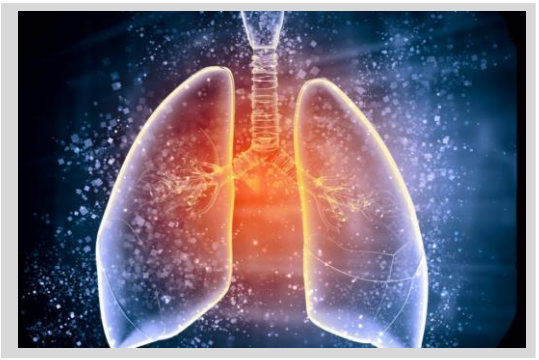
NORTHWESTERN INTERNATIONAL HEALTH

NORTHWESTERN SCIENTISTS DISCOVER CAUSE OF DEADLY SYNDROME AFTER LUNG TRANSPLANTATION

BY ANNA WILLIAMS



Northwestern Medicine scientists have discovered that a subset of immune cells called nonclassical monocytes (NCMs), previously unknown to reside in the lungs, play a key role in driving primary graft dysfunction (PGD), the leading cause of death after lung transplantation.

The study, published in Science Translational Medicine, also demonstrates that targeting these cells could lead to novel treatments for PGD, a complication that currently impacts more than half of transplant patients.

Ankit Bharat, MD, assistant professor of Surgery in the Division of Thoracic Surgery at Northwestern Medicine, was the principal investigator of the study.

"This is a widespread, lethal problem and the biggest reason why lung transplant patients experience both early death and long-term problems. So if you can fix PGD, you can really fix a lot about transplantation," Bharat said. "Now we know what causes it, and we can develop a treatment for it."

Ankit Bharat, MD

PGD is a severe form of lung injury that develops when the recipient's neutrophils — white blood cells — are recruited into the transplanted lung, initiating the inflammatory cascade and causing tissue damage. But while it has been understood that neutrophils were the main effector cells seen in PGD, the mechanisms that drive their influx into the lung were unknown. Further, targeting the patient's neutrophils was not considered a practical strategy for treatment, given that those same cells are critical for defending the body against pathogens.

In the current study, the scientists demonstrated that NCMs hidden in the donor lung are the culprit ultimately responsible for initiating the damaging inflow of neutrophils following transplantation of that lung.

Previously, it had been thought that all donor immune cells are eradicated when the lungs are flushed with a solution prior to transplantation. But the scientists discovered that NCMs, a type of immune cell whose structure and function have only recently been described, are actually retained in the blood vessels of the donor lung.

After identifying these cells in the lungs for the first time, the scientists further demonstrated their fundamental role in developing PGD: NCMs activate a pathway that produces a protein called CXCL2, which acts to attract the damaging neutrophils into the lung.

The findings suggest that targeting NCMs in donor lungs could potentially prevent the development of PGD. "This is a clinically-relevant finding, because it would likely be easy to develop a drug that kills these cells at the time of transplant," said Bharat, also a professor of Medicine in the Division of Pulmonary and Critical Care and a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. "That's a big strength of our findings: Because these are donor-derived cells, you could administer those drugs to the donor lungs before transplant and prevent any potential side effects to the recipient."

The NCMs also don't seem to play a role in a recipient's ability to fight infection, the scientists found, indicating that the cells could be eradicated without weakening the immune system.

The scientists now plan to investigate developing a drug that would eliminate NCMs during transplantation. Similar therapies have already been demonstrated in their animal models.

"We truly believe here that if a patient develops an unsolvable problem, it should be our commitment and duty to do everything we can to take that problem to our scientific laboratories, find a cure and then bring it back to patients," Bharat said. "Hence, while we ensure that patients receive the best technical expertise in the field of lung transplantation, we also want to advance the field by finding cures for such lethal problems to really make a difference in patient outcomes."

Bharat and his collaborators followed a similar path two years ago when they identified the mechanism behind hyperammonemia syndrome, a fatal disorder that affects 5 percent of lung transplant recipients, after it affected one of their patients. The findings, also published in Science Translational Medicine, eventually led to a treatment for a deadly syndrome that had plagued the field of lung transplantation since its inception.

"For several years since it was first identified, recipients have been dying of hyperammonemia. And now with this discovery, everyone can be effectively treated," Bharat said. "I hope that similarly with primary graft dysfunction we can now develop a treatment for this lethal problem."

Zhikun Zheng, MD, a former research fellow, and Stephen Chiu, MD, a postdoctoral fellow in the Bharat Laboratory, were the first authors of the study.

