Wake Forest Institute for Regenerative Medicine

Legislative Report

July 1, 2012 to June 30, 2013

- **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

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. The U. S. Department of Health and Human Services in 2007 called regenerative medicine the "next evolution of medical treatments,"[1] and just four years later, established the National Institutes of Health Center for Regenerative Medicine to provide the infrastructure to support and accelerate its clinical translation. Today, several regenerative medicine-based therapies are 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.[2] 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.[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.

Tissue engineering is the science of growing replacement tissue in the laboratory to replace damaged or diseased tissue and organs. The process usually starts with a three dimensional structure called a scaffold that is used to support cells as they grow and develop. Skin, blood vessels, bladders, trachea, esophagus, muscle and other types of tissue have been successfully engineered; some of these tissues have already been used in treating human disease.

Cell therapies apply living cells to an organ or tissue to promote healing and regeneration from within. Cell therapies are an exciting area of research since it is simpler to heal existing tissues and organs than to replace them. Cell therapies are being delivered today for cartilage reconstruction, bone reconstruction, and in inflammatory and immune response problems. In the future, cell therapies hold promise for treating liver disease, diabetes, neural disorders, renal failure and other chronic conditions.

Healing therapies are similar to cell therapies in that the goal is to restore the function of an existing tissue or organ. However, rather than using cells alone, non-cellular components are used to accelerate the regeneration process. Various strategies are currently being studied with good results, including using biomaterials to aid in cell

[1] *2020—A New Vision: A Future for Regenerative Medicine*, U.S. DHHS (2007).
[2] *Regenerative Medicine at an Inflection Point* BNA Insights, 5 LSLR 476 (2011) E. Herriman
[3] *Progress in the Tissue Engineering and Stem Cell Industry: Are we there yet?* Tissue Engineering: Part B, 18:155 (2012), A. Jaklenec et al.

recruitment for regeneration, and “regenerative pharmacology,” using small molecules to trigger a regenerative effect.

A common misconception about regenerative medicine is that it requires use of stem cells that come from human embryos. This is not accurate. In fact, the goal of many regenerative therapies is to use a patient's own cells. These cells can include adult stem cells (found in many organs and tissues, including brain, bone marrow, and the blood) and progenitor cells (an immature type of cell found in almost every organ in the body). In cases where a patient's own stem cells cannot be obtained, there are several other sources of stem cells. For example, scientists at WFIRM discovered a type of versatile stem cells in amniotic fluid (the fluid that surrounds the developing fetus in the womb), and placenta (also called the afterbirth).

About WFIRM

The ***Wake Forest Institute for Regenerative Medicine*** (www.wfirm.org) is an international leader in translating scientific discoveries into therapies to benefit patients. Its physicians and scientists were the first in the world to engineer laboratory grown organs that were successfully implanted into humans. Today, this team, which has grown to more than 350 scientists and staff, is working to engineer replacement tissues and organs and develop healing cell therapies for more than 30 different areas of the body.

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 store replacement tissues and organs under guidelines of the U.S. Food and Drug Administration (FDA), ensures that a reproducible process is in place. And when the technology is ready to be licensed to a company that can commercialize it for widespread use, WFIRM has the unique infrastructure and community resources to create companies and develop partnerships to expedite the delivery of the technology to patients.

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

Role of State Funding

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

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

North Carolina's Leadership Role

The State of North Carolina is among the states providing critical state support. 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, enabling regenerative technologies to be developed and manufactured in North Carolina, and increasing its economic base by manufacturing and job creation in North Carolina.

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 $1.5 billion since its first round of awards in 2006. As of 2012, three 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.

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.

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

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.

- ***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 Armed Forces Institute for Regenerative Medicine, a $100 million virtual institute that develops regenerative therapies for our wounded warriors. This project 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

The use of improvised explosive devices in Iraq and Afghanistan has caused a significant increase in severe blast trauma. More than 6,700 U.S. military fatalities and more than 51,000 injuries have been reported.[5] While advances in body armor, quicker evacuation from the battlefield, and advanced medical care have improved survival rates, many of the injured come home to face challenges of overcoming severe limb, head, face, and burn injuries that can take years to treat and usually result in significant lifelong impairment. The Department of Defense established the Armed Forces Institute of Regenerative Medicine (AFIRM) in 2008 with the mission of developing new products and therapies to treat severe injuries suffered by U.S. service members. There were two consortia established within AFIRM to accelerate the delivery of regenerative medicine therapies to these severely injured U.S. service members: one headed by Wake Forest Baptist Medical Center (the Wake Forest-Pittsburgh University Consortium or WFPC) and one headed by Rutgers University (the Rutgers-Cleveland Clinic Consortium or RCCC). While these two consortia are distinct and separate entities, they have the same and complementary mission — accelerate regenerative technologies to the wounded warrior. WFIRM, in its role as a consortium co-leader, has continued to grow a national network of regenerative medicine leaders in advancing the AFIRM mission.

