Shriners Hospitals
for Children®— Cincinnati

Pediatric Specialty Care

Burns
Cleft Lip and Palate
Specialized Plastic Surgery

Research that Changes Lives



A look at burn research in Cincinnati

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Introduction

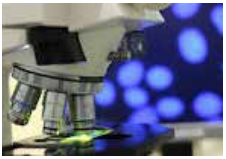
Throughout its history, Shriners Hospitals for Children® has followed a three-pronged mission of medical care, teaching and research. Early on, the organization made a commitment to supporting basic scientific research, the very foundation of science that allows us to understand how and why things happen.




As the health care system has grown and its areas of care have expanded, the research focus has also expanded. Today's Shriners Hospitals for Children are also centers for ongoing clinical research, with staff actively engaged in finding ways to improve a child's quality of life on a daily basis.

The mission of the Shriners Hospitals for Children (SHC) – Cincinnati research unit is to discover new knowledge that improves the quality of care and quality of life of children and families. Research projects are partially supported or, in some cases, fully supported by Medical Research Grants from the Shriners Hospitals for Children. The Cincinnati Research Center focuses on four broad areas that have critical roles in recovery from burn injury:

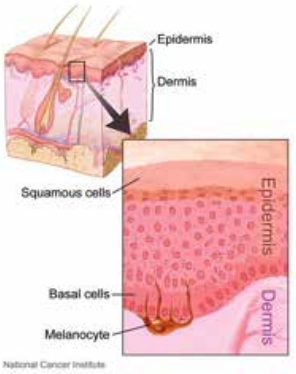
- Wound healing
- Immunology, inflammation, and infection
- Nutrition
- Sleep




Wound Healing Research

Skin substitutes for burn wound closure

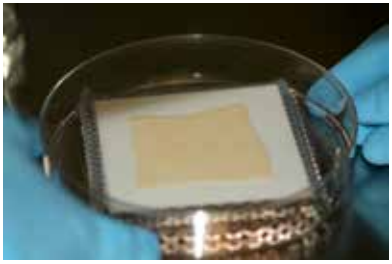
After a burn, wound closure is a critical part of recovery. Burns that destroy part of the upper layer of skin, the epidermis, can usually heal without skin grafting. However, when burns destroy both layers of skin, the epidermis and the dermis, skin grafting is required for healing. In patients with very large burns, skin substitutes can help speed healing and recovery by providing additional material for skin grafting.



Engineered skin substitutes are made through a process called "tissue engineering." This involves the isolation of cells from a patient's unburned skin. These cells are combined with a "scaffold," such as collagen, to provide structural support, and are cultured in the lab to form a skin-like tissue.

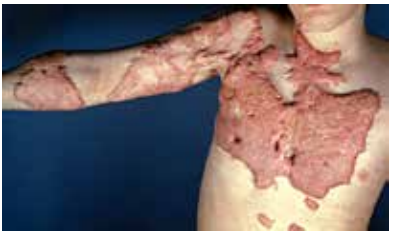
Skin substitutes previously developed by scientists at SHC-Cincinnati were made using two critical cell types: keratinocytes from the epidermis (upper skin layer) and fibroblasts from the dermis (lower skin layer). Clinical trials showed the potential for engineered skin to help healing in patients with very large burns. However, the color of the healed skin substitutes was not a good match for the patients' natural skin color, and structures such as hair were not present.

Current studies at SHC-Cincinnati are developing and testing more complex skin substitutes that include other cell types, in addition to keratinocytes and fibroblasts. Next-generation skin substitutes will contain melanocytes, which are pigment-producing cells, to regulate skin color, and hair follicle stem cells, for regrowth of hair. This research will lead to skin substitutes that look and function more like natural skin.



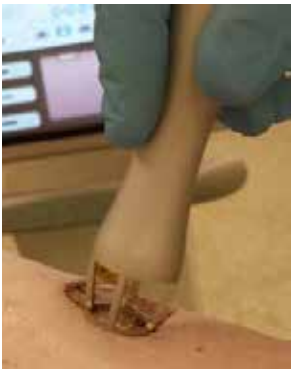
Understanding and treating abnormal scars

Scarring is a natural part of the healing process. Unfortunately, burns can result in abnormal scars that interfere with normal activities, impact self-esteem, and reduce overall quality of life. Hypertrophic scars and keloids are two types of abnormal scars that occur after burn injuries. Scientists at SHC-Cincinnati are studying why and how hypertrophic scars and keloids occur, and are using this knowledge to develop better treatments for these debilitating scars.

