

# PHYSICIANS

SEPTEMBER/OCTOBER 2020

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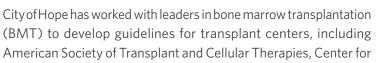


# **Continuing Bone Marrow Transplants During the COVID Era**

ne area of City of Hope that has unique demands put on it by COVID-19 is the Center for Stem Cell Transplantation. Many patients with hematologic disorders

are already immune compromised, either associated with their underlying disease or as a result of the treatments they've been receiving.

Protocols have been put in place to protect patients and their caregivers, to protect health care providers throughout the entirety of the transplant process and to ensure research protocols mitigate risk during this unprecedented time.





Ryotaro Nakamura, M.D. Professor, Department of Hematology & Hematopoietic Cell Transplantation Director, Center for Stem Cell Transplantation

International Blood and Marrow Transplant Research, The Blood and Marrow Transplant Clinical Trials Network and The European Society for Blood and Marrow Transplantation. One person at the table for these discussions is **Ryotaro Nakamura**, **M.D.**, professor in City of Hope's Department of Hematology & Hematopoietic Cell Transplantation and director of its Center for Stem Cell Transplantation.

As department standard operating procedure was implemented, it was further shaped by other City of Hope departments, including infectious diseases, research, transfusion medicine, operations and other service lines.

While there are many facets to the guidance, and it is frequently updated, protocol currently includes PRC testing for COVID-19 before transplant recipients are admitted to the hospital. For related donors, testing is done prior to GCSF mobilization.



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"It is also recommended that many programs pause certain types of transplants as a programmatic rule," said Nakamura. "For example, patients with multiple myeloma whose disease is well controlled and stable are often able to delay their transplant for a few months until a transplant can be performed with less risk than is possible during the current pandemic. But not all transplants can wait."



#### WHEN A TRANSPLANT CAN'T WAIT

As coronavirus spreads, hospitals across the country have had to reallocate resources and implement certain health mandates, pausing elective surgeries for example, to meet COVID-19 patient needs.

"We had one patient who came to us because his transplant was put on hold by another institution. That hospital needed to reallocate resources in response to COVID-19," said Nakamura. "City of Hope, being a cancer hospital, we are a little better situated to take care of those patients in need since we don't have the flow of ambulances coming into ERs, we don't have the direct focus on treating COVID-19." Resources at City of Hope can continue to be used on what we do best, cancer care.

"While transplants are never routine, it is what we do at City of Hope day in and day out," said Nakamura. "Everyone here is familiar with the demands and expectations surrounding transplants, from doctors and nurses to coordinators and staff. It is at the heart of what we do."

# A National Leader in BMT **Survival for 15 Consecutive Years**

I aving one of the largest and most successful bone marrow and blood stem cell transplant centers in the country gives City of Hope the unique ability to quickly address global public health challenges, like COVID-19, that may impact cancer care. As a pioneer in creating breakthrough treatments for all hematologic cancers, including leukemia, lymphoma, multiple myeloma, myelodysplastic syndrome and other blood-related disorders, we are also a world leader in setting standards for stem cell transplantation and in improving long-term outcomes for both children and adults.

In addition to performing more than 16,000 transplants, City of Hope has earned the recognition of "overperforming" in clinical expectations for 15 consecutive years according to an analysis by the Center for International Blood and Marrow Transplant Research.

#### SPECIALIZED CARE FOR PATIENTS

City of Hope recently appointed Eileen Smith, M.D., as the Francis & Kathleen McNamara Distinguished Chair in Hematology and Hematopoietic Cell Transplantation. Smith takes over from Stephen J. Forman, M.D., who led the program for 32 years. Under Smith's leadership, our dedicated, multidisciplinary team combines innovative research discoveries with superior clinical treatments to improve outcomes for patients with various blood cancers, blood abnormalities and other hematologic disorders.

At City of Hope, leading-edge research, treatments and therapies emerge from the Hematologic Malignancies Research Institute. Under the leadership of Forman, who serves as the director of the institute alongside deputy director Larry W. Kwak, M.D., Ph.D., laboratory and physician investigators expand their work and develop new therapies and possible cures for leukemia, lymphoma and multiple myeloma.



