Cover Page

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Wake Forest Institute for Regenerative Medicine

Legislative Report

July 1, 2015 to June 30, 2016

- **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, 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 $16.5 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 how joint initiatives accelerate progress.

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

Regenerative Medicine Initiatives Selected State Programs

California Institute for Regenerative Medicine (CIRM)
CIRM was created 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 $2 billion since its first round of awards in 2006.

New York State Stem Cell Science (NYSTEM)
NYSTEM is a $600 million initiative of the State of New York to provide funding for stem cell biology research and development. The fund, created through legislation authorizing the Empire State Stem Cell Trust Fund and administered by the New York State Department of Health, has awarded $372 million in research grants.

Maryland Stem Cell Research Fund
Established through the Maryland Stem Cell Act to promote stem cell research and development, the Maryland Stem Cell Research Fund has awarded $130 million in research grants to date.

Connecticut Regenerative Medicine Research Fund
The Regenerative Medicine Research Fund, formerly the Stem Cell Research Fund, committed $100 million over a 10 year period to stem cell research.

North Carolina's Leadership Role

North Carolina is among the most forward thinking states in providing critical support to the sector. The State has initiated a recurring annual investment to allow WFIRM to better develop and and more quickly translate its discoveries to patients. With State support of regenerative medicine, North Carolina will maintain its leadership position in this sector by accelerating the clinical translation of scientific discoveries and supporting the development and manufacturing of these regenerative technologies in North Carolina. The result will be rapid 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 the international leader in regenerative medicine – the Wake Forest Institute for Regenerative Medicine. WFIRM is the largest dedicated regenerative medicine organization in the world and its continuing accomplishments have meant a growing reputation in regenerative medicine for North Carolina.

- ***Proven track record***. Several regenerative medicine therapies developed by WFIRM scientists are already in patients, and others are in the pipeline, ready to begin testing in patients within the next few years. Projects

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

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.

- ***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.

- ***WFIRM 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*.** State funds were a critical advantage in WFIRM's selection 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 its selection as sole lead for the second phase. The AFIRM program has brought significant funding to North Carolina WFIRM scientists to rapidly develop new treatments that will benefit both wounded warriors and civilians, a critical need to a state with a proud military history and presence.

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 mission of the AFIRM is to deliver the regenerative-based technologies that will lead to functional and aesthetic recovery from injuries incurred in military service. AFIRM is leading the development of restorative therapies for battlefield trauma. By partnering with health professionals in the Armed Forces, AFIRM serves as a catalyst to bring advances from the nation's leading regenerative medicine laboratories to the warfighter.

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. Equally important, therapies developed by AFIRM will also benefit people in the civilian population.

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. Through WFIRM, North Carolina researchers have played a vital role in the development of therapies for our wounded warriors.

The AFIRM-II team is focused on developing clinical therapies in the following areas:

- Restoration of function to severely traumatized limbs
- Reconstruction for facial and skull injuries through tissue regeneration
- Regeneration of skin 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

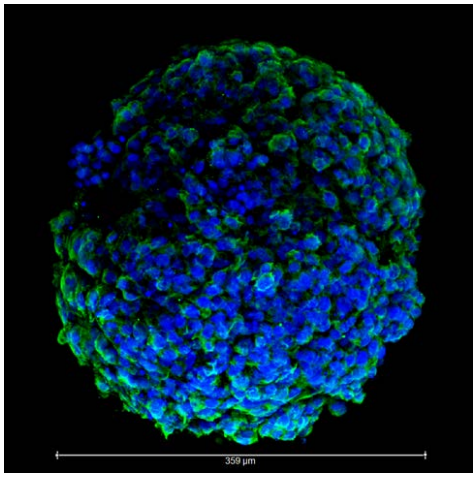
Government sponsors of AFIRM are the U.S. Army Medical Research and Materiel Command, the Office of Naval Research, the Air Force Medical Service, the Office of Research and Development - Department of Veterans Affairs, the National Institutes of Health, and the Office of the Assistant Secretary of Defense for Health Affairs.

The first phase of the AFIRM program focused on getting projects through advanced development, so that the innovations could be used for patients who need them. During the first program, several hundred patients received treatment with AFIRM-funded technologies. The first AFIRM also achieved the first double hand transplant in the U.S. That momentum is continuing under AFIRM-II, with multiple additional clinical trials already initiated and many other projects nearing FDA approval for clinical trials.

