WFIRM

Wake Forest Institute for Regenerative Medicine

Wake Forest University School of Medicine

Overview of the Wake Forest Institute for Regenerative Medicine Training Team, Research, Philosophy & Infrastructure

The current WFIRM faculty roster contains a mixture of established faculty and junior faculty with outstanding promise and collaborative expertise in the field. Overall, our faculty mentors have successfully been awarded over $34 million in funding. The table below provide overviews of seven focus areas:

Areas of Focus for Research Training	T32 Member Faculty
Biomaterials/Enabling Technologies	Atala, Almeida-Porada, Bishop, Bitar, Gorantla, Jackson, Lee, Lu, Marini, Murphy, Opara, Porada, Walker, Yoo
Stem Cells/Cell Therapy	Atala, Almeida-Porada, Bishop, Criswell, Gorantla, Jackson, Lu, Marini, Maxwell, Murphy, Opara, Porada, Sadri-Ardekani, Soker, Williams, Yoo, Zhang
Cardiovascular and Vascular (Blood Vessels, Heart Valves, etc.)	Almeida-Porada, Bishop, Gorantla, Lee, Maxwell, Porada, Soker, Williams, Yoo
Musculoskeletal	Atala, Bitar, Criswell, Gorantla, Jackson, Lee, Soker, Williams, Yoo
Gastrointestinal/Endocrine (Ovary, Liver, Pancreas)	Atala, Bishop, Marini, Opara, Schwartz, Shupe, Soker, Walker, Weis, Yoo, Zhang
Urological (Kidney, Bladder, Urethra)	Atala, Bitar, Jackson, Lee, Murphy, Sadri-Ardekani, Schwartz, Soker, Walker, Williams, Yoo, Zhang
Microphysiological Systems (Body-On-A-Chip)	Atala, Bishop, McNutt, Murphy, Shupe, Soker

Biomaterials/Enabling Technologies. These studies focus on development of biomaterials for tissue and organ replacement, as well as methods for state-of-the-art noninvasive imaging and optimization of regenerating tissues. Concurrent with these investigations are studies to optimize preconditioning of implants using custom-designed bioreactors. Additional areas include projects to develop a "body-on-a-chip" to be used to model the body's response to drugs and harmful chemical and biological agents. Another area includes development of platform technologies to advance RM manufacturing, and ultimately, technologies for developing a GMP-grade universal media to accelerate cell therapy and tissue engineering manufacturing product development. The second is developing a universal bio ink with tunable mechanical properties for additive manufacturing (3D bioprinting). The results of these efforts and future manufacturing-focused project efforts will help to build a library of proven

processes and materials that can be used by researchers and RM companies. Taken together, this work aims to supply novel biomaterials and other technologies critical to efficient clinical translation as well as, biomanufacturing of RM technologies. These studies are funded by the NIH, the DoD, and private foundations with a budget of over $4.5 million annually in grant awards.

Stem cells/Cell Therapy. These studies investigate methods used to isolate amniotic fluid-derived stem cells from multiple species, and induction of pluripotentiality in cells (iPS) using both viral and non-viral methodologies to alter the cell genome. In addition, we are working on the development of other cell sources for tissue engineering/RM, such as stem cells from urine, fat, bone marrow, muscle, nerve, etc., and optimizing methods to isolate and expand these cell types. These studies are funded by the NIH, DoD, and NASA with a combined budget of $5.6 million annually in grant awards.

Cardiovascular Regeneration and Vascular Regeneration. Studies include bioengineering vessels for arteriovenous shunts and bypass grafts. Arterial implants are made from both decellularized and electrospun scaffolds and autologous endothelial and/or smooth muscle cells. Bioengineered heart valve implants are being tested in a sheep model of pulmonary valve insufficiency. Heart valves are bioengineered using decellularized porcine scaffolds seeded with autologous endothelial cells, or unseeded valves in which the surface characteristics have been altered to attract endothelial cells *in situ*. Other studies use a unique sheep model of hemophilia A to explore treatment regimens and the effects of nitric oxide in hemostasis. These studies are funded in part by the NIH, DoD and private foundations through awards of over 3.2 million annually.

Musculoskeletal Regeneration. These studies consist of research into the use of cells, biomaterials and bioreactors for enhanced regeneration and repair of muscle, skin, bone, ligament and cartilage for the treatment of injuries. There is a focus on skin bioprinting, vascularized composite allotransplantation in musculoskeletal regeneration, and development of technologies directed at the entire spectrum of muscle injuries, ranging from compartment syndrome to volumetric muscle loss. These studies are funded by the NIH, the DoD, and other agencies through awards of over $10 million annually.

Gastrointestinal/Endocrinology (liver, pancreas, ovary). These studies focus on cell therapy approaches for the treatment of diabetes, and liver diseases. Studies include the use of cells, scaffolds, encapsulated islets and seeded scaffolds to regenerate damaged pancreatic and hepatic tissue in small and large animals, including nonhuman primates. Studies involve the use of several cell types (amniotic fluid-derived stem cells, induced pluripotent stem cells [iPSC] and stromal cells) and utilize both synthetic polymer and natural scaffolds. Additional studies focus on regeneration of ovarian tissue. The GI program seeks to use RM approaches to treat neuromuscular diseases of the gut. The overriding objective is to develop intrinsically innervated gastrointestinal tissue for implantation. Funding agencies for these studies include the NIH and private foundations with a combined budget of over $2 million annually in grant awards.

