Wake Forest Institute for Regenerative Medicine

Legislative Report

July 1, 2013 to June 30, 2014

- **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

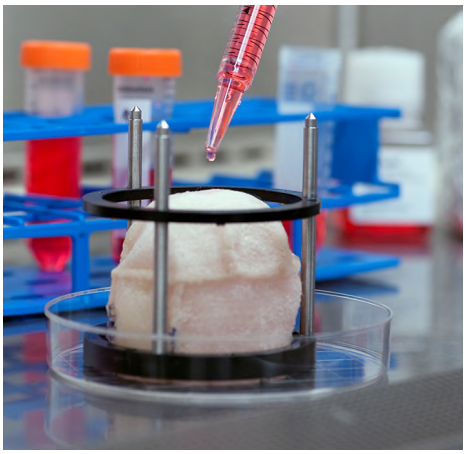
Imagine a day when chronic diseases are treated with an injection of cells ...When functioning nerves are available to replace those damaged by injury ...When diseased organs are routinely exchanged with healthy replacements grown in laboratories.

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. In 2011, regenerative medicine companies generated $3.5 billion in sales and employed almost 14,000 people.[2]

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.

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.[3]

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 $1.8 billion since its first round of awards in 2006. As of 2014, ten 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 $102 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.

[3] 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 in 2013 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 will focus on developing clinical therapies over the next five years focusing on:

- 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 Selected to Lead "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 to develop a "body on a chip" that will be used to develop these countermeasures.

This contractual effort was awarded by Space and Naval Warfare Systems Center, Pacific (SSC Pacific), on behalf of Defense Threat Reduction Agency (DTRA). The goal is to build 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.

Miniature lab-engineered, organ-like hearts, lungs, livers and blood vessels – linked together with a circulating blood substitute – will be used both to predict the effects of chemical and biologic agents and to test the effectiveness of potential treatments.

If successful, the program would significantly decrease the time and cost needed to develop medical countermeasures which would have a direct and positive affect on the ability of the United States government to respond to a chemical or biological attack. Wake Forest Baptist's one-of-a-kind 3-D printer will be used to print the organoids onto the chip. Other partners on the project are Brigham and Women's Hospital, Boston, University of Michigan, the U.S. Army Edgewood Chemical Biological Center, Morgan State University and The Johns Hopkins Bloomberg School of Public Health.

Mission Driven Accomplishments

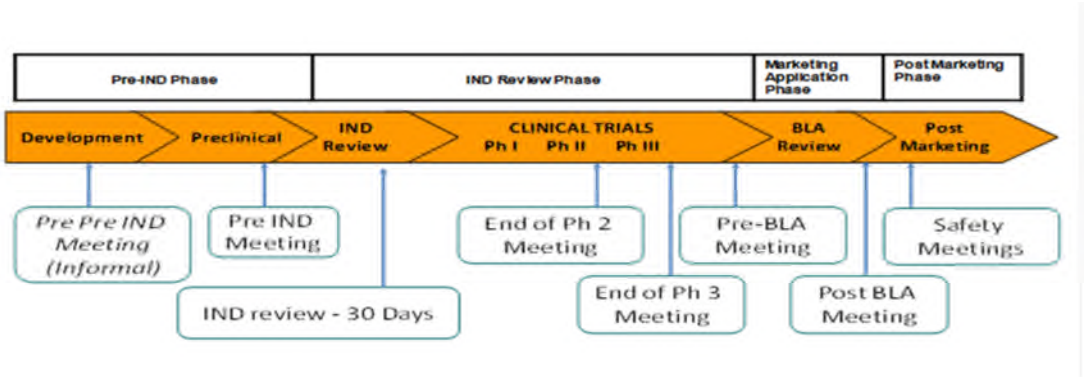
WFIRM's mission is to improve patients' lives by developing regenerative medicine therapies and support technologies. As such, WFIRM's goals have been focused on clinical translation with emphasis on innovation, teamwork and development of platform technologies that address the current scientific challenges. 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.

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 facility includes cell culture/constructs and cell/bioreactor processing laboratories with a class 10,000 air handling capability. Other spaces include cell and materials testing and scaffold fabrication laboratories, warehouse, quarantine, freezer and cryopreservation rooms, and a quality control/analytical lab.

