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Immunotherapy

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Conference Scene - Active immunotherapeutics forum: meeting highlights

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Sections: Choose

The Active Immunotherapy Forum is a new event, a milestone in the field of therapeutic vaccines that, from now on, we should call active immunotherapy.

The Active Immunotherapy Forum was co-organized with the Vaccine Forum in Barcelona and attracted 250 attendees, mainly from the biotech and pharma companies, who are actively involved in the development of such products. The recent boom in immunology and vaccinology research facilitated the growth of the active immunotherapy space with several novel biologic products. These medicines are expected to reach the market in the next 5-10 years especially for the treatment of cancer and infectious diseases. The field can be characterized with expectation for novel medicinal products and with excitement for new developments. Recently, several pharmas expanded from drug to biologic product development, including active immunotherapy. During the presentations Pfizer clearly stated its intention to become the key pharma player in the active immunotherapy field that is presently filled with a few small- and medium-size biotech companies having no product on the market. This superb organized forum not only provided an update on the development of upcoming product candidates, but also extensive discussions on the challenges in this field, including optimization of preclinical research and development, biomarker development, regulatory affairs and clinical trial design. Barcelona was beautiful in June with great food and wine and the attendees had plenty of opportunity for socializing, partnering and networking.

Active immunotherapy for cancer

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Christoph Huber (Emeritus Johannes Gutenberg University, Mainz, Germany) started the **meeting** reviewing the skepticism and the promises on cancer vaccines. The number of clinical trials with cancer vaccines has reached 60 studies per year mainly on the treatment of melanoma, prostate, cervix, breast and lung cancer. A total of 34% of the trials are using peptides or proteins as antigens and another 34% are cellular vaccines. Therapeutic responses with active immunotherapy differ to what we have observed with chemotherapy: a vaccine has a slow effect leading to stabilization rather than disease elimination. Vaccinations are frequently accompanied by antigen-specific immune responses and do not require the application of maximum tolerated doses. Until last year, skepticism towards the therapeutic efficacy of cancer vaccines dominated the expert opinion. The turning point was this year with the demonstration in Phase III placebo-controlled clinical trials of cancer vaccine-induced survival benefits in three different advanced malignant diseases: prostate cancer treated with autologous antigen-presenting cells (APCs) loaded with rhPAP/GM-CSF [1]; follicle lymphoma treated with keyhole limpet hemocyanin (KLH)/GM-CSF [2]; and melanoma treated with GP100:209-217/HD/IL2 [3]. These trials demonstrated that in addition to their effectiveness, antigen-driven active immunotherapies have a favorable toxicity profile. These were compelling enough in 2009 to attract pharmas to this neglected field.

Helen Sabzevari (EDM Serono, Geneva, Switzerland) discussed her company's combination immunotherapy strategy. Since the immune system represents the first line of defense against tumors, they believe that active immunotherapy will be the key to transform a lethal disease to a chronic disease. To develop a safe and effective cancer treatment, they first want to generate a robust immune response with a cancer vaccine then target the tumor microenvironment and minimize immune suppression. Since cancer cells have multiple mechanisms to escape, combination of immunotherapy with chemotherapy, radiation therapy or targeted tumor therapy should be administered to overcome resistance. Their lead product, Stimuvax[®], is a liposomal MUC1 antigen containing vaccine (BLP25) developed for the treatment of non-small-cell lung carcinoma. In the clinic, Stimuvax safety and efficacy (survival end point) was investigated in combination with chemotherapy and radiation therapy. Sabzevari discussed the importance of inducing (e.g., vaccination every 7 days) and to maintaining (e.g., vaccination monthly) a pool of long-lived antigen-specific T cells (memory T cells) that have the ability to kill tumor cells. Even if the initial immunotherapy fails to kill tumor cells, additional chemotherapy or radiation therapy that destroy the tumor environment can help to activate the vaccine-induced memory T cells and induce tumor killing. Active immunotherapy against lung cancer is expected to be a chronic life-long treatment (e.g., monthly vaccination) to be administered in combination with radiation and/or chemotherapy.

