GOAL

To rapidly translate cutting edge adult and pluripotent stem cell and tissue engineering laboratory research into clinical and commercial arenas, to replace and repair diseased tissues and organs, thereby establishing Northeast Ohio as one of the top three regions in the country in stem cell and regenerative medical research.

MISSION

To utilize adult and pluripotent human stem cells and tissue engineering technology to treat human disease.

ABOUT THE NATIONAL CENTER FOR REGENERATIVE MEDICINE

The National Center for Regenerative Medicine (NCRM) builds upon leading research and clinical programs at its founding institutions, Case Western Reserve University (CWRU), Cleveland Clinic (CC), University Hospitals Case Medical Center (UHCMC), Athersys, and The Ohio State University (OSU), in heart disease, cancer, genetic disorders, and neurodegenerative diseases, coupled with a 35-year history of research on non-embryonic stem cells at these institutions. This collaboration of outstanding clinical and research programs, combined with tested and proven experience using non-embryonic stem cell transplantation to treat patients, makes this center unique in the United States.


Figure: Expanding cytolytic natural killer (NK) cells for potential immunotherapy against HIV-1 and cancer - immunofluorescent image of primary NK cells with stained punctate neural cell adhesion molecules (CD56) on the cell surface, and intracellular F-actin and nuclei. Peripheral blood NK cells were isolated from a healthy donor and expanded ex vivo over 300-fold with cytokines that induce a unique CD56brightCD16+ phenotype. Unlike NK cells typically found in blood, these highly activated NK cells specifically kill HIV-infected primary target cells and cancer cell lines, yet are capable of an even more specific antibody-dependent cell-mediated cytotoxicity (ADCC) via persistent CD16 expression.
Dear Colleagues,

At the National Center for Regenerative Medicine, located across the academic centers linked to Case Western Reserve University, in Cleveland Ohio, our mission is to:

Discover and implement regenerative medicine strategies that can effectively treat complex diseases.

To this end, we have assembled accomplished research teams and innovative clinical investigators that help us move exciting discoveries into therapeutic clinical trials by utilizing our core facilities, including: Imaging, iPS production, a clinical cell production facility and the new and remarkable OHIO-Alive facility. As a result, we continue to push the boundaries for new regenerative medicine therapies. Meanwhile our basic science laboratories continue to discover new pathways regulating stem cell growth and differentiation and their malignant transformation, leading to the metastatic phenotype.

Within this annual report, I am happy to note that we have published a summary of the exceptional Cancer Stem Cell conference held last August (page 17), and are anticipating this year’s Mesenchymal Stem Cell conference, (MSC) 2015. These conferences, held in Cleveland, Ohio, highlight our efforts to bring the research and clinical community focused on regenerative medicine and stem cell biology to the city every year.

As you read through our accomplishments and scope, you will realize, as we do, that the National Center for Regenerative Medicine continues to be a leading edge organization committed to outstanding science and timely therapeutic approaches that benefit patients.

Our Best Regards,
It all started with some seed money from the state’s Ohio Third Frontier and luring regenerative medicine rising star, Jeremy N. Rich, MD, away from Duke University. His efforts led to establishing the highly innovative and productive Department of Stem Cell Biology and Regenerative Medicine at Cleveland Clinic’s Lerner Research Institute. In the six short years since his arrival, Rich has recruited seven top scientists and is pursuing recruitment of more outstanding investigators to round out the department.

“The goal was to establish a department that represents the overall commitment made by the state of Ohio and in the context of federal allocations to the National Center for Regenerative Medicine for Northeastern Ohio and specifically to the Cleveland Clinic,” Rich said. “Our department is a continuation of the initial investment into the Lerner Research Institute where 170 investigators focus on a wide range of basic, translational and clinical science research.”

Specifically, his department’s scientists investigate the fundamental biology of adult stem cells, the development of pre-clinical models of stem cell therapeutics, groundbreaking clinical trials and finally, efficient clinical application. Each of the department’s faculty members, including Rich, performs his/her own cutting-edge investigation in specific niches of stem cells.

Rich’s investigation zeros in on malignant glioma brain tumors and the chemotherapy-resistant, stem-like cells that drive this form of cancer with their self-renewal capability and multipotency. He and his team are examining the microenvironment/niche, molecular markers and survival pathways with the goal of one day designing clinical interventions to target these resistant cells more effectively.

Joining him are brain tumor investigators: Jeongpyu Lee, PhD; Shideng Bao, PhD; and Jennifer Yu, MD, PhD.

Additional research in his department includes the work of associate staffer Jan Jensen, PhD, who is investigating the developmental biology of the pancreas. He is exploring the molecular mechanisms controlling insulin-cell development and the ability to apply regenerative medicine to beta islet cells affected in diabetes. “His work has served as the cornerstone for the OH-Alive effort recently funded by the NCRM to bridge the gap between more basic science and translational science approaches,” Rich said. (OH-Alive is an initiative to advance Ohio as one of the leading regions for stem cell therapy).

Other scientists in Rich’s department are studying key stem cell pathways as well.
Research in the Liu Laboratory focuses on two novel approaches to disable cancer stem cells: Turn their own plasticity against them with a network of microRNAs and genes, and more precisely target them with cancer-killing nanoparticle therapeutics.

Directing this research effort is Huiping Liu, MD, PhD, Assistant Professor, Pathology, Case Comprehensive Cancer Center, National Center for Regenerative Medicine, Case Western Reserve School of Medicine, who comes to CWRU from the University of Chicago.

Clearly microRNAs play a pivotal role in regulating cancer stem cell plasticity that not only makes cancer stem cells therapy-resistant, but also promotes their progression toward cancer metastasis. The goal of Liu and fellow scientists is to lead cancer stem cells to a different progression-free fate—either to differentiated benign cells or at least to chemotherapy-sensitive cells.

