Wake Forest Institute for Regenerative Medicine

Legislative Report

July 1, 2014 to June 30, 2015

- **Program Activities, Objectives and Accomplishments**
- **Itemized Expenditures**

Report to
Joint Legislative Commission on Governmental Operations and
Fiscal Research Division
S.L. 2011-145 Section 14.12.(b)

Introduction

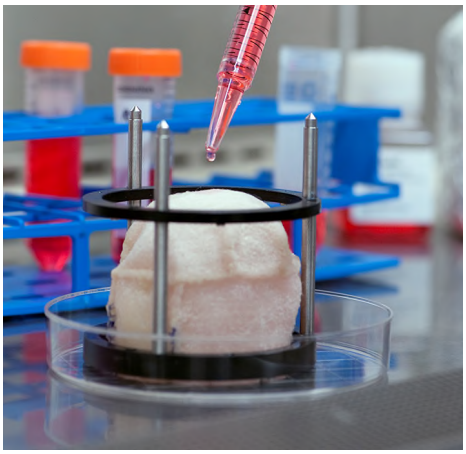
Imagine a day when chronic diseases are treated with an injection of cells ...When functioning nerves are available to replace those damaged by injury ...When diseased organs are routinely exchanged with healthy replacements grown in laboratories.

Once considered by many to be the stuff of science fiction, regenerative medicine – and the promise of growing replacement organs in the laboratory – is starting to become a clinical reality. Referred to as the "next evolution of medical treatments" by the U. S. Department of Health and Human Services, regenerative medicine is already making a mark on clinical care. Several therapies are now in clinical trials, skin and cartilage substitutes are available through regenerative medicine techniques, and laboratory-grown bladders, urethras, tracheas, blood vessels and other tissues have been implanted in patients.

In addition to the potential medical benefits, regenerative medicine also represents the potential for economic benefit through the growth of companies and research institutions dedicated to its technologies. According to industry analysts, regenerative medicine is at an inflection point, on the brink of explosive growth.[1] Between 2008 and 2011, the global market for regenerative medicine products increased three-fold and the number of companies offering products and services doubled. It is estimated that the regenerative medicine market represents $16.4.5 billion in sales and employs almost 14,000 people.[2, 3]

What is Regenerative Medicine?

Regenerative medicine is a multidisciplinary field, bringing together scientists from molecular biology, genetics, cell biology, physiology, pharmacology, biomaterials and nanotechnology, working collaboratively to deliver therapies that repair, replace or regenerate organs and tissues. The field is composed of the sub-disciplines of tissue engineering, cell therapies, and an area often called healing therapies or organoregenesis.



- ***Tissue Engineering*** — growing replacement tissue and organs in the lab. Because a patient's own cells are used, there are no issues with rejection.
- ***Cell therapies*** — using living cells to promote healing and regeneration from within.
- ***Organoregenesis*** — rather than relying on cells alone, various strategies are used to promote regeneration, including biomaterials to aid in cell recruitment and proteins and molecules to trigger a regenerative effect.

[1] *Regenerative Medicine at an Inflection Point* BNA Insights, 5 LSLR 476 (2011) E. Herriman
[2] *Progress in the Tissue Engineering and Stem Cell Industry: Are we there yet?* Tissue Engineering: Part B, 18:155 (2012), A. Jaklenec et al.
[3] *Global Regenerative Medicines Market 2013 – 2020*, Market Research Reports (2014)

About WFIRM

Researchers at the ***Wake Forest Institute for Regenerative Medicine*** (www.wfirm.org) are hard at work to make the future of regenerative medicine a reality. This team was the first in the world to engineer human organs in the laboratory that were successfully implanted in patients. Today, these groundbreaking scientists are applying their expertise to develop cell therapies and replacement tissues and organs for more than 30 different areas of the body

This team—driven by the urgent needs of patients all over the world—is uniquely positioned to make exponential leaps in the development of regenerative medicine therapies for many disease conditions. With a history of success and a focused strategy to get therapies as quickly as possible to patients, the Wake Forest Institute for Regenerative Medicine is the premier research center of its kind.

Once a new technology has been thoroughly tested and is ready for clinical studies, WFIRM is equipped for efficient "translation" from the bench to the bedside. A current good tissue practices (cGTP) and good manufacturing practices (cGMP) compliant facility, which manufactures and stores replacement tissues and organs under guidelines of the U.S. Food and Drug Administration (FDA), ensures that a reproducible process is in place. And when the technology is ready to be licensed to a company that can commercialize it for widespread use, WFIRM has the unique infrastructure and community resources to create companies and develop partnerships to expedite the delivery of the technology to patients.

WFIRM, part of Wake Forest Baptist Medical Center, is located in Wake Forest Innovation Quarter in downtown Winston-Salem, North Carolina. A research and innovation center developed on the site of the former R.J. Reynolds Tobacco Co. manufacturing facilities, the Innovation Quarter has been heralded as a shining example of a community transforming itself into a knowledge-driven economy. When complete, the entire redevelopment will convert more than a million square feet of rehabbed historic buildings into a vibrant, urban community, making it the largest urban research park in the nation. As a premier tenant in the Innovation Quarter, WFIRM is seen as an integral factor in drawing private sector business to the region.

Role of State Funding

Joint government-academic initiatives are playing a pivotal role in realizing the promise of regenerative medicine, providing critical funding that is accelerating translation of scientific discoveries to the clinic. The U.S. Department of Health and Human Services endorsed the government-academic model for regenerative medicine, citing the explosive growth of the nation's semiconductor industry as an example of the joint initiatives can accelerate progress.

State support is also vital to help leverage economic benefits of regenerative medicine. According to a study by Battelle and the Biotechnology Industry Organization, despite challenging state fiscal conditions, states continue to make investments designed to encourage the growth of the bioscience sector, a key driver of economic growth.[4]

Regenerative Medicine Initiatives Selected State Programs

California Institute for Regenerative Medicine (CIRM)
CIRM was created in 2004 through a ballot measure that authorized the sale of $3 billion in general obligation bonds to finance regenerative medicine research and related research facilities in California. CIRM has awarded grants totaling $1.9 billion since its first round of awards in 2006. As of 2015, fifteen CIRM projects were enrolling patients in clinical trials.

