BIOGRAPHICAL SKETCH
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NAME: Legant, Wesley R.

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

POSITION TITLE: Assistant Professor of Biomedical Engineering and 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	Completion Date	FIELD OF STUDY
Washington University, St. Louis, MO	B.S.	12/2005	Biomedical Engineering
University of Pennsylvania, Philadelphia, PA	Ph.D.	05/2012	Bioengineering
HHMI Janelia Research Campus, Ashburn, VA	Postdoctoral	12/2017	Optical Physics

A. Personal Statement

An overarching goal of my work is to answer challenging problems in cell biology through the development and application of novel technologies. Specifically, I aim to develop advanced, custom-built, optical microscopes and quantitative algorithms to study key aspects of cell migration and gene transcription with single molecule resolution and sensitivity. I will accomplish these goals by recruiting students in both engineering and biology programs, integrating them within a cohesive research program, and developing strong collaborations with experts in both mathematics and biology communities. Throughout my graduate and post-doctoral training, I have pursued teaching and outreach. In graduate school, I was awarded a Graduate Assistantship in Areas of National Need (GAANN) fellowship and took additional coursework in how to develop engineering-specific teaching methods for undergraduates. Although my post-doctoral training was at a private research institute, I remained committed to outreach activities by organizing microscopy workshops that were open to the outside community. I also manage an online forum (with >100 members) to aid graduate students and postdoctoral researchers at other institutes to replicate our microscope technologies in their own labs.

As an assistant professor at UNC, I am committed to training graduate students and postdoctoral researchers in a timely manner within a supportive and inclusive research environment. This includes mentoring in both experimental design, research methodology, and critical interpretation of experimental data. As part of my joint appointment in the Biomedical Engineering and Pharmacology departments, I provide a unique training environment that bridges both engineering and biology disciplines and will ensure that students are well positioned to transition to careers in today's interdisciplinary biomedical workforce.

1. Chen, B.C.*, **Legant, W.R.***, Wang, K.*, Shao L., Milkie, D.E., Davidson, M.W., Janetopoulos, C., Wu, X. S., Hammer, J. A., Liu, Z., English, B. P., Mimori-Kiyosue, Y., Romero, D. P., Ritter, A. T., Lippincott-Schwartz, J., Fritz-Laylin, L., Mullins, R. D., Mitchell, D. M., Bembenek, J. N., Reymann, A. C., Bohme, R., Grill, S. W., Wang, J. T., Seydoux, G., Tulu, U. S., Kiehart, D. P., Betzig, E., Lattice light-sheet microscopy: imaging molecules to embryos at high spatiotemporal resolution. Science 346, 1257998 (Oct 24, 2014). PMCID: PMC4336192, ***equal contribution**

2. **Legant, W.R.**, Shao, L., Grimm, J.B., Brown, T., Milkie, D.E., Avants, B., Lavis, L.D., Betzig, E., High density three-dimensional localization microscopy across large volumes. Nature Methods. 13(4): 359-365 (April 2016), PMCID: PMC4889433

3. **Legant, W.R.,** Miller, J.S., Blakely, B.L., Cohen, D.M., Genin, G.M., Chen, C.S., Measurement of mechanical tractions exerted by cells in three-dimensional matrices. Nature Methods 7, 969 (Dec, 2010). PMCID: PMC3056435

4. **Legant, W.R.**, Pathak, A., Yang, M.T., Deshpande, V.S., McMeeking, R.M., Chen, C.S., Microfabricated tissue gauges to measure and manipulate forces from 3D microtissues. Proceedings of the National Academy of Sciences of the United States of America 106, 10097 (Jun 23, 2009), PMCID: PMC2700905

B. Positions and Honors

Positions and Employment

2005-2006 Research Scientist, InVivo Sciences LLC, St. Louis, MO
2006-2012 Graduate Student, Dept. of Bioengineering, University of Pennsylvania, Philadelphia, PA
2011-2012 Whitaker International Fellow, Dept. of Biologically Oriented Materials, ETH, Zurich, Switzerland
2012-2015 Postdoctoral Associate, HHMI Janelia Research Campus, Ashburn, VA
2015-2017 Research Scientist, HHMI Janelia Research Campus, Ashburn, VA
2018- Assistant Professor, Departments of Biomedical Engineering and Pharmacology, University of North Carolina, Chapel Hill

