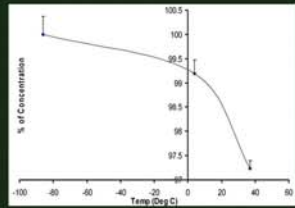
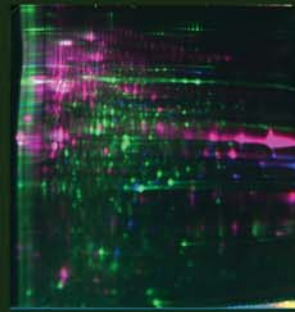
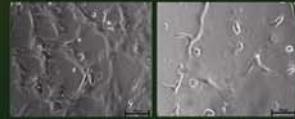


report 2009-10

DR. G. VENKATASWAMY EYE RESEARCH INSTITUTE
Aravind Medical Research Foundation



DR. G. VENKATASWAMY EYE RESEARCH INSTITUTE
Aravind Medical Research Foundation

MISSION

To eliminate needless blindness by providing evidence through research and evolving methods to translate existing evidence and knowledge into effective action.

REPORT 2009-10

INTRODUCTION

The Dr. G. Venkataswamy Eye Research Institute with its state-of-the-art infrastructural facility has been able to make significant contributions in understanding the basic biological mechanisms of eye diseases. Aravind Eye Care System is unique in having the activities of Aravind Medical Research Foundation, Aravind Eye Hospitals, Aurolab and Lions Aravind Institute of Community Ophthalmology integrated to achieve our Mission “To eliminate needless blindness”

Molecular genetics of eye diseases is a proven approach to understand the disease mechanism. At AMRF considerable effort is underway to use this approach to examine several eye diseases (diabetic retinopathy, age related cataract, age related macular degeneration, leber congenital amaurosis, albinism). Apart from the generation of basic information, identification of those genes that are directly involved in the disease process as well as those genes that co-segregate with a particular disease will be of clinical importance. Single Nucleotide Polymorphism (SNP) based approaches are vigorously perused. However, the usefulness of these SNP in clinical medicine is yet to be proven for eye diseases. Recent explosion in the application of next generation and third generation sequencing technologies allows the comparative sequencing of several genomes to understand the contribution of SNPs in disease process and clinical medicine. In the coming years comparative whole genome sequencing approach will be of immense value in the examination of eye diseases.

Protein biomarkers could be used in the analysis of disease process as well as disease management. Disease prediction, disease progression, staging of the disease state and determination of efficacy of disease treatment are all areas of protein biomarkers studies. At Aravind Medical Research Foundation all these areas are explored from the perspective of eye diseases. Protein expression, protein quantitation and determination of protein isoform changes are all areas of intense study. A proteomics laboratory with most modern instruments such as multilaser Typhoon scanner and LC-MS/MS: nano LC- Micro ToF Q Mass Spectrometer has been in operation. Infectious fungal keratitis, diabetic retinopathy, glaucoma, CHED and FECD are some of the disease currently studied using proteomic approaches.

In addition, in the area of translational research we have developed a method to identify and expand in culture adult epithelial stem cells. The stem cell rich cultured epithelium was useful to bring back the vision to people, blind in both eyes. Now, this program is strengthened in the newly established GMP facility.



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BASIC RESEARCH

Molecular genetics of leber congenital amaurosis in South Indian population

Principal investigator : P. Sundaresan, Aravind Medical Research Foundation (AMRF)-Madurai
Co-investigator : P. Vijayalakshmi, Aravind-Madurai
Research scholar : Anshuman Verma
Funding agency : ICMR, UGC (Fellowship)
Duration : 2008 - 2013

Leber's Congenital Amaurosis (LCA) is a genetic disorder in which retinal dysfunction causes severe visual impairment often from birth or early stage of childhood. The vision loss is accompanied by nystagmus and sluggish eye pupil responses. Other features like high refractive errors, photoaversion, nyctalopia, pressing and poking of eyes, keratoconus, cataract etc. may also be associated. The disease is clinically confirmed by certain additional criteria like presence of reduced ERG and exclusion of patients having hearing loss.

Currently there is no treatment available for LCA but one of the emerging possible treatments for a particular type of LCA is gene therapy which has been found successful in animal models like mice and dog. In human it is under phase 2 clinical trial after crossing the promising phase 1 trial results. The gene therapy process essentially requires extensive genetic studies prior to its establishment and application.

So far 15 genes involved in various functional pathways have been identified for disease causing mutation. This accounts for about 60% of LCA cases and for remaining 40% the new candidate genes may have been involved. Our recent report suggests that mutations which are common in European population are rare in India. Therefore, Indian cohort of LCA patients may be useful resource for identifying novel mutations and new LCA genes. In this context we have been screening many LCA genes in Indian LCA cases which include CRX, RPE65, TULP1, SPATA7, and some predicted LCA genes. The study is planned for screening of all known and many possible unknown genes through new generation sequencing which will facilitate the identification of additional genes for LCA.



Master mix preparation for PCR

Molecular genetic analysis of fuchs endothelial corneal dystrophy

Principal investigator : P. Sundaresan, AMRF-Madurai
Co-investigator : M. Srinivasan, Aravind-Madurai
J. Arun Kumar, Aravind-Madurai
Research scholar : B. Hemadevi
Funded by : Department of Science and Technology
Duration : 2007 - 2010

Fuchs Endothelial Corneal Dystrophy (FECD) is a degenerative, bilateral, often asymmetric and slowly progressive disorder. Due to endothelial dysfunction and loss of cells with FECD progression leads to corneal decompensation and impaired vision. The genotypic approach will provide better understanding, identification of the underlying genetic defects and in future enhance the possibility of medical intervention using conventional pharmacological approaches or gene therapy. Heterozygous mutations

in the SLC4A11 gene are known to be associated with the late-onset FECD. Therefore we screened for SLC4A11 gene variants in Indian FECD patients.

Eighty patients with clinically diagnosed FECD and 100 age matched normal individuals were recruited. Genomic DNA was isolated from peripheral blood leukocytes. Mutations in SLC4A11 coding regions were screened using bi-directional sequencing. Fischer's exact test or Pearson's chi squared test were used to predict the statistical association of genotypes with the phenotype. In the screening of SLC4A11 gene, novel c.1659C>T, c.1974C>T and reported c.405G>A, c.481A>C and c.639G>A variants were identified. However all the variations were also present in unaffected control.

This is the first report analysing SLC4A11 gene in a larger series of Indian patients having FECD. Merely silent changes, which showed statistically insignificant association with FECD, were identified. These results suggest that SLC4A11 gene may not be responsible for FECD in patients examined in this study.

Association studies on diabetic retinopathy with type 2 diabetes in South Indian population

Principal investigator : P. Sundaresan, AMRF-Madurai
Co-investigator : P. Namperumalsamy, Aravind-Madurai
: R. Kim, Aravind-Madurai
: Anand Rajendran, Aravind-Madurai
Collaborator : J. Fielding Hejtmancik, NEI/NIH, Bethesda, USA
Research scholar : B. Suganthalakshmi
Funded by : TIFAC-CORE in DR, CSIR and NIH Visiting Fellowship, NIH,
Bethesda, Maryland, USA

The aim of the study was to evaluate SNPs in ten candidate genes, including the RAGE, PEDF or SERPINF1, AKR1B1, EPO, ICAM-1, HFE, EDN1, HTRA1, (previously reported) CFH and ARMS2 were chosen to investigate whether alleles or genotypes of these markers are associated with DR in an Indian population. The possibility of association between polymorphisms of ten genes and DR was examined by genotyping 15 single nucleotide polymorphisms and one dinucleotide repeat polymorphism in 211 diabetes patients with retinopathy (DR) and 237 diabetes patients without retinopathy (DNR). The genes which showed positive association in this screening set were tested further in additional sets of 134 DR and 122 DNR patients. Among the ten loci (16 polymorphisms) screened, SNP rs2070600 (G82S) in the RAGE gene, showed significant association with DR (allelic $P = 0.006$), compared to DNR, including the genotypes (GG, $P=0.006$; GA, $P=0.009$), with the GG genotype OR being 2.25 (95% CI-1.23-4.12). SNP rs2070600 further showed significant association with DR ($P=0.002$) when the sample size was increased by adding the confirmation cohort (allelic $P < 0.01$). In HTRA1, rs11200638 (G>A), showed marginal significance with DR ($P=0.04$). No statistical significance was observed for SNPs in the other eight genes studied.



Genetic analysis for Polymorphism screening

This is the first report analysing the polymorphisms in PEDF, EPO, ICAM-1, HFE, EDN1, HTRA1, CFH and ARMS2 gene in large number of samples for DR case control association study in Indian population.

Genetic and functional dissection of FOXL2 gene involved in the pathogenesis of the Blepharophimosis Syndrome (BPES)

Principal investigator : P. Sundaresan, AMRF-Madurai
Co-investigator : Usha Kim, Aravind-Madurai
Collaborator : Reiner Albert VEITIA, Paris
Research scholar : C. Jayashree
Funded by : Indian Council of Medical Research
Duration : 2008 - 2010

25 BPES affected families and a total of 100 age matched controls were recruited for the genetic study. Among 25 BPES affected cases collected, 12 cases are familial and 13 are sporadic. In these, 4 reported mutations Y91X, S217C, A179G, A224_A234dup and three novel mutations W98R, L108P, A228_A232dup in familial cases and three novel and two reported mutations from sporadic cases were identified using ABI 3130 genetic analyser.

Two novel mutations (p.Leu108Pro, p.Ala253fs) and one reported mutation (p.Ser217Cys) were taken for functional analysis.

To assess the effect of mutations, the transiently transfected wild type and missense (S217C, L108P), frame shift (p.A253fsX272) mutants were fused with plasmid containing green fluorescent protein (GFP) in COS-7 cells. Wild type FOXL2 localises completely to the nucleus in almost all cells. In the case of L108P mutant, it produces 47% nuclear aggregates and 51% of cytoplasmic aggregates in the localisation study. Another missense mutant S217C was mislocalised in cytoplasm. In the (p.A253fsX272) 5bp out frame mutant shows that a fusion protein is indeed produced and observed as 14% cytoplasmic decoration. These findings suggest that impaired protein is unable to accomplish a normal function.



DNA sequencing using ABI 3130 Genetic Analyser

Identification of genetic defects occurring in Indian oculocutaneous (OCA) and ocular albinism (OA) families

Principal investigator : P. Sundaresan, AMRF-Madurai
Co-investigator : P. Vijayalakshmi, Aravind-Madurai
Asim Kumar Sil, Vivekananda Mission Ashram Netra Niramay Niketan,
West Bengal
Research scholar : K. Renugadevi
Funded by : Department of Biotechnology, New Delhi
Duration : 2006 - 2009

While the previous study for mutations in all the known TYR, P, TYRP1, MATP and GPR 143 candidate genes screened twenty three familial cases, the present study aims to screen for the sporadic cases in OCA and OA.

Large panels of sporadic samples were collected from 60 different families in southern and eastern part of Indian cohort. One hundred normal individuals without any ocular anomalies were recruited as a control to confirm the sequence pattern of the novel mutations or polymorphisms



Sample preparation for sequencing reactions

which were identified in the study cases. Genomic DNA was isolated from peripheral blood leukocytes and used as a template for Polymerase Chain Reactions. Mutations in exon-intron boundaries and exonic regions were analysed by bi-directional sequencing using ABI 3130 genetic analyzer. Screening of TYR gene in these sporadic cases revealed the previously reported Arg278X, Arg299His, Gly419Arg, Gln326X, Asp383Asn, Arg402X, c.1379del2bp (TT) mutations and Asp125Asn, Tyr192Ser, Arg402Gln SNPs.

The following SNPs were identified in other candidate genes: OCA2 gene - one novel SNP IVSXX+4A/G; TYRP1 gene - one reported SNP Arg87Arg; MATP gene - three reported SNPs-Thr 329Thr, Leu374Phe, rs45552240-3'UTR and GPR143 gene, one reported SNP - IVS6+10C/G. Among these candidate genes, TYR gene mutations were observed in most of the sporadic cases. Therefore results suggest that prevalence of OCA type 1 is higher than the other OCA types in Indian cohort.

Molecular genetics of keratoconus

Principal investigator : P. Sundaresan, AMRF-Madurai
Co-investigator : M. Srinivasan, Aravind-Madurai
Manoranjan Das, Aravind-Madurai
Research scholar : P. Mohanapriya
Funded by : ALCON - Aravind Eye Care System
Duration : 2008 - 2011

Keratoconus is a bilateral, non-inflammatory, chronic and asymmetric thinning disorder of the cornea that leads to progressive myopic and irregular astigmatism.

Visual system homeobox gene (VSX1), which is expressed in developing cornea, is known to be associated with keratoconus. Therefore, the main objective of the study is to screen for the mutations in the VSX1 gene. So far, 100 patients with clinically diagnosed keratoconus, 100 age matched controls were recruited for the study. Genomic DNA was isolated from peripheral blood leukocytes. Entire coding regions of VSX1 gene were screened for mutations in 26 keratoconus patients and 5 controls by bidirectional sequencing using ABI 3130 genetic analyzer.

Among 26 samples screened, two reported SNPs, rs12480307 (A/G) in exon 3 and rs6138482 (G/A) in intron 3 have been identified. One variation IVS3-23C>T has also identified in one sample, which needs to be confirmed by screening more number of samples. We are in the process of screening the remaining samples to identify the possibility of association of these polymorphisms and keratoconus in our population.

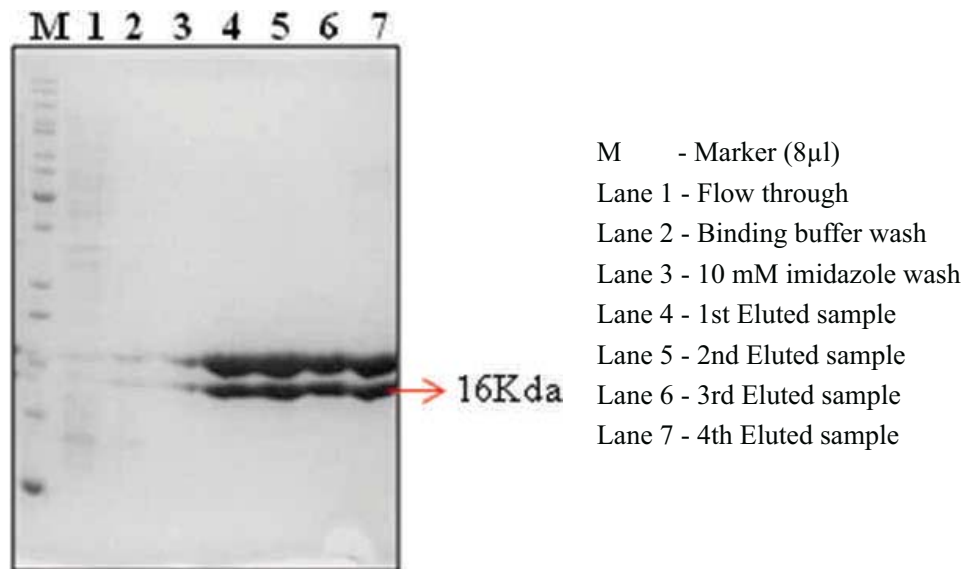
Biophysical characterisation of human myocilin and glaucoma database

Principal investigator : S. Krishnaswamy, Madurai Kamaraj University, Madurai
Co-investigator : P. Sundaresan, AMRF-Madurai
S. R. Krishnadas, Aravind-Madurai
Research scholars : Prasanthi N, Eswari P.J, Rangachari K
Funded by : Department of Biotechnology, New Delhi
Duration : 2006 - 2009

The importance of the present study is to characterise human myocilin protein (55 kDa mol wt, 504aa, Swissprot Q99972) encoded by MYOC gene, which is directly linked to both juvenile and primary open-angle glaucomas.

To study the structural features of myocilin, the C-terminal deleted myocilin (CTD-Myoc) was constructed and expressed by using pET20b (Expression Vector) with presence of pelB (signal peptide) region in Rosetta DE3 pLysS. The results showed two types of protein population, one with pelB and one without pelB region, which may be responsible for mis-cleavage expression product.

C-terminal deleted myocilin protein with pelB region



C-terminal (192-496 residues) without pelB region was expressed in Rosetta DE3 pLysS which produced monomeric protein. The monomeric protein was purified using affinity chromatography and anion exchange chromatography. Secondary structure of C-terminal domain was analysed using CD spectrum.

Glaucoma database

Primary open angle glaucoma is caused by mutation in any one of the candidate genes namely MYOC, OPTN and WDR36. A database has been developed to store and maintain the SNP information related to candidate genes, associated genes that arise from different experiments and also meant to provide an interface for understanding glaucoma at the molecular level. This is created using MYSQL and Perl program is used to fetch the required data from MYSQL. The database is available at bicmku.in:8081/glaucomadb.

Future studies involve the aggregation and crystallographic characterisation of the C6H-Myoc and the deletion mutants.

Screening of LOXL1 gene mutations in exfoliation glaucoma patients

Principal investigator : P. Sundaresan, AMRF-Madurai
Co-investigators : S.R. Krishnadas, Aravind-Madurai
G. Haripriya, Aravind-Madurai
R. Sharmila, Aravind-Madurai
Research scholar : Sushil Kumar Dubey
Funded by : ALCON - Aravind Eye Care System
Duration : 2008 - 2011

Pseudoexfoliation syndrome (PXFS) is an age-related generalised disorder of extracellular matrix of eye and the leading cause of open angle glaucoma. PXFS is characterised by the rapid production and progressive accumulation of abnormal fibrillar material on the anterior segment of the eye. The risk of developing glaucoma is 5 to 10 times more common in eyes with PXFS than in those without it. Pseudoexfoliation syndrome leads not only to severe, chronic open angle glaucoma, but also to lens

subluxation, angle closure, blood-aqueous barrier impairment, and serious complications at the time of cataract extraction.

The objective of the study is to screen three lysyl oxidase like-1 (LOXL1) gene polymorphisms (allele T of rs2165241 in the first intron; allele G of rs1048661 (R141L) and allele G of rs3825942 (G153D) in exon 1) in South Indian patients with pseudoexfoliation syndrome (PXFS) and pseudoexfoliation glaucoma (PXFG). Three hundred patient samples (150 PXFS and 150 PXFG) and 225 age and sex matched control samples were collected from South Indian cohort. The PCR conditions were optimised for the region spanning the three SNPs of LOXL1 gene. Screening of two SNPs (rs1048661 and rs3825942) through restriction fragment length polymorphism and through bi-directional sequencing have been completed and screening of SNP rs2165241 is in progress. The study will determine the frequency of LOXL1 SNPs in individuals with PXFS and PXFG and identification of these genetic markers may allow early recognition of individuals at risk of glaucoma.

A genetic component to the INDEYE study of cataract and age-related macular degeneration in India

Principal investigator : Astrid E Fletcher, London School of Hygiene and Tropical Medicine (LSHTM), London
Co-investigator : D. Nitsch, L Smeeth, LSHTM, London
R. D. Ravindran, Aravind-Pondicherry
P. Sundaresan, AMRF-Madurai
Collaborator : AIIMS, New Delhi and LSHTM, London
Research scholar : Ashwini Shanker
Junior technicians : V. Saravanan, J. Radha
Funding agency : Wellcome Trust
Duration : 2008 - 2011

Aim of the project

- To investigate genetic variants as possible contributors to high rates of cataract in India, complementing the ongoing research on environmental factors being undertaken in the INDEYE study.
- To enrich the sample acquired in the INDEYE study of age related macular degeneration in India with cases from the same geographical location in order to achieve adequate power to test for disease associations in genetic studies.

Progress on the INDEYE genetic study

All the samples from the population based study have been processed in timely manner and DNA extracted (4040 from North India and 4215 from South India). Approximately 400 samples for the enriched case-collection for age-related macular degeneration are awaited. DNA stock was kept, whilst for high throughput genotyping a working stock was generated at calibrated DNA concentration. All the samples were diluted in Deep Well Plates by Semi Automatic Robotic Machine –epMotion 5070. Genotyping was carried out in an automated fashion in 384 well plates with a turn-around time of 7 working days for 1 single nucleotide polymorphism (SNP) to be assayed with Real time PCR and automated data output – thus establishing a high performance high throughput lab at high standards at Aravind Medical Research Foundation. So far large scale genotyping for CFH,



Reaction setup in 384 well plate for Real Time PCR analysis

EPHA2, LOC387715 / ARMS2 HTRA1 genes have been performed. Analyses are still ongoing. As preliminary results evidence was found for genetic variants in the EPHA2 region to be associated with age-related cataract in India, which is in line with previous findings in those of European descent.

