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Chapter 1 : The role of regulatory T cells in cancer immunology | ITT

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Editor who approved publication: Regulatory T cells Treg are generally considered to be significant contributors to tumor escape from the host immune system. Emerging evidence suggests, however, that in some human cancers, Treg are necessary to control chronic inflammation, prevent tissue damage, and limit inflammation-associated cancer development. The dual role of Treg in cancer and underpinnings of Treg diversity are not well understood. This review attempts to provide insights into the importance of Treg subsets in cancer development and its progression. It also considers the role of Treg as potential biomarkers of clinical outcome in cancer. The strategies for monitoring Treg in cancer patients are discussed as is the need for caution in the use of therapies which indiscriminately ablate Treg. A greater understanding of molecular pathways operating in various tumor microenvironments is necessary for defining the Treg impact on cancer and for selecting immunotherapies targeting Treg. In many human cancers and in most mouse models of tumor growth, the frequency of Treg and their suppressor functions are increased as compared to those reported for healthy subjects. Thus, Treg which accumulate in situ and in the peripheral circulation of cancer patients can be viewed as one of multiple attempts by the tumor to promote its own escape from the host immune system by silencing antitumor immune effector cells. On the other hand, it seems equally likely that in tumors characterized by extensive inflammatory infiltrates, such as colon or breast cancers, Treg are necessary for control of chronic inflammation, prevention of tissue damage, and limiting of tumor development associated with inflammation. This ambiguity is fueled by the rapidly emerging evidence for tremendous plasticity and phenotypic as well functional heterogeneity of Treg in man. It is not clear, for example, that Treg found in the TME are the same cells that circulate in the periphery or that their functional repertoire is similar to or different from that of the cells in the peripheral circulation. Overexpression of multiple checkpoint receptors on Treg in the TME suggests that these cells acquire significantly different phenotype and functions once they enter the tumor. Another objective is to impress upon the reader a degree of caution for the use of Treg as biomarkers of cancer progression and for the use of therapies which indiscriminately ablate Treg. The review provides a rationale for exercising this caution and discusses alternative strategies for monitoring activities of human Treg that are based on the current understanding of their diversity. In general, human Treg have been difficult to study for two reasons. The transcription factor, FOXP3, a reliable Treg marker in mice, is not so reliable in man, for it may be absent from some Treg subsets and present on non-Treg, as recently discussed. Specifically, the expression of surface markers such as CD25hi on the cell surface and intracellular FOXP3 has been used to differentiate between these two Treg subsets by flow cytometry, with pTreg exhibiting a much greater heterogeneity in levels of expression of these two markers, 34 â€” 36 as indicated in Figure 1. In the absence of a single specific, stable marker for Treg, combinations of markers are often used to define Treg. It has been suggested that a transcription factor, Kruppel-like factor 2 KLF2 , may be necessary for the development of iTreg. Immunohistochemistry broadly used for Treg detection in formaldehyde-fixed paraffin-embedded human tissues depends entirely on selection of antibodies Abs that work well with such specimens, and as discussed elsewhere, 12 should not depend on expression of FOXP3 alone, as pTreg present in tumors may be negative for this marker. Attempting to bring some measure of consensus to the field, a recent international workshop on Treg was organized by the Collaborative Immunoguiding Program. Therefore, a broader Treg definition, one that allows for the more precise discrimination of tTreg from pTreg in patients with cancer, is needed. As pTreg populations, which likely include subsets of heterogeneous suppressor cells, predominate in cancer, 34 , 45 their localization, numbers, phenotypic signatures, and suppressor functions are of utmost importance. Functional attributes of Treg in patients with cancer We and many others have commented on elevated suppressor functions mediated

