BIOGRAPHICAL SKETCH

NAME: Morsut, Leonardo

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

POSITION TITLE: Assistant Professor of Stem Cell Biology and Regenerative Medicine, and Biomedical Engineering

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Padova, Italy	B.S. & M.S.	1999 - 2004	Medical Biotechnologies
University of Padova, Italy	B.S.	2004 - 2012	Mathematics
University of Padova, Italy	Ph.D.	2007 - 2010	Developmental Biology
University of Padova, Italy	Postdoctoral	2010 - 2011	Mechanobiology
University of California, San Francisco	Postdoctoral	2012 - 2016	Synthetic Biology

A. Personal Statement

My research interests are to understand how complex behaviors in multicellular organisms are achieved as a consequence of cell-cell communication, both for application in regenerative and tumor medicine as well as fundamental understanding. I want to advance a new approach where I combine synthetic biology molecular tools with developmental biology, tissue engineering and engineered cell therapy in a “synthetic developmental biology” discipline.

My training and research experiences provide a favorable background expertise for a successful implementation of this new approach: I have a range of undergraduate and graduate training in multiple fields, from developmental biology to numerical simulations, from mechanobiology to cell signaling and synthetic biology.

In my graduate work, I demonstrated a molecular way in which cells interpret and respond to the nature of their mechanical environment, by identifying the transcription coactivators YAP/TAZ as nuclear relay of extracellular mechanical signals. This work opened the way to the study of how the physical environment shape cellular signaling and transcriptional responses. I studied the signaling in the mouse embryo as well, and the disrupting consequence of removing cell-autonomous negative regulation of morphogen interpretation.

In my postdoctoral training, I developed a new class of synthetic cell-cell contract receptors called synNotch, inspired by the natural Notch receptor that can be easily engineered so that upon recognition of nearly any surface ligand on a partner cell, the receptor will activate a modular transcriptional response. With these tools, I can link nearly any cell-cell contact interaction into a variety of desired responses in the receiver cell.

In my lab at USC I am working on several fronts to explore the potential of the “synthetic development” approach for the next generation of regenerative medicine and tumor therapy applications. Specific focus areas are: developing sensing and response pathways to engineer cells like macrophages for tumor therapy; development of novel synthetic mechanotransduction pathways.

Selected Publications

1. Dupont S*, Morsut L*, Aragona M, Enzo E, Giulitti S, Cordenonsi M, Zanconato F, Le Digabel J, Forcato M, Bicciato S, Elvassore N, Piccolo S. (2011). *Role of YAP/TAZ in mechanotransduction*. Nature, Jun 9;474(7350):179-183.

2. (PATENT) Lim W, Morsut L, Roybal K. *Binding-triggered transcriptional switches and methods of use thereof*. US 9670281 B2. University of California, San Francisco, Apr 12, 2016.

3. Morsut L, Roybal KT, Xiong X, Gordley RM, Coyle SM, Thomson M, Lim WA. (2016). *Engineering customized cell sensing and response behaviors using synthetic Notch receptors*. Cell Feb 11;164(4):780-91. Epub 2016 Jan 28.

4. (INVITED BOOK CHAPTER) Morsut L. (2017) Programming cells to build tissues with synthetic biology: a new pathway towards engineering development and regeneration. In “Regenerative Engineering and

Developmental Biology: Principles and Applications," edited by David M. Gardiner. CRC Press

5. (INVITED REVIEW) Morsut L. Nov 2017 *Engineering multicellular systems: synthetic biology approaches to tissue problems*. Current Opinion in Biomedical Engineering Dec 2017, (4) 163-173

Other publications

Roybal KT, Rupp LJ, Morsut L, Walker WJ, McNally KA, Park JS, Lim WA.
Precision Tumor Recognition by T Cells With Combinatorial Antigen-Sensing Circuits.
Cell 2016 Feb 11;164(4):770-9. Epub 2016 Jan 28.

Roybal KT, Williams JZ, Morsut L, Rupp LJ, Kolinko I, Choe JH, Walker WJ, McNally KA, Lim WA.
Engineering T Cells with Customized Therapeutic Response Programs Using Synthetic Notch Receptors.
Cell 2016 Oct 6;167(2):419-432.e16.

Gilbert, L.A., Larson, M.H., Morsut, L., Liu, Z., Brar, G.A., Torres, S.E., Stern-Ginossar, N., Brandman, O., Whitehead, E.H., Doudna, J.A., Lim, W.A., Weissman, J.S., Qi, L.S. *CRISPR-mediated modular RNA-guided regulation of transcription in eukaryotes*.
Cell 2013 154, 1-10.

