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Kevin R. Loughlin

In recent years, immunotherapy has been the focus of great interest to researchers, clinicians, and the general public. Traditionally cancer therapy has been thought to be limited to surgery, radiation therapy, or chemotherapy. Some clinicians have considered it the so-called fifth pillar of cancer therapy, following surgery, cytotoxic chemotherapy, radiation, and targeted therapy. However, the origins of immunotherapy in cancer treatment reach back at least into the nineteenth century. This article reviews the origins, development, and future of immunotherapy.

## **Kidney Cancer: An Overview of Current Therapeutic Approaches** 419

Nivedita Chowdhury and Charles G. Drake

The management of metastatic renal cell carcinoma (RCC) has evolved rapidly in recent years with several immunotherapy-based combinations of strategies approved as first-line therapies. Targeted strategies, including systemic antiangiogenesis agents and immune checkpoint blockade, form the basis of a therapeutic approach. With rising rates of recurrence after first-line treatment, it is increasingly important to not only adopt a personalized treatment plan with minimal adverse events but also develop predictive biomarkers for response. This review discusses currently available first-line and second-line therapies in RCC and their pivotal data, with specific focus on ongoing clinical trials in the adjuvant setting, including those involving novel agents.

## **Harnessing Natural Killer Cell Function for Genitourinary Cancers** 433

Nina Bhardwaj, Adam M. Farkas, Zeynep Gul, and John P. Sfakianos

Natural killer (NK) cells are potently cytolytic innate lymphocytes involved in the immune surveillance of tumors and virally infected cells. Although much progress has been made in manipulating the ability of T cells to recognize and eliminate tumors, a comprehensive understanding of NK-cell infiltration into solid tumors, and their amenability to immunomodulation, remains incomplete. This article discusses recent studies showing that urologic tumors are infiltrated by NK cells and that these NK cells are often dysfunctional, but that strategies interfering with inhibitory axes have significant potential to alleviate this dysfunction.

## **Immunotherapy for Localized Prostate Cancer: The Next Frontier?** 443

Devin Patel, Rana McKay, and J. Kellogg Parsons

Cancer vaccines, cytokines, and checkpoint inhibitors are immunotherapeutic agents that act within the cancer immunity cycle. Prostate cancer has provided unique opportunities for, and challenges to, immunotherapy drug development, including low tumor mutational burdens, limited expression of PD-L1, and minimal

T-cell intratumoral infiltrates. Nevertheless, efforts are ongoing to help prime prostate tumors by turning a “cold” prostate cancer “hot” and thus rendering them more susceptible to immunotherapy. Combination treatments, use of molecular biomarkers, and use of new immunotherapeutic agents provide opportunities to enhance the immune response to prostate tumors.

**The Potential Role for Immunotherapy in Biochemically Recurrent Prostate Cancer** **457**

Marijo Bilusic, David J. Einstein, Fatima H. Karzai, William L. Dahut, James L. Gulley, Jeanny B. Aragon-Ching, and Ravi A. Madan

Biochemically recurrent prostate cancer represents a stage of prostate cancer where conventional (continued on next page) computed tomography and technetium Tc 99m bone scan imaging are unable to detect disease after curative intervention despite rising prostate-specific antigen. There is no clear standard of care and no systemic therapy has been shown to improve survival. Immunotherapy-based treatments potentially are attractive options relative to androgen deprivation therapy due to the generally more favorable side-effect profile. Biochemically recurrent prostate cancer patients have a low tumor burden and likely lymph node-based disease, which may make them more likely to respond to immunotherapy.

**Immunotherapy for Prostate Cancer: Treatments for the “Lethal” Phenotype** **469**

Susan F. Slovin

Multiple immunologic platforms have provided minimal impact in patients with metastatic castration-resistant prostate cancer, necessitating that novel approaches continue to be developed. Although checkpoint inhibitors have been largely ineffective, there remain small cohorts of patients who have durable responses but lack the conventional indicators for response to this class of drugs, that is, high mutational burden or significant genomic alterations, as seen in other solid tumors. This article presents an update on the evolution of immunotherapeutics that target a more lethal form of prostate cancer and provides the groundwork for future considerations as to how this field should proceed.

**Application of Single-Cell Sequencing to Immunotherapy** **475**

Kristin G. Beaumont, Michael A. Beaumont, and Robert Sebra

Cancer is a highly complex and heterogeneous disease and immunotherapy has shown promise as a therapeutic approach. The increased resolution afforded by single-cell analysis offers the hope of finding and characterizing previously underappreciated populations of cells that could prove useful in understanding cancer progression and treatment. Urologic and prostate cancers are inherently heterogeneous diseases, and the potential for single-cell analysis to help understand and develop immunotherapeutic approaches to treat these diseases is very exciting. In this review, we view cancer immunotherapy through a single-cell lens and discuss the state-of-the-art technologies that enable advances in this field.

**Immunotherapy for Metastatic Prostate Cancer: Current and Emerging Treatment Options** **487**

Dimple Chakravarty, Li Huang, Matthew Kahn, and Ashutosh K. Tewari

The advent of immunotherapy has revolutionized cancer treatment. Prostate cancer has an immunosuppressive microenvironment and a low tumor mutation burden,

resulting in low neoantigen expression. The consensus was that immunotherapy would be less effective in prostate cancer. However, recent studies have reported that prostate cancer does have a high number of DNA damage and repair gene defects. Immunotherapies that have been tested in prostate cancer so far have been mainly vaccines and checkpoint inhibitors. A combination of genomically targeted therapies, with approaches to alleviate immune response and thereby make the tumor microenvironment immunologically hot, is promising.

## **Biotech and Breakthroughs in Immuno-Oncology**

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Jeffrey M. Bockman

The age of immuno-oncology has ushered in a rush within the biopharmaceutical industry. This intense focus has been characterized as a frenzy or overhyped, but represents a substantial investment in new products that hope to harness the immune system against cancer. Such agents include next-generation checkpoint antagonists, immune costimulatory agonists, and a diverse array of novel mechanisms of action and therapeutic modalities targeting immune cell types and the interplay of the host and tumor at the immune synapse. This article surveys the clinical development and investment activity with Immuno-Oncology, specifically prostate, kidney, and bladder cancers.

## **Special Article**

### **Personalized Medicine for the Infertile Male**

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Danielle Velez and Kathleen Hwang

Personalized medicine uses a patient's genotype, environment, and lifestyle choices to create a tailored diagnosis and therapy plan, with the goal of minimizing side effects, avoiding lost time with ineffective treatments, and guiding preventative strategies. Although most precision medicine strategies are still within the laboratory phase of development, this article reviews the promising technologies with the greatest potential to improve the diagnosis and treatment options for male infertility, including sperm cell transplantation, genomic editing, and new biomarker assays, based on the latest proteomic and epigenomic studies.