European Vision Institute-Genoret – An Initiative to Fight Blindness

a report by
José-Alain Sahel

Professor of Ophthalmology, Pierre and Marie Curie University, and Chairman, Department of Ophthalmology IV, National Eye Hospital, Paris

DOI: 10.17925/EOR.2007.00.00.54

Despite major clinical and therapeutic achievements in ophthalmology, the number of people suffering from serious visual impairment is growing. This paradox reflects the fact that we have yet to find ways of stemming and repairing the damage from diseases that affect the retina such as inherited retinal degenerations (IRD) and age-related macular degeneration (ARMD). Visual loss has a devastating impact on physical, social and mental wellbeing and is recognised as major economic burden. A sizeable proportion of the visually impaired suffer from hereditary retinal disorders. However, with the ageing demographics of the European population, ARMD is now the most common cause of visual handicap in the majority of those registered as visually impaired. ARMD affects 8.6% of the visually impaired population over 60 years, and this means 12.5 million people with a potentially blinding disease in Europe as a whole, and 8.3 million people in the EU. These people lose the ability to read, recognise people, watch television and, ultimately, navigate safely around their world.

A Target for Multiple Disease Pathways

The vulnerability of the retina to a wide range of pathogenetic mechanisms reflects the complexity and sensitivity of the numerous steps involved during visual processing at the level of the photoreceptor cells and inner retinal tissue. Over the past 15 years, a massive accumulation of knowledge has led to the recognition that more than 150 genes may be involved in the so-called simple retinal disorders, providing clues for a wide range of specific and ubiquitous functions. Specific functions include visual transduction cascade, structural proteins, circuitry, supporting cells, retinal pigment epithelium and Müller cells, outer segment renewal and vitamin A transport and metabolism. Ubiquitous functions include growth factors, oxidative stress, splicing, transcription factors, lipid metabolism and mitochondrial function. The impairment of some of the latter mechanisms produces a clinical phenotype only at the retinal level. This makes the retinal degenerative diseases a particularly good target for the development of therapies with broad applicability – as well as a sharply targeted focus – and a privileged model system for understanding the biological function of novel genes and proteins. In this sense it is an ideal model for detecting, characterising and potentially rectifying anomalous biological mechanisms (e.g. developmental).

José-Alain Sahel is Professor of Ophthalmology at the Pierre and Marie Curie University, Paris, and Chairman of the Department of Ophthalmology IV at the National Eye Hospital in Paris. He is also full Professor at the Institute of Ophthalmology, University College London (Cumberlege Chair for Biomedical Sciences). He heads a French Institute of Health and Medical Research (INSERM) research laboratory and a clinical investigation centre focused on retinal diseases.

E: j-sahel@quinze-vingts.fr

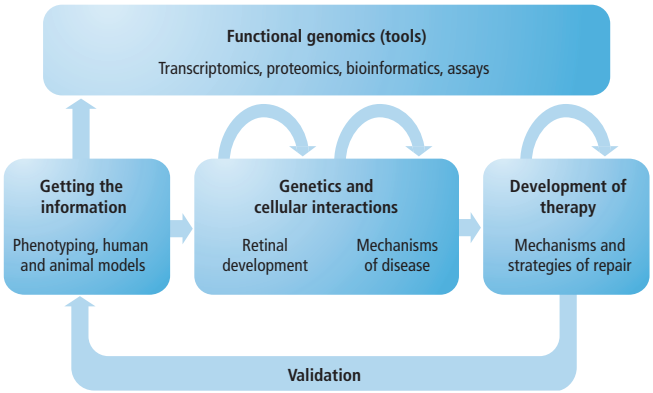
A Major Field of Application for Functional Genomics

This European network is deliberately wide ranging in scope because retinal blindness is complex and multifaceted. Therefore, there is a need for both basic and applied components dealing with the complete range of gene-related studies, starting with development, to genetics and functional genomics, right through to stem cells and gene therapy. There are no easy answers to gene-related and/or age-related blindness. Therefore, we propose a mixture of basic and applied approaches underpinned by the best retina researchers in Europe, all working towards the common goal of increasing our understanding of retinal function in health and disease, which will eventually not only provide a leading model for system biology, but also underpin rational therapies. The application of the methods and concepts of functional genomics is the next crucial step to an in-depth understanding of the function of the numerous genes underlying retinal development, function, maintenance and disease. These, taken in isolation or as a network, provide a basis for the establishment of a thorough and comprehensive integrated understanding of this precious, complex and vulnerable biological system. Together these will form the basis for an efficient analysis and generation of knowledge of fundamental biological processes in retinal development, health and disease. Among the systematic strategies to help understand system biology, we shall prioritise the search for mid-term therapeutic approaches aimed at postponing the onset of blindness. In this respect the importance of preserving, and potentially restoring, central vision is obvious. Therefore, a major focus of our project is the biology of cone cell development, function, maintenance, protection and replacement.

Aim and Structure of European Vision Institute-Genoret

The aim of the European Vision Institute–Functional Genomics of the Retina in Health and Disease (EVI-Genoret) is to build on our understanding of the fundamental molecular and cellular biology of the retina, of its development and the way it is affected by genetic mutation, environmental factors and age. By establishing and utilising a platform of functional genomic technology with broad applicability to the analysis of both the normal physiology and the pathophysiology of retinal function, we hope to gather knowledge about the molecular mechanisms of retinal degenerations, as well as to generate a rationale for future treatment (see *Figure 1*). The project integrates population genetics, clinical and experimental phenotyping, molecular genetic approaches and genomic high-throughput methods of transcriptional and proteomic pattern recognition, as well as in-depth analytical approaches to analyse protein function and its integration into complex protein functional networks. Together these tools will form the basis for efficient analysis and generation of knowledge of fundamental biological processes in retinal health and disease.

Figure 1: A Platform of Functional Genomic Technology



In order to generate an efficient working dynamic, EVI-Genoret is based on five components working in close co-operation around the major fields of knowledge or technologies that we wish to utilise and develop.

Objectives

The objectives of this integrated project are as follows:

- to gather and integrate the information on gene function brought about by the numerous available human, animal and *in vitro* models of retinal development and degeneration;
- to standardise and analyse this information (databases and expression studies);
- to validate the functional assays and models; and
- to facilitate the design of a genomic-based therapy that would potentially benefit patients, but also validate the pathways and targets identified using the approaches described above.

The goal at the completion of the programme would be to help integrate a broad and in-depth understanding of the function and interactions of major cell and gene networks, thereby proposing functional models. EVI-Genoret is an ambitious integrated project that will be achieved by a consortium of 25 groups (10 countries) and small and medium enterprises. This project will lead to the integration of many data resulting from population genetics, clinical and experimental phenotyping, biology of development, as well as functional genomics. At the end, a successful integration of these data in a new database will provide clues to the system biology of this complex system, and will make it possible to identify new therapeutic targets leading to the launch of long-term therapeutic trials.

The programme's main goal is the integration of data produced by EVI-Genoret. To achieve this, we have developed the following procedures:

- Standards and standard operation procedures (SOPs) applicable to individual procedures of clinical and experimental work performed within the project. This provides a basis for transparent quality control of all operations and data generated within the programme. We also elaborated settings and formats for a rapid, harmonised dissemination of EVI-Genoret-validated results to the scientific community.
- Implementation of a system of quality assessment (QA). A quality manager is in charge of the QA. The system of QA will be applicable to standards and standard operation procedures, reliability of data, implementation of the integrated data knowledge bank and assessment of the results. ■