Investing in developing regenerative medicine into new treatments has been described by armed forces leadership as one way to fulfill the nation’s promise to service members who put themselves in harm's way, doing our very best to take care of warriors who come back from the battlefield with serious life-changing injuries. The hope is that the AFIRM program will not only develop new and innovative ways to help them, but will ultimately lead to new treatments to repair these severe injuries as if they never happened.

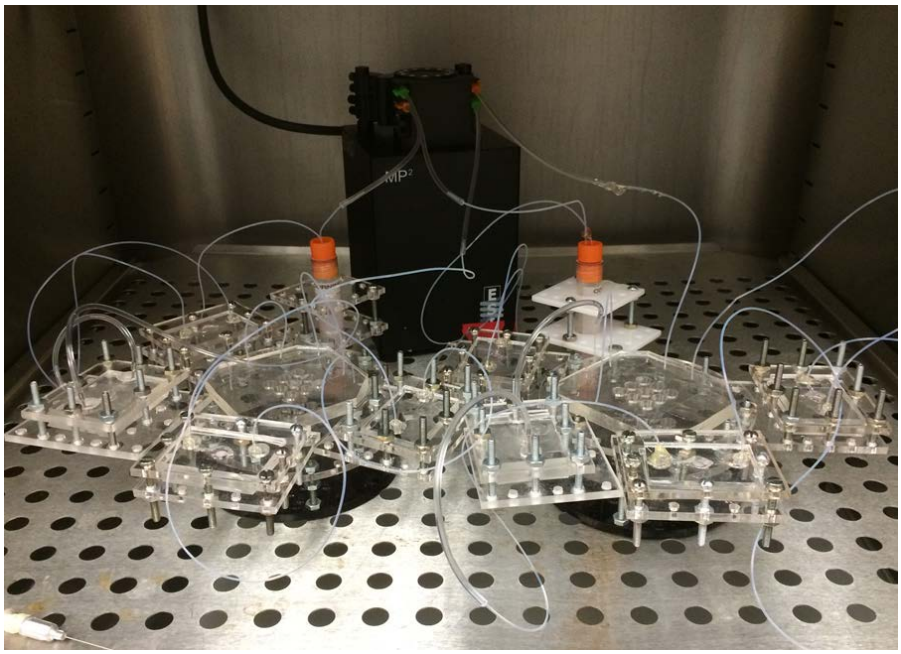
WFIRM makes Significant Breakthroughs in “Body on a Chip” Project

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 ECHO, 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 (traditionally expensive, slow, and with results not always applicable to humans) and greatly accelerate the schedule on which the results might be ready for use in human patients.



The first phase of the ECHO initiative 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, ECHO organoids have demonstrated an astounding degree of fidelity when compared to normal human organs. The heart beats, the lung breathes, the liver detoxifies drugs, and the blood vessels change permeability in response to chemical signals.

The second phase of the ECHO program demonstrated that multiple tissue organoids could be successfully integrated into a single microfluidic circuit and that the integrated platform was able to model the effects of drugs and toxins across multiple organoid types.



By utilizing 3D bioprinting to deposit the tissue organoids (a WFIRM groundbreaking initiative) into the ECHO 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 will be conducted. The breakthroughs achieved in the ECHO program suggest that the technology can be successfully scaled to achieve 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 with regenerative medicine therapies and technologies. As such, WFIRM's goals have been focused on clinical translation with emphasis on innovation, teamwork and the development of platform technologies that address critical and current unmet clinical challenges.

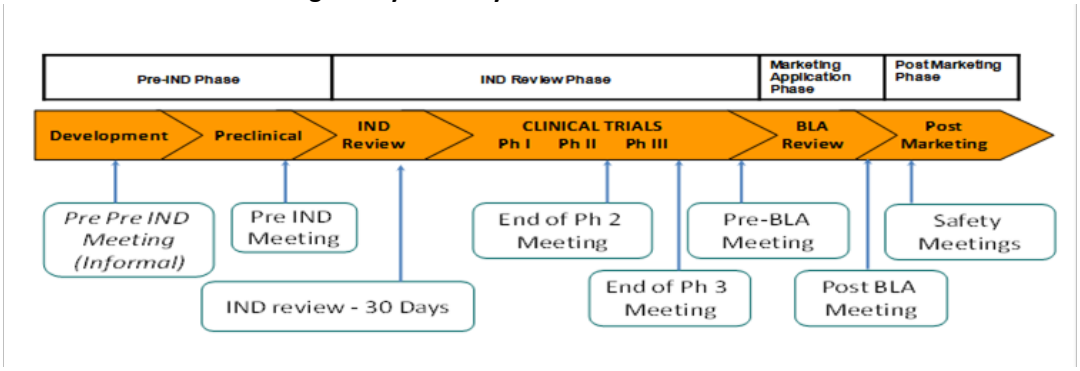
Additional core resources provided by the State of North Carolina have allowed WFIRM to accelerate projects within the AFIRM progam and aided in increasing the visibility of North Carolina to military and federal leadership. State support has been leveraged to attract top scientists from around the nation to North Carolina. The State award has supported the critical 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 the level of complexity and potential risk. Requirements range from the basic regulations for storing 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.

