Name	SILVIA SANTOS
Position	Group Leader (1st 6)
Year joined *(Crick or founder institute)*	2018

Career History

PhD at the European Molecular Biology Laboratory (EMBL) – Heidelberg, Germany
EMBL pre-doc and Marie Curie E-STAR fellow
2004-2008 with Prof Philippe Bastiaens

Post-doc at Stanford University – California, USA
EMBO and HFSP fellow
2009-2014 with Prof Jim Ferrell and Prof Tobias Meyer

Career Development Award (CDA) at London Institute for Biomedical Sciences (LMS), MRC-Imperial College London, London UK
MRC CDA fellow
2014-2017

Major Awards, Honours and Prizes

2004- 2007: Marie Curie fellowship early-stage research training (E-STAR)
2008- 2009: European Molecular Biology Organization (EMBO) post-doctoral fellowship
2009- 2011: Human Frontier Science Program (HFSP) long-term post-doc fellowship
2011: Best poster prize EMBO meeting: The logic of the Cell cycle, France
2012: Mansour Award for best publication, Stanford University
2013: UCL-Crick Excellence Fellowship (declined)
2013: MRC Career Development Award (CDA)
2015: MRC end of the year award
2017: Senior Lecturer Imperial College London, UK
2018: Honorary Associate Professor, UCL, London, UK

Membership of external committees, editorial boards, review panels, SABs etc

Since 2019: Advisory board member for Research Commons (EMBO publishing group)
2015- 2018: Chair of Mentorship at LMS-MRC-Imperial College London
2015, 2020: Scientific advisory committee member for the International Conference of Systems Biology (ICSB)

Lab Name	***Quantitative Cell Biology Laboratory***

Research programme and achievements

During cell decision-making, gene and protein networks dynamically change in response to cues in order to trigger different cellular states. How information is decoded and transmitted in order to commit to specific cell fates has been a fundamental question in cell and developmental biology. In this context, my lab aims to understand how signalling molecules are organised into circuits, and how these circuits are spatio-temporally regulated and remodelled in two important cellular decisions: cell division and cellular differentiation.

The decision to divide is a fundamental decision and the conserved networks that trigger cell division adapt and remodel in a variety of biological contexts including developmental transitions and malignancy. We have been exploring spatio-temporal control of cell division in mammalian cells (Santos SDM et al Cell 2012, Araujo et al Mol Cell 2016) and remodelling of cell cycle networks during developmental transitions, using embryonic stem cells as a model system.

Embryonic stem cells have the propensity to differentiate into the three germ layers. The switch between pluripotency and differentiation in these cells has been our paradigm of choice to understand how protein and gene networks decode cellular signals and thereby encode irreversible commitment to different cell fates (Gunne Braden et al Cell Stem Cell 2020).

Both lines of investigation have a profound impact in the understanding of normal human development, reprogramming and de-differentiation and the transition from healthy to disease states, in particular during cancer.
We use quantitative approaches combining experimental methods (based on single cell live cell imaging, genomics, proteomics and chemical biology) with mathematical modelling. Multidisciplinary approaches have revolutionised the way we ask biological questions and have been crucial to uncover regulatory principles in cell decision-making.

Major achievements
During this quinquennium we have made important scientific contributions to two different fields: developmental biology and cell cycle/chromosome biology:

a. We discovered a new class of genes, deemed *early commitment genes* (ECG), which mediate irreversible commitment to cellular differentiation in human early embryonic stem cells (Gunne-Braden et al Cell Stem Cell 2020)
b. We discovered that cells irreversibly commit to undergoing cellular differentiation unexpectedly early during early human embryonic development (Gunne-Braden et al Cell Stem Cell 2020)
c. We discovered a new role for the transcription factor GATA3 in early differentiation (Gunne-Braden et al Cell Stem Cell 2020, Sullivan et al unpublished)
d. We discovered that positive feedback in the networks that regulate the onset of mitosis allow for modularity in cell division cycles (Araujo et al Mol Cell 2016)
e. We discovered that feedback regulation and protein degradation allow for fine tuning of the period of cell division cycles in early embryonic and somatic divisions (Araujo et al under revision)
f. We discovered that a maternal factor, FGF2, is essential during early mouse development for maintaining correct cell number and proportions of specific lineages (Gharibi et al under revision and Gharibi et al unpublished)
g. We discovered that CDK hyperactivation and spatial control are essential for cell cycle remodeling during the embryonic to somatic transition during cellular differentiation (Padgett and Santos Febs Letters 2020, Gharibi et al unpublished and Padgett et al unpublished)

h. We have developed several genome edited human embryonic stem cell lines expressing biosensors, crucial to perform live cell imaging experiments and dynamic perturbations.
i. We have developed artificial intelligence (AI) based image analysis methods for quantification of live cell imaging experiments
j. We have developed and optimised 2D and 3D models to study early development in the lab. These methodologies are going to be crucial to study the interplay between cell cycle regulation and cellular differentiation and for understanding how cells self-organise and pattern during early development.

