Faculté des Sciences
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Internship proposal - Master 2 Bioinformatics

Specialisation Software Development and Data Analysis

Internship period: Jan-Jun 2024

Internship title	Development and Benchmarking of computational tools to analyze transcriptomic perturbations in single-cell CRISPR-based genetic screen: an application to B cell lymphoid malignancies
Internship supervisor(s)	Sandrine ROULLAND, DR2 INSERM
Laboratory acronym(s)	CIML, Centre d'Immunologie de Marseille Luminy
Laboratory city(ies)	Marseille
Web site(s)	http://www.ciml.univ-mrs.fr/science/lab-bertrand-nadel-sandrine-roulland/genomic-instability-and-human-hemopathies
Team(s)	The 'Genomic Instability and Human hemopathies' team is led by Sandrine Roulland, and gather a multidisciplinary team of biologists, computational biologists and clinicians. The main goals of the team are to understand how tumor and microenvironment heterogeneity contribute to the development and response to therapy in B cell lymphoid malignancies and use this knowledge to identify novel therapeutic vulnerabilities.
E-mail(s)	roulland@ciml.univ-mrs.fr
Internship description	Combining CRISPR-based screens with single-cell RNA-seq (scRNA-seq) in cancer cells appears as a powerful approach for accessing the specific expression profile signatures of cells targeted by distinct genetic perturbation (knock-out in particular) and to infer target gene functions from the observed perturbations. Our team has developed an experimental workflow combining CRISPR/Cas9 genetic screens coupled with scRNA-seq transcriptomic readouts to study the impact the specific genetic alteration on the cell transcriptome of B-cell cancers. Because of the sparsity of scRNA-seq data as well as the expected heterogeneous and sometimes low perturbation signature induced by gene perturbation, an efficient statistical and bioinformatic tool is needed to extract this specific signal and assign gene function in a robust manner. The M2 project aims to benchmark a supervised autoencoder method (SAE) developed by our collaborator in Nice in lung cancer (Truchi et al. Biorxiv 2023, B. Mari Lab, IPMC) versus other recently published tools (MICMOSA/MIXCAPE) to validate the sensitivity

	and specificity of the different approaches in the context of lymphoid tumors. The lymphoid single-cell CRISPR screen dataset has already been produced and sequenced and will be fully available for the project. The Autoencoder tool SAE has been developed by the lab of B. Mari and all unpublished codes will be made available by IPMC for the benchmark. We expect that this benchmarking project will allow to inform on the best single-cell CRISPR tools and to standardize this type of single-cell CRISPR analysis. If successful, the SAE tool could be the object of a development and packaging in a user-friendly approach in order to facilitate its use and exploration of its outputs. The M2 student will benefit during his training at CIML from the professional support of experts bioinformaticians from the COMPUTATIONAL BIOLOGY, BIOSTATISTICS & MODELING (CB2M) in addition to the Roulland team's experts.
Expected skills	Programming skills in Python or R are necessary. Fluency in English and writing skills are required. An interest in multi-omics data analysis is a plus
Confidential (yes/no)	No
Informatics resources	CIML internal network and Mesocentre SAE Code from B. Mari Lab (IPMC, Nice)
Potential PhD project (yes/no)	Yes
References (2 and 3)	1. Schroers-Martin JG*, Brisou G*, Soo J*, Scherer F, Kurtz DM, Sworder B, Khodadoust MS, Jin MC, Bru A, Liu CL, Stehr H, Vineis P, Nathkuman Y, Teras LR, Song JY, Nadel B, Diehn M, Roulland S**, Alizadeh AA**. Tumor-Confirmed Follicular Lymphoma Mutations Are Detectable in Peripheral Blood Years Prior to Clinical Diagnosis. Cancer Discov. 2023 Jun 2;13(6):1310-1323. doi: 10.1158/2159-8290.CD-23-0111.PMID: 36939219 2. Webster DE, Roulland S, Phelan JD. Protocols for CRISPR-Cas9 Screening in Lymphoma Cell Lines. Methods Mol Biol. 2019 1956:337-350 3. Milpied P, Gandhi AK, Cartron G, Pasqualucci L, Tarte K, Nadel B, Roulland S. Follicular Lymphoma Dynamics. Adv Immunol. 2021;150:43-103 4. Truchi et al. A workflow combining single-cell CRISPRi screening and a supervised autoencoder neural network to detect subtle transcriptomic perturbations induced by

	lncRNA Knock-Down. Biorxiv 2023.