by Treg in the peripheral circulation of patients with solid or hematological malignancies. A number of in vitro assays have been developed to measure suppression mediated by Treg. These flow-based assays do not require isolation or culture of Treg and thus are commonly used for monitoring of Treg in human specimens. Other assays require coculture of isolated Treg and CFSE-labeled responder T cells, to quantitate levels of suppression mediated by Treg. The emerging evidence further suggests that in the presence of tumor-derived signals, Treg might be regulated to preferentially use specific inhibitory molecular pathways. Therefore, it may be reasonable to envision the scenario where different solid tumors create microenvironments in which Treg are instructed to preferentially adopt the suppression pathway that best fits with environmental programming in situ. These examples illustrate how human tumors regulate suppressive functions of Treg that are recruited to the TME. Figure 2 Treg accumulating in the TME activated iTreg utilize various suppressive mechanisms to inhibit functions of Teff. The suppressive factors released by iTreg interact with the cognate receptors present on the Teff surface, which process and direct the negative signals to the respective molecular pathways. The final result is a partial or complete loss of effector functions in responder immune cells. The ADO-PGE2 pathway and Treg-mediated suppression ADO is a well-known mediator of diverse regulatory processes in the endocrine, vascular, neurological, renal, pulmonary, and immunological systems. Together, these two factors deliver powerful immunoinhibitory signals to antitumor responder cells. While Treg significance as a prognostic marker is best established in colorectal carcinoma, 81 investigations are in progress to extend and confirm these findings to other solid tumors. Based on measures of the magnitude of immune response silencing by Treg in cancer ie, Treg suppressor functions rather than their phenotype in situ or in the peripheral circulation, it might be possible to arrive at an even better estimate of Treg prognostic significance. Similarly, measures of Treg functions might correlate better with responses to oncological therapies than does their phenotypic enumeration. However, because Treg are heterogeneous, consisting of many subsets of functionally distinct cells, and because no universal distinguishing marker for Treg is currently available, their use as a biomarker of prognosis is limited and has to be taken with caution. Furthermore, current attempts to therapeutically deplete Treg might enhance tumor immunity in some patients but be detrimental in others. It has been reported that expression of surface markers on Treg can be altered in disease 82 and in patients undergoing conventional therapies or immune therapies. As discussed earlier, there is still no consensus as to which marker panel of several available is best, and which subset of Treg should be monitored. Indeed, a considerable body of recent literature deals with various methods for Treg depletion. Table 1 lists the Treg-associated molecules that potentially could be targeted for Treg silencing either by Treg removal or impairment of Treg suppressor functions. To date, a variety of agents, including Abs daclizumab: Strategies that are listed have been used in preclinical studies. Based on favorable preclinical results, some depletion strategies are being used alone or in combination with immunotherapies in human clinical trials Table 2. The table lists clinical trials posted online at http: However, in contrast to successful and meaningful Treg depletion studies in mouse models, it has not been possible to convincingly correlate Treg depletion by these agents with clinical benefits in patients with cancer. Table 2 Immunotherapy clinical trials incorporating strategies for Treg depletion in patients with solid or hematologic malignancies Notes: Clinical trials that were withdrawn or terminated are not listed. For example, in patients with tumors expressing COX-2 such as HNSCC, which are richly infiltrated with iTreg-producing PGE2, inhibitors of the PGE2 pathway celecoxib, indomethacin, diclofenac, ibuprofen have been clinically used with an intent to block immune suppression. This approach has been shown to work both in vitro with human Tregâ€”Teff cocultures 71 and in preclinical models of cancer. An additional benefit of antagonizing ADO-induced suppression may derive from the fact that it involves blocking of Treg suppressor functions without depletion of all Treg and risking the development of autoimmunity. However, Treg, especially those present in the TME, are known to express a variety of the same regulatory molecules. Summary The presence and functions of human Treg in cancer have been intensively investigated. Nevertheless, the role that these suppressor cells play in cancer progression remains controversial. It appears that while contributing to tumor escape from the host immune system, Treg

are also involved in regulating immune responses to self and controlling inflammatory responses that threaten to disrupt tissue integrity. It appears that in cancer, expansion and activation of Treg occur in response to tumor-generated signals, leading to tumor escape. The remarkable plasticity of Treg infiltrating human tumors is reflected in their phenotypic and functional heterogeneity that may influence disease outcome. It appears that genetic and environmental factors promote variability in the expression of Treg cell signature genes, 10 so that Treg gene repertoire differs between individuals. If so, then Treg involvement in human cancer and other diseases will have to be viewed in the light of personalized medicine. This concept underlies the use of Treg as biomarkers of tumor progression and the selection of therapeutic strategies for Treg elimination to help restore antitumor immunity in cancer. The understanding of Treg diversity is critical for either of these strategies to be successful, and a sustained focus on the molecular pathways that Treg use in the TME is likely to facilitate future progress. Disclosure The author reports no conflicts of interest in this work.

