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MEETING REPORT

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CIMT 2017: Anniversary symposium - Report on the 15th CIMT Annual Meeting of the Association for Cancer Immunotherapy

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Introduction

The 15th Annual Meeting of the Association for Cancer Immunotherapy (CIMT) took place May 10–11, 2017, Mainz, Germany during which scientists and CIMT members from all over the world not only celebrated CIMT`s 15th Anniversary but also had the chance to present and discuss the past and current status, and the future of cancer immunotherapy. This annual symposium report highlights and summarizes the sessions held in various fields of this promising cancer therapy.

Keynote

Harnessing the immune system to attack tumor cells has been a holy grail of cancer therapy. The great efforts put into understanding how the activity of T lymphocytes is controlled have begun to pay off, checkpoint inhibitors not only marked the beginning of a new era of cancer immunotherapy termed immune-oncology, but became the forerunners in revolutionizing cancer therapy. In his keynote address, Alexander Eggermont (Gustave Roussy Cancer Campus Grand Paris, Villejuif, France) revisited the checkpoint blockade success story by focusing on key observations, positive as well as negative, made from the plethora of clinical trials pushed forward for the evaluation of CTLA-4 and PD-1/PD-L1 blockade. He deduced the success of checkpoint blockade from the realization that treatment outcome always depends on the presence and the quality of the immune response, even in therapies long thought to act independently of the immune system, such as chemotherapy and targeted therapies. Indeed, the efficacy of chemotherapeutic agents strongly depends on their ability to induce immunogenic cell death.[1-3] Complete responders to BRAF inhibitors display a gene signature profile before treatment enriched for CD8 effector T cells, cytolytic T cells, NK cells and antigen presenting cells,[4] strongly indicating that BRAF inhibitors feed into the immune system and that a "hot" tumor may be a prerequisite for clinical benefit. Eggermont further presented an overview on how chemo-, radio- and targeted therapies are able to support immune action in different ways, and emphasized that the choice of combination partner with immunotherapy should be made dependent on that partner's ability to promote immunogenic cell death.

The most apparent and essential difference in the mechanism of CTLA-4 and PD-1/PD-L1 blockade is their site of action. While CTLA-4 acts mostly central in the lymph nodes and actively prevents activation to counter autoimmunity, PD-1/PD-L1 hinders function of activated T cells in the periphery and the tumor. Despite its stunning effects in responding patients, including those with minimal residual disease, serious adverse effects are associated with the response to CTLA-4 blockade.[5] Efficacy increases with dose, and so does the frequency of treatment- as well as immune-related toxicities of grade 3–5 (especially those of gastrointestinal, endocrine, hepatic and neurologic origin), leading to discontinuation and even death in several patients. These new toxicities in oncology can be controlled, but early identification and intervention is extremely critical.

PD-1/PD-L1 blockade, on the other hand, seems to lack the shortcomings of CTLA-4 blockade but to retain the benefits, providing higher efficacy (overall survival in responding melanoma patients of 45 % after 3 years) and much lower toxicity. In addition, PD-1 blockade has shown clinical efficacy in many cancer entities apart from melanoma, such as squamous and non-squamous non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (SCCHN), renal cell carcinoma (RCC), bladder, gastric, esophageal and liver cancer, mesothelioma, Merkel cell carcinoma (MCC) and Hodgkin's lymphoma (FDA-approved or under approval).

Still, increasing the efficacy and durability of responding patients is only one objective of immune-oncology - more importantly, the fraction of responding patients needs to increase. How to predict responders is one of the key questions in checkpoint blockade therapy. The "cancer immunogram" as proposed by Blank et al.[6] offers a framework for describing the different interactions between cancer and the immune system in individual cases, and intends to focus biomarker research and to help guide treatment choice. PD-L1 expression is suggested to be of major prognostic value. In melanoma, PD-L1

