

BIOGRAPHICAL SKETCH

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NAME: **Serena Carra**

eRA COMMONS USERNAME (credential, e.g., agency login): not applicable

POSITION TITLE: Associate Professor

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)	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of Modena, Italy	Master	10/1992	10/1998	Chemistry and Pharmaceutical Sciences
University of Modena, Italy	Training	10/1998	10/1999	Pharmaceutical Research Methods
University of Catania, Italy	Ph.D.	11/2000	01/2004	Neurobiology
Laval University, Canada	Postdoc	01/2004	05/2007	Molecular Biology
University Medical Center Groningen, The Netherlands	Postdoc	06/2007	05/2009	Molecular Biology
University Medical Center Groningen, The Netherlands	Assistant Professor	06/2009	07/2011	Molecular Biology
University of Modena and Reggio Emilia, Italy	Assistant Professor	07/2011	10/2015	Molecular Biology
University of Modena and Reggio Emilia, Italy	Associate Professor	11/2015	current	Molecular Biology

A. Personal Statement

I dedicated my research to understand the role of chaperones in the maintenance of proteostasis and their implication in rare neurodegenerative and neuromuscular diseases, characterized by cognitive defects including for example Amyotrophic Lateral Sclerosis and other motor neuron diseases. My research contributions were fundamental in shaping the concept of protein quality control of biomolecular condensates, showing the existence of a strong link between phase-separating proteins, condensates dynamics and protein quality control failure, with important implications for cell function and age-related neurodegenerative diseases. My training in pharmaceutical chemistry and neurobiology and the acquired expertise in the field of proteostasis and its novel role in maintaining the dynamics and function of RNA-protein biomolecular condensates positions me to be able to study the molecular mechanisms at the basis of complex diseases, including those associated with mutations in the genes coding for the small heat shock proteins, and to identify potential targets for therapeutic purposes.

B. Positions, Scientific Appointments and Honors

Positions and Employments:

2009-2011 Assistant Professor, University Medical Center Groningen, The Netherlands

2011-2015 Assistant Professor, Rita Levi Montalcini Program, University of Modena and Reggio Emilia, Italy

2015-current Associate Professor, University of Modena and Reggio Emilia, Italy

Other experiences:

2000-2001 Training in Dr. Nicholas Barden Neurosciences lab at Université Laval (CHUL), Canada

Awards as group leader:

- 8th June 2023, Alberto Pio III Award, ROTARY INTERNATIONAL, District 2072°, Italy
- 2022, The Giovanni Armenise Harvard Foundation and AirAlzh, mid-career on neurodegenerative diseases
- 2017, Ferruccio Ritossa Early Career Award, Turku, Finland
- 2011, Rita Levi Montalcini Award, Governmental Award to attract excellent researchers in Italy

Awards as senior post-doc:

- 2009 – 2012, Marie Curie International Reintegration Grant FP7
- 2008, Young Investigator Award National Ataxia Foundation, USA

Elected organizers of international scientific meetings:

- 2nd (2016), 3rd (2018) and 4th (2022) sHSP International Workshop of Cell Stress Society International (CSSI); - 2022, elected co-organizer with Prof. R. Meki of the upcoming (2026) Jacques Monod conference on Protein Phase Transitions; - 2023, elected co-organizer with Prof. U. Hartl of the upcoming (2025) EMBO workshop on protein quality control.

C. Contributions to Science (10 selected publications)

1. Bridging chaperones with the autophagy system.

It was known that small heat shock proteins can cooperate with HSP70 to target proteins for degradation by the proteasome. Yet, in the early 2000, protein degradation by autophagy was still considered to be a “bulk” and rather non-specific event. During her first post-doc, Dr. Carra discovered the HSPB8-BAG3-HSP70 complex and its role in targeting misfolded proteins to autophagy, with important implications in age-related neurodegenerative diseases. She also contributed to show how mechanistically the rare BAG3-P209L and the HSPB8-K141E/N mutations lead to myopathy and motor neuropathy, using cell and Drosophila models. Relevant articles for this contribution are:

[1] **Carra S**, Seguin SJ, Lambert H and Landry J. HspB8 chaperone activity toward poly(Q)-containing proteins depends on its association with Bag3, a stimulator of macroautophagy. **J Biol Chem.** 2008, PMID: 18006506; **FWCI 5.48**

[2] Meister-Broekema M, Freilich R, Jagadeesan C, Rauch JN, Bengoechea R, Motley WW, Kuiper EFE, Minoia M, Furtado GV, van Waarde MAWH, Bird SJ, Rebelo A, Zuchner S, Pytel P, Scherer SS, Morelli FF, **Carra S**, Wehl CC, Bergink S, Gestwicki JE, Kampinga HH. Myopathy associated BAG3 mutations lead to protein aggregation by stalling Hsp70 networks. **Nat. Commun.** 2018, PMID: 30559338. **FWCI 1.71**

2. Protein quality control of stress granules.

Dr. Carra work established an unexpected link between the protein quality control and the dynamics of liquid-liquid phase separated condensates. Carra was a pioneer in showing that chaperones maintain the dynamic properties of membraneless organelles such as stress granules, whose dysfunction is an important pathomechanism in Amyotrophic Lateral Sclerosis. Independent groups followed Dr. Carra research lines and further established the importance of the protein quality control and autophagy in the disassembly and clearance of aberrant SGs. Relevant articles for this contribution are:

[3] Ganassi M, Mateju D, Bigi I, Mediani L, Poser I, Lee HO, Seguin SJ, Morelli FF, Vinet J, Leo G, Pansarasa O, Cereda C, Poletti A, Alberti S, **Carra S**. A Surveillance Function of the HSPB8-BAG3-HSP70 Chaperone Complex Ensures Stress Granule Integrity and Dynamism. **Mol Cell.** 2016, PMID: 27570075; **FWCI 5.84**

[4] Mateju D, Franzmann TM, Patel A, Kopach A, Boczek EE, Maharana S, Lee HO, **Carra S**, Hyman AA, Alberti S. An aberrant phase transition of stress granules triggered by misfolded protein and prevented by chaperone function. **EMBO J.** 2017, PMID: 28377462; **FWCI 10.90**

[5] Boczek EE, Fürsch J, Niedermeier ML, Jawerth L, Jahnel M, Ruer-Gruß M, Kammer KM, Heid P, Mediani L, Wang J, Yan X, Pozniakowski A, Poser I, Mateju D, Hubatsch L, **Carra S**, Alberti S, Hyman AA, Stengel F. HspB8 prevents aberrant phase transitions of FUS by chaperoning its folded RNA binding domain. **Elife.** 2021, PMID: 34487489; **FWCI 2.47**

[6] Mediani L, Antoniani F, Galli V, Vinet J, Carrà AD, Bigi I, Tripathy V, Tiago T, Cimino M, Leo G, Amen T, Kaganovich D, Cereda C, Pansarasa O, Mandrioli J, Tripathi T, Troost D, Aronica E, Buchner J, Goswami A, Sternecker J, Alberti S, **Carra S**. Hsp90-mediated regulation of DYRK3 couples stress granule disassembly and growth via mTORC1 signaling. **EMBO Rep.** 2021, PMID: 33738926. **FWCI 2.41**

3. Discovery and characterization of nucleoli and PML bodies as novel phase separated protein quality control compartments.

Dr. Carra uncovered a role for nucleoli and PML-bodies as phase-separated protein quality control organelles that compartmentalize protein quality control factors and misfolded proteins for their efficient clearance. Failure to dispose misfolded proteins converts nucleoli and PML-bodies into a solid state that immobilizes ubiquitin, limiting its recycling for genome integrity maintenance. Recent studies highlighted that a substantial fraction of nascent peptides is destroyed within minutes after their synthesis by proteasomes. Some of these peptides are generated from upstream open-reading frames and globally these peptides are referred to as the “dark proteome”, being their sequence and structure unknown. This “dark proteome”, located in the cytoplasm and the nucleus, would challenge nuclear proteostasis by potentially competing with mutated and unstable proteins for folding and clearance. Together, these findings make a strong case for further investigations aimed at elucidating the quality control functions of nucleoli and PML-bodies and how dysregulation of these compartments affects genome integrity and contributes to human aging and disease, including Amyotrophic Lateral Sclerosis. Relevant article for this contribution is:

[7] Mediani L, Guillén-Boixet J, Vinet J, Franzmann TM, Bigi I, Mateju D, Carrà AD, Morelli FF, Tiago T, Poser I, Alberti S, **Carra S**. Defective ribosomal products challenge nuclear function by impairing nuclear condensate dynamics and immobilizing ubiquitin. **EMBO J.** 2019, PMID: 31271238. **FWCI 2.28**

4. Discovery of the phase separating properties and nuclear functions of HSPB2 and characterization of its implication in neuromuscular diseases.

Small heat shock proteins (HSPBs) contain intrinsically disordered regions (IDRs), but the functions of these IDRs are still unknown. Dr. Carra reported for the first time the ability of a small heat shock protein to undergo concentration-dependent liquid-liquid phase separation in cells. Morelli et al. show that, in mammalian cells, HSPB2 forms liquid-like nuclear compartments that affect lamin A localization and mobility, with detrimental consequences for chromatin organization and nuclear integrity. Aberrant compartment formation by HSPB2 is regulated by HSPB3, but not by two identified HSPB3 mutants linked to myopathy. These findings support the idea that aberrant HSPB2 phase separation, due to HSPB3 loss-of function mutations, contributes to myopathy.

These data provide new potential mechanisms by which HSPB2 and HSPB3 deregulation contributes to rare neuromuscular diseases, acting at the nuclear level. Relevant article for this contribution is:

[8] Morelli FF, Verbeek S, Bertacchini J, Vinet J, Mediani L, Marmioli S, Cenacchi G, Nasi M, De Biasi S, Brunsting JF, Lammerding J, Pegoraro E, Angelini C, Tupler R, Alberti S, **Carra S**. Aberrant compartment formation by HSPB2 mislocalizes lamin A and compromises nuclear integrity and function. **Cell Rep.** 2017, PMID: 28854361. **FWCI 1.11**

5. Identification of pro-differentiating functions of HSPB3 and characterization of its implication in neuromuscular diseases.

The selective expression of HSPB2 and HSPB3 in differentiating muscle cells was reported during the 1990s, yet the physiological functions of these two chaperones were unknown. The discovery in 2010

of the first mutation in the HSPB3 gene in distal hereditary motor neuropathy further established a link between these two proteins and the neuromuscular system. However, no clear functions were known for HSPB2 and HSPB3 and no pathomechanisms leading to HSPB3-disease were available. Dr. Carra report that localization and activity of the LBR-tether are crucially dependent on the muscle-specific chaperone HSPB3 and that depletion of HSPB3 prevents muscle cell differentiation. Conversely, upregulation of HSPB3 promotes the differentiation of human myoblasts and rhabdomyosarcoma cells, which are myogenic cancer cells that fail to differentiate leading to malignant proliferation. These findings pave the way for a better understanding of HSPB3 implication in the neuromuscular system physiopathology, with implications that may extend to rhabdomyosarcoma. Relevant articles for this contribution are:

- [9] Tiago T, Hummel H, Morelli F, Basile V, Vinet J, Galli V, Mediani L, Antoniani F, Pomella S, Cassandri M, Garone M, Silvestri B, Cimino M, Cenacchi G, Costa R, Mouly V, Poser I, Yeger-Lotem E, Rosa A, Alberti S, Rota R, Ben-Zvi A, Sawarkar R, **Carra S**. Small heat-shock protein HSPB3 promotes myogenesis by regulating the Lamin B receptor. **Cell Death Dis.** 2021, PMID: 33958580; **FWCI 0.92**
- [10] Shemesh N, Jubran J, Dror S, Simonovsky E, Basha O, Argov C, Hekselman I, Abu-Qarn M, Vinogradov E, Mauer O, Tiago T, **Carra S**, Ben-Zvi A and Yeger-Lotem E. The landscape of molecular chaperones across human tissues reveals a layered architecture of core-variable chaperones. **Nat. Commun.** 2021, PMID: 33846299. **FWCI 3.21**

