The tumour take rate is 13% (RCC) and 22% (bladder). At that time 24 (RCC), 6 (bladder) and 1 (prostate) patients-derived models were established in nude mice. It took 1 to 9 months for tumour to developp at the first graft but only 1 to 2 months for subsequent passages. Histopathological parameters are conserved during passages. Molecular parameters are under investigation. Some models responded to the treatment and some other not depending on the drug used, and according to the patient's treatment (when available), validating our models. Predictive biomarkers are under study.
These models are available to test new or existing therapies in these cancers according to tumour characteristics.

### 154 C-kit expression as a novel molecular marker to pre-operatively distinguish benign from malignant thyroid lesions

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**Background:** Thyroid carcinoma represents 90% of all neuroendocrine malignancies. The vast majority of thyroid cancers are papillary thyroid carcinoma (PTC) and their initial presentation is through a thyroid nodule. The best available test in the evaluation of a thyroid nodule is fine needle aspiration which sometimes is not efficient enough to give a specific diagnosis leading to the so called suspicious diagnoses for PTC. Surgery is usually recommended in these cases, but often it is not known what kind of surgery is appropriate: thyroid lobectomy or total thyroidectomy?
It is therefore necessary to develop more accurate early diagnostic assays for the evaluation of thyroid nodules.
Neoplastic processes often result from changes in gene expression patterns. Recent works have documented that *c-kit*, the receptor for stem cell factor, is expressed in a number of nonhematopoietic cell lineages, including normal thyroid epithelium. *Kit* is an important tyrosine kinase receptor in cell differentiation and growth; it functions as an oncogene in many cancers. In our study we found that the transcript level of *c-kit* in PTC tumour cells is extremely low.
**Materials and Methods:** We analyzed preoperative thyroid FNAs of patients with benign and malignant thyroid lesions selected from archived materials of the Section of Cytopathology, Division of Surgical, Molecular and Ultrastructural Pathology, and performed RNA extraction, cDNA synthesis and finally *c-kit* detection by qualitative and quantitative PCR.
**Results:** We observed that: while *c-kit* expression was preserved in a large fraction of goiters and benign adenomas (94%), 91% of malignant thyroid tumours had *c-kit* expression ratio value between 0 and 0.5 ($p = 0.0002$).
It has been suggested in the literature that in some cell types *c-kit* expression positively regulates mitogenesis and is selected for in neoplastic transformation, in other tissues the *c-kit* pathway is involved in morphogenesis and differentiation and is, therefore, negatively selected in the course of tumour progression.
**Conclusions:** In the preoperative settings we could determine a threshold of *c-kit* gene expression levels above or below which it would be possible to give a value indicative of a benign or malignant thyroid lesion. This become more useful in association with other well known molecular markers (BRAF), and also new ones such as LSM7 (a protein involved in pre-mRNA splicing) that we are also investigating in this study.

### 155 Clinical significance of the expression and amplification of the cortactin gene at 11q13 in head and neck squamous cell carcinomas