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expression in pretreatment tumors can be correlated with response rate, progression-free survival and overall survival; however, patients with PD-L1 negative tumors can also achieve durable responses with PD-1 blockade.[7] In other cancers, such as RCC, bladder cancer and MCC, PD-L1 expression does not seem to play a role at all. In a third group comprising NSCLC, SCCHN and especially Hodgkin lymphoma, the expression level of PD-L1 correlates with objective response rates and overall survival (KEYNOTE-010,[8] CheckMate-141[9,10]), emphasizing the importance of stratification according to PD-L1 expression in clinical trial designs for these cancer types. Other parameters of the cancer immunogram, inhibitory tumor metabolism (e.g. LDH, glucose utilization), soluble inhibitors (e.g., IL-6, CRP), and immune cell infiltration (e.g., CD8 T cells, T regulatory T cells, eosinophils) provide hints, but are not at all sufficient for prediction of response. According to Eggermont, tumor sensitivity to immune effectors (e.g., MHC expression, IFNγ sensitivity) may be misleading as a prognostic parameter as immunotherapy may select for escape variants. Tumor foreignness, or mutational load, on the other hand, is predictive for the response to checkpoint blockade in melanoma and NSCLC patients.[11,12] DNA-mismatch repair-deficient colorectal cancer (CRC) patients are more likely to respond,[13] and complete or partial responses were observed in bladder cancer patients with higher mutational load combined with higher CD8 T cell infiltration and effector gene expression.[14] On sequential CTLA-4 and PD-1 blockade, T cell clonality was found to predict response to PD-1 but not CTLA-4 blockade, and high copy number loss was associated with poor response independent of mutational load, suggesting copy number loss as a putative resistance mechanism.[15] Other investigators found that acquired resistance to PD-1 blockade was associated with mutations in interferon receptor signaling and antigen presentation.[16] Eggermont closed the biomarker section by stating that all parameters discusssed in the immunogram may serve as predictive biomarkers, but that prospective trials are needed for their validation. He predicted that comprehensive immunoscoring and profiling may have an important role in this field.

Is the combination of CTLA-4 and PD-1/PD-L1 blockade of any benefit? The CheckMate069 trial (phase II, randomized) for unresectable stage III or IV melanoma demonstrated a median change from baseline tumor burden of −70% in the ipilimumab/nivolumab combination arm compared with +5% with ipilimumab alone at 2 y of follow-up. A current update to Checkmate067 (phase III, randomized) for unresectable or metastatic melanoma produced different interim results depending on end point parameter: response rates and progression-free survival were highest for the combination, followed by nivolumab alone and ipilimumab alone. Overall survival, however, was similar with the combination and nivolumab alone. When retrospectively stratifying according to PD-L1 expression, overall response rates were highest with the combination when PD-L1 expression was negative (< 1 % PD-L1 expression), but were similar to nivolumab alone when PD-L1 was expressed (≥ 1 % PD-L1 expression). Regarding safety, nivolumab alone was much less toxic than ipilimumab alone or the combination.[17] Consequently, stratification according to PD-L1 expression may obviate the need for CTLA-4 and minimize the occurrence of severe adverse events in melanoma therapy. Preliminary results from the ongoing CheckMate012 NSCLC trial demonstrated efficacy across all tumor PD-L1 expression levels for the combination and nivolumab alone, with higher objective response rates with the combination. Interestingly, objective response rates increased with PD-L1 expression especially in the combination arm where up to 90 % were reached when PD-L1 was expressed at more than 50%.[18]

Looking ahead, Eggermont postulated that combination of immunotherapy with other drugs (immuno-combos) will dominate the scene for years to come. Combination of pembrolizumab with IDO inhibitor indiximod, for example, provided durable and ongoing responses in a phase II melanoma trial similar to the combination of ipilimumab and nivolumab, albeit with much lower toxicities (KEYNOTE-006[19]). Combination with agonistic antibodies, e.g., 4–1BB (urelumab), is also under clinical investigation. Breaking tolerance is the primary prerequisite, and PD-1/PD-L1 blockade will be the primary backbone while CTLA-4 may remain key to raise the tail.

Clinical translation, cancer vaccination

Christian Ottensmeier (University of Southampton) opened the first session by revisiting the clinical breakthrough in the treatment of lung cancer by immunotherapy, underlining the success of checkpoint blockade.[20] However, predictive biomarkers are still limited. He highlighted the tumor-infiltrating lymphocyte (TIL) transcriptome as a container of key diagnostic information, since gene expression profiles reveal patients who are likely to respond to checkpoint blockade with late or even no relapse. Ottensmeier and his group set out to break down the whole immune transcriptome information by defining core transcriptional profiles of CD8 TILs in NSCLC, human papillomavirus (HPV)-positive and HPV-negative HNSCC. Core signatures are conserved across these different tumor types, while lymphocyte infiltration determines the expression of immunotherapy response genes. This indicates that different treatments are not restricted to certain types of cancer but need to match the individual patient. Furthermore, Ottensmeier found that CD8 TILs in highly infiltrated NSCLC gain a tissue-resident memory (TRM) signature, characterized by expression of CD103. These TILs are PD-1-positive and capable of proliferation and cytotoxicity, suggesting that they are responsible for a therapeutic response. Consistently, expression of CD103 serves as a better predictor of survival than CD8 expression in lung cancer. Ottensmeier closed his talk by pondering whether phenotype of TILs may be more important than degree of tumor infiltration, and whether TRM may be actively driven by immunotherapy.

