City of Hope Brain Tumor Program

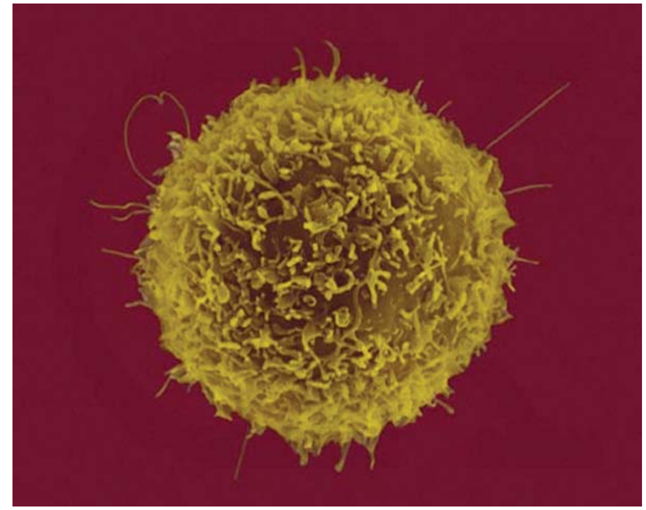
Leading a team of basic scientists, surgeons, physicians, and other health care experts, Dr. Behnam Badie, MD, Director of the Brain Tumor Program is aggressively applying City of Hope's collaborative approach for the greatest patient benefit. Rather than rely on a single methodology, Dr. Badie is bringing together the latest scientific promise from immunotherapy — where our body's immune system is strengthened to attack cancer — along with stem cell, nanotechnology, surgery and other disciplines to battle cancer. This broad collaboration is unique to City of Hope and drives new discoveries to help patients in need of cures now.

Targeting Glioblastoma Through Research

Cellular Immunotherapy: Maximizing A Patient's Immune System

The *Cellular Immunotherapy* program, led by Dr. Michael Jensen, Associate Chair, Division of Cancer Immunotherapeutics & Tumor Immunology, develops innovative treatments that reduce the need for harsh radiation and chemotherapy. Using Dr. Jensen's pioneering technology, we have been able to isolate immune T-cells from a patient's blood sample and then engineer those cells to express an artificial receptor that will seek out and attack cancer cells. In the lab, our researchers then grow billions of identical, reprogrammed T-cells and re-infuse them into the patient in the clinic, where they go to work eliminating the cancer. Under Dr. Jensen's leadership, City of Hope has conducted the first-ever FDA-authorized clinical trials using reprogrammed T-cell therapy for lymphoma, neuroblastoma and glioma.

Presently underway is the glioma study where patients are infused with engineered T-cells that respond to an antigen called *CD8*. An antigen is any foreign substance to which the body reacts by dispatching antibodies such as T-cells. These re-programmed T-cells act as homing devices to take the T-cells to the cancer. Although only glioblastoma patients were initially targeted for treatment, researchers expect to expand this therapy to other brain tumors, including childhood brainstem gliomas, medulloblastoma and neuroblastoma. As this glioma pilot study moves ahead, its results are being used to cultivate the next generation of T-cells.



T-cell lymphocyte

Generation 2 T-cells: Universal T-Cells

One prong of research seeks to formulate a T-cell that is protected from rejection by the patient's own immune system, thus becoming a potential "universal T-cell" for patients everywhere. Specifically, *Generation 2* T-cells will be programmed to be accepted without triggering a rejection reaction. By developing such a T-cell our researchers will have devised a means to mass produce T-cells from one patient on behalf of thousands more. Thus, a "universal T-cell" for all glioma patients is within reach. We anticipate that the first glioma patient to be treated with Generation 2 T-cells will be in Spring 2007 — the first in the world to be treated with this novel therapy.