Urology. Studies include biomolecular and cell therapy for chronic interstitial nephritis, autologous cell-based bioengineered bladders and ureters, autologous cell therapy for urinary incontinence, studies of endogenous bladder regeneration, and gene therapy for erectile dysfunction. These studies are supported by the NIH, DoD and private foundations with combined awards of over $6 million annually.

Microphysiology (Body-On-A-Chip): WFIRM's "Body-on-a-Chip" is an advanced 3D model of the human body using a system of chips and microfluidic devices that creates a structure for the humanoid tissue equivalents, also known as organoids. The system can be designed to fit an area about the size of a matchbox. The bioprinted organoids function in a very similar manner as actual human organs. For example, the heart beats about 60 times each

minute, the lung breathes air from the surrounding environment, and the liver breaks down toxic compounds into harmless waste products. The organoids allow researchers to analyze a drug's impact on an organ. They tested the system using FDA recalled drugs, and although these drugs made it through extensive testing via cell culture, animals, and human clinical trials with no issues, the WFIRM system was able to readily detect toxicity and replicate the damage seen in patients.

Nearly all faculty have a primary appointment at WFIRM with secondary appointments in six other departments/centers at WFU. Faculty from the two other departments are active participants in our research efforts and cross-appointed in WFIRM. This creates an ideal scenario for an integrated approach to translational RM training for PhD students. In addition to strong research and training records, these faculty members collectively are outstanding role models for service to the scientific community, including service on editorial boards, review panels, and organizational committees of scientific societies.

Training Faculty - *Some achievements of WFIRM scientists*

► First to demonstrate that complex, layered tissue structures can be engineered using cells. **(1994)**

► Developed first tissue-engineered product to go to the US Food and Drug Administration for Phase 1 approval for clinical applications, consisting of cells and biomaterials for injectable therapy. **(1995)**

► First to use biomaterials alone, without the addition of cells, implanted in patients for the regeneration of organs. **(1996)**

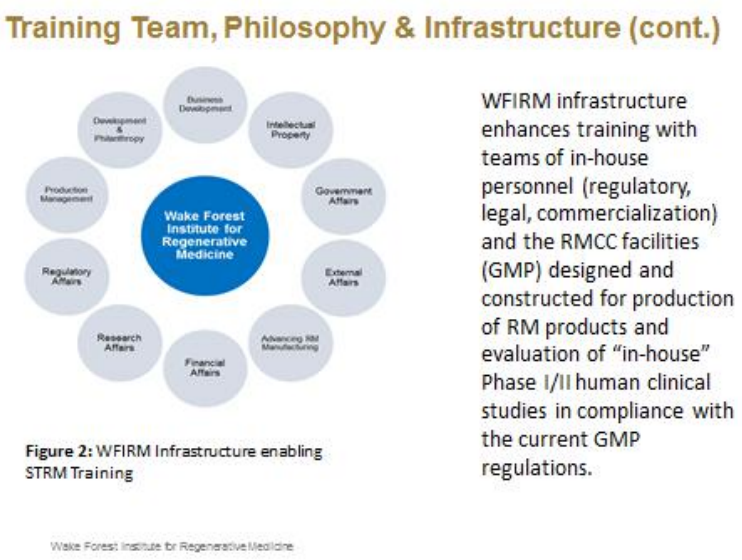


Figure 2: WFIRM Infrastructure enabling STRM Training

► First to create a laboratory-grown organ – engineered bladder tissue (hollow organ) that was successfully implanted in patients. **(1999 first implantation; publication 2006)**

► First to create a functional experimental solid organ, a miniature kidney that secretes urine. **(2003)**

► First to engineer functional, experimental solid organs (penile tissues and livers) using a strategy to recycle donor organs, with potential applications to other solid organs, such as the kidney and pancreas **(2004 and 2010)**

► Led the team that engineered tubular organs (urine conduits) and implanted them in patients. **(2004 first implantation; publication 2011)**

► Led the team that implemented engineered vaginas into four girls with a rare genetic defect. **(2005 first implantation; publication 2014)**

► Founded the Regenerative Medicine Foundation, a non-profit organization dedicated to advancement of regenerative medicine treatments and therapies. **(2005)**

► Provide feasibility of printing living tissue structures to replace injured or diseased tissue in patients. **(2006)**

► Identified and characterized a new source of stem cells derived from amniotic fluid and placenta, which show promise for the treatment of many diseases. **(2007)**

► Selected to co-lead the Armed Forces Institute of Regenerative Medicine, an $85 million, federally funded effort to apply regenerative medicine to battlefield injuries. **(2008)**

► Selected to lead the 2nd phase of the Armed Forces Institute of Regenerative Medicine, a $75-million project. **(2014)**

► Started the first initiative for regenerative medicine manufacturing, through establishment of a joint industrial engineering program **(2008)** and the Regenerative Medicine Manufacturing Society **(2014)**

► Led the team that successfully implanted engineered vaginas into girls with a rare genetic defect. **(2005 first implantation; publication 2014)**

► Developed a 3D bioprinter (the Integrated Tissue and Organ Printing System) over a 14-year period specifically designed to print living tissue structures **(publication 2016)**

► Developed a highly functional body-on-a-chip platform that integrates multiple normal human cell derived tissues with a common "blood" supply system for drug toxicity testing and personalized medicine. **(2017)**

