BIOGRAPHICAL SKETCH

NAME**: Abdelfattah, El Ouaamari**

eRA COMMONS USER NAME: **ELOUAAMARI**

POSITION TITLE**: Assistant Professor in Medicine**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Nice Sophia-Antipolis, France	B.S.	06/2003	Biochemistry
University of Nice Sophia-Antipolis, France	M.S.	06/2005	Life & Health Sciences
University of Nice Sophia-Antipolis, France (PI: Emmanuel Van Obberghen, MD; PhD)	Ph.D.	12/2009	Molecular & Cellular Biology
Joslin Diabetes Center, Harvard University, MA (PI: Rohit N. Kulkarni, MD; PhD)	Research Fellow	2010-2013	Islet Cell & Regenerative Medicine
Joslin Diabetes Center, Harvard University, MA (PI: Rohit N. Kulkarni, MD; PhD)	Research Associate	2013-2017	Islet Cell & Regenerative Medicine

A. Personal Statement

My laboratory (http://elouaamari.org) employs a multidisciplinary approach to unravel the cells, molecules and signaling pathways that regulate the regeneration, survival and function of islet β cells. Throughout my training from graduate school to the postdoctoral fellowship, I produced a body of work centered on islet β-cell biology. My laboratory has extensive experience with a variety of techniques ranging from biochemistry, molecular and cellular biology, mouse genetics and biological imaging to primary co-culture systems, physiology and animal surgery. Our current approach is to use recently developed techniques in neurobiology, molecular neuroscience, single-cell RNA sequencing and proteomics to deconstruct and reconstruct the biological basis of peripheral nerve-dependent regeneration and function of islet β cells and the overall physiological role of vago-islet intercommunication in energy homeostasis. This is a new research direction in my group and in the islet field, and benefits from the tremendous expertise of two neuroscientists co-Is: Drs. Zhiping Pang and Mark Rossi. The studies presented in this application are unprecedented and employ transformative approaches, which, if successful, will shed light on opportunities that can be harnessed for developing neuromodulation- and neuropharmacology-based therapies for individuals with compromised pancreatic β cells.

Ongoing research support:

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El Ouaamari (PI)
07/28/20–06/30/25
Sensory Neuromodulation of Pancreatic β Cells

R01DK131452
El Ouaamari (Co-I)
07/01/22–06/30/27
Synaptic and circuitry mechanisms of central GLP-1 signaling in energy balance

Relevant citations:

1. McEwan S, Kwon H, Tahiri A, Shanmugarajah N, Cai W, Ke J, Huang T, Belton A, Singh B, Wang L, Pang Z, Dirice E, Engel EA and **El Ouaamari A**. Deconstructing the Origins of Sexual Dimorphism in Sensory Modulation of Pancreatic β Cells. *Molecular Metabolism*. 2021; May 21; 53:101260. PMCID: PMC8258979
2. Bou Karam J, Cai W, Mohamed R, Huang T, Meng L, Homan EP, Dirice E, Kahn CR, **El Ouaamari A**. TRPV1 Neurons Regulate β-Cell Function in a Sex-Dependent Manner. *Molecular Metabolism*. 2018; Oct 5; 18:60-67. PMCID: PMC6308974

B. Positions, Scientific Appointments, and Honors

Academic Appointments

2017- Assistant Professor, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ
2013-2017 Instructor in Medicine, Harvard Medical School, Boston, MA

Professional Memberships

2020- Member of the Einstein-Mount Sinai Diabetes Research Center
2018- Member of the Human Islet Research Network
2017- Member of the Penn Diabetes Research Center
2017- Associate Member of the Cancer Institute of New Jersey
2015- Associate Member of the Boston Nutrition Obesity Research Center Jersey
2012- Member of the European Association of the Study of Diabetes
2009- Member of the Francophone Society of Diabetes

