Annex B – **BIOSKETCH**

NAME: Anna Raffaello

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Padova, Italy	MSc	10/1996 – 10/2002	Biology
University of Padova, Italy	PhD	10/2004 – 04/2007	Genetics and Molecular Biology of Development
Harvard Medical School, MA, USA	Visiting fellow	10/2004 – 03/2007	Skeletal muscle pathophysiology
Department of Biology, University of Padova, Italy	Post-doctoral training	10/2007 – 03/2011	Skeletal muscle pathophysiology
Department of Biomedical Sciences, University of Padova, Italy	Post-doctoral training	04/2011 – 03/2013	Mitochondrial calcium in pathophysiology

Positions, Scientific Appointments, and Honors

Positions and Employment:

2018 – present: Associate Professor of Physiology, Department of Biomedical Sciences, University of Padova.

2015 – 2018: Researcher fixed-term (Italian fixed-term type B researcher), Department of Biomedical Sciences, University of Padova, Italy.

2013 – 2015: Researcher fixed-term (Italian fixed-term type A researcher), Department of Biomedical Sciences, University of Padova, Italy.

Scientific and Institutional Appointments (no remuneration received):

2023 – Present: Member of the Academic Senate, University of Padova.

2019 – Present: Member of the Didactic Commission, Department of Biomedical Sciences, University of Padova.

2018 – Present: Faculty Board member, PhD course in Biomedical Sciences, University of Padova.

2019 – Present: Member of the Governing Council of the PhD in Biomedical Sciences, University of Padova.

2021 – Present: Member of the Optional Courses Commission of the School of Medicine, University of Padova.

2019 – 2023: Member of the Department Council of Biomedical Sciences, University of Padova.

2017 – Present: Member of CirMyo - Center for Myology - with administrative headquarters at the Department of Biomedical Sciences, University of Padova.

Honors

2012 – 2013: Awarded a biennial senior research grant from the University of Padova under the "Young Scholars Grants for the awarding of Senior Research Grants and for the support of research of an innovative

and excellent nature proposed by young non-structured researchers" for the research activity titled: "Molecular characterization and physiological relevance of the mitochondrial calcium uniporter."

2011: Award reserved for Post-docs for the best-presented poster: "A 40 kDa protein of the inner membrane is the mitochondrial calcium uniporter", Mitochondrial Dynamics Meeting: from Mechanism to Disease, Sardinia.

2009: First prize reserved for young researchers with the work titled: "JunB, a novel FoxO inhibitor which prevents muscle loss and promotes muscle growth," IV National Congress of the Italian Society of Biomedicine and Space Biotechnology (ISSBB) "A world without gravity", Santa Margherita Ligure.

2008: Ennio Manzin and Mario Fioretti Award - 2nd edition - best oral presentation titled: "JunB transcription factor promotes muscle growth and blocks atrophy", seventh annual retreat of the Venetian Institute of Molecular Medicine (VIMM), Bassano del Grappa.

C. Contributions to Science

I possess a robust background in skeletal muscle physiology and mitochondrial Ca^{2+} signaling.

During my academic journey as a graduate student, I collaborated with Prof. Goldberg's at Harvard Medical School and Prof. Sandri at the University of Padova. There, I directed my focus towards investigating the signaling pathways implicated in skeletal muscle atrophy and growth.

Throughout this period, I characterized the transcriptional changes during denervation and disuse atrophy. My research led to the identification of a set of genes, termed "atrogenes", whose expression is coordinately induced or suppressed in muscle during atrophy. This seminal work, published in the FASEB journal (2007), continues to be actively cited today, accumulating approximately 450 citations. These findings laid the groundwork for further exploration into the molecular mechanisms governing skeletal muscle mass. Additionally, I characterized one of the most downregulated atrogenes, elucidating its pivotal role in muscle hypertrophic growth. This research, published in the Journal of Cell Biology in 2010, has garnered over 100 citations.

Subsequently, as a postdoctoral fellow in the laboratory of Prof. Rizzuto at the University of Padova, I focused on researching the role of mitochondrial Ca^{2+} in skeletal muscle homeostasis.

My significant contribution, widely recognized internationally, was the identification of the long sought Mitochondrial Calcium Uniporter (MCU), the channel responsible for Ca^{2+} ion entry into the mitochondrial matrix. This groundbreaking discovery, published in Nature in 2011, not only marked a significant milestone in my career but also represented a pivotal turning point in the field of Ca^{2+} signaling. The paper has since accumulated over 1500 citations and catalyzed a surge of interest in the role of mitochondrial Ca^{2+} homeostasis in pathophysiology.

As I transitioned to a junior faculty position, I continued to explore the functional intricacies of the MCU machinery. I made substantial contributions to elucidating the MCU complex, including the discovery and characterization of the dominant-negative subunit of the channel pore MCUb (published in EMBO Journal in 2013, with over 350 citations) and uncovering the mechanism of Ca^{2+}-dependent regulation of the channel (published in Molecular Cell in 2014, with over 390 citations).

