MRC PROPOSAL: THE MEMPHIS INSTITUTE OF REGENERATIVE MEDICINE

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, the aim of regenerative therapies is to stop disease progression and restore fully functional healthy tissue. All of us will face deterioration of our organs and tissues based on disease, damage or normal aging. Therefore, the development of methods to repair or replace these organs and tissues via regenerative medicine will be the single most important driver for advancing medical care and economic development for decades to come.

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

We have recruited the world leader in production of 3D bioprinted blood vessels, Revotek International, to Memphis where they will produce blood vessels that will be utilized in the coming months for 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 at UTHSC and the human trials will be conducted via the Clinical Trials Network of Tennessee (CTN2) at UTHSC associated hospitals statewide. As these blood vessels must be shipped to their destination cold and within 24 hours for surgical implantation into humans, we were the perfect site for production with the FedEx hub located within Memphis. Dr. 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 will be full time faculty. Dr. Kang will be the Director of MIRM with Associate Directors leading each site.

MRC is focused on building Memphis's research and we are asking the state to invest $10 million over four years in this unique opportunity. The fast growing segment of Regenerative Medicine will bring additional academic research at all three research entities in Memphis over the next few years. Establishing this institute will encourage applied research investment by the regions' 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 MRC. We believe that this program is a perfect example of what MRC set out to do when it was conceived and supported by the state in 2011: increasing collaborative research, attracting talent, driving jobs and growing investment.

Planned MIRM Innovative Activities

The MIRM projects, for which we are requesting support from the State of Tennessee, are based on collaborations utilizing the synergistic expertise of scientists performing stem cell biology, 3D bioprinting, tissue engineering and additive manufacturing. They are Project (1) **Promoting organ regeneration using 3D-bioprinted vessels** – led by **Dr. James Kang & Dr. Wenjing Zhang**. Vascular repair is the key to trigger and support the regeneration of any failing organ. The technique of 3D bioprinting of blood vessels developed by Revotek (Dr. James Kang, CEO) makes the regeneration of damaged vascular tissue in organ systems possible. Obstructive vascular diseases are responsible for heart attacks, strokes and diabetic angiopathies that effect hundreds of thousands in Tennessee and are the prime candidates for receiving 3D bioprinted vessels. Dr. Kang's team will focus on developing novel approaches to adapt the 3D bioprinting of vessels to multiple failing organs, including heart, kidney, lung, liver, bone, and brain. Research is ongoing for 3D bioprinting of organs, including the liver and the heart.

2) **Modelling of pediatric genetic blood diseases via induced pluripotent stem cells**- led by **Dr. Mitch Weiss. & Dr. Min-Joon Han**. Studies to understand and treat blood diseases are frequently held back by limited availability of diseased tissues, particularly in pediatrics where ethical considerations and small patient size limits tissue procurement. Development of patient-derived induced pluripotent stem cells (iPSCs) can circumvent this problem. Induced pluripotent stem cells can be easily generated from small numbers of patient blood or skin cells, expanded in tissue culture and manipulated to differentiate into mature tissues of interest, including blood cells. Directed in vitro differentiation of patient-derived iPSCs into relevant tissues often recapitulates disease pathologies. Cells generated in this fashion can then be used to study disease mechanisms and new therapies. We have used patient iPSCs to study pediatric leukemias and bone marrow failure syndromes caused by genetic mutations. Now, we are seeking support to expand these efforts so that we can generate new tools to better understand and treat patients with blood disorders.

3) **Innovative approaches to cancer stem cell (CSCs) and cancer initiating cells (CICs)-targeted therapy** – led by **Dr. Sunny Wu & Dr. Gabor Tigyi**. Cancer stem cells (CSC) and **cancer initiating cells (CICs)** are the major source of tumor initiation and metastasis. CSCs/CICs are typically resistant to most current cancer treatments, and play a major role in cancer relapse after rounds of therapies. Cancer treatment induces a selection of drug resistant CSCs/CICs. Targeting these cells will effectively reduce cancer metastases and mitigate therapeutic resistance. Current research programs at UTHSC laboratories are focusing on key mechanisms regulating cancer stem cells self-renewal and differentiation. Novel compounds targeting these pathways, such as autotaxin inhibitors, have been developed at UTHSC and have shown promising CSCs/CICs-targeting efficacy.