Progress has been notable, and the WFIRM translation program reached several regulatory milestones this year:

Phase I clinical study underway. Statistics show that 50% of all women over the age of 65 and 45% of all men will suffer from stress urinary incontinence. A Phase I clinical study is ongoing for the use of muscle progenitor cells in the treatment of this condition; the study will assess safety of the treatment as well as examining efficacy of the therapy in secondary endpoints.

- **IND application submitted.** WFIRM has 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 begin next year.

- **IND applications in preparation**. WFIRM successfully completed the pre-IND application and preclinical studies needed to satisfy requirements to move forward with use of tissue engineered muscle tissue. Cleft lip was selected as the model system for initial clinical studies. Process development is underway in preparation for the IND application to obtain FDA clearance to move the therapy to the clinic. Also in preparation are IND applications for a tissue engineered bladder with urothelial and smooth muscle cells for battle field injuries.

- 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.** Preclinical studies are underway for the clinical development of corporal smooth muscle, bioprinted nasal septum produced with cartilage cells, and endothelial cells for penile reconstruction and tissue engineered innervated internal anal sphincter constructs 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 nasal septum reconstruction, use of placental stem cells for cerebral palsy, amniotic fluid stem cells for 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.

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.

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 communication, 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 17 patents issued in fiscal year 2016 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 350 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 the North Carolina State University Center for Comparative Medicine and Translational Research and the 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 250 organizations 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, past president of the Tissue Engineering & Regenerative Medicine International Society.

Collaborating institutions include the following:

Austria	Ludwig Boltzmann Institute, Wien
Argentina	Universidad Maimónides, Buenos Aires
China	Shanghai Tissue Engineering Research Center, Jiao Tong University School of Medicine, Shanghai
	Nantong University, Nantong
	Suzhou University First Affiliated Hospital, Suzhou, Jiangsu
Egypt	Kasr Al Ainy Teaching Hospital, Cairo University, El Manial
	Assuit University, Assuit
	Zagazig University, El-Zakazik, Ash Sharqia
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
	Soonchunhyang University, Chungcheongnam-do
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 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 1,500 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 and the U.S. and around the world

- **Visiting International Scholar Program**: WFIRM regards the presence of visiting scholars as of strategic importance to fostering international education and the advancement and internationalization of the field to result in the development of new regenerative medicine therapies, products and support technologies. The WFIRM Visiting International Scholars Program (VISP) enables international scientists, clinicians and physician-scientists to participate as Visiting Scholars at WFIRM for a three-month period each fall.

- **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 the North Carolina Association for Biomedical Research and school districts across North Carolina, 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.

- **High Summer Research Exposure Research Program:** 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 provides students with educational and hands-on experiences designed to increase their familiarity with the scientific process, exposure to modern instrumentation and techniques, as well as educate 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 (PI 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, technical communication and scientific presentation wrkshops, GRE and MCAT prep workshops, opportunities to attend professional meetings and co-authoring with faculty, and social activities and community-building.
- Program concludes with research day of student presentations with poster session attended by family members, mentors and faculty.
- 18 undergraduates and 3 medical students participated in the 2016 Summer Research Scholars Program.
- Over the past seven years, WFIRM hosted more than 425 undergraduates during both the summer and academic year. Of these, a total of 168 undergraduate students participated in the competitively selected, Summer Scholars Program with nearly all citing the experience as pivotal in helping them determine next steps in education and career preparation. Nearly 80 percent have reported completion of their undergraduate college degree, with more than 70 percent of those who have completed either currently enrolled or graduated from PhD and MD programs in engineering, medicine, or other STEM 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 23 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 in 2013. 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 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.

