BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: ZARATIEGUI BIURRUN, MIGUEL ANGEL

eRA COMMONS USER NAME (credential, e.g., agency login): ZARATIEGUI

POSITION TITLE: Associate professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Universite Victor Segalen Bordeaux II , Bordeaux, Gironde	BS	06/1997	Maitrise Structural Biochemistry
University of Navarra, Pamplona, Navarra	BS	06/1997	Biochemistry
University of Navarra, Pamplona, Navarra	PHD	06/2002	Gene Therapy
Cold Spring Harbor Laboratory, Cold Spring Harbor, New York	Postdoctoral Fellow	09/2011	Epigenetics

A. Personal Statement

I started my scientific career using viral vectors for gene therapy, and I became fascinated by the phenomenon of epigenetic silencing. From then, my overarching goal has been to study how the cell specifically identifies and silences foreign and selfish DNA. During my postdoctoral work I made significant contributions to the field of epigenetic silencing, studying the mechanisms of heterochromatin deposition mediated by RNA interference in fission yeast. In this work I dissected the mechanism of RNAi processing of small RNA precursors, and how its coupling with the cell-cycle permitted the inheritance of heterochromatin silencing. This led me to investigate the implication of DNA replication, which is the moment where epigenetic inheritance must occur. I discovered that the two main heterochromatic elements, satellite DNA and Transposons, share a striking property: they both block the progression of the replication fork. I went on to show that the different heterochromatin deposition pathways permit the restart of the fork to complete DNA replication, and couple it to heterochromatin inheritance. As a new independent researcher at Rutgers University I went on to further investigate the relationship between DNA replication and transposon biology. While the field of transposons has focused intensely on how they subvert the fundamental process of transcription, I thought that their interactions with the equally fundamental process of DNA replication did not receive adequate attention. I received funding from NIGMS (R01GM105831, later continued as R35131763) to investigate how transposons and their host genomes interact at the level of DNA replication, with a focus on three aspects of transposon biology: i. Insertion target site preference; ii. Transcriptional regulation; and iii. Consequences on host genome stability. This work has illuminated new aspects of the tug-of-war between molecular parasites and their hosts, revealing that transposable elements subvert the processes of transcription, replication and homologous recombination to avert mutation and maintain their foothold in the host genome.
The work in my lab touches on multiple topics in molecular biology: DNA replication and repair, chromatin and transcriptional regulation, RNA interference, Transposon biology, and molecular evolution. My students gain a broad exposure to all these fields, resulting in an integrative view of genome regulation and evolution. We are an intensely collaborative group, and our students often visit other labs to learn techniques and make valuable contacts for their careers. I put a great emphasis on teaching science communication, and actively engage my students in grant and paper writing, as well as encouraging presenting their science at every opportunity through participation in meetings and symposia. I believe that my group provides an excellent learning environment for graduate students and postdocs. In my work as a mentor, I have supervised two graduate students: Jake Jacobs and Eve Reilly. Jake Jacobs graduated in four years an a half, with two first author publications, one of them in the Journal Science.

Eve also graduated in four years and we are preparing her publication to be submitted soon. Both students secured positions in the biotechnology industry, as was their plan. Jake is the manager of the microbiology division at Troy Corporation, and Eve started in September 2019 as an associate consultant at Cello Health BioConsulting. I have also mentored two postdoctoral fellows, and five undergraduate students in their honors theses. My philosophy for mentoring involves a gradual training towards intellectual independence, fostering critical and creative thought through intensive one-on-one and group interactions and activities. I have applied this philosophy in my service as a reviewer for the NSF Graduate Research Fellowship Program, in which the professional development aspect is capital in the identification of valuable candidates for funding. In summary, I believe that my expertise and research interests, and my experience as a mentor, makes me a valuable member of the CINJ.

1. Jacobs JZ, Rosado-Lugo JD, Cranz-Mileva S, Ciccaglione KM, Tournier V, Zaratiegui M. Arrested replication forks guide retrotransposon integration. Science. 2015 Sep 25;349(6255):1549-53. PubMed Central PMCID: PMC4832573.
2. Jacobs JZ, Ciccaglione KM, Tournier V, Zaratiegui M. Implementation of the CRISPR-Cas9 system in fission yeast. Nat Commun. 2014 Oct 29;5:5344. PubMed Central PMCID: PMC4215166.
3. Zaratiegui M, Castel SE, Irvine DV, Kloc A, Ren J, Li F, de Castro E, Marín L, Chang AY, Goto D, Cande WZ, Antequera F, Arcangioli B, Martienssen RA. RNAi promotes heterochromatic silencing through replication-coupled release of RNA Pol II. Nature. 2011 Oct 16;479(7371):135-8. PubMed Central PMCID: PMC3391703.
4. Zaratiegui M, Vaughn MW, Irvine DV, Goto D, Watt S, Bähler J, Arcangioli B, Martienssen RA. CENP-B preserves genome integrity at replication forks paused by retrotransposon LTR. Nature. 2011 Jan 6;469(7328):112-5. PubMed Central PMCID: PMC3057531.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2017 -	Associate professor, Rutgers, the State University of New Jersey, Piscataway, NJ
2011 - 2017	Assistant Professor, RUTGERS, THE STATE UNIV OF N.J.
2004 - 2011	Postdoctoral fellow, COLD SPRING HARBOR LABORATORY
2002 - 2004	Postdoctoral fellow, CIMA, Pamplona
1997 - 2002	Graduate Student and Teaching Assistant, Department of Genetics, University of Navarra, Pamplona

