Cancer Immunotherapy Meets Oncology

In Honor of Christoph Huber

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ISBN 978-3-319-05103-1 ISBN 978-3-319-05104-8 (eBook)
DOI 10.1007/978-3-319-05104-8
Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2014938034

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

This book is a tribute to Professor Dr. Christoph Huber and his lifetime achievements. It is also a testimony to the scientific and medical progress in the growing field of immuno-oncology which is about to improve the standard of care for cancer patients.

In 2002, anticipating the possibilities of immunotherapy in the treatment of cancer, Christoph Huber, together with a core group of basic scientists and clinicians founded the Association for Cancer Immunotherapy (CIMT). Since then, CIMT has grown into the largest European platform and expert meeting with sole focus on cancer immunology.

Over the last 12 years, speakers and contributors of the CIMT faculty have taken us on a dynamic journey: The efforts of numerous scientists in the field have revealed novel mechanisms of how the immune system is able to control tumor growth, while at the same time increasing our general knowledge about the interdependencies of the human immune system. We have witnessed the translation of this knowledge into the first-time approval of vaccines and immune-modulatory antibodies and have seen the formation of the first dedicated regulatory frameworks in Europe and the USA that address the peculiar features of cancer immunotherapies. Recently, clinical trials with adoptively transferred *ex vivo* generated or immunoreceptor-engineered lymphocytes have shown unprecedented effects in patients. Novel combinations of immune-modulatory treatments with immunological and non-immunological treatments promise to lead to further breakthroughs in the near future. Increasing financial constraints in global health-care systems mandate the wise use of innovative drugs. This may be achieved by selecting patients who are most likely to respond to the use of novel immunological and molecular biomarkers. The advent of affordable whole genome sequencing has opened the door to a new discipline of immune-genomics that will lead to better diagnostics and personalized therapies.

Under the chairmanship of Christoph Huber, CIMT has developed into a thriving platform for disseminating the latest research findings among specialists working in academia, industry, and regulatory agencies. Throughout the years, CIMT has invited the most relevant experts in the world. In addition, CIMT has supported young scientists by giving them an opportunity to present their recent findings and awarding prizes for the best abstracts and posters. The CIMT working groups have been instrumental in harmonizing cellular immune assays and the generation of a reporting framework for T-cell assays as well as providing input on new regulatory documents and the

generation of a blueprint for personalized mutanome vaccines that was aligned with the European Medicines Agency. All these achievements would have been impossible without people who are willing to share their innovative ideas for the greater good. Christoph Huber is one of these visionaries who is interested not only in science but also in the people he has been working with, he has mentored, or he has treated as a medical doctor.

Therefore, this book is dedicated to Christoph Huber and all scientists and investigators who share his vision of immune-oncology and work passionately to develop better treatments for cancer patients.

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Immunological and Regulatory Framework for Immuno-oncology

From Basic Immunology to New Therapies for Cancer Patients

Hans-Georg Rammensee

Origins

Paul Ehrlich obviously was fascinated by the then newly discovered adaptive immune receptor molecules able to distinguish between different infectious agents and by the plasticity of the immune system to select such receptors and to make many copies on demand. Constructing "ein Gedankengebäude" to explain the observations made by Emil von Behring and Shibasaburo Kitasato (1890), he not only created the term "Antikörper" (antibody) to describe such adaptive receptors but also considered the problems connected to their development within a mouse or human being, that is, the way how self-reactive antibodies are to be avoided. Presumably within this context, he hypothesized that antibodies, respectively, the immune system, should be able to somehow recognize and attack cancer cells, leading to his famous 1909 postulate of cancer immunosurveillance (Ehrlich 1909): We would have a much higher incidence of cancer without an immune system constantly chasing and destroying newly developing cancer cells. "… Würden diese (*die Schutzvorrichtungen des Organismus*) nicht bestehen, so könnte man vermuten, dass das Karzinom in einer geradezu ungeheuerlichen Frequenz auftreten würde." Independently of Paul Ehrlich, and earlier, two surgeons, Wilhelm Busch (1866) in Bonn (Hartmann 2008) and William B. Coley (1893) in New York (Coley 1991), reported a positive correlation between infection and tumor regression, early hints on TLR ligands and cytokines.

