Global Eye Genetics Consortium

Newsletter #05

Foreword

Applications of Induced Pluripotent Stem (iPS) Cells for Understanding and Treatment of Genetic Eye Diseases

Induced pluripotent stem (iPS) cells were first discovered in 2006 by Shinya Yamanaka and his team. By introducing four specific genes (Oct3/4, Sox2, Klf4, and c-Myc) into adult fibroblasts, they successfully reprogrammed these somatic cells to an embryonic-like pluripotent state. This groundbreaking discovery earned Yamanaka a Nobel Prize in 2012 and revolutionized the field of regenerative medicine. Over the last 15 years iPS cells have demonstrated unparalleled potential for developing precise disease models. Researchers can derive iPS cells from patients with specific genetic disorders, differentiate them into the affected cell types including cells of the eye (retina, retinal pigment epithelium, choroidal cells), and study the disease mechanisms in vitro. This approach has allowed for a better understanding of disease pathology and in several cases leading to the development of targeted therapies.

Despite their potential, there is a significant disparity in iPS cell production based on ethnicity. The majority of iPS cell lines have been derived from individuals of European descent, leading to a lack of representation of diverse genetic backgrounds. This disparity can result in biased research findings and limited applicability of therapies across different ethnic groups. Understanding disease mechanisms and developing treatments that are effective for all populations requires a diverse range of iPS cell lines. Furthermore, ethnicity-specific iPS cells are crucial for addressing health disparities and ensuring that medical research and treatments are inclusive. These cells can help uncover genetic variations and disease susceptibilities unique to different ethnic groups, leading to more effective and personalized treatments. Additionally, studying ethnicity-specific iPS cells can improve the understanding of how genetic diversity impacts disease progression and treatment responses.

To solve the shortage of ethnicity-specific iPS cells, it is essential to increase funding and support for initiatives aimed at creating diverse iPS cell lines. Collaboration between international research institutions, governments, and private organizations can facilitate the establishment of biobanks representing various ethnicities. By addressing these challenges, we can create a more inclusive and equitable landscape for iPS cell research and its applications.Through concerted efforts by international consortia like GEGC, we can overcome the current limitations and harness the full potential of iPS cells to advance personalized and equitable healthcare.

Dr. Kapil Bharti
PhD
Chief Scientific Officer, GEGC
Division of Intramural Research, National Eye Institute, NIH
Bethesda, MD, USA

Recent Events: *The annual GEGC meeting, ARVO, Seattle May 6th, 2024*

The annual GEGC meeting was held on May 6th during ARVO in Seattle this year. The event was attended by over 35 eminent scientists and clinicians from across the globe. This meeting marked a significant milestone in GEGC history, highlighting the integration of induced pluripotent stem cell (iPSC) research with genetic research. The convergence of these fields underscores how advancements in one area can drive progress in the other, enhancing our understanding of biology and improving medical treatments. The GEGC founders wisely incorporated iPSC research into the consortium's primary goals.

Dr. Kapil Bharti, a senior investigator at the National Eye Institute (NEI) and leader of the Ocular and Stem Cell Translational Research Section at NEI, has agreed to serve as the Chief Scientific Officer of GEGC. His leadership is expected to drive innovative research and advancements in uncommon eye diseases. Dr. Gyan "John" Prakash announced the merger of iPSC research with GEGC, and Dr. Bharti emphasized the importance of this integration and the mutual benefits of combining genetics and iPSC research.

This meeting also celebrated the 10th anniversary of GEGC. Dr. Iwata presented the consortium's growth from 25 members to 230 members across 38 countries. He highlighted GEGC's achievements and future vision, followed by an interactive discussion on the organization's next steps.

Dr. Iwata announced changes in the GEGC executive committee:

- Dr. Calvin Pang retired from his role as Chief Scientific Officer and from the Department of Ophthalmology and Visual Science, Chinese University of Hong Kong.