The WFIRM translation program reached several regulatory milestones this year:

- **IND application approved.** WFIRM submitted a full IND application for the use of muscle progenitor cells in the treatment of stress urinary incontinence. The application was approved by the FDA, and the therapy is now in phase I clinical studies.

- **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 two to three years. Also at the definitive preclinical phase is the clinical development of tissue engineered innervated internal anal sphincter construct for fecal incontinence.

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

- **Facility registration**. The FDA regulations require organizations with human cells, tissue, and cellular and tissue-based product to register with the agency. WFIRM is a FDA-registered facility and is now pre-registered for upcoming clinical trials and other clinically relevant human tissue and cell products.

Development continues on multiple cell therapy, tissue engineered and manufacturing and stem cell banking of adult and fetal derived stem cells 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 the 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 muscle repair	Cleft lip deformities
Tissue engineered anal sphincter construct	Fecal incontinence
Banking sperm and testicular tissue	Preserve fertility for young boys with cancer
Amniotic fluid cell therapy	Hemophilia
STEM CELL/TISSUE BANKING/BIOMATERIALS ***Preclinical and Clinical Applications***	
Amniotic fluid stem 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 over 300 national and international patents and

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. WFIRM initiated international participation in their Summer Scholars program, with two students from Cape Town, South Africa taking part in the 2014 class. This program introduces college students to regenerative medicine through a hands-on summer research experience.

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 research 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 a highly active portfolio of community outreach programs through all levels of the community to provide high school, middle school students, and the general public with opportunities to learn more about regenerative medicine.

- **Tours:** Host to more than 1,300 visitors from all walks of life to the WFIRM facility this year alone
- **Lectures:** Presentations by WFIRM faculty at lay events throughout the Triad, the State, and nationally
- **Volunteer Program**: Hands-on research experiences open to high school students, undergraduate students and postdoctoral fellows from the region, the U.S. and around the world
- **Forsyth Tech Intern 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 a month and gain hands-on lab experiences to help them create inquiry-based curriculum materials that integrate valid bioscience concepts and processes.
- **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.

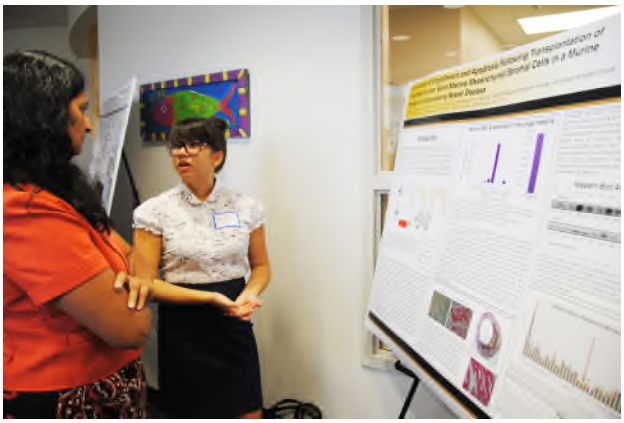
- **Middle and High School Teacher Externships and Classroom Curricula:** In partnership with North Carolina New Schools, high school teachers gain valuable lessons in relevance through externships that provide first-hand experience in the "real world" of regenerative medicine, which is then translated into lessons and curriculum materials for their students and colleagues across the state.

Summer Research Scholars 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
- Program concludes with research day of student presentations with poster session attended by family members, mentors and faculty.
- 24 undergraduates participated in 2014 Summer Research Program.
- Over the past seven years, a total of 127 undergraduates participated in the WFIRM Summer Scholars program with nearly all citing the internship as pivotal in helping them determine next steps in career preparation

