*Genética Molecular e Populacional*

## Course: Regulation of Gene Expression

**Date:** 13rd – 17th May 2013
**Location:**
IBMC – Main auditorium.
**Coordinator:** Alexandra Moreira
**Faculty and invited speakers:** Alexandra Moreira, Mafalda Pinto, Vânia Glória, Sérgio de Almeida, Jernej Ule, Natasha Gromak, Ana Pombo.

**Objectives of the course:**
The life of an mRNA involves many steps that are tightly controlled and often interconnected. Gene expression thus depends on the fate of the mRNA, which is finely determined by a panoply of processes and factors, including pre-mRNA processing, *cis* regulatory elements, RNA binding proteins, miRNAs and mRNA localization. In this course international experts in the area will present state-of-the-art research on the molecular basis of gene expression regulation and mRNA processing during the physiological events that occur in different types of cells and in different systems. Scientific challenges in the field and how they are experimentally addressed will be discussed with the students.

**Outline of the course:** Lectures, tutorials, research seminars, students presentations.

## ***Monday 13rd***

***Morning – Alexandra Moreira***

1. Introduction
2. *Lecture 1*: Overview of transcription and RNA processing; integration of co-transcriptional events.
3. *Lecture 2, research seminar:* Mechanisms of mRNA 3' end formation in Eukaryotes.
    a. Transcription termination
    b. Pre-mRNA cleavage and polyadenylation: Signals and molecular mechanisms; Regulation of mRNA 3' end formation
    c. Poly(A) signals and diseases
4. *Paper dissection*:

    Telmo Henriques, Zhe Ji, Sue Mei Tan-Wong, Alexandre M. Carmo, Bin Tian, Nicholas J. Proudfoot and Alexandra Moreira (2012) Transcription termination between *polo* and *snap*, two closely spaced tandem genes of *D. melanogaster* Transcription 3: 198-212

*Suggested reading:*

1) Kuehner JN, Pearson EL, Moore C. (2011) Unravelling the means to an end: RNA polymerase II transcription termination. Nat Rev Mol Cell Biol. *12*:283-94

***Afternoon - Sérgio de Almeida***

1. *Research seminar:* "Chromatin dynamics during transcription by RNA polymerase II"

*Suggested reading:*

1) Li B, Carey M, Workman JL (2007) The role of chromatin during transcription Cell 128:707-719.
2) de Almeida SF & Carmo-Fonseca M (2012) Design principles of interconnections between chromatin and pre-mRNA splicing" Trends in Biochemical Sciences 37(6):248-53

## ***Tuesday 14th - Alexandra Moreira***

***Morning***

1. *Lecture and research seminar:* Alternative polyadenylation and regulation of mRNA 3' end formation; regulation by the 3'UTR; types and mechanisms of alternative polyadenylation.

2. *Lecture 2 and research seminar*: Regulation of alternative polyadenylation in health and disease.

***Afternoon***

*Paper dissection*:

Pinto, PAB, Henriques, H, Freitas, MO, Martins, T, Domingues, RG, Wyrzykowska, PS, Coelho, PA, Carmo, AM, Sunkel, CE, Proudfoot, NJ and Moreira, A (2011) RNA polymerase II kinetics in polo polyadenylation signal selection, The EMBO Journal, 30: 2431–2444

*Suggested reading:*

1) Moreira, A (2011) Integrating transcription kinetics with alternative polyadenylation and cell cycle control. Nucleus, 2(6)
2) Di Giammartino DC, Nishida K, Manley JL. (2011) Mechanisms and consequences of alternative polyadenylation. Mol Cell. *43*:853-66.
3) Lutz CS, Moreira A (2011) Alternative mRNA polyadenylation in eukaryotes: and effective regulator of gene expression. Wiley Interdisciplinary Reviews – RNA, 2 : 23-31

## ***Wednesday 15th - Natasha Gromak***

***Morning***

1. *Lecture (Part 1)*: Principles of gene expression - Polymerase II CTD code and histone code.
2. *Lecture (Part 2)*: miRNAs and their role in the regulation of gene expression

