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Immunotherapies: cause for measured optimism

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The exciting potential that the field of immunotherapeutics offers for human health and economic reward was showcased at the first *European Therapeutic Vaccine Congress* (27–28 June 2002; London, UK). Data from 19 ongoing or recently completed Phase I–III clinical trials were presented by 11 biotechnology companies and one academic group. Conspicuous by their absence were clinical presentations from pharmaceutical companies, adding further weight to the notion that biotech is the engine of innovation driving this developing discipline. The broad application of immunotherapeutics was reflected in the disease areas covered, which included cancer, chronic infection, autoimmune diseases and inflammation. Novel indications, such as hypertension and drugs of abuse, were also presented.

Immunotherapies for cancer

The field of cancer immunotherapy has been perceived to move slowly but it is now evident that progress has accelerated. Indeed, the majority of presentations were cancer trials and many cases of reduced tumor burden and prolonged survival times were reported. These results are particularly impressive considering that treatment groups are usually in late-stage disease, refractory to conventional therapies and inevitably immunosuppressed. Guy Ely (Biomira; http://www.biomira.com) discussed the problems of assessing responses to cancer immunotherapy and stressed the need for establishing goals that focus on 'patient-first' outcomes, such as quality of life and survival time. It becomes more apparent that 'curing' cancer can not be the endpoint for most trials and that partial tumor regression, disease stabilization and prolonged survival are more realistic targets. This was highlighted by numerous clinical trials targeting mucins as tumor-associated antigens (TAAs) where doubling and tripling of median survival times was reported.

Peter Working (http://www.cellgenesys.com) presented three technologies for cancer vaccination, based on the expression of granuloctye-macrophage colony-stimulating factor (GM-CSF). Autologous or heterologous tumor cells expressing GM-CSF following transfection are used for vaccination. In a Phase I/II lung cancer trial, encouraging anti-tumor responses in patients with advanced stage disease were reported (12% complete responses and 27% stable disease, 9–16 months after treatment). Moreover, 80% of patients in stage Ib/II disease showed no evidence of disease 14 months after treatment. The possibility of side-effects as a result of vaccination against shared self-epitopes and responses to the bystander and allogeneic tumor cells were also discussed.

As the name implies, Dendreon's (http://www.dendrion.com) platform technology is based on dendritic cells (DCs), the most potent inducers of T-cell responses. An approach has been developed to pulse major histocompatibility complex (MHC) class I molecules of DCs with large peptides and proteins, which is a challenging task. In a Phase I/II prostate cancer trial, DCs were pulsed with a GM-CSF fused to a TAA and used to vaccinate patients. Reiner Laus reported impressive immune responses induced in all patients, resulting in tumor regression in 20% of subjects. These data convincingly demonstrated that targeting DCs for antigen presentation is a promising strategy for the induction of potent immune responses. In the light of the need to test vaccines in minimal disease settings, the results of Dendreon's ongoing Phase IIIb prostate cancer trial using patients in an early disease stage is greatly anticipated.

Immunotherapies for chronic infection

Michaele Buschle from Intercell (http://www.intercell.com) described a promising therapeutic vaccine candidate for hepatitis C virus (HCV) infection. This approach targets T-cell immunity by administering MHC class I and II restricted peptides with poly-arginine. Poly-arginine is non-toxic, biodegradable and non-immunogenic, and functions by mediating the charging of antigen-presenting cells (APCs) with antigen, and facilitating APC migration to lymph nodes. This approach offers advantages for production because all the vaccine components are synthetic. Whether the lack of immunogenicity of the poly-arginine impinges on its adjuvanticity remains to be seen. A vaccine comprising five conserved MHC class I and II restricted peptides has been used in a Phase I trial and, for some healthy volunteers, T-cell stimulation was similar to that observed in patients acutely infected with HCV. A Phase II trial in

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patients resistant to IFNα and ribavirin therapy will commence this year.

Joel Haynes from PowderJect (http://www.powderject.com) showed efficient delivery of DNA-loaded gold particles into the epidermis from where transfected Langerhans cells subsequently initiate T-cell responses in the draining lymph nodes. Using hepatitis B surface antigen as a model antigen, they demonstrated induction of T-cell responses and antibody levels in human volunteers. In the absence of a comparison with the classical hepatitis B vaccine, which is based on virus-like particles formed by the hepatitis B surface antigen, the potency of the immune response induced by DNA-vaccination in this case is difficult to assess.

The success of prime-boost strategies in primates has propelled several HIV vaccine candidates into clinical trials. Andrew McMichael from the University of Oxford (http://www.oxford.ac.uk) and Oxxon Pharmaccines (http://www.oxxonpharmaccines.com) reported a clinical trial of a DNA vaccine designed for both prophylactic and therapeutic use. This vaccine is based on HIV A clade gag and comprises linked p24, p17 and p25 epitope sequences; it is delivered via a plasmid, then a year later via modified vaccinia virus Ankara. Unpublished data have shown strong CD8 and CD4 T-cell responses in all volunteers. Therapeutic vaccination focuses on the premise that CD8 T cells have a major role in controlling infection and a new application of this focuses on the treatment of patients undergoing highly active antiretroviral therapy (HAART). During HAART there is a decline in the CD8 response so that when the patient discontinues treatment the existing CD8 levels are insufficient to control virus and a rebound occurs. Hence, many vaccine trials that are designed to boost declining T-cell responses in HAART patients, and thereby prevent viral rebound, are currently under way.