4) **Restoration of function in neuro-ophthalmic diseases with stem cell therapy** – led by **Dr. Shekhar Gangaraju & Dr. George Huang**. Neuro-ophthalmological disorders are life threatening or debilitating diseases. Adult stem cells obtained from patient's discarded tissues could be used to cure these conditions. Current research programs at UTHSC laboratories have been focusing either on reprogramming these adult stem cells to become neuron-like cells having neuron functions or to produce proteins that aid in the regeneration of damaged neurovascular tissues. Neurodegenerative experimental models have shown promise that warrants future studies aimed at preparing these stem cells with consistent potency and efficacy in their functional performance leading to eventual clinical applications.

5) **Engineering of Vascularized Bone from Adipose Tissue Derived Stem Cells** – led by **Dr. Raj Raghow & Dr. Darryl Quarles**. The development of bone graft substitutes to treat skeletal fractures and disunions, and to replace and regenerate lost bone (e.g. osteonecrosis) in aging Tennesseans is an unmet clinical need. In spite of advances in improving the efficacy of bone grafts by incorporating bone progenitor cells and osteogenic growth factors, creating a synthetic bone graft that is structurally and functionally comparable to natural bone has yet to be accomplished. Advances in biomedical hydrogels and novel mechanomimetic drugs to promote stem cell transformation into bone forming cells, combined with ability to generate blood vessels *ex vivo*, may be exploited to create autologous "vascularized" synthetic bone grafts. This project has twin goals (1) to engineer a Synthetic Vascularized Bone Graft and to test it in a pre-clinical model of femoral head osteonecrosis, and (2) to spur clinical application and commercialization of this technology.

6) **Biofabrication of Implantable, Injectable, and Printable Hydrogels for Tissue Regeneration Scaffolds and Delivery Devices**- led by **Dr. Tomoko Fujiwara, Dr. Amber Jennings, Dr. Joel Bumgardner & Dr. Yongmei Wang**. Biomedical hydrogels are biocompatible and biodegradable, and possess mechanical properties that allow their tailoring to produce a controllable range of physical properties and to support a range of medical diagnostic and therapeutic functions and devices. Here, we proposed to develop implantable, injectable, or 3D-printable polymeric hydrogels along with their physical and chemical formulations for specific applications for smart drug delivery systems. Development of novel hydrogels with tunable properties for bioprinting will allow us to mimic morphology of tissues for engineered regenerative implant materials, responsive to industry interests in producing next generation, personalized biomedical devices.

7) **Bioresorbable Polymer Nano-fiber Additive Manufacturing for Tissue Regeneration Templates and Medical Devices**- led by **Dr. Gary L. Bowlin, Dr. Ebrahim Asadi & Dr. Tomoko Fujiwara**. Realizing the promise of regenerative medicine requires production of medical devices, coatings, and/or tissue regeneration templates that mimic the intricate architecture of our tissues and organs with high specificity. To achieve this type of advancement in nanoscale material processing, we will develop a novel

three-dimensional, near-field electrospinning technology that will allow for the precise production of fibrous three-dimensional structures in custom shapes. Initially, we will process biodegradable polymers that mimic the native vascular architecture to develop novel bioresorbable vascular grafts capable of endogenous regeneration. This significant advance in technology will make Memphis a world-leader in polymeric nano-fiber additive manufacturing for biomedical applications. Importantly, once developed, this technology has high applicability and demand in other fields, such as miniature electronic components, flexible devices/sensors, and energy harvesting.

