Wake Forest Institute for Regenerative Medicine

Legislative Report

July 1, 2016 to June 30, 2017

- **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

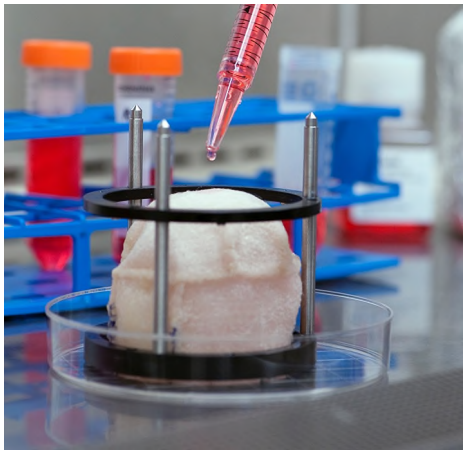
Imagine a day when chronic diseases are treated with an injection of cells ...When functioning nerves are available to replace those damaged by injury ...When diseased organs are routinely exchanged with healthy replacements grown in laboratories.

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 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

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

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 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.

- ***A leader in manufacturing***. Delivering on the promise of regenerative medicine will require significant progress in manufacturing to scale up technologies and make them affordable. WFIRM started the first initiative for regenerative medicine manufacturing in 2008 through establishment of a joint industrial engineering program. Today, WFIRM is part of a 60-member consortium that conducts research to de-risk technologies and speed up the translation to clinical practice.

- ***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-II). The five-year, $75 million federally funded project, which began in 2013, 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 "product 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. The therapies developed through AFIRM will benefit our wounded warriors as well as civilians who incur traumatic injuries.

The first phase of AFIRM, which began in 2008 (AFIRM–I), 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. During AFIRM-I, several hundred patients received treatment with AFIRM-funded technologies. AFIRM-I also achieved the first double hand transplant in the U.S. Through WFIRM, North Carolina researchers have played a vital role in the development of therapies that were supported by AFIRM -I. The AFIRM II continues to build on the success of the first phase of AFIRM, transitioning discoveries to products that can be used in the clinic.

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.

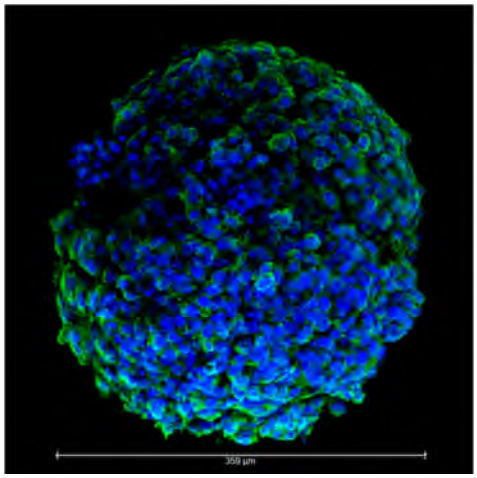
The AFIRM-II program is focused on getting products through advanced development, so

that the innovations could be used for patients who need them. One completed clinical trial in AFIRM II supports a product that can be used to enhance the fit of prosthetic limbs by modifying the skin at the amputation site. Another completed clinical trial involves an acellular scaffold that can be used to repair facial injuries. WFIRM investigators are leading novel clinical trials to test manufactured bladder and urethral tissue in humans. WFIRM investigators are also involved in clinical trials to study skin repair for burn treatment, and muscle regeneration for facial injuries.

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 goal of the AFIRM program is not only develop new and innovative ways to help our wounded warriors, but to ultimately lead to new treatments to repair their severe injuries and restore wounded warriors to full form, function and appearance .

