Preface: More than two decades of modern tumor immunology

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The roots of modern tumor immunology extend back to the pioneering work of William B. Coley, an American surgeon who—at the end of the 19th century—was the first to successfully use a partially inactivated bacterial preparation (the so-called "Coley toxin") for treating soft tissue sarcoma (Coley, 1893), and the revolutionary proposals of Paul Ehlrich, a German-Jewish physician who—at the beginning of the 20th century—introduced for the first time in history the concept of cancer immunosurveillance (Ehrlich, 1909; Rao, Gharib, & Han, 2019). However, with the exception of punctual episodes including the establishment of the Cancer Research Institute of New York (in 1957), whose specific purpose was the development of immunological approaches to treat cancer (Decker et al., 2017), and the publication of the first cancer vaccine study (in 1959) (Graham & Graham, 1959), the field remained virtually unborn until the 1990s. Indeed, the 1990s witnessed not only the discovery that cytotoxic T lymphocyte associated protein 4 (CTLA4) mediates robust immunosuppressive functions, hence constituting a potential target for cancer therapy (Krummel & Allison, 1995; Leach, Krummel, & Allison, 1996), but also the realization that oncogenesis occurs in the context of a bidirectional crosstalk between malignant cells and the immune system of the host (Dighe, Richards, Old, & Schreiber, 1994; Kaplan et al., 1998), laying the foundation for the modern cancer immunosurveillance and immunoediting theories (Dunn, Bruce, Ikeda, Old, & Schreiber, 2002; Dunn, Old, & Schreiber, 2004). In the 2000s, the field gathered additional momentum from preclinical and clinical findings elucidating multiple mechanisms that underlie the ability of the immune system to control developing tumors and the capacity of progressing neoplasms to evade immunosurveillance (Bargou et al., 2008; Dudley et al., 2002; Galon et al., 2006;

Hildner et al., 2008; Jaiswal et al., 2009; Koebel et al., 2007; Majeti et al., 2009; Morgan et al., 2006; Savage et al., 2008; Shankaran et al., 2001), as well as from the discovery that the efficacy of multiple conventional anticancer agents relies (at least in part) on the (re-)activation of tumor-targeting immune responses as a consequence of immunogenic cell death (ICD) induction (Bezu et al., 2018; Casares et al., 2005; Galluzzi, Bravo-San Pedro, Demaria, Formenti, & Kroemer, 2017; Galluzzi, Buque, Kepp, Zitvogel, & Kroemer, 2015, 2017; Galluzzi, Kepp, Chan, & Kroemer, 2017; Galluzzi, Vitale, et al., 2018; Galluzzi, Zitvogel, & Kroemer, 2016; Obeid et al., 2007; Pol et al., 2015). These data paved the way to the cancer immunotherapy revolution of the 2010s (Kelly, 2018).

The 2010s represent indeed the decade in which modern tumor immunology revolutionized the clinical management of multiple tumor types upon the approval of no less than 12 different immunotherapeutic agents for use in cancer patients by the US Food and Drug Administration (FDA) and various equivalent regulatory agencies worldwide (Galluzzi, Chan, Kroemer, Wolchok, & Lopez-Soto, 2018). In January 2019, when this Preface was being redacted, these agents included: (1) sipuleucel T, a myeloid cell-derived product originally approved for the treatment of asymptomatic or minimally symptomatic metastatic castration resistant (hormone refractory) prostate cancer in April 2010 (Hagihara et al., 2019; Kantoff et al., 2010); (2) ipilimumab, a CTLA4-targeting immune checkpoint inhibitor (ICI) (Aranda et al., 2014) initially licensed for use in patients with unresectable or metastatic melanoma who received at least one prior systemic treatment in March 2011 (Hodi et al., 2010; McDermott, Haanen, Chen, Lorigan, & O'Day, 2013; Robert, Schadendorf, Messina, Hodi, & O'Day, 2013), and currently approved for no less than two additional indications (Coens et al., 2017; Eggermont et al., 2015; Eggermont et al., 2016; Geoerger et al., 2017; Merchant et al., 2016); (3) nivolumab, an ICI targeting programmed cell death 1 (PDCD1, best known as PD-1) first licensed for the management of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if $BRAF^{V600}$ mutation positive, a BRAF inhibitor in December 2014 (Weber et al., 2015), and currently available for no less than 10 additional indications (Ansell et al., 2015; Borghaei et al., 2015; Cella et al., 2016; El-Khoueiry et al., 2017; Escudier, Motzer, et al., 2017; Escudier, Sharma, et al., 2017; Ferris et al., 2016; Harrington et al., 2017; Horn et al., 2017; Kazandjian et al., 2016; Kiyota et al., 2017; Motzer et al., 2015; Overman et al., 2017; Sharma et al., 2017; Vokes et al., 2018; Weber et al., 2017; Xu et al., 2017; Younes et al., 2016);