New York State Stem Cell Science (NYSTEM)
NYSTEM is $600 million, 11-year initiative of the State of New York to provide funding for stem cell biology research and development. The fund, created in 2007 through legislation authorizing the Empire State Stem Cell Trust Fund and administered by the New York State Department of Health, has awarded $360 million in research grants.

Maryland Stem Cell Research Fund
Established through the Maryland Stem Cell Act of 2006 to promote stem cell research and development, the Maryland Stem Cell Research Fund has awarded $112 million in research grants to date.

Connecticut Stem Cell Research Fund
Started in 2006, the Connecticut Stem Cell Research Fund commits $100 million over a 10 year period to stem cell research. The Fund is administered through the Connecticut Commissioner of Public Health.

North Carolina's Leadership Role

North Carolina is among the states providing critical support to the sector. The State has initiated a recurring annual investment to allow WFIRM to better develop and translate its discoveries to patients. State support of regenerative medicine will help North Carolina maintain its leadership position in this sector by accelerating the clinical translation of scientific discoveries and enabling regenerative technologies to be developed and manufactured in North Carolina, contributing to job creation and an expanded economic base. While regenerative medicine research initiatives are under way globally, few areas have the critical mass and infrastructure that North Carolina has to engage in the full spectrum of activities required to move from basic research to commercialization and the clinic. Examples of the state's competitive advantages include the following:

- ***World-renowned organization***. North Carolina is home to an international leader in regenerative medicine – the Wake Forest Institute for Regenerative Medicine. WFIRM is the largest dedicated regenerative medicine organization in the world in terms of number of direct employees, and its continuing accomplishments have meant a growing reputation in regenerative medicine for North Carolina.

- ***Proven track record***. Several regenerative medicine therapies developed by North Carolina scientists are already in patients, and others are in the pipeline, ready to begin testing in patients within the next few years. Projects range from treatments designed to help wounds heal to using skin cells to treat burns. The team was the first in the world to successfully engineer human organs in the laboratory and implant them in patients.

[4] Battelle/BIO *State Bioscience Initiatives* 2010

- ***Strong collaborations***. North Carolina scientists are involved in numerous collaborations – which make for stronger science – throughout the nation and world. WFIRM has collaborative agreements with institutes in 10 different countries, and collaborations with numerous universities.

- ***FDA compliant manufacturing facility***. Through WFIRM, regenerative medicine researchers have access to a current good tissue practices and good manufacturing practices facility that allows for the preparation of tissues and cell therapies under U.S. Food and Drug Administration guidelines. This facility helps accelerate clinical translation and commercialization.

- ***AFIRM leadership role*.** By leveraging state funds, WFIRM was selected to co-direct the first phase of the Armed Forces Institute of Regenerative Medicine, a virtual institute that develops regenerative therapies for our wounded warriors, and was selected as sole lead for the second phase. The AFIRM program has brought significant funding to North Carolina scientists to rapidly develop new treatments that will benefit both wounded warriors and civilians.

Accelerating Regenerative Technologies to the Wounded Warrior

WFIRM Leads National Project to Aid Wounded Warriors

WFIRM was selected to lead the second phase of the Armed Forces Institute of Regenerative Medicine (AFIRM). The five-year, $75 million federally funded project focuses on applying regenerative medicine to battlefield injuries. Anthony Atala, M.D., WIFRM's director, is lead investigator for AFIRM-II. He directs a consortium of more than 30 academic institutions and industry partners.

The first phase of AFIRM, which began in 2008, resulted in clinical studies of face transplantation, minimally invasive surgery for craniofacial injuries, a lower-dose anti-rejection regimen after kidney transplantation, scar reduction treatments, fat grafting for reconstructive surgery and new treatments for burns. North Carolina researchers were awarded $22 million in funding for the first phase of the project, 35 percent of total funding.

The AFIRM-II team is focused on developing clinical therapies over the next five years:

- Restoring function to severely traumatized limbs
- Reconstruction for facial and skull injuries through tissue regeneration
- Skin regeneration for burn injuries
- New treatments to prevent rejection of "composite" transplants such as face and hands
- Reconstruction of the genital and urinary organs and lower abdomen including the bladder, anal sphincter and external genitalia

"Everyone had a sense of wow of what was created during AFIRM… Also, the exciting thing about what we do is that, generally, whatever we create for the warfighter can also help the American people, which is a great return on the investment."
—Dr. Kenneth Bertram, USAMRMC's Principal Assistant for Acquisition

The goals of the program are to fund basic through translational regenerative medicine research, and to bring promising technologies and restorative practices into human clinical trials.

The AFIRM-II program is intended to continue the success of the original AFIRM program. The AFIRM-I teams were charged with conducting at least one clinical study of a new treatment for wounded warriors. Instead, due to their expertise, collaborative spirit and dedication to the mission, there were more than 10 clinical studies of potential new therapies. WFIRM is are honored to have the opportunity to continue this important work to benefit those who serve our country.

Therapies developed by AFIRM can also benefit people in the civilian population. AFIRM is a "results-focused" program that not only funds scientific research, but requires that discoveries be tested and compared so that the most promising therapies can be brought to clinical trials.

Government sponsors of AFIRM are the 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.

