BIOGRAPHICAL SKETCH

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NAME: Morsut, Leonardo

eRA COMMONS USER NAME: MORSUT

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

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 training	2010 - 2011	Mechanobiology
University of California, San Francisco	Postdoctoral training	2012 - 2016	Synthetic Biology

A. Personal Statement

My research goals are to understand and control how complex behaviors in multicellular tissues are achieved as a consequence of cell-cell communication for applications in regenerative medicine. I am advancing a novel approach of "synthetic development" where I combine synthetic biology molecular tools with developmental biology, tissue engineering and computational biology for controlling complex tissue formation *in vitro* and *in vivo.*
In my lab at USC I am working on two main fronts: building tissues *in vitro*; using therapeutic cell interventions to reprogram degeneration (e.g. cartilage and bone degeneration, neurodegeneration, etc.) into regeneration.
We showed recently that we can design synthetic developmental trajectories in naïve fibroblasts using a combination of synthetic cell-cell communication pathways and changes in cell adhesion, to control multicellular structure formation, obtaining multilayered structures as well as polarized ones. We want to extend this to other structures, in particular hollow ones (spheres, tubes), as these are the building blocks of more complex tissues.
My training and research experiences provide a favorable background expertise for successful implementation of this new approach. I have a range of undergraduate and graduate training in multiple fields, from developmental biology to numerical simulations, and from mechanobiology to cell signaling and synthetic biology.
In my postdoctoral research, I developed a new class of synthetic cell-cell contract receptors called synNotch. Inspired by the natural Notch receptor, synNotch can be easily engineered to recognize nearly any surface ligand on a partner cell and activate a modular transcriptional response upon binding. With these tools, I can link nearly any cell-cell contact interaction to various desired responses in the receiver cell.
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 shapes cellular signaling and transcriptional responses. I also studied morphogenetic signaling in the mouse embryo, and the disrupting consequence of removing cell-autonomous negative regulation of morphogen interpretation.

Publications (selected)

1. Dupont S*, **Morsut L*,** Aragona M, Enzo E, Giulitti S, Cordenonsi, Zanconato, Le Digabel, Forcato, Bicciato, Elvassore, Piccolo. (2011). *Role of YAP/TAZ in mechanotransduction*. Nature, Jun 9;474(7350):179-183.
2. **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.
3. (INVITED REVIEW) Johnson MB, March AR, **Morsut L**. Engineering multicellular systems: using synthetic biology to control tissue self-organization. Curr Opin Biomed Eng. 2017 Dec;4:163-173.
4. Toda S, Blauch LR, Tang KYS, **Morsut L***, Lim W*. *Self-organized multiucellular structures programmed form engineered cell-cell signaling cascades*. Science, 162(July), p. eaat0271. doi: 10.1126/science.aat0271.

Talks (selected)

- EMBO/FEBS advanced lecture course: Molecular Mechanisms in Signal Transduction and Cancer. Island of Spetses, Greece, **Aug 2007**. *Ectodermin/Tif1*γ *is a critical negative regulator of TGF*-β *signaling*
- Eighth International Conference on Complex Systems, Boston Marriott, Quincy, MA, USA; **Jun 26 – Jul 1, 2011** *Spontaneous emergence of a new robustness motif in networks under intrinsic noise evolution*
- Bioengineering Research Group, University of Padova, host Professor Gianna Toffolo, **Feb 2012**. *From mechanotransduction to synthetic biology*
- Predictive Models for Biomedicine & Environment Unit, Bruno Kessler Foundation, host Cesare Furlanello, **Mar 2012**. *From mechanotransduction to synthetic biology*
- Society for Developmental Biology (SDB) regional meeting – Yosemite – **2017** *New tools to engineer cell-cell communication and development*
- Engineering Development **2017** meeting – EPFL, Lausanne Switzerland – *New approaches to engineering development through engineered cell-cell communications*
- Discovery Center Speaker Series – Thousand Oaks, **Jan 25 2018** - *Old, current and future ways to build tissues for human health*
- SEED 2018 (synthetic biology conference) – Scottsdale – **June 3 2018** – *Programming cells to build tissues*
- Micro and nano-technologies for medicine Conference – Los Angeles - **July 16-20 2018** – *New tools and approaches for controlling tissue development in the lab*
- Engineering Multicellular Self-Organization Conference – Cambridge, UK – **Sept 3-4 2018** – *Controlling morphogenesis via cell-cell signaling + adhesion*

