PhD student Applied Cancer Bioinformatics: Advanced Profiling of Retinoblastoma (36 hrs)

Clinical Genetics

Unravelling the disease progression of Rb at the molecular level and the identification of new treatment possibilities

The project

The hereditary childhood cancer Retinoblastoma (Rb) is a paradigm for tumor suppressor gene function and cancer-genetics research. VU University Medical Center (VUmc) is the national referral centre for Rb. This provides a unique setting to perform bench to bedsite research - also world-wide - due to the combination of basic science with medical expertise, as well as exceptional access to Rb material coupled to clinical data. The (inter)national team of basic researchers, clinicians and the patient support group works together to further improve counseling and care of Rb patients.

Rb is caused by mutations in the exemplar tumor suppressor gene, *RB1*, or, as we recently discovered, by amplification of *MYCN*. Genome-wide mRNA profiling of the $RB1^{-/-}$ tumors suggested a progression model in which genomic copy-number changes at 1q, 2p, 6p and 16q are the drivers of tumor progression. For 2p, *MYCN* could be identified as the driver, emphasizing the overall importance of *MYCN* in Rb tumorigenesis. However, crucial changes characteristic of the different subgroups remain to be further identified. Unfortunately chemotherapy and radiotherapy are associated with an increased risk of second primary tumors, which are often fatal. New treatment modalities, preferably tailored, are thus needed. The aim of this study is to identify crucial alterations linked to subtypes of $RB1^{-/-}$ and $RB1^{+/+}MYCN^{A}$ Rb tumors and to exploit this information to identify unique vulnerabilities. Since the RB1 pathway has been found to be affected in many tumors, studies on Rb are furthermore expected to have a broader significance than for Rb tumors alone. The proposed project is a direct follow-up of the successful PhD in which cancer genomics was applied to classify Rb tumors (e.g. see: Kooi et al., (2016) Scientific Reports;6:25264, doi: 10.1038/srep25264).

Your challenge

Your main tasks and responsibilities are:
- To determine the role of epigenetic changes in Rb tumor progression, in relation to other molecular changes;
- Subsequently, zoom in to determine how *RB1*- or *MYCN*- associated transcriptional changes relate to the distinct Rb subtypes and tumor progression;
- To evaluate the role of changes in translation and the proteome using Ribo-seq and Mass spectrometry;
- To mine the integrated Rb-omics data and pinpoint vulnerabilities that provide indications for treatment options;
- To investigate the existence and relevance of intra-tumor heterogeneity by immunohistochemistry and DNA-sequencing based approaches to determine whether combination therapies are critically needed.

In total, the integrated data are expected to yield important information on Rb carcinogenesis and provide options for novel targeted treatment regimens.

This project provides also the opportunity to contribute to other projects on topics related to bioinformatics (see also link at additional information).

Your profile

We are looking for a candidate who brings the following knowledge and experience:
- You are a highly ambitious bioinformatician or molecular biologist who wants to apply his/her Bioinformatics and Genomics skills to study an important problem in cancer research; you will be part of an interdisciplinary international research team in which basic scientists, and clinicians closely collaborate. For the wet lab experiments, support from a team of skilled technicians will be provided.

- Nevertheless, computational biologists with hands-on experience in molecular biology and genomics experiments are particularly invited to apply;
- In addition, we expect that you are a teamplayer with excellent communication skills;
- Due to the multidisciplinary environment, you are expected to develop proficiencies that are equally relevant to academia and industry.

We offer
Salary scale: OIO (2244 tot 2874 euro based on a 36 hour week), depending on qualifications and experience.
In addition to a good monthly salary we offer, among others, 8,3% extra allowance at the end of the year and 8% holiday allowance. For more information on our conditions, please visit www.werkenbijvumc.nl/arbeidsvoorwaarden (Dutch version with link to English page).

We offer an interdisciplinary stimulating work environment and the opportunity to obtain your PhD on a biologically and clinically exciting subject, as part of a dynamic and international research team. You will have the opportunity to follow high-quality courses offered by the OOA oncology graduate school throughout your PhD.

Additional information
This PhD in Applied Cancer Bioinformatics will be performed at the department of Clinical Genetics, section of Oncogenetics, of VUmc Cancer Center Amsterdam (CCA) in The Netherlands. The section of Oncogenetics has a long-standing tradition in performing forefront research on hereditary cancer-predisposition syndromes, aimed at understanding the molecular cancer biology, as well as improving the diagnostics and care of predisposed individuals.

The CCA houses one of the largest oncology research centers in the Netherlands, joining clinicians and fundamental researchers from the Academic Medical Center (AMC) and the VUmc in Amsterdam. CCA's mission is to improve treatment, life expectancy and quality of life for cancer patients and to reduce the impact of cancer on health care and society. At the CCA, excellent fundamental and translational research programs are intimately connected to clinical studies and clinical care.

Publications Rb PhD student/bioinformatician.
https://www.ncbi.nlm.nih.gov/pubmed/?term=kooi+i.

Interested?
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