In terms of nanoparticles, Liu and colleagues are exploring this pathway to target tumor cells and cancer stem cells directly rather than sending harsh chemotherapy agents coursing throughout the entire body, attacking good cells and cancer cells alike. The lab’s scientists use ultra-fine nanoparticles (10-100 nanometers in size), chemically engineer them using compounds such as peptides, lipids or polymers, and load particles with powerful anti-cancer agents. Liu and colleagues are also working on developing a homing mechanism within therapeutic nanoparticles so they are drawn directly to cancer stem cells and tumor cells to make a targeted attack.

Revealing the mysteries of cancer stem cell programming and effective nanoparticle drug delivery requires a sound understanding of the basic biology of cancer stem cells. The Liu Laboratory relies on state-of-the-art technology to explore cancer stem cell mechanisms with single cell sequencing technology and functional studies. The lab also uses bioluminescence imaging and intravital imaging systems to image the dynamic behavior and interactions of cancer stem cells with immune cells and normal stem cells.

The ultimate goal of the Liu Laboratory research endeavor is to shut down the cancer progression process altogether by targeting cancer stem cells that lead to deadly metastasis.
Justin Lathia, PhD, and colleagues are uncovering the biological workings of cancer stem cells to discover mechanisms for blocking or inactivating their destructive progression to malignancy. Much of his lab’s recent discoveries will be submitted for publication this spring.

“We are interested in the interface between stem cells and cancer. For the most part, we are most interested in malignant brain tumors,” said Lathia, Assistant Professor of the Department of Cellular and Molecular Medicine at the Lerner Research Institute and of the Department of Molecular Medicine in the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University.

Lathia’s lab has been in operation for two years and focuses on three routes of investigation.

The first one involves scavenger receptors and lipid metabolism. Normal immune cells survey tissues, and if scavenger receptors sense damage via cellular debris, these healthy cells evoke an immune response. His lab has discovered that cancer stem cells

INNOVATIVE
CELL THERAPY
APPROACHES
MARK CWRU
ACHIEVEMENTS

A multitude of innovations at Case Western Reserve University (CWRU) makes this institution the stem cell therapy destination for the country, and possibly the world. Hillard Lazarus, MD, has the evidence to prove it.

“We are doing impressive things in stem cell therapy that other institutions are not,” said Lazarus, Director of Novel Stem Cell Therapy at University Hospitals Case Medical Center (UHCMC) and Professor of Medicine at Case Western Reserve School of Medicine.

We have the translational investigators, infrastructure, experience, ground-breaking clinical trials and publishing track record.

A particularly striking example of innovation is an experimental mesenchymal stem cell (MSC) treatment for multiple sclerosis (MS) that brought together investigators from UH Seidman Cancer Center, CWRU and Cleveland Clinic. This Phase 1 trial is testing the safety of utilizing harvested MSCs from a small amount of bone marrow obtained from the hip of the study’s participants. These MSC cells were cultured and expanded for several weeks in the National Center for Regenerative Medicine Cell Production laboratory on the CWRU campus. They were then injected intravenously back into the patient to immune cell activity, yet trigger tissue repair. The research team was led by Jeffrey Cohen, MD, of Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research.

The MS trial follows a long tradition of remarkable MSC research. It was at CWRU that Arnold Caplan, PhD, known as the father of MSCs, joined Lazarus in first applying MSC treatment more than two decades ago. That innovation took root at CWRU and led to today’s wide array of MSC and other cell therapies.

In addition to the MS trial, other MSC investigations focus on Cystic Fibrosis. CWRU scientists, led by Tracey Bonfield, PhD, discovered that injecting human MSCs into animals with a Cystic Fibrosis-like condition resulted in reducing the overabundance of destructive white blood cells infiltrating their lungs; the treated animals subsequently showed healthy weight gain. A next step will be developing human trials for this innovation.

MSCs also show promise in treating spinal disk disease and low back pain, and CWRU scientists are ready to enroll patients into UHCMC trials that are approved for treatment in humans.

Again, a small amount of bone marrow is extracted from a patient’s hip under local anesthesia. Then, MSCs are expanded in the state-of-the-art laboratory, which causes a dramatically increased number of cells, which are then injected into the affected spinal disks. The result should be reduction of inflammation and pain, and regeneration of more cushioning cartilage and bone.

USING BIOLOGY OF CANCER STEM CELLS TO SHUT THEM DOWN

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MSCs may also do wonders for preventing scar formation in the corneas of patients who recently suffered eye infections. Those studies at CWRU could transition soon from animal models to humans. Other conditions that may benefit from the anti-inflammatory and tissue repair properties of MSC treatment include rheumatoid arthritis and lupus.

Significant strides are also taking place at CWRU and UHCMC led by Andrew Sloan, MD, with technology developed by Stanton Gerson, MD, using a patient’s own cells in anti-cancer therapy. An active study in malignant brain tumors seeks to protect a patient’s bone marrow from the harsh effects of chemotherapy that must be given in higher doses to penetrate the brain tissue. The approach involves taking a patient’s own blood stem cells that have been induced to leave the bone marrow where they can be captured in the blood using a standard blood donation instrument similar to that used in a routine blood donation practice. A DNA repair gene is inserted into the stem cells and then the modified blood stem cells are re-injected back into the patient, all before chemotherapy begins. The result is expected to be that chemotherapy attacks the brain tumor but does not damage the bone marrow.

In another anti-cancer trial, a patient’s own T cells, important immune cells whose job is to fight disease, are used as therapy against the skin cancer malignant melanoma. Trials under the supervision of Julian Kim, MD, UHCMC, are about to begin in humans. The idea is to remove a lymph node in the region of the skin cancer, extract the cancer-fighting T cells from it, greatly expand those T cells many hundred-fold and re-inject these cells back near the skin cancer. Animal experiments have demonstrated the potency of this approach.

