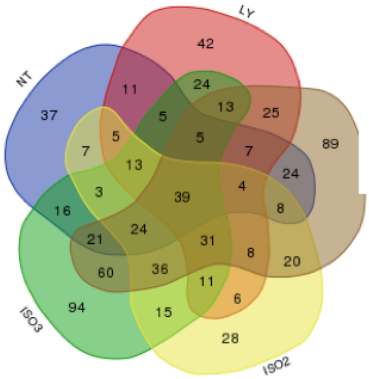


Signal-targeted Therapies & Resistance

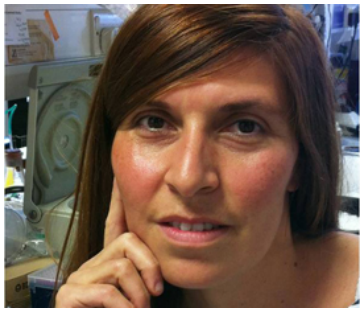
23rd of November 2017

Pierre Fabre's Center for R&D
Cancer Research Center of Toulouse
Oncopole, Toulouse, France

CV of Guest Speakers

Ezra AKSOY

William Harvey Institute



Dr. AKSOY, key expert in PI3K signalling in innate immunity, has created a lab in the William Harvey Institute of London, UK.

She targets her work on the role phosphoinositol metabolism in mucosal immunity, inflammation and regeneration The intestinal mucosa can be considered as a large immunologic organ, lined up with trillions of microbes and plays a major role in the development of oral tolerance and host-defence. Our studies are aimed to understand how phosphatidylinositol signalling by Nod-like receptors and TLRs control innate immunity and translate these signals during host-microbial interplay in the gastrointestinal tract. By employing mouse genetics, we investigate how a single or a set of genes can shape mucosal landscape to the signals derived from the environment (e.g. microbes, particles, toxins) and impact on gut inflammation (inflammatory bowel disease -IBD), oral tolerance and regeneration.

Key publication:

Aksoy E, Taboubi S, Torres D, Delbauve S, Hachani A, Whitehead MA, Pearce WP, Berenjeno IM, Nock G, Filloux A, Beyaert R, Flamand V and Vanhaesebroeck B. *The p110delta isoform of the kinase PI(3)K controls the subcellular compartmentalization of TLR4 signaling and protects from endotoxic shock.* Nature immunology 2012;13:1045-1054. (*co-corresponding author*).

Arkaitz CARRACEDO

CIC bioGUNE

Arkaitz Carracedo obtained his PhD degree under the supervision of Drs. Guillermo Velasco and Manuel Guzman, in the Department of Biochemistry and Molecular Biology of Complutense University in Madrid. His PhD project was focused on the mechanistic understanding of the antitumoral activity of cannabinoids, and the nature of their selectivity between normal and cancer cells. The question underlying this matter, "Which are the distinctive features of cancer cells and how can we use this knowledge for therapy?", has been the driving force in his career.

After obtaining his PhD in 2006, Arkaitz decided to continue his training in the United States under the supervision of Dr. Pier Paolo Pandolfi, first in Memorial Sloan Kettering Cancer Center (NY) and later in Beth Israel Deaconess Medical Center/Harvard Medical School (Boston). During this period, Arkaitz strengthened his knowledge of the biological basis of the cancer cell, the mechanism of resistance to anticancer therapies and the utilization of mouse models of human cancer to study this disease. In 2009 Arkaitz accepted a position at the CIC bioGUNE and was awarded the Ramón y Cajal prize.

He joined CIC bioGUNE in September 2010 with the main objective of studying the unique biological features of cancer cells in vitro and in vivo, with an emphasis on the alterations in cellular metabolism. He became IKERBASQUE Research Professor in 2011 and Associate Professor at University of the Basque Country in 2012.

Key publication:

Torrano V, Valcarcel-Jimenez L, Cortazar AR, Liu X, Urosevic J, Castillo-Martin M, Fernández-Ruiz S, Morciano G, Caro-Maldonado A, Guiu M, Zúñiga-García P, Graupera M, Bellmunt A, Pandya P, Lorente M, Martín-Martín N, David Sutherland J, Sanchez-Mosquera P, Bozal-Basterra L,

Arkaitz CARRACEDO
CIC bioGUNE

Zabala-Letona A, Arruabarrena-Aristorena A, Berenguer A, Embade N, Ugalde-Olano A, Lacasa-Viscasillas I, Loizaga-Iriarte A, Unda-Urzaiz M, Schultz N, Aransay AM, Sanz-Moreno V, Barrio R, Velasco G, Pinton P, Cordon-Cardo C, Locasale JW, Gomis RR, Carracedo A. *The metabolic co-regulator PGC1α suppresses prostate cancer metastasis*. Nat Cell Biol. 2016 Jun;18(6):645-56. doi: 10.1038/ncb3357. Epub 2016 May 23.

