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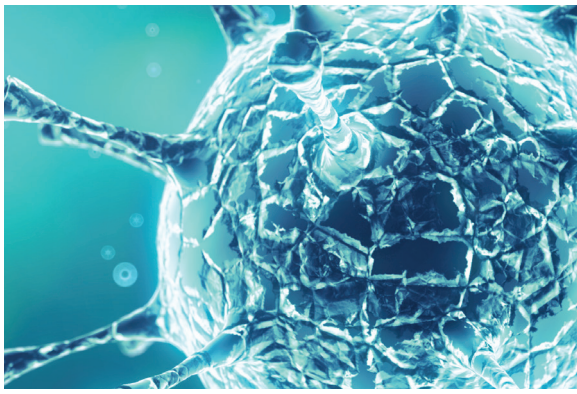
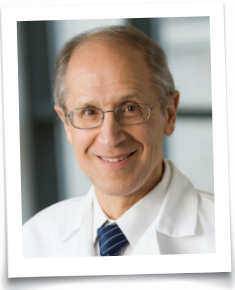
INNOVATIONS IN CANCER



Winter 2017

FROM THE **DIRECTOR**



STANTON L. GERSON, MD

Director, UH Seidman Cancer Center

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Asa & Patricia Shiverick – Jane B. Shiverick (Tripp) Professor of Hematological Oncology,

Case Western Reserve University School of Medicine

Cell therapies have long been among the leading-edge treatments offered at University Hospitals Seidman Cancer Center. UH was among the first in the country to perform bone marrow transplants in 1976, and today is still on the forefront of this life-saving procedure. My colleague Hillard Lazarus, MD, and I along with our colleagues at UH pioneered new treatment approaches for stem cell transplant, including transplantation of stem cells from umbilical cord blood for patients without a donor match.

In this issue of Innovations in Cancer, we focus on cell therapies at UH Seidman Cancer Center – both where we've been and where we're going. We have an extremely strong group of physician-scientists here pursuing these therapies, attacking problems from every angle.

This issue features *Marcos de Lima, MD,* and his efforts to use labor-saving technology to scale up adoptive T cell therapy to fight opportunistic viral infections. It highlights *Ehsan Malek, MD,* and his work on the national project generating a personalized vaccine for multiple myeloma patients. And it includes *Andrew Sloan, MD,* and a trial we worked on together to genetically engineer increased bone marrow tolerance to chemotherapy among patients with glioblastoma.

These are just a few of the cell therapy projects under way at UH. This issue also highlights *Joseph Baar, MD, PhD,* and his work on a breast cancer vaccine targeting blood supply, as well as *Julian Kim, MD,* and his work using adoptive T cells to fight melanoma. *David Wald, MD, PhD,* is also exploring the potential of natural killer (NK) cells. Having unlocked a secret to generating them in large numbers, he and his colleagues here are exploring their potential against hematologic malignancies, sarcoma and colon cancer, using a novel fusion protein to support NK cell survival and proliferation.

With our tradition of excellence, engaged physician-scientists and state-of-the-art Cellular Therapy Service and Laboratory, we at UH Seidman Cancer Center are well-positioned to make the discoveries that will continue to revolutionize cancer care. We look forward to what comes next and invite you to learn more about the progress happening here.

Warm regards,
Stanton L. Gerson, MD

GENE THERAPY AND GLIOBLASTOMA

Novel UH trial creates greater bone marrow tolerance to chemotherapy

In a federally approved clean room in the Cellular Therapy Lab at the Case Comprehensive Cancer Center, clinicians and technicians remove bone marrow-derived stem cells from glioblastoma patients to create stronger cell tolerance to chemotherapy, ushering in a new, highly sophisticated approach to cancer therapy.

This Phase I clinical trial is yielding increased survival rates among selected glioblastoma patients at University Hospitals Seidman Cancer Center, where the clinical protocol was written by Andrew Sloan, MD, Director of the Brain Tumor and Neuro-Oncology Center and the Peter B. Cristal Chair of Neurosurgical Oncology. Dr. Sloan recently received the Neuro-Oncology Award for this trial at the 2016 Annual Meeting of the Congress of Neurological Surgeons in San Diego.

> This trial was designed specifically to protect the bone marrow from damaging chemotherapy,

says Stanton L. Gerson, MD, Director of UH Seidman Cancer Center, the Case Comprehensive Cancer Center and also the National Center for Regenerative Medicine. "We're changing the DNA in their stem cells. We developed this concept 15 to 20 years ago, and only a few cancer centers in the country have been in existence and doing cell therapy as long as we have been."

