2021-11-30

EuReCa International PhD Program

PhD thesis project

2022 Call for application

Identification of Pediatric high-risk tumor master regulators: a pan-cancer study

General information

Call	2022
Reference	2022-13-SCHLEIERMACHER_CAVALLI
Keyword(s)	Computational biology; Pediatric cancer; Genomics data; Tumor heterogeneity; Master regulators.

Director(s) and team

Thesis director(s)	Gudrun Schleiermacher & Florence Cavalli
Research team	Computational Biology and Integrative Genomics of Cancer / Translational Pediatric Oncology
Research department	U900 – Bioinformatics, Biostatistics, Epidemiology and Computational Systems Biology of Cancer / U830 Cancer, Heterogeneity, Instability and Plasticity (CHIP)

Description of the PhD thesis project

The PhD project will be conducted as part of computational biology lab and translational pediatric oncology lab of Drs. Cavalli and Schleiermacher's. The Cavalli lab investigates tumor heterogeneity using genomic approaches to explore clinically relevant aspects of brain and more generally pediatric tumor biology. The Schleiermacher lab aims to characterize biomarkers in solid tumors, particularly neuroblastoma, to study the underlying mechanisms leading to the observed alterations and to develop new therapeutic approaches.

The mechanisms driving treatment resistance and the recurrent tumors of pediatric patients are still largely unknown. Clinicians have very few therapeutic options when a pediatric tumor relapses, it is, therefore, essential to better characterize them, discover the key genes driving recurrences to open the door to further research on novel treatment. An avenue to increase our understanding of aggressive tumors is to identify, the master regulators (MRs) that drive the transcriptional output. Analyzing a unique large-scale pan pediatric cancer dataset generated as part of the national MAPPYACTS and MICCHADO programs (20 tumor types, > 1000 tumors with multi-omics sequencing data; RNA-seq, WES (Whole Exome Sequencing)), coupled with high-level clinical data and CRISRP-Cas9 essential gene screen results, we will identify the MRs of high-risk pediatric tumor types as well as the ones driving the recurrent tumors. Integration of the genomics and clinical data will allow us to further decipher the treatment effects taking into account somatic alterations. In addition, analysis of CIRSPR-Cas9 essential gene screens on cell lines and integration of these results will allow us to further improve our MR identification pipeline and understanding of tumor progression mechanism. We will therefore pinpoint the most relevant genes that will be further validated and increase our understanding of the transcriptional programs driving pediatric tumors evolution.

International, interdisciplinary & intersectoral aspects of the project

For patients for whom sequencing could be performed both at diagnosis (MICCHADO) and at relapse (MAPPYACTS), international collaborations are currently being put in place in particular to analyze aspects of genomic clonal evolution. The project will be done with a co-supervision of a clinician and translational researcher Dr. Schleiermacher and a computational biologist Dr. Cavalli. The bioinformatics student performing this project will benefit from an ideal environment with experts in computation biology coupled to strong interactions with pediatric oncologists and wet lab researchers studying those tumors at Institut Curie allowing a refined and clinically relevant interpretation of the results.

Recent publications

1. **Cavalli FMG***, Remke M*, Rampasek L, Peacock J, Shih DJH, Luu B, Garzia L, Torchia J, Nor C, Morrissy AS, Agnihotri S, Thompson YY, Kuzan-Fischer CM, Farooq H, Isaev K, Daniels C, Cho BK, Kim SK, Wang KC, Lee JY, Grajkowska WA, Perek-Polnik M, Vasiljevic A, Faure-Conter C, Jouvet A, Giannini C, Nageswara Rao AA, Li KKW, Ng HK, Eberhart CG, Pollack IF, Hamilton RL, Gillespie GY, Olson JM, Leary S, Weiss WA, Lach B, Chambless LB, Thompson RC, Cooper MK, Vibhakar R, Hauser P, van Veelen MC, Kros JM, French PJ, Ra YS, Kumabe T, López-Aguilar E, Zitterbart K, Sterba J, Finocchiaro G, Massimino M, Van Meir EG, Osuka S, Shofuda T, Klekner A, Zollo M, Leonard JR, Rubin JB, Jabado N, Albrecht S, Mora J, Van Meter TE, Jung S, Moore AS, Hallahan AR, Chan JA, Tirapelli DPC, Carlotti CG, Fouladi M, Pimentel J, Faria CC, Saad AG, Massimi L, Liau LM, Wheeler H, Nakamura H, Elbabaa SK, Perezpeña-Diazconti M, Chico Ponce de León F, Robinson S, Zapotocky M, Lassaletta A, Huang A, Hawkins CE, Tabori U, Bouffet E, Bartels U, Dirks PB, Rutka JT, Bader GD, Reimand J, Goldenberg A, Ramaswamy V, Taylor MD. Intertumoral Heterogeneity within Medulloblastoma Subgroups. Cancer Cell. 2017 Jun 12;31(6):737-754.e6. doi: 10.1016/j.ccell.2017.05.005. PMID: 28609654; PMCID: PMC6163053. * co-first author