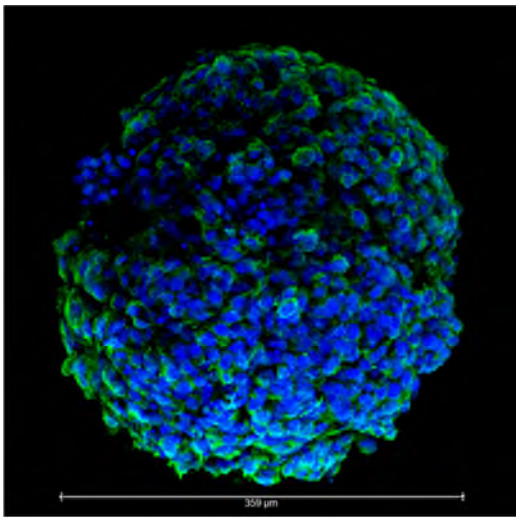
"When warriors come back from the battlefield with serious life-changing injuries, it is our job to find new and innovative ways to help them. Ultimately, we'd like to create new treatments to repair these severe injuries as if they never happened," according to Major General Joseph Caravalho Jr., commanding general of the U.S. Army Medical Research and Materiel Command and Fort Detrick. "The science of regenerative medicine is one of the ways we fulfill our promise to service members who put themselves in harm's way, that we will work our hardest and do our very best to take care of them."

The first phase of the AFIRM program focused on limb repair, craniofacial repair, burn repair, scarless wound repair, and compartment syndrome. The AFIRM program emphasized getting projects through advanced development, so that the innovations could be used for patients who need them. During the first program, more than 200 patients received treatment with AFIRM-funded technologies. The first AFIRM also achieved the first double hand transplant in the U.S.

WFIRM makes Significant Breakthroughs in "Body on a Chip" Project

Whether it's the Ebola virus or sarin and ricin, a key to responding to chemical or biological attacks is having effective antidotes at the ready. To accelerate the development of new therapies, WFIRM is leading a unique $24 million federally funded project, dubbed Ex Vivo Console of Human Organoids or E.C.H.O., that will be used to develop these countermeasures. The goal is to build a 'body on a chip,' a miniaturized system of human organs to

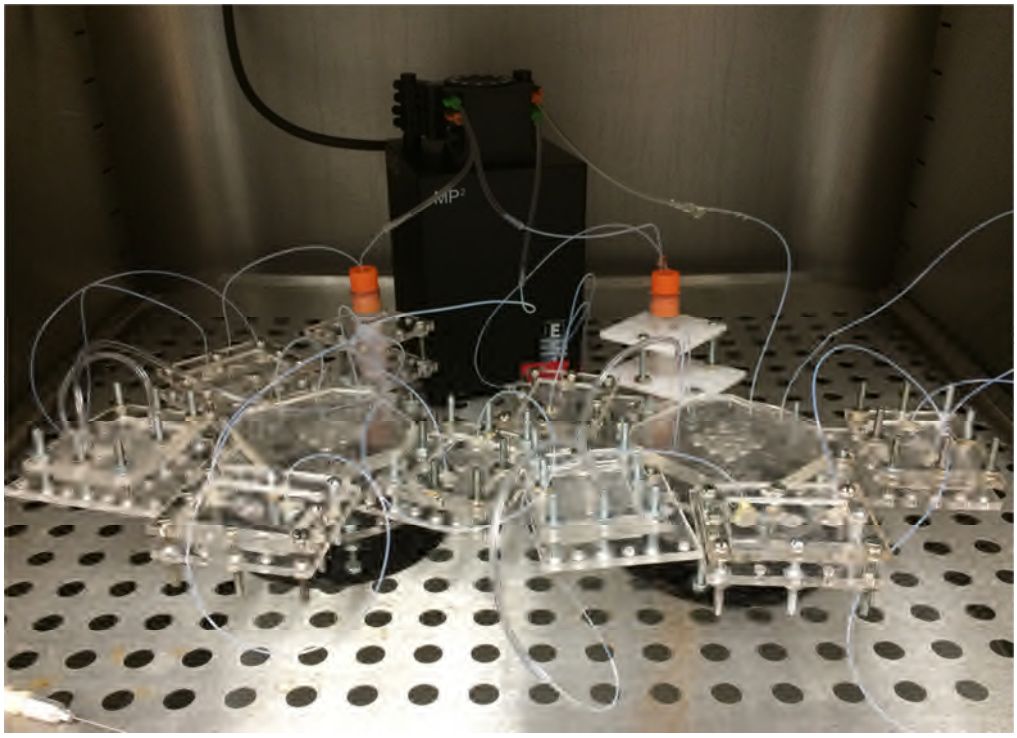
model the body's response to harmful agents and develop potential therapies. This approach has the potential to reduce the need for testing in animals, which is expensive, slow, and has results that aren't always applicable to people.



The first phase of the E.C.H.O. focused on developing micro-engineered 3D human tissues that closely mimic normal human organ physiology. By incorporating all of the cellular and extracellular components found in native tissue, E.C.H.O. organoids have demonstrated an astounding degree of fidelity when compared to normal human organs. The heart beats, the lung breaths, the liver detoxifies drugs, and the blood vessels change permeability in response to chemical signals.

Now in its third year, E.C.H.O. is transitioning into the second phase, during which multiple tissue organoids will be integrated into a single microfluidic circuit. Initial experiments indicate that the integrated platform is able to model the effects of drugs and toxins across multiple organoid types.

By utilizing 3D bioprinting to deposit the tissue organoids into the E.C.H.O. modules, the process may be scaled-up for mass production. This capability will be critical to the last phase of the project in which large scale testing of chemical agents and drugs is to be conducted. With the breakthroughs achieved in the initial phases of E.C.H.O., the team is optimistic about reaching the ultimate goal of the project, a high-throughput platform that accurately models the effects of drugs and toxins in a human being.



