Andrés F. Muro, Curriculum vitae

Personal data:

Name/Surname: Andrés Fernando MURO
Phone Lab: +39-040-3757312
Phone Office: +39-040-3757369
Fax: +39-040-226555
E-Mail address: muro@icgeb.org

Unique Researcher identifying system

ORCID Andrés F. Muro: http://orcid.org/0000-0002-9628-0494
SCOPUS ID Andrés F. Muro: 7006690111
Researcher ID Andrés F. Muro: K-3156-2016

Present Position:

Group Leader of the Mouse Molecule Genetics (MMG) Group at the International Centre of Genetic Engineering and Biotechnology (ICGEB), Trieste, Italy.
Padriciano 99, 34149, Trieste, Italy
Phone: +39-040 3757369
Fax: +39-040 226555
E-mail: muro@icgeb.org
ICGEB Web site: http://www.icgeb.org
MMG Web site: http://www.icgeb.org/mouse-molecular-genetics.html

Education and Training:

- Born in Buenos Aires, Argentina, November 15, 1964
- 1982−1988: Master of Sciences in Molecular Biology, University of Buenos Aires, School of Sciences.
- 1988−1992: Doctor in Biology (PhD., Molecular Biology), University of Buenos Aires, School of Sciences.
- 1992-1995: ICGEB, UNIDO post doctoral fellowship, ICGEB, Trieste, Italy
- 1996-2004: Staff Scientist Position at the Molecular Pathology Group, ICGEB, Trieste, Italy
- 2005-present: Head of the Mouse Molecular Genetics Group, ICGEB, Trieste, Italy

Employment and Research Experience:

Professional Employment:

1989-1990: Teaching Instructor of the Department of Molecular Genetics and Biotechnology, School of Sciences, University of Buenos Aires
1990-1992: Chief Teaching Instructor of the Course of Genetic Engineering, Department of Molecular Genetics and Biotechnology, School of Sciences, University of Buenos Aires and Instituto de Ingeniería Genética y Biotecnología (INGEBI), Buenos Aires, Argentina.

1988-1992: Graduate Student Fellowship, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina, to work at the INGEBI, Buenos Aires, Argentina.
1992-1994: ICGEB-UNIDO post-doctoral fellowship, Molecular Pathology Group of the ICGEB, Trieste, Italy.
1995: Invited Professor at the post-graduate course "Detection and characterization of DNA-binding proteins by in vitro approaches", Campomar Institute and the University of Buenos Aires, Argentina.
1995-2004: Staff Scientist Position at the Molecular Pathology Group of the ICGEB, Trieste, Italy.
2005-present: Group Leader of the Mouse Molecule Genetics Group at the International Centre of Genetic Engineering and Biotechnology (ICGEB), Trieste, Italy.

Past Research Activity:

1988-1992: During my doctoral studies, performed at the Laboratory of Prof. Alberto Kornblihtt (INGEBI, Buenos Aires, Argentina), I analysed the mechanisms regulating transcription of the fibronectin gene. I identified the transcription factors recognising the FN promoter using innovative techniques such as DNA footprinting, gel-shift and *in vitro* transcription using G-free cassettes, with nuclear extracts from rat tissues and tissue culture cells.

1992-1994: During my postdoctoral studies I had two main long-term projects, both based on y gene targeting of mouse embryonic stem cells: a) performing the knockout of the beta-adducin gene, and b) performing the modification of the EDA exon of the fibronectin gene, in order to modify the alternative splicing pattern of the gene *in vivo*. At the same time, a medium term project was focused on the study of the molecular mechanisms of alternative splicing of the fibronectin pre-mRNA.

1994-2004: I continued with the project previously initiated. I determined the basic mechanisms of alternative splicing of the FN EDA exon. This knowledge was crucial to develop the mouse model. I generated both animal models (beta adducin and EDA-fibronectin), and studied the phenotype of both strains. The beta adducin mice presented a red blood cell disease, being beta adducin an important cytoskeletal protein in the red cell. Mice were also hypertensive.

The EDA FN mice presented important defects in wound healing. None of the strains presented pre- or post-natal lethality. EDA-FN mice presented a shorter lifespan.

2005-present: In the first years I continued with the analysis of the mouse strains previously created in the laboratory, showing the molecular defects present in the hepatocyte, and the many behavioural and learning defects. I also continued the study of the EDA-FN mice, detecting new phenotypes and more deeply studying the original ones, such as neurological defects, fibrosis, thrombosis, diabetes, wound healing, life-span, and others.

We generated a new mouse model with a null mutation in the Ugt1a gene, coding for the only enzyme responsible of bilirubin conjugation. The mice reproduced the major features of the human Crigler-Najjar syndrome, and it also reproduced the features of neonatal hyperbilirubinemia. We initiated the study of the molecular mechanisms of bilirubin neurotoxicity and potential therapeutic approaches to cure the disease, ranging from pharmacological therapies to gene therapy.

Present Research Activity:

The main research interest focuses on the study of the functions of genes related to human diseases, using genetically engineered mouse models, and possible therapeutic approaches, ranging from pharmacological therapies, to phototherapy, *in vivo* and *in vitro* gene therapy, gene targeting and gene editing.

Dr. Muro is interested liver diseases, such as neonatal hyperbilirubinemia and the Crigler-Najjar syndrome type I (CNSI), hemophilia B, and two very severe disorders of the urea cycle: ornithine transcarbamylase deficiency OTCD) and citrullinemia type I.

We are addressing the mechanisms at the basis of bilirubin neurotoxicity and the possible therapeutic approaches to cure neonatal hyperbilirubinemia and the Crigler-Najjar syndrome type I. We are studying mechanisms of diseases and therapies, including genes that modify the severity of bilirubin-induced neurological damage, bilirubin-mediated inflammation and cell death, DNA damage, testing pharmacological therapies, gene therapy and gene editing approaches, which are being developed and tested in a CNSI mouse model.

Dr. Muro's laboratory participates to a European network (CureCN) which is developing an Adeno-associated-virus (AAV)-mediated gene therapy approach to treat Crigler-Najjar syndrome type I patients in a H2020-supported Phase I/II clinical trial.

In parallel to the work in CNSI, we are developing an AAV-mediated gene therapy strategy to treat patients suffering from ornithine transcarbamylase deficiency, also with the final aim of transferring the developed therapies to the clinics.

