BIOGRAPHICAL SKETCH
Senior Trainer

NAME: Pelegri, Francisco J.

eRA COMMONS USER NAME: fjpelegri

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California at Berkeley, Berkeley, CA	B.S.	1987	Genetics
Massachusetts Institute of Technology, Cambridge, MA	Ph.D.	1994	Cellular & Developmental Biology
Max-Planck Institute for Developmental Biology, Tuebingen	Postdoc	1994-1999	Zebrafish Developmental Genetics

A. Personal Statement

I have been studying animal embryonic patterning since 1987, when I began my PhD studies in the laboratory of Dr. Ruth Lehmann at M.I.T. on the basis of abdominal segmentation and germ cell identity in Drosophila. Specifically, during my PhD I identified maternal pathways that contribute to the chromatin-mediated regulation of abdominal gap gene expression. My PhD work began a long-time interest in developmental mechanisms that act in the very early embryo. I carried out my postdoctoral studies in the laboratory of Dr. Christiane Nüsslein-Volhard at the Max-Planck Institute in Tübingen, where I led a systematic screen for recessive maternal-effect mutations in the zebrafish using ploidy manipulation methods to facilitate the screen (Pelegri and Schulte-Merker, 1999; Pelegri et al., 2004). We applied the ploidy manipulation methods of standard Heat Shock (inhibition of the first embryonic division) to develop homozygous diploid lines, and Early Pressure (inhibition of the meiotic division) to identify recessive maternal-effect mutations that affect early embryonic processes. Since 1999, my laboratory at the University of Wisconsin - Madison has used a variety of experimental approaches to study these maternal-effect genes and their function.

Early Pressure was not an optimal genetic method for ploidy manipulation, since it results in partial heterozygosity in the resulting gynogenotic offspring, and we have continued attempts to improve ploidy manipulation methods. We originally found that a mutation that affects centriole biogenesis during spermatogenesis promotes whole genome duplication (albeit at a low efficiency for this particular mutation, Yabe et al, 2007). More recently, we developed an improved Heat Shock approach, Heat Shock 2 (HS2, Heier et al, 2015), which inhibits centriole duplication to effectively inhibit the second mitotic division, allowing whole genome duplication with a high efficiency. We are now using HS2 for a variety of applications, including genetic screening for additional adult and parental-effect mutations, analyzing the effect of ploidy levels on the transcriptome, and, as proposed in this application, attempting to dissect the contribution of parental epigenetic marks and self-organizing gene expression networks to gene expression robustness in the early embryo.

We have assembled an outstanding local team of collaborators, which spans the multifaceted expertise required for the proposed project: Melissa Harrison (zygotic genome activation, using Drosophila as a model system), Sushmita Roy (bioinformatics and gene network analysis) and myself (ploidy manipulation and early embryonic development in the zebrafish). Our combine expertise should synergize with an innovative approach to gain novel insights on mechanisms of gene expression regulation in the early vertebrate embryo.

1) Heier, J., Takle, K.A., Hasley, A.O., **Pelegri, F.** (2015) Ploidy manipulation and induction of alternate cleavage patterns through inhibition of centrosome duplication in the early zebrafish embryo. Dev. Dyn. 244, 1300-1312.

2) Yabe, T., Ge, X., and **Pelegri, F.** (2007) The zebrafish maternal-effect gene *cellular atoll* encodes the centriolar component sas-6 and defects in its paternal function promote whole genome duplication. Dev. Biol. 312, 44-60.

3) **Pelegri, F**., Dekens, M.P.S., Schulte-Merker, S. Maischein, H.-M., Weiler, C., and Nüsslein-Volhard, C. (2004). Identification of recessive maternal-effect mutations in the zebrafish using a gynogenesis-based method. Dev. Dyn. 231, 325-336

4) **Pelegri, F.** and Lehmann, R. (1994). A role of *Polycomb* group genes in the regulation of gap gene expression in *Drosophila*. Genetics 136: 1341-1353. *(Highlighted in Trends Genet. 10, 264 (1994)*)

B. Positions and Honors

1999-2007 **Assistant Professor**, University of Wisconsin - Madison, Madison, WI

2007-2012 **Associate Professor,** University of Wisconsin - Madison, Madison, WI