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Chapter 2 : - NLM Catalog Result

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Published online Jun 7. Whiteside , 1 James L. Gulley , 2 Timothy M. Clay Find articles by Timothy M. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Immunotherapy for cancer is based on the concept of inducing the generation and expansion of immune cells that can attack and eliminate cancer. Immunotherapy with therapeutic cancer vaccines aims specifically at inducing tumor antigen-specific T cells. The immune system is a complex, multifaceted cellular network that is not fully understood. Monitoring cellular immune responses is essential for rational cancer vaccine development. The primary objectives of immune monitoring after vaccination are to document the induction of vaccine-specific and tumor-specific immune responses and to correlate the presence and magnitude of vaccine-induced immune responses to clinical outcomes. Immune monitoring could also be used to a define the ability of a given vaccine to generate antigen cascade responses i. Despite advances in the development of immune monitoring assays during the past decade, it has been difficult to establish significant correlations between vaccine-induced immune responses and clinical outcomes. This lack of correlation could reflect the methodological limitations of immunologic assays or the postvaccination absence of antitumor responses sufficiently robust to induce disease-free or overall survival. A wide portfolio of monitoring assays is currently available. However, these assays fail to define surrogate markers that could be used as predictors of clinical response and thus serve to advance vaccine development. The immune monitoring assays currently used in cancer immunotherapy trials such as enzyme-linked immunospot assays, tetramer-based assays, intracellular cytokine flow cytometry, antibody tests, proliferation assays, reverse transcription polymerase chain reaction, and serum cytokine and chemokine profiles have limited usefulness as surrogate markers of clinical efficacy. There is general consensus that further studies are needed to account for the difficulties in establishing the correlation between different aspects of T-cell function and clinical efficacy. Vaccine-induced immune responses against cancer depend on a balance between immune responses of various subsets of effector and suppressor T cells. Because tumor antigens are mostly self-antigens, this balance is shifted toward tolerance in cancer patients, so that generating effective antitumor responses requires breaking of tolerance. Although preclinical data have shown that it is possible to break tolerance to tumor-associated self-antigens, human clinical trials employing cancer vaccines have mostly failed to do so. In an immunocompetent cancer patient, the immune system suppresses attacks against self-antigens, including tumor-associated antigens, particularly in the tumor microenvironment. Recent studies have focused on defining the role of the suppressive component of the antitumor immune response in breaking tolerance and steering the immune system toward autoimmunity. In this respect, monitoring assays that measure the extent of cancer-induced suppression may be especially important. The suppressive compartment of the immune system includes a group of heterogeneous immune cells, including regulatory T cells Tregs , myeloid-derived suppressor cells MDSCs , and tumor-associated macrophages TAMs. One of the major problems in characterizing these cells is their extreme plasticity. Cells normally committed to activating an immune response can transiently acquire suppressive characteristics, as often happens in cancer. While suppressor cells represent an important mechanism by which the immune system fine-tunes specific immune responses, expansion of these cells in cancer patients interferes with antitumor immunity. In humans, it has been difficult to establish a definite phenotype for these cells, and assessment of their functional status has been a special challenge as they are minor lymphocyte subsets lacking well-defined surface markers. Greater understanding of the mechanisms that regulate the homeostasis of these suppressive cells could lead to the development of more effective cancer immunotherapies and better immune monitoring of patients receiving cancer vaccines. Several studies have