Awards and Honors

2019 New Jersey Alliance for Clinical and Translational Science Pilot Award
2019 Charles and Johanna Busch Biomedical Research Grant Award
2019 New Jersey Health Foundation Research Grant Award
2018 Human Islet Research Network New Investigator Pilot Award
2017 Juvenile Diabetes Research Foundation Transition Award
2017 Harvard University Distinction in Teaching Award
2016 Nutrition Obesity Research Center-Harvard Pilot and Feasibility Award
2016 Joslin Diabetes Center Outstanding Research Award
2015 Danish Diabetes Academy Young Investigator Travel Grant Award
2014 Juvenile Diabetes Research Foundation Advanced Postdoctoral Fellowship
2011-2014 Francophone Society of Diabetes Young Investigator Travel Grant Award
2011 American Diabetes Association Young Investigator Travel Grant Award
2010 Francophone Society of Diabetes Research Fellowship
2008 Medical Research Foundation Research
2006 French League against Cancer Research Fellowship

Review activities

2022 Ad-Hoc Grant Reviewer, NIH/NIDDK—Special Emphasis Panel ZDK1 GRB-S (J2)
2021 Ad-Hoc Grant Reviewer, NIH/NCCIH—Special Emphasis Panel ZAT1 JM (12)
Ad-Hoc Grant Reviewer, Utah Diabetes and Metabolism Research Center
Ad-Hoc Grant Reviewer, NIH/NIDDK—Physiology of Obesity and Metabolic Disease
2020 Ad-Hoc Grant Reviewer, NIH/NIDDK—Cellular Aspects of Diabetes and Obesity
2020 Ad-Hoc Grant Reviewer, NRMN Utah Grant Writing Coaching Group
2015 Ad-Hoc Grant Reviewer, Agence Nationale de la Recherche
2015 Ad-Hoc Grant Reviewer, Baker Fund Committee

2015- Ad-Hoc Journal Reviewer, Nature Metabolism, Nature Communications, eLife, PNAS, Molecular Metabolism, American Journal of Physiology-Endocrinology and Metabolism, PLOS One, Journal of Cellular Physiology, Journal of Molecular Biology, Journal of Molecular Endocrinology and Trends in Endocrinology and Metabolism.

2013 Guest Editor, *International Journal of Endocrinology*
2022 Book Editor, *Nanotechnology for Diabetes Management*, Royal Society of Chemistry.

C. Contributions to Science

Identification of novel β-cell growth factors: The expansion of insulin-secreting β-cell pool in prediabetic and insulin-resistant states is a remarkable feature that allows delaying and/or preventing the onset of diabetes in adult rodents and humans. During my postdoctoral training student (Joslin Diabetes Center, PI: Rohit N. Kulkarni, MD; PhD), I focused on understanding how pancreatic β cells adapt to insulin resistance insults with an emphasis on identifying circulating molecules and signaling pathways enhancing growth and/or function of islet β cells. First, I reported that islet β cells undergo major structural and functional changes in response to high demands of insulin [1]. Second, I discovered that liver-derived circulating non-neuronal molecules play an important role in compensatory β-cell response [2]. Finally, I identified a FoxO1-regulated SerpinB1 as a novel β-cell growth factor in models of insulin resistance [3, 4]. This body of work was significant in that it unraveled a new class of molecules that can be leveraged to enhance healthy growth of insulin-secreting cells for patients with diabetes.

