University of Massachusetts Medical School
UMASS

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES
BIOCHEMISTRY AND MOLECULAR PHARMACOLOGY

Ph.D. THESIS DEFENSE

MELISSA ROTUNNO

Mentor: Daryl A. Bosco, PhD

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"IDENTIFYING, TARGETING AND EXPOLOITING A COMMON MISFOLDED, TOXIC CONFORMATION OF SOD1 IN ALS"

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by a loss of voluntary movement over time, leading to paralysis and death. While 10% of ALS cases are inherited or familial (FALS), the majority of cases (90%) are sporadic (SALS) with unknown etiology. SALS and FALS are clinically indistinguishable, suggesting that a common pathogenic mechanism exists for both types. Approximately 20% of FALS cases are genetically linked to a mutation in the anti-oxidizing enzyme Cu,Zn-superoxide dismutase (SOD1). However, misfolded, WT SOD1 lacking any genetic mutation exhibits toxic properties similar to those exhibited by FALS-linked variants, raising the intriguing possibility that misfolded forms of WT SOD1 contribute to SALS pathogenesis. A misfolded conformation of SOD1 that is relevant to both FALS and SALS was identified and characterized during this dissertation. My work revealed that exposure of this misfolded conformation enhances SOD1 toxicity. Based on this information, strategies were designed to prevent exposure of this “toxic” region and stabilize the non-toxic conformation as therapeutic avenues for ALS. Further, the possibility of exploiting this misfolded SOD1 species as a biomarker was explored. A more abundant, over-oxidized form of WT SOD1 in peripheral blood mononuclear cells (PBMCs) from SALS patients was uncovered. We also uncovered a more negatively charged SOD1 species in PBMCs that was reduced in SALS relative to controls. This charged species is hypothesized to modulate the degradation of SOD1, further implicating both misfolded SOD1 and altered protein homeostasis in ALS pathogenesis.

Mentor(s)
Daryl A. Bosco, PhD

Dissertation Exam Committee
Jill Zitzewitz, PhD (Chair)
Robert Brown, MD/PhD
William Royer, PhD
Haining Zhu, PhD