demonstrated that Treg depletion can efficiently enhance vaccine-mediated antitumor immunity in cancer patients. For example, in a randomized placebo-controlled multicenter phase II trial, patients with metastatic castration-resistant prostate cancer were treated with a poxviral-based vaccine containing the transgenes for prostate-specific antigen and 3 costimulatory molecules PSA-TRICOM. This trial demonstrated a direct correlation between the post-vaccination frequency and function of Tregs and overall survival. Analysis of Tregs in real time as part of the immune monitoring of patients could also help to identify the subpopulation of patients who would most likely benefit from vaccine therapy. Similar to Tregs, MDSCs are a heterogeneous cell population that has been difficult to monitor in humans. MDSCs are composed mainly of myeloid progenitor cells that do not completely differentiate into mature macrophages, dendritic cells, or granulocytes. Increased circulating MDSCs have also been correlated with tumor stage and metastatic spread in different types of tumors [3 , 4]. Moreover, it has been demonstrated that MDSCs can be differently affected by standard-of-care therapies such as sunitinib, doxorubicin-cyclophosphamide, and docetaxel, as well as some immunotherapies. These findings suggest a potential use for these cells in immune monitoring of cancer patients receiving immunotherapies. Recent clinical studies have demonstrated a correlation between increased numbers of TAMs and poor prognosis for esophageal, bladder, prostate, endometrial, breast, and lung cancers [5 â€” 8]. These data suggest a possible use of TAMs in the immune monitoring of cancer patients enrolled in clinical trials employing therapeutic vaccines. While the major focus of post-vaccination monitoring is assessment of tumor antigen-specific immune responses, it is important to note that innate immunity mediated by natural killer cells, macrophages, dendritic cells, or granulocytes could significantly contribute to beneficial clinical outcome. Vaccines that engage and promote adaptive and innate antitumor responses appear to be most effective. Thus, at least some aspects of innate immunity should be monitored in clinical trials of antitumor vaccines. The increasing number of immunotherapy clinical trials that use immunologic parameters as primary or secondary endpoints, as well as the availability of an increasing number of monitoring assays, highlights two aspects of immune monitoring. First, selection of assays that are most likely to correlate with clinical outcomes is a critical factor. This should be an informed and hypothesis-driven choice, considering factors such as cost and the need for serial monitoring with multiple assays. As understanding of the mechanisms of immune regulation increases, additional biomarkers will be identified that, hopefully, can be used as surrogate markers for immune responses to cancer vaccines. Second, quality control and assurance are essential for successful immune monitoring of cancer vaccines. All immune monitoring assays need to be standardized for reliability and consistency in order to establish their limitations and overall performance standards. Only standardized monitoring assays are likely to be useful for defining surrogate endpoints of clinical response to antitumor vaccines.

Chapter 3 : Publications Authored by Theresa Whiteside | PubFacts

*Immunologic Monitoring of Cellular Immune Responses in Cancer Vaccine Therapy Theresa L. Whiteside, 1 James L. Gulley, 2 Timothy M. Clay, 3 and Kwong Yok Tsang 3, * 1 Department of Pathology, University of Pittsburgh School of Medicine and University of Pittsburgh Cancer Institute, Pittsburgh, PA , USA.*

 Immunotherapy for cancer is based on the concept of inducing the generation and expansion of immune cells that can attack and eliminate cancer. Immunotherapy with therapeutic cancer vaccines aims specifically at inducing tumor antigen-specific T cells. The immune system is a complex, multifaceted cellular network that is not fully understood. Monitoring cellular immune responses is essential for rational cancer vaccine development. The primary objectives of immune monitoring after vaccination are to document the induction of vaccine-specific and tumor-specific immune responses and to correlate the presence and magnitude of vaccine-induced immune responses to clinical outcomes. Immune monitoring could also be used to a define the ability of a given vaccine to generate antigen cascade responses i. Despite advances in the development of immune monitoring assays during the past decade, it has been difficult to establish significant correlations between vaccine-induced immune responses and clinical outcomes. This lack of correlation could reflect the methodological limitations of immunologic assays or the postvaccination absence of antitumor responses sufficiently robust to induce disease-free or overall survival. A wide portfolio of monitoring assays is currently available. However, these assays fail to define surrogate markers that could be used as predictors of clinical response and thus serve to advance vaccine development. The immune monitoring assays currently used in cancer immunotherapy trials such as enzyme-linked immunospot assays, tetramer-based assays, intracellular cytokine flow cytometry, antibody tests, proliferation assays, reverse transcription polymerase chain reaction, and serum cytokine and chemokine profiles have limited usefulness as surrogate markers of clinical efficacy. There is general consensus that further studies are needed to account for the difficulties in establishing the correlation between different aspects of T-cell function and clinical efficacy. Vaccine-induced immune responses against cancer depend on a balance between immune responses of various subsets of effector and suppressor T cells. Because tumor antigens are mostly self-antigens, this balance is shifted toward tolerance in cancer patients, so that generating effective antitumor responses requires breaking of tolerance. Although preclinical data have shown that it is possible to break tolerance to tumor-associated self-antigens, human clinical trials employing cancer vaccines have mostly failed to do so. In an immunocompetent cancer patient, the immune system suppresses attacks against self-antigens, including tumor-associated antigens, particularly in the tumor microenvironment. Recent studies have focused on defining the role of the suppressive component of the antitumor immune response in breaking tolerance and steering the immune system toward autoimmunity. In this respect, monitoring assays that measure the extent of cancer-induced suppression may be especially important. The suppressive compartment of the immune system includes a group of heterogeneous immune cells, including regulatory T cells Tregs , myeloid-derived suppressor cells MDSCs , and tumor-associated macrophages TAMs. One of the major problems in characterizing these cells is their extreme plasticity. Cells normally committed to activating an immune response can transiently acquire suppressive characteristics, as often happens in cancer. While suppressor cells represent an important mechanism by which the immune system fine-tunes specific immune responses, expansion of these cells in cancer patients interferes with antitumor immunity. In humans, it has been difficult to establish a definite phenotype for these cells, and assessment of their functional status has been a special challenge as they are minor lymphocyte subsets lacking well-defined surface markers. Greater understanding of the mechanisms that regulate the homeostasis of these suppressive cells could lead to the development of more effective cancer immunotherapies and better immune monitoring of patients receiving cancer vaccines. Several studies have

