The Institute of Cancer Research

(University of London)

The Preclinical Modelling of Paediatric Cancer Evolution team

PhD Training Fellow

Sutton

The **Preclinical Modelling of Paediatric Cancer Evolution** team led by Dr. Alejandra Bruna is interested in studying the molecular mechanisms underlying paediatric cancer evolutionary processes leading to therapy resistance and relapse. Our goal is to develop a preclinical framework to help identify more efficient and less toxic therapeutic strategies for children with cancer. We aim to use patient-derived *in vivo* and *ex vivo* improved preclinical tools to increase our understanding of the biology of the disease and the mechanisms underlying the diversity of drug responses. The group is also interested in studying the molecular mechanisms underlying paediatric cancer evolutionary processes to anticipate and therapeutically challenge the unfortunately too often inefficient drug responses seen in the clinic.

Cancer is an evolutionary process fuelled by its most fundamental feature: heterogeneity. Heterogeneity is also the major cause of cancer progression, relapse and therapy resistance. In paediatric cancer research, cancer evolutionary studies are at its infancy despite it is a highly heterogeneous malignancy with an extremely variable response to treatment. There is an urgent clinical need to identify improved therapeutic strategies tailored to the aggressive difficult-to-treat patients as there is currently little consensus on therapeutic strategies and those are rarely successful. Despite this tragic scenario, patients receive intensive chemotherapy and other treatments that come with a high cost for the child. In order to improve preclinical therapeutic testing platforms predictive of drug responses in patients and to develop, accelerate and identify refined and efficacious treatment regimens for children with cancer, the Preclinical Modelling of Paediatric Cancer Evolution team aims to develop and validate a preclinical platform predictive of clinical responses using patient-derived material. Paediatric PDXs (pPDXs), similar to their adult counterparts, capture most of the originating cancer's features, including heterogeneity. pPDXs are therefore also the most suitable laboratory tools to study dynamic molecular changes upon treatment and during cancer progression. Currently, our laboratory is using state-of-the art genomic and functional approaches, including those at single cell resolution, to comprehensively study the principles, biological molecular determinants and clonal dynamics that occur in response to therapy and in relapse in childhood cancers using pPDXs and PDX cell cultures (or pPDTCs). Through a deeper understanding of these processes using improved preclinical models we will aim to anticipate and, consequently, intelligently therapeutically challenge the unfortunately too often inefficient drug responses seen in the clinic.

We have an opportunity for a talented and motivated PhD fellow to focus on identifying enhancer and transcription factor dynamics underlying children's aggressive cancer evolutionary processes. As a consequence of paediatric cancer cell's addiction to its developmental origin, the major driving forces of adaptability in childhood cancers we hypothesize are evolutionary conserved cell-of-origin chromatin configurations of cell plasticity. This hypothesis calls for the need to be creative and develop a new experimental, computational and theoretical framework. To this end, we will use match diagnostic relapse/resistant patient's samples to identify transcription factor activity and other non-genetic

regulatory factors dynamics. This work will involve chromatin immunoprecipitation, genomic and single-cell transcription analysis exploiting in vivo and ex vivo improved patient-derived preclinical models developed in the lab. Functional screens using CRISPR and/or drug screenings will be further used to complement and validate our effort towards deepening our understanding underlying drug-tolerant states and cancer progression dynamics. You will closely interact and support other researchers within the group as well as internal and external collaborative efforts, further assisting a highly collaborative framework in paediatric preclinical modelling. You will have the opportunity to work under your own initiative and apply your excellent problem-solving skills to troubleshoot challenging technical issues. You will drive the project within the laboratory, present your work regularly at the lab meetings, and contribute to the successful running of the lab. You will have the opportunity to present your work at leading national and international meetings.

Applicants will be directly supervised by the lab's Team leader, Dr. Bruna, who recently started her lab at the ICRs aiming to translate and adapt her extensive experience in cancer evolution and preclinical modelling from adult to paediatric cancer. She believes improved preclinical modelling is the means to develop more efficacious treatments in paediatric cancer due to their thankfully paucity. Dr. Bruna ultimately aims to comprehensively characterise the biological mechanisms on the causes and consequences of the choice of evolutionary paths to adapt, refine and improve the design of new therapeutic strategies in children with solid malignancies.