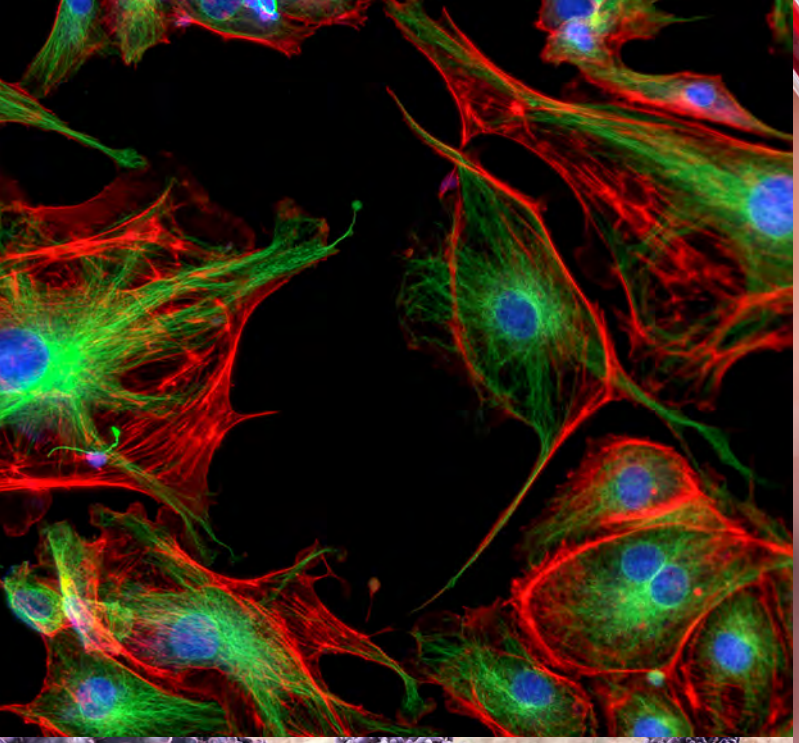

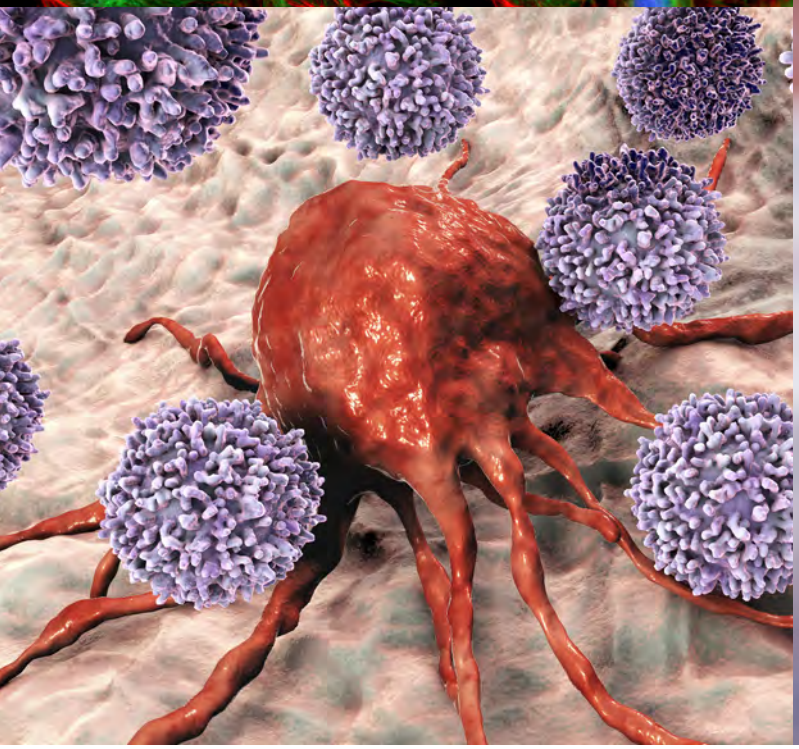

Colorectal cancer:

Towards precision medicine

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Colorectal cancer:
Towards precision medicine

Jérôme Galon and Daniela Bruni at INSERM, Laboratory of Integrative Cancer Immunology, Centre de Recherche des Cordeliers, in France, provide an in-depth look at colorectal cancer

Cancer is one of the most prominent public health challenges and a leading cause of morbidity and mortality worldwide. Colorectal cancer (CRC) is the second most commonly diagnosed cancer in women and third in men, causing nearly 861,000 deaths in 2018 only. It affects the last part of the digestive tract (colon or rectum) and usually begins as a benign, pre-cancerous lesion called polyp. It should be noted that not all polyps develop into cancer. Many subtypes of polyps have been described, including the adenomatous polyps, which bear the highest malignant potential.

Colorectal cancer: epidemiology, aetiology, signs and symptoms

Both environmental and genetic factors, including the presence of hereditary colon cancer syndromes, influence the risk of developing CRC. Modifications in diet (e.g., reduced intake of red and processed meat and sugar) and lifestyle, (such as avoidance of smoking and heavy alcohol use) were shown to substantially reduce the risk of developing CRC, although the relative contribution of each specific factor remains hard to estimate.

Worldwide CRC screening recommendations vary mostly in terms of screening methodologies and timings, but a general consensus emerged on the need to screen average-risk individuals between 50 and 75 years by colonoscopy, to be performed every 10 years. Colonoscopy represents the gold standard for CRC screening due to its ability to explore the entire colon, detect and remove polyps within the same procedure. Such screening is critical, as at the early stages most patients don't experience noticeable symptoms. Significant efforts have been made to increase the awareness of the general public on the importance of screening measures, including the recurring National Colorectal Cancer Awareness Month (Figure 1) every March, and campaigns promoted by U.S. non-profit organisations, such as Colorectal Cancer Alliance, Fight Colorectal Cancer (Fight CRC) and the Paltown community Colontown.

Over time, more evident changes in bowel habits, rectal bleeding, abdominal discomfort, weakness and weight loss might appear, these signs increasing in severity as cancer spreads. As for virtually all types of cancer, early detection and intervention remain to date the most powerful strategies to defeat CRC.

Therapeutic options in CRC

Curative surgery represents the most common treatment option for CRC. However, up to 40% experience cancer recurrence, 80% of which within the first three years post-surgery, most commonly in the form of regional or distant metastases. For rectal cancer, radiation therapy (radiotherapy) may be used before the surgery as so-called "neoadjuvant" therapy to reduce the tumour size and facilitate its resection. As an alternative, radiotherapy can be used after surgery to ensure the destruction of possibly remaining cancer cells. In both cases, chemotherapeutic agents can also be co-administered to increase the effectiveness of radiotherapy. Systemic treatments, such as

Figure 1. The immuno-oncology diagnostics company HalioDx supported the Colorectal Cancer Awareness Month in March 2019 by impersonating the blue awareness ribbon, representing the fight against colorectal cancer. In the middle, Dr Jérôme Galon, co-founder of the company.

chemotherapy, targeted therapy and immunotherapy are also possible therapeutic options in CRC and are most typically administered after surgery.

Current classification of CRC

The classification of polyps and partly that of fully developed CRC, currently relies on a morphological assessment of the bioptic specimen or the resected (pre)cancerous lesion. In addition, for CRC, the extent to which the tumour has spread to close or distant organs constitutes an important classification factor on which diagnosis and prognosis are based. This information is provided by the employment of complementary imaging technologies, such as computed tomography (CT), positron emission tomography and/or colonography. The use of blood-based diagnostic tools represents an attractive, non-invasive, ever-growingly advocated alternative which nevertheless hasn't been able to reach optimal performance.

