Campagne 2020 Contrats Doctoraux Instituts/Initiatives

Proposition de Projet de Recherche Doctoral (PRD)

Appel à projet IUIS - Institut univ d'ingénierie en santé 2020

Intitulé du Projet de Recherche Doctoral : Linking cellular and functional changes in a prospective analysis of age-related macular degeneration.

Directeur de Thèse porteur du projet (titulaire d'une HDR) :

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Unité de Recherche :
Intitulé : Institut de la Vision
Code *(ex. UMR xxxx)* : UMR7210

Ecole Doctorale de rattachement de l'équipe & d'inscription du doctorant : **ED130-EDITE**

Doctorants actuellement encadrés par le directeur de thèse (préciser le nombre de doctorants, leur année de 1ere inscription et la quotité d'encadrement) : 1; 2019; 50%

Co-encadrant :

NOM : **Paques** Prénom : **Michel**
Titre : Professeur des Universités - Praticien H HDR ☒
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Unité de Recherche :
Intitulé : Clinical Investigation Center - CHNO Quinze Vingts
Code *(ex. UMR xxxx)* : 1423

Ecole Doctorale de rattachement : **ED394-Physiologie,Physiopathologie Thérapeutiqu**
Ou si ED non Alliance SU :

Doctorants actuellement encadrés par le co-directeur de thèse (préciser le nombre de doctorants, leur année de 1ere inscription et la quotité d'encadrement) : 2; 2017; 2018; 50%

Cotutelle internationale : ☒ Non ☐ Oui, précisez Pays et Université :

Description du projet de recherche doctoral *(en français ou en anglais)*

3 pages maximum – interligne simple – Ce texte sera diffusé en ligne

Détailler le contexte, l'objectif scientifique, la justification de l'approche scientifique ainsi que l'adéquation à l'initiative/l'Institut.
Le cas échéant, préciser le rôle de chaque encadrant ainsi que les compétences scientifiques apportées. Indiquer les publications/productions des encadrants en lien avec le projet.
Préciser le profil d'étudiant(e) recherché.

CONTEXT

Age-related macular degeneration (AMD) is a major vision threatening disease, causing irreversible visual loss in older adults. The rate of AMD is on the rise, with an estimated 196 million patients projected for 2020 and a staggering 288 million sufferers projected for 2040. This is due to a combination of a growing older population, naturally more susceptible to AMD, and an increase of risk factors including poor antioxidant diet and increased blue-violet light exposure. AMD was ranked by the World Health Organization (WHO) as a priority eye disease, and it is the main cause of blindness in western countries. The deficits in visual function as a result of AMD are debilitating, triggering autonomy loss in activities such as reading, driving, and visio-manual precision tasks. The consequences of visual disability are profound, directly affecting the quality of life, including, but not limited to life satisfaction, productivity, and fulfillment. 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 a prominent visual symptom (e.g., visual acuity loss) brings a subject to the medical doctor. There is thus an urgent need for the development of new sensitive diagnostic tools for functional vision, complementary to clinical gold-standard retina imaging assessments, that can be used for early and systematic screening for this vision-threatening eye disease.

The commonly accepted mechanistic paradigm of AMD development assumes that the primary damage occurs at the level of the retinal pigment epithelium (RPE) and 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), leading in the second half of life to dramatic visual loss (late AMD), due to either neovascularization (wet AMD) or degeneration (dry AMD) of the photoreceptor/RPE unit. While neovascularization can be pharmacologically stabilized by anti-VEGF therapy, there is currently no treatment for the atrophic form of AMD. Therefore, a detailed characterization of RPE differences in healthy and AMD-affected populations, and a better understanding of the temporal and spatial correlations between RPE defects and functional visual losses is a promising direction in the search for novel early diagnostic tools of AMD.

OBJECTIVES & COOPERATION FRAMEWORK

The main objective of this doctoral project is to cross-link cellular changes in the deep retina with visual symptoms of AMD patients. The project will combine state-of-the-art live high-resolution retinal imaging and fine metrics of AMD-related functional visual losses using modern statistical analysis methods in order to discover potential biomarkers of AMD onset and/or stage evolution. Early risk assessment of AMD onset or stage transition based on novel biomedical imaging approaches fits perfectly to the RISK phare program of the IUIS and it can lead to major technological advances in this pressing health issue.

This project relies on a tight collaboration between visual neuroscientists and clinical ophthalmologists. It builds on the existing integration of basic vision science expertise at the Vision Institute (thesis directors: Angelo Arleo and Denis Sheynikhovich, Aging in Vision and Action laboratory) and the clinical research expertise in the Quinze-Vingt National Hospital (thesis co-directors/clinicians: Michel