We are also developing gene-targeting strategies based in the use of the CRISPR/Cas9 platform to insert therapeutic genes into a safe harbor locus.

Research activity is supported through grants from public and private agencies, including Telethon (Italy), Genethon (France), Beneficentia Stiftung (Lichtenstein), AFM-Telethon (France), the local Region Government, and the European Commission (H2020), as well as through collaborations with companies (Bayer, Germany; Selecta Biosciences, US).

Genetically Engineered Mouse Models generated in our laboratory:

a) Knock-out of the beta-adducin (Add2) gene: We generated a null allele of the beta-adducin gene by gene targeting in ES cells. We studied the role of Add2 in the cytoskeleton of erythrocytes, in hypertension and in brain function. Erythrocytes of mutant animals had abnormal shape and properties, with an increase in fragility, reproducing a human syndrome denominated "spherocytic hereditary elliptocytosis". We also showed the involvement of the Add2 gene in hypertension. Mice also presente synaptic plasticity, motor coordination and behavioural deficits, with impairments in long-term potentiation (LTP) and long-term depression (LTD).

b) Knock-in mice devoid of alternative splicing of the fibronectin EDA exon: by gene targeting in ES cells we generated two mouse models devoid of regulated splicing in the EDA exon. Fibronectin is an extracellular matrix protein participating in many physiological processes. One strain contained the EDA splicing sites optimized, thus committing the fibronectin pre-mRNA to undergo constitutive inclusion of the exon. The EDA exon was removed in the other strain, resulting in the constitutive exclusion of the EDA exon from the mature mRNA. We studied the role of FN isoforms in the ECM and plasma, in fundamental processes such as tissue remodelling in regenerative, oncogenic and inflammatory processes.

c) Crigler-Najjar Syndrome (CNSI) and neonatal hyperbilirubinemia: We have generated a mouse model of hyperbilirubinemia by mutating the endogenous UGT1a1 gene. This model closely resembles the major clinical features occurring in babies with CNSI. The CNSI is a condition characterized by severe unconjugated hyperbilirubinemia since birth and lifelong risk of developing bilirubin encephalopathy, with no efficient cure except liver transplantation. We are studying the mechanism of disease and therapeutic approaches, based in AAV-mediated gene therapy, different pharmacological treatments, and we are also setting up protocols to perform gene editing in vivo. We are interested in determining the molecular mechanisms and genetic determinants involved in bilirubin neurotoxicity, in particular in neonatal jaundice and babies with CNSI, and in the possible therapeutic approaches to improve the condition of patients. This project is part of the CureCN network.

d) Ornithine transcarbamylase deficiency: We have generated a null allele of the ornithine transcarbamylase gene (X-linked) using the CRISPR/Cas9 technology. OTCD is the most frequent disease of the urea cycle, in the most severe cases results in early neonatal lethality. There is no cure except liver transplantation. Male mice fully reproduce the main features of OTCD, such as very early postnatal death by hyperamonemmia (24 hs after birth) and elevated levels of urinary orotic acid. We are interested in setting up a therapeutic protocol for OTCD, based on AAV-mediated gene therapy, using specific nanoparticles that induce immunological tolerization against the AAV antigens, allowing re-administration of the therapeutic vector, necessary due to genome viral loss when the first administration is in the neonatal/pediatric age. This project is performed in collaboration with Selecta Biosciences, US.

List of Publications (by chronological order)

Number of peer-reviewed Publications in International Journals: seventy (forty-three as first or last/corresponding author)

1. Bernath, V.A., **A.F. Muro**, A.D. Vitullo, M.A. Bley, J.L. Baranao, and A.R. Kornblihtt, *Cyclic AMP inhibits fibronectin gene expression in a newly developed granulosa cell line by a mechanism that suppresses cAMP-responsive element-dependent transcriptional activation.* **J Biol Chem**, 1990. **265**(30): p. 18219-26.

2. Altschuler, D.L., **A.F. Muro**, A. Schijman, F.B. Almonacid, and H.N. Torres, *Neurospora crassa cDNA clones coding for a new member of the ras protein family.* **FEBS Lett**, 1990. **273**(1-2): p. 103-6.

3. **Muro, A.F.**, L. Puricelli, A.R. Kornblihtt, and E. Bal de Kier Joffe, *Inverse correlation between fibronectin mRNA levels and the metastatic potential of two murine mammary adenocarcinomas.* **Invasion Metastasis**, 1991. **11**(5): p. 281-7.

4. **Muro, A.F.**, V.A. Bernath, and A.R. Kornblihtt, *Interaction of the -170 cyclic AMP response element with the adjacent CCAAT box in the human fibronectin gene promoter.* **J Biol Chem**, 1992. **267**(18): p. 12767-74.

5. Srebrow, A., **A.F. Muro**, S. Werbajh, P.A. Sharp, and A.R. Kornblihtt, *The CRE-binding factor ATF-2 facilitates the occupation of the CCAAT box in the fibronectin gene promoter.* **FEBS Lett**, 1993. **327**(1): p. 25-8.

6. **Muro, A.F.**, C.G. Pesce, and A.R. Kornblihtt, *DNA sequencing by the chemical method: a 10 minute procedure for the G+A reaction.* **Trends Genet**, 1993. **9**(10): p. 337-8.

7. Pesce, C.G., M.S. Rossi, **A.F. Muro**, O.A. Reig, J. Zorzopulos, and A.R. Kornblihtt, *Binding of nuclear factors to a satellite DNA of retroviral origin with marked differences in copy number among species of the rodent Ctenomys.* **Nucleic Acids Res**, 1994. **22**(4): p. 656-61.

8. Tripodi, G., G. Casari, S. Tisminetzky, G. Bianchi, G. Devescovi, **A.F. Muro**, R. Tuteja, and F.E. Baralle, *Characterisation and chromosomal localisation of the rat alpha- and beta-adducin-encoding genes.* **Gene**, 1995. **166**(2): p. 307-11.

9. Tisminetzky, S., G. Devescovi, G. Tripodi, **A.F. Muro**, G. Bianchi, M. Colombi, L. Moro, S. Barlati, R. Tuteja, and F.E. Baralle, *Genomic organisation and chromosomal localisation of the gene encoding human beta adducin.* **Gene**, 1995. **167**(1-2): p. 313-6.