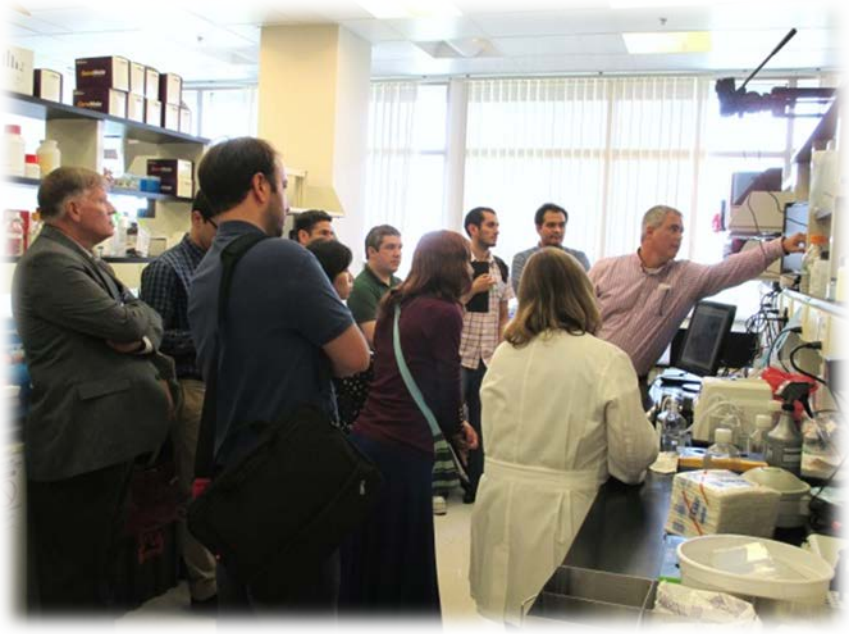
Inaugural trainees, Hannah Baker and JP McQuilling completed their PhD training in 2015. JP McQuilling is now senior research engineer at NuTech Medical with focus on developing allograft derived product and cell based therapies using amniotic fluid stem cells. Hannah Baker is a postdoctoral fellow at the University of Maryland in the Bioengineering Department working on tissue engineered therapies for orthopedic tissues. Trainee Ashely Wagoner successfully completed her program in 2016 and is now a clinical research Trainee fellow at Quintiles, the world's largest provider of biopharmaceutical development and commercial outsourcing services in Research Triangle Park, NC. This position provides regulatory affairs and clinical monitoring experience focusing on therapeutic areas including cardiology, neurology, medical devices, and cancer. Using her clinical operations experience, she obtained a role in strategic planning of clinical trials and drug development.

The 3rd Annual Regenerative Medicine Essentials Course: From the Fundamentals to the Future

The 3rd annual one-week course brought together WFIRM's prominent, world-class experts and nearly 200 course attendees and distinguished course instructors. 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 2016 course were three, new *Into the Lab* workshops. These workshops provided hands-on interaction and demonstrations with cutting-edge technologies and techniques for regenerative medicine applications: 1) 3D bioprinting; 2) decellularization and recellularization of organs and tissues and 3) Intro to Translation. Participants were able to review and interact with these technologies and leading researchers at WFIRM

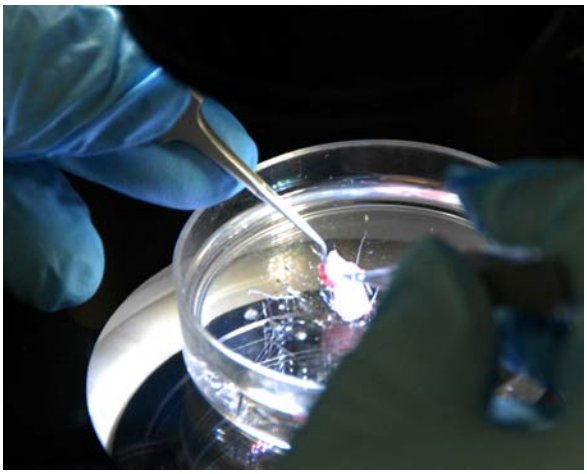


The development of the one-week course was in direct response to the need to provide new members and stakeholders to the regenerative medicine community a firm foundation in this exciting field and is yet another example of WFIRM's proactive leadership role.

