Editorial:

A Decade of Tissue Microarrays: Progress in the Discovery and Validation of Cancer Biomarkers.

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This year, 2008, marks the 10-year anniversary of the development of the modern tissue microarray (TMA). During the last decade, the use of TMAs has grown steadily and accounts for a small but increasing percentage of all cancer biomarker studies performed. The growing popularity of TMA-based studies attests to their benefits in the discovery and validation of new biomarkers. Modern expression-screening platforms such as complementary DNA (cDNA) arrays allow for high-throughput lead discovery in cancer and other diseases. For evaluation of promising candidate genes, however, in situ analysis of high numbers of clinical tissues samples for example, by immunohistochemistry or fluorescence in situ hybridization is mandatory. Tissue microarray (TMA) technology greatly facilitates such analysis. Thus, TMA technology will markedly accelerate the transition from basic research to clinical applications.

What are tissue microarrays? Tissue microarrays (TMA) are a proven method, whereby minute tissue cores (diameter 0.6 mm) are removed from up to a thousand different conventional paraffin blocks and re-assembled in a single empty paraffin block at predefined positions.

By arraying the diverse samples in this manner, a high throughput approach can be applied to the analysis of tissue samples. Sections of the resulting TMA can be utilized for the range of research applicable to conventional tissue sections (Fig.1 and 2), and an entire cohort of cases can be analyzed by staining just one or two master array slides, instead of staining hundreds of conventional slides, yet each spot on the array is similar to a conventional slide in that complete demographic and outcome information is maintained for each case so that rigorous statistical analysis can be done as rapidly as the arrays are analyzed.

This technique was originally described in 1987 by Wan, Fortuna and Furmanski in Journal of Immunological Methods. They published a modification of Battifora's "sausage" block technique whereby tissue cores were placed in specific spatially fixed positions in a block. The technique was popularized by Kononen and colleagues in the laboratory of Ollie Kallioneimi after a publication in Nature Medicine in 1998. This technology should not be confused with DNA microarrays. Tissue microarrays are different from DNA microarrays where each spot on an array

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represents a cloned cDNA or oligonucleotide that binds to the target sequence. With tissue microarrays, each array has patient specific histological samples from cancer infected tissues. The tissue microarray technique is best suited for screening one genetic marker or protein across thousands of samples where as DNA microarrays are best suited to study gene expression across thousands of genes.

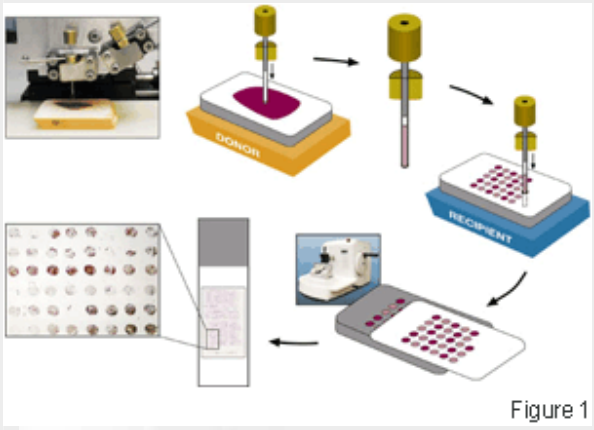

Figure 1

- Figure 1 shows an example of a tissue microarray and its construction. The arrays are assembled by taking core needle "biopsies" from specific locations in pre-existing paraffin-embedded tissue blocks and re-embedding them in an arrayed "master" block.

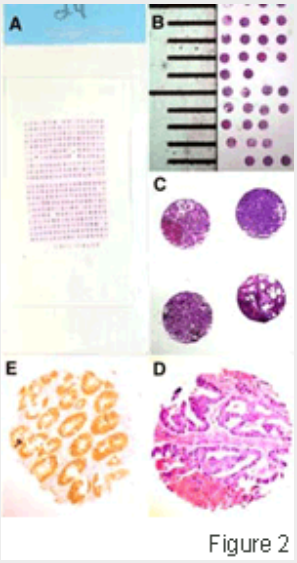

Figure 2

- Figure 2 shows an overview of a completed colon cancer array and higher magnification views of spots from this array. Stains shown in these examples include Hematoxyline and eosin and DAB based-immunoperoxidase.

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Advantages of Tissue Microarrays:

Important advantages of the TMA technology are speed (parallel analysis of up to a thousand tissues), cost efficiency (the same amount of reagents required for a single large-section analysis is sufficient for a thousand samples), and standardisation (the same experimental conditions are applied to all samples). Because of the high numbers of samples usually included in TMAs, they are optimally suited to detect genotype–phenotype associations with high statistical power. Thus, TMA technology will markedly accelerate the transition from basic research to clinical applications.

Can the small cores really be representative of the entire sample?

A suggested drawback of this technique has been that the analyzed material is too small to represent the entire sample. However, it has been demonstrated in numerous studies that this is not the case. In fact, some studies have shown quite clearly that between two to four 0.6mm unique cores from the same sample is all this is necessary to represent an entire section. Using TMA, 1 mm, which is about 2.8 fold larger than that of the 0.6 mm cores commonly used. Use of multiple samples can eliminate variability by rapidly increasing the data points available. Additionally, the available data points can be multiply by using custom TMA with duplicate, triplicate, and quadruplicate cores.

Key Words: tissue microarray; TMA; immunohistochemistry; IHC; fluorescence in situ hybridization; FISH; high-throughout tissue analysis; TMA representatively.