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Chapter 1 : British Society for Immunology |

This research primer is designed to provide a basic overview of immunology for those interested in combining immunotherapy and radiation therapy, and will provide background information for those attending the ASTRO Science Workshop in June of

Elsevier Health Sciences Format Available: The second edition of A Primer of Clinical Psychiatry provides a broad overview of the major topics in psychiatry and provides the clinical skills necessary for competent clinical practice. It also includes an up-to-date overview of the scientific literature behind this fascinating and challenging medical discipline. This book covers in detail the psychiatric interview, the mental state examination, and clinical investigations relevant to psychiatry. All of the major syndromes of psychiatry are addressed including schizophrenia, depressive disorders, bipolar disorder, anxiety, post-traumatic disorders, obsessive-compulsive disorders, eating disorders, somatoform disorders and personality disorders and cover epidemiology, aetiology and clinical aspects, and discussion of specific treatment approaches. A separate section reviews biological and psychosocial aspects of treatment in psychiatry, with worked case examples. A chapter on psychiatric emergencies is included in this section. Discrete chapters cover specialist areas such as child and adolescent psychiatry, old age psychiatry, forensic psychiatry, dual disability and substance use disorders. Enhancing each chapter is a case-based role-play scenario, complete with model answers. Each scenario is set out to model modern pedagogical theory, with roles, setting, tasks, and model answers all articulated and cross-referenced to the core text. Readers can adopt various roles within the scenarios, including that of the doctor general practice registrars, interns, and residents , allied health staff, or patients themselves and their relatives. The scenarios cover everything from basic skills such as taking a history or describing a disorder, to more advanced problems, such as working with the hostile family and assessing risk in the emergency setting. A Primer of Clinical Psychiatry 2nd edition aims to introduce the pertinent facts of clinical psychiatry to medical students and students of mental health disciplines. It will also be a useful resource for established clinicians, including GPs and the more advanced psychiatric trainee or mental health professional. Mary Louise Turgeon Language: The 5th edition of this classic text sets the standard for comprehensive coverage of immunology. Learning objectives at the beginning of each chapter offer a measurable outcome you can achieve by completing the material. Chapter highlights at the end of each chapter provide a summary of the most important information covered in each chapter. Review questions at the end of each chapter are tied to learning objectives further enhance your understanding. Case studies challenge you to apply your knowledge and help strengthen your critical thinking skills. Glossary at the end of the book provides quick access to key terms and definitions. Expanded chapter on Vaccines as the importance of vaccines continues to become more evident. Updated chapter on Molecular Techniques incorporates the newest technology specific to immunology. Key terms at the beginning of each chapter help you learn the important vocabulary in immunology. Case studies with added multiple-choice questions in addition to critical thinking questions will help you apply your knowledge and develop critical-thinking skills. Cellular and Molecular Immunology takes a comprehensive yet straightforward approach to the latest developments in this active and fast-changing field. Lichtman, and Shiv Pillai present sweeping updates in this new edition to cover antigen receptors and signal transduction in immune cells, mucosal and skin immunity, cytokines, leukocyte-endothelial interaction, and more. This reference is the up-to-date and readable textbook you need to master the complex subject of immunology. Recognize the clinical relevance of the immunology through discussions of the implications of immunologic science for the management of human disease. Grasp the details of experimental observations that form the basis for the science of immunology at the molecular, cellular, and whole-organism levels and draw the appropriate conclusions. Stay abreast of the latest advances in immunology and molecular biology through extensive updates that cover cytokines, innate immunity, leukocyte-endothelial interactions, signaling, costimulation, and more. Visualize immunologic processes more effectively through a completely revised art program with redrawn figures, a brighter color palette, and more 3-dimensional art. Find information more quickly and easily through a reorganized chapter structure and a

more logical flow of material. The Immune Response is a unique reference work covering the basic and clinical principles of immunology in a modern and comprehensive fashion. Written in an engaging conversational style, the book conveys the broad scope and fascinating appeal of immunology. The book is beautifully illustrated with superb figures as well as many full color plates. This extraordinary work will be an invaluable resource for lecturers and graduate students in immunology, as well as a vital reference for research scientists and clinicians studying related areas in the life and medical sciences.

