BIOGRAPHICAL SKETCH

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NAME: Jean-Pierre Etchegaray

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

POSITION TITLE: Assistant 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)*	Completion Date MM/YYYY	FIELD OF STUDY
Austral University of Chile, Valdivia, Chile	B.S.	1990	Biological Sciences
Rutgers University, Piscataway, NJ, USA	Ph.D.	1999	Biochemistry & Molecular Biology
MGH-Harvard Medical School, Boston, MA, USA	Post-doc	2001	Development & Chronobiology

A. Personal Statement

I have been focused on elucidating epigenetic mechanisms regulating cell fate transactions in embryonic stem cells and adult tissues. The long-term goal of my research program at Rutgers is to understand how epigenetics affect adult stem cell functions and their implications health and disease. My laboratory has been focusing on epigenetic programs driven by DNA oxidations catalyzed by the Ten-Eleven Translocation (TET) enzymes. TETs are a family of DNA dioxygenases (TET1, TET2, TET3) that produce successive oxidations of 5-methylcytosine (5hmC) into 5-hydroxymethycytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC). My group is investigating how TET-mediated DNA oxidations may function as dynamic epigenetic elements to modulate gene expression in response to tissue stresses and cancer. Earlier, I found that 5hmC promotes expression of developmental genes in early stages of mouse embryogenesis, thereby establishing 5hmC as a positive transcriptional modulator. We recently reported that the histone deacetylase SIRT6 restrains expression of metabolic and developmental genes in embryonic stem cells by sustaining transcriptional pausing at promoter-proximal regions. As both 5fC and 5caC were recently shown to facilitate transcriptional pausing by stalling RNA polymerase II, we are testing the molecular interplay between SIRT6 and TET-mediated 5fC and 5caC in embryonic stem cells, cancer stem cells, and adult intestinal stem cells.

Ongoing and recently completed projects that I would like to highlight include:

NIH NINDS R01 NS118020 (PI: Kim) 2020 – 2025
Role: Co-Investigator
Title: *Choline-dependent metabolism in PNS myelination.*

METAvivor Foundation (PI: Rameshwar) 2021 – 2023
Role: Investigator
Title*: Preventing epigenetic-mediated DNA repair induced by bone marrow niche cells to avert drug resistance*

Busch Biomedical Research Award (PI: Etchegaray) 2020 – 2022
Role: Principal Investigator
Title*: Deciphering epigenetic dynamics driven by TET-mediated DNA oxidations during cellular rejuvenation*

Rutgers Initiative for Multidisciplinary Research Teams (IMRT) Award (PI: Etchegaray) 2019 – 2021
Role: Principal Investigator
Title: *Synergistic Exploration of Epigenetic Mechanisms in Stem Cell-Driven Cancer Initiation*

Citations:

1. **Etchegaray JP**, Lee C, Wade PA, Reppert SM. (2003). Rhythmic histone acetylation underlies transcription in the mammalian circadian clock. *Nature* 421: 177-182.
2. **Etchegaray JP**, Chavez L, Huang Y, Ross KN, Choi J, Martinez-Pastor B, Walsh RM, Sommer CA, Lienhard M, Gladden A, Kugel S, Silberman DM, Ramaswamy S, Mostoslavsky G, Hochedlinger K, Goren A, Rao A, Mostoslavsky R. (2015). The histone deacetylase SIRT6 controls embryonic stem cell fate via TET-mediated production of 5-hydroxymethylcytosine. *Nat Cell Biol* 17: 545-557.
3. **Etchegaray JP** and Mostoslavsky R (2016). Interplay between metabolism and epigenetics: a nuclear adaptation to environmental changes. *Mol Cell* 62: 695-711. PMID: 27259202
4. **Etchegaray JP**, Zhong L, Li C, Henriques T, Ablondi E, Nakadai T, Van Rechem C, Ferrer C, Ross KN, Choi JE, Samarakkody A, Ji F, Chang A, Sadreyev RI, Ramaswamy S, Nechaev S, Whetstine JR, Roeder RG, Adelman K, Goren A, Mostoslavsky R. (2019). The histone deacetylase SIRT6 restrains transcription elongation via promoter-proximal pausing. *Mol Cell* 75: 683-699.

B. Positions and Honors

Previous and Current Appointment:

2019 – present	Assistant Professor, Department of Biological Sciences, Rutgers University, Newark, NJ
2019 – present	Member of the Cancer Institute of New Jersey (CINJ)
2011 – 2018	MGH Cancer Center, Center for Regenerative Medicine, Harvard Medical School.
2002 – 2010	Research Associate, University of Massachusetts Medical School, Worcester, MA, USA.

