

Our group is studying the biology of Tumour Necrosis Factor (TNF) Family Members. These proteins are implicated in the regulation of essential biological processes including proliferation, differentiation, survival and cell death. An altered expression of TNF family members is often associated with pathological situations, such as autoimmune diseases and cancer, which is the particular research interest of our group.

We have vacancies for students who would like to perform their Master- or Diplomarbeit in our group that is part of the *Institut de Génétique Moléculaire de Montpellier* (www.igmm.cnrs.fr). Montpellier is in the South of France, just next to the Mediterranean Sea; the institute is located on the campus of the CNRS (National French Research Council). Knowledge of French is useful but not required, as the operating language in the institute is English. A gratification of about 400€/month can be paid for the respective work.

At present we are following two main lines of research:

- 1.) To clarify the functions of the TNF like ligand APRIL (a proliferation-inducing ligand), which has been first described by Hahne *et al.* in 1998 [1], we have generated transgenic mice in which APRIL acts systemically [2]. We have recently reported that old APRIL transgenic mice develop lymphoid tumors that originate from expansion of the so-called B-1 B cell population [3]. Tumors in the APRIL transgenic mice are highly reminiscent of human B cell chronic lymphoid leukemia (CLL) [3]. In collaboration with Prof. H. Merle-Béral (Hôpital Pitié-Salpêtrière, Paris) we have described that elevated APRIL serum levels are detected in the majority of CLL patients and reflect the progression of disease [4]. Our group is presently testing whether APRIL is implicated in other tumor types and the molecular mechanisms responsible for the APRIL-mediated triggering of tumor cells.
- 2.) Clinicians from the Department of Immuno-Rheumatology of University Hospital of Montpellier are associated to our group and we are analyzing the role of TNF family members in rheumatoid arthritis (RA) and systemic lupus. A hallmark of RA is the pseudo-tumoral expansion of fibroblast-like synoviocytes (FLS), as these cells invade and finally destroy the joint structure. RA FLS have been therefore proposed as a therapeutic target. We have previously described that TNF-related apoptosis-inducing ligand (TRAIL) induces apoptosis in a subset of RA FLS, but an induction of proliferation in the surviving cells [5]. This observation corresponds to the pleiotropic effects of TRAIL observed on primary human tumor cells. The pseudo-tumoral expansion of RA FLS can be easily mimicked *in vitro* and we will therefore take

advantage of this cellular model to analyze the pleiotropic effects triggered by TRAIL using biochemical approaches as well as micorarray experimentation.

References

1. Hahne M, Kataoka T, Schroter M, Hofmann K, Irmeler M, Bodmer JL, Schneider P, Bornand T, Holler N, French LE *et al*: APRIL, a new ligand of the tumor necrosis factor family, stimulates tumor cell growth. *J Exp Med* 1998, 188(6):1185-1190.
2. Stein JV, Lopez-Fraga M, Elustondo FA, Carvalho-Pinto CE, Rodriguez D, Gomez-Caro R, De Jong J, Martinez AC, Medema JP, Hahne M: APRIL modulates B and T cell immunity. *J Clin Invest* 2002, 109(12):1587-1598.
3. Planelles L, Carvalho-Pinto CE, Hardenberg G, Smaniotto S, Savino W, Gomez-Caro R, Alvarez-Mon M, de Jong J, Eldering E, Martinez AC *et al*: APRIL promotes B-1 cell-associated neoplasm. *Cancer Cell* 2004, 6(4):399-408.
4. Planelles L, Castillo-Gutiérrez S, Medema JP, Morales-Luque A, Merle-Béral H, Hahne M: APRIL but not BLyS serum levels are increased in chronic lymphocytic leukemia: prognostic relevance of APRIL for survival. *Hematologica* 2007, 92(9):1284-1285.
5. Morel J, Audo R, Hahne M, Combe B: Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induces rheumatoid arthritis synovial fibroblast proliferation through mitogen-activated protein kinases and phosphatidylinositol 3-kinase/Akt. *J Biol Chem* 2005, 280(16):15709-15718.