Traditional Degree Programs

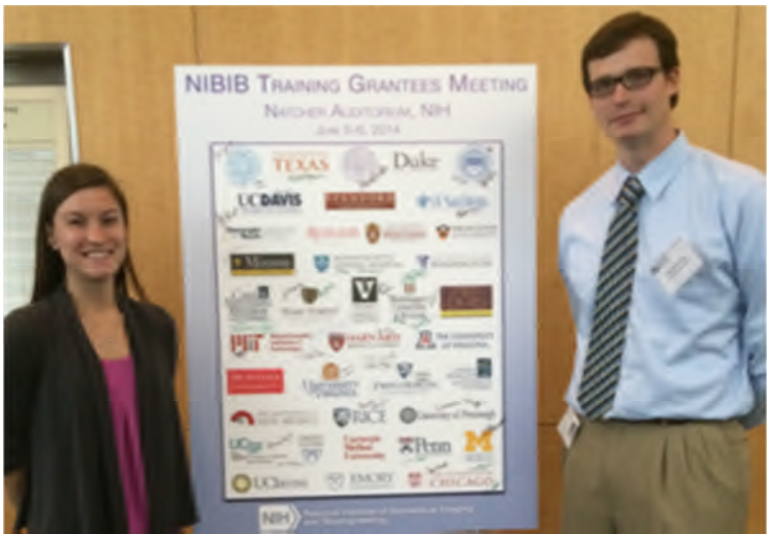
The outstanding research infrastructure, highly collaborative nature and expertise of WFIRM faculty and cutting-edge integrated training program prepare students for research careers in regenerative medicine. WFIRM students interact and exchange ideas on a daily basis with scientifically and culturally diverse students, post-doctoral fellows, technicians and faculty in regenerative medicine. Current enrollment is 24 pre-doctoral (PhD) students and 61 postdoctoral fellows.



National Award for Graduate Training in Regenerative Medicine

WFIRM was awarded a training grant from the National Institute of Biomedical Imaging and Bioengineering this past year. This is a 5-year training grant that 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.

The unique WFIRM infrastructure provides facilities and expertise for translational studies from basic preclinical findings all the way through Phase 2 clinical trials. The program offers 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 will be selected from three tracks within the newly configured structure of the Wake Forest Graduate School: Molecular and Cellular Biosciences, Biomedical Engineering, or Integrative Physiology and Pharmacology.



Inaugural trainees Hannah Baker and JP McQuilling attended the bi-annual National Institute of Biomedical Imaging and Bioengineering Training Grantees Meeting, June 5th to 6th, 2014 in Bethesda, Maryland. Principal investigators and trainees came together to exchange information and share best practices. As the meeting's signage illustrates, WFIRM is indeed in elite company with respect to peer training of pre-doctoral students.

Annual Career Opportunities Day

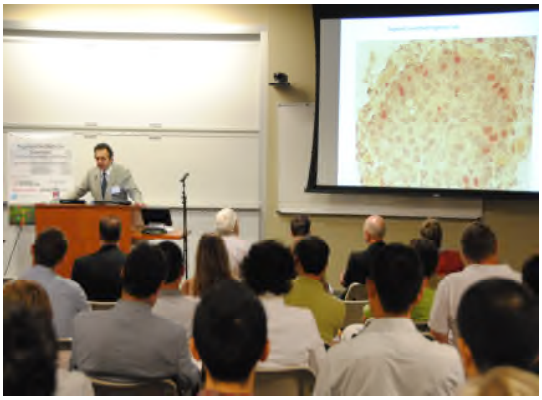
WFIRM's annual Career Opportunities Day is part of the continued efforts to provide best training and career preparation for all of the institute's trainees (graduate students, postdoctoral fellows and research staff). This seminal event brings together successful individuals covering a very broad range of career opportunities related to regenerative medicine. The impressive list of speakers at this year's program included:

- Eric Tomlinson, DSc., Ph.D., Chief Innovation Officer, Wake Forest Baptist Medical Center
- Dwayne Godwin, Ph.D., Dean, Wake Forest Graduate School and Professor of Neurobiology & Anatomy
- Nancy Johnston, North Carolina Biotechnology Center, Executive Director, Piedmont Triad Office
- Joydeep Basu, Director of Process Research & Translation at Tengion, Inc.
- Allison Dobson, Ph.D., Patent Attorney, Kilpatrick Townsend & Stockton LLP

- Kirsten Crapnell, BD Technologies, R&D Leader - Cell Culture Environments/Cell and Tissues
- Cindy Rothschild, Ph.D., Patent Attorney, Kilpatrick Townsend & Stockton LLP
- Ben Corona, United States Army Institute of Surgical Research, Extremity Trauma and Regenerative Medicine Research Physiologist, (former WFIRM Postdoc)
- Rosemarie Hunziker, Ph.D., National Institute of Biomedical Imaging and Bioengineering Director of Tissue Engineering and Regenerative Medicine

Well attended, interactive and highly reviewed by both speakers and participants, the Career Opportunities Day is another example of the forward-looking approach WFIRM has taken to maintain a leadership position in training and education of the required workforce for clinical translation of regenerative medicine technologies.