Inui M, Manfrin A, Mamidi A, Martello G, Morsut L, Soligo S, Enzo E, Moro S, Polo S, Dupont S, Cordenonsi M, and Piccolo S.
USP15 is a deubiquitylating enzyme for receptor-activated SMADs.
Nature Cell Biology 2011 13: 1368-1375, Sep 25

Dupont S, Mamidi A, Cordenonsi M, Montagner M, Zacchigna L, Adorno M, Martello G, Stinchfield MJ, Soligo S, Morsut L, Inui M, Moro S, Modena N, Argenton F, Newfeld SJ, Piccolo S.
FAM/USP9x, a deubiquitinating enzyme essential for TGFbeta signaling, controls Smad4 monoubiquitination.
Cell 2009, 9; 136(1): 123-35, Jan

Martello G, Zacchigna L, Inui M, Montagner M, Adorno M, Mamidi A, Morsut L, Soligo S, Tran U, Dupont S, Cordenonsi M, Wessely O, Piccolo S.
MicroRNA control of Nodal signalling.
Nature 2007 449(7159): 183-8, Sep 13

Porzionato A, Macchi V, Morsut L, Parenti A, De Caro R.
Microvascular patterns in human medullary tegmentum at the level of the area postrema.
J Anat. 2005 206(4):405-10, Apr

B. Positions and Honors

Positions and Employment

2017 - Assistant Professor, Department of Stem Cell Biology and Regenerative Medicine, and Department of Biomedical Engineering, University of Southern California, Los Angeles, CA

Other Experience and Professional Memberships

2015- Member, Society for Developmental Biology (SDB)
2015- Member, Biomedical Engineering Society (BMES)
2016- Member of Organizing Committee, signature international conference on mammalian synthetic biology (mSBW), organized at MIT/BU

Honors

2004 Award for excellence in sport and education from the Italian Association (EISE)
2004 Academic seal for the outstanding curriculum and Final Master Thesis, University of Padova

2006 Competitive graduate fellowship granted by the Telethon Foundation (major Italian charity)
2007 Poster prize at the EMBO/FEBS advanced lecture course in Spetses, Greece
2010 Study Prize from Telethon Foundation
2010 University of Padova postdoctoral fellowship ("assegno di ricerca")
2012 European Molecular Biology Organization (EMBO) postdoctoral fellowship
2012 Human Frontiers Scientific Program (HFSP) long-term postdoctoral fellowship
2015 NIH/NIBIB K99/R00 Pathway to Independence Award

C. Contribution to Science

1. My PhD work was devoted to the study of morphogenetic signaling in the early mouse embryo. As a PhD student in Stefano Piccolo's lab at the University of Padova, Italy, I studied cell-cell communication signaling in the mouse embryo and the disrupting consequence of removing cell-autonomous negative regulation of morphogen interpretation. Cell-cell communication pathways are a key determinant of multicellular behavior. The way in which cells communicate with one another shapes every event of tissue formation and development. Specifically, during gastrulation, the three germ layers are generated thanks to sophisticated control over both the signaling and the response to morphogenetic signaling. With my graduate work on the knockout mouse for Ectodermin, an intracellular inhibitor of the TGF-beta/Smad4 pathway, I showed how removing an intracellular component of the response to growth factor stimuli completely impedes the formation of the three germ layers during mouse gastrulation. This work underscored the importance of morphogenetic interpretation during complex morphogenetic events, and contributed additional insights on the molecular roles of morphogenetic pathways signaling transducers in shaping morphogenetic responses.
   I performed this work during my graduate work in the Stefano Piccolo Lab, at the University of Padova, Italy; I designed experiments, performed them, analyzed data, and worked as first-author.
   a. Morsut L**,** Yan KP, Enzo E, Aragona M, Soligo SM, Wendling O, Mark M, Khetchoumian K, Bressan G, Chambon P, Dupont S, Losson R, Piccolo S. (2010). Negative control of Smad activity by Ectodermin/Tif1γ patterns the mammalian embryo. Development 137(15):2571-8, Aug 1