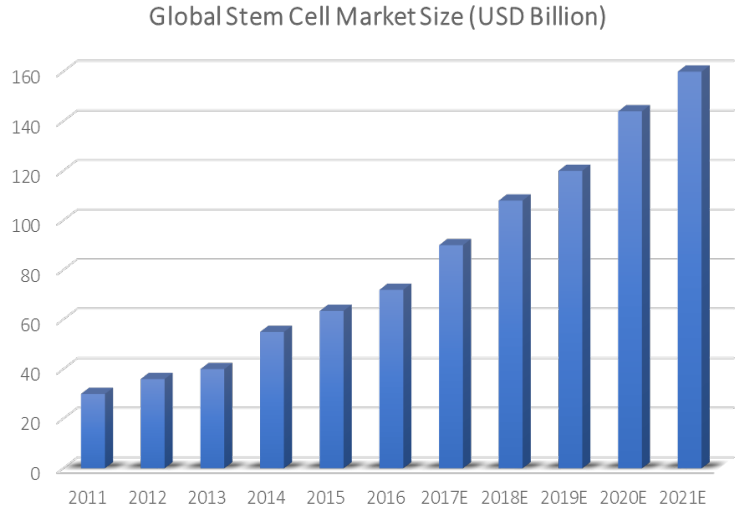
8) **Additive Manufacturing of Magnesium-Based Biodegradable Orthopedic Devices for Guided Bone Regeneration**-led by **Dr. Ebrahim Asadi, Dr. Gary L. Bowlin, Dr. Amy Abell & Dr. Ranganathan Gopalakrishnan**. Next generation devices for bone disease treatments must be manufactured to match the anatomy of a specific patient, integrate proper scaffold structure into the device to allow guided bone regeneration, possess bone-like mechanical properties to avoid abnormal bone density developments, and biodegrade to eliminate risk of body rejection and secondary revision surgeries. Tapping the largely unexplored potential of magnesium, this research will employ novel additive manufacturing technology that, when combined with patient-specific CT-scans will allow fabrication of patient-specific magnesium devices and offer a platform for other relevant applications such as fabrication of biodegradable vascular stents. In addition, aerosol-base printing technology will be developed to allow for custom release of therapeutic agents printed or coated on the devices.

While listed as individual, highly interdisciplinary projects, it should be noted that numerous synergistic, cross-project collaborations will also be developed as a direct result of the initial projects leading to further innovations, medical advancements, intellectual property, and economic development.

Economic Development

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. Governments are working with the scientific community to eliminate hurdles to realize the enormous potential these products bring to patients, providers, and the general economy. All of the projects above will result in an extensive patent portfolio, leading to numerous new business startups and/or technologies licensed to existing companies. These existing companies will include Revotek USA, Medtronic and other bio-companies in Memphis. FedEx will be the carrier for transporting the 3D bioprinted organs and tissues to patients worldwide.

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 infraction, diabetes, liver disorder, etc.



Sourc: GBI Research <<Stem Cell Research Market to 2017-GBI Research 2011>>;Mordor Intelligence <<Stem Cell Market - Growth, Trends and Forecasts (2017-2022).

Revotek USA will be located at UTHSC’s Plough Center by January 2018. According to Revotek CEO, Dr. James Kang, “If we simply consider 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 3000-5000 new jobs in 10 years.”

Workforce Development

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 UM and UTHSC 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 bioprinting, 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 citizen’s careers (Tennessee Conference of Graduate Schools, *Tennessee Graduate Schools: Building the Workforce for the Future*, 2017).

With state support of regenerative medicine research and manufacture, Tennessee will join many other States that have jump-started their regenerative medicine-based industries.

Budget

Budgets appear in the order that the projects appear in the preceding narrative.

PROJECT	YEAR 1	YEAR 2	YEAR 3	Year 4	Project Total
Project 1: Promoting organ regeneration using 3D-bioprinted vessels	250,000	250,000	250,000	250,000	1,000,000
Project 2: Modelling of pediatric genetic blood diseases via induced pluripotent stem cells	500,000	500,000	500,000	500,000	2,000,000
Project 3: Innovative approaches to cancer stem cell (CSCs) and cancer initiating cells (CICs)-targeted therapy	250,000	250,000	250,000	250,000	1,000,000
Project 4: Restoration of function in neuro-ophthalmic diseases with stem cell therapy	250,000	250,000	250,000	250,000	1,000,000
Project 5: Engineering of Vascularized Bone from Adipose Tissue Derived Stem Cells	250,000	250,000	250,000	250,000	1,000,000
Project 6: Biofabrication of Implantable, Injectable, and Printable Hydrogels for Tissue Regeneration Scaffolds and Delivery Devices	300,000	300,000	300,000	300,000	1,200,000
Project 7: Bioresorbable Polymer Nano-fiber Additive Manufacturing for Tissue Regeneration Templates and Medical Devices	300,000	300,000	300,000	300,000	1,200,000
Project 8: Additive Manufacturing of Magnesium-Based Biodegradable Orthopedic Devices for Guided Bone Regeneration	400,000	400,000	400,000	400,000	1,600,000
Annual Total	$2,500,000	$2,500,000	$2,500,000	$2,500,000	$10,000,000