BIOGRAPHICAL SKETCH

NAME: Teruel, Mary

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date	FIELD OF STUDY
Duke University, Durham, NC	Postdoctoral	12/2000	Cell Biology
Stanford University, Stanford, CA	Ph.D.	01/1996	Aeronautical Engineering
Stanford University, Stanford, CA	M.S.	08/1989	Aeronautical Engineering
University of Pennsylvania, Philadelphia, PA	B.S.	05/1985	Mechanical Engineering

A. Personal Statement

The overarching goal of my research is to understand the dynamic control principles underlying cell differentiation, a process of fundamental importance for creating, maintaining, and repairing tissues and organs in all multicellular organisms. My laboratory merges mathematics and engineering with experimental validation of theories using *in vitro* and *in vivo* cell differentiation models. We use adipogenesis (fat cell differentiation) as an experimentally accessible *in vitro* model system that is also of great medical relevance since defects in adipogenesis and adipocyte function underlie the current worldwide epidemics in obesity, insulin resistance, diabetes, and cardiovascular disease. We have developed endogenously-tagged cell lines, microfluidics, and targeted mass spectrometry methods to make this system uniquely useful to study cell differentiation. We are uncovering general principles of how cell-to-cell variability (noise), feedback, and thresholds control cell differentiation processes and are particularly interested in how oscillating hormonal stimuli, which cells experience physiologically, control differentiation rates. Finally, we validate our *in vitro* results in mouse models in order to facilitate translating our basic science findings into potential therapies to treat human patients for diseases arising from defects in cell differentiation and to optimize tissue regeneration. Below are examples of papers my laboratory has published:

1. Bahrami-Nejad Z*, Zhao ML*, Tholen S, Hunderdosse D, Tkach KE, van Schie S, Chung M, and **Teruel MN.** (2018). A transcriptional circuit filters oscillating circadian hormonal inputs to regulate fat cell differentiation. ***Cell Metabolism*** Apr 3, 27(4):854-868.e8. *equal contribution. *Highlighted in **Nature, NIH Research Matters,** and by the **Faculty of 1000**.*

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. 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 signaling editors of **Science.***

4. Kovary KM, Taylor B, Zhao ML, and **Teruel MN.** (2018). Expression variation impairs analog and enables binary signaling control. ***Molecular Systems Biology*** May 14;14(5):e7997. PMID: 29759982.

B. Positions and Honors

Positions and Employment

2017- present Member of the NIH P50 Stanford Diabetes Research Center

2015 - present Faculty Fellow, Stanford Institute for Chemistry, Engineering, and Medicine for Human Health (CHEM-H)

2014 - present Member of the Stanford Cancer Institute

2013 - present	Co-Investigator and Director of the Technology Core, Stanford NIH Center for Systems Biology (P50)
2012 - present	Member of the Stanford Cardiovascular Institute
2012 - present	Assistant Professor, Dept. of Chemical & Systems Biology, Stanford University, Stanford, CA.
2007 - 2011	Senior Research Scientist, Dept. of Chemical & Systems Biology, Stanford University.
2007 - 2009	Visiting Scientist with Professor Ruedi Aebersold, Institute for Molecular Systems Biology, ETH Zürich, Zürich, Switzerland.
2001 - 2007	Senior Research Scientist, Dept. of Molecular Pharmacology, Stanford University.
2001 - 2005	Microscopy, Imaging, and Analysis Consultant for the Alliance for Cellular Signaling.
1998 - 2000	Postdoctoral Fellow, Dept. of Cell Biology, Duke University, Durham, NC.
1995 -1998	Microscopy Engineer, Dept. of Cell Biology, Duke University, Durham, NC.
1989 - 1995	Research Assistant with Prof. John Eaton, NASA Ames Research Center and the Dept of Mechanical Engineering, Thermosciences Division, Stanford University.
1988 - 1989	Research Assistant with Prof. Robert MacCormack, Dept. of Aeronautics & Astronautics, Stanford University. Computation of Hypersonic Duct Flow.
1988	Research Assistant with Prof. Peter Banks, Dept. of Electrical Engineering, Stanford University. Shuttle Electrodynamic Tether System Project
1986 - 1987	Test Engineer, Kronos Incorporated, Waltham, MA.
1985 - 1986	Helicopter Structural Test Engineer, Kaman Aerospace Corporation, Bloomfield, CT

