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Utilizing Genomics and Identifying Biomarkers to Develop Targeted Therapies in Cancer

For over a century, scientists have observed tumor development within the human body, which were presumed to arise from somatic mutations that persisted as cells continually underwent mitotic divisions. As more discoveries arose in the field of genetics and molecular biology, researchers began to identify cancer as a genetic disease, utilizing more advanced technologies in order to study these abnormalities at the chromosomal and genomic levels. Moreover, the completion of the human genome sequencing effort at the turn of the twenty-first century strengthened the study of cancer genomes by not only providing various techniques, such as the polymerase chain reactions, but also by developing more systematic methods to sequence cancer genomes and identify relevant biological pathways. This genetic understanding of biological functions has and will continue to revolutionize the field of cancer diagnostics and therapeutics by enabling scientists to identify specific biomarkers within individual cancers in order to develop targeted therapies and personalized medicine for the individual patient (Stratton, 2011). The development of bevacizumab, an anti-vascular endothelial growth factors (VEGF) antibody, arose from this approach to targeting cancer, and thus far, has shown promising results as a therapeutic agent; however, the identification of potential biomarkers will improve the effectiveness of this anti-VEGF agent as well as other drugs in patients.

Among the various research topics in the field of cancer biology, scientists have conducted intensive research on the process of angiogenesis and cancer metastasis – the process

of developing new blood vessels. This event plays a crucial role in cancer metastasis by providing tumor cells with the necessary conditions to spread to other tissues through the lymphatic and blood vessels. Particularly, researchers have identified the role of vascular endothelial growth factors (VEGF) in mediating angiogenesis. These relationships arose from studies of the human VEGFA gene through the understanding of the regulation of VEGF gene expression. Various growth factors – epidermal growth factor, TGF-α, TGF-βm keratinocyte growth factor, insulin-like growth factor-1, FGF and platelet-derived growth factor – in conjunction with inflammatory cytokines such as IL-1α and IL-6 were found to upregulate VEGF mRNA expression in various cancerous cell lines, thereby supporting the claims that VEGF facilitates angiogenesis (Ferrara et al, 2003).

From the understanding of the biology of VEGF and its receptors through gene expression array studies along with other in vitro and in vivo models, researchers were able to develop various anti-VEGF monoclonal antibodies on the notion that VEGF-targeted therapies would utilize these agents to hinder the development of new blood vessels, and therefore deprive the metastatic tumors of the essential nutrients and oxygen (Lee et al, 2008). This included the development of bevacizumab at Genentech, which recently gained approval from the United States Food and Drug Administration to serve as the first-line therapy for metastatic colorectal cancer.

Given their understanding of VEGF as a regulator of angiogenesis, Genentech produced promising results through both their in vivo and clinical models. Their in vivo studies showed that the compound possessed a similar binding affinity as the original antibody and within mice, bound and neutralized human VEGF-A isoforms and bioactive proteolytic fragments (Ferrara et al, 2004). In humans, from phase III clinical trials, bevacizumab, in conjunction with traditional

chemotherapy, demonstrated increased overall survival in “colorectal and lung cancer patients as well as a progression-free survival in breast cancer patients” by targeting both cancer cells and endothelial cells (Jain et al, 2006). When used with irinotecen/5-fluorouracil/leucovorin or paclitaxel, bevacizumab showed approximately 4.4-month and 4.8-month increase in overall survival in previously untreated, metastatic colorectal cancer patients and previously untreated progression-free breast cancer patients, respectively. With a combination of paclitaxel and carboplatin, the compound also provided for an increase in overall survival in lung cancer patients at about a 2-month increase (Full date table can be viewed: http://www.nature.com/nrclinonc/journal/v3/n1/fig_tab/ncponc0403_T2.html).

The development of bevacizumab represents a step towards a more targeted approach in cancer therapeutics: researchers utilize genomics in order to identify specific genes or pathways that exhibit abnormal patterns in human tissues, from which they could develop drugs that selectively target these markers to reduce the cell viability of cancer cells without yielding other poor clinical outcomes or side effects. Unlike the specificity of this method, nontargeted therapies for cancer, such as chemotherapy, cause much collateral damage as radiation indiscriminately affects all tissues, including the surrounding normal tissues and organs to cancer regions. While the results of the clinical trials seem to support possible widespread clinical applications at face value, the mechanism of action for bevacizumab in patients remains mostly unknown for researchers, consequently leaving the possibility for major safety concerns, such as “increased morbidity, and a number of treatment-related deaths from bowel perforations, thromboembolic events, and hemorrhage” (Jain et al, 2006). This is the result of the lack of knowledge of any proven biomarkers – biological indicators that provide identification of patient response to the prescribed therapies – in anti-VEGF therapy.

