recently discovered class of genes transcribing small non-coding RNAs, namely microRNAs, was found to play important regulatory roles in normal development and physiology in plants and animals. Mature microRNAs are 20−22 nucleotides molecules that can regulate gene expression through RNA interference effecter complex (RISC) mediated mRNA degradation and translational suppression via complimentary pairing to predominantly 3′-untranslated region (3′-UTR) of their targeted messenger RNAs. Increasing number of studies has demonstrated a perturbation of the normal expression patterns of microRNAs in many human cancers.

Main Message: In order to investigate the microRNAs expression signatures in pediatric malignancies, we profiled a panel of pediatric tumor xenografts and cell lines belonging to 6 diagnostic categories using an in-house developed microRNA microarray. This panel included rhabdomyosarcoma (RMS), neuroblastoma (NB), Ewing's sarcoma, osteosarcoma, Wilm's and brain tumors. Each of our microRNA microarrays contains 336 human microRNAs probes based on Sanger Center's microRNA registry release 7. By unsupervised hierarchical clustering using all high quality data the cancers were primarily grouped according to their diagnosis. Using a parametric statistical analysis we identified 18 miRNAs that were differentially expressed between RMS and NB several of which were confirmed by real-time RT-PCR methods. We subsequently confirmed the expression of several cancer-specific microRNAs in the corresponding clinical tumor samples indicating their potential use for the diagnosis of these cancers.

In order to investigate the potential targets and functional roles of these microRNAs, we performed parallel gene expression profiling study on the same set of xenograft samples using Affymetrix U133 Plus 2 chips, and calculated the correlations between the expression of microRNAs and messenger RNAs. This resulting data matrix will identify potential targets of miRNA which will require experimental validation. Furthermore, we performed knock down and over expression studies with several NB and RMS specific miRNAs. We found that the over expression of mir-133a caused a profound growth suppression and induction of apoptosis in a RMS cell line.

Conclusions: Our findings showed the potential use of microRNAs for the diagnosis of pediatric cancers. Furthermore our results will reveal new insights into the function, and identify potential therapeutic uses of these small RNAs in these pediatric cancers.

S20

Novel biomarkers for prognosis and therapy response in ovarian cancer

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Introduction: New biomarkers for diagnosis, prognosis, monitoring and prediction of therapeutic response in ovarian cancer are needed.

Main Message: Recently, we have delineated the complete organization of the human kallikrein locus, which comprises 15 genes with significant homology. We have produced recombinant proteins and developed ELISA methodologies for quantitative assessment of all kallikrein proteins in serum and tissue extracts. We found that some tissue kallikreins, including KLK5, KLK6, KLK8, KLK10, KLK11 and KLK13 are over-expressed in ovarian cancer tissue, in comparison to normal ovarian tissue. We found that these KLKs have prognostic value in ovarian cancer. More recently, we have analyzed panels of kallikreins, as well as other biomarkers, in our efforts to develop a multiparametric prognostic and predictive model for this disease. We developed a combined marker which provided an area under the curve (AUC) of 0.97 for discriminating normal from cancer groups. Univariately, KLK5 and KLK6 were positively associated with progression. Increasing levels of KLK13 were associated with chemotherapy response with an odds ratio of 2.32. The predictive power of KLK13 to chemotherapy response was improved with a panel of 5 biomarkers with AUC of 0.75. After adding other clinical parameters, the AUC increased to 0.91. This data suggests that a group of kallikreins and multiparametric combinations with other biomarkers and clinical parameters can significantly assist with ovarian cancer classification, prognosis and response to chemotherapy.

Conclusions: In conclusion, human tissue kallikreins represent novel biomarkers for ovarian cancer diagnosis, prognosis and prediction of response to chemotherapy. These biomarkers, assessed individually and/or in combination with other biomarkers, may assist with delivery of individualized treatments in ovarian cancer.

S21

Biomarkers of brain tumors to temozolamide treatment

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Introduction: Glioblastomas are the most malignant brain tumors with a median survival of less than 15 months despite modern therapies. The accumulation of diverse aberrations in regulatory processes enables tumor cells to bypass the effects of most classical therapies available. Molecular alterations underlying such mechanisms comprise aberrations on the genetic level, such as point mutations of distinct genes, or amplifications and deletions, while others result from epigenetic modifications such as aberrant methylation of CpG islands in the regulatory sequence of genes.

Main Message: In a candidate gene approach the epigenetic inactivation of the MGMT gene was evaluated as a predictive factor for benefit from the alkylating agent temozolomide that was added concomitant and adjuvant to radiotherapy. MGMT is a repair enzyme known to rapidly revert the highly toxic O6-methylguanine to its native state, guanine, in a suicide reaction – hence, blunting most of the treatment effect of the alkylating drug. The translational