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BIOGRAPHICAL SKETCH

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NAME: Galmozzi, Andrea

eRA COMMONS USER NAME: GALMOZZI

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Milan, Milan, Italy	B.S.	02/2006	Biotechnology
University of Milan, Milan, Italy	Ph.D.	12/2010	Biochemistry
Scripps Research, La Jolla, CA	Postdoctoral Fellow	10/2018	Chemical Physiology

A. Personal Statement

I am an Assistant Professor at the University of Wisconsin-Madison. My group studies the molecular basis of physiology and the transcriptional regulation of metabolism. During my training, I have used multiple experimental approaches, including mouse models, chemoproteomics, transcriptomics, metabolomics, phenotypic screenings, chemical and genetic tools, to describe new molecular pathways that may provide novel therapeutic avenues to treat metabolic disease. My previous work initially focused on understanding the role of histone deacetylases in the control of glucose and lipid metabolism in liver and skeletal muscle (*Galmozzi et al., Diabetes 2013*), and extended to cutting-edge chemoproteomic methods during my postdoctoral training at the Scripps Research Institute, where I carried out innovative studies that include the discovery of the poorly characterized protein Pgrmc2 as the first intracellular heme chaperone described in mammals and its critical role for adipocyte function (*Galmozzi et al., Nature 2019*), the generation of a proteome-wide map of protein ligandability using fully functionalized, traceable fragment probes (*Parker*, Galmozzi* et al., Cell 2017 – *co-first authors*), and the generation of the first reporter mouse to monitor in real-time the expression of Ucp1, a central component of the thermogenic machinery of brown and beige adipose tissue, in live animals, a model that allowed us to identify small molecules that increase Ucp1 expression in brown adipose tissue and enhance energy expenditure *in vivo* (*Galmozzi*, Sonne* et al., Cell Reports 2014 – *co-first authors*).
As an independent investigator, I intend to apply the expertise I have acquired on a wide range of experimental methodologies to understand adipose tissue pathophysiology in metabolic disorders, including obesity, type 2 diabetes, cancer-associated cachexia, and aging-related metabolic derangement.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

08/2021 – Associate Director, Mouse Phenotyping & Surgery Core, UW Comprehensive Diabetes Center
02/2021 – Member, UW Carbone Cancer Center
01/2021 – Affiliate Faculty, Department of Biomolecular Chemistry, UW – Madison SMPH, WI
10/2020 – Assistant Professor, Dept. of Medicine (Endocrinology), UW – Madison SMPH, WI
2018 – 2020 Staff scientist, The Scripps Research Institute, La Jolla, CA
2011 – 2018 Postdoctoral fellow, The Scripps Research Institute, La Jolla, CA
2007 - 2010 Ph.D. Student, University of Milan, Italy
2006 - 2007 Research Fellow, University of Milan, Italy
2004 - 2006 Undergraduate Researcher, University of Milan, Italy

Scientific Appointments

2022- Member, American Diabetes Association

2021-	Member, UW Comprehensive Diabetes Center
2013 - 2015	Member, American Heart Association
2012 - 2013	Member, American Association for Cancer Research
2007 - 2011	Member, Italian Society for the Study of Atherosclerosis
2006 - 2011	Member, Italian Society of Biochemistry

Honors

2022	Invited Speaker – Biochemistry Seminar Series, University of Minnesota, Minneapolis, MN.
2022	Rheos Short Talk Award - 2nd Metabolism in Health and Disease Fusion Conference, Cancun, Mexico
2021	Invited Speaker – Boston Nutrition Obesity Research Center Adipose and Metabolic Tissues Seminar Series, Boston, MA.
2021	Invited Speaker – Postdoctoral Association at UCLA, Los Angeles, CA
2021	Invited Speaker – Weill Cornell Emerging Investigators in Metabolism Series, New York, NY.
2020	Seahorse Bioscience Travel Award
2019	Invited Speaker – Endocrine Grand Rounds Lecture series, UCSD School of Medicine, San Diego, CA.
2019	Invited Speaker – Rising Stars Lecture Series, National Institutes of Health, Bethesda, MD.
2019	Invited Speaker – National Center for Advancing Translational Sciences, NIH, Rockville, MD.
2019	Agilent Technologies Travel Award
2018	Invited Speaker – University of Milan, Italy
2018	Agilent Technologies Travel Award
2015	Keystone Symposia Scholarship
2015	Seahorse Bioscience Travel Award
2014	American Heart Association Postdoctoral Fellowship (USA)
2011	Young Researcher Award, Italian Society for the Study of Atherosclerosis (Italy)
2011	Cariplo Foundation Postdoctoral Fellowship (Italy)
2009	Keystone Symposia Scholarship
2007	Undergraduate Young Researcher Award, Italian Society for the Study of Atherosclerosis (Italy)
2007	“Progetto Ingegno” Predoctoral Fellowship (European Community)
2006	Telethon Foundation Predoctoral Fellowship (Italy)