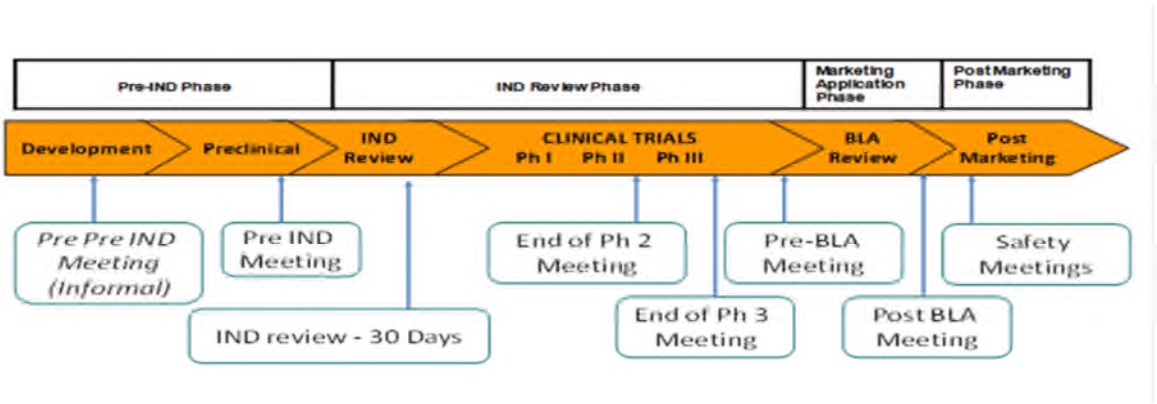
Mission Driven Accomplishments

WFIRM's mission is to improve patients' lives by developing regenerative medicine therapies and support technologies. As such, WFIRM's goals have been focused on clinical translation with emphasis on innovation, teamwork and development of platform technologies that address the current unmet clinical challenges. Additional core resources provided by the State of North Carolina have allowed projects within the federally funded AFIRM to accelerate progress and aided in increasing the visibility of North Carolina to military and federal leadership. State support has been leveraged to attract top scientists from around the nation to North Carolina. The State award has supported the work and training of scientists and synergized the growth and productivity of WFIRM and its Regenerative Medicine Clinical Center.

Robust Clinical Translation Program

Achieving the WFIRM mission means getting new technologies to the clinic safely and rapidly, and that requires satisfying strict FDA quality and safety requirements. The specific regulatory requirements for a given therapy are determined by the FDA and are dependent on level of complexity and potential risk. Requirements range from the basic regulations to store cells and tissue for future clinical use, known as current good tissue practices (cGTP), to current good manufacturing practices (cGMP). In addition, there are numerous requirements associated with investigational new drug applications (IND) for treatment of certain clinical indications with biological cells, tissues, and constructs. The regulatory pipeline for clinical translation, illustrated in the schematic below, is a complex undertaking that involves a series of iterations of data collections and FDA meetings.

Regulatory Pathway for Clinical Translation



Key to the efficient translation strategy is a central FDA cGTP- and cGMP-compliant processing facility, integrated regulatory management, and strong researcher and clinician participation. The cGMP/cGTP compliant facility, physically located at WFIRM and designed and built to support clinical trials to Phase II specifically for AFIRM, is part of the commitment from the state of North Carolina to support the clinical programs for AFIRM. The facility of approximately 4,000 square feet is fully equipped for processing and cryopreservation of human cell and tissue products as well as providing biomaterial design and fabrication.

The WFIRM translation program reached several regulatory milestones this year:

- **Phase I clinical study underway.** Phase I clinical study is ongoing for the use of muscle progenitor cells in the treatment of stress urinary incontinence. The study will assess safety of the treatment as well as examining efficacy of the therapy in secondary endpoints.

- **IND application submitted.** WFIRM submitted a full IND application for the use of urothelial and smooth muscle cells for treatment of urethral defects. If approved, the phase I clinical study will get underway in the next year.

- As an **FDA registered facility** we are storing testicular tissue and sperm as well as placental master cell banks for potential future clinical use. Currently we are performing tumorgenicity, toxicity and biodistribution studies with placental cells for intravenous infusion.

- **Definitive preclinical studies underway.** WFIRM successfully completed the pre-IND application and meeting process to establish the scope of preclinical studies needed to satisfy requirement to move forward with use of tissue engineered muscle tissue. Cleft lip was selected as the model system for initial clinical studies. If the preclinical studies are successful, and the IND application approved by the FDA, the therapy could move to the clinic within one to two year. Also at the definitive preclinical phase are the clinical development of corporal smooth muscle and endothelial cells for penile reconstruction and tissue engineered innervated internal anal sphincter construct for fecal incontinence.

- **Pre-IND meetings.** Several WFIRM technologies are at or nearing pre IND submissions and pre IND meeting discussions with the FDA, including use of amniotic fluid stem cells for cerebral palsy and hemophilia, and tissue engineered vagina. If the preclinical study plan is approved and the studies are successful, the IND application is expected to be submitted to the FDA within one to two years.

- **Pre-Pre-IND submitted for tissue engineered cartilage**. Pre-pre-IND documents were submitted following meetings with FDA to discuss pilot and definitive studies for a WFIRM program advancing the clinical use of tissue engineered cartilage.

Development continues on multiple cell therapy, tissue engineered and manufacturing and stem cell banking projects, including muscle progenitor cells for treatment of urinary incontinence, tissue engineered muscle repair

for cleft lip deformities, and tissue engineered innervated internal anal sphincter construct for fecal incontinence. Preclinical process development and regulatory submissions are under way for a number of earlier stage projects. An overview of selected candidates in the clinical development pipeline is shown in the table below.

Selected Projects in Clinical Development Pipeline	
CELL THERAPY/TISSUE ENGINEERING/BIOMATERIALS	
Project	***Indication***
Muscle progenitor cell therapy	Urinary incontinence
Tissue engineered urethra	Urethral defects
Tissue engineered bladder	Fibrotic contracted bladder secondary to trauma
Tissue engineered corpora	Injury to the penile corpora cavernosa
Tissue engineered vagina	Underdeveloped or injured vaginas
Tissue engineered nasal septum	Nasal septal reconstruction
Tissue engineered muscle repair	Cleft lip deformities
Tissue engineered anal sphincter construct	Fecal incontinence
STEM CELL/TISSUE BANKING/BIOMATERIALS ***Preclinical and Clinical Applications***	
Placental cells	
Muscle precursor cells	
Sperm	
Testicular tissue	

Integrated Intellectual Property and Technology Transfer

WFIRM's strategy has been, and continues to be, overcoming technical challenges to clinical translation through innovation. Robust intellectual property protection is essential to the effective translation and commercialization of therapies and innovations, and WFIRM has integrated intellectual property into the day-to-day operations through a dedicated technology transfer team that operates within the Institute.

