MARIE SKŁODOWSKA-CURIE POSTDOCTORAL FELLOWSHIPS 2024

EXPRESSION OF INTEREST FOR HOSTING MARIE CURIE FELLOWS

HOST INSTITUTION

NOVA Medical School I (iNOVA4Health Research Unit)

RESEARCH GROUP AND URL

Molecular Mechanisms of Disease
https://www.nms.unl.pt/en-us/research/research-groups/research-group/n/molecular-mechanisms-of-disease

SUPERVISOR (NAME AND E-MAIL)

Miguel Seabra
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SHORT CV OF THE SUPERVISOR

Miguel C Seabra (MCS) graduated in Medicine in 1986 at Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Portugal. Fascinated by a career in science, MSC enrolled in a PhD in Biochemistry and Molecular Biology at the University of Texas Southwestern Medical Center at Dallas, USA (UTSW) supervised by Nobel laureates MS Brown and JL Goldstein, with a Fulbright and Gulbenkian fellowship. Soon, after accomplished her PhD thesis in 1992, MCS started his own lab as an Assistant Professor in 1994 at UTSW. In 1997, MCS moved his lab to Imperial College London, UK where he became full Professor in 1999 and head of Section of Molecular Medicine.
In 2007, MCS moved to his hometown of Lisbon, Portugal, as Professor of Biomedicine and head of Biochemistry and Cell Biology at Nova Medical School (NMS). Since then and until 2015 MCS maintained a position as Honorary Professor at Molecular Medicine, NHLI, Faculty of Medicine, Imperial College London, UK. Since 2016 MSC is Honorary Professor at the UCL Institute of Ophthalmology, University College London, UK.
In 2012, MCS became president of Fundação para a Ciência e Tecnologia (FCT) the public grant-funding body in Portugal in all areas of science. Whilst president of FCT, MCS served one term as president of Science Europe, a Brussels-based organization combining research-funding and research-performing European organizations. In 2016, MCS returned to NMS as a group leader of the Molecular Mechanisms of disease Lab, and as Full Professor.
In 2021, MCS created a new lab at Fundação Champalimaud to implement a Global Eye Research Initiative in collaboration with the LV Prasad Institute in India with the goal of developing and implementing low-cost solutions for common eye diseases.
MCS is a holder of a patent on AAV2-Choroideremia gene therapy (UK patent application 1103062.4 and international application PCT/GB/12/050376, entitled "AAV-vectors for use in gene therapy of choroideremia", filed by the University of Oxford, jointly with R. MacLaren and Matt During)
MCS trained so far 23 postdoctoral fellows and 37 PhD students. These have become successful academic professors and research group leaders, entrepreneurs, industry workers, science communication, policy and administration experts. Overall, he has received over 13 million Euros in competitive grants as group leader in USA, UK and Portugal.

5 SELECTED PUBLICATIONS

- Flores R, Fradinho AC, Pereira RS, Mendes JM, Seabra MC, Tenreiro S, Carneiro Â. Identifying Imaging Predictors of Intermediate Age-Related Macular Degeneration Progression.Transl Vis Sci Technol. 2023 Jul 3;12(7):22. doi: 10.1167/tvst.12.7.22.
- Flores R, Carneiro Â, Neri G, Fradinho AC, Quenderra B, Barata MJ, Tenreiro S, Seabra MC.Choroidal Vascular Impairment in Intermediate Age-Related Macular Degeneration. Diagnostics (Basel). 2022 May 22;12(5):1290. doi: 10.3390/diagnostics12051290.

- Flores R, Carneiro Â, Tenreiro S, Seabra MC. Retinal Progression Biomarkers of Early and Intermediate Age-Related Macular Degeneration. Life (Basel). 2021 Dec 27;12(1):36. doi: 10.3390/life12010036.
- Escrevente C, Falcão AS, Hall MJ, Lopes-da-Silva M, Antas P, Mesquita MM, Ferreira IS, Cardoso MH, Oliveira D, Fradinho AC, Ciossek T, Nicklin P, Futter CE, Tenreiro S, Seabra MC. Formation of Lipofuscin-Like Autofluorescent Granules in the Retinal Pigment Epithelium Requires Lysosome Dysfunction. Invest Ophthalmol Vis Sci. 2021 Jul 1;62(9):39. doi: 10.1167/iovs.62.9.39.
- Flores R, Carneiro A, Serra J, Gouveia N, Pereira T, Mendes JM, Coelho PS, Tenreiro S, Seabra MC. Correlation study between drusen morphology and fundus autofluorescence. Retina. 2021 Mar 1;41(3):555-562. doi: 10.1097/IAE.0000000000002881.

PROJECT TITLE AND SHORT DESCRIPTION

Testing new NRF2 activators in an Age-related macular degeneration (AMD) mouse model

AMD is a serious medical unmet need and there is no treatment whatsoever available for the more common early, intermediate and late “dry” forms of AMD. The primary cause of pathology appears to be retinal pigmented epithelium (RPE) degeneration. Miguel Seabra´s lab have developed a model system that recapitulates some AMD features *in vitro*; feeding RPE monolayers in culture with photoreceptors outer segments (POS) leads to accumulation of autofluorescent granules similar to lipofuscin *in vivo*, resembling RPE stress and disease. Notably, our results show that overexpression of the transcriptional regulator NFE2L2/NRF2, involved in antioxidant defences, or drugs that activate this transcription factor, can prevent the formation and/or resolve autofluorescent granules in this *in vitro* model.
We have recently set-up a combination of techniques (OCT, ERG, etc) to evaluate the structure and function of the mouse retina. We are currently validating and extending the *in vitro* results using mouse models. One such model of AMD is inducible upon sodium iodate (NaIO3) injection which leads to retinal degeneration, characterized by retinal RPE damage, oxidative stress and inflammation. We plan to use and characterise other AMD mouse models.
Firstly, we aim to evaluate molecular and cellular markers of disease on the AMD mouse models treated or not with FDA-approved NRF2 activators**.** NRF2 KO mice will be used as controls. We expect that candidate drugs, already selected in our *in vitro* studies, will improve AMD phenotypic features. We hope that using different therapeutic approaches will be a proof-of-concept study to establish the potential of both pharmacological or genetic approaches exploring the NRF2 pathway for AMD and eventually other age-related diseases. The data derived from this project will be useful in guiding the design of early phase clinical trials (translational research), while contributing to defining a reasonable risk for the therapy in the intended patients.
This ongoing project is funded by “La Caixa Foundation” (NASCENT HR22-00569).

SCIENTIFIC AREA WHERE THE PROJECT FITS BEST*

Life Sciences (LIF)

***Scientific Area where the project fits best** – Please select/indicate the scientific area according to the panel evaluation areas: Chemistry (CHE) • Social Sciences and Humanities (SOC) • Economic Sciences (ECO) • Information Science and Engineering (ENG) • Environment and Geosciences (ENV) • Life Sciences (LIF) • Mathematics (MAT) • Physics (PHY)