Memphis Research Consortium

MEMPHIS INSTITUTE OF REGENERATIVE MEDICINE

2019 PROPOSAL

EXECUTIVE SUMMARY

The 20th century was a period of monumental change in medicine, with dramatic advances in our understanding of disease and the development of drugs and devices to treat those maladies. The 21st century is shaping up to be a time of dramatic advancement in regenerative medicine. The goal of regenerative medicine is not the treatment of symptoms; rather, it is to stop disease progression and restore fully functional healthy organs. All of us will face deterioration or loss of tissues and organs based on trauma, chronic injuries, or aging. Therefore, the development of methods to repair or replace these tissues and organs by means of regenerative medicine may well be the single most important driver for advancing medical care and economic development for decades to come.

The Memphis Institute of Regenerative Medicine (MIRM) has brought together the expertise of the **University of Tennessee Health Science Center (UTHSC)**, the **University of Memphis (UofM)**, **St. Jude Children's Research Hospital**, and industry leaders (Revotek and Medtronic) to perform basic, clinical, and translational research in the areas of stem cell biology, 3D bio-printing, and tissue engineering. The goal is to translate scientific discoveries into new organ repair and replacement therapies for people suffering from organ damage.

We have recruited a world leader in the production of 3D bioprinted blood vessels, Revotek USA, to Memphis where the company will produce blood vessels that will be utilized in the first FDA-approved human trials of stem cell derived bioprinted blood vessels. The blood vessels will be produced in the Plough Center for Sterile Drug Delivery Solutions at UTHSC and the human trials will be conducted via the Clinical Trials Network of Tennessee (CTN2) associated with hospitals statewide. These blood vessels must be shipped to their destination cold and within 48 hours for surgical implantation into humans, and Memphis is the perfect site for production with FedEx Corporation's worldwide headquarters and hub located in Memphis. Dr. Y. James Kang, CEO and Scientific Director of Revotek, has been recruited as a part-time faculty member at UTHSC along with his colleague Dr. Wenjing Zhang, who is full-time faculty. Dr. Kang is the Executive Director of MIRM with Dr. Gabor Tigyi (UTHSC Associate Vice Chancellor for Global Partnerships and Industry Relations) serving as Deputy Director.

A major current focus of the Memphis Research Consortium (MRC) is to build Memphis's research capacity for regenerative medicine. We are asking the State of Tennessee to invest $2.5 million to help launch MIRM. This state investment in the health of all Tennesseans will be matched by $2.5 million in contributions by our industry partners: Revotek USA, Medtronic, and FedEx. Our industry partner contributions include contracts for services, discounted shipping rates, in-kind donations of staff and expertise and philanthropic support.

The fast-growing segment of regenerative medicine will bring very substantial new federal and non-federal research grants to all three research institutions in Memphis over the next few years. Establishing this institute will encourage applied research investment by the region's medical device industry. Rather than a long recruitment process, our new institute starts immediately with faculty and staff, with national visibility and reputation. Lastly, rather than hoping for startups in the future, this program already brings a high potential early-phase, fully-capitalized startup company poised for growth, ready to hire employees in Memphis and across the state.

Consequently, the state's investment of funds will bring significant investment in ongoing research by federal agencies and private corporations, one of the goals of the MRC. We believe this program is a perfect example of what the MRC was established to do when it was conceived and supported by the state in 2011: Increasing collaborative research, attracting talent, driving jobs, and growing investment.

We appreciate the University of Tennessee Health Science Center's provision of $880,000 to initiate the Memphis Institute of Regenerative Medicine's research projects. These funds are being used to seed four working groups including: (1) Novel 3D Biofabrication Methodologies and Manufacturing for Enhanced Tissue Regeneration and Implantable Devices; (2) Cell Interactions with 3D Bioprinted Vessels – Basic and Translational Approaches; (3) Stem Cell-enhanced Tissue Regeneration: Engineering of Vascularized Bone/Cartilage Graft from Adipose-derived Stem Cells; and (4) Gene Editing of Hematopoietic and Cancer Stem-like Cells.