Based on the results of the cited diagnostic tools, CRC staging is determined according to the TNM (T for tumour, N for node, M for metastasis) classification provided by the American Joint Committee on Cancer (AJCC) and Union Internationale Contre le Cancer (UICC). The first parameter (T) is based on the size of the original (primary) tumour; the second (N) and third (M) take into account the spreading of cancer to nearby lymph nodes or distant organs, respectively. Therefore, an alphanumerical code is assigned to describe anatomically each CRC, by which healthcare providers classify patients in five main stages, ranging from stage 0, or cancer in situ, only involving the colon/rectum inner lining (mucosa), to stage IV, in which the tumour spread to distant organs (metastatic stage); the stages in between these two extremes gradually see the involvement of the underlying muscular layer, near tissues, organs and lymph nodes. Accordingly, patients' survival varies along the stages: the estimated ~90% survival rate at five years post-diagnosis (meaning that 90% of patients will have the same likelihood as healthy people of living at least five years from the time of diagnosis) of a localised

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CRC falls down to ~14% in case of metastatic disease.

In addition to anatomical features, the most recent revision of the TNM staging classification (8th edition, 2017) acknowledges, amongst others, the presence of specific genetic mutations and background, (such as microsatellite instability) for their ability to predict the response to specific types of therapy. Indeed, this classification provides a framework for estimating not only patients' life expectancy but also for guiding therapeutic interventions.

Beyond the TNM classification: Towards a TNM-I?

The TNM classification is undoubtedly powerful, but the fact that patients within the same stage display very different clinical outcomes clearly shows its limitations. By solely relying on anatomopathological and genomic parameters, this stratification system is essentially tumour-centric.

The recent year witnessed the (re)birth of the field of tumour-Immunology, with the success of cancer immunotherapy, acknowledged as Breakthrough of the Year 2013 by the journal Science and recognised with the Nobel Prize in Physiology or Medicine 2018, awarded to James Allison and Tasuku Honjo for their discovery of durable, immune-activating anti-cancer strategies. Indeed, cancer immunotherapies are the only treatments leading to long-lasting tumour regression even in patients with metastases.

Nowadays, the immune system is recognised as a crucial component of modulating cancer development. The strength of the immune system is also reflected by the intrinsic prognostic value held by specific immune components, such as the cytotoxic T cells. Cytotoxic T cells are the ultimate effectors of cancer cell killing. Dr Galon was the first to demonstrate that a tumour-specific immune reaction is a better predictor of survival than traditional staging[1], where high tumour-associated cytotoxic T cell densities correlate with longer survival[2]. Thus, he proposed an immune classification of cancer-based on a newly-developed tool, the Immunoscore®, which measures the density of specific immune cells (i.e., $CD3^+$ and $CD8^+$) at pre-defined areas within CRCs[1,3]. More specifically, the Immunoscore is obtained by a digital enumeration of labelled $CD3^+$ and $CD8^+$ cells within distinct regions of the tumour (centre and invasive margin), hence providing a score ranging from 0 to 4 for increasing T cell densities.

We initiated and recently completed a worldwide study to validate Immunoscore globally, endorsed

and coordinated by the Society for Immunotherapy of Cancer (SITC). An international consortium involving more than 3,000 CRC patients in 13 different countries, validated a standardised consensus Immunoscore as the first immune classification of cancer patients[3]. By displaying a prognostic value superior to the TNM classification, the Immunoscore was found to better stratify patients in terms of disease-free and overall survival at all CRC stages. Thus, the adoption of a TNM-I (I for Immune) staging has been proposed to improve CRC classification[4]. This would have important repercussion in terms of patients' management and clinical decisions, with specific implications depending on the CRC stage.