B. Positions and Honors

Positions and Employment

2007 – 2010	PhD Student, Genetic and Molecular Biology of Development, University of Padova, Italy. (Advisor: Stefano Piccolo)
2010 – 2011	Postdoctoral Scholar, University of Padova, Italy. (Advisor: Stefano Piccolo)
2012 – 2017	Postdoctoral Fellow, University of California – San Francisco, USA. (Advisor: Wendell A. Lim)
2017 -	Assistant Professor, Department of Stem Cell Biology and Regenerative Medicine, and Department of Biomedical Engineering, University of Southern California, Los Angeles, CA
2018 -	Director, Center CIEBOrg: Center for Integrated Electronics and Biological Organisms, Viterbi School of 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 yearly 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. I studied stem cell behavior and discovered that the transcription coactivators YAP/TAZ are nuclear relays 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 used to read and respond to different mechanical environments (e.g. stiffness, geometrical confinement, etc.). In our 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 stem cell and developmental biology, regenerative medicine, and morphogenesis. It has been cited more than 1500 (Google Scholar).
   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

2. A common theme in multicellular self-organization of tissues is the use of cell-cell signaling networks to induce morphological changes. To be able to control this feature of cellular systems synthetically, we need to develop molecular tools and link them to networks in order to design developmental trajectories.
   During my postdoctoral training, I developed a new class of synthetic cell-cell contact receptors called synNotch. Inspired by the natural Notch receptor, the synNotch receptor can be easily engineered so that upon recognition of nearly any surface ligand on a partner cell, it can 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 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 cellular programs: from the selective detection and destruction of tumor cells, to neighbor-dependent induced differentiation.
   The synNotch pathways were highlighted as Notable advances in the end of the year issue of *Nature Medicine* (2016). They have attracted substantial interest from the academic world and, as a patent, has been licensed to a startup company (CDL, recently bought by Gilead Sciences) that is working on optimizing its function for applications in immunotherapy.

   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. (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.
   c. 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.
   d. 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.

3. In a subsequent project, I supervised postdoctoral scholar Satoshi Toda in the Wendell Lim Lab to use the modular synNotch juxtacrine signaling platform to engineer artificial genetic programs in which specific cell-cell contacts induced changes in cadherin cell adhesion. Despite their simplicity, these minimal intercellular programs were sufficient to achieve many hallmarks of natural developmental including robust self-organization into multi-layer structures, formation through sequential steps, divergence of cell types, symmetry breaking, and regeneration upon injury. The ordering power of these networks derives from interlinked cascades of signaling and morphological responses. Signal-induced spatial changes modify positional signals for individual cells leading to iterative cycles of cell fate branching. These results demonstrate the potential to engineer customized self-organizing tissues or materials.
   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. 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).

a. Toda S, Blauch LR, Tang KYS, Morsut L*, Lim W*. *Self-organized multiucellular structures programmed form engineered cell-cell signaling cascades*. *Science*, 162(July), p. eaat0271. doi: 10.1126/science.aat0271.
b. Johnson MB, March AR, **Morsut L**. (INVITED REVIEW) *Engineering multicellular systems: using synthetic biology to control tissue self-organization*. **Curr Opin Biomed Eng**. 2017 Dec;4:163-173.
c. **Morsut L**. *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** (September 1, 2017) (INVITED BOOK CHAPTER)

Complete list of publications link:
https://www.ncbi.nlm.nih.gov/sites/myncbi/leonardo.morsut.1/bibliography/50105771/public/?sort=date&direction=descending

D. Additional Information: Other Funding

Ongoing Research Support
Startup fund from the Department of Stem Cell Biology and Regenerative Medicine of USC

R00 EB021030-03 Morsut (PI) 08/01/17 – 04/31/20
750,000$ - 3 years
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 mouse embryonic stem cells to drive their differentiation to precursors of the different lineages (ectoderm, mesoderm, endoderm).
Role: PI

Completed Research Support
K99 EB021030-01 Morsut (PI) 08/1/15 – 01/31/17
250,000$ - 2 years
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
$184,000 - 3 years
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