2. I studied stem cell behavior and discovered a molecular way in which cells interpret and respond to the nature of their mechanical environment, by identifying the transcription coactivators YAP/TAZ as nuclear relay of extracellular mechanical signals.
   A lot of phenomenological and molecular work was known at that time about the mechanotransduction effect on stem cells, but relatively little was known about the signaling pathways that cells use to read and respond to different mechanical environments (e.g. stiffness, geometrical confinement, etc.). In this work, we identified the transcription coactivators YAP/TAZ as both reader and effector of those mechanical stimuli, in mesenchymal stem cells, endothelial cells and mammary epithelial cells. This work added a key piece to the study of how the physical environment shapes cellular signaling and transcriptional responses. This is recognized as a cornerstone paper that started the study of YAP/TAZ in mechanotransduction, enabling discoveries in fields of developmental biology, cancer biology and morphogenesis.
   I performed this work in the Stefano Piccolo Lab, where I was staying after my PhD for a postdoctoral period. I developed a collaboration with bioengineers from the Nicola Elvassore group at the Engineering Department of the University of Padova. I designed and performed the experiments, acting as first author (indicated by equal contribution).
   a. Dupont S*, Morsut L*, Aragona M, Enzo E, Giulitti S, Cordenonsi M, Zanconato F, Le Digabel J, Forcato M, Bicciato S, Elvassore N, Piccolo S. (2011). Role of YAP/TAZ in mechanotransduction. Nature 474(7350): 179-183, Jun 9

3. In development, complex multicellular structures form based on genetically encoded algorithms that specify how cells will collectively interact and regulate each other's fates. To be able to constructively use this "programming language" we need to have synthetic biology tools to engineer the cells to modify their behavior. During my postdoctoral training, I developed a new class of synthetic cell-cell contract receptors called synNotch, inspired by the natural Notch receptor that can be easily engineered so that upon recognition of nearly any surface ligand on a partner cell, the receptor will activate a modular transcriptional response. With these tools, I can link nearly any cell-cell contact interaction to a variety of desired

responses in the receiver cell. We showed that the synNotch pathways do not crosstalk with native pathways or with each other, thus providing multiple novel channels for cell-cell communication. We show that these receptors can be used to flexibly construct new multi-cellular programs—they can direct localized differentiation, self-sorting behaviors and complex pattern formation in epithelial layers. This synthetic receptor platform represents a novel set of control points that the user can exploit to guide self-organization of multicellular ensembles in structural and functional tissues with user-defined high-level properties (e.g., shape, resistance to injury, regeneration).

The synNotch pathways were highlighted as Notable advances in the end of the year issue of Nature Medicine. They have attracted substantial interest from the academic world, being cited by several reviews (total of 75 citations as of September 2017). As a patent, it has been licensed to a startup company (CDL) that is working on optimizing its function for applications in immunotherapy.

Synthetic signaling pathways pave the way for more rational engineering of multicellular interactions, with applications in cell therapy for cancer, regenerative medicine, as well as basic understanding of tissue development principles.

In the work that describes the synthetic Notch pathway concept, I worked as first author, ideating the research and executing the experiments. For the application work on immunotherapy, I worked in collaborated with Kole Roybal, supporting the implementation of the synNotch system in immune cells.

a. Morsut L, Roybal KT, Xiong X, Gordley RM, Coyle SM, Thomson M, Lim WA. (2016). Engineering Customized Cell Sensing and Response Behaviors Using Synthetic Notch Receptors. Cell Feb 11;164(4):780-91. Epub 2016 Jan 28.
b. Roybal KT, Rupp LJ, Morsut L, Walker WJ, McNally KA, Park JS, Lim WA. (2016). Precision Tumor Recognition by T Cells With Combinatorial Antigen-Sensing Circuits. Cell Feb 11;164(4):770-9. Epub 2016 Jan 28.
c. Roybal KT, Williams JZ, Morsut L, Rupp LJ, Kolinko I, Choe JH, Walker WJ, McNally KA, Lim WA. (2016). Engineering T Cells with Customized Therapeutic Response Programs Using Synthetic Notch Receptors. Cell Oct 6;167(2):419-432.e16.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/50105771/

D. Additional Information: Research Support

Ongoing Research Support

R00 EB021030-03 Morsut (PI) 08/01/17 – 07/31/20
Engineering Synthetic Receptor Systems That Can Detect Specific Cell-Cell Contact
The goal of this study is to implement the synthetic Notch system developed during the K99 phase in stem cells to drive their differentiation to different lineages.
Role: PI

Completed Research Support

K99 EB021030-01 Morsut (PI) 08/1/15 – 01/31/17
Engineering Synthetic Receptor Systems That Can Detect Specific Cell-Cell Contact Signals
The goal of this study was to develop and characterize the synthetic Notch pathway as a way to engineer cells with novel input/output functions.

Human Frontiers Science Program (HFSP), long-term postdoctoral fellowship, 01/2013-08/2015
Optogenetic and synthetic biology study of developmental phenomena
The goal of this project was to explore synthetic biology approaches in multicellular mammalian contexts; this study was the foundation for the rationale underlying the invention of the synthetic Notch pathway.

European Molecular Biology Organization (EMBO), postdoctoral fellowship, 04/2012-01/2013
Study of new approaches to multicellular dynamics

The goal of this project was to explore multicellular dynamics with a combination of simulations and screening of effector genes