EuReCa International PhD Program

PhD thesis project

2021 Call for application

Immune and epigenetic biomarkers assessments based on a basket prospective trial with Pembrolizumab and Vorinostatin patients with late stage squamous cell carcinoma

General information

Call	2021
Reference	2021-08-LETOURNEAU_SERVANT
Keyword(s)	Squamous cells carcinoma; epigenetics; immunotherapy; biomarkers; bioinformatics

Director(s) and team

Thesis director(s)	Christophe Le Tourneau & Nicolas Servant
Research team	Bioinformatics and Computational Systems Biology of Cancer
Research department	U900 - Bioinformatics, Biostatistics, Epidemiology and Computational Systems. Biology of Cancer

Description of the PhD thesis project

Squamous cell carcinomas (SCCs) may originate from various locations in the body, are sometimes related to HPV (Human Papilloma Virus) infection and are shown to harbour similar molecular alterations justifying a common therapeutic strategy.

Based on the literature and preliminary results, we hypothesize that SCCs share common molecular features that support the clinical development of an immunotherapy in combination with an epidrug. In the frame of an ERAPERMED project supplemented by a funding from the Agence de la Recherche contre le Cancer, we set up the PEVOSQ basket trial that evaluates this combination in SCC patients. The trial received regulatory approval and started including patients in September 2020.

The PEVOSQ prospective phase II basket trial aims to evaluate the antitumor activity of pembrolizumab in combination with vorinostat in patients with late stage SCC of the head and neck, cervix, lung, anus, vulva and penis. Multi-omics integrative analysis will be performed on samples collected at different time points during patient treatment and follow-up in order to better understand the mechanisms of response or resistance to this combination.

More specifically, the multiomics analyses will include:
- WES (Whole Exome Sequencing) on DNA from patients' tumors and blood (PBMC) at baseline,
- RNAseq on tumor samples for RNA analysis from patients at baseline,
- Global and genome-wide epigenetic analysis to evaluate the possible role of key epigenetic modifications as predictors of response to investigational drugs, (techniques under discussion, and may include DNA-methylome-genomic-scale, ChIP-seq, ATAC-seq)
- Circulating HPV DNA by droplet digital dPCR (ddPCR) on HPV positive patients to assess the predictive value of circulating HPV

International, interdisciplinary & intersectoral aspects of the project

The project is a European project that includes a multidisciplinary international consortium.

In the PEVOSQ clinical trial, SCC patients with different types of squamous cell carcinomas (SCCs) are treated with a combo of immunotherapy with an epidrug. It will allow to run integrative molecular and immune analyses to better understand the mechanism of response and resistance to immune-checkpoint blockade in combination with an epidrug.

It involves European teams actively involved in translational research and with complementary skill and expertise in cancer epigenetics, bioinformatics, cancers, pharmacogenomics and medical oncology.

The proposal is at the frontier of two complementary domains which are

i) bioinformatics and data analysis
ii) (epi)genetics and cancer biology.

Recent publications

1. Müller S, Sindikubwabo F, Cañeque T, Lafon A, Versini A, Lombard B, Loew D, Wu TD, Ginestier C, Charafe-Jauffret E, Durand A, Vallot C, Baulande S, **Servant N**, Rodriguez R. CD44 regulates epigenetic plasticity by mediating iron endocytosis. Nat Chem. 2020 Oct; 12(10):929-938.

2. Ragazzini R, Pérez-Palacios R, Baymaz IH, Diop S, Ancelin K, Zielinski D, Michaud A, Givelet M, Borsos M, Aflaki S, Legoix P, Jansen PWTC, **Servant N**, Torres-Padilla ME, Bourc'his D, Fouchet P, Vermeulen M, Margueron R. EZHIP constrains Polycomb Repressive Complex 2 activity in germ cells. Nat Commun. 2019 Aug 26; 10(1):3858.

3. Bertucci F, Ng CKY, Patsouris A, Droin N, Piscuoglio S, Carbuccia N, Soria JC, Dien AT, Adnani Y, Kamal M, Garnier S, Meurice G, Jimenez M, Dogan S, Verret B, Chaffanet M, Bachelot T, Campone M, Lefeuvre C, Bonnefoi H, Dalenc F, Jacquet A, De Filippo MR, Babbar N, Birnbaum D, Filleron T, **Le Tourneau C***, André F*. Genomic characterization of metastatic breast cancers. Nature. 2019 May; 569(7757):560-564.

4. Lecerf C, Kamal M, Vacher S, Chemlali W, Schnitzler A, Morel C, Dubot C, Jeannot E, Meseure D, Klijanienko J, Mariani O, Borcoman E, Calugaru V, Badois N, Chilles A, Lesnik M, Krhili S, Choussy O, Hoffmann C, Piaggio E, Bieche I, **Le Tourneau C**. Immune gene expression in head and neck squamous cell carcinoma patients. Eur J Cancer. 2019 Nov; 121:210-223.

5. **Le Tourneau C**, Borcoman E, Kamal M. Molecular profiling in precision medicine oncology. Nat Med. 2019 May; 25(5):711-712.

Expected profile of the candidate

The present position is oriented toward the quantitative and qualitative applications of Next Generation Sequencing for exome sequencing, RNA-seq, ChIP-seq, ATAC-seq, etc.
The PhD student will work in close collaboration with bioinformaticians, biologists and clinicians and must have a strong interest in working on medical projects.

Profile:
- Advanced university degree (MSc) in computer science or bioinformatics (or equivalent)
- Previous experience in analysis of sequencing data is highly recommended
- Good knowledge in genetics and cancer biology is highly recommended