10. Kornblihtt, A.R., C.G. Pesce, C.R. Alonso, P. Cramer, A. Srebrow, S. Werbajh, and **A.F. Muro**, *The fibronectin gene as a model for splicing and transcription studies.* **FASEB J**, 1996. **10**(2): p. 248-57.

11. Gajovic, S., **A.F. Muro**, and F.E. Baralle, *Appearance of vaginal duplication in outbred CD1 mice.* **Veterinarski Arhiv**, 1997. **67**(4): p. 145-150.

12. Urtreger, A., F. Porro, L. Puricelli, S. Werbajh, F.E. Baralle, E. Bal de Kier Joffe, A.R. Kornblihtt, and **A.F. Muro**, *Expression of RGD minus fibronectin that does not form extracellular matrix fibrils is sufficient to decrease tumor metastasis.* **Int J Cancer**, 1998. **78**(2): p. 233-41.

13. **Muro, A.F.**, A. Iaconcig, and F.E. Baralle, *Regulation of the fibronectin EDA exon alternative splicing. Cooperative role of the exonic enhancer element and the 5′ splicing site.* **FEBS Lett**, 1998. **437**(1-2): p. 137-41.

14. Urtreger, A.J., J.A. Aguirre Ghiso, S.E. Werbajh, L.I. Puricelli, **A.F. Muro**, and E. Bal de Kier Joff, *Involvement of fibronectin in the regulation of urokinase production and binding in murine mammary tumor cells.* **Int J Cancer**, 1999. **82**(5): p. 748-53.

15. **Muro, A.F.**, M. Caputi, R. Pariyarath, F. Pagani, E. Buratti, and F.E. Baralle, *Regulation of fibronectin EDA exon alternative splicing: possible role of RNA secondary structure for enhancer display.* **Mol Cell Biol**, 1999. **19**(4): p. 2657-71.

16. Cramer, P., J.F. Caceres, D. Cazalla, S. Kadener, **A.F. Muro**, F.E. Baralle, and A.R. Kornblihtt, *Coupling of transcription with alternative splicing: RNA pol II promoters modulate SF2/ASF and 9G8 effects on an exonic splicing enhancer.* **Mol Cell**, 1999. **4**(2): p. 251-8.

17. Baralle, M., L. Vergnes, **A.F. Muro**, M.M. Zakin, F.E. Baralle, and A. Ochoa, *Regulation of the human apolipoprotein AIV gene expression in transgenic mice.* **FEBS Lett**, 1999. **445**(1): p. 45-52.

18. Sorol, M.R., R.L. Pastori, **A.F. Muro**, S. Moreno, and S. Rossi, *Structural and functional analysis of the cAMP binding domain from the regulatory subunit of Mucor rouxii protein kinase A.* **Arch Biochem Biophys**, 2000. **382**(2): p. 173-81.

19. **Muro, A.F.**, M.L. Marro, S. Gajovic, F. Porro, L. Luzzatto, and F.E. Baralle, *Mild spherocytic hereditary elliptocytosis and altered levels of alpha- and gamma-adducins in beta-adducin-deficient mice.* **Blood**, 2000. **95**(12): p. 3978-85.

20. Marro, M.L., O.U. Scremin, M.C. Jordan, L. Huynh, F. Porro, K.P. Roos, S. Gajovic, F.E. Baralle, and **A.F. Muro**, *Hypertension in beta-adducin-deficient mice.* **Hypertension**, 2000. **36**(3): p. 449-53.

21. Yang, H., S.C. Francis, K. Sellers, M. DeBarros, C. Sun, C. Sumners, C.M. Ferrario, M.J. Katovich, **A.F. Muro**, and M.K. Raizada, *Hypertension-linked decrease in the expression of brain gamma-adducin.* **Circ Res**, 2002. **91**(7): p. 633-9.

22. **Muro, A.F.**, A.K. Chauhan, S. Gajovic, A. Iaconcig, F. Porro, G. Stanta, and F.E. Baralle, *Regulated splicing of the fibronectin EDA exon is essential for proper skin wound healing and normal lifespan.* **J Cell Biol**, 2003. **162**(1): p. 149-60.

23. Porro, F., L. Costessi, M.L. Marro, F.E. Baralle, and **A.F. Muro**, *The erythrocyte skeletons of beta-adducin deficient mice have altered levels of tropomyosin, tropomodulin and EcapZ.* **FEBS Lett**, 2004. **576**(1-2): p. 36-40.

24. Echeverria, V., A. Ducatenzeiler, L. Alhonen, J. Janne, S.M. Grant, F. Wandosell, **A.F. Muro**, F. Baralle, H. Li, K. Duff, M. Szyf, and A.C. Cuello, *Rat transgenic models with a phenotype of intracellular Abeta accumulation in hippocampus and cortex.* **J Alzheimers Dis**, 2004. **6**(3): p. 209-19.

25. Chauhan, A.K., A. Iaconcig, F.E. Baralle, and **A.F. Muro**, *Alternative splicing of fibronectin: a mouse model demonstrates the identity of in vitro and in vivo systems and the processing autonomy of regulated exons in adult mice.* **Gene**, 2004. **324**: p. 55-63.

26. Buratti, E., **A.F. Muro**, M. Giombi, D. Gherbassi, A. Iaconcig, and F.E. Baralle, *RNA folding affects the recruitment of SR proteins by mouse and human polypurinic enhancer elements in the fibronectin EDA exon.* **Mol Cell Biol**, 2004. **24**(3): p. 1387-400.

27. Arrisi-Mercado, P., M. Romano, **A.F. Muro**, and F.E. Baralle, *An exonic splicing enhancer offsets the atypical GU-rich 3' splice site of human apolipoprotein A-II exon 3.* **J Biol Chem**, 2004. **279**(38): p. 39331-9.

28. Fededa, J.P., E. Petrillo, M.S. Gelfand, A.D. Neverov, S. Kadener, G. Nogues, F. Pelisch, F.E. Baralle, **A.F. Muro**, and A.R. Kornblihtt, *A polar mechanism coordinates different regions of alternative splicing within a single gene.* **Mol Cell**, 2005. **19**(3): p. 393-404.

