Newsletter July 2020

INSIDE THIS NEWSLETTER

"Targeting neuroinflammation to combat pathological pain in neurodegenerative diseases and chronic pain syndromes."

Professor Marzia Malcangio

TOBeATPAIN's Mission

TOBeATPAIN is a research training programme funded by the Horizon 2020 programme of the European Union (Marie Skłodowska-Curie Grant Agreement No 764860).

Coordinated by Professor Marzia Malcangio at the Institute of Psychiatry, Psychology & Neuroscience, King's College London, the TOBeATPAIN network is providing eleven researchers with a unique training platform across different research/training environments and cultures working with 3 biotech SMEs, 2 large companies and 1 non-profit research charity. Our partners are: Karolinska Institutet, Medizinischen Universität Innsbruck, Universitätsklinikum Jena, Universitätsklinikum Würzburg, Kancera AB, Bionorica GmbH, Eli Lilly and Company Ltd, Mabtech AB, European Research and Project Office GmbH (EURICE) and the Alzheimer's Society.

TOBeATPAIN is exploring the links between neuroinflammation and pathological pain that occurs as a result of diseases within the brain as well as in the peripheral nervous system. Our hope is to identify the critical non-neuronal cellular players and mediators involved in pathological pain signaling in neurodegenerative diseases characterized by neuro-inflammation and in chronic pain syndromes.

Spotlight on Public Engagement…

By Dr Susan Duty (King's College London)

An important aspect of the TOBeATPAIN training programme is to provide a platform for interaction with the general public, whether this be to young budding scientists or to adults from a non-science background wishing to find out more about our scientific world. This year, two of our Early Stage Researchers (ESRs) have helped to inspire those at the start of their scientific journey. Fátima Gimeno-Ferrer (ESR8) and Zerina Kurtovic (ESR5), hosted school students in their places of work - Universitätsklinikum Jena, UKJ and Kancera, respectively - to see first-hand what a scientist does and to hear, in straightforward, easily understandable terms about the theory behind the scientific projects they are engaged with.

European Researchers' Night is a public event aimed at bringing researchers closer to the general public, in everyday settings, to showcase the diversity of current research and highlight the positive roles of research on society. In September, 2019 this event was held at the Natural History Museum in London and one of our ESRs, Xhoana Lama (ESR2) was excited to take part. One of the activities Xhoana contributed to was the 'EU pub', designed to give members of the public a chance to have a relaxed chat with a scientist over a drink. As Xhoana says, "Because the format was informal, conversations were flowing more fluidly, and this helped remind people that scientists are just normal people too!"

During the period of Covid-19 lockdown, with limited scope for face-to-face interaction with the public, we turned our attention to producing videos for their information. George Sideris Lampretsas (ESR1), Xhoana Lama (ESR2) and Rita Silva (ESR11) have produced a wonderfully animated video to explain the role of neuroinflammation in pain. This includes hand-drawn cartoons to illustrate the role of the brain in monitoring pain, amongst other fun and easily understood analogies. Meanwhile, I have videorecorded interviews with some of our project supervisors who explain in lay terms how pain features in the disorders on which they are focused in the TOBeATPAIN network. Why not visit the Public Engagement tab on our website to take a look at these useful resources?

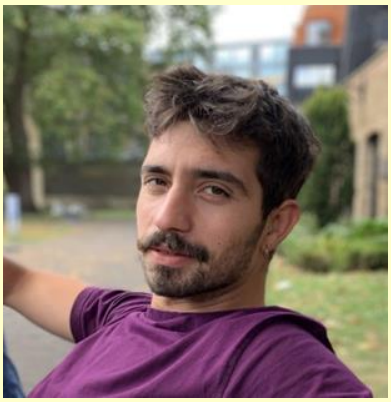
Early Stage Researcher (ESR) Project Updates…

Neuroinflammation and pain in Alzheimer's disease

By George Sideris Lampretsas (ESR1)

Before joining the TOBeATPAIN European Training Network, I graduated from the School of Pharmacy at the Aristotle University of Thessaloniki in Greece. During my 5-year bachelor, my main research project focused on RNA editing in Alzheimer's disease in post-mortem tissues, while I have also spent six months working on ER-stress and protein synthesis machinery in APP/PS1 mice in Idibell in Barcelona.