# THE INSTITUTE FUNCTIONS AS A MATRIX OF SEVEN SPECIALIZED CENTERS:

#### **Gehr Family Center for Leukemia Research**

The center works to broaden research and treatment options for acute myeloid, acute lymphoblastic, chronic myelogenous and chronic lymphocytic leukemias, as well as myelodysplastic syndrome and myeloproliferative neoplasms.

Led by Guido Marcucci, M.D., and Anthony Stein, M.D.



Guido Marcucci, M.D. *Director* 



Anthony Stein, M.D. Associate Director

#### **Toni Stephenson Lymphoma Center**

With a focus on lymphoma, including Hodgkin and non-Hodgkin lymphoma, researchers at this center are working to develop immune-based, nontransplant therapies.

Led by Larry Kwak, M.D., Ph.D., and Alexey Danilov, M.D., Ph.D.



Larry W. Kwak, M.D., Ph.D. Director Dr. Michael Friedman Professor in Translational Medicine



Alexey Danilov, M.D., Ph.D. Associate Director

# Judy and Bernard Briskin Center for Multiple Myeloma Research

Researchers are aggressively pursuing new research and improved treatments for multiple myeloma and amyloidosis.

Led by Amrita Krishnan, M.D., and Jonathan Keats, Ph.D.



Amrita Krishnan, M.D. Director



Jonathan Keats, Ph.D. (TGen) Associate Director

#### **Center for Stem Cell Transplantation**

The team focuses on the advancement of hematopoietic stem cell transplants, including improving cure rate and reducing toxicity.

Led by Ryotaro Nakamura, M.D., and David Snyder, M.D.



Ryotaro Nakamura, M.D. *Director* 



David S. Snyder, M.D. Co-director

#### **Cellular Immunotherapy Center**

Experts are finding new ways to harness the immune system to fight cancer, including CAR T cell therapy.

Led by Stephen J. Forman, M.D., and Christine Brown, Ph.D.



Stephen J. Forman, M.D. *Director* 



Christine Brown, Ph.D. Associate Director The Heritage Provider Network Professor in Immunotherapy

#### **Center for Gene Therapy**

This center conducts research on genetic modification of stem cells.

Led by John Zaia, M.D., and Kevin Morris, Ph.D.



John A. Zaia, M.D. Director Aaron D. Miller and Edith Miller Chair for Gene Therapy



Kevin Morris, Ph.D. *Associate Director* 

#### **Center for Survivorship and Outcomes**

By maintaining lifelong follow-up with hematology patients treated at City of Hope, researchers can incorporate data from health outcomes after the completion of therapy that allows for a deeper understanding of health challenges faced by survivors short and long term.

Led by Saro Armenian, D.O.



Saro H. Armenian, D.O., M.P.H. *Director* 

The research done at the Hematologic Malignancies Research Institute is one of the reasons clinical outcomes are so successful at City of Hope. "It is the commitment of our physicians and nurses, and the creativity of our programs' scientists that has lead to our success and recognition every year," said Forman. "It is a remarkable achievement, especially considering that our patients often have more advanced cases of blood cancer when they come to us than at many other programs in the country."

Care and consideration for our patients extends beyond treatment. Each year, we celebrate our survivors and their families, who live across the United States and all over the world.

Looking forward, our program is focused on minimizing the side effects of therapies and preventing recurrence, increasing its effectiveness and expanding its reach to save the lives of more patients.

To refer a patient, please contact (800) 826-4673.

# Making Bone Marrow Transplant Safe and Available to All

#### HALF-MATCHES IN BONE MARROW TRANSPLANTS **PROVIDE COUNTLESS SECOND CHANCES**

he haploidentical transplant program at City of Hope is setting a new gold standard in the treatment of leukemia and other blood cancers.

The gold standard for transplants has historically involved harvesting stem cells from a close relative, usually a sibling, with human leukocyte antigens (HLA) markers identical to the patient's. While occurring in 30% of cases, 70% of patients do not have a relative match and thus could have a long wait to track down an unrelated 100% matched donor from the National Bone Marrow Registry.



Monzr Al Malki, M.D. Assistant Clinical Professor, Department of Hematology & Hematopoietic Cell Transplantation

Minorities suffered the most. For example, African American patients who did not have a match in their family had less than a 10% chance of finding a donor in the unrelated registry.

Additionally, possible matches can be from halfway around the world, so collecting the donor's cells and completing the transplant process takes several months. Additionally, anything less than an exact match increases the likelihood of graft failure, as well as graft-versus-host disease (GVHD), which can lead to fatal complications.