2. Morrissy AS*, **Cavalli FMG***, Remke M*, Ramaswamy V, Shih DJH, Holgado BL, Farooq H, Donovan LK, Garzia L, Agnihotri S, Kiehna EN, Mercier E, Mayoh C, Papillon-Cavanagh S, Nikbakht H, Gayden T, Torchia J, Picard D, Merino DM, Vladoiu M, Luu B, Wu X, Daniels C, Horswell S, Thompson YY, Hovestadt V, Northcott PA, Jones DTW, Peacock J, Wang X, Mack SC, Reimand J, Albrecht S, Fontebasso AM, Thiessen N, Li Y, Schein JE, Lee D, Carlsen R, Mayo M, Tse K, Tam A, Dhalla N, Ally A, Chuah E, Cheng Y, Plettner P, Li HI, Corbett RD, Wong T, Long W, Loukides J, Buczkowicz P, Hawkins CE, Tabori U, Rood BR, Myseros JS, Packer RJ, Korshunov A, Lichter P, Kool M, Pfister SM, Schüller U, Dirks P, Huang A, Bouffet E, Rutka JT, Bader GD, Swanton C, Ma Y, Moore RA, Mungall AJ, Majewski J, Jones SJM, Das S, Malkin D, Jabado N, Marra MA, Taylor MD. Spatial heterogeneity in medulloblastoma. Nat Genet. 2017 May;49(5):780-788. doi: 10.1038/ng.3838. Epub 2017 Apr 10. PMID: 28394352; PMCID: PMC5553617. * co-first author

3. Bellini A, Pötschger U, Bernard V, Lapouble E, Baulande S, Ambros PF, Auger N, Beiske K, Bernkopf M, Betts DR, Bhalshankar J, Bown N, de Preter K, Clément N, Combaret V, Font de Mora J, George SL, Jiménez I, Jeison M, Marques B, Martinsson T, Mazzocco K, Morini M, Mühlethaler-Mottet A, Noguera R, Pierron G, Rossing M, Taschner-Mandl S, Van Roy N, Vicha A, Chesler L, Balwierz W, Castel V, Elliott M, Kogner P, Laureys G, Luksch R, Malis J, Popovic-Beck M, Ash S, Delattre O, Valteau-Couanet D, Tweddle DA, Ladenstein R, **Schleiermacher G**. Frequency and Prognostic Impact of ALK Amplifications and Mutations in the European Neuroblastoma Study Group (SIOPEN) High-Risk Neuroblastoma Trial (HR-NBL1). J Clin Oncol. 2021 Oct 20;39(30):3377-3390. doi: 10.1200/JCO.21.00086. Epub 2021 Jun 11. PMID: 34115544.

4. Bellini A, Bessoltane-Bentahar N, Bhalshankar J, Clement N, Raynal V, Baulande S, Bernard V, Danzon A, Chicard M, Colmet-Daage L, Pierron G, Le Roux L, Planchon JM, Combaret V, Lapouble E, Corradini N, Thebaud E, Gambart M, Valteau-Couanet D, Michon J, Louis-Brennetot C, Janoueix-Lerosey I, Defachelles AS, Bourdeaut F, Delattre O, **Schleiermacher G.** Study of chromatin remodeling genes implicates SMARCA4 as a putative player in oncogenesis in neuroblastoma. Int J Cancer. 2019 Nov 15;145(10):2781-2791. doi: 10.1002/ijc.32361. Epub 2019 May 31. PMID: 31018240; PMCID: PMC6771805.

5. Jiménez I, Chicard M, Colmet-Daage L, Clément N, Danzon A, Lapouble E, Pierron G, Bohec M, Baulande S, Berrebi D, Fréneaux P, Coulomb A, Galmiche-Rolland L, Sarnacki S, Audry G, Philippe-Chomette P, Brisse HJ, Doz F, Michon J, Delattre O, **Schleiermacher G.** Circulating tumor DNA analysis enables molecular characterization of pediatric renal tumors at diagnosis. Int J Cancer. 2019 Jan 1;144(1):68-79. doi: 10.1002/ijc.31620. Epub 2018 Oct 26. PMID: 29923174.

Expected profile of the candidate

Applicants should have a strong desire to increase the knowledge of pediatric tumors biology through bioinformatics analyses. He/she should have a strong background in bioinformatics, statistics, or computer science with knowledge and interest in biology. Wet lab experience is a plus but not compulsory. The applicant should show solid capacity for independent and creative thinking and a desire to work closely with clinicians and biologists. Experience in statistical analysis using R is essential and working in a Unix environment is desired.