PROJECT UPDATE



Chronic pain is a common condition in the elderly with Alzheimer's Disease (AD) that often remains undertreated as patients may experience difficulty in reporting pain. In this project, we are using transgenic mice models of AD to test the hypothesis that neuroinflammation in the CNS contributes to alteration in pain-like-behaviour in AD mice in models of inflammatory arthritis. By employing imaging and molecular biology techniques, we have observed that persistent inflammatory pain is associated with pronounced neuroinflammation in the pain-related-brain areas, in the form of activated microglia. In addition, the development of mechanical hyperalgesia is associated with exacerbation of the underlying AD pathology. The next set of experiments will aim to identify microglial signature in the brain of AD mice with and without persistent pain.

The project is supervised by Professor Marzia Malcangio (King's College London) with a secondment planned at Eli Lilly (6 months).

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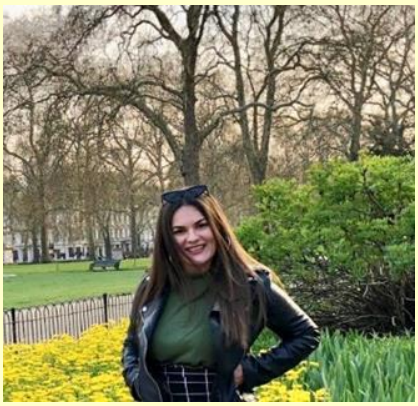
Neuroinflammation and pain in Parkinson's disease

By Xhoana Lama (ESR2)

Before embarking on the TOBeATPAIN programme I studied at the Department of Biological Applications and Technology of the University of Ioannina where I became fascinated with neuroimmunology. I subsequently conducted my master's thesis at the Biomedical Research Foundation of the Academy of Athens then received an Erasmus+ scholarship to conduct a placement in University Hospital Frankfurt.

PROJECT UPDATE



Pain is one of the most debilitating non-motor signs of Parkinson's disease (PD) but is poorly understood and inadequately treated by current analgesics in patients; 45% of people report no pain relief or improvement by existing medications. Neuroinflammation is a hallmark of PD and has already been implicated in the neurodegenerative side of PD. However, whether neuroinflammation is involved in pain in PD is still unexplored. So far, we have completed a preliminary study in the 6-OHDA rat model of PD that has presented mixed results owing to a variable lesion size produced in the animals. Doses of 6-OHDA will be increased to generate a more consistent lesion. Nevertheless, these preliminary studies enabled us to optimise all the behavioural nociceptive and motor tests and the post-mortem immunohistochemistry and RNA extraction protocols as well as some FACS analysis protocols.

The project is supervised by Dr Susan Duty & Professor K Ray Chaudhuri (King's College London). Secondments are planned at the Universitätsklinikum Würzburg (UKW) with Dr Nurcan Üceyler.

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Neuroinflammation and cerebral pain processing in fibromyalgia and osteoarthritis

By Silvia Fanton (ESR3)

Before joining the TOBeATPAIN network, I graduated from a Bachelor's degree in Cognitive Psychology and Psychobiology and a Master's degree in Cognitive Neuroscience and Clinical Neuropsychology (entirely held in English) at the University of Padua (Italy). I also took part in a Summer School at the Experimental and Applied Psychology Lab at Vrije University in Amsterdam and spent two semesters abroad, the first one in Linköping (Sweden) and the second one as a research trainee in the Department of Neuroscience at KI.