In the century thereafter, a tremendous amount of work searching for manifestations of such cancer immunity was performed, mostly leading to nothing or to discoveries seemingly unrelated to cancer. One such prominent case was the discovery of histocompatibility antigens (Klein 1986), following the observation that transplanted mouse tumors are readily rejected by recipient mice, but normal tissue from the other mouse as well, because the mice at that time were not inbred sufficiently (reviewed in (Klein 1986)).

Modern Cancer Immunology

It took almost 50 years until Richmond Prehn and Joan Main were able to show that at least methylcholanthrene-induced tumors could be rejected by an immune reaction in syngeneic mice (Prehn and Main 1957), and shortly thereafter, in 1960, George Klein and colleagues found tumor rejection to be also possible for an autologous tumor (Klein et al. 1960). The decades to follow brought a long row of ups and downs in the perception of the relevance of cancer immunity by the scientific community. A severe blow to the cancer immunosurveillance theory was the thymusless nude mouse, showing no higher incidence of spontaneous cancer than fully

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C.M. Britten et al. (eds.), *Cancer Immunotherapy Meets Oncology*,
DOI 10.1007/978-3-319-05104-8_1,

immunocompetent mice, as reported by Osiasis Stutman in 1974, again with a chemically induced tumor model (Stutman 1974). Another blow to the belief in cancer immunity was Prehn's experiment in 1972, demonstrating that, in opposite to Ehrlich's view, an immune reaction could also enhance rather that inhibit tumor growth (Prehn 1972). This experiment actually picked up an older observation of 1962 from the Old group (Boyse et al. 1962). (This collection of phenomena can now be put into the drawer of "tumor-promoting inflammation" (Hanahan and Weinberg 2011).) During all these years, a rather small number of scientists still were of the opinion that there must be something to it and continued to invest in experiments to discover mechanisms and target structures of cancer immunity, by studying both antibody and T-cell responses. Some of the leading figures were Lloyd Old et al. (2005), Robert North (1982), and Thierry Boon et al. (1988), to name only a few who influenced my own education. It took until the 1980s to molecularly identify in the mouse the first nonviral tumor antigen recognized by T cells, with a contribution from Mainz (Thomas Wölfel) (De Plaen et al. 1988). This actually turned out to be a mutated antigen, and in collaboration with the Boon group, we were able to identify and to quantify the mutated peptide presented on the MHC molecules of the tumor cells (Wallny et al. 1992). The first human T-cell epitope representing a tumor antigen again was reported by the Boon group in 1991 (van der Bruggen et al. 1991) and again with essential contribution from the University of Mainz (Alexander Knuth). Tumor-associated antigens spontaneously recognized by antibodies were analyzed early on by Lloyd Old and Edward Boyse in mice (Old and Boyse 1964), extended by Old's group to patients' sera (Pfreundschuh et al. 1978) and brought to high throughput in the 1990s by the SEREX approach, pioneered by Ugur Sahin, Özlem Türeci, and Michael Pfreundschuh (Sahin et al. 1997; Tureci et al. 1997).

Since the days of Paul Ehrlich, a full century was required to understand the basic molecules and mechanisms our immune system uses for its daily tasks in fighting infections. We still are far away from having gained complete knowledge but what we know to date is just sufficient to manipulate the immune system such that it can attack and destroy cancer cells. Currently, several of such attempts are proving to be successful. After getting to know the structures and functions of antibodies, T-cell receptors, MHC molecules and their ligands, cytokines and their receptors, cells of the innate immune system including their receptors and ligands, T-cell populations (chapter by T. Bopp et al.), and their co-receptors and inhibitory receptors, we now start to get insight into the complex interactions between immune mechanisms attacking tumors and the counteracting measures of tumors to defend themselves against this attack, formulated by Bob Schreiber into the "immunoediting" concept (Schreiber et al. 2011).

Modern Cancer Immunotherapy

The first hopes into cancer immunotherapy were raised by the discovery of the first cytokines, the interferons, in the 1950s by Alick Isaacs and Jean Lindenmann (1957) and later in the mid-1970s by the invention of making monoclonal antibodies on demand by Georges Köhler and Cesar Milstein (1975).