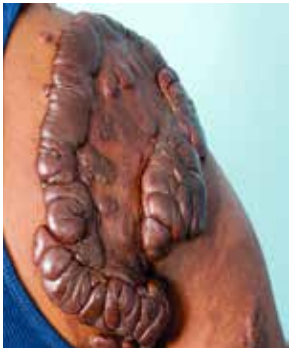


Hypertrophic scars are thick, raised scars that can be itchy, painful, and can restrict a patient's range-of-motion. Hypertrophic scars are relatively common after burns. There are several treatment options for patients with hypertrophic scars, but they are not all effective for every patient. Researchers are studying two of the most common treatments—compression garments and laser therapy—to help determine the best way to treat and prevent hypertrophic scars.

Compression garments are currently considered the "standard of care" for suppression of scarring, and have been used for many years to prevent hypertrophic scarring after burns. These tight-fitting, elastic garments, which are worn up to 23 hours per day, are thought to decrease scarring by maintaining pressure on the skin. However, some burn patients still develop hypertrophic scars, even when compression garments are used. Researchers are studying how pressure affects healing to better understand how compression therapy can be used to prevent hypertrophic scars from forming. This research can lead to more effective compression garments for scar prevention.



Laser therapy is gaining popularity for treatment of many skin disorders, including hypertrophic scars. Although lasers can improve the appearance of hypertrophic scars in some patients, their effectiveness has not been fully proven. In addition, several different types of lasers are in use, which can have different effects on scar tissue. Researchers and clinicians at SHC-Cincinnati, in collaboration with investigators at The Ohio State University, are studying how lasers affect the scarring process to determine the best way to use lasers for treatment of hypertrophic scars.



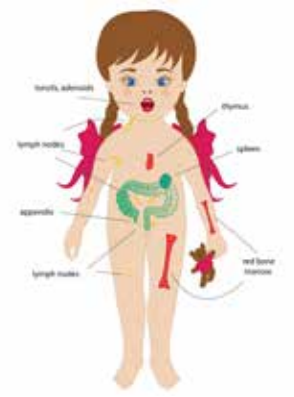
Keloids are a less common but more severe form of abnormal scarring that can occur after burns. Like hypertrophic scars, keloids are thick, raised scars that can be itchy, painful, and can restrict range of motion. However, unlike hypertrophic scars, keloids bulge out and extend beyond the boundary of the original wound, and tend to increase in size for months or even years after injury. Keloids can happen in anyone, but are more common in patients with darker skin pigmentation, such as African Americans. The reasons for this increased risk are not known, and the underlying causes of keloids are not well understood. Keloids are very difficult to treat. There are many different treatment options for keloid patients, but no currently available treatment works for every patient, and recurrence is very common.

Researchers at SHC-Cincinnati are studying keloid scars to learn why and how keloids form after wounding, and to determine why they are more common in certain patient populations. This knowledge will be used to develop more effective treatments for keloid scars. This research may also help clinicians identify patients at greatest risk for keloid formation, and provide improved strategies for keloid prevention.

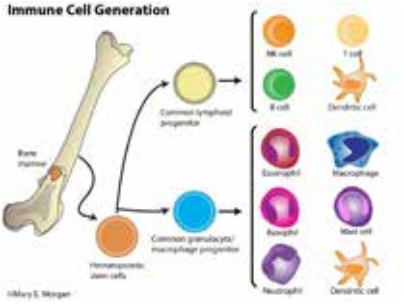
Immunology, Inflammation, and Infection

Research at SHC-Cincinnati aims to understand how the body's immune system responds to burn injury and fights infection.

Immunology is the study of the immune system, the system that protects against disease. Many different tissues and organs make up the immune system, including the spleen, lymph nodes, thymus, and bone marrow. These structures produce numerous different cell types involved in the immune response.



Inflammation is one of the first responses of the immune system to infection, and usually involves redness, swelling, heat, and pain due to increased blood flow and release of specific chemicals by cells after injury.



Infection occurs when a patient's body is invaded by disease-causing agents, such as bacteria. Bacterial infection in burn patients can lead to sepsis, a severe inflammatory response that can cause shock, organ failure, or death.

Burn injury can cause massive changes to the entire immune system, resulting in reduced immune function, increased susceptibility to infection, and excessive inflammation, which can lead to death if not properly controlled. Research at SHC-Cincinnati seeks to understand these processes for development of better therapies for burn patients.

