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## Preface

Cancer immunotherapies, which include cancer vaccines, are novel therapeutic modalities being added to the armamentarium for cancer management/treatments that are finally becoming available to cancer patients around the world. In contrast to chemo- and radio-therapies, cancer vaccines are not normally associated with severe side effects, and unlike these therapies which directly kill the tumor cells and normal rapidly dividing cells in the body, cancer vaccines and other immunotherapies exert their effect by stimulating the body's immune system to focus on the cancer cells alone, remove them, and consequently reduce the severity of the disease, generally without toxicity. Given these characteristics, cancer vaccines offer cancer patients a more focused and gentler means of cancer treatment that is far less detrimental to their bodies and is cognizant of the patient's wish for a better quality of life.

The status of the patient's immune system is the vital biological element affecting the outcome of cancer immunotherapy. However, each individual's immune status is in turn affected by factors including age of the person, stage of the disease, prior treatment (chemotherapy or radiation therapy), tumor-induced immunosuppression, and the overall well-being of that person. As the term "immunotherapy" implies, the cells of the immune system perform the primary role in mediating the outcome of an immunotherapeutic regimen.

Most cancer vaccines to date have been designed to treat cancers that have already developed and therefore are termed "therapeutic." The purpose of these cancer vaccines is to stop cancer cell growth and eventually reduce the tumor burden. Some experts in the field believe that cancer vaccines may be best suited to prevent cancer from returning or to eliminate cancer cells that were not killed by other, more conventional treatments.

Whether used as adjunctive or stand-alone therapies, the development of effective cancer vaccines requires a thorough understanding of the innate and adaptive immune system, immune effector cells, and cancer cells. However, despite the plethora of clinical and basic knowledge of cancer and the immune system, the issue boils down to the simple fact that the immune system, in most cases, does not see cancer cells as being "nonself" and thus dangerous. Even when the immune system does recognize some element of danger, it does not usually mount a clinically significant response against well-established tumors. This is mainly due to the fact that cancer cells have developed mechanisms that make it challenging for the immune system to target them for removal. The most significant issue is that cancer cells express normal "self"-antigens on the cell surface in addition to specific cancer-associated antigens, giving the abnormal cells an advantage against immune surveillance. Furthermore, during their rapid proliferation, these cancer cells frequently undergo further genetic mutations that may consequently lead to the loss or down-regulation of the cancer-associated antigens. Finally, cancer cells generate soluble factors that function to suppress an anticancer immune response.

Producing an effective therapeutic cancer vaccine has proven to be challenging. To be effective, cancer vaccines must achieve two objectives. First, cancer vaccines must stimulate

a robust tumor-specific immune responses against the correct target. Second, the immune responses must be potent enough to overcome the means by which cancer cells evade the adaptive immune response.

Therapeutic cancer vaccines can be divided into two broad categories, namely, (1) whole-cell vaccines, which encompass autologous, allogeneic, and dendritic cell vaccines, and (2) peptide or protein antigen vaccines. Dendritic cell vaccines fall into both “camps,” since this category can include the use of peptide and/or protein antigens as well as whole-cell lysates in the production of these vaccines.

The whole-cell vaccine approach encompasses the use of inactivated whole-tumor cells and/or whole-cell lysate as the vaccine. As such, these whole-cell vaccines present an array of tumor cell-associated antigens to the patient’s immune system. The approach of using whole-tumor cell as a vaccine eliminates the significant problem of having to identify the crucial antigen(s) for that cancer, most of which remain unknown, but almost always requires some type of immune adjuvant.

Peptide or protein antigen vaccines can be comprised of synthetic or purified native moieties that are representative of the tumor cell antigens displayed by the target tumors. These antigens can be used to immunize patients and have been shown to generate an immune response capable of destroying cells in the body that display these antigens. These types of cancer vaccines are dependent upon knowing the major tumor cell markers/antigens, their structure, and, if peptides are generated, the important epitope(s) required to generate a tumor-specific immune response. Dendritic cells, which orchestrate the function of immune cells, are often used as the “delivery vehicles” for these synthetic peptides and proteins to the immune system.

Researchers continue to acquire the elements and knowledge required in order to design cancer vaccines that can potentially accomplish both goals, i.e., to evoke a tumor-specific response and overcome the immuno-evasive mechanisms employed by the tumor cells. The purpose of this current volume is to gather many of the methods that have been developed to manufacture these cancer vaccines under one cover. The chapters are grouped according to the purpose or the aim of the cancer vaccine, namely, the manipulation and modification of immune cells; the manipulation and modification of tumor cells; and the manipulation of immune/tumor interactions and various delivery mechanisms. The volume also covers the subject of cancer vaccines in a more global sense with its section on the advances, challenges, and future of cancer vaccines.

In bringing this volume together, we have attempted to gather experts in the various subspecialty fields of cancer vaccines to share their expertise with current and future cancer vaccinologists, researchers, and clinicians. To this end, the authors have shared their experiences and given helpful “tips” through the Notes section in each chapter to aid in the development of future cancer vaccine design. It is hoped that the methods and protocols that have already been developed will lead to the further generation of cancer vaccines that are both safe and efficacious and that cancer vaccines will be the standard of care in the very near future.

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