The arrangement promotes frequent and informal communications, better flow of information and closer working relationships between the researchers, commercialization team and technology transfer staff, all of which contribute to higher quality protection and better prospects for faster, more effective commercialization, building portfolios around key technology areas. WFIRM faculty members have been very productive in generating intellectual property. The WFIRM patent portfolio includes 33 national and international patents issued in fiscal year 2015 and numerous patent applications for technological advances in all aspects of regenerative medicine, from cell and gene therapy to bioprinting and tissue engineering.

Collaborations

WFIRM strongly believes that collaborative teamwork is the key to success. Collaborations create opportunity for scientific exchanges at the very highest levels, extend the translation of clinical techniques to the most appropriate places, and increase the visibility and reputation of WFIRM and the State of North Carolina. WFIRM currently has established over 300 collaborative relationships within the region, nationally and internationally.

Regional

WFIRM has strong relationships within the Wake Forest Baptist Medical Center and Wake Forest University, collaborating with nearly every department and more than 75 scientists from across the institution. Research collaborations are under way with a number of regional companies, including four based in the Piedmont Triad. Collaborations continue with North Carolina State University Center for Comparative Medicine and Translational Research and North Carolina State University Edward P. Fitts Department of Industrial and Systems Engineering. These collaborations are directed at bringing together advances in regenerative medicine with cutting edge science in other disciplines to reduce cost and improve effectiveness. Both collaborations expand training opportunities to develop the North Carolina work force infrastructure.

National

WFIRM scientists are engaged in active research collaborations with more than 200 researchers across the country. The collaborators represent the best and brightest drawn from academic, industrial, and government laboratories.

International

WFIRM has established research collaborations with leading laboratories around the world. WFIRM faculty maintain leadership roles in international scientific societies, including Dr David Williams as global president of the Tissue Engineering & Regenerative Medicine International Society.

Collaborating institutions include the following:

Austria	Ludwig Boltzmann Institute, Wien
China	Shanghai Tissue Engineering Research Center, Jiao Tong University School of Medicine, Shanghai Nantong University, Nantong
Egypt	Kasr Al Ainy Teaching Hospital, Cairo University, El Manial Assuit University, Assuit
Germany	European Center for Medical Technologies and Applications, Cologne Institute for Tissue Engineering and Regenerative Medicine ITERM, Lukas Hospital, Neuss Aachen University Institute of Applied Medical Engineering, Aachen
Hungary	University of Szeged Institute of Surgical Research, Szeged
Ireland	National University of Ireland at Galway and Regenerative Medicine Institute of Ireland at Galway
Israel	Rambam Medical Center, Haifa
Japan	Tokyo Woman's Medical University, Institute of Advanced Biomedical Engineering & Science, Tokyo
Korea	Kyungpook National University and Kyungpook National University Hospital Daegu Korea Institute of Science and Technology, Seoul
Russia	First Moscow State Medical University, Moscow
South Africa	University of Cape Town
Switzerland	University Hospital Basel, ICFS, Basel
Taiwan	Taipei Medical University, Taipei

Education and Outreach

Consistent with its philosophy of making regenerative medicine training widely accessible and the educational need to engage our region's talent as well as attract new talent to cutting-edge biomedical research that reflects the strengths of North Carolina, WFIRM maintains a wide variety of educational offerings from traditional graduate and post-graduate education to programs for undergraduate students, K-12 students and teachers, and the general public.

Community Outreach

WFIRM maintains an active portfolio of community outreach programs at throughout the community at all levels to provide high school, middle school students, and the general public with opportunities to learn more about regenerative medicine.

- **Tours:** Host to more than 1,500 visitors from all walks of life to the WFIRM facility this year alone.
- **Lectures:** Presentations by WFIRM faculty at formal and informal events throughout the Triad, the State, and nationally.
- **Volunteer Program**: Hands-on research experiences open to high school students and teachers, undergraduate students, medical students and postdoctoral fellows from the region, the U.S. and around the world.
- **Forsyth Tech Internship Program:** Internships offering hands-on research experience for Forsyth Technical Community College students pursuing careers in biotechnology.

- **National Center for Biotechnology Workforce Bioscience Industrial Fellowship Project:** Faculty and staff from North Carolina's community colleges identified as high-impact educators become fellows for one month each year and gain hands-on lab experiences to help them create inquiry-based curriculum materials that integrate valid bioscience concepts and processes.
- **Middle and High School Teacher Externships and Classroom Curricula:** In partnership with North Carolina New Schools and the North Carolina Association for Biomedical Research, middle and high school teachers gain valuable lessons in relevance through externships that provide first-hand experience in the "real world" of regenerative medicine, which is then translated into lessons, curriculum materials and educational workshops for teachers and their students across the state.
- **Summer Exposure Program for High School Students:** This mini-exposure program is designed for high

school students to address questions such as: What's it like to be a regenerative medicine scientist? Participants meet with practicing regenerative medicine researchers, students and other experts and explore regenerative medicine fundamentals and applications. A mentoring component educates participants on what it takes to prepare for a career in regenerative medicine.

- **Post-Baccalaureate Research Education Program (PREP):** The unique aspects of this post-baccalaureate research program funded by the National Institute of General Medical Sciences (Principal Investigator Dr. Debra Diz) are to provide a transition between undergraduate and graduate schools for under-represented minorities.

The WFIRM Summer Scholars Research Program

- Highly competitive 10-week program open to undergraduate science and engineering and medical students.
- Students are assigned to one of a broad range of funded projects focused on various aspects of tissue engineering and regenerative medicine.
- Under guidance of researcher-mentor teams, students perform their own research and data analysis.
- Additional features include a special short course, seminar series, professional development and community activities.
- Program concludes with research day of student presentations with poster session attended by family members, mentors and faculty.
- 19 students participated in the 2015 Summer Research Scholars Program.
- Summer Scholars consistently cite the experience as pivotal in their career preparation, and nearly three-quarters have gone on to PhD and MD programs in engineering, medicine, or related fields.