JEFFERY WAYNE, MD RECEIVES HUMANITARIAN AWARD

CANCER CARE/ONCOLOGY | OCTOBER 09, 2017

The Melanoma Research Foundation awarded Jeffrey Wayne, MD, oncologist at Northwestern Memorial Hospital with the humanitarian award at the 3rd Annual Wings of Hope Gala. Each year the foundation awards a leader in the local medical community who has committed to fighting melanoma through exemplary patient care, cutting-edged research and scientific leadership.

"When it came down to selecting this year's honoree we knew Dr. Wayne fit the bill," said Steve Silverstein, Melanoma Research Foundation Board Chair. "His efforts in the community, among colleagues and with his patients are superb and it was truly an honor to present him with this year's award."

"I am humbled by this honor from the Melanoma Research Foundation," said Dr. Wayne. "When I arrived at Northwestern Memorial Hospital 16 years ago, and was tasked with building a comprehensive melanoma program, I could have never imagined being afforded such an honor. What was perhaps the best part of the evening for me was watching my 5 of my patients come up to the stage to share their stories and receive their courage awards. There is no better feeling for a cancer surgeon than to see his or her patients overcome the odds, and to know that you played some small role in their success."

https://www.nm.org/about-us/northwestern-medicine-newsroom/nm-news-blog/jeffrey-wayne-md-receives-humanitarian-award

THE SKIN CANCER INSTITUTE AT NORTHWESTERN MEDICINE

The Skin Cancer Institute within the Robert H. Lurie Comprehensive Cancer Center is deeply committed to providing advanced care for melanoma and reversing the growing prevalence of all forms of skin cancer. The Skin Cancer Institute provides advanced care through continued high-impact research, education and training. The Institute also offers multidisciplinary leadership that coordinates dermatology, surgical oncology, medical oncology and radiation oncology care with translational research.

Our five areas of excellence are:

- Melanoma
- Cutaneous T-cell lymphoma
- Epithelial cancer, basal and squamous cell cancers
- Skin cancer education
- Skin complications of cancer therapies

Leading-edge clinical and lab-based research to benefit our patients with cancer is a critical component of the Skin Cancer Institute.

https://www.nm.org/conditions-and-care-areas/cancer-care/dermatologic-cancers/melanoma/specialists-and-care-centers

SPOTLIGHT ON NORTHWESTERN MEDICINE'S MARIANJOY REHABILITATION HOSPITAL

HOSPITALS, REHABILITATION/PHYSICAL THERAPY

In 2014, the Marianjoy Assistive Rehabilitation Technology Institute (MARTI) of Northwestern Medicine, opened on the main Wheaton campus, offering patients access to a new Aquatic Therapy center, a unique Driver Rehabilitation Center, a nationally recognized Swallowing and Voice Center, the Northwestern Medicine Aphasia Center at Marianjoy and other innovative programs. In 2016, the Tellabs Center for Neurorehabilitation and Neuroplasticity (TCNN) opened, dramatically expanding the treatment options and making Marianjoy Rehabilitation Hospital one of few facilities offering such a range of technologies.

More than 45,000 patients receive inpatient care, outpatient therapy and physician services at Marianjoy Rehabilitation Hospital annually and some of the most experienced specialists in stroke, brain and spinal cord injury practice at the hospital. In addition to our accredited stroke, brain injury and pain programs, experts specialize in treating a variety of diagnoses, from orthopaedic physical therapy for hip and knee replacements, to neuromuscular rehabilitation for conditions like multiple sclerosis or Guillain-Barré syndrome.

A campus designed for holistic care

Marianjoy Rehabilitation Hospital was designed with the patient experience in mind. Each floor of the hospital is divided into treatment areas focused on specific diagnostic conditions, and every patient room features floor-to-ceiling windows to provide views of the surrounding beautiful 60-acre wooded campus in Wheaton, Illinois.

Throughout the campus, patients can enjoy a variety of gardens intended to meet a range of mental, physical and spiritual needs. Several gardens are designed with a combination of surface textures to practice walking and balancing in real-world environments. Patients and their families can enjoy the many accessible tree-lined paths or bright, airy and welcoming lobbies.

TELLABS CENTER FOR NEUROREHABILITATION AND NEUROPLASTICITY- CUTTING EDGE TECHNOLOGY WITH WORLD CLASS CARE

- **Ekso GT™ Robotic Exoskeleton**
  Stimulates neuroplasticity through adaptively supportive walking system to reeducate the brain and muscles
- **ZeroG® Gait and Balance Training System**
  Enables practice with movement and balance in a safe, controlled environment
- **Armeo® Power Robotic Arm Exoskeleton and Armeo® Spring Arm & Hand Therapy**
  Stimulates brain and muscle activity to regain lost arm movement
- **Woodway Split-Belt Treadmill**
  Customizable therapy and assessment tool that can be interfaced with the ZeroG® system
- **KineAssist-MX®**
  A safe system for patients to practice walking and balance in simulated motion challenges
- **RealEyesX DVR™ Binocular Video Goggles**
  Enables therapists to diagnose and treat dizziness and vestibular disorders
- **NuStep Recumbent Trainer**
  Moderate exercise platform allowing for neuroplastic "priming" to achieve better functional outcomes
- **Bioness® Integrated Therapy System**
  Customizable visuomotor system evaluates and improves visual-motor activities
- **RE-WALK™ Bionic Leg and Suit**
  Wearable robotic exoskeleton enables patients with lower limb weakness to stand, walk, and even take stairs independently
- **Bertec Balance Advantage™ System CDP**
  Virtual reality computerized system enables diagnosis and treatment of balance impairments system