Research Activities

Research Proposal Applications

WFIRM faculty submitted over 100 research proposals totaling nearly $108 million to more than 22 different agencies, foundations, and companies during fiscal year 2016.



Research Awards

New and continuing awards provided $30 million in grant funding. Included in the ongoing awards in FY16 were:

- ***AFIRM II*** WFIRM was selected to lead the Warrior Restoration Consortium, with more than 30 participating institutions, in a

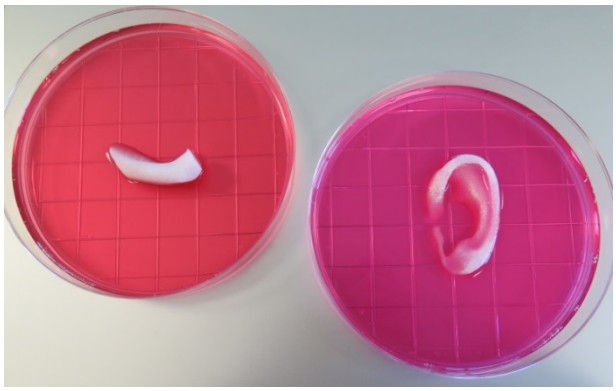
comprehensive program of $75 million in research over 5 years. The program, which includes more than 60 projects in 5 program areas, of extremity regeneration, craniomaxillofacial regeneration, skin regeneration, composite tissue allotransplantation, and genitourinary repair, started in September 2013.

- ***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 lung tumor organoids for the development of personalized medicine. If successful, this research could lead to more effective cancer treatments.

News and Publications

WFIRM researchers published 169 peer-reviewed papers and publications during fiscal year 2016 and also shared their work at scientific conferences. Notable scientific reports and news included:

Scientists Prove Feasibility of "Printing" Replacement Tissue



Using a sophisticated, custom-designed 3D printer, scientists at Wake Forest Institute for Regenerative Medicine have proved that it is feasible to print living tissue structures to replace injured or diseased tissue in patients.

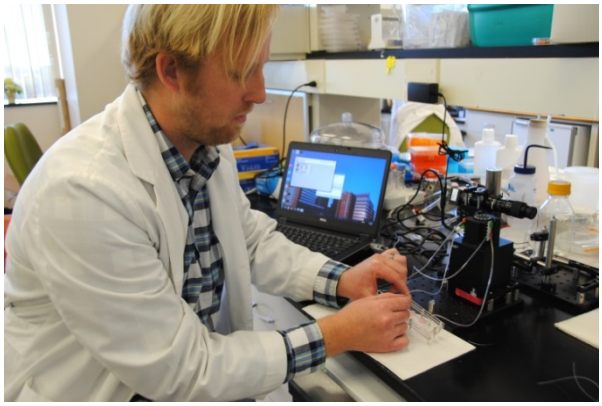
Reporting in Nature Biotechnology, the scientists said they printed ear, bone and muscle structures. When implanted in animals, the structures matured into functional tissue and developed a system of nerves and blood vessels. Most importantly, these early results indicate that the structures have the right size, strength and function for use in humans.

"This novel tissue and organ printer is an important advance in our quest to make replacement tissue for patients," said Anthony Atala, M.D., institute director and senior author on the study. "It can fabricate stable, human-scale tissue of any shape. With further development, this technology could potentially be used to print living tissue and organ structures for surgical implantation."

With funding from the Armed Forces Institute of Regenerative Medicine, a federally funded effort to apply regenerative medicine to battlefield injuries, Atala's team aims to implant bioprinted muscle, cartilage and bone in patients in the future.

The Integrated Tissue and Organ Printing System (ITOP), developed over a 10-year period by WFIRM scientists, overcomes a variety of prior challenges in 3D bioprinting. The system deposits both bio-degradable, plastic-like materials to form the tissue "shape" and water-based gels that contain the cells. In addition, a strong, temporary outer structure is formed. The printing process does not harm the cells.

Model of Tumor Spreading May Help Doctors Pinpoint Best Treatment



Advances in personalized medicine allow doctors to select the most promising drugs for certain types of malignant tumors. But what if before initiating treatment, they could go a step further and use a mini-model of the human body to see how each patient's actual tumor responds to the drugs and learn if and where the tumor is likely to spread?

That's the idea behind a new invention by scientists at Wake Forest Institute for Regenerative Medicine. In the journal Biotechnology and Bioengineering, the team reports on its "metastasis-on-a-chip" system believed to be one of the first laboratory models of cancer spreading from one 3D tissue to another.

