# ACTA DE LA REUNIÓN DE LA COMISIÓN DE SEGUIMIENTO DEL PROYECTO CONSOLIDER CSD2009-00080

Madrid, 3 de diciembre de 2012

**ASISTENTES:**

- Marian Marrodan Ligorit, Gerente
- Juan Valcarcel, investigador coordinador

- Marina Villegas Gracia, Subdirectora General de Proyectos de Investigación.
- Lisardo Bosca Gomar, gestor de biomedicina.

Se reúnen los miembros de la Comisión de Seguimiento del proyecto Consolider CSD2009-00080 denominado "An integrated approach to post-transcriptional regulation of gene expression and its role in human disease"con el siguiente orden del día:

- **Situación del proyecto**

Projects have made significant progress, resulting in more than 25 publications on the topic and more than 60 communications to international meetings. The work was very positively reviewed by an external panel (A.Krainer, CSHL; T.Cooper, Baylor Coll. Med.; J.Cáceres, MRC) attending our annual meeting.

**1) Highlights of scientific achievements**

**a) Molecular mechanisms of RNA processing**

* nuclear function of CPEB1 in cell proliferation and cancer (Bava **Nature**, in press, collab. between the Mendez and Valcárcel groups)
* function of hnRNP A1 in splice site proofreading (Tavanez **Mol Cell**)
*role of RNA secondary structures in 3' splice site recognition (Plass **RNA**)
*widespread use of alternative UTRs in sex-specific regulation (Mihailovich **RNA**)
*role of Gemin 5 in IRES-dependent translation (Piñeiro **NARa**, **NARb**)
*improved methods for U1-based gene silencing with therapeutic applications (Blazquez **NAR**; Knoepfel **Antiviral Res**)
*improved conjugated chemistry for novel antisense-based RNA regulation (Sánchez **Bioconj Chem**)
*computational prediction of gene regulation from epigenomics data (Althammer **Comp Funct Genomics**)

**b) RNA in cancer biology**

* mutation profile of RNA processing factors in Chronic Lymphocytic Leukemia (Ramsay et al, **Leukemia**, collab. between the Quesada and Valcárcel groups)
* identification of biomarkers in metastatic colorectal cancer (Abajo **Br J Cancer**, Rodriguez et al **Eur J Cancer**)
* mechanisms of TGFb activation in glioblastoma (Eichhorn et al, **Nature Medicine**)
*mechanisms of E2F1-dependent oncogenic addiction in melanoma (Verhaegen **Oncogene**)
* efficient transduction of adenoviral vectors in cirrhotic livers (Sobrevals **Gene Ther**)

Additional work in progress (with collaborative manuscripts in preparation) includes:

* predictive value of lncRNA expression in CLL, ALL and Hepatitis virus infection

* role of miRNAs in cancer stem cells and resistance to radio- and chemotherapy

* modulation of melanoma cell proliferation and invasion by RNA binding proteins CUGBP, DDX46 as well as by dsRNA nanocomplexes

* role of CPEBs in stem cell differentiation and in glioma and melanoma progression (including angiogenesis) using mouse knock outs; structural characterization of RNA binding by CPEBs

* role of RNA binding proteins RBM5, 6, 10 and EWS in cancer progression

* function of UNR in cell transformation and melanoma / colon cancer progression

* functional networks of splicing regulation in cancer and mechanisms of anti-tumor drugs targeting RNA processing factors

* structural characterization of Gemin5-IRES interaction and identification of small molecules that can inhibit viral translation

* optimization of peptide-PNA chimeras as modulators of RNA processing

- In addition, RNAREG PIs contributed commissioned reviews in **Nature Rev Drug Discov**, **Science**, **Nature Struct Mol Biol, CSH Pers Biol**, **Cell Res**, **Int J Mol Sci, Curr Mol Med, Ageing Res Rev** and **Pigment Cell Melanoma Res.**

**2) Highlights of outreach activities**

**a)** **Organization of international meetings** attended by numerous members of RNAREG groups: **RNA Biology in Cancer and Other Diseases** Barcelona May 3-4 org. J.Valcárcel and M.Sánchez -RNAREG YI-; **Cold Spring Harbor Laboratory Asia "RNA Biology"** Suzhou Oct 8-12, org. F.Gebauer and others; **Cell Symposium Functional RNAs**, Sitges Dec 2-4, org. by J.Valcárcel and Cell editors.

