

ALLIANCE FOR CANCER
GENE THERAPY'S MARATHON MAN:
DR. MICHAEL T. LOTZE



Dr. Michael Lotze (right) with Dr. Christoph Bergman of Essen, Germany.



At age six, Michael Lotze drew pictures of himself with a stethoscope around his neck and his mother was thrilled that young Michael would clearly follow in the footsteps of her father, Michael's grandfather, and become a valued Western Pennsylvania general practitioner.

What Michael's mother could not predict was that soon after receiving his medical degree from Northwestern University Feinberg School of Medicine within the Honors Program in Medical Education, and launching training in surgery, he traded his scalpel and stethoscope for a microscope and laboratory, beginning a journey leading to breakthrough cell and gene therapy in the fight against cancer.

BLENDING SCIENCE—MYSTERY—HOPE

Alliance for Cancer Gene Therapy (ACGT) founding Scientific Advisory Council member Dr. Michael T. Lotze is Professor of Surgery and Bioengineering; Vice Chair of Research within the Department of Surgery; Assistant Vice Chancellor Health Sciences at Pittsburgh Clinical Medicine, and Director of Strategic Partnerships within the University of Pittsburgh. He has worked in the field of Immunology and Clinical medicine for over 35 years and believes that a fundamental understanding of cancer biology and immunology is essential to making progress in Oncology. He is the co-inventor of 10 patents in dendritic cell vaccines and antigen discovery and serves as Associate Editor of the *Journal of Immunotherapy*. He has over 500 publications in peer-reviewed journals.

In tandem with all of Michael Lotze's outstanding scientific accomplishments, he has completed 60 marathons in seven countries and will compete in the New York City Marathon for the third time in 2011! How does his love for long-distance running connect with his passion for scientific cancer research? "It stimulates the mind and body, it creates a deep understanding of focus, it motivates the attainment of goals and it allows one to establish objectives that are beyond immediate reach. I have been involved in cancer research and the field of Immunotherapy for over 35 years. The challenges, mysteries, setbacks,

victories and the hope are all marathons. In scientific research you must go the distance, never half way."

ZENO'S PARADOX. THE TORTOISE AND THE HARE!

Dr. Lotze says, "Setting goals brings to mind Zeno's Paradox." Zeno's Paradoxes are a set of problems generally thought to have been devised by Zeno of Elea to support Parmenides' (*Ancient Greek Philosopher*) doctrine that all is one. That which is in locomotion must arrive at the halfway stage before it arrives at the goal. Says Lotze, "If you set your goal as successively reaching in intervals the halfway point, you will never get to the finish line! In cell and gene therapy research you must go the distance or you will be diverted time and again by Zeno's Paradox!"

THE CANCER MYSTERY "FIGHTING FIRE WITH FIRE"

Gene Therapy: Gene therapy is the replacement or modification of a defective or missing gene. One area of gene therapy is immunotherapy in which researchers genetically modify a patient's immune cells so they recognize antigens produced by cancer cells, thus destroying them and eliminating the tumor.
T-cell: A type of white blood cell that is of key importance to the immune system

and is at the core of adaptive immunity, the system that tailors the body's immune response to specific pathogens. T-cells are like soldiers who search out and destroy the targeted invaders.

"When I began my career, cancer was a great mystery. There was little or no biological understanding of the disease. The good news today is that some of that mystery has been lifted. We now know that cancer is fundamentally a disease of the genes and of cells. We have also come to understand that cancer cell and gene therapy is really about fighting fire with fire. It is about introducing through immunology, modified genes and killer cells (T-cells) that kill cancer cells!"

"The very beginning of gene therapy and the first clinical trials were cooked up by Michael Blaese and me. (*Dr. Michael Blaese was then in the Metabolism Section of the NCI and subsequently, Chief of the Clinical Gene Therapy Branch of the National Human Genome Research Institute*). Dr. Blaese had been very interested in immune deficiencies and thought that gene therapy might be a way to cure some of these disorders. Since we were already giving T-cells to cancer patients, we talked about developing a new protocol that marked the T-cells as a strategy to purposefully launch genetic manipulation of the cell, which eventually became the first gene therapy."