29. Chauhan, A.K., F.A. Moretti, A. Iaconcig, F.E. Baralle, and **A.F. Muro**, *Impaired motor coordination in mice lacking the EDA exon of the fibronectin gene.* **Behav Brain Res**, 2005. **161**(1): p. 31-8.

30. Gajovic, S., D. Mitrecic, L. Augustincic, A. Iaconcig, and **A.F. Muro**, *Unexpected rescue of alpha-synuclein and multimerin1 deletion in C57BL/6JOlaHsd mice by beta-adducin knockout.* **Transgenic Res**, 2006. **15**(2): p. 255-9.

31. Costessi, L., G. Devescovi, F.E. Baralle, and **A.F. Muro**, *Brain-specific promoter and polyadenylation sites of the beta-adducin pre-mRNA generate an unusually long 3'-UTR.* **Nucleic Acids Res**, 2006. **34**(1): p. 243-53.

32. Moretti, F.A., A.K. Chauhan, A. Iaconcig, F. Porro, F.E. Baralle, and **A.F. Muro**, *A major fraction of fibronectin present in the extracellular matrix of tissues is plasma-derived.* **J Biol Chem**, 2007. **282**(38): p. 28057-62.

33. White, E.S., F.E. Baralle, and **A.F. Muro**, *New insights into form and function of fibronectin splice variants.* **J Pathol**, 2008. **216**(1): p. 1-14.

34. **Muro, A.F.**, F.A. Moretti, B.B. Moore, M. Yan, R.G. Atrasz, C.A. Wilke, K.R. Flaherty, F.J. Martinez, J.L. Tsui, D. Sheppard, F.E. Baralle, G.B. Toews, and E.S. White, *An essential role for fibronectin extra type III domain A in pulmonary fibrosis.* **Am J Respir Crit Care Med**, 2008. **177**(6): p. 638-45.

35. Chauhan, A.K., J. Kisucka, M.R. Cozzi, M.T. Walsh, F.A. Moretti, M. Battiston, M. Mazzucato, L. De Marco, F.E. Baralle, D.D. Wagner, and **A.F. Muro**, *Prothrombotic effects of fibronectin isoforms containing the EDA domain.* **Arterioscler Thromb Vasc Biol**, 2008. **28**(2): p. 296-301.

36. Babaev, V.R., F. Porro, M.F. Linton, S. Fazio, F.E. Baralle, and **A.F. Muro**, *Absence of regulated splicing of fibronectin EDA exon reduces atherosclerosis in mice.* **Atherosclerosis**, 2008. **197**(2): p. 534-40.

37. Bazigou, E., S. Xie, C. Chen, A. Weston, N. Miura, L. Sorokin, R. Adams, **A.F. Muro**, D. Sheppard, and T. Makinen, *Integrin-alpha9 is required for fibronectin matrix assembly during lymphatic valve morphogenesis.* **Dev Cell**, 2009. **17**(2): p. 175-86.

38. White, E.S., R.L. Sagana, A.J. Booth, M. Yan, A.M. Cornett, C.A. Bloomheart, J.L. Tsui, C.A. Wilke, B.B. Moore, J.D. Ritzenthaler, J. Roman, and **A.F. Muro**, *Control of fibroblast fibronectin expression and alternative splicing via the PI3K/Akt/mTOR pathway.* **Exp Cell Res**, **2010**. **316**(16): p. 2644-53.

39. Porro, F., M. Rosato-Siri, E. Leone, L. Costessi, A. Iaconcig, E. Tongiorgi, and **A.F. Muro**, *beta-adducin (Add2) KO mice show synaptic plasticity, motor coordination and behavioral deficits accompanied by changes in the expression and phosphorylation levels of the alpha- and gamma-adducin subunits.* **Genes Brain Behav**, **2010**. **9**(1): p. 84-96.

40. Morgan, M., A. Iaconcig, and **A.F. Muro**, *CPEB2, CPEB3 and CPEB4 are coordinately regulated by miRNAs recognizing conserved binding sites in paralog positions of their 3'-UTRs.* **Nucleic Acids Res**, **2010**. **38**(21): p. 7698-710.

41. Kohan, M., **A.F. Muro**, E.S. White, and N. Berkman, *EDA-containing cellular fibronectin induces fibroblast differentiation through binding to alpha4beta7 integrin receptor and MAPK/Erk 1/2-dependent signaling.* **FASEB J**, 2010. **24**(11): p. 4503-12.

42. White, E.S. and **A.F. Muro**, *Fibronectin splice variants: understanding their multiple roles in health and disease using engineered mouse models.* **IUBMB Life**, 2011. **63**(7): p. 538-46.

43. Kohan, M., **A.F. Muro**, R. Bader, and N. Berkman, *The extra domain A of fibronectin is essential for allergen-induced airway fibrosis and hyperresponsiveness in mice.* **J Allergy Clin Immunol**, **2011**. **127**(2): p. 439-446 e1-5.

44. Morgan, M., A. Iaconcig, and **A.F. Muro**, *Identification of 3' gene ends using transcriptional and genomic conservation across vertebrates.* **BMC Genomics**, 2012. **13**: p. 708.

45. Curlin, M., K. Kapuralin, **A.F. Muro**, F.E. Baralle, K. Chowdhury, and S. Gajovic, *Stam2 expression pattern during embryo development.* **Gene Expr Patterns**, 2012. **12**(1-2): p. 68-76.

46. Bortolussi, G., L. Zentilin, G. Baj, P. Giraudi, C. Bellarosa, M. Giacca, C. Tiribelli, and **A.F. Muro**, *Rescue of bilirubin-induced neonatal lethality in a mouse model of Crigler-Najjar syndrome type I by AAV9-mediated gene transfer.* **FASEB J**, **2012**. **26**(3): p. 1052-63.

47. Booth, A.J., S.C. Wood, A.M. Cornett, A.A. Dreffs, G. Lu, **A.F. Muro**, E.S. White, and D.K. Bishop, *Recipient-derived EDA fibronectin promotes cardiac allograft fibrosis.* **J Pathol**, **2012**. **226**(4): p. 609-18.

48. Nedeljkovic, M., L. Costessi, A. Iaconcig, F. Porro, and **A.F. Muro**, *Long-distance regulation of Add2 pre-mRNA3'end processing.* **RNA Biol**, 2013. **10**(4): p. 516-27.