### ***Noon – Vânia Glória: "At the crossroads between transcription and splicing regulation of CD6 exon 5 alternative splicing" - PhD Seminar Series***

*Suggested reading:*

1) Castro, MAA, Oliveira, MI, Nunes RJ, Fabre, S, Barbosa, R, Peixoto, A, Brown, MH, Parnes, JR, Bismuth, G, Moreira A, Rocha, B and Carmo, A (2007) Extracellular isoforms of CD6 generated by alternative splicing regulate targeting of CD6 to the immunological synapse. J. Immunol., 178: 4351-4361.
2) Lynch KW. (2007) Regulation of alternative splicing by signal transduction pathways. Adv Exp Med Biol. 623:161-174.

***Afternoon – Natasha Gromak***

1. *Lecture*: A. Inter-connection between gene expression steps.
    a. Transcriptional termination
    b. RNA splicing.
    c. RNA/DNA hybrids (R-loops) in health in disease.

2. *Paper dissection*:

   K Skourti-Stathaki, N. J. Proudfoot and N. Gromak (2011) Human senataxin resolves RNA/DNA hybrids formed at transcriptional pause sites to promote Xrn2-dependent termination**.** Molecular Cell 42(6): 794-805

## ***Thursday 16th - Jernej Ule***

### *Morning*

1. Introduction
2. *Lecture 1*: Overview of strategies to study regulation of pre-mRNA processing and mRNA translation in a genome-wide manner.
3. *Lecture 2, research and paper dissection:* Insights from genome-wide studies
   a. Positional principles (RNA maps)
   b. Dynamics of RNP assembly
   c. Evolution
4. *Paper dissection:*

   Zarnack K, König J, Tajnik M, Martincorena I, Eustermann S, Stévant I, Reyes A, Anders S, Luscombe NM, Ule J. (2013) Direct competition between hnRNP C and U2AF65 protects the transcriptome from the exonization of Alu elements. Cell 152(3):453-66

*Suggested reading:*

Riley KJ, Steitz JA. (2013) The "Observer Effect" in genome-wide surveys of protein-RNA interactions Mol Cell. 49(4): 601-4.

### *Afternoon - RNA biology in the brain*

1. Introduction
2. *Lecture 1*: Four ways of causing disease via aberrant protein-RNA interactions.
3. *Lecture 2, research and paper dissection:* RNA biology in the differentiation of neurons and glia.
   a. PTB and Nova proteins: pre-mRNA processing
   b. Staufen proteins: mRNA localisation, RNA granules
   c. miRNAs
4. *Paper dissection:*

   Huang YW, Ruiz CR, Eyler EC, Lin K, Meffert MK (2012) Dual regulation of miRNA biogenesis generates target specificity in neurotrophin-induced protein synthesis. Cell. 148(5):933-46

*Suggested reading:*

Modic M, Ule J, Sibley CR. (2013) CLIPing the brain: Studies of protein-RNA interactions important for neurodegenerative disorders. Mol Cell Neurosci. Apr 10.

## ***Friday 17th - Ana Pombo***

***Morning –*** Preparation of the students projects to be the discussed in the afternoon. Teachers will be available.

***Noon – Ana Pombo: 'Chromatin 'communities' associated with RNA polymerase II' - IBMC Seminar Series***

***Afternoon –*** Students projects presentation and discussion. Students should arrange in 3 groups. Each group will make an oral presentation of a research project based on a topic that has been discussed this week. A formal presentation is not required, but it should be well structured, with a clear rationale. The students should focus on making a strong and solid proposal addressing some open questions in this field.

**Closing session and evaluation**

***6pm - Drinks with students***

**Teachers contacts list:**

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| **Alexandra Moreira**<br><br>Gene Regulation – IBMC, Univ Porto<br>alexandra.moreira@ibmc.up.pt | **Natasha Gromak**<br><br>University of Oxford, UK<br>natalia.gromak@path.ox.ac.uk |
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