Key Personnel Biographical Sketch

BIOGRAPHICAL SKETCH

NAME: Teruel, Mary, Nunez

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

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date	FIELD OF STUDY
University of Pennsylvania, Philadelphia,PA	B.S.	05/1985	Mechanical Engineering
Stanford University, Stanford, CA	M.S.	06/1989	Aeronautical Engineering
Stanford University, Stanford, CA	Ph.D.	01/1996	Aeronautical Engineering
Duke University, Durham, NC	Postdoctoral	01/1998-01/2000	Cell Biology

A. Personal Statement

I am very experienced working at the interface of engineering, medicine, and biology to design, build, and implement new technology and analysis tools to understand fundamental principles in cell signaling and differentiation, especially in the context of obesity, diabetes, cardiovascular disease, and cancer. As an independent investigator, I worked with my group members to successfully develop the first quantitative robust targeted mass spectrometry methodology and analysis tools to quantitatively measure adipogenesis and adipocyte function, as well as molecular tools such as adipocyte cell lines with endogenously-tagged PPARG and CEBPB and fluorescence imaging approaches that can – for the first time – allow differentiation to be quantitatively measured live in thousands of single cells over the multi-day timecourse of adipogenesis. My laboratory also developed the first quantitative molecular model of fat cell differentiation. Below are examples of papers my laboratory has published:

1. Ahrends R, Ota A, Kovary KM, Kudo T, Park BO, Teruel MN. (2014). Controlling low rates of cell differentiation through noise and ultra-high feedback. ***Science.*** Jun 20; 344:1384-9. PMID: 24948735. *Awarded an Editors' Choice rating by the Science magazine signaling editors.*
2. Park BO, Ahrends R, Teruel MN. (2012). Consecutive positive feedback loops create a bistable switch that controls preadipocyte to adipocyte conversion. ***Cell Reports.*** Oct 25; 2(4): 976-90. Epub 2012 Oct. 11. PMID: 23063366.
3. Abell E*, Ahrends R*, Bandara S, Park BO, Teruel MN. (2011). Parallel adaptive feedback enhances reliability of the Ca2+ signaling system. ***Proc Natl Acad Sci U S A***. Aug 30;108(35):14485-90. *equal contribution. *Awarded a "Must Read" and "Exceptional" rating by the Faculty of 1000.*
4. Ota A, Kovary KM, Wu OH, Ahrends R, Costa MJ, Shen W, Feldman BJ, Kraemer FB, Teruel MN. (2015). Using SRM mass spectrometry to profile nuclear protein abundance differences between adipose tissue depots of insulin resistant mice. ***Journal of Lipid Research.*** May; 56(5):1068-78. PMID: 25840986.

B. Positions and Honors

Positions and Employment

1985 - 1986 Helicopter Structural Test Engineer, Kaman Aerospace Corporation, Bloomfield, CT.
1986 - 1987 Test Engineer, Kronos Incorporated, Waltham, MA.
1988 Research Assistant with Prof. Peter Banks, Dept. of Electrical Engineering, Stanford University. Shuttle Electrodynamic Tether System Project.
1988 - 1989 Research Assistant with Prof. Robert MacCormack, Dept. of Aeronautics & Astronautics, Stanford University. Computation of Hypersonic Duct Flow.

1989 - 1995	Research Assistant with Prof. John Eaton, NASA Ames Research Center and the Dept of Mechanical Engineering, Thermosciences Division, Stanford University.
1995 -1998	Microscopy Engineer, Dept. of Cell Biology, Duke University, Durham, NC.
1998 - 2000	Postdoctoral Fellow, Dept. of Cell Biology, Duke University, Durham, NC.
2001 - 2005	Microscopy, Imaging, and Analysis Consultant for the Alliance for Cellular Signaling.
2001 - 2007	Senior Research Scientist, Dept. of Molecular Pharmacology, Stanford University.
2007 - 2009	Visiting Scientist with Professor Ruedi Aebersold, Institute for Molecular Systems Biology, ETH Zürich, Zürich, Switzerland.
2007 - 2011	Senior Research Scientist, Dept. of Chemical and Systems Biology, Stanford University.
Nov. 2011-	Assistant Professor (tenure-track), Dept. of Chemical and Systems Biology, Stanford University, Stanford, CA.
Nov. 2011-	Member of the Stanford Cardiovascular Institute
July 2013-	Co-Investigator and Director of the Technology Core, Stanford NIH Center for Systems Biology (P50)
May 2014-	Member of the Stanford Cancer Institute
May 2015-	Faculty Fellow, Stanford Institute for Chemistry, Engineering, and Medicine for Human Health (CHEM-H)
Nov 2016-	Assistant Professor (By courtesy), Dept. of Bioengineering, Stanford University, Stanford, CA.