Numerous projects are in development for both neoplastic and non-neoplastic disorders,” Lazarus said. “We are trying to extend our observations from in vitro and preclinical animal models into patients, as well as expand our significant clinical experiences. People will come here for the cell therapy. Perhaps they will not be candidates for one type of therapy, but they may be for another one. Innovation is a real draw to entice people to come here as an innovative yet regulated stem cell destination.”

have their own scavenger receptors critical to their functioning and that ligands in necrotic areas can trigger cancer stem cells to proliferate and self-renew at higher rates. Many of these ligands are lipids, the building blocks for energy storage and utilization, and generating new cell membranes. This novel scavenger receptor pathway allows cancer stem cells to consume increased levels of raw materials enabling them to store and utilize energy. This mechanism of action then facilitates the formation of new cell membranes required for the generation of additional tumor cells, thereby sustaining tumor growth.

This is an exciting finding because it establishes the interface between stem cells and lipid metabolism,” Lathia said. “Through collaborations here, we have tapped into clinically relevant small molecules to treat brain tumors.

The second route of research involves his lab’s discovery of how cancer stem cells directly communicate with one another and the ability to disrupt that communication. One mechanism of communication is the exchange of molecules via specialized cellular channels. When cancer stem cells lose their potency and differentiate, the cellular channels. When cancer stem cells exchange of molecules via specialized communication channels change as well. These various communication channels have different ion specificity and rates of permitting cell-to-cell communication.

“It is really important for cancer stem cells to communicate for tumor progression to occur,” Lathia said. “We have identified agents that compromise this communication process. Combined with chemotherapy, these agents spark a potent effect. We are at the cusp of getting these into the clinic because the compounds are already FDA approved.”

Still another avenue of investigation explores the interaction between cancer stem cells and myeloid-derived suppressor cells (MDSCs). This interaction sets into motion localized immune suppression enabling tumor growth. In collaboration with Michael Vogelbaum, MD, PhD, a neurosurgeon at Cleveland Clinic, the team has discovered that immune suppressive cell types, specifically MDSCs, interact with cancer stem cells and accumulate in the tumor microenvironment, suppressing normal immune system function.

“If you disrupt the interaction either by removing the MDSCs or possibly targeting a series of related factors, you can get the intact immune system to work better to prevent tumor growth,” Vogelbaum said. “We have low doses of clinically relevant chemotherapeutic agents to target MDSCs, so this is work that can begin almost immediately. These drugs are being given to patients right now for other cancers, so we just need to get the dosing right. To get all these innovations to patients, that is the future direction. There is still a multitude of projects in the lab focusing on other mechanisms and pathways.”
The work of David Dean, PhD, and colleagues certainly qualifies as promising. He received AFIRM II funding to investigate cell-based therapies for segmental defects of the mandible (lower jaw and teeth). He recently became an Associate Professor in the Department of Plastic and Reconstructive Surgery at Case Western Reserve University (CWRU) School of Medicine. His craniofacial regenerative research will be carried out with colleagues at CWRU.

Bone regeneration is paramount to building one complete mandible capable of holding dental implants and enabling the ability to chew. Even a small split, and certainly wider gaps, in the mandible cause significant problems, he said, in the ability to chew without excruciating pain and difficulty speaking. Disuse of chewing muscles leads to atrophy in a short amount of time, and then over time, the structure of the face withers with the long-term disuse of chewing muscles. A solid mandible is also required to clutch the titanium screws required to hold dental implants in place.

Currently, therapeutic approaches simply attempt to fill the space of the critical-sized segmental defect gap, which is not entirely sufficient. The craniomaxillofacial regeneration project by Dean and colleagues aspires to go so much farther with a cell-based therapy model. The process would begin with obtaining a CT scan of a patient’s affected jaw, developing a computer model to replicate that mandible precisely, 3D print a scaffold of the jaw, apply mesenchymal stem cells to the scaffold and then grow bone on that scaffold in a bioreactor. This stem cell-seeded scaffold can then be shipped to any location and act just like a bone graft for the patient.

“With critical-sized defects, it is not enough just to fill the gap because solid bone is needed to hold a dental implant which, effectively, is a bone screw to which we attach a dental crown,” Dean said. “No region of the skeleton will regenerate much more than an inch of bone on its own, so that’s why we need to regenerate bone for the mandible. The goal is to regenerate bone of high enough quality that it is sufficient to sustain its original function.”

CWRU team members collaborating on this craniomaxillofacial regeneration project, in addition to Dean, include:

• Stanton L. Gerson, MD, Director, National Center for Regenerative Medicine, Case Comprehensive Cancer Center and Seidman Cancer Center; Distinguished University Professor, Case Western Reserve University; Asa & Patricia Shiverick and Jane (Shiverick) Tripp Professor of Hematological Oncology, Case Western Reserve University; Associate Dean, Oncology, Case Western Reserve School of Medicine

• Arnold I. Caplan, PhD, Director of the CWRU Skeletal Research Center and Professor of Biology and General Medical Sciences (Oncology) at Case Western Reserve School of Medicine

• Donald P. Lennon, DDS, Director of the Cell Culture Facility and Senior Research Associate at Case Western Reserve University Skeletal Research Center

• Jiayang Sun, PhD, Professor of Statistics at Case Western Reserve School of Medicine

• Jane Reese Koç, MT, MBA, Operations Director, Cellular Therapy Services, NCRM and University Hospitals Seidman Cancer Center, Case Western Reserve University

• Clare Rimmac, PhD, Professor of Musculoskeletal Mechanics and Materials at University Hospitals Case Medical Center and Associate Dean of Research at Case Western Reserve University School of Engineering

The craniomaxillofacial regeneration project by Dean and colleagues joins other AFIRM II research projects throughout the United States developing advanced treatments for wounded soldiers. Members of the AFIRM II team are referred to as the Warrior Restoration Consortium comprising 28 core academic partners, including Case Western Reserve University, Cleveland Clinic, The Ohio State University Wexner Medical Center and the University of Cincinnati. The ultimate goal of the AFIRM II is making wounded soldiers whole by restoring form and function.

