BIOGRAPHICAL SKETCH

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NAME: Chiara Di Malta

eRA COMMONS USER NAME (credential, e.g., agency login): dimalta

POSITION TITLE: Assistant Investigator

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Federico II University, Naples, Italy	BS	10/2005	Biological Sciences
Open University, London, UK and Telethon Institute of Genetics and Medicine (TIGEM), Naples, Italy	PHD	09/2012	Genetics/Cell biology
TIGEM, Pozzuoli, Italy	POST DOC	12/2020	Cell biology/mouse genetics
TIGEM, Pozzuoli, Italy	Assistant Investigator	present	Cell Biology and Disease Mechanisms

A. Personal Statement

My long-term research interests involve the study of pathogenetic mechanisms underlying rare genetic diseases. My PhD experimental thesis was aimed at studying the neurodegenerative phenotype of the Lysosomal Storage Disorders (LSDs), rare genetic diseases due to the accumulation of undigested material inside the lysosomes. Thanks to mouse genetics and cell biology approaches, I discovered that dysfunction of astrocytes, due to lysosomal storage, triggers neurodegeneration in a mouse model of Multiple Sulfatase Deficiency, an extremely severe LSD. The results of this study were published on PNAS journal and I'm listed as first author. In the meantime, I collaborated to two important studies leading to the identification of the transcription factor EB (TFEB) as the master regulator of lysosomal biogenesis and autophagy. These predoctoral studies were done at TIGEM (2007-2009) and at Baylor College of Medicine, Houston (TX) (2009-2012). This training allowed me to acquire a solid background on mouse genetics, cell biology and molecular biology and to develop initiative and independent thinking. As postdoctoral researcher I focused my attention on TFEB and on other members of MiT/TFE family of transcription factors (in particular TFE3 and MITF), known oncogenes deregulated in different malignancies. By studying the signaling pathways regulating lysosomal adaptation to nutrient availability, I identified a new transcriptional regulation, mediated by MiT/TFE factors, controlling mTORC1 signaling in response to nutrients. This mechanism is essential to ensure an efficient switch between catabolic and anabolic pathways in health conditions, but its deregulation underline the growth of cancers associated to MiT/TFE hyperactivation, in particular Renal Cell Carcinoma (RCC) due to chromosomal translocation of TFE3 or TFEB. This discovery was published on Science journal and I'm the first author of the paper. In the last three years of my research activity as postdoctoral researcher, I've been studying a genetic disease called Birt-Hogg-Dube' (BHD) syndrome, whose affected individuals have an increased risk to develop kidney cancer. This disease is due to loss of function mutations in the gene encoding FLCN and second-hit mutation is required for tumor development. I demonstrated that TFEB is constitutively

nuclear and hence hyper-active in cellular and murine models of this disease and its genetic inactivation completely rescued renal cystogenesis and precancerous lesions in a BHD mouse model, restoring mouse viability. These findings were published on Nature journal and I'm co-first author of the paper. More recently, the analysis of BHD patient-derived tumor samples revealed increased activation of TFEB/TFE3-mediated transcriptional program and we showed that silencing either of the two genes rescued tumorigenesis in human BHD renal tumor cell line-derived xenografts (CDXs), thus demonstrating in disease-relevant models that both TFEB and TFE3 are key drivers of renal tumorigenesis in BHD. This study was published on Embo Molecular Medicine journal, and I'm both first and co-corresponding author of the paper.
As an independent investigator at Tigem since January 2021, I intend to dissect how lysosomal dysfunction contributes to kidney cystogenesis and cancer, with the purpose to open new therapeutic avenues for the treatment of these pathologies. In parallel, I also will explore conditions in which increased activation of the lysosome may be beneficial, as demonstrated by my most recent publication on Acta Pharmaceutica Sinica B, in which we discovered that pharmacological activation of TFEB is beneficial for the treatment of Nonalcoholic fatty liver disease (NAFLD).