1. **El Ouaamari A**, Zhou JY, Liew CW, Shirakawa J, Dirice E, Gedeon N, Kahraman S, De Jesus DF, Bhatt S, Kim JS, Clauss TR, Camp DG 2nd, Smith RD, Qian WJ, Kulkarni RN. Compensatory Islet Response to Insulin Resistance Revealed by Quantitative Proteomics. *Journal of Proteome Research*. 2015; Aug 7; 14(8):3111-3122. PMCID: PMC4615688
2. **El Ouaamari A**, Kawamori D, Dirice E, Liew CW, Shadrach JL, Hu J, Katsuta H, Hollister-Lock J, Qian WJ, Wagers AJ, Kulkarni RN. Liver-derived Systemic Factors Drive β Cell Hyperplasia in Insulin-Resistant States. *Cell Reports*. 2013; Feb 21; 3(2):401-10. PMCID: PMC3655439
3. **El Ouaamari A**, Dirice E, Gedeon N, Hu J, Zhou JY, Shirakawa J, Hou L, Goodman J, Karampelias C, Qiang G, Boucher J, Martinez R, Gritsenko MA, De Jesus DF, Kahraman S, Bhatt S, Smith RD, Beer HD, Jungtrakoon P, Gong Y, Goldfine AB, Liew CW, Doria A, Andersson O, Qian WJ, Remold-O'Donnell E, Kulkarni RN. SerpinB1 Promotes Pancreatic β Cell Proliferation. *Cell Metabolism*. 2016; Jan 12; 23(1):194-205. PMCID: PMC4715773
4. **El Ouaamari A**, O-Sullivan I, Shirakawa J, Basile G, Zhang W, Roger S, Thomou T, Xu S, Qiang G, Liew CW, Kulkarni RN, Unterman TG. Forkhead Box Protein O1 (FOXO1) Regulates Hepatic Serine Protease Inhibitor B1 (serpinB1) Expression in a Non-Cell-Autonomous Fashion. *Journal of Biological Chemistry*. 2019; Jan 18; 294(3):1059-1069. PMCID: PMC6341384

Identification of pancreatic signaling pathways for β-cell regeneration: The pancreas contains several cellular and molecular signals that contribute to β-cell expansion. Insulin itself has been described as mitogenic for β cells—but the molecular mechanism of insulin-induced β-cell proliferation is not known. In collaboration with Dr. Jun Shirakawa, we identified a new FoxM1/PLK1/CENP-A pathway that regulates insulin-stimulated mitotic cell-cycle progression in mouse and human β cells [1]. With Dr. Hannah Welters, we demonstrated that the expression of PPARγ β cells is dispensable for normal and adaptive β-cell replication and function [2]. More recently, I collaborated with Dr. Ercument Dirice to show that pancreatic ductal cells constitute, during extreme insulin demand, an extra reserve for β-cell regeneration through a mechanism of differentiation/neogenesis [3]. These studies are of utmost relevance because they shed light on additional targets that can be harnessed, within the pancreas, to increase functional β-cell mass.

1. Shirakawa J, Fernandez M, Takatani T, **El Ouaamari A**, Jungtrakoon P, Okawa ER, Zhang W, Yi P, Doria A, Kulkarni RN. Insulin Signaling Regulates the FoxM1/PLK1/CENP-A Pathway to Promote Adaptive Pancreatic β Cell Proliferation. *Cell Metabolism*. 2017; 25, 868-882. PMCID: PMC5382039
2. Welters HJ, **El Ouaamari A**, Kawamori D, Meyer J, Hu J, Smith DM, Kulkarni RN. Rosiglitazone Promotes PPARγ-Dependent and -Independent Alterations in Gene Expression in Mouse Islets. *Endocrinology*. 2012; 153, 4593-4599. PMCID: PMC3512010
3. Dirice E, De Jesus DF, Kahraman S, Basile G, Ng RWS, **El Ouaamari A**, Teo AK, Bhatt S, Hu J, Kulkarni RN. Human Duct Cells are a Source of β-Cell Reserve in the Compensatory Response to Insulin Resistance. *JCI insight*. 2019; 4(8):e99576. PMCID: PMC6538348

Deconstructing organ-islet intercommunication in β-cell regeneration: Current diabetes translational research capitalizes on integrative physiology and systems biology to identify β-cell trophic factors. Over the last few years, I have collaborated with several investigators to identify new sources of such molecules. Within the Joslin Diabetes Center, I worked with Drs. Jeremie Boucher and C. Ronald Kahn and showed that ablation of insulin/IGF1 receptors in adipose tissue in mice results in lipodystrophy phenotype associated with β-cell

hyperplasia [1], thus indicating adipocytes as a direct source of β-cell growth repressors or indirect intermediates in larger organ crosstalk regulating β-cell replication. With Drs. Garima Singhal and Eleftheria Maratos-Flier, we demonstrated that the endocrine growth factor FGF21 reduces β-cell growth *in vivo* [2]. Together, these studies provided clues on how organ-organ crosstalk can be manipulated to expand or limit the β-cell pool size.