MIRM PARTICIPANTS AND INNOVATIVE PROJECTS

Project One: Novel 3D Biofabrication Methodologies and Manufacturing for Enhanced Tissue Regeneration and Implantable Devices

Project Leaders: Gary Bowlin (UofM) and Ebrahim Asadi (UofM)

Participants: UTHSC - Valeria Mas, Donald Thomason, Marko Radic; Univ. of Memphis – Amy Abell, Ebrahim Asadi, Gary Bowlin, Jessica Jennings, Ali Fatemi, Eugene Eckstein, Jasbir Dhaliwal, Joel Bumgardner, Ranganathan Gopalakrishnan, Tomoko Fujiwara, Yongmei Wang

Innovative Objective: This group aims to integrate state-of-the-art metallic, polymeric, and hybrid (combination of metal and polymer) additive manufacturing (AM) technologies with multi-disciplinary expertise that can contribute to establishing novel 3D biofabrication methodologies to create successful tissue regenerative platforms and devices. Initially, this group will pursue the following three lines of research with the aim of integrating them in the future years:

(1) Biofabrication of Implantable, Injectable, and Printable Hydrogels for Tissue Regeneration Scaffolds and Delivery Devices (Dr. Tomoko Fujiwara, Dr. Amber Jennings, Dr. Joel Bumgardner, and Dr. Yongmei Wang): We will design and produce two series of novel 3D-printed hydrogel scaffolds by biodegradable synthetic and natural polymers, with capabilities of (1) stimuli-responsive changes in shape and strength by pH, temperature, or external electrical fields; (2) controlled delivery of therapeutic molecules for tissue regeneration; and (3) support for cell growth and development into specific tissues such as bone and cartilage.

(2) Bioresorbable Polymer Nano-fiber Additive Manufacturing for Tissue Regeneration Templates and Medical Devices (Dr. Gary L. Bowlin, Dr. Ebrahim Asadi, Dr. Tomoko Fujiwara, and Marko Z. Radic (UTHSC): We expect to design and fabricate a novel, three-dimensional, near-field electrospinning system that will allow the precise production of fibrous three-dimensional structures in custom shapes replicating different tissues and organs. We will validate and verify the engineered, three-dimensional near-field electrospinning system using the development of a biomimicking artery (new vascular graft designs for bypass procedures) and liver lobule architecture (a liver building block for use in total liver regeneration) as the first prototypes.

(3) Additive Manufacturing of Magnesium-Based Biodegradable Orthopedic Devices for Guided Bone Regeneration (Dr. Ebrahim Asadi, Dr. Gary L. Bowlin, Dr. Amy Abell, Dr. Ranganathan Gopalakrishnan, and Dr. Ali Fatemi): We expect to develop an additive manufacturing process and standard practice based on powder-bed fusion direct metal laser sintering for fabrication of Magnesium alloys as well as an aerosol-based coating technology to control the degradation rate. For the first year,

we will focus on WE43 magnesium alloy (traditionally and additively manufactured) and hydroxyapatite for aerosol coating. The effectiveness of the process, alloy, and coating in the first year will be determined based on (1) mesenchymal stem cell viability and differentiation, (2) geometrical accuracy, (3) microhardness, (4) fatigue performance, and (5) degradation rate and innate immune system response.