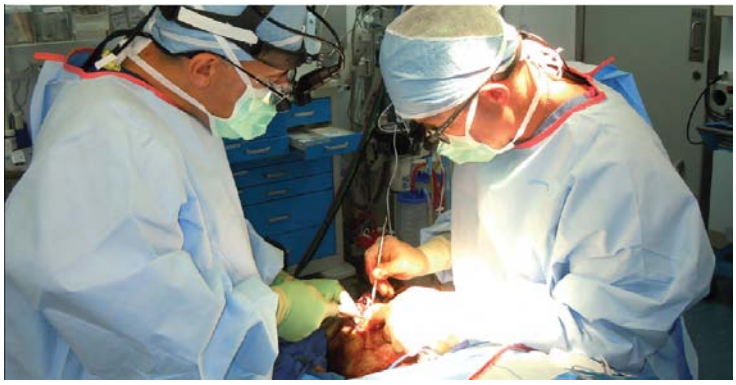
Five Major Program Areas within AFIRM

There are five areas of research emphasis within AFIRM-WFPC focused on developing regenerative therapies to address burn, craniofacial, and compartment syndrome related injuries, limb and digit regeneration and healing without scarring.

[5] http://www.defense.gov/news/casualty.pdf (August 2013)

Craniofacial Regeneration Program

Craniofacial trauma is among the most debilitating forms of injury facing civilian and military populations due to the important aesthetic and functional role of the craniofacial complex. Blast injuries and injuries from high velocity projectiles, such as those encountered on the battlefield, present a range of therapeutic challenges and often require a staged repair. A significant need exists for the development of novel regenerative medicine approaches for the generation of both soft and hard tissues to overcome the current clinical barriers to craniofacial reconstruction. Like all programs within AFIRM, this program consists of several multidisciplinary, multi-institutional collaborative research teams to address the core issues associated with traumatic injuries.

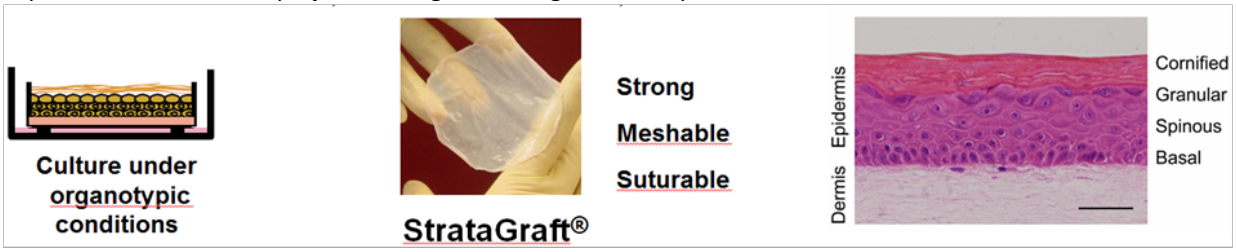


Burn Program

Unquestionably, one of the most visible and life-threatening injuries to military service personnel are severe burns. The current standard of care for burn injuries remains early excision and autografting, and has not fundamentally changed in over 30 years. The multi-institutional and multidisciplinary Burn Program's principal "thrust" is to significantly advancing the operative management of burn injuries, as burn wound "closure" remains the single greatest threat to the burn-injured warfighter. All six of the originally funded AFIRM projects, and the three added clinical trials, in the Burn Program complement each other and offer significant potential for synergy, which has been and will be leveraged at every opportunity. In addition to an ongoing 100-patient trial using a cell spraying technology nearing completion, a second burn project has begun treating dozens of patients.

***AFIRM Clinical Trial in North Carolina:* "Spray-On" Skin**

- Using a small piece of skin, the skin cells are converted into a spray form that be applied over a larger area (80% of the body) with good results.
- 100 patient FDA-approved clinical trial is nearing completion.