Generation 3 T-cells: Stacking the Deck Against Cancer

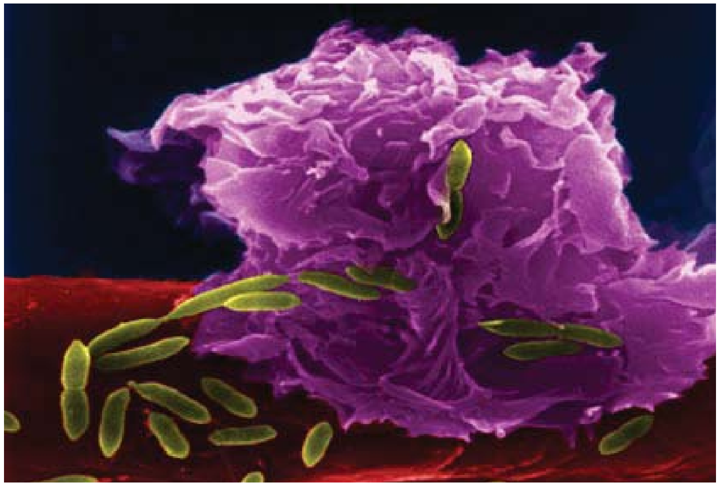
Concurrently, while the autoimmune-resistant T-cell is being developed, our researchers will adapt it to create *Generation 3* T-cells. The goal is to create the technology to enable researchers to add additional cancer-fighting therapeutic material to strengthen the T-cell's impact against cancer. Dr. John Rossi, Chairman and Professor of Molecular Biology at City of Hope, will team up with Dr. Jensen to use *interfering ribonucleaic acid* (RNAi) inside T-cells to make them even more effective cancer combatants. Current plans involve development of a drug using RNAi by January 2007 for Phase I trial.

Neural Stem Cells: One-Way Tickets to Glioblastoma

Neural stem cells selectively travel to tumor cells. Dr. Karen Aboody, MD, conducts ground-breaking research to exploit this finding, allowing her to use neural stem cells as a delivery vehicle that target tumor cells with therapeutic agents. These cells can be genetically modified to produce therapeutic gene products and effectively deliver them throughout a brain tumor mass to target and infiltrate tumor cells.

Macrophages and Microglia: Harnessing the Immune System's Clean-up Crew

Macrophages are immune cells that act as scavengers feeding upon dead cells, foreign substances, and other debris in the body. *Microglia* are macrophages specific to the central nervous system. Microglia are normally inactive but become activated in response to inflammation, infection and trauma. Once activated, they proliferate and migrate to the site of injury. Dr. Badie is researching ways to "change the microglia" and use it as a therapy for post-surgical brain tumor patients, where the re-engineered microglia delivers therapeutic agents to the tumor site. He also wishes to extend the life of T-cells using microglia and test their



Macrophage

efficacy in mouse models against cancer. This mouse study will likely garner data in a year, placing us two years away from launching a Phase I clinical trial targeting glioblastoma.

Nanotubes: Small and Lethal Envelopes Used to Kill Cancer

Carbon nanotubes are the size of a fraction of a cell. In collaboration with NASA, Dr. Badie and Mr. Kateb, Director of Research and Development of the City of Hope Brain Tumor Program, have embarked on using nanotubes to deliver chemicals and stimulants inside macrophages. These macrophages become couriers to areas of inflammation, like tumor cells, where the nanotube's deadly payload is deposited. Current efforts are geared towards developing the best nanotube prototype.

There is also a separate study underway to combine the homing characteristics of macrophages with nanotubes. Dr. Badie is developing methods of having nanotubes hold theraupeutic drugs or other healing agents, and then inserting this nanotube package into a macrophage that delivers its payload to the tumor. He is also exploring ways to have the nanotube contain products that activate the macrophage to attack the tumor directly. Current expectations are to develop a clinical trial that targets glioblastoma within two years.

Minimally Invasive Surgery: Future Generation Surgery Now

We use minimally invasive procedures which reduce trauma to the patient and assist in quicker healing. Some of the approaches being used at City of Hope include:

Stereotactic Surgery — This procedure allows neurosurgeons to target any area in the brain with sub-millimeter accuracy, and is particularly useful to perform biopsies, implant devices and remove brain metastases or other localized tumors. Stereotactic surgery involves a small incision in the body, usually performed without anesthesia. Most patients undergoing this operation leave the hospital after one or two days after surgery. When this procedure is appropriate, it provides patients with a safe, rapid and accurate means to sample or treat tumors with minimal risks.

Intra-operative Cortical Mapping — During the course of tumor removal surgery, sensitive brain areas such as those related to speech, motor or the sensory cortex centers are avoided through mapping. This surgical assistance dramatically reduces risk of neurological injury while enhancing the degree of tumor removal.