Traditional Degree Programs

The outstanding research infrastructure, highly collaborative nature and expertise of WFIRM faculty and cutting-edge integrated training program prepare students for research careers in regenerative medicine. WFIRM students interact and exchange ideas on a daily basis with scientifically and culturally diverse students, post-doctoral fellows, technicians and faculty in regenerative medicine. Current enrollment is 25 pre-doctoral (PhD) students and 52 postdoctoral fellows.

NIH Pre-doctoral Training Program: Studies in Translational Regenerative Medicine

WFIRM was awarded a training grant from the National Institute of Biomedical Imaging and Bioengineering. The program includes traditional didactic course work, a variety of WFIRM-wide training activities, participation in cutting-edge research projects, grant writing and scientific presentations and exposure to ethical issues in regenerative medicine. Inaugural trainees of the program, Hannah Baker and JP McQuilling, were awarded their doctoral degrees in 2015.

The unique WFIRM infrastructure provides facilities and expertise for translational studies from basic preclinical findings all the way through Phase II clinical trials. The program includes six areas of research focus: 1) urological, 2) cardiovascular, 3) musculoskeletal, 4) endocrine tissue, 5) stem cells, and 6) biomaterials/enabling technologies. Each area of focus contains at least five faculty members with complementary expertise, who will participate in the training and supervision of graduate students as co-

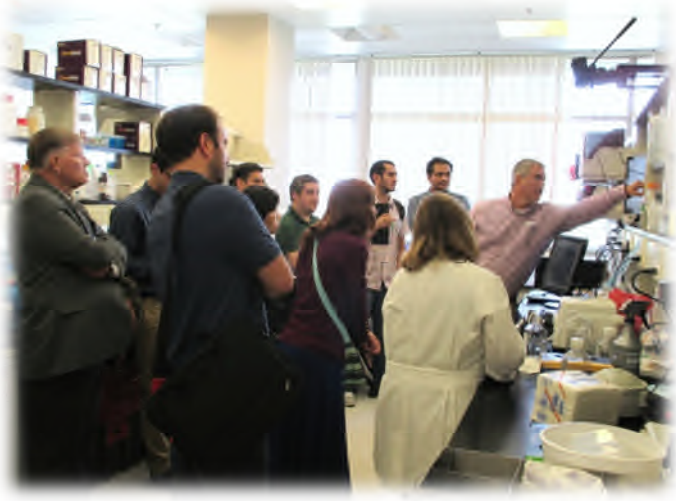
mentors. Students are selected from four tracks within the newly configured structure of the Wake Forest Graduate School: Molecular and Cellular Biosciences, Biomedical Engineering, Integrative Physiology and Pharmacology or Neuroscience.

The 2nd Annual Regenerative Medicine Essentials Course: From the Fundamentals to the Future

The 2nd, annual one-week course brought together WFIRM's prominent, world-class experts and distinguished experts from across the U.S. as faculty together with more than 125 course attendees. Organized as an interactive, educational and scientific course, the purpose was to promote the participation and education of all stakeholders, providing attendees from North Carolina, as well as a substantial presence of national and international participants, a firm foundation in this exciting field.

The course provided a state-of-the-art review of various aspects of regenerative medicine including background material, the key scientific components of the field of regenerative medicine, ethical, economic and other issues important to regenerative medicine. The course

integrates information, technologies and skills from biological sciences, engineering, legal, commercial, regulatory and ethical disciplines. Sessions address the science behind regenerative medicine, its application to human disease and its importance to modern society. New to the 2015 course were two, new *Into the Lab* workshops. These workshops provided hands-on interaction and demonstrations with two cutting-edge technologies and techniques for regenerative medicine applications – 3D bioprinting and decellularization/ recellularization of organs and tissues. Participants were able to review and interact with these technologies and leading researchers at WFIRM

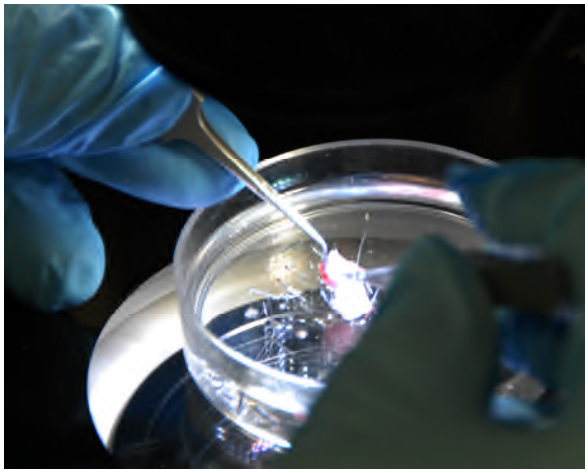


The development of the one-week course was in direct response to the need to provide new members and stakeholders to the regenerative medicine community a firm foundation in this exciting field and is yet another example of WFIRM's proactive leadership role.

Research Activities

Research Proposal Applications

WFIRM faculty submitted 100 research proposals totaling nearly $85 million to more than 22 different agencies, foundations, and companies during fiscal year 2014.



Research Awards

New and continuing awards provided $34 million in grant funding. Included in the ongoing awards in FY15 were:

- ***AFIRM II*** WFIRM was selected to lead the Warrior Restoration Consortium, with more than 30 participating institutions, in a comprehensive program of $75 million in research over 5 years. The program, which includes more than 60 projects in 5 program areas, of extremity regeneration, craniomaxillofacial regeneration, skin regeneration, composite tissue allotransplantation, and genitourinary repair, started in September 2013.
- ***Translational Regenerative Medicine Training Program*** WFIRM received an award from the National Institutes of Health under a highly competitive grant mechanism designed to provide continuing and stable support for the training of outstanding graduate students. Funding from this grant represents national recognition for WFIRM's accomplishments and provides additional resources for training the next generation of clinicians, scientists and thought leaders in regenerative medicine.

