

PERSONAL INFORMATION

Family name, Name: Settembre, Carmine
Nationality: Italian
Date of birth: 21st June 1978
URL for web site: <https://www.tigem.it/Staff/settembre>

EDUCATION

2008 Ph.D. in Molecular Medicine, University of Naples Federico II, Italy. Supervisor: Andrea Ballabio
2002 Pharmaceutical Chemistry Degree, University of Naples Federico II, Naples, Italy

CURRENT POSITION(S)

2018 Associate Professor of Histology, University of Naples Federico II, Italy
2013 Associate Investigator, Telethon Institute of Genetics and Medicine (TIGEM), Italy

PREVIOUS POSITIONS

2013 – 2018 Assistant Investigator, Telethon Institute of Genetics and Medicine, Naples, Italy
2012 – 2018 Assistant Professor of Medical Genetics, University of Naples Federico II, Italy
2011 – 2012 Assistant Professor, Inst. for Molecular Genetics, Baylor College of Medicine, Houston TX
2009 – 2011 Postdoc Fellow, Inst. for Molecular Genetics, Baylor College of Medicine, Houston TX
2007 – 2009 Visiting scientist, Columbia University in the city of New York, NY

FELLOWSHIPS AND AWARDS

2021 – 2026 Recipient of the ERC Consolidator Grant
2020 – 2022 Recipient of the ERC Proof of Concept Grant
2017 Ian Boyle Award, European Calcified Tissue Society
2017 – 2021 Member of the EMBO Young Investigator Program
2016 – 2021 Recipient of the ERC Starting Grant
2013 Annual Rotary/CNR young biologist Award
2013 – 2018 Dulbecco Telethon Institute Career Award
2008 – 2010 EMBO Long-term Fellowship Award
2006 Young Investigator Awards for Outstanding Science, European Human Genetics Conference

SUPERVISION OF GRADUATE STUDENTS AND POSTDOCTORAL FELLOWS (if applicable)

2011 – to date Prof. Settembre has supervised 8 post-doctoral fellows, 6 PhD students, 3 graduate students. Among them, Alison Forrester is now applying for a faculty position, Rosa Bartolomeo and Marilina Piemontese are staff scientists at pharmaceutical companies. Two graduate students are now enrolled in PhD programs. Ten of them are currently employed in the Settembre laboratory.

TEACHING ACTIVITIES (if applicable)

2018 – to date Associate Professor of Histology and embryology, University of Naples Federico II, Italy
2013 – 2018 Assistant Professor of Medical Genetics, University of Naples Federico II, Italy
2013 – to date Lecturer, European School of Molecular Medicine (SEMM), PhD in System Medicine, Italy

ORGANISATION OF SCIENTIFIC MEETINGS (if applicable)

2020 Organizer and Scientific Committee Member, Autophagy Early-Career Investigator's On-line Seminar

series

- 2018 Organizer and Scientific Committee Member, EMBO Workshop 'Lysosomes and metabolism', Italy
2015 Organizer and Scientific Committee Member, Forum in Bone and Mineral Research, Torino, March 6-7, 2015, Torino, Italy

INSTITUTIONAL RESPONSIBILITIES (if applicable)

- 2019 – 2020 Member of the Admission Committee, European School of Molecular Medicine (SEMM), PhD in System Medicine, Italy
2014 – 2020 Internal Advisor, European School of Molecular Medicine (SEMM), PhD in System Medicine, Italy
2014 – 2015 Member Examiner Committee of 4 PhD defenses; Open University/c.o. Tigem, Italy
2013 – to date Faculty, Telethon Institute of Genetics and Medicine (TIGEM), Italy

REVIEWING ACTIVITIES (if applicable)

Ad hoc reviewer for several international peer-reviewed journals, including: Science, Nature Cell Biology, Nature communication, Developmental Cell, Molecular Cell, EMBO Molecular Medicine, EMBO Journal, eLife, Journal of Clinical Investigation, Plos Biology, Human Molecular Genetics, Journal of Cell Biology. Member of the editorial boards of Life Science Alliance, Traffic and Cells Journals.
Ad hoc Reviewer of ERC starting and Consolidator grants

MEMBERSHIPS OF SCIENTIFIC SOCIETIES (if applicable)

- 2017 – to date Directory Board, Forum of Bone and Mineral Research, Italy
2017 – 2021 EMBO Young Investigator Programme
2014 – to date European Calcified Tissue Society
2013 – to date Italian Association of Cell Biology and Differentiation
2013 – to date Forum of Bone and Mineral Research, Italian Society of the Histology and Embryology

MAJOR COLLABORATIONS (if applicable)

- Maurizio Molinari Institute for Research in Biomedicine (IRB), Bellinzona, Switzerland
Ivan Dikic Goethe University Frankfurt, Germany
Mattias Mann Max Planck Institute of Biochemistry, Martinsried, Germany
Andrea Ballabio Telethon Institute of Genetics and Medicine (TIGEM), Italy
Antonella De Matteis Telethon Institute of Genetics and Medicine (TIGEM), Italy
Paolo Grumati Telethon Institute of Genetics and Medicine (TIGEM), Italy

CAREER BREAKS (if applicable)

I have been awarded my PhD on October 27th, 2008. My son Samuele was born on February 13, 2012. I took a 90 days paternity leave from February 12th to May 12th, 2012.

