All major treatment modalities surgery, radiation and chemotherapy had significant impact on survival. When ranking studies according to survival gain, the three highest ranking studies were: Danohue 1997 (BCNU + HFRT), Fukushima 2003 (MCNU + TNF-alpha) and Levin 2203 (PCV + DFMO). When grouping studies according to agent groups, nitrosurea rank above temozolomide, which are still above other groups. Numerous novel appraches such as tumorvaccination with dendritic cells, and EGFR tragetted therapies, provide hope for future further improvement. However, none of theses clinical reports rank higher then the cehmotherapeutic studies.
This literature analysis indicates that, nitrosurea and temozolomide as well as DMFO are promising treatments. Patient numbers in clinical trials represent the crucial factor limiting speed to gain knowledge. Novel approaches need to move to clinical trials with higher patient numbers. Multiinstitutional collaborations are necessary to overcome this problem. In pediatrics, these collaborations have to exceed national boarders.

EACR Special session

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Oncogenic Herpesviruses: Understanding the latent–lytic switch

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Kaposi's sarcoma (KS) was first described in 1872 as a rare disseminated sarcoma of the skin. However, widespread human immunodeficiency virus (HIV) infection has since turned KS into an epidemic disease. A key concern is the major epidemic of KS in Africa. KS is now the most common adult tumour reported in parts of Africa. Furthermore, childhood KS in Africa is becoming more common and unlike adults who usually have a slow-growing form of KS, childhood KS is aggressive and rapidly fatal.
The etiological agent of KS, is the most recently identified human tumour virus, Kaposi's sarcoma associated herpesvirus virus (KSHV). Like other herpesviruses, KSHV has two distinct forms of infection, latent persistence and lytic replication. Although, latent persistence of the KSHV genome has been implicated in tumourigenesis, it is evident that lytic replication plays an important part in the pathogenesis and spread of KSHV infection. Therefore, it is essential to study the molecular mechanisms of reactivation and the control of lytic gene expression for a better understanding of KSHV pathogenesis.
Herein, we will describe the characterisation of the KSHV ORF 50 protein. We demonstrate that it is the key protein responsible for reactivation from the latent state and initiating the lytic replication cycle. KSHV ORF 50 is produced as immediate early protein, it autoregulates its own expression and activates transcription of various viral and cellular genes. Moreover, sustained transient expression of ORF 50 in KSHV latently infected cell lines leads to the stimulation of its own expression and consequently viral lytic replication. This implicates the KSHV ORF 50 protein as the molecular switch for reactivation and initiation of the lytic replication cycle. We will also describe a novel KSHV ORF 50–cellular protein interaction. We have shown that HMG-A can directly interact and significantly enhance KSHV ORF 50-mediated transactivation, suggesting it has an important role in KSHV ORF 50-mediated reactivation and the initiation of the lytic replication cycle. These results will lead to a better understanding of the molecular mechanisms of reactivation and the control of lytic gene expression which are implicated in KSHV pathogenesis.

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IGF-1 receptor in cancer: the perfect target, searching the perfect bullet

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The insulin-like growth factor 1 receptor (IGF-1R) plays an essential role in malignant processes in at least different ways: 1) it is a promoting factor; 2) it is an anti-apoptotic factor; and 3) it is quasi-obligatory for the establishment and maintenance of the malignant phenotype. Several signaling pathways, including MAP kinase pathways and phosphatidylinositol 3-kinase pathway are activated by IGF-1.
Phosphorylation is known as being the central process governing IGF-1R signaling. However, recently we described the involvement of ubiquitination on IGF-1R function. We demonstrated that Mdm2 serves as a ligase in ubiquitination of the IGF-1R and thereby causes its internalization and degradation. A process discovered as the means by which IGF-1R is turned off, quite surprisingly has been found to provide support for signal transduction. This newly signaling mechanism involves two families of proteins Mdm2 and β-arrestins [1–3].
Our results reveal the involvement of ubiquitination in the IGF-1R signaling pathways. A twin function for IGF-1R ubiquitination mediated by MDM2 is demonstrated: internalization and down-regulation of the receptor in conjunction with activation of the IGF-1R signaling pathway.
The vast expression of IGF-1R in neoplastic cells and tissues combined with its crucial roles in cancer cell growth is making this tyrosine receptor an attractive target to combat malignant diseases. A variety of approaches aimed at targeting IGF-1R has been utilized to prove the concept, or are being developed for potential anticancer therapies. Recently, we demonstrated that the cyclolignan PPP inhibited phosphorylation of IGF-1R without interfering with insulin receptor activity, as well as it reduced phosphorylated Akt, caused apoptosis and induced tumour regression in xenografted mice. PPP did not compete with ATP but interfered with phosphorylation in the activation loop of the kinase domain, in which it specifically blocked phosphorylation of the tyrosine (Y) 1136 residue, while sparing the two others (Y1131 and Y1135) [4].
Currently it is well established that IGF-1R is crucial in many physiological processes like growth, differentiation and aging as well as it is an important player in disease development. Particular attention has been paid at its role in cancer and today the IGF-1R is generally regarded as one of the most promising targets for cancer therapy. However, we have to learn how to use it.

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Role of p27kip1/stathmin interaction in the regulation of cell motility

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The relationship between cell movements and cell cycle progression is a topic far to be completely clarified. Recent data from several laboratories suggest that some of the cell cycle related proteins, such as Cyclins, CDKs and CKIs (CDK Inhibitors) directly participate also in the regulation of cell movements.
We investigated the role of the CKI $p27^{kip1}$ in the regulation of cell proliferation and motility in cells in contact with the Extracellular Matrix (ECM).
$p27^{kip1}$ (hereafter p27) is a well known cell cycle inhibitory protein that acts by binding and inhibiting the cyclins/CDKs complexes, preferentially targeting the activity of the Cyclin A/CDK2 and Cyclin E/CDK2 complexes in the nucleus of the cells. Exclusion of p27 from the nucleus results in the loss of its cell cycle progression inhibition while its potential role in the cytoplasm has been for long time unexplored.
Our work demonstrates that in mouse fibroblasts and in sarcoma derived cell lines cell-ECM contact induces a rapid translocation of p27 from the nucleus to the cytoplasm. When located in the cytoplasm, p27 is able to inhibit cell migration. This activity of p27 relies in the C-terminal portion of the protein, since a deletion mutant that lacks the last 28 aminoacids fails to inhibit cell motility although retains the ability to inhibit cell cycle progression. Thus, p27 displays two different activities that could be separated by using different deletion mutants. Based on this notion we identified as p27-interactor the Microtubules-destabilizing protein stathmin. We demonstrated that *in vitro* and *in vivo* p27 is able to bind and inhibit the activity of stathmin thus increasing the cellular MT-stability and that this increase was eventually linked to the inhibition of cell migration. High expression of stathmin and low expression of p27 result in enhanced cell migration while high p27 levels in the cytoplasm and low stathmin expression decreased cell motility through different ECM substrates. Accordingly, in a panel of human sarcomas p27/Stathmin cytoplasmic expression is high in primary tumors and low in metastatic diseases.
In conclusion, our work contributes to identify a new function for p27 protein that strictly connects the regulation of cell cycle progression with the modifications of the MTs network, thus providing new insights in the comprehension of tumor progression and metastatization that could eventually results in new therapeutic approaches in the treatment of metastatic cancers.