Synaptic Function, Dysfunction and Repair

Monday 1st – Tuesday 2nd April 2019

Auditório Professor Manuel Machado Macedo

CEDOC/NOVA Medical School

Universidade NOVA de Lisboa

Day 1 – Monday 1st April 2019

1.30pm – ***Registration***

2.00pm – **Professor Giampietro Schiavo,** University College London**, *Welcome and Opening Address* - *The Discoveries Centre for Regenerative & Precision Medicine***

2.10pm – Session 1: **Synaptic Function**

Session Chair: **TBC**

2.10pm – Talk 1: **Professor Miguel Seabra**, Universidade NOVA de Lisboa, ***Cellular ageing and chronic disease: mechanisms and interventions***

2.40pm – Talk 2: **Rita Teodoro,** CEDOC, Universidade NOVA de Lisboa, ***Neuronal membrane blebbing as a novel mechanism of activity-dependent bouton formation***

3.10pm – Talk 3: **Mónica Sousa,** IBMC, ***The regulation axonal contractility and propagation velocity***

3.40pm – Talk 4: **João Relvas,** IBMC, ***Talk Title TBC***

4.10pm – ***tea/coffee break & exhibit TBC***

4.40pm – Session 2: **Synaptic Dysfunction and Repair**

4.40pm – Talk 1: **Dr Marc Busche,** UK Dementia Research Institute, University College London, ***Circuit changes underpinning progression in Alzheimer's disease***

5.10pm – Talk 2: **Cláudia Almeida,** CEDOC, Universidade NOVA de Lisboa, ***Impact of late-onset Alzheimer's disease risk factors on synapses***

5.40pm – Talk 3: **Miguel Oliveira,** Univ Minho, ***Nanobiomaterials advances for the Central Nervous System and Peripheral Nerve Regeneration***

6.10pm – *Closing remarks and questions*

6.30-7.30pm – ***Evening Reception***

Find out more about the Discoveries Centre at http://www.thediscoveriesctr.eu/
The project has received funding from the European Union's Horizon 2020 research and innovation programme, under grant agreement No 739572

Day 2 – Tuesday 2nd April 2019

9.00am – ***Tea & Coffee***

9.30am – Session 3: **Synaptic Dysfunction and Repair**

Session Chair: **TBC**

9.30am – Talk 1: **Professor Stephanie Schorge**, UCL School of Pharmacy, ***Brain Hacking with Viruses: Gene therapy for epilepsy***

10.00am – Talk 2: **Catarina Brito,** ITQB, Universidade NOVA de Lisboa & IBET, ***Modelling neuronal microenvironment dynamics in disease***

10.30am – Talk 3: **Helena Vieira,** CEDOC, Universidade NOVA de Lisboa, ***Targeting microglia for the improvement of neuronal function***

11.00am – Coffee Break
11.30 – Session 4: **Synaptic Function**

11.30am Talk 1: **Vanessa Morais,** IMM, ***Synaptic mitochondria: In search of its functional fingerprint***

12.00pm – Talk 2: **Teresa Summavielle,** Universidade do Porto**,** ***Psychostimulant-elicited synaptic modulation through regulation of Cdc42***

12.30pm – Talk 3: **Odete Cruz e Silva,** Universidade de Aveiro, ***Protein phosphatases and the synapse***

1.00pm – Closing remarks and Farewell

1.05pm – ***Lunch***

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Speaker Abstracts

Day 1

Session 1:

Professor Miguel Seabra, Universidade NOVA de Lisboa

Cellular ageing and chronic disease: mechanisms and interventions

Ageing is the most important risk factor in the common chronic diseases, including neurodegenerative diseases. I will review the current ideas on cellular ageing, with a focus on loss of proteostasis and lysosomal dysfunction. Then I will use age-related macular degeneration as an example and will discuss our attempts to develop cellular models of the disease and study early events in the degenerative process. Finally, I will discuss possible interventions into the ageing process and how they might be applied to age-related degenerative diseases.