Injecting cells with a treated human gene at first met with extraordinary resistance. In the 1960s, the Cambridge, Massachusetts City Council actually outlawed the science at both M.I.T. and Harvard University laboratories. The modern period of cell therapy started in the 1970s and gene therapy in the 1990s. Dr. Lotze adds, "We have come a long way. We have now seen the first

approved cell therapy for the treatment of some prostate cancers. However, there as yet is no approved gene therapy for cancer treatment in the United States. Everything remains in trials. It is exciting indeed that Dr. Carl June's breakthrough* clinical trials at the University of Pennsylvania, funded by ACGT, suggest that gene and cell therapy is going to soon be very much a part of modern therapy."

"EXCEEDING ALL EXPECTATIONS!"

ACGT Research Fellow Dr. Carl June and his team at the University of Pennsylvania's Abramson Cancer Center and Perelman School of Medicine have made great strides in the treatment of advanced CLL (chronic lymphocytic leukemia), the most common type of the blood disease that strikes 15,000 people in the U.S. and kills 4,300 every year. The treatment uses genetically modified versions of the patient's own T-cells, and has shown remission for up to a year in a small group of patients, several of whom are in complete remission. The protocol, which involves removing the patient's white blood cells and modifying them, then infusing the new cells back into the patient's body following chemotherapy, provides a tumor-attack roadmap for the treatment of leukemia and other cancers including those of the lung and ovaries and myeloma and melanoma. This is the first demonstration of the use of gene transfer therapy to create "serial killer" T-cells aimed at cancerous tumors. "Within three weeks, the tumors, which were several pounds each, had been obliterated in a way that was much more complete than we ever expected," said senior author Carl >>



Dr. Michael Lotze (right) with Dr. Carl June



June, MD, director of Translational Research and a professor of Pathology and Laboratory Medicine in the Abramson Cancer Center, who led the work. "The results exceeded our expectations quite a bit; our entire team is really excited, and as well, the patients are excited."

"APPROVED GENE THERAPY FOR CANCER IN THREE TO FIVE YEARS!"

Michael Lotze believes the finish line for cell and gene therapy is in sight. "I suggest that gene-modified cells are going to be part of modern cancer therapy. We may still be at the halfway mark of Zeno's Paradox for gene therapy, but my suspicion is that within the next three to five years we will see an approved gene therapy for cancer!"

"Compared to where I started thirty years ago we are now at a level of sophistication in clinical trials where we can pluck out the T-cell receptor, modify it, recognize a particular molecule on a tumor cell and then modify the patient's own cells and introduce them back into the body as cancer-killing cells. Is that a breakthrough? Absolutely! Is it effective? Absolutely! Are there people who are cured? Possibly! Only long term follow through will determine whether these tumors will never come back. Those of us in the tumor immunology field feel that we are not going to cure cancer without the involvement of T-cells. I think the greatest breakthroughs yet to come will be when we have consilience** between cancer biology and tumor immunology."

WITH CLINICAL TRIALS THERE IS HOPE

The digital world's access to information can create both hope and despair for cancer patients. Each day brings both good news and disappointing false starts regarding new treatments for cancer. Worldwide human trials are reported with mixed results. How does Dr. Lotze feel about patient access to trials? "I think that the new therapies available in clinical trials should be readily available for desperate patients. People deserve to live with hope. Participation in clinical trials offers that hope."

ARE CLINICAL TRIALS FOR EVERYONE?

"I believe clinical trials are for almost everyone. It has been shown repeatedly that the quality of care in a clinical protocol often offers patients better care than in conventional therapy. Some patients will not qualify for clinical trials. Some may make the very difficult choice to have no therapy. There are more clinical trials open in the field of cancer treatment than for any other disease. Sadly, many clinical trials are starving for patients." Clinical trial information is available at www.acgtfoundation.org

CANCER AND FITNESS

Long-distance runners are obviously focused on fitness and the take on the subject by ACGT's nationally renowned cancer research scientist, who is also a physician, presents a poignant viewpoint. Dr. Lotze: "Setting medicine and treatment aside, being trim and fit may be the only way to increase longevity. One of the major benefits of regular exercise and staying fit is that you clear yourself of cells that can create problems for you over time."

T.R. AND MICHAEL LOTZE?

With whom would Michael Lotze like to have a philosophical conversation? Surprisingly the answer was not a scientist, but rather an amateur botanist and outdoor adventurer who became the twenty-sixth President of the United States. Teddy Roosevelt! Says Lotze, "Having just read *T.R.* by Edmund Morris, here is a man who overcame a childhood plagued with illness and who long before it became popular threw himself headlong into a physical fitness regimen to cure his ailments. It worked! T.R. also never set a goal of half the distance. Whether it was establishing our National Parks, making the Panama Canal a reality, dealing with the oil, railroad, and steel trusts or living off the land for a year in the Dakota Territory, Teddy Roosevelt was all about hope. He was innovative, put big ideas on the line and was willing to take risks regardless of personal popularity."