Immunoscore in stage I/II CRC

The SITC-led international study enabled to assess the prognostic value of the consensus Immunoscore in patients with early-stage (I and II) CRC, whose tumours are most commonly and exclusively subjected to surgical resection. Currently, there are no guidelines directing the use of additional therapeutic approaches, such as (neo)adjuvant chemotherapy. Our analysis confirmed and validated the inverse correlation between Immunoscore and risk of recurrence at both stages: the highest the former, the lowest the latter[3,5]. Therefore, the Immunoscore may constitute a valuable risk-assessment tool which reliably identifies a subgroup of stage I and II patients with a heightened risk of relapse. For these patients, a more intensive surveillance programme after curative resection may be recommended.

Immunoscore in stage III CRC

The prognostic value of the consensus Immunoscore was assessed in stage III CRC patients' subgroup from the SITC-led study. In line with previous findings, the time to recurrence and overall survival were higher in high Immunoscore patients, gradually reducing with decreasing Immunoscore.

Nearly one in four of all CRCs are stage III at diagnosis[6]. These patients are typically subjected to primary tumour resection plus chemotherapy. Of note, adjuvant chemotherapy in stage III has been recommended, as it was shown to improve overall survival, albeit only on an estimated 20% of CRC patients. Hence, we attempted to improve clinical management of stage III CRC patients by assessing the power of Immunoscore to stratify patients according to their response to chemotherapy, measured in terms of tumour recurrence. The Immunoscore-based stratification can indeed identify subgroups of patients for which chemotherapy is advisable or not. Thus, the Immunoscore could constitute a valuable tool to stratify patients for which chemotherapy is beneficial. Conversely, unresponsive patients can be spared the unnecessary hazards and toxicity of this therapeutic approach and, in an attempt to increase their life expectancy, could be proposed to enrol ad hoc clinical trials.

Immunoscore in stage IV CRC

Metastatic (stage IV) disease is a leading cause of morbidity and mortality in most cancers, including CRC. Liver and lung are the dominant metastatic sites for CRC patients.

We previously showed that a weak adaptive tumour-associated immunity leads to early signs of invasiveness around the tumour, (such as venous emboli, lymphatic invasion and perineural invasion), a first step towards metastatic invasion[7]. The tumour microenvironment and Immunoscore were then shown to be critical determinants of dissemination to distant metastasis[8], demonstrating the importance of the cytotoxic immune cells in controlling the latest stage of the disease.

A great degree of heterogeneity, both in terms of tumour cells features as well as associated immunity, has been found amongst primary tumours and metastases. Such heterogeneity contributes greatly to treatment failure, for three main reasons: (I) Prognosis evaluation may be confounded, leading to inadequate therapeutic strategies and ultimately to recurrence; (II) Treatment targeting specific components may be ineffective as these components may be not

present at all tumour sites; (III) Resistant tumour subclones may emerge during treatment, leading to the inefficacy of treatment and progressive disease. To date, this so-called intra-tumour heterogeneity still represents a major challenge. From an immune point of view, the immune landscape, as well as the Immunoscore, have also been shown to vary greatly in space and time[9]. Nevertheless, the Immunoscore is one of the best predictors of favourable clinical outcome, together with other immune and non-immune (i.e., the size of the metastasis) features.

Based on these parameters, including Immunoscore, we created a predictive model of metastatic recurrence, which was able to rightly predict the risk of metastatic recurrence in CRC patients[9]. This model was built based on the information acquired on each resected metastatic lesion from individual CRC patients. Strikingly, high-Immunoscore within metastasis is also associated with very prolonged patients' survival, even when the metastases are located in the brain[10], which are notoriously associated with a dismal outcome.

In clinical practice, it's not always feasible to remove surgically all metastases and the cited heterogeneity could potentially limit the strength of this immune approach. In fact, the Immunoscore calculated on the least T cell-infiltrated metastasis is the one with the strongest association with CRC patients' outcome[11]. However, the Immunoscore was shown to perform accurately predict survival even when performed on a single biopsy, even though a better estimation can be achieved by exploiting multiple biopsies or larger tumour areas[11].

