Published in final edited form as:

Colorectal Cancer. 2013 ; 2(6): 487–489. doi:10.2217/crc.13.65.

Challenges and strategies for identifying biomarkers for colorectal cancer

Bruno Conte¹ and **Scott Kopetz^{*,1}**

¹Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 426, Houston, TX 77030, USA

Since biologic therapies became a routine in the clinical practice of colorectal cancer (CRC), they have been shown to improve survival and have provided a new avenue for predictive biomarker research with the goal of improving outcomes. The targeted nature of these therapies has provided opportunities to propose and interrogate biomarkers related to the respective agents' mechanisms of action. *KRAS* mutation is currently the most recognized molecular predictive marker in CRC, predicting efficacy of anti-EGF receptor (anti-EGFR) antibodies.

The discovery of the predictive ability of *KRAS* was considered a pivotal example of personalized medicine, and accelerated interests in biomarker discovery in CRC. However, over the past 5 years, predictive biomarkers for biologic therapy of CRC, other than *KRAS*, have been slow to appear. The incidence of *KRAS* mutation is approximately 30–45%, and in many countries testing with PCR technology remains costly and is accessible only in specialized centers [1]. There is also a significant uncertainty regarding how to better interpret data on *KRAS* mutations given the controversy about the findings of alternate *KRAS* codons, including the mixed results on anti-EGFR sensitivity in the less common codon 13 mutations. To highlight the rapidly changing landscape, recent data suggest that expanded *RAS* testing, to include *NRAS* and codons 61 and 146 of *KRAS*, may provide additional benefit in treatment prediction [2]. This provides a backdrop to the challenges and future prospects for identifying predictive biomarkers.

Biomarkers are the backbone of personalized medicine. Molecular abnormalities from DNA, RNA and proteins of cancer cells provide explanations for the exquisite, unregulated behavior of cancer cells. From a biologic perspective, each anomaly is a marker of the malignant state. In clinical oncology, the term biomarker often implies that a specific molecular change has the capacity to predict outcome in response to a particular therapy and also stratify prognosis. In addition, biomarkers have the potential to reveal important insights regarding carcinogenesis and the mechanism of action of drugs [3].

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*Author for correspondence: Tel.: +1 713 792 2828; skopetz@mdanderson.org.

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Competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Recently the field of oncology has been adopting a more individualized medicine approach, or so-called ‘precision medicine’. Given this exciting perspective, the investigative field of biomarkers that are prognostic and/or predictive of a tumor’s response is an intensive and prosperous area of research. The discovery of new biomarkers for CRC is imperative and its requirement is dramatically increasing considering all the myriad of molecular knowledge that are available, but unfortunately this is not always paralleled by the ability to reliably detect or mediate this knowledge [4].

In recent years, the framework for the investigation of novel biomarkers and therapeutics has been driven primarily by the desire to improve the activity of novel therapeutics (and thereby increase the likelihood of subsequent US FDA approval). This current biomarker development model, which we term the ‘targeted-based’ model, is based on a target drug’s mechanism of action and the particular interaction with its signaling pathway. *BRAF* inhibitors (e.g., vemurafenib or dabrafenib) are examples of this model, as over 60% of metastatic melanoma has a *BRAF* mutation and exhibited an interesting clinical benefit for this disease in the mutated population. Unfortunately this was not demonstrated in metastatic CRC, suggesting that in this disease, *BRAF* mutation inhibition has a different biologic behavior [5, 6]. The need to continue developing biomarkers that are specific to individual drugs currently in development has arisen, for example, from successes in the model with an ALK inhibitor in a biomarker-directed subset of lung cancer.

But there are more examples of failures of this model – not due to insufficient effort or resources, but owing to the difficult underlying mechanism of action of the agents. For example, regorafenib, a recently approved tyrosine kinase inhibitor for metastatic CRC, lacks a predictive biomarker, as well as the other biologic agents routinely used, such as bevacizumab and ziv-afercept. The more widespread failures of this approach have blunted some enthusiasm for predictive biomarkers, and highlight some complexities and hurdles that need to be addressed to improve the success rate.

