

2 master thesis projects available for Bioinformatics students at the IRCCS Regina Elena National Cancer Institute at the Fanciulli lab under the supervision of Dr. Giacomo Corleone. The projects will provide students with the opportunity to gain experience in a variety of bioinformatics techniques, including ATAC-seq, RNA-seq, and ChIP-seq. Students will also have the opportunity to collaborate with a team of experienced researchers and to contribute to cutting-edge research in cancer genomics.

To apply for one of these projects, please make a request to Dr. Corleone together with the CV/letter of interest at [giacomo.corleone@ifo.it](mailto:giacomo.corleone@ifo.it)

### **1) Investigating the role of transposable elements in the development and progression of multiple myeloma**

Multiple myeloma (MM) is a haematological malignancy characterized by the clonal proliferation of plasma cells within the bone marrow. Despite significant efforts in understanding the underlying pathogenesis of MM and the development of novel therapeutic approaches, it remains an incurable disease (*Kumar & Rajkumar, Nat.Rev.Clin.Oncol., 2018*) Recent evidence suggests that MM carcinogenesis involves epigenetic alterations, in addition to genetic factors. Transposable elements (TEs) are mobile DNA sequences that can insert themselves into the genome at random. TEs are thought to play a role in cancer development by disrupting gene expression and promoting genomic instability (*Grundy et al., FEBS J., 2022; Burns et al., Nat.Rev.Canc., 2017*)

Objectives:

The objective of this project is to investigate the role of TEs in the development and progression of MM. Specifically, we will:

- 1) Dissect the chromatin accessibility profile of a cohort of MM patients (~95 patients) comprising disease at the diagnosis and recurrence.
- 2) Investigate the activity of TEs using state-of-the-art computational approaches.
- 3) Identify the genes that are regulated by TEs in MM cells.
- 4) Determine the role of TEs in the activation of proliferative mechanisms in MM cells.

Methods:

We will use a combination of methods to investigate the role of TEs in MM, including: Chromatin immunoprecipitation sequencing (ChIP-seq) to identify the binding sites of TEs in MM cells.

Next-generation sequencing (NGS) to quantify the expression of TEs in MM cells.

Computational analysis to identify the genes that are regulated by TEs in MM cells.

In vitro and in vivo experiments to determine the role of TEs in the activation of proliferative mechanisms in MM cells.

Expected outcomes:

A better understanding of the role of TEs in the development and progression of MM.

The identification of new therapeutic targets for MM.

The development of new methods for diagnosing and treating MM.

## 2) ATAC-seq-based large-scale analysis of eccDNAs in colorectal cancer

Colorectal cancer (CRC) is a leading cause of cancer-related death worldwide. Despite extensive genomic studies, the molecular mechanisms underlying CRC development and progression are still not fully understood. Extrachromosomal circular DNA (eccDNAs) are small, circular DNA molecules that are found in both cancer and normal cells. eccDNAs are thought to play a role in cancer development by promoting genomic instability and by providing a reservoir of genetic material that can be used to drive tumor growth (Zhao *et al*, *eLife*, 2022).

### Objectives:

The objective of this project is to investigate the role of eccDNAs in the development and progression of CRC. Specifically, we will:

- 1) Apply, refine, and develop a method to detect eccDNAs (Kumar *et al.*, *Science Adv.*, 2020) in the largest cohort of ATAC-seq produced to date of colorectal cancer comprising ~1000 samples together with ~100 matched healthy tissues (Heide *et al*, *Nature*, 2022).
- 2) Investigate the impact of eccDNAs on gene expression and epigenetic regulation in CRC cells.
- 3) Identify target eccDNAs to be knocked out (KO) using CRISPR-Cas technology and investigate the associated KO phenotype in CRC cell lines.

### Methods:

We will use a combination of methods to investigate the role of eccDNAs in CRC, including:  
ATAC-seq to identify eccDNAs in CRC samples.  
RNA-seq to investigate the impact of eccDNAs on gene expression in CRC cells.  
ChIP-seq to identify the binding sites of transcription factors on eccDNAs in CRC cells.  
CRISPR-Cas technology to knock out target eccDNAs in CRC cell lines.

### Expected outcomes:

The development of new methods for identifying eccDNAs from ATAC-seq.  
A better understanding of the role of eccDNAs in the development and progression of CRC.  
The identification of new therapeutic targets for CRC.  
The development of new methods for diagnosing and treating CRC.