Main achievements in recent years:

**Free radicals are constantly produced in the body by metabolism and cellular respiration; but this physiological production is controlled by efficient “antioxidant” defence systems. Under certain circumstances, imbalance arises, either because of antioxidant deficiency or overproduction of radicals. The excess of derivatives of oxygen (or ROS, reactive oxygen species) becomes toxic for major components of the cell: this reaction is called oxidative stress.**

**1- Chronic oxidative stress promotes aging and metastatic spread:**

In last years, the “Stress and Cancer” laboratory has identified two new molecular players of the oxidative stress response, the miR-200 family of microRNA and the transcription factor JunD. We showed that a chronic oxidative stress accelerates aging through accumulation of HIF (Hypoxia-Inducible Factor) and modulation of insulin signaling (Gerald, Cell, 2004; Laurent, *Cell Metabolism*, 2008).

Consistent with the fact that cancer is one obvious pathology observed in elderly, we discover that persistent ROS increase tumour development and metastatic spread, by deeply modifying tumour micro-environment. Conversion of fibroblasts into myofibroblast result from ROS-mediated accumulation of pro-angiogenic (HIF) and pro-inflammatory (SDF-1/CXCL-12) components. These studies established that HER2 tumours, which are characterized by a high rate of nodal metastases, exhibit a high proportion of myofibroblasts and a signature of oxidative stress (Toullec, *EMBO Mol. Med.*, 2010; Scholer-Dahirel, Cell cycle, 2013; Costa, *Sem. Cancer Biol.*, 2014).
2- Oxidative stress increases tumour development, but improves chemosensitivity.

We combined expression data from miR-200 family members and global transcriptomic profiling to identify different molecular subgroups of ovarian cancers. By this method, we defined two sets of patients according to a dual signature, related to “oxidative stress” and “fibrosis”. Interestingly, the “stress” and “fibrosis” signatures have a clear impact on patient survival. Indeed, the “stress” patients survive significantly longer than the “Fibrosis”
patients, effect associated with a more effective tumour resection at the time of surgery and a greater sensitivity to chemotherapy. In conclusion, oxidative stress response can have a dual function in tumours: while it increases tumour growth, it also enhances sensitivity to chemotherapy. This is what we call the "Paradoxical effects of Reactive Oxygen Species or ROS" (Mateescu, et al., *Nature Medicine*, 2011; Batista, *Int. J. Biochem & Cell Biol.*, 2013).

Given the role of miR-200 family members in stress response and ovarian tumorigenesis, studying the mechanisms of their regulation was of major interest. We discovered that miR-200c/141 transcription is intimately linked to this one of an immediate upstream gene, *PTPN6*, in all physiological conditions tested. First, a bypass of the regular *PTPN6* polyadenylation signal allows the transcription of the downstream miR-200c/141. Second, the promoters of the *PTPN6* and miR-200c/141 transcription units physically interact through a 3-dimensional DNA loop and exhibit similar epigenetic regulation. Our findings highlight that transcription of intergenic miRNAs is a novel outcome of transcriptional read-through and reveal a yet unexplored type of DNA loop associating two closely located promoters. These mechanisms have significant relevance in
ovarian cancers and stress response, pathophysiological conditions in which miR-200c/141 exert key functions (Batista, *Nature Communications*, 2016).

3- **Inhibition of autophagy as a new means of improving chemotherapy efficiency in triple-negative breast cancers**

We confirmed the role of oxidative stress in chemosensitivity in breast cancers. Indeed, we identified autophagy, a catabolic process that helps cells to circumvent cell stress, as a new means of chemoresistance in triple-negative breast cancers (TN BC). Despite intensive efforts to improve BC treatments, patients with TN BC still exhibit poor survival, with half developing resistance to chemotherapy. By combining analyses of independent cohorts of BC patients, 3D culture experiments and human primary derived-tumour xenografts, our study is the first to reveal autophagy as a new prognostic factor and a promising chemotherapeutic target in treating TN BC patients (Lefort, *Autophagy*, 2014).

4- **MAP3K8/COT is a new predictive marker for MEK inhibitors in high-grade ovarian cancers**

Ovarian cancer is a silent disease with a poor prognosis that urgently requires new therapeutic strategies. In low-grade ovarian tumours, mutations in the MAP3K *BRAF* gene activate MEK. We demonstrated that the other MAP3K, MAP3K8, accumulates in high-grade ovarian carcinomas and is a new prognostic marker for these tumours. MAP3K8 controls cancer cell proliferation and migration by regulating key players in G1/S transition and adhesion dynamics. In addition, MAP3K8 exhibits a reliable predictive value for the effectiveness of MEK inhibitor treatment. Our data highlight key roles for MAP3K8 in high-grade ovarian cancers and indicate that MEK inhibitors could be a useful treatment strategy, in combination with conventional chemotherapy (Gruosso, *Nature Communications*, 2015).
Stress and Cancer

U830 Cancer, Heterogeneity, Instability and Plasticity (CHIP)
Key publications

Year of publication 2020

**A subset of activated fibroblasts is associated with distant relapse in early luminal breast cancer**  

**Single-Cell Analysis Reveals Fibroblast Clusters Linked to Immunotherapy Resistance in Cancer**  
*Cancer Discovery* : [DOI : 10.1158/2159-8290.CD-19-1384](https://doi.org/10.1158/2159-8290.CD-19-1384)

Yann Kieffer, Claire Bonneau, Tatiana Popova, Roman Rouzier, Marc-Henri Stern, Fatima Mechta-Grigoriou (2020 Mar 17)  
**Clinical Interest of Combining Transcriptomic and Genomic Signatures in High-Grade Serous Ovarian Cancer**  

**Cancer-associated fibroblast heterogeneity in axillary lymph nodes drives metastases in breast cancer through complementary mechanisms**  
*Nature Communication* : 11 : 1-20 : [DOI : 10.1038/s41467-019-14134-w](https://doi.org/10.1038/s41467-019-14134-w)

Year of publication 2019

**PML-Regulated Mitochondrial Metabolism Enhances Chemosensitivity in Human Ovarian Cancers**  

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Cell Metabolism

Year of publication 2018


Nature communications: DOI: 10.1038/s41467-018-03348-z.