► Developed miniature 3D human brains (organoids), the first engineered tissue equivalent to naturally resemble the normal human blood brain barrier, containing all six major cell types found in organs. (publication 2018)

► Developed an engineered uterus that can sustain pregnancy and live delivery pre-clinically. (publication 2020)

► WFIRM team won 1st and 2nd place in the NASA Vascular Tissue Challenge, creating vascularized liver tissues with two different 3D bioprinting methods. (2021)

► First to study viral threats for the prevention of pandemics by combining organoids and Artificial Intelligence to find relationships between infection and human biology. (2022)

FACULTY RESEARCH INTERESTS

***Anthony Atala, MD, Professor and Director of WFIRM*:** Dr. Atala's research is known world-wide for many ground-breaking advances in RM. Many firsts have resulted from his research. Sixteen applications of technologies developed in his lab have been used clinically. He is PI for several grants, including NIH and DoD research (AFIRM, XCEL, MTEC) which span creating a "body-on-a-chip" platform and RM strategies for wounded soldiers. Other projects include rapid prototyping 3D organ printing technology exploring novel biomaterial/cell combinations. Dr. Atala and his team use a multidisciplinary approach to achieve the goal of engineering complex functional tissues. Trainees benefit from extensive interaction with Dr. Atala and his team with diverse scientific backgrounds at all levels, from undergraduate to MDs, PhDs, and MD/PhDs. Dr. Atala has mentored over 190 postdoctoral fellows, 64 graduate students and 42 undergraduates, and is a strong role model/mentor for PhD students interested in clinical translation of basic research.

***Graca Almeida-Porada, MD, PhD, Professor and Director Fetal Research and Therapy Program*.** Dr. Almeida-Porada's research focuses on the development of cell and gene therapies for genetic disorders, prior to birth and during infancy, taking these therapies all the way from the bench to the clinic. To overcome the current barriers to fetal transplant and gene therapy she investigates hematopoietic and immunologic development, studies the biology and function of novel stem cell populations, and explores innovative methods of bone marrow conditioning and stem cell expansion. Dr. Almeida-Porada also uses human organoid platforms with integrated microfluidics, that consolidate a variety of important physiological parameters such as 3D architecture, cell-cell/cell-matrix interactions, and circulation, to allow a better mimicry of in vivo conditions, to address the impact and safety of different gene delivery systems. She is the editor-in-chief of Current Stem Cell Reports and the co-founder of the International Fetal Transplantation and Immunology Society. Dr. Almeida-Porada is fully committed to train the next generation of scientists in particular women and underrepresented minority students. She has been the thesis advisor and/or serve(d) on the thesis committee of more than 50 graduate students and post-doctoral fellows.

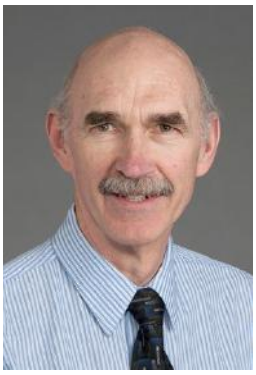
***Colin Bishop, PhD, Professor*:** Dr. Bishop has been involved in molecular genetics and developmental biology over 25 years studying the molecular biology of the mammalian Y chromosome, the genetics of sex determination, reproductive failure and stem cell biology. Recent previous appointment was at Baylor College of Medicine where he held position of Professor (tenured) in the departments of Obstetrics & Gynecology and Molecular & Human Genetics. In 2006, he determined to re-orientate his research towards the emerging field of RM and joined WFIRM, where he directs the Genetics and Developmental Biology program. The main thrust of his current funded research involves development of several human micro organoids (liver, cardiac, blood vessel lung, brain and testis) using primary cells in combination with differentiated iPS cells in unique 3D culture systems. The objective is to develop a human "body-

on-a-chip" for rapid, more predictable drug screening than can be obtained using animals. In particular, his group has developed multicellular 3D human liver, heart and testis organoids which self-organize, remain viable and functional for more than four weeks. They have been fully characterized using a large number of organ specific parameters with publications on their utility in drug screens. Over his 30-year career, Dr. Bishop has mentored more than 25 graduate and 35-post-doctoral fellows coupled with a portfolio of European, NIH and DoD funding.

***Tracy Criswell, PhD, Assistant Professor*:** Dr. Criswell received her PhD in cellular biology from Case Western Reserve University followed by a postdoctoral fellowship in cancer biology at Vanderbilt University. Her expertise in cell biology and cell signaling is broadly applicable to the field of regenerative medicine. Dr. Criswell's research interests broadly involve examining the effect of sex and age on regenerative medicine and tissue engineering therapies, specifically on identifying novel therapies to aid skeletal muscle regeneration after acute and chronic injuries. She developed a novel rodent model of compartment syndrome that has led to several discoveries related to the pathogenesis of skeletal muscle injury and the consequent regenerative processes. Her current research areas of focus include: 1) the development of biological and pharmacological therapies for the treatment of acute skeletal muscle injury; 2) the identification of sex-specific changes in skeletal muscle regeneration after injury, across the lifespan; 3) engineering ovarian tissue for the regulation of hormones in women during the menopausal transition; and 4) the development of micro-physiological systems that mimic the hormonal changes that occur in women as they age (adolescence – puberty – child-bearing – peri-menopause – post-menopause). In addition to research, Dr. Criswell serves as Program Director for the Master of Science in Translational Biotechnology program and has been actively involved in educational, mentoring, and outreach activities throughout her tenure at WFIRM. She has mentored undergraduate and graduate (MS, PhD, MD) students, national and international visiting scientists and postdoctoral fellows at WFIRM, including under-represented minority (URM) students involved in the WF Post-baccalaureate Research Education (PREP) Scholars program. Dr. Criswell is passionate about increasing diversity, equity, and inclusion at Wake Forest and in STEM fields in general. She currently serves as Chair of Women in Medicine and Science (WIMS) and faculty lead of the White Affinity Group for Racial Equity (WAGRE) and is co-director of the Inclusion, Diversity, Equity Accelerator (IDEA) for the Wake Forest Biomedical Sciences Graduate School.

