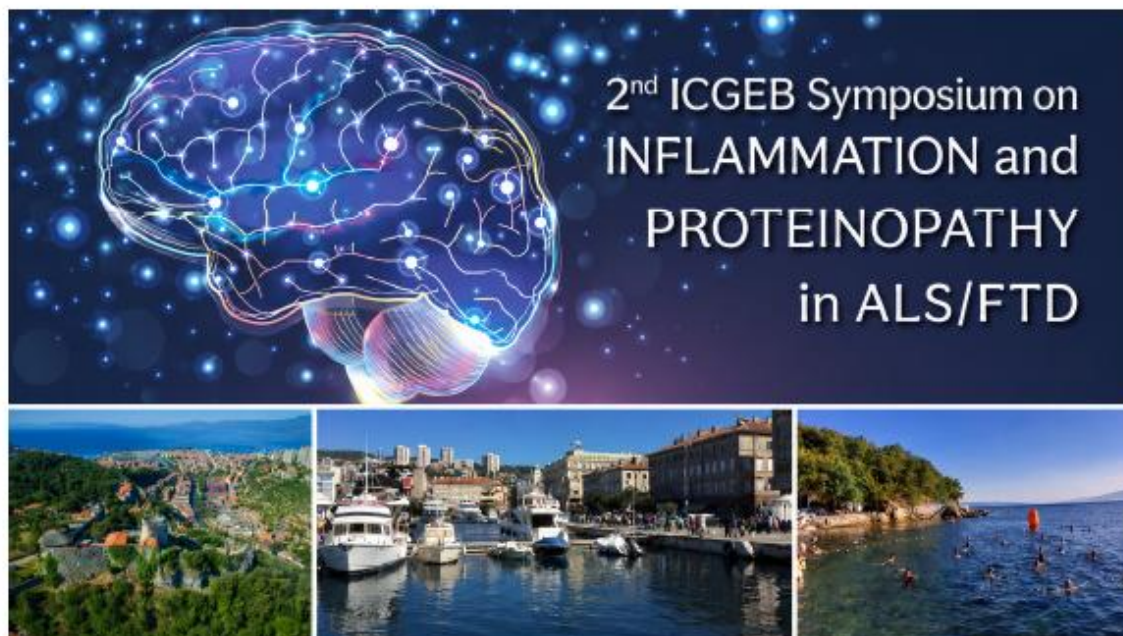




ABSTRACT BOOK

SCIENTIFIC COMMITTEE

Andrea Markovinovic Krajacic (Faculty of Medicine, Rijeka, Croatia)
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 Kristina Pilipović (Faculty of Medicine, Rijeka, Croatia)
 Vlatka Sotošek (Faculty of Medicine, Rijeka, Croatia)
 Ivana Marić (Faculty of Medicine, Rijeka, Croatia)

ORGANIZING COMMITTEE

Josip Peradinović, Ema Jalšić, Ivona Čargonja, Bojana Čulev, Toni Franjkić, Mariana Fučić, Željka Minić,
 Iva Kristić, Ivana Bertović, Dario Brizić, Nikolina Kovačević & Damjan Jonas Močnik



Cozzi, Marta

Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti" (DiSFeB),
Università degli Studi di Milano, Milan, Italy

Authors: Marta Cozzi¹, Stefania Magri², Barbara Tedesco¹, Veronica Ferrari¹, Marta Chierichetti¹, Laura Cornaggia¹, Ali Mohamed¹, Veronica Marchesi¹, Margherita Piccolella¹, Mariarita Galbiati¹, Paola Rusmini¹, Valeria Crippa¹, Cinzia Gellera², Riccardo Cristofani¹, Franco Taroni², Angelo Poletti¹

¹Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti" (DiSFeB), Università degli Studi di Milano, Milan, Italy

²Unit of Medical Genetics and Neurogenetics, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

Shared behaviours of ALS and NEIMY KIF5A mutants: similarities between a neurodegenerative and a neurodevelopmental molecular phenotypes

KIF5A is a neuron-specific kinesin involved in anterograde axonal transport. Frameshift mutations affecting KIF5A tail cause ALS or neonatal intractable myoclonus (NEIMY), a neurodevelopmental syndrome. Despite the phenotypic differences between ALS and NEIMY, the underpinning KIF5A mutations share abnormal reading frame and stop codon, producing elongated KIF5A variants with 40 aberrant amino acids in common. We therefore compared the behaviour of the ALS-KIF5A (N999Vfs*40) and NEIMY-KIF5A (C975Vfs*73) mutants to identify their unique and shared features. Bioinformatic analysis of ALS- and NEIMY-KIF5A sequences revealed that their aberrant tail is composed of poorly soluble residues. Notably, one low-solubility sequence was present in NEIMY-KIF5A but absent in ALS-KIF5A. Consistently, both mutants displayed low detergent solubility, but NEIMY-KIF5A accumulated into larger and less dynamic inclusion with respect to ALS-KIF5A. The increased aggregation tendency of NEIMY-KIF5A was also accompanied by more pronounced wild-type KIF5A sequestration compared to ALS-KIF5A, indicating a stronger negative dominance. Moreover, both ALS- and NEIMY-KIF5A inclusions were positive for SQSTM1/p62, which could only reach the rim of NEIMY-KIF5A aggregates. Interestingly, both ALS- and NEIMY-KIF5A accumulated upon proteasomal blockage, while autophagy inhibition did not change their levels, showing that the ubiquitin-proteasome system is predominantly involved in their degradation. Finally, both NEIMY- and ALS-KIF5A poorly co-distributed with mitochondria, well-established KIF5A cargoes, although the overall mitochondrial distribution was not significantly altered in cells.

Our observations indicate that most molecular behaviours characterising ALS-KIF5A are exacerbated for NEIMY-KIF5A, consistently with a more severe phenotype, and that a combination of gain- and loss-of-function mechanisms underpins both KIF5A-linked diseases.