



# A promising road in colorectal cancer treatment: personalized immunotherapy based on molecular and immune classification system

SeungJu Jackie Oh<sup>1</sup>, Woojin Lee<sup>2</sup>, A. Craig Lockhart<sup>3</sup>

<sup>1</sup>Department of Philosophy-Neuroscience-Psychology, Washington University in St. Louis, St. Louis, Missouri, USA; <sup>2</sup>College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul, Korea; <sup>3</sup>Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA

*Correspondence to:* A. Craig Lockhart, Professor of Medicine. Director, Developmental Therapeutics Program, Siteman Cancer Center, Department of Medicine, Washington University School of Medicine, Campus Box 8056, 660 S. Euclid Avenue, St. Louis, Missouri, USA.

Email: lockhartac@wustl.edu.

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Immunotherapy has increasingly proven to be a key treatment modality that can make a significant impact on the lives of many cancer patients. In particular, immune checkpoint inhibitors targeting the programmed cell death protein 1 (PD-1) pathway have led to remarkable clinical benefits in various cancers, including melanoma and lung cancer, and active investigations are ongoing to expand their therapeutic utility in other cancer types (1). In fact, several clinical trials have revealed a link between high somatic mutation prevalence and the clinical success in PD-1 axis blockade. Considering that colorectal cancers (CRC) are known to have very high rates of somatic mutations in comparison to other solid cancers (2), the potential of immunotherapeutic agents in treating patients with CRC is encouraging (3,4). However, in harnessing the full potential of immunotherapy, several key questions need to be addressed: which patients are to be treated in order to maximize therapeutic benefits; how would immunotherapy be combined with other treatment modalities; and how would optimal biological dosing be determined with minimal toxicity as well as cost-effectiveness (5).

Recently, Becht and colleagues conducted transcriptomic analyses of the immune, fibroblastic and angiogenic microenvironment using 1,388 CRC samples from three independent discovery and validation cohorts, and MCP-counter algorithm that can assess immune and stromal cell

infiltration (6). Their objective was to further integrate the immune and inflammatory microenvironment data within the four recently proposed CRC consensus molecular subtypes (CMSs): CMS1 [microsatellite instability (MSI) immune], CMS2 (canonical), CMS3 (metabolic), and CMS4 (mesenchymal) (7). Their results revealed a high degree of correlation between CMS classifications and microenvironmental signatures, yielding both expected and unexpected results. The good-prognosis CMS1 group was found to have high expression of immune signatures. Surprisingly, the CMS4 group with the worst prognosis of the four subgroups displayed high expression of immune signatures as well. Substantial contextual differences, however, were noted between the CMS1 and CMS4 groups. While the CMS1 group was characterized by overexpression of genes specific to cytotoxic lymphocytes, the CMS4 group showed overexpression of markers of lymphocytes and cells of monocytic origin with strong angiogenic and inflammatory components. On the other hand, the CMS2 and CMS3 groups were found to display low immune and inflammatory signatures (*Table 1*).

As discussed by Becht and colleagues (6), their findings may provide important insights into clinical investigations of immunotherapeutic agents in patients not only with CRC and but also other types of cancers. Relevant to this, Le and colleagues recently reported the results of a Phase II trial

**Table 1** Distinct immune-related signatures of the four colorectal cancer consensus molecular subtypes (CMSs) based on the major findings by Becht and colleagues (6)

Characteristics	Colorectal cancer consensus molecular subtypes (CMS)			
	CMS 1 [microsatellite instability (MSI) immune]	CMS 2 (canonical)	CMS 3 (metabolic)	CMS 4 (mesenchymal)
Prevalence	14%	37%	13%	23%
Prognosis	Good	Intermediate		Poor
Immune and inflammatory signatures	Strong	Weak		Strong
Contextual gene expression signatures (using MCP-counter algorithm)	High expression of markers of cytotoxic lymphocytes	Low expression of markers of cytotoxic lymphocytes		High expression of markers of fibroblasts, monocytic cells and endothelial cells
Tumor infiltration profiles (using immunohistochemistry)	High densities of CD8 T cells & CD68 macrophages	Low densities of CD8 T cells & CD68 macrophages		High densities of CD8 T cells & CD68 macrophages, High density of cancer-associated fibroblasts

with pembrolizumab, an anti-PD-1 immune checkpoint inhibitor, in 41 patients randomized into three cohorts: cohort A with mismatch-repair (MMR) deficient CRC patients, cohort B with MMR proficient CRC patients, and cohort C with MMR deficient non-CRC patients (4). In this study, the immune-related objective response rates were markedly dependent upon the MMR status; 40% (4 of 10 patients) and 0% (0 of 18 patients) for cohort A (MMR-deficient CRC) and cohort B (MMR-proficient CRC), respectively. While the results from this study support the predictive value of the MMR status for the response to pembrolizumab, molecular and immune classification systems with more refined and dynamic markers may offer better predictive power in identifying responders and non-responders to anti-immune checkpoint therapies than the MMR status alone. Especially in the cases of CMS2 (canonical) and CMS3 (metabolic) groups, other strategies will be needed to optimize their treatment outcomes since the two were characterized to have low immune signatures by Becht and colleagues (6). Specifically within the immunotherapy context, other approaches such as adoptive T cell therapies may be more suitable for patients with CMS2 and CMS3 CRC. In addition, how more conventional anticancer therapies such as chemotherapy or radiation therapy interact with immune therapies or alter the immune milieu within an individual's cancer have not been fully investigated and may also impact the treatment of these CRC subtypes.

As reflected by an almost 10-fold jump in overall median survival from what it was in the initial stages of CRC research in the 1960's, major advances have been made in CRC therapy over the past decades. From the introduction

of 5-fluorouracil (5-FU) and other chemotherapies to the gradual evolution of targeted therapies and immunotherapies, the past fifty years of CRC research have witnessed a number of pivotal moments. As suggested by Becht and colleagues (6), integrated molecular and immune classifications of CRC and their application to personalized CRC therapy may be a noteworthy advancement in guiding the selection of therapies that can maximize clinical benefits while minimizing unwanted side effects to CRC patients.

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