Cataract genetics—role of EPHA2

There was a borderline association between rs7543472 TT and any form of cataract when compared to rs7543472 CC with an Odds Ratio (OR) of 1.31 with 95% confidence interval (0.97, 1.77); $p=0.074$. This association reflected mainly the association of rs7543472 TT with cortical cataract with OR 2.06 (1.14, 3.70); $p=0.015$ and posterior subcapsular cataract (PSC) with OR 1.73 (1.20, 2.51); $p=0.004$. There was weaker association of rs7543472 TT with nuclear cataract with OR 1.37 (1.01, 1.88); $p=0.045$. Thus, evidence was found for association of rs7543472 with age-related cataract in the Indian population, in particular for cortical and posterior sub-capsular forms.

Early stages of AMD in India

This is the first study to investigate whether the complement factor Y402H variant was associated with early age-related macular degeneration similar to what has been described for populations of European ancestry. There were 4772 participants aged 60 and above who had an eye examination including fundus photography. Of these 1276 (27%) had un-gradable fundus photographs mainly because of advanced cataract. Early AMD stage 1 (soft distinct drusen or pigmentary irregularities) was graded in 28%, and stage 2 in 4.9% (soft indistinct ($\geq 125\mu\text{m}$) or reticular drusen only or soft distinct drusen ($\geq 63\mu\text{m}$) with pigmentary irregularities). Late AMD was graded in 0.8% ($n=40$). Fundus grading used the Wisconsin Age-Related Maculopathy Grading System. 1862 had no signs of early or late AMD (AMD 0). Overall the genotype frequencies of Y402H were 48%, 42% and 10% for the common homozygote (TT), heterozygote (CT) and rare homozygote (CC), respectively, and were in Hardy-Weinberg equilibrium. Genotype frequencies were similar in controls and those with ungradable images. For early AMD Stage 1 the relative risk ratios, 95% confidence intervals and p for trend were 0.86 (0.75-1.00) and 0.95 (0.74-1.22) $p=0.3$ for CT and CC genotypes versus TT, respectively, for early AMD stage 2, 0.89 (0.70-1.14) and 0.78 (0.48-1.25) $p=0.3$ respectively, and for late AMD 1.70 (0.79-3.62) and 2.35 (0.81-6.76) $p=0.07$. These analyses were adjusted for age, sex, socioeconomic status, tobacco smoking and diabetes status and clustering by village. Hence, in contrast to what has been described for European populations, there was no evidence for an association between the Y402H risk genotype and early AMD in India. For late AMD the results suggest similar results to those in European populations but these are not conclusive due to the small number of late AMD cases.

Transcriptome and proteome analysis of ALR2 gene and its involvement in the pathogenesis of diabetic retinopathy

Principal investigator : P. Sundaresan, AMRF-Madurai
Co-investigator : Kim Ramasamy, Aravind-Madurai
Collaborators : G. Banuprakash Reddy, Nasreen Z. Ethesam, National Institute of Nutrition, Hyderabad
Research scholar : G. Gowthaman
Funded by : Department of Biotechnology
Duration : 2009 - 2012

Diabetic Retinopathy (DR) is the most common micro vascular complication of the retina due to diabetes mellitus and the leading cause of blindness worldwide. Diabetic retinopathy is multifactorial and its pathogenic mechanism remains unclear. One of the most important candidate gene is ALR2 (Aldose reductase), a rate limiting enzyme in Polyol pathway which gets activated at the hyperglycemic condition. The main objective is to study the molecular and functional aspects of ALR2 in pathogenesis of DR.

We have collected 82 samples from diabetic patients without retinopathy and 102 samples from proliferative diabetic retinopathy. Seven field fundus photography and biochemical tests like blood

sugar, HbA1C, blood urea, serum creatinine and total cholesterol has been done for all collected samples. Bi-directional sequencing was performed to detect the variations in the ALR promoter region for 100 samples and identified three novel mutations.

Parallel red blood cell samples were also collected for the above patients and controls. Bio chemical analysis of RBC is being carried out in National Institute of Nutrition, Hyderabad to determine the ALR2 and SDH (Sorbitol De Hydrogenase) activities.

Molecular mechanism of neovascularisation in proliferative diabetic retinopathy and Eales' disease

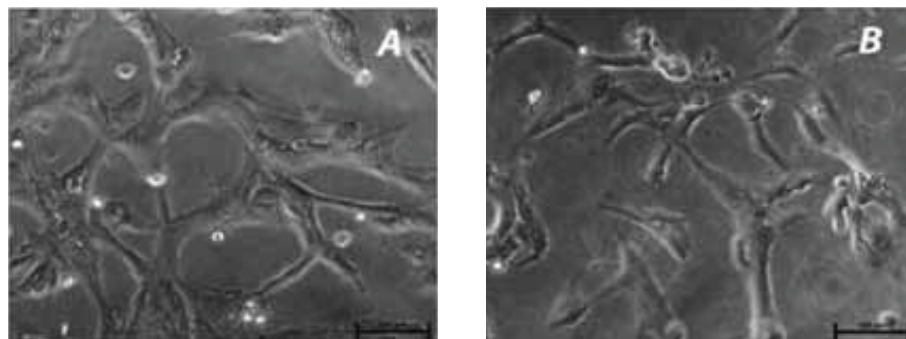
Investigators : Alan Stitt, Centre for Vision and Vascular Sciences, Queens University, Belfast, UK.
: VR. Muthukkaruppan, AMRF-Madurai
: D. Shukla, Aravind-Madurai
: R. Kim, Aravind-Madurai
: P. Namperumalsamy, Aravind-Madurai
Research scholar : P. Murugeswari
Duration : 2009 - 2010
Funded by : Commonwealth Split-Site Scholarship, TIFAC-CORE in Diabetic Retinopathy and Department of Science and Technology

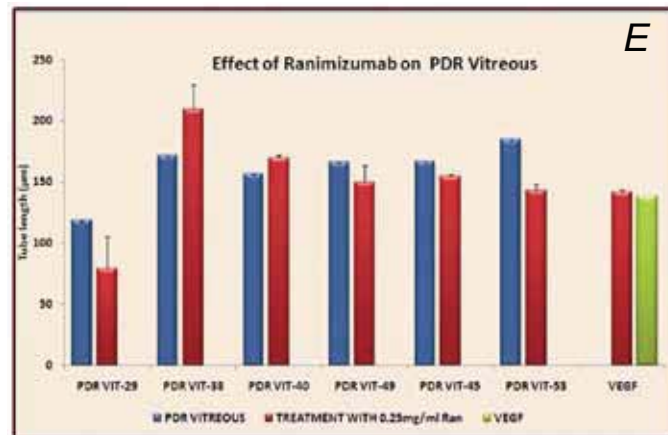
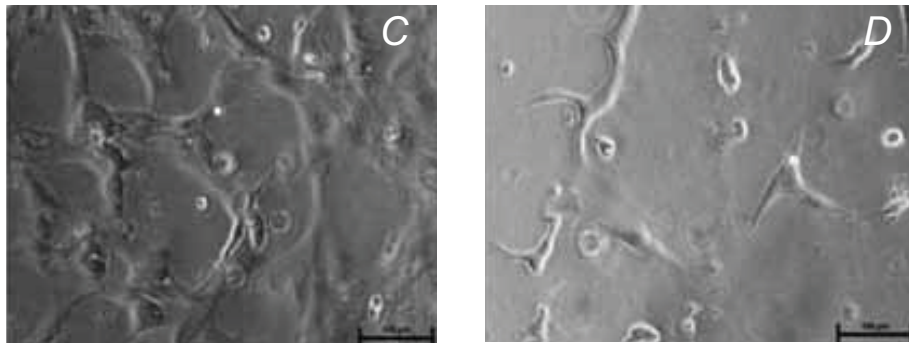
There is an increasing emphasis on inflammatory processes in the aetiology and mechanism of diabetic retinopathy (DR). Eales' Disease (ED) is an overt inflammatory eye disease that can result in retinal neovascularisation. This study determined the effect of anti-VEGF (Ranibizumab) antibody in secretion of cytokines in vitro by ARPE-19 cells (human retinal pigment epithelial cell line). ARPE-19 cells were treated with Ranibizumab and/or IL6 neutralising antibody for 24 hours and the supernatants were quantified for various cytokines by Cytokine Biochip Array (Randox, UK) and ELISA.

In addition, this study characterised in vitro the angiogenic potential of vitreous from DR (n=9), ED (n=5) and Macular Hole (MH)(n=5), with known concentrations of various cytokines (IL-6, IL-8, MCP-1) and growth factor (VEGF). Tubulogenesis assay was performed using Human Dermal Microvascular Endothelial cells (HDMECs) and tube length was quantified using Nikon-NIS-Elements software.

In addition to the anticipated reduction in VEGF, Ranibizumab treatment reduced the secretion of Pro-inflammatory cytokines (IL-6, IL-2, and MCP-1; $P < 0.001$) by ARPE-19 cells. PDR and ED vitreous showed significant ability to induce tube formation, compared with the untreated controls ($p < 0.05$; $p < 0.01$). Angiogenic capacity of vitreous samples were neutralised, when mixed with Ranibizumab (0.25mg/ml) or anti-IL6 (0.1ug/ml), (mean fold decrease ranging from 0.2 to 1.2) - (Figure 1 and 2).

This study indicates that in addition to VEGF, inflammatory cytokines (IL6 and MCP-1) also play a central role in inducing retinal neovascularisation in PDR and ED. The angiogenic ability of PDR/ED vitreous is neutralised by anti-VEGF or anti-IL-6 antibody.





- A. Representative image of Human Dermal Microvascular Endothelial Cells cultured on Matrigel and exposed to PDR vitreous for 48 hours, showing the formation vascular capillary like tubes
- B. Addition of ranibizumab with the PDR vitreous reduced the tube formation
- C. HDMEC culture exposed to ED vitreous for 48 hours
- D. Addition of ranibizumab with the ED vitreous
- E. Quantification of tube length induced by PDR vitreous and its reduction after treatment with Ranimizumab

Topical kinetics of voriconazole (1% & 0.1%) in humans

Principal investigator : S. Senthilkumari, AMRF-Madurai
 Co-investigator : N. Venkatesh Prajna, Aravind-Madurai
 Lalitha Prajna, Aravind-Madurai
 Haripriya Aravind, Aravind-Madurai
 Collaborator : T. Velpandian, Dr. R. P. Centre, AIIMS
 Source of funding : Champalimaud-AMRF Research Grant (# 25B)
 Duration : One year (January 2009 – 2010)

Voriconazole (VZ) is a new broad-spectrum antifungal agent reported to have good intraocular penetration following oral, systemic and topical administration. However, single dose kinetics of topical voriconazole is lacking which is essential to design the dosing regimen for the management of sight-threatening fungal keratitis. Therefore, the present study was undertaken with the following objectives.

The objectives of the present study are

1. To evaluate single dose kinetics of VZ in humans
2. To optimise multiple dosing in rabbit model
3. To evaluate the stability of 0.1% VZ by tandem mass spectroscopy

In the present study single dose ocular kinetics of topical VZ in humans as well as single and multiple dosing in rabbits were evaluated at different time intervals. The stability of the reconstituted

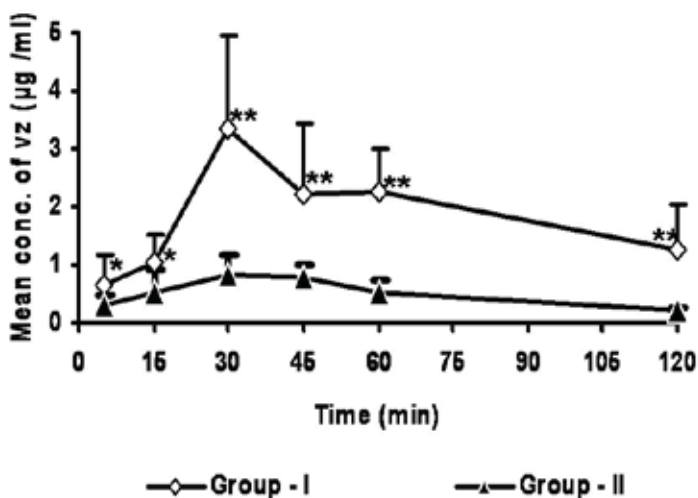


Fig 1: Mean aqueous conc. of VZ - time profile in humans

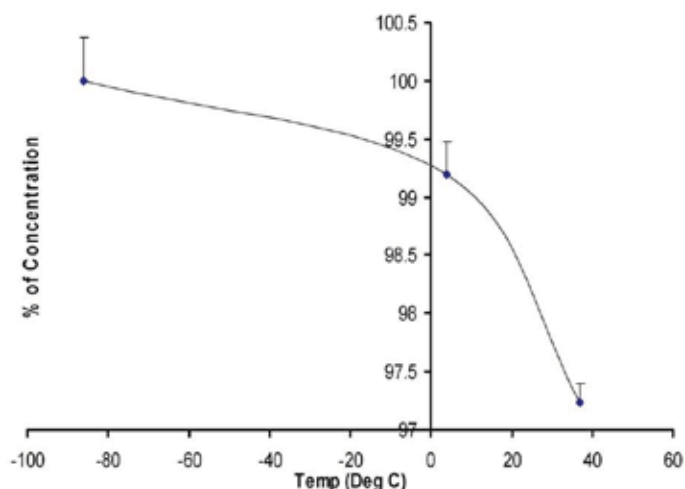


Fig 2: Stability of 0.1% VZ at different temperatures

formulation was also evaluated. Objective 1 was conducted at Department of Ocular Pharmacology, AMRF and the other two objectives were carried out in association with Dr. T. Velpandian, Dr. R. P. Centre, AIIMS, New Delhi. For single dose human ocular kinetics of topical VZ, 119 patients undergoing cataract surgery were divided into two groups viz. group I and group II. A single drop of 1% and 0.1% topical VZ were received by group I and group II patients respectively and aqueous humor was collected at different time intervals. In another experiment, New Zealand albino rabbits were used for both single dose and multidose ocular kinetics of topical VZ.

Single dose ocular kinetics of 1% VZ in humans showed a maximum mean aqueous concentration of 3.333 +/- 1.61 µg/ml in 30 min whereas 0.1% showed maximum mean aqueous concentration of 0.817 +/- 0.36 µg/ml. The achieved aqueous concentration after single drop of 1% VZ is sufficient enough to reach the MIC 90 of most of the causative organisms.

The reconstituted VZ formulations were stable at -86° C and 4° C for 30 days with a maximum degradation of 3% observed in the formulations incubated at 37° C.

Conclusion

Single dose topical kinetics of VZ (1% and 0.1%) in humans was elucidated. Multidose kinetics at 1 hour interval showed better aq .conc (above 2µg/ml) à meeting MIC 90 for all organisms. Frequency of instillation may be designed for “every 1 hour regimen” to maintain the therapeutic concentration above 2µg / ml in the aqueous humour for the successful therapy.

Evaluating the relationship between Pharmacokinetics (PK) and efficacy of Methotrexate (MTX) in patients with non-infectious uveitis

Principal investigator : S. Senthilkumari, AMRF-Madurai
 Co-investigator : S. R. Rathinam, Aravind-Madurai
 Project assistant : J. Thilagavathi
 Duration : Two years
 Source of funding : AMRF, Madurai

Low dose Methotrexate (MTX) is very effective in the treatment of chronic non-infectious uveitis and may be used as a glucocorticoid- sparing therapeutic drug. In most cases, it is reported to be safe and

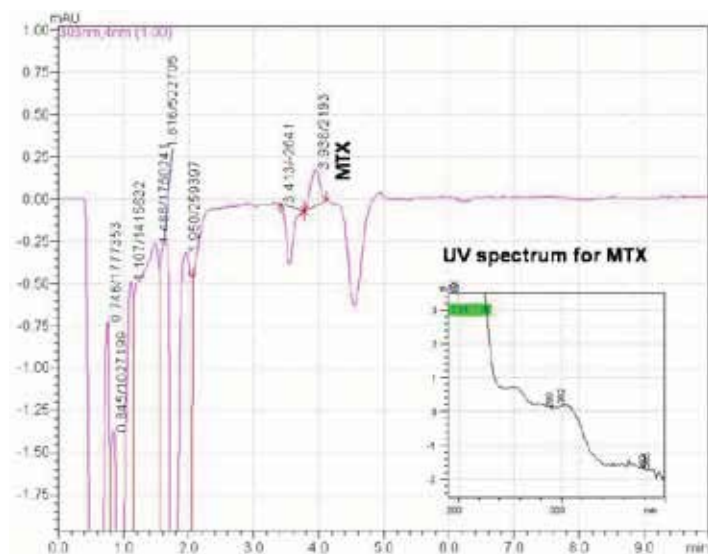
well tolerated by children and older patients with uveitis. However, pharmacokinetic guided dosing regimen is not established yet in patients with noninfectious uveitis. Therefore, the present study is undertaken and this study may offer guidance for optimising dosing regimen for individual patients and diminish side effects with better clinical efficacy.

The objectives of the present study are

- To optimise a very sensitive HPLC method for the quantification of methotrexate (MTX) in biological fluids.
- To analyse the trough plasma levels (C0) of MTX in uveitis patients receiving oral MTX.
- To evaluate the clinical efficacy of MTX by using parameters like vitreous haze, presence or absence of anterior chamber cells and visual acuity.
- To correlate the relationship between the trough plasma levels and efficacy of MTX in patients receiving oral MTX.

A sensitive HPLC method was developed for measuring the MTX concentration in biological fluids using Shimadzu HPLC system with PDA detector. The analytical separation was achieved with mobile phase consisting of Tris phosphate buffer (pH 5.7): ACN (94:6) in the ratio of 94:6 v/v which

was pumped at the flow rate of 1ml/min into RP-18 Purosphere Star column (150X4.6 mm; 3µm). The quantification of MTX was carried out at 303nm.



In order to optimize the extraction protocol for estimating MTX in plasma, blood samples were collected from patients who were attending the Uvea Clinic of Aravind Eye Hospital after getting their written consent. Plasma was separated and MTX was extracted by treating with double the volume of 10%TCA, vortexed and centrifuged at 10,000rpm for 10 mins. The resulting supernatant was vacuum concentrated at 40°C for 3 hours.

The residue was reconstituted by adding 100µl of tris: ACN (9:1) and injected into HPLC column. Representative chromatogram showing the separation of MTX in patient plasma sample is shown above. The LOD was found to be 30 ng/ml and LOQ was found to be 60 ng/ml. The recovery of the MTX was found to be 80-90%.

Pathogenesis and molecular mechanism of age-related macular degeneration

- Principal investigator : VR. Muthukkaruppan, AMRF-Madurai
 Co-investigators : Anand Rajendran, Aravind-Madurai
 T. Amala RajaSundari, Post Doctoral Fellow, AMRF-Madurai
 Collaboration : Centre for Vision and Vascular Science Queen’s University, Belfast, UK
 Research scholar : S.Sudha Priya, M. Minu Jenifer
 Funded by : AMRF

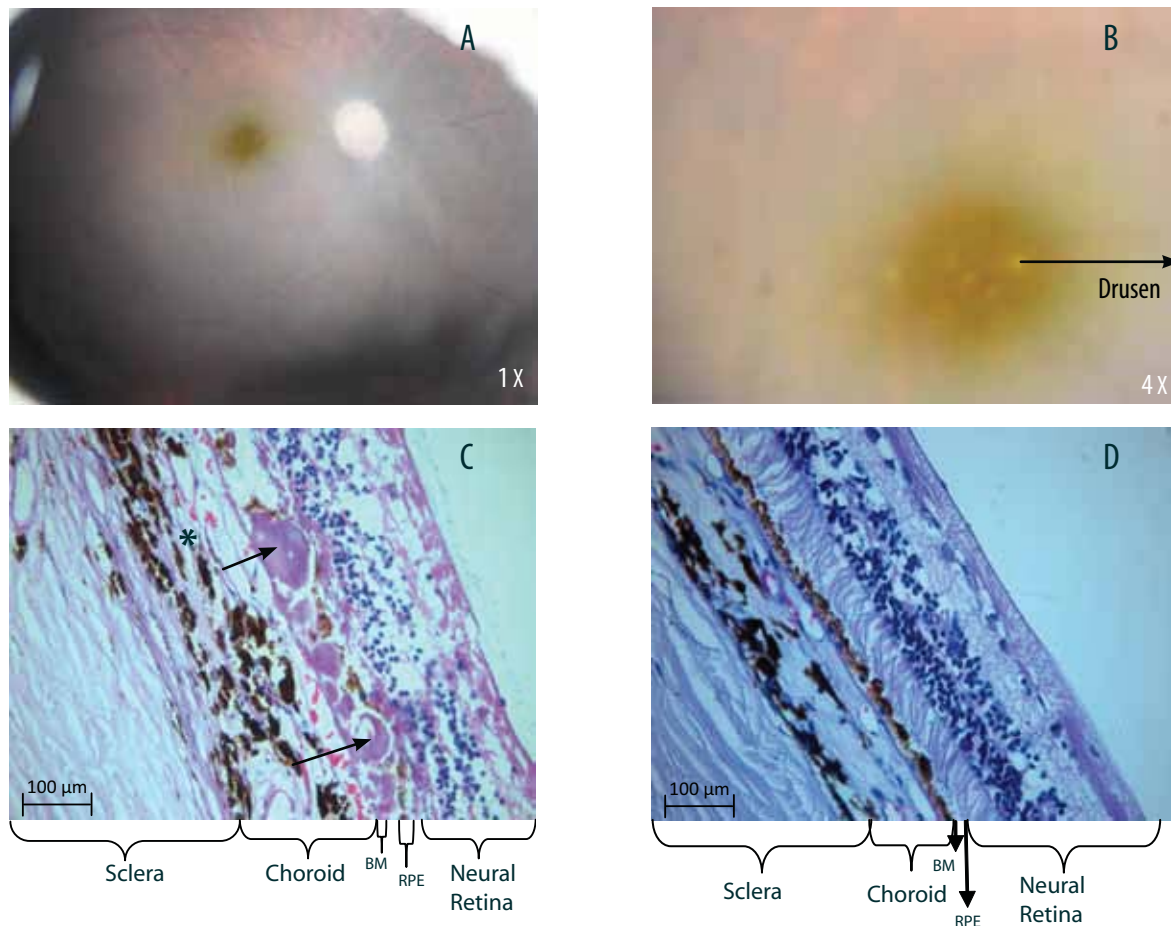
Age-related macular degeneration is a late-onset, complex disorder of the eye with a multi-factorial etiology in elderly people. It results in progressive and irreversible loss of central vision affecting the macula of the eye and involves the Retinal Pigment Epithelium (RPE), Bruch’s Membrane (BM) and choriocapillaries. It is the third leading cause of blindness worldwide. In India, the prevalence ranges between 1.4% – 1.8% above the age of 40 years in different epidemiological studies. It is estimated that by the year 2020, at least 80 million people will be affected by AMD globally.