Autoimmunity, inflammation and allergy

Anders Essen-Moller (Diamyd; http://www.diamyd.com) presented a vaccination strategy against type I diabetes. The aim is to induce an immune response against a glutamic acid decarboxylase (GAD) thought to be recognized by self-specific lymphocytes in auto-immune type I diabetes. The difference between 'protective' anti-inflammatory immune responses and 'destructive' immune responses is poorly understood. Therefore, despite extensive safety testing in animal models and a Phase I clinical trail demonstrating tolerability, a note of caution should be maintained.

Alk-Abello's (http://www.alk-abello.com) favored strategy for allergen-targeting immunotherapies is the induction of specific IgG responses based on the premise that protection from allergy correlates with competitive IgG levels, rather than T cells. Furthermore, negative regulation of FcεRI signaling by FcγRII costimulation in human blood basophils is an additional mechanism, which could potentiate the protective effect of allergen specific IgG. Lars Jacobsen highlighted the complexities of manufacturing immunotherapeutic allergens that meet modern pharmacological standards. Difficulties include country-specific regulations, product standards and manufacturing. It was argued that an effective allergy vaccine should include all naturally occurring antigens. For the vaccine itself to be non-anaphylactogenic, the company is pursuing a challenging scheme to engineer recombinant allergens that induce IgG responses but that do not bind IgE.

Anand Gautum described Pharmexa's (http://www.pharmexa.com) technology for inducing cytotoxic T lymphocyte (CTL) responses and/or high titre antibodies with either DNA or protein-based vaccines, respectively. In both cases, a foreign T-helper cell epitope is inserted into a permissible site within the target antigen, thereby attempting to overcome T-cell tolerance. Phase I/II clinical trials are ongoing with both technologies targeting HER-2 and TNFα. Although passive antibody therapies directed against TNFα have proven highly successful, frequent infusion of 100 mg quantities is required and allotypic responses might occur. Active vaccination to induce neutralizing antibodies against self molecules and to ameliorate disease has the potential to overcome many of the drawbacks of monoclonal antibody therapy. Key questions to be addressed are safety and the maintenance of efficacious antibody titres with human compatible antigens. Some encouraging preliminary safety data in animals demonstrated no reinforcement of anti-TNFα antibodies by endogenous TNFα.

Other indications

A Phase I trial (Protherics; http://www.protherics.com) of a vaccine to treat hypertension demonstrated no side-effects and reduced blood pressure in volunteers on a low salt diet. The vaccine comprises the peptide-hormone precursor angiotensin I cross-linked to keyhole limpet hemocyanin administered subcutaneously in alhydrogel. Safety remains a primary concern and it will be essential to induce strong antibody responses in the host in the absence of potential inflammatory T cells. Reversibility of the antibody response is another concern. J.F. Glover pointed out that less reversibility could be useful because their regimens seem to require frequent boosting to maintain high antibody titres. Early results from a Phase IIa trial were promising and showed an antibody half-life of 85 days, with titres persisting for six months. Blood pressure data was not reported and could be complicated by the number of patients (17) used in the trial.

Xenova (http://www.xenova.co.uk) and Nabi (http://www.nabi.com) are developing B cell vaccines against cocaine

and nicotine addiction with therapies based on 'removing the addictive kick'. High levels of anti-drug antibodies would sequester the drug and blunt the peak levels in the brain. Preclinical data demonstrated good antidrug titres and efficacy in models of dependency. However, John St Clair Roberts (Xenova) reported difficulties in attaining long-lived, high-titre anticocaine antibody responses in a Phase IIa trial. If supplemented with psychological counseling, drug-vaccination could be the therapy of the future for substance abuse.

Communication and terminology

Alistair Nunn (Bioscience Communications; http://www.biosciencecommunications.com) addressed the need to deliver concise coordinated messages to markets, investors, regulatory authorities, patient advocacy groups and governments. It is essential to realistically manage the expectations created by our technologies and vital to initiate the lead and adopt the high-ground when it comes to dealing with negative issues.

The theme of communication was extended to discuss the nomenclature used in the concept of therapeutic vaccination. The debate centered on the idea that the word 'vaccine' carries with it many preconceived notions, and these might not always be beneficial to this emerging biotechnology sector. Modern prophylactic vaccines aim to be without side effects and have efficacy rates close to 100%, levels that are unachievable and not expected for therapeutic vaccines. Indeed, therapeutic T-cell vaccines might be associated with side effects. Rigid, orthodox views on regulatory issues and drug pricing are not desirable to this new class of drug. Moreover, there exists an active and irrational anti-vaccine lobby, the attention of which we could well do without*.

Summary

The concept of immunotherapy still has many hurdles to overcome. These not only include biological and technical ones but also economic downturns and the inevitable failures in clinical trials that have negative impacts on the entire industry. However, there is reason for great optimism as shown by the increasing number of innovative approaches yielding promising results. This meeting revealed the tip of the iceberg and those faced with the challenges of this burgeoning field are keenly anticipating the results that will come in the next five years. If these approaches deliver just a fraction of their potential, the gains for human health will be more than worth the effort and the industry will fly high.

*An initiative was put forward at the meeting to form a working group to address the issue of terminology and nomenclature. Those interested in contributing to the initiative should contact John Lyttle at PowderJect (John.Lyttle@powderject.com).