49. Losino, N., A. Waisman, C. Solari, C. Luzzani, D.F. Espinosa, A. Sassone, **A.F. Muro**, S. Miriuka, G. Sevlever, L. Baranao, and A. Guberman, *EDA-containing fibronectin increases proliferation of embryonic stem cells.* **PLoS One**, 2013. **8**(11): p. e80681.

50. Hirshoren, N., M. Kohan, M. Assayag, T. Neuman, F. Vernea, **A.F. Muro**, R. Eliashar, and N. Berkman, *Extra domain-A fibronectin is necessary for the development of nasal remodeling in chronic allergen-induced rhinitis.* **Ann Allergy Asthma Immunol**, 2013. **110**(5): p. 322-7.

51. Danussi, C., L. Del Bel Belluz, E. Pivetta, T.M. Modica, **A.F. Muro**, B. Wassermann, R. Doliana, P. Sabatelli, A. Colombatti, and P. Spessotto, *EMILIN1/alpha9beta1 integrin interaction is crucial in lymphatic valve formation and maintenance.* **Mol Cell Biol**, 2013. **33**(22): p. 4381-94.

52. Costessi, L., F. Porro, A. Iaconcig, M. Nedeljkovic, and **A.F. Muro**, *Characterization of the distal polyadenylation site of the ss-adducin (Add2) pre-mRNA.* **PLoS One**, 2013. **8**(3): p. e58879.

53. Porro, F., L. Bockor, A. De Caneva, G. Bortolussi, and **A.F. Muro**, *Generation of Ugt1-deficient murine liver cell lines using TALEN technology.* **PLoS One**, 2014. **9**(8): p. e104816.

54. Costessi, L., F. Porro, A. Iaconcig, and **A.F. Muro**, *TDP-43 regulates beta-adducin (Add2) transcript stability.* **RNA Biol**, 2014. **11**(10): p. 1280-90.

55. Bortolussi, G., L. Zentillin, J. Vanikova, L. Bockor, C. Bellarosa, A. Mancarella, E. Vianello, C. Tiribelli, M. Giacca, L. Vitek, and **A.F. Muro**, *Life-long correction of hyperbilirubinemia with a neonatal liver-specific AAV-mediated gene transfer in a lethal mouse model of Crigler-Najjar Syndrome.* **Hum Gene Ther**, 2014. **25**(9): p. 844-55.

56. Bortolussi, G., G. Baj, S. Vodret, G. Viviani, T. Bittolo, and **A.F. Muro**, *Age-dependent pattern of cerebellar susceptibility to bilirubin neurotoxicity in vivo in mice.* **Dis Model Mech**, 2014. **7**(9): p. 1057-68.

57. Vodret, S., G. Bortolussi, A.B. Schreuder, J. Jasprova, L. Vitek, H.J. Verkade, and **A.F. Muro**, *Albumin administration prevents neurological damage and death in a mouse model of severe neonatal hyperbilirubinemia.* **Sci Rep**, 2015. **5**: p. 16203.

58. Pulakazhi Venu, V.K., P. Uboldi, A. Dhyani, A. Patrini, R. Baetta, N. Ferri, A. Corsini, **A.F. Muro**, A.L. Catapano, and G.D. Norata, *Fibronectin extra domain A stabilises atherosclerotic plaques in apolipoprotein E and in LDL-receptor-deficient mice.* **Thromb Haemost**, 2015. **114**(1): p. 186-97.

59. Bortolussi, G., E. Codarin, G. Antoniali, C. Vascotto, S. Vodret, S. Arena, L. Cesaratto, A. Scaloni, G. Tell, and **A.F. Muro**, *Impairment of enzymatic antioxidant defenses is associated with bilirubin-induced neuronal cell death in the cerebellum of Ugt1 KO mice.* **Cell Death Dis**, 2015. **6**: p. e1739.

60. Ronzitti, G., G. Bortolussi, R. van Dijk, F. Collaud, S. Charles, C. Leborgne, P. Vidal, S. Martin, B. Gjata, M.S. Sola, L. van Wittenberghe, A. Vignaud, P. Veron, P.J. Bosma, **A.F. Muro**, and F. Mingozzi, *A translationally optimized AAV-UGT1A1 vector drives safe and long-lasting correction of Crigler-Najjar syndrome.* **Mol Ther Methods Clin Dev**, 2016. **3**: p. 16049.

61. Malara, A., C. Gruppi, G. Celesti, B. Romano, L. Laghi, L. De Marco, **A.F. Muro**, and A. Balduini, *Brief Report: Alternative Splicing of Extra Domain A (EIIIA) of Fibronectin Plays a Tissue-Specific Role in Hematopoietic Homeostasis.* **Stem Cells**, 2016. **34**(8): p. 2263-8.

62. Gortan Cappellari, G., R. Barazzoni, L. Cattin, **A.F. Muro**, and M. Zanetti, *Lack of Fibronectin Extra Domain A Alternative Splicing Exacerbates Endothelial Dysfunction in Diabetes.* **Sci Rep**, 2016. **6**: p. 37965.

63. Vodret, S., G. Bortolussi, J. Jasprova, L. Vitek, and **A.F. Muro**, *Inflammatory signature of cerebellar neurodegeneration during neonatal hyperbilirubinemia in Ugt1 -/- mouse model.* **J Neuroinflammation**, 2017. **14**(1): p. 64.

64. Porro, F., G. Bortolussi, A. Barzel, A. De Caneva, A. Iaconcig, S. Vodret, L. Zentilin, M.A. Kay, and **A.F. Muro**, *Promoterless gene targeting without nucleases rescues lethality of a Crigler-Najjar syndrome mouse model.* **EMBO Mol Med**, 2017. **9**(10):p.1346-1355.

65. Bockor, L., G. Bortolussi, S. Vodret, A. Iaconcig, J. Jasprova, J. Zelenka, L. Vitek, C. Tiribelli, and **A.F. Muro**, *Modulation of bilirubin neurotoxicity by the Abcb1 transporter in the Ugt1-/- lethal mouse model of neonatal hyperbilirubinemia.* **Hum Mol Genet**, 2017. **26**(1): p. 145-157.