The first successful cancer immunotherapy, however, was a special kind of adoptive T-cell transfer, the donor lymphocyte infusion in the setting of bone marrow transplantation. This was a result from the development of bone marrow transplantation into irradiated recipients as a treatment of leukemias performed by the Edward Donnall Thomas lab with Rainer Storb in Seattle, who observed that the detrimental graft-versus-host reaction regularly occurring in human patients or outbred dogs, but not within inbred mice, was beneficial since it seemed to have an effect against leukemia (Weiden et al. 1979). This observation could be attributed to donor leukocytes in the late 1980s by Hans-Jochem Kolb (1990), who then systematically developed the use of DLI (donor leukocyte infusion) for the treatment of leukemia relapses after the original

bone marrow transplantation (Weiden et al. 1979). Such donor-derived T cells, including those already present in the bone marrow graft, induced not only graft-versus-host disease but also a graft-versus-leukemia effect. The recurrence of leukemia after transplantation could be successfully treated by additional transfer of a small number of leukocytes from the original donor, which in many cases led not only to an aggravation of GvHD but also to complete cure. Other early successes in antigen nonspecific cancer immunotherapy were the development of cytokines, in particular interferon alpha in hairy cell leukemia, where Christoph Huber was a pioneer (Gastl et al. 1985a, b; Huber et al. 1985; Aulitzky et al. 1985), and the use of a TLR ligand, BCG, for the treatment of bladder carcinoma (De Jager et al. 1991).

The first attempts of using monoclonal antibodies for passive immunotherapy of cancer were by the groups of Stuart Schlossman et al. (1980) and Ronald Levy and Miller (1981). It took, however, until the late 1990s to use monoclonal antibodies for passive immunotherapy of cancer on a routine basis, pioneered by Ralph Reisfeld et al. (1992), Gert Riethmüller et al. (1998), and others. In 1997, the first antibody was approved by the FDA for the treatment of cancer – rituximab (Grillo-Lopez et al. 2000) – directed not against a cancer antigen but rather against a cell type-specific antigen, CD20, expressed on normal cells dispensable for survival, the B cells.

Three principal problems in these developments were (1) the task to produce humanized antibodies in suitable formats to achieve sufficient production rates in cell cultures as well as to avoid anti-antibody reactions in the recipient, (2) achieving efficient effector function in the patient, and (3) finding the right antigen. The first problem has been largely solved by now, and the second is being solved at present by enhancing Fc-receptor interaction or by using bispecific antibodies capable of recruiting T cells with their superior proliferative potential, as pioneered by Uwe Staerz et al. (1985), Gundram Jung et al. (1986, 2001), and Gert Riethmüller (Topp et al. 2011). The third problem, finding suitable target structures on the surface of cancer cells that are not, or at least not much, expressed on normal cells, is still unsolved. Finding cancer cell surface antigens as target structures for therapeutic antibodies essentially follows three strategies:

1. Using information derived from cancer biology; epithelial carcinomas, for example, express epithelial markers, such as Epcam (Riethmuller et al. 1998). In growth factor receptor-driven cancers, in particular, this receptor or others of the EGFR family can be used as target, as pioneered by Axel Ullrich for HER2/neu in breast cancer (Hudziak et al. 1987; Fischer et al. 2003).
2. Looking at the antibody response produced spontaneously by cancer patients, as followed by the SEREX technology.
3. By systematically comparing cell surface antigens of tumor cells with that of normal cells, an approach that has been attempted surprisingly late in a systematic way, but then very successfully as shown by the work of Özlem Türeci and colleagues (Sahin et al. 2008).

The design of present and future cancer immunotherapies is drawing essential benefit from the revelations of cancer biology in the last 30 years. The insight that not only viral but also cellular oncogenes (Doolittle et al. 1983; Waterfield et al. 1983; Downward et al. 1984) are causative for cancer development, and the first indications that mutations in genes regulating cellular signaling or DNA repair such as K-Ras or p53 (Vogelstein et al. 1988; Hollstein et al. 1991) already hinted toward interesting targets for cancer immunotherapy. This is true in particular for T cells, since we know that HLA molecules present peptides from all cellular compartments, including nuclear proteins. Indeed, Thomas Wölfel showed that T cells specific for peptides representing mutated gene products can spontaneously develop in melanoma patients (Wolfel et al. 1995), and Gustav Gaudernack introduced peptide vaccination against K-ras mutations in a clinical trial followed over many years, with encouraging clinical results (Weden et al. 2011). The recent methodological improvements in genome sequencing have been used to systematically analyze the spectrum of mutations in many individual cancers, the result being an amazing heterogeneity of number and sites