Vaccination with autologous DCs can induce strong de novo immune responses with clinical benefit for melanoma patients and has proven to be safe and feasible.[21] According to Carl Figdor (Radboud University), limiting issues such as labor-intensive cell culture and product variations can be overcome by synthetic solutions. Figdor and colleagues develop synthetic DCs (sDCs) that mimic the features of natural DCs. Hence, sDCs need to accommodate modules that enable migration to the lymph nodes, presentation of antigens and provide necessary costimuli. He stated that a large interaction area between

T cells and sDCs as well as molecular movement are essential to form an immunological synapse. Figdor's approach is therefore based on polymers that form flexible, filamentous sDCs, which exhibit remarkable T cell activation capacity after tuning length, stiffness and anti-CD3 antibody density.[22] Loading of anti-CD3 and anti-CD28 antibodies on the same polymer resulted in superior T cell activation relative to the antibodies coupled to different polymers or soluble antibodies.[23] This finding is particularly interesting as it suggests that the T cell receptor (TCR) complex and CD28 need to be in close proximity for optimal T cell priming. A deeper look into formation of the immunological synapse, optimization of coupling methods and orientation of molecules, and addition of advanced T cell modulating moieties warrants further understanding.

The session continued with advancements in the field of cancer vaccination when Ugur Sahin (BioNTech) presented the latest progress in the development of individualized RNA vaccines. Initially, he stressed the value of mutanome targeting to deal with tumor heterogeneity and individual immune profiles. Summarizing preclinical findings, he showed that mutations identified by next-generation sequencing are frequently immunogenic and that a high frequency of epitopes is MHC II-restricted.[24,25] The therapeutic efficacy of MHC II-restricted neoantigens is based on alteration of the immune profile in the tumor microenvironment and on CD40L-mediated CD4 T cell help, which induces CD8 T cell responses against unrelated antigens by antigen spreading.[25] After explaining standardized processes for the preparation of high-quality personalized drug products, Sahin reported on the outcome of the IVAC MUTANOME trial. Thirteen patients with advanced melanoma received personalized RNA vaccination, which elicited robust CD4 and CD8 T-cell responses against neoantigens in all patients. The vaccine showed an excellent safety profile along with a reduced metastatic recurrence rate after treatment. One patient, however, showed progression after temporary disease control. This was associated with deletion of both *B2M* alleles, which resulted in immune escape through loss of MHC I expression, indicative for high selective pressure instigated by the therapy. Sahin announced that the next clinical trial would utilize liposomal RNA vaccines for systemic targeting of DCs, which has shown superior activity over intranodal application of naked RNA.[26] Finally, as a consequence of preclinical and clinical observations, Sahin stated that a combination therapy of RNA vaccination with PD-1/PD-L1 blockade would be developed in a collaborative study with Genentech, with clinical evaluation starting by the end of 2017.

Adoptive T-cell therapy, innate immunity, cancer epigenetics

Johanna Olweus (University of Oslo, Norway) first summarized recent advances in adoptive cell therapy. Tumor infiltrating lymphocyte (TIL) therapy relies on isolation, expansion and reinfusion of autologous TILs, which led to 40 % objective responses in treated (24 % in all enrolled) patients in several clinical trials between 1994 and 2016.[27] Autologous T cells can also be genetically modified, as is the case for chimeric-antigen receptor (CAR) therapy. Especially in acute lymphoblastic leukemia, these cells are highly effective with complete response rates between 70 and 90 %.[28-30] Another modality for engineering T cells is to target the cancer mutanome, the sum of all mutations in a tumor, which could potentially be immunogenic (neoantigens). However, only 1–3 % of neoantigens were so far identified to be recognized by patient TILs.[31-33] To broaden T-cell reactivities against neoantigens independently of patient immunity, Olweus' and Ton Schumacher's groups screened healthy donors for responses against the mutanome of 3 melanoma patients. In this way, several T-cell receptors were found that specifically recognized tumor mutations that were ignored by the respective patient tumor-infiltrating T cells.[34] Further, neo-antigens showed more stable MHC-I binding than non-immunogenic peptides, a fact that may be used to better predict responder peptides for T cell recognition. In another approach to identify novel T cell epitopes, Olweus and colleagues developed a sensitive and cost-effective MAP-array to detect autoantibodies, which might reflect T-cell reactivities, as T and B cells cooperate in immunity. These findings might help improve TCR construct design and specific cancer targeting to finally increase the number of eligible patients for therapy with engineered T cells.

