BIOGRAPHICAL SKETCH

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NAME: Michael Andres Cortazar Osorio

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

POSITION TITLE: Posdoctoral Research Fellow

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
University of Colorado, Anschutz Medical Campus Aurora, Colorado, USA	Ph.D.	August/2018	Molecular Biology
Universidad del Valle Cali, Valle del Cauca, Colombia	B.S.	April/2011	Chemistry

A. Personal Statement

My long-term goal is to establish a research group to study cellular mechanisms of RNA quality control and their contribution to the disease phenotype of cystic fibrosis. Understanding how cellular machineries normally cope with errors in RNA transcripts can significantly stimulate the development of new strategies to treat genetic diseases caused by failure of such mechanisms. To achieve my long-term goal, I have the following specific goals for the postdoc period: 1. To become an expert in the study of nonsense-mediated RNA decay (NMD) and its role in cystic fibrosis, 2. To build collaborations with scientists and medical doctors at CU Anschutz currently investigating cystic fibrosis to strengthen my awareness and knowledge about the etiology and pathology of this disease. 3. To participate in scientific meetings and courses dedicated to the understanding of molecular mechanisms leading to cystic fibrosis and strategies to eliminate the burden of this disease, and 4. To build mentoring and leadership skills in preparation for launching my independent research career as a principal investigator.

I am well positioned to achieve my goals as a postdoc because of my strong training in genomics and regulation of gene expression as a graduate student in the laboratory of Dr. David Bentley. There, I learned to investigate RNA biogenesis and apply several high-throughput sequencing techniques. I successfully implemented ChIP-seq to investigate association of proteins with chromatin, Bru-Seq to measure transcription and splicing on chromatin and DRIP-seq to study RNA-DNA hybrids, or R-loop structures. I also learned to design novel sequencing libraries. I developed 5' Bru-seq, which maps 5' phosphates on uncapped nascent transcripts genome-wide (in preparation for publication). During the course of my graduate studies, I became proficient in the programming languages Python and R to process and analyze the results from sequencing libraries. These skills allowed me to efficiently advance in the analysis of complex sequencing datasets. I have also gained experience implementing the CRISPR/Cas9 system to successfully edit the genome of mammalian cells.

B. Positions and Honors

Positions and Employment

2018 – Present Postdoctoral Fellow, University of Colorado Anschutz Medical Campus
2011 – 2018 Graduate Student, University of Colorado Anschutz Medical Campus
2005 – 2011 Undergraduate student, Universidad del Valle, Colombia

Honor

2017 – 2018 RBI Scholar Award (Graduate Fellowship)**,** RNA Bioscience Initiative, University of Colorado School of Medicine

C. Contributions to Science

1. Transcriptional elongation and termination. Although transcription initiation is well studied, little is known about the molecular determinants of transcription termination. As a graduate student in the laboratory of Dr. David Bentley, I discovered that RNA Pol II slows down as it approaches the termination site and this slowdown is critical for transcription termination. We further found that the phosphatase PNUTS-PP1 dephosphorylation of Spt5 is essential for Pol II braking. These discoveries were possible because of my direct calculations of transcription elongation rates genome-wide in mammalian cells. My work in the Bentley lab contributed to the understanding of how the speed of transcription elongation is controlled and proposed a new model that explains transcription termination at 3' ends of human genes.

a. **Michael A. Cortazar**, Ryan M. Sheridan, Benjamin Erickson, Nova Fong, Kira-Glover-Cutter, Kristopher Brannan and David L. Bentley. Control of RNA pol II speed by PNUTS-PP1 and Spt5 dephosphorylation facilitates termination by a "sitting duck torpedo" mechanism, Mol. Cell. (2019).
b. Benjamin Erickson, Ryan M. Sheridan, **Michael A. Cortazar**, and David L. Bentley. Dynamic turnover of paused pol II complexes at human promoters, Genes Dev. (2018).
c. **Michael A. Cortázar** and David L. Bentley "The exonuclease Xrn2 induces premature termination and poly(A) site dependent termination of polymerase II transcription by targeting nascent transcripts", Transcription and Chromatin EMBL Conference, August 2016, Heidelberg, Germany. *(Poster presentation).*
d. Nova Fong, Kristopher Brannan, Benjamin Erickson, Hyunmin Kim, **Michael A. Cortazar**, Ryan M. Sheridan, Tram Nguyen, Shai Karp, and David L. Bentley. Effects of transcription elongation rate and Xrn2 exonuclease activity on RNA polymerase II termination suggest widespread kinetic competition, Mol. Cell. (2015).