The clinical features of AMD are the hard and soft drusen formation in the early stages, and geographical atrophy, RPE detachment, choroidal neovascularization and disciform scarring in later stages. The histopathological studies showed two distinct types of deposition such as basal laminar (BLamD) and basal linear (BLinD) deposits. There is also an involvement of macrophages in choroidal neovascular membrane including increased VEGF expression. Autoantibodies with the ability to react with several antigens in retinal tissues have been reported, indicating their involvement in AMD pathogenesis.

The objectives of our present study are:

1. To identify the AMD changes in the donor eyes using histopathology and immunohistochemistry
2. To evaluate the role of autoantibodies in the pathogenesis of AMD, and
3. To elucidate the mRNA profile of several factors (IL-6, VEGF, TNF- α , PEDF etc) in RPE /choroid of AMD donor eyes.

So far 146 eyes from 76 donors (15 to 93 years of age) from Rotary Aravind International Eye bank have been examined for AMD changes in the macula using the stereo dissection microscope with fiber optics lighting. Among them four donor eyes showed the AMD-like phenotypic changes, such as soft drusen, and geographical atrophy. By histopathological examination, one of the donor eyes (75 years) was confirmed as the early AMD phenotype, based on the Alabama age-related macular degeneration grading system for donor eyes (Fig. 1).



*Fig. 1 Donor eye aged 75 years showing early AMD phenotype with drusen. Photograph taken with epi-illumination at A) 1X, B) 4X magnification and C) Histopathological section of macular region. Arrows showing soft drusen with indistinct boundary, located between retinal pigment epithelium (RPE) and Bruch's membrane (BM). Note: Mild disorganization and reduced pigments in RPE. D) Histological section of macular region of 81 year donor; showing normal features. **RPE- Retinal Pigment Epithelium, *- Choriocapillary***

The mRNA expression profile was analysed using the RPE/choroid of donor eyes; RNA was isolated using RNeasy mini kit, Qiagen. The cDNA was prepared using Super Script™ III First-Strand System, Invitrogen and the converted cDNA was subjected to real time PCR using SYBR Green master-mix for Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) - a housekeeping gene, Interleukin-6 (IL-6) and Vascular Endothelial Growth Factor (VEGF). Simultaneously, retinal pigment epithelial cells (ARPE19 cell line) were used for standardisation of methods. The quantity of RNA extracted from the donor RPE/choroid was less when compared to ARPE19 cells, however it was sufficient for the molecular analysis. The amplification plot obtained for the ARPE-19 cells for IL-6, VEGF and GAPDH is shown in Fig 2a, 2b and 2C. In donor RPE/choroid sample (67 yrs), the amplification plot for GAPDH, IL-6 and VEGF was found at late cycle compared to ARPE 19 cells (Table 1). Further studies are underway to elucidate the mRNA profile of RPE/choroid of donor eyes.

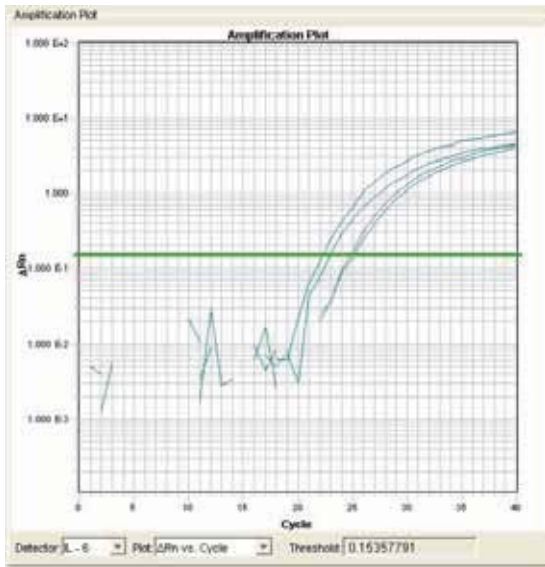


Fig 2a: ARPE19 cell line showing the amplification plot for IL-6 gene

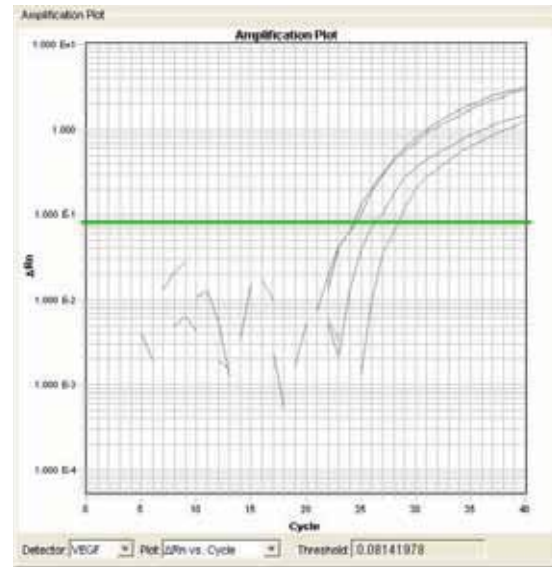


Fig 2b: ARPE19 cell line showing the amplification plot for VEGF gene

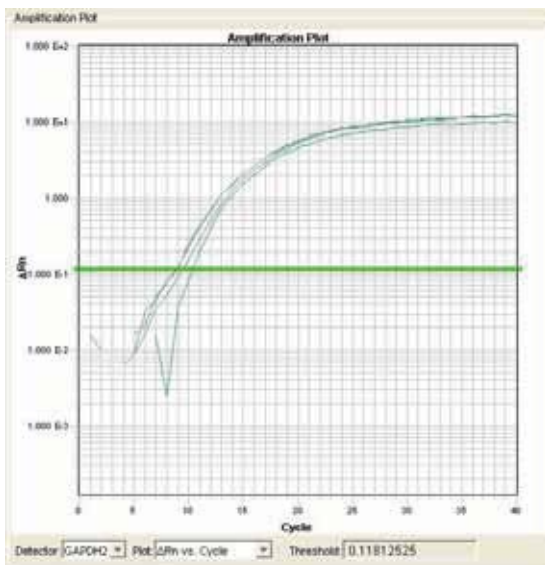


Fig 2c: ARPE19 cell line showing the amplification plot for GAPDH gene

Table 1: Threshold Cycle (Ct) value of the genes expressed in RPE/Choroid of the donor eye & ARPE 19 cells

Sample	Ct Value		
	GAPDH	IL-6	VEGF
ARPE 19	9.6	22.6	24.3
RPE / Choroid (67 yrs)	24.9	26.9	34.9

Corneal surface reconstruction using cultured human limbal epithelial cells

Principal investigator : Gowri Priya Chidambaranathan, AMRF - Madurai
Co-investigator : M. Srinivasan, Aravind-Madurai
N. Venkatesh Prajna, Aravind-Madurai
VR. Muthukkaruppan, AMRF-Madurai
Research scholar : T. Lalitha
Funded by : Aravind Eye Hospital
Duration : 2009

To treat unilateral Limbal Stem Cell Deficient (LSCD) patients, autologous limbal biopsy from the contralateral eye was cultured as explant cultures for 12-15 days. A ten-fold increase in the stem cell content after culturing was established by 2-parameter analysis of native and cultured epithelium. Such *ex vivo* expanded epithelial sheet was transplanted onto the affected cornea of 11 unilateral LSCD patients for corneal surface reconstruction during 2009-2010. Success of transplantation was defined as anatomical (clear cornea, reduction in blood vessels and conjunctivalisation) and/or visual improvement (improvement of at least three lines in Snellen's visual acuity measurement). Of the total 23 patients so far recruited in this study, six had both visual and anatomical improvement, five had anatomical improvement alone, five were lost to follow up and the remaining 7 showed no improvement.

Developing xenobiotic-free culture conditions to generate stem-cell rich epithelium for corneal surface reconstruction

Investigators : Gowri Priya Chidambaranathan, AMRF-Madurai
VR. Muthukkaruppan, AMRF-Madurai
N. Venkatesh Prajna, Aravind-Madurai
Usha Kim, Aravind-Madurai
Research scholars : S. Jeyalakshmi, T. Lalitha
Duration : 2008 - 2011
Funded By : ALCON Anterior Segment Research Grant

Corneal surface reconstruction using cultured epithelial sheets involves the use of various xenobiotic substances like-growth-arrested murine fibroblast (3T3) as feeder layer, human amniotic membrane (HAM) and medium supplements like fetal bovine serum (FBS) and cholera toxin. With growing concerns regarding the potential transmission of adventitious agents such as prions and animal viruses, this study aims to culture cells for human transplantation under xenobiotic-free conditions.

We have already established that the use of autologous serum instead of FBS and human limbal fibroblast in place of 3T3, is equally efficient for expansion of stem cells. We have now demonstrated the efficacy of a functional equivalent of cholera toxin based on colony forming efficiency (CFE). The percentage of CFE was significantly higher (4.05%) in cultures with this new compound than in its absence (0.97%). Further studies on the use of certified reagents for media preparation and identification of alternate substrates like fibrin gel/contact lens are now being carried out.

In addition, we have established the infrastructure for good manufacturing practice (GMP), which will be used for *ex vivo* expansion of stem cells for corneal surface reconstruction.

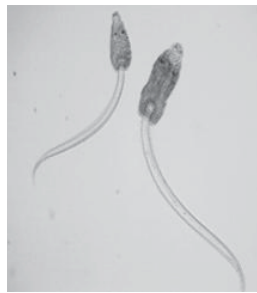
Etiology and immunopathogenesis of presumed trematode induced uveitis

Principal investigator : S.R. Rathinam, Aravind-Madurai
Co-investigator : Lalitha Prajna, AMRF-Madurai
Collaborator : Veena Tandon - North Eastern Hill University, Shillong, India
Duration : 2008 - 2011
Funded by : ALCON – AMRF Fellowship
Research scholar : Lalan Kumar Arya

Uveitis due to trematode infection was identified by the presence of tegument of trematode in the sub-conjunctival scleral nodule in children who were exposed to village pond or river water in various districts of Tamilnadu and Kerala (Am Academy of Ophthalmology, 2001 and Am J Ophthalmology, 2002). In order to confirm the etiology of the disease in relation to environmental source, snails were collected from village ponds to obtain cercaria. Anterior chamber granuloma, sub-conjunctival granuloma and AC fluid were collected from 24 patients treated in Aravind Eye Hospital, Madurai. By using the universal primer specific for trematodes, we have carried out PCR followed by molecular sequencing and BLAST analysis. Preliminary studies established the identity of the environmental cercaria, using calf liver cercaria as positive control. Further, this study will be extended to the immunopathogenesis of the trematode induced uveitis to understand the host immune response against the disease progression.



Subconjunctival granuloma



Environmental cercaria



PCR product of environmental cercaria DNA with F.gigantica (positive control)

Cytokine profile in aqueous humor of parasitic granuloma

Principal investigator : Gowri Priya Chidambaranathan, AMRF-Madurai
 Co-investigators : SR. Rathinam, Aravind-Madurai
 VR. Muthukkaruppan, AMRF-Madurai
 Duration : 2008 - 2011
 Research scholar : Merlin Premalatha
 Funded by : ALCON Anterior Segment Research Grant

Granulomatous anterior uveitis caused by a water-borne trematode accounts for one third of the paediatric uveitis cases (Am. J. Ophthalmology, 2002). In order to understand the associated pathogenesis, the profile of infiltrating cells and cytokines in the aqueous humor (AH) was studied in trematode-induced granulomatous uveitis patients.

After getting informed consent, AH was collected from 12 trematode-induced granulomatous uveitis patients, 10 Fuch's heterochromic uveitis patients, 5 lens induced uveitis patients, and 10 cataract patients. Analysis of AH from trematode-induced granulomatous uveitis patients by Giemsa staining revealed the presence of eosinophils, a characteristic of parasitic infection. On the other hand, in lens induced uveitis macrophages were observed (Table 1) in addition to other cell types. In Fuch's heterochromic uveitis, infiltrating cells were too small in number to be counted and they were totally absent in AH of cataract controls.

Cytometric bead array was used to estimate Th1/Th2 cytokines (IL-2, IL-4, IL-6, IL-10, TNF- α , and IFN- γ) in AH and serum (5 samples/group) by flow cytometry. The signatory Th1 cytokine IFN- γ along with IL-6 and IL-10 were higher in both trematode induced and lens induced uveitis patients compared to Fuch's uveitis and cataract controls (Table 2). Further studies are being carried out to understand whether these cytokines are responsible for the formation of granuloma or in the clearance of trematode. Understanding the pathogenesis will help in the initiation of accurate treatment.

Table: 1 Profile of infiltrating cells (%mean \pm SD) in the aqueous humor of Trematode-induced uveitis and Lens-induced uveitis patients

Diagnosis (No. of Cases)	Lymphocytes	Monocytes	Neutrophils	Eosinophils	Macrophages
Trematode-induced Uveitis (12)	41.91 \pm 20.07	8 \pm 9.36	38 \pm 24.70	12.08 \pm 24.87	0
Lens-induced Uveitis (6)	33.5 \pm 30.5	4.5 \pm 4.8	55 \pm 41.25	0	7 \pm 15.27

Table: 2 Cytokine profile in the AH of Trematode induced uveitis patients and control

Diagnosis	Concentration (pg/ml) – Median (Minimum, Maximum)					
	IFN- γ	TNF α	IL 10	IL 6	IL 4	IL 2
Trematode-induced uveitis (5)	2 (0, 25.6)	0	3.5 (0,50.5)	858.7 (4.3, >5000)	0 (1.8, 2.7)	0
Lens induced uveitis (5)	2.1(0, 9.4)	0 (0,2.2)	10.8 (2.9, 199.2)	2272.3 (2272.3,>5000)	2.1 (0, 2.8)	0 (0, 1.4)
Fuch's heterochromic uveitis (5)	0	0	0	93 (6.2, 147.3)	0	0
Cataract (5)	0	0	0	1.8 (1.7,472.5)	0	0



Cytokine analysis using Flow Cytometer

Antigenic mimicry between leptospiral and human lens proteins

Principal investigator : Gowri Priya Chidambaranathan, AMRF-Madurai
Co-investigator : SR. Rathinam, Aravind-Madurai
VR. Muthukkaruppan, AMRF-Madurai
Research scholar : Merlin Premalatha
Duration : 2008 - 2011
Funded by : ALCON Anterior Segment Research Grant

Development of cataract in young patients is one of the important anterior segment findings in leptospiral uveitis. In horses, antigenic mimicry between leptospiral proteins and cornea/lens proteins has been suggested as a possible cause for recurrent uveitis. Hence the objectives of this study are to identify cross-reacting proteins between leptospiral and human lens antigens by *in-silico* analysis and to experimentally confirm the antigenic mimicry between these proteins.

Serum samples were collected after getting informed consent from 29 leptospiral uveitis patients, 18 non-leptospiral uveitis patients, 18 age related cataract patients and 18 population controls. Lens protein was prepared from 21 – 30 year old donor eyes and leptospiral protein was prepared from Semarang patoc Patoc I.

Serum samples from leptospiral uveitis patients reacted with a 21kDa lens protein and a 36kDa leptospiral protein in Western blot analysis, while the control sera showed minimal reaction with these proteins. In addition, the whole proteome of human, retrieved from ExpASY Proteomics Server, Human Protein Initiative and the whole proteome of *Leptospira* from HAMAP –high quality automated and manual annotation of microbial proteomes was analysed for sequence similarity using FASTA software. The major hits were with house-keeping enzymes. However, on the basis of our result from Western blot analysis and a report on mimicry between leptospiral protein – LruA and equine α crystalline B, specific similarity search by *in-silico* analysis showed some identity. Further studies are being carried out to identify and characterise the proteins identified by Western blot using LC-MS/MS and also to verify whether they are cross-reactive.

International leptospirosis MAT proficiency testing scheme

Principal investigator : Gowri Priya Chidambaranathan
Co-investigator : S.R. Rathinam
Research scholar : Merlin Premalatha

Microscopic Agglutination Test (MAT) is the gold standard for serodiagnosis of leptospiral infection. Since the test involves the use of a panel of live leptospiral serovars to be used as antigens, quality assurance for the MAT is important. In order to improve the performance of the individual laboratories, the International Leptospirosis Society encourages all laboratories to participate in the International Leptospirosis MAT proficiency testing scheme, a collaborative project of the Royal Tropical Institute, Amsterdam, the County Hospital, Hereford, and the National Serology Reference Laboratory, Australia in Melbourne. The objectives of the scheme are (a) to evaluate the participants for the quality of their MAT testing, and (b) to encourage a general improvement in the performance of MAT testing and in leptospirosis diagnosis throughout the world.

Lyophilized coded serum panels are sent to participants annually. Samples are analysed using a panel of leptospiral serovars available in the participating centres and the results are submitted to the Proficiency testing scheme. After all results are received, participants receive a preliminary report, identifying the samples. Later they receive a comprehensive final report, comparing and analysing results from different laboratories. AMRF has been participating in this test from 2005 (Round 4) and has submitted the results for round 8 on February 22, 2010. This validation is more important for periodical quality testing of our laboratory since this test is used not only for research purpose but also as a service to other hospitals in and around Madurai for serodiagnosis of leptospiral infection–systemic / ocular. AMRF also get samples from Aravind satellite hospitals.

Molecular insights into the etiology of infectious uveitis

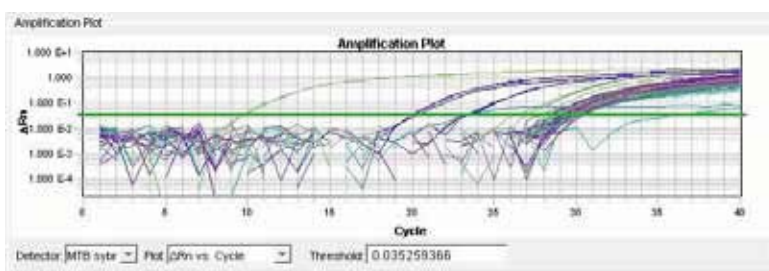
Principal investigator : Lalitha Prajna, Aravind-Madurai
Co-investigator : Rathinam Sivakumar, Aravind-Madurai
Research scholar : J. Cornelia Reena
Funding agency : Department of Biotechnology, New Delhi
Duration : 2008 - 2011

Uveitis, which involves infection and inflammation of the iris, ciliary body and the choroid of the eye, can cause debilitating pain and can lead to serious and permanent visual loss due to complication like cataract and glaucoma. Infectious uveitis occurs in greater frequency in developing countries from 11.9% to 50% of overall cases. The most common infectious etiologies are viruses like Herpes simplex, Varizella zoster and Cytomegalovirus, bacteria like Tryponema pallidum, *M. tuberculosis*, and leprosy and parasites like Toxoplasmosis. The laboratory diagnosis of these various etiologies is very important for exact treatment. Ocular fluids like vitreous and aqueous humor are analysed by gold standard techniques of culture, but this is time consuming and not sensitive due to very small volume of sample.

