

BIOGRAPHICAL SKETCH

NAME: Alessandro Bartolomucci

eRA COMMONS USER NAME: ABARTOLO

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
University of Parma, Parma, Italy	BS	07/1999	Biology
University of Milan, Milan, Italy	Ph.D	05/2003	Psychobiology
CNR, Rome, Italy	Postdoctoral	08/2006	Neuroscience and Physiology

A. Personal Statement

My laboratory is primarily interested in metabolic physiology, stress physiology and social determinants of health and aging. We developed a unique integrative approach to investigate the molecular physiology of obesity and chronic stress-related disease which combines behavioral and genetic models, metabolic, neuroendocrine and imaging techniques in living animals as well as sophisticated molecular and structural biology analyses of neuropeptides.

The major research topics include: 1) the functional role of *Vgf*-derived peptides in obesity and metabolism and their development as innovative drug targets for obesity-related disease; 2) autonomic nervous system regulation of white and brown adipocyte functions in obesity; 3) stress-induced cardiovascular and metabolic diseases; 4) social determinants of health, disease and aging.

I completed my pre-doc and postdoctoral training in behavioral neuroscience, psychobiology and metabolism. Recruited to the Univ Minnesota in 2010 I was promoted to Associate Professor with indefinite tenure in 2016 and Professor in 2022. I have been awarded the 2016-17 Fesler-Lampert Chair in Aging Studies, the Ancel Keys Biomedical Scholar in Physiology and Metabolism, and I'm Director of the Physiology Core facility of the Medical School. Since 2023 I also hold a Professorship at the Dept of Medicine of the University of Parma.

I have mentored 8 junior faculty, 5+ postdocs, 9 Graduate students, and I have had 40+ undergraduates and 10+ scientists/technicians work in the lab. Of the PhD students and postdocs, all are in academic positions or research positions in the biotechnology industry. 90% of the undergraduates entered graduate school or medical school.

Key citations

Lyons CE, Pallais JP, McGonigle S, Mansk RP, Collinge CW, Yousefzadeh MJ, Baker DJ, Schrank PR, Williams JW, Niedernhofer LJ, van Deursen JM, Razzoli M, Bartolomucci A. Chronic social stress induces p16-mediated senescent cell accumulation in mice. **NATURE AGING**, 2025 Jan;5:48-64..

Razzoli M, Nyuyki-Dufe, Chen B, Bartolomucci A. Contextual determinants of healthspan, lifespan and epigenome in mice under chronic social stress. **THE PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (PNAS)**. 2023;120(16):e2211755120.

Kivimäki M#, Bartolomucci A#, Kawachi I#. The multiple roles of life stress in metabolic disorders. **NATURE REVIEW ENDOCRINOLOGY**, 2023;19:10–27. #co-corresponding author.

Snyder-Mackler N, Burger JR, Gaydosh L, Belsky D, Noppert G, Campos FA, Bartolomucci A, Yang C, Aiello A, O'Rand A, Harris KM, Shively C, Alberts SC, Tung J. Social determinants of health and survival in humans and other animals. **SCIENCE**, 2020;368 (6493); eaax9553.

Relevant grants I would like to highlight:

NIH/NIA R61/R33 AG078520 Bartolomucci (PI) 09/01/22 - 08/31/2027
Mouse models for the influence of the social environment on health and aging

NIH/NIA R24 AG065172 Bartolomucci (PI), Tung, Harris, Snyder-Mackler (MPI) 03/01/2020 – 02/28/2030
Research Network on Animal Models to Understand Social Dimensions of Aging

NIH/NIA U54 AG076041-01 Niedernhofer, Aferis, PIs 09/30/21- 08/31/26
Minnesota Tissue Mapping Center for Senescent Cells
Role: Co-Investigator (key personnel)

NIH/NIA U54 AG079754-01 Bernlohr D, Budinger S, Sundeep K (PIs) 08/02/22-07/31/26
Midwest Murine-Tissue Mapping Center (MM-TMC)
Role: Co-Investigator (key personnel)

PE0000006 Uccelli A, PI 01/01/2023 - 12/31/2025
National Recovery and Resilience Plan (NRRP), Mission 4 Component 2 Investment 1.3 - European Union – NextGenerationEU
Title: MNESYS - A multiscale integrated approach to the study of the nervous system in health and disease.
Role: Project Leader
Project total cost: Euros 114 millions.
Total cost Bartolomucci Lab: Euros 124,000 + 100,000 in equipment + 1 Researcher (RTDa funded for 3 years).