Project Two: Cell Interactions with 3D Bioprinted Vessels - Basic and Translational Approaches

Project Leaders: Y. James Kang (UTHSC) and Wenjing Zhang (UTHSC)

Participants: UTHSC - Enkhe Purejav, Jeffrey Towbin, John Jeffries, Lu Lu, Mustafa K. Dabbous, Robert W. Williams, Umar Boston, Weikuan Gu, Wenjing Zhang, Y. James Kang, Steve Goodman; St. Jude - Stephen Gottschalk; Medtronic - Roger Harrington

Innovative Objective: Vascular diseases are responsible for heart attacks, strokes, and diabetic angiopathies that are affecting hundreds of thousands of patients in Tennessee. Replacement of blood vessels with a bypass graft is the main clinical strategy to treat such advanced vascular diseases. There are two resources of vascular grafts currently used in clinical practice, autologous veins/arteries and prosthetic vascular grafts; however, both have fatal defects such as unavailability or thrombosis and calcification. Moreover, the lack of growth and remodeling of the replacement conduits when used in treating congenital heart defects cause high morbidity and mortality in such patients. The technique of 3D bioprinting of blood vessels developed by Revotek (Dr. Y. James Kang, CEO) makes the regeneration of autogenous blood vessels possible, which would overcome all the drawbacks mentioned above. This technique has been succesfully used in monkeys and pigs, and is in the application process for FDA approval for the first human trial of stem cell derived bioprinted blood vessels in Memphis. With the progress in the translational aspect, it is urgent to develop a good animal model for understanding the underlying mechanisms, which will in turn improve the clinical application of this technolgoy. We thus carry out this study to specifically address the following aims:

(1)Develop Mouse Model of Vascular Implantation Using Stem Cell Derived 3D Bioprinted Blood Vessel: We will modify the bioink using adipose tissue-derived stem cells (ADSCs) from a mouse and modify the platform of the bioprinter to generate a small blood vessel graft with an inner diameter of less than 1mm. This stem cell vascular graft will be implanted into the same strain of mouse as an infra-renal aortic or interposition conduit. *In vivo* ultrasonography and microcomputed tomography will be used to evaluate graft patency and morphology before final histologic and immunohistochemical evaluation at different time points.

(2) Identify Critical Gene Variants that Cause Differences in Blood Vessel Regenerations Using a System Genetic Strategy: We hypothesize that there is natural genetic variation in ADSCs biology and in their regenerative capacity, and will test this in BXD mice. The BXDs are an immortal family of 154 genetically unique and fully sequenced strains of mice that can be replicated in large numbers in different laboratories and environments. The BXD family is the most completely studied mammalian population and is widely used to study gene-by-phenotype, gene-by-treatment, and gene-by-environment effects. In this work, we will isolate and propagate ADSCs from at least 30 BXD family members. Phenotypes such as their surface epitopes, rates of proliferation, differentiation potential as well as transcriptome profile will be assisted and collected. With the already acquired genotype and sequencing data for all BXD strains from GeneNetwork (Drs. RW Williams and L Lu), and bioinformatics tools, we will be able to identify gene variants related to ADSCs behavior. Next, we will select 4 to 6 strains based on the data generated above to produce ADSC derived 3D bioprinted vessels and implant these into animals of the same strain, sex, and age.

3) Define and Validate the Gene Variants That Control Regeneration Capacity Under Normal Condition: With data from Aim 2, genes related to regenerative variation will be identified. CRISPR/*Cas9* techniques will be used to validate gene functions. After modification of genes by CRISPR/*Cas9*, ADSCs will be used to produce 3D bioprinted vessel for implantation. The alterations of phenotypes will be determined as described in Aim 1 and through comparison with wild-type animals.

The results of this project will provide novel opportunities to deeply explore regenerative medicine and its interface with precision medicine. We would be able to generate data on the influence of different diseases such as diabetes, atherosclerosis, hypertension, and key cofactors such as aging, sex, and strains on blood vessel regeneration. This will provide critical and individualized guidance for the clinical application of the novel 3D bioprinting of stem cell vascular grafts in patients.