- Dr. Paul Baird retired from his position as Vice President of GEGC and from the Department of Surgery, Ophthalmology, Faculty of Medicine, Dentistry, and Health Sciences, University of Melbourne, Australia. He was succeeded by Dr.Yingbin Fu, Associate Professor at Baylor College of Medicine, Houston, Texas, USA.

Dr. Fu outlined his plan to secure a research grant in age-related macular degeneration (ARMD) from NIH, which could significantly fund GEGC's research initiatives. Dr. Shailja Tibrewal, Secretary General of GEGC and Senior Consultant at Dr. Shroff's Charity Eye Hospital, New Delhi, India, spoke about the power of collaborative research, citing the Bodhya Eye Consortium in India. This consortium has collectively published nine articles on common and rare eye diseases.

Prof. Natarajan, Vice President of GEGC and associated with the Aditya Jyot Foundation for Twinkling Little Eyes, Mumbai, India, was announced as the new treasurer of GEGC. He discussed surgical advances in inherited retinal disorders, a rapidly growing field in genetic eye research.

The meeting featured interactive discussions on various topics, including:

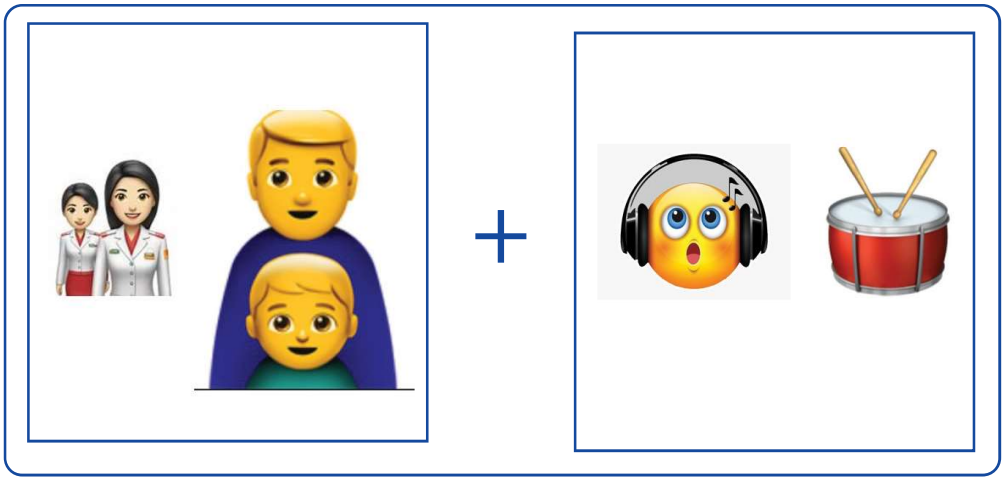
- Creating platforms for uniform data collection
- Enhancing international collaboration to accelerate genetic research
- Collective grant writing
- Opportunities to collaborate with pharmaceutical companies and biotech firms
- Connecting researchers from various institutions to foster joint research projects

In his closing remarks, Dr. Gyan "John" Prakash expressed optimism that the research conducted would translate into real-world benefits for patients with genetic eye diseases.

Upcoming Events

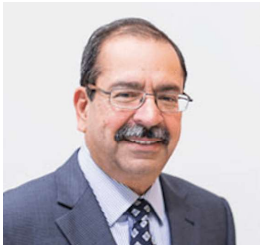
Trivia

Guess this Disease



HINT: Skull bones fusion confusion!