A COMPLEX PROCESS

The novel glioblastoma trial involves removing hematopoietic stem cells from the patient's body, reengineering them in the lab and then retransplanting them. By introducing a drug-resistant gene, the treatment team can escalate the chemotherapy dose without as much concern for the toxicity to the bone marrow.

The process is challenging. Stem cells can be difficult to define, manipulate and keep viable in a culture outside the body. It is critical that the gene is placed in a stem cell that can differentiate from other mature blood cells in the body.

"We did extensive safety studies to make sure the gene did not insert into the DNA in a place that would lead to unwanted gene activation," says Jane Reese-Koc, MBA, MT, Operations Director of the Cellular Therapy Lab, adding that the lab is required by the U.S. Food and Drug Administration to track all gene insertions.

PATIENT AS SUPERMAN

Consider 52-year-old glioblastoma patient Andy Simon, who arrived at his final chemotherapy treatment dressed as Superman. He was feeling so strong throughout his chemotherapy regimen that he ran in multiple 5K races and worked 50-hour weeks. Simon entered the clinical trial following imaging complete resection of the tumor by Dr. Sloan.

"Thus far, the trial has been safe for our patients," Dr. Gerson says. "Glioblastoma multiforme is a tough disease. It's one in which if we can give them more chemotherapy and they can tolerate it, they may do better. This trial gives the patient an opportunity to be involved in a new treatment. We really do partner with our patients as participants."

For more information on this trial, email **CancerInnovations@UHhospitals.org.**

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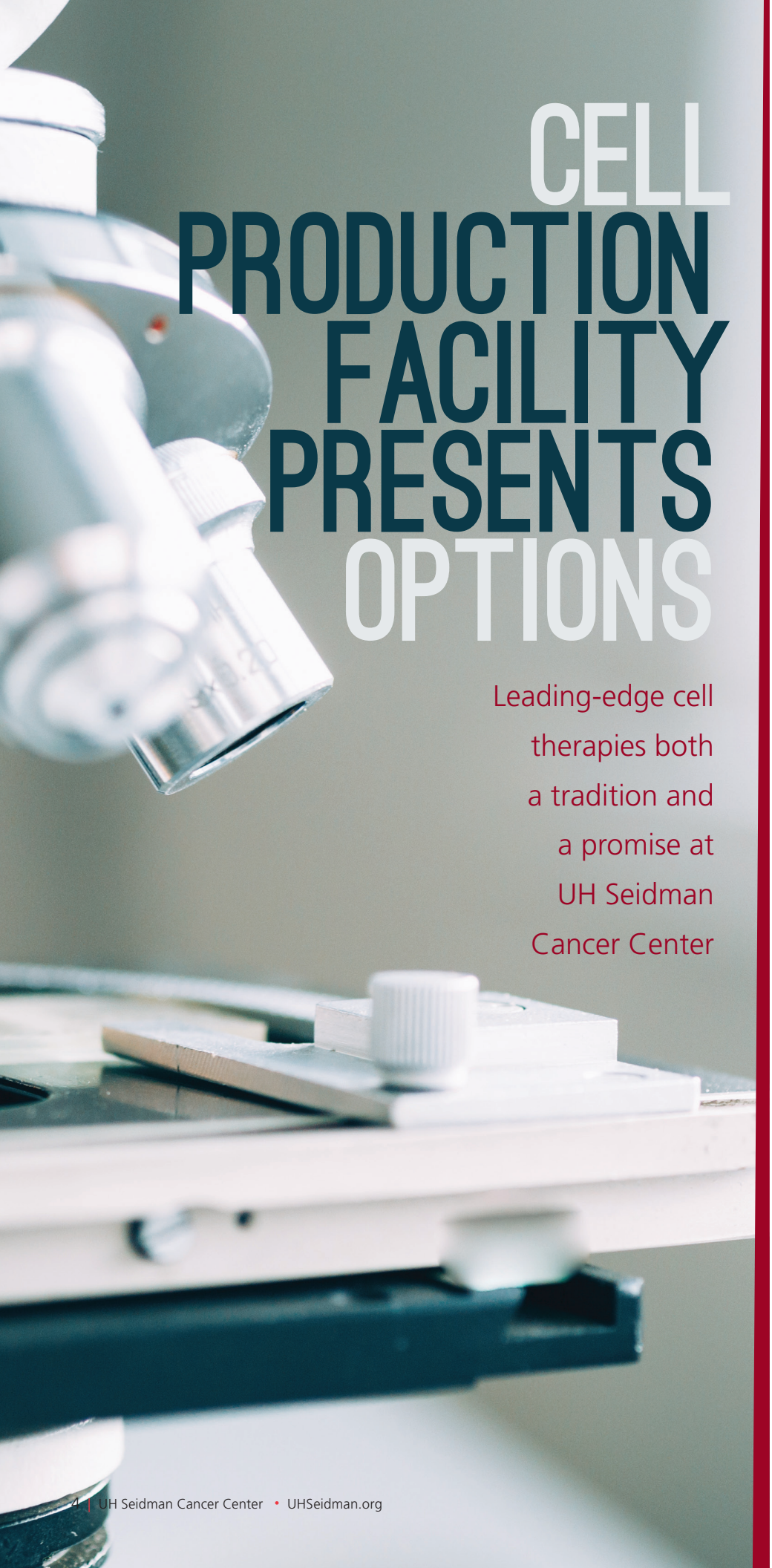