In haploidentical transplant, however, donor cells have to only match half the patient's HLA markers, and the donor is typically a family member. The advantage of having a haploidentical transplant is that it increases the chance of finding a donor as almost everyone has at least one haploidentical relative, so transplants can take as little as two to three weeks.

### City of Hope doctors have performed nearly 300 haploidentical transplants in the last five years.

The research that led to this breakthrough focused on T cells. It turns out that when the T cells were removed, patients did not get GVHD. Additionally, the same drug used to treat patients before bone marrow transplant (cyclophosphamide) could be given post-transplant to limit GVHD, without hampering the T cell's ability to mop up any surviving cancer cells.

"Haploidentical transplants are faster, easier and more costeffective for patients," said Monzr Al Malki, M.D. "This is the future." Al Malki is an assistant clinical professor in the Department of Hematology & Hematopoietic Cell Transplantation and director of the Unrelated Donor BMT Program and the Haploidentical Transplant Program at City of Hope. "What makes me happy is no longer having to say to a patient, 'Sorry, we don't have a donor for you."

#### **OVERCOMING BARRIERS IN GRAFT-VERSUS-HOST DISEASE**

While the chance of getting graftversus-host disease (GVHD) depends on the HLA matching, age and gender of the donor and recipient, GVHD is a long-term side effect of allogeneic stem cell transplant patients. Occurring in over 50% of cases, GVHD causes donor's T lymphocytes cells to attack the patient's cells, including healthy tissue of the recipient's body such as



Defu Zeng, Ph.D. Professor, Department of Immunology and Theranostics

gut, liver, lung and skin. Symptoms can be mild to severe and often include mouth ulcers, gastrointestinal distress and rashes.

Currently, immunosuppressants are used to minimize the degree of GVHD. However, they can also diminish the anticancer effects of the donor T cells. Through experimental work, an international team of researchers led by City of Hope's Defu Zeng, Ph.D., professor in the Department of Immunology and Theranostics, found a way to prevent GVHD after stem cell transplants, while retaining the transplants' positive effects on fighting leukemia and lymphoma.

The study findings confirm that depletion of a specific type of donor T cells (CD4+) soon after transplants prevents GVHD while preserving strong anti-cancer effects. The depletion of CD4+ cells causes another type of T cell (CD8+) to halt the destruction of normal tissue, yet strengthen their ability to fight cancer, hence the donor CD8+ T cells can eliminate tumor cells without causing GVHD.

"If successfully translated into clinical application, this regimen may represent one of the novel approaches that allow strong GVL effects without causing GVHD," says Zeng. "This kind of regimen has the potential to promote widespread application of allogenic HCT as a curative therapy for hematological malignancies." A clinical trial is soon to open in order to translate this novel discovery into clinical application that helps improve patient outcomes.

# Age is no longer a barrier for bone marrow transplants

ity of Hope was one of the first institutions to use transplantation in the treatment of patients with leukemia who were over the age of 50. This was accomplished by developing transplant regimens that relied less on the intensity of chemotherapy and radiation and more on the anti-tumor effects of the graft itself, known as the graft-versus-tumor effect.

Many types of leukemia, particularly acute myeloid leukemia (AML) and myelodysplasia, are clonal disorders involving hematopoietic stem cells that are more common in older adults. Because of age and the risk of toxicity, these patients were often not candidates for transplant. City of Hope clinical investigators have developed new transplant regimens that could be used to treat older patients with hematologic malignancies, particularly those over the age of 70. In a study led by Monzr Al Malki, M.D., over 50 patients over the age of 70 were transplanted using a transplant regimen developed at City of Hope. The results showed that more than more than 95% of the patients achieved complete donor engraftment and 70% had a two-year overall leukemia-free survival. Transplant-related complications and morbidities did not differ from the



Patient Leif Voeltz at the 43rd Annual Bone Marrow Transplant Reunion in 2019

commonly expected ones seen in younger patients. This led them to conclude that age is no longer a barrier for transplant, opening up the opportunity for a curative therapy in older people with leukemia and myelodysplasia.

Thus, patients with acute lymphoblastic leukemia, AML, myelodysplasia and myeloproliferative disorders are now evaluated like their young counterparts for transplant with the hope that these patients can also achieve a long-term cure of their bone marrow disorder.

