UNIVERSITE BIOLOGIE BRETAGNE SANTE LOIRE

Year 2018 /2019

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin: Next ID or Phase 2 Université Transdisciplinaire**
Thesis title: **Implementation of a 3D-printed model of human mucosa to study virus/host interactions**		3 keywords: 3D bioprinting Mucosa/skin equivalent Host/pathogen interactions
Unit / team: **UMR1064 INSERM/CRTI**		
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Socio-economic and scientific context (approximately 10 lines):

The 3D printing of living cells / tissues is one of the last revolutions in the field of biological engineering and regenerative medicine. We propose to use this automated, reliable and reproducible technology to develop a unique experimental model of immunocompetent human mucosa and explore, for the first time, the entry into the mucosa of species-specific viruses. Our primary objective through this collaborative project is the development of an immuno-competent human mucosal equivalent, that is to say containing the major dendritic cell subpopulations of the mucous membranes, Langerhans cells (CL) in the body. epithelium and interstitial dendritic cells (DCs) in the underlying connective tissue. By development, we mean the development of all manufacturing processes as well as the characterization of biomaterials and cells used to achieve our goal. Thus we plan to carry out on this first phase of the tender (i) the identification of the biomaterials of natural or synthetic origins used to form the model, (ii) the choice of the primary human cells used, (iii) analysis of cell viability over time (impact of biomaterials used, availability of nutrients, oxygen, etc.), (iv) analysis of the macrostructural evolution of the reconstructed tissue as a function of time (Phenotypic / functional stability, absence of surface keratinization), (v) phenotypic-functional monitoring of integrated dendritic cells (ability to interact with epithelial / stromal cells, permissiveness to CMV infection in a complex environment, presentation of antigen, modulation of the transcriptome, etc.).

Working hypothesis and aims (approximately 8 lines):

The objective is to fabricate a vascularized human mucosa using 3D bioprinting and to use it to set up an innovative model to study human/transplant-related viruses interactions.

WP2 : 4D bioprinting of the connective tissue with or without the epithelial layer. A subsequent addition of immune cells will be addressed in this package. Extrusion and sprayning cells are two deposition mthods that will be used here.

WP3 : Validation of the model, ie cell viability phenotypes over time will be assessed.

WP4 : Macrostructural evolution of the 3D-printed model follow-up, ie variability assessment over time (hours to 21 days).

WP5 : Does this model support viral infections (HCMV for instance) ? Do immune cells play a role in the viral infection, either deleterious or beneficial for the virus ? Testing blocking agents, ie antiviral compounds.

This project relies mainly on cutting-edge tissue engineering/3D bioprinting techniques as well as on imaging techniques for the analysis part.

Main milestones of the thesis (approximately 12 lines):

Milestone 1: Getting a model of mucosa (malphigian epithelium relying on a 3D-printed connective tissue) resembling a native human genital mucosa. The validation phase will lie on the use of imaging, (RT-)qPCR, cytometry, RNAseq (single cell and bulk) (collaboration with Centrale Nantes).

Milestone 2: Set up insertion of immune cells (ie myeloid DC).

Milestone 3: The model recapitulates viral infections (HCMV) in a native tissue. Immune cells play a role in the various parameters like the viral spreading.

Milestone 4: Identification of new antiviral compounds.

Scientific and technical skills required by the candidate (2 lines):

The candidate must be interested in immunology, virology and bio-engineering. (S)He must be enthusiastic, conscientious, hard-worker, prone to teamworking but independent. Speaking/writting english fluently is suitable.

3 publications from the team related to the topic (last 5 years):

1) **Chéneau C et al, J Infect Diseases, in press. (Halary F: last author)**
2) **Gergen J et al, PLoS One. 2018 Feb 15;13(2). (Halary F: co-last author)**
3) **Halary F et al. METHODS AND COMPOSITIONS FOR TREATING INFECTIONS. January 2018. PCT/EP2018/051406 (Patent)**

National and international collaborations:

National : Pr JY Hascoët (Centrale Nantes, bioprinter's owner), Pr A Touzé (Tours), Dr C Bressollette-Bodin and Dr D McIlroy (Nantes).
International : Dr M Messerle/Dr EM Borst (Hannover, Germany), Pr C Sinzger (Tübingen, Germany).