- New locus has been mapped for retinitis pigmentosa
- One function of the protein optineurin identified, relating to glaucoma
- Second stem cell culture room established, for patient studies
- Published 54 peer-reviewed research papers, including in Proc. Natl.Acad. Sci. US
- Five Ph D degrees obtained during 2008-2010
- India's highest research award (Bhatnagar Prize) to Dr. Santosh Honavar
- 4 students received international travel fellowships to ARVO and to Gordon Conference

Activity profile of C-TRACER since 2008

Salient features of the research

Stem cell biology and therapy

- Limbal stem cell based therapy, initiated at LVPEI in 2001, has since grown into a standard mode of treatment to repair the damaged ocular outer surface of patients, who have suffered chemical and fire injuries. To date, we have completed over 700 such treatments, and have analyzed the long-term outcomes of about 405 of these. The results will shortly appear in print. They have already been presented at the 2009 Cold Spring Harbor Meeting on Stem Cells at Long Island, NY, USA, 2010 Gordon Research Conference at Ventura, CA, USA, and at the 2010 ARVO meeting at Ft. Lauderdale, FL, USA.
- Where the limbal tissue is not available, we have taken tissue from the oral mucosa, cultivated them just as we do for limbal cells, and transplanted them on over 30 patients. Some of them have responded well already, while we are studying the progress of others.
- Induced pleuripotent stem cell (iPSC) preparation: Based on the recent report by Yamanaka, that stem cells can be generated from any cells in the body, by introducing specific genes (or protein factors), we have started generating such iPSCs, so as to ultimately study and correct cells of patients with some forms of retinitis pigmentosa. While this is a long-term project, which would take a few years, we have already succeeded in generating iPSCs of mice, and have moved to humans.

Molecular and Functional Genetics

- Research in primary open angle glaucoma (POAG) has focused on gene identification based on pathways leading to complement activation and extracellular matrix (ECM) remodeling. Using customized microarray and resequencing, we have been able to understand that the genomic profile in the Indian cohort is different from other populations, complement genes may have a limited role in pathogenesis and the ECM-related genes exhibit a stronger association to POAG that needs to be validated functionally.
- We have discovered a genetic biomarker that enhances the susceptibility to primary congenital glaucoma (PCG). This marker in the *CYP1B1* promoter enhances the risk to patients harboring mutations, has a reduced expression and is associated with poor prognosis in terms of intraocular pressure (IOP) control post operatively.
- Our recent work on age-related macular degeneration (AMD), has led to the identification of a new ECM gene, *TIMP3*. Using customized arrays, we have been able to pinpoint to two specific intronic variations that are strongly associated with AMD susceptibility and is also supported by data from other populations. The findings have been reported in PNAS.
- Based on multiple pathways leading to retinopathy of prematurity (ROP), we are currently engazed in identifying genetic risk factors for this disease based on a candidate gene approach.
- A new locus has been mapped for retinitis pigmentosa based on linkage analysis in a large family. Fine mapping of the region has yielded a narrow disease interval and the hunt for the RP-associated gene is in progress.
- The gene *OPTN*, which codes for the protein optineurin, is associated with normal tension and primary open angle glaucomas. However, what the actual function(s) of the protein optineurin is in the cell, and which of these functions are affected upon mutation, leading to glaucoma, is not understood. To this end, we have embarked on a study of the biochemistry and cell biology of optineurin and its mutants (particularly the mutant E50K, which leads to a severe phenotype). Our studies reveal that optineurin

is involved in protein trafficking in the cell, in particular in the process of recycling endosomes (which govern cellular homeostasis); the mutant E50K impairs this process, leading to cellular malfunction and eventual death of retinal ganglion cells, associated with glaucoma. This work has been published.

