BIOGRAPHICAL SKETCH

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NAME: Fabián Morales-Polanco

eRA COMMONS USER NAME: FABIANMP

POSITION TITLE: Postdoctoral Scholar

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	COMPLETION DATE	FIELD OF STUDY
Stanford University, USA (Judith Frydman Laboratory)	Postdoc	2019-present	Biology – Biochemistry
The University of Manchester, UK. (Mark Ashe and Christian Grant Laboratories)	Ph.D	09/2018	Biotechnology and Enterprise
The University of Manchester, Business School, UK	Other	04/2015	Biotechnology and Enterprise
Universidad de Chile – Sciences Faculty, Chile	MENG (equivalent)	04/2014	Biotechnology Engineer
Universidad de Chile, Sciences Faculty, Chile	Licentiate	12/2012	Molecular Biotechnology Engineering
Universidad de Chile, Faculty of Medicine, Chile.	Other	12/2008	Medical Technology

A. Personal Statement

My research centers on proteostasis in eukaryotic cells, specifically studying translation, clearance mechanisms, and their implications for health and disease. I have expertise in diverse techniques related to protein quality control, RNA biology, and aging-related molecular mechanisms. Through my contributions, I have uncovered novel processes in RNA biology, functional protein interactions, and misfolded protein clearance. In the Frydman lab, I investigate changes in the interactome of nuclear and cytoplasmic protein quality control inclusions (INQ and JUNQ). Using a proximity labeling approach with APEX2 in yeast, I am trying to elucidate the different roles of chaperones, E3 ligase complexes, and ubiquitination pathways, deepening our understanding of proteostasis and misfolded protein diseases. I also specialize in leading microscopy techniques, exploring novel pathways for clearing misfolded proteins in eukaryotes. Collaborating with Emily Sontag, I studied the convergence of INQ and JUNQ at Nuclear-Vacuolar Junctions (NVJs), crucial for spatial protein quality control and cellular health.

I have also been working on trying to understand how ageing impacts translation. In collaboration with Kevin Stein, I investigated the molecular mechanisms underlying aging and age-related diseases, providing insights into proteostasis deterioration and impaired ribosome-associated quality control pathways. These findings contribute to our understanding of age-related protein misfolding diseases and potential therapeutic interventions.

During my PhD at the University of Manchester, I conducted groundbreaking research on the co-localization and translation of glycolytic mRNAs within Core Fermentation or CoFe Granules. This challenged existing views and illuminated regulatory mechanisms governing metabolic pathways through RNA localization and translation. I demonstrated active mRNA translation within these granules, providing insights into cellular mechanisms governing enzyme synthesis and proteostasis.

Beyond research, I am dedicated to scientific communication and mentorship. I effectively convey complex scientific concepts through presentations and mentor undergraduate and high school students, fostering their enthusiasm for scientific inquiry. With a solid academic background and a strong commitment to advancing scientific knowledge and improving human health, I am poised to make significant contributions in proteostasis research. In summary, my research focuses on proteostasis, with expertise in protein quality control, RNA biology, and translation. I have made novel discoveries and collaborations that deepen our understanding of proteostasis and misfolded protein diseases. With a passion for scientific communication and mentorship, I am dedicated to advancing our understanding of cellular mechanisms and improving human health.

Positions and Honors

Professional Positions

2019-present	Postdoctoral Scholar at Judith Frydman Laboratory- Stanford University, US.
2015 – 2018	Teaching Assistant (Various courses) - The University of Manchester, UK.
2014 – 2018	Graduate Student at Mark Ashe and Christian Grant Laboratories- University of Manchester, UK
2015	Funder and Scientific Chief Developer of the startup “Biowater Solutions”.
2012 – 2014	Engineering student and researcher in Biotechnology - Centre for Biotechnology and Bioengineering CeBiB, Faculty of Physical Sciences and Mathematics, Chile.
2011 – 2011	Research Assistant, Fundación “Ciencia para la Vida”, Startup Chile, Chile.
2010 – 2012	Researcher and project developer, Biopacific Ltda., Chile
2010 – 2011	Research assistant, Michael Handford, Claudia Stange and Margarita Carú Laboratories, Universidad de Chile, Chile.
January 2008	Teaching Assistant at the Molecular Biology Summer School for Chilean students, Faculty of Medicine, Universidad de Chile, Chile