CELL PRODUCTION FACILITY PRESENTS OPTIONS

Leading-edge cell therapies both a tradition and a promise at UH Seidman Cancer Center

University Hospitals Seidman Cancer Center is at the forefront of cell therapy, with multiple clinical trials available to patients that will ultimately lead to new treatments.

Using living cells to replace, regenerate or enhance a healing process in the patient's body is facilitated in large part by UH Seidman Cancer Center's Cellular Therapy Service. At the center of this program stands the Cellular Therapy Laboratory, designed to support investigator-initiated trials and produce high clinical-grade cellular therapy products to benefit patients. This 3,000-square-foot, state-of-the-art facility, located in the Wolstein Research Building at Case Western Reserve University, has six ISO7 clean rooms that control environmental conditions and limit airborne particles.

The Cellular Therapy Laboratory manufactures large numbers of cells for physicians who use them in clinical trials targeting cancer, as well as conditions such as multiple sclerosis and cystic fibrosis. State-of-the-art equipment enhances cell manufacturing efficiency and extends the possibilities for new treatments.

The preparation and use of cellular products require adherence to the rigorous regulations set forth by the U.S. Food and Drug Administration. The facility also is accredited by the Foundation for the Accreditation of Cellular Therapy.

HISTORICAL LEADERS, BREAKING NEW GROUND

UH Seidman Cancer Center has long been a leader in stem cell therapy. Researchers here have built on more than 30 years of groundbreaking work using stem cells to treat cancer and other diseases. UH was among the first in the country to perform bone marrow transplants in 1976, and today is still on the leading edge of this life-saving procedure. Hillard Lazarus, MD, Stanton

Gerson, MD, and their colleagues pioneered new treatment approaches for stem cell transplant, including transplantation of stem cells from umbilical cord blood for patients without a donor match.

Translating work from the lab to patients has inspired UH physicians to continue to advance the field. Dr. Lazarus and his colleagues have done pioneering work in bone marrow and stem cell transplantation and have developed new treatment approaches to help patients battle their cancer more successfully than ever before. His team developed the use of stem cells from umbilical cords to treat leukemia and also discovered a new type of stem cell, mesenchymal stem cells (MSCs).

For his part, Dr. Gerson, an expert in stem cells and DNA repair, has identified a gene therapy that creates drug-resistant stem cells capable of selectively repopulating the recipient without the need for high-dose, toxic chemotherapy.

This strategy is now used experimentally and clinically throughout the country. He has developed clinical trials on using MSCs as a therapeutic infusion for blood stem cell transplantation and for the correction of genetic disorders, as well as inhibitors of DNA repair to improve the efficacy of anti-cancer agents.

Dr. Gerson collaborated in his early research with Arnold Caplan, PhD, Professor of Biology at Case Western Reserve University. Together they produced publications and patents related to MSCs and then oversaw four first clinical trials using these cells. Dr. Gerson has also developed transgenic mouse models that examine the role of critical genes in the stability of stem cell populations over the lifetime of the animal. These studies may predict stem cell diseases of aging and cancer. His research has generated 12 patents in the area of gene therapy and cancer drug development that have been licensed to three companies.

