GABBA Programme
2012 – NEURODEGENERATIVE DISEASES
June 4-8, IBMC

Coordination – Saraiva, MJ (IBMC and ICBAS)
Faculty – Gomes Pereira M (Paris)
Jensen PH (Aarhus)
Maciel P (U Minho)
Pereira C (U Coimbra)

June 4
10-12.30 a.m. – Saraiva, MJ
Introduction, course presentation; cell death; neurodegeneration – general concepts

4 - 6.30 p.m. - Pereira, C
Main trends in Alzheimer Disease pathogenesis. The role of mitochondria.

June 5
10-12.30 a.m. – Jensen , PH
Main trends in Parkinson Disease pathogenesis. Synuclein biology in Health and Disease.

2.30 – 5 p.m. – Gomes Pereira, M
Main trends in Myotonic Distrophy Pathogenesis. Repeat instability and toxic RNA.

June 6
12 p.m. Jensen, PH
Seminar: "How does alpha-synuclein aggregates impact on cell function and survival ?"

2.30 – 5 p.m. Journal Clubs on Parkinson and MD

June 7
10- 12.30 a.m. – Maciel, P
Main trends in Machado Joseph and Huntington disease

2.30 – 5 p.m. – Saraiva MJ
Main trends in Systemic Amyloidoses: Familial Amyloid Polyneuropathy as a model.

June 8

2.30 – 5 p.m. Journal Clubs on MJD and FAP

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Suggested reviews

Introduction

Garden GA, La Spada AR (2012). Intercellular (mis)communication in neurodegenerative disease. Neuron **73**:886-901.

Hetz C (2012). The unfolded protein response: controlling cell fate decisions under ER stress and beyond. Nat Rev Mol Cell Biol.**13**:89-102.

Alzheimer Disease

Gibson GE, Shi Q. (2010). A mitocentric view of Alzheimer's disease suggests multi-faceted treatments. J Alzheimers Dis.**20** Suppl 2:S591-607.

Karran E, Mercken M, De Strooper B. (2011). The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. Nat Rev Drug Discov. **10**:698-712.

Parkinson Disease

Vekrellis K, Xilouri M, Emmanouilidou E, Rideout HJ, Stefanis L. (2011). Pathological roles of α-synuclein in neurological disorders. Lancet Neurol. **10** :1015-25.

Hardy J. (2010). Genetic analysis of pathways to Parkinson disease. Neuron. **68**:201-6.

Myotonic Dystrophy

Sicot, G., Gourdon, G. and Gomes-Pereira, M. (2011) Myotonic dystrophy, when simple repeats reveal complex pathogenic entities: new findings and future challenges. *Hum Mol Genet*, **20**, R116-123.

de Leon, M.B. and Cisneros, B. (2008) Myotonic dystrophy 1 in the nervous system: from the clinic to molecular mechanisms. *J Neurosci Res*, **86**, 18-26.

Meola, G. and Sansone, V. (2007) Cerebral involvement in myotonic dystrophies. *Muscle Nerve*, **36**, 294-306.

Machado Joseph Disease

Baptista MS, Duarte CB, Maciel P (2012). Role of the ubiquitin-proteasome system in nervous system function and disease: using C. elegans as a dissecting tool. Cell Mol Life Sci. Mar 3. [Epub ahead of print].

Costa Mdo C, Paulson HL(2012).Toward understanding Machado-Joseph disease. Prog Neurobiol. **97**:239-57. Epub 2011 Nov 23.

Familial Amyloidotic Polyneuropathy

Saraiva MJ, Magalhães J, Ferreira N, Almeida MR (2012). Transthyretin deposition in familial amyloidotic polyneuropathy. Current Medicinal Chemistry. **19**: 2304-2311.

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Journal Club

Parkinson

Luk KC, Kehm VM, Zhang B, O´Brien P, Trojanowski JQ, Lee VMY (2012), Intracerebral inoculation of pathological alfa-synuclein intiates a rapidly progressive neurodegenerative synucleinopathy in mice. J Exp Med **209**: 975-986.

Myotonic Distrophy

Zu, T., Gibbens, B., Doty, N.S., Gomes-Pereira, M., Huguet, A., Stone, M.D., Margolis, J., Peterson, M., Markowski, T.W., Ingram, M.A. *et al.* (2011) Non-ATG-initiated translation directed by microsatellite expansions. *Proc Natl Acad Sci U S A*, **108**: 260-265.

Machado Joseph Disease

Teixeira-Castro A, Ailion M, Jalles A, Brignull HR, Vilaça JL, Dias N, Rodrigues P, Oliveira JF, Neves-Carvalho A, Morimoto RI, Maciel P (2011). Neuron-specific proteotoxicity of mutant ataxin-3 in C. elegans: rescue by the DAF-16 and HSF-1 pathways. Hum Mol Genet. **20**:2996-3009.

FAP

Magalhães J, Saraiva MJ (2011). Clusterin overexpression and putative role in transthyretin deposition in familial amyloidotic polyneuropathy. J Neurop and Exp Neurol. . **70**:1097-106.