Honors

2012 - 2015	Searle Scholar, Kinship Foundation, Chicago
2004 - 2006	Post-Doctoral Fellowship (EX2004-1234), Ministry of Education and Research, Spain
2002 - 2004	Post-Doctoral Fellowship, Center of Applied Medical Research (CIMA), Pamplona, Spain
1998 - 2002	Pre-Doctoral Fellowship (CICYT SAF98-0001), Ministry of Education and Research, Spain
1996 - 1997	Erasmus Fellowship Program, Université Victor Segalen Bordeaux II, France
2009	Ramon y Cajal Reincorporation Program (Declined), Ministry of Science and Education, Spain
1998	2nd National Prize for the Bachelor Degree in Biochemistry, Ministry of Education and Research, Spain
1997	1st Prize Bachelor Degree in Biochemistry, University of Navarra, Pamplona, Spain.

C. Contribution to Science

1. RNAi dependent Heterochromatin formation depends on pericentromeric long non-coding RNA that are processed into small RNA. This work uncovered the mechanistic basis for the intriguing observation of the dependence of heterochromatin on RNAi. We showed that the target of RNAi is not

DNA, but nascent non-coding RNA contained in the centromeric satellites. Further, silencing of reporter genes embedded in heterochromatin (the long unexplained phenomenon of Position Effect Variegation, PEV) depends on non-coding transcripts invading the reporter genes, bringing them under the control of RNAi. This work confirmed the RNA-centric model of RNAi action, and provided an elegant explanation to PEV. I was co-first author in the resulting publication with my collaborator Danielle Irvine.

a. Irvine DV, Zaratiegui M, Tolia NH, Goto DB, Chitwood DH, Vaughn MW, Joshua-Tor L, Martienssen RA. Argonaute slicing is required for heterochromatic silencing and spreading. Science. 2006 Aug 25;313(5790):1134-7. PubMed PMID: 16931764; NIHMSID: NIHMS268997.

2. RNAi processing is coupled to, and facilitates, DNA replication. This work revealed that RNAi and heterochromatin are necessary for seamless replication of satellite DNA, explaining another puzzling long standing observation, the loss of genome integrity in heterochromatin mutants. The involvement of RNA in heterochromatic silencing is paradoxical, considering the heterochromatin prevents RNA synthesis. Working under my direct supervision, Anna Kloc showed that non-coding RNA processed by RNAi were in fact activated during a small window of the cell cycle, coinciding with DNA replication, and that this brief burst of RNAi activity prepares for heterochromatin reestablishment in the wake of the replication fork. I was second author in this publication (Kloc et al., 2008). This discovery set the stage for my comprehensive investigation of the coupling of RNAi, DNA replication and genome integrity. I mapped the origins of replication within centromeric satellites, showing that they were intercalated between the non-coding genes processed by RNAi. Knowing that transcription of these elements is maximal during DNA replication, I showed that this leads to replisome-RNA polymerase collisions, which resolution depends on RNAi-mediated release of RNA polymerase to make way for the advancing replisome. If RNAi is inactive, these collisions are resolved instead by engaging Homologous Recombination (HR), which when performed on repetitive DNA can lead to deleterious rearrangements. I was first author in the resulting publication.

a. Holmes A, Roseaulin L, Schurra C, Waxin H, Lambert S, Zaratiegui M, Martienssen RA, Arcangioli B. Lsd1 and lsd2 control programmed replication fork pauses and imprinting in fission yeast. Cell Rep. 2012 Dec 27;2(6):1513-20. PubMed Central PMCID: PMC3909218.
b. Zaratiegui M, Castel SE, Irvine DV, Kloc A, Ren J, Li F, de Castro E, Marín L, Chang AY, Goto D, Cande WZ, Antequera F, Arcangioli B, Martienssen RA. RNAi promotes heterochromatic silencing through replication-coupled release of RNA Pol II. Nature. 2011 Oct 16;479(7371):135-8. PubMed Central PMCID: PMC3391703.
c. Kloc A, Zaratiegui M, Nora E, Martienssen R. RNA interference guides histone modification during the S phase of chromosomal replication. Curr Biol. 2008 Apr 8;18(7):490-5. PubMed Central PMCID: PMC2408823.