Scarless Wound Healing Program

Military trauma creates not only large wounds but also large scars. These scars are often very visible and can draw unwanted attention to the wounded warrior. In some instances the scars become so thick that they can limit movement of joints and greatly restrict the patient's ability to move. The costs associated with treatment of tissue fibrosis in the U.S. are estimated to be over $4 billion per year. Current treatment regimens involving surgery, silicone sheeting, anti-inflammatory medications and laser/radiation have been disappointing. This is largely due to

a lack of understanding of the fibrotic process. The pathophysiology of scar formation suggests the need to regulate numerous aspects of the wound environment, including cells, extracellular matrix, mechanics and biochemical signaling.

The WFPC approach encompasses a broad continuum of technologies aimed at modulating the tissue response to injury. Collectively, these projects represent a collaborative effort to address every aspect and stage of wound repair in a single research program, with the overarching aim of developing a more effective wound management paradigm. Thus the WFPC Scarless Program is composed of a synergistic combination of seven leading research groups focusing on every aspect of scarless wound healing. Industrial partners have contributed to the initiation of two clinical trials. This program utilizes complementary approaches (device, pharma, biotechnology) to balance short- and long-term objectives.

Compartment Syndrome and Limb & Digit Programs

Tissue wounds to the extremities are among the most common battlefield injuries sustained by troops during Operations Iraqi Freedom and Enduring Freedom. Particularly common trauma injuries caused by improvised explosive devices are blast and projectile injuries. Thus there is a need to develop technologies which address both limb and digit salvage and the consequences of amputated parts. While sometimes the damage is obvious, other times injuries are complicated by compartment syndrome (CS). In CS, trauma- related tissue swelling creates increased compartment pressures and this leads to ischemia and infarction of tissues. CS dramatically amplifies the battlefield injury and quickly leads to permanent muscle, nerve and vascular cell death. Soldiers that develop CS have prolonged recovery times and rarely recover complete muscle function, and they usually do not return to active duty at the same level of performance. Most CS injuries of the extremities result in permanent disability.

This program aims to develop regenerative medicine technologies using a number of approaches from autologous and progenitor cells that offer a safe and potentially effective new therapeutic avenue to amplify the body's endogenous regenerative response to injury, to hand transplants, to biomaterials approaches — all with the goal to improve the functional recovery of the injured soldier. The regenerative medicine technologies, which have already been used by AFIRM investigators and others safely and effectively for civilian tissue injuries, provide a promising approach to solve an important unmet need in the treatment of battlefield injuries.

Clinical Trials Underway

During the fifth year of operation, WFPC has continued to advance technologies to clinical trials. The following table shows the number of Department of Defense nationwide approved trials currently under AFIRM-WFPC. Beyond these clinical trials, a string of clinical trials nearing the enrollment phase are coming to fruition. Utilizing well-established, proven research investigators, the AFIRM has been able to expand the rehabilitative medicine knowledge base, develop models of injury, and test advanced technology products.

AFIRM Technologies Reaching Clinical Trials
A Comparative Study of the ReCell® Device and Autologous Split-thickness Meshed Skin Grafting in the Treatment of Acute Burn Injuries (Phase III) (J. Holmes MD)
StrataGraft® Skin Tissue as an Alternative to Autografting Deep Partial-Thickness Burns (J. Holmes, MD)
Human Upper Extremity Allotransplantation (A. Lee, MD)
Autologous Adipose Derived Stem Cell Therapy For Soft Tissue Reconstruction After Facial Trauma (P. Rubin, MD)
Structural Fat Grafting for Craniofacial Trauma: Effect of Concentrating Endogenous Stromal Cells in the Fat Graft using the Tissue Genesis Cell Isolation System Device (P Rubin, MD)
Clinical Evaluation of the Neodyne Dressing for Diminished Scarring (G. Gurtner, MD)
Skin Bioreactor for Treatment of Facial Injuries (SJ Lee PhD)

Future AFIRM Programs: AFIRM II and the Warrior Restoration Consortium

Last year, the U.S. Army Medical Research and Materiel Command, with 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 announced the continuation of AFIRM and solicitated applications for the AFIRM II program. AFIRM II, expected to be funded in 2013, will include progams in the areas of extremity renegeration, craniomaxillofacial regeneration, skin regeneration, composite tissue allotransplantation, and genitourinary repair. WFIRM was selected by the current four major partner institutions to lead the Warrior Restoration Consortium as prime contractor in response to the AFIRM II solicitation. If awarded, the WFIRM-led Warrior Restoration Consortium could begin operations in 2013.

