

The Laboratory for Stem Cell and Cancer Research (<http://labriccardofodde.nl>) at the department Pathology of the Erasmus MC Cancer Center plans to appoint a:

Post-doc

[Research Topic: Paneth cell as the cell of origin of intestinal cancer]

36 hours per week

JOB DESCRIPTION

A 3 years post-doctoral position will be available from February 2019 on in the laboratory to work on a project funded by the Dutch Cancer Society (EMCR 2018-11407) entitled “Secretory Paneth-like cells as the origin of intestinal cancer”.

The cell of origin of cancer is often thought to have stem- and/or progenitor-like features which satisfy the need for active proliferation, self-renewal and differentiation capacity. This was elegantly demonstrated in the intestine where loss-of-function mutations in the Apc tumor suppressor gene successfully initiate adenoma formation only when they occur in the Lgr5+ stem cells. However, next to this “bottom-up” scenario, additional “top-down” models of intestinal tumorigenesis have also been proposed where more committed and even fully differentiated and post-mitotic intestinal cells are likely to initiate colon cancer especially in the context of tissue injury and inflammation, as in the case of inflammatory bowel diseases (IBD; Crohn’s disease and ulcerative colitis).

Paneth cells (PCs) are specialized secretory cells and the main source of antimicrobial peptides in the small intestine where they are primarily located. Moreover, they provide essential physical support and secreted signals to ensure stem cell function. In the colon, where Paneth cells are not present, Paneth-like cells play secretory and niche-like functional roles analogous to those of PCs in the small intestine. As shown by our laboratory, upon inflammation PCs behave as quiescent stem-like cells capable of re-entering the cell cycle and de-differentiate thus contributing to the tissue regenerative response. Here, we propose that Paneth cells and their equivalent in the colon, because of their quiescent stem cell features may represent the cells of origin of IBD-related intestinal cancer.

To this aim, we will model sporadic colon cancer in the mouse by inducing chronic inflammation (multiple DSS cycles). This protocol was previously shown to mimic lag, incidence, frequency, histopathology, and ratio of carcinoma to adenoma of sporadic and IBD-associated colon cancer in man. Different readily available Paneth- specific Cre-Lox mouse models based on expression of the lysozyme (Lyz), defensin 6 (D6), and c-Kit genes will be employed to monitor and lineage-trace Paneth(-like) cells during tumor onset and progression towards malignancy. In a parallel approach, single and combined mutations in the Apc, Kras, and Tp53 genes will be introduced in Paneth cells to study their de-differentiating and tumor-initiating capacities both in vitro and in vivo.

The identification of the cell(s) of origin of colon cancer is critical to the development of preventive and therapeutic strategies. Their detailed analysis and characterization is likely to reveal molecular or cellular features that could be exploited to prevent cancer onset or block its progression. Paneth cells are likely to

play a central role in diet- and inflammation-associated sporadic bowel cancer and as such represent a source of targets for future prevention and treatment programs.

WORK ENVIRONMENT

A healthy population and excellence in healthcare through research and education. This is what Erasmus MC stands for. Conducting groundbreaking work, pushing boundaries and leading the way. In research, education, and healthcare. We are practical people with a high level of expertise, working hard to improve and renew the healthcare of today and the public health of tomorrow.

Information about the Institute.

Since 1998, first the Josephine Nefkens Institute (JNI) and since 2014 the Erasmus MC Cancer Institute, have represented the core of research on cancers carried out within the Erasmus University Medical Centre. The Erasmus MC Cancer Institute encompasses various research groups and departments from the Erasmus MC and the Daniel den Hoed Cancer Centre (DDHK) working on the molecular basis of cancer, its prevention and treatment. The JNI focuses on solid tumors and hosts more than 200 among scientists and clinicians appointed within four different departments (Pathology, Medical Oncology, Urology, Neuro-Oncology) collaborating in a multi-disciplinary fashion over 4000 m2 of laboratories and research facilities. Central to the JNI is the department of Pathology, where a team of pathologists, biomedical scientists, and research technicians join forces to implement and improve high standards of diagnostic pathology and experimental research on the major tumour types including breast, brain colon and urogenital cancers.

Since 2003, the research group led by R. Fodde within the Department of Pathology (<http://labriccardofodde.nl>) has been focussing on the role played by stem cells in tumour onset, progression and the formation of distant metastases in a broad spectrum of malignancies. The present appointment, based on a project funded by Dutch Cancer Society .

QUALIFICATIONS AND SKILLS

Experience with experimental mouse models (Cre/Lox, mouse models for cancer), cancer research, molecular and cellular biology, and stem cells/organoids is highly desirable. Holding the Dutch authorization to work with experimental animals (Article 9 of the Experiments on Animals Act) is a strong prerequisite though not essential, especially for foreign applicants. Equivalent Felasa-approved certificates obtained abroad may apply.

TERMS OF EMPLOYMENT

The gross monthly salary amounts a maximum of € 4.216,- (scale 10), depending on your level of education and relevant experience and based on a full-time working week of 36 hours. The terms of employment are in accordance with the Collective Bargaining Agreement for University Medical Centers (CAO UMC).

INFORMATION AND APPLICATION

To apply for this position, please **send a letter of motivation, a CV, and at least two references together with their contact information**, to: Riccardo Fodde, professor of Experimental Pathology, r.fodde@erasmusmc.nl.

For other information please visit our laboratory's web site: <http://labriccardofodde.nl> or contact prof. Fodde directly by mail.