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An Efficient Algorithm for Biomarker Identification

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Background: Studies on cancer biomarkers have reported an ability to identify the presence of breast cancer in small and retrospective studies. We explored a breast cancer detection test utilizing an array of protein biomarkers in an attempt to define a reliably reproducible model.

Methods: 376 women, 35 to 75 years old, were enrolled treatment naive from community breast biopsy ($n = 244$) and screening mammography referrals ($N = 132$). Biopsy patients were further divided into breast cancer positive ($n = 35$) and benign breast conditions ($n = 209$) groups based on subsequent tissue pathology. Serum was analyzed for IL-2, IL6, IL8, IL12, TNF alpha, HGF, EGF, FGF, and VEGF utilizing either bead-based multiplex or ELISA methodology. Marker data were combined with each subject's demographic and clinical information and analyzed with a proprietary iterative regression analysis.

Results: A subset of the original biomarkers was shown to be statistically significant ($P < 0.05$) and used to create the final score predictive of the presence or absence of breast cancer. This score yielded an AUROC of 0.830 with a specified sensitivity of 63% and specificity of 86%.

Conclusion: These findings demonstrate in a clinical trial the ability of a select set of biomarkers to correlate with the presence or absence of breast cancer in an enriched population of patients. A prospective clinical trial is underway to validate the numbers presented here. Additional trials of differing study design are warranted to quantify the clinical utility in an unselected population.

Generation of an antibody microarray for the early detection ovarian cancer markers

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Neoclone has a Phase II SBIR contract to develop a high-throughput monoclonal antibody microarray for the diagnosis of early stage ovarian cancers. These arrays will be produced using the glass slide based platform of GenTel Biosciences, and after development and validation of the assay system with fluorescence detection these arrays will be provided to EDRN investigators for testing with human samples.

NeoClone Biotechnology develops monoclonal antibodies (mAbs) using a novel ABL-MYC retroviral technology. Our process targets antigen-specific B cells and transforms them into stable plasmacytomas, secreting high levels of immunoglobulins. We can rapidly and efficiently produce large numbers of antigen-specific antibody producing cell lines. This process is ideal for the generation of antibodies to be used in diagnostic applications where high clonal diversity is important for selecting antibodies with specific characteristics, such as high affinity and specificity as well as stability and compatibility with different detection platforms. NeoClone is in the process of developing a panel of mococlonal antibodies to several ovarian cancer markers, including CA-125, CA 15-3, CA 19-9 and CA 72-4. In collaboration with GenTel Biosciences antibodies specific to a minimum of 16 cancer markers will be printed in a microarray for multiplex detection of these biomarkers in human serum. Preliminary data suggest that such microarrays will detect these biomarkers with a linear dose response over at least two logs of target concentration.

An efficient algorithm for biomarker identification

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One challenge for biomarker identification is how to handle high dimensional mass spectral data. Various feature selection algorithms have been applied, including the Wilcoxon test, Area under the ROC curve, Fisher score, J5 test, Simple separability criterion,t-test score, Weighted separability criterion, principal component analysis (PCA), Wavelet-based algorithms and

the genetic algorithm, to name a few. However, each of them has its own limitations. We present an efficient feature selection algorithm, recently developed by the authors, for the biomarker identification task. Advantages of the proposed algorithm are as follows. 1) It selects peaks rather than a combination of all available peaks such as those selected by transformation based methods (PCA, Wavelet), 2) It considers interactions among peaks and measures the correlations in terms of amount of explained variances by the peaks, 3) It is computationally efficient, 4) It automatically handles extremely unbalanced data sets where the number of instances in some classes are significantly more than those in other classes, and 5) The algorithm produces a list of near-optimal combinations for all possible number of peaks with sensitivity and specificity calculated for each of the combinations. Users can then choose the best peak combination based on its sensitivity and specificity. We applied the proposed algorithm to MALDI-MSI mass spectra to identify biomarkers for prostate cancer and the effectiveness of the proposed method is clearly demonstrated.

Autoantibody approach for serum-based detection of head and neck cancer

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Currently, no effective tool exists for screening or early diagnosis of head and neck squamous cell carcinoma (HNSCC). Here we describe an approach for cancer detection based on analysis of patterns of serum immunoreactivity against a panel of biomarkers selected using microarray-based serological profiling and specialized bioinformatics. We biopanned phage-display libraries derived from 3 different HNSCC tissues to generate 5,133 selectively cloned tumor antigens. Based on their differential immunoreactivity on protein microarrays against sera from 39 cancer and 41 control patients, we reduced the number of clones to 1,021. The performance of a neural network model (Multilayer Perceptron) for cancer classification on a dataset of 80 HNSCC and 78 control samples was assessed using ten-fold cross-validation repeated 100 times. A panel of 130 clones was found to be adequate for building a classifier with sufficient sensitivity and specificity. Using these 130 markers on a completely new and independent set of 80 samples, an accuracy of 84.9% with sensitivity of 79.8% and specificity of 90.1% was achieved. Similar performance was achieved by reshuffling of the dataset and by using other classification models. The performance of this classification approach represents a significant improvement over current diagnostic accuracy (sensitivity of 37% to 46% and specificity of 24%) in the primary care setting. The results shown here are promising and demonstrate the potential use of this approach toward eventual development of diagnostic assay with sufficient sensitivity and specificity suitable for detection of early stage HNSCC in high risk populations.

Harnessing DNA repair enzyme activity for use as biomarkers for risk assessment and early detection of lung cancer

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DNA repair provides a major defense against cancer in humans as indicated by the high cancer predisposition of individuals with hereditary germ-line mutations in DNA repair genes. Several studies have shown that reduced DNA repair plays a similarly important role in sporadic cancers. However the scarcity of functional specific DNA repair assays that are suitable for epidemiological studies slows down the progress in this field.

Our goal is to develop a series of DNA repair biomarkers for cancer risk assessment and early detection, and apply them to large-scale screening directed towards cancer prevention in general, and lung cancer prevention in particular. Our approach is based on functional DNA repair assays, and specifically enzymatic DNA repair activities. We have previously developed an enzymatic activity assay for the repair of the oxidative DNA lesion 8-oxoguanine in extracts from human