Current grants (Please indicate "No funding" when applicable):

<i>Project Title</i>	<i>Funding source</i>	<i>Amount (Euros)</i>	<i>Period</i>	<i>Role of the PI</i>
BONEPHAGY - Defining the role of the FGF – autophagy axis in bone physiology	ERC STARTING GRANT	1.586.430,00	01/01/2017 - 30/06/2022	PI
RE-STORE Pharmacological restoration of selective autophagy for the treatment of skeletal disorders'	ERC POC	120.000,00	01/01/2021 - 30/06/2022	PI
Dissecting the role of selective autophagy dysfunction in MPS pathogenesis.	MPS SOCIETY	75.000	01/01/2021 - 31/12/2022	PI
Modulation of selective autophagy to treat Vascular Ehlers Danlos Syndrome	FONDAZIONE TELETHON	50.000	01/04/2022 - 31/3/2023	PI

Early achievements track-record

Below I summarize the main scientific achievement I have obtained during the last 10 years. As a post-doctoral fellow and assistant professor at the Baylor College of Medicine I demonstrated that **lysosomes and autophagosomes are transcriptionally co-regulated** by a previously uncharacterized **lysosome-to-nucleus signalling mechanism** relying on the nutrient sensing kinase mTORC1 and the transcription factor TFEB. This signaling mechanism participates to metabolic adaptation to nutrient scarcity in liver. Notably this regulatory pathway is conserved across the evolution and allowed organismal survival to starvation periods (Settembre et al, **Science** 2011; Settembre et al, **EMBO J**, 2012; Settembre et al, **Nat Cell Biol**, 2013).

As an independent scientist my group investigated the role of autophagy and lysosome biogenesis during bone growth. We demonstrated that during post-natal development in mice, **autophagy is induced in chondrocyte of the growth plate to regulate levels of type II collagen (Col2)**, the major component of cartilage extracellular matrix. Chondrocyte autophagy is regulated by the growth factor FGF18 through the activation of the FGFR4 and FGFR3 receptors via JNK signaling. JNK controls autophagy and lysosome biogenesis through the VPS34–beclin-1 complex and TFEB activation. Notably, TFEB induces the expression of the ER-phagy receptor FAM134B promoting chondrocyte's ER-phagy. These studies demonstrated that: 1) catabolic pathways may be positively regulated by growth factor signaling and play anabolic roles during organismal growth and 2) selective autophagy can be regulated during development by transcriptional mechanisms (Cinque et al., **Nature** 2015; Cinque et al. **EMBO** 2020).

In parallel, my laboratory also characterized the relationship between autophagy and collagens. We found that **autophagy selectively recognizes the misfolded fraction of ER-retained procollagens** via a complex formed **by the ER chaperone Calnexin and the ER-phagy receptor FAM134B**. In turn, FAM134B binds the autophagosome membrane-associated protein LC3 and delivers a portion of ER containing both calnexin and procollagens to the lysosome for degradation. This work describes ER-phagy as ER-quality control mechanism for clearance of ER-associated misfolded clients (Forrester et al. **EMBO** 2018). Notably, we also demonstrated that a **collagen trafficking defect due to impaired autophagy accounts for the skeletal**

manifestation in lysosomal storage disorder mouse models. Both genetic and pharmacological modulation of autophagy rescues collagen trafficking defects and skeletal phenotype in preclinical models of lysosomal storage disorders. These findings identified new potential therapeutic approaches for the treatment of LSDs (Bartolomeo et al. **Journal of Clinical Investigation** 2017).

I have demonstrated the capacity to secure funding for my laboratory. In particular, in the last year my lab was supported by an **ERC starting grant** and in 2020 the **ERC proof of concept grant**, among many others. In 2017 I become a member of the **EMBO Young Investigator Programme**, that select the best young researchers in the life sciences in EMBC Member or Associate Member States.

TOP 10 PUBLICATIONS (out of >60 publications in peer reviewed journals, total impact factor 721.332, H-index 35, Total citations 13146 (self-citation excluded))