Honors

2018	Recipient of the Stanford McCormick/Gabilan Award given to a faculty member at Stanford for their work in supporting the mentoring, training and encouragement of women pursuing the study of medicine, in teaching medicine, and engaging in medical research.
2018	Recipient of the inaugural Diabetes Knowledge Award (DKA) awarded by the Stanford Diabetes Research Center for the most impactful, original diabetes-related publication from Stanford in 2017-2018.
2013 – present	Stanford Gabilan Fellow
2007	Biochemical Journal Young Investigator Award
2000 - 2006	National Institutes of Health (NGHRI) Quantitative Mentored Career Development Award
1998 - 2001	National Institutes of Health Postdoctoral Fellowship
1989 – 1993	National Air and Space Administration (NASA) Graduate Student Fellowship

B. Contribution to Science

1. Adipogenesis / PI3K signaling / Insulin resistance

I have a deep interest that my basic science findings can someday be used to treat human disease, and this is a main motivation for my focus on adipogenesis and adipocyte function since defects in these lead to insulin resistance, diabetes, cardiovascular disease, and many types of cancer. My work in the adipocyte field includes my development of a sensitive total-internal reflection (TIRF) 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 on using bioinformatics and fluorescence imaging to comprehensively identify proteins downstream of PI3K signaling which regulates insulin action and glucose uptake capability (Park,...Teruel, ***Molecular Cell,*** 2007). In a series of papers, my laboratory developed and experimentally validated the first quantitative molecular model, based on stochastic differential equations, explaining how adipocyte progenitor cells undergo terminal differentiation, and how mammalian cells can adjust the fraction of cells that differentiate (Park,...,Teruel, ***Cell Reports*** 2012; Ahrends,...,Teruel, ***Science***, 2014; Bahrami-Nejad,...,Teruel, ***Cell Metabolism***, 2018). My lab has also developed novel targeted proteomics approaches that allow us to validate our in vitro findings, as well as to identify new regulatory mechanisms, in mouse models and in human patients (Ota,...,Teruel, ***Journal of Lipid Research***, 2015). Of note, our recent paper, Bahrami-Nejad et al (***Cell Metabolism,*** 2018) won the inaugural Diabetes Knowledge Award awarded by the Stanford Diabetes Center for the most impactful, original diabetes-related publication from Stanford in

2017-2018 and also was chosen by the NIH National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) to be highlighted in ***NIH Research Matters***.

a) 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

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) Khor VK, Ahrends R, Shen W, Cortez Y, **Teruel MN,** Salman A, and Kraemer FB. (2014). The proteome of cholesteryl-ester-enriched versus triacylglycerol-enriched lipid droplets. ***Plos One***. Aug 11; 9(8):e105047. PMID: 25111084.

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.

Our findings have opened up several areas of research in my lab including to understand 1) how the different feedbacks identified in our earlier papers can be used to restore insulin sensitivity and normal adipocyte differentiation and function under insulin resistant conditions, and 2) the molecular mechanisms and timing underlying the systemic insulin resistance, significant fat mass increase, and adipocyte dysfunction that occurs in mice when circadian glucocorticoid oscillations are lost.

2. Oscillatory Control of Cell Differentiation and Tissue Regeneration

Glucocorticoid and other differentiation-inducing hormones are secreted in mammals in circadian oscillations. Loss of this circadian oscillation pattern during stress and disease correlates with increased fat mass and obesity in humans, raising the intriguing question of how hormone secretion dynamics affect the process of adipocyte differentiation. In Bahrami-Nejad *et al* (***Cell Metabolism,*** 2018), we used live, single-cell imaging of the key adipogenic transcription factors CEBPB and PPARG, endogenously tagged with fluorescent proteins, and discovered that pulsatile circadian hormone stimuli are rejected by the adipocyte differentiation control system. In striking contrast, equally strong persistent signals trigger maximal differentiation. We identify the mechanism of how hormone oscillations are filtered as a combination of slow and fast positive feedback centered on PPARG. Furthermore, we confirmed in mice that flattening of daily glucocorticoid oscillations significantly increases the mass of subcutaneous and visceral fat pads. Our results provide a molecular mechanism for why stress, Cushing's disease, and other conditions for which glucocorticoid secretion loses its pulsatility may lead to obesity. Given that oscillating hormones are ubiquitous in mammals, the temporal filtering mechanism we discovered likely represents a general principle for the control of cell differentiation.

