2020 European Grand Prix for Young Researcher – SCOR

NAME: Mancuso

FIRST NAME: Renzo

CURRICULUM VITAE *(1 page)*

Education/training
2010 to 2014 PhD in Neuroscience, Universitat Autònoma de Barcelona, Spain.
2009 to 2010 Master in Neuroscience, Universitat Autònoma de Barcelona, Spain.
2004 to 2009 Degree on Biology, Universitat Autònoma de Barcelona, Spain.

Appointments
Since Sept 2019 - Staff scientist at the Laboratory for the Research of Neurodegenerative disease. VIB Center for Brain & Disease Research. KU Leuven Department of Neuroscience.
2017 to 2019 - Postdoctoral fellow at the Laboratory for the Research of Neurodegenerative disease. VIB Center for Brain & Disease Research. KU Leuven Department of Neuroscience.
2015 to 2017 - Postdoctoral fellow at CNS Inflammation group. Centre for Biological Sciences, University of Southampton. Southampton, UK. Wellcome Trust NIMA Consortium.
2010 to 2014 - Pre-doctoral fellow. Universitat Autònoma de Barcelona, Spain.

Research projects
2019 to 2021 - Targeting non-neuronal Alzheimer's disease risk genes with antisense oligonucleotides. Flanders Innovation & Entrepreneurship (VLAIO) with Janssen Pharmaceuticals. PI: Renzo Mancuso. 427,000€
2019 to 2022 - Microglia and neuroinflammation: transducers of amyloid beta toxicity in human Alzheimer's disease. FWO Research project. PI: Renzo Mancuso. 564,996€
2018 to 2021 - Microglia and neuroinflammation: transducers of Ab toxicity in human AD. Alzheimer's Association Research Fellowship (AARF). PI: Renzo Mancuso. $174,070.40

Fellowships and awards
2017 - Nominated for the Young Investigator Award by the Catalan Society of Biology (Societat Catalana de Biologia), Spain.
2015 - Outstanding PhD thesis award by the Universitat Autònoma de Barcelona, Spain.
2010 to 2014 - National competitive Training Programme for Academic Staff (FPU) fellowship by the Ministry of Education and Science, Spain.

Thesis supervision
Since 2018 - From genetics to the cellular phase of Alzheimer's disease: untangling the role of lipid pathways in microglia responses to amyloid pathology. PhD project by Nicola Fattorelli at VIB - KU Leuven, Belgium
Since 2018 - The effects of gamma secretase inhibition on biological functions of microglia. PhD project by Pengfei Hou at VIB - KU Leuven, Belgium.

Teaching activities
2019 - Masters Biomedical Sciences at KU Leuven. Microglial function during homeostasis and in neuroinflammation. (Coordinator: Prof. Lucia Chávez-Gutierrez)
2011-2013 - Teaching assistant Medicine degree. Faculty of Medicine. Universitat Autonoma de Barcelona

Conferences and symposiums
Speaker at AD/PD and FENS Brain Conference, and UK-DRI Connectome meetings and iPSC-microglia workshops. Poster presentations at multiple symposiums including AD/PD, GRC or FENS.

PRESENTATION OF PREVIOUS PROJECTS *(1 page)*

Please detail briefly your personal involvement on this/these research project(s) (4 lines/project).

Project 1

PhD in neuroscience

I performed my PhD in amyotrophic lateral sclerosis, developing new functional biomarkers and therapeutic interventions aiming at reducing neuronal degeneration. I accomplished this successfully and published 17 original research papers, 10 of them as first author, and a 2 review articles.

Project 2

Microglia modulation as Alzheimer's disease modifier (Wellcome Trust NIMA Consortium

I investigated how microglia impact tau pathology in the group of Prof Hugh Perry, where I led a comprehensive study together with multiple partners and provided first evidence of microglia as driver of tau pathology and cell death. I am corresponding author of this work published in Brain and am advisor of the Consortium during the clinical testing of the compound.

Project 3

Microglia and neuroinflammation: transducers of amyloid beta toxicity in human

I lead this project in the lab of Prof. Bart De Strooper. I have fully developed a model of human microglia transplantation in the mouse brain to study genetic interactions in the context of AD (I am corresponding author of the recent publication in Nat Neurosci). I am now using this system to study the role of APOE in the response of human microglia to amyloid-beta.

Project 4

From genetics to the cellular phase of Alzheimer’s disease: untangling the role of lipid

I supervise this PhD project carried out by Nicola Fattorelli, investigating how rare loss-of-function mutations in multiple genes related to lipid/cholesterol metabolism affect human microglia response to amyloid-pathology in vitro and in vivo (using cutting-edge human microglia chimeric models)

Project 5

The effects of gamma secretase inhibition on biological functions of microglia

I supervise this PhD project carried out by Pengfei Hou, investigating how pharmacological and genetic modulation of gamma secretase modify microglial biological processes, using an array of approaches in both in vivo and in vitro, as well as mouse and human systems.