Chapter 2 : A primer on tumour immunology and prostate cancer immunotherapy

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Nayak Find articles by Jasmir G. Drachenberg Find articles by Darrel E. Introduction Prostate cancer is the most commonly diagnosed non-cutaneous malignancy and the third leading cause of cancer death in Canadian men. Recent recommendations questioning the benefit of prostate-specific antigen PSA screening 2 have highlighted the requirement to uncouple the diagnosis from treatment for localized disease in order to reduce over-treatment of biologically indolent disease. Despite recent interest in the earlier delivery of cytotoxic chemotherapeutics for men with advanced disease, prostate cancer remains, for the most part, androgen-dependent. In a non-curative setting, ADT remains a mainstay of treatment. Although most patients are initially responsive, progression to castration-resistant prostate cancer CRPC eventually occurs and is associated with a median time until death of less than three years. An increasing understanding of the mechanisms of survival in prostate cancer cells with castrate levels of serum testosterone has led to multiple new therapies, including bone-targeted agents and next-generation androgen receptor inhibitors. Unfortunately, progression to a chemo-resistant, androgen-independent state is the norm. Exploring other therapeutics, including those processes and pathways involved in resistance to standard therapies, is key to further improving the quality and quantity of life of these patients. Immunotherapy represents one potentially innovative and complementary management strategy for those with advanced prostate cancers. For urologists, medical oncologists, and other clinicians that regularly care for men with prostate cancer, remaining up-to-date with these new therapies and their underlying immunological concepts will allow them to offer, and better explain, the most appropriate therapies for their patients. Here we review the basic concepts in tumour immunology that underlie cancer immunotherapy with a primary focus on prostate cancer immunotherapies. Hallmarks of anti-tumour immune responses A few key concepts are worth reviewing with respect to what is known about immune detection and elimination of tumour cells. The notion that the immune system acts as an extrinsic tumour suppressor by preventing the proliferation of neoplastic cells was first proposed by Ehrlich in the early 20th century. Both divisions of the immune system, the innate 11 and adaptive, 12 have been shown to be involved in tumour immune surveillance and thus have been targets across immunotherapies. Anti-tumour innate immune responses Innate immune cells are responsible for the initial immediate response to tissue damage and play a role in preventing and facilitating tumour progression. Macrophages are initially recruited and can be classified as pro-inflammatory M1 cells and anti-inflammatory M2 cells, with a functional spectrum existing between the two ends. One potential therapeutic target for tumour-associated macrophages is the receptor for colony-stimulating factor 1, a vital growth factor for macrophages and their differentiation, migration, and survival. They recognize foreign and altered cells by two mechanisms: In contrast, the altered-self mechanism refers to the process by which damaged cells express specific ligands â€" TAAsâ€" that trigger natural killer cell activity. DCs have many receptors that recognize specific pathogen-associated molecular patterns and environmental signals. Anti-tumour adaptive immune responses The adaptive immune system is constituted by T and B lymphocytes that mediate specific functions via cell surface or secreted effector molecules. Adaptive immunity has long been recognized in the eradication of tumour cells. The antigens that trigger these responses are often peptide fragments of TAAs from the initial tumour cell destruction by innate effectors, such as natural killer cells, cytotoxic chemotherapy or radiation therapy, or tumour cell lysis by oncolytic viruses. Once activated, CTLs undergo clonal expansion, resulting in a population of cytotoxic cells specific to that tumour antigen. Th1, Th2, Th17, and regulatory T cells Tregs based upon their function and the cytokines they secrete. In general, Th1 cells are involved in intracellular immunity and Th2 in extracellular humoral immunity. Th17 cells are unique in their expression of IL Tregs are an important subset of CD4 T cells that are able to suppress effector T cells and also maintain immune tolerance. Tregs constitutively express CTLA-4 and targeting this important regulator to decrease Tregs in tumours has resulted in significant clinical benefit. Humoral immunity The humoral arm, mediating its