AFIRM II is funded through a cooperative agreement with U.S. Army Medical Research and Materiel Command, the Office of Naval Research, the Air Force Medical Service, the Office of Research and Development - Department of Veterans Affairs, the National Institutes of Health, and the Office of the Assistant Secretary of Defense for Health Affairs.
TESAR LAB MAKES GROUND-BREAKING STRIDES IN STEM CELL RESEARCH

The laboratory of Paul Tesar, PhD, is perfecting stem cell reprogramming processes for directly converting fibroblasts — an abundant structural cell present in the skin and most organs — into oligodendrocytes, a type of cell responsible for myelinating the neurons of the brain. The capability to produce myelinating cells offers hope for therapies in multiple sclerosis, cerebral palsy and rare genetic disorders called leukodystrophies, all of which cause the destruction and non-replacement of myelinating cells critical to the insulating sheath that protects neurons and neurotransmission throughout the body. The Tesar lab demonstrated that induced Oligodendrocyte Progenitor Cells (OPCs) could regenerate new myelin coatings around nerves after being transplanted to mice.

“’We want to leverage the power of this technology,’ Tesar said. ‘Our hope is that downstream, we would be able to transition this technology to humans to evaluate whether remyelination would provide an effective treatment and potentially even a cure for myelination-based disorders.’”

In addition to this current investigation, the Tesar lab explores the fundamental properties of early stem cell development to learn how the body is built. His lab made a significant contribution late this spring to the discovery of seed enhancers in pluripotent stem cells.

That long road will require fine-tuning processes for regenerating OPCs to optimize efficiency. Further research is needed to understand the long-term stability of these cells post-transplantation. For now, it appears the reprogrammed cells are stable and will not transform to some other state. Additionally, even more in vivo work in animal models is required to ensure efficacy and safety of this reprogramming technology.

The ability to produce an unlimited supply of OPCs has other important research implications as well. Human brain cells are, after all, inaccessible for experiments for the most part. Thanks to stem cell reprogramming technology, Tesar and colleagues can develop an ample supply of OPCs to investigate the cellular and molecular underpinnings at work in these special stem cells.

This research involved examining two closely related stem cell types that represent the earliest phases of development — embryonic stem cells and epiblast stem cells, first described in research by Tesar in 2007. Seed enhancers represent a whole new class of enhancers that serve as landmarks within pluripotent stem cells and guide how these special cells develop to serve different purposes within the body. Enhancers are sections of DNA that control the expression of nearby genes, and unlike most enhancers only active at specific times or places in the body, seed enhancers play roles from before birth to adulthood.

Seed enhancers are present, but dormant, in the early mouse embryonic stem cell population. In the more developed mouse epiblast stem cell population, they become the primary enhancers of their associated genes. As the cells mature into functional adult tissues, the seed enhancers grow into super enhancers. Super enhancers are large regions that contain many enhancers and control the most important genes in each cell type.

The seed enhancer discovery published June 5, 2014, offers promise that scientists eventually will be able to direct pluripotent stem cells in ways that prevent disease or repair damage from injury or illness.
OH-Alive is a research program operating from the Global Cardiovascular Innovation Center in Cleveland that focuses on optimizing new conditions for the production of adult stem cells. The program, made possible by a grant from the Ohio Third Frontier initiative, develops new manufacturing methods and intellectual properties that will advance cell therapy’s impact on Northeast Ohio. NCRM aims for OH-Alive to establish a core facility that houses the expertise and equipment necessary to optimize the production and development of cellular therapy materials for clinical trials.

OH-Alive was created as a collaborative force to develop research synergies across the field and to commercialize new technologies as they are developed. The Ohio Third Frontier grant enables NCRM, through OH-Alive, to cover every stage of cell therapy manufacturing “from concept to clinical application,” says Michael Gilkey, MBA, MS, Director, OH-Alive and Director of Strategic Partnerships, NCRM. One example of this synergism is OH-Alive’s X-Evo system, a combination of a Biospherix Xvivo barrier isolator with a TECAN Freedom EVO 150 fluidics robot. This pairing is the first of its kind and represents an exciting evolution in developmental biology.

OH-Alive’s goal is to establish and support its own contract research organization. Creating a stable, commercially viable company will ensure that the program’s clusters of cooperation will have a firm home-base in Northeast Ohio.

Such accomplishments can only come from working with numerous partners. In addition to funding from Ohio Third Frontier and the NCRM, companies such as BioOhio, BioSpherix, NanoFiber Solutions, Renovo Neural, and TECAN, work together with key academic collaborators like CWRU, Cleveland Clinic, and University Hospitals, to contribute to OH-Alive’s success. Additionally, collaborative educational programs will continue to generate an interested, enthusiastic workforce to sustain the system on all fronts, ensuring further growth and study-involved partners.

The Ohio Third Frontier represents an unprecedented and bipartisan commitment to expand Ohio’s technological strengths and promote commercialization that leads to economic prosperity throughout Ohio. Designed to build world-class research programs, nurture early-stage companies, and foster technology development that makes existing industries more productive, Ohio Third Frontier creates opportunity through innovation and is a strong and vital partner of the National Center for Regenerative Medicine.
The Cleveland Cord Blood Center (CCBC) collects, preserves, and stores the umbilical cord blood of Northeast Ohio’s diverse population in order to safely incorporate harvested cord blood stem cells into patients’ treatments. With funding from the Ohio Third Frontier Wright Program Project (WPP), CCBC is one step closer to applying these cells to the treatment of a wider range of diseases. Eventually, ailments as diverse as autism, diabetes, and sickle cell may be treated with cord blood stem cells.