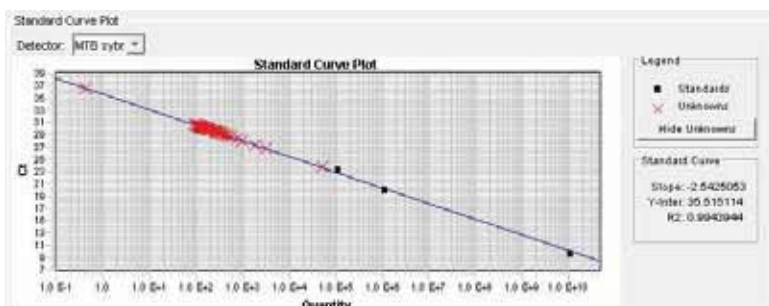
Molecular techniques like Polymerase Chain Reaction (PCR) can provide rapid as well as more accurate results in a short time. More recently the advent of Real Time PCR has come in practice and can be used for the specific diagnosis of various infectious agents causing Uveitis, and is more sensitive than the conventional PCR and the other advantages are that it can be used for determining the pathogenic load, gene expression and regulation and allelic discrimination in the samples. Other than the established causes of infectious Uveitis, novel infectious agents like Chikungunya and Dengue have been associated with Uveitis following wide spread epidemic outbreaks in the recent past. Diagnostic modalities for these and other infectious agents are also being explored. The objective of this study is to investigate the cause of infectious Uveitis and to confirm the etiology by molecular techniques like Real Time PCR and sequencing for identifying the organism and strain variations for bacterial, viral and parasitic causes. Phylogenetic analysis of the specific viruses and bacteria are also studied.

The Real Time PCR conditions were standardised for the *M. tuberculosis* and sixteen ocular fluid samples from clinically suspected cases were analysed. The nested PCR identified only seven cases of the *M. tuberculosis* infection, where as the Real Time PCR picked up four more cases additional. The sensitivity and specificity of the Real Time PCR was found to be 63% and 100% respectively.

The figure below is a representation of the standardisation and application of Real Time PCR for Mycobacterim tuberculosis.



Amplification plot of Mycobacterium tuberculosis samples



Standard curve plot for positive control

Characterisation and speciation of *Aspergillus* and *Fusarium* species from corneal ulcer

Principal investigator : Lalitha Prajna, Aravind-Madurai
Research scholar : J. Lakshmi Priya, AMRF-Madurai
Funding agency : Aravind Eye Hospital

Aspergillus sp and *Fusarium sp* are the most common fungal pathogens causing corneal ulcer. Conventional identification methods based on culturing and microscopy are time consuming and also not accurate in identifying species. In order to solve this issue, molecular techniques like PCR and sequencing have been developed to identify the different species. Identification of a pathogen at the species level will give us upper hand to develop specific treatment options, susceptibility testing with new antifungal drugs and for epidemiological purposes. The objective of this study is to characterise and speciate *Aspergillus* and *Fusarium* species human corneal ulcers. DNA was extracted from these fungal mycelia and amplified using universal fungal ITS (Internal Transcribed Spacer) PCR primers, which is followed by gene sequencing using the ABI 3130 genetic analyser and compared in the nucleotide database using BLAST to identify the species. The conditions for sequencing were standardised using ATCC culture of *A. flavus*, *A. fumigatus* and *Candida parapsilosis*. On analysing the twelve clinical fungal isolates by the conventional culture method, showed nine were *A. flavus* and three were identified as *Fusarium sp*. On sequencing the ITS region of these fungal isolates three out of the nine *A. flavus* were found to be *A. oryzae* and all the *Fusarium* isolates were identified as *F. solani*. Identification of the organism up to species level will be helpful for understanding the pathogen and also in studying the pathogenesis of fungal keratitis.

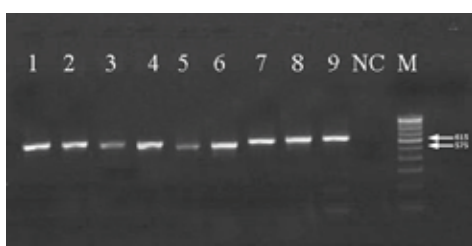


Figure 1. PCR Result of ITS region Lane 1-6: *A. flavus*. Lane 7-9 :*Fusarium sp*, NC : Negative control, M :Marker(100bp)

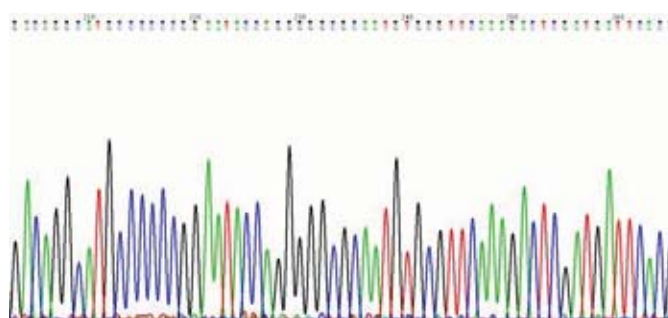


Figure 2. Chromatogram of *A. flavus* targeting ITS region

The pathogenesis of fungal keratitis in human corneal tissue by *Fusarium sp* and *Aspergillus sp*

Principal investigator : Lalitha Prajna, Aravind-Madurai
Co-investigator : Venkatesh Prajna, Aravind-Madurai
K. Dharmalingam, Madurai Kamaraj University, Madurai
Eric Pearlman, Case Western Reserve University, Cleveland, USA
Research scholar : R. Siva Ganesa Karthikeyan
Funding agency : ALCON
Duration : 2008 - 2011

Corneal diseases are one of the major causes of vision loss and blindness throughout the world. The predominant fungal species reported in South India is *Fusarium sp* followed by *Aspergillus sp* which accounts for nearly 42.82% and 26% of the total fungal infection respectively.

Progression of mycotic keratitis may be augmented by the activation of resident corneal cells or inflammatory cells, particularly polymorphonuclear leucocytes, which release proteinases, resulting in extensive degradation of the corneal tissue matrix. In the initial response, neutrophils and the macrophages recognise the conserved motif on pathogens called PAMP (pathogen associated molecular

patterns) through the pattern-recognition receptors (PRR). Toll-like receptors (TLR) are the well characterised PRR's which recognize the PAMPs and induces the production of signals responsible for the activation of genes that are essential for an effective host defense, especially proinflammatory cytokine genes.

In the current study, we have characterised the innate immune response in early stages of fungal infection by examining corneal scrapings from the fungal infected patients using Real Time PCR for the following genes of the PRRs' such as, TLR- 2, TLR- 4, TLR- 9, Dectin-1, Dectin-2, NALP3, and ASC (apoptosis-associated speck-like protein) as well as cytokines (IL-1 α , IL-1 β , IL-4, IL-8, IL-17, IL-18, IL-23, TNF- α and IFN- γ). We also characterised cellular infiltration in the later stages of disease by immunohistochemistry of infected corneas after transplant. Immunofluorescence was carried out to detect fungal β -glucan in the infected tissues. Our results showed a higher expression of the PRRs mainly TLR-2, TLR-4 and Dectin-1, which is crucial for the fungal recognition and also up-regulation of chemotactic and inflammatory cytokines. These cytokines recruits the inflammatory cells into the infected cornea. The major population of inflammatory cells comprised the neutrophils and macrophages. The presence of the T-cells was also found which indicates the involvement of the adaptive immune response. Detailed understanding of the host response in the fungal infection helps in the future development of the better immune intervention to prevent the damage to the cornea by inflammatory cell.

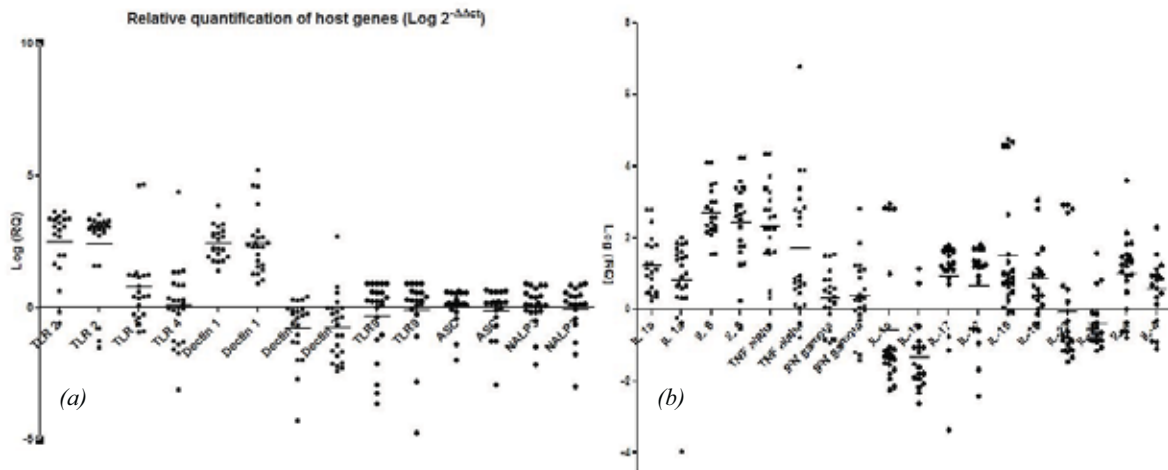


Figure 1. Gene expression pattern of PRRs (a) and cytokines (b)

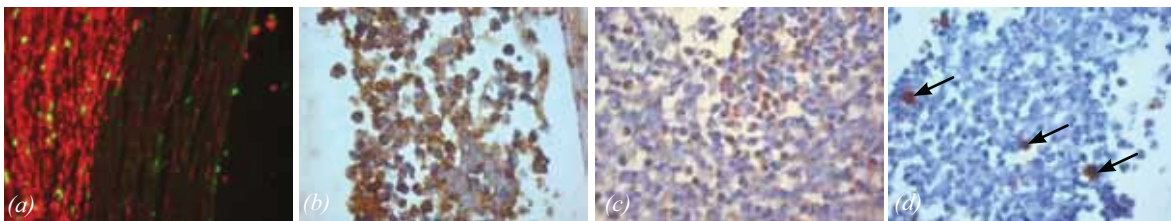


Figure 2. a) Immunofluorescence staining of the fungal filaments (green) and the corneal tissue (red). Immunohistochemistry staining of fungal infected corneal tissue section showing the presence of b) Neutrophils c) Macrophage d) CD3+T cell

Pathogen host interaction in human mycotic keratitis

Principal investigator : N. Venkatesh Prajna, Aravind-Madurai
Co-investigator : K. Dharmalingam, Madurai Kamaraj University
: S. Lalitha, Aravind-Madurai
Research scholars : S. Ananthi, P. Narmatha Devi, M. Sangeetha, S.R. Bhuvanaree
Funded by : Department of Biotechnology, New Delhi
Duration : 2007 - 2009

Mycotic keratitis is a major cause of corneal blindness in India. A proper understanding of the pathogenesis may help in refining the existing treatment. Ocular fungal infections or ophthalmic mycoses are being increasingly recognised as the cause of morbidity and certain types of ophthalmic mycoses may even be life threatening.

In order to understand the pathogenesis of this condition, the team has started examining the proteome profiles of infected tear, clinical isolates from infected corneal scrapings and corneal buttons from the fungal keratitis patients. The data shows that tear can be used as a clinical source to study the proteome wide responses in patients with fungal keratitis.

In continuation, now we have optimised the sample preparation for the corneal button which is a transparent, avascular, and highly specialised connective tissue that provides $\approx 70\%$ of the total refraction in the optical system of the eye. Infected corneas were collected from culture positive fungal keratitis patients at the time of transplantation which would be an ideal sample to study the late stage of the disease pathogenesis. Preliminary experiments show differential expression of proteins in infected corneas when compared to cadaver cornea control (Fig. 1).

The profile of secreted proteins from *Aspergillus flavus* was analysed to examine the expression of profiles of clinical isolates. Comparison between ATCC and clinical isolates showed clear variation in the expression of secreted proteins in clinical isolates. These differences are also found to be seen among the different clinical isolates. The quantification of these regulated proteins using Differential In-Gel Electrophoresis (DIGE) is under progress (Fig. 2).

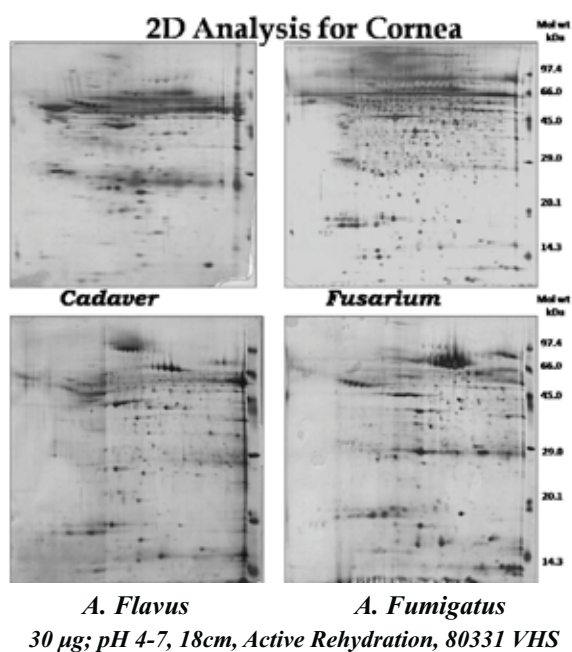
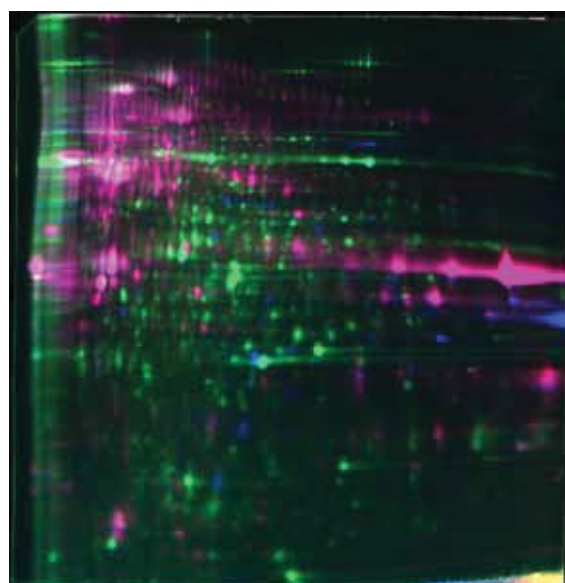


Fig. 1 Differential expressions of the corneal protein profile were observed in *A. flavus*, *A. fumigatus* and *Fusarium* infected cornea



Green spots - Clinical Isolate 1617
Pink spots - ATCC
Blue spots - Common to both the ATCC and CI

Fig. 2. DIGE analysis of ATCC and Clinical isolate 1617

Proteomic profiling of serum in proliferative diabetic retinopathy

Investigators : VR. Muthukkarrupan, AMRF-Madurai
K. Dharmalingam, School of Biotechnology, MKU
T.P Vignesh, Aravind-Madurai

Research scholar : M. Valar Nila

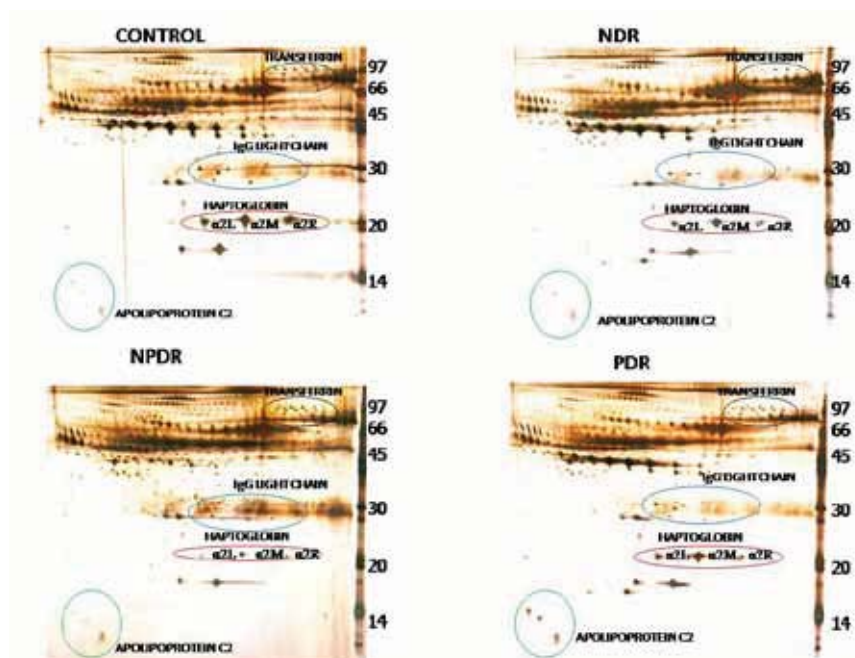
Funded by : TIFAC-CORE in Diabetic Retinopathy

Indian population is particularly vulnerable to diabetes (40 million). Among the diabetes patients, development of microvascular complications, such as retinopathy, precedes macrovascular events which might lead to death. As of now no dependable protein biomarkers are there that could be routinely used in clinical set up to predict the susceptibility of Diabetic Mellitus patients to retinopathy, even though there are several candidate proteins shown to be differentially regulated.

Based on the previous study, the team started examining a larger sample set. Study includes four major categories of samples, Diabetes without Retinopathy (NDR), Non-Proliferative Diabetic Retinopathy (NPDR), Proliferative Diabetic Retinopathy (PDR), Age Matched Normal Controls. The initial attempt was to examine the above samples, using Two Dimensional Polyacrylamide Gel Electrophoresis (2D PAGE) analysis. There are several proteins shown to be altered in their expression levels in PDR compared to control and DM patients. Among the 56 identified proteins, Apolipoprotein and Haptoglobin $\alpha 2$ chain - isoform $\alpha 2M$, are significantly up regulated in PDR.

Also some recent results clearly show that NPDR and PDR are linked with major macrovascular complications such as stroke, coronary heart disease, heart failure and nephropathy. It has been proposed that apart from being a microvascular complication, in future studies DR should be viewed as an early biomarker of widespread systemic deleterious effects in diabetic patients. In parallel the available proteomic techniques will be used to examine the proteome (stage specifically) of serum, vitreous fluid and Fibrovascular membrane for the disease specific differential regulation. From the putative list of differentially regulated proteins, ELISA will be developed and 2D western methods to validate these using a much larger sample size from southern India.

Serum proteome profile and Differential Expression of Proteins in DR



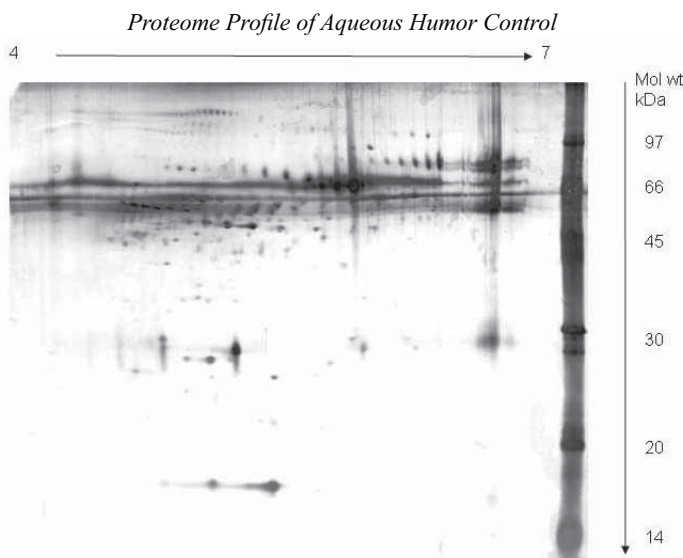
Transferrin, IgG Light chain, Apolipoprotein C2 and $\alpha 2$ chain of Haptoglobin are showing difference between the stages of DR. All the Haptoglobin isoforms were upregulated in PDR condition

Identification of biomarkers for primary open angle glaucoma

Principal investigator : S.R. Krishnadas, Aravind-Madurai
Co-investigator : P. Sundaresan, AMRF-Madurai
K. Dharmalingam- Madurai Kamaraj University, Madurai
US Collaborator : John W Crabb, Cole Eye Institute, Cleveland, USA
Research scholar : I. Paul Pown Raj
Funding agency : Department of Biotechnology, New Delhi
Duration : 2009 - 2012

Primary open angle glaucoma (POAG) is one of the leading causes of blindness in the elderly population worldwide. Slowing or preventing the progression of this disease is an urgent public health goal and early detection of the disease becomes the need of the hour. The objective of the project is to identify protein biomarkers specific for POAG.