**b)** **Young and Associate Investigator Program**: with the incorporation of 6 new PIs at our annual meeting, 13 groups form the extended network of associated groups that actively collaborate and share resources with the 12 core groups.

Distribution of Indirect Costs:
After examining and considering the justification for the request on distribution of indirect costs, an Amendment regarding the modification of clause ten of the Convenio de Ejecución will be prepared.

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Firma Subdirectora General de proyectos de Investigación

Firma Gestor Científico

## ANNEX

**Highlight of publications by RNAREG consortium in 2012**


1. Abajo, A., Boni, V., Lopez, I., Gonzalez-Huarriz, M., Bitarte, N., Rodriguez, J., Zarate, R., Bandres, E., and Garcia-Foncillas, J. (2012). Identification of predictive circulating biomarkers of bevacizumab-containing regimen efficacy in pre-treated metastatic colorectal cancer patients. Br. J. Cancer 107, 287–290.
2. Althammer, S., Pagès, A., and Eyras, E. (2012). Predictive models of gene regulation from high-throughput epigenomics data. Comp. Funct. Genomics 2012, 284786.
3. Bava, FA., Eliscovich, C., Ferreira, PG., Miñana, B., Ben-Dov, C., Guigó, R., Valcárcel, J. and Méndez, R. "CPEB1 coordinates alternative 3'UTR formation with translational regulation". Nature, *In press*.
4. Blázquez, L., and Fortes, P. (2013). U1 snRNP control of 3´-end processing and the therapeutic application of U1 inhibition combined with RNA interference. Curr. Mol. Med.
5. Blazquez, L., Gonzalez-Rojas, S.J., Abad, A., Razquin, N., Abad, X., and Fortes, P. (2012). Increased in vivo inhibition of gene expression by combining RNA interference and U1 inhibition. Nucleic Acids Res. 40, e8.
6. Bonnal, S., Vigevani, L. and Valcárcel, J. (2012). The splicesosome as a target of antitumour drugs. Nature Reviews in Drug Discovery, 11: 847-859 (2012).
7. Eichhorn, P., L. Rodón, A. Gonzàlez-Juncà, A. Dirac, M. Gili, E. Martínez-Sáez, C. Aura, I. Barba, V. Peg, A. Prat, I. Cuartas, J. Jimenez, D. García-Dorado, J. Sahuquillo, R. Bernards, J. Baselga and Seoane, J. (2012). USP15 stabilizes the TGF-beta receptor I and promotes oncogenesis through the activation of the TGF-beta signal in glioblastoma. Nature Medicine 18, 429-435.
8. Fernández-Miranda, G., and Méndez, R. (2012). The CPEB-family of proteins, translational control in senescence and cancer. Ageing Res. Rev. 11, 460–472.
9. Gebauer, F. (2012). Versatility of the translational machinery during stress: changing partners to keep dancing. Cell Res. 22, 1634–1636.
10. Gebauer, F., Preiss, T., and Hentze, M.W. (2012). From cis-regulatory elements to complex RNPs and back. Cold Spring Harb Perspect Biol 4, a012245.
11. Knoepfel, S.A., Abad, A., Abad, X., Fortes, P., and Berkhout, B. (2012). Design of modified U1i molecules against HIV-1 RNA. Antiviral Res. 94, 208–216.
12. Mannava, S., Omilian, A.R., Wawrzyniak, J.A., Fink, E.E., Zhuang, D., Miecznikowski, J.C., Marshall, J.R., Soengas, M.S., Sears, R.C., Morrison, C.D., et al. (2012). PP2A-B56α controls oncogene-induced senescence in normal and tumor human melanocytic cells. Oncogene 31, 1484–1492.
13. Mihailovich, M., Wurth, L., Zambelli, F., Abaza, I., Militti, C., Mancuso, F.M., Roma, G., Pavesi, G., and Gebauer, F. (2012). Widespread generation of alternative UTRs contributes to sex-specific RNA binding by UNR. RNA 18, 53–64.
14. Nadal-Ribelles, M., Conde, N., Flores, O., Gonzalez-Vallinas, J., Eyras, E., Orozco, M., De Nadal, E., and Posas, F. (2012). Hog1 bypasses stress-mediated down-regulation of transcription by RNA polymerase II redistribution and chromatin remodeling. Genome Biol. 13, R106.
15. Papasaikas, P. and Valcárcel, J. (2012) Splicing in 4D. Science, 338: 1547-1548.
16. Piñeiro, D., Fernández, N., Ramajo, J., and Martínez-Salas, E. (2012a). Gemin5 promotes IRES interaction and translation control through its C-terminal region. Nucleic Acids Res.
17. Piñeiro, D., Ramajo, J., Bradrick, S.S., and Martínez-Salas, E. (2012b). Gemin5 proteolysis reveals a novel motif to identify L protease targets. Nucleic Acids Res. 40, 4942–4953.