PROJECT UPDATE

The overall purpose of my PhD project is to increase the understanding about the still largely unknown mechanisms responsible for the chronification of musculoskeletal pain by focusing, specifically, on the transition from nociceptive to nociplastic pain. With this scope, rheumatoid arthritis and disc degenerative disease (DDD) will be explored as models of the former, while fibromyalgia (FM) will be examined as a prototype of the latter.

Progress made so far includes:

1. Investigating the influence of a functional polymorphism of the translocator protein gene on endogenous pain modulation, brain metabolism, and cerebral pain processing in fibromyalgia (FM) patients and healthy controls (HC) – writing manuscript
2. Applying temporal network theory to fMRI data in the investigation of pain processing in rheumatoid arthritis – data organization started, data pre-processing and analysis to begin
3. Testing for possible association between autoimmune antibodies and changes in brain morphology, cerebral pain processing, and brain metabolism in FM and HC – planning completed, data collection to start
4. Examining pain processing in disc degenerative disease – ongoing data collection

The project is supervised by Professor Eva Kosek (Karolinska Institutet). I have undertaken a secondment at MABTECH AB, Stockholm (which you can read about in our research blog) with further secondments planned for Kancera and for Universitätsklinikum Würzburg (UKW) under supervison of Professor Claudia Sommer.

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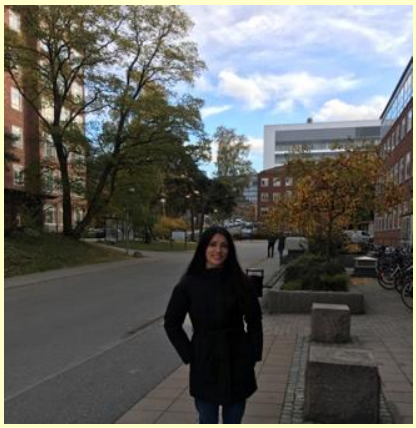
Role of brain and spinal cord (micro)glia in arthritis- and fibromyalgia-associated pain

By Joana Menezes (ESR4)

I studied Human Biology at the historical Evora University at a bachelor level followed by a Master degree in Molecular Genetics and Biomedicine at Nova University in Lisbon. I spent the second year of my Master's in the BRAINlab at the University of Copenhagen. Up until joining the TOBeATPAIN project I was working as a research assistant at the Neurobiology Research Unit (NRU), Rigshospitalet, under supervision of Professor Jens Mikkelsen.

PROJECT UPDATE



My project is focused on chronic pain in Fibromyalgia (FM). The Svensson lab is part of a collaboration that recently found evidence of an autoimmune component in FM and developed a disease-relevant mouse model. These mice injected with IgG from FM patients develop pain-related behavior.
I am analyzing gene expression levels in different cell cultures that have been exposed to FM IgG or controls IgG. I have for e.g. found that N2A neuronal cells have a significant increase in CACNA1B and P2RX3 mRNA levels when exposed to FM IgG. This approach can give us insights if the presence of FM IgG induces changes in genes in different cells. This can helpful to explore FM IgG-associated pain mechanisms in vivo. Through my PhD work in the Svensson lab, and through collaborations within the TOBeATPAIN network, I am confident that we will identify new strategies to reduce the burden of chronic pain and improve the quality of life for the millions suffering from pain.

This project is supervised by Dr Camilla Svensson (Karolinska Institutet) with secondments planned at the University of Jena with Professor Hans-Georg Schaible and Kancera with Dr. T. Olin.

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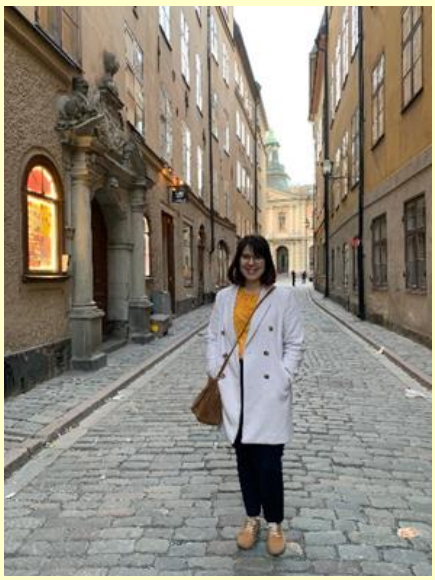
Role of microglia and macrophages and the CX3CL1/CX3CR1 pathway in arthritis-induced pain

