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The broad objective of our research is to understand how epithelial cells interact with their microenvironment during migration in gut homeostasis and cancer invasion (Figure 1). We use a gut as a model system, and our strategy is to combine different models such as 3D cell cultures, tissue explants, mouse models and human samples coupled with different microscopy techniques and biophysical modeling.

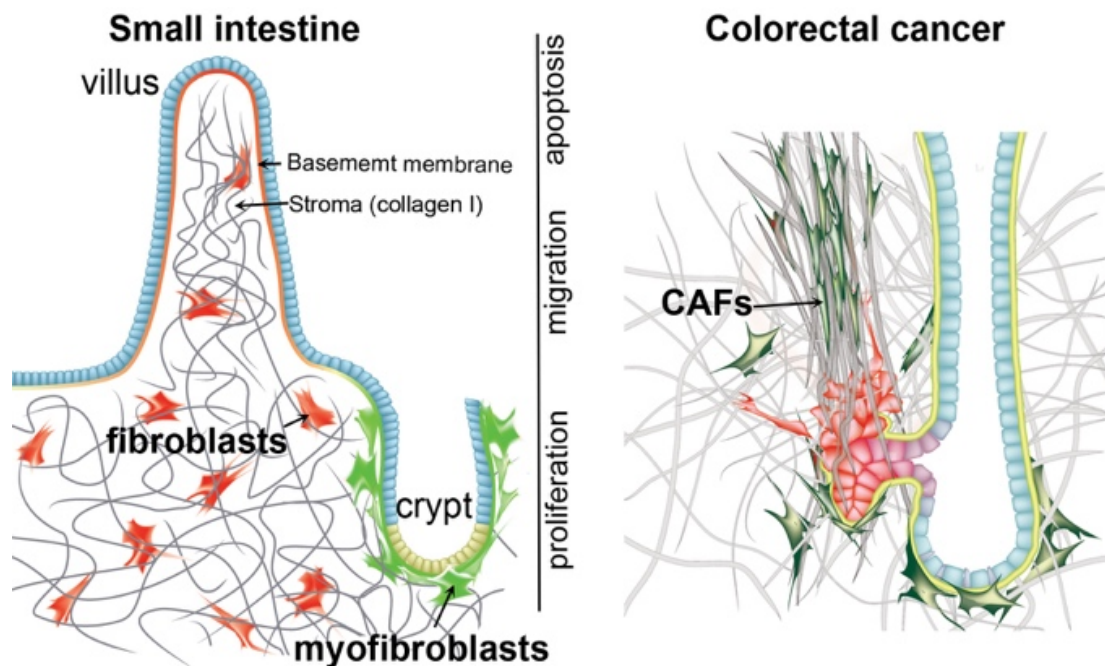


Figure 1

### Epithelial cell migration in gut homeostasis

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. What is the mechanism responsible for the movement of intestinal cells? In the crypts, epithelial cells move passively as a consequence of the pushing force generated by dividing cells. However, we found that along the villi, cells move actively using Arp2/3-dependent actin cytoskeleton (Krndija et al., Science, 2019) (Movie 1). We also found that cells migrate collectively with minimal rearrangements; and exhibit dual-polarity – apicobasal, and front-back, characterized by actin-rich basal protrusions oriented in the direction of migration. We are currently investigating the cue for directional cell migration towards the villus top and what role the actomyosin and cell-matrix adhesions play in this process. In collaboration with Stephanie Descroix (UMR168, IPGG) we are developing a device – reconstituted Gut-on-Chip – that will allow us to test the impact of individual parameters such as physical constraints, peristalsis and the extracellular matrix (ECM) on epithelium homeostasis.

#### **Movie 1: Epithelial migration along the villus (Denis Krndija)**

**Gut explants derived from Villin: CreERT2/mTmG mouse. Mosaic expression of GFP (green) in epithelial cells in the villus, other epithelial cells, and stroma (red).**

#### **Role of stromal cells in gut homeostasis**

Fibroblasts are one of the major components of the stroma. There has been tremendous progress in understanding the importance of the chemical signals that fibroblasts produce for homeostasis of stem cell niche in the intestine. However, the way fibroblasts use mechanical forces to shape the extracellular matrix and consequently dictate the response of epithelial cells remains unexplored. We aim to understand how fibroblast contractility impacts epithelial cell proliferation, differentiation, and migration in homeostasis. In collaboration with Ana-Maria Lennon's lab (Institut Curie, U932) we are also investigating the role of other stromal cells, such as dendritic cells and macrophages, in intestinal physiology.