Determining the right dose of antibiotics

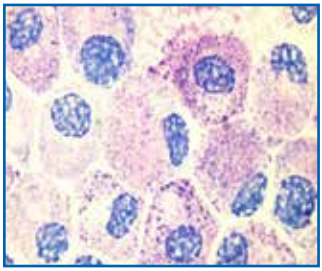
Approximately 75% of deaths in patients with large burns are due to sepsis. These life-threatening infections are often caused by antibiotic-resistant bacteria. Overuse of antibiotics can lead to increased numbers of antibiotic-resistant bacteria, so it is important to use only the amount of antibiotics needed to fight infection. Because burn injury causes major changes in metabolism, it can be hard to determine the right dose of antibiotics or other drugs for burn patients. Some burn patients may need double or even triple the amount of a drug that a non-burn patient needs to have the same effect. It is very important for doctors treating burn patients, especially children with burns, to use the right dose of an antibiotic drug—one that kills the bacteria without harming the patient. Doctors often lack the information they need to help determine the right dose.

Pharmacokinetics is the term used to describe how a drug is processed by the body: how it is absorbed, distributed, metabolized, and eliminated. At Shriners Hospitals for Children – Cincinnati, researchers are studying the pharmacokinetics of various drugs after burn injury. This knowledge is being used to determine the best treatment regimen for each burn patient. This improves care by optimizing the killing of infection-causing bacteria, without increasing the risk of negative side effects or increasing bacterial resistance to antibiotics.

Bone marrow cells that fight infection

Scientists at SHC-Cincinnati are studying the role of a group of immature bone marrow cells, called Myeloid-Derived Suppressor Cells, or "MDSC", in burn injury and recovery. MDSCs are immature bacteria-eating cells that are induced by inflammation, and have the ability to regulate other cells of the immune system. The presence of MDSC is correlated with protection against infection and pneumonia after burns.

Researchers are studying the mechanisms by which burn injury causes increased production of MDSC. By learning how to control the levels of these cells, new ways to control sepsis can be developed.

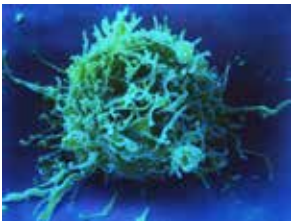


Mast cells in burns, wound healing, and post-burn infection

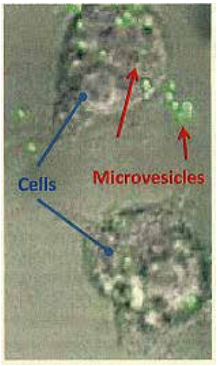
Mast cells are present in many different tissues of the body, where they are involved in inflammatory responses such as hypersensitivity and allergic reactions. When activated, a mast cell rapidly releases various hormones and chemicals into the body, including histamine and heparin. Mast cells are an important part of wound healing and management of burn injuries.

Studies at SHC-Cincinnati seek to identify the chemicals made by mast cells that are involved in burns, wound healing, and post-burn infection. This research can help identify important targets for development of new treatments to promote wound healing.

Prevention of hospital-acquired infection



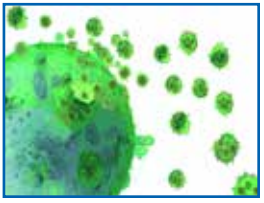
Nosocomial infections are infections that are acquired during hospitalization. Prevention of nosocomial infection is an important issue in all hospitals, including SHC-Cincinnati. Changes to the immune system after burns put burn patients at greater risk of nosocomial infection. One of these changes is a drop in the number of T cells, a group of immune cells that are important for fighting infection. Researchers at SHC-Cincinnati are studying drugs that reverse the loss of T cells caused by burns, which may lead to new therapies to reduce nosocomial infections in burn patients.



Changes in blood after burns

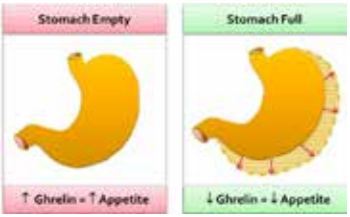
Burn injury can cause anemia, which is a reduction in the number of circulating red blood cells. Some changes that occur in the blood are due to small fragments of cells, measuring only about 1/100 the width of a human hair, which circulate throughout the body. These tiny cell fragments are called microvesicles.

Microvesicles can have different effects depending on their cell type of origin. In addition, the types of microvesicles found in the body are changed by burn injury. Researchers at SHC-Cincinnati discovered that burns cause an increase in a type of microvesicle particle that interferes with blood clotting. During infections, a different type of microvesicle is found in the body, which may interfere with the ability of white blood cells to kill bacteria. Studies have also shown that microvesicle formation may affect storage of red blood cells, reducing the effectiveness of blood used for blood transfusions. By studying microvesicles, researchers hope to develop therapies to control changes in the blood that happen after burn injury.