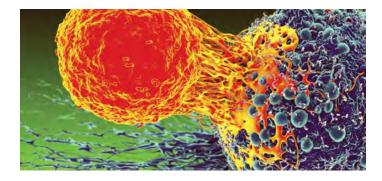
# Among the First to Utilize CAR T Cell Therapy as a Bridge to Stem Cell Transplant

or many patients with leukemia, induction therapy is administered to bring about remission, often paving the way to a potentially curative transplant. Sometimes, however, the therapy is not effective, and patients develop drug-resistant disease that precludes successful curative treatment. Transplant physicians at City of Hope were some of the first to develop CART cell therapy as a potential bridge therapy to bone marrow transplant for patients with leukemia and lymphoma.

CAR T cell treatment is a cellular immunotherapy that reengineers the patient's own immune cells to recognize and attack cancer cells. The specially engineered immune cells can kill cancer cells even in chemo-resistant cases, leading to a remission that makes it an effective bridge to transplant. The remission rate at City of Hope for adult patients with acute lymphoblastic leukemia (ALL) utilizing CD19 CAR T cells is close to 100%, and many patients have gone on to successful transplant following this immunotherapy procedure. Similar to transplant, there is no age barrier for the use of CAR T cells

for the treatment of leukemia, lymphoma and now multiple myeloma, with patients in their 70s being successfully treated.

City of Hope is home to one of the most comprehensive CART cell programs in the world with 45 clinical trials either current or completed, targeting various hematologic and solid tumors, including brain tumors. Having expertise in both stem cell therapy and cellular immune therapy within the same program facilitates collaborations that lead to new therapies and better outcomes for patient with these diseases.



For all CART inquiries (patient, physician, clinical trials), contact (833) 310-CART (2278). For all other clinical trials, contact (626) 218-1133 or visit clinicaltrials.coh.org.

# CITY OF HOPE **CURRENT OPENINGS**

ity of Hope is home to award-winning health care and has earned some of the top honors in the nation. Here at the forefront, we are looking for professionals who have distinguished themselves and are dedicated to excellence and care, just as we are. We welcome you to explore careers with City of Hope as we continue to expand throughout Southern California, including our **new Orange County cancer campus** opening in 2022.

## Current Openings\*

#### Gastrointestinal Oncology, Genitourinary Oncology, Thoracic Oncology, Women's Oncology

 Program Leaders (medical oncologists or surgeons) Irvine

#### **Department of Diagnostic Radiology**

- Body Imager: Onco-radiology, experience preferred
- Body Imager: Musculoskeletal, experience preferred
- PET/MR Radiologist, Body Imager
- Interventional Radiologist, Associate level preferred

#### Department of Hematology & Hematopoietic Cell Transplantation

- Leukemia Translational Clinician, Assistant-Associate Professor level
- Myeloma Clinician, Assistant-Associate Professor level **Duarte**
- Hematologist Associate Clinical Professor, fellowship trained **Irvine**

#### Department of Medical Oncology & Therapeutics Research

- Clinical Cancer Genomics
- Gastrointestinal Oncology
- Melanoma/Skin Oncology Duarte
- General Medical Oncology Clinical Faculty Antelope Valley, Simi Valley, Glendora/West Covina

#### Department of Medicine

- · Gastroenterology, Interventional Endoscopist
- General Neurology
- Nocturnist
- Pulmonary/Critical Care Duarte



#### Department of Pathology

- Surgical Pathologists Head and Neck, GU and Soft Tissue
- Pathology Informatics **Duarte**

#### Department of Radiation Oncology

- Radiation Oncologists Associate Clinical Professor, fellowship trained specializing in:
  - · Image-guided respiratory-gated lung stereotactic body radiation therapy
  - Stereotactic radiosurgery
  - Adaptive radiotherapy
  - High dose rate brachytherapy Irvine

#### Department of Supportive Care Medicine

• Palliative Medicine — Geriatrics experience preferred **Duarte** 

#### **Department of Surgery**

- Chief, Gynecologic Oncology
- Chief, Plastic Surgery
- Chief, Surgical Oncology
- General Oncologic Surgery Clinical Faculty Corona, Upland
- Gynecologic Oncologist Clinical Faculty South Bay, West San Fernando Valley
- Urologic Oncology Clinical Faculty Antelope Valley/Santa Clarita
- Surgeons Experienced, fellowship-trained
  - Breast Surgery
  - GOS/Colon and Rectal Surgery
  - Gynecologic Oncology
  - General Urology

Irvine

For a complete list of our current opportunities, please visit the Physician Careers webpage at CityofHope.org/MDrecruitment.