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

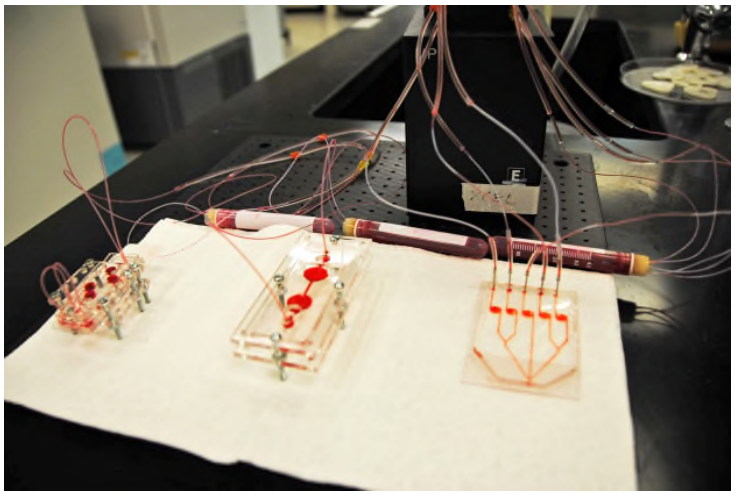
Whether it's the threat of an emerging virus, a new chemical warfare agent, or an unidentified environmental toxin, the key to developing an effective solution is having a reliable test platform for developing and testing countermeasures. To accelerate the development of new therapies, WFIRM is leading a unique $24 million federally funded program to build such a platform. The system that has been developed, which has been named the Ex Vivo Console of Human Organoids or ECHO, represents a 'body on a chip' device. The platform is comprised of miniaturized human organs that accurately model the effects of harmful agents and respond to antidote therapies. The body on a chip approach reduces the need to rely animal experimentation, which is expensive, slow, and often produces unreliable results.



The first phase of the ECHO program 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. The final phase showed the potential for discovering downstream effects of drugs by causing target organs to release factors that travel to other organs where they produce a response that would not be picked up by single organ

systems. The system is currently being used to test even more subtle biological events such as environmental pollutant toxicity and cancer metastases.



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 for large-scale testing of chemical agents and drugs. The breakthroughs achieved by the ECHO program provide a high-throughput platform that can be used to develop and test a variety of drugs and countermeasures with the potential to improve the lives of people across the United States.

Mission Driven Accomplishments Due to the State Award

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.

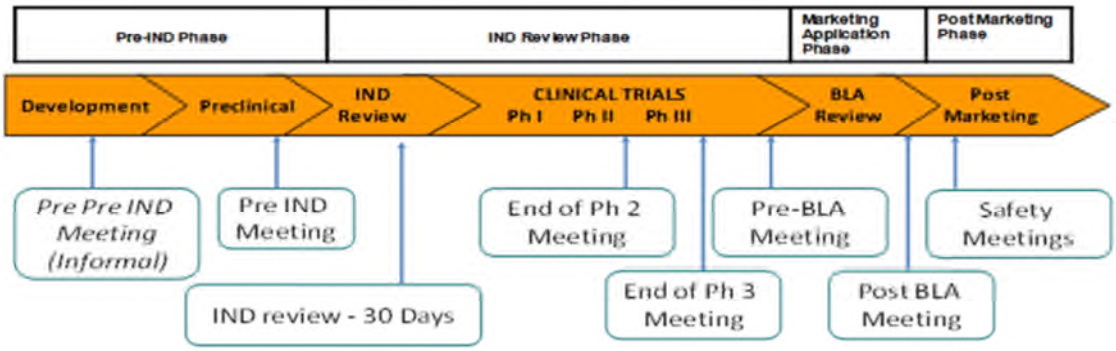
Additional core resources provided by the State of North Carolina have allowed WFIRM to accelerate projects within the AFIRM program and aided in increasing the visibility of North Carolina to military and federal leadership. State support has been leveraged to attract top scientists from around the 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.

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 early phase clinical trials 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.

Regulatory Pathway for Clinical Translation



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

- **Phase I clinical study completed.** 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 has just completed for the use of muscle progenitor cells in the treatment of this condition. The study data is being assessed for safety of the treatment as well as examining efficacy of the therapy in secondary endpoints. With successful data, an IND will be submitted for a Phase II study.

- **Phase I clinical study underway**. Phase I clinical study underway for tissue engineered urethra for urethral tissue repair due to battlefield injury. A phase I study just kicked off a recruitment

effort. The study will be assessed by primary endpoints for safety and secondary endpoints for efficacy of the therapy.

- **IND applications submitted.** WFIRM submitted two IND applications for the use of engineered tissue for the repair of battlefield urologic injuries for soldiers with battlefield injury. If approved, the clinical studies will begin in the coming 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 approved to store tissues for potential future clinical use.

- **Definitive preclinical studies under way. Definitive preclinical studies under way.** Preclinical studies are underway for the clinical development of bioprinted nasal septum produced with cartilage cells.

