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MEETING REPORT

IMMUNOTHERAPEUTICS AND IMMUNOMONITORING

GTCBIO'S FOURTH ANNUAL CONFERENCE, SAN DIEGO, CA, USA, JANUARY 30-31, 2012

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SUMMARY

GTCBio's Fourth Immunotherapeutics and Immunomonitoring conference attracted clinical immunologists, pathologists, pharmacologists and scientists from the U.S., Canada, Europe and other parts of the world to hear discussions of the most promising and cutting edge developments in the field. Experts from biotech and pharmaceutical companies and academia presented novel immune-based therapeutic and immunomonitoring technologies. Also discussed was the clinical feasibility and commercial potential of the newest data obtained from leading biomedical research laboratories.

Key words: Immunomonitoring – Vaccines – Antibodies – Cancer

qPCR IMMUNOMONITORING AT EPIONTIS

Ulrich Hoffmueller from Epiontis described his company's qPCR-based immunomonitoring platform, which has the advantage of using frozen tissue samples or frozen whole blood. Unlike antibody detection/measurement, the measurement of cell-mediated immune responses, which is the basis of important decisions in early-stage human studies, is complicated and requires fresh samples. Data were shared for measuring T-regulatory cells in a head-to-head comparison with flow cytometry data. Since the transport of fresh blood needed for current methods is a challenge, the flexibility of Epiontis' immunomonitoring methods in specimen requirement was considered a major advantage. For example, the technology allows the monitoring of T cells in blood or tissue. Low amounts (50-100 µL blood or 1 µg DNA) of whole blood, buffy coat and peripheral blood mononuclear cells (PBMCs) (EDTA, citrate or heparin preservation) may be used to measure T-cell numbers.

NEXVAX2

ImmusanT's celiac disease peptide vaccine NexVax2 (ImmusanT/Nexpep/BTG) was described by Bob Anderson and Leslie J. Williams from the company. Over 90% of celiac disease patients carry certain HLA allotypes (HLA DQ2) restricted by CD4 T cells specific for peptides derived from dietary gluten that orchestrate the immune response causing chronic intestinal damage. Celiac disease is the only human immune-mediated disease for which there is definitive understanding of the epitopes recognized by disease-relevant T cells. High-throughput T-cell epitope mapping defined three peptides recognized by the majority of gluten-specific T cells mobilized in blood by oral gluten challenge. NexVax2 is an equimolar solution of two 16- and one 15-mer peptides designed for HLA $DQ2^+$ celiac disease, which is being developed as a highly specific immunotherapy to restore immune tolerance to gluten and allow return to normal diet. Proof of concept has been shown in genetically modified mice expressing HLA DQ2 and a T-cell receptor specific for one of the five epitopes in NexVax2. A phase I clinical trial in 34 HLA $DQ2^+$ volunteers with celiac disease following a gluten-free diet supported the safety, tolerability and the predicted bioactivity of NexVax2. Functional T-cell assays using NexVax2 peptides show promise as companion and standalone diagnostic tests for celiac disease, and also to monitor immunotherapy. It was explained how the clinical need, market size, definitive epitope mapping, controlled in vivo antigen challenge, accessibility of tissue from the target organ and

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diagnostics measuring relevant T cells in blood make celiac disease an ideal indication to develop and refine effective peptide-based immunotherapy.

IMMUNOGEN'S TECHNOLOGY

ImmunoGen's proprietary technology empowers antibodies by fusing them to tumor cell-killing drugs or cytokines, thereby combining the exquisite specificity of antibodies with the potent cytotoxic effects of drugs or cytokines. This approach should spare non-targeted (healthy) cells, reducing many of the known toxic effects of systemically administered cytokines. ImmunoGen's selective antitumor fusion proteins are one molecule that is genetically engineered and recombinantly produced in mammalian cells. An example of the company's antibody–cytokine fusion proteins is antibody–IFN-alpha, where IFN-alpha is used as a payload. The selection of IFN-alpha was based on many features of this cytokine that resulted in its clinical use for the treatment of several solid and hematological cancers; it remains the standard of care for the treatment of metastatic melanoma.

