Conference Scene

The 3rd International Cancer Vaccine Conference

The 3rd International Conference on Cancer Vaccines/Adjuvants/Delivery for the Next Decade (CVADD): Meeting Highlights 11–13 November, 2009, Dublin, Ireland

The 3rd International Conference on Cancer Vaccines/Adjuvants/Delivery for the Next Decade (CVADD) was organized to support the translation of basic research achievements into clinical practice and to bridge the gap between academic studies and innovations of pharmacologic companies. A clear discrepancy between high rates of immune anti-tumor responses and poor clinical effects makes necessary to improve cancer vaccination. This challenge stimulated a fruitful discussion on strategies of immunization, adjuvants, delivery systems, novel antigens, targets and monitoring of the immune response.

The 3rd International Conference, Cancer Vaccines/Adjuvants/Delivery for the Next Decade (CVADD 2009) took place in Dublin, Ireland, on 11–13 November 2009. The main aims were to discuss the state of the art of cancer vaccination with special attention to clinical application. This article provides a short overview of novel concepts, strategies and clinical achievements in this field following the 2nd CVADD conference in Heidelberg, Germany (2005). Approximately 150 participants from academia and pharmacologic companies were attracted by the scientific program that consisted of presentations from 44 international experts. Good memories remain not only from the lively discussions of ten scientific sessions and eight posters, but also from the beauty of ancient Dublin and the social evenings downtown with local food and drinks.

Biological underpinning of cancer vaccines

The conference was opened by the lecture of Malcolm Mitchell (University of Texas, TX, USA) who presented a brief history of cancer vaccine development. He stressed that cancer vaccines have produced major clinical remissions and, similar to other cancer treatments, should be judged solely on their ability to prolong survival. Andrew Sewell and David Price (Cardiff University, Wales, UK) focused on the possibilities of improving T-cell receptors to bind natural tumor antigens. Effective T-cell anti-tumor responses and successful clinical outcome after vaccination will be determined by avidity, clonotype, phenotype and functional activity of tumor

antigen-specific CD8 T cells. Matthew Mescher (University of Minnesota, MN, USA) presented a broad overview of signals required for efficient CD8 T-cell activation. The size of antigen-bearing surface was shown to determine the level of CD8 T-cell anti-tumor response. Other important parameters for this response are IL-12 and IFN- α produced by dendritic cells (DCs), as well as the help from CD4 T cells secreting IL-2. An interesting study to improve the efficacy of DC-based vaccination was reported by Walter Storkus (University of Pittsburgh, PA, USA). DCs genetically modified to express high levels of the transcription factor T-bet were able to induce a strong polarization of naive T cells to exert Th1 responses independent of IL-12. The data suggest a novel mechanism for induction of Th1 immunity.

Basic concepts & models

Based on the studies on universal breast cancer antigen mammaglobin A, June Kan-Mitchell (University of Texas, TX, USA) stressed a role of subdominant antigenic epitopes for successful cancer vaccination. Subdominance is not a function of poor immunogenicity, but rather suggests that useful responses to this epitope can be suppressed by competing CD8 T-cell subsets. A comprehensive overview of cancer vaccine models in mice was presented by Guido Forni (University of Turin, Italy). For efficient vaccination, it is critically important to know target tumor antigens, vaccine adjuvants and delivery, prime–boost strategy, immunosuppression mechanism and right combination

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with other therapies. Genetically engineered mice were suggested as an adequate preclinical system for vaccine development. Giorgio Parmiani (San Raffaele Foundation Scientific Institute, Milan, Italy) discussed different aspects of peptide vaccination and the use of heat shock protein (Hsp)-96 as an adjuvant. Stroma cells and cancer stem cells were proposed as new targets for effective vaccination. An interesting approach of a xenogenous DNA immunization in melanoma was reported by Miguel Perales (Memorial Sloan-Kettering Cancer Center, NY, USA). This type of vaccination could be combined with the adoptive transfer of allogeneic T cells that led to an increased survival and tumor growth suppression in mice.

Manipulation & monitoring of the immune response

Jianda Yuan (Memorial Sloan-Kettering Cancer Center, NY, USA) analyzed in his presentation T-cell-mediated anti-tumor immune responses and clinical benefits of melanoma patients after DNA vaccination combined monoclonal antibodies against CTLA-4, PD1 or 4-1BB markers. Combining CTLA-4 blockade with vaccine therapy represents an efficient strategy of immunotherapy that results not only in an enhancement of immune reactivity but also in tumor regression. A detailed analysis of cytokine profile and T-cell phenotype in pancreatic cancer patients with unexpected long-term survival after vaccination was reported by Jon Kyte (Oslo University Hospital, Norway). In general, these patients contained high numbers of tumor-specific memory T cells, increased concentrations of IFN- γ and decreased levels of IL-10 and IL-4. Theresa Whiteside (University of Pittsburgh, PA, USA) emphasized a key role of different subpopulations of CD4 regulatory T cells in tumor-induced immunosuppression. She focused on Tr1 cells expressing CD39, which mediate suppression by IL-10, TGF- β_1 and adenosine secretion, and whereby accumulation strongly correlate with the tumor progression. New strategies to block regulatory T-cell induction in tumor-bearing hosts by inhibiting PI3 kinase or MAPK signaling pathways in DCs were discussed by

Kingston Mills (Trinity College, Dublin, Ireland). This modulation was demonstrated to increase the anti-tumor effector T-cell responses and clinical efficiency of DC vaccines.