Nicole Provost (Dendreon, Seattle, USA) gave an overview on the development of Provenge[®] (Sipuleucel-T), the company lead active immunotherapeutic product for prostate cancer. Sipuleucel-T is an autologous cellular therapy: at day 0 patients undergo leukapheresis at a clinical site in the USA and the specimen is shipped to Dendreon's manufacturing center where the cells are purified and treated with antigen. After extensive quality control, the cellular product is shipped back to the clinical site where the cells are infused back into the patients. The antigen, used for the priming of the cells, is a fusion protein of prostate acid phosphatase and GM-CSF. The company faced plenty of challenges during product development, including the development of a potency assay. After several years of hard work, they found that CD54 expression on the surface of the large APCs together with the number of CD54^{high} cells correlate with the biological activity of Sipuleucel-T. Now, Sipuleucel-T product release is based on potency (CD54 upregulation on APCs and CD54⁺ APC counts), total nucleated cell counts, identity, viability and sterility.

Dendreon began clinical development with noncontrolled trials and demonstrated safety and immunogenicity after three infusions. Two Phase III clinical trials resulted significant 4.5 months average survival benefits after 36 months in Sipuleucel-T-treated patients compared with placebo. The company submitted the biologics licence application to the US FDA and all of us hope for approval. Sipuleucel-T might become the first product that induces new immune responses in cancer patients with pre-existing immune responses against a self-antigen and has the potential to create a new treatment paradigm in the oncology field.

Optimizing preclinical research & development to increase success in the clinic

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Heather L Davis (Pfizer) gave an introduction of the active immunotherapy strategy of Pfizer. It was a clear demonstration

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that this large pharma intends to take leadership in both the vaccine and the active immunotherapy fields. Pfizer has already established in-house antigen discovery and adjuvant working groups. Davis showed impressive results on their complex testing system of combinations of model antigens and adjuvants. This preclinical test system will provide a rational strategy for selecting the best adjuvant matching with the antigen. Pfizer did not disclose any therapeutic targets and we were left excited to learn more regarding their product-development strategy. However, my impression was that Pfizer is looking for one or more novel strategies to obtain safe and efficacious therapeutic vaccine products and to establish a new market. Therapeutic vaccines will be products defined as 'first in class' because of their novel targets or new mechanisms of action or both. Davis disclosed some of their innovative ideas of how their development of vaccine and immunotherapeutic products will be different from the presently accepted drug development protocols. Davis defined that the safety of therapeutic vaccines is different from prophylactic vaccines or drugs: it is important that the product adverse event profile is acceptable for the target population. For example, it should be carefully evaluated whether induction of autoimmunity for a vaccine indicated for the treatment of oncology patients can be acceptable or not, especially if this adverse events is associated with efficacy. Efficacy also needs to be redefined because it was clear from the presentations and discussions at the conference that the accepted clinical end points may be not the best for novel vaccines. For example, it seems that the immune responses and drugs not only have different mechanisms of action, but also different speeds of action. Efficacy of drugs is generally measured in weeks or months. By contrast, the efficacy of immune responses might be measured in months or years. Immune system efficacy might require the measurement of cumulative long-term effects, for example, survival benefits. I believe that the stakeholders of this space should work together to define new clinical end points to facilitate the development and approval of active immunotherapeutic products.

Deirdre McIntosh (ERA Consulting, London, UK) discussed the European requirement for the 'first-in-man' clinical trials with immunotherapy products. Advances in immunotherapy have led to the generation of novel but potentially 'high-risk' products for human use. First-in-man trials are the most critical ones in terms of safety as they are based on data extrapolated from animal and *in vitro* testing for substances with an unknown action in humans. McIntosh emphasized the outcome of the investigation on the disaster of the trial with TGN1412 in March 2006 and how the EMEA revised the regulations of 'high-risk' medicinal products. TGN1412 was a monoclonal antibody developed to treat leukemia and autoimmune diseases. The first-in-man trial in six healthy volunteers resulted in a cytokine-release syndrome with multiorgan failure. This syndrome did not occur in the cynomolgus monkeys, the animal model used to select the first human dose; therefore, the preclinical development did not predict a safe initial human dose. An Expert Scientific Group (ESG) was set up following this disaster to review what could be learned from the trial and make future recommendations to increase safety. Therefore, after 2006, the European agency requires, in addition to the previous package:

- Interpretation of nonclinical studies
- Use of human *in vitro* studies
- Selection of microdosing as starting dose
- Dosing intervals between subjects
- Preparation for adverse effects

'High-risk' medicinal products were defined as:

- Biological molecules with a novel mechanism of action
- New agents with a highly species-specific action
- New drugs directed towards immune system targets

In particular, for agents targeting the immune system, potential unintended effects should be investigated with human material. ICH M3 Guidance on Non Clinical Safety Studies for the Conduct of Pharmaceuticals will be finalized in June 2009.

Adjuvants: the next-generation platforms in vaccine development

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Martin Friede (WHO) gave a provocative introduction. He posed the question of how the ideal vaccine or active immunotherapy development should be and how it compares with the present practice. Ideally, we should select a disease target and establish the target immune response that needs to be elicited to combat the disease. Then we should select an adjuvant known to develop the target immune response and then go ahead with the development of a vaccine with either prophylactic or therapeutic indications. However, rational selection of an adjuvant is rarely possible because of intellectual property, safety, manufacturing, stability and compatibility issues.

Derek O'Hagan (Novartis) introduced Novartis' adjuvant strategy. The company has a commitment to the development of prophylactic vaccines, but it was unclear whether they plan venture to the therapeutic area. The company view was that new-generation vaccines would comprise of recombinant proteins formulated with novel adjuvants. Second-generation adjuvant formulations include more than one component, but there are concerns whether these adjuvants can be safely used in a diverse human population. It is expected that in the next few years, several new adjuvants will obtain licensure. Agencies require sponsors to understand the mechanism of action of these new adjuvants *in vivo* and define their physicochemical properties. MF59 is Novartis' lead adjuvant consisting of squalene obtained from shark liver and an emulsifying agent. MF59 is approved in several Novartis' vaccines and has a favorable safety database including over 33,000 subjects. Novartis has put effort into understanding its mechanism of action: it was a surprise that MF59 does not activate dendritic cells, but instead induces transcription of genes at the injection site. It induces certain chemokines that attract macrophages, monocytes and granulocytes to the injection site to generate a local immunostimulatory environment. MF59 is generally more potent than alum. Novartis second-generation adjuvant is a combination adjuvant of MF59 and CpG (TLR9 agonist). In mice, this combination can redirect Th2 type responses to Th1 type. Novartis also established an adjuvant discovery platform with high-throughput, screening of small-molecule immune potentiators (SMIPs). They want to develop synthetic adjuvants with a well-defined chemical structure and take advantage of more than 10 years of drug-development expertise to establish the safety profile of SMIPs. The objective of Novartis is to develop synthetic vaccines similar to the traditional vaccines: size is important (they believe that it should be ~1 micron) and O'Hagan exemplified the new synthetic vaccine as a 1 µm poly(lactide-co-glycolide) microparticle with SMIP and antigens.

Eszter Nagy (Intercell, Vienna, Austria) demonstrated the progress on the Company's lead adjuvant IC31. It consists of two synthetic components: a positively charged peptide (KLK) and a single-stranded oligonucleotide (ODN1a). IC31 activates dendritic cells, enhances antigen delivery and supports the induction of Th1-type immune responses. IC31 adjuvant has been tested in preclinical models and human subject (intramuscularly). The other adjuvant technology of Intercell that was acquired together with Iomai Corporation is a patch-based system. The vaccine is formulated into the patch and applied to the skin. The resolubilization takes place on the skin. The patch has been investigated in the clinic against *Escherichia coli*, a bacterial diarrhea-causing pathogen. These bacteria secrete a toxin, a dried form of which was used within the patch. The toxin both serves as antigen and adjuvant. A Phase II trial demonstrated antibody induction against the toxin and a decrease of diarrheas. The company is in the process of industrializing the manufacturing processes to begin Phase III trials for traveler's diarrhea indication.