Bahrami-Nejad Z*, Zhao ML*, Tholen S, Hunderdosse D, Tkach KE, van Schie S, Chung M, and **Teruel MN.** (2018). A transcriptional circuit filters oscillating circadian hormonal inputs to regulate fat cell differentiation. ***Cell Metabolism*** Apr 3, 27(4):854-868.e8. *equal contribution. *Highlighted in* ***Nature,*** *the* ***Faculty of 1000, and NIH Research Matters***.

Our findings have opened up several areas of research in my lab including to understand 1) how cell-intrinsic cell cycle and circadian clock oscillators interact or are entrained by cell-external hormonal oscillations to gate cell differentiation, 2) how phase-shifts and memory of different physiological hormone oscillations such as insulin and cAMP-inducing signals cause such a profound effect on adipogenesis, and 3) how loss of the oscillatory glucocorticoid pattern, such as would happen due chronic stress or irregular sleep schedules, results in adipose-specific cell differentiation and hypertrophy *in vitro* and *in vivo*.

3. Identifying and modulating noise to control mammalian cell fate-decisions

The advent of single cell approaches has made it clear that noise (cell-to-cell variability) is inherent in all cell populations, but how noise originates, propagates, and affects cell signaling outcome has been largely unexplored. Our goal is to identify and understand the different mechanisms that can be used to stabilize noisy signaling systems and how noise can be modulated to resolve the conflict that noise is harmful for analog signaling but at the same time is needed for robust control of binary cell-fate decision signaling. In Abell *et al*, **(*PNAS,*** 2011), we applied a novel combined mass spectrometry and modeling strategy to the calcium signaling system to understand how eukaryotic cells can prevent signaling failure despite the inherent noise in expression of individual signaling components. In Ahrends *et al* (***Science***, 2014), we used computational modeling and

quantitative proteomics to show that noise, combined with multiple feedback loops in the regulatory circuits, enables the stable and infrequent differentiation required to homeostatically maintain tissue size. In Shi *et al* (***Molecular Cell***, 2017), we developed a quantitative mass spectrometry approach to understand variation in ribosomal composition in stem cells. In Kovary *et al* (***Molecular Systems Biology*****,** 2018), we developed single-cell mass spectrometry and imaging strategies to more accurately measure the variation of proteins between individual cells and found it to be much less than has been assumed in the literature. We discovered that covariation provides a key mechanism for fractional activation of population-level binary signaling outputs and were able to use our results to develop a model of how covariance and number of pathway components can be used to increase the variation in a signaling system in order to balance opposing needs for low noise in accurate single-cell analog signaling and high noise for accurate population-level binary signaling.

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. *Awarded a "Must Read" and "Exceptional" rating by the Faculty of 1000.*

b) 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 signaling editors of* ***Science.***

c) Shi Z, Fujii K, Kovary KM, Genuth NR, Röst HL, **Teruel MN**, Barna M. (2017). Heterogeneous Ribosomes Preferentially Translate Distinct Subpools of mRNAs Genome-wide. ***Molecular Cell*** Jul 6;67(1):71-83.e7. Epub 2017 Jun 15. PubMed PMID: 28625553.

d) Kovary KM, Taylor B, Zhao ML, and **Teruel MN.** (2018). Expression variation impairs analog and enables binary signaling control. ***Molecular Systems Biology*** May 14;14(5):e7997. PMID: 29759982.

Our findings have opened up several areas of research in my lab including to understand how different system architectures (i.e. double negative versus positive feedback) or how modulating dynamic inputs (i.e. phase-shifting orthogonal oscillating hormonal signals) can be advantageously used with noise to optimally control particular cell fate decisions such as to increase the fraction of differentiated cells or to enable de-differentiation).

