COLLOQUIA IN CELLULAR SIGNALLING

Venue: Medical University Vienna, Center for Physiology and Pharmacology, Institute of Pharmacology, Waehringerstrasse 13a, 1090 Vienna, "**Leseraum**". (Harald Sitte, Tel.: (01) 40160 31323, harald.sitte@meduniwien.ac.at)

Friday 12.06.2015 11:00 s.t. **Lukas Kenner (host:** H. Sitte**)**

Ludwig Boltzmann Institute for Cancer Research (LBI-CR)
Klinisches Institut für Pathologie (KIP)
Medizinische Universität Wien
LBI-CR: Währingerstrasse13A
KIP: Währingergürtel 18-20
1090 Vienna

"Transcription factors in oncogenesis: from ALCL to prostate cancer"

Lukas Kenner (lukas.kenner@meduniwien.ac.at**)**

Abstract:
Anaplastic large cell lymphoma (ALCL) is a malignant T-cell Non-Hodgkin lymphoma and frequently associated with the t(2;5) translocation resulting in expression of the Nucleophosmin-Anaplastic Lymphoma Kinase (NPM-ALK) fusion protein. Recent studies by us identified AP-1 transcription factors (TF) JUNB and cJUN as downstream effectors of NPM-ALK. These TFs directly upregulate platelet derived growth factor receptor B (PDGFRB) expression in the lymphoma cells and promote tumor progression and dissemination in a murine NPM-ALK lymphomagenesis model. Genetic ablation of cJUN and JUNB in this model did not affect tumor incidence, however lymphomas displayed reduced progression, indicated by reduced vascularization as well as a loss of dissemination. This resulted in extended survival; therapeutic inhibition of PDGFRB with the kinase inhibitor imatinib markedly prolonged the life of NPM-ALK transgenic mice. Moreover, imatinib treatment in a late-stage patient with refractory NPM-ALK-positive PDGFR-expressing ALCL resulted in rapid, complete and sustained remission.
In the second part of my talk I will focus on Prostate cancer (PCa), which is the most prevalent cancer in men. Hyperactive STAT3 is thought to be oncogenic in PCa. However, targeting of the IL-6/STAT3 axis in PCa patients failed to provide therapeutic benefit. Here, we show that genetic inactivation of *Stat3* or *IL-6* signaling in a *Pten*-deficient PCa mouse model accelerates cancer progression leading to metastasis. Mechanistically, we identify $p19^{ARF}$ as a novel direct Stat3 target. Loss of Stat3 signaling disrupts the ARF-Mdm2-p53 tumor suppressor axis bypassing senescence. Strikingly, we also identify *STAT3* and *CDKN2A* mutations in primary human PCa. *STAT3* and *CDKN2A* deletions co-occurred with high frequency in PCa metastases. In accordance, loss of STAT3 and $p14^{ARF}$ expression in patient tumors correlates with increased risk of disease recurrence and metastatic PCa. Thus, STAT3 and ARF are sensitive prognostic markers to stratify high from low risk PCa patients. Our findings challenge the current view of the therapeutic benefit or risk of IL-6/STAT3 inhibition.