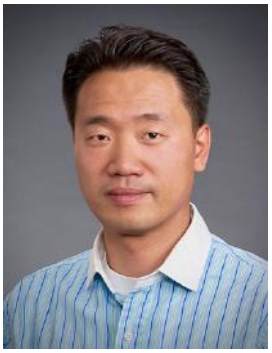
***Vijay Gorantla, MD, PhD, Professor*:** Dr. Gorantla is Director of the Vascularized Composite Allotransplantation program at WFIRM. He played a key role in the Nation's first and second hand transplant programs at the University of Louisville and University of Pittsburgh before being recruited to WFIRM. Dr. Gorantla is lead Investigator on multiple translational and clinical studies funded by the DoD totaling over $10M dollars in funding. Over the last decade, he has been active in basic and translational research in the restoration or rehabilitation of disabilities secondary to complex limb loss, traumatic brain injury, or vision loss. These include complex microvascular models to study limb or eye transplantation, non-invasive high resolution vascular imaging strategies with ultrahigh field MRI and ultrasound biomicroscopy, adipose and mesenchymal stem cell therapies for immunomodulation and neuromuscular regeneration, and novel strategies for bone healing and regeneration using bioresorbable and biocompatible

materials. Over the past 10 years, Dr. Gorantla has mentored 8 graduate students and 20 postdoctoral fellows. He has also served as primary or co-primary faculty advisor for several medical scientist training programs (MD/PhD), many of whom have moved on to successful independent clinical or academic research careers.



***John D. Jackson, PhD, Associate Professor*:** Dr. Jackson received his PhD degree in medical sciences (experimental hematology) from the University of Nebraska Medical Center, Omaha, Neb. He received post-doctoral training in the laboratory of Dr. Donna Rennick at DNAX Research Institute, Palo Alto, Calif. At DNAX Research Institute, Dr. Jackson was involved in research directed to the study of the role of cytokines on the regulation of hematopoietic and immune systems. In 1990, Dr. Jackson joined the Department of Pathology and Microbiology at the University of Nebraska Medical Center, Omaha, as an assistant professor. He was also appointed technical director of the Cell Processing Laboratory at the University of Nebraska Medical Center which provided support for the bone marrow transplantation program. His research focus during this time was directed toward the effects of cytokines and other agents on hematopoietic mobilization for transplantation as well as hematopoietic and immunological recovery following transplantation. In 2010, Dr. Jackson joined WFIRM where research interests broadened to include tissue engineering of skin, thymus, inner ear, kidney, corporal tissue and ovary.

***Patrick Michael McNutt, PhD, Associate Professor*:** Dr. McNutt completed his undergraduate training at Wake Forest University with Bachelor degrees in both Biology and Chemistry. He received his Ph.D. in Molecular Biology from Princeton University in the lab of Dr. Malcolm Steinberg. After completing an active-duty military obligation from 2000-2010, which included assignments at Fort Benning, Madigan Army Medical Center, Baghdad, Iraq, and the U.S. Army Medical Research Institute for Chemical Defense (USAMRICD), he accepted a faculty position at USAMRICD where he built a large research team focused on understanding corneal pathophysiologies in mustard-exposed rabbit eyes, developing new therapeutics for botulinum neurotoxin paralysis, and treating neurotoxicity caused by exposure to nerve agents. In the fall of 2020, he accepted a faculty position at the Wake Forest Institute for Regenerative Medicine (WFIRM), where he is currently an Associate Professor. Dr. McNutt has a broad background in Cellular and Molecular Biology and a decade of practical experience in fundamental and translational research involving ocular toxicology, neurotoxicology and neuropharmacology. His personal goal at WFIRM is to apply the knowledge and technical expertise he developed as a Department of Defense scientist to develop translational treatments for biological and chemical threats faced by the general population, with an emphasis on regenerative pharmacology and therapeutic screening using human microphysiological models. The scope of his research program requires a highly collaborative environment. In addition to existing NIH-funded academic collaborations with New York University, Tufts University and University of California, Irvine, he has extensive collaborations with industry partners to advance novel therapies and dedicated Department of Defense funding to conduct translational studies for regulatory approval of a novel botulism countermeasure under the Animal Rule. Dr. McNutt serves on the Wake Forest Biosafety Committee and the Intramural Research Committee. He is also a Colonel in the U.S. Army Reserves. Dr. McNutt's publication record can be reviewed at https://orcid.org/0000-0002-5703-4565.