Project Three: Regenerative Strategies In Osteoarthritis Using Adipose-Derived Stem Cells

Project Leaders: Karen Hasty (UTHSC)

Participants: UTHSC - Edward Rosloniec, Hongsik Jake Cho, James Beaty, Fred Azar, Karen Hasty, L. James Kang, Wenjing Zhang, Raja Shekhar Gangaraju, Susan Miranda, Zhousheng Xiao, Rajendra Raghow, Min Pi, George Huang, David Brand, Tao Lu Lowe, Larry Reiter, John Stuart, Santos Martinez, Richard A. Smith, Anastasios Karydis; St. Jude – Paul Taylor

Innovative Objective: Osteoarthritis (OA) is a complex disease involving the breakdown of articular cartilage and subchondral bone. The long range goal of this group is to re-establish the functional integrity of the joint including the osteochondral interface. We will use adipose-derived stem cells (ADSC) from subcutaneous fat tissues for osteochondral repair in femoral knee defects of rats who have extensive, surgically-created chondral or osteochondral defects in the femur. ADSC will be enzymatically isolated and encapsulated using Revotek technology to create bioactive units (Biosynspheres) that can be transplanted directly in vivo with or without resuspension in collagen matrices modified to promote cell differentiation (**Brand, Lowe**). Our hypothesis is that Revotek technology will allow development of a bifunctional unit (cartilage/bone) as illustrated in Figure 1. The Biosynsphere technology combined with incorporation of chemical modifiers will provide cellular protection from the oxidative and toxic environment in the post-traumatic/osteoarthritic joint. Chondro-inductive or osteoinductive agents formulated for sustained release (**Lowe**) and/or protective free radical scavenging microparticles (**Hasty**) will be incorporated into Biosynspheres or the collagen matrices. For chondral replacement, we will use a micromass of encapsulated ADSC at a high cell density in a type II collagen matrix whereas for bone reconstruction we will use stem cells in a type I collagen matrix. Constructs will be implanted into the osteochondral defect. Osteogenic and chondrogenic constructs will be overlayed to create the bilayered tissue needed for reconstruction of an intact joint surface. An engineered chitosan scaffold (in collaboration with

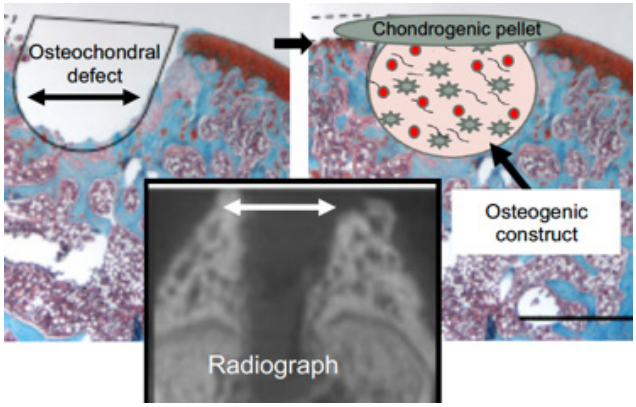


Fig 1. Osteochondral defect in knee reconstruction with bilayered construct; a chondrogenic pellet (type II collagen/Biosynspheres) overlay onto an osteogenic (type I collagen /Biosynsphere) construct.

MIRM Group 1 members, **Bumgardner, Jennings)** will be tested as an innovative interpositional barrier between the differentiating cartilagenous and subchondral osteogenic layers.

At various intervals after treatment, the rat femur will be evaluated (**Cho**) by optical imaging (IVIS) using near infrared-labeled monoclonal antibody to type II collagen (MabCII) for cartilage matrix regeneration or by X-ray (Lumina II XR) for regrowth of the subchondral bone. After healing for 4, 8 or 16 weeks, the joints will be harvested for analysis by histopathology (**Martinez**) and quantitative MicroCT (**Brand, Karydis**) analyses as endpoint read-outs. Histopathological scoring of cartilage regeneration and re-establishment of the calcified cartilage layer and its associated tidemark will be done to evaluate recovery of normal articular cartilage architecture and its relationship to the subchondral bone. In vivo double staining with calcein and tetracycline can give an accurate measurement of the mineral apposition rate (**Miranda**). For monitoring of the persistence of the ADSC in both chondral or osteochondral defects, cells will be labeled with near infrared fluorescent dyes for short-term studies (< 4weeks) or for long-term studies using ADSC isolated from GFP-transgenic donor rats. Biosynsphere/collagen constructs will be engineered with or without agents formulated as slow release compounds that stimulate proliferation and/or osteogenesis (eg. platelet derived growth factor-BB), platelet rich plasma, or chondrogenic differentiation (eg.scSOX9) included either in the matrix or within the encapsulated contents of the Biosynspheres. In some cases, the inductive agent will be targeted to the engineered chondrogenic construct after implantation into the chondral defect using intra-articular injections (**Stuart**) of MabCII-targeted liposomes loaded with inductive agents such as TGF beta3 or scSOX9 protein (in collaboration with VivoScript, Costa Mesa,