demonstrated that Treg depletion can efficiently enhance vaccine-mediated antitumor immunity in cancer patients. For example, in a randomized placebo-controlled multicenter phase II trial, patients with metastatic castration-resistant prostate cancer were treated with a poxviral-based vaccine containing the transgenes for prostate-specific antigen and 3 costimulatory molecules PSA-TRICOM. This trial demonstrated a direct correlation between the post-vaccination frequency and function of Tregs and overall survival. Analysis of Tregs in real time as part of the immune monitoring of patients could also help to identify the subpopulation of patients who would most likely benefit from vaccine therapy. Similar to Tregs, MDSCs are a heterogeneous cell population that has been difficult to monitor in humans. MDSCs are composed mainly of myeloid progenitor cells that do not completely differentiate into mature macrophages, dendritic cells, or granulocytes. Increased circulating MDSCs have also been correlated with tumor stage and metastatic spread in different types of tumors [3 , 4]. Moreover, it has been demonstrated that MDSCs can be differently affected by standard-of-care therapies such as sunitinib, doxorubicin-cyclophosphamide, and docetaxel, as well as some immunotherapies. These findings suggest a potential use for these cells in immune monitoring of cancer patients receiving immunotherapies. Recent clinical studies have demonstrated a correlation between increased numbers of TAMs and poor prognosis for esophageal, bladder, prostate, endometrial, breast, and lung cancers [5 â€” 8]. These data suggest a possible use of TAMs in the immune monitoring of cancer patients enrolled in clinical trials employing therapeutic vaccines. While the major focus of post-vaccination monitoring is assessment of tumor antigen-specific immune responses, it is important to note that innate immunity mediated by natural killer cells, macrophages, dendritic cells, or granulocytes could significantly contribute to beneficial clinical outcome. Vaccines that engage and promote adaptive and innate antitumor responses appear to be most effective. Thus, at least some aspects of innate immunity should be monitored in clinical trials of antitumor vaccines. The increasing number of immunotherapy clinical trials that use immunologic parameters as primary or secondary endpoints, as well as the availability of an increasing number of monitoring assays, highlights two aspects of immune monitoring. First, selection of assays that are most likely to correlate with clinical outcomes is a critical factor. This should be an informed and hypothesis-driven choice, considering factors such as cost and the need for serial monitoring with multiple assays. As understanding of the mechanisms of immune regulation increases, additional biomarkers will be identified that, hopefully, can be used as surrogate markers for immune responses to cancer vaccines. Second, quality control and assurance are essential for successful immune monitoring of cancer vaccines. All immune monitoring assays need to be standardized for reliability and consistency in order to establish their limitations and overall performance standards. Only standardized monitoring assays are likely to be useful for defining surrogate endpoints of clinical response to antitumor vaccines.

Chapter 4 : Theresa L. Whiteside, Ph.D. | Department of Immunology | University of Pittsburgh

Immunologic Monitoring of Cellular Immune Responses in Cancer V accine Therapy Theresa L. Whiteside, 1 James L. Gulley, 2 Timothy M. Cl ay, 3 and K wong Y ok T sang 3.