With these future applications in mind, the WPP grant supports the CCBC’s steps to commercialize promising intellectual properties. Specifically, the center’s cord blood product, LeuCord™, which prepares non-embryonic umbilical cord stem cells for clinical applications in hematology and regenerative medicine. The WPP partnership that includes CWRU, Cleveland Clinic, CCBC, and BioInVision, are directly responsible for creating jobs in Northeast Ohio, which has in turn stimulated employment within the center’s partnering hospitals. Taking the steps to commercialize LeuCord™ has expanded the center in several ways. First, it was able to purchase equipment that allowed the center to file for a Biologics License with the FDA. Another immediate benefit of their expansion was healthy job generation. CCBC has nearly doubled its staff since 2010, and Marcie R. Finney, MS, Associate Director, Cleveland Cord Blood Center, estimates that more than 20 additional full-time positions have been created in partner hospitals associated with CCBC.

The WPP has developed the center’s new commercial directions while simultaneously strengthening established programs of ethically sound collection and use of umbilical cord blood stem cells. The combined support from the WPP grant and CWRU will enable further growth. Having already treated over 200 patients with cord blood stem cells, CCBC will continue to positively impact patients’ lives in the future.
Stem cell science has a devoted industry partner in Athersys, Inc. The company nurtures promising discoveries from lab bench beginnings to final development of life-saving therapeutics for everything from graft versus host disease (GvHD) to stroke.

“We are committed to stem cells and regenerative medicine,” said Gil Van Bokkelen, chairman and CEO of Athersys, Inc. “We currently have five clinical stage programs with MultiStem®, our proprietary clinical stem cell therapy, that addresses areas of substantial unmet medical need where current treatments are inadequate.”

Athersys is currently conducting Phase 2 clinical trials for patients who have suffered a stroke or who are being treated for inflammatory bowel disease (IBD), the partnership with Pfizer. In addition, the company is planning to initiate a Phase 2 trial in myocardial infarction (heart attack) with patients later this year and is planning for a Phase 2/3 study for preventing GvHD in leukemia patients. These cutting-edge programs culminate from a decade of exploration by Athersys and its international network of collaborators seeking more effective ways to treat neurological, cardiovascular, inflammatory and immune disease. Athersys is also involved in other clinical areas where a current standard of care is lacking and has obtained exciting results from earlier clinical trials.

The company also encourages new ways of thinking. For example, the vision of stem cells had once revolved around simply replacing damaged or injured tissue. However, the view at Athersys is that some cells are capable of promoting healing and tissue repair through the regulated production of proteins and other factors, and by dynamically interacting with other cell types.

“We have seen over and over again the ability of the cells we work with to reduce inflammatory damage while they also protect injured or at-risk tissue, promote formation of new blood vessels and upregulate key repair processes in the body,” Van Bokkelen said. “We believe that by harnessing these capabilities and delivering new treatments in a scalable and consistent way, we could help change medicine as we know it and establish a leading company in the process.”

One striking example involves the work of Athersys in stroke treatment. Currently, frontline stroke care calls for administering the clot-dissolving drug tPA within three to four hours after stroke. Because of this tight time window, only five – 10 percent of stroke patients actually present in time to receive tPA. Published studies from Athersys and independent collaborators have led to an exciting new approach that could redefine stroke medicine. Using standard models of stroke, the company has shown that administration of MultiStem™ even several days after a stroke produced remarkable results. The company is currently conducting an international Phase 2 study at leading stroke centers in the United States and the United Kingdom for stroke patients to receive MultiStem™ within one to two days after a stroke.

“If we see anything like the results from our preclinical studies, we believe it could revolutionize stroke care,” Van Bokkelen said. “We treated animals out to a week after a stroke and saw dramatic recovery.”

Impressive discoveries have made stem cells and regenerative medicine an international phenomenon. Nevertheless, he advised, caution is in order to deliver consistent, practical and cost-effective solutions.

“We must continue to build a strong foundation of data while also learning from our mistakes,” Van Bokkelen said. “The clinical validation is extremely important, but also showing we can provide scalable solutions is critical for achieving long-term success. We believe that is exactly what Athersys will be able to deliver.”

Van Bokkelen praises fellow collaborators, most notably the visionary work of Arnold Caplan, PhD, from Case Western Reserve University School of Medicine and a host of outstanding scientists and investigators from the National Center for Regenerative Medicine and other institutions in Ohio and throughout the world.

“We are certainly learning from the collaborative work we do with others, as well as the experience of these great pioneers in stem cells and regenerative medicine,” Van Bokkelen said. “In many ways, we are forging new paths, and we believe we are well positioned to take innovation to a higher level.”
The Seidman Cancer Center is conducting a ground-breaking stem cell therapy clinical trial that could increase survival length in patients with glioblastoma multiforme (GBM), the most common primary brain tumor. The Phase 1 clinical trial, funded by a $2.4 million Small Business Technology Transfer grant, with Lentigen, utilizes genetically engineered hematopoietic stem cells (HSCs) in combination with chemotherapy drugs temozolomide (TMZ) and O\textsubscript{6} benzylguanine (BG) to treat GBM. The idea is to move the needle toward increasing survival in GBM patients beyond the current median of only 15 months. Leading the clinical trial is Jeffrey Cohen, MD, Director of the Mellen Center for Multiple Sclerosis Treatment, Cleveland Clinic.