2022XZ7MBC Nisoli, PI 10/01/2023 - 4/17/2026
PRIN: PROGETTI DI RICERCA DI RILEVANTE INTERESSE NAZIONALE – Bando 2022
The sexual dimorphic effects of amino acid diets in metabolic syndrome
Role: PI, UNIPR research unit.
Total cost: Euro 79,378

AI4ChemoBrain Calza, PI 10/14/2023-04/3/2026
Programmi Operativi Regionali finanziati con Fondo europeo di sviluppo regionale (POR-FESR) Emilia Romagna.
A machine learning/artificial intelligence model for personalized medicine: development of a predictive demonstrator of cognitive impairment during chemotherapy based on omics data
Role: PI, UNIPR research unit.
Total cost: euro 63,206

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022-	Professor, Dept. Integrative Biology and Physiology, University of Minnesota.
2022-	Associate Professor, Dept. Medicine and Surgery, University of Parma, Italy.
2020-present	Core Leader, Institute for Diabetes, Obesity and Metabolism, University of Minnesota.
2018-present	Ancel Keys Biomedical Scholar in Physiology and Metabolism, University of Minnesota.
2015-present	Director, Physiology Core, University of Minnesota Medical School.
2019-2021	Member, Cellular Aspects of Diabetes and Obesity (CADO), standing NIH Study Section.
2021-2023	Member, Pathophysiology of Obesity and Metabolic Disease – POMD, standing NIH Study Section.
2016-2022	Associate Professor, Dept. Integrative Biology and Physiology, University of Minnesota.
2010-present	Member, Center for Neurobehavioral Development, University of Minnesota.
2012-present	Faculty member. Lillehei Heart Institute, University of Minnesota.
2012-present	Faculty Mentor. The Minnesota Obesity Training Program, T32 DK083250.
2015-present	Faculty Mentor, Training Grant in Diabetes, Endocrinology And Metabolism, T32 DK007203.
2016-present	Faculty Mentor, Training Grant In Functional Proteomics of Aging, T32 AG029796.
2016-present	Faculty Member, Center on Aging, University of Minnesota, USA.

2016-present	Member, Institute for the Biology of Aging and Metabolism, University of Minnesota.
2016-present	Steering Committee, Medical Discovery Team, Biology of Aging, University of Minnesota.
2016-present	Member, Masonic Cancer Center, University of Minnesota.
2018-present	Member, Institute for Engineering and Medicine, University of Minnesota, USA.
2010-2020	Steering Committee, Graduate Program in Integrative Biology and Physiology, UMN.
2010-2014	Board Member for Neuroendocrinology, Italian Society for Neuroscience
2010-2016	Assistant Professor, Dept. Integrative Biology and Physiology, University of Minnesota.
2006-2010	Tenured Project Leader, Dept. Evol. Funct. Biol, Univ. Parma, Italy
2004-2005	Adjunct Professor of General Biology, School of Psychology, Univ. Parma, Italy
2003-2006	Post Doc fellow, Institute of Neuroscience, National Research Council, Rome, Italy
08/2007	Visiting Professor – University of Sao Paulo, Sao Paulo, Brasil.
01-05/2002	Visiting Scientist, Lab. Integr. Neurobiol., INRA-INSERM, Bordeaux, France.
2000-2003	Graduate student, Dept. Evol. Funct. Biol, Univ. Parma, and Univ. Milan, Italy
09/1999-04/2000	Research Fellow, Lab. Clin. Neurobiol., German Primate Center, Goettingen, Germany
1997-1999	Intern, Dept. Evol. Funct. Biol, Univ. Parma, Italy

Honors and Awards:

Awards: 1999 Graduate student fellowship, Univ. Padova, Italy; 2002 Travel award, European Science Foundation; 2004 Poster prize, European Behavioral Pharmacology Society; 2005 Young investigator Award, Italian Society for Neuroscience; 2010 Research Presentation Grant, Disease Models & Mechanisms - The Company of Biologist; 09/2012 Committee member. Xth International Catecholamine Symposium, CA 9/9-12 2012; 2012 Finalist, ISSNAF Young Investigator Award, Washington, DC, October 25th 2012; 2016 Fesler-Lampert Chair in Aging Studies, Center on Aging, University of Minnesota; 2018 Ancel Keys Biomedical Scholar in Physiology and Metabolism; 2019 Nominated Standing Member of the NIH study section, Cellular Aspects of Diabetes and Obesity. Recipient of the special program “brain gain”, the Italian Ministry of Research.

