Preface: New Immunological Approaches to Cancer Therapy Dedicated to Dr. Michio Nishida

In 1909, Paul Ehrlich proposed that the incidence of cancer would be much greater were it not for the vigilance of our immune systems to seek out and destroy newly formed tumor cells, thus giving rise to the initial concept of immune surveillance. This hypothesis remained controversial until later in the 20th century when the tools and knowledge to examine this concept started to become available and the idea could be tested. In early murine tumor experiments, the notion of tumor-specific antigens became entangled with data from allograft rejection experiments and whether or not they were one and the same. However, after the development of syngeneic strains of mice, which could be immunized against implanted syngeneic tumors, the concept of tumor-specific antigens was resurrected. As a consequence, it was surmised that if there was an immune reaction against tumors, there must be distinctive structures on tumor cells that could be recognized and distinguished from normal structures by the immune system.

In 1957, Sir Macfarlane Burnet and Lewis Thomas both speculated that if tumor cells possessed new antigenic potential, lymphocytes could act as sentinels in recognizing and eliminating continuously arising, nascently transformed cells. Thus, the idea of using endogenous or exogenous immunological means to control tumor growth began to seriously take root. Although its history had its ups and downs, with the availability of new tools, animal models, and fresh knowledge, it seemed that these ideas might finally be realized.

Antibody effector functions were initially underappreciated and many early attempts to use mouse monoclonal antibodies were unsuccessful. The development of chimeric and eventually humanized and fully human antibodies with customized effector functions was able to address some of these issues. Jumping ahead to today, the concept of using monoclonal antibodies to attack tumor cells is now well established.

The first article in this issue briefly describes the development of the first monoclonal antibody developed and approved for the treatment of cancer: the anti-CD20 chimeric antibody rituximab. The development of this antibody encountered much resistance due to the prevailing wisdom at the time that monoclonal antibodies did not work as therapeutic treatment for human tumors. It took the perseverance of the team at IDEC (idiotype technology) Pharmaceuticals, Inc. to develop this antibody and the confidence of Genentech to take a chance on its codevelopment with IDEC for the treatment of non-Hodgkin’s lymphoma. This collaboration resulted in one of the most successful monoclonal antibodies developed to date. In the following 20 years, many new features had been discovered about the CD20 molecule and several “improved” antibodies have been advanced. In Oldham, Cleary, and Cragg (page 7) describe the current understanding of the CD20 molecule, newer anti-CD20 antibodies that have been developed, and the likely future for targeting this somewhat mysterious molecule.

Although rituxan was a clinical and commercial success, the future for single antibody molecules that rely on their endogenous effector functions to generate robust antitumor effects may be limited. Monoclonal antibodies have been used, among other functions, to deliver toxic payloads to tumors. Blot, Richardson, and Coronella describe recent advances in antibody drug conjugates (ADCs) on page 25. Again, although not a new concept, the right tools to exploit this approach fully were not available until recently.

Similarly, the discovery of the function of so-called checkpoint inhibitor molecules has only recently been appreciated, although many of these molecules have been in the literature for two decades or more. Sathish (page 69) describes the recent advances in this field, which has become one of today’s hottest areas in cancer research. Also reviewed is the role of these molecules in suppressing T-cell responses and enhancing tumor destruction by blocking their inhibitory function.

Another way of manipulating T-cell responses to attack tumors is by the insertion of chimeric antigen
receptors (CARs), which recognize tumor cells, into T cells so that they can provide the necessary activation signals to generate cytotoxic T cells. The CAR–T-cell approach is described by Achkova and Maher (page 47). Although very encouraging data emerged from treatment of hematological cancers and melanoma, the question for the future is whether they can be equally successful when applied against other solid tumors.

Cytokines can efficiently activate T cells in vitro but when used in vivo they have not been quite as successful, primarily because of the lack of specific delivery. Probst and Neri (page 83) have extensively explored the use of cytokines that activate immune cells at the site of the tumor by using antibodies to deliver the payload. Again, unleashing the power of activated T cells at the site of the tumor, and in combination with other checkpoint inhibitors, described in this volume by Sathish (page 69), could prove to be a powerful combination.

Finally, Wuellner and Grabulovski (page 101) describe framework structures that can be used as cancer therapeutics, as alternatives to antibodies. Although there have been many proposed alternative antibody structures, only a small number have survived rigorous examination and have been shown to have practical benefit. They can be generated in vitro and selected to bind almost any target, and their versatility and modularity make them ideal as new alternatives as targeting agents.

This volume is dedicated to the memory of Michio Nishida who had a lifelong interest in immunological approaches to cancer and played a pivotal role in helping to develop rituximab. The field is moving rapidly, and this volume is an attempt to bring together many of the key players in today’s current field of tumor immunology and review some of the active areas of cancer research. Today is a very exciting time in cancer biology and now that many of the tools and databases needed are available, we all expect to see new and exciting clinical data to emerge in the next few years.

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