66. Bockor, L., G. Bortolussi, A. Iaconcig, G. Chiaruttini, C. Tiribelli, M. Giacca, F. Benvenuti, L. Zentilin, and **A.F. Muro**, *Repeated AAV-mediated gene transfer by serotype switching enables long-lasting therapeutic levels of hUgt1a1 enzyme in a mouse model of Crigler-Najjar Syndrome Type I.* **Gene Ther**, 2017. **24**(10): p. 649-660.

67. Vodret, S., G. Bortolussi, A. Iaconcig, E. Martinelli, C. Tiribelli, and **A.F. Muro**, *Attenuation of neuro-inflammation improves survival and neurodegeneration in a mouse model of severe neonatal hyperbilirubinemia.* **Brain Behav Immun**, 2018. **70**: p. 166-178.

68. Rawat, V., G. Bortolussi, S. Gazzin, C. Tiribelli, and **A.F. Muro**, *Bilirubin-Induced Oxidative Stress Leads to DNA Damage in the Cerebellum of Hyperbilirubinemic Neonatal Mice and Activates DNA Double-Strand Break Repair Pathways in Human Cells.* **Oxidative Medicine and Cellular Longevity**, 2018. **In Press**.

69. Malara, A., C. Gruppi, G. Celesti, V. Abbonante, G. Viarengo, L. Laghi, L. De Marco, **A.F. Muro**, and A. Balduini, *Alternatively spliced fibronectin extra domain A is required for hemangiogenic recovery upon bone marrow chemotherapy.* **Haematologica**, 2018. **103**(2): p. e42-e45.

70. Bortolussi, G. and **A.F. Muro**, *Advances in understanding disease mechanisms and potential treatments for Crigler–Najjar syndrome.* **Expert Opinion on Orphan Drugs**, 2018. **6**(7): p. 425-439.

Book chapters

Book title: Farmacologia Molecular; 1995 - Editor: Marcelo Kazanietz. Chapter title: Regulación de la expresión de genes por AMP cíclico, by Andrés Muro

Book title: Paediatric Hepatology and Liver Transplantation; Springer Medicine Books; 2018 – Editor: Lorenzo D'Antiga. Chapter title: Gene therapy in paediatric liver disease, by Andrés Muro, Lorenzo D'Antiga and Federico Mingozzi

Patents filed

- **2014 – European Patent Office - Treatment of Crigler-Najjar syndrome – Patent No. 14305622.4 - 1410**

- **2015 – WIPO - Treatment of Hyperbilirubinemia – International Publication Number: WO 2015/162302 A3 – Abstract:** The invention relates to a nucleic acid sequence useful in the treatment of hyperbilirubinemia, in particular in the treatment of Crigler-Najjar syndrome. More particularly, the nucleic acid sequence of the present invention is a codon-optimized UGT1A1 coding sequence.

Participations to scientific meetings, invitation to conferences, organization of meetings and courses (selected)

2007-01-14 EMBO-ICGEB meeting on "pre mRNA processing and disease". "Cortina d'Ampezzo, Italy. Oral Presentation: The role of the EDA splice variant of fibronectin in lung fibrosis. **A.F. Muro**

2007-04-22 Gordon Conference on "Fibronectin, Integrins & Related Molecules". Il Ciocco, Barga, Italy. Oral Presentation: Development and Progression of Liver and Lung Fibrosis is Dependent on the Extra Type III Domain A of Fibronectin. **A.F. Muro**

2007-11-26 "Gene Expression and RNA Processing". San Carlos de Bariloche, Argentina. ICGEB, University of Bs As, CONICET, and the European Alternative Splicing Network (EURASNET). In vivo role of Alternative Splicing: The Fibronectin Paradigm. **A.F. Muro** and F.E. Baralle.

2008-01-31 International meeting on Bilirubin metabolism: Trieste yellow Retreat. Trieste, Italy. Co-organizer with Prof. Claudio Tiribelli. Oral Presentation: New animal models in the study of UCB metabolism and toxicity. **A.F. Muro**

2008-07-28 13th Annual meeting of the RNA Society. Berlin, Germany. Tissue-specific alternative polyadenylation of the adducin pre-mRNA. L. Costessi, M. Nedeljkovic, F. Porro and **A.F. Muro**.

2008-01-31 Trieste Yellow Retreat. ICGEB, Trieste, Italy. Oral Presentation: "New animal models in the study of UCB metabolism and toxicity." **A.F. Muro**.

2009-03-11 International meeting on Bilirubin metabolism: Trieste yellow Retreat. Trieste, Italy. Co-organizer with Prof. Claudio Tiribelli. Oral Presentation: The Gunn mouse: a new experimental model for understanding BIND. **A.F. Muro**

2009-04-22 Inter Disciplinary Focus Meeting (European Alternative Splicing Network, EURASNET) 'Mouse models for alternative splicing'. Assisi, Italy. Oral presentation: Tales from a mouse model: New insights into form and function of fibronectin splice variants. **A.F. Muro**

2009-05-07 Invited speaker University of Udine. Oral Presentation: Tales from a mouse model: new insights into form and function of fibronectin splice variants. **A.F. Muro**

2009-09-16 EMBO Meeting: Messenger RNA 3' ends & gene expression. Oxford, UK. Regulation of CPEB2 subfamily members through their 3'UTRs. M. Morgan, **A.F. Muro**

2010-03-08 International meeting on Bilirubin metabolism: Trieste yellow Retreat. Trieste, Italy. Co-organizer with Prof. Claudio Tiribelli.

2010-10-22 Invited speaker to Virginia Commonwealth University (VCU), Richmond, VA, USA. "A new mouse model for Crigler-Najjar syndrome and possible therapeutic approaches". **A.F. Muro**

2011-03-07 XVI Telethon Convention, Riva del Garda, Italy. A new mouse model for Crigler-Najjar syndrome and possible therapeutic approaches. Bortolussi, G.; Zentilin, L.; Giraudi, P.; Dapas, M.; Bellarosa, C.; Giacca, M.; Tiribelli, C.; **Muro, A.F**.

2011-02-21 Invited speaker at the course "Mouse Genetics: Models for human diseases" Trieste, Italy. "Disease Models and Translation: Fibronectin" **A.F. Muro**

2011-04-07 European Network for the Advancement of Clinical Gene Transfer and Therapy (CliniGene-NoE). A new mouse model for Crigler-Najjar syndrome and possible therapeutic approaches. Bortolussi, G.; Zentilin, Baj, G. L.; Dapas, M.; Bellarosa, C.; Giacca, M.; Tiribelli, C.; **Muro, A.F**.