Young Min Ju, PhD, Assistant Professor: Dr. Ju received his Ph.D. degree in Biomedical Engineering from the University of South Florida, FL. After completing his Ph.D. degree and post-doctorate training at the Wake Forest Institute for Regenerative Medicine (WFIRM), he became a faculty at WFIRM. Dr. Ju's research focuses on various aspects of developing various biomaterials for > 25 years, including 3D scaffold design, surface modification of scaffold, cell-biomaterials interaction, control release drug delivery system, 3D bioprinting, and implantable medical device (e.g. implantable biosensors). Dr. Ju has been involved in multiple research projects concerning the development of engineering complex functional bioengineered tissue including *in situ* musculoskeletal tissue regeneration using a multi-growth factor delivery system, the development of cardiovascular tissue regeneration using the electrospun scaffold with dual micro-/nanofiber architecture, and other functional tissue regenerations (e.g. bone, heart valve, trachea, corporal tissue). More recently, Dr. Ju has applied his expertise to the development of a novel biomaterial system including decellularized tissue scaffold for 3D bio-printed muscle tissue engineering applications and wound care skin graft that delivers regenerative bioactive factors (e.g. conditioned media factors) as well as the development of the universal bioreactor platform for the clinical manufacturing of a wide range of regenerative medicine products.

***Ji Hyun Kim, PhD, Assistant Professor*:** Dr. Kim's research has focused on developing and fabricating three-dimensional (3D) biomimetic tissue-engineered constructs and cell-based treatments for treating diseased or damaged tissues, including skeletal muscle, nerve, kidney, heart, and blood vessels. Dr. Kim's research interests are to bioengineer complex and composite tissue constructs to restore normal tissue function using tissue-engineering technologies for transplantation. Dr. Kim has developed functional skeletal muscle tissue constructs with structural mimicry and innervation capability for implantation using 3D bioprinting technology for pelvic floor muscle and limb regeneration. In another project, Dr. Kim has worked on establishing therapies to restore skeletal muscle tissue functions using autologous cells/tissues for clinical translations, which have been approved by the FDA for a Phase I safety study. Another research interest is to develop novel strategies to overcome the vascularization challenge of the current tissue-engineering approaches and to engineer implantable clinically relevant sized tissue constructs for long-term tissue survival and function by accelerating vascularization. Dr. Kim's recent active research includes the biofabrication of implantable vascular kidney tissue constructs using autologous renal cells, iPSC-derived renal organoids, and growth factors for accelerating vascular integration for treating kidney diseases. She has developed stem cell Secretome-based recombinant protein therapies as a cell-free, off-the-shelf product for the treatment of kidney diseases and wound care and accelerating healing.

***Sang Jin Lee, Ph.D., Professor*:** Dr. Lee and his team have been working on the development and fabrication of 3D biomaterial systems for tissue-engineered constructs, which include cardiovascular, musculoskeletal, and urological tissues. To work on that, his research team has focused on the development of novel smart scaffolding systems that support regenerative medicine approaches. The novel scaffolding systems combined with

drug/protein delivery systems, nano/micro-scaled topographical features, and hybrid materials could actively participate in functional tissue regeneration. Recently, his research team has focused on 3D bioprinting strategy that can manufacture complex, multi-cellular living tissue constructs. To establish a clinically relevant bioprinting workflow, his team has developed multiple biomaterial formulations as bioinks that provide the tissue-specific biological microenvironment needed for the successful delivery of cells to discrete locations within the 3D tissue architectures. Because of these previous works, he has authored more than 150 scientific publications and reviews, has edited 2 textbooks, and has written 35 chapters in several books. As PI or co-investigator on NIH- and DOD-funded grants, his team performed the fundamental works for the proposed study by developing functional tissue scaffolds that possess biological and biomechanical properties and provide a favorable microenvironment that supports the growth of cells. Since 2004, Dr. Lee has mentored 176 trainees at all career levels which include 19 graduate students, 33 postdoctoral fellows, 8 research trainees, 36 visiting scholars, 8 laboratory technicians, 13 undergraduate students, 30 summer internship undergraduate students, 2 high school internship students, and 27 international graduate students.

***Baisong Lu, PhD, Assistant Professor*:** Dr. Lu is working on developing safe and efficient CRISPR/Cas9 delivery methods for gene therapy. Recently, his group developed virus-like particles and exosomes for delivering Cas9 mRNA or Cas9 ribonucleoprotein (a complex between Cas9 and single guide RNA). Currently, he is developing lipid nanoparticles for efficient RNA delivery into deep organs. In addition to delivery method development, he is also using these newly developed genome editing CRISPR/Cas9 system to develop treatments for amyotrophic lateral sclerosis, Duchenne muscular dystrophy and Friedreich ataxia. In addition, he is developing a lentiviral vector based on gene therapy for Dent's disease, a rare genetic disease.

***Frank Marini, PhD, Professor*:** Dr. Marini's research focuses on interactions between developing tissue and its stroma. This focus includes investigation of interactions between regenerating muscle and bladder tissue and its supporting stroma/ECM. Dr. Marini is an expert in mesenchymal stem cells and their application in cell therapy and cell and gene therapy of cancer. An NIH and DoD funded investigator, his was the first group to demonstrate the tropism of mesenchymal stem cells and tissue resident progenitor cells for tumor microenvironments, and importantly the role of mesenchymal stem cells within tumors to form stromal elements. Dr. Marini contributes his vast expertise in optical imaging using imaging platforms such as confocal and multispectral multiphoton. His group has developed several noninvasive imaging modalities for identifying stem cells in vivo and have applied them to large animal models and recently patient clinical trials. Additionally, he is the Cell Imaging core director (AKA the microscope core) and has tremendous experience in sophisticated microscopy. His imaging methodologies have important applications to evaluate of tissue formation *in vivo*, and therefore, will provide important enabling technologies for RM. Over the past 30 years Dr. Marini has mentored 14 students, 5 doctoral fellows, 4 medical fellows and graduated 1 MS, and 5 PhD students. All 5 PhD students have continued successful paths in science-

related fields. Notably, his recent postdoc was awarded a K99/R00 and has been recruited to Thomas Jefferson as Assistant Professor.