2. Coupling of transcription with splicing and chromatin structure. Chromatin is dynamically disassembled and re-assembled as RNA pol II traverses a gene. Additionally, transcription is coupled with splicing of the growing nascent transcript. I contributed to the understanding of how transcription elongation dynamics influence chromatin structure and the splicing process. Additionally, in my doctoral thesis and oral presentation, I described the effects of slowing down pol II with the topoisomerase I inhibitor, camptothecin, on R-loop formation in the human genome.

a. Tassa Saldi, **Michael A. Cortazar**, Ryan M. Sheridan and David L. Bentley. Coupling of RNA polymerase II transcription elongation with pre-mRNA splicing, J. Mol. Biol. (2016).

b. Nova Fong, Tassa Saldi, Ryan M. Sheridan, **Michael A. Cortazar** and David L. Bentley. RNA pol II dynamics modulate co-transcriptional chromatin modification, CTD phosphorylation, and transcriptional direction, Mol. Cell. (2017).

c. **Michael A. Cortázar**. Understanding the effects of camptothecin treatment on RNA polymerase II transcription. The Seventeenth of Biennial meeting of Post-Initiation Activities of RNA Polymerases (October 2014), Pembroke, Virginia. (*Oral Presentation).*

3. Mechanism and function of chromatin modifiers. Factors that create, recognize or remove histone post-translational modifications are referred to as writers, readers and erasers respectively. As a first-year graduate student in the laboratory of Dr. Tatiana Kutateladze, I provided evidence that the histone H3K4-specific demethylase KDM5B can recognize its substrate and enzymatic product via two different protein PDH finger domains. I investigated binding of the three KDM5B PHD finger domains to modified histone tails

using NMR and $^{1}H,^{15}N$ heteronuclear single quantum coherence (HSQC) titration experiments. Results from my titration experiments were the basis to propose a model in which this enzyme recognizes its substrate, but it is able to bind its product to maintain association with histone tails and spread its demethyase activity on chromatin.

a. Brianna J. Klein, Lianhua Piao, Yuanxin Xi, Hector Rincon-Arano, Scott B. Rothbart, Danni Peng, Hong Wen, Connie Larson, Xi Zhang, Xia Zheng, **Michael A. Cortazar**, Pedro V. Peña, Anthony Mangan, David L. Bentley, Brian D. Strahl, Mark Groudine, Wei Li, Xiaobing Shi, and Tatiana G. Kutateladze. The histone-H3K4-specific demethylase KDM5B binds to its substrate and product through distinct PHD fingers, Cell Reports (2014).

4. Mechanisms of escape from NMD. As a postdoc in the Jagannathan lab, I recently contributed to a review on the current understanding of molecular mechanisms of escape from NMD.

a. Michael C. Dyle, Divya Kolakada, **Michael A. Cortazar**, Sujatha Jagannathan. How to get away with nonsense: Mechanisms and consequences of escape from nonsense-mediated RNA decay, WIREs RNA (2019).

5. The role of liver X receptor (LXR) agonists in chronic kidney disease. Phosphate homeostasis is regulated by the coordinated action of the intestinal and renal sodium–phosphate (NaPi) transporters, and the loss of this regulation causes hyperphosphatemia. Chronic kidney disease further exacerbates this effect. As a summer intern in the laboratory of Dr. Moshe Levi, I contributed to the completion of a study that documented a novel role for the LXR-activating ligands, DMHCA and TO901317, in the inhibition of the major renal and intestinal Na-Pi transporters. Such inhibition can reduce serum phosphate levels in mice. The relevance of that study was that it suggested that LXR-activating ligands, such as DMHCA, might be a promising therapeutic agent in the prevention of hyperphosphatemia and its cardiovascular consequences.

a. Yupanqui A. Caldas, Hector Giral, **Michael A. Cortázar**, Eileen Sutherland, Kayo Okamura, Judith Blaine, Victor Sorriba, and Moshe Levi. Liver X Receptor (LXR) Activating Ligands Modulate Renal and Intestinal Phosphate (Na-Pi) Transporters. *Kidney International* (July 2010).
b. Yupanqui A. Caldas, Hector Giral, **Michael A. Cortázar**, Eileen Sutherland, Kayo Okamura, Judith Blaine, Victor Sorriba, and Moshe Levi. Liver X Receptor agonists modulate the expression of intestinal and renal NaPi transporters. *Kern Aspen Lipid Conference*, August 2010, Aspen, Colorado. *(Poster presentation)*.

A. Additional Information: Research Support

RNA Bioscience Initiative Scholar Award 2017-2018
University of Colorado Anschutz Medical Campus, Aurora, CO
Dissertation title: *"Termination of RNA polymerase II transcription by the 5'-3' exonuclease Xrn2"*.
Role: PI