2011-04-16 Annual meeting of the Italian Society of Crigler Najjar (CIAMI). Oral presentation: New frontiers for the cure of the Crigler-Najjar syndrome. **A.F. Muro**

2011-06-06 International meeting on Bilirubin metabolism: Trieste yellow Retreat. Trieste, Italy. Co-organizer with Prof. C. Tiribelli

2011-09-27 International meeting on "Gene expression and RNA processing", organized by A.R. Kornblihtt. Iguazú, Argentina. Polyadenylation mechanisms of the Add2 pre-mRNA Costessi, L., Porro, F., Nedeljkovic, M., Iaconcig, A. and **Muro, A.F.**

2012-05-28 7th International Congress on Heme Oxygenase and related enzymes, Edinburgh, UK. Oral presentation: Bilirubin neurotoxicity: In vivo studies using a new mouse model of the Crigler-Najjar Syndrome type I. **A.F. Muro**

2012-06-21 International meeting on Bilirubin metabolism: Trieste yellow Retreat. Trieste, Italy. Co-organizer with Prof. C. Tiribelli.

2013-03-11 XVII Telethon Convention, Riva del Garda, Italy. Life-long liver-specific AAV-mediated gene therapy in a Crigler-Najjar mouse model. Bortolussi, G.; Bockor, L.; Zentilin, L.; Mancarella, A.; Bellarosa, C.; Giacca, M.; Tiribelli, C.; **Muro, AF.**

2013-04-08 Invited speaker at the course "Mouse Genetics: Models for human diseases" Trieste, Italy. "Disease Models and Translation: Fibronectin". A.F. Muro

2013-08-29 International meeting on Bilirubin metabolism: Trieste yellow Retreat. Trieste, Italy. Co-organizer with Prof. Claudio Tiribelli.

2014-05-19 Annual meeting of the American Society of Gene and Cell Therapy (ASGCT). Washington, USA. Transduction with Codon Optimized hUGT1a1 AAV vectors for more efficient Crigler-Najjar Syndrome Gene Therapy G. Bortolussi, F. Collaud, G. Ronzitti, S. Charles, C. Leborgne, S. Martin, P. Bosma, F. Mavilio, F. Mingozzi and **A.F. Muro**

2015-03-16 Invited speaker at the course "Mouse Genetics: Models for human diseases" Trieste, Italy. "Disease Models and Translation: Crigler-Najjar syndrome"

2015-05-13 18th Annual meeting of the American Society of Gene and Cell Therapy (ASGCT). New Orleans, USA. Oral Presentation: AAV8-mediated liver gene targeting without nucleases rescues lethality in a mouse model of the Crigler-Najjar syndrome. **A.F. Muro**

2015-05-13 18th Annual meeting of the American Society of Gene and Cell Therapy (ASGCT). New Orleans, USA. Untranslated region optimization increases transgene mRNA and protein levels, resulting in enhanced therapeutic efficacy of AAV vector gene transfer in vivo for Crigler-Najjar syndrome Ronzitti G., Bortolussi G., Collaud F., Charles S., **Muro A**., Mingozzi F.

2015-05-13 18th Annual meeting of the American Society of Gene and Cell Therapy (ASGCT). New Orleans, USA. Long-term correction of Crigler-Najjar syndrome and scale-up of production of an optimized AAV8 vector expressing the UGT1A1 transgene G. Bortolussi, F. Collaud, R. van Dijk, G. Ronzitti, S. Charles, S. Martin, C. Le Bec, M. Hebben, F. Mavilio, P. Bosma, **A.F. Muro,** F. Mingozzi

2015-08-29 International meeting on Bilirubin metabolism: Trieste yellow Retreat. Trieste, Italy. Co-organizer with Prof. Claudio Tiribelli. Oral presentation: *"Gene therapy approaches using a mouse model of the Crigler-Najjar syndrome Type I"* **A.F. Muro**

2015-10-29 European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). Meeting on "Targeting liver disease at DNA level." Venice, Italy. Oral presentation: Scientist´s view: Aspects of feasibility, efficacy and safety of vector based gene therapy. **A.F. Muro**

2016-06-09 Invited speaker at the meeting "Be Liver", Papa Giovanni XXIII Hospital, Bergamo, Italy. Oral presentation: "Gene therapy in animal models with liver genetic diseases" **A.F. Muro**

2016-10-19 Annual Meeting of the European Society of Gene and Cell Therapy (ESGCT). Florence, Italy. Long-term correction of hyperbilirubinemia in animal models of Crigler-Najjar syndrome with an optimized AAV8-UGT1A1 vector. G Ronzitti G Bortolussi R van Dijk F Collaud S Charles C Leborgne M Simon Sola L van Wittenberghe A Vignaud P Veron P J Bosma **A F Muro** F Mingozzi

2017-05-10 20th Annual meeting of the American Society of Gene and Cell Therapy (ASGCT). Washington, USA. Liver transduction efficacy with AAV vectors in juvenile Ugt1a1-deficient mice G. Bortolussi, F. Collaud, A. Iaconcig, S. Charles, G. Ronzitti, **A.F. Muro** and F. Mingozzi

2017-10-17 Annual Meeting of the European Society of Gene and Cell Therapy (ESGCT). Berlin, Germany. Development of a novel adeno-associated viral vector in combination with tolerogenic nanoparticles for the treatment of Ornithine Transcarbamylase Deficiency. G. De Sabbata, G. Bortolussi, F. Collaud, F. Boisgerault, A. P. Ilyinskii, T.K. Kishimoto, L. D'Antiga, F. Mingozzi, **A.F. Muro**

2018-05-16 21st Annual meeting of the American Society of Gene and Cell Therapy (ASGCT). Washington, USA. AAV-Directed Liver Gene Therapy for Crigler-Najjar Syndrome. F. Collaud, G. Ronzitti, G. Bortolussi, L. Guianvarc'h, P. Veron, S. Charles, P. Vidal, M. Simon Sola, C. Leborgne, S. Rundwasser, L. Dejoint, L, S. Martin, C. Le Bec, P. J. Bosma, **A.F. Muro**, M. Hebben, F. Mingozzi

