BIOGRAPHICAL SKETCH

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NAME: Espinosa, Joaquin Maximiliano

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

POSITION TITLE: Executive Director, Linda Crnic Institute for Down Syndrome; Professor of Pharmacology

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
Universidad Nacional de Mar del Plata, Argentina	B.S.	06/1995	Biology
Universidad de Buenos Aires, Argentina	Ph.D.	06/1999	Biology
The Salk Institute for Biological Studies, CA	Post-Doc	08/2004	Molecular Biology

A. Personal Statement

For nearly three decades, I have investigated molecular mechanisms relevant to human health and disease. As detailed below under *Contributions to Science*, my team has made important discoveries about the mechanisms of action of major tumor suppressors and oncogenes, the mechanisms that orchestrate the cellular response to hypoxia, basic mechanisms of gene expression control, and the mechanisms by which trisomy 21 dysregulates cellular and organismal function in people with Down syndrome.

Between 2004 and 2015, I led my research team at the University of Colorado Boulder, and during six of those years I held an appointment with the Howard Hughes Medical Institute (HHMI) as an Early Career Scientist (2009-2015). My research program has been funded by NIH since 2006. In 2015, I moved my research team to the University of Colorado Anschutz Medical Campus to take the post of Associate Director for Science at the Linda Crnic Institute for Down Syndrome. In July 2017, I became the Executive Director of the Crnic Institute.

At the Crnic Institute, I oversee a research and training program involving >60 labs performing research on various aspects of Down syndrome at >20 academic departments and divisions across the University of Colorado system, including many teams at the Anschutz Medical Campus and the Boulder campus. This program has effectively become the largest group of Down syndrome researchers in the world. I also manage the interactions with our clinical affiliates, the Anna and John J. Sie Center for Down Syndrome at Children's Hospital Colorado, the Adult Down Syndrome Clinic at Denver Health, and the Alzheimer's and Cognition Center. In addition, I direct the Crnic Institute's Human Trisome Project (HTP, NCT02864108), a large pan-omics cohort study of the population with Down syndrome, which has recruited >1,550 participants so far and enabled many important discoveries, leading to innovative clinical trials of immunomodulatory therapies to improve health outcomes in Down syndrome (NCT04246372, NCT05662228). I also serve as the Leader of the Administrative and Outreach Core of the INCLUDE Data Coordinating Center, which administers the INCLUDE Data Hub, a first-in-kind researcher portal facilitating access to and analysis of data generated from cohort studies of Down syndrome.

Examples of past or ongoing projects that I would like to highlight are:

R33AR077495
Espinosa (contact PI) – Bruckner – Rachubinski - Gurnee
09/12/2022 - 04/30/2025
JAK Inhibition in Down Syndrome

R61HD109748
Espinosa (contact PI) – Santoro – Sannar

09/09/2022-06/30/2024
Mechanistic investigations of therapies for Down syndrome Regression Disorder.

U2CHL156291
Resnick (contact), **Espinosa**, Carroll, DiGiovanna, Ferretti, Galbraith
09/01/2025 – 08/31/2030
The INCLUDE Data Coordinating Center

B. Positions, Scientific Appointments and Honors

Positions

2017 Executive Director, Anna and John J. Sie Endowed Chair in Genomics, Linda Crnic Institute for Down Syndrome, University of Colorado School of Medicine.
2015 Professor with Tenure, Department of Pharmacology, University of Colorado School of Medicine.
2010 Director, Functional Genomics Shared Resource of the University of Colorado.
2004 Assistant Professor > Associate Professor with Tenure > Visiting Professor, Department of Molecular, Cellular, and Developmental Biology, University of Colorado Boulder.

Scientific Appointments

2020 Leader, Administrative and Outreach Core, NIH INCLUDE Project Data Coordinating Center.
2015 Editorial Board, Trends in Cancer.
2013 co-Editor in Chief, Transcription.
2012 Member of various review panels for NIH and the National Science Foundation (NSF).
2011 Editorial Board, Cell Reports.

Honors

2018 Pueschel-Tjossem Memorial Research Award from the National Down Syndrome Congress.
2007 The Mortar Board Society Teaching Award.
2006 March of Dimes Basil O'Connor Junior Investigator Award.
2003 The Leukemia and Lymphoma Society Special Post-Doctoral Fellowship.
2000 The Pew Charitable Trusts Latin American Post-Doctoral Fellowship.
1996 Gold Medal, Rotary Club International. Prize to student with best qualifications in his or her discipline graduated from the Universidad Nacional de Mar del Plata.