Other Experience and Professional Membership

2005 Teaching Assistant for Quantitative Physiology course, Washington University, St. Louis
2009 Teaching Assistant for Cells to Tissues Bioengineering Course, University of Pennsylvania
2010 Co-chair, Gordan-Kenan Research Seminar, Signal Transduction by Engineered ECMs
2016 Organizer, Lattice light sheet microscopy workshop, Janelia Research Campus

Honors

2002-2005 Calvin M. Woodward Fellow (1/2 tuition, 4 years at Washington University in St. Louis)
2006 Valedictorian and Graduation Speaker (Washington University in St. Louis)
2006-2007 Graduate Assistance in Areas of National Need Fellowship
2007-2010 National Science Foundation Graduate Research Fellowship
2011-2012 Whitaker International Fellowship
2015 Newcomb Cleveland Prize for most outstanding research article in the journal Science
2019 Searle Scholars Program - Searle Scholar Award
2019 Arnold and Mabel Beckman Foundation - Beckman Young Investigator Award
2019 National Institute of Health – New Innovator Award
2019 David and Lucile Packard Foundation – Packard Fellow

C. Contribution to Science

1. **Microfabricated cell cultures.** In my undergraduate and early graduate work, I generated microfabricated cell culture platforms to measure and manipulate the forces that arise during tissue remodeling. Although larger, centimeter-scale, engineered tissue constructs had been used for many years, miniaturization via microfabrication permitted simultaneous control and microscopic measurement of cellular forces and extracellular events such as matrix remodeling. This work further enabled high throughput measurements of hundreds of constructs in parallel. We used this system to investigate the effects of matrix and boundary rigidity on the contractile force and protein expression in model cardiac and skin tissues. With funding from the Whitaker International Fellowship, I worked for one year in Viola Vogel's group at ETH Zurich to combine this system with fluorescent biosensors and determined how mechanical forces lead to changes in extracellular matrix protein conformation and signaling. In total, this contribution was significant because it was one of the first microfabricated "organ on chip" systems. This platform was awarded a US patent for drug screening using microfabricated cardiac tissue constructs, was the basis for the formation of a startup company, was rapidly adopted by other group members and outside collaborators, and has enabled research and publications in diverse areas of biology and engineering.

    a. Marquez, J.P.*, **Legant, W.R.***, Lam, V., Cayemberg, A., Elson, E., Wakatsuki, T., High-throughput measurements of hydrogel tissue construct mechanics. Tissue Engineering. Part C, Methods 15, 181 (Jun, 2009). PMCID: PMC2819830, ***equal contribution**

b. **Legant, W.R.**, Pathak, A., Yang, M.T., Deshpande, V.S., McMeeking, R.M., Chen, C.S., Microfabricated tissue gauges to measure and manipulate forces from 3D microtissues. Proceedings of the National Academy of Sciences of the United States of America 106, 10097 (Jun 23, 2009), PMCID: PMC2700905

c. **Legant, W.R.**, Chen, C.S., Vogel, V., Force-induced fibronectin assembly and matrix remodeling in a 3D microtissue model of tissue morphogenesis. Integrative biology: quantitative biosciences from nano to macro 4, 1164 (Oct, 2012). PMCID: PMC3586566

d. Chen, C.S., Margulies, K., Boudou, T., **Legant**, **W.R.,** Yang, M.T., "In vitro microphysiological system for high throughput 3D tissue organization and biological function." U.S. Patent 9,512,396, issued December 6, 2016.

2. **Precision measurements of 3D cellular forces.** In my later graduate work, I combined novel biomaterials, 3D imaging, and mathematical modeling to perform first-of-their-kind measurements of the forces that cells use to drive their migration through a 3D matrix. Such "traction force microscopy" had been developed and applied previously to cells grown on flat planar substrates and has been a key technique to aid in models of cell migration. However, extending these 2D measurements quantitatively into 3D matrices was a long standing and critical challenge in the field. Overcoming this challenge required the generation of a synthetic linearly elastic hydrogels that would support both cell adhesion and invasion as well as new advances in finite element modeling and linear inverse source solutions. Together, I used these materials and methods to describe the role of matrix rigidity and adhesiveness on angiogenic sprouting (a), to quantify the forces cells exert as they spread and invade into a 3D matrix (b), to demonstrate that cells exert rotational torques about cell-matrix contacts (c), and to study the requirement for matrix remodeling in stem cell differentiation (d). This work was significant because it combined advances in biomaterials, imaging, and mathematical modeling to reveal diverse roles for mechanical forces in physiologically relevant 3D settings.