Honors and Awards

2023	ISFS Fellow 2023 - The Intersections Science Fellowship| Research showcase platform connecting talented postdocs with institutions for faculty recruitment.
2023	MERIT Emerging Leader 2023 | Memorial Sloan Kettering (MSK), New York, US.
2020 - 2024	Pew Fellow 2020 | Postdoctoral fellowship awarded for young scientists with outstanding contributions to Biomedical Sciences.
2019	Recipient of a Protein Folding at the Ribosome Travel Award | Organization Committee.
2017	Best poster presentation award | 28th International Conference on Yeast Genetics and Molecular Biology (ICYGMB), Springer.
2015	Best poster Presentation award | Translation UK conference, The Biochemical Society.
2015	Selected for the Lean Launchpad Program for 10 Startups | Synbicite, Imperial College of London, UK. Our team underwent a transformative entrepreneurial experience acquiring expertise in commercializing synthetic biology technology.
2013	Engineering degree with Maximum Distinction | Universidad de Chile
2013 - 2018	Recipient of a Doctoral Fellowship | Conicyt, Chile.
2012	Licentiate in Molecular Biotechnology with Maximum Distinction | Universidad de Chile

B. Contributions to Science

Deciphering the context-dependent change on protein interactions within different Spatial Protein quality control compartments. During my research in the Frydman lab, I have focused on exploring the interactome of two important PQC compartments: the INQ (Intranuclear Quality control compartment) and JUNQ (Juxtanuclear Quality control compartment). These compartments play a crucial role in managing misfolded proteins in eukaryotic cells. Although our understanding of these compartments is still limited, initial investigations have revealed important factors within the INQ, including Btn2, Sis1, and Hsp70, indicating a complex network of interactions. Additionally, the E3 ligase complex Rad6-Bre1 has been implicated in recruiting Mus81-Mms4 to the INQ, highlighting the involvement of ubiquitination and protein degradation pathways. Chaperones such as Hsp104, Hsp70, and Hsp40 have also been identified in the INQ, suggesting their potential roles in protein refolding and disaggregation. However, further research is needed to fully unravel the INQ and JUNQ interactome, including the identification of resident proteins, mapping protein-protein interactions, understanding the impact of posttranslational modifications, and conducting comparative studies across species. Through my work as the first author on an upcoming manuscript, currently in preparation, I have made significant progress in studying the spatial interactors of misfolded proteins at different stages of misfolding using the APEX2 methodology. Notably, our findings suggest that the chaperone Hsp26 may play a critical role in the phase separation process, leading to the formation of distinct compartments for misfolded proteins. I am eager to share these findings with the scientific community and continue exploring the complexities of proteostasis in future research endeavors.

i. Pinto S*., Wangeline M*., **Morales-Polanco F*.,** & Frydman, J. (2023). Molecular Mechanisms of Protein Quality Control and Misfolded Protein Sequestration. *Molecular Cell (In revision)*, *5*, 67-94. Review

*Authors contributed equally to this work

A subcellular organization for the orchestrated co-translational folding and assembly of protein complexes in the eukaryotic cell: Unraveling the mechanisms. Protein complex biogenesis is essential for diverse biological functions, yet the cellular mechanisms involved remain elusive. While cotranslational and posttranslational assembly principles are emerging, the absence of polycistronic mRNAs in eukaryotes raises questions about how unassembled subunits are orchestrated in these cells. Throughout my time at the Frydman lab, I have dedicated my efforts to unraveling the intricate processes governing protein complex assembly in eukaryotic cells. During my doctoral research, I made an intriguing discovery regarding the co-localization of glycolytic mRNAs within phase-separated droplets known as Glycolytic mRNA or CoFe Granules. Do these granules have the potential to facilitate the assembly of glycolytic protein complexes during rapid cell growth? Building upon this finding, I further investigated the impact of ribosomal kinetics during translation elongation on the formation of functional protein complexes. By employing Selective Ribosome Profiling (SeRP) and Disome Selective Profiling (DiSP) in yeast, we gained insights into the non-uniqueness of assembly pathways for glycolytic enzymes. Moving forward, my research will delve deeper into the molecular mechanisms underlying condensate formation, the conservation of ribosomal kinetics, the effects of age-related changes on protein complex formation, and therapeutic manipulations targeting ribosomal kinetics and condensates. Through these investigations, I aim to advance our understanding of cellular biology and contribute to improving human health. Currently, I am preparing the manuscript in which I am the first author, documenting these significant findings.

