Research and activity plan

Research plan

Small nucleolar RNAs (snoRNAs) are non-coding RNAs whose genes are hosted in the introns of protein-coding and non- protein-coding genes. snoRNAs guide the modification of specific residues in RNA (pseudouridylation for the H/ACA box snoRNAs and ribose methylation for C/D box snoRNAs). However, their functions are largely unexplored. Interestingly, a significant fraction of snoRNA sequences are found as retained introns of specific mRNA isoforms expressed from their host gene (or snoRNA retaining transcripts - snoRTs). Our preliminary results suggest that snoRTs localize in the cytoplasm, where they can associate with ribosomes and selected mRNAs. While several snoRTs are highly abundant, they have been entirely missed by gene-based RNA-seq analyses. Thus, we ignore the mechanisms behind their biogenesis, and their function in cell physiology and pathology. We observed that snoRTs expression is associated with primary breast cancer features, and that they interact with proteins involved in tumorigenesis. This evidence suggests that snoRTs could be highly relevant in cancer. The need to understand snoRTs biogenesis and function is thus evident. We also found that the human pseudouridine-synthase DKC1 could bind to snoRTs in the cytoplasm. snoRTs could thus allow the pseudouridylation complex to act on targets in the cytoplasm. We hypothesize these targets to comprise mRNAs and rRNAs accessible on ribosomal subunits, enabling snoRTs to act as post-transcriptional regulators and affect rRNA modification.
The work we propose aims at understanding how snoRTs are produced and processed in the cell. To this end, we will characterize the sequence of full-length snoRTs and their shorter 3’- counterparts, that are abundantly present in proliferating cells in order to find sequence or secondary structure motifs guiding their biogenesis.

The definition of these sequence features can help in defining the mechanism involved in their processing and possibly their functional features enabling future developments in the field.

Activity plan

To investigate the biogenesis of full-length and 3’ snoRTs the selected candidate will design and implement a bioinformatic pipeline to evaluate the presence of shared caracteristics among the 3’-snoRTs capable snoRNA.

The evaluation will include a sequence based motif search and, given the known complexity of snoRNA secondary structure, a predictive structure based search.

The findings obtained through this bioinformatic pipeline will be further validated using publicly available nanopore-based TCGA datasets. This validation will ultimately guide the development of a robust model for the identification of novel 3'-snoRTs.

Modulo richiesta assegno

TITOLO DEL PROGETTO			
TUTOR			
ASSEGNO FINANZIATO DA PROGETTO COMPETITIVO *(barrare la casella corrispondente)*	X SI	☐ NO	*Punti*
SE IL FINANZIAMENTO È COMPETITIVO L'ENTE FINANZIATORE			
PROGETTO/ATTIVITÀ A SCOPO COMMERCIALE *(es. sperimentazione profit)*	☐ SI	X NO	
CARATTERISTICHE DEL PROGETTO (*biomedico/osservazionale/clinico-interventistico/multidisciplinare*)	biomedico		
STATO DI APPROVAZIONE DEL PROGETTO DA PARTE DEL COMITATO ETICO (*se necessario per il tipo di studio barrare o evidenziare la casella corrispondente*)	☐ Ottenuto	☐ Da ottenere	

DESCRIZIONE DEL PROGETTO *(max 800 parole)* — *Punti*

(1)obiettivi, (2)materiali e metodi, (3) risultati/impatto attesi, (4) attività formativa e (5) di ricerca dell'assegnista

1 - Our preliminary results suggest that snoRTs localize in the cytoplasm, where they can associate with ribosomes and selected mRNAs. While several snoRTs are highly abundant, they have been entirely missed by gene-based RNA-seq analyses. Thus, we ignore the mechanisms behind their biogenesis, and their function in cell physiology and pathology. We observed that snoRTs expression is associated with primary breast cancer features, and that they interact with proteins involved in tumorigenesis. This evidence suggests that snoRTs could be highly relevant in cancer. The need to understand snoRTs biogenesis and function is thus evident. We also found that the human pseudouridine-synthase DKC1 could bind to snoRTs in the cytoplasm. snoRTs could thus allow the pseudouridylation complex to act on targets in the cytoplasm. We hypothesize these targets to comprise mRNAs and rRNAs accessible on ribosomal subunits, enabling snoRTs to act as post-transcriptional regulators and affect rRNA modification. The work we propose aims at understanding how snoRTs are produced and processed in the cell. To this end, we will characterize the sequence of full-length snoRTs and their shorter 3'- counterparts, that are abundantly present in proliferating cells**.** The primary objective of this research is to identify sequence motifs or structural patterns that play a critical role in guiding the biogenesis of both full-length and 3'-snoRTs. These motifs and patterns are likely associated with specific snoRNA features that influence the processing and maturation pathways leading to the formation of distinct snoRT types.

2 - The research will leverage bioinformatics methodologies to achieve its objectives. This may involve the utilization of existing computational tools, or the development of in-house pipelines specifically tailored to the project's needs. The chosen approach will be determined based on the specific requirements of the analysis and the availability of suitable existing tools.

3 - The research is expected to lead to the identification of key characteristics that govern snoRT biogenesis. This knowledge will be instrumental in the development of a model capable of identifying novel 3'-snoRTs.

4 – The candidate is expected to possess basic bioinformatics knowledge. This experise is expected to be further enhanced through participation in relevant conferences and workshops in the fiels (e.g. those organized by Translacore or other external entities).

5 -The chosen candidate will have to develop a comprehensive strategy to achieve the project's overarching aim. This strategy will encompass the design and implementation of the bioinformatics pipeline, data analysis, model development, and the interpretation of the obtained results.

DESCRIZIONE DELLE ATTIVITÀ DELL'ASSEGNISTA *(per i **nuovi** assegni: max 400 parole; competenze richieste, scansione temporale della formazione, scansione temporale dell'attività, obiettivi primari e secondari)* *(per i **rinnovi**: max 600 parole – da integrare con la relazione dell'assegnista; formazione raggiunta, attività effettuata, obiettivi raggiunti/competenze acquisite, formazione ancora da acquisire (se pertinente), scansione temporale dell'attività durante il rinnovo)*	*Punti*
To investigate the biogenesis of full-length and 3' snoRTs the selected candidate will design and implement a bioinformatic pipeline to evaluate the presence of shared characteristics among the 3'-snoRTs capable snoRNA. The evaluation will include a sequence-based motif search and, given the known complexity of snoRNA secondary structure, a predictive structure based search. The findings obtained through this bioinformatic pipeline will be further validated using publicly available nanopore-based TCGA datasets. This validation will ultimately guide the development of a robust model for the identification of novel 3'-snoRTs.	

Commissione proposta 3 commissari + 1 supplente	Lorenzo Montanaro
	Davide Treré
	Marianna Penzo
	Federico Zacchini (supplente)

Scheda attività assistenziale (se prevista)

ATTIVITÀ ASSISTENZIALI DELL'ASSEGNISTA/ N. ORE SETTIMANA

AZIENDA SANITARIA PRESSO CUI SI SVOLGERÀ L'ATTIVITÀ

Si ricorda che, come previsto dagli Accordi sull'impiego nell'attività assistenziale dei Titolari di assegni di ricerca, sottoscritti tra l'Università di Bologna e le Aziende Ospedaliere di riferimento, una volta stipulato il contratto con il vincitore della selezione, il tutor deve consegnare alla Direzione Medica Ospedaliera la relativa modulistica, nella quale andranno riportate le attività qui segnalate.