#### **Cancer cell invasion**

The long-lasting interest of our team is the mechanism of cancer cell migration during the first steps of cancer metastasis. Until now, cancer cell migration has been described at the so-called “invasive front”, the region where cancer cells reach stromal tissue. The core of tumors has been considered as a relatively immobile tissue. However, using tumor explants and long-term 3D imaging we found that cancer cells in the tumor core are remarkably motile and that a collective behavior of neighboring cells is giving rise to large-scale tissue dynamics (Staneva et al., J Cell Science, 2019). After escaping the primary tumor, cancer cells migrate through the stroma either as single cells or in groups. We are investigating biomechanical advantages for cancer cells to migrate collectively. Cells migrate through the stroma by extending membrane protrusions which are stabilized by focal adhesions that link the actin cytoskeleton to the underlying extracellular matrix (Movie 2). We are interested in how focal adhesions are formed (Geraldo et al., EJCB, 2012; Elkhatib et al, Curr Biology, 2014) and we showed that cancer cells use focal adhesions to attach to endothelial fibronectin deposits, which allow them to extravasate and form metastasis in the liver (Barbazan et al., Cancer Research, 2017).

**Movie 2: Cancer cell invasion (Sara Geraldo)**

**Cancer cells (green) invade the extracellular matrix (pink) in the living mouse observed by intravital two-photon microscopy.**

**Cancer-associated fibroblasts (CAFs) in cancer invasion**

The tumor microenvironment plays an essential role in tumor progression. The basement membrane represents a first physical barrier that prevents spreading of the primary tumor to adjacent tissues. We found that in the presence of primary human colon CAFs, cancer cells invade the basement membrane in a protease-independent manner. Using live imaging showed that CAFs use mechanical forces to remodel the basement membrane, leading to the formation of gaps through which cancer cells can migrate (Glentis et al., 2017) (Movie 3). Besides secreting growth factors that can stimulate invasive migration of cancer cells, CAFs can also actively excavate passageways in the ECM and lead cancer cell invasion. We found that CAFs assemble fibronectin fibrils via integrin  $\beta 3$  that triggers invasion of cancer cells through the stroma (Atieh et al., 2017) (Movie 4). Currently, we are investigating if the specific organization of CAFs, their contractile capacity, and the matrix they produce can stimulate invasion of cancer cells, resistance to therapy, and tumor relapse.

**Movie 3: Cooperation of CAFs and cancer cells in basement membrane invasion (Alexandros Glentis).**

**CAFs (red) help cancer cells (green) to invade basement membrane (mesentery, cyan).**

**Movie 4: Cooperation of CAFs and cancer cells in the invasion of stroma (Youmna Attieh).**

**CAFs (red) remodel collagen I matrix (cyan) and help cancer cells (green) to invade.**

## Key publications

**Year of publication 2019**

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Denis Krndija, Fatima El Marjou, Boris Guirao, Sophie Richon, Olivier Leroy, Yohanns Bellaiche, Edouard Hannezo, Danijela Matic Vignjevic. (2019 Aug 16)

**Active cell migration is critical for steady-state epithelial turnover in the gut.**

*Science* : 365(6454) : 705-710 : [DOI : 10.1126/science.aau3429](https://doi.org/10.1126/science.aau3429)

Ralitzza Staneva, Fatima El Marjou, Jorge Barbazan, Denis Krndija, Sophie Richon, Andrew G Clark, Danijela Matic Vignjevic (2019 Feb 16)

**Cancer cells in the tumor core exhibit spatially coordinated migration patterns.**

*Journal of cell science* : [DOI : jcs220277](https://doi.org/10.1242/jcs.220277)

#### Year of publication 2018

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Jorge Barbazán, Danijela Matic Vignjevic (2018 Oct 12)

**Cancer associated fibroblasts: is the force the path to the dark side?**

*Current opinion in cell biology* : 71-79 : [DOI : S0955-0674\(18\)30133-9](https://doi.org/10.1016/j.cocub.2018.09.009)

Andrew G Clark, Anthony Simon, Koceila Aizel, Jérôme Bibette, Nicolas Bremond, Danijela Matic Vignjevic (2018 Sep 1)

**3D cell migration in the presence of chemical gradients using microfluidics.**

*Methods in cell biology* : 133-147 : [DOI : S0091-679X\(18\)30070-0](https://doi.org/10.1016/j.mcb.2018.08.007)

Ralitz Staneva, Jorge Barbazan, Anthony Simon, Danijela Matic Vignjevic, Denis Krndija (2018 Mar 12)

**Cell Migration in Tissues: Explant Culture and Live Imaging.**

*Methods in molecular biology (Clifton, N.J.)* : 163-173 : [DOI : 10.1007/978-1-4939-7701-7\\_13](https://doi.org/10.1007/978-1-4939-7701-7_13)

#### Year of publication 2017

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Alexandros Glentis, Philipp Oertle, Pascale Mariani, Aleksandra Chikina, Fatima El Marjou, Youmna Attieh, Francois Zaccarini, Marick Lae, Damarys 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)