4. **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 I described in earlier reviews (Teruel and Meyer, ***Cell,*** 2000 and Meyer and Teruel, ***Trends in Cell Biology,*** *2003*), the historic concept of linear signaling pathways is an anachronism and that signaling components need to be considered to be highly dynamic and connected together in networks full of cross-talk and feedback loops. This argues that there is a critical need to develop new approaches to quantitatively measure the dynamics of multiple signaling parameters on a large scale in single-cell. In one strategy, I addressed 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 can 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 (i.e. Ahrends et al, ***Methods Mol. Biol.,*** 2015; Niewiadomski et al, ***Cell Reports,*** 2015; Shi et al, ***Molecular Cell,*** 2017; Khor et al, ***Plos One,*** 2014; Chu et al, ***J. Biol. Chem.,*** 2013).

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

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

c) **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.*

d) Ahrends R, Niewiadomski P, **Teruel MN,** Rohatgi R. (2015). Measuring Gli2 phosphorylation by selected reaction monitoring mass spectrometry. ***Methods Mol Biol.*** 1322:105-23. PMID: 26179043.

My lab is very skilled at developing technology as needed to address important open questions in cell signaling. Our most recent technology focus has been to develop custom fluidic devices that can be used together with longterm, multi-day fluorescence imaging to understand how oscillatory hormonal dynamics can control cell differentiation. We have built custom devices since we cannot use standard PDMS-based microfluidics for many

of our applications due to the hydrophobic nature of many hormones and small molecules we are studying, which would mean they would leach into the PDMS. The dynamic stimulus protocols we are able to apply longterm with our custom devices are also proving very useful for uncovering negative and positive feedbacks, as well as other system architecture timing and structure parameters.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40592858/?sort=date&direction=descending

SELECTED INVITED LECTURES

November 2019	ICSB 2019 - 20th International Conference on Systems Biology, Chair and speaker of session on "Developmental Systems Biology", Okinawa, Japan.
October 2019	University of Cincinnati and Cincinnati Children's Hospital Research Foundation
June 2019	Gordon Research Conference on Developmental Biology, Mount Holyoke, MA.
April 2019	University of Chicago, Committee on Molecular Metabolism and Nutrition Program (Students' Choice, invited by the graduate students in the program), Chicago, IL.
March 2019	CHSL Meeting on Systems Biology: Networks, Cold Spring Harbor, NY.
February 2019	2019 Winter Qbio Meeting, Oahu, Hawaii
January 2019	Keystone Symposia on Signal Dynamics and Signal Integration in Development and Disease, Keystone, CO.
January 2019	University of Southern California (USC), Molecular & Computational Biology Program, Los Angeles, CA.
January 2019	Boston University, Dept. of Biomedical Engineering, Boston, MA
January 2019	Boston University, Dept. of Biochemistry, Boston, MA.
December 2018	Weill-Cornell School of Medicine, Dept. of Biochemistry, New York City, NY.
December 2018	American Society of Cell Biology (ASCB) Annual Meeting, Session on Systems and Synthetic Biology of Decoding Complex Cellular Rhythms, San Diego, CA.
December 2018	University of Michigan, Dept. of Biomedical Engineering, Ann Arbor, MI.
December 2018	UC Santa Cruz; Dept. of Molecular, Cell, and Developmental Biology; Santa Cruz, CA.
October 2018	UC Berkeley, Dept. of Bioengineering, Berkeley. CA.
July 2018	Green Center for Systems Biology and Dept. of Cell Biology, UT Southwestern, Dallas, TX.
July 2018	CSHL Course on Single Cell Analysis, Cold Spring Harbor, NY.
July 2018	The Francis Crick Institute, London, England.
May 2018	Quantitative Biology Seminar Series, UC San Diego, San Diego, CA. "Students' Choice". Invited by the graduate students in the UCSD Quantitative Biology PhD program.
May 2018	Solvay Workshop on "Dynamics of biological systems: Modelling genetic, signaling and microbial networks", The International Solvay Institutes, Brussels, Belgium.
March 2018	Dept. of Cell Biology/Institute of Cell Dynamics, Johns Hopkins University, Baltimore, MD.
February 2018	SysBio 2018: 8th Advanced Lecture Course on Systems Biology, Innsbruck, Austria.
January 2018	Dept. of Systems Biology, Harvard University, Cambridge, MA.
January 2018	Institute of Genomics and Systems Biology, University of Chicago, Chicago, IL.
November 2017	Institute of Systems Biology and Dept. of Biomedical Engineering, Yale University, New Haven, CT.
May 2017	1st Latin-American Systems Biology Conference, Mexico City, Mexico.
April 2017	Stanford Diabetes Research Symposium, Stanford, CA.
February 2017	Fifth Annual Winter Quantitative Biology (q-bio) Conference, Kauai, Hawaii.
January 2017	Keystone Symposia on Obesity and Adipose Tissue Biology, Keystone, CO.
January 2017	UCSF/Gladstone Institutes Seminar, UC San Francisco, San Francisco, CA.
November 2016	NIH/NIDDK Workshop on the Adipose Tissue Niche, Bethesda, MD.
October 2016	University of Mississippi Medical Center, Jackson, MS.August 2015 EMBO workshop on Cell and Developmental Systems, Arolla, Switzerland.
October 2016	Biozentrum/University of Basel, Basel, Switzerland.
July 2016	q-bio 2016: Quantitative and Systems Biology in Nashville Conference, Nashville, TN.
September 2015	14th Human Proteome Organization World Congress – HUPO 2015, Session on Protein Networks and Systems Biology, Vancouver, Canada.