(4) pembrolizumab, a PD-1-targeting ICI originally licensed for the treatment of advanced or unresectable melanoma patients who are no longer responding to ipilimumab and BRAF inhibitors (when indicated) in September 2014 (Hodi et al., 2016; Joseph et al., 2018; Patnaik et al., 2015; Ribas et al., 2016; Robert et al., 2018, 2014), and currently approved for no less than 10 additional indications (Alley et al., 2017; Balar, Castellano, et al., 2017; Brahmer et al., 2017; Brogden et al., 2018; Chatterjee et al., 2016; Chen et al., 2017; Chow et al., 2016; Doi et al., 2018; Frenel et al., 2017; Fuchs et al., 2018; Gandhi et al., 2018; Garon et al., 2015; Hsu et al., 2017; Hui et al., 2017; Le et al., 2017, 2015; Muro et al., 2016; Nanda et al., 2016; O'Neil et al., 2017; Ott, Elez, et al., 2017; Ott, Piha-Paul, et al., 2017; Patnaik et al., 2015; Petrella et al., 2017; Plimack et al., 2017; Reck et al., 2016; Robert et al., 2015; Schachter et al., 2017; Seiwert et al., 2016; Shaverdian et al., 2017; Tahara et al., 2018; Zinzani et al., 2017); (5) cemiplimab, yet another ICI specific for PD-1 originally approved for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma in September 2018 (Migden et al., 2018); (6) durvalumab, an ICI specific for CD274 (best known as PD-L1) originally licensed for the treatment of locally advanced or metastatic urothelial carcinoma progressing during or following platinum-containing chemotherapy in May 2017 (Levy, Massard, Soria, & Deutsch, 2016; Powles et al., 2017), and currently also available for the management of patients with unresectable nonsmall cell lung carcinoma (Antonia et al., 2017); (7) avelumab, a PD-L1-targeting ICI originally approved for the treatment of adult and pediatric patients with metastatic Merkel cell carcinoma in March 2017 (D'Angelo et al., 2018; Kaufman et al., 2016, 2018), and currently licensed also for use in patients with locally advanced or metastatic urothelial carcinoma progressing during or following platinum-containing chemotherapy (Apolo et al., 2017; Heery et al., 2017); (8) atezolizumab, yet another PD-L1 inhibitor originally approved for the treatment of locally advanced or metastatic urothelial carcinoma progressing during or following platinum-containing chemotherapy in May 2016 (Balar, Galsky, et al., 2017; Necchi et al., 2017; Perez-Gracia et al., 2018; Rosenberg et al., 2016), and currently approved for no less than two additional indications (Fehrenbacher et al., 2016; Hida et al., 2018; Rittmeyer et al., 2017); (9) PEGylated interferon alpha 2B, a recombinant cytokine (Garcia-Martinez et al., 2018) originally approved for the treatment of stage III melanoma patients after surgery in March 2011 (Bottomley et al., 2009; Bouwhuis et al., 2010; Di Trolio et al., 2012; Eggermont et al., 2008; Eggermont et al., 2010; Fusi et al., 2009);

(10) talimogene laherparepvec, an oncolytic virus originally approved for the treatment of metastatic, unresectable melanoma patients in October 2015 (Andtbacka et al., 2015; Pol et al., 2018; Pol, Kroemer, & Galluzzi, 2016; Vacchelli et al., 2013), (11) tisagenlecleucel, a preparation of autologous T cells engineered to express a chimeric antigen receptor (CAR) (Borrie & Maleki Vareki, 2018; Raikar et al., 2018) that recognizes CD19, originally approved for the treatment of pediatric and young adults with acute lymphocytic leukemia who relapsed or are refractory to recommended prior therapy in August 2017 (Maude et al., 2018), and now also licensed for the therapy of subjects with various B-cell lymphomas relapsing on or refractory to recommended prior therapy (Schuster et al., 2019); and (12) axicabtagene ciloleucel, another variant of CAR-expressing T cells specific for CD19 (Kellner, Peipp, Gramatzki, Schrappe, & Schewe, 2018), originally approved for the treatment of several variants of refractory or relapsing B-cell lymphoma in October 2017 (Neelapu et al., 2017).