2012-Present **Professor,** University of Wisconsin - Madison, Madison, WI

1984-1987 Undergraduate Honors: President's Undergraduate Fellowship (1985-1986, University of California at Berkeley); Summer Undergraduate Research Fellowship, (1986, Genetics Society of America), Highest Honors (U.C. Berkeley), Special Departmental Citation (Department of Genetics, U.C. Berkeley)
1995-1997 Long Term Postdoctoral Fellowship, European Molecular Biology Organization
1999 New Faculty Startup Supplement, University of Wisconsin Medical School/Howard Hughes Medical Institute Faculty Development Program in Molecular Mechanisms of Disease
2001-2003 Basil O'Connor Starter Scholar Research Award, March of Dimes Birth Defects Foundation
2008-2012 NIH DEV-2 study section, regular member
2011-2012 Romnes Faculty Research Fellowship, U.W. Madison
2015-2016 Vilas Research Investigator Award, U.W. Madison

C. Contribution to Science

1. Identification of maternal-effect mutations in zebrafish. For my postdoctoral training, I joined the laboratory of Dr. Christiane Nüsslein-Volhard at the Max Planck Institute in Tübingen, where I contributed to the completion of ongoing screens for zygotic mutations in the zebrafish. My primary interest, however, was to implement a gynogenesis-based screen in this organism in order to identify recessive mutations in maternal-effect genes while at the same time providing streamlined genetic tools for the analysis of adult traits. In 1998-1999, I implemented gynogenetic methods to carry out the first forward genetics maternal-effect screen in the zebrafish or any other vertebrate, using the gynogenesis promoting technique of Early Pressure (EP) to inhibit cytokinesis for the second meiotic division of the egg. This method allowed the identification of 14 maternal-effect mutations. As an independent investigator at the University of Wisconsin – Madison, we focused on the molecular, cellular and embryological analysis of a subset of those mutations. At the same time, we have continued to develop methods to study the function of maternal-effect genes, such as the use of vitro oocyte maturation for the functional manipulation and expression of maternal genes, and improved gynogenetic protocols leading to full genome homozygosity with increased efficiencies. In addition to their use in genetic screens for parental and intergenerational effects, the use of these improved gynogenetic methods should facilitate the identification of genes influencing adult traits of biomedical relevance..

1) Heier, J., Takle, K.A., Hasley, A.O., **Pelegri, F.** (2015) Ploidy manipulation and induction of alternate cleavage patterns through inhibition of centrosome duplication in the early zebrafish embryo. Dev. Dyn. 244, 1300-1312.

2) Nair, S., Lindeman, R.E, **Pelegri, F.** (2013) In vitro oocyte culture-based manipulation of zebrafish maternal genes. Dev. Dyn. 242, 44-52*. (cover in vol 242, issue 2)*

3) **Pelegri, F**., Dekens, M.P.S., Schulte-Merker, S. Maischein, H.-M., Weiler, C., and Nüsslein-Volhard, C. (2004). Identification of recessive maternal-effect mutations in the zebrafish using a gynogenesis-based method. Dev. Dyn. 231, 325-336

4) **Pelegri, F.** and Schulte-Merker, S. (1999) *A gynogenesis-based screen for maternal-effect genes in the zebrafish,* Danio rerio . *In* The Zebrafish: Genetics and Genomics *(H. W. Detrich, L. I. Zon, and M. Westerfield, Eds.) Academic Press, San Diego. Meth. Cell Biol., Vol. 60, pp. 1 - 20.*

2. Germ plasm segregation in the early zebrafish embryo. The report of the localization pattern of the RNA for the gene *vasa* by the Hopkins laboratory in 1997 provided our first assay to test our identified maternal-effect mutations for defects in germ plasm segregation. Applying this assay to our collection of maternal mutants we found two mutations, in the genes *nebel* and *aura,* which produced effects on *vasa* RNA localization without having defects in furrow induction. These findings led us to analyze in detail processes involved in the segregation of germ plasm ribonucleoparticles (RNPs). Our achievements include the definition of the major stages of germ plasm RNP multimerization during the early cleavage stages, the identification of the role of cytoskeletal networks in germ plasm RNP aggregation prior to the initiation of cell division, the mechanism of furrow recruitment of germ plasm RNPs in coupling to the machinery driving cytokinesis, the novel role of the Chromosomal Passenger Complex (CPC) protein Mot/Survivin as a linker between the cytoskeleton and germ plasm RNPs, and the subcompartmentalization of animal vs. vegetal germ plasm RNPs within the germ plasm mass.

1) Eno, C., Solanki, B., Pelegri, F. (2016) aura (mid1ip1l) regulates the cytoskeleton at the zebrafish egg-to-embryo transition. Development, 143, 1585-1599.