C. Contributions to Science

(***** denotes equal author contribution; # denotes correspondence by PI)

1. **Development of biological tools to study adipose tissue function**. The understanding of the mechanisms underlying adipocyte differentiation and function has greatly benefited from the use of cells cultured *in vitro*. To provide a more physiologically relevant model to study the complexity of white and brown adipose tissue, we have developed a protocol to simultaneously isolate and expand in culture primary white and brown adipocyte progenitors that can be differentiated *in vitro* into mature adipocytes. Compared to immortalized cell lines, primary cells are a heterogeneous population that more closely reflect the variety of cell types present in adipose depots *in vivo*. The primary advantage of isolating primary cells from newborn, rather than adult mice, is that the adipose depots are actively developing and are, therefore, a rich source of proliferating preadipocytes (a). In collaboration with Dr. Shingo Kajimura, we also generated a reporter mouse to visualize in real time the expression of uncoupling protein 1 (UCP1), a key component of brown adipose tissue (BAT) thermogenesis, in live animals. Discovery of compounds that promote UCP1 expression in is an important stride towards the goal of pharmacological stimulation of BAT function in obese individuals. Using this model, we developed a cell-based screen to isolate small molecules that increased UCP1 expression, identified the pathways targeted by these compounds, and validated their effects *in vivo*. This mouse model has been submitted to Jackson Laboratories (Jax stock number 026690). (b).
These works provide highly sensitive and accessible tools for academic research.

   a. **Galmozzi A**#, Kok BP, Saez E. Isolation and Differentiation of Primary White and Brown Preadipocytes from Newborn Mice. **J Vis Exp**. 2021 Jan 25;(167). PubMed PMID: 33554974.

b. **Galmozzi A***, Sonne SB*, Altshuler-Keylin S, Hasegawa Y, Shinoda K, Luijten IH, Chang JW, Sharp LZ, Cravatt BF, Saez E, Kajimura S. ThermoMouse: an *in vivo* model to identify modulators of UCP1 expression in brown adipose tissue. **Cell Reports**. 2014 Dec 11;9(5):1584-93. PubMed PMID: 25466254.

2. **Discovery of adipocyte functional pathways using chemical probes**. The vast majority of proteins lack small-molecule ligand. In collaboration with the laboratory of Ben Cravatt, we generated Fully Functionalized traceable Fragment-based probes (FFFs) to enable the identification of fragment-protein interactions in live cells. We detected >2000 interacting proteins, including transporters, transcription factors, and uncharacterized proteins. Strikingly, the majority of them (>80%) had no known small-molecule ligands, and only 18% were already classified in DrugBank. Integrating this chemoproteomic platform with phenotypic screening, we isolated a fragment hit that increased lipid accumulation in adipocytes and identified its molecular target as PGRMC2, a protein with no prior link to adipogenesis (*a*). Further characterization of PGRMC2 led us to understand the role of this protein in adipocyte function. We found that PGRMC2 is a heme-binding protein localized in the ER and the nuclear envelope that plays a critical role in intracellular trafficking of signaling (or labile) heme. Heme is a prosthetic group required by numerous proteins and a key signaling molecule in multiple biological processes. Heme synthesis is completed in mitochondria, but how this highly reactive metabolite is delivered to hemoproteins in other cellular compartments remains poorly defined. We showed that PGRMC2 is required for delivery of labile, or signaling heme, to the nucleus, and that this process is critical to control the stability of heme-responsive transcriptional repressors Rev-Erbα and BACH1. Deletion of PGRMC2 in adipose tissue caused severe mitochondrial defects that rendered adipose-specific PGRMC2-null mice unable to activate adaptive thermogenesis and more susceptible to develop glucose intolerance and insulin resistance, when fed a high fat diet. In contrast, obese-diabetic mice treated with a PGRMC2 activator showed a substantial improvement of diabetic features. This work described PGRMC2 as the first intracellular heme chaperone identified in mammals, and revealed the impact of alterations in adipose tissue heme dynamics on systemic physiology. These studies also suggest that pharmacological modulation of PGRMC2 activity may be useful to revert obesity-associated defects in adipocyte function (*b*).

a. Parker CG*, **Galmozzi A***, Wang Y, Correia BE, Sasaki K, Joslyn CM, Kim AS, Cavallaro CL, Lawrence RM, Johnson SR, Narvaiza I, Saez E, Cravatt BF. Ligand and target discovery by fragment-based screening in human cells. ***Cell***. 2017 Jan 26;168(3):527-541.e29. PubMed PMID: 28111073.

b. **Galmozzi A**, Kok BP, Kim AS, Montenegro-Burke JR, Lee JY, Spreafico R, Mosure S, Albert V, Cintron-Colon R, Godio C, Webb WR, Conti B, Solt LA, Kojetin D, Parker CG, Peluso JJ, Pru JK, Siuzdak G, Cravatt BF, Saez E. PGRMC2 is an Intracellular Heme Chaperone Critical for Adipocyte Function. ***Nature*****.** 576(7785), 138 (2019). PubMed PMID: 31748741.