B. Positions, Scientific Appointments, and Honors

2006-2007: Undergraduate fellow, laboratory of Prof. Giuseppe D'Alessio, Department of Structural and Functional Biology, University "Federico II" of Naples (Italy).
2007-2009: PhD student, laboratory of Prof. Andrea Ballabio, TIGEM, Naples (Italy)
2009-2012: Visiting PhD student at Dept. of Human Genetics-Baylor College of Medicine, Houston (Texas), laboratory of Prof. Andrea Ballabio.
2012-2020: Postdoctoral fellow, laboratory of Prof. Andrea Ballabio, TIGEM, Naples (Italy).
2017-2019: Junior Principal Investigator STAR (Sostegno Territoriale alle attivita' di ricerca) research grant, University "Federico II", Naples (Italy).
2020- to present: Research Associate University "Federico II", Naples (Italy).
2021- to present: Assistant Investigator Telethon Institute of Genetics and Medicine, Pozzuoli (NA, Italy).

2007-2008 Open University PhD fellowship award (ranked first).
2018 Annual Rotary/CNR young biologist award, Naples, Italy.
2017 Minerva Prize Anna Maria Mammoliti for the scientific research, Campidoglio, Rome (Italy).
2020 Kidney Cancer Young Investigator Award

C. Contributions to Science

Early career: As an undergraduate student in the laboratory of Professor Giuseppe D'Alessio at Department of Structural and Functional Biology of Federico II University, I collaborated to a study aimed at characterizing the mechanism of action of ERB-hRNase, an antitumor immuno-conjugate targeting ErbB2 positive carcinoma cells and made up of a human anti-ErbB2 scFv called Erbicin with human pancreatic RNase. We found that the antitumor action of ERB-hRNase was fully dependent on its RNA degrading activity. In the meantime, I was involved in a project focused to characterize the angiogenic activity of zebrafish ribonucleases. This undergraduate training allowed me to become familiar with biochemistry and cell biology techniques.

a. Intracellular route and mechanism of action of ERB-hRNase, a human anti-ErbB2 anticancer immunoagent. De Lorenzo C, **Di Malta C**, Calì G, Troise F, Nitsch L, D'Alessio G. *FEBS Lett*. 2007 Jan 23;581(2):296-300. doi: 10.1016/j.febslet.2006.12.034. Epub 2007 Jan 2. PMID: 17208233

b. Characterization of the angiogenic activity of zebrafish ribonucleases. Monti DM, Yu W, Pizzo E, Shima K, Hu MG, **Di Malta C**, Piccoli R, D'Alessio G, Hu GF. *FEBS J*. 2009 Aug;276(15):4077-90. doi: 10.1111/j.1742-4658.2009.07115.x. Epub 2009 Jun 22. PMID: 19549190

Graduate Career: My main PhD research project was focused to the study of the mechanisms leading to the neurodegeneration in lysosomal storage disorders (LSDs). I generated a mouse model for a severe LSD, the

multiple sulfatase deficiency (MSD) in which the disease could be induced in a tissue specific fashion (conditional Sumf1 mouse line). By analyzing the different contribution of both neuronal and non- neuronal populations to the observed neurodegeneration in MSD models, I demonstrated a role for astrocytes dysfunction in the neurodegeneration observed in LSD model. Mechanistically, I found that astrocytes were unable to support neuronal functions because of an intrinsic autophagy defect. This work was published on PNAS, and I was listed as first author. This work was very important to make me acquire intellectual independence and a strong expertise in mouse genetics. In parallel, I contributed to two important research projects that led to the identification and characterization of the Transcription factor EB (TFEB) as a master regulator of lysosome biogenesis and autophagy function. I contributed to the design of the experiments and performed several of them. In particular, I'm listed as second author in the Science manuscript reporting the identification of TFEB-mediated transcriptional regulation of autophagy machinery, as proof that my contribution was fundamental for the success of the research project. This collaboration was extremely productive and led me to acquire a solid background in the lysosomal biology. Furthermore, this work was instrumental for make me acquire both a deep understanding of the molecular pathways converging on TFEB and the necessary technical skills required for my subsequent research work as postdoctoral fellow.