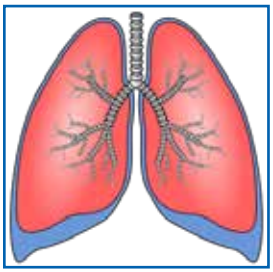


Muscle wasting after burn injury

Metabolic changes are common after burns. Major burns cause a hypermetabolic response, or an increase in metabolism, that can last even after the burn wounds have healed. To help fuel this increase in metabolism, the body breaks down skeletal muscle. This muscle loss results in decreased strength, making rehabilitation difficult.



Researchers at SHC-Cincinnati are studying the "hunger-hormone" ghrelin, which is normally produced in the stomach. When the stomach is empty, ghrelin is secreted; it acts on brain cells to increase hunger, and acts in the digestive system to prepare the body for food intake. Researchers discovered that ghrelin levels are decreased by burn injury; laboratory studies showed that increasing ghrelin levels could increase food intake and reduce muscle wasting. Current research involves the development of drugs based on the structure and activity of ghrelin for treatment of burn-induced muscle wasting.



Lung injury and infection after burns

Pneumonia, a bacterial infection of the lung, is a potentially lethal complication that can occur after burn injury. The lungs can also be harmed by smoke inhalation or inflammation. Researchers at SHC-Cincinnati are interested in finding new ways to fight lung infection and injury in burn patients.

Keratinocyte Growth Factor (KGF) is a protein produced by the lung that may have a protective role by increasing resistance to bacterial infection. Researchers found that KGF causes lung airway cells to increase production of bacteria-fighting factors. This suggests that KGF may be a promising therapeutic for burn patients. Current studies are testing whether KGF might be helpful in post burn pneumonia.

Nutrition

Meeting the nutritional needs of burn patients

Because of the metabolic changes that occur after burns, meeting the nutritional needs of burn patients can be challenging. Nutrition researchers have studied and tested formulations with various levels and types of proteins, fats, vitamins, minerals, probiotics, and fiber to determine the best combination to help improve recovery in burn patients. One formulation developed at SHC-Cincinnati has been commercially developed and is being sold under the trade name IMPACT™. It is currently used to improve outcomes in surgical and trauma patients.

Nutritional supplements to reduce inflammation

Nutrition researchers and clinicians at SHC-Cincinnati are interested in the development of nutritional supplements that reduce inflammation and fight infections in burned individuals. Dietary components that boost immune function are called immunonutrients. Recent studies showed that some of the nutrients supplied in IMPACT™ might be immunonutrients. Some immunonutrients, such as fish oil and arginine, may help reduce inflammation and fight wound infection. They could potentially be used to help diseases involving inflammation, such as cardiovascular disease and type II diabetes. Current studies aim to test immunonutrients in humans to determine their safety and effectiveness.

Sleep

The important role of sleep in recovery from burns

A good night's sleep is not just refreshing for the mind. There is compelling evidence that sleep has many health-related benefits. Sleep may even be an important predictor of longevity! Sleep is also vital for optimum recuperation from injury and illness. For patients with severe burns, getting sufficient sleep is difficult. Studies at Shriners Hospitals for Children – Cincinnati are unraveling the causes and effects of sleep deficiency after burns.

Researchers evaluate sleep using a painless test called polysomnography, which involves measuring brain waves, muscle tension, and eye movements using electrodes attached to the face and head. This test has been used to show that burn injury affects a patient's internal clock, known as the circadian rhythm. This contributes to sleep deprivation, a problem that continues long after the burn wound has healed.

The research team at SHC-Cincinnati is examining different types of interventions, such as sleep medications and alternative medicine approaches, to increase the time spent in deep, restorative sleep. This research will help determine new approaches for maximizing the quality of sleep, and, consequently, improve the outcomes in children recovering from burns.

Special Shared Facilities

Many scientific instruments, resources, or methods are very expensive—too expensive for a single laboratory to afford. ***Shared Facilities*** are shared resources or laboratories available for use by multiple researchers, providing a cost-effective way to access high-tech equipment and expensive services. SHC-Cincinnati has multiple Shared Facilities for use by Shriners researchers and members of the Cincinnati research community, including the University of Cincinnati and Cincinnati Children's Hospital Medical Center.

Flow Cytometry Shared Facility:

Flow cytometry has many applications in basic research, clinical practice, and clinical trials. A flow cytometer is a sophisticated instrument that uses laser technology to measure various properties of cells, including size and activation state. It can also be used to detect the presence or absence of certain proteins inside cells or on a cell's surface. These properties may be used to sort and purify specific cell populations of interest. Analysis using flow cytometry is based on scattering of laser light or measurement of fluorescence. The SHC flow cytometry shared facility has the ability to use up to five lasers, which permits measurement of up to 20 different parameters of cells.

