PROJECT 2 (optional)

DoS: ALESSANDRA BOLETTA

Title: Loss of genome repair mechanisms in the initiation and progression of renal cell carcinomas

Curriculum: BAIO

Link to OSR/UniSR personal page: https://research.hsr.it/en/divisions/genetics-and-cell-biology/molecular-basis-of-cystic-kidney-disorders.html

Project description (*Number of characters*, *including spaces*: 2.000 - 3.000):
Renal Cell Carcinomas (RCCs) are common cancers originating from the epithelia lining the tubule of the nephron and it is diagnosed in more than 350,000 people worldwide each year. Investigation over the years and identification/testing of novel potential therapies has so far been limited by the fact that faithful animal models of the disease are not available. We developed a new mouse model of RCC by inactivation of the *Tsc1* gene through the activity of a kidney-specific Cre (KspCre) causing upregulation of the mTORC1 cascade in a restricted segment of the nephron (*Tsc1kKO*). These mice develop cysts, cystadenomas and carcinomas with full penetrance and a reproducible timing (Pema et al, Nat Comm, 2013; Drusian et al, Cell Reports, 2018). Transcriptional profiling of the *Tsc1* mutant lesions identified alterations in the MisMatch Repair (MMR) Machinery, which appears to be secondary to profound metabolic reprogramming occurring in these renal lesions. Aim of the project will be to test whether the alterations observed in MMR can justify the progressive accumulation of tumoral lesions due to enhanced accumulation of somatic mutations. Single cells transcriptional profiling will be carried out in *Tsc1kKO* mice intercrossed with mT/mG mice (i.e. carrying green cells when the KspCre is active). Furthermore, accumulation of somatic mutiations over time will be studied in collaboration and under the supervision of Dr. Irene Franco, who has developed an innovative technology to identify somatic mutations in pre-cancerous cells of the kidney (Franco et al, *Genome Biology*, 2019). Data will be corroborated by analysis of cells derived from early lesions in patients. Findings will be validated and mechanistically characterized in the multiple cellular, tissues and animal models available in the lab. The project is funded by AIRC.

Skills to be acquired by the student:

Upon completion of this project the student will be able to design and execute a scientific project in the field of oncology. Specifically on the use of cellular and animal models for renal cell carcinomas, on production and interpretation of transcriptomic and genomic data, as well as pharmacological studies on orthotopic xenografts.

References (max. 3)

- Pema M, Drusian L, Chiaravalli M, Castelli M, Yao Q, Ricciardi S, Somlo S, Qian F, Biffo S, Boletta A. mTORC1-mediated inhibition of polycystin-1 expression drives renal cyst formation in tuberous sclerosis complex. Nat Commun. 2016 Mar 2;7:10786. doi: 10.1038/ncomms10786.

- Drusian L, Nigro EA, Mannella V, Pagliarini R, Pema M, Costa ASH, Benigni F, Larcher A, Chiaravalli M, Gaude E, Montorsi F, Capitanio U, Musco G, Frezza C, Boletta A. mTORC1 Upregulation Leads to Accumulation of the Oncometabolite Fumarate in a Mouse Model of Renal Cell Carcinoma. Cell Rep. 2018 Jul 31;24(5):1093-1104.e6. doi: 10.1016/j.celrep.2018.06.106.

- Franco, I., H. T. Helgadottir, A. Moggio, M. Larsson, P. Vrtacnik, A. Johansson, N. Norgren, P. Lundin, D. Mas-Ponte, J. Nordstrom, T. Lundgren, P. Stenvinkel, L. Wennberg, F. Supek and M. Eriksson (2019). "Whole genome DNA sequencing provides an atlas of somatic mutagenesis in healthy human cells and identifies a tumor-prone cell type." Genome Biol 20(1): 285.