Alongside, considerable translational advances have been made in the 2010s, including (but not limited to): (1) the realization of the major impact of the immunological tumor microenvironment on disease outcome among cancer patients treated with a variety of therapeutic regimens beyond immunotherapy (Atherton et al., 2018; Bantug, Galluzzi, Kroemer, & Hess, 2018; Chevrier et al., 2017; De Henau et al., 2016; Herbst et al., 2014; Humbert & Hugues, 2019; Lavin et al., 2017; Li et al., 2019; Mariathasan et al., 2018; Riaz et al., 2017; Spranger, Bao, & Gajewski, 2015; Straussman et al., 2012; Tauriello et al., 2018; Zheng et al., 2017); (2) the identification of the gut microbiota as a major determinant of the sensitivity of cancer patients to multiple treatments including ICIs (Bhutiani et al., 2018; Gopalakrishnan et al., 2018; Iida et al., 2013; Routy et al., 2018; Vetizou et al., 2015; Viaud et al., 2013); (3) the discovery that novel antigens expressed by cancer cells as a consequence of nonsynonymous mutations play a key role in tumor progression and response to treatment (Gubin et al., 2014; Janikovits et al., 2018; Ozcan, Janikovits, von Knebel Doeberitz, & Kloor, 2018; Rizvi et al., 2015; Schumacher & Schreiber, 2015; Vitale et al., 2019); (4) the elucidation of innate immune mechanisms that provide a major contribution to both natural and therapy-elicited immunosurveillance (Andre et al., 2018; Dou et al., 2017; Ferrari de Andrade et al., 2018; Galluzzi, Vanpouille-Box, Bakhoum, & Demaria, 2018; Harding et al., 2017; Lopez-Soto, Gonzalez, Smyth, & Galluzzi, 2017; Mackenzie et al., 2017; Oyer, Gitto, Altomare, & Copik, 2018; Ruscetti et al., 2018;

van Montfoort et al., 2018; Vanpouille-Box et al., 2017; Vanpouille-Box, Demaria, Formenti, & Galluzzi, 2018); and (5) the identification of exosomes as a prominent vehicle for malignant cells to condition distant anatomical sites and interface with the host immune system (Chen et al., 2018; Diamond et al., 2018; Gabrusiewicz et al., 2018; Hoshino et al., 2015; Mirzaei et al., 2018; Yaddanapudi et al., 2019; Zhang et al., 2015). Finally, major technological advances have been achieved in the 2010s, including (but not limited to): (1) the development of reliable and cost-effective platforms for single cell DNA or RNA sequencing (Alemany, Florescu, Baron, Peterson-Maduro, & van Oudenaarden, 2018; Mulqueen et al., 2018; Zhang et al., 2018); (2) the design of robust algorithms enabling not only the analysis of large single cell omic datasets (Becht et al., 2019; Grobner et al., 2018; Wu et al., 2014), but also various other *in silico* functions that are widely employed in modern tumor immunology, such as neoantigen and TCR motif prediction (Balachandran et al., 2017; Brown & Holt, 2019; Dash et al., 2017; Formenti et al., 2018; Glanville et al., 2017; Hundal et al., 2019; Karasaki et al., 2017); (3) the refinement of the CRISPR/Cas system for gene editing (Halperin et al., 2018; Hille et al., 2018; Kalhor et al., 2018; Nishimasu et al., 2018; Shen et al., 2018; Wang et al., 2018; Yan et al., 2019); and (4) the introduction of mass cytometry (Chevrier et al., 2017; Galluzzi, Yamazaki, & Demaria, 2017; Lavin et al., 2017; Spitzer & Nolan, 2016; Wierz, Janji, Berchem, Moussay, & Paggetti, 2018). Beyond any reasonable doubt, the preclinical, clinical and technological progress we witnessed in the 2010s will pave the way to an exciting decade of achievements in the fields of tumor immunology and immunotherapy as the 2020s are on their way.

In *Tumor Immunology and Immunotherapy* (a group of volumes of the *Methods in Enzymology* series), world leaders in the field gathered to provide the first comprehensive compendium of methods for the study of cancer immunology in both its fundamental and translational components. Each of the chapters of *Tumor Immunology and Immunotherapy* provides a detailed description of one or a few protocols that are suitable for the characterization of (components of) the tumor–host interaction, *in vitro*, *in vivo* or *in silico*. The book consists of five volumes: "Molecular Methods," "Cellular Methods—Part A," "Cellular Methods—Part B," "Integrated Methods—Part A," and "Integrated Methods—Part B," and is equally addressed to expert researchers who may want to extend their technical portfolio, and to beginners in this exciting and rapidly growing field of investigation.