



Ana-Maria Lennon-Duménil
Chef d'équipe, DR2 INSERM
ana-maria.lennon@curie.fr
Tel: +33 1 56 24 64 27

We work at the interface of cell biology, immunology and biophysics. We aim at deciphering the fundamental cell biological mechanisms that control the spatio-temporal regulation of antigen presentation.

In this context, we develop two main axis of research:

- 1. the coordination between cell migration and antigen uptake and presentation in dendritic cells**
- 2. the role of cell polarity in immune synapse formation and antigen presentation in B lymphocytes. Our ultimate goals are to unravel the molecular basis accounting for the behavior of antigen presenting cells in tissues and to understand how it impacts immune responses in vivo.**

The coordination between cell migration and antigen uptake and presentation in dendritic cells

We found that dendritic cell locomotion and antigen uptake involve common regulatory molecules. This led to the description of the first cell biological mechanism that allows the coordination between cell migration and cell function. This unexpected discovery opened a new

research line in our lab whose main goal is to decipher the molecular mechanisms and physical principles that govern dendritic cell migration and to understand how they are linked to their function as immune sentinels. We highlight the central role of the actin-based molecular motor Myosin II in coordinating dendritic cell migration and antigen macropinocytosis by imposing on immature dendritic cells an intermittent migration mode that favors environment patrolling. We further show the key role of the endoplasmic reticulum calcium channel IP₃ Receptor 1 in the regulation of Myosin II activity and localization in migrating dendritic cells. We are currently combining microfabricated and biophysical tools with live imaging to understand how Myosin II and various players of the actin cytoskeleton couple antigen uptake to cell migration *ex vivo* as well as in tissues such as the skin and the gut. We are further investigating how the biochemical and physical extracellular cues of these tissues impact on the molecular mechanisms responsible for the coordination between dendritic cell migration and function. Whether and how such mechanisms and cues have a role in tumor cell migration is also being explored. Identifying the mechanisms that control dendritic cell migration will help using these cells as vaccines in cancer immunotherapy.

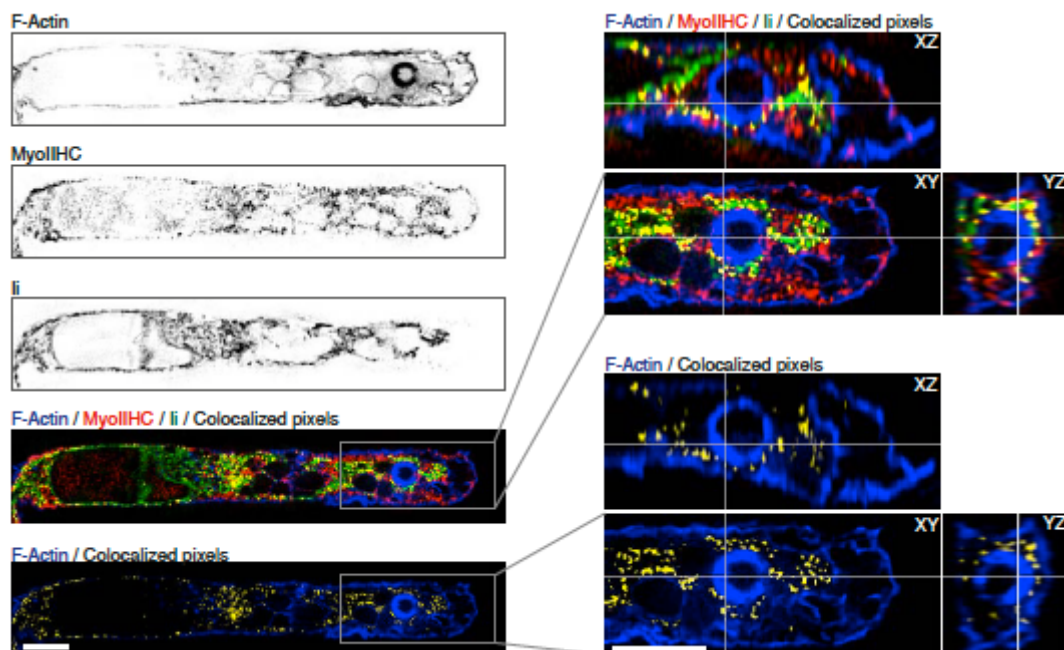


Figure 1: A dendritic cell fixed during migration in a micro-channel and stained for actin (blue), Myosin II (green) and CD74 (red). Macropinosomes (giant vesicles used to uptake antigens) are highlighted in the rectangle at the cell front.