The Cleveland Clinic’s Mellen Center enrolled and treated participants, drawing upon its large MS patient base and MS clinical trial experience. Case Western Reserve School of Medicine’s National Center for Regenerative Medicine prepared the MSCs for the study through its cell-production facility, which has earned a solid track record with the FDA for safety in MSC development and administration. Additionally, the study’s immunologic assessment was completed at McGill University in Montreal, Quebec, Canada.

For the eight-month study, all 24 participants with documented MS activity went through the treatment: Bone marrow was extracted from the patient’s hip, MSCs isolated from the marrow, isolated MSCs grown in culture to increase their numbers and then re-infused back into the patient. Extensive safety monitoring during a six month period included blood studies, brain MRI scans, and physical and neurological examinations.

Next steps? A Phase 2 study, which hinges on obtaining the necessary funding. Plans are already on the drawing boards for the Phase 2 stage of assessing the effectiveness of using MSCs with the goal of inducing repair of MS-damaged nerve-cell sheaths in the brain and spinal cord.
## 2014-2015 TRIALS

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A clinical trial launched in Fall 2014 for a dendritic cell (DC) vaccine is being developed to treat metastatic breast cancer. Thirty HLA-A2 positive women enrolled in the four-year, single-arm, prospective pilot clinical trial at University Hospitals Seidman Cancer Center, Cleveland Clinic and University of Pittsburgh. Leading the project is principal investigator, Joseph Baar, MD, PhD, a breast cancer oncologist and Associate Professor of Medicine, Case Western Reserve School of Medicine, and co-principal investigator Walter J. Storkus, PhD, Professor of Immunology and Dermatology, University of Pittsburgh School of Medicine.

Funded by a $996,000 investigator-initiated research grant from the Susan G. Komen Foundation, the study is testing the safety and efficacy of a dual treatment strategy. Patients first receive a round of sequential administration of the cytotoxic chemotherapy agent, gemcitabine, proven effective at blocking metastatic breast cancer and at impairing the activity of cells known to suppress the immune system, such as regulatory T cells and myeloid-derived suppressor cells. Then, the DC vaccine will be administered after chemotherapy. However, in order for the vaccine to be effective, all trial participants must be positive for HLA-A2, a specific protein that is expressed on cells in approximately 50 percent of women.

The DC vaccine, referred to as the DC1-TBVA vaccine, will be developed from the patients’ own DCs that will be programmed to generate an immune attack on tumor blood vessels. The objective is to starve the tumor by withholding its blood and oxygen supply.

The dendritic cell vaccine will be developed from the patients’ own dendritic cells, and manufactured under Good Manufacturing Practice (cGMP) conditions in the NCRM state-of-the-art clean room facility for patients at Cleveland Clinic and University Hospitals Seidman Cancer Center.

Historically, breast cancer vaccine strategies have failed because cancer cells evade immune cells. They escape by either changing or by not expressing the exact cancer cell antigens that the vaccine was developed to sense, thereby stalling any immune attack on the tumor.

**The trial’s investigators hypothesize that the environment supporting the cancer cells would serve as a better target than the cancer cells themselves. Hence, the DC1-TBVA vaccine will generate killer T cells to attack the cancer’s lifeline, the tumor blood vessels.**

The clinical trial will assess the standard safety and clinical response endpoints. In addition, the investigators want to determine whether gemcitabine and DC1-TBVA vaccination generate T-cell immunity against tumor blood vessels and whether changes in myeloid-derived suppressor cells and regulatory T cells correlate with the generation of anti-TBVA T-cell immunity. Reaching these immunity endpoints would translate into a decisive success with this clinical trial.
BEST PRACTICES: CELLULAR THERAPY INTEGRATED SERVICES

Multiple cell therapy trials conducted by National Center for Regenerative Medicine investigators utilize the Center’s Cellular Therapy Integrated Service (CTIS).

CTIS provides regulatory, quality oversight, GMP-compliant cell manufacturing for Phase I/II studies as well as technical and environmental control expertise to support novel investigational therapies. The preparation and use of cellular products requires adherence to the rigorous regulations set forth by the FDA. Regulations such as Good Tissue Practices (cGTP), for minimally manipulated cell products and Good Manufacturing Practices (cGMP), for those which undergo more manipulation are stringently followed.

CTIS also includes a 3,000 square foot Cellular Therapy Manufacturing lab with 6 state-of-the-art ISO7 clean rooms which produce clinical grade cellular therapy products. The Cellular Therapy Lab is dedicated to scale-up translational studies to support investigator and industry sponsored clinical trials involving cellular therapy. It is one of only three facilities within an academic center in the State of Ohio that supports GMP-compliant therapy cell manufacturing.

The Cellular Therapy Lab staff have extensive experience in all aspects of cellular therapy and cGMP Phase I/II manufacturing of autologous and allogenic cellular products. This includes support for novel cell therapies such as dendritic cell, hematopoietic stem cell, T cell, and mesenchymal stromal cell expertise, as well as preparation of cell products for standard stem cell transplantation.

CTIS is located on the sixth floor of the Wolstein Research building on the campus of Case Western Reserve University and is proximal to University Hospitals Case Medical Center.

CTIS CAPABILITIES:
• Preparation and/or processing of cell products for experimental IND-based cell therapies.
• Full-spectrum service from minimally manipulated to extensively cultured cells produced in compliance with FDA mandated guidelines.
• Competency in all cell manipulations including purification, culture and cytokine expansion, antigen exposure, cell differentiation protocols, and gene transfer.
• Comprehensive support starting with IND preparation and regulatory guidance to development of Standard Operating Procedures and product delivery reimbursed by users.
• A defined Quality Management program, including quality assurance, quality control and a Cellular Therapy Review and Monitoring Board.

