Midwest Stem Cell Therapy Center

Annual Report

Legislative Update

Senate Ways and Means Committee / Senate Public Health and Welfare Committee
House Appropriations Committee / House Health and Human Services Committee
March 28, 2018

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and the MSCTC team members

I. OVERVIEW

Over the past decade, adult stem cell transplantation has emerged as an effective therapeutic option for organ repair. Emerging evidence from numerous scientific reports, both from animal models and human studies, supports the notion that adult stem cells are able to heal damaged tissues and restore function. These adult stem cells from bone marrow, umbilical cord blood, and other sources have the potential to cure diseases for which no effective treatment is available at this time. Indeed, growing scientific evidence supports the efficacy of adult stem cell therapy for diverse pathological conditions, including heart attacks, stroke, spinal cord injury, and many others. However, there was no comprehensive center or program in Kansas or in the surrounding region until a senate bill (No. 199) was passed by the Kansas Legislature to enable the establishment of Midwest Stem Cell Therapy Center (MSCTC) in July 2013.

II. GOALS

The goals of MSCTC are broad:

- Focus on activities that advance adult, cord blood and related stem cell and non-embryonic stem cell research and therapies for patient treatment;
- Serve as a core facility to produce clinical grade stem cells from adult tissues, cord blood and related materials for use in clinical trials and therapies;
- Facilitate the delivery of adult, cord blood and related stem cell therapies to Kansas City and Midwest region hospitals where appropriate;
- Partner and collaborate with the blood and marrow transplant center of Kansas to foster a regional network of physicians trained in adult, cord blood and related stem cell therapy applications;
- Create and maintain a database resource for physicians and patients that provides a comprehensive global list of available stem cell clinical trials and therapies;
- Initiate clinical trials with adult, cord blood and related stem cells;
- Create education modules to train and educate physicians and research scientists about peer-reviewed adult, cord blood and related stem cell therapy applications for patients;

- Distribute information to Kansas physicians about methods for successful treatments with adult, cord blood and related stem cells through basic and clinical research;
- Inform the public on available adult, cord blood and related stem cell therapeutic options.

To assure that each of the goals is accomplished and that the Midwest Stem Cell Therapy Center reaches the expectations of the Kansas Legislature, a broad and multi-faceted approach has been developed as outlined below.