Building upon my expertise in skeletal muscle and mitochondrial Ca^{2+} homeostasis, I endeavored to dissect the role of MCU in various facets of muscle pathophysiology. I contributed to uncover the impact of mitochondrial Ca^{2+} homeostasis on muscle trophism (published in Cell Reports in 2015, with over 150 citations) and identified a splicing isoform of the channel regulator MICU1, named MICU1.1, exclusively expressed in skeletal muscle and I elucidated its mechanism of action. I published these findings as a senior author in Molecular Cell in 2016 (with over 100 citations).

Furthermore, I investigated the role of MCU in macrophages within the context of skeletal muscle regeneration. I demonstrated that the dominant-negative subunit of the channel, MCUb, modulates the polarization state of macrophages, thereby influencing muscle regeneration post-injury. This research,

published as a senior author in Science Signaling in 2021, contributed significantly to our understanding of the intricate interplay between mitochondrial Ca^{2+} signaling and skeletal muscle regeneration.

D. Relevant Publications

1. Vecellio Reane D, Cerqua C, Sacconi S, Salviati L, Trevisson E, **Raffaello A**. The Splicing of the Mitochondrial Calcium Uniporter Genuine Activator MICU1 Is Driven by RBFOX2 Splicing Factor during Myogenic Differentiation. Int J Mol Sci. 2022 Feb 24;23(5):2517. PMID: 35269658.
2. Feno S, Munari F, Reane DV, Gissi R, Hoang DH, Castegna A, Chazaud B, Viola A, Rizzuto R, **Raffaello A**. The dominant-negative mitochondrial calcium uniporter subunit MCUb drives macrophage polarization during skeletal muscle regeneration. Sci Signal. 2021 Nov 2;14(707):eabf3838. PMID: 34726954.
3. Vecellio Reane D, Vallese F, Checchetto V, Acquasaliente L, Butera G, De Filippis V, Szabò I, Zanotti G, Rizzuto R, **Raffaello A**. A MICU1 Splice Variant Confers High Sensitivity to the Mitochondrial Ca2+ Uptake Machinery of Skeletal Muscle. Mol Cell. 2016 Nov 17;64(4):760-773. PMID: 27818145.
4. Mammucari C, Gherardi G, Zamparo I, **Raffaello A**, Boncompagni S, Chemello F, Cagnin S, Braga A, Zanin S, Pallafacchina G, Zentilin L, Sandri M, De Stefani D, Protasi F, Lanfranchi G, Rizzuto R. The mitochondrial calcium uniporter controls skeletal muscle trophism in vivo. Cell Rep. 2015 Mar 3;10(8):1269-79. PMID: 25732818.
5. Patron M, Checchetto V, **Raffaello A**, Teardo E, Vecellio Reane D, Mantoan M, Granatiero V, Szabò I, De Stefani D, Rizzuto R. MICU1 and MICU2 finely tune the mitochondrial Ca2+ uniporter by exerting opposite effects on MCU activity. Molecular Cell. 2014 Mar 6;53(5):726-37. PMID: 24560927.
6. **Raffaello A**, De Stefani D, Sabbadin D, Teardo E, Merli G, Picard A, Checchetto V, Moro S, Szabò I, Rizzuto R. The mitochondrial calcium uniporter is a multimer that can include a dominant-negative pore-forming subunit. EMBO J. 2013 Aug 28;32(17):2362-76. PMID: 23900286.
7. Rizzuto R, De Stefani D, **Raffaello A**, Mammucari C. Mitochondria as sensors and regulators of calcium signalling. Nat Rev Mol Cell Biol. 2012 Sep;13(9):566-78. PMID: 22850819.
8. De Stefani D, **Raffaello A***, Teardo E, Szabò I, Rizzuto R. A forty-kilodalton protein of the inner membrane is the mitochondrial calcium uniporter. Nature. 2011 Jun 19;476(7360):336-40. PMID: 21685888. (*co-first author)
9. **Raffaello A**, Milan G, Masiero E, Carnio S, Lee D, Lanfranchi G, Goldberg AL, Sandri M. JunB transcription factor maintains skeletal muscle mass and promotes hypertrophy. J Cell Biol. 2010 Oct 4;191(1):101-13. PMID: 20921137.
10. Sacheck JM, Hyatt JP, **Raffaello A**, Jagoe RT, Roy RR, Edgerton VR, Lecker SH, Goldberg AL. Rapid disuse and denervation atrophy involve transcriptional changes similar to those of muscle wasting during systemic diseases. FASEB J. 2007 Jan;21(1):140-55. PMID: 17116744.
11. **Raffaello A**, Laveder P, Romualdi C, Bean C, Toniolo L, Germinario E, Megighian A, Danieli-Betto D, Reggiani C, Lanfranchi G. Denervation in murine fast-twitch muscle: short-term physiological changes and temporal expression profiling. Physiol Genomics. 2006 Mar 13;25(1):60-74. PMID: 16380408.