CURRENT CELL THERAPY TRIALS AT UH SEIDMAN CANCER CENTER

UH Seidman Cancer Center faculty are building on a strong legacy of cell-based cancer therapies with these clinical trials:

Breast cancer vaccine:
Joseph Baar, MD, PhD, is piloting a new approach for select women with metastatic breast cancer – a vaccine targeting tumor blood supply. Attempts to develop a breast cancer vaccine have repeatedly met with failure because the cancer cells evade immune cells, either by changing or not expressing the molecular targets that the immune cells seek.

Genes and glioblastoma:
Neuro-oncologist Andrew Sloan, MD, and Dr. Gerson have developed a novel trial for glioblastoma patients. It involves removing hematopoietic stem cells from the patient's body, reengineering them in the lab and then retransplanting them. By introducing a drug-resistant gene, the treatment team can escalate the chemotherapy dose without as much concern for the toxicity to the bone marrow.

T cells and melanoma:
Julian Kim, MD, has developed a novel technique to generate large numbers of activated T cells, which can then be transferred back into the same patient to stimulate the immune system to mount a protective immune response against the disease. The clinical team aims to use this technique – offered at only a few institutions worldwide – in attacking other cancers.

Hematologic malignancies:
Stem Cell Transplant Director Marcos de Lima, MD, new to UH from M.D. Anderson Cancer Center, has shown that injecting combined human cord blood cells and mesenchymal stromal cells directly into bone marrow results in better engraftment in mice. He and his team are now testing the approach in adult patients with hematologic malignancies. This project addresses the lack of matched donor cells, a persistent challenge in hematologic malignancies.

T cells to treat viral infections in stem cell transplant patients:
Dr. de Lima and Paolo Caimi, MD, will soon launch a trial using virus-directed T cells from the transplant patient's donor or donor's family member to treat opportunistic viral infections, including cytomegalovirus, BK, Epstein-Barr and adenovirus. A new automated cell processor will make the process quicker and easier to manage.

Personalized vaccine for multiple myeloma patients:
Dr. Lazarus and Ehsan Malek, MD, are participating in a national effort through the Blood and Marrow Transplant Clinical Trials Network to test a personalized vaccine against multiple myeloma derived from the patient's own tumor cells after autologous hematopoietic stem cell transplant.

Natural killer (NK) cells and hematologic malignancies, sarcoma and colon cancer:
Having unlocked a secret to generating NK cells in large numbers, David Wald, MD, PhD, and his colleagues are exploring their potential against hematologic malignancies, sarcoma and colon cancer, using a novel fusion protein to support NK cell survival and proliferation.

For more information on any of these trials or to refer a patient, email **CancerInnovations@UHhospitals.org**.

PERSONALIZED MEDICINE: A REAL OPTION FOR MULTIPLE MYELOMA PATIENTS

Individualized vaccine is created from each patient's unique cancer cells

The 2015 approval by the U.S. Food and Drug Administration of two new monoclonal antibodies – elotuzumab (Empliciti®) and daratumumab (Darzalex®) – and an oral proteasome inhibitor – ixazomib (Ninlaro®) – has given new hope to patients with multiple myeloma. At University Hospitals Seidman Cancer Center and just over a dozen other centers nationwide, all multiple myeloma patients with relapsed disease have access to these new therapies. But they also have access to another experimental option: a personalized myeloma vaccine.

"Preclinical and clinical data indicate that myeloma-associated tumor antigens elicit humoral and cellular immune responses in myeloma patients," says Ehsan Malek, MD, a hematologist at UH Seidman Cancer Center participating in a trial of the new myeloma vaccine. "These findings strongly suggest that the immunotherapeutic strategies, such as immune checkpoint inhibitors, therapeutic myeloma vaccines and adoptive cellular therapies, are promising avenues of clinical research that may be most applicable in the minimal residual disease state following autologous hematopoietic stem cell transplant."

At UH Seidman Cancer Center, all newly diagnosed, standard-risk multiple myeloma patients who are eligible for autologous stem cell transplantation are asked to participate in the myeloma vaccine trial. The Phase II, multicenter trial is sponsored by the Blood and Marrow Transplant Clinical Trials Network. Hematologist and oncologist Hillard Lazarus, MD, is the principal investigator at UH.

HOW IT WORKS

When a patient is diagnosed with multiple myeloma, UH physicians and scientists, in collaboration with investigators at Dana Farber Cancer Institute, use "treatment-naïve" cancer cells to create a dendritic cell vaccine to enhance the individual patient's immune system, increasing its ability to recognize and kill myeloma cells. This vaccine is generated on-site at the Cellular Therapy Laboratory.