III. COMPONENTS AND PROGRESS REPORT

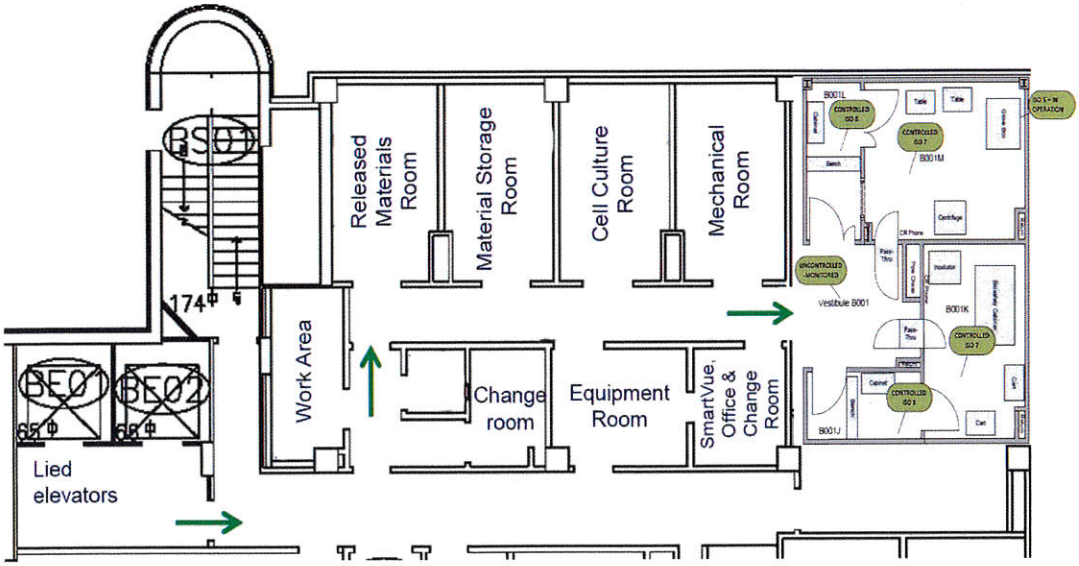
A. ADVISORY BOARD

- A 15-member Advisory Board representing various stake-holders has been assembled with periodic reappointment or replacement of individual members at intervals specified in the bill.
  - Information related to individual members is available at www.kumc.edu/msctc.
- The Board meets Quarterly and, as necessary, to assure continued MSCTC progress
  - The next meeting is scheduled on June 7, 2018.

B. SCIENTIFIC AND ADMINISTRATIVE PERSONNEL

1. Center Director: Recruited
2. GMP Manager: Open
3. GMP consultant: Recruited
4. Financial assistant (part-time): Recruited
5. Research Associate, Production: Recruited
6. Quality Control Supervisor (part-time): Recruited
7. Quality Assurance Supervisor: Recruited
8. Research Scientist (25% effort): Recruited

C. FACILITY FOR CLINICAL GRADE CELL PROCESSING/MANUFACTURING



Over the past year, the space allocated for MSCTC within KU Medical Center has decreased from approximately 8200 ft^2 of space (including office [1260 ft^2], laboratories [5100 ft^2] and GMP manufacturing [1000 ft^2] areas) to approximately 3680 ft^2 of space (including office [1150 ft^2], laboratories [1115 ft^2] and GMP manufacturing [1000 ft^2] areas). The space is utilized for R&D related to cell isolation and expansion, process development, analytical methods development, quality control testing and clinical grade manufacturing. The reduction in laboratory space limits the basic research and early developmental research plans due to the need to segregate certain functions from a regulatory standpoint. The manufacturing area is an FDA registered facility and is designed and operates to meet FDA compliance and environmental quality requirements as outlined in the Good Manufacturing Practice (GMP) and Good Tissue Practices (GTP) guidelines.

'Good Manufacturing Practice' guidelines define the quality standards for the production and testing of medicinal products, medical devices, and other pharmaceutical products as required by the Food and Drug Administration (FDA). In addition to GMP requirements, the 'Good Tissue Practice' guidelines define the requirements that govern the methods used in, and the facilities and controls used for, the manufacture of Human Cell Therapy and Gene Therapy Products in a way that prevents the introduction, transmission, or spread of communicable diseases by these products. The concepts underlying all of these guidelines are directed at the ultimate goal of safeguarding the health of the patient. GMP/GTP guidelines cover quality and safety standards in all aspects of the manufacturing process, including the infrastructure, buildings, equipment, personnel training, ingredients, the manufacturing process, and quality control process. Having a fully functional GMP/GTP facility and the supporting infrastructure is a necessary aspect of processing and manufacturing clinical grade cellular products.

MSCTC's FDA registered GMP facility (FEI# 3011110834):

- Adheres to GMP and GTP regulations
- Follows appropriate Standard Operating Procedures relevant for the characterization and manufacturing processes required to assure the availability of consistent adult stem cells
- Maintains the highest standards of Quality Control (QC) and Quality Assurance (QA)
- Educates and trains all relevant personnel
- Serves current MSCTC efforts well with capacity for up to 6 batches of adult stem cells per week if staffed and equipped to address volume

Location: Lower level of Lied building within the KUMC campus

Services being offered:

- Processing adult stem cells for the purpose of therapeutic transplantation in patients
  - Source of adult stem cells include bone marrow, the Wharton's Jelly fraction of human umbilical cord and cells provided by industry sponsors
  - Developing cell culture and cell expansion processes as well as characterization methodology suitable for specific therapeutic purposes