Paques and Kate Grieve, Clinical Investigation Center). The Aging in Vision and Action team is at the cutting edge of visual functional investigations through the development of psychophysical, neuroscientific and statistical analysis procedures to assess real-life vision. The study of age-related degradation of visual functions is the core research of the team, which focuses on experimental and theoretical approaches to the study of how aging shapes both sensory and cognitive aspects of vision. The team contributed to the field through longitudinal and cross-sectional studies of age-related visual functional changes (1–3). A recent milestone activity led to the establishment of a new study population of ~350 voluntary subjects, including AMD patients, each of them deeply phenotyped through ophthalmological, visual, audio-vestibular, sensorimotor, neuropsychological, and cognitive screening (4). Cross-sectional experiments using participants from this cohort already characterized age-related functional changes in terms of contrast sensitivity (5–7), motion perception (8,9), active visual exploration (10), and visuospatial cognition (11). From a data-analytic perspective, neural models and machine learning techniques developed in the team provided insights on multistage visual processing (12), gaze stabilization (13), and spatial coding (14). The team at the Clinical Investigation Center (CIC) of the Quinze-Vingt National Hospital has been a pioneer in the development and clinical application of high-resolution retinal imaging in humans (15). The team played a pivotal role in several recent contributions to the field: the development of new protocols for 3D histology, the development of clinical imaging tool at a resolution comparable to microscopy (16), the development of novel protocols for visual testing, and the identification of novel mechanisms contributing to AMD progression (under publication). The team recently obtained one of the first imaging of RPE cells in Europe (17), paving the way to the exploration of RPE diseases.

WORKPLAN

During the first phase of the project, the doctoral candidate will collect new retinal imaging data (at the CIC) and perform deep visual screening (at Vision Institute and CIC) from the cohort of AMD patients. She/he will process raw experimental data and will extract statistical variables both on the retinal level (i.e., imaging results for RPE/photoreceptor cells, optical coherence tomography, ocular pressure, and stray light measures) and visual functioning (in the ongoing cohort study an extensive battery of visual tests is routinely conducted on all subjects, including measures of visual acuity, contrast sensitivity, color sensitivity, and visual field extent). In the second phase of the project, she/he will use multivariate statistical approaches to analyze differences in retinal variables between healthy and AMD-affected participants and she/he will assess the principal factors linking retinal and visual functional variables in AMD. In the third phase, she/he will carry out a detailed characterization of visual measures (i.e., potential candidates for functional biomarkers of AMD onset/stage evolution resulting from phase 2), aiming at increasing their predictive value and offering a set of functional visual screening tests with a high predictive potential towards AMD. While we will evaluate the specificity of the proposed test battery in phase 3 using available cohort data from healthy subjects, we will measure its sensitivity through longitudinal analyses in an early-AMD population.

DESIRED PROFILE OF THE PHD CANDIDATE. The candidate is required to hold a MSc in statistics, biostatistics or related fields. Theoretical and/or practical knowledge of vision science (optometry, eye diseases) is a strong plus.

PUBLICATIONS OF THE HOST UNITS RELEVANT TO THE PROJECT

1. Naël V et al. Vision loss and 12-year risk of dementia in older adults: the 3C cohort study. Eur J Epidemiol 34, 141-52 (2019).

2. Naël V et al. Visual impairment, undercorrected refractive errors, and activity limitations in older adults: […]. Investig Ophthalmol Vis Sci 58, 2359-65 (2017).

3. Naël V et al. Prevalence and associated factors of uncorrected refractive error in older adults in a population-based study [...] JAMA Ophthalmol 137, 3-11 (2019).

4. Lagrené K et al. Healthy and pathological visual aging in a French follow-up cohort study. Investig. Opthalmology Vis Sci 60, 5915 (2019).

5. Silvestre D et al. Adding temporally localized noise can enhance the contribution of target knowledge on contrast detection. J Vis 17, (2017).

6. Silvestre D et al. Internal noise limiting contrast sensitivity. Sci. Rep. 8, 2596 (2018).

7. Silvestre, D. et al. Healthy aging impairs photon absorption efficiency of cones. Investig. Ophthalmol. Vis. Sci. 60, 544–51 (2019).

8. Allard, R. & Arleo, A. Reducing luminance intensity can improve motion perception in noise. Sci. Rep. 7, 43140 (2017).

9. Allard, R. & Arleo, A. Factorizing the motion sensitivity function into equivalent input noise and calculation efficiency. J. Vis. 17, 17 (2017).

10. Bécu M et al. Age-related preference for geometric spatial cues during real-world navigation. Nat Hum Behav 4, 88-99 (2020).

11. Ramanoël S et al. Age-related differences in functional and structural connectivity in the spatial navigation network. Front Neural Circuits 13, 69 (2019).

12. Li T et al. Panoramic visual representation in the dorsal visual pathway and its role in reorientation. bioRxiv 827667 (2020).

13. Sheynikhovich D et al. Unsupervised detection of microsaccades in a high-noise regime. J Vis 18, 19 (2018).

14. Li T et al. Modeling place cells and grid cells in multi-compartment environments: Entorhinal–hippocampal loop as a multisensory integration circuit. Neural Networks 121, 37–51 (2020).

15. Paques M et al. Adaptive optics ophthalmoscopy: Application to age-related macular degeneration and vascular diseases. Prog Retin Eye Res 66, 1-16 (2018).

16. Xiao P et al. In vivo high-resolution human retinal imaging with wavefront-correctionless full-field OCT. Optica 5, 409 (2018).

17. Grieve K et al. In vivo near-infrared autofluorescence imaging of RPE cells with 757 nm excitation. Biomed Opt Express 9, 5946-61 (2018).

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à envoyer simultanément par e-mail à l'ED de rattachement et au programme :
cd_instituts_et_initiatives@listes.upmc.fr avant le 30 mars.