C. Contributions to Science

1. Interferon hyperactivity in Down syndrome: from petri dish to clinical trials. Since the creation of the Crnic Institute at the University of Colorado, my team became interested in the study of trisomy 21 (T21) and its many impacts on human biology. In 2013, funded by a pilot grant from the Crnic Institute, we embarked on a series of functional genomics studies to understand the signaling events triggered by T21, which illuminated consistent activation of the interferon (IFN) response in diverse cell types from people with DS (Sullivan et al, *eLIFE* 2016). This discovery, which could be explained by the fact that four IFN receptors are encoded on chromosome 21, led to the hypothesis that many of the clinical and developmental hallmarks of DS are driven by chronic hyperactivation of this important aspect of the immune system. This hypothesis gained support from several follow up studies, including a large plasma proteomics analysis revealing signs of chronic autoinflammation with elevation of many IFN-inducible cytokines (Sullivan et al, *Scientific Reports* 2017); a large plasma metabolomics study showing that T21 activates the IFN-inducible kynurenine pathway, leading to elevated levels of neurotoxic tryptophan catabolites (Powers et al, *Nature Communications* 2019); and deep studies of the immune system of people with DS, revealing widespread immune dysregulation with rampant hypersensitivity to IFN stimulation (Waugh et al, *Cell Reports* 2019; Araya et al, *PNAS* 2019). Importantly, these results indicated that attenuation of the IFN response with JAK inhibitors could have therapeutic benefits in DS. This idea was successfully tested in mouse models of DS displaying lethal immune hypersensitivity (Tuttle et al, *Cell Reports* 2020). Furthermore, we reported the first known cases of JAK inhibition in DS for treatment of alopecia areata (Rachubinski et al, *JAAD Case Reports* 2019) and psoriatic arthritis (Pham et al, *Rheumatology* 2021). More recently, we demonstrated that triplication of the IFNRs contributes to multiple hallmarks of DS in a mouse model (Waugh et al, *Nature Genetics* 2023) and completed a multi-omics investigation of the interferonopathy of DS in hundreds of research participants with DS (Galbraith et al, *Science Advances* 2023).

These efforts led to two ongoing clinical trials to test the impact of JAK inhibition on diverse health outcomes in DS, where I serve as the contact PI (NCT04246372, NCT05662228). Key publications are:

a. Sullivan, K.D., Lewis, H.C., Hill, A.A., Pandey, A., Jackson, L.P., Cabral, J.M., Smith, K.P., Liggett, L.A., Gomez, E.B., Galbraith, M.D., DeGregori, J., and **Espinosa, J.M.** Trisomy 21 consistently activates the interferon response. *eLIFE* e16220, **2016**. PMID: 27472900.

b. Powers, R.K., Culp-Hill, R., Ludwig, M.P., Smith, K.P., Waugh, K.A., Minter, R., Tuttle, K.D., Lewis, H., Rachubinski, A.L., Granrath, R.E., Wilkerson, R.B., Kahn, D.E., Joshi, M., D'Alessandro, A., Costello, J.C., Sullivan, K.D., and **Espinosa, J.M.** Trisomy 21 activates the kynurenine pathway via increased dosage of interferon receptors. *Nature Communications* 10(1):4766, **2019.** PMID: 31628327.

c. Araya, P., Waugh, K.A., Sullivan, K.D., Núñez, N.G., Roselli, E., Smith, K.P., Granrath, R.E., Rachubisnki, A.L., Enriquez Estrada B., Butcher E.T., Minter, R., Tuttle, K.D., Bruno, T.C., Maccioni, M., and **Espinosa, J.M.** Trisomy 21 dysregulates T cell lineages toward an autoimmunity-prone state associated with interferon hyperactivity. *Proceedings of the National Academy of Sciences* 116(48):24231-24241, **2019.** PMID: 31699819.

d. Waugh, K.A., Minter, R., Baxter, J., Chi, C., Galbraith, M.D., Tuttle, K.D., Eduthan, N.P., Kinning, K.T., Andrysik, Z., Araya, P., Dougherty, H., Dunn, L.N., Ludwig, M., Schade, K.A., Tracy, D., Smith, K.P., Granrath, R.E., Busquet, N., Khanal, S., Anderson, R.D., Cox, L.L., Estrada, B.E., Rachubinski, A.L., Lyford, H.R., Britton, E.C., Fantauzzo, K.A., Orlicky, D.J., Matsuda, J.L., Song, K., Cox, T.C., Sullivan, K.D., **Espinosa, J.M.** Triplication of the interferon receptor locus contributes to hallmarks of Down syndrome in a mouse model. *Nature Genetics* 55(6):1034-1047, **2023**. PMID: 37277650.