Summary of future programme

Our future research has three main aims: a) to shed light into embryonic to somatic cell cycle transitions during cellular differentiation in early human development; b) to understand how early embryonic cells decode intracellular signals and signals from the embryo niche and specify specific fates; c) to understand the interplay between cell cycle regulation and cellular differentiation in early development.
We will continue to rely on multi-disciplinary approaches, based on single cell imaging, 2D and 3D models for embryogenesis and genomic approaches and combine these with mathematical models and computations.

Research outputs

Padgett, J., & Santos, S. D. M. (2020). *From clocks to dominoes: lessons on cell cycle remodelling from embryonic stem cells*. FEBS Letters, 594(13), 2031-2045. DOI: 10.1002/1873-3468.13862
This manuscript is the first review we published on cell cycle regulation. It focuses on how the cell cycle remodels during differentiation of human embryonic stem cells. We highlighted that these cells are an incredbily trackable system to understand embryonic-to-somatic transition and highlight the incredible variability in cell cycle regulation in human cells (from early embryonic, pluripotent, somatic to post-mitotic).

Sullivan, A. E., & Santos, S. D. M. (2020). *An optimized protocol for ChIP-Seq from human embryonic stem cell cultures*. STAR Protocols 1, 2. DOI: 10.1016/j.xpro.2020.100062
This manuscript is a methods paper. While at the Crick we have developed methods and optimised protocols to work with human embryonic stem cells, namely ChIPsequencing to perfom high quality and highly reproducible sequencing. While working closely with the Advanced Sequencing facility we were asked to share our protocols with several labs at the Crick, since our data with ASF was of consistently good quality. We decided to submit one of these methods to be useful for the wider community of stem cells/developmental biologists.

Gunne-Braden, A., Sullivan, A., Gharibi, B., Sheriff, RSM., Maity, A., Wang, Y-F., Edwards, A., Jiang, M., Howell, M., Goldstone, R., Wollman, R., East, P. and Santos, SDM*. (2020) *GATA3 mediates a fast, irreversible commitment to BMP4-driven differentiation in human embryonic stem cells*. Cell Stem Cell 26, 693-706. DOI: 10.1016/j.stem.2020.03.005
This manuscript was the first demostrations that irreversible commitment to cellular differentiation during early development happens unexpectedly early. The paper reflects our interdisciplinary work, combining single cell imaging, mathematical modelling and -omics approaches. We discovered a new class of genes which we termed early

commitment genes (ECG) that are responsible for the pluripotency-to-differentiation transition. It was also our first manuscript in developmental biology, a new field outside of our lab's expertise.

Ochoa, D., Jonikas, M., Lawrence, R. T., El Debs, B., Selkrig, J., Typas, A., Santos, S D M, Beltrao, P. (2016). ***An atlas of human kinase regulation*****. Molecular Systems Biology, 12(12). DOI: 10.15252/msb.20167295**
This manuscript was an interdisciplinary study combining bioinformatics, modelling and experimental approaches to understand regulation of phosphorylation in human cells. The study also developed a computational method to derive activation of kinases from proteomics data. We helped validated our collaborators' methodology with imaging approaches and human embryonic stem cells.

Araujo AR., Gelens L., Sheriff RSM. and Santos SDM* (2016). ***Positive feedback keeps duration of mitosis temporally insulated from upstream cell cycle events*****. Molecular Cell 64, 362-375. DOI: 10.1016/j.molcel.2016.09.018**
This manuscript was our lab's first manuscript. It was an important discovery in the cell cycle field: that despite high variability in cell cycle dynamics in mammalian tissues, duration of mitosis is kept surprisingly constant. We described the molecular basis for this: positive feedback regulation in the networks that regulate the onset of mitosis and mitotic progression. The paper mirors well our interdisciplinary work, combining single cell imaging, mathematical modeling and omics approaches. The study is a collaboration with Dr Gelens, a long term collaborator from the University of Leuven in Belgium.