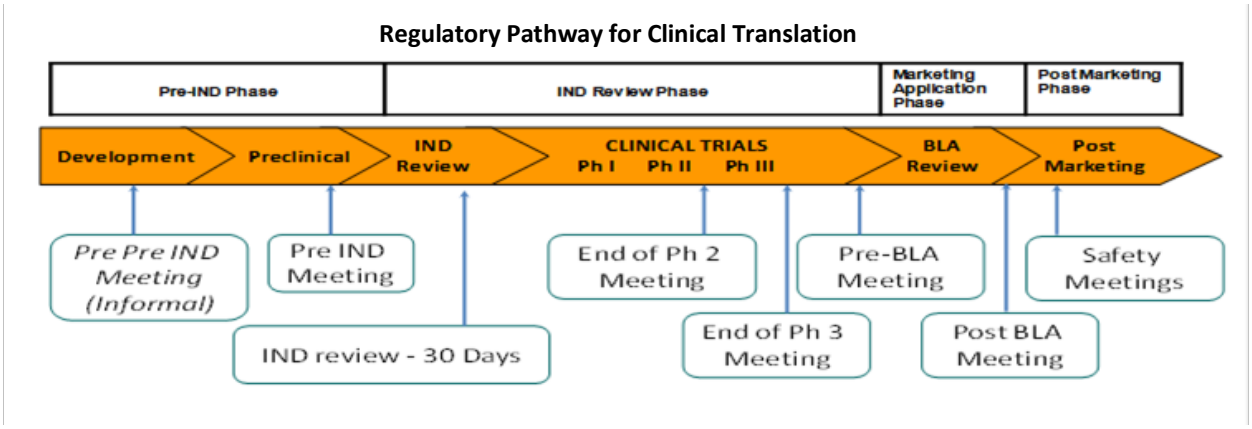
Mission Driven Accomplishments

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.



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 under review.** WFIRM submitted a full IND application for the use of muscle progenitor cells in the treatment of stress urinary incontinence. The application is currently under review by the FDA. If the application is approved, the therapy would move to phase I clinical studies in next year.

- **Definitive preclinical study 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.

- **Pre-IND meeting completed.** WFIRM completed the pre IND meeting and has proposed definitive preclinical studies in connection with the clinical development of tissue engineered innervated internal

anal sphincter construct for fecal incontinence. 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 years.

- **Facility registration**. The FDA regulations require establishments with human cells, tissue, and cellular and tissue-based product to register with the agency. WFIRM submitted its application to become 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 underway for a number of earlier stage projects including development of a bioengineered cornea, use of particle oxygen generators for wound healing, and self-seeding heart valves. 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	Chronic kidney injury
Amniotic fluid cell therapy	Hemophilia
STEM CELL/TISSUE BANKING/BIOMATERIALS ***Preclinical and Clinical Applications***	
Amniotic fluid stem cells	
Muscle precursor cells	
Sperm	
Testicular tissue	
Particle oxygen generators	
TISSUE ENGINEERING/STEM CELL/TISSUE BANKING ***Process Development***	
Placental stem cells	
Adipose-derived stem cells	
Bioengineered Cornea	

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 approximately 250 patents and applications generated from over 165 invention disclosures.

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 175 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 from around the world. Collaborations include the following institutions:

Austria Ludwig Boltzmann Institute, Wien

China Shanghai Tissue Engineering Research Center, Jiao Tong University School of Medicine, Shanghai
Beihang University, Beihang

	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
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, WFIRM maintains a wide variety of educational offerings, from traditional graduate and post-graduate education to programs for the general public.

Community Outreach

WFIRM maintains a very active outreach program 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 600 visitor groups per year from all walks of life to the WFIRM facility
- **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 around the world
- **Forsyth Tech Intern Program:** Internships offering hands-on research experience for Forsyth Technical Community College students pursuing careers in biotechnology

- **Post-Baccalaureate Program:** Post-baccalaureate research program for minority funded by the National Institute of General Medical Sciences (Principal Investigator Dr. Debra Diz)

Traditional Degree Programs

The outstanding research infrastructure, highly collaborative nature and expertise of WFIRM faculty and cutting-edge integrated training program prepare students for research careers in regenerative medicine. WFIRM students interact and exchange ideas on a daily basis with scientifically and culturally diverse students, post doctoral fellows, technicians and faculty in regenerative medicine. Current enrollment is 25 pre-doctoral (PhD) students and 71 postdoctoral fellows.

