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Days of Molecular Medicine '03

In the 200 years since Edward Jenner established a vaccine strategy to induce immunity to smallpox, the field of immunotherapy has become a respected route to effect the treatment of cancer, autoimmunity and infectious disease. In an effort to gauge the current state of affairs in this field, *Nature Medicine*, in conjunction with the University of California, San Diego Institute of Molecular Medicine (IMM) and the Salk Institute, cosponsored the Days of Molecular Medicine 2003 meeting on 'Immunotherapy: A Technology Platform for Molecular Medicine' in La Jolla, California.

We brought together leading experts from academia and industry to discuss recent advances and obstacles in immunotherapy. Topics spanned a diversity of approaches in preclinical settings and human studies, including cell-based strategies, antibody-mediated approaches, targeting of cytokines and their receptors or co-stimulatory pathways, and an array of DNA, RNA and peptide strategies. The range of disease indications included cancer, autoimmune disorders, graft rejection and graft-versus-host disease, as well as atherogenesis and infectious disease. The intersection of academia and industry and current efforts to improve upon existing relationships were also debated (see News, page 379).

The goal of immunotherapy is to modulate immune responses to ameliorate disease. But, as succinctly put by Thomas Waldmann in his keynote address, although active immunotherapy is effective at preventing recurrent disease in humans in the context of an acute self-limiting infection, significant hurdles remain for chronic disease, cancer and transplantation.

Nevertheless, some clinical success has been achieved. To date, the US Food and Drug Administration has approved 11 monoclonal antibodies. Ron Levy told of the generation of anti-idiotype antibodies (tailor-made therapies for individual cancers) and the subsequent development of rituximab, a more generally applicable antibody approach to treating $CD20^+$ B-cell lymphomas. In the area of cell-based strategies, Megan Sykes discussed the use of non-myeloablative conditioning and hematopoietic stem cell transfer to treat patients with hematopoietic malignancies without inducing graft-versus-host disease. Marc Feldmann presented the rationale for targeting tumor necrosis factor (TNF) to treat rheumatoid arthritis.

Refreshingly, we learned that success in the clinic does not abrogate interest in improving accepted therapies to further reduce side effects, increase targeting specificity or expand the candidate patient population. This was evident in talks by both Waldmann and Nabil Hanna on new biotin-streptavidin strategies to increase the efficacy of CD20-specific antibody targeted to tumor tissue. Similarly, Mark Sliwkowski presented efforts to develop a new antibody specific for HER-2 (also known as Neu or ErbB2) to treat breast cancers expressing low levels of HER-2.

The field is, of course, not without its setbacks, and the recent HIV vaccine trial by VaxGen is not an isolated instance of the difficulties of immunotherapy (see News, page 376). Anti-TNF therapies inhibit both pro- and anti-inflammatory responses and are associated with increased frequency of lymphoma and reactivation of tuberculosis. Likewise, treatment of breast cancer with the monoclonal antibody Herceptin is limited to tumors with high HER-2 expression and is associated with cardiotoxicity. Induction of solid graft tolerance requires an immunosuppressive regimen. Radionuclide-coupled antibodies have poor tissue penetration and may damage healthy tissue. HIV vaccine strategies have yet to demonstrate efficacious induction of both a neutralizing antibody response and cell-mediated immunity, as well as eradication of the latent viral reservoir.

Despite these cautionary notes, the mood at the symposium was very positive and the excitement that surrounds these researchers is a clear indication that immunotherapy is a vibrant field with an exciting future.

Current strategies in various stages of testing include tolerance-induction regimens for solid organ transplantation, use of antigen-specific T-cell clones and targeting of activated dendritic cells to secondary lymphoid organs (considered to be a central goal of active immunotherapy for cancer treatment). Not all fields are poised for the introduction of new immunotherapeutic strategies, however. As suggested by Peter Libby for the field of atherogenesis, and echoed by Mario Stevenson on the therapeutic application of RNA interference, a better fundamental understanding of the biology is still required before we can entertain its clinical application.

Modulating the activating arm of the immune system alone is not likely to be sufficient to induce long-lasting efficacy of treatment; targeting inhibitory signals will also prove crucial for successful immunotherapy. In particular, efforts must be directed at the inhibitory signals transduced by negative regulators of the co-stimulatory family of molecules; Cbl-b, a negative regulator of T-cell receptor signaling; the inhibitory Fc-γRIIB receptor that may dampen the effects of therapeutic antibodies; and regulatory T cells. Factoring these variables into therapeutic strategies may increase the likelihood of successful treatment of chronic disease without inducing autoimmunity or increasing susceptibility to infection.

We continue this exciting series of symposia next year in Cambridge, UK. In collaboration with IMM and the Wellcome Trust, we will present a meeting devoted to the interplay of neurohormonal and metabolic pathways in human disease. We hope you will join us for a penetrating look at integrative physiology and its implications for disease.