Meet Our Members



Dr. Nitin Verma is a highly accomplished ophthalmologist and a prominent figure in the medical community, particularly within the realm of ophthalmology. Born into a family with a background in professional engineering, Dr. Verma's journey led him to pursue a career in medicine, specifically in the field of ophthalmology.His professional journey commenced in 1981 when he began his ophthalmology training at the Dr. RP Centre for Ophthalmic Sciences at the All-India Institute for Medical Sciences in New Delhi. Under the comprehensive training program offered there, he gained expertise in various subspecialties of ophthalmology, encompassing clinical practice, research, and surgical skills. Following his training, he worked for two years in Germany, conducting research on silicon IOLs (intraocular lenses). In 1994, Dr. Verma moved to Papua New Guinea, where he established an eye health program with a focus on postgraduate teaching. His commitment to improving eye health extended further when he relocated to Darwin in 1997, where he played a pivotal role in running the Aboriginal Eye Program in the Top End. During this time, he underwent the process of assessment for recognition as a Specialist International Medical Graduate (S-MIG) in Australia, eventually becoming a Fellow of the Royal Australian and New Zealand College of Ophthalmologists (FRANZCO) in 2000.Dr. Verma's contributions to ophthalmology extend beyond clinical practice. He has been actively involved in various initiatives aimed at international development and outreach, particularly in the Asia-Pacific region. Notably, he founded the East Timor Eye Program in 2000, which has evolved into the national Eye Service in Timor Leste, training numerous ophthalmologists and eye health professionals over the years. Since its inception the prevalence of blindness in Timor Leste has been reduced from 7.7% to 2.9%. Now the Program is established, the focus has switched to building capacity in the local Timorese eye health workforce through education, clinical service delivery, training and on the job mentoring in addition to advocating government funded programs to improve the eye health of the Timorese people.He has now turned his attention to the South Pacific and is working hard towards ensuring self-sufficiency in eye care in the region. His dedication to internationaldevelopment in ophthalmology has earned him accolades and recognition, including the RANZCO Distinguished Service Award in 2006,College Medal in 2023 and appointments as Honorary Consul for Timor Leste in Tasmania and the Dean of the Consular Corps. In addition to his clinical and humanitarian work, Dr. Verma has been deeply involved in professional organizations such as RANZCO, where he served in various capacities, including as President. During his tenure, he spearheaded initiatives to advance equity in eye care, promote sustainability, and enhance professional development opportunities for ophthalmologists.Outside of his professional endeavors, Dr. Verma is a devoted family man, sailor and a skilled woodworker, finding solace and fulfillment in the meticulous craft of woodturning.Dr. Nitin Verma's multifaceted contributions to ophthalmology, international development, and professional leadership underscore his commitment to improving eye health and well-being on a global scale.

Professor Guy LJ Chen holds the positions of Professor in the Department of Ophthalmology and Visual Sciences and Head of the Graduate Division ofOphthalmology and Visual Sciences at The Chinese University of Hong Kong. Additionally, he serves as an Honorary Consultant at the Prince of Wales Hospital and the Hong Kong Eye Hospital, specializing in vitreoretinal and macular diseases.

Professor Chen is actively engaged in cutting-edge ophthalmic research, focusing prominently on the molecular and clinical genetics of major eye diseases. His research spans a wide spectrum including macular and retinal diseases such as age-related macular degeneration, polypoidal choroidal vasculopathy, central serous chorioretinopathy, diabetic retinopathy, retinitis pigmentosa, and other inherited retinal dystrophies. He also investigates glaucoma, myopia, and the genetic profiling of myopia progression and ocular traits in children. Together with his team, Professor Chen has identified numerous new disease genes, loci, mutations, association profiles, and biomarkers that have significantly advanced understanding and treatment options for these conditions.

With an impressive academic record, Professor Chen has authored over 200 papers in SCI internationally indexed peer-reviewed journals, with a notable H-index of 52 as of July 2024. He has co-authored a number of articles in high-impact journals, including JAMA, Nature Medicine, Nature Genetics, Lancet Oncology, Lancet Global Health, Nature Communications, JAMA Network Open, and Ophthalmology.

