Title: Studying the dynamics of micro eye movements to identify biomarkers of AMD retinal disease

Age-related macular degeneration (AMD) is a major cause of irreversible visual loss. The deficits in visual function as a result of AMD are debilitating, triggering autonomy loss in activities such as reading, driving, and visuo-manual precision tasks. Despite the prevalence, rate of growth, and impact of AMD, its diagnosis is made too late: 69% AMD patients ignore their condition, and 78% have irreversible loss when first diagnosed. This is partially due to the fact that only prominent visual symptoms bring a patient to the medical doctor. There is a need for early and systematic screening for this vision-threatening eye disease, through new diagnostic tools for functional vision, complementary to gold-standard retina imaging of the eye structure. Existing histological findings and mechanistic hypotheses have not yet led to a comprehensive "standard model" of AMD. The commonly accepted mechanistic paradigm assumes that the primary damage occurs at the level of the RPE/Bruch's membrane, compromising the metabolic exchange underpinning retina photoreceptor functions. During the course of AMD, various genetic and metabolic cues trigger decades of low-grade inflammation of the RPE/photoreceptor interface (early AMD), sometimes leading to dramatic visual loss (late AMD) caused by neovascularization and subsequent degeneration of the photoreceptor/RPE unit. At present, neovascularization can be pharmacologically stabilized by anti-VEGF therapy (i.e., wet AMD treatment). However, there is currently no treatment for the atrophic form of AMD (dry AMD), despite the identification of ~80% of the genetic variants and more than 50 phase 3 clinical trials performed during the past decade. It is hence a key target of this project to obtain a better phenotyping of RPE cells as well as a better understanding of the temporal and spatial correlations between RPE defects and functional visual losses. This has the potential to bridge the gap between the onset/progression of RPE degeneration and the consequent visual symptoms in dry AMD patients. This project brings together vision neuroscience, clinical ophthalmology and computer sceince. It builds on the existing collaboration between the teams led by A. Arleo (Vision Institute) and M. Paques (Clinical Investigation Center, CHNO Quinze-Vingts). The goal is to improve the understanding, early diagnosis, and treatment of dAMD. Cellular level psychophysics (linking visual symptoms to cellular-scale changes) has the potential to help us uncover functional signatures of structural pathogenic processes, possibly generating new anatomo-functional biomarkers of AMD. Beside co-directors D. Sheynikhovich (Vision Institute) & M. Paques, the candidate will be supervised on a daily basis by J. Gautier, a postdoc specialized in retina imaging and stimulation, currently working at Vision Institute and CHNO Quinze-Vingts.

This project is structured along 3 axes:

1. Multiscale dynamic imaging of cell morphology changes during dAMD. We will establish cellular/structural phenotypes to characterize dynamic patterns of the evolution of dAMD at different temporal and spatial scales. It will combine conventional and high-resolution temporal and spatial imaging to identify spatially distant synchronous events as well as to describe the dynamics of retinal layer-specific morphology changes.

2. Structure-function relationship in AMD. We will identify functional deficits that are correlated with cellular level disease-dependent structural changes in AMD patients. Psychometric analyses of visual loss will link spatiotemporal changes of cell morphology to visual perception performances (e.g., to study how structural disorganization/changes of the photoreceptor/RPE arrays caused by AMD may lead to early/progressive perceptual hallmarks of disease, such as metamorphopsia, decline of photon absorption rate, and subtle changes in fixational micro-eye movement and scanning dynamics).

3. Data mining, statistical analysis, predictive models. We will also study the linking of structural and functional measures through machine learning and in silico modeling (already implemented and used in our teams), to establish predictive statistical models of AMD onset/evolution.