June 2016	Japanese Society of Cell Biology Annual Meeting, Kyoto, Japan.
February 2016	Biophysical Society Annual Meeting, Symposium on Synthetic Biology and Systems Biology, Los Angeles, CA.
December 2015	American Society of Cell Biology (ASCB) Annual Meeting, Minisymposium on Signaling and Differentiation, San Diego, CA.
November 2015	Dept. of Biomedical Engineering, Georgia Tech and Emory University, Atlanta, Georgia.
October 2015	Keystone Symposium on Diabetes: New Insights into Molecular Mechanisms and Therapeutic Strategies, Kyoto, Japan.
July 2015	International Conference on the Systems Biology of Disease, German Cancer Institute, Heidelberg, Germany.
May 2015	Program in Vascular Biology, UCLA, Los Angeles, CA.
April 2015	Friedrich Miescher Institute (FMI) for Biomedical Research, Basel, Switzerland.
April 2015	EMBO|EMBL Symposium: Cellular Heterogeneity: Role of Variability and Noise in Biological Decision Making, Heidelberg, Germany.
March 2015	Society for Developmental Biology, West Coast Meeting, Yosemite, CA.
February 2015	Third Annual Winter Quantitative Biology (q-bio) Conference, Maui, Hawaii.
December 2015	American Society of Cell Biology Annual Meeting, Philadelphia, PA.
October 2014	Cell Press Symposia: Systems Approach to Metabolic Diseases, Chicago, IL
July 2014	NIH National Centers for Systems Biology Annual Meeting, San Diego, CA.
June 2014	Sanofi/Aventis, Frankfurt, Germany.
February 2014	Second Annual Winter Quantitative Biology (q-bio) Conference, Kona, Hawaii.
October 2013	University of Chicago, Institute of Genomics and Systems Biology, Chicago, IL.
August 2013	Quantitative Biology (q-bio) 2013 Conference on Cellular Information Processing, St. Johns College, Santa Fe, NM.
June 2013	International Conference on the Systems Biology of Disease, German Cancer Institute, Heidelberg, Germany.
November 2012	Uppsala University, Department of Medical Cell Biology, Uppsala, Sweden.
November 2012	EMBL Symposium: From Functional Genomics to Systems Biology, Heidelberg, Germany.
July 2012	Kern Lipid Conference on Systems Biology and Cardiometabolic Diseases, Aspen, CO.
March 2012	U.S. Human Proteome Organization (HUPO) Annual Meeting, San Francisco, CA.

D. Research Support

NIH 1 R01 DK106241 Teruel (PI) 6/1/15-5/31/20
"Controlling tissue size by noise and feedback"

NIH 1 RO1 DK101743 Teruel (PI) 2/1/15-1/31/20
"Controlling the rate of terminal cell differentiation: experiments and theory"

NIH RO1- DK114217 Feldman (PI) 7/1/18-6/30/22
"Integrated Systemic and Adipose Depot-Specific Regulation of Adipogenesis"
Role: Co-Investigator

Stanford BioX Seed Grant Teruel (PI) 10/1/14-9/30/19
"Hormonal control of fat cell differentiation"

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"