

A BLUEPRINT TO ADVANCE COLORECTAL CANCER IMMUNOTHERAPIES

In November 2017, the Cancer Immunology Research journal accepted and published A Blueprint to Advance Colorectal Cancer Immunotherapies. This paper was written as a collaboration supported by Fight Colorectal Cancer (Fight CRC) and the Cancer Research Institute (CRI) over an 18-month period.

This is a huge deal for scientists and patients! Here's what happened and why:



The blueprint is a collaboration between stakeholders, including clinicians, scientists, industry, patients and advocates, who are all invested in the development of novel approaches for patients with colorectal cancer. This comes at a time when unprecedented development of novel immune agents is intersecting with our deeper understanding of colorectal molecular subtypes and of the complexities of the tumor microenvironment.

- Dung Le, M.D., Co-Chair of the IO Work Group

BACKGROUND

Immunotherapy (immuno-oncology or IO): is an approach to cancer treatment that uses a person's own immune system to fight diseases. Colorectal cancer (CRC) had been resistant to IO until recent research identified a subgroup of patients (MSI-H) who were receptive to certain IO treatments in a clinical trial.

MSI-H patients are candidates for IO treatment

Results from a study published in 2015 showed patients with a certain abnormality in their tumor, called defective mismatch repair (DMMR), or microsatellite instability high (MSI-H), responded well to a type of IO (PD1-inhibition; PDL-1 checkpoint blockade), with prolonged benefit.

The groundbreaking study indicated that a patient's MSI status could predict their response to IO. (Le, et al. 2015.) However, only 15% of CRC tumors are MSI-H. The study didn't apply to the other 85% of CRC patients with microsatellite stable (MSS) tumors. More research is needed.

The Work Group

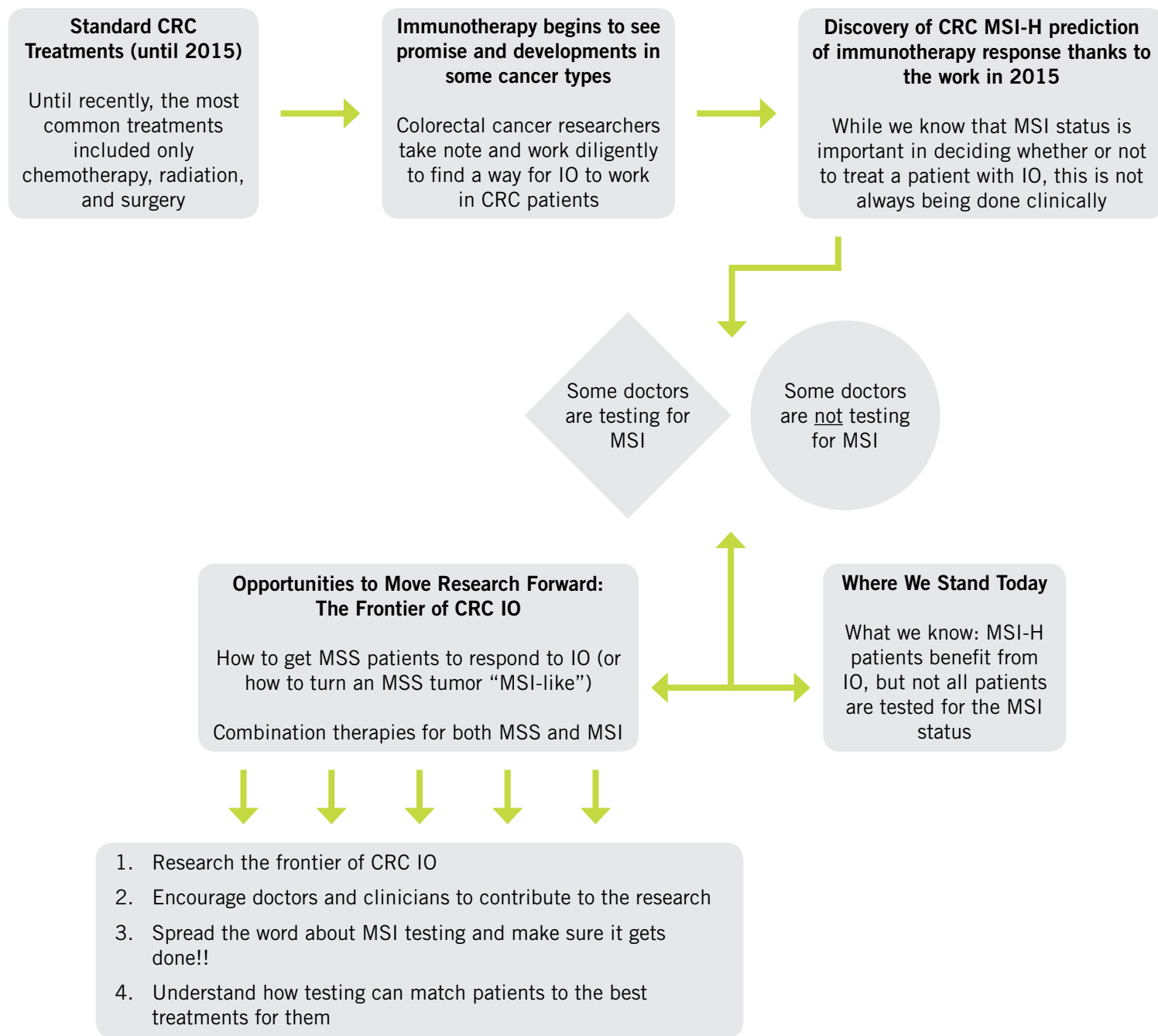
Fight CRC and CRI convened the Immunotherapy Work Group in 2015 thanks to a legacy gift donated to Fight CRC from the family of the late Gordon Cole. CRI matched the funds. Through this effort, we hosted a meeting and formed the work group. The work group efforts are to:

- Convene multi-disciplinary experts in the fields of CRC and IO
- Synthesize research and identify gaps in translational and clinical research
- Follow the path of the science and advise

In 2016 the work group wrote a blueprint outlining next steps and potential for the advancement for CRC IO. The initial finds of the blueprint were presented by Dr. Al Benson (Co-chair) during the American Association of Cancer Research (AACR) annual meeting the same year.

In the blueprint, the IO work group assessed how to implement what we know now and how to move research forward so that all patients have access to IO treatment.

Below is a description of what was presented at the 2016 AACR meeting and a summary of what was published in Cancer Immunology Research journal:



Specific Examples from the Blueprint:

- Ensure MSI and immunoscore testing are done for all CRC patients
- Identify biomarkers that predict responses to certain drugs in small Phase I studies and update clinical guidelines as needed
- Use studies that focus on a tumor's gene mutation, NOT cancer type, with biopsies before, during, and after treatment
- Utilize strategies to turn MSS into "MSI-Like" tumors so that they can receive the same benefits of IO that MSI-H tumors receive
- Collect stool samples pre, during, post treatment to study the microbiome
- Development of liquid biopsy technology
- Use the framework described in the publication that supports research identifying immunologic factors that may be used to improve IO for CRC patients, with the goal that the biomarkers and treatment strategies identified will become part of routine management of CRC
- Ensure researchers are kept up to date on what research others are doing so that they don't repeat efforts
- Create better mouse models for combination strategies
- While specific reasons are unclear, T-cells (essential for human immunity) could be a broad reason why checkpoint blockade (IO) in MSS patients does not work
- It is unknown if biomarkers with prognostic value like the immunoscore (which shows how a person's tumor interacts with the immune system) and interferon signatures (certain pattern of gene expression) will predict benefit for IO therapies in MSS CRC. If they do predict benefit, these and other biomarkers with a potential for an immune response need to be included in clinical guidelines.
- Using insights from small Phase I studies in preclinical model application
- Use of germ-free animal studies to learn more about the role of the microbiome



Immunotherapy is getting us closer to the common goal of curing cancer. The continued time and effort Fight CRC and CRI put into research and working together on the IO project is priceless.

-Wendy Lewis, Fight CRC Research Advocate, Stage III Colon Cancer Survivor

PATIENT IMPACT

With an article published in the Cancer Immunology Research (CIR) journal, we're excited to be arm-in-arm with those taking us further into the future of medicine. Here's what the blueprint means for patients and some of its implications so far:

- The IO Work Group continues to meet regularly to achieve its goals. With Fight CRC's leadership, the group will continue to meet and ensure the patient viewpoint is represented amongst the world's top experts in IO.
- Six-time Jeopardy! champion Cindy Stowell, who died from colon cancer in 2016, donated her winnings to cancer IO research at CRI, and the funds were put toward a research grant awarded to Dr. Cynthia Sears to study the "gut microbiome and immune microenvironment." This grant was awarded based on insights from the blueprint. The ongoing work in this area will continue to provide a meaningful way for patients and their loved ones to support and donate to research. This type of work could not be done without advocates like Gordon Cole, Cindy Stowell, and others affected by CRC.
- To support the trials and ongoing research, Fight CRC partnered with Tom Marsilje, Ph.D. on the Late Stage MSS-CRC Trial Finder. Patients with MSS-CRC can search through our curated list of clinical trials and help advance treatment options. **[TrialFinder.FightCRC.org](https://www.trialfinder.org/FightCRC.org)**

More Resources

[Check out our presentation from 2016 AACR](#)

[Learn more about our partnership with CRI](#)

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