By Zerina Kurtovic (ESR5)

Before joining the TOBeATPAIN network, I obtained my bachelor's degree in Molecular Biology and Genetics at the Istanbul Technical University and my master's degree at Ludwig Maximilian University in Munich. During this period, I gained insights into different research areas like aging studies, the cell biology around cytokinesis, immunology and neuroimmunology. I did my master thesis as a visiting student at the University of Cambridge, as a part of the Multiple sclerosis genetics group.

PROJECT UPDATE



I am focusing on studying macrophage-associated pain mechanisms in animal models of rheumatoid arthritis. In order to do an in-depth analysis of the effect of CAIA (collagen antibody induced arthritis) on macrophages, we have established protocols to analyze dorsal root ganglion (DRG) macrophages with flow cytometery. Next, we have, together with collaborators, sorted CD45+ cells from the DRGs from naïve mice for scRNA-seq. We have also explored macrophage numbers and sex-differences in terms of inflammation and mechanical hypersensitivity in the CAIA model. We are currently addressing if KAN145, Kancera´s CX3CR1 antagonist, has an effect on arthritis scores and mechanical hypersensitivity in the CAIA model.

The project is supervised by Professor Camilla Svensson and co-supervised by Dr. Sally Abdelmoaty and Dr. Harald Lund as a part of the TOBeATPAIN grant. Secondments are planned at the University of Jena with Professor Hans-Georg Schaible and the University of Innsbruck with Professor Michaela Kress.

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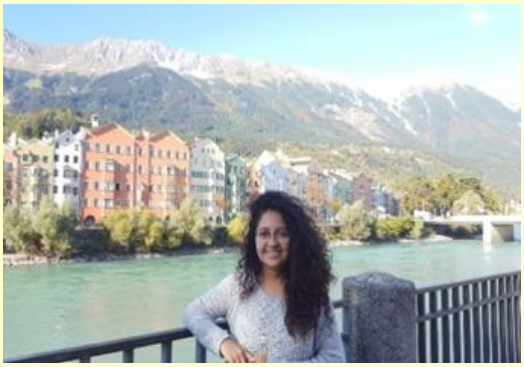
Neuroinflammation and pain in a mouse model for Fabry disease

By Jeiny Luna-Choconta (ESR6)

Before getting involved in the TOBeATPAIN research training program, I studied a bachelor's degree in Biology in the Universidad Nacional de Colombia; however, my bachelor thesis took place in Clinical Parasitology Lab at the Universidad Nacional del Sur, Bahia Blanca, Argentina. Afterward, I completed a master's degree in Neuroscience at Universidad Miguel Hernandez and I had the opportunity to begin research on the interaction of brain-resident macrophages under neuroinflammatory conditions in Cellular plasticity and Neuropathology Lab at Instituto de Neurociencias, Alicante, Spain.

PROJECT UPDATE



Fabry disease (FD) is an X-linked lysosomal storage disorder. It is caused by deficiency of α-galactosidase-A and accumulation of globotriaosylceramide (Gb3). The central nervous system dysfunctions are associated with the deposition of Gb3 in blood vessels of the brain, causing vascular dementia disorder in Fabry patients.
During the first year of my project we obtained results confirming significant Gb3 accumulation in hippocampus, specifically in the dentate gyrus in adult FD mice. Furthermore, we find alterations of microglia morphology in the hippocampus of aged FD mice. In order to delineate the underlying pathogenesis, we are now analyzing microRNA-mRNA interactions and working memory deficits associated with FD.