Strategies of immunization

The role of myeloid-derived suppressor cells (MDSCs) in the immunosuppressive tumor microenvironment was addressed in several presentations of this session. Viktor Umansky (German Cancer Research Center, Heidelberg, Germany) demonstrated in a *ret* transgenic mouse melanoma model (resembling the human situation) that neutralization of MDSC activity by phosphodiesterase-5 inhibitor Viagra® (Pfizer, UK) resulted in the improved survival of the mice. This correlated with the intratumoral accumulation of CD8 T cells with enhanced activity. Rolf Kiessling (Karolinska Institute, Stockholm, Sweden) reported that MDSCs contain high levels of arginase I and Stat-3. In melanoma patients, increased amounts of MDSCs expressing phenotypic markers of mature and immature DCs were found to correlate with disease progression. Enzo Bronte (University of Padua, Italy) discussed a role of C/EBP β transcription factor as a master regulator of MDSC function. C/EBP β -knockout mice showed a drastic decrease in CD11b⁺Gr1⁺ MDSC numbers, decreased arginase and nitric oxide synthase activity in CD11b⁺ cells and better response to anti-tumor immunotherapy with tumor-specific T cells. Volker Schirmacher (German Cancer Research Center, Heidelberg, Germany) analyzed different randomized clinical vaccination studies in cancer patients. He stressed that individualized cancer vaccine using Newcastle disease virus could bring clinical benefits, since infection of tumor cells with Newcastle disease virus provides them with danger signals facilitating anti-tumor T-cell reactivity. The role of Incomplete Freund Adjuvant in vaccination was addressed by Willem Overwijk (MD Anderson Cancer Center, TX, USA). In mouse system, incomplete Freund's adjuvant induced a long-term tolerance and can be replaced by IL-2, IL-23 and anti-CD40 antibodies to stimulate durable T-cell responses.

DNA vaccines

Two sessions were focused on different approaches of DNA anti-tumor vaccination. Chien-Fu Hung (John Hopkins University, MD, USA) presented a broad overview of innovative vaccines for gynecological cancers. The efficiency of DNA vaccination could be increased via modification of antigen-presenting cells or via combination with chemotherapy, which changes the tumor microenvironment by reducing the number of MDSCs and Tregs and inducing release of tumor antigens. Advantages of DNA vaccination were analyzed by Freda Stevenson (University of Southampton, UK). These vaccines stimulate innate immunity, deliver additional molecules enhancing anti-tumor immunity, present tumor antigens in the appropriate form and are safe. Christian Ottensmeier (University of Southampton, UK) described beneficial effects of the vaccination of patients with recurrent prostate cancer using the DNA-coding tumor-specific transmembrane glycoprotein PSMA. This vaccine was applied intramuscularly via electroporation. Advantages of this method of DNA delivery were discussed by Jacob Mathiesen (Inovio AS, Oslo, Norway). Intramuscular injection of plasmid DNA followed by electrical stimulation (electroporation) allows achieving therapeutic levels of encoded proteins and eliciting efficient immune responses. Two early-phase DNA vaccine clinical trials in humans using electroporation-enhanced delivery are now in progress.

An elegant approach of the Immunobody Platform permitting DNA vaccination with T-cell epitopes encoded within antibody molecules was presented by Lindy Durrant (University of Nottingham, UK). Such vaccination was demonstrated to induce high avidity CD8 memory T cells with enhanced anti-tumor activity and will be tested in the Phase I clinical trial in melanoma patients. Douglas McNeel (University of Wisconsin, WI, USA) reported a clinical trial using DNA vaccine-encoding tumor-specific antigen prostatic acid phosphatase in patients with biochemically recurrent prostate cancer. He stressed the safety and immunological efficacy of this DNA vaccine, which should be later tested in the Phase II trial. Nirnajan

Sardesai (Inovio Biomedical Corporation, PA, USA) demonstrated the results of the ongoing clinical trial in patients with cervical cancer vaccinated with a DNA construct encoding tumor-specific protein E7 from HPV16. The majority of the vaccinated patients showed strong specific cellular or humoral responses. Based on preclinical mouse models and clinical trials in melanoma patients, Drew Hannaman (ICHOR Medical Systems, CA, USA) also stressed that DNA vaccination via electroporation is able to improve anti-tumor immune responses compared with regular plasmid DNA injection.

