**PROJECT 1**

**DoS**: Prof. Giuseppe Querques

Title: Complement system in age-related macular degeneration: understanding its prognostic role

Curriculum: Experimental and Clinical Medicine

Link to OSR/UniSR personal page:
http://www.unisr.it/k-teacher/querques-giuseppe/

**Project description**

Age-related macular degeneration (AMD) is a leading cause of central vision loss. Although the exact mechanisms leading to this disease are complicated and not well known, previous studies suggested that this disease may be associated to the complement system.[1] Severe vision loss in AMD is the result of macular neovascularization in the majority of cases (85%) while geographic atrophy (GA) is also a significant causal factor (15% of cases). The development of one or both of these complications characterizes the late form of AMD (Ferris et al., 2013). Late AMD is preceded by the early and intermediate stages; the latter is characterized by medium and large drusen formation and associated pigmentary abnormalities. Patients with neovascular exudative AMD are usually treated with anti-vascular endothelial growth factor (VEGF) intravitreal injections.

The complement system is an ancient defense mechanism against infectious microbes. It has many other important physiological functions, including clearance of apoptotic cells and immune complexes, and other roles related to tissue homeostasis.[2]
The effect of environmental exposures and behaviors on AMD risk may be at least partly mediated through the complement cascade. As an example, smoking tobacco has consistently been found to increase risk of AMD and tobacco was demonstrated to activate the classical complement system pathway. Furthermore, AREDS reported that high dietary intake of omega-3 long chain polyunsaturated fatty acids was associated with lower risk of neovascular AMD. The Blue Mountains Study supported these findings and furthermore observed that weekly consumption of fish and weekly consumption of nuts decreased risk of AMD, while high LDL cholesterol raised risk. A possible link with the complement system is in HDL, which is protective against AMD and contains complement proteins, including clusterin, vitronectin, C3, C4A, C4B, and C9.

Genome-wide association studies first revealed associations between AMD and variants in the complement genes.[3] However, these studies failed to investigate associations between complement polymorphisms and differences in response to treatments.

In details, an increase in complement activation may lead to a macular scar formation with consequent severe vision loss. Therefore, we hypothesize that polymorphisms in complement genes (clusterin, vitronectin, C3, C4A, C4B, and C9) may cause differences in treatment response to anti-VEGF.

This PhD project will employ the following methods:

- Patients with treatment-naïve exudative neovascular AMD will be enrolled.
- Patients will be followed-up for 1 year.
- Patients will be treated with a fixed-regimen anti-VEGF treatment (monthly ranibizumab)
- Monthly examinations will be performed in order to assess visual acuity, response to treatment (absence of exudation at each follow-up), presence of signs of macular fibrosis (scar)

- Patients will be evaluated for the presence of polymorphisms. In details, blood samples will be collected from included patients and SNPs of clusterin, vitronectin, C3, C4A, C4B, and C9 genes will be evaluated.

Our primary outcome is to understand whether there is any association between complement polymorphisms and development of macular fibrosis (detected using optical coherence tomography – OCT) within 1 year after the initiation of anti-VEGF therapy.

Additional outcomes will include the associations between complement polymorphisms and response to treatment evaluated in terms of visual acuity gain and absence of anatomic evidence of exudation.

Our results may have translational relevance. In details, the identification of complement polymorphisms may grant the chance to identify a sub-group of patients with a poorer prognosis related to a more likely development of macular scar. Furthermore, our results may allow to further clarify mechanisms involved in the macular fibrosis that may constitute new therapeutic targets.

The PhD student will be directly involved in the enrollment of patients, execution of clinical examinations, arrangement of genetic test, analysis of data, writing of papers.

**Skills to be acquired by the student:**

1. To conduct an investigative study in Experimental and Clinical Medicine.
2. To perform statistical analysis and write scientific papers.
3. To use instruments typically used in Ophthalmological clinical practice.
4. To understand and develop procedures relevant for Ophthalmological clinical practice.

**References** (max. 3)

1. Hageman GS, Luthert PJ, Victor Chong NH, Johnson LV, Anderson DH, Mullins RF. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. Prog Retin Eye Res 2001; 20: 705–732.
2. Nonaka M, Kimura A. Genomic view of the evolution of the complement system. Immunogenetics 2006; 58: 701–713.
3. Montes T, Tortajada A, Morgan BP, Rodriguez de Cordoba S, Harris CL. Functional basis of protection against age-related macular degeneration conferred by a common polymorphism in complement factor B. Proc Natl Acad Sci USA 2009; 106: 4366–4371.