List of peer-reviewed publications by Carra:

<https://www.carralab.unimore.it/publications/>

Invitation to write news and views and conference proceedings, as group leader:

- Ecroyd H, ...Benesch JLP, **Carra S**. The beauty and complexity of the small heat shock proteins: a report on the proceedings of the fourth workshop on small heat shock proteins. **Cell Stress Chaperones** 2023, PMID: 37462824;
- Alberti S, **Carra S**. A shared fate for nuclear and cytosolic inclusions. **Nat Cell Biol.** 2023, PMID: 37081163;
- Cable J et al., Targeted protein degradation: from small molecules to complex organelles-a Keystone Symposia report, **Ann N Y Acad Sci** 2022, PMID: 35000205;
- Alberti S, **Carra S**. Nucleolus: A Liquid Droplet Compartment for Misbehaving Proteins. **Curr Biol.** 2019, PMID: 31593669;
- **Carra S**, et al., Small heat shock proteins: multifaceted proteins with important implications for life. **Cell Stress Chaperones** 2019, PMID: 30758704;
- Weihl CC, Udd B, Hanna M; ENMC workshop study group. 234th ENMC International Workshop: Chaperone dysfunction in muscle disease Naarden, The Netherlands, 8-10 December 2017. **Neuromuscul Disord.** 2018, PMID: 30424919;
- **Carra S**, et al. The growing world of small heat shock proteins: from structure to functions. **Cell Stress Chaperones** 2017, PMID: 28364346.

Invited presentations to major conferences:

To date, I presented over 60 invited lectures at international conferences and workshops; a selection of the most relevant are listed here:

- 2024, EMBO, EMBL Symposium: Cellular mechanisms driven by phase separation. Heidelberg, Germany;
- 2024, Third European C9orf72 workshop, Munich, Germany;
- 2023, SIBBM, Frontiers in Molecular Biology. Beyond Genomics: Next Generation Molecular Biology. Bari, Italy;
- 2023, EMBO Workshop, Protein quality control: From molecular mechanisms to therapeutic intervention, Srebreno-Dubrovnik, Croatia;
- 2022, Jacques Monod Conference "Protein phase transitions in ageing and age-related diseases: from atomic resolution to cellular solutions", France;
- 2021, FASEB Conference on Protein Aggregation: Function, Dysfunction, and Disease;
- 2021, PhasAGE International Conference "Phase Transitions in Aging and Age-related Diseases";

- 2021, Targeted Protein Degradation: From Small Molecules to Complex Organelles". Keystone eSymposia;
- 2019, Gordon Research Conference, Amyotrophic Lateral Sclerosis (ALS) and Related Motor Neuron Diseases, Mechanisms of Motor Neuron Degeneration and Therapeutic Intervention, Mount Snow, US;
- 2019, Protein quality control: From mechanisms to disease, Costa de la Calma, Mallorca, Spain;
- 2018, First Autumn School on Proteostasis, Medils, Split, Croatia;
- 2018, EMBO, EMBL Symposium: Cellular Mechanisms Driven by Liquid Phase Separation, Heidelberg, Germany;
- 2018, SIBBM, Italian Society of Biophysics and Molecular Biology, Frontiers in Molecular Biology, La Sapienza University;
- 2017, 234th ENMC (European NeuroMuscular Centre) workshop on Chaperone, Naarden, The Netherlands;
- 2017, The 8th international congress on stress proteins in biology and medicine, Turku, Finland;
- 2017, EMBO Conference, Protein Quality Control: Success and failure in health and disease, Sant Feliu de Guixols, Girona, Spain;
- 2016, Protein Homeostasis in Health and Disease, Cold Spring Harbor, New York, USA.