First Annual WFIRM Career Opportunities Day

WFIRM launched an annual Career Opportunities Day, 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 brought together successful individuals covering a very broad range of career opportunities related to regenerative medicine. The impressive list of speakers at the inaugural program included:

- Eric Tomlinson, DSc., Ph.D., Chief Innovation Officer, Wake Forest Baptist Medical Center
- Masood Machingal, Ph.D., Center for Technology Transfer and Commercialization, Vanderbilt University
- Nancy Johnston, Executive Director, North Carolina Biotechnology Center, Piedmont Triad Office
- Richard Payne, Ph.D., Director, Biomaterials Development, Tengion, Inc.
- Kirsten Crapnell, BD Technologies, R&D Leader - Cell Culture Environments / Cell and Tissues
- Cindy Rothschild, Ph.D., Patent Attorney, Kilpatrick Townsend & Stockton LLP
- Dave Baer, Ph.D., Institute for Surgical Research (ISR) Director of Research, Combat Casualty Care

This cutting-edge event, well attended, interactive and highly reviewed by both speakers and participants, 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.

Connecting the Future with the Past: Two significant collections highlighting the history of medicine are housed at WFIRM, giving visitors the opportunity to appreciate the progress of medical science.

- Collections of medical artifacts amassed by former Bowman Gray professor and local obstetrician Dr. Jack Monroe. Included are a number of decorative bleeding bowls, bowls with a sliced-out portion to fit under the patient's neck or elbow when a vein was slit, the oldest dating back to 1690, and a metal trepanner, a device used to drill into the skull, to relieve swelling caused by a kick to the head.

- The History of Medicine in Pictures, a series of prints from the 1950s, donated by Dr. Jesse Meredith, emeritus chair of surgery at Wake Forest Baptist Medical Center.

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

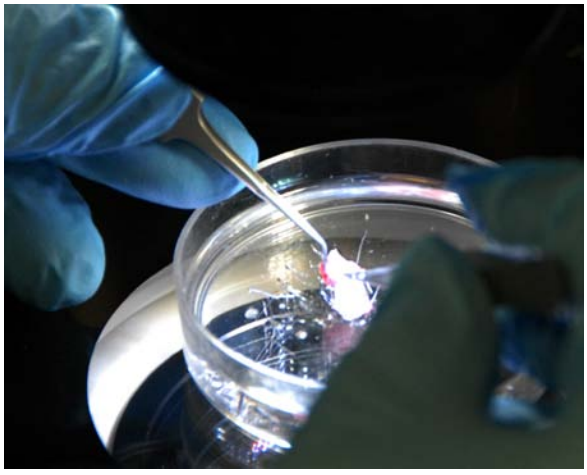
engineering and regenerative medicine.

- Program concludes with research day of student presentations attended by family members, mentors and faculty.

Research Activities

Research Proposal Applications

WFIRM faculty submitted 80 research proposals totaling nearly $160 million to more than 25 different agencies, foundations, and companies during fiscal year 2013. Among this year's applications was a proposal to establish an NIH-funded Translational Regenerative Medicine Training Program at WFIRM**.** The National Institutes of Health (NIH) provide funding for training of graduate students via the Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grant (T32) program. This highly competitive grant mechanism was designed to provide continuing and stable support for the training of outstanding graduate students. The WFIRM application, assigned to the National Institute of Biomedical Imaging and Bioengineering (NIBIB), received an excellent initial evaluation. Funding of this training grant would represent national recognition for WFIRM's accomplishments and potential, and provide additional resources for training the next generation of clinicians, scientists and thought leaders in regenerative medicine.



Research Awards

New and continuing awards provided $29.9 million in grant funding. Included in the new awards in FY13 was an award from the Space and Naval Warfare Systems Center Pacific for the Xvivo Capability for Evaluation and Licensure Program. Dubbed "Body on a Chip," this unique $24 million project aims to build a miniaturized system of human organs to model the body's response to harmful agents and potential therapies. This approach has the potential to reduce the need for testing in animals and will be used to develop countermeasures to chemical or

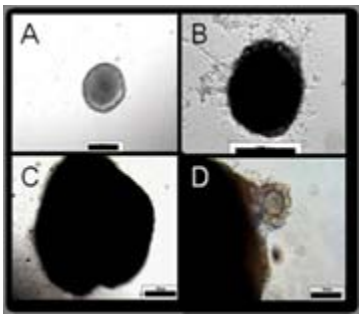
biological attacks. WFIRM is the lead institution on the program proposal that brings together leading experts from a range of disciplines and includes six different institutions.

News and Publications

Scientific Publications

WFIRM researchers published 197 peer-reviewed papers in 80 different scientific journals during fiscal year 2013 and also shared their work at scientific conferences. Notable reports included:

Lab-engineered Eggs – A Potential Solution for Infertility?