D. Training and Education Initiatives

- **Components**
  - Midwest Conference on Cell Therapy and Regenerative Medicine
    - Disseminating knowledge related to the use of adult stem cells in human clinical trials
    - Educating scientists on the latest research techniques and development requirements
    - Informing the public about the latest adult stem cell treatment options
    - Train students and postdoctoral fellows in stem cell research and related techniques
  - Seminars and Local School Outreach, Grand Rounds and Seminars
    - Inform the public, scientists, and clinicians about available and developing adult stem cell treatments – through web portals and global resources: database of available treatments and clinical trials, publication of stem cell "consumer reports" and 1:1 conversations with those enquiring about stem cells
    - Professional and public forums similar to town hall or similar meetings
    - Elementary and secondary school science and health introduction to adult stem cells and their applications
- **Accomplishments:**
  - Five successful conferences on adult stem cell therapy with the 5th Annual Midwest Conference on Cell Therapy and Regenerative Medicine was held on September 15-16, 2017
    - 38 speakers and panelists and approximately 130 attendees
    - Monsignor Tomasz Trafny, Head of Science and Faith department in the Pontifical Council for Culture at The Vatican, gave a Keynote Address
  - The MSCTC website provides extensive and disease-specific information on adult stem cell therapy, both preclinical and human studies.
    - Numerous original and review articles are freely accessible to the public
  - A total of six students have thus far gained first-hand, meaningful scientific experience in adult stem cell research and therapy. They include 4 Medical Students (KU School of Medicine), one undergraduate student from the Ohio State University, and one high school student from New York, NY.
  - The MSCTC is now tied into ClinicalTrials.gov, NIH/FDA database for global clinical trials
    - Provides immediate access to the most current clinical trial information on a global basis
    - Defined searches in the most sought after areas of stem cell therapy available
- **Plans:**
  - The 6thMidwest Conference on Cell Therapy and Regenerative Medicine (Sep 14-15, 2018) will be held at the Sheraton Overland Park hotel in Kansas

- Post regular unbiased commentaries on articles published on stem cell therapy in scientific journals as well as lay media
- Update the MSCTC Facebook webpage with trending scientific information regarding adult stem cell therapy

E. Clinical Trials and Therapy

- **Accomplishments**
  - Completed follow-up phase of PreSERVE AMI trial that tested autologous bone marrow CD34+ cell therapy in patients with reduced cardiac function following ST-Elevation Myocardial Infarction (STEMI)
    - Randomized, double-blind, placebo-controlled Phase 2 trial in patients with reduced cardiac function after ST-Elevation Myocardial Infarction (STEMI) (heart attack)
    - Multicenter clinical trial sponsored by Amorcyte (Neostem)
    - Enrollment and long-term follow-up completed. Study closed.
  - **Completed and closed the ALLSTAR clinical study (sponsored by Capricor, Inc.)**
    - **Intracoronary injection of cardiac stem cells in patients with heart attacks**
  - **Completed and closed the ACTIsSIMA clinical trial (sponsored by San Bio)**
    - **Injection of modified adult bone marrow stem cells (SB623) into brains of patients with chronic motor deficit resulting from ischemic stroke**
  - **Completed pre-clinical studies and filed an Investigational New Drug application (IND) with the Food and Drug Administration (FDA) related to treatment of Graft vs Host Disease with MSCTC-0010, the first adult stem cell product developed within the Midwest Stem Cell Therapy Center**
  - Continuing to collaborate with a California company to recover and bank adult stem cells under a 20-year contract
    - Revenue continues to be realized
  - Completed development of the MSCTC strategic plan with the help of the KUMC Organizational Improvement Office (OIO). The plan is comprehensive and relates to all aspects of the center's operation, with special focus on supporting our clinical trials and therapeutic efforts.
    - The strategic plan is currently being implemented
- **Plans:**
  - Address FDA questions related to the IND submission and gain approval to open the Phase I human clinical study
  - Continue to identify and collaborate with internal research laboratories who are identifying possible disease specific adult stem cell applications
  - Foster collaborations with external Midwest Universities, Centers and Institutions to bring opportunities identified at these institutions to fruition

- Continue to identify and establish external opportunities to utilize the MSCTC core skills in the evaluation of adult stem cell applications to improve human health
- Future initiatives will include:
  - Establish cryopreserved batches of bone marrow, Wharton's Jelly and adipose tissue MSCs as well as induced-pluripotent stem cells for evaluation in multiple diseases
  - Expansion and transplantation of hematopoietic adult stem cells

F. Regulatory

The MSCTC continues to maintain translational and regulatory efforts focused on the requirements for R&D that occur during discovery, proof of concept and pre-clinical evaluation and culminates in the submission of a New Drug Application (NDA) to the FDA requesting marketing approval.