Honors

1989 – 1993	National Air and Space Administration (NASA) Graduate Student Fellowship
1998 - 2001	National Institutes of Health Postdoctoral Fellowship
2000 - 2006	National Institutes of Health (NGHRI) Quantitative Mentored Career Development Award
2007	Biochemical Journal Young Investigator Award
2013 – present	Stanford Gabilan Fellow

C. Contribution to Science

1. **Adipogenesis / PI3K signaling / Insulin resistance**

I have been studying adipogenesis and adipocyte function for 15 years now, beginning with developing a very sensitive total-internal reflection microscopy approach to for the first time measure glucose transporter translocation and PI3K signaling simultaneously in single adipocyte cells (Tengholm, Teruel,..., ***Science Signaling,*** 2003) and with a particular emphasis on understanding PIP3-signaling that regulates insulin action and glucose uptake capability (Park,...Teruel, ***Molecular Cell,*** 2007). Defects in adipogenesis and adipocyte function are highly implicated in causing insulin resistance and diabetes, and because of this, I have focused a great deal of effort in the lab into understanding the molecular mechanisms that control adipogenesis. We succeeded in developing the first quantitative molecular model of adipogenesis and uncovering the protein network architecture that controls adipogenesis (Ahrends,...,Teruel, ***Science***, 2014). I have a strong interest in understanding how to restore adipogenesis and adipocyte function as a means of treating in insulin resistance. My lab has developed novel targeted proteomics approaches that will allow us to validate our in vitro findings, as well as identify new mechanisms, in mouse models and in human patients (Ota,...,Teruel, ***Journal of Lipid Research***, 2015).

a) Tengholm A, Teruel MN, Meyer T. (2003). Single cell imaging of PI3-kinase activity and glucose transporter insertion into the plasma membrane by dual color evanescent wave microscopy. ***Science Signaling.*** Feb 11; (169):PL4. PMID:12582202.

b) Park WS, Heo WD, Whalen JH, O'Rourke NA, Bryan HM, Meyer T, Teruel MN. (2008). Identification of PIP3-regulated proteomes from C.elegans to human by model prediction and live imaging. ***Molecular Cell.*** May 9;30(3):381-92. PMID:18471983

c) Ahrends R, Ota A, Kovary KM, Kudo T, Park BO, Teruel MN. (2014). Controlling low rates of cell differentiation through noise and ultra-high feedback. ***Science.*** Jun 20; 344:1384-9. PMID: 24948735.

d) Ota A, Kovary KM, Wu OH, Ahrends R, Costa MJ, Shen W, Feldman BJ, Kraemer FB, Teruel MN. (2015). Using SRM mass spectrometry to profile nuclear protein abundance differences between adipose tissue depots of insulin resistant mice. ***Journal of Lipid Research.*** May; 56(5):1068-78. Epub Apr 3. PMID: 25840986.