The role of cell polarity in immune synapse formation and antigen presentation in B lymphocytes

We have highlighted the membrane trafficking events and associated molecular mechanisms involved in antigen extraction and processing at the B cell synapse. We found that MHCII-

containing lysosomes are recruited at the synapse where they locally undergo exocytosis, allowing synapse acidification and the extracellular release of hydrolases that promote the extraction of the immobilized antigen. Lysosome recruitment and secretion results from the CDC42-dependent polarization of the microtubule-organizing center (MTOC). Regulation of B lymphocyte polarity therefore emerges as a central mechanism that couples antigen extraction to antigen processing and presentation. In addition, we have identified the Par3 subunit of the ancestral polarity complex as essential for MTOC and lysosome polarization. Interestingly, we further showed that Par3 is recruited to the B cell immune synapse where it interacts with the microtubule-based molecular motor Dynein to allow centripetal transport of BCR micro-clusters for proper signaling. We are currently using a multidisciplinary approach that combines proteomics, siRNA-based screening and live imaging to identify the molecular mechanisms involved in B cell polarization. A specific focus is given to the proteins that regulate the interface between the actin and microtubule cytoskeleton -including molecular motors- and membrane trafficking. Furthermore, we are investigating how local extracellular cues regulate B lymphocyte polarity and B cell responses *in vivo*. The molecules identified might represent valuable targets to modulate B cell responses in pathological contexts.

Key publications

Year of publication 2019

Anita Kumari, Judith Pineau, Pablo J Sáez, Mathieu Maurin, Danielle Lankar, Mabel San Roman, Katharina Hennig, Vanessa F Boura, Raphael Voituriez, Mikael C I Karlsson, Martial Balland, Ana-Maria Lennon Dumenil, Paolo Pierobon (2019 Jun 30)

Actomyosin-driven force patterning controls endocytosis at the immune synapse.

Nature communications : 2870 : [DOI : 10.1038/s41467-019-10751-7](https://doi.org/10.1038/s41467-019-10751-7)

Year of publication 2016

M Raab, M Gentili, H de Belly, H R Thiam, P Vargas, A J Jimenez, F Lautenschlaeger, Raphaël Voituriez, A M Lennon-Duménil, N Manel, M Piel (2016 Apr 15)

ESCRT III repairs nuclear envelope ruptures during cell migration to limit DNA damage and cell death

Science (New York, N.Y.) : [DOI : 10.1126/science.aad7611](https://doi.org/10.1126/science.aad7611)

Dorian Obino, Francesca Farina, Odile Malbec, Pablo J Sáez, Mathieu Maurin, Jérémie Gaillard, Florent Dingli, Damarys Loew, Alexis Gautreau, Maria-Isabel Yuseff, Laurent Blanchoin, Manuel Théry, Ana-Maria Lennon-Duménil (2016 Mar 19)

Actin nucleation at the centrosome controls lymphocyte polarity

Nature communications : 10969 : [DOI : 10.1038/ncomms10969](https://doi.org/10.1038/ncomms10969)

Hawa-Racine Thiam, Pablo Vargas, Nicolas Carpi, Carolina Lage Crespo, Matthew Raab, Emmanuel Terriac, Megan C King, Jordan Jacobelli, Arthur S Alberts, Theresia Stradal, Ana-Maria Lennon-Dumenil, Matthieu Piel (2016 Mar 16)

Perinuclear Arp2/3-driven actin polymerization enables nuclear deformation to facilitate cell migration through complex environments.

Nature communications : 10997 : [DOI : 10.1038/ncomms10997](https://doi.org/10.1038/ncomms10997)

Year of publication 2015

Pablo Vargas, Paolo Maiuri, Marine Bretou, Pablo J Sáez, Paolo Pierobon, Mathieu Maurin, Mélanie Chabaud, Danielle Lankar, Dorian Obino, Emmanuel Terriac, Matthew Raab, Hawa-Racine Thiam, Thomas Brocker, Susan M Kitchen-Goosen, Arthur S Alberts, Praveen Sunareni, Sheng Xia, Rong Li, Raphael Voituriez, Matthieu Piel, Ana-Maria Lennon-Duménil (2015 Dec 8)

Innate control of actin nucleation determines two distinct migration behaviours in dendritic cells

Nature cell biology : 43-53 : [DOI : 10.1038/ncb3284](https://doi.org/10.1038/ncb3284)

Mélanie Chabaud, Mélina L Heuzé, Marine Bretou, Pablo Vargas, Paolo Maiuri, Paola Solanes, Mathieu Maurin, Emmanuel Terriac, Maël Le Berre, Danielle Lankar, Tristan Piolot, Robert S Adelstein, Yingfan Zhang, Michael Sixt, Jordan Jacobelli, Olivier Bénichou, Raphaël Voituriez, Matthieu Piel, Ana-Maria Lennon-Duménil (2015 Aug 15)

Cell migration and antigen capture are antagonistic processes coupled by myosin II in dendritic cells

Nature communications : 8122 : [DOI : 10.1038/ncomms8526](https://doi.org/10.1038/ncomms8526)