ii. **Morales-Polanco, F**., Lee, J. H., Barbosa, N. M., & Frydman, J. (2022). Cotranslational mechanisms of protein biogenesis and complex assembly in eukaryotes. *Annual Review of Biomedical Data Science*, *5*, 67-94. Review

A new pathway for misfolding proteins clearance in eukaryotes: Nuclear and Cytosolic misfolded protein Inclusions are Cleared at Nuclear-Vacuolar Junctions. Clearing misfolded proteins is essential for cellular health and the spatial sequestration of misfolded proteins into membrane-less inclusions is a fundamental protein quality control (PQC) strategy. In our research, we investigated the clearance of misfolded proteins in yeast cells and discovered a novel pathway for their removal. We observed that cytoplasmic misfolded proteins concentrate in a compartment called JUNQ, while nuclear misfolded proteins sequester into a compartment known as INQ. Interestingly, we found that INQ and JUNQ are positioned on opposite sides of the nuclear envelope, and they converge near Nuclear-Vacuolar Junctions (NVJs) through a signal associated with nuclear pores. To understand the molecular mechanisms involved, we focused on the ESCRT-II/-III protein Chm7, which is localized at the nuclear envelope and essential for the convergence of INQ and JUNQ at NVJs. By disrupting NVJs or deleting the ATPase Vsp4, necessary for membrane invagination into the vacuole, we observed impaired clearance of both INQ and JUNQ. Surprisingly, deleting the NVJ or Vps4 resulted in the egress of nuclear INQ into the cytoplasm, indicating a pathway for extruding misfolded protein compartments from the nucleus. Furthermore, we identified the involvement of other ESCRT family members, including Vps23, Vps24, and Vps15, in the homing of INQ and JUNQ, and their deletion led to the budding of INQ from the nucleus, resulting in the accumulation of nuclear misfolded proteins in the cytoplasm. These findings highlight the intricate coordination between nuclear and cytoplasmic spatial protein quality control mediated by perinuclear ESCRT and the nuclear envelope. I am honored to have this work recently published in the prestigious journal Nature Cell Biology, as a co-first in conjunction of Emily Sontag (Ph.D.). This significant work has been presented at IFOM, Milan, and will also be featured in talks at the 31st International Conference on Yeast Genetics and Molecular Biology in Florence, Italy, and at the Institute of Molecular Biology of Barcelona.

i. Sontag, E. M*., **Morales-Polanco, F*.,** Chen, J. H., McDermott, G., Dolan, P. T., Gestaut, D., ... & Frydman, J. (2023). Nuclear and cytoplasmic spatial protein quality control is coordinated by nuclear–vacuolar junctions and perinuclear ESCRT. *Nature Cell Biology*, 1-15.

*Authors contributed equally to this work

RNA granules harboring translationally competent mRNAs encoding glycolytic enzymes and translation factors. During my time with the research team in Manchester, I came across an interesting observation: the colocalization of two glycolytic mRNAs in actively growing yeast cells. This discovery intrigued me, as it hinted at a potential regulatory mechanism for metabolic pathways through RNA localization and translation. However, no prior reports in the literature had described such a phenomenon. Undeterred, I dedicated substantial effort to investigate further and successfully demonstrated that a majority of glycolytic mRNAs localize to phase-separated entities in yeast and human cells. To gain a deeper understanding, I conducted comprehensive live cell and single-molecule FISH studies in yeast, revealing the active translation of mRNAs within these granules. This finding significantly contributes to our understanding of how cells regulate the synthesis of essential enzymes while maintaining proteostasis. Moreover, it challenges existing views and opens new avenues for research in protein folding, assembly of oligomeric complexes, and their potential involvement in neurodegenerative amyloid diseases. In summary, my research sheds light on the localization and translation of glycolytic mRNAs within RNA granules, offering valuable insights into cellular mechanisms governing enzyme synthesis and proteostasis. These findings present exciting opportunities for future investigations in protein folding, oligomeric complex assembly, and their implications for neurodegenerative diseases.

i. **Morales-Polanco, F**., Bates, C., Lui, J., Casson, J., Solari, C. A., Pizzinga, M., ... & Ashe, M. P. (2021). Core Fermentation (CoFe) granules focus coordinated glycolytic mRNA localization and translation to fuel glucose fermentation. *IScience*, *24*(2).

ii. Pizzinga, M., Bates, C., Lui, J., Forte, G., **Morales-Polanco, F**., Linney, E., ... & Ashe, M. P. (2019). Translation factor mRNA granules direct protein synthetic capacity to regions of polarized growth. *Journal of Cell Biology*, *218*(5), 1564-1581.