Eric Vivier (Centre d'Immunologie de Marseille-Luminy, France) introduced a class of innate immune cells of which most were only recently discovered and classified as innate lymphoid cells (ILCs). The ILCs can be subdivided into subsets analogously to adaptive T cells: the helper-like ILCs, ILC1, 2 and 3, which express T-bet, GATA-3 and RORγt, respectively[35] as well as the EOMES-positive killer ILCs discovered already in 1975 as Natural Killer (NK) cells.[36,37] Vivier then continued to highlight therapeutic concepts for targeting especially the NK subset. He reported intermediate results of a small phase I clinical trial using autologous NK cell adoptive transfer for the treatment of mostly refractory AML patients (NCT01853358). There was no control arm, but 2-year survival rates were 78 % and adverse graft-versus-host disease was lower than in other donor-lymphocyte infusion studies. Further, an antibody blocking the function of the inhibitory receptor KIR on NK cells was successful in treating mouse model tumors expressing class I, which are otherwise resistant to NK cell attack.[38-40] Lirilumab is currently tested in several clinical studies, with an objective response rate of 24 % in a phase I/II study in combination with nivolumab in patients with SCCHN (NCT01714739), which would mean a doubling of the response rate compared with nivolumab monotherapy (Checkmate 141[41]). Treatments targeting other ILC subsets have not been developed yet, but ILCs express immune checkpoints that might potentially be targeted.[42]

Manel Esteller (University of Barcelona, Spain) highlighted the lacking interaction between the fields of immunotherapy and cancer epigenetics. Epigenetic drugs inhibit DNA methyltransferases and histone-related enzymes such as histone deacetylases and acetylases, sirtuins or histone methylases, and thus alter expression of a variety of genes.[43] However, whether they activate the immune system within tumors is currently unknown. These drugs eventually work, in part, because cancer cells show epigenetic alterations that silence tumor suppressor genes by DNA methylation of so-called CpG islands in regulatory regions.[44] Epigenetic alterations not only occur between cancer and normal cells, but also among patients, tumors are

rather heterogeneous. Around 10 % of some 500,000 analyzed CpG sites were differentially methylated in different parts of colorectal cancer such as the central bulk and the invasive front.[45] Epigenetic profiling can also be used for cancers of unknown primary, cancers of very poor prognosis where metastases can be detected but the original site remains obscure. In a retrospective study, Esteller's team developed algorithms to identify the original tissue of lesions of unknown primary based on DNA methylation profiles.[46] Finally, Esteller closed the circle by introducing a project where epigenetics and tumor immunotherapy converge: a multicentric study that envisions to uncover epigenetic determinants of effective treatment with immune checkpoint inhibitors with the aim to better predict therapeutic response in human tumors.

Antibodies, helper T-cell physiology

Özlem Türeci (Cluster for Individualized ImmunoIntervention, Germany) opened the session by outlining the development of IMAB362, an investigational first-in-class antibody drug specific for the tight junction protein Claudin 18.2 (CLDN18.2). For many years monoclonal antibody (mAb) development in solid cancers focused on blocking growth factor pathways. Immune checkpoint inhibition became a second meanwhile clinically validated and successful concept. With IMAB362, a third paradigm is pursued, namely to select mAb targets based on cancer cell specificity rather than critical biological function and use mAbs for high precision recruitment of the patient`s anti-tumoral immune-effector mechanisms. CLDN18.2 is not expressed in normal cells except for gastric mucosa, where it is compartmentalized within the tight junction architecture and not accessible to IMAB362.[47] However, a variety of cancer indications (e.g., gastric, esophageal, pancreatic, biliary, lung) express CLDN18.2.[48] IMAB362 exerts tumor-cell killing via antibody-dependent cell mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) and by activating these mechanisms modulates the tumor microenvironment. IMAB362 is being clinically developed for 1st line treatment of patients with CLDN18.2-positive advanced gastroesophageal cancer. Data from a recent randomized phase II, open-label study was presented that assessed the safety and antitumor activity of IMAB362 in combination with standard of care chemotherapy, which includes immunogenic cell death inducers.[49-51] Addition of IMAB362 to chemotherapy highly significantly improved both overall and progression-free survival compared with chemotherapy alone and was generally well tolerated with largely manageable adverse events. In the subgroup of highly CLDN18.2-positive patients near-doubling of the median overall survival was observed. Most importantly, IMAB362 not only moved the median but raised the tail of the overall survival curve. Future directions include confirmatory clinical trials and further dissection of immunomodulatory effects of IMAB362 associated with promoting an inflammatory tumor microenvironment.