- **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 hemophilia, and tissue engineered vagina. If the preclinical study plan is approved and the studies are successful, the IND application will 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. 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 34 patents issued in fiscal year 2017 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 more than 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 workforce infrastructure.

National

WFIRM scientists are engaged in active research collaborations with more than 275 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 Initiatives
Sharing the Promise of Regenerative Medicine

WFIRM offers a complete range of educational and training programs ranging from traditional graduate, post-graduate and professional development training to programs for undergraduate students, K-12 students, teachers, and the general public. Our goal is to train the next generation of scientists, clinicians and technicians, engage our region's talent, and attract new talent to cutting-edge biomedical research that reflects the strengths of North Carolina.

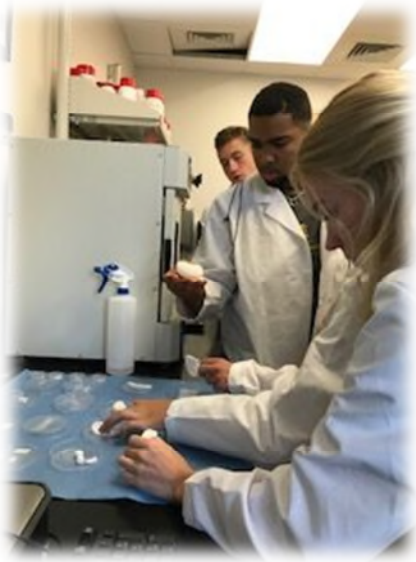
Programs for K-12 and the Community

With the goal to engage, inspire, and broaden learning opportunities for our youth and the general public, WFIRM has an active portfolio of both formal and informal K-12 and community outreach programs. These programs provide middle- and high-school students, teachers, and the general public opportunities to learn more about the science behind the field of regenerative medicine and the implications for health care technologies and therapies of the future. We also offer career and training opportunities for youth as they begin to plan and consider their own educational and career pathways.

- **Tours:** Host to nearly 1,700 visitors from all walks of life to the WFIRM facility this year alone

- **Lectures:** Presentations by WFIRM faculty at formal and informal events throughout the Triad, the State, and nationally

- **Volunteer Program**: Hands-on research experiences open to high school students and teachers, undergraduate students, medical students and postdoctoral fellows from the region, the U.S. and around the world



- **Visiting International Scholar Program**: WFIRM regards the presence of visiting scholars as of strategic importance to fostering international education, collaboration and internationalization of the field to result in the development of new regenerative medicine therapies and products. The WFIRM Visiting International Scholars Program enables international scientists, clinicians and physician-scientists to participate as Visiting Scholars for a 3-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, the Medical Careers and Technology (MedCAT) Pipeline Program of the Wake Forest Baptist Maya Angelou Center for Health Equity 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 School Summer Research Exposure Research Program:** This 5-week exposure program is designed for high school students to address questions such as: What's it like to be a regenerative medicine scientist? High school students attend the 1-week Regenerative Medicine Essentials course, meet with practicing regenerative medicine researchers, students and other experts and explore regenerative medicine fundamentals and applications. A mentoring component provides students 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.

- **The Wake Forest Summer Immersion Program** is a hands-on learning experience. Students dive deep into a field of study with access to world-class faculty, researchers, and industry professionals. WFIRM offers high school students direct exposure to the field of regenerative medicine through partnership with the Immersion program's Biosciences and Engineering Institute providing special lectures, demos and tours to nearly 500 high school student participants.

- **Post-Baccalaureate Research Education Program (PREP):** This unique post-baccalaureate research program, funded by the National Institute of General Medical Sciences (PI Dr. Debra Diz), provides a transition between undergraduate and graduate school for under-represented minorities.

Programs for Undergraduate Students

The WFIRM Summer Scholars Research Program: Students accepted into this highly competitive, 10-week program conduct an individually tailored research project under the supervision of WFIRM faculty and staff. Open to undergraduate science, engineering and medical students, projects are focused in a variety of areas, from biomaterials and cell biology to biochemistry and tissue engineering. Under the guidance of researcher-mentor teams, students perform their own research and data analysis. Additional features include attending the immersive 1-week Regenerative Medicine Essentials Course, a special seminar series on hot topics, technical communication and scientific presentation workshops andGRE and MCAT prep workshops;opportunities to engage in roundtable discussions with medical and graduate students and to co-author with with faculty; and social activities and community-building. The program concludes with a final research day of student presentations with a poster session attended by family members, mentors and faculty. Twenty-one undergraduates and three medical students participated in the 2017 Summer Research Scholars Program.

