Corso di dottorato in Scienze Biomolecolari
PhD in Biomolecular Sciences
Ciclo 39 / Cycle 39
A.Y. 2023-2024

Reserved scholarships E

Progetti finanziati nell'ambito dei Dipartimenti di Eccellenza 2023-2027.
Curriculum Scienze Biomolecolari
Il vincitore sceglierà il progetto di ricerca dall'elenco sottostante.

MUR-funded grants - Departments of Excellence 2023-2027.
Biomolecular Sciences Curriculum
The winner will choose from the list available below the research project.

Principal Investigator	Project title
1 – Fulvio Chiacchiera	*Decrypting metastatic potential of primary liver tumors*
2 – Paolo Macchi, Alessandro Provenzani & Toma Tebaldi	*Transcriptome signature analysis in pediatric and adolescent myelodysplastic syndrome using a Single Cell approach*

Project 1

Decrypting metastatic potential of primary liver tumors

Laboratory:
Laboratory of Stem Cells and Cancer Genomics (https://www.cibio.unitn.it/956/laboratory-of-stem-cells-and-cancer-genomics)

Principal Investigator: Fulvio Chiacchiera

Synthetic description of the activity and expected research outcome
The possibility to predict the metastatic potential of a primary liver tumour and identify those genetic and epigenetic mechanisms involved in metastasis formation and growth would be a turning point for prognosis and therapy. A considerable lack of knoledge exist about the mechanisms involved in the formation of lung metastasis from primary hepatocellular carcinoma. This is mainly due to the lack of reliable models spontaneously recapitulating all the steps required for metastasis formation. We generated a novel hepatocellular carcinoma mouse model in which the growth of sporadic primary tumours followed by the formation of lung metastasis similarly to what can be observed in humans. We plan to use these models to characterize the transcriptional programs activated during the metastatic process, the genetic and epigenetic alterations involved, and to identify key features of potentially metastatic clones when still confined in the primary tumor. Complementary approaches will be used to successfully finalize this project. We will use spatial transcriptomics and proteomics to characterize primary tumours and metastatic lesions and single-cell transcriptomics to characterize the immune cells associated with these lesions. By performing whole exome sequencing of both primary tumors and metastatic cells we will obtain important informations about additional mutations eventually required for this transition and by performing ChIPseq experiments we will charachterize the alterations of the epigenetic landscape that charachterize primary tumors and metastatic lesions. The involvement of specific transcription factors will be inferred by the analysis of the differentially-activated transcriptional regulatory elements, providing important mechanistic evidence and possibly identifying actionable targets. The data obtained will shed light on the genetic and epigenetic mechanisms involved in cancer cell dissemination helping to identify specific traits charachterizing potentially metastatic clones that can be used to stratify primary liver tumors. The translatability of the data obtained will be explored in collaboration with the pathology unit of S. Chiara Hospital.

Candidate's profile (skills and competencies)
We are looking for passionate and curious open-minded candidates able to take risks and willing to fail. A mental attitude tuned towards problem solving and to collaborative work is required. He/she should hold a master's degree in biology, biotechnology, medicine, or related fields. Experience in topics such as genomic and epigenomics, mouse genetics, or histology, is preferred but is not mandatory. Willingness to work in vivo and strong ethical values are mandatory.

Project 2

Transcriptome signature analysis in pediatric and adolescent myelodysplastic syndrome using a Single Cell approach

Laboratory:
Laboratory of Molecular and Cellular Neurobiology (https://www.cibio.unitn.it/108/laboratory-of-molecular-and-cellular-neurobiology)

Principal Investigator: Paolo Macchi, Alessandro Provenzani & Toma Tebaldi

Synthetic description of the activity and expected research outcome
Description
Pediatric and adolescent myelodysplastic syndrome (MDS) is a very rare and still unexplored childhood preleukemic condition. It is characterized by bone marrow myeloid precursors or blasts that acquire sequential genetic alterations, resulting in disrupted maturation and uncontrollable proliferation (1-3).
Single-cell RNA sequencing (scRNA-seq) allows to analyse the transcriptome of complex tissues at a single-cell level and can identify differential gene expression as well as new cell-specific markers and cell types. ScRNA-seq plays an important role in various aspects of cancer research; it reveals the heterogeneity of tumor cells, monitors the progress of tumor development and enables the study of intercellular communication and the interaction of tumor and non-malignant cells to reveal their role in tumorigenesis (4-8).
Genetic mutations of malignant blast cells (subclones) can provide information on the perturbed function of genes and their corresponding pathways. While some insights into the relationship between genetic and transcriptional heterogeneity have been gained from bulk analysis (9), further characterization on the single-cell level is needed to more accurately dissect the pathway and regulatory features associated with distinct genetic subclones and to characterize intra-individual transcriptional heterogeneity.
Here, we will apply a single cell expression strategy to uncover major sources of the transcriptional differences and intra-individual transcriptional heterogeneity in pediatric and adolescent MDS. To our knowledge this is the first single-cell RNA sequencing study in pediatric and adolescent MDS.
Aims

In this project the candidate will apply scRNA-seq to pediatric and adolescent bone marrow mononuclear cells and bioinformatics analysis will be performed to explore the cell cluster differences and differentially expressed genes that may affect the development of pediatric and adolescent MDS. This may provide new targets for the disease treatment.
Furthermore, the candidate will assess the intra-individual transcriptional heterogeneity by identifying expression profile signature unique to subsets of malignant precancerous blast cells within each sample. These intra-individual transcriptional differences could highlight deregulated genes and pathways in potentially resistant subclones or reveal epigenetic changes driven by subclonal genetic alterations.
Expected results
Single-cell RNA sequencing provides a powerful means to characterize malignant cell populations in complex samples. In pediatric and adolescent MDS, scRNA-seq will differentiate the cell types in a complex population combination, promote the recognition of new cell types and contribute to the understanding of the physiological processes and the exploration of novel treatment options.
Furthermore, we will uncover the transcriptional changes at the single cell level of pediatric and adolescent MDS by scRNA-seq technology and identify novel molecular markers and major enrichment biological pathways through bioinformatics analysis. These markers may be important targets for future treatment of childhood and adolescent MDS.
This project will provide an atlas of pediatric and adolescent MDS cell states, regulators and gene targets with implications for precision medicine and immune therapies. We hope to identify new ways to deploy existing therapeutic strategies.

1. Rau AT, Shreedhara AK, Kumar S. Myelodysplastic syndromes in children: where are we today? The Ochsner journal. 2012.
2. Schwartz JR, Ma J, Lamprecht T, Walsh M, Wang S, Bryant V, et al. The genomic landscape of pediatric myelodysplastic syndromes. Nature communications. 2017.
3. Locatelli F, Zecca M, Pession A, Maserati E, De Stefano P, Severi F. Myelodysplastic syndromes: the pediatric point of view. Haematologica. 1995.
4. Mario L. Suvà, Itay Tirosh. Single-Cell RNA Sequencing in Cancer: Lessons Learned and Emerging Challenges, Molecular Cell, Volume 75, Issue 1, 2019, Pages 7-12, ISSN 1097-2765, https://doi.org/10.1016/j.molcel.2019.05.003