In order to study the proteome wide changes, plasma, serum, and aqueous humor have been collected from more than 80 patients in four different categories depending on the severity of the disease. The standardisation of 2D gel electrophoresis for the protein profiling is in progress. The differential expression in POAG samples in comparison with control group will give emphasis on the proteins involved in POAG pathogenesis. Identifying those specific proteins and correlation of expression level with disease will allow the development of a diagnostic method for use in clinical practice.



Aqueous Humor – Control: 18cm, 4-7, Cup loading, 50ug, Glutaraldehyde Silver, 43003vhs

INDEYE REVIEW MEETING

INDEYE Review meeting was held at Aravind Medical Research Foundation from February 8-9, 2010 to review the progress of the project “A genetic component to the INDEYE study of cataract and age-related macular degeneration in India”.

FROM LEFT, FIRST ROW: Dr.R.D.Ravindran, Aravind-Pondicherry, Dr.VR.Muthukkaruppan, Director-AMRF, Dr. Usha Chakravarthy, Professor, Department of Ophthalmology, Queen's University, Belfast, Dr. Astrid Fletcher, Professor, London School of Hygiene & Tropical Medicine, London, Dr.Monica Camparini, Dr. Giovanni Maraini, Professor, University of Parma, Parma, Dr.J.Fielding Hejtancik, Professor, Department of Genetics, National Eye Institute, USA, FROM LEFT SECOND ROW: Mr. Saravanan, AMRF, Dr. Praveen Vasisht, AIIMS, New Delhi, Dr. Liam Smeeth, Dr. Dorothea Nitsch, Professor, London School of Hygiene & Tropical Medicine, London, Dr. P. Sundaresan, Senior Scientist, AMRF, Ms.Ashwini, Ms. Mohana Priya, Ms. Radha, AMRF, Dr. Badri Aravind-Pondicherry



PUBLICATIONS

INDIAN J PEDIATRICS

2009; 76(5):513-517

GURUSWAMY NEETHIRAJAN,
ABRAHAM SOLOMON, SUBBAIAH
RAMASAMY KRISHNADAS,
PERUMALSAMY VIJAYALAKSHMI,
PERIASAMY SUNDARESAN

- *Genotype/phenotype association in Indian congenital aniridia*

MOLECULAR VISION

2009;15:1781-1787

PERIASAMY SUNDARESAN,
P.VIJAYALAKSHMI, STEWART
THOMPSON, AUDREY C.KO, JOHN
H.FINGERT, EDWIN M.STONE

- *Mutations that are a common cause of leber congenital amaurosis in northern America are rare in southern India*

HUMAN GENETICS

2009 125 (3): 340

RENUGADEVI K, SIL AK,
PERUMALSAMY V, SUNDARESAN P.

- *Novel human pathological Mutations. Gene symbol: OCA2. Disease: albinism, oculocutaneous II*

CORNEA

2010;29:302-306

J S MEHTA, B HEMADEVI, E N
VITHANA, J ARUNKUMAR, M
SRINIVASAN, N V PRAJNA, DT TAN,
A TIN, P SUNDARESAN.

- *Absence of phenotype-genotype correlation of patients expressing mutations in the SLC4A11 gene*

BMC OPHTHALMOLOGY

2010; 10:3

HEMADEVI B, SRINIVASAN M, ARUN
KUMAR J, PRAJNA NV, SUNDARESAN
P.

- *Genetic analysis of patients with Fuchs endothelial corneal dystrophy in India*

HUMAN MOLECULAR GENETICS

2010 Jan 15;19(2):287-98

YE M, BERRY-WYNNE KM, ASAI-
COAKWELL M, SUNDARESAN P,
FOOTZ T, FRENCH CR, ABITBOL M,
FLEISCH VC, CORBETT N, ALLISON
WT, DRUMMOND G, WALTER MA,
UNDERHILL TM, WASKIEWICZ AJ,
LEHMANN OJ.

- *Mutation of the bone morphogenetic protein GDF3 causes ocular and skeletal anomalies*

BMC MEDICAL GENETICS (SUBMITTED)

SUGANTHALAKSHMI BALASUBBU,
SUNDARESAN PERIASAMY, ANAND
RAJENDRAN, KIM RAMASAMY,
NAMPERUMALSAMY PERUMALSAMY,
J.FIELDING HEJTMANCIK

- *Association analysis of nine candidate gene polymorphisms in Indian patients with type 2 diabetic retinopathy*

MOLECULAR VISION (SUBMITTED)

KATHIRVEL RENUGADEVI, ASIM
KUMAR SIL, VIJAYALAKSHMI
PERUMALSAMY, PERIASAMY
SUNDARESAN

- *Spectrum of candidate genes mutation associated with Indian familial oculocutaneous and ocular albinism patients*

CURRENT EYE RESEARCH (IN PRESS)

SENTHILKUMARI S, LALITHA P,
VENKATESH PRAJNA N, HARI PRIYA
A, NIRMAL J, PANKAJ G,
VELPANDIAN T.

- *Single and multidose ocular kinetics of extemporaneous formulation of topical voriconazole in human and evaluation of its stability*

PROTEOME SCIENCE (IN COMMUNICATION)

ANANTHI S, SANTHOSH RS,
VENKATESH PRAJNA N, LALITHA P,
DHARMALINGAM K.

- *Development of an effective sample preparation method for the tear proteome analysis using 2-D gel electrophoresis*

MAJOR EQUIPMENT (NEW ADDITIONS)



*Vir Tis Bench Top Freeze Dryer
(Lyophiliser)*



CHRIST Rotational Vacuum concentrator



Typhoon Trio (GE Healthcare)

AWARDS



DR. P. SUNDARESAN was awarded the ICMR AWARD 2009 and Prize for biomedical research for scientists belonging to underprivileged communities for the year 2006 from Mr. Ghulam Nabi Azad, Union Minister - Health and Family Welfare, Government of India.



MS. AMALA RAJA SUNDARI, Research Scholar has been declared to have qualified for the degree of Doctor of Philosophy (Ph.D) for her thesis on “Serological and Molecular characterisation of Rubella virus in children with Ocular defects of Congenital Rubella Syndrome” on 26th April 2009 by the Madurai Kamaraj University.



DR. SHEETAL received the “Best Cornea Free Paper Session Award” in Tamil Nadu Ophthalmic Association (TNOA) meeting, August 2009, Coimbatore on “COMET – a promising technique for treating patients with bilateral LSCD due to chemical injury”.

PARTICIPATION IN CONFERENCES AND WORKSHOPS

ARVO 2009 annual meet

Fort Lauderdale, Florida, May 3-7

Dr. P. Sundaresan made a poster presentation on “Novel mutations of the transcription factor FOXL2 and functional effects in BPES patients”.

Dr. P. Sundaresan with Ms. Pamela Sieving, Informationist, NIH Library, USA, Dr. Irene Hussels Maumnee, Professor of Medicine and Pediatrics, Wilmer Eye Institute, Baltimore, USA

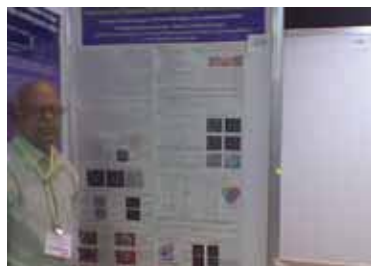


International Society for Stem Cell Research (ISSCR)

Barcelona, Spain, July 8 -11

VEERAPPAN MUTHUKKARUPPAN¹, PARTHASARATHY ARPITHA¹, SIVARAMAKRISHNAN VAISHALI¹, CHIDAMBARANATHAN GOWRI PRIYA¹, USHA KIM², VENKATESH PRAJNA².

¹Dr.G.Venkataswamy Eye Research Institute, Aravind Medical Research Foundation, Madurai, ²Aravind Eye Hospital,



Madurai. Poster presentation on - *Adult human buccal epithelial stem cells: Identification, ex-vivo expansion and transplantation for corneal surface reconstruction*

Dr.VR.Muthukkaruppan visited the Centre for Regenerative Medicine, University of Modena, Italy and discussed with Dr. Graziella Pellegrini, Professor of Cell Biology on the establishment of GMP facility to generate epithelial stem cells for



ocular surface reconstruction. It is proposed to enter an agreement with University of Modena for collaboration between AMRF and Centre for Regenerative Medicine, University of Modena.

Dr. VR. Muthukkaruppan also visited the Institute of Ophthalmology, University college of London to discuss with Dr. Julie Daniels, Head, and Cells for sight Transplantation and Research Programme on the various aspects of their GMP facility and ocular stem cell culture protocols.

Dr. VR. Muthukkaruppan visited the Centre for Vision and Vascular Science, Queens University, Belfast to meet Dr. Alan Stitt, Director of Research to discuss on various aspects of mechanism of diabetic retinopathy and age related macular degeneration. Dr. Stitt has indicated his willingness to develop collaboration by signing MoU between AMRF and Queens University.

68th Annual conference of AIOS 2010

Kolkata, January 21 - 24

Dr.P.Sundaresan presented

- *Glaucoma - hereditary patterns based on genetic mutations and chromosome alterations - a crash course of genetics ophthalmology.*

Dr. P. Sundaresan with Dr. Gerald R. Schultz and Dr.A.J. Aldave at Kolkata



Dr. Gowri Priya at 6th annual meeting of International Leptospirosis Society

Sixth annual meeting of International Leptospirosis Society

Cochin, September 21-24, 2009

Dr.Gowri Priya attended and presented two oral presentations on:

- *Infecting leptospiral serovars among uveitis patients - 10 year study*
- *Antibody dynamics in leptospiral uveitis patients.*

2nd National Hands-on workshop

AIIMS, New Delhi, February 3-5, 2010

2nd National Hands-on workshop on advanced bioanalytical techniques in pharmacokinetics studies from method development to data interpretation and symposium on “contemporary technologies and concepts revolutionizing drug discovery strategies”.

Dr. S. Senthilkumari participated as a moderator in the meeting.

ARVO-ISOCB 2009 (International Society for Ocular Cell Biology)

Portugal, September 9-12

P. MURUGESWARI¹, R. KIM², D.SHUKLA², P.NAMPERUMALSAMY², VR. MUTHUKARUPPAN¹, A.W. STITT³.

Dr. S. Senthilkumari at AIIMS, New Delhi



¹Dr. G. Venkataswamy Eye Research Institute, Aravind Medical Research Foundation, Madurai, ²Vitreous and Retina Service, Aravind Eye Hospital, Madurai, ³Centre for Vision and Vascular Science, Queens University Belfast, Northern Ireland, United Kingdom.

Poster presentation on

- *Cytokine profile and angiogenic potential of vitreous from patients with proliferative diabetic retinopathy and Eales' disease by*

Ms. P. Murugeswari who has worked with Dr. Alan Stitt, Centre for Vision and Vascular Science, Queen's University, Belfast for a year as Commonwealth Fellow.

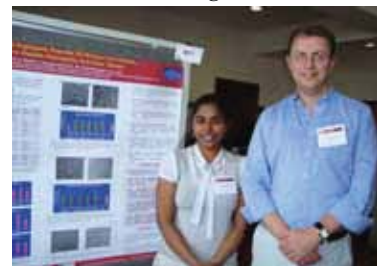
Biotechnology Fusion of Advanced Research and Teaching conference

Madurai, January 2-4

M. VALAR NILA¹, T. P. VIGNESH², VR. MUTHUKARUPPAN¹, K. DHARMALINGAM³

¹Dr. G. Venkataswamy Eye Research Institute, Aravind Medical Research Foundation, Madurai, ²Vitreous and Retina Service, Aravind Eye Hospital,

Ms. P. Murugeswari, Dr.Alan Stitt at Portugal





M. Valar Nila and S. Ananthi with poster at Hyderabad



Dr. T.S. Rao, Advisor, Department of Biotechnology and Dr. Marcus Macht, Bruker, Germany chairing the session

Madurai, ³Madurai Kamaraj University, Madurai. Poster presentation on
- *Proteomic profiling of serum in proliferative diabetic retinopathy.*

ANANTHI S¹, VENKATESH PRAJNA N², LALITHA P², DHARMALINGAM K³

¹Dr. G. Venkataswamy Eye Research Institute, Aravind Medical Research Foundation, Madurai, ²Aravind Eye Hospital, Madurai, ³Madurai Kamaraj University, Madurai. Poster presentation on
- *Corneal proteome profile in fungal keratitis patients*

5th AOHUPO Congress, 14th ADNAT Convention & 1st PSI Conference on New Perspectives in Proteome Research

Hyderabad, February 21-25

M.VALAR NILA¹, T.P. VIGNESH², VR. MUTHUKARUPPAN¹,

K. DHARMALINGAM³.

¹Dr. G.Venkataswamy Eye Research Institute, Aravind Medical Research Foundation, Madurai, ²Vitreous and Retina Service, Aravind Eye Hospital, Madurai, ³Madurai Kamaraj University, Madurai. Poster presentation on
- *Proteomic analysis of serum in patients with diabetic retinopathy.*

ANANTHI S¹, VENKATESH PRAJNA N², LALITHA P², DHARMALINGAM K³

¹Dr. G. Venkataswamy Eye Research Institute, Aravind Medical Research Foundation, Madurai, ²Aravind Eye Hospital, Madurai, ³Madurai Kamaraj University, Madurai. Poster presentation on
- *Comparative analysis of the tear and cornea protein profile in mycotic keratitis patients.*

Workshop on Mass Spectrometry in clinical proteomics

One day workshop on Mass Spectrometry in clinical proteomics was conducted on September 30, 2009. The workshop included following lectures by the experts in the field of Mass Spectrometry.

DR. MARCUS MACHT, (BRUKER, GERMANY)

- *Comprehensive proteomics analysis using ESI-QT of Mass Spectrometry*

DR. RANJAN MOGRE, (DIONEX, MUMBAI)

- *Multidimensional LC in proteomics*

PROF. K. DHARMALINGAM, MADURAI KAMARAJ UNIVERSITY

- *Experimental approaches to clinical proteomics*

VISITORS

The Director General of Indian Council of Medical Research (ICMR), **DR. V.M. KATOCH**, along with Senior Deputy Director General, M. Rajamani visited AMRF on 16th June 2009. Dr. N. Venkatesh Prajna, Cornea specialist took them around various laboratories in Aravind Medical Research Foundation.

DR. R.B SRIVASTAVA, Member Secretary, LSRB and Director, Life Sciences, DRDO HQ, New Delhi and **DR. RP TRIPATHI**, Director, Institute of Nuclear Medicine and Allied Sciences, Delhi visited Aravind Medical Research Foundation on 8th August 2009, to review the DRDO project on "Buccal epithelial culture and transplantation".



DR. RUDY A. HARTSKEERL, Head and Coordinator of the Leptospirosis Unit, Royal Tropical Institute, Amsterdam, The Netherlands and Dr. Manjula Sritharan, Professor, Department of Animal Sciences, University of Hyderabad visited AMRF on September 28-30. During their visit they discussed the possibility of developing an international collaborative project on leptospirosis with Dr.SR.Rathinam, Dr.Gowri Priya, Dr.VR.Muthukkaruppan.



DR. S. SWAMINATHAN, Director and **DR. UMA MAHESWARI**, Professor, Centre for Nanotechnology and Advanced Biomaterials (CeNTAB), School of Chemical & Biotechnology, SASTRA University, Thanjavur visited AMRF on October 3 to explore the possibility of developing collaboration in Nanotechnology.



DR. ERIC PEARLMAN, Case Western Reserve University, Cleveland visited AMRF on January 25 and gave the lecture on “Innate immunity in Pseudomonas aeruginosa keratitis”. He also had a discussion on the collaboration on Fungal Keratitis with Dr. K. Dharmalingam, Senior Professor of Biotechnology, Madurai Kamaraj University, Dr. N.V. Prajna, Chief of Cornea clinic and Dr. Lalitha Prajna, Chief Microbiologist, Aravind Eye Hospital.



PROF. TIEN-YIN WONG, Director, Singapore Eye Research Institute, visited AMRF on January 9. Dr. Tien-Yin Wong indicated that his research groups would be interested to develop collaborative projects with Aravind Medical Research Foundation.



DR. MORTON F.GOLDBERG, Joseph E Green, Professor of Macular Degeneration and Retinal Diseases, Former Director, Wilmer Ophthalmological Institute, Johns Hopkins University, USA visited AMRF on January 9 and discussed with students about the ongoing projects.



DR. RITA BANERJEE, Department of Science and Technology, Prof. BD. Banerjee, University College of Medical Science, Prof. Bharathi P. Salimath, Mysore University and Dr. P.V. Salimath, Central Food Technological Research Institute (CFTRI), Mysore visited AMRF on February 22. Dr. Rita Banerjee discussed with AMRF scientists on the various opportunities and support provided by Department of Science and Technology, New Delhi, India.



MR. TOBIAS WIMMER, Research fellow, Department of Ophthalmology, University Eye Hospital Giessen and Marburg GmbH, Giessen, Germany Visited Department of Genetics, Aravind Medical Research Foundation from March 1-21, 2010 under the DST-DAAD project based personnel exchange (Indo-German) programme. Dr.P.Sundaresan and Dr. Markus Preising are the Investigators for the project entitled “Molecular Genetics of Albinism in the Indian population”.



Tobias and Renukadevi, research scholar at AMRF were able to establish the methods needed to clone human Albinism candidate gene into HEK293 (human embryonic kidney) for the expression of wild type and mutant type proteins. They cloned a wild type-receptor gene sequence into PcDNA3.1(+) by restriction digestion and ligation of the two DNA Fragments. These circular constructs were then transformed into competent Escherichia coli. The insertion and orientation of wild type DNA sequence in PcDNA3.1(+) was confirmed by restriction digestion and Big Dye Termination sequencing methods. Mr. Tobias Wimmer gave a seminar on “Control of the retinal angiogenesis by the regulated expression of VEGF-binding molecules”.

Dr. Eric Pearlman and his student **SIXTO LEAL**, Case Western Reserve University, Cleveland, Ohio visited AMRF on January 24th, 2010. Dr. Eric Pearlman spent a week at AMRF to discussing the ongoing as well as possibility of the future collaborative research work in immunopathogenesis of the human corneal ulcers. Sixto leal who has been interested in animal models to study the immunopathogenesis of the fungal keratitis spent three weeks at the Department of Microbiology, AMRF to establish the immunohistochemical and immunofluorescence techniques to characterise cell population and to identify fungus in the paraffin embedded archival corneal tissues. Mr. Sixto presented seminar on “Pathogenesis of Aspergillus keratitis”.



MR. CHRISTOPHER BAHL, PhD student from the Department of Biochemistry Dartmouth Medical School, USA, visited AMRF lab from March 8 – 31 . He is working on X-ray crystallography to predict and analyse the protein structures. Cif (Cystic fibrosis transmembrane conductance regulator inhibitory factor) is one of the virulence factors found to be involved in the pathogenesis of the Pseudomonas aeruginosa. The main purpose of his visit was to analyse cif gene expression in the P. aeruginosa isolated from the corneal ulcer. A panel of P. aeruginosa strains isolated from ocular infections from Aravind Eye Hospital, and environmental isolates from the surrounding area are used. On analysing the clinical samples 94 % of the ocular isolates express this protein whereas, it is only 40% in case of the environmental isolates. This may give us an idea that Cif may play a role during ocular infection. Investigating a potential role for Cif during eye infection will augment our understanding of P. aeruginosa ocular pathogenesis. Mr. Christopher Bahl gave a seminar on “Cif: A Novel Epoxide Hydrolase Virulence Factor Secreted by Pseudomonas aeruginosa”.



DR. AMRITLAL MANDAL, Research Associate, Department of Physiology, University of Arizona, USA visited AMRF and gave a seminar on “Hydrostatic Pressure induced activation of Sodium Hydrogen exchanger in optic nerve head astrocytes: Role of Calcium on March 31.

CLINICAL RESEARCH

GLAUCOMA SERVICES

At Madurai

Health literacy and other barriers to follow-up after initial diagnosis of glaucoma in south Indian population

Investigators : Dr. Manju R. Pillai
Dr. SR Krishnadas
Setting : Glaucoma Clinic, Aravind-Madurai

Purpose

To determine the association of health-literacy and other social and demographic factors with the probability of return for follow-up in newly identified glaucoma patients in South India.