WFIRM researchers moved a promising step closer to helping infertile, premenopausal women produce enough eggs to become pregnant. As presented at the 2012 American College of Surgeons Annual Clinical Congress, the research team stimulated ovarian cell production using a mouse model and observed as the cells matured into very early-stage eggs that could possibly be fertilized. Several fertility disorders can leave premenopausal women without an adequate amount of eggs or with enough sex hormones to stimulate egg production. The goal of the study was to spur the ovaries to produce the female sex hormones estrogen and progesterone as well as stimulate egg production. The team will next work to create more mature structures that could be used for fertilization.

Novel Hybrid Printer for Cartilage

The printing of three-dimensional tissue was demonstrated with a novel hybrid printer that simplifies the process of creating implantable cartilage. The printer was used to engineer cartilage constructs that could potentially one day be implanted into injured patients to help re-grow cartilage in specific areas, such as the joints. The printer is a combination of two low-cost fabrication techniques: a traditional ink jet printer and an electrospinning machine. Combining these systems allowed the scientists to build a structure made from natural and synthetic materials. Synthetic materials ensure the strength of the construct and natural gel materials provide an environment that promotes cell growth. In this study, cartilage constructs printed with the system were inserted into mice to see how they performed in a real life system. After eight weeks of implantation, the constructs appeared to have developed the structures and properties that are typical of elastic cartilage, demonstrating their potential for insertion into a patient. Hybrid printing of mechanically and biologically improved constructs for cartilage tissue engineering applications. Xu T, Binder KW, Albanna MZ, Dice D, Zhao W, Yoo JJ, Atala A. Biofabrication. 2013 Mar;5(1)

Research Supports Promise of Cell Therapy for Bowel Disease

WFIRM researchers and colleagues have identified a special population of adult stem cells in bone marrow that have the natural ability to migrate to the intestine and produce intestinal cells, suggesting their potential to restore healthy tissue in patients with inflammatory bowel disease (IBD). IBD refers to two conditions – ulcerative colitis and Crohn's disease – in which the intestines become red and swollen and develop ulcers, probably as the result of the body having an immune response to its own tissue. Because current therapies aren't always effective, scientists hope to use stem cells to develop an injectable cell therapy to treat IBD. In addition, the team has also

identified stem cells in cord blood that are involved in blood vessel formation and also have the ability to migrate to the intestine. The scientists hope that a mixture of the cells could be used as an injectable therapy to treat IBD. The cells would theoretically induce tissue recovery by contributing to a pool of cells within the intestine. EphB2 isolates a human marrow stromal cell subpopulation with enhanced ability to contribute to the resident intestinal cellular pool. Colletti E, El Shabrawy D, Soland M, Yamagami T, Mokhtari S, Osborne C, Schlauch K, Zanjani ED, Porada CD, Almeida-Porada G. FASEB J. 2013Jun;27(6):2111-21. Distinct contribution of human cord blood-derived endothelial colony forming cells to liver and gut in a fetal sheep model. Wood JA, Colletti E, Mead LE, Ingram D, Porada CD, Zanjani ED, Yoder MC, Almeida-Porada G. Hepatology. 2012 Sep;56(3):1086-96.

Stem Cells Identified in Urine

Could harvesting stem cells for therapy one day be as simple as asking patients for a urine sample? WFIRM researchers and colleagues have identified stem cells in urine that can be directed to become multiple cell types. Their advantage for potential clinical use is that they can be obtained through a simple, non-invasive low-cost approach that avoids surgical procedures. The research team has successfully directed the stem cells from urine to become bladder-type cells, such as smooth muscle and urothelial, the cells that line the bladder. But the urine-derived cells could also form bone, cartilage, fat, skeletal muscle, nerve, and endothelial cells, which line blood vessels. The multipotency of the cells suggests their use in a variety of therapies. Multi-Potential Differentiation of Human Urine-Derived Stem Cells: Potential for Therapeutic Applications in Urology STEM CELLS Accepted manuscript online: 10 MAY 2013, Shantaram Bharadwaj, Guihua Liu, Yingai Shi, Rongpei Wu, Bin Yang, Tongchuan He, Yuxin Fan, Xinyan Lu, Xiaobo Zhou, Hong Liu, Anthony Atala, Jan Rohozinski and Yuanyuan Zhang

WFIRM Receives Edison Award

WFIRM received a gold Edison Award for innovations in bioprinting. The Edison Awards™, which recognize and honor innovative new products, services and business leaders, are named after renowned inventor Thomas E. Edison. The awards program is conducted by Edison Universe, a non-profit organization dedicated to fostering future innovators.

