IDENTIFICATION OF BLADDER CANCER BIOMARKERS
BY GENOMIC APPROACHES

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Bladder cancer is one of the most frequent human cancer which develops on two tracks, papillary and non-papillary that correspond to clinically different forms of the disease. Most bladder cancers are chemically induced with tobacco smoking being the leading risk factor. Recent advances of bladder cancer research for which our laboratory has significantly contributed have enhanced the understanding of the origin of bladder cancer from urothelial progenitor cells via field effects along papillary/luminal non-papillary/basal pathways. Here we present the contribution to the development of novel, both diagnostic and therapeutic, biomarkers using genomic high throughput technologies.

The analysis of hits associated with growth advantage of preneoplastic lesions allowed us to identify six chromosomal regions mapping 3q22, 5q22.2 -5q23.3, 9q22.12, 10q26.1, 13q14 and 17p13 that may be critical for the development of bladder cancer and contain a distinct class of genes referred to us forerunner (FR) genes involved in the clonal expansion of precursor conditions. We concentrated our efforts on one of these regions; which contain a model tumor suppressor RB1. We used high-resolution whole-organ mapping with SNPs, which facilitated the identification of five positional candidate FR genes (ITM2B, LPAR6, MLNR, CAB39L and ARL11) mapping contiguously to RB1. We hypothesized that identification of novel forerunner genes and the investigation of their involvement in early occult phases of human bladder preneoplasia may not only provide important mechanistic clues to the development of human cancer but also identify a novel class of early detection markers capable of detecting the clinically and microscopically occult phases of human cancer development [3,4].

We used the whole-organ histologic and genetic mapping strategy coupled with next generation whole exome sequencing using complemented with genotyping using Illumina HumanOmni2.5_8 chips and whole genome methylation analyses to define the molecular alterations that were associated with the progression of muscle-invasive bladder cancer in one surgical specimen.

We identified a total of 18 structurally significant mutations, three of which appeared to be clear “driver” mutations that had been annotated previously. Alterations in chromatin hyper- and hypomethylation predominated in all of the regions that contained normal-appearing urothelium or low-grade dysplasia. In total, 31 genes were hypermethylated and 26 genes were hypomethylated. Copy number alterations were numerous (n=242) in areas that contained high-grade dysplasia suggesting that genomic instability preceded the emergence of driver mutations in what ultimately emerged as the dominant tumor subclone. Chromosomal gains (n=216) vastly outnumbered losses (n=26).