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OTHER PROGRAM AFFILIATIONS

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Cancer is a complex disease that evolves over time and becomes more malignant by acquiring multiple mutations at the DNA level, as well as in the way proteins function in the cell. While a single initial defect can promote tumor appearance, additional mutations may favour development of the disease to more aggressive stages of malignancy.

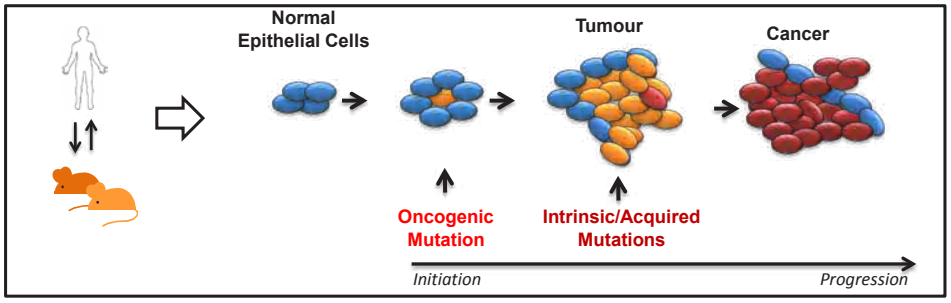
The PI3K-Akt-mTOR cascade is a key intracellular signalling pathway that mediates several biological processes including cell growth, proliferation, metabolism and migration. As such it is not surprising that mutations in key regulators of this pathway are frequently associated with cancer. PTEN (*phosphatase and tensin homology on chromosome 10*) is a major negative regulator of the PI3K-Akt-mTOR pathway and is frequently inactivated or silenced in a range of human cancer and cancer syndromes.

Our research focuses on the identification and characterization of signalling pathways and molecular networks responsible for the correct functioning of cells in mammals with a special focus on the tumour suppressor PTEN.

Through a combination of *in vitro* studies and *in vivo* analyses, we utilise recently generated mouse models to investigate how loss of PTEN functions alters normal cell behaviour to promote uncontrolled cell growth and survival, at a systemic level and in a tissue specific manner. The final goal of these studies is to identify new therapeutic targets for the development of novel treatments or treatment modalities of human diseases, including cancer.

Research Projects

1. **To define the functional role of PTEN in suppression of breast tumourigenesis**
2. **To characterise the contribution of the mTOR signalling pathway to brain cancer formation and progression**



Selected significant publications:

1. **Papa A**, Wan L, Bonora M, Salmena L, Song MS, Hobbs RM, Lunardi A, Webster K, Ng C, Newton RH, et al. 2014. Cancer-associated PTEN mutants act in a dominant-negative manner to suppress PTEN protein function. *Cell* 157, 595-610.
2. Liu P, Begley M, Michowski W, Inuzuka H, Ginzberg M, Gao D, Tsou P, Gan W, **Papa A**, Kim BM, et al. 2014. Cell-cycle-regulated activation of Akt kinase by phosphorylation at its carboxyl terminus. *Nature* 508, 541-545.
3. Juvekar A, Burga LN, Hu H, Lunsford EP, Ibrahim YH, Balmana J, Rajendran A, **Papa A**, Spencer K, Lyssiotis CA, et al. 2012. Combining a PI3K inhibitor with a PARP inhibitor provides an effective therapy for BRCA1-related breast cancer. *Cancer Discovery* 2, 1048-1063.
4. Bernardi R, **Papa A**, Egia A, Coltella N, Teruya-Feldstein J, Signoretti S, and Pandolfi PP. 2011. Pml represses tumour progression through inhibition of mTOR. *EMBO Molecular Medicine* 3, 249-257.
5. Iraci N, Diolaiti D, **Papa A**, Porro A, Valli E, Gherardi S, Herold S, Eilers M, Bernardoni R, Della Valle G, et al. 2011. A SP1/MIZ1/MYCN repression complex recruits HDAC1 at the TRKA and p75NTR promoters and affects neuroblastoma malignancy by inhibiting the cell response to NGF. *Cancer Research* 71, 404-412.