Methods

An ongoing prospective cohort study of Tamil-speaking individuals enrolled at the time of newly diagnosed glaucoma at Aravind Eye Hospital in Madurai, India is being conducted. Tamil translations of two validated literacy assessments are used to evaluate health-literacy: “Rapid Assessment of Adult Literacy in Medicine” (REALM) and “Test of Functional Health Literacy in Adults” (TOFHLA). An additional oral questionnaire is administered to assess age, gender, level of education, socioeconomic status, marital status, distance and mode of transportation used to attend clinic appointments, and need for an escort. Glaucoma therapy is initiated on the date of enrollment, and follow-up is scheduled approximately 1 week to 2 months later at the physician’s discretion. Data of subjects who have had follow-up of at least 2 weeks longer than their initial scheduled follow-up appointment was analysed. This analysis evaluated factors associated with failure to return for initial follow-up examination.

Results

To date, 147 subjects have had sufficient follow-up to assess factors associated with failure to return for follow-up. In univariate analysis, REALM score with literacy grade 3 was associated with a lower probability of returning for follow-up (57.8% vs. 83.3%, $p=0.006$). Subjects who failed to return also had fewer dependents than those who returned for follow-up (mean: 0.47 vs. 1.03 dependents, $p=0.03$). Multivariate logistic regression analysis identified these factors as being independently associated with a higher risk of failure to return for follow-up; REALM score literacy grade 3 (Odds Ratio (OR)=4.06, $p=0.008$), and fewer dependents (OR=1.82 for each fewer number of dependents, $p=0.04$). After adjusting for literacy and number of dependents, male gender also was associated with a higher risk of failure to return for follow-up, but the difference did not reach statistical significance (OR=2.72, $p=0.06$).

Conclusion

In this population, illiteracy is a significant risk factor for failure to return after initial diagnosis of glaucoma, particularly among men. In addition, the added responsibility of dependents may increase adherence to recommended follow-up. Future analysis with a larger sample size will more clearly delineate factors associated with the probability of returning for initial follow-up, as well as for subsequent follow-up appointments.

A multi-centre, double-masked study of the safety and efficacy of Travoprost APS compared to TRAVATAN® in patients with open-angle glaucoma or ocular hypertension

Investigators : Dr. Manju R. Pillai
Dr. Prashanth
Dr. Vijaya
Dr. Nithiverma
Setting : Glaucoma Clinic, Aravind-Madurai

Objective

The primary objective of this study is to compare the efficacy and safety of Travoprost APS (Polyquad preserved) to TRAVATAN Solution (BAK preserved), both dosed once-daily in the evening, in patients with open-angle glaucoma or ocular hypertension.

Design

Prospective, parallel assignment, double-masked, randomised controlled trial.

Methodology

Screened patient were under wash out period for concomitant anti glaucoma drugs. Eligibility visit 1 and 2 was to assess IOP. 17 Patients were enrolled in this study. Eligible patients were randomly allotted into one of the treatment arms.

Travoprost APS - Once daily PM
TRAVATAN® - Once daily PM

Patients were followed up at week 2, week 6 and month 3. Post operative evaluation included ETDRS, slit lamp examination, IOP, dilated fundus, HFA and CCT. Total number of enrolled patients was 371.

Conclusion

Travoprost APS is found to be non inferior to TRAVATAN in IOP lowering efficacy and the safety profile of Travoprost APS is consistent with the established safety profile of TRAVATAN.

Pharmacoeconomics of various brands of Timolol for patients with glaucoma or ocular hypertension

Investigators : Dr. Manju R. Pillai
Dr. Krishnadas
Setting : Glaucoma Clinic, Aravind-Madurai

Objective

To compare cost effectiveness of Aurotim (Aurolab, India), Timolet (Sun Pharmaceutical, India) and Glucomol (Allergan, India) in subjects with glaucoma or ocular hypertension.

Design

Prospective, open label, active comparator, pharmacoeconomics, randomised controlled trial.

Methodology

30 subjects were randomised into 3 arms in 1:1:1 ratio. Screening procedures including best corrected visual acuity (BCVA), pachymetry, anterior segment and fundus examinations, IOP at 9:00 AM and 12:00 PM time points and visual field were performed. Medication was given to subjects with meticulous counselling. Pamphlets were also provided to the subjects. During the follow up visits in the first, second and third months follow up visits, outcome variables would be captured. Analysis would be performed to compare three brands of timolol. Pharmacoeconomics outcome measurements are cost effective and patient weighted average IOP reduction. Pharmacoeconomics endpoints are Average Cost

Effectiveness Ratio (ACER), Incremental Cost Effectiveness Ratio (ICER), cost per mm Hg reduction, cost per 1% reduction in IOP, drop count, daily cost, volume per drop and number of days of usage per bottle.

A Multicentre, open label, active control, parallel group randomized study to demonstrate non inferiority of Brinzolamide 1% Ophthalmic suspension compared with Dorzox (Dorzolamide) 2% Ophthalmic solution in treatment of elevated intra-ocular pressure in patients with primary open angle glaucoma or ocular hypertension

Investigators : Dr. Krishnadas
Dr. George varghese
Dr. Ramakrishan
Setting : Glaucoma Clinic, Aravind-Madurai

Objective

To demonstrate non-inferiority and safety of Brinzolamide 1% ophthalmic suspension compared to Dorzox (dorzolamide) 2% ophthalmic solution in treatment of elevated intra-ocular pressure in patients with primary open angle glaucoma or ocular hypertension.

Design

12 weeks prospective, open label, randomised, active control, parallel group, multicentre study.

Methods

25 subjects would be randomised into 2 arms in 1:1 ratio. The study includes patients with either primary open angle glaucoma or ocular hypertension with intra-ocular pressure >24 <36 mmHg in at least one eye at 9.00 am. Eligible patients are randomized on the same day. Ocular examinations at screening/baseline include bilateral IOP measurement by Goldman's applanation tonometry, Snellen visual acuity, slit lamp, gonioscopy, dilated ophthalmoscopy and perimetry. Demographic parameters, physical examination, ocular and medical history are recorded at baseline and women of childbearing potential would undergo pregnancy test. They are followed up at 4th week, 8th week and 12th week after randomisation to assess safety and efficacy outcomes.

At Tirunelveli

1. Fluocinolone Acetonide for the treatment of diabetic macular edema

Principal investigator : Dr. R. Ramakrishnan
Assessing investigators : Dr. Divya Lakshmi K.S
Dr. Naveen Narendranath
Dr. Nithila E.G.Paul
Treating investigator : Dr. Manjunath
Funding agent : Alimera Sciences, Inc.
Duration : June 2007 - September 2010

Triamcinolone acetonide has come a long way in the treatment of diabetic macular edema, however side effects like cataract and glaucoma in the treated eyes continue to be a problem. The outcome of the FAME study is to find out the effectiveness of fluocinolone acetonide in various concentrations for the treatment of diabetic macular edema and to understand the potential side effects of instituting this therapy. Currently 15 patients are following up with us of the 19 initially selected. It is a randomised, double masked, parallel group, multi centre, dose finding comparison of the safety and efficacy of 0.5 micrograms and 0.2 micrograms FLUOCINOLONE ACETONIDE intravitreal inserts to sham injection in subjects with diabetic macular edema.

Rinzolamide 1% ophthalmic solution for the treatment of primary open angle glaucoma and ocular hypertension

Principal investigator : Dr. R. Ramakrishnan
Co-investigator : Dr. Devandra Maheswari
Dr. Mohideen Abdul Kader
Funding agent : ALCON Laboratories (India) Pvt Ltd.
Duration : 3 Months

Topical CAIs such as Brinzolamide and Dorzolamide are effective in reducing IOP and possess a more favourable adverse event profile than their oral predecessor (acetazolamide). They can be prescribed alone or often as an adjunctive therapy. They should be considered as therapy of choice for patients with contraindications for beta-blockers, especially patients with pulmonary and heart disease. Brinzolamide belongs to a new class of heterocyclic sulfonamide CAIs that is typically active for reducing IOP.

Brinzolamide 1.0% Ophthalmic suspension is well tolerated and does not produce many of the side effects associated with the CAIs that are given systemically making it an attractive treatment for patients with glaucoma, in whom compliance with therapy can be an issue. Brinzolamide ophthalmic suspension 1% dosed three times per day (TID) in patients with elevated IOP, produced significant reductions in IOPs (4-5mmHg). It is Multicentre, open-label, active control, parallel-group randomised study to demonstrate non inferiority of BRINZOLAMIDE 1% ophthalmic suspension compare with DORZOX (Dorzolamide) 2% ophthalmic solution in patients with primary open angle glaucoma or ocular hypertension.

At Coimbatore

A multicenter, open label, active control, parallel-group, randomised study to demonstrate non-inferiority of BRINZOLAMIDE 1% ophthalmic suspension compared with DORZOX (Dorzolamide) 2% ophthalmic solution in treatment of elevated intra-ocular pressure in patients with primary open angle glaucoma or ocular hypertension

Principal investigator : Dr. Parthasarathi Sathyan
Co-investigator : Dr. Ganesh Venkata Raman
Funding source : Alcon laboratories(India) Pvt Ltd.
Period : 12 weeks

Abstract

Primary Open Angle Glaucoma (POAG) is a chronic progressive condition with a loss of optic nerve fibers characterised by changes at the optic disc. In addition POAG is characterised by open anterior chamber angle, visual field abnormalities and Intra-Ocular Pressure (IOP) that is too high for the continued health of the eye. The term Ocular hypertension (OH) is used to describe IOP above an upper normal value of 21mmHg when there is no optic nerve damage. Brinzolamide belongs to a new class of heterocyclic sulfonamide CAIs (Carbonic Anhydrase Inhibitor) that is topically active for reducing IOP. It has high affinity and inhibitory potency against human CA II, an isoenzyme of carbonic anhydrase found in ciliary epithelia, which are involved with aqueous humor secretion. Brinzolamide ophthalmic suspension 1% dosed three times per day (TID) in patients with elevated IOP, produced significant reductions in IOPs. The study also demonstrate that Brinzolamide was significantly less associated with ocular discomfort (burning and stinging) than Dorzolamide. The main purpose of this prospective is to demonstrate non-inferiority of topical Brinzolamide dosed TID compared with Dorzolamide dosed TID in IOP reduction in patients with POAG or OH.

At Pondicherry

A multicentre, open label, active control, parallel-group randomised study to demonstrate non inferiority of brinzolamide 1% ophthalmic suspension compared to dorzox (dorzolamide) 2% ophthalmic solution in treatment of elevated intra-ocular pressure in patients with primary open angle glaucoma or ocular hypertension

Principal investigators : Dr. R. Venkatesh
Co-investigator : Dr. S. Kavitha
Funding agency : Alcon Laboratories Pvt. Ltd.,
Duration : February 2009 - 2010

Objectives

Primary objective

To demonstrate non-inferiority of brinzolamide 1% ophthalmic suspension compared to dorzox (dorzolamide) 2% ophthalmic solution in treatment of elevated intra-ocular pressure in patients with primary open angle glaucoma or ocular hypertension

Secondary objective

To assess the safety of brinzolamide 1% ophthalmic suspension compared to dorzox (dorzolamide) 2% ophthalmic solution in treatment of elevated intra-ocular pressure in patients with primary open angle glaucoma or ocular hypertension.

RETINA AND VITREOUS SERVICES

At Madurai

A randomised, double masked, active controlled, phase 3 studies of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF trap in subjects with neovascular Age-related Macular Degeneration (AMD)

Investigator : Dr. R. Kim
Dr. Anand Rajendran
Dr. Umesh
Dr. Praveen Murali
Setting : Retina Clinic, Aravind-Madurai

Objective

Primary objective is to assess the efficacy of intravitreally (ITV) administered VEGF Trap compared to ranibizumab in preventing moderate vision loss in subjects with all subtypes of neovascular AMD.

Design

Multicentric, double- masked, randomised, active controlled, phase 3 study.

Methods

1240 subjects were randomised in a 1:1:1:1 ratio with a fixed block size to 1 of 4 dosing regimens: 0.5mg VEGF Trap-Eye administered every 4 weeks (0.5Q4) or 2mg VEGF Trap-Eye administered every 4 weeks (2Q4) or 2mg VEGF Trap-Eye administered every 8 weeks (2Q8) or 0.5mg ranibizumab administered every 4 weeks. Subjects assigned to (2Q8) received the 2 mg injection every 8 weeks with one additional dose at week 4 and received sham injections at interim monthly visits (every 4 weeks) during year 1 of the study. Subjects are being evaluated every 4 weeks for safety and best corrected visual acuity (BCVA) using the 4 meter ETDRS protocol. Quality of Life (QOL) is evaluated using the

NEI VFQ-25 questionnaire. Optical Coherence Tomography (OCT) and Fluorescein Angiography (FA) examinations are conducted periodically. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea are evidenced by FA in the study eye. 13 subjects have been enrolled into this study.

A safety and efficacy assessment of Vitreosolve® for ophthalmic intravitreal injection for inducing posterior vitreous Detachment in non-proliferative diabetic retinopathy subjects

Investigator : Dr. R. Kim
Dr. Somnath
Setting : Retina Clinic, Aravind-Madurai

Objective

To evaluate the safety and efficacy of Vitreosolve® ophthalmic intravitreal injection for inducing a posterior vitreous detachment in native diabetic retinopathy subjects.

Methodology

30 subjects with Non-Proliferative Diabetic Retinopathy (NPDR) were randomly assigned into one of the two study arms

- Intravitreal injection of 0.10 ccs (100 microliters) 18.0% of Vitreosolve® (study drug).
- Intravitreal injection of 0.10 ccs (100 microliters) 0.10 % of Vitreosolve® (study control).

Each subject received an intravitreal injection, at the start of the study after the baseline visits, and at 1 month post the first injection. Treatment was administered in single eye of each patient. Patients were evaluated at baseline, day of injection (day 0) (within 2 weeks of baseline photos) and study days: 1 day, 7 days, and 1 month post injection. Then the patients were reinjected and followed at 30th day, 60th day, 120th day and 180th day post second injection. If the follow up session is unreliable, the OCT and clinical exam will be used to determine the presence or absence of a PVD.

CLINICAL STUDIES

Ongoing

A study of featureless retina in diabetic retinopathy: Clinical and angiographic features and therapeutic implications

Principal investigator : Dr. Dhananjay Shukla
Co-investigator : Dr. Anuradha Dhawan
Status : Data Collection over. Analysis partly over

Objective

The study aims to put forward guidelines for clinical-investigational clues to diagnose featureless retina in diabetic retinopathy patients and determine its angiographic and systemic associations.

A retrospective analysis of patients with idiopathic macular telangiectasia: Natural history, incidence of visual loss and investigations of causes of visual loss

Principal investigator : Dr. Dhananjay Shukla
Co-investigator : Dr. Shashank
Dr. Sachin
Dr. Sumi Gupta
Status : Data Collection over. Analysis partly over

Objective

To study the natural history, incidence of visual loss and causes of visual loss in IMT.

Pigment Epithelial Detachment (PED) in Chronic Central Serous Retinopathy (CSCR)

Principal clinician : Dr. Dhananjay Shukla
Team : Dr. Jay Kalliath, Dr. Sangamitra Kanungo
Status : Data Collection over

Objective

To demonstrate the advantage of OCT over fluorescein angiography in detecting occult PED's in Chronic CSCR

Radial optic neurotomy for ischaemic central retinal vein occlusion: a case-control study

Principal clinician : Dr. Dhananjay Shukla
Team : Dr. Anand Rajendran, Dr. Sathya Kakade
Status : Data Collection over

Objective

To evaluate radial optic neurotomy as a treatment option for ischaemic central retinal vein occlusion against conventional treatment with photocoagulation.

Brilliant blue dye for internal limiting membrane peeling in macular surgery

Principal clinician : Dr. Dhananjay Shukla
Team : Dr. Jay Kalliath
Status : Data Collection over
Presented at AAO 2009 as Poster

Objective

To evaluate brilliant blue dye for internal limiting membrane peeling in macular surgeries like macular hole, epimacular membrane and tractional macular edema.

Laser photocoagulation for diabetic macular edema with serous retinal detachment

Principal clinician : Dr. Dhananjay Shukla
Team : Dr. Jay Kalliath
Status : Data Collection over

Objective

To evaluate the results of focal or grid photocoagulation for diabetic macular edema with serous retinal detachment as documented by optical coherence tomography.

Optical coherence tomography for subhyaloid haemorrhage of various etiologies

Principal clinician : Dr. Dhananjay Shukla
Team : Dr. Jay Kalliath
Status : Data Collection over

Objective

To determine the plane of cleavage in subhyaloid haemorrhage of various etiologies by optical coherence tomography

A study of combined occlusion of central retinal artery and vein

Principal clinician : Dr. Dhananjay Shukla
Team : Dr. Sanghamitra Kanungo, Dr. Anuradha Dhawan
Status : Data Collection over

Objective

To determine the systemic associations, diagnostic pitfalls and management options in combined occlusion of central retinal artery and vein

Vitreotomy for macula-threatening tractional retinal detachment in diabetic retinopathy

Principal clinician : Dr. Jay Kalliath
Team : Dr. Dhananjay Shukla

Objective

To evaluate the visual and surgical outcomes of macula-threatening tractional retinal detachment in unstable proliferative diabetic retinopathy.

Silicone oil tamponade in 23 gauge sutureless vitrectomy: long term anatomical and functional outcome

Principal clinician : Dr. Naresh Babu
Team : Dr. R.Kim
Dr. Bharat Ramchandani

Objective

To describe the feasibility of silicone oil tamponade as an option with sutureless 23 gauge vitrectomy system in varied vitreo-retinal etiologies.

Yag hyaloidotomy with gas tamponade as a viable option for pre macular haemorrhage in PDR against surgical intervention by pars plana vitrectomy

Principal clinician : Dr. Naresh Babu
Team : Dr. Bharat Ramchandani

Objective

To put up a viable and equally successful minimal intervention procedure for pre macular haemorrhage in PDR patients

IVTA Vs Macular PHC for diffuse diabetic macular edema—prospective study

Principal investigator : Dr. Anand Rajendran
Co-investigator : Dr. Sumi
Dr. Priyanka Mohini

Objective

To compare IVTA alone Vs Macular PHC alone treatment of diffuse diabetic macular edema.

Isolated intravitreal bevacizumab therapy for choroidal neovascular membranes of multiple aetiologies

Principal clinician : Dr. Anand Rajendran
Team : Dr. Bharat Ramchandani
Dr. Jay Kalliath
Dr. Shashank Rai Gupta

Objective

To report an angiographic and tomographic analysis of intravitreal bevacizumab monotherapy on choroidal neovascular membranes of various aetiologies.

Intravitreal bevacizumab as a preoperative adjuvant for diabetic macular tractional detachments with active new vessels

Principal clinician : Dr. Anand Rajendran
Team : Dr. R.Kim
Dr. Deepak A
Dr. Anuradha Dhawan

Objective

To determine the visual and anatomic outcome of intravitreal bevacizumab as a preoperative adjuvant for diabetic macular tractional detachments with active new vessels

Intravitreal bevacizumab therapy for polypoidal choroidal vasculopathy

Principal clinician : Dr. Anand Rajendran
Team : Dr. Shashank Rai Gupta

Objective

To evaluate intravitreal bevacizumab therapy for Polypoidal choroidal vasculopathy.

Retinochoroidal coloboma - a comparison of laser barrage photocoagulation versus natural history

Principal clinician : Dr. Anand Rajendran
Team : Dr. Bharat Ramchandani
Dr. Manish Tandon

Objective

To analyse the role of laser barrage of RCC without retinal detachment when compared to observation.

AT COIMBATORE

Comparison of the safety and efficacy of fluocinolone acetonide intravitreal inserts to sham injection in subjects with diabetic macular edema

Principal investigator : Dr. V. Narendran (Treating investigator)
Co-investigators : Dr. V.R. Saravanan
Dr. Rodney J Morris
Funding source : Alimera Sciences
Period : 3 year study with start date 22-November - 2006

Abstract

This study is designed to assess the safety and efficacy of ASI -001A and ASI-001B Fluocinolone Acetonide (FA) intravitreal inserts in subjects with clinically significant diabetic macular edema (DME) who have had at least 1 macular treatment. The primary objective is to determine whether either dose level of the injectable insert is superior to the control group with respect to the proportion of subjects who have an increase of 15 or more letters of BCVA (VA responders) at month 24 compared to baseline. Totally 25 subjects expected to be enrolled in the study and the Hospital randomized over 37 subjects. The subjects will be assessed by evaluating ocular AEs, visual acuity, IOP, concomitant medications, fluorescein angiograms, color fundus photographs, and slit lamp/dilated Ophthalmoscopy. And systemic safety will be assessed by evaluating non-ocular AEs, vital signs, concomitant medications and clinical laboratory tests. Summaries will be provided for each treatment group.