Study Sections/Grant Review: NIH, Pathophysiology of Obesity and Metabolic Disease [POMD] standing member, 2021-2023; NIH, Cellular Aspects of Diabetes and Obesity Study Section [CADO], standing member 2019-2021; NIH ZAG1 ZIJ-4 (J5) Second Stage Review NIA P01. Ad hoc, December 3-4 2019; NIH, 2019/05 ZDK1 GRB-N (M1) 1 - High Impact, Interdisciplinary Science in NIDDK Research Areas (RC2), ad hoc; 2018 NIH, CADO, ad hoc; National Science Foundation (NSF), Physiological Mechanisms and Biomechanics Program (PMB) ad hoc; American Association for the Advancement of Science (AAAS) Research Competitiveness Program, Connecticut Bioscience Innovation Fund; German Research Foundation; Israel Science Foundation; The French National Research Agency (ANR); University of North Carolina, Nutrition Obesity Research Center (NORC). Pilot/Feasibility Grant Program; Alzheimer's Society; University of Alabama, Nutrition Obesity Research Center (NORC) Pilot/Feasibility Grant Program; British Alzheimer Research Society; Netherlands Organization for Scientific Research.

Editorial responsibility: Adipocytes (2022-present), PLoS ONE (Editor, 2006-2021), Scientific Reports (Editor, 2016-2021), Frontiers in Nutrition (Associate Editor, 2014-present), Genes and Nutrition (Editorial Board, 2011-present), Stress (Editorial Board, 2015-present), Frontiers in Behavioral Neuroscience (Review Editor, 2007-present).

Guest Editor: “Social dimensions of health and aging: population studies, preclinical research and comparative research using animal models” (Neuroscience and Biobehavioral Reviews). “Novel Insights Into Adipose Tissue Biology: Role in Inter-Organ Communication and Metabolic Diseases” (Adipocyte). “Genes and Nutrition at the crossroad of obesity and metabolic disease” (Genes and Nutrition). “The Obese Species” (Disease, Models & Mechanisms). “Stress-Induced Depression and Comorbidities: From Bench to Bedside” (PLoS ONE). “Advancements in Neuroendocrine and Autonomic Control of Metabolic Functions and their Pathological Significance” (Eating and Weight Disorders).

Meeting organization: “Toward a mechanistic understanding of protective and damaging effects of social determinants of health”. Minneapolis, September 22-24 2022. Meeting lead organizer. “Influence of Social Inequalities and Social Stress on Metabolic Health” American Diabetes Association’s Scientific Sessions. Symposium organizer and Chair. June 25-29, 2021 in Washington, DC; “Stress, Metabolism and Aging”, Chair and lead organizer, University of Minnesota, May4th 2017; “The Obese Species” Co-director (Bartolomucci A, Parmigiani S, Rodgers J, Vidal-Puig A) Ettore Majorana Foundation and Centre of Scientific Culture, Erice, Italy, 10/21-26 2011; European Behavioral Pharmacology Society workshop on “Eating behaviour and obesity” Organizing committee member, September 7-9, 2012. Lecce, Italy. “Granins, catecholamines and the

cromaffin cells” Co-Chair. Xth International Catecholamine Symposium. Pacific Grove, CA Sept 9th-12th 2012.

C. Contribution to Science

My laboratory has pioneered the research on *Vgf* gene derived peptides with special reference to their role in metabolic functions, neuroendocrine regulation and pain. We have identified a VGF peptide designated TLQP-21 in the rodent brain and later we identified its expression in sympathetic nerve terminals innervating the adipose organ and identified for the first time its role as enhancer of beta-adrenergic induced-lipolysis. We recently generated a selective TLQP-21 deficient knock-in mouse which is currently available at Jackson Lab (JAX Stock No. 039020 B6;129S-Vgftm5Srjs/AbarJ).