Celine GONGORA

Institute for Research on Cancer of Montpellier

Dr. Celine Gongora is team leader at the IRCM, Montpellier, France. Her work focuses on the resistance to tyrosine kinases inhibitors in colon cancer.

One of the main causes of cancer treatment failure is the development of drug resistance, the mechanisms of which is pleiotropic by nature and involves multiple pathways that need to be targeted to potentiate tumor response. Our new group, emerging from P. Martineau's has already demonstrated that the two kinase inhibitors sorafenib and the MAPK14 inhibitor SB202190 can overcome irinotecan resistance, and was the first to identify predictive gene signature in CRC for response to treatment using patients' samples. Our future research project will focus on identification of new alternative strategies for the optimization of anticancer treatment used in colorectal cancer (CCR) and prostate cancer (PCa). Based on specific molecular signatures obtained from patients and from drug-resistant models we are developing functional approaches either exploratory or focused on specific genes of interest.

Key publication:

Marzi L, Combes E, Vié N, Ayrolles-Torro A, Tosi D, Desigaud D, Perez-Gracia E, Larbouret C, Montagut C, Iglesias M, Jarlier M, Denis V, Linares LK, Lam EW, Martineau P, Del Rio M, Gongora C. *FOXO3a and the MAPK p38 are activated by cetuximab to induce cell death and inhibit cell proliferation and their expression predicts cetuximab efficacy in colorectal cancer*. Br J Cancer. 2016 Nov 8;115(10):1223-1233. doi: 10.1038/bjc.2016.313. Epub 2016 Sep 29.

Thierry AR, Mouliere F, El Messaoudi S, Mollevi C, Lopez-Crapez E, Rolet F, Gillet B, Gongora C, Dechelotte P, Robert B, Del Rio M, Lamy PJ, Bibeau F, Nouaille M, Loriot V, Jarrousse AS, Molina F, Mathonnet M,

Celine GONGORA
Institute for Research on Cancer of Montpellier

Pezet D, Ychou M. *Clinical validation of the detection of KRAS and BRAF mutations from circulating tumor DNA*. Nat Med. 2014 Apr;20(4):430-5. doi: 10.1038/nm.3511. Epub 2014 Mar 23.

Emilio HIRSCH

University of Torino

Emilio Hirsch is Professor of Biology at the Medical School of the University of Torino. He provided seminal contributions in the characterization of phosphoinositide 3-kinases (PI3K) as drug targets in inflammation (Science 2000, Immunity 2002), cancer (Science Signaling 2008, Cancer Cell 2011 and 2014), heart failure (Cell 2004, Molecular Cell 2011, Circulation 2011 and 2012), obesity (Science Signaling 2014). He produced the first knock-out mice for a PI3K catalytic subunit and demonstrated the role of PI3Kgamma in chemotaxis of leukocytes (Science 2000; PNAS 2007, Blood 2012). He developed, together with Merck-Serono, the first isoform selective PI3Kgamma inhibitor (Nat Med 2005) and recently launched an academic spin off exploiting his patented PI3K inhibitors for topical treatment. He was the first to demonstrate that PI3K are not only enzymes but also scaffold proteins (Cell 2004, Mol Cell 2011), showing that knock-in of a catalytically inactive mutant better models drug targeting than knock-out-mediated elimination of the protein. He demonstrated that PI3Kbeta is a scaffold controlling receptor endocytosis (Sci Signal 2008) and that PI3Kgamma interacts with PKA to integrate PI3K and cAMP signaling (Cell 2004; Mol Cell 2011; Circulation 2012). More recently, he shifted his attention to class II PI3Ks and defined the role of PI3KC2alpha in endocytosis (Nature 2013) and primary cilium function (Dev Cell 2014). He is author of 202 publications, his works received around 12000 citations and his h-index (Harzing's Publish or Perish) is 61.

Key publication:

Kaneda MM, Cappello P, Nguyen AV, Ralainirina N, Hardamon CR, Foubert P, Schmid MC, Sun P, Mose E, Bouvet M, Lowy AM, Valasek MA, Sasik R, Novelli F, Hirsch E, Varner JA. *Macrophage PI3Kγ Drives Pancreatic Ductal Adenocarcinoma Progression.* Cancer Discov. 2016 Aug;6(8):870-85. doi: 10.1158/2159-8290.CD-15-1346. Epub 2016 May 13.

Emilio HIRSCH
University of Torino

Costa C, Ebi H, Martini M, Beausoleil SA, Faber AC, Jakubik CT, Huang A, Wang Y, Nishtala M, Hall B, Rikova K, Zhao J, Hirsch E, Benes CH, Engelman JA. *Measurement of PIP3 levels reveals an unexpected role for p110β in early adaptive responses to p110α-specific inhibitors in luminal breast cancer*. Cancer Cell. 2015 Jan 12;27(1):97-108. doi: 10.1016/j.ccell.2014.11.007. Epub 2014 Dec 24.