The research team is working to further develop the system in hopes that it can one day be used to quickly reveal the best way to treat an individual patient's cancer.

"We believe the metastasis-on-a-chip system has potential for making meaningful advances in cancer investigation and drug discovery," said Aleks Skardal, Ph.D., lead author and an assistant professor of regenerative medicine.

The current version of the system models a colorectal tumor spreading from the colon to the liver, the most common site of metastasis. Skardal said future versions could include additional organs, such as the lung and bone marrow, which are also potential sites of metastasis. The team also plans to model other types of cancer, such as the deadly brain tumor glioblastoma.

"We are currently exploring whether other established anti-cancer drugs have the same effects in the system as they do in patients," said Skardal. "If this link can be validated and expanded, we believe the system can be used to screen drug candidates for patients as a tool in personalized medicine. If we can create the same model systems, only with tumor cells from an actual patient, then we believe we can use this platform to determine the best therapy for any individual patient."

Alumni of Summer Program for Students Win Awards for Research

Savannah Est

Sarah Grebinnikov

Two alumni of the Wake Forest Institute for Regenerative Medicine's Summer Scholar's program have been honored for scientific research they conducted during the 2015 program. Savannah Est, a biomedical engineering junior at the University of Washington, is one of 60 students nationwide selected to participate in the 20th annual Posters on the Hill event, a selective poster session sponsored by the Council on Undergraduate Research (CUR). Sarah Grebinnikov, a microbiology major at the University of Oklahoma, was awarded honorable mention in the competition.

Summer Scholars is a 10-week annual program offering college students the opportunity to conduct research projects under the supervision of institute scientists. By exposing students to multidisciplinary projects that address real-world clinical needs, Summer Scholars aims to motivate students to pursue graduate studies and careers in the biomedical sciences. Est, whose Summer Scholars project focused on 3D printing a trachea, worked under the supervision of Anthony Atala, MD, director of the Institute for Regenerative Medicine, and Sean Murphy, Ph.D., assistant professor.

Grebennikov's project, conducted under the direction of Thomas Shupe, Ph.D., assistant professor of regenerative medicine, focused on engineering a mini-blood vessel for a "body on a chip" system to test the effects of biologic weapons on the body and develop potential therapies.

Researchers Report Possibility of Using Unused Human Pancreata to Build New Organs

Researchers have been working for years to develop an artificial pancreas in the lab to help the millions of people with type 1 diabetes. But what if the answer is to "recycle" the more than 300 human pancreata from organ donors that aren't currently being used?

Online ahead of print in the Annals of Surgery, regenerative medicine researchers at Wake Forest Institute for Regenerative Medicine and colleagues report on the potential to use human pancreata as the "hardware" of a new-generation, bio-artificial pancreas. The pancreas is a large gland near the stomach that secretes insulin to regulate the metabolism of glucose and other nutrients.

Currently, about 25 percent of the approximately 1,300 pancreata recovered for transplant cannot be used due to defects and other reasons.

"We see these unused organs as potential 'hardware." The 'software' would be the patient's own cells, so that there would be no issues with rejection," said lead author Giuseppe Orlando, M.D., Ph.D., a transplant surgeon and regenerative medicine researcher. "We believe this research represents the first critical step toward a fully human-derived artificial pancreas."

Currently, most patients who have type 1 diabetes must take injections of insulin because their bodies do not produce insulin to regulate blood sugar levels. Other options, such as a pancreas transplant or transplant of insulin-producing islet cells are rarely offered due to the lack of suitable pancreas donors and the toxic effects of anti-rejection drugs. In the U.S., for every 10,000 patients with type 1 diabetes, only three will receive a pancreas transplant or islet transplant in their lifetime, according to the authors.

The goal of the research was to test the suitability of pancreata from organ donors as a platform for building a new bio-artificial pancreas. "The early results are encouraging and pave the way for further investigations to understand the interactions between the organ structures and cells and to identify the optimal cell type to achieve complete regeneration of the endothelium and islets," said Orlando.

New Discoveries Advance Efforts to Build Replacement Kidneys in the Lab

Researchers at Wake Forest Baptist Medical Center report progress in their quest to build replacement kidneys in the lab. The teams' goal is to make use of the more than 2,600 kidneys that are donated each year, but must be discarded due to abnormalities and other factors. The scientists aim to "recycle" these organs to engineer tailor-

made replacement kidneys for patients.