Fellowships and Awards:

2020	Busch Biomedical Foundation Award
2019	Initiative for Multidisciplinary Research Team (IMRT) grant award, Rutgers University
2015	International Society for Stem Cell Research (ISSCR) Travel Award. Invited speaker
2011	Pilot and Feasibility grant from the NCI Federal Share Proton Beam Program, to study the role of SIRT6 in pluripotency and differentiation
2002	Society for Research on Biological Rhythms (SRBR) Travel Award. Invited speaker
2000	Postdoctoral Fellowship: The Sleep, Circadian and Respiratory Training Program, HL07901, Harvard Medical School

Patent:

2001	U.S. Patent 6333191. Nucleic acids sequence, stress-induced protein and uses thereof. Inventors: Inouye M, Jones P, **Etchegaray JP**, Jiang W, Pollitt NS, Goldstein J. Assignee: Robert Wood Johnson Medical School, Rutgers University (formerly UMDNJ), (Newark, NJ)

C. Contributions to Science

1. Epigenetic mechanisms sustaining circadian rhythms: We identified epigenetic mechanisms underlying circadian clock function in mammals. The circadian clock is an intrinsic cell autonomous timekeeping system controlling daily rhythms of gene expression to sustain tissue homeostasis in response to daily light-dark cycles. Dysfunctional circadian rhythms are implicated in multiple pathologies and diseases including learning/memory impairments, psychiatric illness, neurodegenerative diseases, immunodeficiency, diabetes, metabolic syndrome, accelerated aging and cancer. We discovered that circadian rhythms are strictly dependent on epigenetic dynamics involving daily rhythms of histone acetylation and methylation at promoter regions of timekeeping genes that are essentially required for circadian clock function. More specifically, we found the histone acetyltransferase p300 and the histone methyltransferase EZH2 from the polycomb repressive complex 2 (PRC2) to drive transcription of timekeeping genes within 24-hour periodicity. This was the first demonstration of epigenetic dynamics within 24-hour time windows. Additionally, we demonstrated the essential role of post-translational modifications in maintaining circadian rhythms. We found that phosphorylation of circadian timekeeping transcription factors maintain 24-hour rhythms.

a. **Etchegaray JP** Lee C, Wade PA, Reppert SM. (2003). Rhythmic histone acetylation underlies transcription in the mammalian circadian clock. *Nature* 421: 177-182. PubMed PMID: 12483227

b. **Etchegaray JP** Yang X, DeBruyne JP, Peters AH, Weaver DR, Jenuwein T, Reppert SM. (2006). The polycomb group protein EZH2 is required for mammalian circadian clock function. *J Biol Chem* 281: 21209-21215. PubMed PMID: 16717091
c. Lee C, **Etchegaray JP** Cagampang FR, Loudon AS, Reppert SM. (2001). Posttranslational mechanisms regulate the mammalian circadian clock. *Cell* 107: 855-867. PubMed PMID: 11779462
d. **Etchegaray JP** Machida KK, Noton E, Constance CM, Dallmann R, Di Napoli MN, DeBruyne JP, Lambert CM, Yu EA, Reppert SM, Weaver DR. (2009). Casein kinase 1 delta regulates the pace of the mammalian circadian clock. *Mol Cell Biol* 29: 3853-3866. PubMed PMID: 19414593; PubMed Central PMICD: PMC2704743

2. Epigenetic mechanisms in embryonic stem cell function: We found DNA oxidations by the Ten-Eleven Translocation (TET) enzymes to induce expression of developmental genes upon differentiation of embryonic stem cells (ESCs) towards the neural lineage. TET enzymes can change the epigenetic landscape by oxidizing methylated DNA into 5hmC, 5fC and 5caC. We demonstrated that TET-mediated DNA oxidations are required for early stages of embryonic development in both mouse and humans. In a collaborative project, we found new DNA methylation pathways in mouse pluripotent stem cells. Additionally, we found the histone deacetylase Sirtuin-6 (SIRT6) can repress the expression of the pluripotency genes *Oct4*, *Sox2* and *Nanog*. Consequently, SIRT6 deficiency improves reprogramming efficiency of somatic cells into induced pluripotent stem cells (iPSCs). Concordantly, catalytically inactive SIRT6 caused the upregulation of *Oct4* and *Sox2* leading to developmental malformations during human embryogenesis. Recently, we demonstrated a new role for SIRT6 in transcription by sustaining pausing of RNA polymerase II (Pol II) at promoter-proximal regions.