From 2007-2017, WFIRM hosted nearly 450 undergraduates during both the summer and academic year. Of these, a total of 187 undergraduate students participated in the competitively reviewed and 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, and more than 70 percent of those have either completed or are

currently enrolled in a PhD or MD program in engineering, medicine, or other STEM related fields.

NSF Grant Recognizes Successful WFIRM Summer Scholars Program: Based on the strength of WFIRM's long-standing commitment to undergraduate research, the institute has been awarded a National Science Foundation (NSF) grant to engage undergraduate students in research at the interface of engineering and biology in challenging areas of tissue engineering and regenerative medicine (TERM) each summer. The three-year grant will focus on enhancing participation and interest of under-represented minority groups, women, first generation students, veterans and non-traditional students attending 2- and 4-year universities with limited access to TERM research. The NSF and the Department of Defense have both identified TERM research as high priority areas.

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 27 pre-doctoral (PhD) students and 59 postdoctoral fellows.

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

WFIRM maintains a training program funded the National Institute of Biomedical Imaging and Bioengineering. The training program in translational regenerative medicine (RM) provides an integrated mechanism to support training of pre-doctoral students in the broad and expanding discipline of RM with particular emphasis on training students to better understand and utilize the inter-relationships among biomedical engineering, molecular biology, genetics and physiology in the science and, ultimately, clinical translation of RM. The principal goal of this training program is to attract and train the next generation of independent investigators required for significant scientific progress in the field of regenerative medicine. Training includes traditional didactic course work, a variety of WFIRM-wide training activities, participation in cutting-edge research projects, training in onsite GMP facilities, externship opportunities, grant writing, scientific presentations, and exposure to ethical issues in RM.

The unique WFIRM infrastructure provides facilities and expertise for translational studies from basic preclinical findings all the way into clinical trials. The program includes six areas of research focus: urological, cardiovascular, musculoskeletal, endocrine tissue, stem cells, and biomaterials/enabling technologies. Each area of focus contains at least five faculty members with complementary expertise, participate in the training and supervision of graduate students as co-mentors. Students are selected from all four tracks within the Wake Forest Graduate School: Molecular and Cellular Biosciences, Biomedical Engineering, Integrative Physiology and Pharmacology or Neuroscience.

4th Annual Regenerative Medicine Essentials Course: From the Fundamentals to the Future

The 4th annual one-week course brought together WFIRM's prominent, world-class experts with colleague experts from across the globe. Summer 2017 marked the largest course to date with nearly 300 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, regulatory, manufacturing 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.

Additional aspects of the 2017 course included three, *Into the Lab* workshops. These workshops provided hands-on interaction and demonstrations with cutting-edge technologies and techniques for regenerative medicine applications. 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 Applications and Awards

WFIRM faculty submitted more than100 research proposals totaling more than $100 million to more than 20 different agencies, foundations, and companies during fiscal year 2017. New and continuing awards provided more than $30 million in grant funding.

Included in the ongoing awards in FY17 were an NIH-funded Biomedical Technology Resource Center project aimed at advancing techniques to create complex tissues and parts for the body, such as for organs and bone, the NSF funded undergraduate summer research program and federally funded regenerative medicine manufacturing innovation initiative as part of the RegenMed Development Organization activities, as described below.

Publications and Scientific Reports

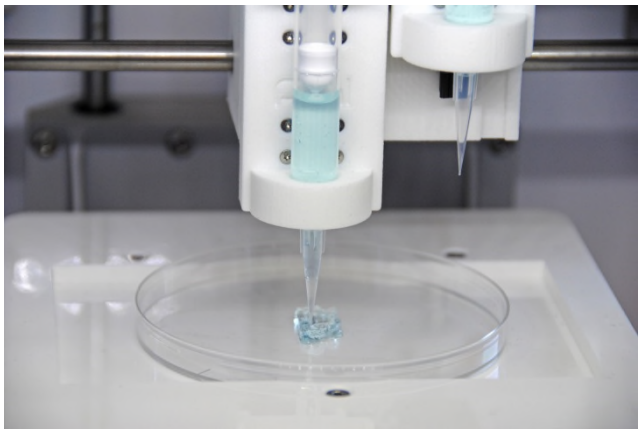
WFIRM researchers published 141 peer-reviewed papers and publications during fiscal year 2017 and also shared their work at scientific conferences. Notable scientific reports and news included:

WFIRM Plays Leading Role in Effort to Advance Manufacturing of Regenerative Medicine Therapies

WFIRM played a leading role in the development of new initiatives to apply advanced manufacturing to regenerative medicine. The goal is to speed up the availability of replacement tissues and organs to patients. The initiatives include a five-year, $20 million effort awarded to the RegenMed Development Organization.