<sup>\*</sup>Positions are subject to change.

#### **NEW HOPE**

City of Hope recently welcomed the following new physicians to its medical staff:

#### **IDOROENYI AMANAM, M.D.**

Assistant Clinical Professor, Department of Hematology & Hematopoetic Cell Transplanation Location: Duarte

#### **HANNAH ASGHARI, M.D.**

Assistant Clinical Professor, **Department of Medical Oncology** & Therapeutics Research Location: Antelope Valley

#### **BRIAN BALL, M.D.**

Assistant Clinical Professor, Department of Hematology & Hematopoietic Cell Transplantation Location: Duarte

#### **RUSHA BHANDARI, M.D., M.S.**

Clinical Professor, **Department of Pediatrics** Location: Duarte

#### PETER CURTIN, M.D.

Clinical Professor, Department of Hematology & Hematopoietic Cell Transplantation Location: Duarte

#### ZAIN JABRI, M.D.

Assistant Clinical Professor, **Department of Medicine** Location: Duarte

#### YULIAN KHAGI, M.D.

Assistant Clinical Professor, **Department of Medical Oncology** & Therapeutics Research Location: Corona

#### **ERIC D. MECUSKER, D.O.**

Assistant Clinical Professor, Department of Supportive Care Medicine Location: Duarte

#### **REZA MOSTOFI, M.D.**

Assistant Clinical Professor, **Department of Medical Oncology** & Therapeutics Research Location: South Bay

#### RAMYA MUDDASANI, D.O., M.S.

Assistant Clinical Professor, **Department of Medicine** Location: Duarte

#### **ANDREW NGUYEN, M.D.**

Assistant Clinical Professor, Division of Surgical Oncology, **Department of Surgery** Location: South Bay

#### **RANJAN PATHAK, M.D.**

Assistant Clinical Professor, **Department of Medical Oncology** & Therapeutics Research Location: Duarte

#### ALFREDO PUING, M.D.

Assistant Clinical Professor, Department of Medicine, **Division of Infectious Diseases** Location: Duarte

#### MOHAMMAD SADI, M.D.

Assistant Clinical Professor, **Department of Medicine** Location: Duarte

#### **DUPINDER SINGH, M.D.**

Assistant Clinical Professor, Department of Medicine, **Division of Gastroenterology** Location: Duarte

#### F. MARC STEWART, M.D.

Clinical Professor and Vice Chair of Hematology & Hematopoeitic Cell Transplantation Location: Duarte

#### **NEEL TALWAR, M.D.**

Assistant Clinical Professor, Department of Medical Oncology & Therapeutics Research Location: Upland

#### RANDY TAPLITZ, M.D.

Chair and Clinical Professor, Department of Medicine Location: Duarte

#### ROMA TICKOO, M.D., M.P.H.

Assistant Clinical Professor, Department of Supportive Care Medicine Location: Duarte

#### MARIA MERCEDES CHANG VILLACRESES, M.D.

Assistant Clinical Professor, Department of Diabetes, Endocrinology & Metabolism Location: Duarte

#### MIGUEL A. VILLALONA, M.D.

Professor, Department of Medical Oncology & Therapeutics Research

#### Location: Duarte

#### **CHRISTINA WEI, M.D.**

Assistant Clinical Professor, Department of Pathology, Division of Anatomic Pathology Location: Duarte

#### **DEBRA WONG, M.D.**

Assistant Clinical Professor, **Department of Medical Oncology** & Therapeutics Research Location: Duarte

#### **OUR LOCATIONS**

City of Hope's clinical network extends the institution's reach to more patients by bringing premier care to local communities across Los Angeles, Ventura, San Bernardino, Orange and Riverside counties.