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Faculty

Mário Gomes-Pereira – mario.pereira@inserm.fr

Myotonic dystrophy type 1 (DM1) is caused by the expansion of a non-coding CTG trinucleotide repeat expansion in the *DMPK* gene. The CTG repeat size is highly unstable, with a marked tendency to further expand in intergenerational tansmissions and in somatic tissues. Like in many other trinucleotide repeat expansion disorders, longer trinucleotide repeats are associated with more severe symptoms and an earlier age of onset. Experimental evidence suggests that repeat size mutation results from mis-repair of alternative repeat-containing DNA structures. We are currently dissecting further the mechanisms of trinucleotide repeat expansion using transgenic mice and cell cultures.

Although traditionally seen as a muscle disease, clinical, neuropsychological, imaging, histopathological and molecular evidence demonstrates significant brain dysfunction in DM1, characterised by highly debilitating cognitive deficits and behavioural changes. The development of mouse models revealed that toxic CUG repeats accumulate in nuclear foci, affecting the activity of splicing regulators and disrupting downstream transcripts. However, it is still unclear to what extent DM1-associated spliceopathy contributes to the neurological symptoms; nor do we know which disease intermediates and pathways are affected in the central nervous system. We are using transgenic mice as well as cell cultures derived thereof to decipher the molecular mechanisms of DM1 neuropathogenesis in a multi-faceted project, involving molecular, electrophysiological and behavioural approaches.

It is our long-term aim to develop rational therapeutic strategies, grounded on the dissection of the mechanisms of DM1 molecular pathogenesis.

Poul Henning Jensen - PHJ@BIOKEMI.AU.DK

Main focus is aggregation of alpha-synuclein (AS) and the cellular impact of such aggregates. This has involved characterizing its axonal transport and identifying ligands for monomeric and aggregated species. Such ligands have been related to proteasomal function, microtubule associated proteins, calcium regulatory proteins and cytoprotective proteins like parkin and DJ-1. A line has focussed on developing cellular models that recapitulate aggregate- and phosphorylation dependent degenerative processes that believed to be at play in brain. Using such models recent work has been on transcriptional responses to AS aggregation and this has revealed both pro- and antidegenerative pathways that currently are being investigated in AS transgenic mice models.

Currently working on characterizing a conditional p25a transgenic mice with the aim of using it to promote AS aggregation in AS tg models.

Interest in biomarker studies and developed a range of antibodies, one being selective for aggregated AS, that are used in numerous cellular and tissue studies.

Patricia Maciel - pmaciel@ecsaude.uminho.pt

The goal of my group is to study the genetic basis of the nervous system function and dysfunction, with a strong focus on human disease-related aspects, using molecular genetics, genomics, transcriptomics, proteomics, cell biology and behavioral analysis.

We address neurodegenerative and neurodevelopmental diseases and go from human genetics studies to cell and animal models, using *C. elegans* and mouse as model organisms. Departing from the identification of human neurological disease-related genes, by positional cloning - based on linkage analysis or association studies, by copy number variation identification - using aCGH, or by mutation identification using massive parallel sequencing technologies, we employ functional genomics strategies to characterize the role of the identified genes in the nervous system. This can be done by silencing gene expression, using RNAi strategies or obtaining gene knockouts, or by over-expressing the gene, in cell or animal models. If diseases are caused by gain-of-function rather than loss-of-function mutations, generation of transgenic cellular or animal models expressing the mutant variants of the gene may be required. Importantly, the models generated to understand the function of genes in the nervous system and to model pathogenesis, once validated, can be used to search for therapeutic targets and test the efficacy of therapeutic strategies.

We focus on one neurodegenerative disease, Machado-Joseph disease/Spinocerebellar ataxia type 3 (hereon referred to as MJD), and on several neurodevelopmental disorders, encompassing intellectual disability, autism spectrum disorders and epilepsy. Although the exploratory nature of the human genetic studies may lead us to different biochemical and cellular pathways, emerging themes in our research are the mechanisms of proteostasis, the ubiquitin-proteasome system (UPS) and chromatin remodeling/epigenetic mechanisms.

Claudia Pereira – claudia.mf.pereira@gmail.com

Maria João Saraiva – mjsaraiv@ibmc.up.pt

The main objectives of our team are related to the identification and characterization of ethio-physiopathological mechanisms of familial amyloidotic polyneuropathy (FAP), a peculiar form of neuropathy first described by the eminent Portuguese neurologist Corino de Andrade, which is characterized by the deposition of amyloid derived from transthyretin (TTR), in special on the peripheral nerves; we search for preventive, diagnostic and treatment forms of this disease. The technologies developed for these purposes are used, however, in studies of other TTR related disorders, in basic research of human physiology specially those associated with transport of thyroid hormones and vitamin A, natural ligands of TTR, and in general with TTR.

We develop also research on signalling pathways involved in brain injury, particularly those related to Alzheimer disease and brain ischemia using unique animal models developed in our laboratory. We seek neuroprotective strategies to rescue phenotypes related to these degenerative conditions.