The host institution for this project is in the Institut. für Physiologie und Medizinische Physik at the Medizinische Universität Innsbruck, under the supervision of Prof. Michaela Kress and co-supervision of Dr. Michiel Langeslag (MUI) and Prof. Ray Chaudhuri (KCL). A secondment is planned at Eli Lilly.

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Mechanisms of spinal neuroinflammation and hyperexcitability in models of joint inflammation

By Anutosh Roy (ESR7)

Before joining the TOBeATPAIN innovative training network, I was graduated in Zoology with Honours from the University of Calcutta and later obtained my MSc degree in Molecular & Human Genetics from Jiwaji University, Gwalior. Later I attended Summer School of Molecular Medicine in Jena, Germany and also received prestigious travel award from DAAD, Germany for the same.

PROJECT UPDATE

Spinal hyperexcitability is a hallmark of many chronic pain states including joint inflammation. At the moment, we are investigating the chronification mechanism of spinal hyperexcitability from acute phase in nociceptive neurons as planned in our hypothesis. We assume EGF might be an important player in this chronification process. We used an EGF inhibitor (Gefitinib), which reasonably reduces spinal hyperexcitability following long term spinal IL-6/IL-6sR application. In addition, a Stat3 inhibitor did not reduce neuronal activity as expected. In controls the substance surprisingly increases neuronal activity in vivo. We tested these two inhibitors in vitro in different cell lines, (Rat DRGs, Mice BV2). There they blocked Stat3 activity effectively. However, at the same time another pro-inflammatory signaling protein (p38) increased. Currently we are trying to find whether there is a link between Stat3 and P38 signalling pathways.

The host institution for this project is University of Jena: Supervisor is Prof. Hans Georg Schaible; Co-supervisor is Dr. Andrea Ebersberger (UKJ). A secondment is planned for King's College London (KCL), UK under the supervision of Prof. Marzia Malcangio.

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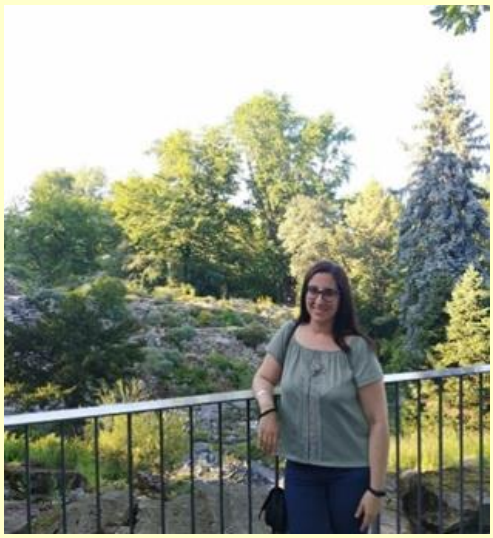
Impact of neuroinflammation and neurodegeneration on brain and spinal cord homeostasis: relevance to nociception

By Fátima Gimeno-Ferrer (ESR8)

Before joining TOBeATPAIN, I was graduated in Biochemistry and Biomedical Sciences from the University of Valencia (UVEG) and then I obtained my MSc in Research in Molecular, Cellular and Genetics Biology in the UVEG as well. Also, I did a postgraduate in Medical Genetics in the same university. During my studies in Valencia I took part in different internships and part of this work has been published from 2017 onwards.

PROJECT UPDATE



In my project I study the interaction of homeostasis and neuroinflammation and neurodegeneration. During this 1.5 year in the Institut für Physiologie in Jena, I have characterized brain excitability in the neuroinflammation model. For that aim I performed in vivo electrophysiology experiments in rats as well as histology. We could conclude that there is a change in brain homeostasis under a neuroinflammatory state. Apart from my work in Jena, I could do my first secondment in the Medizinische Universität Innsbruck where I could test the same model with Multielectrode Array technology, confirming our previous data. We are pleased with the current status of the project with promising results.