***Josh Maxwell, PhD, Assistant Professor*:** Dr. Maxwell's research focuses on the elucidation of various aspects of pediatric cardiac dysfunction, repair, and preservation. His lab is currently testing molecular- and cellular-based approaches to restore cardiac function after cardiac injury or disease. Specifically, Dr. Maxwell is interested in examining the paracrine effect of many cell-based therapies including human cardiac progenitor cells and bone marrow-derived mesenchymal stem cells on native cardiac cells and determining the mechanism by which these cells can repair and preserve the function of the failing heart. Using small animal models, his lab is studying the effect of cell and secretome delivery on heart function and repair in a RVHF model (pulmonary artery banding) and an ischemia reperfusion model of myocardial infarction. Additionally, Dr. Maxwell's laboratory uses their experience with confocal calcium (Ca^{2+}) imaging in primary cardiac myocytes to investigate the control of intracellular Ca^{2+} and its role in the regulation of excitation-contraction and excitation-transcription coupling in normal animals and animals with RVHF. Dr. Maxwell also has projects using iPSC-CMs for drug and cardiac toxicity testing and works closely with engineers to create biomaterials for the delivery of cellular therapies and cardiac repair. Over the past 7 years Dr. Maxwell has mentored over 25 undergraduates and 2 medical fellows and is highly active in the education and mentoring programs at WFIRM.

***Sean Murphy, PhD, Assistant Professor*:** Dr. Murphy received his BSc degree in molecular biology from the University of Western Australia and his PhD in stem cell therapy from Monash University, Melbourne. His research focuses on the application of regenerative medicine and tissue engineering strategies to develop new clinical treatments for lung disease. His lab has shown that perinatal cells are an effective anti-inflammatory therapy for the treatment of lung disease. This work has culminated in a Phase I clinical trial for the treatment of bronchiopulmonary dysplasia in pre-term infants. He has also developed perinatal tissue-derived biomaterials for treatment for skin wounds and burns which is currently in a Phase I clinical trial as well as licensed for commercialization. Dr. Murphy has applied tissue engineering technologies to develop a lung organ tissue equivalent (OTE) model which is being applied for modeling pulmonary fibrosis, exposure to toxic gases and bacterial and viral infection. Combination of these OTE models with drug screening and artificial intelligence/machine learning tools promises to improve our understanding of lung disease and injury and accelerate to development of effective therapeutics and drugs.

***Emmanuel C. Opara, PhD, Professor*:** Dr. Opara directs the Diabetes Program at WFIRM, and is Co-Director of the Islet Transplantation Program at WFBMC. His research applies engineering tools to diabetes research. He has been involved in diabetes research for >30 years, has a successful track record of developing bioartificial organs to treat hormone deficiencies and extensive experience in recruitment and supervision of URM students. Dr. Opara has authored more than 120 scientific publications and is sole inventor or co-inventor on >1 dozen patents (national and international) related to islet cell encapsulation, tissue engineering, and drug delivery. Dr. Opara most recently served as the Director of the BME Graduate Program at WF Campus and sits on the Curriculum and Executive Committee of the BME Program (Track 7), one of the tracks from which T32 trainees are drawn. One of inaugural fellows of this T32 program, John McQuilling, whose work resulted in >13 publications during his PhD studies, was mentored by Dr. Opara. Dr. Opara has trained 5 surgery residents, 12 postdoctoral fellows, 6 PhDs, 7 MS students. He has also trained 36 medical/undergraduate students who have either completed their medical education or gone on to graduate/medical schools. Dr. Opara has an impressive track record of successfully mentoring >2 dozen URM students who successfully completed their undergraduate, graduate/medical school or fellowship programs and went on to the next level of their careers.

***Christopher Porada, PhD, Professor*:** Dr. Porada's research focus is to develop safer and more efficient means of accomplishing gene transfer into clinically relevant cell types in vivo and achieving immunological tolerance to the therapeutic transgene. The ultimate goal is to use this knowledge to develop safe, effective treatments for monogenic diseases such as hemophilia which could be administered shortly after, or prior to, birth. In addition to his studies on direct *in vivo* gene delivery, Dr. Porada has spent over 10 years studying stem cell-based gene therapy, employing hematopoietic stem cells and mesenchymal stem cells as delivery vehicles for a variety of marker and therapeutic transgene cassettes. As such, he has a great deal of experience transducing bone marrow-derived stem cells with a variety of viral vectors, and with tracking/characterizing stem cell engraftment after transplantation. More recently, as a NASA investigator, he has been applying his knowledge of hematopoiesis and stem cell assay systems to define the effects of solar particle event and galactic cosmic ray radiation on the human hematopoietic system, with ultimate goal of defining the risk of leukemogenesis astronauts will face during long-duration missions in deep space. He has been involved in mentoring 8 undergraduate students, 6 master and PhD students and 2 post-doctoral fellows.