In order to reduce the risk for these poor clinical outcomes from the usage of bevacizumab, or any other compound intended for targeted therapy in cancers, it is necessary for researchers and clinicians to understand individual cancer cases in order to determine appropriate optimal treatment regiments and therapeutic recommendations, as there exist genetic variations between patients, and subsequently, tumors. Moreover, they will need to be able to predict the responses of different tumor types to the prescription of these compounds in order to possess better knowledge of patient compatibility and outcomes (Jain et al, 2006). For these clinicians and researchers, there are three types of biomarkers that hold clinical relevance: "prognostic biomarkers (that predict disease outcome without further treatment), predictive biomarkers (that foretell response to a specific therapy), and pharmacodynamic biomarkers (that help decide on the optimal dose of a drug for an individual patient)" (Bernards, 2010). Therefore, with such a wide range of utility and applications, the discovery and validation of biomarkers becomes especially crucial to improving the efficacy of current targeted therapies and reducing potential unintended damage from their usage.

However, since the complete mechanism of action by bevacizumab in the regulation of angiogenesis remains elusive, biomarker discovery has been particularly difficult. Consequently, the associated outcomes in the phase III clinical trials of bevacizumab as labeled above and in the table linked above do not reflect the usage of biomarkers as well as the consideration of other variables, including dose-dependency per individual patients and evaluations, such as K-ras, BRAF, and p53 mutations and microvascular density (Jain et al, 2006). While scientists have singled out potential biomarkers, including "classical diagnostic or prognostic biomarkers, as well as newly developed, target-based and mechanism-based biomarkers," none has proven to be predictive in clinical situations due to lack of accessibility in some tumors, low concentrations

within the human body, poor resolution, unclear origins, and dependency on alterable factors (Surrogate markers under testing for the evaluation of the efficacy of anti-VEGF agents included here: http://www.nature.com/nrclinonc/journal/v3/n1/fig_tab/ncponc0403_T4.html). Therefore, this particular situation (bevacizumab) not only emphasizes the urgency for biomarker discovery but also, highlights some of the many challenges to finding and establishing clinically feasible biomarkers.

While current research has identified and called for the necessity of biological indicators within novel cancer therapeutic approaches, various barriers continue to inhibit the progress of biomarker discovery (Sawyers, 2008). Currently, within some clinical trials, clinicians utilize predictive and pharmacodynamic biomarkers to assess efficacy of tested drugs. However, there are many physical barriers to collecting these results, as it is difficult to acquire multiple tumor samples from patients due to the stipulations of clinical trial set ups as well as the invasive nature of the biopsy procedure. However, as a response, researchers have tried to characterize the "molecular composition of [the] tumor" instead by utilizing blood sampling to study the changes in the serum proteins; however, such methods also have their limitations as few biomarkers are known. Besides the technical challenge of acquiring tumor samples, researchers also find difficulty with determining which measurements would provide the most information about a patient's response to the therapy. In order to accomplish this, researchers could not utilize a 'data-driven' approach, as the issues with the acquisition of samples remain unresolved; instead, they must genotype the DNA in the tumor, either through preclinical or clinical models, with the former eventually validated in the latter. This method, albeit more 'discovery-based,' could include gene expression profiling of the entire cancer genome, which could reveal previously

unidentified proteins, genetic modifications, and pathways, among many other clinically related findings.

Lastly, should these previous barriers be surpassed, researchers must also consider the funding that would be required to develop complex assays that could be used within the clinics. For this to occur, there must be financial incentives for pharmaceutical companies to undergo the long and expensive process of biomarker discovery, assay development, and validation of the commercially available product. While collectively, these barriers may seem to inhibit progress towards research and development of these biomarkers, increasingly successful evidence from limited clinical trials thus far are presenting evidence to large pharmaceutical companies that drugs created in conjunction with their biological companion diagnostics could greatly increase the pool of patients eligible for certain drugs; moreover, such results also have stimulated the rise of "adaptive trials," a new type of clinical trial that provide for greater rates of biomarker validation through biomarker-driven hypotheses (Bernards, 2010).

As evident in many recent published studies, the field of genomics has and will continue to transform the field of cancer therapeutics, by enabling scientists to not only identify certain genetic targets but also, co-develop compounds and their biomarkers in order to increase the efficacy of treatment and reduce the possibility of collateral damage to the patient. Although, this approach to medicine will require extensive funding, research, and time, the ultimate success of targeted therapy would improve the quality of care for all cancer patients by enabling clinicians to understand the individual needs of each patient. These medical providers will understand how the patient will react to various treatment options, which then will enable them to select the most optimal therapies and maximize overall survival and quality of life for patients. At this point, the field of oncology would very closely approach the idea of personalized medicine.

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