“We are excited to be at the forefront of this next frontier in regenerative medicine,” said Anthony Atala, M.D., director of WFIRM. “Just like the invention of the moving assembly line reduced the cost of cars and made them commonplace, the field of regenerative medicine must develop standardized manufacturing processes to successfully make replacement tissues and organs more widely available.”

The award to RegenMed Development Organization was funded by a public-private partnership that involves the U.S. Army Medical Research and Materiel Command awarded the project. The goal of this partnership, known as the Medical Technology Enterprise Consortium (MTEC), is to accelerate progress in regenerative medicine manufacturing. The MTEC awarded funds will be matched by a consortium of regenerative medicine industry leaders and non-profit organizations organized by RegenMed Development Organization.



Under the RegenMed Development Organization award, WFIRM will participate in two projects. One is to develop standardized “bio-inks” that can be used to print replacement tissues and organs. The second is to develop standardized cell culture media -- liquids that support cell growth. These products are used in most all regenerative medicine projects because of the millions of cells that must be grown for each patient.

Researchers Make Significant Progress in Engineering Digestive System Tissues

WFIRM researchers reaches important milestones in their quest to engineer replacement tissue in the lab to treat digestive system conditions – from infants born with too-short bowels to adults with inflammatory bowel disease, colon cancer, or fecal incontinence.

Reporting in Stem Cells Translational Medicine, the research team verified the effectiveness of lab-grown anal sphincters to treat a large animal model for fecal incontinence, an important step before advancing to studies in humans. And in Tissue Engineering, the team reported success implanting human-engineered intestines in rodents.

"Results from both projects are promising and exciting," said Khalil N. Bitar, Ph.D., AGAF, senior researcher on the projects, and professor of regenerative medicine at the institute. "Our goal is to use a patient's own cells to engineer replacement tissue in the lab for devastating conditions that affect the digestive system."

Sphincter Project: The lab-engineered sphincters are designed to treat passive incontinence, the involuntary discharge of stool due to a weakened ring-like muscle known as the internal anal sphincter. The muscle can lose function due to age or can be damaged during child birth and certain types of surgery, such as cancer.

"The regenerative medicine approach has a promising potential for people affected by passive fecal incontinence," said Bitar. "These patients face embarrassment, limited social activities leading to depression and, because they are reluctant to report their condition, they often suffer without help."

Intestine Project: The intestine project is aimed at helping patients with intestinal failure, which is when the small intestine malfunctions or is too short to digest food and absorb nutrients essential to health. Patients must get nutrition through a catheter or needle. The condition has a variety of causes. Infants can be born with missing or dysfunctional small intestines. In adults, surgery to remove sections of intestine due to cancer or other disease can result in a too-short bowel. Intestinal transplant is an option, but donor tissue is in short supply and the procedure has high mortality rates.

"A major challenge in building replacement intestine tissue in the lab is that it is the combination of smooth muscle and nerve cells in gut tissue that moves digested food material through the gastrointestinal tract," said Bitar.

Through much trial and effort, his team has learned to use the two cell types to create "sheets" of muscle pre-wired with nerves. The material is already approved by the U.S. Food and Drug Administration for certain applications. In the current study, the tubular structures were implanted in

rats. Results showed that the muscle cells began releasing materials that would eventually replace the scaffold as it degraded. In addition, the tubes developed a cellular lining as the body's epithelial cells migrated to the area. The rats gained weight and studies showed that the replacement intestine was healthy in color and contained digested food.

WFIRM Sponsors International Bioprinting Conference

WFIRM hosted an international conference on 3D bioprinting in May 2017 in Winston-Salem. The event, which was attended by close to 150 scientists from around the world, was the second international event the institute sponsored.

"Hosting events like this gives us the opportunity to share our institute's scientific advancements with our colleagues, but also allows us to introduce Winston-Salem to researchers from around the world," said Anthony Atala, M.D., director of the institute and a conference organizer.