- ***Exploratory/Developmental Grant*** from the National Heart, Lung and Blood Institute to utilize bioengineered liver constructs as a novel vehicle for cord blood expansion. If successful, this research could significantly increase the availability of cord blood, which is used in the treatment of leukemia and more than 80 other diseases.

News and Publications

WFIRM researchers published 230 peer-reviewed papers and publications during fiscal year 2015 and also shared their work at scientific conferences. Notable scientific reports and news included:

Milestone Reached in Work to Build Replacement Kidneys in the Lab

WFIRM researchers addressed a major challenge in the quest to build replacement kidneys in the lab. Working with human-sized pig kidneys, the scientists developed the most successful method to date to keep blood vessels in the new organs open and flowing with blood. The work is reported in journal Technology.

"Until now, lab-built kidneys have been rodent-sized and have functioned for only one or two hours after transplantation because blood clots developed," said Anthony Atala, M.D., director and professor at the Wake Forest Institute for Regenerative Medicine and a senior author on the study. "In our proof-of-concept study, the vessels in a human-sized pig kidney remained open during a four-hour testing period. We are now conducting a longer-term study to determine how long flow can be maintained."

If proven successful, the new method to more effectively coat the vessels with cells (endothelial) that keep blood flowing smoothly, could potentially be applied to other complex organs that scientists are working to engineer, including the liver and pancreas.

Researchers Make Progress Engineering Digestive System Tissues

New proof-of-concept research at WFIRM suggests the potential for engineering replacement intestine tissue in the lab, a treatment that could be applied to infants born with a short bowel and adults having large pieces of gut removed due to cancer or inflammatory bowel disease.

Lead researcher Khalil N Bitar, Ph.D., a professor at the institute, reported the results this week at Digestive Diseases Week in Washington, D.C. He also updated attendees on a related project to engineer anal sphincters for patients with fecal incontinence.

"Results from both projects are promising and exciting," said Bitar. "Our latest effort, to find a new solution for the urgent need for gut-lengthening procedures, shows we can meet the basic requirements for regenerating segments of the gastrointestinal tract."

Research in Rodents Suggests Potential for "In Body" Muscle Regeneration

What if repairing large segments of damaged muscle tissue was as simple as mobilizing the body's stem cells to the site of the injury? New research in mice and rats, conducted at WFIRM, suggests that "in body" regeneration of muscle tissue might be possible by harnessing the body's natural healing powers.

Reporting online ahead of print in the journal Acta Biomaterialia, the research team demonstrated the ability to recruit stem cells that can form muscle tissue to a small piece of biomaterial, or scaffold that had been implanted in the animals' leg muscle. The secret to success was using proteins involved in cell communication and muscle formation to mobilize the cells.

"Working to leverage the body's own regenerative properties, we designed a muscle-specific scaffolding system that can actively participate in functional tissue regeneration," said Sang Jin Lee, Ph.D., assistant professor of regenerative medicine and senior author. "This is a proof-of-concept study that we hope can one day be applied to human patients."

Wake Forest Baptist One of a Few Centers Worldwide Offering Fertility Preservation Option to Young Boys with Cancer

Wake Forest Baptist Medical Center is one of a few centers in the world – and the only one in North Carolina – offering young boys with cancer the opportunity to participate in a research study focused on fertility preservation and restoration.

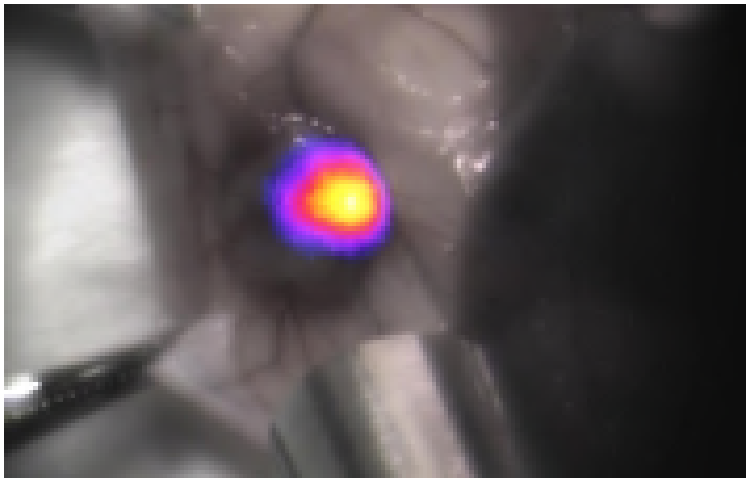
The research, conducted by WFIRM under the direction of Anthony Atala, M.D., institute director, gives boys who have a high risk of becoming sterile the option to "bank" a small piece of testicular tissue prior to treatment.

"The average survival rates for childhood cancer are around 80 percent, but a side effect of some treatments can be permanent sterility," said Thomas W. McLean, M.D., a pediatric cancer specialist, who co-leads the experimental biological bank with Hooman Sadri-Ardekani, M.D., Ph.D., a male infertility specialist at WFIRM. "Preserving or restoring the ability of our patients to one day have children is an important aspect of their treatment."

From the stored tissue, researchers can extract spermatogonial stem cells (SSCs), which are responsible for the continuous production of sperm throughout adult life. Physicians and scientists hope that when the boys reach adulthood, the cells can be transplanted back into their testicles through a simple injection and they will be able to produce sperm.

Scientists Invent System to Improve Effectiveness of Cancer Surgery

With the goal of making it easier for surgeons to detect malignant tissue during surgery and hopefully reduce the rate of cancer recurrence, scientists have invented a new imaging system that causes tumors to "light up" when a hand-held laser is directed at them.



"A surgeon's goal during cancer surgery is to remove the tumor, as well as enough surrounding tissue to ensure that malignant cells are not left behind," said Aaron Mohs, Ph.D., assistant professor at WFIRM and a co-inventor of the system. "But how do they know when they've removed enough tissue? Our goal is to provide better real-time information to guide the surgery."