Patients are also screened for oncogenic fusions by targeted RNAseq and for germline cancer predisposition alleles and evidence of clonal hematopoiesis. Hartshorn, PhD, Program Director, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health Albeit the case for long-term, out-of-clinic monitoring has been obvious for many chronic diseases, the case for cancer has not been as clear. This talk will focus on these efforts currently and prospectively as well as the overall vision to coordinate a much broader initiative to improve our understanding of cancer progression and improve the delivery of cancer care. Therefore, harmonization of various tests will be essential to establish diagnostics. In this presentation, we will discuss an application of human germline genetics and primary human tumor tissues for the characterization and translational biomarker discovery of a novel drug candidate. Complex molecular signals are measured and reported in an easy to interpret report. Case study data with control samples and patient materials will be discussed. Webb Chair in Health Innovation, Arizona State University The clinical benefits of immune checkpoint inhibitors in a variety of malignancies are unprecedented. Unfortunately, the level of positive therapeutic response is not consistent across different tumor classes and even in responsive tumor lineages non-responders still dominate. The need for comprehensive immunophenotyping to identify the mechanisms underlying these differential responses and better predict responder patients is an urgent clinical and economic imperative. Despite the current success of these therapies, not all patients respond to immunotherapy, and even those that do often experience toxicities. Combination approaches are the keys to improving clinical response. High throughput next-generation sequencing technologies enable us to explore the mechanisms of responses as well as resistance. Emerging dual biomarkers tumor mutational burden and gene expression profile allow us to understand novel translational biomarkers to stratify patients effectively for personalized cancer immunotherapy. This presentation will discuss these tests and future more sophisticated tests for protein, including expression in the microenvironment and the tumor, mRNA, as expression signatures, and DNA, including tumor mutational burden. However, the extent to which patients derive benefit is diverse and the determinants of response to therapy are ill-defined. We have sought to define the genomic and immunologic determinants of response to immune checkpoint blockade therapies such as anti-CTLA-4 and anti-PD Our work has shown that tumor mutational burden, clonality, and the tumor immune landscape help dictate clinical response to immune-based therapies. In addition to PD-L1 staining and tumor mutational burden, factors such as immune cell compositions and checkpoint molecule profiles, antigen presenting machinery and immune resistance signals, should also be considered when evaluating a patient for immunotherapy. In this talk, a novel chip-based assay to monitor tumor microenvironment using FFPE tissue will be presented. Attendees choose to join a specific group, and the small, informal setting facilitates sharing of ideas and active networking. Details on the topics and moderators are available on the conference website. Whiteside, PhD, Professor, Pathology, Immunology and Otolaryngology, University of Pittsburgh Cancer Institute Plasma-derived exosomes are emerging as promising non-invasive correlates of cancer progression. In patients with solid tumors or hematological malignancies, plasma exosomes carry a cargo enriched in immunosuppressive proteins. As immune suppression is one of the hallmarks of cancer progression, circulating exosomes rich in inhibitory molecules are implicated in mediating systemic immune suppression. However, plasma has a rich content in cells, extra-cellular vesicles and biomolecules that inform about tumor features, the microenvironment and the status of the immune response. Progress in defining the tumor microenvironment in solid tumors by means of liquid biopsy will be presented. Implementation of ctDNA-based assays across clinical and research settings highlights important assay characteristics and suggests future clinical applications. Gelb, MD, MS, FASCP, FCAP, Clinical Advisor, Exploratory

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Biomarkers The objectives of this presentation are 1 to review the biological background by which somatic mutations can lead to the generation of private, highly immunogenic tumor antigens neoantigens , 2 discuss association of neoantigens with mutational burden, mismatch repair and immune checkpoint expression, and 3 to provide an outlook on clinical applications involving assessment of neoantigens and mutational load with regards to response to immune-checkpoint blockade in solid tumors. Identifying neoantigens accurately from the exome sequence is a key parameter for the development of such responses and remains a significant variable of the overall process. TESLA is a consortium-based approach involving over 30 groups to identify key parameters in neoantigen prediction. An update on the progress of the program will be discussed. The personalized vaccine is delivered in combination with immune checkpoint blockade, to keep TSNA-induced T-cells active in the immunosuppressive tumor microenvironment.