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**Background:** Despite major advancements in cancer diagnosis and treatment, the survival rate for patients with head and neck squamous cell carcinoma (HNSCC) has only marginally improved over the past few decades. It is therefore essential to identify new markers that can distinguish differences in tumour condition and augment the predictive power of the current clinical markers. Amplification of the 11q13 region is a prevalent genetic alteration in head and neck squamous cell carcinoma (HNSCC). We investigated the clinical significance of cortactin (CTTN) and cyclin D1 (CCND1) amplification in HNSCC tumour progression.
**Material and Methods:** CTTN and CCND1 amplification was analysed by differential and real-time PCR in a prospective series of 202 laryngeal/pharyngeal carcinomas. CTTN mRNA and protein expression were respectively determined by real-time RT-PCR and immunohistochemistry, and correlated with gene status. Molecular alterations were associated with clinicopathological parameters and disease outcome.
**Results:** CTTN and CCND1 amplifications were respectively found in 75 (37%) and 90 (45%) tumours. Both correlated with advanced disease; however, only CTTN amplification was associated with recurrence and reduced disease-specific survival ($p = 0.0022$). Strikingly, CTTN amplification differentially influenced survival depending on tumour site ($p = 0.0001$ larynx versus $p = 0.68$ pharynx) and was an independent predictor of reduced survival in the larynx ($p = 0.04$). Furthermore, CTTN overexpression correlated significantly with reduced disease-specific survival ($p = 0.018$). *CTTN* gene status strongly correlated with CTTN expression. All tumours harbouring *CTTN* amplification showed elevated mRNA/protein levels; however, CTTN overexpression occurred at a higher frequency (57%, mRNA and protein) indicating that additional mechanisms contribute to the regulation of CTTN expression in HNSCC.
**Conclusion:** These data indicate that although *CTTN* and *CCND1* amplification may be both biologically relevant features that cooperatively contribute to cancer development and progression, the strong relationship of *CTTN* amplification/overexpression with prognosis and disease outcome reinforces its role as driver of 11q13 amplification in HNSCC. CTTN emerges as a valuable prognostic marker to identify patients with laryngeal tumours at high-risk of recurrence and poor outcome that could benefit from more intensive treatment and follow-up.

### 156 Profile, target genes and regulation of microRNAs in ovarian carcinoma tumour progression

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**Background:** MicroRNAs(miRNAs) are small non-coding RNAs, that exert their regulatory effect post-transcriptionally by binding the 3′-UTR oftheir target mRNA and inhibiting gene translation to protein. Depending on whether miRNAs target oncogenes or tumour suppressor genes, they may be referred to as tumour suppressors or oncogenes respectively. Cellular miRNA expression is tightly regulated. One of thepost-transcriptional regulatory mechanisms involves changes in expression of miRNA machinery proteins, i.e., Dicer, and miRISC components such as the Argonaute (Ago) family members. Numerous studies, using different profiling approaches, have unraveled that miRNA expression is deregulated in various human cancers.
Ovarian canceris the leading cause of death from gynecological cancers in western countries. The disease is asymptomatic in the early stages, and is usually diagnosed at anadvance stage. Primary solid tumours, solid metastases, and effusions to theperitoneal and pleural cavities (ascites) characterize the tumour as itprogresses.
The aim of thestudy was to characterize the difference in miRNA expression pattern between primary ovarian solid carcinomas and effusion-derived cells, using freshly frozen samples. We also assessed changes in regulation of miRNA by evaluating theexpression of the machinery proteins at these two sites.
**Material and Methods:** Using microRNA-array platforms, we identified three sets of miRNAs: one set is highly expressed in both primary solid carcinomas and effusions. The second set is relatively upregulated in effusions, and the third set is relatively downregulated in effusions. The most significant miRNAs were validated byreal-time PCR.
**Results:** Our results show concordance between the training and the independent test cohortsfor the downregulated miR-145 and miR-214 and for the upregulated let-7f, miR-182, miR-210, miR-200c, miR-222 and miR-23a in effusions. Using in-silicotarget prediction programs we identified potential target genes for the miRNAsof interest listed above, we investigated the changes of those genes in ourcohort. We analyzed the expression levels of Zeb1, a confirmed target ofmiR-200c as well as c-Myc, that was found to be a predicted target of miR-200c. In addition, we analyzed Pak1 and PTEN, both predicted targets of miR-222. We found inverse correlations between the expression levels of the indicated miRNAs and of the predicted target genes.
We further analyzed the miRNA processing machinery genes that regulate miRNA generationand action. We found significantly higher expression of Ago1, Ago2 and Dicer ineffusion-derived cells compared to primary carcinoma tumours. These alterationsin expression levels indicate on difference in miRNA regulation between the two sites.
**Conclusions:** In summary, miRNAexpression profiles and the changes in miRNA processing machinery genes reveala new level of regulatory elements in ovarian carcinoma tumour progression.