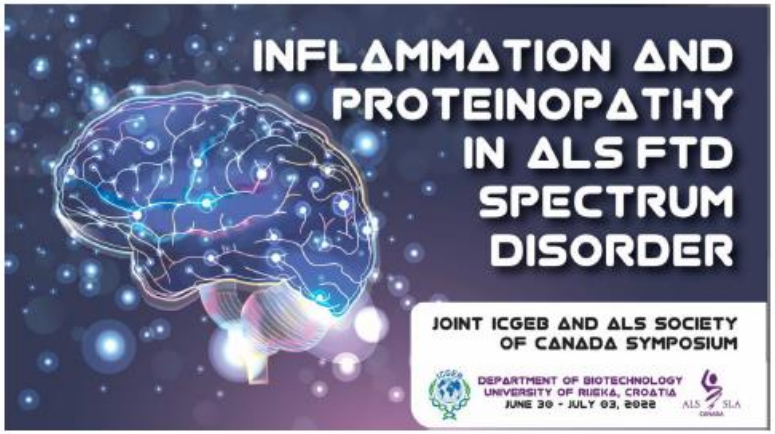


# ABSTRACT BOOK

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### How PQC inhibition modulates miRNA loading in large and small extracellular vesicles

Extracellular vesicles (EVs) are membrane-enclosed particles released from all eukaryotic cells that carry proteins, lipids, RNA and DNA. They are classified in two main types of EVs: large vesicles (LVs) and small vesicles (SVs). In our previous studies we observed that both LVs and SVs play a role in the disposal of neurotoxic aggregates of the TAR DNA-binding protein 43 (TDP-43) and its C-terminal fragments of 35 (TDP-35) and 25 KDa (TDP-25), associated with Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD).This release increased when the protein quality control (PQC) system [i.e. chaperone proteins, the ubiquitin proteasome system (UPS) and the autophagic pathway] was impaired, a common condition observed both in ALS and FTD. Since TDP-43 is an RNA-binding protein and it is involved in miRNA biogenesis, we wondered whether PQC impairment could also affect miRNA content in EVs. LVs and SVs were isolated from medium of NSC-34 cells, treated or not with the UPS inhibitor MG132 or with the autophagy inhibitor NH4Cl, by differential centrifugation and characterized by Nanosight. MicroRNA libraries were generated using Small RNA-Seq Library Prep Kit (Lexogen) and sequenced on a NextSeq 500/550 (Illumina). Interaction prediction was carried out on TarBase v.8 database. We found a total of 91 Differentially Expressed (DE) (log Fold Change (FC) >1 and <-1) microRNAs in treated-EVs compared to untreated EVs. No DE miRNA were found in NH4Cl-LVs, only 7 miRNAs were DE in MG132-LVs and of the 82 miRNAs in MG132-SVs and 66 in NH4Cl-SVs, 43 were in common. Interestingly, the most enriched pathway targeted by commonly DE SVs-miRNAs is the prion disease. In conclusion our observation suggests that, in disease condition, EVs are enriched in both toxic TDP-43 species and potentially harmful miRNA, and thus they may contribute to the propagation of the disease from affected to healthy cells.