Importantly, the myeloma vaccine is personalized for each patient, based on his or her specific disease.

"Myeloma is among the most heterogeneous malignancies," Dr. Malek says. "Therefore, strategies to use patients' own tumor cells to generate a patient-specific myeloma vaccine are warranted. This is a big step toward precision medicine and individualized therapy for multiple myeloma patients. It's important to make the immune system activated against the antigens expressed by a person's particular cancer. That's the exciting thing about personalized medicine."

After the myeloma vaccine is created in the laboratory and the patient undergoes an autologous stem cell transplant, he or she receives the vaccine – designed to stimulate his or her own T cells against the myeloma. Before doctors inject a patient, vaccine function is scrutinized to determine whether it is capable of stimulating T cells recognizing the myeloma cells.

OTHER MYELOMA PROJECTS IN THE PIPELINE

Dr. Malek and his colleagues at UH Seidman Cancer Center are also working on natural killer cell therapies for multiple myeloma, as well as other hematologic malignancies. They hope to have a new trial open soon. Also, they're collaborating with physicians and scientists from Cleveland Clinic – their partners in the Case Comprehensive Cancer Center – to develop and test another myeloma vaccine, this one targeted against the myeloma antigen DKK. This project is led by UH's Dr. Lazarus in collaboration with Fred Reu, MD, and Qing Yi, MD, from Cleveland Clinic.

For more information on treatment for multiple myeloma at UH, including the personalized vaccine, or to refer a patient, please email **CancerInnovations@UHhospitals.org**.

EHSAN MALEK, MD

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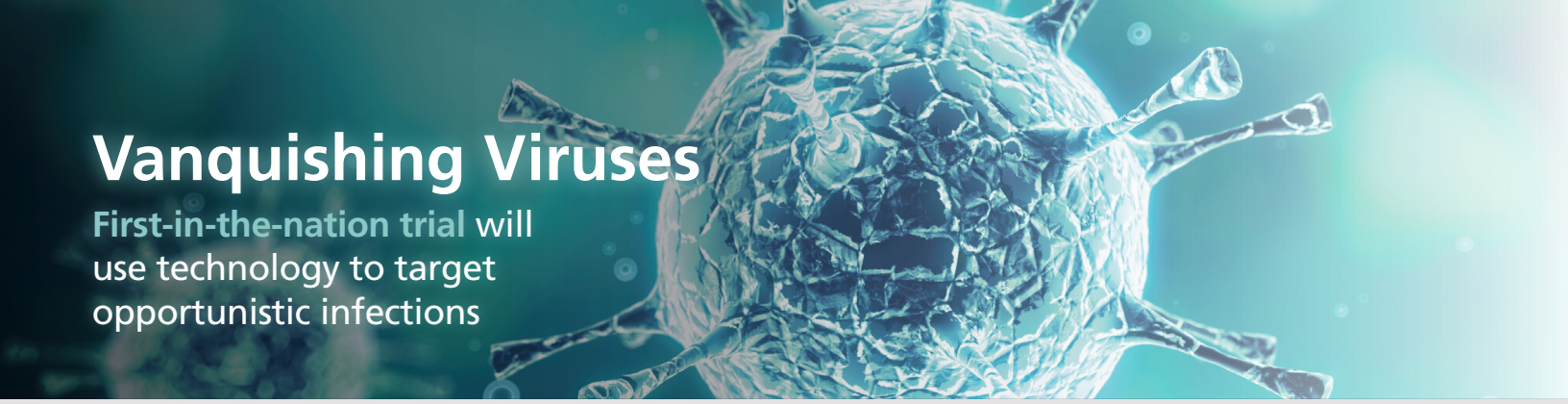

Vanquishing Viruses

First-in-the-nation trial will use technology to target opportunistic infections

Opportunistic viral infections remain a significant risk after hematopoietic stem cell transplantation (HSCT). Current antiviral therapies are often inadequate to combat these infections, putting both the graft and the patient at risk.

"It's an ongoing problem," says Marcos de Lima, MD, Director of the Hematologic Malignancies and Stem Cell Transplant Program at University Hospitals Seidman Cancer Center. "Today, we use more mismatched transplants using haploidentical (mismatched related donors) or cord blood. It's great because you can potentially transplant everybody, but the limitation is that there are more significant issues during recovery after transplant and more of these opportunistic infections."