This project takes place in the Institut für Physiologie I/Neurophysiologie of the Universitätsklinikum Jena (Germany) and is supervised by Prof. Frank Richter as part of the TOBeATPAIN network. I have already completed one secondment at Medizinischer Universität Innsbruck, under the supervision of Prof Michaela Kress which you can read more about in our research blog. Other secondments are planned for the Karolinska Institutet (Department of Physiology & Pharmacology) and the Company Mabtech.

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Neuroinflammation in pain and nerve degeneration and regeneration in peripheral neuropathies

By Patricia García Fernández (ESR9)

Before joining the TOBEeATPAIN network, I studied my bachelor and master degrees in Madrid. My bachelor degree was in Biotechnology, clinical expertise, in the Technical University of Madrid. My master degree was in Molecular and Cellular Integrative Biology (MCIB) at the Menendez-Pelayo International University, in collaboration with the Spanish National Research Council.

PROJECT UPDATE

The balance of pro- and anti-inflammatory mediators after nerve injury and in polyneuropathies not only determines painfulness of the disease, but also modulates nerve degeneration and regeneration. This project will evaluate the profiles of pro- and anti-inflammatory cytokine and chemokine expression and secretion in peripheral blood leukocytes, cerebrospinal fluid (CSF) and CSF lymphocytes, macrophages and Schwann cells isolated from patients' nerve biopsies.
Recently, I have achieved the culture of Schwann cells from sural nerve biopsies from patients with polyneuropathies and now I am isolating them from fibroblasts to obtain a pure culture.
Furthermore, I have found two populations of immune cells in the epidermis and dermis of patients with polyneuropathies: Langerhans cells and Dendritic cells. Currently, I am characterizing these two populations and their marker expression in these patients.
Moreover, I am analyzing the morphology of Langerhans cells with an automatic software, developed by a collaborator group. Some other parts of the project are been taken care by one master student and three medical students under my supervision.

This project is being supervised by Professor Claudia Sommer at the Universitätsklinikum Würzburg (UKW) with secondments planned for the University of Jena with Dr. A. Ebersberger and Bionorica with Dr. S. Schoenbichler.

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Assessment of medical marijuana bioactive substances in a mouse model of neuropathic pain

By Cristiana Dumbrăveanu (ESR10)

Before joining TOBeATPAIN, I graduated from Alexandru Ioan Cuza University of Iaşi with a bachelor's degree in Biology and a master's degree in Microbial and cellular biotechnologies. During my studies I took advantage of the opportunities that the university offers, and I completed a practical traineeship at Konstanz University, Germany and a semester of study and research at Clarkson University, New York.

PROJECT UPDATE

Although pharmacological targeting of peripherally expressed cannabinoid CB1 receptors has pronounced analgesic effects and CB2 receptor activation suppresses neuroinflammation in the CNS, the use of medical marijuana is still limited mainly because, apart from tetrahydrocannabinol (THC) and cannabidiol (CBD), its active components have not been studied in sufficient detail.

… focused to characterise the analgesic action of medical marijuana preparations with and without THC and CBD in the spared nerve injured (SNI) mouse model for neuropathic pain and assess the bioavailability of medical marijuana bioactive substances to correlate it with analgesic and anti-inflammatory effects.

The endocannabinoid system includes four receptors, the metabotropic receptors CB1, CB2, GPR55, and the ionotropic receptor TRPV1 that are known to bind cannabinoids. Cannabinoid receptors activation mediates downstream signaling pathways that are responsible for their analgesic effects.

Working with HEK-293 cells expressing CB1 and performing real-time cAMP imaging by FRET we confirmed that natural cannabinoid THC was able to inhibit cAMP level. CBD, a negative allosteric modulator at CB1 receptor, showed inhibitory effects at low concentrations. The microfluorimetric calcium assay in HEK-293 cells expressing TRPV1 channel indicated that both compounds, THC and CBD, induced small calcium influx by activating TRPV1.