First, Yelena Kovtun described the company's approach in cytotoxic compound labeling of already marketed/approved humanized monoclonal antibodies (MAbs), and introduced the antibody–drug conjugate (ADC) technology, noting that currently there are at least 25 ADCs in the clinic. In August 2011, the FDA granted conditional approval to brentuximab vedotin (Adcetris™), a conjugate of an anti-CD30 antibody and the microtubule-disrupting agent auristatin E, for the treatment of relapsed Hodgkin's lymphoma and relapsed systemic anaplastic large cell lymphoma. Trastuzumab emtansine (trastuzumab-DM1, T-DM1; Genentech/Chugai/Roche), a conjugate of trastuzumab (Herceptin®) and the microtubule-binding agent DM1, demonstrated compelling activity and impressive tolerability in phase II clinical trials as a first-line treatment in patients with HER2-positive metastatic breast cancer; results of phase III trials are expected in 2012. Both the cancer-binding drug and the payload (an agent that induces cell death) are FDA-approved. ImmunoGen uses IP-protected methods to couple/optimize products, some of which have been in clinical trials; the company hopes to finalize the approval steps.

Iqbal Grewal described maytansinoids (DM1 and DM4) and their mechanism of cell killing. The maytansinoids are conjugated to tumor-targeting antibodies via several linkers developed at ImmunoGen (SMCC, SPP, SPDB, PEG4Mal and SulfoSPDB). The linkers allow for the design of well-tolerated antibody–maytansinoid conjugates that are highly potent against "hard-to-kill" cancers, e.g., solid tumors that express target antigen heterogeneously and/or are resistant to traditional chemotherapy. Also discussed was IFN-alpha as a cytokine that ImmunoGen has coupled to an antibody. The company is currently building a robust portfolio of antibody–IFN-alpha fusion drug candidates for lymphomas, leukemias and solid tumors. Both preclinical and clinical studies have demonstrated the sensitivity of a variety of tumor cell types to soluble IFN-alpha, the payload used to arm its antibodies. ImmunoGen's lead drug candidate IGN-002 fuses IFN-alpha to an anti-CD20 antibody. Anti-CD20 antibodies are a proven target in oncology, with Genentech's rituximab (Rituxan®) and Spectrum Pharmaceuticals' ibritumomab tiuxetan (Zevalin®) currently being used for induction and maintenance therapy in patients with non-Hodgkin's lymphoma (NHL). IGN-002 fuses two FDA-approved and widely used therapeutic agents into a single molecule, which has the potential of being more effective and safer than either soluble IFN-alpha or anti-CD20 antibodies when used alone or in combination.

SYMPHOGEN'S ANTIBODY MIXTURE

Peter Sejer Andersen from Symphogen described the "antibody mixture" as the next wave of antibody therapies. The use of a mixture will enhance the "avidity" of antibody therapies, imitating the nature of the immune system and eliciting protection against pathogens. Symphogen has many such products and, with partners, has conducted clinical trials. This strategy further ensures targeting, in particular when the expression of a surface receptor that one antibody targets is lowered/stopped, a mechanism that some cancers use to evade the immune system. Using a mixture of peptides also enhances/facilitates the involvement of an immune-mediated insult to cancer cells, e.g., via the complement cascade. Symphogen specializes in the discovery of recombinant antibodies, identifying the optimal antibody mixtures and manufacturing such products, while reducing the time from antibody discovery to lead selection.