18. Plass, M., Codony-Servat, C., Ferreira, P.G., Vilardell, J., and Eyras, E. (2012). RNA secondary structure mediates alternative 3'ss selection in Saccharomyces cerevisiae. RNA 18, 1103–1115.
19. Ramsay, A.J., Rodríguez, D., Villamor, N., Kwarciak, A., Tejedor, J.R., Valcárcel, J., López-Guillermo, A., Martínez-Trillos, A., Puente, X.S., Campo, E., López-Otín, C., and Quesada, V. (2012). Frequent somatic mutations in components of the RNA processing machinery in chronic lymphocytic leukemia. Leukemia Nov 28. doi: 10.1038/leu.2012.344.
20. Rodríguez, J., Zarate, R., Bandres, E., Boni, V., Hernández, A., Sola, J.J., Honorato, B., Bitarte, N., and García-Foncillas, J. (2012). Fc gamma receptor polymorphisms as predictive markers of Cetuximab efficacy in epidermal growth factor receptor downstream-mutated metastatic colorectal cancer. Eur. J. Cancer 48, 1774–1780.
21. Sánchez, A., Pedroso, E., and Grandas, A. (2012). Conjugation reactions involving maleimides and phosphorothioate oligonucleotides. Bioconjug. Chem. 23, 300–307.
22. Sobrevals, L., Enguita, M., Rodriguez, C., Gonzalez-Rojas, J., Alzaguren, P., Razquin, N., Prieto, J., and Fortes, P. (2012). AAV vectors transduce hepatocytes in vivo as efficiently in cirrhotic as in healthy rat livers. Gene Ther. 19, 411–417.
23. Soengas, M.S. (2012). Mitophagy or how to control the Jekyll and Hyde embedded in mitochondrial metabolism: implications for melanoma progression and drug resistance. Pigment Cell Melanoma Res 25, 721–731.
24. Tavanez, J.P., Madl, T., Kooshapur H, Sattler, M. and Valcárcel, J (2012). hnRNP A1 proofreads 3' splice site recognition by U2AF. Molecular Cell, 45: 314-329.
25. Verhaegen, M., Checinska, A., Riblett, M.B., Wang, S., and Soengas, M.S. (2012). E2F1-dependent oncogenic addiction of melanoma cells to MDM2. Oncogene 31, 828–841.
26. Weill, L., Belloc, E., Bava, F.-A., and Méndez, R. (2012). Translational control by changes in poly(A) tail length: recycling mRNAs. Nat. Struct. Mol. Biol. 19, 577–585.
27. Zarate, R., Boni, V., Bandres, E., and Garcia-Foncillas, J. (2012). MiRNAs and LincRNAs: Could They Be Considered as Biomarkers in Colorectal Cancer? Int J Mol Sci 13, 840–865.