1. Boucher J, Softic S, **El Ouaamari A**, Krumpoch MT, Kleinridders A, Kulkarni RN, O'Neill BT, Kahn CR. Differential Roles of Insulin and IGF-1 Receptors in Adipose Tissue Development and Function. *Diabetes*. 2016; 65, 2201-2213. PMCID: PMC4955980
2. Singhal G, Fisher FM, Chee MJ, Tan TG, **El Ouaamari A**, Adams AC, Najarian R, Kulkarni RN, Benoist C, Flier JS Maratos-Flier, E. Fibroblast Growth Factor 21 (FGF21) Protects against High Fat Diet-Induced Inflammation and Islet Hyperplasia in Pancreas. *PLoS One*. 2016; 11, e0148252. PMCID: PMC4752212

Identification of new targets enhancing β-cell regeneration in type 1 diabetes: Although immune cells are, generally, considered detrimental to islet health, studies have reported the occurrence of β-cell replication concomitant with initial immune cell infiltration prior to the onset of type 1 diabetes. The nature of the immune factors contributing to β-cell replication in this particular context is unknown. In collaboration with Dr. Ercument Dirice, we set out to reveal the underpinnings of this biology. Using *in vivo* models and *in vitro* co-culture systems, we demonstrated the ability of T cells to increase β-cell proliferation and identified secretory molecules mediating these mitogenic effects [1]. With Dr. Dirice, we revealed that simulation of β-cell proliferation early in life prevents the development of type 1 diabetes in genetically susceptible mice [2]. Together, these data highlight the possibility of β-cell replenishment in type 1 diabetes despite sustained autoimmunity.

1. Dirice E, Kahraman S, Jiang W, **El Ouaamari A**, De Jesus DF, Teo AK, Hu J, Kawamori D, Gaglia JL, Mathis D, Kulkarni RN. Soluble Factors Secreted by T Cells Promote β-Cell Proliferation. *Diabetes*. 2014; 63, 188-202. PMCID: PMC3868047
2. Dirice E, Kahraman S, De Jesus DF, **El Ouaamari A**, Basile G, Baker RL, Yigit B, Piehowski PD, Kim MJ, Dwyer AJ, Ng RWS, Schuster C, Vethe H, Martinov T, Ishikawa Y, Teo AK, Smith RD, Hu J, Haskins K, Serwold T, Qian WJ, Fife BT, Kissler S, Kulkarni RN. Increased β-Cell Proliferation Prior to Immune-Cell Invasion Prevents Progression of Type 1 Diabetes. *Nature Metabolism*. 2019; 5, 509-518. PMCID: PMC31423480

Characterization of the role of microRNAs in β-cell growth and function: My “encounter” with β cells took place at a very exciting time in RNA biology—the discovery of microRNAs and the advent of technologies to study their function. As a graduate student (University of Nice Sophia Antipolis, PI: Emmanuel Van Obberghen, MD; PhD), I sought to determine the physiological relevance of microRNAs in pancreatic β cells. As the protocols to quantify these molecules were not optimal at that time, my early experiments geared towards setting up a qPCR method to quantify microRNA precursors. I was the first to determine that microRNAs are physiologically regulated by glucose in insulin-producing INS-1 and MIN-6 cell lines are rat pancreatic islets. I worked particularly on miR-375, a microRNA discovered by the Stoffel Lab, known to be selectively expressed in pancreatic islets. I discovered that miR-375 downregulates the protein levels of PDK1, an important regulator of the insulin signaling pathway, and consequently regulates glucose-induced insulin secretion and β-cell proliferation [1].

1. **El Ouaamari A**, Baroukh N, Martens GA, Lebrun P, Pipeleers D, Van Obberghen E. miR-375 Targets 3'-Phosphoinositide-Dependent Protein Kinase-1 and Regulates Glucose-Induced Biological Responses in Pancreatic Beta-Cells. *Diabetes*. 2008; Oct; 57(10):2708-17. PMCID: PMC2551681

Complete list of published work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1N36msrj7ueAQ/bibliography/public/