Professor Chen is also actively involved in securing research funding, serving as the principal investigator for 10 major local (Hong Kong), national (China), and international competitive research grants, totalling more than HK$10 million.Professor Chen's dedication to advancing global ophthalmic knowledge is further underscored by his extensive international academic service. He served as the Co- congress President and Co-chair of the Scientific Program Committee of the Asia-Pacific Vitreo-retinal Society (APVRS) Annual Congress 2023 Hong Kong. He also served as Council Member of APVRS, and Secretary General of the Hong Kong Vitreo-retinal Society (HKVRS). He has delivered over 50 invited lectures and chaired more than 20 sections at prestigious international conferences including the World Ophthalmology Congress, Asia-Pacific Academy of Ophthalmology (APAO) Congress, and International Symposium of Ophthalmology. He has also obtained a number of international awards, including the Constable Lecture Award in the APVRS Annual Congress 2019.Professor Chen's contributions continue to shape the field of ophthalmology throughhis groundbreaking research and leadership in genetic studies and disease prevention.

Dr. Ch. Mohan Rao, an eminent Indian molecular biologist, has made significant contributions to biophysics and molecular biology. He is celebrated for his pioneering research in heat-shock proteins and molecular chaperones in health and disease. A DNA-based diagnostic chip developed by him in a multi-institutional project is commercialised and won the "Product of the Year" award in India and was recognised as a major unmet need in biotechnological products in the Asia-Pacific region.

He has obtained a BSc degree from Osmania University, and an MSc (chemistry) from Kaktiya University. Dr. Rao received his PhD in chemistry from the University of Hyderabad in 1984, focusing on photoacoustic spectroscopy of chemical and biological systems.His illustrious career includes serving as the Director of the Centre for Cellular and Molecular Biology (CCMB), Hyderabad, where he significantly advanced molecular biology research and initiated translational research projects; has developed a separate building complex for Biomedical Research and innovation. Subsequently, he was appointed as a "Distinguished Scientist" at the Council of Scientific and Industrial Research (CSIR). Dr. Rao has held prestigious global positions, including visiting associate at the National

Institutes of Health and visiting professorships at Osaka University, Tokyo University in Japan, Visiting Scientist at the University of Texas Medical Branch, USA, Adjunct Professor at RMIT University, Melbourne, Australia, Inter-Academy visiting professor at University of Paris, France etc. He is also an adjunct professor at the University of Hyderabad. He is currently Senior Professor Emeritus at the BITS, Hyderabad. His exceptional scientific contributions have earned him numerous accolades, including the 1999 Shanti Swarup Bhatnagar Prize for Science and Technology in the Medical Sciences category, India's highest science award. He is a fellow of esteemed organizations such as the Indian National Science Academy, National Academy of Sciences, India, Indian Academy of Sciences, and The World Academy of Sciences. Dr. Rao has been honoured with an honorary doctorate by Kakatiya University and the Distinguished Alumnus Award by the University of Hyderabad.

Beyond his research and academic achievements, he has played pivotal roles in various scientific societies, serving as President of the Society of Biological Chemists (India), the Indian Biophysical Society, the Andhra Pradesh Academy of Science, and the Telangana Academy of Sciences. Additionally, he was elected member of IUPAB, FAOBMB, and the Asian Pacific Protein Association.

Dr Vivek Singh is an alumnus of MS University, where he completed his master's degree in microbiology and biotechnology. He earned his PhD at the School of Biotechnology, Banaras Hindu University, Varanasi, India, and went on to complete a four-year post-doctoral fellowship at the prestigious Cole Eye Institute, Cleveland Clinic, Ohio, USA. Currently, Dr Singh is a Senior faculty member at the Centre for Ocular Regeneration, LV Prasad Eye Institute, Hyderabad.