3. Transposon silencing is coupled to DNA replication. This work unified transposon and satellite elements into a single entity that requires heterochromatin for DNA replication, resulting in a structure that both silences and stabilizes repetitive elements. The fission yeast Long Terminal Repeat (LTR) retrotransposons are silenced by a family of DNA binding factors collectively known as CENP-B. I observed that CENP-B mutants also displayed a dramatic loss of genome integrity, reminiscent of that observed in RNAi mutants. I showed that the replication fork is arrested at the LTR by the action of a DNA binding factor called Sap1. Much like in the case of centromeric satellites and RNAi, CENP-B mutants lose the ability to manage these fork barriers, and become dependent of HR, which once again leads to genome instability. I was first author in the resulting publication.

a. Daulny A, Mejía-Ramírez E, Reina O, Rosado-Lugo J, Aguilar-Arnal L, Auer H, Zaratiegui M, Azorin F. The fission yeast CENP-B protein Abp1 prevents pervasive transcription of repetitive DNA elements. Biochim Biophys Acta. 2016 Oct;1859(10):1314-21. PubMed Central PMCID: PMC5391875.

b. Holmes A, Roseaulin L, Schurra C, Waxin H, Lambert S, Zaratiegui M, Martienssen RA, Arcangioli B. Lsd1 and lsd2 control programmed replication fork pauses and imprinting in fission yeast. Cell Rep. 2012 Dec 27;2(6):1513-20. PubMed Central PMCID: PMC3909218.

c. Zaratiegui M, Castel SE, Irvine DV, Kloc A, Ren J, Li F, de Castro E, Marín L, Chang AY, Goto D, Cande WZ, Antequera F, Arcangioli B, Martienssen RA. RNAi promotes heterochromatic silencing through replication-coupled release of RNA Pol II. Nature. 2011 Oct 16;479(7371):135-8. PubMed Central PMCID: PMC3391703.

d. Kloc A, Zaratiegui M, Nora E, Martienssen R. RNA interference guides histone modification during the S phase of chromosomal replication. Curr Biol. 2008 Apr 8;18(7):490-5. PubMed Central PMCID: PMC2408823.

4. Transposition depends on replication fork arrest. LTR retrotransposons exhibit a wide variety of insertion site preferences. We have uncovered a universal property of transposon targets: they arrest the replication fork. During my work on transposon silencing and instability I remarked that LTR were frequently associated with genomic Sap1 binding sites, and speculated that genome- bound Sap1 could be guiding insertion site selection (Zaratiegui et al., 2011b). We tested this explicitly by correlating genomewide patterns of Sap1 binding and transposon insertion preferences. Strikingly, this analysis revealed that transposition required not just Sap1 binding, but also its activity as a replication fork barrier. Together with the insertion preference of other LTR transposons for different fork-arresting elements, like tRNA and satellite DNA, this observation points to an ancestral insertion preference for LTR retrotransposons towards fork arrest regions. This work explains the distribution of transposons in eukaryotic genomes, as well as the cross-regulation between transposon life cycle and DNA replication. I was last and corresponding author in the resulting publication.

   a. Zaratiegui M. Cross-Regulation between Transposable Elements and Host DNA Replication. Viruses. 2017 Mar 21;9(3) PubMed Central PMCID: PMC5371812.

   b. Jacobs JZ, Rosado-Lugo JD, Cranz-Mileva S, Ciccaglione KM, Tournier V, Zaratiegui M. Arrested replication forks guide retrotransposon integration. Science. 2015 Sep 25;349(6255):1549-53. PubMed Central PMCID: PMC4832573.

5. Implementation of the CRISPR-Cas9 system in fission yeast. The use of CRISPR-Cas9 genome editing tools in fission yeast was precluded by the lack of an expression system allowing transcription of arbitrary sequences. We solved this problem by repurposing the precursor of a structural RNA of RNAse P to express gRNA with precise 5’ and 3’ ends. Using a proof of principle model we were able to show specific and selection-free gene editing with >95% efficiency. This work opened the CRISPR toolset for use in fission yeast. The plasmids have been distributed to more than a hundred labs around the world. I was last and corresponding author in this publication.

   a. Rodríguez-López M, Cotobal C, Fernández-Sánchez O, Borbarán Bravo N, Oktriani R, Abendroth H, Uka D, Hoti M, Wang J, Zaratiegui M, Bähler J. A CRISPR/Cas9-based method and primer design tool for seamless genome editing in fission yeast. Wellcome Open Res. 2016;1:19. PubMed Central PMCID: PMC5445975.

   b. Jacobs JZ, Ciccaglione KM, Tournier V, Zaratiegui M. Implementation of the CRISPR-Cas9 system in fission yeast. Nat Commun. 2014 Oct 29;5:5344. PubMed Central PMCID: PMC4215166.