

## Advances in the Molecular Profiling of Tumor Tissue

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In the realm of cancer care, complete sequencing of the human genome has supported a move away from the traditional paradigm in which histopathologically defined disease is treated primarily with cytotoxic chemotherapy, toward the use of molecularly targeted drugs. The cancer genome typically contains numerous mutations; however, a select number are considered "driver" mutations. When specific drugs are developed either targeting these driver mutations, or pathways associated with these mutations, they are also termed "actionable" mutations. Early success stories demonstrated in breast cancer with trastuzumab in ERBB2 amplified cancer, imatinib in Philadelphia chromosome positive chronic myelogenous leukemia, erlotinib in EGFR mutated non-small cell lung cancer, cetuximab in KRAS wild-type colorectal cancer and vemurafenib in BRAF-mutant melanoma. The Cancer Genome Atlas is a comprehensive program in cancer genomics that began in 2006 and has been the foundation of the molecular profiling movement. As a result of the associated and consequential genomic discoveries, there are now hundreds of compounds in clinical development targeting more than 100 actionable mutations in cancer-related genes representing multiple cellular pathways.

Cancer treatment has entered a new frontier. The advent of new sequencing technologies such as next generation sequencing (NGS) allows for rapid, relatively inexpensive profiling of individual cancer genomes. This technologic advancement offers the opportunity to "individualize" cancer care.

Despite all of the hype regarding molecular profiling of individual tumors certain caveats need to be considered: 1: The fact that a given mutation is actionable in a tumor

from one organ does not necessarily mean it is actionable in another. For example, encouraging results have been obtained targeting the BRAF mutation in melanoma; however, these same compounds are not active against BRAF mutated colonic cancer. 2: It appears that many tumors are able to develop resistance towards drugs targeting single mutations and in all likelihood combination therapy targeting several mutations or multiple steps along a single pathway will be necessary to combat resistance. 3: Several other cancer-associated pathways other than actionable mutations are being successfully targeted. Angiogenesis, the immune microenvironment, tumor sensitization, induction of cell death, tumor vaccines and monoclonal antibody delivery of toxic molecules are but a few of these novel therapeutic pathways.

The success of molecular profiling will require continued collaboration between oncologists, biostatisticians, pathologists, geneticists, policy-makers and members of the pharmaceutical industry in order to develop new clinical models that enable rapid translation of many new biomarkers and cancer targets into new clinical tests and therapeutic interventions to benefit cancer patients.

### Guest Editors

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