Dr Singh combines stem cell biology, molecular biology, and bioengineering in his laboratory to tackle scientific questions related to ocular surface diseases. His research focuses on corneal wound healing, regenerative biology, Dry Eye, animal models in ophthalmology, and the development of biomaterials. Dr Singh's recent accolades include being named a Tata Innovation Fellow for 2024 and being inducted as a Life member of the National Academy of Sciences, India (NASI) and as an Associate Fellow of the Telangana Academy of Sciences. Appointed to the board of the International Society of Eye Research (ISER) - Early Career Researcher Education Committee. Dr Singh serves as an Associate Editor for Frontiers in Medicine and has authored around 100 peer-reviewed papers. He has also secured more than 15 national and international research grants and the prestigious Sree Padmavathi Venkateswara Foundation award.

His other notable achievements include receiving the Young Scientist Award in 2017 at the 86th annual Conference of the Society of Biological Chemists. Under his leadership, his team has obtained DCGI approval for two clinical trials involving new cell-based therapies. Furthermore, his group has developed a reliable, low-cost encapsulation method for transporting mesenchymal stem cells (MSCs), thereby making MSC therapies accessible to remote and underserved patients in India. Outside of his research, Dr Singh enjoys a variety of interests including badminton, swimming, exploring cuisines, and travelling the world whenever possible. His dedication to advancing ophthalmic science and commitment to scholarly excellence make Dr. Vivek Singh a standout figure in the field of ocular regenerative medicine.

Ophthalmic Genetics News

Around the World

(1) Tease-3 Study Interim Data in Stargardt Disease Shows Some Promise

At the 42nd American Society of Retina Specialists (ASRS) Annual Scientific Meeting, held from July 17-20 in Stockholm, Sweden, Alkeus Pharmaceuticals Inc. presented promising interim data from its TEASE-3 study on the treatment of early-stage Stargardt disease using gildeuretinol acetate (ALK-001). The study's findings indicated that patients treated with gildeuretinol acetate exhibited no disease progression and remained asymptomatic over therapy periods ranging from 2 to 6 years. This highlights the critical importance of early intervention for patients with confirmed ABCA4 genetic mutations to prevent the progressive loss of central vision.

Stargardt disease is a severe cause of blindness in children and young adults, affecting over 150,000 people globally, and currently, there is no approved treatment. Gildeuretinol acetate, a novel deuterated vitamin A molecule, was designed to reduce the dimerization of vitamin A without disrupting vision. Preclinical studies have shown that gildeuretinol can decrease vitamin A dimerization to normal levels seen in unaffected individuals, thereby preventing retinal degeneration and loss of visual function.

The TEASE-3 trial, which is part of a series of four clinical studies (TEASE-1, TEASE-2, TEASE-3, and TEASE-4), is an open-label study focused on early-stage Stargardt disease patients. These patients are genetically confirmed and show early signs of the disease on retinal imaging but have not yet experienced symptoms of vision loss. Each participant has a sibling with Stargardt disease, sharing identical gene mutations and irreversible vision loss, providing a unique comparative perspective.

The primary endpoint of the TEASE-3 study is to assess disease progression over two years, evaluated through retinal imaging and functional outcome measures. Following this initial two-year treatment period, patients continue to receive gildeuretinol in an open-label long-term extension study. The study has enrolled a total of six patients, who receive the treatment as a once-a-day pill.

The interim results from TEASE-3 suggest that gildeuretinol acetate has significant potential in altering the course of Stargardt disease, offering hope for early-stage patients and potentially paving the way for new therapeutic approaches in managing this currently untreatable condition.

1- Pharmaceuticals A.Alkeus Pharmaceuticals Announces Presentation of a TEASE 3 study update showing progression stalled in Early-Stage Stargardt Disease Patients Treated with Gildeuretinol. GlobeNewswire News Room. Published July 18, 2024. Accessed July 18, 2024. https://www.globenewswire.com/news-release/2024/07/18/2915423/0/en/Alkeus-Pharmaceuticals-Announces-Presentation-of-a-TEASE-3-Study-Update-Showing-Progression-Stalled-in-Early-Stage-Stargardt-Disease-Patients-Treated-with Gildeuretinol.html

- News (ophthalmologytimes.com)