1. Cinque L, De Leonibus C, Iavazzo M, Krahmer N, Intartaglia D, Salierno FG, De Cegli R, Di Malta C, Svelto M, Lanzara C, Maddaluno M, Wanderlingh LG, Huebner AK, Cesana M, Bonn F, Polishchuk E, Hübner CA, Conte I, Dikic I, Mann M, Ballabio A, Sacco F, Grumati P, **Settembre C**. MiT/TFE factors control ER-phagy via transcriptional regulation of FAM134B. *EMBO J*. 2020 Sep 1;39(17):e105696. [IF 9.889](#)
2. Forrester A, De Leonibus C, Grumati P, Fasana E, Piemontese M, Staiano L, Fregno I, Raimondi A, Marazza A, Bruno G, Iavazzo M, Intartaglia D, Seczynska M, van Anken E, Conte I, De Matteis MA, Dikic I, Molinari M, **Settembre C**. A selective ER-phagy exerts procollagen quality control via a Calnexin-FAM134B complex. *EMBO J*. 2019 Jan 15;38(2) [IF 9.889](#)
3. Bartolomeo R, Cinque L, De Leonibus C, Forrester A, Salzano AC, Monfregola J, De Gennaro E, Nusco E, Azario I, Lanzara C, Serafini M, Levine B, Ballabio A, **Settembre C**. mTORC1 hyperactivation arrests bone growth in lysosomal storage disorders by suppressing autophagy. *J Clin Invest*. 2017 Oct 2;127(10):3717-29. [IF 13.251](#)
4. Cinque L, Forrester A, Bartolomeo R, Svelto M, Venditti R, Montefusco S, Polishchuk E, Nusco E, Rossi A, Medina DL, Polishchuk R, De Matteis MA, **Settembre C**. FGF signalling regulates bone growth through autophagy. *Nature*. 2015 Dec 10;528(7581):272-75. [IF 38.138](#)
5. Goginashvili A, Zhang Z, Erbs E, Spiegelhalter C, Kessler P, Mihlan M, Pasquier A, Krupina K, Schieber N, Cinque L, Morvan J, Sumara I, Schwab Y, **Settembre C**, Ricci R. Insulin secretory granules control autophagy in pancreatic β cells. *Science*. 2015 Feb 20;347(6224):878-82. [IF 34.661](#)
6. **Settembre C**, Fraldi A, Medina DL, Ballabio A. Signals from the lysosome: a control centre for cellular clearance and energy metabolism. *Nat Rev Mol Cell Biol*. 2013 May;14(5):283-96. [IF 36.458 – Cit.826](#)
7. **Settembre C** *, De Cegli R, Mansueto G, Saha PK, Vetrini F, Visvikis O, Huynh T, Carissimo A, Palmer D, Klisch TJ, Wollenberg AC, Di Bernardo D, Chan L, Irazoqui JE, Ballabio A*. TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop. *Nat Cell Biol*. 2013 Jun;15(6):647-58. (*co-corresponding authors) [IF 20.058 – Cit.451](#)
8. Di Malta C, Fryer JD, **Settembre C***, Ballabio A*. Astrocyte dysfunction triggers neurodegeneration in a lysosomal storage disorder. *Proc Natl Acad Sci U S A*. 2012 Aug 28 (*co-last authors) [IF 9.737 – Cit.63](#)
9. **Settembre C**, Zoncu R, Medina DL, Vetrini F, Erdin S, Erdin S, Huynh T, Ferron M, Karsenty G, Vellard MC, Facchinetti V, Sabatini DM, Ballabio A. A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFEB. *EMBO J*. 2012 Mar 7;31(5):1095-108. [IF 9.822 – Cit.919](#)
10. **Settembre C**, Di Malta C, Polito VA, Garcia Arencibia M, Vetrini F, Erdin S, Erdin SU, Huynh T, Medina D, Colella P, Sardiello M, Rubinsztein DC, Ballabio A. TFEB links autophagy to lysosomal biogenesis. *Science*. 2011 Jun 17;332(6036):1429-33. [IF 31.201 – Cit.1491](#)

BOOK CHAPTERS

1. **Settembre C**, Ballabio A. Lysosomal adaptation: how the lysosome responds to external cues. Cold Spring Harb Perspect Biol.
2. Ballabio A, Medina D, **Settembre C**. TFEB/ CLEAR Network. In: Lysosomes and lysosomal Diseases. Series: Methods in Cell Biology. Eds Platt F, Platt N. Series Eds Wilson L, Tran P. Elsevier B.V, Chapt 10.

GRANTED PATENTS

1. Co-inventor WO2012120044, Title: "TFEB variants and uses thereof".
2. Co-inventor WO2012120048, Title: "TFEB phosphorylation inhibitors and uses thereof".
3. Co-inventor WO2013186398, Title: "TFEB for use in treating obesity or metabolic syndrome"
4. Co-inventor US 62/233687, Title: "treatments of bone growth disorders"- Priority date: 28/09/2015

INVITED PRESENTATIONS

I have been invited to more than 40 national and international meetings and international institutes as seminar speaker. Below I list only the ones in which I was invited as keynote speaker.

1. **Keynote speaker**, The AIM Center's 2020 International eSymposium November 9, 2020
2. **Keynote speaker**, 3rd Nordic Autophagy Society Conference, Utrecht, NL, May 22-24, 2019
3. **Keynote speaker**, Interuniversity Institute of Myology (IMM) meeting, Assisi, Italy, October 11-14, 2018
4. **Keynote speaker**, 14th International Symposium of the Portuguese Society of Metabolic Disorders, Porto, Portugal, March 15-17, 2018
5. **Keynote Speaker**, European Symposium on Lysosomal Storage Disorders (ESLSD), Vienna, Austria October 12-14, 2017
6. **Keynote speaker**, 5th Belgian Symposium on Tissue Engineering (BSTE), Leuven, Belgium, May 4-5, 2017
7. **Keynote speaker**, San Raffaele Departmental Retreat, Milan, Italy, September 24, 2015