SUICIDE MOLECULES KILL ANY CANCER CELL

TIME TRAVELING HUNDREDS OF MILLIONS OF YEARS TO UNLEASH ONE OF NATURE'S ORIGINAL KILL SWITCHES

BY MARLA PAUL

CHICAGO - Small RNA molecules originally developed as a tool to study gene function trigger a mechanism hidden in every cell that forces the cell to commit suicide, reports a new Northwestern Medicine study, the first to identify molecules to trigger a fail-safe mechanism that may protect us from cancer.

The mechanism -- RNA suicide molecules -- can potentially be developed into a novel form of cancer therapy, the study authors said.

Marcus Ernst Peter, PhD

Cancer cells treated with the RNA molecules never become resistant to them because they simultaneously eliminate multiple genes that cancer cells need for survival. "It's like committing suicide by stabbing yourself, shooting yourself and jumping off a building all at the same time," said Northwestern scientist and lead study author Marcus Peter. "You cannot survive."

The inability of cancer cells to develop resistance to the molecules is a first, Peter said.

"This could be a major breakthrough," noted Peter, the Tom D. Spies Professor of Cancer Metabolism at Northwestern University Feinberg School of Medicine and a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

Peter and his team discovered sequences in the human genome that when converted into small double-stranded RNA molecules trigger what they believe to be an ancient kill switch in cells to prevent cancer. He has been searching for the phantom molecules with this activity for eight years.

"We think this is how multicellular organisms eliminated cancer before the development of the adaptive immune system, which is about 500 million years old," he said. "It could be a fail-safe that forces rogue cells to commit suicide. We believe it is active in every cell protecting us from cancer."

This study, which will be published Oct. 24 in eLife, and two other new Northwestern studies in Oncotarget and Cell Cycle by the Peter group, describe the discovery of the assassin molecules present in multiple human genes and their powerful effect on cancer in mice.

Looking back hundreds of millions of years

Why are these molecules so powerful? "Ever since life became multicellular, which could be more than 2 billion years ago, it had to deal with preventing or fighting cancer," Peter said. "So nature must have developed a fail-safe mechanism to prevent cancer or fight it the moment it forms. Otherwise, we wouldn't still be here." Thus began his search for natural molecules coded in the genome that kill cancer.

"We knew they would be very hard to find," Peter said. "The kill mechanism would only be active in a single cell the moment it becomes cancerous. It was a needle in a haystack."

But he found them by testing a class of small RNAs, called small interfering (si) RNAs, scientists use to suppress gene activity. siRNAs are designed by taking short sequences of the gene to be targeted and converting them into double- stranded RNA. These siRNAs when introduced into cells suppress the expression of the gene they are derived from.

RNA suicide molecules could be used for a novel form of cancel therapy. Peter found that a large number of these small RNAs derived from certain genes did not, as expected, only suppress the gene they were designed against. They also killed all cancer cells. His team discovered these special sequences are distributed throughout the human genome, embedded in multiple genes as shown in the study in Cell Cycle.

When converted to siRNAs, these sequences all act as highly trained super assassins. They kill the cells by simultaneously eliminating the genes required for cell survival. By taking out these survivor genes, the assassin molecule activates multiple death cell pathways in parallel.

The small RNA assassin molecules trigger a mechanism Peter calls DISE, for Death Induced by Survival gene Elimination.

Activating DISE in organisms with cancer might allow cancer cells to be eliminated. Peter's group has evidence this form of cell death preferentially affects cancer cells with little effect on normal cells.

To test this in a treatment situation, Peter collaborated with Dr. Shad Thaxton, associate professor of urology at Northwestern Medicine, to deliver the assassin molecules via nanoparticles to mice bearing human ovarian cancer. In the treated mice, the treatment strongly reduced the tumor growth with no toxicity to the mice, reports the study in Oncotarget. Importantly, the tumors did not develop resistance to this form of cancer treatment. Peter and Thaxton are now refining the treatment to increase its efficacy. "Our research may be tapping into one of nature's original kill switches, and we hope the impact will affect many cancers," he said. "Our findings could be disruptive."