(2) Italian investigators suggest genetic syndrome link with rare eye tumor

Francesco Fortarezza and colleagues in Italy have reported a notable case involving a 9-year-old boy diagnosed with medulloepithelioma of the ciliary body (MECB) linked to DICER1 tumor predisposition syndrome. MECB, a rare primitive neuroepithelial tumor and the most common congenital neoplasm of the non-pigmented epithelium of the ciliary body, was identified in the boy, who presented with vision impairment in his left eye, microphthalmos, and a retrolental cyclitic membrane. Examination revealed a fleshy, whitish-pink mass in the ciliary body, confirmed by B-scan ultrasound, which showed intralesional cysts and total retinal detachment. The right eye was unaffected with 20/20 vision.

Genetic analysis revealed a mutation in exon 25 (p.E1813D) of the DICER1 gene, which is associated with malignant MECB. The mutation identified (NM_177438.3:c.4465-4468dup p.(Gly1490Valfs*3)) is predicted to introduce a premature stop codon, suggesting it is likely pathogenic. This case is significant as it represents MECB as the initial manifestation of a germline DICER1 mutation, highlighting the importance of recognizing this rare association. DICER1 syndrome increases the risk of several tumors, including pleuropulmonary blastoma and thyroid tumors, and has been linked to at least seven cases of MECB associated with pleuropulmonary blastoma. However, this case is unique in that it involves both a germline mutation and evidence of thyroid disease, emphasizing the need for genetic counseling and monitoring for affected individuals. This case underscores the importance of considering DICER1 syndrome in the diagnosis and management of rare tumors like MECB.

Sources:
- News (ophthalmologytimes.com)
- Fortarezza F, Midena G, Parrozzani R, Dei Tos AP. DICER1 syndrome discovered through an eye tumor. JAMA Ophthalmol. 2024; Published online May 30, 2024. doi:10.1001/jamaophthalmol.2024.1697
- González IA, Stewart DR, Schultz KAP, et al. DICER1 tumor predisposition syndrome: an evolving story initiated with the pleuropulmonary blastoma. Mod Pathol. 2022;35:4-22. doi: 10.1038/s41379-021-00905-8

Last Issue Trivia Solution

SOLUTION

Ocular Genetics Word search

m	d	.	h	c	.	p	s	v	r	v	e	c	t	o	r	c	.
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palindromic (E,7,11)
hereditary (E,5,2)
homozygous (E,6,1)
sequencing (E,4,6)
voretigene (E,2,9)
karyotype (E,9,12)
recessive (E,4,5)
mendelian (E,1,10)
dystrophy (E,9,4)
axenfeld (E,1,8)
genotype (S,18,4)
pedigree (E,8,7)
mutation (E,9,8)
aicardi (E,1,4)
crispr (E,1,7)
vector (E,3,12)
exome (E,12,9)

Recent publications of GEGC members

Suga A, Mizobuchi K, Inooka T, Yoshitake K, Minematsu N, Tsunoda K et al (2024) A homozygous structural variant of RPGRIP1 is frequently associated with achromatopsia in Japanese patients with IRD. Genetics in Medicine Open 101843, doi:10.1016/j.gimo.2024.101843. (Full text available on ScienceDirect)

This study investigates the genetic underpinnings of achromatopsia (ACHM), a form of inherited retinal dystrophy (IRD) characterized by complete color blindness and other visual impairments. On whole genome sequencing for 10 ACHM families, the researchers identified a specific deletion involving exon 18 of RPGRIP1 in homozygous state segregating with diseased individuals in 5/10 analyzed family. This variant appears to play a crucial role in the etiology of the disease within the Japanese population subset. Biallelic RPGRIP1 variants are mainly associated with Lebers Congenital Amuarosis (LCA) phenotype. However, some IRD cases with RPGRIP1 pathogenic variants have been clinically diagnosed as cone rod dystrophy (CORD) in variable regions and populations. Hence, with its novel association with achromatopsia phenotype it can be concluded that RPGRIP1 may be causal for a spectrum of photoreceptor associated phenotypes, from functional defects primarily in cones (ACHM and CORD) to photoreceptor degeneration in both rods and cones (LCA and early-onset retinitis pigmentosa).