The institute received the "Game Changer Award" in the science and medical category for two unique printers designed by institute scientists to print living cells and biomaterials rather than ink. The goal of the bioprinting projects is to print replacement tissues and organs for human patients.

Bioprinting of Stem Cells

In a recent study in Stem Cells Translational Medicine researchers have shown that stem cells derived from amniotic fluid (AFSC) function well in wound closure and re-epithelialisation, partly through increased secretion of trophic factors. AFSC were deposited through a bioprinting process; this entails the depositing of two layers of a fibrin-collagen gel containing cells in between layers of thrombin at wound sites. Histological sections of skin samples taken at week two found well-defined, organized epidermal layers of the regenerated skin in the AFSC treated mice, while the control animals exhibited poorly defined epidermal layering. Additionally, the treated wounds demonstrated noticeably thicker regenerating tissue with a greater number of blood vessels as compared to control. These data point towards AFSC as being optimal cell types for bioprinting towards a more effective treatment for burns and skin wounds, partially via increased neovascularization and blood vessel maturation, likely due to the secretion of trophic factors. The advantages using AFSC are obvious; they have extended life in vitro (up to 250 passages), are multipotential and may have increased differentiation and expansion potential, and show a degree of immunomodulatory activity. With all this in mind, it is possible that bioprinter-mediated deposition of AFSC could be highly important in a clinical setting with the potential for tissues and organs to be built from

scratch. Bioprinted amniotic fluid-derived stem cells accelerate healing of large skin wounds. Skardal A, Mack D, Kapetanovic E, Atala A, Jackson JD, Yoo J, Soker S. Stem Cells Transl Med. 2012 Nov;1(11):792-802.

News Media Coverage

Coverage by Top Media Outlets

The Institute's work was covered by the following print, broadcast and web outlets. *The media outlets in bold type also visited WFIRM.*

60 Minutes Australia ABC.com **Andri Poli Photographer** **Associated Press** Baylor Innovations Magazine **BBC** BeSpoke International Bloomberg **Canadian News Program** **CBS Newspath** Christian Science Monitor City Life Toronto **Catalyst: Australian Science Program** CNN.com **Discovery Channel "This Changes Everything"** Discovery News Elite Magazine (Ft. Bragg) **Esquire**	**New York Magazine** **News 14** NBC **Filmaker and artist: Lynn Hirshman** Fox 8 Tampa: Spiderman **Global News (Canada's 60 Minutes)** IEEE Pulse Magazine **Ivanhoe Broadcast News** Iris Krasnow – Book author Kiplinger Letter LA Times Louisville Courier Journal Military Officer Magazine National Geographic **National Geographic Photographer** National Public Radio – New York National Public Radio Science Friday Nature	NCSU Alumni Magazine Oprah Magazine Popular Mechanics Popular Science Reuters **Smithsonian Channel** **Robert Smith: Artist** Science Magazine Scientific American **Smithsonian Magazine** Talk Radio Network's "Science Fantastic" Time Magazine USA Today Voice of America Wall Street Journal **WFMY** **WGHP**

International Coverage

WFIRM scientists were interviewed by journalists from around the world:

Austria	Iceland
Australia	Italy
Belgium	Mexico
Brazil	Poland
Columbia	Spain
England	Russia
France	Switzerland
Germany	United States

Selected News Coverage

- The work of Dr. Atala and the Wake Forest Institute for Regenerative Medicine made several "Best of 2012" lists:
  - The institute's project to print organs and tissues was named by Time Magazine.com as one of "5 Discoveries that will change the Future of Organ Transplants." http://healthland.time.com/2013/06/06/5-discoveries-that-will-change-the-future-of-organ-transplants/?iid=hl-main-lead#slide/the-problem-with-transplants/?&_suid=137062931441900728543155710 31
  - Atala was named to AARP Magazine's "Power List – 50 People Who Make Your Life Better." The list includes 10 people over age 50 recognized for "Moving Us to a Healthier Future." for his team's work to engineer replacement organs in the lab.