Selected invited lectures:

- 2023, Condensate Colloquium Series organized by Pappu, Alberti, Gladfelter and Mahamid;
- 2022, Neurobiology, Experimental Neurology, VIB-KU Leuven, Center for Brain & Disease Research, Leuven, Belgium;
- 2020, Cellular and protein homeostasis webinars, Organisers: P. De Los Rios, P. Goloubinoff, A. Barducci and N. Nillegoda;
- 2020, University La Sapienza, Rome, Italy, Webinars in: "Molecular and cellular mechanism of DISEASES";
- 2020, European Research Institute for the Biology of Ageing, ERIBA, Groningen, The Netherlands;
- 2020, Lecture for The Department of Biomedical Sciences, University of Lausanne, Switzerland;
- 2019, CRMB, Montpellier, France;
- 2019, International Centre for Genetic Engineering and Biotechnology, Trieste, Italy;
- 2019, Department of Biomedical Sciences, University of Padova, Italy;
- 2018, CIBIO, University of Trento, Italy;
- 2018, Italian Institute of Technology, Genoa, Italy;
- 2017, The Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli, Naples, Italy.

Other contributions to the research community: Review activity for journals (in alphabetical order): BBA - Molecular Cell Research; Biomolecular Concepts; Cell Death and Differentiation; Cell Death and Disease; Cell Reports; Cell Stress and Chaperones; Essays in Biochemistry; eLIFE; Expert Review of Proteomics; FEBS Letters; Frontiers; Journal of Cell Biology; Journal of Molecular Neuroscience; Heliyon; iScience; Mechanisms of Ageing and Development; Molecular Neurobiology; Nature Cell biology; Nature Communication; Neurobiology of Aging; Neuropathology and Applied Neurobiology; Neuroscience; Plos One; Redox; TIBS; Trends in Pharmacological Sciences; The International Journal of Biochemistry & Cell Biology. Review activity for scientific foundations: Ataxia UK, Deutsche Forschungsgemeinschaft, ERC 2020 Grant Calls, Portuguese Foundation for Science and Technology, Israel Science Foundation, Czech Science Foundation, FWF Austrian Science Fund, Swiss Science Foundation, BIRAX British Council; Neurobiology Division at the MRC (Cambridge, UK).

Public engagement: 2021, Member of the panel discussion about Diversity and Inclusion at the FASEB meeting "Targeted Protein Degradation"; 2020, dissemination event to introduce students of G. Fassi middle school to microscopy techniques, with Centro Grandi Strumenti (CIGS), Univ. of Modena; 2019, "Magic Hour", dissemination event to introduce high school students of Liceo M. Fanti to biomedical research; 2018 and 2019, organization of concerts with primary school students and music conservatoire for fundraising campaign for Telethon Italy; 2018, dissemination event for the Italian Muscular Dystrophy Association.

D. Research Support

To date, I obtained research support from the following national, European and international funding agencies:

- 2008, National Ataxia Foundation (USA),
- 2009, Marie Curie Actions (EU, FP7 program),
- 2010, Prinses Beatrix Fonds/Dutch Huntington Association,
- 2011, 2017, 2019, 2023, Italian Ministry of University and Research (MUR),
- 2011, Italian Ministry of Health (MoH),
- 2011, 2012, 2021, Association française contre les myopathies (AFM),
- 2012, 2015, 2022, Telethon-Italy,
- 2012, 2015, 2019, 2023, Agency for Research on Amyotrophic Lateral Sclerosis (AriSLA),
- 2015, The Italian Cariplo Foundation,
- 2016, 2017, The Ministry of Foreign Affairs and International Cooperation (MAECI),
- 2016, JPND Neurodegenerative Disease Research (EU),
- 2017, Italian Medicines Agency (AIFA),
- 2022, The Muscular Dystrophy Association (MDA), USA
- 2022, Mid-career award on neurodegenerative diseases (AHA-MCA) supported by Armenise Harvard Foundation, Agency for Research on Alzheimer (AriAlzh).

Ongoing research support:

- Feb. 2024 – Feb. 2026 Italian Ministry of University and Research (MUR), project PRIN 2022WBHCSM
- March 2023 – March 2026 Agency for Research on Amyotrophic Lateral Sclerosis (AriSLA), project SUMOsolvable
- Dec. 2022 – Dec. 2025 Armenise Harvard Foundation and AriAlzh, project AHA-MCA 2022
- Sept. 2022 – Sept. 2025 The Muscular Dystrophy Association (MDA), USA, project 952599
- April 2022 – Nov. 2025 Telethon-Italy, project GMR22T1003