Individualized Molecular Medicine: Linking Functional Proteomics to Select Therapeutics Targeting the PI3K Pathway for Specific Patients

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1 Introduction

In 1970s, President Nixon declared a war on cancer and signed the National Cancer Act with an expectation of finding a cure. For at least a subset of cancers such as childhood leukemias, we have made remarkable progress to the point where survival is an expectation rather than a rarity. Although we do not have one panacea for all human cancers, 30 years later, we understand that each type of cancer and potentially each person’s cancer is different, and it will take the development of rationale combination therapies to cure all cancers. To reach Nixon’s idealistic goal, medical oncology care will need to become individualized. Specifically targeted drugs continue to receive FDA approval and guide treatment selection on the basis of the underlying dysfunctional genetic, transcriptional, or protein regulation driving their tumor progression.

For individual treatment selection to become a reality, it is critical to have methods in place to determine where, exactly, the genetic defect in each tumor is and to monitor the response to treatment of the patient’s tumor and of the protein product of the genetic defect. Thus, oncology will rely heavily on laboratory analysis of the molecular abnormalities from an individual’s biopsy. Repeated biopsies will guide every treatment decision along the way to recovery. Following validation of targets and targeting through biopsies, it may become feasible to move to less invasive approaches such as molecular imaging. Indeed, a major goal is to develop approaches that link the concurrent development and validation of targeted therapeutics, molecular markers, and molecular imaging.

Although the idea of an individually tailored drug regimen has been around for some time and other diseases, such as HIV, are treated in this manner, cancer is such a complex disease that the latest technological developments have only now made it possible to begin unraveling this complexity. This complexity also makes the development of effective personalized therapies both challenging and expensive.
However, personalized therapies are already being used in particular cancers with targeted therapeutics such as gefitinib and imatinib mesylate for tumors that have mutations in the drug targets.

Breast cancer serves as the “poster child” for the implementation and validation of individualized treatment on the basis of biological and genetic abnormalities or molecular markers. After the diagnosis of breast cancer, the expression of estrogen, progesterone, and ErbB2 receptors is measured in all patients to determine the most appropriate course of treatment, either based on hormonal therapy or trastuzumab, combined with other approaches on the basis of the molecular diagnostics results. Here, molecular diagnostics allows the presence of the target to drive the selection of patients who are likely to benefit from a specific treatment. This example demonstrates how molecular medicine can be extended to all cancer types. However, despite the utility of these approaches in breast cancer, only about 40% of patients with the underlying aberration respond to the targeted therapeutic. The presence of the target is not sufficient to faithfully predict response. Thus, it is necessary to develop additional predictive markers to identify likely responders as well as more effective combination therapies. In contrast, the negative predictive value of molecular diagnostics for hormone receptors and ErbB2 is striking with no or extremely few patients without the marker responding.

Although the availability of targeted treatment options like trastuzumab to selectively inhibit ErbB2 receptors is advantageous, the majority of breast cancer patients do not have an amplification of the ErbB2 receptor. Novel inhibitors that target more common protein aberrations without toxic side effects are desperately needed. However, it is essential to note that even within the small population of ErbB2-overexpressing breast cancers, individualized molecular medicine yields a very high patient benefit.

Breast cancer with its frequent early diagnosis presents an additional opportunity for molecular diagnostics and personalized therapy. For patients with small localized disease, the chance of recurrence after local therapy such as surgery and/or radiation is low. Indeed, there is a consensus that patients with low risk disease do not require additional chemotherapy to their management, particularly because of the short and long-term toxicity of treatment. However, the patient and physician are faced with the conundrum of not knowing in which patient the disease is likely to recur. This results in an overtreatment of patients who could have been cured by surgery alone. Recently molecular marker sets with the potential to identify patients who do not require additional chemotherapy or patients who potentially will not respond to chemotherapy have been identified and undergone initial validation. The Oncotype Dx and Agendia approaches are undergoing large scale evaluation to establish their utility in patient management. These studies point the way but markers with high sensitivity and specificity of predicting outcomes and response to therapy are sorely needed.

For effective implementation of new cancer therapies, the development of pharmaceuticals requires two important informational components: who would benefit the most from treatment and what biomarker can be used to measure the response. A biomarker determines whether the appropriate dose is given or can identify early