   a. Miller, J.S., Shen, C.J., **Legant, W.R.**, Baranski, J.D., Blakely, B. L., Chen, C.S., Bioactive hydrogels made from step-growth derived PEG-peptide macromers. Biomaterials 31, 3736 (May, 2010). PMCID: PMC2837100

   b. **Legant, W.R.,** Miller, J.S., Blakely, B.L., Cohen, D.M., Genin, G.M., Chen, C.S., Measurement of mechanical tractions exerted by cells in three-dimensional matrices. Nature Methods 7, 969 (Dec, 2010). PMCID: PMC3056435

   c. **Legant, W.R.***, Choi, C.K.*, Miller, J.S., Shao, L., Gao, L., Betzig, E., Chen, C.S., Multidimensional traction force microscopy reveals out-of-plane rotational moments about focal adhesions. Proceedings of the National Academy of Sciences of the United States of America 110, 881 (Jan 15, 2013). PMCID: PMC3549134, ***equal contribution**

   d. Khetan, S., Guvendiren, M., **Legant, W.R**., Cohen, D.M., Chen, C.S., Burdick, J.A., Degradation-mediated cellular traction directs stem cell fate in covalently crosslinked three-dimensional hydrogels. Nat. Mater. 12, 458–465 (2013). PMCID: PMC3633615

3. **Light sheet and super-resolution microscopy:** In my postdoctoral work, I worked closely with a small team of scientists to pioneer groundbreaking techniques in super-resolution and light sheet microscopy. Specifically, we developed the lattice light sheet microscope which dramatically increases speed and reduces phototoxicity compared to confocal or widefield microscopes. We used this instrument both in diffraction-limited and super-resolution imaging modalities to investigate specimens ranging in size from single molecules to small embryos. Since our initial demonstration of the technique, I have worked together on many collaborative projects to develop additional computational analysis and to apply this instrument to address fundamental problems in cell biology and gene transcription. This work was significant because it described the theory, development and implementation of a new microscope that greatly expands our ability to study cells in 3D settings. This work was awarded several US patents (on which I am a co-inventor), has been commercially licensed, and has been rapidly adopted by other groups throughout the world. To support

these efforts, I have organized build workshops at Janelia, videos of which are freely available online, and I manage an online user forum (with over 100 members) where people share troubleshooting and build tips. As part of this proposal, I will continue to build these resources by freely sharing developments for our new microscope, image analysis, and microfluidic devices. In my ongoing research, I am further developing these systems together with microfabricated cell culture platforms to study the mechanisms that cells use to migrate through complex 3D environments.

a. Chen, B.C.*, **Legant, W.R.***, Wang, K.*, Shao L., Milkie, D.E., Davidson, M.W., Janetopoulos, C., Wu, X. S., Hammer, J. A., Liu, Z., English, B. P., Mimori-Kiyosue, Y., Romero, D. P., Ritter, A. T., Lippincott-Schwartz, J., Fritz-Laylin, L., Mullins, R. D., Mitchell, D. M., Bembenek, J. N., Reymann, A. C., Bohme, R., Grill, S. W., Wang, J. T., Seydoux, G., Tulu, U. S., Kiehart, D. P., Betzig, E., Lattice light-sheet microscopy: imaging molecules to embryos at high spatiotemporal resolution. Science 346, 1257998 (Oct 24, 2014). PMCID: PMC4336192, ***equal contribution,** *awarded the Newcomb Cleveland prize for most outstanding article published that year in the journal Science.*

b. **Legant, W.R.**, Shao, L., Grimm, J.B., Brown, T., Milkie, D.E., Avants, B., Lavis, L.D., Betzig, E., High density three-dimensional localization microscopy across large volumes. Nature Methods. 13(4): 359-365 (April 2016), PMCID: PMC4889433

c. Liu, Z, **Legant, W.R.,** Chen, B.C., Li, L., Grimm, J.B., Lavis, L.D., Betzig, E., Tjian, R., 3D imaging of Sox2 enhancer clusters in embryonic stem cells. eLife. 2014; 3:e04236. PMCID: PMC4381973

d. Valm, A.M.*, Cohen, S.*, **Legant, W.R.**, Melunis, J., Hershberg, U., Wait, E., Cohen, A.R., Davidson, M.W., Betzig, E. Lippincott-Schwartz, J., Applying systems-level spectral imaging and analysis to reveal the organelle interactome. Nature 546, 7656 (Jun 1, 2017). PMCID: PMC5536967, *equal contribution

Complete List of Published Work in My Bibliography, NCBI:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1B_plcl_WnV5q/bibliography/42378457/public/?sort=date&direction=ascending