Project Four: Gene Editing of Hematopoietic and Cancer Stem-like Cells

Project Leaders: Mitchell J. Weiss (St. Jude) and Gabor Tigyi (UTHSC)

Participants: St. Jude - Mitch Weiss, Min-Joon Han; UTHSC – Gabor Tigyi, Neil Hayes, Zhaohui “Sunny” Wu, Junming Yue

Innovative Objective: The evolution of stem cell transplantation techniques and the discovery of genome-editing methodologies represent the two breakthroughs in life-science research of the 21st century. Our objective is to develop improved, clinically applicable, gene editing technologies and targeted delivery of small molecules to manipulate non-malignant and malignant stem cells. The initial focus of this project is to develop and validate new robust technologies, in preclinical models, for (1) the targeted delivery of the gene editing molecular machinery and (2) small molecules into different types of stem cells using unique nanotechnology platform(s). Stem cell-targeted delivery of molecular cargos is likely to have a major impact on translational research toward novel clinical therapies of hematopoietic diseases, malignancies, and beyond.

The specific aims of our proposed collaboration are:

(1) Develop new nanoparticle-based delivery methods for cargos including (1) gene editing molecular machinery and (2) small molecules into predefined subsets of non-malignant and malignant stem cells. Validate these new techniques *in vitro* using a battery of tests to ascertain the efficacy and specificity of the targeting and the functional efficacy of the delivered cargos.

(2) Obtain proof-of-principle for the efficacy and specificity of the new stem cell-targeted nanoparticle-based delivery methods in preclinical animal models predictive of human diseases.

Treatment of Hemoglobinopathies: Sickle cell disease (SCD) and β-thalassemia are common, debilitating anemias caused by mutations in the *HBB* (β-globin) gene. Genome editing of hematopoietic stem cells (HSCs) *via* Cas9 and related proteins can alleviate these disorders, either by correcting the pathological mutations or by introducing new mutations that de-repress fetal β-globin genes (*HBG1* and *HBG2*) in adult red blood cells to compensate for the loss of normal β-globin. Numerous laboratories, including St. Jude investigators, have demonstrated a proof-of-principle for these approaches. However, delivery of these gene editing molecular machineries has been quite challenging. To address this issue and facilitate rapid clinical translation of this approach, we will develop novel nanoparticle formulation using our patented delivery systems for the efficient and non-toxic delivery of genome editing machineries to HSCs.

Treatment of Cancer Stem-like Cells (CSCs): CSCs are the primary source of tumor initiation, metastasis, and therapy resistance. CSCs are resistant to most current cancer treatments, and play a major role in cancer relapse and metastasis after rounds of conventional chemo/radiation therapies. These treatments generally induce a selection of drug- and radiation-resistant CSCs, which are refractory to a broad spectrum of therapeutic agents. Targeting CSCs will effectively reduce cancer metastases and mitigate therapeutic resistance. However, current modalities are suboptimal for the treatment of this small but crucial cell population.

We are currently focusing on key mechanisms, such as ATX/LPA and Wnt/β-Catenin signaling, regulating CSCs self-renewal, differentiation, and the development of resistance to chemo and radiation therapy. We have identified two novel mechanisms induced in CSC in response to chemotherapeutics and radiation exposure. Novel drug candidate small molecule compounds targeting these pathways have been developed on our campus and shown promising efficacy in reversing the therapy resistance of CSCs.