Inaugural Regenerative Medicine Essentials Course: From the Fundamentals to the Future

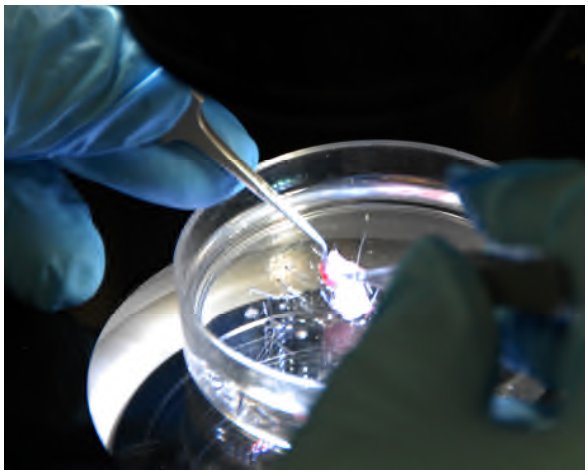


The inaugural, annual one-week course brought together WFIRM's prominent, world-class experts and distinguished experts from across the U.S. as faculty. Organized as an interactive, educational and scientific course, the purpose was to promote the participation and education of all stakeholders, providing 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 the field addressing the fundamental principles and progress in tissue engineering and regenerative medicine in recent years, including background material, key scientific components, ethical, economic and other issues important to the field. 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 70 research proposals totaling nearly $75 million to more than 22 different agencies, foundations, and companies during fiscal year 2014.

Research Awards

New and continuing awards provided $32 million in grant funding. Included in the new awards in FY14 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 239 peer-reviewed papers during fiscal year 2014 and also shared their work at scientific conferences. Notable scientific reports and news included:

Lab-engineered Vaginal Organs Implanted in Patients

WFIRM led a team of scientists that reported the first human recipients of laboratory-grown vaginal organs. The team achieved long-term success in four teenage girls who received vaginal organs that were engineered with their own cells.

The pilot study was the first to demonstrate that vaginal organs can be constructed in the lab and used successfully in humans. Anthony Atala, WFIRM director, said the technology may represent a new option for patients who require vaginal reconstructive surgeries and is one more example of how regenerative medicine strategies can be applied to a variety of tissues and organs.

The girls in the study were born with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, a rare genetic condition in which the vagina and uterus are underdeveloped or absent. The treatment could also potentially be applied to patients with vaginal cancer or injuries, according to the researchers. The girls were between 13 and 18 years old at the time of the surgeries. Data from annual follow-up visits show that even up to eight years after the surgeries, the organs had normal function.

Tissue-engineered autologous vaginal organs in patients: a pilot cohort study. Raya-Rivera AM, Esquiliano D, Fierro-Pastrana R, López-Bayghen E, Valencia P, Ordorica-Flores R, Soker S, Yoo JJ, Atala A. Lancet. 2014 Apr 9. pii: S0140-6736(14)60542-0. doi: 10.1016/S0140-6736(14)60542-0. [Epub ahead of print)

Oxygen-Generating Compound Shows Promise for Saving Tissue after Severe Injury

The same compound in a common household clothes detergent shows promise as a treatment to preserve muscle tissue after severe injury. WFIRM researchers hope the oxygen-generating compound could one day aid in saving and repairing limbs and tissue.

The research in rats found that injections of the compound sodium percarbonate (SPO) can produce enough oxygen to help preserve muscle tissue when blood flow is disrupted. Some commercial detergents generate oxygen bubbles to help clean clothes or remove stains. Researcher modified the material so it can be injected into muscle and provide a boost of oxygen to slow down muscle death until surgery can restore blood flow. Potential applications include treating amputations, crush injuries from car accidents or even blast injuries suffered by those in combat zones.

