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MEETING REPORT

# 11th International Symposium on Minimal Residual Cancer (ISMRC): 3–5 May 2018, Montpellier, France

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International ISMRC meetings started in 1996 and have established themselves, every other year, as a premier event focusing on minimal residual cancer in patients with solid tumors. After great cities like Munich, Berlin, Oslo, San Francisco, Hamburg, Athens, Osaka and Paris, the 11th International Symposium of Minimal Residual Cancer (ISMRC) took place May 3–5 2018 at the convention center 'Corum' in Montpellier, France (http://www.ismrc2018.com). Forty-two international key opinion leaders and experts in the field of cancer have been invited; thirty different sponsors accepted to support this important congress and 400 participants from 31 different countries registered proposing 119 abstracts.

The 11th ISMRC has been a great opportunity to gather during 3 days, researchers and clinicians from academia and industry to share information about the most recent technical developments, clinical trials, biology discoveries and late breaking news and establish long lasting collaborations in cancer research.

The program covered multiple aspects of cancer biology with emphasis on metastasis including cancer stemness, cancer dormancy, epithelial-mesenchymal transition as well as immunomodulation of tumor cells and evolution of cancer. The translational part of the program had a specific focus on *LIQUID BIOPSY* in a broad sense including circulating tumor cells (CTCs), circulating nucleic acids (DNA, miRNA), exosomes and platelets with an emphasis on clinical validation studies (Fig. 1).

Metastasis in cancer patients can occur after long latency periods of up to more than 10 years, a process called "cancer dormancy". The source of these late relapses are disseminated tumor cells (DTCs) or small micrometastases undetectable by current imaging procedures. Recent advances in the development of sensitive and specific immunoassays and PCR-based technologies have made this stage of "minimal residual cancer" (MRC) become visible.

At the 11th ISMRC, international experts focusing on basic mechanisms of cancer metastasis and translational studies to detect and characterize cancer cells or their products such as nucleic acids or exosomes in the blood of cancer patients ("liquid biopsies").

The first part of the ISMRC focused on basic mechanisms of cancer metastasis with emphasis on the early stages of tumor cell dissemination and colonization of distant organs [1–5]. In this context, the high plasticity of cancer cells plays an important role in metastasis [6]. Carcinoma cells can undergo an epithelial-to-mesenchymal transition (EMT) [7–9], which is associated with cancer cell stemness leading to an increased invasiveness and resistance to chemotherapy [10, 11]. EMT and cancer stem cells were therefore also the prime topics of the experts presenting their research at ISMRC [12]. Another key area of investigation was cancer dormancy, which is controlled by the features of the DTCs and the surrounding microenvironment (e.g., changes in the BM environment may induce the escape from dormancy). Most DTCs in cancer patients are initially in a dormant (i.e., non-proliferative) stage and they can display a cancer stem cell phenotype, which might help DTCs to survive systemic chemotherapy and evade immune recognition and eradication. After induction of proliferation DTCs can be eradicated by the surrounding immune cells until some mutations occur (e.g., LOH in MHC genes) that enable the DTCs to escape immuno-surveillance [13, 14]. Moreover, 'evolutionary ecology to oncology' was also a fascinating topic with potential crucial implications for novel treatment strategies [15].

The second part of the symposium was dedicated to clinical studies on "liquid biopsy", a new diagnostic concept

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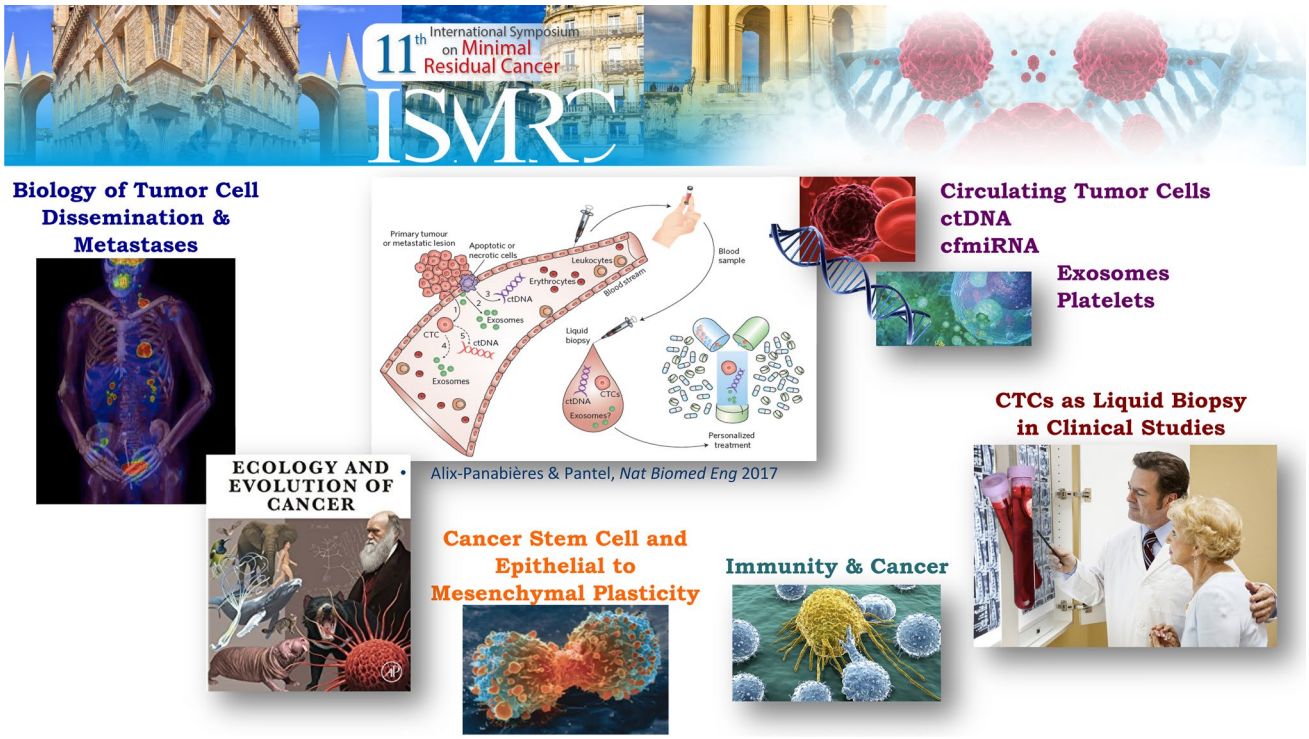


