



**FEBS International  
Workshop**  
**“New Developments  
in RNA Biology”**



**Ilha de Tavira (by Câmara Municipal de Tavira)**

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**Tavira, Algarve, Portugal**

# WELCOME FROM THE ORGANIZERS

Dear Participants:

It is our pleasure to welcome you to FEBS workshop on RNA Biology. RNA has emerged from the “shadow” of DNA and it has become one of the hottest research areas of molecular biology. The study of RNA biology has implications not only for the control of many diseases but also for the understanding of gene expression, translation, and ultimately evolution. In recent years, ribozymes, miRNA, siRNAs and many other functional noncoding RNA have been discovered and evidences indicate that RNA dictates the expression of genetic information and can control the metabolism. RNA is also very important in development, differentiation, and the onset of diseases. The major objective of the workshop is to promote the dialog between experts concerned with different areas of RNA Biology such as Transcription, Ribosomal RNA/tRNA, RNA structure, RNA degradation and quality control, and small RNAs. The number of participants will certainly promote fruitful exchanges, discussions and will contribute to the advancement of Science in the RNA field. Welcome!

The organizers, **M. Leonor Cancela** and **Cecília M. Arraiano**

## LOCAL ORGANIZING COMMITTEE

**Ricardo B. Leite**

**Vincent Laizé**

**Paulo J. Gavaia**

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**Rute G. Matos**

**Sandra Viegas**

**Susana Domingues**

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## Matrix Gla protein expression: a complex process involving the use of alternative promoters, multiple splicing events and microRNAs

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Matrix Gla protein (MGP) is a secreted vitamin K-dependent protein (VKD) located in the extracellular matrix and capable of binding calcium through its  $\alpha$ -carboxyglutamate residues. Although identified in 1983, transcriptional and post-transcriptional mechanisms regulating its expression remain unclear. In human, homozygous null-mutations in MGP gene originate the Keutel syndrome, a rare disease with multiple phenotypes associated to abnormal extracellular matrix deposition and calcification, which can be fatal in young adults. Accordingly, KO mice die 6 to 8 weeks after birth due to extensive calcifications in the vascular system, lungs and cartilages, confirming that MGP is a potent physiologic inhibitor of calcification. In all species but mammals, the MGP gene contains 5 exons and two promoters, with distinct transcripts resulting from alternative splicing. Interestingly, in zebrafish, we have also identified distinct transcript variants combining domains from two adjacent genes, MGP and osteocalcin (OC), another VKD protein considered to be evolutionarily related to MGP. This results in proteins with altered biochemical and functional characteristics and recapitulates what was observed in sturgeon, a fish with ancestral features which contains a hybrid form of MGP and OC. Recently, a new exon was identified in primate MGPs which encodes an additional in-frame protein domain distinct from any other sequence already identified, This results in a longer protein with a predicted increase in its calcium binding capability. Bioinformatic analysis has positioned this exon within a DNase I hypersensitive region, a hyperacetylated domain and a site of enhancer/insulator interaction, which could be involved in the regulation of this alternative splicing event. Because this form has only been observed in human fetal RNA, it may represent a variant linked to development and /or cell differentiation. Both short and long human MGP variants contain the same 3'UTR region, with putative binding sites for miR-148a, conserved in humans and primates, and miR-155, conserved in vertebrates. Luciferase assays indicate that both microRNAs repress MGP expression and inhibition of miR-148a by a specific microRNA inhibitor significantly induces MGP protein expression in human osteosarcoma MG-63 cells, confirming its regulatory potential. Altogether, our data indicate a complex regulation of the MGP gene, both at transcription and post-transcription levels, with what appears to be primate/human specificities.

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