PUBLICATIONS *(1 page)*

Select the five publications that you consider as the most significant by their anteriority and their impact. For each reference, indicate the interest of the paper (2 lines/reference) and the number of citations.

Publication 1

Stem-cell-derived human microglia transplanted in mouse brain to study brain disease

Mancuso R, Van Den Daele J, Fattorelli N et al. Nat Neurosci. 2019 Dec;22(12):2111-2116
Interest: I pioneered the development of human microglia chimeras to study genotype -phenotype interactions in microglia in vivo. This has been major breakthrough in the field.
Number of citations: 9

Publication 2

CSF1R inhibitor JNJ-40346527 attenuates microglial proliferation and neurodegeneration

Mancuso R et al. Brain 2019 Oct 1;142(10):3243-3264
Interest: this is the first evidence of microglia as driver of tau pathology and cell death. It also settled the base for the current clinical testing of CSF1R inhibitors in Alzheimer's disease.
Number of citations: 6

Publication 3

Early microgliosis precedes neuronal loss and behavioural impairment in mice with a

Clayton EL & Mancuso R et al. Hum Mol Genet. 2017 Mar 1;26(5):873-887.
Interest: this study revealed a very early microglial involvement in the CHMP2B mouse model of frontotemporal dementia, indicating that microglia are a central player in driving dementia
Number of citations: 47

Publication 4

CSF1R blockade slows the progression of amyotrophic lateral sclerosis by reducing

Martínez-Muriana A & Mancuso R et al.Sci Rep. 2016 May 13;6:25663.
Interest: we showed that microglia/macrophages contribute to ALS both in the CNS and PNS, and that modulation of these cells slows down disease and protects from neurodegeneration.
Number of citations: 62

Publication 5

Sigma-1R agonist improves motor function and motoneuron survival in ALS mice

Mancuso R et al. Neurotherapeutics. 2012 Oct;9(4):814-26.
Interest: this study showed for the first time that modulation of motorneuron excitability by boosting Sigma-1R is beneficial in ALS, and opened new therapeutic avenues.
Number of citations: 109

PRESENTATION OF RESEARCH PROJECT TO COME

Title of the research project :

Dissecting the role of APOE and lipid metabolism in human microglia in Alzheimer's disease

The overall goal of my research is to define the role of microglia and neuroinflammation in the pathogenesis of Alzheimer's disease (AD). AD shows a slow disease process with a long incubation phase between the first biochemical alterations (i.e. accumulation of amyloid-beta and tau) and cognitive manifestations that can last decades. This means that, in addition to the biochemical insults, there are profound multicellular alterations that are an integral part of the disease process, and a major challenge now is to understand the interplay between these distinct cellular components within the context of the demented human brain.
Genetics provide crucial insights to uncover the cellular players involved in AD. Studies in twins estimate that 58-79% of susceptibility is defined by genetics . Apart from well-known low-frequency causative mutations (e.g. APP or PS), multiple other genetic polymorphisms increase the risk for AD. The APOE polymorphism is the major risk factor (12-fold increased risk), and multiple genome-wide association studies (GWAS) have uncovered at least 42 other loci that confer susceptibility for AD, the majority of which are enriched or specifically expressed in microglia, placing these cells in the very core of the pathogenesis of dementia. Data mining approaches suggest that all these AD risk genes operate in a limited number of disease pathways. The major pathways involved, all microglia-related, are: 1) genes linked to a "cholesterol" or "lipid" pathway (APOE, CLU1, ABCA7, PLCG2 and SORL1), 2) inflammation processes (TREM2, CR1, CD33, HLA-DRB5, HLA-DRB1, INPP5D, MS4A6A, etc.) and 3) endocytosis (BIN1, SORL1, PICALM and CD2AP). The definition of these categories is still very broad, and almost all genes are actually implicated in more than one pathway (i.e. the lipid pathway genes are all implied in inflammation, genes implied in endocytosis are often interacting with lipids to internalize, etc.). Functional data to validate these links are vastly missing, and this will be a corner stone of the research I plan to develop during the coming years.
One of the major challenges when trying to define the impact of human genetic variability on disease susceptibility and progression is the lack of good models that recapitulate all features of AD. From a microglia perspective, this is even clearer as the immune system is constantly subjected to a very strong evolutionary pressure, and a significant number of AD risk candidate genes either do not have good mouse homologues or they are exclusively expressed in human but not mouse microglia. For example, the APOE polymorphism, the major genetic risk factor for AD, does not exist in rodent, mouse Siglec-3 lacks an ITIM motif, there is no real homologue for CR1, the locus of MS4A4A is highly divergent, etc. To overcome this limitation, I plan to use a microglia xenograft model I recently developed where iPSC-derived cells are transplanted into the mouse brain. This allows human cells to adopt a brain resident phenotype by living in their native brain environment, where they can be further exposed to amyloid-beta plaques
I hypothesise that microglial activation and neuroinflammatory imbalance are central drivers of AD. Building up from human genetics and using iPSC technology and humanised systems I plan to determine what are the major phenotypic/functional manifestations derived from microglia carrying genetic alterations in cholesterol/lipid metabolism pathways, and how that influences their response to amyloid-beta and further impact modifying disease course.

