Dendritic cells reach out to the clinic

Named for their morphological characteristics, dendritic cells of the immune system have become a hot area of research among clinical scientists. With new advances in the isolation and purification of these cells, dendritic cells are actively being studied as to their ability to initiate an immune response by presenting antigen in the context of the major histocompatibility complex (MHC) and priming specific resting T cells to that antigen. And, not surprisingly, several biotechnology companies are looking to harness that ability toward commercial ends.

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During last December's annual meeting of the American Society for Hematology in Orlando, Florida, there were a large number of papers describing the use of dendritic cells for antitumor and infectious disease immunotherapy. Since dendritic cells are very potent antigen-presenting cells (APCs), but are difficult to concentrate in large numbers from various tissues, the majority of the current research has focused on *in vivo* and *in vitro* expansion of stem cells by using hematopoietic growth factors such as granulocyte macrophage colony-stimulating factor (GM-CSF) and the Flt-3 ligand (FL).

Using a mouse tumor model, David H. Lynch and colleagues at Immunex Corp. (Seattle, WA) reported that daily subcutaneous injections with FL for 19 days resulted in tumor regression of implanted fibrosarcomas in mice. Seventy percent of the challenged mice demonstrated tumor regression, and of these, 38 percent had complete regression of the tumor. Lynch noted that tumor regression in his experiments was correlated with *in vivo* expansion of dendritic cell population through FL pretreatment. The researchers also noted that tumor regression only occurred in animals with an intact immune system, and appeared to be specifically mediated by $CD8^+$ T cells.

Volker Reichardt and his colleagues at the Stanford University Medical Center reported a novel approach of using dendritic cells as a vaccine in treating four patients with multiple myelomas. Three months after high-dose chemotherapy and peripheral blood stem cell transplantation, the patients were vaccinated with autologous dendritic cells that had been antigen-pulsed *ex vivo* with immunoglobulin proteins produced by the myeloma specific for each individual patient (idiotypic Ig). Using a buoyant density separation device developed by Activated Cell Therapy, Inc (Mountain View, CA), the Stanford group were able to isolate enough dendritic cells from the peripheral blood to generate cytotoxic T cells to the idiotype protein from autologous serum using an *in vitro* assay. Since the proteins and cells are from the same patient, the paper drew speculation that *ex vivo* antigen-pulsing induced a maturation process that allowed the dendritic cells to present antigen to specific resting T cells. The goal of the group is to follow the patients to determine the level of minimal residual disease following dendritic cell vaccination.

It now appears that both Immunex and Activated Cell Therapy (ACT) are pursuing the commercial use of dendritic cells as an immunotherapy to treat cancer and infectious diseases. Immunex is using Flt-3 ligand as an adjuvant to expand the *in vivo* cell population, whereas ACT is using an *ex vivo* antigen-pulsed therapeutic regimen to treat diseases. ACT is currently testing their approach in patients with B-cell lymphomas and this month have initiated clinical studies to vaccinate patients with prostate cancer using a recombinant prostrate-specific antigen. It will be interesting to see in the future whether dendritic cells will extend into the armamentarium of clinicians.

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Addressing aboriginal health

A new Cooperative Research Centre (CRC) for Aboriginal and Tropical Health is to be established at the Northern Territory University. The new institution is one of six new CRCs announced last December, and will be headquartered at the Menzies School of Health Research in Darwin.

According to John Mathews, director of Menzies and interim director of the new CRC, "health in northern and central Australia continues to suffer because of its tropical environment and frontier lifestyle, because of the social disadvantage of the Aboriginal population, because health consumers and some of the health work force are inadequately informed or resourced, because of divided responsibility and poorly informed administration, and because of the high cost of delivering complex services over long distances to a sparse population."

One major health problem is infectious disease, the result of overcrowding and poor living conditions, according to Mathews. Studies of the Nguiu community by a Menzies team has found 20 different serotypes of *Pneumococcus* and 50 different strains of non-typable *Haemophilus* to be endemic in children, who are infected soon after birth. Multiple strains of group A *Streptococci* have also been found to infect between 10 and 50 percent of children in most rural communities, causing skin sores and rheumatic fever. Diabetes and kidney and heart disease are also major health problems in the Territory.

The new CRC was set up to address these problems and to develop means of overcoming the cross-cultural communication problems that presently hamper the delivery of effective health-care services to Aboriginal communities. Rural Aborigines generally mistrust western medicine, regarding hospitals as places where people die.

The biomedical research focus of the new CRC will initially be the molecular aspects of strain diversity in infectious agents, and to develop and test new ways to deliver health care to rural communities. Another area of investigation will be mapping genetic markers that determine susceptibility to kidney disease and diabetes mellitus.

Core participants in the new CRC include Menzies, Territory Health Services, Northern Territory University, Flinders University and the Cochran Centre, Danila Bilba Medical Services and the Central Australian Aboriginal Congress.

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