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Title: Cancer-associated oncogenic BARD1 isoforms: From biomarker expression studies to development of a blood test for early detection of lung cancer

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Body: BARD1 protein binds to, stabilizes, and enhances the tumor suppressor functions of BRCA1. However, highly upregulated expression of aberrant BARD1 isoforms correlates with decreased patient survival in NSCLC. BARD1 isoforms are tumor drivers and act antagonistically to E3 ubiquitin ligase functions of BARD1-BRCA1 heterodimer. In particular, isoform BARD1β is promoting cell proliferation by stabilizing Aurora kinases. Since BARD1β and BARD1π are upregulated and correlated with poor prognosis in lung cancer they might act as suitable biomarkers of NSCLC detection/progression. We developed a blood test based on BARD1 isoforms by performing ELISA tests with antibodies against different regions of BARD1 for detection of BARD1 isoforms in blood of NSCLC patients. We also generated a peptide library representing 60 epitopes mimicking BARD1 isoforms, for detection of autoimmune antibodies recognizing epitopes expressed by BARD1 isoforms. Significant differences between serum samples from 60 chemotherapy-naive NSCLC patients and from 40 healthy volunteers have been found. Applying a combination of seven peptides, lung cancer was detected with 87 percent sensitivity and 68 percent specificity. Thus, antibodies against BARD1 isoforms are telltales of NSCLC and their detection can be further developed towards a blood test. Experiments including larger patient and control group numbers, different types of lung cancer are currently ongoing, and should optimize test conditions and define the target patient set.