***Hooman Sadri-Ardekani, MD, PhD, Assistant Professor (Mentor-in-Training)*:** Dr. Hooman Sadri-Ardekani is Director of the male fertility research program at WFIRM and the Department of Urology. He established the first in vitro propagation system for human Spermatogonial Stem Cells (SSCs) (JAMA 2009 and 2011), recognized as a milestone in auto transplantation of human SSCs (Nature Reviews Urology February 2010). He is running a national comprehensive referral program to preserve fertility in high risk infertility patients in different ages, from childhood to adolescence to adults; including but not limited to those with cancer, Klinefelter syndrome, spinal cord injury, diabetes and multiple sclerosis. His research areas include: 1) Male reproductive medicine and biology; 2) Stem cell

therapies for male infertility; and 3) Tissue engineering 3D human testis organoid platform for in vitro spermatogenesis, androgen replacement, toxicology and drug screening. During the past 5 years, Dr. Sadri has mentored one graduate student, 6 undergraduate students, 4 postdoctoral fellows, 2 research residents and 3 high school students.

***Marshall Schwartz, MD, Professor and Surgeon, Department of Urology, WFIRM*:** As a distinguished surgeon and physician-scientist with a long history of NIH funding and mentoring of >25 surgery residents and physician-scientists over the past 48 years, Dr. Schwartz has been involved in basic science research mostly focused on GI physiology and nutrition. He became interested in the potential role of GI peptides and their potential role in treating intestinal failure from massive intestinal resection, inflammatory bowel disease, and intestinal ischemia-reperfusion injury and was the first investigator to show that certain GI peptides (now known as growth factors) were effective in increasing intestinal function and nutrient absorption. Studies are now on-going in the clinical application of this basic science investigation. As a pediatric surgeon, he has been most focused on intestinal failure in infants and children. In premature infants there is a disease process of unknown etiology referred to as necrotizing enterocolitis (NEC) which has become the main cause of intestinal failure in the pediatric age group. His motivation for coming to WFIRM was to study the role of stem cells in the prevention or amelioration of the severity of NEC and in those premature infants who lose much of their intestine from NEC with the aim to tissue engineer a small intestine that will enable them to get their nutrition enterally rather than from an intravenous source (referred to as parenteral nutrition). Dr. Schwartz has been involved in mentoring, education, and running ACGME-accredited training programs in general surgery and pediatric surgery for 36 years. He has directly mentored over 60 research fellows, 11 PhD candidates, and 7 post doctorates in his basic science research laboratory. In addition, he has been involved in the clinical and didactic training of >500 surgical residents and fellows in general surgery and pediatric surgery.

***Thomas Shupe, PhD, Assistant Professor*:** Dr. Shupe is a University of Maryland graduate who earned masters and doctoral degrees from Albany Medical College. He has 25 years of experience in developing and *in vitro* and *in vivo* models for human disease. He began his career in cancer and stem cell biology research and has identified several alternative pathways for carcinogen metabolism that are activated during liver regeneration. He has also been a key player in the characterization of several molecular factors that govern the phenotypes of both liver stem cells and liver tumor cells. More recently, Dr. Shupe has transitioned to the field of regenerative medicine and was the first to publish a method for the decellularization of intact liver. These decellularized matrices are currently under evaluation as scaffolds for clinical scale liver bioengineering. Together with colleagues at the Institute, Dr. Shupe has developed methods for incorporating decellularized tissue matrices into cell culture substrates that provide exceptional support for human primary cells. He serves as the scientific coordinator for the WFIRM "Body-on-a-Chip" program and is PI for a project developing chemically defined and animal product-free cell growth media.

***Shay Soker, PhD, Professor*:** Dr. Soker received his BA in agriculture and MA in microbiology and molecular genetics from the Hebrew University of Jerusalem, and his doctorate in biology from the Technion-Israel Institute of Technology. Dr. Soker is a professor of regenerative medicine, Biomedical Engineering, Cancer Biology and Physiology & Pharmacology, and the Chief Science Program Officer at WFIRM. Dr. Soker is an expert in the field of angiogenesis. Dr. Soker's research focuses on multiple aspects of regenerative medicine including ways to enhance the vascularization and innervation of bio-engineered tissues using growth factors and specialized biomaterials, identification of new sources of cells and biomaterials for tissue engineering and real-time imaging technologies. Some of his research projects have been translated into clinical applications in patients including the use of cells, biomaterials and bioengineered tissues to repair muscles, skin wounds and damaged urological tissues. In parallel, Dr. Soker has applied his expertise to developing 3D small tissue constructs as tissue models of human development and disease, namely body-on-a-chip. This technology enables screening of existing drugs on a personalizes basis and development of new drugs and test them on cells derived from individual patients. Based on his work, a new Wake Forest Organoid Research Center (WFORCE) was recently established, on which he serves as the scientific director.