Conclusions

Thus far, the Immunoscore has been validated in multiple clinical studies involving more than 5,000 CRC patients. To promote the translation of these scientific findings into the clinic, Dr Galon co-founded HalioDx, an immuno-oncology diagnostics company based in Marseille, France, with a U.S. subsidiary, HalioDx Inc. Awarded with the Seal of Excellence Certificate by the European Commission and winner of the first-place prize in the Worldwide Innovation Challenge, HalioDx provides Immunoscore testing for in vitro diagnostic use (CE-IVD for European Community countries; performed in CLIA-certified laboratories for the U.S.). The Immunoscore is currently used in routine practice for Stage II and III colon cancer patients.

The limited accuracy of the current CRC staging system warrants for the addition of further parameters. Taken together, the presented evidence shows how the latest advances in the field of tumour-Immunology and the newly developed tools, such as the Immunoscore can effectively improve CRC patients' clinical management at all stages. It is our hope that our encouraging results and successful achievements will ultimately contribute to saving the lives of CRC patients.

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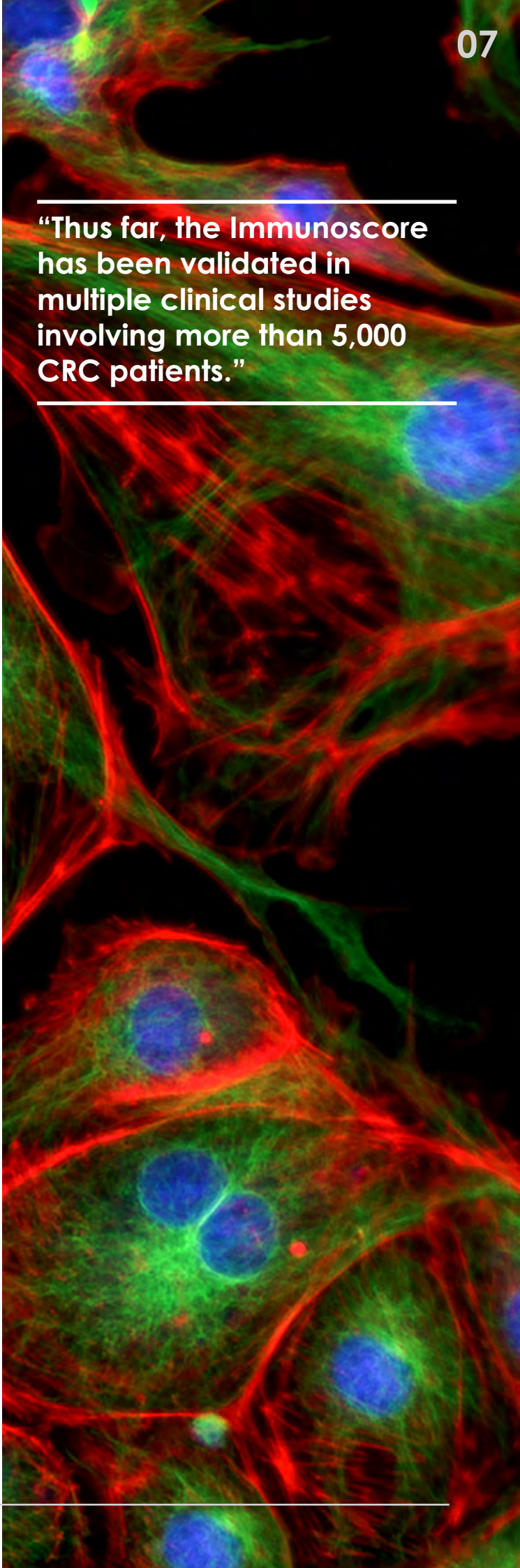

"We aim to understand tumor progression and immune reaction against cancer from pre-cancerous lesion to metastasis by using integrative biology and bioinformatics, to improve the immunotherapeutic management of cancer patients. Our research projects are focusing on the analysis of the pre-existing immunity and its modulation."

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