3. **Biological application of ABPP for the discovery of Enzyme Modulators**. One of the works I contributed to develop during my postdoctoral training at Scripps has been the first one to integrate phenotypic screens and chemoproteomic techniques to rapidly identify and pharmacologically validate new targets of metabolic interest. Using a combination of phenotypic screening in adipocytes and the chemoproteomic method Activity-Based Protein Profiling (ABPP), we isolated serine hydrolase-directed small molecules that enhanced adipocyte lipid storage, identified their targets, and showed that obese-diabetic mice treated with one of these molecules (targeting the serine hydrolase Ces3) were more resistant to insulin sensitivity (a; b). Our group also implemented ABPP technology, which has been extensively used to discover enzyme inhibitors, to identify small molecule enzyme activators. We showed that using kinetically controlled ABPP assay, it is possible to isolate compounds that stimulate serine hydrolase activity (c).

a. Dominguez E, **Galmozzi A**, Chang JW, Hsu KL, Pawlak J, Li W, Godio C, Thomas J, Partida D, Niessen S, O'Brien PE, Russell AP, Watt MJ, Nomura DK, Cravatt BF, Saez E. Integrated phenotypic and activity-based profiling links Ces3 to obesity and diabetes. **Nature Chemical Biology**. 2014 Feb;10(2):113-21. PubMed PMID: 24362705.

b. **Galmozzi A**, Dominguez E, Cravatt BF, Saez E. Application of activity-based protein profiling to study enzyme function in adipocytes. **Methods in Enzymology**. 2014;538:151-69. PubMed PMID: 24529438.

c. Kok BP, Ghimire S, Kim W, Chatterjee S, Johns T, Kitamura S, Eberhardt J, Ogasawara D, Xu J, Sukiasyan A, Kim SM, Godio C, Bittencourt JM, Cameron M, **Galmozzi A**, Forli S, Wolan DW, Cravatt

BF, Boger DL, Saez E. Discovery of small-molecule enzyme activators by activity-based protein profiling. **Nature Chemical Biology**. 2020 Sep;16(9):997-1005. PubMed PMID: 32514184.

4. **Dissecting the role of Histone Deacetylases in the control of metabolism.** Epigenetic modifications are sensitive to environmental and nutritional cues and abnormalities in epigenetic regulation are associated with multiple metabolic disorders. One of the most common epigenetic modifications is acetylation of histones, balanced by the action of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Pan-HDAC inhibitors have been used to treat epilepsy and mood disorders in children, resulting also in reduced plasma cholesterol levels as a side effect. Based on this clinical evidence, we performed a detailed dissection of the events underlying the regulation of the rate-limiting enzyme that controls bile acid biosynthesis in the liver, Cholesterol 7-hydroxylase (CYP7A1), and found that bile acids repress CYP7A1 transcription rapidly by recruiting HDAC7 onto the CYP7A1 promoter, whereas the canonical FXR-dependent negative feedback occurs only after several hours. HDAC Inhibition prevented Cyp7a1 transcriptional repression and leads to reduction of blood cholesterol in mice (a). Small molecules globally inhibiting histone deacetylases have also shown antidiabetic effects. Using class-selective HDAC inhibitors we showed for the first time that class I HDAC inhibition, but not class II, promotes oxidative metabolism, reduces body weight, increases energy expenditure and insulin sensitivity in a mouse model of obesity and type 2 diabetes. These effects are largely due to relief of Hdac3 repression of Pgc-1α expression in muscle, and increased oxidative capacity of adipose tissue consequent to augmented Pparγ expression and activity. We also showed that class I selective HDAC inhibitors cause a significant beigeing/browning of white adipose tissue that contributes to the increased fat burning, reduced body weight, and improved capacity to clear glucose (b). These observations suggest that class I selective HDAC inhibitors may have promise in pathological conditions characterized by suppressed oxidative metabolism, insulin resistance, obesity and associated disorders such as type 2 diabetes.

a. Mitro N, Godio C, De Fabiani E, Scotti E, **Galmozzi A**, Gilardi F, Caruso D, Vigil Chacon AB, Crestani M. Insights in the regulation of cholesterol 7alpha-hydroxylase gene reveal a target for modulating bile acid synthesis. **Hepatology**. 2007 Sep;46(3):885-97. PubMed PMID: 17654698.

b. **Galmozzi A***, Mitro N*, Ferrari A, Gers E, Gilardi F, Godio C, Cermenati G, Gualerzi A, Donetti E, Rotili D, Valente S, Guerrini U, Caruso D, Mai A, Saez E, De Fabiani E, Crestani M. Inhibition of class I histone deacetylases unveils a mitochondrial signature and enhances oxidative metabolism in skeletal muscle and adipose tissue. **Diabetes**. 2013 Mar;62(3):732-42. PubMed PMID: 23069623.

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