2. Advancing functional genomics, systems biology, and open science approaches. With the advent of functional genomics and systems biology approaches, our team assumed a leadership position in this field by creating the Functional Genomics Shared Resource of the University of Colorado in 2010. This facility has served 300+ research teams across the state of Colorado, providing access to shRNA, ORF, and CRISPR libraries, as well as the protocols to use these tools. In parallel, our team developed a large portfolio of -omics technologies and the data analysis pipelines required to make discoveries from these high-content datasets. A key achievement in this area is the development of the Human Trisome Project (HTP), an ambitious study of the population with DS including a multidimensional biobank, deep clinical data, and pan-omics datasets, along with a public researcher portal that enables real-time data access and analysis (TrisomExplorer). The HTP has been a true discovery accelerator, supporting the investigations of IFN signaling in DS mentioned above, and many other studies (e.g., Culp-Hill et al, *Blood Advances* 2017; Galati et al, *Developmental Cell* 2018; Ligget et al, *Blood Advances* 2021, Araya et al, *Cell Reports* 2022). Our leadership in this area was recognized in 2020 with a collaborative agreement with NIH to design and launch the NIH INCLUDE Project Data Coordinating Center and Data Hub, where I serve as Leader of the Administrative and Outreach Core. With the arrival of the COVID-19 pandemic, we organized a team of collaborators to launch the COVIDome Project to quickly generate and release multi-omics datasets through an online portal known as the COVIDome Explorer (Sullivan et al, *Cell Reports* 2021), enabling important discoveries, such as a new staging model for COVID-19 pathology (Galbraith et al, *eLIFE* 2021) and studies of specialized interferon action in COVID-19 (Galbraith et al, *PNAS* 2022). These examples illustrate the global impact of our research program, where we go well beyond publishing discoveries and datasets by creating knowledge ecosystems that enable discoveries by many others. Recent example publications in the field of functional genomics and systems biology are:

a. Galbraith, M.D., Kinning, K.T., Sullivan, K.D., Baxter, R., Araya, P., Jordan, K.R., Russell, S., Smith, K.P., Granrath, R.E., Shaw, J.R., Dzieciatkowska, M., Ghosh, T, Monte, A.A., D'Alessandro, A., Hansen, K.C., Bennett, T.D., Hsieh, E.W., **Espinosa, J.M.** Seroconversion stages COVID19 into distinct pathophysiological states. *Elife* 10:e65508, **2021.** PMID: 33724185.

b. Sullivan, K.D., Galbraith, M.D., Kinning, K.T., Bartsch, K., Levinsky, N., Araya, P., Smith, K.P., Granrath, R.E., Shaw, J.R., Baxter, R., Jordan, K.R., Russell, S., Dzieciatkowska, M., Reisz, J.A., Gamboni, F., Cendali, F., Ghosh, T., Monte, A.A., Bennett, T.D., Miller, M.G., Hsieh, E.W.Y., D'Alessandro, A., Hansen, K.C., **Espinosa, J.M.** The COVIDome Explorer Researcher Portal. *Cell Reports* 36(7):109527. **2021.** PMID: 34348131.

c. Galbraith, M.D., Kinning, K.T., Sullivan, K.D., et al., **Espinosa, J.M.** Specialized interferon action in COVID19. *Proceedings of the National Academy of Sciences*, 119(11):e2116730119, **2022**. PMID: 35217532.

d. Galbraith, M.D., Rachubinski, A.L., Smith, K.P., Araya, P., Waugh, K.A., Enriquez-Estrada, B., Worek, K., Granrath, R.E., Kinning, K.T., Eduthan, N.P., Ludwig, M.P., Hsieh, E.W.Y., Sullivan, K.D., **Espinosa, J.M.** Multidimensional definition of the interferonopathy of Down syndrome and its response to JAK inhibition. *Science Advances* July 26 doi: 10.1126/sciadv.adg6218. **2023.** PMID: 37379383.