The conference focused on the physical and chemical processes used in 3D printing replacement tissues and biomedical devices. The events aimed to attract the best and brightest early-career researchers to join in discussions and present their work in poster sessions.

WFIRM Part of NIH-Funded Center for Engineering Complex Tissues

WFIRM is part of a National Institutes of Health (NIH)-funded Biomedical Technology Resource Center aimed at advancing techniques to create complex tissues and parts for the body, such as for organs and bone. The NIH awarded a $6.25 million grant to the newly established Center for Engineering Complex Tissues, for which WFIRM and Rice University will serve as key partners with the University of Maryland.

Anthony Atala, WFIRM director, and James Yoo, WFIRM professor, associate director, and chief scientific officer, will serve as co-principal investigators.

The center will serve as a national hub for transforming current tissue engineering and 3-D printing technologies into new and improved platforms for everyday uses in regenerative medicine.

"We are proud to be part of this collaborative effort to advance the field of 3-D bioprinting," Atala said. "We believe bioprinting represents one of the most promising strategies for increasing the number of patients who can benefit from replacement tissues and organs."

WFIRM Awarded Education Grant

WFIRM was awarded a National Science Foundation (NSF) grant to engage undergraduate students in research at the interface of engineering and biology in challenging areas of tissue engineering and regenerative medicine (TERM) each summer.

Based on the strength of WFIRM's long-standing Summer Scholars program, the $366,423 three-year grant will focus on enhancing participation and interest of under-represented minority groups, women, first generation students, veterans and non-traditional students attending 2- and 4-year universities with limited access to TERM research. The NSF and the Department of Defense have both identified TERM research as high priority areas.

The Summer Scholars program is unique in that students are placed into an interdisciplinary, team-based approach to TERM research. The program also boasts open spaces where faculty mentors and the entire WFIRM research team collaborate, allowing for simultaneous exposure to TERM research projects beyond the students' own individual research projects.

"A significant challenge in TERM is developing the next generation of science and engineering experts, who are cognizant of the interdisciplinary challenges and approaches needed to solve TERM problems," said Joan Schanck, MPA, WFIRM Academic Research Program Officer who oversees educational programming. "Engineers need to understand the biological dimensions of their work to advance their own engineering knowledge and interact knowledgeably with biologically trained counterparts and vice versa."

News Media Coverage

Coverage by Top Media Outlets

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

- Newsweek
- R&D Magazine
- NBC News
- Mashable
- AARP Bulletin
- CNN.com

- Dermatology Times
- Popular Science
- Vice.com (Tonic – science platform)
- Saturday Evening Post
- NBC's MACH (science platform)
- CNBC
- New Scientist
- IEEE Pulse magazine
- The Scientist
- TechCrunch
- EdTech Magazine
- Military.com
- Science
- BioTechniques
- Laboratory Equipment
- Business Times
- Industry Week
- Share America
- Futurism
- Science Nordic (Denmark)
- CBS.Ca (Canada)
- Espana magazine
- El Mercurio newspaper (Chile)
- YTN TV (So. Korea)
- Focus Gesundheit (Germany)
- EBS TV (So. Korea)

Selected News Coverage

AARP Bulletin: The bulletin, one of the world's largest circulation publications, interviewed Dr. Atala about this work.
http://www.aarp.org/health/conditions-treatments/info-2017/organ-donation-crisis-advances.html

The Wall Street Journal: A round up of insights into the booming stem-cell research arena, which included comment from WFIRM Director Anthony Atala.
https://www.wsj.com/articles/stem-cell-treatments-become-more-available-and-face-more-scrutiny-1472496352

R&D Magazine: WFIRM's Director Anthony Atala is chosen as Innovator of the Year.
https://www.rdmag.com/article/2016/12/regenerative-medicine-physician-named-2016-innovator-year

Fast Company: WFIRM was named the winner in the Health category of Fast Company's 2017 World Changing Ideas Awards for its work in 3D bioprinting.
https://www.fastcompany.com/3068873/announcing-the-winners-of-the-2017-world-changing-ideas-awards

Newsweek: A WFIRM researcher's findings on the effects of deep space radiation and the development of leukemia were widely reported.