a. A gene network regulating lysosomal biogenesis and function. Sardiello M, Palmieri M, di Ronza A, Medina DL, Valenza M, Gennarino VA, **Di Malta C**, Donaudy F, Embrione V, Polishchuk RS, Banfi S, Parenti G, Cattaneo E, Ballabio A. *Science*. 2009 Jul 24;325(5939):473-7. doi: 10.1126/science.1174447. Epub 2009 Jun 25. PMID: 19556463

b. TFEB links autophagy to lysosomal biogenesis. 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. *Science*. 2011 Jun 17;332(6036):1429-33. doi: 10.1126/science.1204592. Epub 2011 May 26. PMID: 21617040

c. Astrocyte dysfunction triggers neurodegeneration in a lysosomal storage disorder. **Di Malta C**, Fryer JD, Settembre C, Ballabio A. *Proc Natl Acad Sci U S A.* 2012 Aug 28;109(35):E2334-42. doi: 10.1073/pnas.1209577109. Epub 2012 Jul 23. PMID: 22826245

d. Autophagy in astrocytes: a novel culprit in lysosomal storage disorders. **Di Malta C**, Fryer JD, Settembre C, Ballabio A. *Autophagy*. 2012 Dec;8(12):1871-2. doi: 10.4161/auto.22184. Epub 2012 Oct 9. PMID: 23047468

Postdoctoral career: As a postdoctoral fellow I focused my attention on the study of TFEB and how it regulates lysosomal function in health and pathological conditions. In particular, I found that TFEB, as well as its homologs TFE3 and MITF, regulates at a transcriptional level the activity of mTORC1, by inducing the expression of RagD/C GTPases, small GTPases deputed to mTORC1 lysosomal recruitment. This mechanism is important to ensure a fast switch between catabolic and anabolic pathways according to nutritional availability but is deregulated in malignancies associated to the increased activity of MiT/TFE factors. In particular, analysis of RCC due to chromosomal translocation of TFE3 or TFEB revealed excessive levels of RagD/C, leading to mTORC1 hyper-activation, which fuels tumor growth. In the last three years of my research activity as postdoc I studied the BHD syndrome, a genetic disease due to mutations in the *FLCN* gene and associated to kidney cystogenesis and cancer development. I understood that FLCN is strictly required to inhibit TFEB activity, which become constitutive nuclear and hence hyperactive when FLCN is missing. By exploiting a mouse genetic approach, I demonstrated that TFEB depletion fully rescued kidney cysts and pre-cancerous lesions of kidney-specific FLCN-KO mouse. This discovery suggests that the main tumor suppressor function of FLCN is to inhibit TFEB hyper-activity which, otherwise, promotes cystogenesis and cancer development. For both my postdoctoral studies I pursued my own ideas, conceived the projects and designed the required experiments to accomplish them.

a. Transcriptional activation of RagD GTPase controls mTORC1 and promotes cancer growth. **Di Malta C**, Siciliano D, Calcagni A, Monfregola J, Punzi S, Pastore N, Eastes AN, Davis O, De Cegli R, Zampelli A, Di Giovannantonio LG, Nusco E, Platt N, Guida A, Ogmundsdottir MH, Lanfrancone L,