a. **Etchegaray JP** Chavez L, Huang Y, Ross KN, Choi J, Martinez-Pastor B, Walsh RM, Sommer CA, Lienhard M, Gladden A, Kugel S, Silberman DM, Ramaswamy S, Mostoslavsky G, Hochedlinger K, Goren A, Rao A, Mostoslavsky R. (2015). The histone deacetylase SIRT6 controls embryonic stem cell fate via TET-mediated production of 5-hydroxymethylcytosine. *Nat Cell Biol* 17: 545-557. PubMed PMID: 25915124; PubMed Central PMICD: PMC4593707
b. **Etchegaray JP** Zhong L, Li C, Henriques T, Ablondi E, Nakadai T, Van Rechem C, Ferrer C, Ross KN, Choi JE, Samarakkody A, Ji F, Chang A, Sadreyev RI, Ramaswamy S, Nechaev S, Whetstine JR, Roeder RG, Adelman K, Goren A, Mostoslavsky R. (2019). The histone deacetylase SIRT6 restrains transcription elongation via promoter-proximal pausing. *Mol Cell* 75: 683-699. PubMed PMID: 31399344; PubMed Central PMICD: PMC6907403
c. Ferrer CM, Alders M, Postoma AV, Park S, Klein MA, Cetinbas M, Pajkrt E, Glass A, van Koningsbruggen S, Christoffels VM, Mannens MMAM, Knegt L, **Etchegaray JP** Sadreyev RI, Denu JM, Mostoslavsky G, van Maarle MC, Mostoslavsky R. (2018). An inactivating mutation in the histone deacetylase SIRT6 causes human perinatal lethality. *Genes Dev* 32: 373-388. PubMed PMID: 29555651; PubMed Central PMICD: PMC5900711
d. Choi J, Clement K, Huebner AJ, Webster J, Rose CM, Brumbaugh J, Walsh RM, Lee S, Savol A, **Etchegaray JP** Gu H, Boyle P, Elling U, Mostoslavsky R, Sadreyev R, Park PJ, Gygi SP, Meissner A, Hochedlinger K. (2017). DUSP9 modulates DNA hypomethylation in female mouse pluripotent stem cells. *Cell Stem Cell* 20: 706-719. PubMed PMID: 28366588; PubMed Central PMICD: PMC5524993

3. Epigenetic mechanisms in cancer stem cells: Recently, we found expression of TET enzymes to be implicated in the formation of breast cancer stem cells that are resistant to chemotherapy.

a. Sandiford O, Donnelly R, El-Far M, Williams L, Sinha G, Parmarthi SH, Sherman L, Ferrer A, DeVore D, Patel S, Naaldijk Y, Alonso S, Barak P, Bryan M, Ponzio N, Narayanan R, **Etchegaray JP**, Kumar R, and Rameshwar P. (2021) Mesenchymal stem cell secreted small microvesicle instructs breast cancer cells to undergo stepwise dedifferentiation towards dormancy at bone marrow perivascular region. *Cancer Research* 81: 1567-1582. PubMed PMID: 33500249
b. Ferrer AI, Trinidad JR, Sandiford O, **Etchegaray JP**, Rameshwar P. (2020). Epigenetic dynamics in cancer stem cell dormancy. *Cancer Metastasis Rev* 39: 721-738. PubMed PMID: 32394305
c. Ferrer A, Roser CT, El-Far MH, Savanur VH, Eljarrah A, Gergues M, Kra Ja, **Etchegaray JP**, Rameshwar P. (2020). Hypoxia-mediated changes in bone marrow microenvironment in breast cancer dormancy. *Cancer Lett* 488: 9-17. PubMed PMID: 32479768

4. **Non-coding RNA driven epigenetic mechanisms involved in cancer**: We are investigating epigenetic mechanisms driven by long non-coding RNAs (lncRNAs) that promote cell fate transitions into malignant states.

a. Kumar S, Gonzalez EA, Rameshwar P, **Etchegaray JP** (2020). Non-coding RNAs as mediators of epigenetic changes in malignancies. *Cancers (Basel)* 12: 3657. (COVER). PubMed PMID: 33291485; PubMed Central PMICD: PMC7762117.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=etchegaray%20jp