CRBM External Seminar
*Thursday **June 22nd** 11:00 am Salle Marcel Dorée*

The hereditary N363K mutation adds glioblastoma to a canonical tumor spectrum by combining DNA damage with replication infidelity

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Malik did his PhD in Germany under the supervision of Ed Hurt, working on nuclear pore complexes in *Saccharomyces cerevisiae*. He joined French academic research in 2004 as a postdoctoral researcher in the team of Dr. Marcel Méchali at the *Institute of Human Genetics*, IGH, in Montpellier, where he was recruited in 2008 as a staff scientist (CR1). For 13 years, he worked on several factors key in DNA replication and introduced knock-out mouse models in the team. Since his research moved from a very DNA replication-centered focus to a wider replication-associated DNA damage assessment, he moved end 2016 to the *Cancer Research Center of Toulouse*, CRCT, where he joined the group of Dr. Jean-Sébastien Hoffmann. There, he deployed his own research line by obtaining numerous grants, which took him to a more medical-oriented character in his research. This is why, beginning 2021, he came back to Montpellier to join Dr. Jérôme Moreaux's group, at IGH-CHU Saint Éloi, working on Multiple Myeloma, where he provides a deep molecular structuration to the translational research of this team. Malik will discuss with us his most recent publication to illustrate how deep understanding of molecular processes sheds light into relevant clinical applications.

Presentation summary

The exonuclease domain of DNA polymerases epsilon catalytic subunit (POLE) removes misincorporated nucleotides, a process called proofreading. POLE exonuclease mutations cause colorectal and endometrial cancers with an extreme burden of single nucleotide substitutions. We recently reported that, particularly, the hereditary POLE exonuclease mutation N363K predisposes in addition to aggressive giant cell glioblastomas. We knocked-in this mutation homozygously into human cell lines and compared its properties to knock-ins of the like-wise hereditary POLE L424V mutation and to a complete proofreading-inactivating mutation (exo-null). We found that N363K cells have higher mutation rates, display a growth defect, replication stress and DNA damage. In non-transformed cells, these burdens lead to aneuploidy within macroscopically normal nuclei. In contrast, transformed N363K cells phenocopy the enlarged and disorganized nuclei of giant cell glioblastomas. Taken together, our data characterize a POLE exonuclease domain mutant that not only causes single nucleotide hypermutation, but in addition DNA damage and chromosome instability, leading to an extended tumor spectrum. By expanding our understanding of the polymerase exonuclease domain, our data help refine the classification and treatment of POLE-mutated tumors.

Selected Publications:

Labrousse, G, Perre,PV, Parra, G, Jaffrelot, M, Leroy, L, Chibon, F, Escudie, F, Selves, J, Hoffmann, JB, Guimbaud, R, **Lutzmann M.** The hereditary N363K POLE exonuclease mutant extends PPAP tumor spectrum to glioblastomas by causing DNA damage and aneuploidy in addition to increased mismatch mutagenicity. **NAR Cancer**, 2023, Vol. 5, No. 2

Lutzmann, M, Bernex, F, Da Costa De Jesus, C, Hodroj, D, Marty, C, Plo, I, Vainchenker, W, Tosolini, M, Forichon, L, Bret, C, Queille, S, Marchive, C, Hoffmann, JS, Méchali, M. MCM8- and MCM9 deficiencies cause lifelong increased hematopoietic DNA damage driving p53-dependent myeloid tumors. **Cell Rep.** 2019, 28: 2851-2865.

Lutzmann M, Grey, C, Traver, S, Ganier O, Maya-Mendoza A, Ranisavljevic N, Bernex F, Nishiyama A, Montel N, Gavois E, Forichon L, deMassy B, Méchali, M. MCM8- and MCM9- deficient mice reveal gametogenesis defects and genome instability due to impaired homologous recombination. **Mol. Cell** 2012, 47: 523-534.