2) Nair, S., Marlow, F., Abrams, E., Kapp, L., Mullins, M., Pelegri, F. (2013) The chromosomal passenger protein Birc5b organizes microfilaments and germ plasm in the zebrafish embryo. PLoS Genetics 9, e1003448.

3) Theusch, E.V., Brown, K.J. and Pelegri, F. (2006). Separate pathways of RNA recruitment lead to the compartmentalization of the zebrafish germ plasm. Dev. Biol. 292, 129-141.

4) Pelegri, F., Knaut, H., Maischein, H.-M., Schulte-Merker, S., and Nüsslein-Volhard, C. (1999). A mutation in the zebrafish maternal-effect gene nebel affects furrow formation and vasa RNA localization. Curr. Biol. 9, 1431-1440. (Featured article)

3. Analysis of early zebrafish embryonic development. We have pioneered the analysis of maternal-effect genes in the zebrafish by carrying out their positional cloning and in-depth characterization of the endogenous processes in wild-type and mutant embryos. We showed that *futile cycle* encodes the KASH-domain protein Lrmp involved in centrosome-nuclear attachment in the zygote, and that its products exhibit cell-cycle regulation to facilitate protein targeting to the nuclear membrane. We also identified a role for *hecate*, which encodes the vesicle-associated signaling factor Grip2a, in the bundling of microtubules at the vegetal pole, and discovered the role in the process of axis induction of an amplification loop involving an off-center symmetry-breaking event and a subsequent general transport mechanism. We also characterized the function of six additional genes with a role in cell division and their role in germ plasm segregation (see above and Research description), as well as the function of *mission impossible*, which encodes a DEAH-box helicase likely involved in a posttranscriptional regulation network important for the activation of zygotic genes. The functions of these genes encompass a wide range of areas, which provides me with broad experience relevant to this application, and constitute some of the very first examples of detailed mechanistic characterization of early vertebrate developmental processes.

1) Ge, X., Grotjahn, D., Welch, E., Holguin, C., Lyman-Gingerich, J., Dimitrova, E., Abrams, E., Marlow, F., Yabe, T., Mullins, M., **Pelegri, F.** (2014) Hecate/Grip2a acts to reorganize the cytoskeleton in the symmetry-breaking event of embryonic axis induction. PLoS Genetics 10, e1004422.

2) Lindeman, R.E., **Pelegri, F.** (2012) Localized products of *futile cycle/lrmp* promote centrosome-nucleus attachment in the zebrafish zygote. Curr. Biol. 22, 843-85.

3) Putiri, E., **Pelegri, F.** (2011) The zebrafish maternal-effect gene *mission impossible* encodes the DEAH-box helicase Dhx16 and is essential for the expression of downstream endodermal genes. Dev. Biol. 353, 275-289.

4) Yabe, T., Ge, X., Lindeman R., Nair, S., Runke G., Mullins M.C., **Pelegri, F.** (2009) The maternal-effect gene *cellular island* encodes Aurora B kinase and is essential for furrow formation in the early zebrafish embryo. PloS Genetics 5, e1000518. *(Featured article)*

4. Role for Polycomb-group genes in patterning of gap genes in the Drosophila embryo. During my Ph.D. studies in the laboratory of Ruth Lehman at MIT I carried out screens for genetic modifiers of maternal-effect mutations

involved in abdominal development. A group of these mutations fell within genes of the Polycomb Group complex, at the time known to confer a negative repressive state to chromatin of the homeotic gene cluster. My analysis showed that chromatin regulators also act to control gap genes, and constitute one of the first examples for a wider role of chromatin regulators on gene expression.

1) **Pelegri, F.** and Lehmann, R. (1994). A role of *Polycomb* group genes in the regulation of gap gene expression in *Drosophila*. Genetics 136: 1341-1353. *(Highlighted in Trends Genet. 10, 264 (1994)*)

URL to a list of published work (My Bibliography):
http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/40776348/

D. Research Support

Current

NIH R01 GM065303 3/1/02 – 12/31/17
Cytokinesis and RNA Segregation in Zebrafish Development
Coordination of processes involved in cell division and germ plasm segregation during early zebrafish development

Role: PI

Completed

NIH R21 HD068949 4/1/11-3/31/13 (no cost extension to 3/31/14)
Single centriole-mediated gynogenesis in the zebrafish
Development of gynogenesis as a tool to facilitate zebrafish genetics
Role: PI

2011-2012 Romnes Faculty Research Fellowship, U.W. Madison

2015-2016 Vilas Research Investigator Award, U.W. Madison