Active immunotherapy for HIV disease

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One promising and attractive alternative strategy to HIV vaccine is a therapeutic vaccine for HIV/AIDS. During the past decades, HIV vaccine development was focused on the prophylactic vaccines for two main reasons: key opinion leaders believed that it is easier and faster to develop vaccines that induce a protective immune response in healthy people. Even when it turned out that a prophylactic vaccine might not completely protect against infection, the herd effect was taken into consideration, especially in impacting survival. Consequently, most of the funding was directed to research, product and clinical development for prophylactic HIV vaccines, especially to candidates based on proteins with adjuvants and adenovirus

vectors. The field suffered from several efficacy trials failures. First, we learned that a recombinant envelope protein vaccine increased HIV-specific antibodies but failed to show protection. Recently, recombinant adenovirus vaccine showed induction of potent and functional HIV-specific T cells, but these immune responses did not confer protection, instead more people in the vaccinated group became infected. HIV vaccine research moved from antibodies to T cells and is now moving back to antibodies and to basic research. At the conference, we felt that a balanced scientific, preclinical and clinical strategy with financial support for development of not only the prophylactic but also the therapeutic vaccine would be the best way to proceed.

Genetic Immunity's (Budapest, Hungary) lead product, DermaVir Patch, developed for HIV treatment, is based on the observation that during primary HIV infection, induction of a therapeutically effective immune response is feasible. We have developed three platform technologies to induce long-lasting immune responses to delay or reverse disease progression. Our ATIGENeering team designed a single plasmid DNA that expresses nine HIV antigens capable of forming a virus-like particle. This DNA is condensed to a pathogen-like nanoparticle to target and express the DNA-encoded antigens in dendritic cells. The nanomedicine (DermaVir) is transdermally administered with our novel DermaPrep device that *in vivo* targets the nanomedicine to the lymph node dendritic cells. This is the organ where dendritic cells expressing antigens initiate immune responses. The mechanism of action of DermaVir Patch immunization was demonstrated in mice and monkeys. Preclinical proof-of-concept experiments on SIV-infected macaques showed potent induction of memory T-cell responses and a significant reduction of viral load and increase in survival. A Phase I proof-of-concept clinical study also demonstrated dose-dependent induction of long-lasting memory T cells in all the immunized HIV⁺ patients. The product safety profile is excellent, the major side-effect observed was transient erythema. The safety, immunogenicity and preliminary efficacy of DermaVir Patch immunotherapeutic nanomedicine is presently being investigated in Phase II clinical trials in different HIV⁺ patient population in the USA, Germany and Italy.

Giuseppe Pantaleo (University of Lausanne, Switzerland) discussed the perspectives of immunotherapy in HIV infection. Pantaleo transmitted optimism in this field despite, the first generation of products were not investigated properly. Neither the target patient population nor the number of patients was adequate to show therapeutic efficacy. He pointed out the limitations of several product candidates: high dose and high manufacturing cost. Then Pantaleo reported on Gene Transport Unit (GTU[®]) technology application for immune therapy, a work supported by FIT Biotech, Finland. GTU is a vector that allows for multiple copies of a plasmid to efficiently spread into dividing cells. A protein of the bovine papillomavirus supports the segregation of plasmid DNA. The gene expression, when compared with conventional vectors, could be up to 100-times higher, therefore GTU technology permits significantly longer gene expression. FIT GTU-HIV vaccine is a DNA expressing a codon-optimized fusion protein originating from six HIV genes. This HIV immunotherapy (three primes and two boosts) was investigated in South Africa in a placebo-controlled trial in HIV⁺ patients who never received antiretroviral drug therapy. Intramuscular administration of 1 mg DNA of GTU-HIV vaccine via biojector resulted in a statistically significant 0.47-log reduction of viral load and a 72-increase in CD4 counts. Intradermal administration resulted in a 0.16-log viral load reduction and 18-increase of CD4 counts (not statistically significant).