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2015 SCIENTIFIC RETREAT

The NCRM Annual Scientific Retreat was held at the Tinkham Veale University Center on the campus of Case Western Reserve University in March 2015. Nearly 100 attendees from collaborating intuitions attended presentations and panel discussions on topics including harnessing NK cells, drug discovery, immunotherapy, clinical trials, tissue engineering and stem cell research ethics.

RENEW PROGRAM PROVIDES TRAINING FOR TOMORROW’S STEM CELL SCIENTISTS

RENEW (Regenerative Medicine Education Network) continues to stimulate stem cell biology now and into the future by cultivating a cadre of well-trained scientists to bring stem cell innovations to the marketplace. In conjunction with Rutgers University, the program is funded by a T32 training grant from the National Institutes of Health (NIH), RENEW provides a web-based course to post-doctoral graduates, clinicians, and industry scientists to gain experience with stem cell biology and regenerative medicine. Most importantly, it connects these up-and-coming scientists directly with NCRM primary investigators during sessions that run for 15 weeks.

During the RENEW program, leading stem cell researchers host live lectures focused on various topics related to regenerative medicine. The sessions are not expressly organized as a building-block progression, but taken together, they provide a broad swath of what regenerative medicine encompasses. With this in mind, lecturers present summative discussions at the beginning and end of the course. As with all of NCRM’s educational programs, RENEW has significance for broader commercial applications for the future.

“Already boasting past involvement of international participants from Brazil, The Netherlands, Russia, and Ireland, the NCRM aspires to turn RENEW into a formal course at Case Western Reserve University by Spring 2016.”

We look to actively recruit course participants from across the country and abroad. The RENEW course will serve as a launch pad for the Masters of Science program in Regenerative Medicine which is currently in the pipeline for review and approval.
EDUCATION

ENGAGE

The ENGAGE summer program is a 10-week internship organized by the NCRM for undergraduate students to gain direct, real-world experience in a functioning lab setting. Entering its eighth year, ENGAGE promotes and supports undergraduate student participation in research and creative projects in the study of stem cells and regenerative medicine.

With the support of CSC 2014, and a new NIH SEPA grant, NCRM can offer 10 undergraduate students full funding – $3,500 in stipends and material costs – to work alongside principal investigators in NCRM. The Mesenchymal Stem Cell conference’s support of ENGAGE came from a record-breaking conference attendance that provided funding for ENGAGE interns.

This initial investment stimulates future employment. “Most undergraduates don’t really have true experience working in the lab,” said Michael Gilkey, MBA, MS, Director, OH-Alive and Director of Strategic Partnerships, NCRM. ENGAGE wants to change this. Getting students into labs sooner gives them a better understanding of careers in research earlier in their education. This will in turn convince more students to choose careers in regenerative medicine. This end result is in line with NCRM’s goal for all of its educational programs: Training a strong regenerative medicine job force. With the cooperation of the MSC conference, CWRU and partnering primary researchers, NCRM continues to make this possible. ENGAGE helps ongoing research, gives students relevant experience for the future, and provides the educational exposure that leads to future employment.

NIH SEPA GRANT

The National Institutes of Health (NIH) awarded The Great Lakes Science Center (GLSC), and through GLSC, NCRM—support of a Science Education Partner Award (SEPA) grant as an added component of NCRM’s summer ENGAGE program. The SEPA grant funds two undergraduate interns as they are paired with high school students, acting as mentors for the younger scholars, in addition to the responsibilities and benefits associated with the ENGAGE internship. On top of their work with primary investigators, the two interns have an exciting chance to teach as they learn.

The SEPA grant adds another layer of educational involvement to ENGAGE. Students from the MC2 STEM High School, located in the GLSC, work with the two funded ENGAGE undergraduates. This creates a further emphasis on step-wise training, which is an already important aspect of the NCRM’s approach to educational programs. By incorporating work from the MC2 students, NCRM and ENGAGE have extended the program’s reach from primary investigators to a high school level. The trickle down of knowledge that starts with postgraduate and faculty investigators is filtered through graduate students on down to ENGAGE undergrads, and, in turn, their assigned high school mentees. This idea works in concert with CWRU’s participation in the Clinical & Translational Science Collaborative (CTSC), which seeks new and innovative approaches to educating high school students in the sciences.

Funding from the SEPA grant strengthens ENGAGE’s already collaborative learning, and represents another chance for NCRM to offer innovative educational programs. Partnering with MC2 students benefits all involved. The younger students are exposed to learning opportunities typically unavailable to them, and their ENGAGE undergraduate mentors learn through teaching, another important aspect of their ongoing education.
CANCER STEM CELL CONFERENCE

2014 Highlights
In August 2014, the National Center for Regenerative Medicine (NCRM) convened its inaugural International Cancer Stem Cell (CSC) conference in Cleveland. With the goal to remove the roots of cancer, eliminate metastatic seeds, and overcome therapy resistance, the conference gathered over 320 investigators, including 55 invited world-class speakers, 25 short oral presenters and 100 poster presenters, to gain an in-depth understanding of CSCs and explore therapeutic opportunities targeting CSCs.

CSC conference discussion topics included: genetics and epigenetics; cancer origin and evolution; microenvironment and exosomes; metabolism and inflammation; metastasis and therapy resistance; single cell and heterogeneity; and plasticity and reprogramming, among many other new concepts. The conference also provided investigators reports on clinical trials targeting CSCs and emphasized the urgent need for strategically designing combinational CSC-targeting therapies against cancer.

The CSC conference became the third conference in the world focused on cancer stem cells, joining a European conference and a U.S. west coast conference.

