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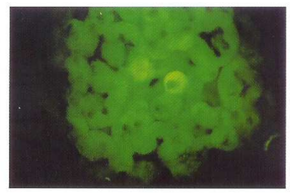
FROM ROCKET FUEL TO T-CELLS

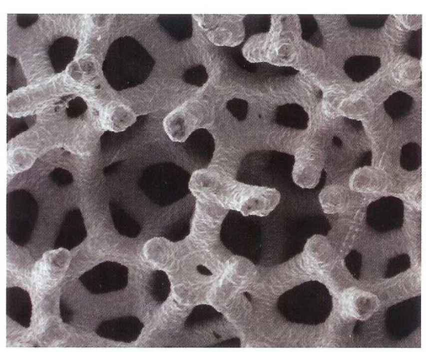
Cancer sufferers are typically faced with limited treatment options and often opt for chemotherapy in the absence of other choices. Because damage to patients' immune system is a significant side effect of chemotherapeutics, Melbourne, Australia-based CyGenics has developed an autologous stem cell therapy intended to rebuild these cancer patients' tattered immunological responses. The company recently filed an investigational new drug application (IND) with FDA for Phase I/II clinical trials in Melbourne, using T-cells produced in its T-cell growth platform to reconstitute the immune system of patients with lymphoma, leukemia, and related blood diseases. In these safety and efficacy trials, CyGenics will extract hematopoietic stem cells and skin cells (fibroblasts and epithelial cells) from approximately two dozen patients, then use those cells to grow new T-cells to be transfused back into the original patients.



Photos courtesy of CyGenics

GFP-transfected HEK 293 cells, growing in the matrix device after 8–10 days in culture.

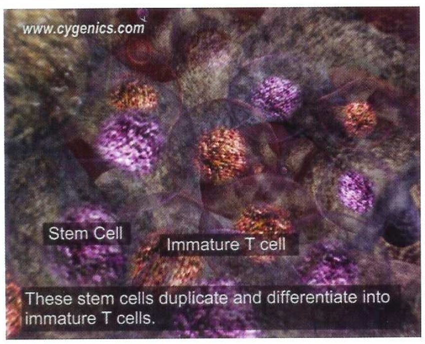
CyGenics' platform is based on a carbon–metal matrix scaffold initially developed for the aerospace industry. According to Mark Pykett, former CEO of CyGenics' subsidiary Cytomatrix, NASA commissioned the materials engineering company Ultramet to develop the matrix as a catalytic converter for rocket engine fuel combustion. Ultramet employees noticed that the matrix's microscopic interconnected struts and pores looked a lot like the natural three-dimensional structure of bone and other orthopedic implant devices, and contacted the orthopedic company Implex to see if it might in fact be a good implant. Implex performed a few animal studies in which the material, called CellFoam at the time, was implanted into cortical (hard) bone, with a small part of the matrix protruding into the medullary cavity of the bone (where bone marrow hematopoiesis occurs). After histological examination showed hematopoiesis occurring in the device — for example, growth of red blood cells, white blood cells, platelets, bone marrow trabeculae, and stromal cells — as well as cortical bone growth, Implex licensed the matrix for bone implantation. Implex (now part of Zimmer) has developed the matrix, which it now calls Trabecular Metal, for a wide variety of prosthetic bone applications.

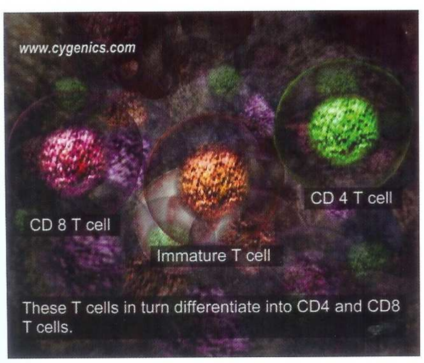


Scanning electron microscope photograph of the Cytomatrix scaffold.

"Later, when Cytomatrix came along, we thought it would be good for growing other cells as well, so we also did some pilot studies with a variety of cell types and found it worked well, so we licensed it [from an Ultramet offshoot called Tantalum Cellular products] for all other cell growth applications," says Pykett. In particular, the matrix's potential as a vehicle for *ex vivo* expansion of stem cells did not go unnoticed, and in 2003, the Singaporean cord blood bank Cordlife acquired Cytomatrix for $11 million with the goal of using the matrix to expand umbilical cord blood stem cells. CyGenics was formed in April 2004, and is comprised of Cordlife and Cytomatrix, with the Australian cell culture product company Cell Therapies Pty Ltd rounding out the trio.

Growing stem cells in a bone marrow surrogate solved a vexing problem in stem cell transplantation research: In *ex vivo* expansion of stem cells in bioreactors, augmentation with growth factors such as cytokines is typically required to spur cell division, and although large numbers of cells (40- to 50-fold increases) can be produced using this method, the cells rapidly lose much of their pluripotent potential. Because the Cytomatrix scaffold closely resembles the cells' natural environment, the cells produce extracellular matrix material as well as their own growth factors, resulting in a heterogeneous environment that can sustain stem cells for more than six months and fully retains their ability to differentiate into a wide range of tissues while multiplying up to six-fold. CyGenics' initial focus for the stem cell-loaded matrix is to rebuild T-cell responses in patients with a chemotherapy-damaged thymus.





CyGenics grows stem cells and differentiates them into functional T-cells which replace damaged T-cells.

To use the growth scaffold as an artificial thymus, CyGenics first introduces the extracted fibroblasts and epithelial cells, followed by the hematopoietic stem cells, which adhere to the skin cells. The stem cells then generate their own growth factors and proliferate while differentiating into immature T-cells. After the T-cells have undergone further differentiation into $CD8^+$, $CD4^+$, natural killer, and regulatory T-cells, they are harvested and injected back into the cancer patient that the original cells came from. The upcoming Phase I/II clinical trials are intended to show that autologous T-cells manufactured in this way can restore immune function damaged by chemotherapy. CyGenics also intends to develop T-cell production kits, comprised of matrix devices with liquid reagents, for autologous immunotherapy and license the technology to other companies.

For the upcoming trials of CyGenics' T-cell production platform, Cell Sciences will use the Cytomatrix scaffold to produce the cells at the Centre for Blood Cell Therapies at Peter MacCallum Cancer Centre in Melbourne. CyGenics intends to complete the trials by mid-2006, with Phase III trials to follow, both alone and with partners. Professor Miles Prince, chair of hematology service of the MacCallum Cancer Centre, said in a statement, "The potential of T-cell therapy to boost the immune system and reduce the risk of infections that occur following cancer treatment is enormous. The primary limitation today is that there is no simple way to produce or replace T-cells that have been damaged by the treatment given to patients. We are excited to be working on trials that may well put an end to this limitation." ■