Dr Rita O. Teodoro, CEDOC, Nova Medical School

Neuronal membrane blebbing as a novel mechanism of activity-dependent bouton formation

Activity-dependent structural plasticity is a key feature of nervous system development and function. Despite this, the mechanism by which activity-dependent boutons form remains unclear. Using the *Drosophila* neuromuscular junction, we show in real time that, in response to depolarization, boutons form by a mechanism that is clearly distinct from growth-cone mediated bouton formation and, instead, resembles fast amoeboid migration. Amoeboid migration, also known as blebbing, is a pressure-driven mechanism used by some cells to migrate in 3-D environments and that is favored in conditions of high confinement and low adhesion. We show that activity-dependent boutons have the hallmarks of blebs and that changing the levels of synaptic activity in motor neurons or muscle results in predictable changes in bouton formation. We suggest that structural plasticity requires a fine balance between mechanical forces and biochemical signaling, and we introduce blebbing as a novel way to regulate presynaptic morphology.

Mónica Sousa, IBMC

The regulation axonal contractility and propagation velocity

After contacting their targets, axons increase their diameter to enable fast conduction of action potentials. In the adult, axonal caliber varies by almost 100-fold in different tracts. When considering a given axon, its diameter can further oscillate depending on organelle transport, neuronal activity, or deformations imposed by movement or degeneration. However, the fine-tune mechanisms controlling diameter throughout the lifetime of an axon, remain largely elusive. Here, we will present our most recent findings on the mechanisms regulating of axon diameter, with a specific focus on the role played by the actin-spectrin based membrane periodic skeleton, and their implications in neuronal biology.

Session 2:

Dr Marc Busche, UK Dementia Research Institute, University College London

Circuit changes underpinning progression in Alzheimer's disease

Alzheimer's disease (AD) is one of the most severe and devastating brain disorders anyone can experience; it affects millions and costs the health care system billions. While most research in the last decade has focused on pathology and proteins, recent technological breakthroughs in single-cell and circuit approaches have shifted the focus towards a better understanding of what is happening to cells and circuits in the brain during the progression of the disease. I will summarize recent work demonstrating how the major proteins involved in AD, tau and Abeta, affect neural circuit function, disrupting normal activity patterns, leading to cognitive impairments. I will further present data on the effects of anti-Abeta and anti-tau therapeutic approaches on those cellular and circuit dysfunctions.

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Dr Cláudia Almeida, CEDOC, Universidade NOVA de Lisboa

Impact of late-onset Alzheimer's disease risk factors on synapses

Synapse loss is the best correlate of Alzheimer's disease (AD) progression, but the identification of its causal mechanisms has been a challenge given the multifactorial etiology of late-onset AD (LOAD). While genetic predisposition is one of the factors accelerating the disease onset, its contribution to synapse loss is unknown. GWAS identified *CD2AP* and *BIN1* gene variants associated with AD among the top 20 biggest genetic risk factors. Bringing together our background in Alzheimer's and cell biology expertise, we are now investigating how LOAD mutations in Bin1 and CD2AP, regulators of endosomal trafficking, drive synapse dysfunction.

Dr Miguel Oliveira, Institute 3Bs (I3Bs), Universidade do Minho

Nanobiomaterials advances for the Central Nervous System and Peripheral Nerve Regeneration

Biomaterials have been attracting great deal of attention for delivery of cells and drugs to the central nervous system (CNS) and peripheral nerve system (PNS). Their versatility, processability and possibility of tuning its physico-chemical and biological properties are most advantageous and can offer a wide range of avenues to tackle the challenges of nerve regeneration. In this talk, the current biomaterials advances and latest tissue engineering strategies used for CNS and PNR pursued in the pre-clinical setting are explored and overviewed. In particular, recent advances that make use of biomaterials, neurotrophic factors, and cell-based therapies associated with nerve guidance conduits and hydrogels, alone or in combination, are presented. I will conclude by exploring the challenges and prospects of exploration of hydrogels in combination with imaging possibilities (e.g. Mn MRI) to overcome some clinical challenges associated with CNS and PNS disorders.