Vincenzo Cerundolo (MRC Human Immunology Unit, University of Oxford, UK) devoted his talk to amino acid degrading enzymes and their role in tumor immune escape. Already in 2013, Cerundolo's group demonstrated that acute myeloid leukemia (AML) blasts express and release the enzyme arginase 2 (Arg2), leading to significantly increased Arg2 serum levels in patients with AML during disease progression and suppression of T cell proliferation.[52] Furthermore, the study demonstrated that Arg2 expressing AML blasts are capable of polarizing neighboring monocytes toward an M2-like immunosuppressive phenotype and suppress the proliferation and differentiation of human $CD34^+$ progenitors. In the course of his talk, Cerundolo provided insights into his unpublished follow-up studies and elaborated how, in contrast to T cells, AML blasts manage to thrive and survive in an Arg2 nutritionally stressed environment. Based on differential gene expression analysis of THP-1 and T cells upon arginine deprivation, 4 target genes involved in the arginine metabolism have been identified. Subsequent studies provided a mechanistic rationale for the role of the identified genes in arginine deprivation-mediated cancer immune escape and potential pharmacological intervention.

Olivier Lantz (Institute Curie, France) pointed out that main research emphasis in cancer immunology has been put on $CD8^+$ T cells, albeit sufficient evidence for a significant role of $CD4^+$ T cells in antitumor responses in men,[53,54] and mouse.[55,56] Péguillet and colleagues demonstrated that differentiated effector T cells are present in patients with cancer and exhibit cytotoxic features. During neoadjuvant chemotherapy of breast cancer, an increase of $CD25^-CD127^-CD4^+$ T cells correlated with clinical responses.[57] An increased frequency of $CD25^-CD127^-CD4^+$ T cells has been confirmed in metastatic uveal melanoma and chronic infection. Notably, this $CD4^+$ T cell population did not secrete T_H2-related cytokines IL-10 and IL-17 but granzyme B, indicative of their cytotoxic function. Taken together, these data sets strongly support a significant contribution of $CD4^+$ T cells in tumor regression. Given the correlative nature of human studies, animal models are essential for mechanistic studies. The reasons for why antitumor $CD4^+$ T cellresponses have been largely overseen in preclinical studies are multifaceted. However, this may be partially attributable to the lack of suitable tumor models. Obviously, most tumor cells do no express MHC class II molecules and depletion of $CD8^+$ T cells completely abolishes tumor regression in many transplantable tumor models. By generating an MCA101-based tumor cell line with inducible expression of the MHC-II restricted model antigen DBY, Flament and colleagues demonstrated that antigen release from tumor cells results in efficient priming of tumor-specific, polyfunctional $CD4^+$ T cells in the tumor draining lymph node capable of circulating to the tumor and secrete IFN-γ.[58] Notably, this tumor model will be very useful to gain a better understanding of how to efficiently generate antitumor $CD4^+$ T cell responses for therapeutic purposes.