One important hurdle that needs to be considered for target-based biomarker development is tumor heterogeneity. There is increasing evidence suggesting intratumoral variation between the primary and metastatic sites, between regions of the same tumor and in the same region at different points in the disease course [7, 8]. The assumption that a targeted drug could work for one specific mutation along the entire natural history of the tumor may result in a costly, time-consuming clinical trial that fails to demonstrate benefit. At a minimum, the degree of intratumoral, intertumoral, temporal and treatment-induced heterogeneity should be determined for each biomarker with as much clarity as possible before embarking on efforts to utilize this biomarker for patient selection [9]. Instead, a more comprehensive analysis of the intrinsic biology is needed, which is independent of the status of a single biomarker and less susceptible to this heterogeneity.

A second important limitation for biomarker development is the feasibility of screening patients for experimental studies. Logistics considerations are important because the frequency of many bio-markers of interest is low [10]. As an example, two genes of interest for target-based prospective trials are *PIK3CA* and *BRAF*, which are present in 15 and 5% of CRC tumors, respectively. For a prospective enriched clinical trial that addresses these two

abnormalities, 500 patients need to be screened to treat 75 and 25, respectively, so the majority of the patients will not have the mutations of interest and will not be able to participate. Such a high screen failure rate is of particular concern in the refractory metastatic setting where patients have a limited timeframe to initiate experimental therapy. Thus, as biomarker research evolves, several important ethical and practical issues emerge and need to be carefully handled [11].

There is increased recognition that this target-based model is insufficient to handle the complexity of CRC. CRC is the common designation for a group of different cancers with unique etiology, outcomes, clinical behavior and response to therapy. Recently, there has been substantial effort to define these molecular subsets based on molecular features such as gene expression patterns [12,13].

This recognition leads to an alternative approach to colorectal biomarker development: the 'taxonomy-based' biomarker model. It provides more comprehensive data regarding the tumor biology, pathology, clinical features and also is independent from considerations of specific therapies. It acknowledges that CRC consists of a group of heterogeneous cancers with diverse sets of genetic and epigenetic changes, which accumulate during carcinogenesis, but that commonality is present within these subgroups [14, 15]. This taxonomy-based model will require a common definition of these subtypes, and a re-evaluation of samples to determine the most appropriate assay, or combination of them, to ultimately classify precise molecular signatures for CRC subtypes.

Unlike the target-based model, this taxonomy-based model will provide a framework that is independent of the specific therapy. As such, the effort put forward in taxonomy-based biomarker development provides an enduring benefit, even if particular therapies are not effective. Similarly, once such a classification framework is established, subsequent enrichment trials will be feasible.

However, to achieve a clinically applicable classification framework, the taxonomy-based model has to address inherent challenges such as the reliability and cost of the molecular tests in the Clinical Laboratory Improvement Amendment environment. As these signatures may be difficult to clinically apply, parallel efforts may be required to identify and validate surrogate markers for CRC taxonomy groups, so that these surrogate markers can overcome the regulatory and technical issues of the new generation of gene expression-based molecular assays.

The goal of personalized medicine or precision therapy is to use biomarkers to select patients who will have the best chance to respond to specific systemic therapies. To accomplish this goal, we believe that a more comprehensive taxonomy-target biomarker development model is needed, instead of the current target-based model. The proposed taxonomy model should integrate features of the tumor biology, pathology and clinical aspects to better define colorectal groups of patients and finally provide them with the best treatment available. While difficult, this approach is more likely to provide an enduring benefit to the field and improve the outcomes of patients.

Acknowledgments

Financial disclosure

S Kopetz is supported by NIH R01CA172670 and Texas Cancer Prevention & Research Institute of Texas grant RP110584.

No writing assistance was utilized in the production of this manuscript.

Biographies

Bruno Conte

Scott Kopetz

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