2016 CSC Contact:
Charlene Mitchell
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EDUCATION

COLON CANCER: TARGETING NEIGHBORING CELLS

Tumor-generating action in colon cancer may well have contributions from neighboring cells, the fibroblasts. Pursuing this line of investigation is Emina Huang, MD, in her research at the Lerner Research Institute where she serves as Vice-Chair of the Stem Cell Biology and Regenerative Medicine Center.

The colorectal surgeon came to the Lerner Research Institute last year from the University of Florida and earlier from the University of Michigan where she has studied the origins of tumor-initiating cancer stem cells in ulcerative colitis.

Colorectal cancer is the third leading cause of cancer deaths in the United States, with approximately 146,000 new cases and 50,000 deaths expected in 2015. Current therapeutic regimens have limited efficacy and thus new treatments are critical.

Funded by two grants from the National Cancer Institute for approximately $2.5 million, Huang and colleagues at the Lerner Research Institute are exploring fibroblasts’ contribution to tumor initiation, establishment and promotion. They are examining the mechanism of action in both the cancer stem cells and neighboring fibroblasts that regulate tumor initiation.

They are seeking to uncover what promotes healthy colon epithelium regeneration and what goes awry in the process of oncogenesis, because gut tissue regenerates every three to five days. Investigators are exploring everything from genetic disorders to intercellular cross talk to define operational targets and zero in on target sites of the epithelium.

There appears to be a connection between the dysfunction of colon epithelium regeneration, inflammation and cancer. Inflammation-related processes occur in 20 percent of all cancers and are associated with either infectious or inflammatory etiologies. Huang and colleagues are working to learn the precise steps from inflammation to colitis-associated cancer and whether that progression can be blocked.

Her research is particularly pressing, given that 20 to 30 percent of the American population is overweight and obesity triggers a mild degree of inflammation. Huang also wishes that her findings will extend investigations of cancers involving other major organ systems.

SAVE THE DATE
September 13-16, 2016
Cleveland, OH
Cancer Stem Cell Conference
National Center for Regenerative Medicine Directory

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<th>Neurology</th>
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CC (Cleveland Clinic)

CSU (Cleveland State University)
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Membership benefits include:

- Access to NCRM grant opportunities
- Access to all NCRM Core Facilities (40 total across CWRU, UHCMC, and Cleveland Clinic Campuses)
- Access to invited lecturers and collaborative biotech company personnel

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DEVELOPMENT

**FAMILY’S GIFT SUPPORTS RESEARCH JOURNEY FROM DISCOVERY TO TREATMENT**

A born and bred farmer, Lionel Long with his wife Irmgard by his side, muses that he started his hydraulic company with two flat rocks and a hammer. With years of hard work and sacrifice under their belts, the couple is in a position to provide philanthropic support to the National Center for Regenerative Medicine.

Love for their daughter, Juli, who has Multiple Sclerosis (MS), and the desire to improve the lives of others with the disease, led the couple to NCRM member and director of the Pluripotent Stem Cell Facility, Paul Tesar, PhD. Each are contributing to a mutual mission – to develop cutting-edge technologies for treating nervous system disorders, specifically MS.

Mr. Long knew he’d found something special when he met Tesar, whom he described as “a real dynamo,” after hearing about his research breakthroughs. In particular, he was impressed with the Tesar laboratory’s ability to induce repair of myelin, the protective sheath covering neurons that is damaged in diseases like MS.

Supporting research as it transverses the bridge from Tesar’s laboratory benches to ultimately the Cleveland Clinic patient rooms where Juli receives care, was of paramount importance to the Longs.

“Paul and many others at the NCRM are on the threshold of developing new promising treatments for MS,” said Long, who counts three businesses under his ownership. “Our family’s gift of financial support ensures that their breakthrough research won’t die on the vine.”

**PHILANTHROPY**

The infinite potential of stem cell therapy is limited only by the resources available to explore this emerging treatment pathway. Philanthropy, therefore, can play a vital role in advancing scientific endeavors that align with your specific medical interests.

The National Center for Regenerative Medicine represents an assembly of leading scientists and technology whose purpose and passion is to advance human health through stem cell medicine. Your gift at any level can support this work directly, be it through research funds for immediate use, or endowed professorships that attract and retain top talent or major investments to establish new specialized research programs. Whether you’d like to spark a novel research track in a disease that is meaningful to you, or support the Center’s existing strengths – such as heart disease, cancer, genetic disorders, wound healing, or immunological, musculoskeletal and neurodegenerative diseases – our staff is open to starting a conversation to structure a philanthropic invest that is right for you.

Your gift to stem cell medicine leads to a tangible outcome: advancing discoveries into cures that will become available to all patients. Young and old, civilian or veteran – your support impacts countless lives, from those who participate in clinical trials today, to those who will benefit from the cures of tomorrow.

To learn more about how you can make a difference to advance future stem cell therapies from the NCRM, please contact Jason Gray, Executive Director, External Affairs at 216.368.4420 or jason.gray@case.edu or Sophie Sureau, Senior Director of Development, at 216.368.0631 or sophie.sureau@case.edu.

Visit us at case.edu/medicine/ncrm.

Sophie Sureau and Jason Gray

Above image by artist, Megan Kern
**RESEARCH PARTNERS**

- Case Center for Imaging Research (CCIR)
- Case Comprehensive Cancer Center (CCCC)
- Cleveland Cord Blood Center (CCBC)
- Center for Clinical Research at UHCMC
- Cleveland Clinic Orthopedic Research Center
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- Functional Electronic Stimulation Center (FES)
- Global Cardiovascular Innovation Center (GCIC)
- Lerner Research Institute (LRI)
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VISION OF THE FUTURE

To transform medical therapy through the use of cells and other therapies to heal tissues and organs. And to create the commercial and academic infrastructure in Northeast Ohio to establish a vibrant industry of high-tech biotechnology and support services that are attractive to cell-therapy institutions across the United States.