HLA ligandome, clinical immunomonitoring

HLA molecules present small peptide ligands that potentially evoke a T-cell response. These candidate T-cell epitopes can be obtained via affinity chromatography or acidic elution, separated by liquid chromatography and analyzed by mass spectrometry.[59,60] Using HLA ligandomics, Stefan Stevanović (University of Tübingen, Germany) showed that the HLA ligand profiles are very similar among primary tumor and renal

cell cancer (RCC) metastasis.[61] Importantly, HLA class I in RCC is broadly expressed and in many cases even significantly overexpressed compared with normal kidney tissue,[62] a finding that was reproduced for ovarian cancer. Both factors, abundant expression of MHC molecules as well as presentation of antigens in primary tumor and metastasis are crucial factors for successful cancer vaccination. Already in 2002, Stevanović and colleagues presented a concept where HLA ligands derived from genes overexpressed or exclusively expressed in the tumor were probed for the ability to be recognized by T cells.[63] The so-called Xpresident® platform was used to discover multiple shared tumor antigens which gave rise to IMA901, a peptide-based therapeutic vaccine for RCC. Despite a promising phase II trial,[64] a larger phase III trial of IMA901 in addition to the standard first-line therapy with sunitinib did not meet its primary end point of overall survival benefit. A different approach is now being pursued in glioblastoma patients vaccinated against shared as wells as neo-antigens identified by a combination of ligandome analysis with exome and RNA sequencing (GAPVAC, NCT02149225).

The interplay between tumor biology and the anti-tumor immune response was also the topic of Patrick Hwu (MD Anderson Cancer Center, TX, USA) who focuses on modulating signaling pathways for improving sensitivity or overcoming resistance to cancer immunotherapy. One way in which tumors are able to dampen T-cell responses is by hijacking the β-catenin, BRAF/MAPK or PI3K pathways. An active β-catenin pathway was shown to correlate with low infiltration of T cells, explained by reduced expression of $CD103^+$ DC attracting chemokines and a subsequent failure of T-cell priming.[65] A similar phenotype was observed in melanomas harboring the BRAF V600E mutation. Blocking excessive BRAF signaling resulted in reduced VEGF expression, increasing T-cell infiltration.[66,67] As for BRAF mutations, aberrant PI3K/AKT signaling in PTEN-loss tumors (PTEN blocks PI3K signaling) results in increased expression of VEGF and correlates with lower T-cell infiltration and reduced efficacy of adoptive T-cell therapy.[68] Blocking of PI3Kβ in combination with PD-1 resulted in significantly reduced tumor growth in a PTEN loss tumor model. Trying to identify novel markers of resistance to immunotherapies, Hwu and colleagues screened compound, shRNA and ORF libraries for effects on the cytotoxic capacity of autologous tumor-reactive T cells. One compound identified, the HSP90 inhibitor ganetespib, increased T-cell mediated killing via upregulation of interferon signaling and showed synergistic efficacy with an anti-CTLA-4 antibody in mice. ShRNA mediated knock down of glycolysis-related genes increased T-cell killing by reducing lactic acid, the end product of glycolysis. Overexpression of Mex3b in tumor cells reduced HLA-I expression resulting in limited T-cell mediated cytotoxicity. Interestingly, a meta-analysis of melanoma patients treated with an anti-PD-1 antibody revealed higher expression of Mex3b among non-responders.

Especially in vaccination trials, diligent clinical immunomonitoring is key, stated Marij Welters (Leiden University Medical Center, Netherlands), who is specialized in tracking the "wanted" and "unwanted" immune responses in cancer patients. Beneficial responses from $CD4^+$ and $CD8^+$ T cells can be easily identified by IFNγ ELISpot or by flow cytometry-based intracellular cytokine staining. However, the experimental protocol as well as the definition of response criteria vary strongly between investigators.[69-71] Even more difficult is the monitoring of undesirable regulatory T cells (Tregs) or myeloid-derived suppressor cells (MDSC). There are at least 3 different definitions of Tregs[72] and 10 putative MDSC subsets,[73] and different laboratories apply different gating protocols to define these cell types. In pursuit of harmonizing immunomonitoring, the CIMT immunoguiding program (CIP) managed by Welters and 7 other colleagues was initiated. The CIP published several protocols for immunomonitoring showing that protocol harmonization resulted in significantly reduced inter-laboratory variation.[69-73] Applying the harmonized guidelines, Welters et al. were able to scrutinize the anti-tumor mode of action of gemcitabine in ovarian cancer showing a therapy-induced decrease of the Treg to T cell ratio and a reduced subpopulation of MDSCs.[74]

Conclusion

This year`s annual meeting was a tribute to 15 y of success for CIMT as well as cancer immunotherapy, providing an overview on what this type of cancer therapy with great promise can achieve for the successful treatment of cancer. Further preclinical and clinical developments in this field will also be reflected about during the third CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference this coming fall (September 6–9, 2017 in Mainz, Germany).

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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