Imaged-Guided Surgical Navigation — This method relies on the patient's MRI to guide a surgeon in removing the tumor. The exacting contours of a tumor marked onto the MRI assists our surgeons in providing extremely accurate approaches to tumors located beneath the brain surface and in removing tumors that are hard to see or are located in "high-risk" sensitive brain areas. Such comprehensive and delicate procedures, combined with advanced technology serve our patients in accelerating their recovery, improving complete tumor removal, reducing neurological morbidity and shortening hospital stays.

Functional Imaging: Gauging Brain Function During Scans

One of the latest forms of imaging involve what are called functional MRIs — scans that identify specific areas in the brain that control certain functions, such as speech or movement. By identifying exactly how a person's brain cancer affects their thinking and physical functions, our surgeons can avoid damage to those brain areas when removing the tumor. Another advancement our team seeks to add involves functional imaging of blood and volume flow, where the degree of blood vessel growth or *angiogenesis* is measured. Angiogenesis is a sign of early tumor growth, recurrence and increased likelihood of distant metastases. By determining the extent of angiogenesis our doctors can gauge tumor presence sooner and treat patients as early as possible.

Next Generation Technology in Imaging

Our researchers are continually exploring the latest imaging technologies to sharpen our view of tumors, and thereby enhance our care to patients. One major effort involves the pursuit of *intra-operative tumor imaging* (IOTI). There are four technologies currently identified by our researchers as tools for future adoption:

- Ultra Violet — Jet Propulsion Laboratory developed a camera which displays the ultra-violet light (UV) characteristics of tumors. Dr. Badie and co-investigator Kateb are presently preparing a protocol in collaboration with JPL to use this novel technology in imaging glioblastoma, a first-time ever use of such sophisticated instrumentation in a clinical setting.

- Nanoparticles — Aside from their therapeutic applications, nanoparticles are also are potentially useful in imaging stem cells. Currently, Dr. Aboody has joined forces with Dr. Badie and Mr. Kateb to explore the use of nanoparticles inserted into stem cells to track their performance in a patient. These researchers believe that a MRI taken of these nanoparticles can flag where the stem cells have traveled in assessing patient clinical data. The present timeline to develop a viable nanoparticle for stem cell use is by 2008. This venture is another ground-breaking effort involving this nascent technology.

- Infrared — This form of imaging provides easier differentiation of tumor matter from healthy cells using infrared. An immediate benefit of infrared technology to our doctors in treating glioblastoma is greater precision concerning its contours apart from neighboring healthy cells.

- Optical Coherence Tomography — This is used to image the retina. Micro-ultrasound based, it is the equivalent of cutting and staining the retina, making biopsies much more targeted. Dr. Badie and Mr. Kateb are presently preparing a protocol to use this novel technology to guide brain tumor biopsies.

- Intra-operative MRI — This instrument would be performed post-surgery upon the patient while in the surgical suite. It would provide immediate feedback on the surgery's success in removing the tumor. In the future, we plan to use this technology to better direct the delivery of our cell-based therapies such as T-cell, neural stem cells and activated microglia.

The union of each of these technologies when used together will lend greater precision, certainty and information about each patient's tumor, thereby enhancing treatment and care.

Novel UV imaging technology, built in collaboration with NASA researchers and Dr. Badie's team, will provide more detail of brain cancers for better diagnosis and treatment.

City of Hope's Dedication to Advancing Better Care

Dramatic advances in treating cancer are the result of painstaking, yet urgent, scientific exploration and discovery followed by refinement through clinical research. Because we conduct more clinical studies than any other hospital of our kind in the nation, City of Hope plays a critical role in advancing medical care for patients everywhere.

The essence of City of Hope is translating biomedical research into innovative diagnosis, treatment and prevention regimens for cancer and other serious illnesses. Likewise, our Brain Tumor Program is dedicated to this model in applying multiple modalities from the surgical and immunotherapeutic fronts to conquer cancer while enhancing patient care.

Through pioneering basic and clinical research we are transforming today's technologies — and providing tomorrow's care today. Of course, to conduct this vital basic and clinical research, we continue to rely on the benevolence of generous friends. Your support of City of Hope will live on as a legacy of health and healing.

We invite you to partner with City of Hope in pursuing the research that will save the lives of people around the world.