Newsweek

http://www.newsweek.com/nasa-mars-space-suits-radiation-space-radiation-mars-travel-space-travel-space-584657

Politico: A comprehensive, in-depth portrait of Winston-Salem's downtown which includes The Innovation Quarter, home to WFIRM. The article highlights WFIRM research with the subhead, "The North Carolina city was once a major producer of cigarettes in the country. Now it's manufacturing human organs."
http://www.politico.com/magazine/story/2016/10/winston-salem-technology-tobacco-town-214377

Smithsonian Magazine: WFIRM Director Anthony Atala is featured as an American Ingenuity Award winner for 3D printing with the Integrated Tissue and Organ Printing System, or ITOP.
http://www.smithsonianmag.com/innovation/miracle-maker-anthony-atala-winner-smithsonian-ingenuity-awards-2016-life-sciences-180961121/?utm_source=facebook.com&utm_medium=socialmedia

Smithsonian Magazine

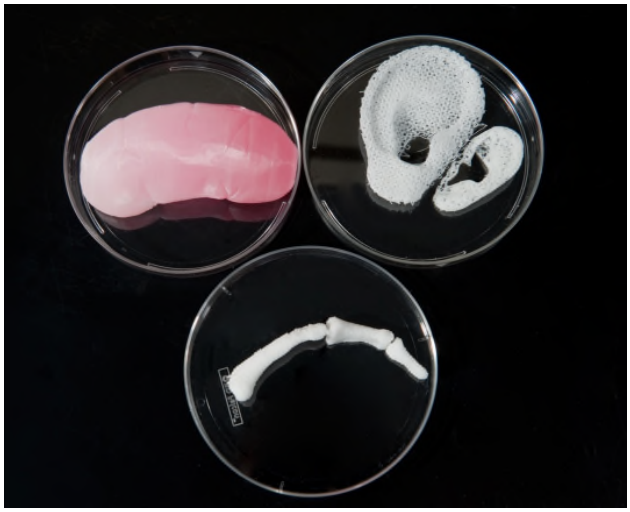
Engineering.com: An article that takes a step by step look at how organs and tissues are manufactured using 3D printing technology.
http://www.engineering.com/3DPrinting/3DPrintingArticles/ArticleID/13395/What-Does-It-Take-to-Engineer-a-Liver.aspx

UNC-TV Science Now: This show segment took viewers into the WFIRM lab to see how 3D organs and tissues are bioprinted.
http://science.unctv.org/content/video/printing-3d-organs

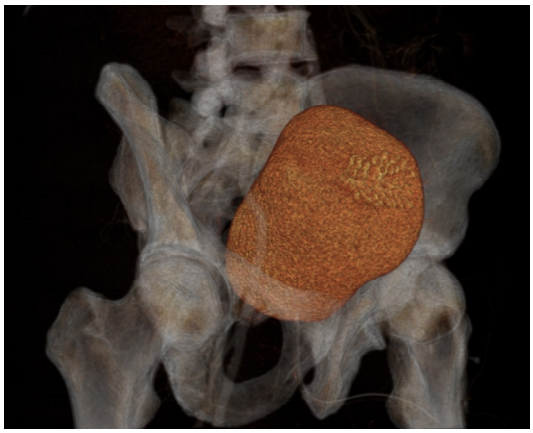
The Translational Scientist: A Q&A with WFIRM Director Anthony Atala about the future of regenerative medicine.
https://thetranslationalscientist.com/issues/0616/the-organ-grower/

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, 2017

Royalties generated from subject projects:	0
Unrestricted Revenues:	
Institutional Support	3,416,222
Gift Income	128,812
Other Income	762,565
Total Unrestricted Revenues	4,307,599
Restricted Revenues:	
State of North Carolina	7,042,516
Federal Government	18,779,052
Foundation	280,765
Industry, Individual, Endowment, & Other	339,659
Total Restricted Revenues - cash basis, not accrual	26,441,992
Total Revenues	30,749,591
Restricted Expenditures:	
AFIRM Expenditures	12,481,562
Other Federal Expenditures	6,328,109
GMP & Translation Related Expenditures	6,938,665
Other Restricted Expenditures	1,403,236
Total Restricted Operating Expense	27,151,572
Unrestricted Expenditures:	
Administration, Legal, & patents	3,529,137
Department Research	58,863
Education	71,775
Total Unrestricted Operating Expense	3,659,775
Capital (renovations, equipment, & software) Funded by Wake Forest, State of NC, & Federal	1,058,487
Total Expenditures	31,869,834
NET	(1,120,243)