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## AIMS OF EVI-GENORET

To build on our understanding of the fundamental molecular and cellular biology of the retina, of its development and the way it is perturbed by genetic mutation, environmental factors and age.

To gather and integrate the information on gene function brought about by the numerous human, animal and in vitro models of retinal development and degeneration available.

To standardize and analyze this information (databases and expression studies)

To validate the information (functional assays and models)

To facilitate the design of genomic-based therapy that would obviously potentially benefit patients but also validate the pathways and targets identified using the above-described approaches.

## GOALS OF EVI-GENORET

The goal at the completion of the program would be to help integrate a broad and in depth understanding of the function and interactions of major cells and genes networks, thereby proposing functional models.

The key questions and issues faced in addressing these questions are:

- 1) Obtaining the information provided by the clinical conditions and animal models
- 2) Analyze the information: Functional genomic tools
- 3) Validate the information
- 4) Design genomic-based therapy

## Component Phenotyping



1. Phenotyping, tissue and DNA collection in patients with AMD /MRD
  - \* Harmonisation of Material and Methods
  - \* Phenotypic assessment by imaging techniques , visual function
  - \* Phenotype-Genotype correlation
2. Assessment of retinal function and morphology and evaluation of therapeutic strategies in animal models of retinal degeneration
  - \* Develop and test autofluorescence, angiography, SLO, double flash and bright flash ERG in mice
  - \* Optomotor response

## Component Functional Genomics



1. Transcriptional regulation in healthy and degenerating retinal tissue
  - \* Analysis of transcriptional regulation patterns
  - \* Characterization of cone specific gene promoters
  - \* Identification of new retinal specific expressed genes
2. Proteomic analysis of retinal tissue
  - \* profiling of large sets of protein-protein inter. from rods and cones
  - \* protein-protein interactions screening of Y2H libraries
3. Bioinformatics and comparative genomics
  - \* transcriptomic data analysis, identification and annotation of genes
  - \* integration and model design
4. Functional analysis and functional assays
  - \* functional validation of candidate genes, proteins and pathways

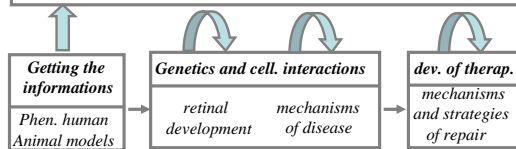
## Component Therapy



1. Strategies for controlling gene expression
  - \* AAV and lentivirus mediated delivery of siRNA;
  - \* non viral delivery of oligonucleotides, electrotransfert of plasmids
2. Functional genomics of the host retinal response to cell and tissue based therapies
  - \* transplantation (development of cell lines, characterization)
  - \* host response : RETCHIP
3. Therapeutics using agents derived from functional genomics
  - \* Test small compounds to activate endogenous Thioredoxins (RdCVF)
  - \* test these compounds in rd1 mouse
  - \* evaluation of neuroprotective effect of hypoxic exposure

## Functional Genomics (tools)

Assays, Transcriptomics, Proteomics, Bioinformatics



## validation

### Horizontal tools



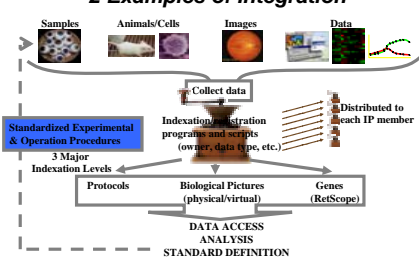
1. Database and Quality Control
  - \* Dev. of standards and information networking system integrating the experimental and operation procedures as well as the CRFs provided by the members
  - \* Implementation of a system of Quality Assessment
2. Management
  - \* Daily management of the project, meetings, periodic reports to the EC, overall administration, risk management and conflict resolution.
  - \* Dissemination of the results, validation methods and standards to the scientific community, major stakeholders (Retina International) and patients.
3. Ethics
  - \* to disseminate the knowledge about all relevant regulations to the partners, to point out the ethically sensitive issues of each subproject and to inform the researchers about them, to establish ways to discuss them with the stakeholders, to proposed solutions and to contribute to their implementation
4. Training
  - \* To provide efficient management tools for organizing all aspects of training, to provide central recruitment of both courses and trainees, to organize on team site EVI GENORET courses, central courses and lab rotation, to provide training assessment of both courses and trainees as well as counselling

## Component Development



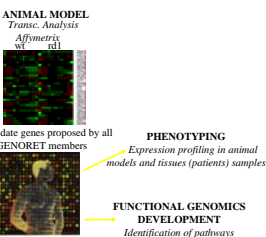
1. Expression of key developmental regulators in the retina, and in stem cells
  - \* Development of ISH platform (HTS) and SOPs ;
  - \* spatiotemp. gene expression in dev. and PN mouse eyes
2. Derivation and characterisation of stem cells with therapeutic potential
  - \* expression studies of cultured stem and progenitor cells;
  - \* develop renewable retinal stem and progenitor cell lines
3. Functional studies of eye development pathways in model systems

## 2 Examples of Integration



Centralized Databases

Dev. of RETCHIP



## Component Genetics



1. Genetic mapping and gene identification of a novel monogenic retinal dystrophy
  - \* genetic mapping of new loci for MRD, RP, LCA, CRD ;
  - \* positional cloning ;
  - \* mutation screening of candidate genes
2. Role of RPE-expressed genes in monogenic and complex retinal disorders, including age-related macular degeneration.
  - \* Identification of RPE genes candidate for MRD / AMD ;
  - \* Mutation analysis of novel RPE expressed genes.