2. **Spatial-temporal control of cell signaling**

Experiments by myself and others started to suggest that cell signaling was very dynamic and built on rapid and reversible diffusion and co-localization of proteins and second messengers as opposed to the historic "hardwired signaling concept" where receptors and other signaling proteins stay largely in place. I then started to delve deeper into developing microscopy approaches and GFP-based biosensors to track signaling processes in space and time in order to dissect the dynamic mechanisms in signal transmission and to gain a spatial and temporal understanding of intracellular signal transduction that would not be possible by using biochemical approaches.

a) Teruel MN, Meyer T. (2000). Translocation and reversible localization of signaling proteins: a dynamic future for signal transduction. ***Cell.*** Oct 13;103(2):181-4. PMID:11057890.

b) Oancea E, Teruel MN, Quest AF, Meyer T. (1998). GFP-tagged cysteine-rich domains from Protein Kinase C as fluorescent indicators for diacylglycerol signaling in living cells. ***J Cell Biol.*** Feb 9;140(3):485-98. PMID: 9456311.

c) Teruel MN, Chen W, Persechini A, Meyer T. (2000). Differential codes for free Ca2+-calmodulin signals in nucleus and cytosol. ***Curr Biol.*** Jan 27;10(2):86-94. PMID:10662666.

d) Codazzi F, Teruel MN, Meyer T. (2001). Control of Astrocyte Ca2+ Oscillations and Waves by Oscillating Translocation and Activation of Protein Kinase C. ***Curr Biol.*** Jul 24;11(14):1089-97. PMID:11509231

2. **Development of highly-parallel fluorescence microscopy and mass-spectrometry approaches to - systematically and on a large-scale - quantitate signaling network parameters in mammalian cells**

As we described in our review (Meyer and Teruel, 2003, ***Trends in Cell Biology***), it became more and more apparent that the historic concept of linear signaling pathways was an anachronism and that instead signaling components were highly dynamics and connected together in networks full of cross-talk and feedback loops. There was a critical need to develop new approaches to quantitatively measure the dynamics of multiple signaling parameters on a large scale in single-cell. I helped to address this need by developing microscopy approaches such as the one described in Teruel and Meyer (***Science,*** 2002) and targeted mass spectrometry approaches (Abell,...,Teruel, ***PNAS,*** 2011; Ahrends,...,Teruel, ***Science,*** 2014) that could systematically quantitate protein translocation and abundance changes on the network level. My laboratory also developed and applied targeted mass spectrometry approaches to quantitate phosphorylation stoichiometry, protein complex formation, as well as lipid droplet composition, as described in other publications listed in MyBibliography.

a) Meyer T, Teruel MN. (2003). Fluorescence imaging of signaling networks. ***Trends Cell Biol.*** Feb;13(2):101-6. PMID:12559761.

b) Teruel MN, Meyer T. (2002). Parallel single cell monitoring of receptor-triggered membrane translocation of a calcium sensing protein module. ***Science.*** Mar 8;295(5561):1910-2. PMID:11884760. *Awarded an "Editors' Choice" rating by the Science Magazine signaling editors.*

c) Abell E, Ahrends R, Bandara S, Park BO**,** Teruel MN. (2011). Parallel adaptive feedback enhances reliability of the Ca2+ signaling system. ***Proc Natl Acad Sci U S A***. Aug 30;108(35):14485-90. Epub 2011 Aug 15. *Awarded a "Must Read" and "Exceptional" rating by the Faculty of 1000.*

d) Ahrends R, Ota A, Kovary KM, Kudo T, Park BO, Teruel MN. (2014). Controlling low rates of cell differentiation through noise and ultra-high feedback. ***Science.*** Jun 20; 344:1384-9. PMID: 24948735. *Awarded an Editors' Choice rating by the Science magazine signaling editors.*

3. **Uncovering feedback loop architecture in signaling and transcriptional networks**

Using the experimental methods that we developed (described above), together with computational modeling, my laboratory was able to identify that multiple parallel adaptive feedback loops allow cells to transmit signals correctly despite large cell-to-cell variations in the concentrations of individual signaling proteins. We first focused our attention on the ubiquitous and fundamental calcium signaling system (Abell,...Teruel, ***PNAS*** 2011). We also identified the network architecture that controlled adipogenesis and could permit low rates of terminal cell differentiation (Park,...Teruel, ***Cell Reports,*** 2012; Ahrends,...,Teruel, ***Science,*** 2014). I listed the fourth paper below to illustrate that I am also very willing to develop molecular tools as needed to

understand signaling networks. In this paper (Galvez, Teruel,..., ***Genome Biology***, 2007), I played a big role in developing the molecular biology protocols to make diced pool siRNA libraries and to use them successfully to carry out screening to identify signaling modules in mammalian cells.