Investigation of efficacy and safety in wet AMD-view2 study

Principal investigator : Dr. Narendran Venkatapathy
Co-investigators : Dr. V.R. Saravanan
Dr. Rodney J Morris
Dr. Parag K Shah (Un-blinded SI)
Funding source : Bayer Schering Pharma
Period : 3 year study with 15 months enrollment period
(Start date- December 2006- Study Ends by 2011)

Abstract

To assess the efficacy of intravitreally (ITV) administered study drug compared to ranibizumab (in a non-inferiority paradigm) in preventing moderate vision loss in subjects with all subtypes of neovascular AMD and to assess the safety and tolerability of repeated ITV administration of Study drug in subjects with all subtypes of neovascular AMD for up to 2 years. Subjects will be evaluated every 4 weeks for safety and best corrected visual acuity (BCVA) using the 4 meter Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Quality of Life (QOL) will be evaluated using the NEI VFQ-25 questionnaire. Optical Coherence Tomography (OCT) and Fluorescein Angiography (FA) examinations will be conducted periodically. The effect of repeated ITV administration of study drug in vision-related quality of life (QOL) in subjects with all subtypes of neovascular AMD, as assessed using the NEI VFQ-25 will be analysed. Out of 200 subjects from India (Overall 1240 randomised subjects) the Hospital has randomised over 17 patients and 90% have entered their Second Phase of the Study (Maintenance Phase).

A multicenter, open study assessing the efficacy and safety of Ranibizumab (intravitreal injections) as adjunctive therapy to laser in patients with visual impairment due to Diabetic Macular Edema(DME)

Principal investigator : Dr. Narendran Venkatapathy
Co-investigators : Dr. Saravanan
Dr. Rodney J. Morris
Funding source : Novartis
Period : 1 year study with start date August-2009

Abstract

This study is designed to assess the efficacy and safety of Ranibizumab with the patients affected with Diabetic Macular Edema in atleast one eye and eligible for the laser treatment. The primary objective is to determine the efficacy of the drug. Patients are provided with 3 injections along with the laser treatment provided after the first injection. After completion of third injection patients are reviewed for every month with the usual procedures such as Vital signs, BCVA (Best Corrected Visual Activity), OCT (Optical Coherence Tomography) to find the efficacy of the Ranibizumab. Overall 19 cases have been enrolled and all have crossed their loading phase.

A 12 month randomised pilot study to compare the efficacy and safety of PDT (standard Fluence) plus intravitreal Lucentis vs. PDT (reduced Fluence plus intravitreal Lucentis)

Principal investigator : Dr. Narendran Venkatapathy
Co-investigators : Dr. Saravanan
Dr. Rodney J. Morris
Funding Source : Novartis
Period : 1 year study (Start date August-2007 to end date May-2009)

Abstract

This 1 year study was conducted at 10-12 Ophthalmology centres all over the country, enrolling a total of 60 Patients. The study was planned in such a way that subjects were asked to visit the site 13 times (13 Visits with Baseline, Month 1 to 12). The results will be analyzed for better understanding and to determine how effective is the use of combination therapy of Visudyne PDT with Lucentis and whether Visudyne administered with a reduced light dose is better than Visudyne administered with the standard light dose.

AT PONDICHERRY

Fame study

A randomised, parallel group, multicentre, dose finding, comparison of the safety and efficacy of ASI-001A 0.5G/Day And ASI-001B 0.2 G/Day Fluocinolone Acetonide Intravitreal Inserts To Sham Injections In Subjects With Diabetic Macular Edema

Principal investigator : Dr. R.D. Ravindran
Co-investigators : Dr. T.A. Aniruddha
Dr. Pankaja Dhoble
Duration : November 2006 - April 2010
Funding agency : SIRO Clinpharm Pvt.Ltd., Mumbai

Primary Objectives

The primary objectives are to determine whether either dose level of the injectable insert is superior to the control group with respect to the proportion of subjects who have an increase of 15 or more letters of BCVA (VA responders) at months 18 and 36 compared to baseline.

This trial will have two primary efficacy variables which will be split into 3 co-primary endpoints across 18 and 36 months. The first primary variable will represent a clinically significant visual acuity improvement and will be tested at months 18 and 36, and the second will represent a clinically significant worsening in the diabetic retinopathy scale and will be tested at month 36.

Secondary objectives

Secondary study objectives are

1. to choose the optimum dose level of intravitreal fluocinolone acetonide,
2. to compare the 2 dose levels versus the control group at other timepoints, and
3. to evaluate the efficacy of ASI-001A and ASI-001 B in DME and diabetic retinopathy using other relevant measures.

VITREOSOLVE : A phase 3 safety and efficacy study of Vitreosolve® for ophthalmic intravitreal injection for inducing posterior vitreous detachment in Retinopathy subjects

Principle investigator : Dr. R.D. Ravindran
Co-investigator : Dr. T.A. Aniruddha
Sponsor : Vitreo Retinal Technologies, Inc.
Duration of the study : 2008 - 2009

Objective

The objective of this study is to evaluate the safety and efficacy of Vitreosolve ® Ophthalmic intravitreal injection for inducing posterior vitreous detachment

VEGF trap–eye: investigation of efficacy and safety in wet AMD

A randomised, double masked, active controlled, phase 3 study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap-Eye in subjects either neovascular Age-related macular Degeneration (AMD)

Principal investigator : Dr. Pankaja Dhoble
Co-investigator : Dr. T.A. Aniruddha
Sponsor : Bayer Healthcare, Bayer Schering Pharma
Study duration : 2008 – 2011

Primary objective

To assess the efficacy of intravitreally (ITV) administered VEGF Trap-Eye compared to ranibizumab (in a non-inferiority paradigm) in preventing moderated vision loss in subjects with all subtypes of neovascular AMD.

Secondary objectives

To assess the safety and tolerability of repeated ITV administration of VEGF Trap-Eye in subjects with all subtypes of neovascular AMD for up to 2 years.

To assess the effect of repeated ITV administration of VEGF Trap-Eye in vision-related quality of life (QOL) in subjects with all subtypes of neovascular AMD, as assessed using the NEI VFQ-25.

To describe systemic exposure to the study drug.

ORBIT AND OCULOPLASTY SERVICES

AT MADURAI

National retinoblastoma registry

Investigators : Dr. Usha Kim
Co-investigator : Dr. R. Kim
Funded by : Indian Council of Medical Research (ICMR)
Duration : 36 months

The purpose of this study is to have a uniform, national, hospital based registry which will have a reliable database for all patients of retinoblastoma. The various parameters like age, sex, area, and staging of the disease, histological typing, uniform treatment protocol and response to treatment will be assessed.

Paediatric tumours are emerging as a national priority as they are curable in nature. The importance of this research proposal is that retinoblastoma is a treatable disease. The epidemiology of the disease has to be studied and this will enable us to identify the research areas in retinoblastoma and plan strategies to decrease the mortality and increase the global salvage rate. The overall aim of the research is to start a National retinoblastoma registry where retinoblastoma cases will be uniformly recorded from various centres treating retinoblastoma.

Inclusion of patients will be done after taking informed consent from the parents. Standard protocol of management will be followed after receiving informed consent. In doing so all centres involved in retinoblastoma management will be able to share and gain in all aspects of management of this potentially curable childhood cancer.

Randomised, double blind, active controlled study of the efficacy, surgical outcome and complications of Silicone Rod Sling in frontalis sling suspension surgery

Principal investigator : Dr. Usha Kim
Co-investigators : Dr. Kamalpreet

Objective

To compare the efficacy, surgical outcome and complication of Aurosling to Ethibond material in frontalis sling suspension surgery

Methodology

Patients eligible on the basis of inclusion and exclusion criteria will be included in this study after getting informed consent. Frontalis sling suspension surgery using Aurosling or Ethibond will be done. Patients will be followed up for observing the surgical outcome, amount of Ptosis correction and post surgical complication in all cases. The results will be statistically analysed

Socket reconstruction using Bio-engineered autologous oral mucosal epithelium

Principal investigator : Dr. Usha Kim
Dr. Kamalpreet
Co-investigator : Dr. Gowri Priya Chidambaranathan
Dr. VR. Muthukkaruppan
Period : January 2007- May 2009

The loss of eye is often followed by scar tissue contracture if not taken care of properly. Custom-made conformers can be used to enlarge unfavorably small sockets, improve hygiene, assist the clinician develop the final shape for the definitive prosthesis fitting. In order to retain the conformers in the socket, there is a need for a healthy epithelial support. In cases where the socket contraction is maximal, it is not possible to reconstruct the socket for the epithelial support with alternative tissue sources like dermis, conjunctival tissue etc., Therefore, it is essential to identify another alternative source in such cases. The objective of the present proposal is to use the patients own nonkeratinized buccal mucosal tissue for ex vivo expansion of buccal epithelium for socket reconstruction.

Oral Clonidine premedication in patients undergoing dacryocystorhinostomy under local anaesthesia

Investigator : Dr. Ravichander
Dr. Usha Kim
Dr. P.M. Aravind
Setting : Orbit Clinic, Aravind Eye Hospital, Madurai

Objective

The primary objective of this study is to evaluate the efficacy and safety of oral clonidine as a premedication in patients undergoing elective external dacryocystorhinostomy under local anaesthesia. Prospective, Double masked, Placebo controlled, Randomised controlled trial (RCT). 50 Subjects undergoing elective external dacryocystorhinostomy under local anaesthesia. Screened patients will randomly receive either placebo or 150 microgram clonidine tablet 90-120 minutes before the time of surgery. Blood pressure and heart rate will be recorded before the administration of medication. Pain (intra-operative and postoperative) will be recorded using the visual analog scale from 1-100. Postoperative request for additional analgesia, nausea or emetic episodes and dryness of mouth will be noted in the immediate post surgery period.

Prospective clinical evaluation of Dacryocystorhinostomy (DCR) with lacrimal intubation

Investigator : Dr. Usha Kim
Dr. P.M. Aravind
Dr. Kamal Preet
Setting : Orbit Clinic, Aravind Eye Hospital, Madurai

Objective:

To investigate the safety and efficacy of Aurolab silicone intubation for the management of Naso Lacrimal duct obstruction.

Design

Prospective, interventional clinical investigation. 30 subjects were recruited for this study. Informed consent were taken from the willing subjects. Diagnosis was made on history of epiphora, regurgitation test, lids examination, nasal examination, probing and syringing. Standard procedure of DCR was adopted in all cases with only anterior flaps suturing. Silicone tube was inserted and anchored to the nasal cavity near the external nostril. At the first follow-up skin sutures were removed. Tightness and mobility of the silicone tube was checked. At 3 months after surgery, the silicone tube will be removed and the lacrimal passage will be irrigated. The potency of lacrimal passage will be investigated by irrigation. A successful outcome will be defined as resolution of symptoms like epiphora and discharge and a patent lacrimal system on irrigation. Patients will be followed up on the tenth day and at first, third, sixth and twelfth months. As of now 30 patients have been recruited.

CORNEA SERVICES

AT MADURAI

AURO KPRO

Clinical investigator : Dr. Jeena Mascarenhas
Clinical trials have been started with the first indigenously manufactured keratoprosthesis – Aurokpro. The outcome measures are improvement in visual acuity and retention of the device.

Mycotic Ulcer Treatment Trial (MUTT)

Principal Investigator : Dr.N.Venkatesh Prajna
Project : Dr.Thomas Lietman
Sponsor : NEI
Study Centre : Aravind Eye Hospital (Madurai, Puducherry)

Study Objectives

The objective of the MUTT study is to determine which topical antifungal treatment, Voriconazole or Natamycin, results in a better visual acuity and in better clinical outcome for a subgroup of organisms. The study also aims to determine whether there is a co-relation between antifungal susceptibility and clinical outcome in fungal keratitis. The primary outcome is best spectacles corrected visual acuity three month after enrollment. This is a fixed block, randomised double masked controlled trial.

Steroids for corneal ulcer trial

This study in collaborations with proctor foundation and funded by NIH, has been completed.

SICCA study

Principal investigator : Dr. M. Srinivasan

Funding agency : NIH

The purpose of SICCA study is to be a part of the multicentric international registry of dry eye patients.

AT TIRUNELVELI

Steroids for Corneal Ulcer Trial

Principal investigator : Dr. M. Srinivasan

Co-investigator : Dr. R. Meenakshi
Dr. D. Lional Raj

Funding Source : Proctor Foundation, USA

Period : September 2006 - February 2010

The proposed study is a randomised, double-masked, placebo-controlled trial to determine whether adding topical steroids to conventional antibiotic therapy improves the outcomes of central bacterial corneal ulcers. Five hundred corneal ulcers presenting to the Aravind Eye Hospitals Cornea Clinics (Madurai, Tirunelveli, and Coimbatore), Dartmouth-Hitchcock Medical Center and the Proctor Foundation, University of California, San Francisco will be randomised to receive antibiotic plus steroid or antibiotic plus placebo. The primary outcome will be best spectacle-corrected visual acuity at three months. Bacterial keratitis, a suppurative bacterial infection of corneal stroma can range from a mild disease responsive to topical antibiotics, to a severe condition associated with dense scarring, perforation or loss of vision.

The objectives of the study are

- To determine whether adding topical steroids to the treatment of a bacterial corneal ulcer improves post-treatment visual acuity
- To determine whether the addition of topical steroids results in a higher frequency of adverse outcomes
- To determine whether outcomes depend on the causative organism

The primary outcome of the trial will be the best spectacle –corrected log MAR visual acuity three months after enrollment, using best spectacle-corrected enrollment visual acuity as a covariate.

The study is randomised, double-masked, placebo-controlled trial to determine whether adding topical steroids to conventional antibiotic therapy improves the outcomes of central bacterial corneal ulcers. The study is done in collaboration with Proctor foundation (UCSF). The study was started in Sep'06 at Tirunelveli. The duration of study was 3 years with an extension period till Feb2010. We have enrolled 156 patients at Tirunelveli, 238 patients at Madurai, 91 patients at Coimbatore, 7 patients at Proctor and 8 patients at Dartmouth. The last patient was enrolled on 22.02.2010 at Tirunelveli.

AT PONDICHERRY

Mycotic Ulcer Treatment Trial (MUTT)

Investigators : Dr. Thiruvengada Krishnan
Dr. N. Shivananda

Specific aims

1. To determine which topical anti-fungal treatment, voriconazole or natamycin, results in better visual acuity.
2. To determine which agent, voriconazole or natamycin, results in better clinical outcomes for subgroups of organisms.

3. To determine whether there is a correlation between antifungal susceptibility and clinical outcomes in fungal keratitis.
4. To determine whether scraping of the epithelium results in better visual acuity (Only for the pilot study)

Study design

The proposed study is a fixed block randomised, double-masked, controlled trial to which treatment, natamycin or voriconazole, is more effective than natamycin in the treatment of filamentous fungal corneal ulcers.

CATARACT AND IOL SERVICES

AT MADURAI

Posterior capsular opacification after implantation of square edge PMMA, Round edge PMMA and hydrophobic acrylic intraocular lenses: A prospective, randomised comparative trial

Investigators : Dr. Haripriya Aravind
 Dr. S. Aravind
 Dr. Raghavendra

Setting : Cataract Clinic, Aravind Eye Hospital, Madurai

Objective

To compare posterior capsular opacification (PCO) with Square edge PMMA, Round edge PMMA and Square edge hydrophobic acrylic intraocular lenses after in-the-bag implantation. Study design is a prospective, double masked, Randomised Controlled Trial (RCT). This study was registered at clinicaltrials.gov. 50 patients received square edge PMMA in one eye and round edge PMMA in fellow eye. In another group, 50 patients received square edge PMMA in one eye and Square edge hydrophobic acrylic in fellow eye. Patients are followed up at sixth month and first, second, third, fourth and fifth year post operatively. Outcome measures are visual acuity and PCO. To evaluate PCO and the position of the anterior capsulorhexis, retroillumination digital photographs were taken and PCO was analysed using EPCO software. 94 enrolled patients underwent both eye surgeries. 93 were followed up at first year, 89 subjects were followed up at second year and 84 were followed up at third year. Fourth year follow-up will start from May 2010.

Clinical evaluation of hydrophobic foldable IOLs

Investigators : Dr. Haripriya Aravind
 Dr. S. Aravind
 Dr. Niraj Agarwal

Setting : Cataract Clinic, Aravind Eye Hospital, Madurai

Objective

To evaluate the safety and efficacy of Hydrophobic Foldable Intraocular Lenses Aurovue (Aurolab) in cataract surgery. Study design is unilateral, prospective, open label clinical trial. This IRB approved study is being carried out in compliance with ISO, GCP and FDA standards and is registered at www.clinicaltrials.gov. Pilot study was completed with the sample size of 20. Aurovue lens was implanted by phacoemulsification. Patients are followed up on day 1, 2, 3, 7, 15 and first, second, third, and sixth month and first year post operatively. Main study is going on and the sample size is 120 subjects. To evaluate PCO and the position of the anterior capsulorhexis, retroillumination digital photographs were taken and PCO was analyzed using EPCO software. Enrollment was started on March 29, 2007. The accrual enrollment period was 18 months. Patients are followed up on day 1, 10, 40, 120 and at first, second and third year post operatively. As of now, 109 patients have completed second year follow up.

Both the pilot and main study outcome measures are visual acuity and lens status. Third year follow up is ongoing.

Capsule wash for paediatric eyes

Investigators : Dr. Haripriya Aravind
Dr. P. Vijayalakshmi
Dr. Rupal Trivedi (Storm Eye Institute, USA)
Setting : Cataract Clinic, Aravind Eye Hospital, Madurai

Objective

The objective of this study was to determine whether AquaLase® capsule wash decreases posterior capsule opacification (PCO) in paediatric eyes. This was a prospective; double masked randomised controlled trial (RCT). This study included bilateral strata and unilateral strata. For bilateral strata the sample size was 22 including 10% follow up loss. For unilateral strata the sample size was 6. Visually significant cataract patients aged between 6 and 15 were eligible for the study. Phacoemulsification with in the bag implantation of square edge hydrophobic acrylic intraocular lens was done in all subjects according to critically defined surgical protocol. For bilateral strata, capsule wash solution was randomly allotted. One group (Group 1) of eyes was washed with AquaLase® solution and another group (Group 2) of eyes was not washed with AquaLase® solution. Subjects were followed up on first day and at first, third, sixth, twelfth, eighteenth and twenty – fourth month post surgery. During follow up visits digital images focusing lens capsule with good red glow were taken for the study eyes.

To analyse the effect of CTR on Anterior Capsular Opening (ACO) in eyes with retinitis pigmentosa

Investigators : Dr. Rathini David
Dr. Haripriya Aravind
Setting : Cataract Clinic, Aravind Eye Hospital, Madurai

Objective

To analyse the effect of CTR on Anterior Capsular Opening (ACO) in eyes with Retinitis Pigmentosa. Study design is a prospective; double masked randomised controlled trial (RCT). Patient will be allotted into with CTR or non CTR group using randomisation table. Phacoemulsification with in the bag implantation of foldable IOL will be done for 40 patients. CTR will be placed for with CTR arm. Patients will be followed up at first, third, sixth, ninth and twelfth month post operatively. ACO will be evaluated using EPCO software.

Calculation of extent of anterior capsule contraction will be calculated using the following formula

$$\text{Extent of Anterior Capsule Contraction} = \frac{\text{Reduction of ACO (\%)}}{\text{Baseline ACO (\%) (1day Post operative)}} \times 100$$

This is the first time a study of this nature was conducted to assess the role CTR in ACO in Retinitis Pigmentosa patients, however no statistical significance in the rate of capsule contraction was found in the CTR and control group.

Hemodynamic response to routine phacoemulsification among normal healthy ophthalmic surgeons during high volume cataract surgery

Investigators : Dr. P.M. Aravind, Dr. Haripriya
Setting : Cataract Clinic, Aravind Eye Hospital, Madurai

Objective

To investigate the hemodynamic response to the stress of performing routine phacoemulsification (PE) among healthy ophthalmic surgeons in a high volume cataract surgical setup.

Methods

Fourteen surgeons, formally trained in PE, having different levels of experience and skill were recruited in a tertiary eye care hospital for this observational, cross sectional study. After establishing their baseline blood pressure (BP) and heart rate (HR) they underwent continuous electronic monitoring of their hemodynamic parameters as they performed multiple PEs. The overall procedure of PE was divided into five serial stages: wound construction, capsulorhexis, PE proper (nucleofractis+emulsification), irrigation-aspiration and IOL implantation. The HR corresponding to each phase and the BP at the end of each surgery were recorded.

Results

The results showed that a mean pulse difference from baseline was at a peak during stage 3. Change in systolic and diastolic BP over the course of multiple surgeries analysed using repeated measure ANOVA was not significant. Stratification of the group based on age, gender, years of experience and number of surgeries showed no statistical significance in BP. Two surgeons who showed consistently high HR during surgery were counselled by a physician to better manage their stress.