3. Cancer biology: advanced studies of the p53 tumor suppressor. As a post-doctoral fellow at the Salk Institute, I set up a new project and obtained results that changed long-held views on how the tumor suppressor p53 works. My research discarded the once prevalent 'latency model' of p53 regulation, dissected the mechanism of p53 coactivation by the acetyl-transferase p300 (Espinosa and Emerson, *Molecular Cell* 2001), and revealed the action of stimulus- and promoter-specific transcriptional complexes within the p53 network (Espinosa et al, *Molecular Cell* 2003). As an independent investigator, I continued to study the mechanisms controlling p53 activity through a multidimensional research program, from biochemistry to functional genomics. We discovered many molecular mechanisms exerting differential effects on p53 target genes involved in cell cycle arrest versus apoptosis (e.g., Gomes et al, *Genes and Development* 2005; Donner et al, *Molecular Cell* 2006; Gomes et al, *Genes and Development* 2010; Allen et al, *eLIFE* 2015; Andrysik et al, *Genome Research* 2017; Tatavosian et al, *Cell Death and Differentiation* 2023). We also investigated the molecular mechanisms that define the cellular response to p53 activation in response to inhibitors of the p53-MDM2 interaction, including ambitious functional genomics experiments to identify strategies to enhance the efficacy of these drugs (e.g., Henry et al, *The EMBO Journal* 2012; Sullivan et al, *Nature Chemical Biology* 2012; Andrysik et al, *Cell Reports* 2013; Rissotto et al, *Cell Reports* 2020; Andrysik et al, *Nature Communications* 2022; Szwarc et al, *Cell Reports* 2023). Our results in this area have provided the rationale for clinical trials where MDM2 inhibitors are combined with other targeted biological therapies to induce tumor cell death. We also revealed mechanisms by which p53 family members modulate p53 activity and other cancer-relevant pathways (e.g., Gallant-Behm et al, *Genes and Development* 2012; Abraham et al, *Cell Reports* 2018). Key publications are:

a. **Espinosa, J.M.** and Emerson, B.M. Transcriptional regulation by p53 through intrinsic DNA/chromatin binding and site-directed cofactor recruitment*. *Molecular Cell* 8(1):57-69, **2001**. PMID: 11511360. *Selected by Cell Press as 'Featured Article', by *Science* magazine for its 'Editor's Choice' column, and by Faculty of 1000 as 'Exceptional'.

b. **Espinosa, J.M.,** Verdún, R.E. and Emerson, B.M. p53 functions through stress- and promoter-specific recruitment of transcription initiation components before and after DNA damage. *Molecular Cell* 12(4):1015-1027, **2003**. PMID: 14580351. *Selected by Faculty of 1000 as 'Must Read'.

c. Allen, M.A., Andrysik, Z., Dengler, V.L., Mellert, H.S., Guarnieri, A., Freeman, J.A., Sullivan, K.D., Galbraith, M.D., Luo, X., Kraus, W.L., Dowell, R.D. and **Espinosa, J.M.** Global analysis of p53-regulated transcription identifies its direct targets and unexpected regulatory mechanisms. *eLIFE* 3:e02200, **2014**. PMID: 24867637.

d. Andrysik, Z., Sullivan, K.D., Kieft, J., and **Espinosa, J.M.** PPM1D suppresses p53-dependent transactivation and cell death by inhibiting the Integrated Stress Response. *Nature Communications* 13 (7400), **2022**. PMID: 36456590.

4. Decoding the hypoxic response in health and disease. Another key area of research in the lab is the study of the cellular response to hypoxia. Our team made significant contributions to the understanding of how cells sense and respond to low levels of oxygen, with an emphasis on studies of the hypoxia-inducible factors (HIFs). In collaboration with the Mostoslavsky's lab, we elucidated the mechanism by which the sirtuin family member SIRT6 represses basal HIF1A activity (Zhong et al, *Cell* 2010). We then discovered that HIF1A employs the CDK8-Mediator coactivator complex to stimulate transcriptional elongation at its target genes (Galbraith et al, *Cell* 2013), and identified the TIP60 complex as a conserved coactivator of HIF1A (Perez-Perri et al, *Cell Reports* 2016). We discovered that the kinase activity of the HIF1A cofactor CDK8 is required for metabolic reprogramming and glycolysis in cancer cells (Galbraith et al, *Cell Reports* 2017). Using an innovative multi-omics platform, we characterized the immediate early response to hypoxia in great detail, leading to the identification of context-dependent tumor suppressive and oncogenic gene modules within the hypoxic response driven by HIF1A (Andrysik et al, *Nature Communications* 2021). Example publications in this area are:

a. Zhong, L., D'Urso, A., Toiber, D., Sebastian, C., Henry, R.E., Vadysirisack, D.D., Guimaraes, A., Marinelli, B., Wikstrom,J.D., Nir, T., Clish, C.B., Vaitheesvaran, B., Iliopoulos, O., Kurland, I., Dor, Y., Weissleder, R., Shirihai, O.S., Ellisen, L.W., **Espinosa, J.M.** and Mostoslavsky, R. The histone deacetylase Sirt6 regulates glucose homeostasis via HIF1A*. *Cell* 140(2):280-293, **2010**. PMID: 20141841. *Selected by Faculty of 1000 as 'Must Read'.

b. Galbraith, M.D., Allen, M.A., Bensard, C.L., Wang, X., Schwinn, M.K., Qin, B., Long, H.W., Daniels, D.L., Hahn, W.C., Dowell, R.D. and **Espinosa, J.M.** HIF1A employs CDK8-Mediator to stimulate RNAPII elongation in response to hypoxia. *Cell* 153(6):1327-39, **2013**. PMID: 23746844.

c. Perez-Perri, J.I., Dengler, V.L, Audetat, A.K., Pandey, A., Bonner, E.A., Urh, M., Mendez, J., Daniels, D.L., Wappner, P., Galbraith, M.D., and **Espinosa, J.M.** TIP60 is a conserved coactivator of HIF1A. *Cell Reports* 16(1):37-47, **2016.** PMID: 27320910.

d. Andryzik, A., Bender, H., Galbraith, M.D., **Espinosa, J.M.** Multi-omics analysis reveals contextual tumor suppressive and oncogenic gene modules within the acute hypoxic response. *Nature Communications* 12(1):1375, **2021.** PMID: 33654095.

5. Basic studies of gene expression control mechanisms. Since my pre-doctoral work at the University of Buenos Aires studying trans-splicing in parasitic trypanosomes, I have been fascinated by mechanisms of gene expression control, from chromatin assembly to post-translational regulation of mRNA stability. Funded by multiple NSF awards and NIH grants, our team and its many collaborators made significant contributions to this field. Some prominent examples are studies of RNA polymerase II elongation and pausing (e.g., Glover-Cutter et al, *Nature Structural and Molecular Biology* 2008; Donner et al, *Nature Structural and Molecular Biology* 2010); studies of the Mediator coactivator complex (e.g., Meyer et al, *The EMBO Journal* 2008; Knuesel et al, *Molecular and Cellular Biology* 2009; Steinparzer et al, *Molecular Cell* 2019); and investigations of diverse chromatin remodeling and modifying complexes (e.g., Smallwood et al, *Genome Research* 2012; Nichol et al, *Cell Reports* 2016; Strahl et al, *Cell Reports* 2016; Liang et al, *Cell* 2017). Key publications are:

a. Gomes, N.P., Bjerke, G., Llorente, B., Szostek, S.A., Emerson, B.M. and **Espinosa, J.M.** Gene-specific requirements for P-TEFb activity and RNA polymerase II phosphorylation within the p53 transcriptional program*. *Genes and Development*, 20(5):601-12, **2006.** PMID: 16510875. *Selected by *Genes and Development* editors for a special 'Perspective' appearing in *Genes and Development* 20(6):643-7 and by Faculty of 1000 as 'Recommended'.

b. Donner, A.J., Szostek, S.A., Hoover, J.M. and **Espinosa J.M.** CDK8 is a stimulus-specific positive coregulator of p53 target genes*. *Molecular Cell* 27(1):121-133, **2007.** PMID: 17612495**.** *Selected by the ISI portal as one of the Top 50 articles in the Cell Cycle field in 2009.

c. Donner, A.J., Ebmeier, C.C., Taatjes, D.J. and **Espinosa, J.M.** CDK8 is a positive regulator of transcriptional elongation within the serum response network. *Nature Structural and Molecular Biology* 17(2):194-201, **2010**. PMID: 20098423. *Selected for the cover of the February 2010 issue of *Nature SMB* and by Faculty of 1000 as 'Recommended'.

d. Gomes, N.P. and **Espinosa, J.M.** Gene-specific repression of the p53 target gene PUMA via intragenic CTCF-Cohesin binding. *Genes and Development,* 24(10): 1022-34, **2010.** PMID: 20478995. *Selected by *Nature Cancer Reviews* for its 'Highlight' section and by Faculty of 1000 as 'Recommended'.

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