We have also developed novel nanoparticle-based drug delivery methods suitable for targeting CSCs. Targeted delivery of these small molecule inhibitors into CSCs will provide a major improvement in the cancer treatment. The intellectual property portfolio of these methods and small molecules has been patented, thus enabling their industrial-level development for regulatory approval and for their use in clinical practice. One such set of anti-metastatic compounds has been recently licensed to a drug development company RxBio Inc., by the University of Tennessee Research Foundation for accelerated preclinical and clinical development and FDA regulatory approval. This Tennessee biotech company will work in collaboration with UTHSC investigators to accelerate the regulatory approval of these compounds that are under exclusive world-wide patent protection and generate new high-paying jobs in the state.

This research will provide evidence at a mechanistic level for the pharmacological reversal of CSC resistance to the current first-line taxane treatment via blockade of ATX. This evidence will be obtained using human xenograft and murine cancer metastasis models. This application will establish ATX as a novel anticancer drug target and ATX inhibitors as novel therapeutic adjuvants for the treatment of metastatic and therapy-resistant cancers.

INDUSTRIAL PARTNERS

Revotek

Regenerative therapies have the potential to revolutionize the practice of medicine. Industry, governments, and the general population are becoming aware of these innovative technologies, and view them as “disruptive game-changers” in the field of medicine.

Revotek is a vertically integrated 3D bio-printing company currently specializing in vascular structures for research and clinical applications. In December 2016 during a series of animal trials, Revotek became the first known company in the world to successfully print and implant 3D bioprinted blood vessels that were fully accepted into living hosts using bio-ink derived from each recipient’s own fat tissue. Revotek has been granted 14 patents to date with an additional 56 under review with new submissions added regularly as they continue developing their technology and methods.

As of January 2018, Revotek USA moved into the UTHSC Plough Center for Sterile Drug Delivery Solutions. Revotek USA is currently in discussions with the US FDA seeking approval to begin clinical trials for our 3D bio-grafts. These groundbreaking clinical trials will be conducted via the Clinical Trials Network of Tennessee (CTN2).

Medtronic

The first goal of the Medtronic Mission Statement is, “To contribute to human welfare by application of biomedical engineering in the research, design, manufacture, and sale of instruments or appliances that alleviate pain, restore health, and extend life.” One of their major approaches to reach this goal involves 3D Bioprinting and Tissue Regeneration. In FY18, Medtronic invested $2.3 billion in research and development, launched 72 new clinical studies, completed 81 clinical studies, and had 320 ongoing clinical studies accounted for. Their products and therapies improve the lives of two people every second.

Medtronic has four operating segments: Cardiac and Vascular, Minimally Invasive Therapies, Restorative Therapies, and Diabetes. Each group is separated into business divisions that deliver a wide range of medical technologies, therapies, services and solutions.

With their Spinal Division located in Memphis, Medtronic has been involved with the Memphis Institute of Regenerative Medicine since its inception. Roger Harrington, former Senior Director of Biologics R&D at Medtronic, is a Member of MIRM and, along with Dr. Steven Goodman, Vice Chancellor for Research at UTHSC, was a central contributor to the creation of the Institute. Roger is a participant in the blood vessel MIRM Group 2.

FedEx Corporation

When most living creatures are taken out of their natural environment the amount of time and stressors of being away can mean the difference between life and death. The same is true with Revotek’s 3D bioprinted blood vessels and tissues. When Revotek representatives visited Memphis in 2017, they were looking for Revotek USA’s future US headquarters. They needed a city that could support their research, education, commercialization, and business development as well as one that could quickly transport biological materials as sensitive as 3D bioprinted blood vessels and tissues.