Normally, when blood flow to muscle tissue is reduced due to severe injury, the muscle begins to die. Providing extra oxygen to oxygen-deprived muscle following injury is currently a major medical challenge. The few treatments that are available are primarily aimed at increasing the oxygen-carrying capacity of blood and require an intact system of blood vessels to carry that fluid, which we don't always have in damaged tissue.

The research found that even after exercising isolated leg muscles in the absence of oxygen, the muscles injected with the SPO compound could generate 20 percent more force than untreated muscles. Additional work is needed to determine if SPO will be effective in larger muscles and can be dispersed throughout the muscle, as well as if it can be applied to humans.

Oxygen generating biomaterials preserve skeletal muscle homeostasis under hypoxic and ischemic conditions.
Ward CL, Corona BT, Yoo JJ, Harrison BS, Christ GJ. PLoS One. 2013 Aug 26;8(8):e72485. doi: 10.1371/journal.pone.0072485. eCollection 2013. PMID: 23991116 [PubMed - indexed for MEDLINE]

Finding Hiding Place of Virus Could Lead to New Treatments

Discovering where a common virus hides in the body has been a long-term quest for scientists. Up to 80 percent of adults harbor the human cytomegalovirus (HCMV), which can cause severe illness and death in people with weakened immune systems. Now, researchers at WFIRM have found that stem cells that encircle blood vessels can be a hiding place, suggesting a potential treatment target.

The virus, which is part of the herpes family, is unnoticed in healthy people. In people with weakened immune systems, including those with HIV, undergoing chemotherapy, or who are organ or bone marrow transplant

recipients, the virus can become re-activated. Once re-activated, HCMV can cause a host of problems – from pneumonia to inflammation of the liver and brain – that are associated with organ rejection and death.

The WFIRM team hypothesized that cell populations in the body's tissues may be able to harbor the virus and suspected that perivascular cells that surround blood vessels were a likely culprit. Their suspicions were confirmed when testing revealed that perivascular cells are susceptible to HCMV infection and that the virus can grow within these cells.

Knowing the identity of the cells opens the possibility of targeting treatments to stop its re-activation. Perivascular stromal cells as a potential reservoir of human cytomegalovirus.

Soland MA, Keyes LR, Bayne R, Moon J, Porada CD, St Jeor S, Almeida-Porada G. Am J Transplant. 2014 Apr;14(4):820-30. doi: 10.1111/ajt.12642. Epub 2014 Mar 4. PMID: 24592822 [PubMed - in process]

News Media Coverage

Tissue Engineering Breakthrough

A highlight of news coverage during FY 14 was the **almost 1,000 news stories** reporting on the implantation of lab-engineered vaginal organs into four young women with a rare genetic disorder.

Four young women received engineered vaginas as a result of Wake Forest Institute for Regenerative Medicine research.

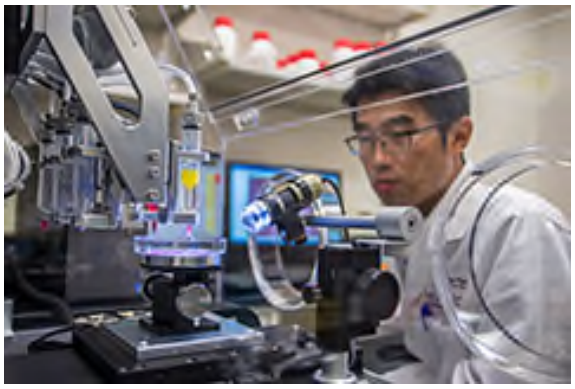
The breakthrough was covered by such media outlets as:

- Associated Press
- CBS Newspath
- CNN
- Huffington Post
- Newsweek
- Washington Post
- Wall Street Journal

Coverage by Top Media Outlets

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

- BBC News
- Bloomberg News
- CNN.com
- Discovery News
- Fox News
- Military Officer Magazine
- National Journal
- National Pubic Radio's Science Friday
- Newsweek
- Popular Science
- Scientific American
- Reuter's Health
- Stars and Stripes
- The Economist
- Today Show.com