Comparison of phacoemulsification vs. SICS: A randomised control trial

Investigators : Dr. Haripriya Aravind, Dr. Tamilarasi
Setting : Cataract Clinic, Aravind Eye Hospital, Madurai

Objective is to compare the surgical outcomes of Phacoemulsification (PE) with small incision cataract surgery (SICS) in patients with senile cataract and the improvement in quality of life using two cataract extraction methods. Study design is a multicentric, prospective, interventional, randomised controlled trial. 140 patients were randomized in 1:1 ratio. For PE group, phacoemulsification was done under topical anesthesia using Infiniti machine, 3 mm clear corneal incision and phaco chop technique with in the bag placement of single piece foldable (SN6OWF) IOL. For SICS group, small incision cataract surgery was done under retro bulbar anesthesia through superior scleral tunnel (7 mm) with in the bag placement of single piece PMMA (MZ6OBD) IOL. Surgical time, amount of BSS, ophthalmic viscosurgical device (OVD), sutures used and any intra operative complications were recorded. Patients are followed up at second week, first, third, sixth and twelfth month post operatively. Post operative evaluation includes visual acuity, slit lamp examination, IOP, corneal astigmatism using manual keratometer, contrast sensitivity and quality of life (QOL) evaluation using visual function questionnaire -14. As of now 103 subjects completed sixth month follow up.

Role of wetlab training in donor eyes and simulator for learning capsulorhexis

Investigators : Dr. Haripriya Aravind
Dr. Neeraj kumar
Dr. Parna Deb Roy
Dr. Tan Preet Pal Singh
Setting : Aravind Eye Hospital, Madurai

Objective

To compare the role of donor eyes and EYESi surgical simulator in capsulorhexis training of novice surgeons

Method

It is a prospective clinical trial in which eight residents with experience of ECCE were included in the study and they were divided into two groups. Each group contains four residents. Group -1 initially underwent wet lab capsulorhexis training on simulator and group -2 on donor eyes over a period of 15 days each. This was followed by their capsulorhexis scoring for initial nine SICS cases under supervision of investigator.

The criteria for scoring included

- Raising flap
- Circularity
- Time
- Tissue protection
- Completion of rhexis

Each criterion was scored as 1 on completion or else it was scored as 0.

On the basis of individual scores in both the groups, the validity of both the tools ie simulator and donor eyes will be compared. As of now, scores of 7 residents have been recorded and the study is ongoing.

Cataract and its treatment – patient awareness and public myths

Investigators : Dr. Aravind Palanisamy Murugesan
Dr. Haripriya Aravind
Mr. Heber John David
Dr. Madhushekhar

Aim

To study level of public awareness about cataract – the disease and its management

Methods

A detailed 26 point questionnaire designed with experts in public screening and biostatistics, was administered to a study group of 351 patients and attendants who came to a tertiary eye care centre for treatment of defective vision or cataract surgery review. It captured information about the educational, demographic and socioeconomic background of the respondents and their exposure to popular informative media. It assessed the general awareness about the disease, its treatment and the latest surgical management. Special focus was on the common myths in cataract surgery

Results

The major source of information about cataract was by word of mouth (22.81%); newspaper (12.5%), radio (5.63%) and Internet (2.19%) were the other accessed sources. The majority (27%) believed they didn't get any exposure about cataract through any media. The awareness about cataract and its need for timely surgery was quite high (68.68 to 80%) but the knowledge about the type of surgery and the advantages of phaco was dismally low (24.28%). Many thought phaco was a laser (41.28%), including those who had undergone counselling and surgery (47.73%)

Conclusion

Access to sources of public information about cataract is limited. Word of mouth spread remains the mainstay and multiple wrong notions about phaco prevail. A public oriented campaign to spread the right information about cataract and its management is needed

Comparison of secondary PCIOL, iris fixated IOL and scleral fixated IOL

Investigators : Dr. Haripriya Aravind
Dr. Tamilarasi
Dr. Chhanda Ghosh
Setting : Aravind Eye hospital, Madurai

Aim

To evaluate and compare the technique, intraoperative and post operative complications and visual outcome of secondary PCIOL, iris fixated (IF) and scleral fixated IOL (SFIOL).

Methods

In this retrospective study 148 eyes of 148 aphakic patients underwent secondary IOL implantation between January 2007 and December 2008. Patients were divided into 3 groups-group 1-secondary PCIOL (n=60), group 2-secondary IFIOL (n=67), group-3 SFIOL (n=21). Detailed anterior and posterior segment evaluation, biometry and IOL power calculation by IOL master was done in all patients. Surgery was conducted under retrobulbar anesthesia in all patients. Patients were followed up on day 1 and at first, third and sixth month.

UVEA SERVICES

AT MADURAI

A double – masked, Placebo-controlled, multicentric, parallel group, dose ranging study to assess the efficacy and safety of LX211 as therapy in subjects with non-infectious intermediate, anterior and intermediate, posterior or pan-uveitis

Principal investigator : Dr. SR. Rathinam, Aravind-Madurai
Dr. B. Manohar Babu, Aravind-Coimbatore
Co-investigator : Dr. Venu Nadella, Aravind-Madurai
Duration : 18months – 12months recruitment, 6 months follow up

Objective

LX211 is likely to have an improved safety profile compared to cyclosporine. A lower therapeutic dose can be used and the correlation of dose with blood concentrations has been improved. The objective was to study the safety and efficacy of LX211 as treatment and as maintenance in subjects with uveitis.

LX 211-01 : Treatment of active sight threatening non infectious intermediate, anterior and intermediate, posterior or pan-uveitis
LX211-02 : Treatment of clinically quiescent sight threatening, non-infectious intermediate, anterior and intermediate, posterior or pan uveitis
LX211-03 : Treatment of active sight threatening non infectious anterior uveitis

Protocol: CAIN457C 2303 : A 24 week multicenter, randomised, double-masked, placebo controlled study to assess the difference in the rate of recurrent exacerbations in Behçet's patients with posterior or panuveitis treated with AIN457 vs. placebo adjunctive to standard-of-care immunosuppressive therapy

Principal investigator : Dr. S.R. Rathinam, Aravind-Madurai
Co-investigator : Dr. S. Balamurugan, Aravind-Madurai
Duration : 6 months

Objectives

To determine if subcutaneous AIN457 given adjunctive to standard-of-care immunosuppressive therapy is more effective than placebo given adjunctive to standard-of-care immunosuppressive therapy in reducing the rate of recurrent ocular exacerbations in Behçet's disease.

Protocol CAIN457C2301: A 24 week multicenter, randomised, double-masked, placebo controlled, dose -ranging phase 3 study of AIN 457 versus placebo for maintaining uveitis suppression when reducing systemic immunosuppression in patients with quiescent ,non-infectious intermediate, posterior or panuveitis (ENDURE study)

Principal investigator : Dr. S.R. Rathinam, Aravind-Madurai
Dr. B. Manohar Babu, Aravind-Coimbatore
Co-investigator : Dr. S. Balamurugan, Aravind-Madurai
Dr. Narendran, Aravind-Coimbatore

Funding agency : NOVARTIS
Duration : 6 months

Objectives

To determine the efficacy of subcutaneous AIN457 compared to placebo for maintaining suppression of intraocular inflammation and prevention of an active intermediate, posterior or panuveitis recurrence during the withdrawal of concomitant immunosuppressive therapy in adults with quiescent, non-infectious, uveitis affecting the posterior segment.

PAEDIATRIC OPHTHALMOLOGY SERVICES

AT MADURAI

A2Z Child blindness and eye health project

Project executive : Dr. P. Vijayalakshmi
Funding agency : Academy for Educational Development
Duration : 1st October 2008 to 31st July 2010 (22 months)
Purpose : To strengthen the existing paediatric service
Service area : Aravind Eye Hospital, Madurai

Objective

- To increase the number of children surgically treated
- To identify and provide spectacles to the needy children in the schools
- To create awareness about paediatric eye diseases among teachers
- To screen for ROP and to treat the indicated babies in NICUs
- To create awareness about ROP among paediatricians and Gynaecologist.

Main activities

- Cataract surgery
- School screening
- Paediatric eye camps
- ROP Screening.

Reporting method

All the reports should be submitted in A2Z prescribed format

Quarterly

- Performance report
- Financial report
- Monitoring and evaluation report

Annual report should cover entire report of 12 months in same quarterly report format.

Deliverable

School Screening camp

- 450 teachers to be trained
- 70 school screening camps conducted
- 70,000 students to be screened (0-15 yrs.)
- 4,400 spectacles distribution

Paediatric eye camp

- 14 paediatric eye camps conducted
- 4,800 children to be screened (0-15 yrs.)

- 800 spectacles distribution
- Cataract surgeries (0 - 15 years)
- 525 children should receive foldable IOLs
- ROP Screening
- 500 babies to be screened for ROP
 - 90 laser procedures will be provided to the ROP babies

Effect of square edge PMMA IOL in preventing lens epithelial cell migration in paediatric cataract surgery: A randomized controlled trial

Investigators : Dr. P. Vijayalakshmi, Dr. Shashikant Shetty
 Setting : Paediatric Clinic, Aravind Eye Hospital, Madurai

Objective

To compare posterior capsule opacification (PCO) with Square edge PMMA and Acrysof intraocular lenses in paediatric cataract surgery. Study design is double masked, Randomized Controlled Trial. Paediatric patients with bilateral cataract of 5 to 10 years of age willing to participate in the study are enrolled into this study. Sample size is 30 paediatric patients. Enrolment was started on August, 2006. 19 patients were enrolled in this study. Follow up period is 30th day, 180th day, 360th day and 720th day post operatively. Digital photographs were taken during each follow up and PCO was analysed using EPCO software. 14 subjects completed one year follow up and second year follow up is ongoing.

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- *Leptospiral uveitis in the developing world*

OPERATIONS RESEARCH

Comparison of Uptake of spectacles for refractive error across different delivery systems – A cluster randomised controlled trial

Principal investigator : Dhivya T. Ravilla
Co-investigators : Mr. Sanil Joseph
Mr. R.D. Thulasiraj
Mr. V. Vijayakumar
Mr. Vinod Mitta
Mr. Jeyaram Ilayaraja

Introduction

Refractive services remain restricted to urban areas and the traditional means of receiving spectacles is through hospital-based or individual optical shops. Aravind Eye Hospitals' outreach camps extend refractive correction services to rural areas by prescribing, fitting and dispensing spectacles on-the-spot. The effectiveness of immediate spectacles dispensing has not been assessed in literature. This study compares the uptake of spectacles for refractive error across different delivery models.

Objectives

- To compare uptake of spectacles across different refractive service delivery models
- To compare costs in acquiring spectacles
- To measure the impact of spectacle correction on quality of life

Current Status:

Completed. Getting ready for publication.

Gender analysis of Cataract Surgical Services in South India

Principal investigator : Mr. Sanil Joseph
Co-investigators : Mr. R.D. Thulasiraj
Mr. Jeyaram Ilayaraja

Interest in gender issues in blindness programs is relatively recent and is still not appreciated by many organisations or individuals who work in the field of eye care. This issue of gender inequity in eye care was first exposed in a meta-analysis of population-based surveys conducted in Asia, Africa and industrialised countries between 1980 and 2000; results of which were published in 2001. Results showed that approximately two out of every three blind people in the world are women, most of who are older, and ninety percent of who live in poverty. The Gender Study at Aravind investigated socio-demographic and clinical characteristics among the users of cataract surgical services at Aravind Eye Hospitals looking for inequity both between and among different socio-economic levels.

Current Status

Completed. Getting ready for publication

Human resource practices which influence employee satisfaction and patient satisfaction

Internal guide	:	Mr. R.D. Thulasiraj
External guide	:	Dr. V.R. Muraleedharan, Professor and Head of Department, Humanities and Social Sciences, IIT Madras Dr. T.J. Kamlanabhan, Professor, Department of Management Studies, IIT Madras
Research scholar	:	Ms. Preethi Pradhan, LAICO

Introduction

Extant literature has demonstrated there is strong link between employee satisfaction and patient satisfaction. To take this evidence further, hospitals are keen to understand which of the human resources practices can influence patient satisfaction and employee satisfaction. There is a dearth of evidence in the health care sector which has attempted to decode this. This study set in the eye care sector examines these three concepts of patient satisfaction, employee satisfaction and human resource practices and the linkages between them from a developing country perspective like India. This study aims to contribute to policy which deals with human resource in health besides tool development.

Objectives of the study

- To develop an instrument for measuring patient satisfaction
- To validate an instrument for measuring employee satisfaction and perception of human resources in the eye hospital context
- To compare employee satisfaction, patient satisfaction and perception of human resource practices in the government sector as well as in the private not for profit sector
- To study whether the link between employee perception of human resource practices on patient satisfaction is mediated by employee satisfaction

Current status

Chapter corrections are in the final stage. Thesis will be submitted by July 2010.

PRODUCT DEVELOPMENT

Aurovue new metal injector

January 2010

Aurolab's IOL division introduced the metal injector for Hydrophobic Acrylic lens – Aurovue. This new improved delivery system was developed to bring delivery system user friendly to the surgeon. This delivery system is gaining acceptance in the ophthalmic society.



Aurolac

January 2010

Aurolab's suture division launched Aurolac, Lacrimal Intubation. This product finds its application in DCR surgeries. DCR or Dacryocystorhinostomy is a surgery performed to create a new drain between the eye and nose when the current tear drain becomes blocked or obstructed. Aurolac comprises of Medical graded silicone for excellent biocompatibility & longer retention time and Malleable and convenient probes for easier insertion through the canaliculi & nasolacrimal duct. This medical graded silicone provides tension free post operative period for surgeons.



Nanocut

January 2010

Aurolab's Blade division launched "Nanocut" Superior Technology blades.



Aurosil plus

August 2009

Aurolab's pharmaceutical division launched "Aurosil Plus" Silicone Oil 5000 mm²/s (cSt). This product is used for prolonged tamponade after surgical treatment for severe retinal detachment. As soon as the product is launched we have got the CE Certificate also.



Eye drops

Aurolab's pharmaceutical division has also launched the following eye drops during last year.

"TOB-DEX" Tobramycin 0.3% + Dexamethazone sodium phosphate 0.1% antibiotics with steroid drug introduced on July 2009.

"G-FLOX" Gatifloxacin 0.3% antibiotic drug introduced on September 2009

"AUROPROST" Latanoprost 0.005% agent for glaucoma introduced on November 2009. Our Auroprost is the only brand which is economically priced when compared with all other available brands to serve even the poorer.

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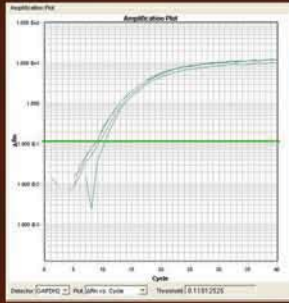
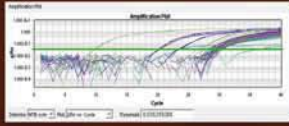
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RESEARCH SCHOLARS AT AMRF

Scholar's Name	Guide	Project
T. Amala Raja Sundari Post Doctoral Fellow	Dr. VR. Muthukkaruppan Dr. Anand Rajendran	Molecular Biology of human retinal pigment epithelial cells and age related macular degeneration
B. Suganthalakshmi Pre Doctoral Fellow	Dr. P. Sundaresan Dr. SR. Krishnadas	Association studies for glaucoma and mutation screening for congenital cataract
P. Murugeswari JRF-ALCON	Dr. VR. Muthukkaruppan Dr. R. Kim Dr. D. Shukla	Pathogenic mechanism of diabetic retinopathy
S. Ananthi JRF-DBT	Dr. N.V. Prajna Dr. K. Dharmalingam	Pathogen host interaction in human mycotic keratitis
B. Hemadevi JRF-DST	Dr.P.Sundaresan Dr. J. Arun Kumar Dr. M. Srinivasan	Genetic and functional analysis of Fuch's Endothelial Corneal Dystrophy (FECD) and Congenital Hereditary Endothelial Dystrophy (CHED) in Indian patients
S. Jeyalakshmi JRF-ALCON	Dr. C. Gowri Priya Dr. N.V. Prajna Dr. VR. Muthukkaruppan	Characterisation of buccal epithelial stem cells
K. Renugadevi JRF-DBT	Dr. P. Sundaresan Dr. P. Vijayalakshmi	Identification of genetic defects occurring in Indian Oculocutaneous (OCA) and Ocular Albinism (OA) families
Ashwini Shanker Senior Technician-INDEYE	Dr. P. Sundaresan Dr. R.D. Ravindran	A Genetic component to the INDEYE study of cataract and age related macular degeneration in India
T. Lalitha Senior Technician-AEH	Dr. C. Gowri Priya Dr. N.V. Prajna Dr. VR. Muthukkaruppan	Ex vivo expansion of limbal epithelial cells for transplantation
M. Lalan kumar Arya JRF-ALCON	Dr. SR. Rathinam Dr. Lalitha Prajna	Etiology and Immunopathogenesis of trematode induced Uveitis
Anshuman Verma JRF-UGC	Dr. P. Sundaresan Dr. P. Vijayalakshmi	Molecular genetics of Leber congenital amaurosis in South Indian population
Sushil Kumar Dubey JRF -ALCON	Dr. P. Sundaresan Dr. SR. Krishnadas	Screening of LOXL1 gene mutations in exfoliation glaucoma patients
R. Siva Ganesha Karthikeyan JRF-ALCON	Dr. Lalitha Prajna Dr. K. Dharmalingam	Elucidating the virulence genes involved in the pathogenesis of corneal ulcers by <i>Aspergillus sps</i> and the study of host response via the expression of Toll-like receptors
S. Sudhapriya JRF ALCON	Dr. VR. Muthukkaruppan Dr. Anand Rajendran	Histopathology of human donor retina in relation to AMD
M. Valar Nila Senior Technician-AMRF	Dr. K. Dharmalingam Dr. VR. Muthukkaruppan	Proteomic profiling of serum in proliferative diabetic retinopathy

Name	Guide	Project
C. Jeyashree JRF -ICMR	Dr. P. Sundaresan Dr. Usha Kim	Genetics and functional dissection of FOXL2 gene involved in the pathogenesis of the Blepharomosis syndrome (BPES)
P. Mohanapriya Junior Technician-ICMR	Dr. P. Sundaresan Dr. Usha Kim	Genetics and functional dissection of FOXL2 gene involved in the pathogenesis of the Blepharomosis syndrome (BPES)
N. Prasanthi Senior Technician-AMRF	Dr. P. Sundaresan Dr. S. Krishnaswamy Dr. SR. Krishnadas	Biophysical characterisation of human myocilin and glaucoma database
V. Saravanan Junior Technician-INDEYE	Dr. P. Sundaresan Dr. R.D. Ravindran	A Genetic component to the INDEYE study of cataract and age related macular degeneration in India
J. Radha Junior Technician-INDEYE	Dr. P. Sundaresan Dr. R.D. Ravindran	A Genetic component to the INDEYE study of cataract and age related macular degeneration in India
J. Cornelia Reena JRF-DBT	Dr. Lalitha Prajna Dr. SR. Rathinam	Molecular insights into the etiology of infectious uveitis
Minu Jenifer Senior Technician-ALCON	Dr. VR. Muthukkaruppan Dr. Anand Rajendran	GMP facility and autoantibody profile in age related macular degeneration
Prasanya Selvam Senior Technician-AMRF	Dr. C. Gowri Priya Dr. VR. Muthukkaruppan	Monoclonal antibody and expression of p63 in relation to stemness in corneal epithelial cells
Paul Pown Raj JRF-DBT	Dr. SR. Krishnadas Dr. P. Sundaresan Dr. K. Dharmalingam	Identification of biomarkers for primary open angle glaucoma
Merlin Premalatha Senior Technician-ALCON	Dr. C. Gowri Priya Dr. SR. Rathinam	Antigenic mimicry between Leptospiral and human lens proteins
G. Gowthaman JRF-DBT	Dr. P. Sundaresan Dr. R. Kim	Transcriptome and Proteome analyses of ALR2 and its involvement in the pathogenesis of diabetic retinopathy
SR. Bhuvanasree Senior Technician-AMRF	Dr. K. Dharmalingam Dr. Lalitha Prajna	Proteomic analysis of <i>Aspergillus-flavus</i> secretome, isolated from fungal keratitis patients
J. Thilagavathi Project Assistant-AMRF	Dr. Senthilkumari	HPLC Analysis
J. Lakshmi Priya Senior Technician -AEH	Dr. Lalitha Prajna	Characterisation and speciation of <i>Aspergillus</i> and <i>Fusarium</i> species from corneal ulcer



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