Suga A, Minegishi Y, Yamamoto M, Ueda K, Iwata T (2024a) Compound heterozygous mutations in a mouse model of Leber congenital amaurosis reveal the role of CCT2 in photoreceptor maintenance. Communications Biology 7: doi:10.1038/s42003-024-06384-2. (Full text available on PubMed)

Leber congenital amaurosis (LCA) is a severe form of inherited retinal dystrophy that leads to blindness or severe visual impairment from birth or early childhood. It is caused by mutations in various genes involved in photoreceptor function and maintenance. CCT2 (Chaperonin Containing TCP1 Subunit 2) is a gene that encodes a subunit of the chaperonin complex, essential for the folding of proteins crucial for cell function. This study aimed to investigate the role of CCT2 in photoreceptor maintenance using a mouse model carrying compound heterozygous mutations that mimic the genetic context of LCA in humans. The researchers developed a mouse model with the desired compound heterozygous mutations in the CCT2 gene. Retinal structure and function of the mutant mice were analyzed through histological examination, electroretinography (ERG), and other molecular techniques. The impact of CCT2 mutations on the chaperonin complex's function and its interaction with photoreceptor proteins were assessed. It was observed that the Cct2 mutant mice exhibited progressive retinal degeneration, with significant loss of photoreceptor cells. This degeneration was observed to start early and worsen with age, mirroring the clinical progression of LCA in humans. ERG recordings revealed a marked decrease in photoreceptor response, indicating functional impairment of the retina in mutant mice. The study found that the mutations in CCT2 disrupted the proper folding of critical photoreceptor proteins, leading to their mislocalization and aggregation, which contributed to photoreceptor cell death. This demonstrated that CCT2 is essential for the maintenance of photoreceptors, likely through its role in ensuring the proper folding and function of key photoreceptor proteins.

Fu Y, Zhang Z, Webster KA, Paulus YM. Treatment Strategies for Anti-VEGF Resistance in Neovascular Age-Related Macular Degeneration by Targeting Arteriolar Choroidal Neovascularization. Biomolecules. 2024 Feb 21;14(3):252. doi: 10.3390/biom14030252. (Full text available on PubMed)

Neovascular age-related macular degeneration (nAMD) is a leading cause of blindness in the elderly. It is characterized by choroidal neovascularization (CNV) under the retina. Anti-vascular endothelial growth factor (anti-VEGF) therapies are the standard treatment for nAMD, but some patients develop resistance to these therapies. This study investigates alternative treatment strategies specifically by targeting arteriolar CNV, a subtype of CNV that may contribute to resistance. The researchers analyzed clinical data from patients with nAMD who developed resistance to anti-VEGF therapy. The characteristics of arteriolar CNV were examined through imaging techniques, such as optical coherence tomography angiography (OCTA), and molecular profiling to understand the underlying mechanisms of resistance. Animal models of nAMD were used to test new treatment strategies that specifically target arteriolar CNV. The study confirmed that a subset of nAMD patients with resistance to anti-VEGF had distinct lesions with a higher density of pericytes and increased expression of pro-angiogenic and pro-fibrotic factors. The resistance in arteriolar CNV was linked to the activation of alternative angiogenic pathways, such as platelet-derived growth factor (PDGF) and angiopoietin pathways, which were not adequately suppressed by anti-VEGF therapy alone. In animal models, combination therapies that inhibited both VEGF and these alternative pathways were more effective in reducing arteriolar CNV and improving retinal function compared to anti-VEGF monotherapy. The study demonstrates that targeting this subtype of CNV with combination therapies that address both VEGF and alternative angiogenic pathways offers a promising strategy to overcome resistance and improve outcomes for patients with nAMD.

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