- Voice of America
- UK Wired News
- Yahoo! News – South Africa

International Television Coverage

Crews from around the world visited WFIRM to produce stories on regenerative medicine for their viewers. These included:

- CNN's Inside Man
- Daily Planet, a Discovery Channel news program syndicated in 120 countries
- France 24: broadcast in three languages and reaches 245 million households

Selected News Coverage

Stars and Stripes: Research into regenerating tissue to benefit severely wounded warriors
http://www.stripes.com/news/special-reports/wounded-warriors/research-into-regenerating-tissue-to-benefit-severely-wounded-warriors-1.270006

Charlotte Observer: Wake Forest to lead high-tech medical research for severely wounded warriors
http://www.charlotteobserver.com/2014/02/25/4723881/wake-forest-to-lead-high-tech.html#.U9ElO7HFjKc

The Business Journal: Wake Forest leading research to counter chemical, biological weapons
http://www.bizjournals.com/triad/news/2013/09/10/wake-forest-research-hopes-to-counter.html

Popular Science: How 3D Printing Body Parts will Revolutionize Medicine
http://www.popsci.com/science/article/2013-07/how-3-d-printing-body-parts-will-revolutionize-medicine

BBC: Body on a Chip uses 3D printed organs to test vaccines
http://www.bbc.com/news/technology-24125678

Discovery News: "10 Amazing Parts Created Outside the Body"
http://news.discovery.com/tech/biotechnology/10-bionengineered-body-parts-130722.htm

CNN: Artificial eyes, plastic skulls: 3-D printing the human body
http://edition.cnn.com/2014/04/17/tech/innovation/artificial-eyes-3d-printing-body/index.html#cnn-disqus-area

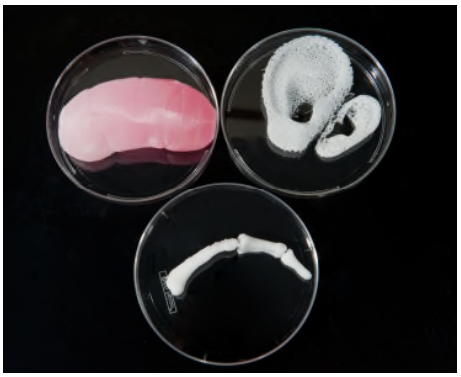
CBSNewspath: Doctors grow sex organs for patients with rare genetic condition
http://www.cbsnews.com/videos/doctors-grow-sex-organs-for-patients-with-rare-genetic-condition/

Winston-Salem Journal: Editorial: Regenerative Medicine: Wake Forest Institute a point of pride
http://www.journalnow.com/opinion/editorials/editorial-regenerative-medicine-wake-forest-institute-a-point-of-pride/article_f3bb58a6-a620-11e3-88b9-0017a43b2370.html

BBC: Doctors implant lab-grown vagina
http://www.bbc.com/news/health-26885335

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, 2014
NOT FINAL - Preliminary Data Only

Revenues (Actual)**:**	
Unrestricted Revenues:	
Institutional Support	2,994,079
Gift Income	157,775
Other Income	66,899
Total Unrestricted Revenues	3,218,753
Restricted Revenues:	
State of North Carolina	7,018,273
Federal Government	13,760,034
Foundation	655,663
Industry, Individual, Endowment, & Other	298,342
Net Prepaid Income Used	6,478,481
Total Restricted Revenues - cash basis, not accrual	28,210,793
Total Revenues	**31,429,546**
Restricted Expenditures:	
AFIRM Expenditures	12,123,331
Other Federal Expenditures	8,625,441
GMP & Translation Related Expenditures	4,684,962
Other Restricted Expenditures	1,778,433
Total Restricted Operating Expense	27,212,167
Unrestricted Expenditures:	
Administration, Legal, & Patents	1,619,087
Department Research	1,582,374
Education	126,339
Total Unrestricted Operating Expense	3,327,800
Capital (renovations, equipment, & software)	716,847
Total Expenditures	**31,256,814**
Net	**172,732**