Champalimaud Symposia

- *The First Antonio Champalimaud symposium* was held on January 30, 2008. Prof N K Ganguly, UNESCO Centre for Translational Research and Training, New Delhi, delivered the First Champalimaud Lecture on 'Translational Research: Scenario and Opportunities in India'. Prof Robert Folberg of the University of Illinois Chicago campus, Chicago, USA, explained how technology could be used to maximize the impact of distance education in ophthalmology. Prof Jost Jonas from the University of Heidelberg, Germany, presented the results and policy implications of the Beijing Eye Study, while Dr Miguel Castelo-Branco from Coimbra, Portugal, described a model of genotype-phenotype correlations in ocular disease. Prof Brien Holden, CEO, Institute of Eye Research, Australia, detailed the progress of translational research in the area of refractive error.
- *The Second Champalimaud Symposium* was held on January 30, 2009. We had lectures by Dr Jeremy Nathans of Johns Hopkins University, Baltimore, MD, USA, (who won the Champalimaud Prize for Vision Research, 2008); Dr William M Bourne of Mayo Clinic, Rochester, MN, USA; Dr Virender S Chauhan of the International Centre for Genetic Engineering and Biotechnology, New Delhi; and Dr K Vijay Raghavan of the National Centre for Biological Sciences, Bangalore. In addition, research updates were provided by colleagues of the LVP family.
- *The Third Champalimaud Symposium* was held on January 30, 2010. We had lectures by Dr. Janey Wiggs of the Massachusetts Eye and Ear Infirmary, Harvard University, Cambridge, MA, USA, Dr. Dave Friedman of the Wilmer Eye Institute, Johns Hopkins University, Baltimore, MD, USA, and Dr. Borja Corcostegui of the Faculty of Medicine, Universitat Autonoma de Barcelona, Spain, and also from some of the faculty of the LVPEI family.

Research publications from C-TRACER, Hyderabad since 2008

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Honours & Awards to C-TRACER Researchers

- D. Balasubramanian has been re-elected as a member of UNESCO's International Basic Science Programme Panel, Paris, France (April 2009-March 2012)
- D. Balasubramanian has been elected as Fellow of the German Academy of Sciences Leopoldina, 2009.
- Professor D. Balasubramanian has been chosen to be awarded the Biospectrum Life Time Achievement Award in Biotechnology 2009.
- Santosh Honavar, MD has been awarded the Shanti Swarup Bhatnagar Prize of India in Medical Sciences, 2009
- Geeta Vemuganti has been (i) nominated for and elected as ARVO Program Committee Member (AP section); and (ii) chosen as a guide for the 6- Month Fellowship Program in Ophthalmic Pathology, and (iii) invited as a r eviewer for project proposals submitted to the Medical Council Research Committee (Translational Stem Cell Research Committee), UK
- Subhabrata Chakrabarti has been invited to join the Editorial Board of the journal Diabetes Review Letters, and the journal International Glaucoma Review.
- Ms. Vidya Parsam, Research Fellow in Chitra Kannabiran's group was awarded this year's KV Rao Foundation Young Scientist Prize (plaque and cash prize of Rs 10000).
- Dr. Indumathi Mariappan has been awarded a grant by the Department of Biotechnology, Government of India on Induced Pleuripotent cells.
- A bilateral Indo-Tunisian project on "Genetic comparison of primary congenital glaucoma in India and Tunisia – understanding the possible founder effects" approved by Department of Science and Technology, Government of India. This is for exchange of people and samples between us and Tunisian colleagues.
- Dr. Subhabrata Chakrabarti has been chosen as a Young Affiliate (from India) of the Academy of Sciences for the Developing World (TWAS), 2009-2013.
- Dr. Ashok Kumar Reddy received the IAMM Silver Jubilee Prize for Best Paper in Parasitology at 33rd National Congress of the Indian Association of Medical Microbiologists, held at Mysore, during 6-8 November, 2009.
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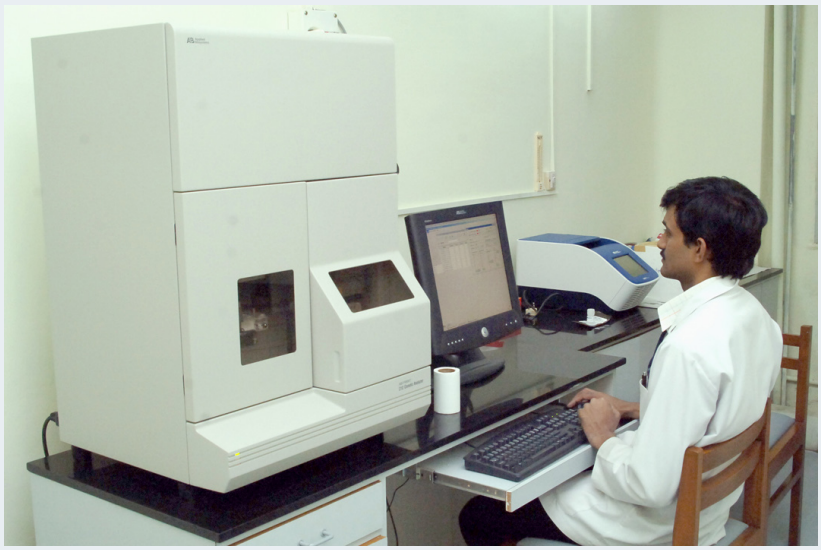

LVPEI
So that all may see

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