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## HUMAN KALLIKREINS (hKs) AS NOVEL SERUM BIOMARKERS FOR DIAGNOSIS, PROGNOSIS AND MONITORING OF EPITHELIAL OVARIAN CARCINOMA

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We recently reported the complete genomic organization of the human kallikrein gene locus on chromosome 19q13.4, which represents that largest cluster of serine proteases within the whole human genome. All kallikreins share significant homologies at the DNA and amino acid level and are hormonally regulated by steroids. We examined the prognostic value of multiple kallikreins in ovarian cancer by measuring protein levels in ovarian cancer tissue extracts or mRNA by RT-PCR. We found that kallikreins 4, 5, 6, 7, 8, 9, 10 and 11 are all prognostic indicators of ovarian cancer outcomes. We have further demonstrated strong associations between kallikrein expression and tumor stage, grade, histotype, residual tumor post-surgery, response to chemotherapy, as well as disease-free and overall survival. We also recently developed the first methods for quantification of multiple kallikreins in serum. We found that the concentration of at least 6 kallikreins, hK5 hK6, hK7, hK8, hK10 and hK11, is frequently increased in serum of ovarian cancer patients, but not in serum of patients with benign ovarian lesions. At least two of these new biomarkers, hK6 and hK10, have recently demonstrated their diagnostic and prognostic value. Their diagnostic sensitivity at 90% specificity is 54%. About 35% of CA125 negative ovarian cancer patients were hK10 positive at 90% specificity. The use of these two markers in stage I-II patients results in a 21% increase in sensitivity compared to CA125 alone. Moreover, hK6/hK10 serum levels are a powerful predictor of both PFS and OS in uni- and multivariate analyses. Thus, multiple kallikreins appear to be useful as diagnostic and prognostic markers in serum, and we are now performing a multiparametric analysis of at least 6 hKs together with CA125 in order to further enhance sensitivity and specificity of this novel panel of biomarkers.