Financial trends in the vaccine & immunotherapy fields

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Steve Chatfield (Health Protection Agency, UK) moderated this exciting section. Vaccine development is becoming a more attractive investment:

- Vaccine market is growing from US\$8.6 billion to 27.9 billion (2015);
- Vaccines will be not limited to prophylactic indication; therapeutic vaccines for oncology, infectious diseases, CNS and allergies will enter to the market;
- Large pharmas are entering the space and this creates opportunities for biotech and venture capitalist;
- Developing countries will grow, creating a huge market opportunity.

These days, it is very difficult to raise venture capital (VC) funding for vaccine development: for financing of vaccine development VCs want proof-of-concept (preferable in humans), management, strong IP protection and scientific credibility. Since initial public offering is not an option these days for VC exit, selling the IP or the company to pharmas that want to complete the pipeline remains the only exit strategy for VC. If the exit strategy is trade-sale, the biotech company should avoid having multiple partnership with pharmas. If the exit strategy is initial public offering multiple partnerships becomes an advantage. Despite all of the advances in the vaccine space, most VCs do not look for investment in companies developing vaccines and immunotherapies. However, successful announcements, such as the Dedreon's Phase III trial, are expected to change this phenomenon. At present, until the end of Phase II development, vaccine companies must look for government funding, especially these days when VCs are not taking new investments.

Jeff Southerton (Pfizer) explained that the company's deal-making strategy with academic institutes, biotech and pharma ranges from collaborations to identification or validation of new pharmaceutical targets, license agreements to access novel technologies or products, acquisition of entire companies or their assets. Pfizer seeks to extend and build upon its current capabilities in the biotherapeutic and vaccine space. Pfizer recognized that opportunities in the vaccine field are much larger than the conventional prophylactic vaccine business. Immune-based interventions are not limited to the infectious disease space but will extend in multiple therapeutic areas, including allergy, respiratory, oncology and CNS. Pfizer intends to create a balanced portfolio of therapeutic and prophylactic vaccines in multiple therapeutic areas. The reason for this shift is that the vaccine market is expected to grow rapidly. Shifts from old to new technologies will move the field beyond prevention of infectious diseases. Novel immune-based treatment approaches are already close to the market, especially in the oncology field. Pfizer expects that for 2015, the world vaccine revenue will be (US\$ billions): 11.2 pediatric; 3.7 influenza; 3.8 hepatitis virus; 5.5 therapeutic oncology; and 3.7 others.

Financial & competing interests disclosure

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Bibliography

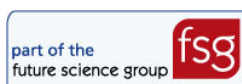
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- 1 . Malcolmf JB, Barone B, Given RW, Fabrizio MD, Schellhammer PF: Prospective longitudinal comparison of quality of life outcomes following treatment of localized prostate cancer. AUA April 2009 www.aaupub.org/abstracts/2009/236.pdf
- 2 . Schuster SJ, Neelapu SS, Gause BL *et al.*: Idiotype vaccine therapy (BiovaxID) in follicular lymphoma in first complete remission: Phase III clinical trial results. 2009 ASCO Annual Meeting Proceedings. *J. Clin. Oncol.* <http://meeting.ascopubs.org/cgi/content/abstract/27/15S/2?maxtoShow=&HITS=20&hits=20&RESULTFORMAT=&fulltext=schuster&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT>
- 3 . Schwartzentruber DJ, Lawson D, Richards J *et al.*: A Phase III multi-institutional randomized study of immunization with the gp100: 209-217(210M) peptide followed by high-dose IL-2 compared with high-dose IL-2 alone in patients with metastatic melanoma 2009 ASCO Annual Meeting Proceedings *J. Clin. Oncol.* <http://meeting.ascopubs.org/cgi/content/abstract/27/18S/CRA9011>

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