#### **MAIN CAMPUS**

1500 E. Duarte Road, Duarte, CA 91010

#### **COMMUNITY PRACTICE SITES**

#### **Antelope Valley**

44151 15th St. West, Lancaster, CA 93534

301 W. Huntington Drive, Suite 400, Arcadia, CA 91007

1280 Corona Pointe Court, Suite 112, Corona, CA 92879

412 W. Carroll Ave., Suite 200, Glendora, CA 91741

#### Mission Hills

15031 Rinaldi St., Suite 150, Mission Hills, CA 91345

#### **Newport Beach**

1601 Avocado Ave., Newport Beach, CA 92660

630 S. Raymond Ave., Suite 220, Pasadena, CA 91105

#### Santa Clarita

23823 Valencia Blvd., Suite 250, Santa Clarita, CA 91355

1157 Swallow Lane, Simi Valley, CA 93065

#### South Bay

5215 Torrance Blvd., Torrance, CA 90503

#### South Pasadena

209 Fair Oaks Ave., South Pasadena, CA 91030

#### **Thousand Oaks**

425 Haaland Drive, Suite 101 Thousand Oaks, CA 91361

1100 San Bernardino Road, Suite 1100, Upland, CA 91786

#### West Covina

1250 S. Sunset Ave., Suite 303, West Covina, CA 91790

#### RADIATION ONCOLOGY COMMUNITY PRACTICE SITES

#### **Arcadia Radiation Oncology**

301 W. Huntington Drive, Suite 120, Arcadia, CA 91007

#### **Glendale Radiation Oncology**

720 E. Colorado St., Glendale, CA 91205

#### **Riverside Radiation Oncology**

6939 Palm Court, Riverside, CA 92506

#### San Bernardino Radiation Oncology

401 E. Highland Ave., Suite D, San Bernardino, CA 92404

#### Santa Clarita Radiation Oncology

26357 McBean Parkway, Suite 150, Valencia, CA 91355

#### **Sherman Oaks Radiation Oncology**

5522 Sepulveda Blvd., Sherman Oaks, CA 91411

#### **Temecula Radiation Oncology**

44274 George Cushman Court, Suite 100, Temecula, CA 92592

#### West Hills Radiation Oncology

7301 Medical Center Drive, Suite 100, West Hills, CA 91307

#### Wildomar Radiation Oncology

36450 Inland Valley Drive, Suite 101, Wildomar, CA 92595

To refer a patient, call **800-826-4673 (HOPE)** or visit CityofHope.org/refer-a-patient.





Clinical Marketing Dept. 1500 E. Duarte Road Duarte, CA 91010-3000

#### **PHYSICIAN News:**

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Attn: Olive Suarez, MHA, Editor Clinical Marketing Dept. City of Hope 1500 E. Duarte Road Duarte, CA 91010 physiciannews@coh.org

# CANCER EXPERTISE ACCELERATES COVID-19 RESEARCH

With research expertise on deadly viruses similar to SARS-CoV-2, cancer and vulnerable immune systems, experts at City of Hope were primed to quickly begin COVID-19 research.

Two vaccine development projects are currently underway. The vaccine being developed by **Don Diamond**, **Ph.D.**, viral

immunologist with the Department of Hematology & Hematopoietic Cell Transplantation and co-investigators Flavia Chiuppesi, Ph.D., and Felix Wussow, Ph.D., both research professors, relies on a subunit strategy whereupon synthetic copies of immunogenic viral components get inserted into a carrier virus.

This technique has been used by the group in the past to develop a novel



Don Diamond, Ph.D.
Professor, Department of
Department of Hematology
& Hematopoietic Cell
Transplantation

Triplex vaccine against cytomegalovirus (CMV), a virus that can cause pneumonia and other serious complications in patients with weakened immune systems, similar to coronavirus.

Findings from a phase 2 randomized, placebo-controlled clinical trial showed that bone marrow and stem cell transplant patients who received Triplex were 50% less likely to develop health complications related to the virus than patients who did not take Triplex. The measurable immune response and study findings illustrate the promise of applying this vaccine approach toward COVID-19.

Larry W. Kwak, M.D., Ph.D., the Dr. Michael Friedman Professor in Translational Medicine, is building upon infrastructure he established when pioneering a therapeutic vaccine for the treatment of non-Hodgkin lymphoma. Kwak will fuse naked DNA sequences encoding SARS-CoV-2 proteins with a chemokine adjuvant to stimulate a strong immune response. In addition to being expedient, this approach may also



Larry W. Kwak, M.D., Ph.D. Vice President and Deputy Director, Comprehensive Cancer Center Director, Toni Stephenson Lymphoma Center

benefit immune compromised patients, as the vaccine relies on genetic sequences rather than live or attenuated virus.