Histology Shared Facility:

Histology is the study of the microscopic anatomy of cells and tissues. This usually involves the fixation (to prevent decay) and sectioning (to make ultra-thin slices) of tissue samples to permit detailed structural analysis. Preparation of tissue for histology requires a great deal of training, specialized equipment, and many different types of chemical dyes used to visualize structures within cells.

Clinical Research Shared Facility

Clinical research refers to the testing of new medications, procedures, and devices in patients for safety and efficacy. Clinical research must comply with numerous local and federal regulations to ensure the safe and appropriate treatment of human subjects. Clinical research nurses are very knowledgeable about applicable regulations and assist with initiating and conducting clinical trials. Nurses act as liaisons between researchers and clinicians, and assist clinicians in planning and conducting experiments in patients, as well as collection and analysis of data. Research nurses in the Clinical Research Shared Facility help with essentially all of the clinical research activities conducted at the SHC-Cincinnati.

Analysis of data is a critical component of research, whether that research is done at a laboratory bench or in a clinical setting. Statistical analysis uses mathematical methods to identify trends in data, and ensures the validity of conclusions drawn from a particular study. For medical and biological research, a biostatistician helps with sample size estimation (determining number of patients needed for a study), data management and data analysis. The SHC-Cincinnati research department employs a staff biostatistician to help researchers involved in both preclinical and clinical research with study design and statistical analysis of data.

Who we are

Leadership & Administration

Petra Warner, MD	Hospital Chief of Staff
John van Aalst, MD	Director of Research
Denise Byrum, MS	Research Operations Coordinator

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George Babcock, PhD	Immunology, infection, microvesicles
Kevin Bailey, MD	Plastic surgery, scar reduction
Ambi Balasubramaniam, PhD	Muscle wasting, burn metabolism
Steven Boyce, PhD	Skin tissue engineering, scar reduction
Charles Caldwell, PhD	Immunology, infection
Jason Gardner, PhD	Immunology, infection
Michele Gottschlich, PhD	Sleep research, nutrition, cleft lip & palate
Dan Healy, PharmD	Antimicrobial pharmacokinetics, pharmacodynamics
David Hildeman, PhD	Immunology, infection
J. Howard James, PhD	Burn metabolism
W. John Kitzmiller, MD	Plastic surgery, scar reduction
Francis McCormack, MD	Lung disease, lung infection
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Santa Ono, PhD	Immunology, mast cells
Brian Pan, MD	Cleft lip & palate, otoplasty
Heather Powell, PhD	Skin tissue engineering, scar reduction
Timothy Pritts, MD, PhD	Surgery, inflammation, microvesicles
Sulaiman Sheriff, PhD	Muscle wasting, burn metabolism
Dorothy Supp, PhD	Skin tissue engineering, scar reduction

Special Shared Facilities

Karen Domenico	Flow Cytometry Special Shared Facility
Mary Rolfes, MLT/HT, ASCP	Histology Special Shared Facility
Laura Fowler, RN, BSN, CCRC	Clinical Research Coordinator, Clinical Research Special Shared Facility
Judy Nelson, RN, CCRC	Clinical Research Nurse, Clinical Research Special Shared Facility
Laura James, MS	Biostatistics, Clinical Research Special Shared Facility

About Shriners Hospitals for Children

Shriners Hospitals for Children® is a health care system with locations in the U.S., Canada and Mexico, dedicated to improving the lives of children by providing pediatric specialty care, conducting innovative research, and offering outstanding teaching programs for medical professionals. Our 22 facilities provide advanced care for children with orthopaedic conditions, burns, spinal cord injuries, and cleft lip and palate, regardless of the families' ability to pay. Generally, care is provided until age 18, although, in some cases, it may be extended to age 21. All care and services are provided in a family-centered environment.

Shriners Hospitals for Children — Cincinnati is a regional referral pediatric burn and plastic surgery center serving the Midwest and Southeastern United States. With some of the country's most experienced plastic surgeons, Shriners Hospitals for Children – Cincinnati treats children with pediatric burns and many non-burn conditions such as cleft lip and palate, ear deformities, hairy nevus, hand malformations, and post-trauma deformities. The hospital is Magnet™ designated.

Shriners Hospitals for Children is a 501(c)3 non-profit organization and relies on the generosity of donors. All donations are tax deductible to the fullest extent permitted by law.

For more information, please visit
shrinershospitalcincinnati.org

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