Day 2

Session 3:

Professor Stephanie Schorge, UCL School of Pharmacy

Brain Hacking with Viruses: Gene therapy for epilepsy

Gene therapy for rare genetic diseases is rapidly moving into clinical trials. In this talk we highlight a slightly different approach to using gene therapy to replace a mutated gene. Using the extensive data on how neuronal excitability is altered in epilepsy, even in the absence of mutations, we are identifying different approaches to dampen excitability, and consequently to reduce the frequency of seizures. This talk uses three different strategies we have taken to highlight how flexible gene therapy can be, and the advantages and disadvantages of synthetic, exogenous and endogenous protein expression for manipulating neuronal activity, not just in epilepsy, but in any neurological disorder characterised by well-defined changes in neuronal excitability.

Dr Catarina Brito, ITQB, Universidade Nova de Lisboa & iBET

Modelling neuronal microenvironment dynamics in disease

The neuronal microenvironment modulates physiological functions and pathological processes, including synaptic function. The major challenge in studying the underlying mechanisms is the lack of human cell models in which the dynamics of the extracellular space is recapitulated without the confounding effects of heterologous ECM components. This talk will describe advances in 3D cell culture for concomitant differentiation of neurons, astrocytes and oligodendrocytes from induced pluripotent stem cells. Neurospheroids preserve synaptic and ion transport machinery and accumulate typical neural ECM components, such as structural proteoglycans. We have been exploiting neurospheroids to model Mucopolysaccharidosis type VII, a neuronopathic lysosomal storage disease caused by deficient β-glucuronidase (β-gluc) activity, to gain insight into the interplay between reduced β-gluc activity, GAG accumulation and its impact on neuronal activity and connectivity.

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Dr Helena L.A. Vieira, CEDOC, NOVA Medical School, Universidade Nova de Lisboa

Targeting microglia for the improvement of neuronal function

Microglia, the "resident immunocompetent cells" of the central nervous system (CNS), are key players in innate immunity and for maintaining brain homeostasis and neuronal function. Carbon monoxide (CO) is an endogenous produced gasotransmitter with anti-inflammatory and cytoprotective activities. This talk explores whether and how CO modulates microglia to sustain neuronal plasticity/survival via anti-inflammatory signaling. This work describes a non-cell autonomous role of CO *via* regulation of glial-neuron communication and promotion of neuroprotection.

Session 4:

Dr Vanessa Morais, iMM – Instituto de Medicina Molecular | João Lobo Antunes, Faculty of Medicine, University of Lisbon

Synaptic mitochondria: In search of its functional fingerprint

Neurons are morphologically polarized cells and mitochondria have been observed in all neuronal sub-compartments. However, this distribution has been shown to be heterogeneous, with presynaptic and postsynaptic terminals containing more mitochondria than other neuronal domains. Additionally, these neuronal compartment- specific mitochondria appear to have different dynamics and morphological features, raising the question of whether these are functionally similar or actually have specialized functions adapted to the environment where they reside. Therefore, defining the intrinsic properties preferentially used by synaptic mitochondria to maintain their overall health is of particular relevance in the context of neuron function.

Mitochondria homeostasis is a process involving an intimate crosstalk between energy production, quality control and mitophagy. Perturbances of this intricate system are widely speculated to contribute to neurodegeneration. Our work focuses on elucidating these mitochondrial mechanisms crucial for brain function, and how a dysregulation in these processes can be fatal for the mitochondria itself or for the neuron.

Teresa Summavielle, Universidade do Porto

Psychostimulant-elicited synaptic modulation through regulation of Cdc42

Drug-induced modulation of neuronal morphology is associated with the long-lasting alterations underling addiction. We hypothesized that modulating of RhoGTPases, particularly of cdc42, could control such changes. Primary hippocampal neuronal cultures were exposed to methamphetamine (Meth) showing increased neurite growth and higher spine density. Using FRET reporter probes, we specifically determined that cdc42 is activated at dendritic spines and that expressing an inactive form of cdc42 prevents Meth-induced effects. Based on an RNAseq for neurites exposed to Meth, we next explored the role of intersectin1, a cdc42 specific activator. Through either an intersectin1/cdc42 interaction inhibitor (ZCL278) or a siRNA silencing approach, we significantly reduced Meth-effects. To confirm the relevance of our findings in vivo, we used an AAV9 to allow neuronal expression of GFP in wild type mice, which were later exposed to Meth in the presence or absence of ZCL278. Collectively, our data shows a relevant role for cdc42 and its regulators in the context of addiction.

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