a) Abell E, Ahrends R, Bandara S, Park BO, Teruel MN. (2011). Parallel adaptive feedback enhances reliability of the Ca2+ signaling system. ***Proc Natl Acad Sci U S A***. Aug 30;108(35):14485-90. Epub 2011 Aug 15.

b) Park BO, Ahrends R, Teruel MN. (2012). Consecutive positive feedback loops create a bistable switch that controls preadipocyte to adipocyte conversion. ***Cell Reports.*** Oct 25; 2(4): 976-90. Epub 2012 Oct. 11. PMID: 23063366

c) Ahrends R, Ota A, Kovary KM, Kudo T, Park BO, Teruel MN. (2014). Controlling low rates of cell differentiation through noise and ultra-high feedback. ***Science.*** Jun 20; 344:1384-9. PMID: 24948735.

d) Galvez T, Teruel MN, Heo WD, Jones JT, Kim ML, Liou J, Myers JW, Meyer T. (2007). An siRNA screen of the signaling proteome identifies the PI3K-mTOR signaling pathway as a regulator of transferrin uptake. ***Genome Biol.*** 8(7):R142. PMID: 17640392.

4. **Understanding how noise controls low rates of cell differentiation**

This study addresses the question of how organisms control the rate of terminal cell differentiation. The answer to this question is of fundamental importance to all multicellular organisms that have to create and maintain organs and tissues of defined size. We addressed this question using adipocyte differentiation since it is arguably one of the most accessible experimental systems for investigating terminal differentiation in mammalian cells. Understanding adipogenesis also has great medical relevance since defects in adipogenesis underlie obesity, insulin resistance, diabetes, and cardiovascular disease.

Precursor cells in adult mammalian tissues differentiate at very low rates; for example, only 10% of adipocytes (fat cells) are replaced per year. If all precursor cells responded to the same threshold of stimulus, these low rates would not be possible. Noise in the system (variability in the abundance of key proteins in different cells) could allow only a few cells to differentiate, but then such variability would allow dedifferentiation as well, which is not observed. Here we used computational modeling and protein measurements in single cells to show that multiple feedback loops in the regulatory circuits, along with noise, can allow both stable and infrequent differentiation. These results provide a conceptual framework of how organisms use noise to effectively control low rates of differentiation without sacrificing the robustness of the differentiated state. The results of this study will likely have broad relevance to all terminal differentiation processes including those in cardiac, neuronal, and other tissues.

a) Ahrends R, Ota A, Kovary KM, Kudo T, Park BO, Teruel MN. (2014). Controlling low rates of cell differentiation through noise and ultra-high feedback. ***Science.*** Jun 20; 344:1384-9. PMID: 24948735.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1xSIwjyqjuoQG/bibliography/40592858/public/?sort=date&direction=ascending

SELECTED INVITED LECTURES

March 2011	U.S. Human Proteome Organization (HUPO) Annual Meeting, Raleigh, NC.
August 2011	U.C. Berkeley, Dept. of Nutritional Science and Toxicology, Berkeley. CA.
March 2012	U.S. Human Proteome Organization (HUPO) Annual Meeting, San Francisco, CA.
July 2012	Kern Lipid Conference on Systems Biology, Lipidomics and Cardiometabolic Diseases, Aspen, CO.
November 2012	EMBL Symposium: From Functional Genomics to Systems Biology, Heidelberg, Germany.
November 2012	Uppsala University, Department of Medical Cell Biology, Uppsala, Sweden.
June 2013	International Conference on the Systems Biology of Disease, German Cancer Institute, Heidelberg, Germany.
August 2013	Quantitative Biology (q-bio) 2013 Conference on Cellular Information Processing, St. Johns College, Santa Fe, NM.
October 2013	University of Chicago, Institute of Genomics and Systems Biology, Chicago, IL.
February 2014	Second Annual Winter Quantitative Biology (q-bio) Conference, Kona, Hawaii.