Adjuvants & adjuvanticity

Angus Dalgleish (University of London, UK) discussed a necessity to include in the combinatory treatment of cancer patients Toll-like receptor (TLR) agonists (e.g., Aldara™, Graceway Pharmaceuticals, LLC, TN, USA), cytokines (e.g., IL-2 and -15) and low-dose chemotherapy, which can reduce Treg and increase CD4 and CD8 T-cell numbers. Perfect adjuvant capacities of IRX-2, a cytokine-based, cell-derived biologic agent that stimulates antigen-presenting cells (APCs) and significantly enhances T-cell responses to tumor-specific epitopes were reported by Paul Naylor (IRX Therapeutics, NY, USA). Promising carrier and adjuvant functions of virosomes (prepared *in vitro* virus-like particles) were demonstrated by Christian Moser (Pevion Biotech, Bern, Switzerland). Virosome-based trivalent peptide vaccine targeting Her-2/neu is currently under investigation in the Phase I trial in breast cancer patients. Karl-Jochen Kallen (CureVac, Tuebingen, Germany) demonstrated that mRNA-based vaccines possess excellent self-adjuvanting capacities and can induce effective responses by CD8 and CD4 memory T cells via stimulation of TLR7.

Novel antigens & targets

Advantages of p53 synthetic long peptide vaccine (p53-SLP) applied in patients with recurrent ovarian cancer in a Phase II trial were reported by Hans Nijman (University of Groningen, The Netherlands). This vaccine is not only safe and well tolerated and but also induces p53-specific T-cell responses in ovarian cancer patients.

Ronald Rooke (Transgene SA, Strasbourg, France) described TG-4010, a second-generation modified vaccinia Ankara virus encoding MUC1 and IL-2 for the potential treatment of a variety of MUC-1 expressing tumor types. Phase II trials are underway for non-small-cell lung cancer, metastatic renal cancer and prostate cancer.

The application of modified vaccinia Ankara virus has been also discussed in the presentation of Richard Harrop (Oxford Biomedica, Oxford, UK). Vaccinia Ankara has been engineered to deliver the tumor antigen 5T4 and has been evaluated in a Phase II trial in metastatic renal cell cancer patients, in which the vaccine was administered alone or in combination with IFN- α_{2b} . At the end of the session, Harpreet Singh (Immatics Biotechnologies, Tuebingen, Germany) analyzed the current state of the development of multi-peptide vaccines for immunotherapy of cancer patients.

New vaccines, adjuvants & methods of delivery

This session started with the presentation of Neil Marshall (Trinity College, Dublin, Ireland). He proposed a promising approach for the development of effective anti-tumor vaccines by using PI3K β and δ inhibitors to encourage DC away from a regulatory phenotype and towards an anti-tumor response. Karen Lingnau (Intercell, Vienna, Austria) presented IC31 as of potential benefit for cancer immunotherapy adjuvant, IC31 acts through the transcription factor MyD88 and strongly stimulates Th1 response. Jan Nesselhut (Institute for Tumor Therapy, Duderstadt, Germany) pointed out that the disease progression in patients with colon, lung and breast cancer strongly correlated with the accumulation of CD4⁺CD25⁺CD39⁺ Tregs. Moreover, CD39⁺ cells represent a major subset of Tregs in cancer patients.

Andrew Sikora (Mount Sinai School of Medicine, NY, USA) evaluated the role of IFN- α as a vaccine adjuvant in peptide vaccination in melanoma patients, and as an enhancer of maintenance of adoptively transferred gp100-specific CD8 T cells

with an effector memory phenotype. This new insight provides a rationale for clinical trials, in which vaccination is combined with standard-of-care IFN- α therapy for melanoma. Jan Michalek (Masaryk University, Brno, Czech Republic) analyzed five already published protocols of maturation cocktails for DC maturation and subsequent vaccination. Last, Stephanie McArdle presented the results of standardization of the ELISPOT assay performed in eleven laboratories across Europe and the USA. The laboratories were provided with identical reagents and were asked to follow the same protocol. A high reproducibility of results among different laboratories led to the conclusion that ELISPOT may be an ideal candidate for robust and reproducible monitoring of T-cell activity *in vivo*.

Future perspective

The CVADD 2009 meeting (similar to the previous two CVADD meetings) has brought together experts in the field of cancer vaccination and immunomonitoring from different countries working on the preclinical animal models, with cancer patients and in pharmacologic companies. These experts discussed how to manipulate the immune system to generate efficient tumor-specific immune responses. Although immunotherapy protocols have not yet delivered substantial clinical benefits, the results of recent preclinical studies and clinical trials suggest that we are on the edge of a real breakthrough in cancer immunotherapy. It has been clearly demonstrated that successful strategies of this treatment should be based on the application of different vaccines, adjuvants and delivery systems combined with the neutralization of the immunosuppressive tumor microenvironment. The CVADD 2009 meeting revealed that by supporting open intensive communication between researcher, clinicians and pharmacologic companies as well as sharing ideas, plans and results of clinical trials, we could accelerate the progress in the area of cancer vaccination and eventually save the life of patients.