"We believe the two studies we are reporting provide critical information to the booming field of organ bioengineering as it applies to the kidney," said Giuseppe Orlando, M.D., Ph.D., a transplant surgeon and regenerative medicine researcher. Orlando is part of a team at the Wake Forest Institute for Regenerative Medicine aiming to recycle human kidneys. Another group at the institute is doing the same thing with pig kidneys.

The process begins by washing the discarded organs in a mild detergent to remove all cells. The idea is to replace these cells with a patient's own kidney stem cells, making a tailor-made organ that would not be rejected and wouldn't require the use of powerful anti-rejection medication. But are the organs a suitable platform for engineering after going through the process to remove cells?

To help answer that question, the researchers evaluated whether the washing process affects a small sac of capillaries in kidneys called the glomerulus. These vessels, which are vital to the kidney's role of filtering contaminants out of the body, operate at a pressure that is at least three times higher than other capillaries in the body. The scientists injected resin into the structures to measure vessel size and used pulse-wave technology to measure pressure within the vessels. The researchers also screened the kidney structures to see if they retained growth factors that play an important role in function.

In the journal Transplantation, the research team reports that the size, structure and function of the micro-vessels in the glomerulus are preserved after the cell-removal process. In addition, vital proteins known as growth factors that regulate cell growth and function are retained within the kidney structures.

"These results indicate that discarded human kidneys are a suitable platform for engineering replacement kidneys and that when cells are added, the structures behave as an effective and viable biosystem," said Orlando.

News Media Coverage

Coverage by Top Media Outlets

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

- Beijing Bulletin
- Channel News Asia
- CNN International
- Discover Magazine
- Huffington Post
- International Business Times
- MD News
- Military.com
- Military Times
- Nature News
- National Public Radio
- New York Times
- Newsweek
- Science Daily

- Scientific American
- The Scientist
- UK Telegraph

Selected News Coverage

CNN International: A publication by the WFIRM bioprinter team in Natural Biotechnology was featured in almost 400 media outlets, including this informative video report.
http://edition.cnn.com/videos/world/2016/02/18/printer-3d-organs-intv.cnn

Huffington Post: The institute's work in 3D printing is included in this article, "These Advances in Lab-Grown Organs Might Save your Life One Day."
http://www.huffingtonpost.com/entry/lab-grown-organs-transplant-technology_562122cee4b08d94253ee660

UK Telegraph: A pentagon-funded project to engineer replacement genital tissue for wounded warriors is under way at the institute as part of the Armed Forces Institute of Regenerative Medicine.
http://www.telegraph.co.uk/news/worldnews/northamerica/usa/12090097/US-military-funds-research-into-lab-grown-testicles-for-wounded-soldiers.html

Philanthropy Roundtable: Dr. Atala is quoted on the need for research funding in the article about the power of philanthropy.
http://www.philanthropyroundtable.org/topic/excellence_in_philanthropy/the_power_of_science_philanthropy

WFIRM's 3D printing research was featured in a Fox8 Newsmaker segment.
https://www.youtube.com/watch?v=LiL2k3W8NKI

WFIRM's 3D printing research was featured by CBS New York.
http://newyork.cbslocal.com/2016/02/17/3d-printing-tissue/

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, 2016

Royalties generated from subject projects:	0
Unrestricted Revenues:	
Institutional Support	3,264,142
Gift Income	122,060
Other Income	397,524
Total Unrestricted Revenues	3,783,725
Restricted Revenues:	
State of North Carolina	7,065,023
Federal Government	21,146,025
Foundation	368,949
Industry, Individual, Endowment, & Other	215,689
Total Restricted Revenues - cash basis, not accrual	28,795,686
Total Revenues	32,579,411
Restricted Expenditures:	
AFIRM Expenditures	15,251,495
Other Federal Expenditures	5,896,987
GMP & Translation Related Expenditures	5,802,097
Other Restricted Expenditures	1,550,567
Total Restricted Operating Expense	28,501,146
Unrestricted Expenditures:	
Administration, Legal, & patents	3,268,641
Department Research	50,366
Education	131,957
Total Unrestricted Operating Expense	3,450,964
Capital (renovations, equipment, & software) Funded by Wake Forest, State of NC, & Federal	328,054
Total Expenditures	32,280,164
NET	299,247