24 months post-doctoral offer in mouse genetic and molecular and cellular biology

Epithelial stem cell and cancer laboratory
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Title of the project: Investigating mechanisms of anorectal pre-cancerous development in a model of intra-epithelial neoplasia

Context: In humans and mouse, epithelial tumours frequently develop in transition zones which represent the junction between two types of epithelia such as between the anus and the rectum *(McCauley et al., 2017)*. We have recently developed a mouse model of human anorectal tumors at transition zones to follow the early steps of tumor progression from healthy to pre-neoplastic stage. In these mice, the transformation occurs only at a restricted area allowing to clearly address the cellular and molecular mechanisms in both the epithelial and the immune compartments that contribute to the establishment of the tumor.

Project: The goal of the proposal is to characterize the pre-tumoral immune environment of future transition zone tumors and understand how its presumed specific characteristics modulate the susceptibility to tumor development.

The project will be divided in two axes:

1. Identify at the single cell level the malignant events that could represent early neoplastic changes occurring during the hyperplasic to pre-malignant transition at the anorectal TZ

2. Investigate the role of T cell anal transition zone stromal fractions in mediating epithelial hyperplasia to pre-neoplasic progression

This project is based on the use of a mouse model and a three-dimensional organoid culture of transition zone to examine in more depth at a single-cell level whether specialized subsets of lymphocytes present at transition zones are directly linked to susceptibility to carcinogenesis.

Required expertise: Interested applicants should have a PhD degree in Biology, Genetics, Biochemistry, or an equivalent field as well as a background in molecular cell biology techniques. Ideally, these will include experience with mouse genetics, mammalian cell culture, cell imaging and cell sorting (Flow cytometry). Experience in immunology and bioinformatics is welcome, but not essential. Prospective candidates will be part of a highly collaborative research team and expected to be highly motivated.

Contact:
Send your candidature including a CV, a motivation letter and contact information for academic references letters to geraldine.guasch-grangeon@inserm.fr

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Main publications:

Matrka MC., Cimperman KA., Haas SR., **Guasch G.,** Ehrman LA., Waclaw RR., Wikenheiser-Brokamp KA, Wells SI. Dek Overexpression in Murine Epithelia Increases Overt Esophageal Squamous Cell Carcinoma Incidence. ***Plos Genetics.*** 2018 14(3):e1007227.

McCauley, HA., Chevrier V., Birnbaum D**., Guasch G.** De-repression of ELMO1 in cancer stem cells drives progression of TGFβ-deficient squamous cell carcinoma from transition zones. ***ELife.*** 2017, pii: e22914.

McCauley, H.A. and **Guasch G.** Three Cheers For The Goblet Cell: Maintaining Homeostasis In Mucosal Epithelia. ***Trends In Molecular Medicine.*** 2015, 21:492-503.

McCauley H.A, Liu C-Y, Attia A, Wikenheiser-Brokamp KA, Zhang Y, Whitsett JA, and **Guasch G.** TGFβ signaling inhibits goblet cell differentiation via SPDEF in the conjunctival epithelium. ***Development.*** 2014 141:4628-4639.