EMCs IN CANCER VACCINES

The identification of an important driver of epithelial mesenchymal cells (EMCs) as a target candidate to be used in an anti-EMC vaccine was discussed by Claudia Palena (National Cancer Institute). Epithelial–mesenchymal transition (EMT) is a change of normal epithelial cells to EMT, and is known to promote tumor dissemination by enhancing the motility and invasiveness of cancer cells. Mesenchymal-like phenotypes are not normal cells, but they share many features of cancer cells, cause serious pathological conditions and are believed to be facilitators of metastasis. Dr. Palena's group identified a molecule, brachyury, that is a driver of EMT in human tumors. Since the molecule is specific for the EMT process, it is a good candidate for vaccine development where anti-brachyury-specific immune responses are elicited; the development of such a vaccine, known as GI-6301, is under way by GlobeImmune.

NANOPARTICLE VACCINES

Pirouz Daftarian from the University of Miami reported the creation of a novel nanoparticle vaccine vehicle designed to have intrinsically both targeting and immunupotentiating abilities (Fig. 1). Data were shared from two different animal models: melanoma and cutaneous leishmaniasis. Two vaccinations using the nanoparticle platform complexed with DNA-harboring antigens from melanoma or *Leishmania major* were enough to cure mice with established melanoma or those with large leishmaniasis lesions. A recent report showed this therapeutic nanoparticle-based vaccine to rescue mice from melanoma. The vaccine nanoparticle platform (also called PDD) is based on the conjugation of generation 5 poly(amidoamine) (G5 PAMAM) dendrimers, an antigen-loading surface, with MHC class II-targeting peptides that serve to selectively deliver the dendrimers to APCs, while enhancing their immunostimulatory potency. The peptide–dendrimer platform specifically targets B cells, monocytes and dendritic cells, and escorts the cargo into these cells. In vitro, haptens, antigens or DNA conjugated with this plat-

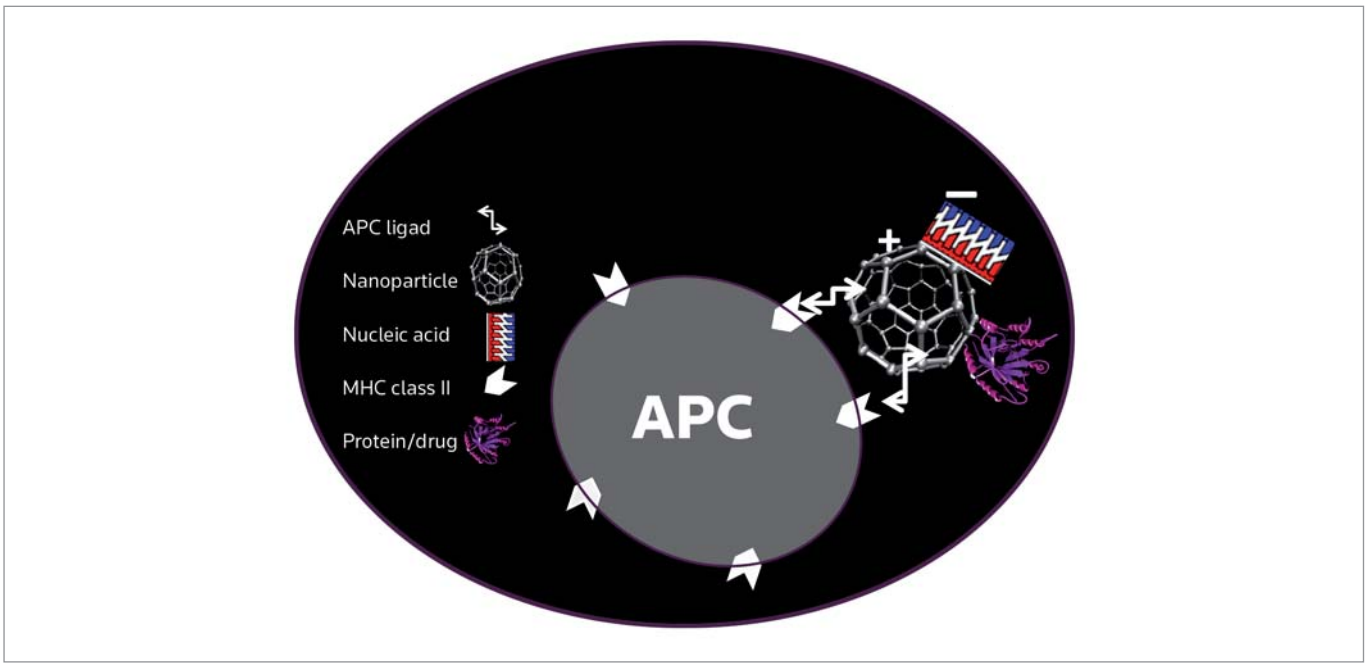

Figure 1. Nanoparticle-based vaccine.