PRESENTATION OF RESEARCH PROJECT TO COME

Objective 1: Dissecting the role of APOE in human microglia in amyloid pathology. My first aim is to determine the differential response of human microglia harboring different APOE alleles to amyloid pathology in vitro and in vivo. I anticipate that APOE4/4 microglia will produce an exacerbated response and result in an acceleration of tau pathology.
Aim 1.1. Defining the major transcriptional networks induced by amyloid-beta in iPSC-derived microglia in vitro.
Aim 1.2. Elucidating the role of microglial APOE in amyloid pathology in vivo using cutting edge microglia xenograft models.

Objective 2: Linking lipid metabolism pathways and microglial response to amyloid pathology. I will assess how manipulation of lipid/cholesterol genes alters microglial function and modifies response to amyloid pathology. I will focus on the established AD risk genes ABCA7, BIN1, CLU, PICALM, PLCG2 and SORL1. Importantly, these genes haven been not only linked in GWAS, but rare loss-of-function mutations were identified in each of them by targeted sequencing in independent AD cohorts, which means they can be studied using a KO strategy.
Aim 2.1. Generation of isogenic lines KO for genes of lipid metabolism pathways.
Aim 2.2. In vitro analysis of mutant iPSC-derived microglia.
Aim 2.3. Implication of lipid/cholesterol metabolism pathways in human microglia cell states in vivo in response to amyloid-plaques.

Objective 3. Generation of relevant lipid metabolism mutants and impact on mouse pathology. Based on the outcome of Objective 2, I expect to obtain candidates lipid risk genes that, when knocked down, are able to either restore homeostatic microglia functions or exacerbate disease associated phenotypes. I plan to select the best hits among all analysed genes and then study their impact upon the mouse brain and investigate their ability to modify pathology in-depth
Aim 3.1. Generation of stem cell lines harbouring single mutations
Aim 3.2. In vivo assessment of the best hits using microglia chimeras
Aim 3.3. Validation in human tissue carrying the specific mutations

Expected results
I predict that lipid metabolism has a strong impact on the response of microglia to amyloid beta plaques. Objective 1 will unravel for the first time what are the phenotypic alterations triggered by amyloid-beta accumulation in human microglia and define which is the contributory role of human microglial APOE in the pathology of AD in vivo. I predict that APOE4/4 microglia will display exacerbated activation phenotypes and induce higher extents of pathology, therefore linking APOE increased risk of AD to an amplified microglia activation. Objective 2 will dive deeper into a number of rare genetic mutations with strong link to AD and related to lipid metabolism. I predict that some of these mutations will induce a dramatic effects on the phenotype of human microglia phenotype. I will then select the hits displaying the larger cell autonomous effects and explore their impact upon amyloid pathology in Objective 3. Therefore, the last objective will study the impact of microglia bearing AD genetic mutations upon disease progression. I predict that mutations recovering microglial homeostasis will have a positive impact on mouse brain pathology, whereas mutations leading to increased disease associated states will accelerate the disease process. Overall, this project will provide first evidence on how genotype affect human microglial response to AD in vivo, and are able to modify disease course. This will represent a major breakthrough in the field an I consider I am in the best position to carry out this very exciting research.

SUMMARY FOR GENERAL PUBLIC INFORMATION *(15 lines)*

Alzheimer's disease (AD) is a degenerative brain disorder and the most common cause of dementia. AD is characterized by the extensive accumulation of abnormal proteins in the brain, in the form of amyloid beta (Aβ) plaques and tau tangles. Genetics is the major risk factor of AD, and we know that most of this risk is found in genes mainly expressed in microglia, the immune cells of the brain. Several of these risk genes are associated with lipid or cholesterol metabolism, and linked to inflammatory processes. Therefore, microglia have a central role in AD, but a link is missing between genetics and how they modify microglial response to AD pathology. However, mouse and human display major genetic differences, therefore limiting our ability to study how genes impact microglia function in mice. To overcome lack of similarity of AD human risk genes in mouse models, I recently developed a humanized microglial chimera model that allows to study genetic risk and AD pathogenesis in a unique way. I propose with this project to use a combination of cell culture and chimeric AD mice to study the role of APOE (major risk factor of AD) and other lipid-associated AD risk genes (i.e. ABCA7, BIN1, CLU, PICALM, PLCG2 and SORL1) in human microglia. This represents an unparalleled approach to elucidate the effect of lipid risk genes manipulation on human microglia responses to amyloid pathology.

Explain in 2 lines what is/are your major(s) contribution(s) in the field:

I showed how microglia drive tau pathology and created a cutting-edge platform to study human microglia in vivo in AD that I will use to unravel the role of APOE in human microglia in AD.