- **Accomplishments**
  - GMP/GTP Facilities registration for the following:
    - Expanded GMP/GTP facilities registration for various stem cell sources including
      - bone marrow
      - umbilical cord
      - umbilical cord blood
      - adipose tissue
      - induced Pluripotent Stem Cells
      - Gene-editing activities within the facilities
  - Developing Wharton's Jelly MSC-specific IND for the treatment of GvHD
  - Completed all preclinical studies required for the IND application. The IND application has been filed awaiting approval for the Phase I human clinical study
- **Plans:**
  - Address FDA questions related to the MSCTC-0010 IND and initiate human clinical trials for GvHD

G. Basic Research Program

- **Core group of stem cell researchers**
  - Basic scientists/Translational researchers
    - Buddhadeb Dawn, M.D.
    - Neil Dunavin, M.D.
    - Hartmut Jaeschke, Ph.D.
    - Rajasingh Johnson, Ph.D.
    - Joseph McGuirk, M.D.
    - Hiroshi Nishimune, Ph.D.
    - Doug Myers, M.D.
    - Deryl Troyer, Ph.D.
    - Mark Weiss, Ph.D.

- Ben Woolbright, Ph.D.
- Yu-Ting Xuan, Ph.D.

- Clinician researchers
  - Kamal Gupta, M.D.
  - Clay Quint, M.D.
  - Sunil Abhyankar, M.D.
  - Sid Ganguly, M.D.
  - Richard Barohn, M.D.
  - Mazen Dimachkie, M.D.
  - Mark Wiley, M.D.
  - Randall Genton, M.D.
  - Ashwini Mehta, M.D.
  - Matt Earnest, M.D.
  - Peter Tadros, M.D.
  - Louis Wetzel, M.D.
- Need to continue to recruit additional scientists and clinicians from other specialties
  - Postdoctoral fellows and Research Associates

- **Accomplishments**
  - Amyotrophic Lateral Sclerosis (ALS/Lou Gehrig's Disease)
    - Collaboration with KUMC Neurology Department researchers (Drs. Nishimune, Barohn)
    - Studies continue to progress well with positive results
  - Liver failure
    - Collaboration with KUMC Pharmacology, Toxicology & Therapeutics (Drs. Jaeschke)
    - Further research being conducted to better define mechanism
    - Pre-IND discussions underway
  - Cardiovascular
    - Collaboration with investigators within KU Cardiovascular Research Institute
    - Studies in MI Mouse models to be initiated
  - Repair of spinal cord
    - MSCTC demonstrated the generation of two types of neurons from Wharton's Jelly MSCs
    - Next steps awaiting funding
  - Stroke and Traumatic Brain Injury
    - MSCTC demonstrated the generation of two types of neurons from WJMSCs
    - Initial studies awaiting funding
  - Cartilage Repair
    - MSCTC studies have proven the potential of WJMSCs to differentiate into chondrocytes
    - Next steps defined and awaiting funding

- **Plans**:
  - **Complete proof of principle studies in mouse models of ALS and initiate pre-IND effort**
  - **Conduct an informal discussion on the development of adult stem cells in the treatment of acetaminophen-induced liver injury leading to human clinical trials with the FDA**
  - Examine the potential of adult stem cell therapy for other liver diseases
  - Evaluate the potential of umbilical cord MSCs for heart repair following a heart attack
  - **Explore adult stem cell therapy for Traumatic Brain Injury when funding is available**
  - Explore adult stem cell therapy for cartilage repair when funding is available