***Stephen J. Walker, PhD, Professor with Tenure*:** Dr. Walker is a molecular developmental biologist and geneticist whose main research focus is identification of molecular biomarkers for complex disease. Dr. Walker is an expert in functional genomics and bioinformatics and in the application of molecular profiling to better describe complex disease sub-phenotypes. His NIH and private foundation funded research has resulted in: (1) the first ever molecular description of gastrointestinal inflammation in GI-symptomatic children with autism, (2) a putative blood-based biomarker for GI inflammation in children with ASD, (3) clinical sub-phenotyping in interstitial cystitis/bladder pain syndrome that distinguishes a bladder-centric disease phenotype from a systemic pain syndrome phenotype, and (4) a molecular description of post-transplant repair and regeneration activity in the peripheral blood of kidney transplant patients. Since his appointment to the Wake Forest Institute for Regenerative Medicine in 2007, Dr. Walker has mentored 4 PhD students, 3 Master's students, 9 Urology Residents and 4 Fellows in the Female Pelvic Health and Reconstructive Surgery Fellowship program. He has mentored an additional 16 undergraduate students and 5 students from the Work-Based Learning Program from Forsyth Technical Community College.

Victoria Gail Weis, PhD, Assistant Professor: Dr. Weis received her PhD in Cell and Developmental Biology from Vanderbilt University followed by postdoctoral fellowships in Epithelial Biology Center at Vanderbilt University and in Regenerative Medicine at Wake Forest Institute for Regenerative Medicine. Dr. Weis's research interests are in gastrointestinal biology and translational science with a special emphasis within the neonatal/pediatric patient population. Dr. Weis integrates a diverse set of methods and model platforms to elucidate various aspects of neonatal intestinal pathophysiology in both Necrotizing Enterocolitis (NEC) disease and in health development. Additionally, using a small animal model of NEC and an in vitro model of intestinal epithelium, Dr. Weis's

laboratory studies the use of placental stem cell-based therapies (cell therapy and secretome therapy) to induce intestinal repair in NEC disease. Her current research areas of focus include: 1) Developing an advanced placental stem cell-based therapy for NEC, 2) Identifying the critical cellular/molecular mechanisms of repair in the neonatal intestine and NEC disease, 3) Developing high-throughput in vitro model platforms for 'preclinical-to-translational' NEC and neonatal intestinal research, and 4) Developing photoacoustic imaging as a non-invasive method to assess biophysical indicators of neonatal intestinal health and function.

***J. Koudy Williams, DVM, Professor*:** Dr. Williams graduated from Iowa State University of Science and Technology with a BS followed by a DVM. He began his career at the medical center 30 years ago with the Department of Comparative Medicine focusing on the use of male and female nonhuman primates as models of coronary heart disease. At the Institute, he focuses on the use of male and female cynomolgus primates as models of regenerative medicine approaches to lower urinary tract diseases. He is currently funded by the NIH to explore cell and chemokine therapies for urinary incontinence and post-prostatectomy erectile dysfunction and is also actively involved in Armed Forces Institute of Regenerative Medicine projects to regenerate the lower urinary tract for wounded warriors. Williams' major service to WFIRM is to provide assurance to the DEA for the use of controlled substances and technical training in preclinical work. He also serves as the Core Leader of the Surgery Core.

***James J. Yoo, MD, PhD, Professor*:** Dr. Yoo is a surgeon and researcher who received his Bachelor's degree in biology from the University of Illinois in 1984. He earned his MD, MS and PhD all from Korea University College of Medicine, Seoul, Korea. Dr. Yoo's research efforts have been directed toward the clinical translation of tissue engineering technologies and cell-based therapies by developing new therapeutic modalities for the functional repair and replacement of diseased tissues and organs. His background in cell biology and medicine has facilitated the transfer of numerous cell-based technologies from the bend-top to the bedside. His extensive experience in cell culture, biomaterials design, surgical techniques and animal handling has contributed to achieving functional tissues and organs for successful pre-clinical and clinical studies.

***Yuanyuan Zhang, MD, PhD, Associate Professor*:** Dr. Zhang received his M.D. from Nanchang Medical University, and PhD degree at University of Lausanne in Switzerland. Dr. Zhang has extensive experience in stem cells, tissue engineering, biomaterials, regenerative medicine and 3D models for drug testing for > 25 years. He was the first to demonstrate that stem cells exist in urine and that those cells (urine-derived stem cells, i.e. USCs), possess self-renewal and multipotent capacity and trophic effects. As a novel stem cell source, USCs provide paracrine factors and also give rise to different cell types for tissue repair. Furthermore, patient-specific renal stem cells can act as novel and non-invasive biomarkers of renal tumor, other kidney diseases and the aging related physical dysfunction. More recently, he and his team demonstrated that 3D renal organoids generated from USC or USC-generating iPSC (u-iPSC) might be used for renal disease modeling, drug screening and therapeutic application. Dr. Zhang has a productive record of 240 original peer-reviewed medical research and review articles. As a PI, Dr. Zhang led NIH-funded studies in the fields of 1) 3D in vitro models of urine derived stem cells for assessment of mitochondrial toxicity and nephrotoxicity (2020 R21 and 2021 R03); 2) Patient derived urinary stem cells as novel and non-invasive biomarkers for chronic kidney diseases (2018, NIH CKD Consortium); 3) Autologous stem cells for urinary incontinence (2014, NIH R56); and 4) Urinary tract tissue reconstruction with bone marrow stem cells (2006, NIH R21). Furthermore, Dr. Zhang have isolated, cultured and characterized stem cells from other body fluids, such as breast milk, amniotic fluid, joint synovial fluid and menstrual blood, for potential use in various tissue repair or disease diagnosis. He has specific training and expertise in bioinformatics analysis required for the clinical applications with a novel artificial intelligence (AI) technology to make accurate diagnosis, and identify the optimal timing and type of invasive intervention(s) to improve clinical outcomes.