form are efficiently shuttled/transfected into murine, rat, non-human primate and human APCs, making the platform a good candidate for translation to human trials. Parts of extensive tests of PDD in vitro and in vivo were recently published, and demonstrated that PDD effectively delivered cargos to APCs and produced significant immune responses. The platform has shown unprecedented efficacy in established melanoma, as well as in mice infected with cutaneous leishmaniasis. Another ongoing study is aimed at making more robust cocaine vaccines, where the conjugation of cocaine derivatives to PDD results in a controlled nanosystem that has inherent adjuvant activity (PADRE), targets APCs and displays cocaine derivatives to APCs. Some new data were also shared on the delivery of antifungal drugs selectively into dendritic cells and macrophages to treat leishmaniasis, and obligatory intracellular pathogens of macrophages and other phagocytic cells. This approach should overcome the shortcomings of traditional vaccine strategies, and should be superior to costly and complicated personalized dendritic cell-based vaccines.

TREATING B-CELL LYMPHOMAS

Sattva S. Neelapu from the MD Anderson Cancer Center summarized clinical trials aiming to cure B-cell lymphomas, including personalized vaccines made of a patient's own tumor specimens with various adjuvants. Follicular lymphoma is the most common low-grade B-cell non-Hodgkin's lymphoma. Despite advances in therapy that usually achieve complete remission initially, most patients with advanced-stage follicular lymphoma eventually relapse and die of the disease; therefore, novel therapeutic strategies are needed to eliminate minimal residual disease. The clonal tumor immunoglobulin expressed on the surface of malignant B cells, termed idiotype (Id), has been found to be safe and immunogenic as a tumor-specific antigen for therapeutic vaccination in phase I/II trials against follicular lymphoma and other B-cell malignancies. In a recently completed randomized, double-blind, controlled, multicenter phase III clinical trial, vaccination with patient-specific tumor-derived Id protein significantly prolonged disease-free survival compared with the control group that received a non-specific immune stimulant; these were the first positive results for a phase III vaccine trial against lymphoma. However, two other phase III Id vaccine trials did not show clinical benefit; reasons for the disparate outcomes between various clinical trials need to be analyzed.

TARGETING EFGRvIII

The EGFR variant III (EGFRvIII) was reported by Albert Wong (Stanford University Medical Center) to be a major molecular target for cancer diagnosis (biomarker) and therapy. Dr. Wong's studies focused on glioblastoma multiforme, the most common and aggressive malignant primary brain tumor in humans; however, the results generated in the studies also have implications for other cancers, including lung, breast, ovarian and prostate cancer. EGFRvIII is an important and unique gene mutation in some types of tumors and could be used as the basis for a peptide vaccine as a therapeutic for brain tumors, as well as a cancer stem cell marker. EGFRvIII is frequently expressed in glioblastoma stem cells; therefore, it may be used as a biomarker of such stem cells. Since targeting brain tumor stem cells and not normal stem cells would be needed to identify specific markers, this finding has therapeutic, as well as diagnostic, applications. Patients who carry this mutation should benefit from

an immunotherapy being conducted in a clinical trial by Celldex Therapeutics, known as as rindopepimut (PF-4948568).

DISCLOSURES

The author states no conflicts of interest.

The website for this meeting can be found at http://www.gtcbio.com/component/conference/?file=home&cn=4th+Immunotherapeutics+and+Immunomonitoring+Conference&cid=52.