This project is being supervised by Dipl.-Ing. A. Neumann, (Bionorica research GmbH, Innsbruck), co-supervisor: Prof. M. Kress (Medical University of Innsbruck). The secondment will take place at Karolinska Institute, Stockholm.

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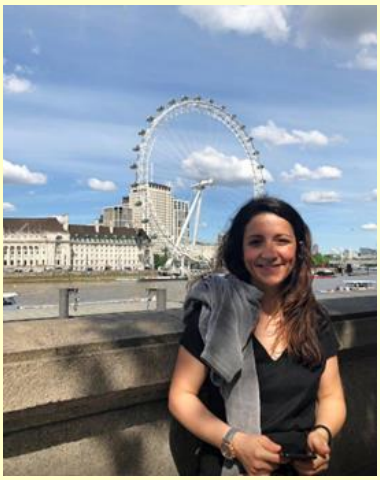
Neuroinflammation and CNS hyper-excitability in chronic pain and neurodegeneration mice models

By Rita Silva (ESR11)

Before joining the TOBeATPAIN European Network, I studied Biochemistry at the Faculty of Sciences in the University of Porto. Parallel to my undergraduate studies, I was also a paramedic. Seeing first hand the impact of pain, I moved to the Faculty of Medicine at University of Porto, where I completed internships and, inclusive, my Master in Neurobiology thesis in the pain field.

PROJECT UPDATE

Alzheimer's disease (AD) and chronic pain are amongst the biggest co-morbidities needed to be addressed in the growing ageing population. Neuroinflammation plays a significant, and possibly differential role in the sensory versus cognitive components of chronic pain under neurodegenerative conditions. This project aims to uncover how neuroinflammation in the brain, driven by a neurodegenerative disorder such as Alzheimer's disease (AD), affect pain behavior and neuronal excitability in mouse animal models. Until recently, I focused in challenging spinal cord slices and organotypic cultures in vitro with an inflammatory mediator to assess changes in neuronal excitability, microglial gene expression and cytokine release. However, differences were not observed in vitro. The next experiments will be done in vivo, using an AD mouse model with a spare nerve injury where inflammation is present in the spinal cord, and assess pain-related behaviors. I will also verify if brain areas involved in the descending pain inhibitory system known to be affected in AD patients are affected in this animal model.



This project is being supervised by Professor Marzia Malcangio (King's College London) with a secondment having been taken at Lilly Pharmacueticals under the supervision of Dr Emanuele Sher.

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Training Events

Upcoming Network Training Workshops

September 2020: Hosts Kancera AB and Karolinska Institutet. Scientific Workshop - Pharmacokinetics and multi-cytokine quantification - and Transferable Skills – Society Innovation and patenting

January 2021: Hosts Medizinische Universitat Innsbruck, Austria. Winter School and Transferable Skills – Business Entrepreneurship and Innovation

July 2021: Hosts King's College London, England. Scientific Workshop - Genomics and bioinformatics - and Transferable Skills – Science, Media and Communication

January 2022: Hosts Universitat Klinikum Jena, Germany Project Conference and Transferable Skills – Grant Proposal Writing

July 2022: Hosts King's College London. Project AGM

Training Sessions Undertaken this Year

July 2019: Hosts Universitätsklinikum Würzburg, Germany. Annual Meeting and Transferable Skills –IP and commercial exploitation

February 2020: Hosts Medizinische Universitat Innsbruck, Austria. Scientific Workshop - Mass spectrometry analysis - and Transferable Skills – Leadership and Research Governance

Visit here for more details and reviews of past events.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie Grant Agreement No 764860.

Dissemination

Network members have presented their work at conferences including:

Neuroscience Conference in Chicago, 19-23 /10/ 2019

98th Meeting of German Physiological Society, 30/9 – 2/10, 2019.

11th Congress of the European Pain Federation (EFIC), Valencia, 4-7/9/2019

Reviews of these meetings and journal club presentations given by ESRs 1,2 and 3 can be found on our website here.

Published articles can be found on our website here.

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