**Fig. 1** Different topics covered by the 11th ISMRC Montpellier—France

introduced in 2010 [16] for the analysis of CTCs and now extended to material (in particular DNA) released by tumor cells in the peripheral blood of cancer patients [17, 18]. Over the past decade, various methods have been developed to detect CTCs and ctDNA in the peripheral blood of cancer patients [18–21]. While reliable information can be easily obtained in patients with advanced disease, early stage cancer patients usually present with very low concentrations of CTCs and ctDNA. At present, most CTC assays rely on epithelial markers and the majority of CTCs detected are single isolated cells. The clinical relevance of 'mesenchymal' CTCs lacking any epithelial markers as well as CTC clusters are still under investigation. Strong interests for detecting viable CTCs and for expanding them ex vivo has been highlighted in different cancer types and it remains a crucial challenge in this field of expertise. Although most published studies have been performed on patients with carcinomas and melanomas, CTCs have been also detected in the peripheral blood of patients with primary brain tumors (glioblastomas) despite the blood–brain barrier [22]. Moreover, breast cancer CTCs associated with brain metastases could be recently characterized at the molecular level [23].

*Liquid biopsy* assays are currently being validated for early detection of cancer, which is supposed to reduce cancer related mortality. Despite remarkable progresses, liquid biopsy-based detection of early stages of cancer remains a challenge, in particular in breast cancer. New blood-based biomarkers for early detection currently validated in clinical trials include miRNAs, exosomes and tumor-educated platelets.

In patients with diagnosed cancer, CTCs and ctDNA analyses [24] can obtain independent information on prognosis in early and advanced stages of disease. In particular, CTC counts at initial diagnosis are able to refine the current risk stratification by TNM staging in early stage breast cancer. Moreover, early detection of relapse by sequential ctDNA (or CTCs) analysis of blood samples obtained post-surgery during the follow up is possible and may be used in future trials to stratify patients to "post-adjuvant" therapies [25].

Another key application of *liquid biopsy* is to identify therapeutic targets or mechanisms of resistance of metastatic cells in individual patients. While the analysis of ctDNA focuses on mutations relevant for cancer therapy (e.g., EGFR, KRAS or ESR1 mutations), CTCs offer a wide spectrum of analyses at the DNA, RNA and protein levels [17, 18, 26, 27]. Metastatic cells might have unique characteristics that can differ from the bulk of cancer cells in the primary tumor currently used for stratification of patients to systemic therapy. Moreover, monitoring of CTCs and ctDNA before, during and after systemic therapy (e.g., chemotherapy, hormonal therapy, antibody therapy) might provide unique information for the future clinical management of the individual cancer patient and might serve as surrogate marker for response to therapy [28–34]. In the context

of recent success in antibody-mediated blockade of immune checkpoint control molecules, expression of the PD-L1 on CTCs might be of interest as potential predictive marker [35–38]. Moreover, the expression of androgen receptor variant seven in CTCs may predict resistance to anti-androgen therapy in prostate cancer, while mutations in the estrogen receptor gene (ESR1) provides information on resistance to hormone therapy in breast cancer [39, 40]. Additional therapeutic targets detected on CTCs in cancer patients include the estrogen receptor and HER-2 oncogene [18]. Single cell RNAseq analysis of CTCs may provide more comprehensive information on relevant pathways.

For functional analysis of CTCs, the development of in vitro and in vivo test systems has started, which might also serve as models for drug testing. In particular, the development of CTC lines [41] and xenografts [42, 43] derived from CTCs can provide novel insights into the biology of tumor cell dissemination and may be used to discover new pathways to target specifically metastatic cells.

Besides CTCs and ctDNA the analysis of circulating microRNAs, exosomes or tumor-educated platelets may provide complementary information as "liquid biopsy" [44]. E.g., the integrin composition of exosomes seems to determine the organ site of metastatic niches [45] and the RNA expression pattern of tumor-educated blood platelets [46] reveals information on tumors in cancer patients.

In conclusion, *liquid biopsy* analysis can be used to obtain new insights into metastasis biology, and as companion diagnostics to improve the stratification of therapies and to obtain insights into therapy-induced selection of cancer cells. Different approaches such as CTC or ctDNA analysis will provide complementary information [47]. Technical and clinical assay validation is very important and can be achieved in international consortia such as the European IMI Cancer-ID network (http://www.cancer-id.eu).

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