June 2014	Sanofi/Aventis, Frankfurt, Germany.
July 2014	NIH National Centers for Systems Biology Annual Meeting, San Diego, CA.
October 2014	Cell Symposia: Systems Approach to Metabolic Diseases, Chicago, IL.
December 2015	American Society of Cell Biology Annual Meeting, Philadelphia, PA.
February 2015	Third Annual Winter Quantitative Biology (q-bio) Conference, Maui, Hawaii.
March 2015	Society for Developmental Biology, West Coast Meeting, Yosemite, CA.
April 2015	EMBO|EMBL Symposium: Cellular Heterogeneity: Role of Variability and Noise in Biological Decision Making, Heidelberg, Germany.
April 2015	Friedrich Miescher Institute (FMI) for Biomedical Research, Basel, Switzerland.
May 2015	Program in Vascular Biology, UCLA, Los Angeles, CA.
July 2015	International Conference on the Systems Biology of Disease, German Cancer Institute, Heidelberg, Germany.
August 2015	EMBO workshop on Cell and Developmental Systems, Arolla, Switzerland.
September 2015	14th Human Proteome Organization World Congress – HUPO 2015, Session on Protein Networks and Systems Biology, Vancouver, Canada.
October 2015	Keystone Symposium on Diabetes: New Insights into Molecular Mechanisms and Therapeutic Strategies, Kyoto, Japan.
November 2015	Dept. of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, Georgia.
December 2015	American Society of Cell Biology (ASCB) Annual Meeting, Minisymposium on Signaling and Differentiation, San Diego, CA.
February 2016	Biophysical Society Annual Meeting, Symposium on Synthetic Biology and Systems Biology, Los Angeles, CA.
June 2016	Japanese Society of Cell Biology Annual Meeting, Kyoto, Japan.
July 2016	q-bio 2016: Quantitative and Systems Biology in Nashville Conference, Nashville, TN.
October 2016	Biozentrum/University of Basel, Basel, Switzerland.
October 2016	University of Mississippi Medical Center, Jackson, MS.
November 2016	NIH/NIDDK Workshop on the Adipose Tissue Niche, Bethesda, MD.
November 2017	Stanford Regenerative Medicine (ReMS) Seminar, Stanford, CA.
January 2017	UCSF/Gladstone Institutes Seminar, UC San Francisco, San Francisco, CA.
January 2017	Keystone Symposia on Obesity and Adipose Tissue Biology, Keystone, CO.
February 2017	Fifth Annual Winter Quantitative Biology (q-bio) Conference, Kauai, Hawaii.
April 2017	Stanford Diabetes Research Symposium, Stanford, CA.
May 2017	1st Latin-American Systems Biology Conference, Mexico City, Mexico.
November 2017	Institute of Systems Biology and Dept. of Biomedical Engineering, Yale University, New Haven, CT.
January 2018	Dept. of Systems Biology, Harvard University, Cambridge, MA.
February 2018	Institute of Genomics and Systems Biology, University of Chicago, Chicago, IL.
March 2018	SysBio 2018: 8th Advanced Lecture Course on Systems Biology, Innsbruck, Austria.
March 2018	Dept. of Cell Biology/Institute of Cell Dynamics, Johns Hopkins University, Baltimore, MD.

D. Research Support

Stanford BioX Seed Grant Teruel (PI) 10/1/14-9/30/18
"Hormonal control of fat cell differentiation"

NIH 1 R01 DK106241 Teruel (PI) 8/1/15-7/31/19
"Controlling tissue size by noise and feedback"

NIH 1 RO1 DK101743 Teruel (PI) 2/1/15-1/31/19
"Controlling the rate of terminal cell differentiation: experiments and theory"

NIH 1 P50 GM107615-01 Ferrell (PI) 7/1/13 – 6/30/18
Role: Co-Investigator and Director of the Technology Core
"Systems Biology of Collective Cell Decisions"
The overarching aim of this Center is to understand the systems-level basis for cellular decision-making in the interrelated processes of proliferation, migration, and differentiation.