



On the Trail of Genomic Pioneers



Meet Justin M. Balko, Pharm.D., Ph.D.
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1. Would you tell us more about your educational background and research experience?

I earned my Doctor of Pharmacy (Pharm.D.) degree at the State University of New York (SUNY) Buffalo in 2004. From 2004 until 2009, I completed my Ph.D. in Pharmaceutical Sciences from the University of Kentucky, specializing in Clinical and Experimental Therapeutics.

My doctoral work at the University of Kentucky was focused on improving patient outcomes in non-small cell lung cancer by a *priori* selection of patients who will respond to small molecule inhibitors of EGFR using gene expression predictors of response (GEPR). This work was extended through identification of the MAPK pathway as an important module within the context of the EGFR dependent phenotype. This was accomplished specifically by validating cytotoxic synergy *in vitro* between inhibitors of EGFR and MEK, a component of the MAPK pathway. Finally, we furthered our predictive work by transposing the GEPR of EGFR inhibitor sensitivity to metastatic colorectal cancer, where we found that the efficacy of our predictive profile was conserved in mCRC patients treated with the EGFR-targeted monoclonal antibody cetuximab.

Following the completion of my doctorate, I moved to my current position, which is a research fellow in the laboratory of Carlos Arteaga, M.D. at Vanderbilt Ingram Cancer Center, in the division of hematology/oncology.

2. Your paper demonstrates gene expression as a predictor of sensitivity to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI). Could you briefly explain this and how it could be a valuable clinical tool?

The role of EGFR mutations in predicting response to EGFR TKI has been well established in recent years. Certainly a number of other biomarkers of response to these agents have been validated *in vitro*, but lack substantial clinical data as to their efficacy. KRAS mutations, certainly well established as playing a predictive role in the response of colorectal tumors to cetuximab, remain a controversial biomarker in lung cancer.

Our GEPR, based on the expression of 180 mRNAs, may offer improved predictions of EGFR inhibitor sensitivity over single gene biomarkers. Incorporating a large number of variables better accounts for high levels of inter-patient variability that cannot be captured easily in single gene assays. Thus, we believe that ultimately, multivariate biomarkers will hold promise to guide patient and oncologist therapeutic decisions. Certainly, any method which can both enhance response rates to therapeutics by enriching the treated population for responders while minimizing treatment costs could be a valuable tool. This is underscored by the recent moves to reduce overall healthcare costs.

3. How could pharmacogenomics help in lung cancer research?

Lung cancer is a disease characterized by diverse oncogenic activity. A large number of



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independent and inter-dependent pathways are activated in lung cancers, and only once these pathways and their importance is understood will we achieve effective therapies for the majority of patients. Pharmacogenomics offers the ability to capture the heterogeneity of lung cancer by identifying transcriptional 'readouts' of activated pathways and cellular processes. These readouts can be used to both identify patients who will benefit from certain therapies, as well as identify common pathways or signatures of activated pathways that can be taken advantage of through novel therapeutics.

4. What is the use of biological markers in cancer research?

Biological markers can impact all stages of cancer research, including screening and diagnosis, characterization of tumor subtypes, prognostic indicators, and markers of response or pharmacodynamic activity of drugs. Currently single feature biological markers are already in place in many cancer treatment paradigms. Thus, the use of biological markers is not a novel idea, although novel biomarkers are being routinely identified in the laboratory. The true impact of these markers however will depend on extensive validation, a field which has lagged behind. Essentially, the application of pharmacogenomics has improved our ability to identify potential biomarkers, but the number of these biomarkers being extensively validated is comparably low. Thus, I believe that the impact of new biomarkers will depend

precariously upon our ability to validate their utility clinically. Without routine enrollment in cancer biomarker trials and the availability of patient samples to validate potential markers upon, we could fall short of this goal. Significant work remains to be done in this field.

5. Where do you see your research heading in the future?

I believe that the future of my research will be to continue to identify clinical scenarios where the application of pharmacogenomic methods may afford the opportunity to reduce unnecessary therapies and treatments and to maximize benefit in the treated population. There are a number of solid malignancies to which survival and treatment remains suboptimal. Application of pharmacogenomics to these areas will allow for discovery of new biomarkers to be used for the identification and stratification of responsive patient subgroups. I hope to devote the majority of my future research to not only identifying these biomarkers, but also validating them both biologically and clinically in an effort to directly impact and improve patient care.

6. A great deal of your work focuses on cancer research. What would you say are the most important things that have been discovered in recent years and what will be role of genomics in it in the years to come?

I believe that the most important findings in recent years are the observations that 1) molecular diagnostics can be a cost effective way to enhance therapeutic decisions (for example, KRAS testing in CRC, EGFR mutation testing in NSCLC, and multivariate gene expression



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assaying in breast cancer such as Oncotype Dx and MammaPrint), 2) Complex multivariate biological assays are better able to capture heterogeneity of cancer as a disease, and can be used to better stratify response, prognosis, and disease subtypes than previously used methods, and 3) A large amount of molecular information is encoded within the tumor through expression patterns of genes. Specifically item 3 underlies my belief that genomics will play an increasing role in the diagnosis, classification, prognosis, and treatment decisions in cancer therapy. This point is underscored by the well developed technology and technical understanding of the genomics field.

7. What are specific goals of your research?

The specific goals of my research at this time are to identify biomarkers of endocrine therapy resistance in breast cancer patients. Additionally, I am working on the application of genomics to identify subsets of breast cancers that may be more aggressive and may require alternative strategies to improve survival.

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