INVESTMENT IN RESEARCH BUILDS ECONOMIES

Michael Lotze believes that continued cutbacks in scientific research are devastating to solving many of the great medical mysteries and to society as a whole.

"Despite the economic difficulties in the America of 2011, the great success of the economy over the past two decades has been the consequence of innovation and funding of a broad range of research. In medicine, investing in areas such as the National Institute of Health, philanthropic organizations like ACGT and the space race, without which we would not have today's computer technology, biotechnology, and evolving gene therapy have all paid handsome dividends. It is all about the willingness to take risks. Yes, you can cut expenditures but if you pare down research, science and education, you are looking at a bleak future across the entire economic and social spectrum. The critical role for organizations like ACGT is to keep hope alive for a group of hard working scientists whose goals are trying to solve problems and uncover many more scientific mysteries. A short time ago I was running in the Rachel Carson (*Rachel Carson is the author of The Silent Spring*) 35-Mile Foot Race with Carl June, and he said to me, 'I would have been unable to do my work without the funding from ACGT.'"

For Michael Lotze a break from the laboratory is in the works. He is heading to Kenya with his family in search of new mysteries. Yes, he is running in the Lewa Marathon with the Kenyans. □ **WRITTEN BY GHH**

This is the second in a series of articles profiling the Research Stars of the Alliance for Cancer Gene Therapy, a public charity based in Stamford, Connecticut, that supports scientific research in the area of cancer cell and gene therapy. This series will culminate with the celebration of the tenth anniversary of ACGT at a dinner on April 19, 2012 at the Hyatt Regency in Greenwich, Connecticut in honor of ACGT Co-Founder, the late Edward Netter. For details, please go to www.acgtfoundation.org

"Compilations" and "Collective Works"

One of the more difficult tasks confronting attorneys who counsel creative artists is explaining such terms as "compilation", "collective work" and "derivative work", all separately defined in the first section of the Copyright Act. This column will try to explain "compilation" and "collective work".

Under the Copyright Act, a "compilation" is a work formed by the collection in assembling of pre-existing materials or data that are selected, coordinated, or arranged in such a way that the resulting work as a whole constitutes an original work or authorship. The term "compilation" includes collective works (emphasis added).

A "collective work" is a work such as a periodical issue, anthology or encyclopedia, in which a number of contributions, constituting separate and independent works in themselves, are assembled into a collective whole.

Other examples of collective works are: magazines, software programs, collections of songs by third parties and retrospective collections of a particular artist's films. The resulting "collection" may become a separately-protectable work, if certain requirements are met.

It is important that compilers understand that compilations and collective works, to be eligible for copyright protection, must involve some originality in the selection coordination and arrangement of the materials. It is this selection, coordination and arrangement - - and not the

underlying original elements - - that protect compilations and collective works. A useful example is a magazine - - a collection of articles by its publisher. The authors may own copyrights in the individual articles; the publisher will generally own the copyright in the magazine as a whole. In short, there are two distinct sets of copyrights which overlap, but which are, individually, protectable.

Keep in mind the phrase in the first section of the Copyright Act, original work of authorship. How difficult is it to establish originality? The case law seems to say that originality is not difficult to establish at all. It depends on the act of selection and editing, which the courts have held to be a "highly creative endeavor". On the other hand, where there is no originality - - where the selection process is purely mechanical, as in the simple al-

phabetical arrangement of names in a phone book - - copyright protection will be much more difficult to obtain.

In short, artists, editors, film producers and publishers seeking copyright protection for "compilations" or "collective works", will stand a much better chance if there is selection, coordination or arrangement sufficient to constitute an original work of authorship. The considered selection of prints of a certain artist, or of several stories of a prolific author, would satisfy the selection, coordination or requirement of the Copyright Act. On the other hand, the arrangement of a list of 10,000 names in alphabetical order would almost certainly not satisfy this requirement.

We will deal with the ambiguities of "derivative works" in the next article.

**In his 1998 book *Consilience: The Unity of Knowledge*, Pulitzer Prize-winning author Edward O. Wilson discusses methods that have been used to unite the sciences. Wilson uses the term "consilience" to describe the synthesis of knowledge from different specialized fields of human endeavor.