2018-10-16 Annual Meeting of the European Society of Gene and Cell Therapy (ESGCT). Lausanne, Switzerland. Oral Presentation: AAV-mediated promoterless gene targeting coupled to SaCas9 nuclease to efficiently correct liver metabolic diseases. A. De Caneva, F. Porro, G. Bortolussi, R. Sola, M. Lisjak, A. Barzel, M. Giacca, M.A. Kay, K. Vlahovicek, L. Zentillin and **A.F. Muro**

2018-10-16 Annual Meeting of the European Society of Gene and Cell Therapy (ESGCT). Lausanne, Switzerland. Development of a novel AAV-based gene therapy in combination with tolerogenic nanoparticles for sustained treatment of Ornithine Transcarbamylase Deficiency. G. De Sabbata, F. Boisgerault, C. Guarnaccia, G. Bortolussi, F. Collaud, A. Iaconcig, M. Simon Sola, S. Charles, C. Leborgne, E. Nicastro, P. Ilyinskii, T.K. Kishimoto, L. D'Antiga, F. Mingozzi, **A.F. Muro**

2019-03-06 Co-organizer of the ICGEB course "Mouse genetics; models for human diseases", Trieste, Italy

Academic Activities:

PhD thesis directed: Nine (Open University, London, UK, 6; SISSA, Trieste, 1; Scuola Normale Superiore di Pisa, 1; Trieste University, 1).

Graduate thesis directed: Five (Trieste University, 5; Bologna University, 1)

Since 2004/01, teaching staff and member of the ICGEB International PhD course of the Open University, UK (http://www.open.ac.uk)

Since 2013/10 Member of the teaching staff of the PhD course in Research in Biomedical Sciences and Biotechnology (*"Collegio docenti del Corso di Dottorato di Ricerca in Scienze biomediche e biotecnologiche"*) at the University of Ferrara, Italy.

Since 2013 Teaching staff of the course "Erasmus week" at the University of Trieste, organized by Prof. Guidalberto Mandfioletti with students of the University of Trieste and University of Paris-Diderot and University of Paris-Descartes.

Since 2017, member of the Editorial Board as a Review Editor of the journal "Frontiers Genetics and Molecular Biosciences – RNA".

Member of the American Society of Gene and Cell Therapy (ASGCT) since 2014

Member of the European Society of Gene and Cell Therapy (ESGCT) since 2015

Reviewer for the following international Scientific Journals

Biochemical Biophysical Acta (BBA), Brain Research, Circulation, Disease Markers, EMBO Molecular Medicine, Expert Opinion in Orphan Diseases, Gene, Human Gene Therapy, Human Genetics, Human Molecular Genetics, Journal of Hepatology, Journal of Neuroinflammation, Journal of Pathology, Molecular and Cellular Biology, Molecular and Cellular Biochemistry, Molecular Therapy - Methods &

Clinical Development, Molecular Therapy-Nucleic Acids, Neurotoxicity Research, Nuclei Acids Research, PlosOne, Scientific Reports

Examiner of PhD thesis:

Examiner of eighteen (18) PhD Thesis from Trieste University (Italy), 1; University of Udine (Italy), 1; Open University (UK), 4; University of Torino (Italy), 1; University of Ferrara (Italy), 11.

Financed projects

07/2008-07/2012 Friuli-Venezia-Giulia Regional Grant. Creation of a regional Mouse Phenotyping network for the study of human diseases in the Friuli-Venezia-Giulia region. (€276.000)

Role: Principal Investigator

2008 BAYER HeathCare AG. In vivo determination of the function of fibronectin EDA domain in neo-angiogenesis. (€20.000)

Role: Collaborator

2008-2012 NIH RO1 grant. Role of EIIIA fibronectin in pulmonary

fibrosis. (€30.000)

Role: Collaborator

10/2010-10/2014 Telethon (Italy) project GGP10051 "New diagnostic and therapeutic approaches for the Crigler−Najjar Syndrome Type I"; Network of five Italian laboratories: ICGEB (L. Zentilin); SISSA (S. Gustincich); University of Udine (G. Tell); Centro Studi Fegato (C. Tiribelli). (€436.090 for the whole project; €145.500 to the group)

Role: Principal Investigator – Coordinator of the whole project

6/2012-6/2014 Beneficentia Stiftung – Lichtenstein. "Crigler-Najjar Syndrome Type I: understanding the causes of bilirubin toxicity in brain and possible therapeutic approaches." (€30.000)

Role: Principal Investigator

2012-2014 AXA Research Fund (France). Neonatal jaundice: *In vivo* bilirubin neurotoxicity in a Ugt1 ko mouse model. (€100.000).

Role: Principal Investigator

6/2015-6/2017 Beneficentia Stiftung – Lichtenstein. "Crigler-Najjar Syndrome Type I: towards more efficient therapeutic approaches (€50.000)

Role: Principal Investigator

2014-2015 Fondazione San Paolo, Italy. " Identification of the molecular mechanism linking the alpha sinuclein gene to Parkinson Disease" (€50.000)

Role: Principal Investigator

5/2015-5/2016 Collaboration agreement with Genethon (France) in the project: "Crigler-Najjar syndrome type I: Towards a clinical trial. Pre-clinical studies to improve gene therapy vectors and protocols in a mouse model of the disease" (€30.000)

Role: Principal Investigator

5/2016-6/2018 Collaboration agreement with Genethon (France) in the project: "Crigler-Najjar syndrome type I: Towards a clinical trial. Pre-clinical studies to improve gene therapy vectors and protocols in a mouse model of the disease (€143.000)

Role: Principal Investigator

6/2016-5/2018 Collaboration agreement with the biotechnology company Selecta Biosciences (Boston, USA) in the project:" Developing novel AAV gene therapy for Ornithine Transcarbamylase Deficiency (OTC). Pre-clinical studies in mouse models aimed to develop a medical product to be later used in a clinical trial." (€320.000)

Role: Principal Investigator

04/2018-12/2019. AFM-Telethon (France). Project #21826 Liver metabolic diseases: CRISPR/SaCas9-mediated gene targeting of a promoterless ASS1 cDNA to cure citrullinemia type I. (€40.000)