Perera RM, Zoncu R, Pelicci PG, Settembre C, Ballabio A. *Science*. 2017 Jun 16;356(6343):1188-1192. doi: 10.1126/science.aag2553. PMID: 28619945

b. MiT/TFE Family of Transcription Factors, Lysosomes, and Cancer. Perera RM, **Di Malta C**, Ballabio A. *Annu Rev Cancer Biol.* 2019 Mar;3:203-222. doi: 10.1146/annurev-cancerbio-030518-055835. Epub 2018 Nov 28. PMID: 31650096

c. Transcriptional regulation of mTORC1 in cancer. **Di Malta C**, Ballabio A. *Oncotarget*. 2018 Dec 4;9(95):36734-36735. doi: 10.18632/oncotarget.26229. eCollection 2018 Dec 4. PMID: 30613362

d. Transcriptional Regulation of Autophagy: Mechanisms and Diseases. **Di Malta C**, Cinque L, Settembre C. *Front Cell Dev Biol*. 2019 Jul 2;7:114. doi: 10.3389/fcell.2019.00114. eCollection 2019. PMID: 31312633

e. A substrate-specific mTORC1 pathway underlies Birt-Hogg-Dubé syndrome. Napolitano G*, **Di Malta C***, Esposito A, de Araujo MEG, Pece S, Bertalot G, Matarese M, Benedetti V, Zampelli A, Stasyk T, Siciliano D, Venuta A, Cesana M, Vilardo C, Nusco E, Monfregola J, Calcagnì A, Di Fiore PP, Huber LA, Ballabio A. *Nature*. 2020 Jul 1. doi: 10.1038/s41586-020-2444-0. Online ahead of print. PMID: 32612235. *co-first authors.

Most recent publications:

- Di Malta C*, Zampelli A, Granieri L, Vilardo C, De Cegli R, Cinque L, Nusco E, Pece S, Tosoni D, Sanguedolce F, Sorrentino NC, Merino MJ, Nielsen D, Srinivasan R, Ball MW, Ricketts CJ, Vocke CD, Lang M, Karim B, Lanfrancone L, Schmidt LS, Linehan WM*, Ballabio A*. TFEB and TFE3 drive kidney cystogenesis and tumorigenesis. *EMBO Mol Med*. 2023 May 8;15(5):e16877. doi: 10.15252/emmm.202216877. Epub 2023 Mar 29. *** co-corresponding authors.**

- Akwa Y†, **Di Malta C**†, Zallo F†, Gondard E, Lunati A, Diaz-de-Grenu LZ, Zampelli A, Boiret A, Santamaria S, Martinez-Preciado M, Cortese K, Kordower JH, Matute C, Lozano AM, Capetillo-Zarate E, Vaccari T, Settembre C, Baulieu EE, Tampellini D. Stimulation of synaptic activity promotes TFEB-mediated clearance of pathological MAPT/Tau in cellular and mouse models of tauopathies. *Autophagy.* 2023 Feb;19(2):660-677. doi: 10.1080/15548627.2022.2095791. Epub 2022 Jul 22. **† equal contribution**. **Please, note that this publication is without the co-authorship of my PhD supervisor.**

- Du X†, **Di Malta C**†, Fang Z, Shen T, Niu X, Chen M, Jin B, Yu H, Lei L, Gao W, Song Y, Wang Z, Xu C, Cao Z, Liu G, Li X. Nuciferine protects against high-fat diet-induced hepatic steatosis and insulin resistance via activating TFEB-mediated autophagy–lysosomal pathway. *Acta Pharmaceutica Sinica B. 2022 Jun;12(6):2869-2886. doi: 10.1016/j.apsb.2021.12.012.* **† equal contribution**. **Please, note that this publication is without the co-authorship of my PhD supervisor.**

Complete List of Published Work in My Bibliography:
https://pubmed.ncbi.nlm.nih.gov/?term=di%20malta%20c&sort=pubdate

D. Additional Information: Research Support and/or Scholastic Performance

Research Support

May 2017- May 2019	STAR research grant, University “Federico II”, Naples (Italy)
October 2020- October 2021	Kidney Cancer Young Investigator Award
January 2021- December 2023	Worldwide Cancer Research Grant
January 2021- December 2023	Telethon grant
January 2023-December 2027	My First Airc Grant (MFAG)
October 2023-October 2025	PRIN 2022-MUR-Italy