To address this problem, Dr. de Lima and his colleagues at UH Seidman Cancer Center and the Case Comprehensive Cancer Center at Case Western Reserve University will soon launch a first-in-the-nation cell therapy trial aimed at treating four common viral infections in HSCT patients.

DISTINCTIVE DEVICE

The trial relies heavily on an automated cell processing device called the CliniMACS Prodigy system, which uses a gamma interferon capture system. First, the team will secure cells from the patient's donor or the donor's family member. Then the cells will be exposed to the particular virus antigen. Viruses to be included in this trial include cytomegalovirus, Epstein-Barr, adenovirus and BK. Through a series of magnetic interactions within the Prodigy device, only cells that respond to the viral antigen will secrete the gamma interferon and be captured.

> "At the end, you end up with a small, but very strong, selected population of T cells."

"We will be able to separate out these particular T lymphocytes with the Prodigy system," Dr. de Lima says. "At the end, you end up with a small, but very strong, selected population of T cells. The basic assumption is that because the donor had those T cells, he or she must have been previously exposed to that virus. Because of this, then you can prevent off-target activity, such as graft versus host disease. The T cells are very specific against the virus, so they are less likely to cause off-target damage."

Creating virus-specific T cells to restore immunity and combat viral infections is in itself not a new idea. Cell-based immunotherapy, using adoptive T cell transfer, has been shown to be safe and effective in the treatment of viral infections after HSCT, including adenovirus, cytomegalovirus and Epstein-Barr.

The difference is in the speed and convenience provided by the Prodigy system.

"This is not a new idea, but the automated approach makes it very user-friendly," Dr. de Lima says. "In the past, an approach like this was very labor-intensive. Technology now makes it easier, which we think will be a big advantage for our HSCT patients."

He predicts that this is just one of the major cell therapy advances cancer patients will see from UH Seidman Cancer Center in the days and weeks ahead.

"Centers like ours that have cell processing and bone marrow transplant programs are well-positioned as the science develops and expands," he says. "In the future, we expect to see a lot more combinations of cell therapies and drugs. For us, embracing these projects will be almost second nature."

For more information on this pending clinical trial at UH Seidman Cancer Center, please contact Dr. de Lima or Paolo Caimi, MD, at **216-844-0130**.

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Cleveland's Stanton L. Gerson, MD, Named AACI President

Stanton L. Gerson, MD, has been named President of the Association of American Cancer Institutes (AACI).

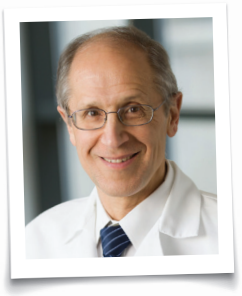
Dr. Gerson is Director of University Hospitals Seidman Cancer Center and the National Cancer Institute (NCI)-designated Case Comprehensive Cancer Center at Case Western Reserve University. He is also Asa and Patricia Shiverick – Jane Shiverick (Tripp) Professor of Hematological Oncology, Case Western Reserve University School of Medicine, founding Director of the National Center for Regenerative Medicine, Distinguished University Professor at Case Western Reserve University and a member of the NCI Board of Scientific Advisors.

During his two-year term as AACI President, Dr. Gerson will launch an initiative that addresses a major objective of the Obama administration's Cancer Moonshot Initiative: promoting collaborations with researchers, doctors and patients to improve patient outcomes and health care value in the community.

"The need to facilitate this process is especially great at community points of care where access to newer technology, decision-making expertise to handle 'omics' and other advanced diagnostics, clinical trials or multidisciplinary care may lag that available at larger cancer center sites," Dr. Gerson says.

To meet that challenge, Dr. Gerson proposes marshalling the collaborative and synergistic knowledge and experience of AACI cancer centers to create a model of care that can provide access to patients currently seen in the community. In the coming months, AACI will convene a steering committee that will chart the direction of Dr. Gerson's initiative at the network sites of major cancer centers.

Dr. Gerson has been an active member of AACI for the past 14 years, including service on the board of directors (2007 – 2009). An internationally recognized cancer researcher, Dr. Gerson has been active in stem cell, hematologic malignancies and developmental therapeutics programs. He has received multiple NIH grants and has published more than 236 articles, 270 abstracts and 37 book chapters. He also has received 18 patents for stem cell and drug discoveries.



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