The broad objective of our research is to understand how epithelial cells interact with their microenvironment during migration, focusing on the mechanism of cell migration and the role of actin cytoskeleton in this process.

We use gut as model system to study cell migration in homeostasis, wound healing and cancer invasion (Fig. 1). Our research strategy combines molecular and cell biology techniques with live-cell imaging. In particular, we use 2D and 3D in vitro cell cultures; tissue slices cultured ex vivo; and transgenic mouse models.

Role of actin cytoskeleton in cell migration. Cells initiate migration by extending membrane protrusions, lamellipodia and filopodia, that are driven by actin polymerization. Using 2D and 3D chemotactic chambers we are investigating if filopodia are guiding organelles responsible for directed cell migration. Newly extended cellular protrusions are stabilized by adhesions that link the actin cytoskeleton to the underlying extracellular matrix. It is not clear how tensile forces generated by stress fiber contraction, strengthen adhesions at the cell front but disassemble adhesions at the cell rear allowing cell translocation. We have shown that actin bundling by fascin regulate contraction and consequently fate of adhesions.

Cell migration in gut homeostasis and wound healing. The entire intestinal epithelium is renewed every week due to cell division in the crypts coupled with cell migration towards the villi and loss of cells by apoptosis at the tip of villi (Fig. 1A). However, the mechanism responsible for the migration of intestinal cells remains largely unknown. Our goal is to determine if epithelial cells migrate passively because of the pushing force generated by cell division in the crypts, actively using specialized cellular protrusions or if they are transported by underlying fibroblasts and basement membrane (BM).
Figure 1. Actin cytoskeleton in cell invasion:
Cooperation of cancer cells and fibroblasts during invasion. Uncoupling cell proliferation from apoptosis and possibly from cell migration can lead to pathologies such as cancer. In carcinoma in situ, the BM represents a physical barrier that prevents spreading of the primary tumor to adjacent tissues. Cancer cells can perforate BM (Fig 2A), but stromal cells such as carcinoma-associated fibroblasts (CAFs) also secrete matrix proteinases. Our objective is to understand who is invading whom – do cancer cells invade the stroma or is the stroma invading tumor? Using co-cultures we are investigating if cancer cells and fibroblasts have overlapping or distinct functions that need to be combined to perforate the BM (Fig 2B). Once the BM is degraded, cancer cells migrate through the stroma towards the blood vessels, allowing dissemination of the tumor and formation of metastasis. We are interested in how CAFs stimulate invasion of cancer cells: by secreting diffusible pro-invasive molecules, preparing "the road", "carrying" cancer cells and/or by providing direction. By imaging cancer cells in vivo, we are studying how cells migrate in and interact with complex environments in the living animal (Fig 2C).
Finally, in collaboration with physicists from the Institute Curie, we are also investigating if, in addition to cellular and biochemical tumor microenvironment, mechanical pressure imposed by stroma can stimulate invasion of cancer cells.

Key publications

Year of publication 2017

Alexandros Glentis, Philipp Oertle, Pascale Mariani, Aleksandra Chikina, Fatima El Marjou, Youmna Attieh, Francois Zaccarini, Marick Lae, Damaris Loew, Florent Dingli, Philemon Sirven,
Marie Schoumacher, Basile G Gurchenkov, Marija Plodinec, Danijela Matic Vignjevic (2017 Oct 15)  
*Cancer-associated fibroblasts induce metalloprotease-independent cancer cell invasion of the basement membrane.*  
_Nature communications_: 924 : [DOI: 10.1038/s41467-017-00985-8](https://doi.org/10.1038/s41467-017-00985-8)

Koceila Aizel, Andrew G Clark, Anthony Simon, Sara Geraldo, Anette Funfak, Pablo Vargas, Jérôme Bibette, Danijela Matic Vignjevic, Nicolas Bremond (2017 Oct 13)  
*A tuneable microfluidic system for long duration chemotaxis experiments in a 3D collagen matrix.*  
_Lab on a chip_: [DOI: 10.1039/c7lc00649g](https://doi.org/10.1039/c7lc00649g)

Youmna Attieh, Andrew G Clark, Carina Grass, Sophie Richon, Marc Pocard, Pascale Mariani, Nadia Elkhatib, Timo Betz, Basile Gurchenkov, Danijela Matic Vignjevic (2017 Sep 22)  
*Cancer-associated fibroblasts lead tumor invasion through integrin-β3-dependent fibronectin assembly.*  
_The Journal of cell biology_: [DOI: jcb.201702033](https://doi.org/jcb.201702033)

*Liver metastasis is facilitated by the adherence of circulating tumor cells to vascular fibronectin deposits.*  

**Year of publication 2016**

Youmna Attieh, Danijela Matic Vignjevic (2016 Aug 31)  
_The hallmarks of CAFs in cancer invasion._  
_European journal of cell biology_: 493-502 : [DOI: S0171-9335(16)30136-4](https://doi.org/S0171-9335(16)30136-4)

**Year of publication 2015**

Andrew G Clark, Danijela Matic Vignjevic (2015 Jul 18)  
_Modes of cancer cell invasion and the role of the microenvironment._  
_Current opinion in cell biology_: 13-22 : [DOI: 10.1016/j.ceb.2015.06.004](https://doi.org/10.1016/j.ceb.2015.06.004)