Novel molecular mechanisms underlying ageing and age-related diseases. Ageing poses a significant challenge to cellular proteostasis, which plays a crucial role in age-related protein misfolding diseases like

Alzheimer's, Parkinson's, and cancer. During my postdoctoral studies at the Frydman lab, I collaborated with another postdoctoral fellow Kevin Stein, and we investigated the impact of ageing on translation kinetics using Caenorhabditis elegans and Saccharomyces cerevisiae models. Through ribosome profiling and pause analysis, we observed a remarkable finding: ribosome pausing increased at specific positions in aged yeast and worms, leading to ribosome collisions and compromised ribosome-associated quality control. Intriguingly, long-lived yeast mutants exhibited reduced age-dependent ribosome pausing, resulting in extended lifespan and improved flux through the ribosome-associated quality control pathway, effectively mitigating the detrimental effects of ageing. Moreover, our research revealed that aged cells displayed heightened pausing and aggregation of multiple proteostasis components, thereby initiating a self-perpetuating cycle of proteostasis collapse. These findings significantly advance our understanding of ageing and age-related protein misfolding diseases. Furthermore, the conserved nature of these mechanisms across species presents numerous intriguing avenues for future investigations. This significant work has been recently published in *Nature*.

i. Stein, K. C., **Morales-Polanco, F**., van der Lienden, J., Rainbolt, T. K., & Frydman, J. (2022). Ageing exacerbates ribosome pausing to disrupt cotranslational proteostasis. *Nature*, *601*(7894), 637-642.

Additional information: Research Support and/or Scholastic Performance

Relevant talks and Presentations:

2023 Oct	Selected talk, ISFS Fellows Symposium.
2023 Aug	Selected talk, 31st International Conference on Yeast Genetics and Molecular Biology (ICYGMB) | Florence, Italy.
2023 Aug	Invitation Seminar, Instituto de Biología Molecular de Barcelona IBMB CSIC | Barcelona, Spain.
2023 Aug	Selected talk | The MERIT emerging leaders Symposium | Memorial Sloan Kettering Cancer Centre, New York, US
2023 Jun	Invitation Seminar | IFOM, Milan, Italy.
2023 March	Talk, Pew Meeting in the Biomedical Sciences | Puerto Rico
2022 Dec	Poster and talk, Pew Meeting in the Biomedical Sciences | Costa Rica.
2021 Apr	Talk, Virtual Pew Meeting in the Biomedical Sciences.
2022 Mar	Poster, Pew Meeting in Biomedical Sciences | Los Angeles, US.
2019 Dec	Invitation Seminar, Elke Deuerling lab | University of Konstanz, Germany.
2019 Dec	Poster, Protein Folding at the ribosome meeting | Berlin, Germany.
2019 Jun	Poster, RNA conference | Krakow, Poland (Author)
2017 Nov	Talk, Chilean Society seminars on Science diffusion | Manchester, UK.
2017 Oct	Poster and flash talk, 28th International Conference on Yeast Genetics and Molecular Biology (ICYGMB) | Prague, Czech Republic
2016 Nov	Talk, Seminars on Regulation of Gene Expression | The University of Manchester, UK.
2016 Jul	Poster, Translation UK | University of Aberdeen, Scotland.
2015 Jul	Poster, Translation UK | University of Aberdeen, Scotland.
2015 Jul	Poster, Summer Post-graduate Research Symposium |The University of Manchester, UK
2015 May	Talk, Lean LaunchPad “Biowater solutions”, finalist | The Imperial College of London

Teaching and mentoring experience:

2020-2023	Mentor of Cooper Veit and Dario Coonor Alvarez, Undergraduate research internship | Stanford University.
2014-2018	Teaching assistant. Courses: Molecular Biology, Biochemistry, Cellular Biology, Microbiology, Yeast Biology, Human Physiology, Pharmacology, Enzymology, Neurobiology, Laboratory skills, Biotechnology, and Genetics. My role was to direct and help students on their practical experiments.
2008	Mentor of high school students on Molecular Biology | Universidad de Chile, Chile.