Headquartered in Memphis, FedEx Corp. has been enlisted as the carrier for transporting the 3D bioprinted blood vessels and tissues to patients worldwide. FedEx's networks reach more than 220 countries and territories, linking more than 99 percent of the world's GDP. Selecting FedEx as a partner was key in terms of the importance of being able to transfer these 3D bioprinted blood vessels and tissues quickly for medical use. Ongoing conversations between the MIRM and FedEx leadership teams have focused on shipping and testing various shipment methods to ensure the 3D bioprinted blood vessels produced will survive the shipment process. The shipping will include far more than the blood vessels, as other MIRM researchers will have their own shipping needs. Further, we anticipate the current and future MIRM membership (65 members and constantly growing) to produce substantial new intellectual property and resulting spin-off companies which will require shipping through our FedEx industry partner.

ECONOMIC AND WORKFORCE DEVELOPMENT

The global stem cell market size is projected to reach USD 160 billion by 2021, at a compound annual growth rate (CAGR) of 19.8%. The current global stem cell market size and projection are based on the following stem cell applications: regenerative medicine in neurology, orthopedics, oncology, hematology, cardiovascular disease, myocardial infarction, diabetes, liver disorder, etc.

Governments are working with the scientific community to eliminate hurdles to realize the enormous potential these applications bring to patients, providers, and the general economy. All of the Memphis Institute of Regenerative Medicine's projects will result in an extensive patent portfolio, leading to numerous new business start-ups and/or technologies licensed to existing companies. These existing companies will include Revotek USA, Medtronic, and other bio-companies in Memphis as well as FedEx.

According to Dr. Y. James Kang, "If we simply consider that our new technology can only take 3-5% of the current market share every year starting from 2020, it can arrive at $5-8 billion a year in regenerative medicine, and $30-45 billion a year in the cardiovascular disease market. Again, this is only based upon current markets, not projected on newly open markets in the future. On job opportunities, it can be easily projected that there will be 300-500 new high-tech jobs added to Memphis every year, reaching 3,000-5,000 new jobs in 10 years."

The Memphis Research Consortium is making a $2.5 million request to the State of Tennessee to fund the Memphis Institute of Regenerative Medicine's current research projects. This will allow the Memphis Institute of Regenerative Medicine's members to obtain the preliminary data required to apply for federal grant opportunities to further support our basic, clinical, and translational research.

Aging and other related diseases are problems we all have to face. With state and federal support of regenerative medicine research and manufacturing, Tennessee will join many other states that have jump-started their regenerative medicine-based industries.