Published online ahead of print in IEEE Transactions on Biomedical Engineering (TBME), Mohs and co-authors report on their prototype system that combines a fluorescent dye that localizes in tumors with a real-time imaging system that allows the surgeon to simply view a screen to distinguish between normal tissue and the "lighted" malignant tissue.

Search for Biomarkers Aimed at Improving Treatment of Painful Bladder Condition

Taking advantage of technology that can analyze tissue samples and measure the activity of thousands of genes at once, scientists at WFIRM are on a mission to better understand and treat interstitial cystitis (IC), a painful and difficult-to-diagnose bladder condition.

"We are looking for molecular biomarkers for IC, which basically means we are comparing bladder biopsy tissue from patients with suspected interstitial cystitis to patients without the disease. The goal is to identify factors that will lead to a more definitive diagnosis, and then use this information to tailor treatments to the patient," said senior author Stephen J. Walker, Ph.D., associate professor.

The team's initial work, published online ahead of print in the Journal of Urology, found that tissue from IC patients with low bladder capacity had a significantly different gene expression profile than both IC patients with normal bladder capacity and study participants without IC. The findings suggest there may be a sub-type of IC.

News Media Coverage

Coverage by Top Media Outlets

Director Anthony Atala's research was profiled in both Smithsonian Magazine and Discover Magazines. He was also interviewed for a special WebMD video report on 3D printing. In addition, he was named to "The Worldview 100, a list compiled by Scientific American of the world's top leaders in biotechnology."

During the year, WFIRM's research was covered in a wide variety of other national and international news outlets including:

- Canada's CBC News
- Channel News Asia
- Forbes.com
- Fox News
- Huffington Post

- International Business Times
- Gizmondo UK
- Military Times
- Nature.com News
- NPR's Diane Rehm Show
- Parade Magazine
- Popular Mechanics
- UK Guardian
- U.S. News & World Report
- Wall Street Journal

Selected News Coverage

Web MD: Dr. Atala is interviewed for this special Robin Roberts report on the Future of Health
http://www.webmd.com/news/breaking-news/future-of-health/default.htm#3d-printing-toc/3d-printing

US News and World Report: WFIRM is included in a "Biotechnology to the Rescue" article in the 2014 "Best Hospitals" issue
http://health.usnews.com/health-news/hospital-of-tomorrow/articles/2014/09/02/biotechnology-to-the-rescue

UK Guardian: Report on project to benefit wounded warriors with severe genital injuries
http://www.theguardian.com/education/2014/oct/04/penis-transplants-anthony-atala-interview

Diane Rehm Show: Advances in 3-D printing
http://www.theguardian.com/education/2014/oct/04/penis-transplants-anthony-atala-interview

Smithsonian Magazine: Soon, Your Doctor Could Print a Human Organ on Demand
http://www.smithsonianmag.com/innovation/soon-doctor-print-human-organ-on-demand-180954951/?no-ist

UNC-TV: Reports on 3D printing and "Cancer on a Chip" Research
http://video.unctv.org/video/2365418965/; http://video.unctv.org/video/2365426373/

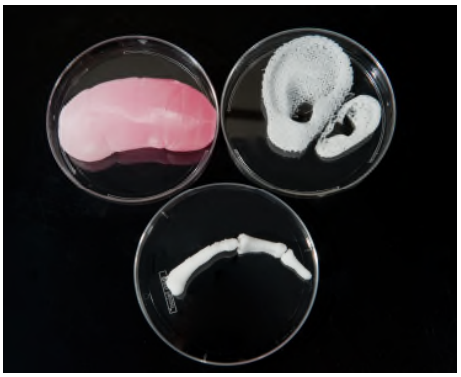
Popular Mechanics: Report on the Body on a Chip project
http://www.popularmechanics.com/science/health/a15071/artificial-heart-cells-beating-video-wake-forest/

Medical News Today: Report on engineering digestive tissue
http://www.medicalnewstoday.com/releases/294141.php

Fierce Biotech Research: project to engineer replacement human kidneys
http://www.fiercebiotechresearch.com/story/regenerative-med-researchers-advance-work-recycling-discarded-kidneys/2015-06-03

The Future

Moving forward, the State of North Carolina's investment in regenerative medicine will continue to play a pivotal role in the institute's ability to "translate" promising scientific discoveries into real-world therapies that can benefit both wounded warriors and the general population.



Already, state support of infrastructure, including the FDA-compliant facility for producing cells and tissues for clinical trials, is enabling the accelerated development of new therapies and helping to ensure that treatments developed in N.C. have the potential to lead to new jobs here.

The institute will continue to leverage state support to attract additional federal and private funding – helping cement North Carolina's role as a leader in the burgeoning regenerative medicine industry.

For more information, please visit the WFIRM website, www.wfirm.org

Wake Forest Institute of Regenerative Medicine
Statement of Revenues and Expenses
Fiscal Year Ending June 30, 2015
NOT FINAL - PRELIMINARY DATA ONLY

Royalties generated from subject projects:	0
Unrestricted Revenues:	
Institutional Support	3,273,948
Gift Income	243,546
Other Income	32,510
Total Unrestricted Revenues	3,550,004
Restricted Revenues:	
State of North Carolina	7,037,889
Federal Government	27,275,640
Foundation	1,146,745
Industry, Individual, Endowment, & Other	241,094
Net Prepaid Income Used/(Deferred)	(1,041,155)
Total Restricted Revenues - cash basis, not accrual	34,660,213
Total Revenues	**38,210,217**
Restricted Expenditures:	
AFIRM Expenditures	18,411,175
Other Federal Expenditures	8,518,469
GMP & Translation Related Expenditures	4,856,405
Other Restricted Expenditures	2,250,651
Total Restricted Operating Expense	34,036,700
Unrestricted Expenditures:	
Administration, Legal, & patents	1,940,450
Department Research	1,386,348
Education	119,451
Total Unrestricted Operating Expense	3,446,249
Capital (renovations, equipment, & software) Funded by Wake Forest, State of NC, & Federal	573,552
Total Expenditures	**38,056,501**
NET	**153,716**