- a) Sahu BS, Razzoli M, McGonigle S, Pallais JP, Nguyen ME, Sadahiro M, Jiang C, Lin WJ, Kelley KA, Rodriguez P, Mansk R, Cero C, Caviola G, Palanza P, Rao L, Beetch M, Alejandro E, Sham YY, Frontini A, Salton SR, Bartolomucci A. Targeted and selective knockout of the TLQP-21 neuropeptide unmasks its unique role in energy homeostasis. **Mol Metab.** 2023;76:101781. PMID: 37482186; PMCID: PMC10400922.
- b) Possenti R, Muccioli G, Petrocchi P, Cero C, Cabassi A, Vulchanova L, Riedl M, Manieri M, Frontini A, Giordano A, Cinti S, Govoni P, Graiani G, Quaini F, Ghe C, Bresciani E, Bulgarelli I, Torsello A, Locatelli V, Sanghez V, Larsen B, Petersen J, Palanza P, Parmigiani S, Moles A, Levi A, Bartolomucci A. Characterization of a novel peripheral pro-lipolytic mechanism in mice: role of VGF-derived peptide TLQP-21. **BIOCHEMICAL JOURNAL**, 2012;441:511-22.
- c) Bartolomucci A, Possenti R, Loh YP, Mahata S, Fisher-Corbie R, Salton S. The Extended Granin Family: Structure, Functions and Biomedical Implications. **ENDOCRINE REVIEWS**. 2011;32:755-97. PMC3591675.
- d) Bartolomucci A, G. La Corte, R. Possenti, V. Locatelli, A.E. Rigamonti, A. Torsello, E. Bresciani, I. Bulgarelli, R. Rizzi, F. Pavone, F.R. D'Amato, G. Mignogna, A. Giorgi, M.E. Schininà, A.M. Rinaldi, G. Elia, C. Brancia, G.-L. Ferri, R. Conti, B. Ciani, T. Pascucci, G. Dell'Omo, E.E. Muller, A. Levi, A. Moles. TLQP-21, a VGF-derived peptide, increases energy expenditure and prevents the early phase of diet-induced obesity. **PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCE USA** 2006.103,14584-14589. PMC1600003.

We established that TLQP-21 activates lipolysis and opposes obesity via C3aR1 activation: 1) we identified critical amino acids in the receptor binding pocket and the peptide pharmacophore, crucial to understand the biochemical mechanism of receptor activation and design of C3aR1 agonists; 2) we characterized the TLQP-21/C3aR1-mediated pro-lipolytic and anti-obesity mechanism in mice; 3) we identified the co-evolution of critical amino acids in the binding pocket and the peptide pharmacophore in the *Murinae* sub-family of rodents (including rats and mice) which resulted in enhanced potency at the C3aR1; 4) We characterized a ligand mediated biased C3aR1 signaling and its functional significance for lipolysis and immune function using several human and murine cellular models. We are currently characterizing the molecular mechanism of TLQP-21 anti-obesity and pro-lipolytic effect using novel genetic mouse models as well as rodent and human cellular systems.

- a) Rodriguez P, Laskowski LJ, Pallais JP, Bock HA, Cavalco NG, Anderson EI, Calkins MM, Razzoli M, Sham YY, McCorvy JD, Bartolomucci A. Functional profiling of the G protein-coupled receptor C3aR1 reveals ligand-mediated biased agonism. **J Biol Chem.** 2024 Jan;300(1):105549. PMID: 38072064; PMCID: PMC10796979.
- b) Sahu BS, Rodriguez P, Nguyen ME, Han R, Cero C, Razzoli M, Piaggi P, Laskowski LJ, Pavlicev M, Muglia L, Mahata SK, O'Grady S, McCorvy JD, Baier L, Sham YY, Bartolomucci A. peptide/receptor co-evolution explains the lipolytic function of the neuropeptide TLQP-21. **CELL REPORTS**, 2019;28:2567–2580. PMC6753381
- c) Cero C, Razzoli M, Han R, Sahu BS, Patricelli J, Zaidman N, Guo ZK, Miles JM, O'Grady S, Bartolomucci A. The neuropeptide TLQP-21 opposes obesity via C3aR1-mediated enhancement of adrenergic-induced lipolysis. **MOLECULAR METABOLISM**, 2017 6(1):148-158. PMC5220279.
- d) Cero C, Vostrikov V, Verardi R, Severini C, Gopinath T, Braun PD, Sassano MF, Gurney A, Roth BL, Vulchanova L, Possenti R, Veglia G, Bartolomucci A. The TLQP-21 Peptide Activates the G-protein-coupled receptor C3aR1 via a Folding-upon-Binding Mechanism. **STRUCTURE**, 2014. 22:1744–1753. PMC4353613.

We developed a unique ethological model of chronic social stress in mice and established a social-rank-dependent vulnerability to psychopathologies and neurological abnormalities. We demonstrated that subordinate mice (low social rank, a model of low socio-economic status) manifest a complex syndrome characterized by a depression-like behavior, increased anxiety, neuroimmune, neuroendocrine and cardiovascular abnormalities (including hypertension). After having characterized the stress-induced neurobehavioral and endocrine pathophysiology we directed our experimental effort to the impact of stress on metabolic functions, feeding behavior, obesity and vulnerability to type 2 diabetes as well as molecular markers of Alzheimer's disease. Importantly, lifelong social subordination anticipates the onset of many aging-related diseases, increases molecular markers of cellular senescence and causes epigenetic changes consistent with accelerated biological age. Finally, we also demonstrated that chronic social stress is a major risk factor to precipitate genetic diseases in mouse models such as the *mdx* mouse model of Duchenne Muscular Dystrophy.