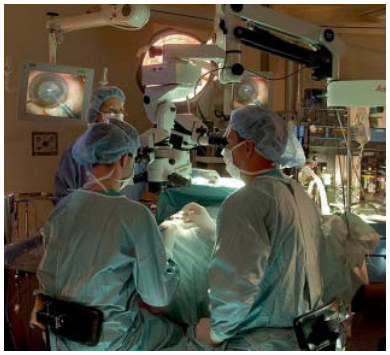
- Atala was named by the World Stem Cells Regenerative Medicine Congress as one of the "Top 50 Most Influential People on Stem Cells Today." http://www.cirm.ca.gov/sites/default/files/files/press_release/Top_50_Global_Stem_Cell_Influencers.pdf

- The institute's success engineering human urine tubes in the lab was included in a Discover News feature, "10 Amazing Parts Created Outside the Body." http://news.discovery.com/tech/biotechnology/10-bionengineered-body-parts-130722.htm

WFIRM's 3-D printing research was featured on a Smithsonian Channel program, "The Real Story: Star Trek" and was also included in a Smithsonian magazine cover story on 3-D printing. The project is led by WFIRM faculty members James Yoo, M.D., Ph.D., professor, and Sang Jin Lee, Ph.D., assistant professor.

- Research by Giuseppe Orlando, M.D., assistant professor of surgery and regenerative medicine researcher, and colleagues' project to engineer replacement kidneys using organs that have been rejected for transplant was covered by The Scientist and many other publications. http://www.thescientist.com/?articles.view/articleNo/35694/title/Recycling-Kidneys/

- The work of Emmanuel Opara, Ph.D., professor of regenerative medicine, to create artificial ovaries in the lab to provide a more natural form of hormone replacement therapy for women was covered by U.S. News & World Report.com and a variety of other media outlets. *http://health.usnews.com/health-news/news/articles/2013/03/29/artificial-ovaries-could-potentially-deliver-hormone-therapy*



- A WFIRM collaboration with Ocular Systems and the N.C. Eye Bank has resulted in a new company that aims to apply regenerative medicine to corneal transplants. The project includes faculty members Shay Soker, Ph.D., professor, and Tracy Criswell, Ph.D., assistant professor, and Jin San Choi, M.S., Ocular Systems scientist. The company's formation was covered by numerous Triad media. http://www.digtriad.com/news/local/article/262590/327/Regenerative-Medicine-Sets-Sight-On-Corneas

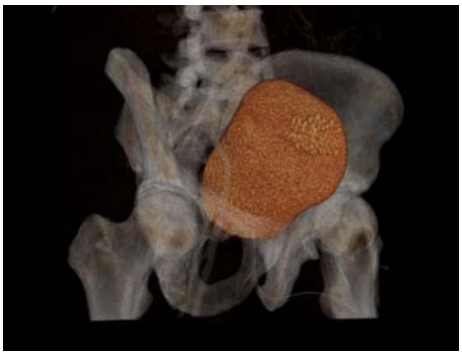
- A project by James Yoo, Ph.D., professor, and Sunyoung Joo, M.D., to engineer eggs in the laboratory with the potential to treat infertility was reported by CBS Newspath, and distributed to affiliates nationwide. www.wcax.com/story/20035896/hope-for-patients-who-cant-get-pregnant . The research was also reported by Voice of America http://www.voanews.com/content/researchers-re-create-eggs-to-treat-infertility/1522569.html

- Professor Graca Almeida-Porada, M.D., Ph.D., was interviewed by EverydayHealth about her research involving the potential of stem cells to treat bowel disease: http://www.everydayhealth.com/digestive-health/are-stem-cells-the-key-to-fighting-ibd.aspx

- The Institute's work was included in an Associated Press roundup article on regenerative medicine that was published around the world. An accompanying video story featured many images from the institute. Video: http://landing.newsinc.com/shared/video.html?freewheel=90121&sitesection=ap&VID=24887648

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, 2013
NOT FINAL - Preliminary Data Only

Revenues (Actual)**:**	
Unrestricted Revenues:	
Institutional Support	2,603,825
Gift Income	497,210
Other Income	17,163
Total Unrestricted Revenues	3,118,198
Restricted Revenues:	
State of North Carolina	7,717,228
Federal Government	11,427,618
Foundation	1,181,039
Industry	287,740
Individual & Other	362,884
Deferred Income	3,856,474
Total Restricted Revenues	24,832,983
Total Revenues	**27,951,182**
Expenditures:	
Salaries/Wages/Fringe	9,291,662
Purchased Services	12,000,151
Laboratory Supplies & Expenses	2,438,408
Facilities & Administration	3,822,417
Total Operating Expense	27,552,638
Capital (renovations, equipment, & software)	261,927
Total Expenditures	**27,814,565**