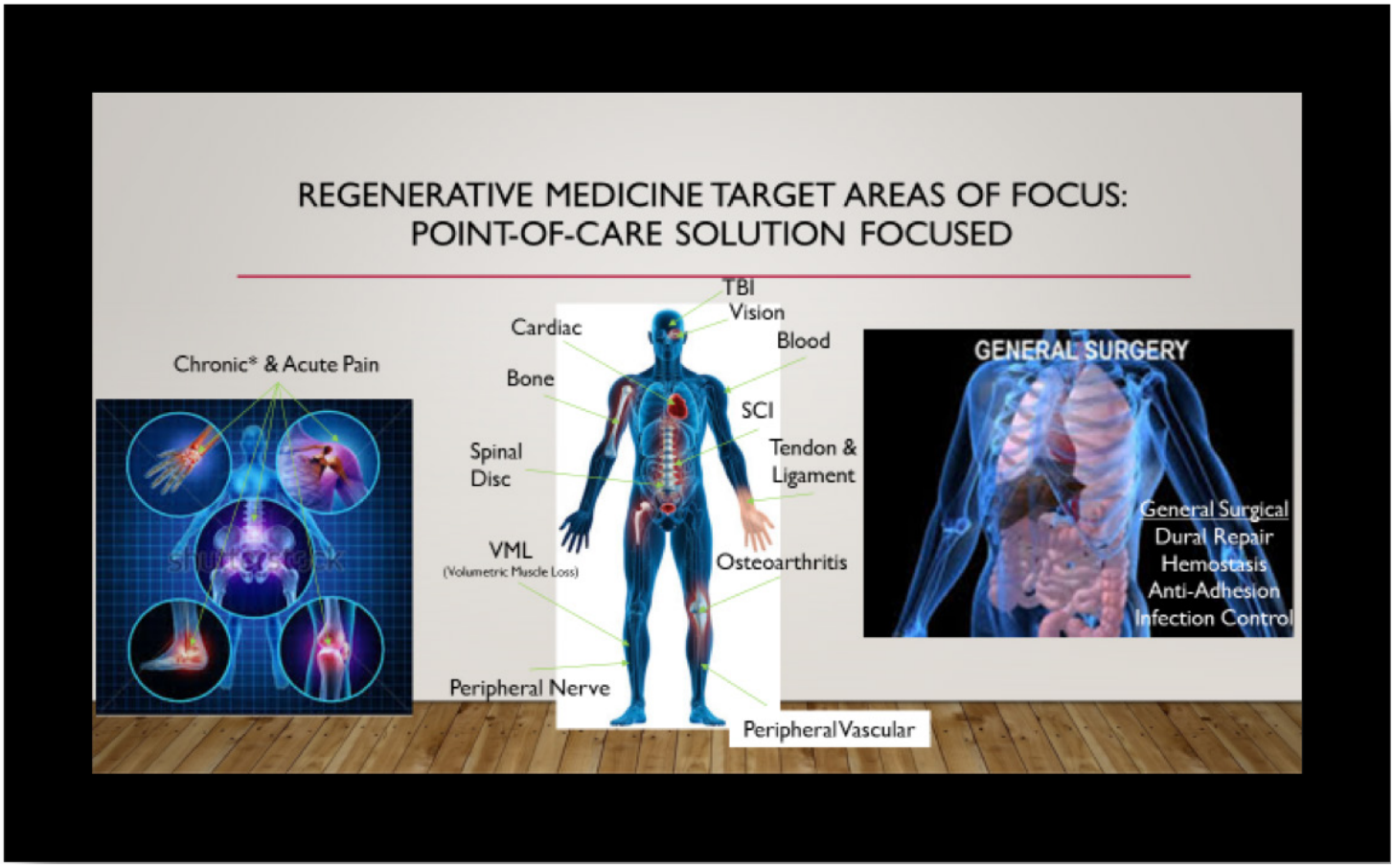
"This is a completely new paradigm for healthcare, we will be changing the world."

- Dr. Y. James Kang

As described above, this exponentially growing regenerative medicine industry will require a highly trained work force. The University of Memphis will develop a graduate certificate program in Additive Manufacturing Technology. This program will also be packaged and offered as an intensive institute

for the region's practicing engineers and scientists. The UofM and UTHSC's joint BME program already offers graduate courses in tissue engineering, biomaterials, and advanced biomaterials. Furthermore, UTHSC and Revotek are collaborating on graduate courses on 3D bio-printing, and tissue and organ production.

These workforce development efforts will play a large role in providing the estimated additional 2,075 graduate degree-holding workers per year required to meet the projected demand in Tennessee by year 2022, with an economic benefit to the State of $3.3B over these Tennessee citizens' careers (Tennessee Conference of Graduate Schools*, Tennessee Graduate Schools: Building the Workforce for the Future*, 2017).



PROPOSED BUDGET

PROJECT	YEAR 1
Project 1: Novel 3D Biofabrication Methodologies and Manufacturing for Enhanced Tissue Regeneration and Implantable Devices	$500,000
Project 2: Cell Interactions with 3D Bioprinted Vessels – Basic and Translational Approaches	$500,000
Project 3: Engineering of Vascularized Bone/ Cartilage Graft from Adipose Tissue Derived Stem Cells	$500,000
Project 4: Gene Editing of Hematopoietic and Cancer Stem-like Cells	$500,000
Competitive Pilot Project Funds, Equipment, and Operational Support	$500,000
Annual Total	**$2,500,000**

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