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Chapter 5 : Theresa L. Whiteside, Ph.D. | Program in Microbiology and Immunology | University of Pittsbur

Dr. Whiteside's research interests are in Tumor Immunology and Immunotherapy with special focus on mechanisms of tumor-induced immunosuppression, cytokine networks, development of anticancer vaccines, immunology of human head and neck cancer and the role of natural immunity in the control of cancer progression.

Interleukin enhances NK cell cytotoxicity in patients with acute myeloid leukemia by upregulating the activating NK cell receptors. Immune Responses to Malignancies. Impact of HIV on liver fibrosis in men with hepatitis C infection and haemophilia. Tumor-derived microvesicles induce, expand and up-regulate biological activities of human regulatory T cells Treg. Adenosine and prostaglandin E2 cooperate in the suppression of immune responses mediated by adaptive regulatory T cells. Shipping of therapeutic somatic cell products. In vitro chemosensitivity of head and neck cancer cell lines. Mechanisms of T-cell protection from death by IRX-2, a new immunotherapeutic. Mechanisms of tumor escape from the immune system: Adenosine-producing Treg, exosomes and tumor-associated TLRs. Special Issue on Tumor Microenvironment, 98 2: Tumor-derived macrophage migration inhibitory factor modulates the biology of head and neck cancer cells via neutrophil activation. Prolactin receptor is a negative prognostic factor in patients with squamous cell carcinoma of the head and neck. Targeting human regulatory T cells Treg in patients with cancer: Exp Opin Biol Ther, 11 9: Clin Cancer Res, 17 IRX-2 a novel biologic, favors the expansion of T effector over T regulatory cells in a human tumor microenvironment model. A short course of neoadjuvant IRX-2 induces changes in peripheral blood lymphocyte subsets of patients with head and neck squamous cell carcinoma. The Role of the Adenosinergic pathway in immunosuppression mediated by human regulatory T cells Treg. Increased lymphocyte infiltration in patients with head and neck cancer treated with the IRX-2 immunotherapy regimen. Cancer, [Epub ahead of print Oct. Cyclin B1 expression and p53 status in squamous cell carcinomas of the head and neck. A gynecologic oncology group phase II trial of two p53 peptide vaccine approaches: Disarming suppressor cells to improve immunotherapy. Suppression of natural killer-cell and dendritic-cell apoptotic tumoricidal activity in head and neck cancer patients. Head and Neck, In Press, Kato H, Whiteside TL. Expression of IL and IL receptors on peripheral blood lymphocytes and monocytes in human head and neck squamous cell carcinoma. IRX-2, a novel immunotherapeutic, enhances and protects NK-cell functions in cancer patients. Myeloid-derived suppressor cell measurements in fresh and cryopreserved blood samples. What are regulatory T cells Treg regulating in cancer and why? Immune modulation of T cells and natural killer cells by tumor-derived exosomes. Elsevier, London, In Press, Develoments in clinical cell therapy. The tyranny of statistics in medicine: A critique of unthinking adherence to an arbitrary p value. Immunologic monitoring of cellular immune responses in cancer vaccine therapy. This site is designed and maintained by Enterprise Provider Solutions.

Chapter 6 : Immunologic Monitoring of Cellular Immune Responses in Cancer Vaccine Therapy

Monitoring cellular immune responses is essential for rational cancer vaccine development. The primary objectives of immune monitoring after vaccination are to document the induction of vaccine-specific and tumor-specific immune responses and to correlate the presence and magnitude of vaccine-induced immune responses to clinical outcomes.

Chapter 7 : [Full text] The role of regulatory T cells in cancer immunology | ITT

Monitoring of Immune Therapies. By Theresa L. Whiteside. View abstract. A complete guide to molecular and cellular immunology for practicing clinicians, clinical.

Chapter 8 : Theresa L. Whiteside, PhD

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The use of new immune biomarkers and the ability to assess responses to therapy by noninvasive monitoring promise to improve early cancer diagnosis and prognosis. Personalized immunotherapy based on individual genetic, molecular, and immune profiling is a potentially achievable future goal.

Chapter 9 : Immuno-Oncology Biomarkers 1 | Biomarkers & Immuno-Oncology World Congress

Theresa Whiteside, PhD - University of Pittsburgh Cancer Institute â€¢ Use of Molecular Assays to Assess Cellular Therapies David Stroncek, MD - Cell Processing, DTM, CC, NIH.