functions primarily by secreting antibodies and cytokines, is now gaining attention in the field of tumour immunology, with its anti- and pro-tumourigenic roles across cancers. However, as part of tumour immuno-editing, tumour cells often gain properties to escape detection and establish themselves and present as disease. Elimination of tumour cells occurs by innate and adaptive immune mechanisms. Pro-inflammatory cytokines, released by the growing tumour, macrophages, and surrounding stromal cells, activate and recruit several immune effectors. NK-mediated tumour destruction releases tumour associated antigens, which induce adaptive immune responses. Elimination via CTL activation can result in the selection of tumour cells with reduced immunogenicity and thus become resistant to immune effectors. This results in tumour growth favouring non-immunogenic phenotypes. Some of these factors can lead to increased extra-cellular matrix that binds tumour antigens; fibroblasts and endothelial cells compete with DCs for antigens, effectively reducing the amount of TAAs and contributing to tumour progression. The promise of immunotherapies in prostate cancer Consequent to the tumour immunosurveillance theory, the past decade has witnessed significant successes in cancer immunotherapies that rely on enhancing the effectiveness of host anti-tumour immune responses in multiple ways. Prostate cancer is often a slow proliferative disease, causing many cytotoxic agents to be ineffective. However, it provides the time needed to mount an immune response, even in patients with advanced or metastatic disease. Passive immunotherapy uses anti-tumour agents generated in vitro. Monoclonal antibodies can be generated against specific tumour surface markers. For prostate cancer, these agents are still early in development and have mainly focussed on PSMA. The T cells are engineered with surface receptors that recognize specific TAAs, termed chimeric antigen receptors. This essentially bypasses the steps of tumour recognition, T cell activation, and amplification required in the body. Several clinical trials are testing transfer of tumour-infiltrating lymphocytes, CTLs, Th cells, and Tregs. Immunotherapeutic vaccines can be separated into four classes: The cells are then activated with a recombinant fusion protein consisting of PAP linked to granulocyte-macrophage colony stimulating factor GM-CSF , an immune cell activator. However, there remain several unanswered questions that have limited its uptake in North America. The whole tumour cell is used as the antigen, rather than just the PAP, as in sipuleucel-T, facilitating both humoural and cellular immune responses. DNA-based vaccines DNA-based vaccines consist of bacterial plasmids constructed to contain the coding sequence of a targeted antigen, which can be taken up by cells. These transformed cells express genes that can induce an immune response. Bacterial plasmids are attractive in their simplicity, stability, and cost-effectiveness, which can be encoded with adjuvants and cytokines to increase their immune response. Viral-based vaccines Prostvac-VF is a vaccine comprised of two recombinant viral vectors that each encode for PSA and three immune costimulatory molecules including: This helps to overcome the host anti-vector antibody responses to the original vector. GM-CSF is co-administered to further boost immune response. The virus infects APCs, promoting cell surface protein expression and interaction with T-cells that facilitate a targeted immune response and cell-mediated tumour cell destruction. Under normal conditions, these mechanisms help maintain self-tolerance, duration, and strength of immune responses, and aim to minimize damage to surrounding self-tissues. Recent successful immunotherapies have extensively exploited these mechanisms to enhance immune-mediated tumour cell destruction. CTLA-4 based immunotherapy T cell activation initiates several downstream functions, such as cytokine production, cell cycle progression, and effector differentiation. T cell activation induces expression of inhibitory signals, which limit and control the immune response. CTLA-4 is a co-inhibitory signal that binds B7 with greater affinity. CTLA-4 blockade removes the inhibition and results in T cell activation against tumour cells. Several current trials are testing ipilimumab in patients with prostate cancer as a monotherapy and in combination settings. To date, mono-therapy with ipilimumab in a phase III trial assessing men with castration-resistant disease was negative overall; however, there has been demonstration of good biochemical response and there was a signal of a survival benefit in subgroups of patients with favourable prognostic features. This interaction inhibits downstream T cell receptor signalling, preventing T cell activation leading to their exhaustion and subsequent apoptosis. Similar to CTLA-4 targeting by ipilimumab, PD-1 is an additional but non-redundant pathway for which inhibition results in a targeted anti-tumour response. There has been recent success with anti-PD-1 therapy in advanced melanoma, with the FDA approval of pembrolizumab in September , and nivolumab in

December for metastatic melanoma. These two checkpoint regulators have different, non-overlapping mechanisms of action and can thus ideally be used in combination to maximize immune response. This would increase the response from PD-1 targeting. Results of a phase III study evaluating combination treatment of ipilimumab and nivolumab vs. Most of us in the urological community have likely always been believers to some degree, given modest past successes in renal and bladder cancer. However, this has been a long time coming since the first observations in the early twentieth century by Coley using heat-killed bacterial infections to initiate an anti-tumour response. This progress has been a result of significant advances in our understanding of the complex nature of the regulatory events in cytotoxic T cell-mediated immune responses, particularly antigen presentation, activation and immuno-editing in the cancer microenvironment. We hope this review serves as a primer of the intricacies of the immune system and cancer immunotherapy, as well as highlights some of the promising novel immuno-therapeutic approaches being investigated in prostate cancer. Undoubtedly, these are early days and despite some encouraging and long-lasting responses in some heavily pre-treated patients with prostate cancer, there remains a great deal of both experimental and clinical investigation. There is substantial evidence suggesting that linking different immunotherapeutic approaches, as well as combining other local or systemic cancer therapies, will likely be required to realize synergistic benefits. This could be a daunting task, given the non-classic cancer responses to immunotherapy and co-evolving immune escape mechanisms, the need for knowledge-based trials to help inform dosing, timing, and sequencing, as well as the need to develop precise criteria for patient selection. Finally, as these novel therapies become more available, those in the urological community will need to become better educated regarding the recognition and management of immune-related adverse effects in order to maximize clinical benefit. Graham has served as an unpaid consultant and is a shareholder for Nometics, Inc. Siemens has participated or is participating in clinical trials for Janssen, Amgen, Astellas, and Ferring. The remaining authors declare no competing financial or personal interests. This paper has been peer-reviewed. Saad F, Miller K. Current and emerging immunotherapies for castration-resistant prostate cancer. Canadian Task Force on Preventive Health Care Recommendations on screening for prostate cancer with the prostate-specific antigen test. Kapoor A, Siemens DR. And nowâ€¦a message from our experts. Can Urol Assoc J. Abiraterone in metastatic prostate cancer without previous chemo-therapy. N Engl J Med. Immunotherapy in prostate cancer: Review of the current evidence. Neoantigens in cancer immunotherapy. Immune surveillance of tumours. Balancing the innate immune system in tumour development. Immune-mediated mechanisms influencing the efficacy of anticancer therapies.

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The Primer on Tumor Immunology and Cancer Immunotherapy is designed to provide a foundation for understanding core immunology principles as they relate to basic and clinical research in immunotherapy of cancer.

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