- a) Lyons CE, Pallais JP, McGonigle S, Mansk RP, Collinge CW, Yousefzadeh MJ, Baker DJ, Schrank PR, Williams JW, Niedernhofer LJ, van Deursen JM, Razzoli M, Bartolomucci A. Chronic social stress induces p16-mediated senescent cell accumulation in mice. **NATURE AGING**, 2025;5:48-64.
- b) Collinge CW, Razzoli M, Mansk R, McGonigle S, Lamming DW, Pacak CA, van der Pluijm I, Niedernhofer L, Bartolomucci A. The Mouse Social Frailty Index (mSFI): A Novel Behavioral Assessment for Impaired Social Functioning in Aging Mice. **GEROSCIENCE**, 2024 in press
- c) Razzoli M, Nyuyki-Dufe, Chen B, Bartolomucci A. Contextual determinants of healthspan, lifespan and epigenome in mice under chronic social stress. **THE PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (PNAS)**. 2023;120(16):e2211755120.
- d) Razzoli M, Nyuyki-Dufe K, Gurney A, Erickson C, McCallum J, Spielman N, Marzullo M, Patricelli J, Kurata M, Pope EA, Touma C, Palme R, Largaespada DA, Allison DB, Bartolomucci A. Social stress shortens lifespan in mice. **AGING CELL**, 2018:e12778. PMC6052478.

Through our integrative physiology approach we identified novel functional roles of sympathetic nerves and nerve-derived factors (neurotransmitters and neuropeptides) in adipose tissue functions. This line of research led to the identification of the synergism between norepinephrine/beta-adrenergic receptor signaling and the neuropeptide TLQP-21/C3aR1 signaling (see above) in lipolysis in white adipocytes, as well as between norepinephrine/beta-adrenergic receptor signaling and ATP/purinergic receptors signaling in adipogenesis and uncoupling in brown adipocytes. We also developed innovative optogenetic and neuromodulation approaches designed to achieve selective sympathetic stimulation of adipose fat pads to modulate organ functions with the ultimate goal of preventing and treating obesity and diabetes.

- a) Sveidahl Johansen O, Ma T, Hansen JB, Markussen LK, Schreiber R, Reverte-Salisa L, Dong H, Christensen DP, Sun W, Gnad T, Karavaeva I, Nielsen TS, Kooijman S, Cero C, Dmytriyeva O, Shen Y, Razzoli M, O'Brien SL, Kuipers EN, Nielsen CH, Orchard W, Willemsen N, Jespersen NZ, Lundh M, Sustarsic EG, Hallgren CM, Frost M, McGonigle S, Isidor MS, Broholm C, Pedersen O, Hansen JB, Grarup N, Hansen T, Kjær A, Granneman JG, Babu MM, Calebiro D, Nielsen S, Rydén M, Soccio R, Rensen PCN, Treebak JT, Schwartz TW, Emanuelli B, Bartolomucci A, Pfeifer A, Zechner R, Scheele C, Mandrup S, Gerhart-Hines Z. Lipolysis-induced transcription of the constitutively active receptor GPR3 drives adipose thermogenesis. **CELL**, 2021;184(13):3502-3518.e33
- b) Lyons C, Razzoli M, Larson E, Svedberg D, Frontini A, Cinti S, Vulchanova L, Sanders M, Thomas M, Bartolomucci A. Optogenetic-induced Sympathetic Neuromodulation of Brown Adipose Tissue Thermogenesis. **FASEB J**, 2020;34(2):2765-2773.
- c) Razzoli M, Emmett M, Lazar M, Bartolomucci A. Beta-adrenergic receptors control brown adipose UCP1 tone and cold response without affecting its circadian rhythmicity. **FASEB J**, 2018, 2018;32(10):5640-5646. PMC6133705
- d) Razzoli M, Frontini A, Gurney A, Mondini E, Cubuk C, Katz LS, Cero C, Bolan PJ, Dopazo J, Vidal-Puig A, Cinti S, Bartolomucci A. Stress-induced activation of the brown adipose tissue prevents obesity in conditions of low adaptive thermogenesis. **MOLECULAR METABOLISM** 2016;5:19-33. PMC4703853

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/alessandro.bartolomucci.1/bibliography/47326263/public/?sort=date&direction=descending>.