H. COMMUNICATION AND MARKETING

Communication and Marketing efforts within the MSCTC are focused on building a brand and increasing awareness of the Center. Focus during FY17 and the first half of FY18 has been to secure donations through individual donors, groups and disease specific societies, and establishing awareness of the capabilities of the MSCTC with companies conducting basic research and clinical trials to drive third party manufacturing. Long-term, this function continues to be expected to help drive awareness and growth of the MSCTC nationally and internationally through the identification of communication channels that take advantage of current technology, continuously disseminating information related to the status, achievement of objectives and competitive advantage of the MSCTC. Additionally, we will continue to work with KU Endowment and KUMC Senior Leadership to connect with donors interested in supporting the MSCTC and continuing to build the MSCTC brand.

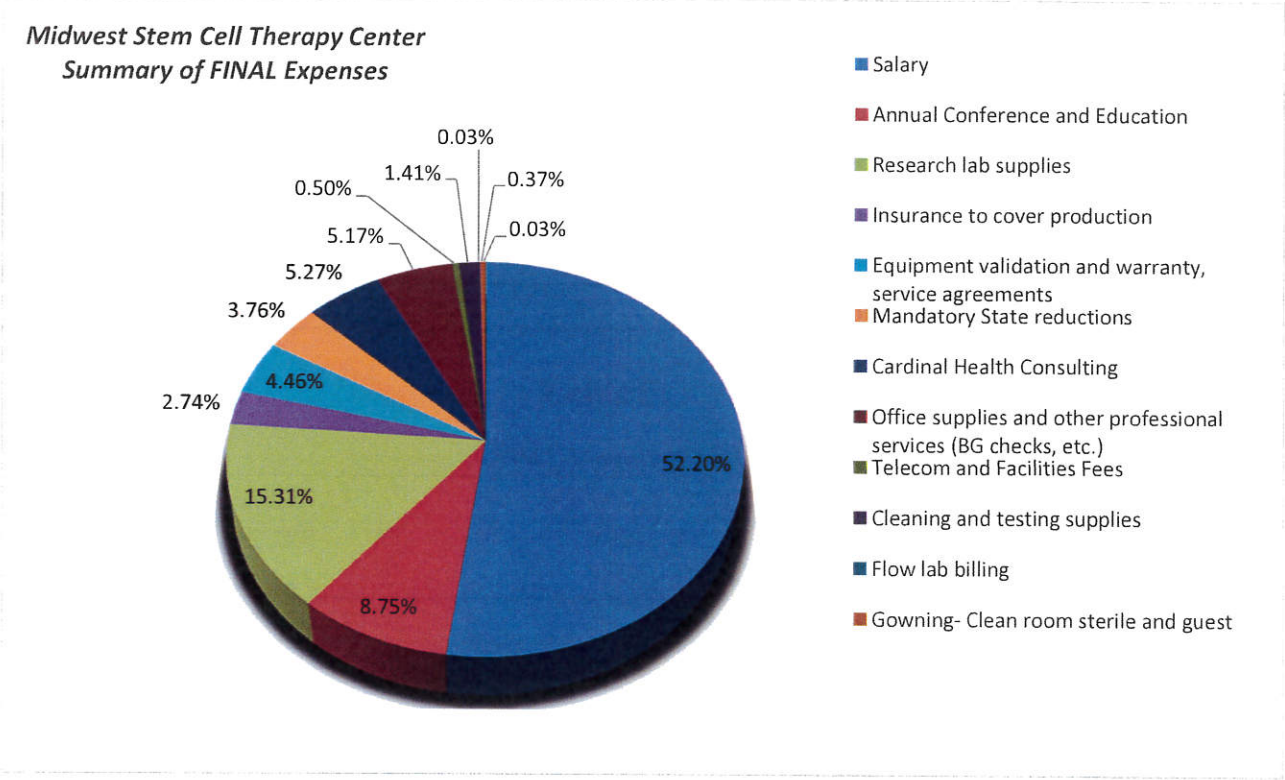
- **Accomplishments**:
  - Marketed the Midwest Stem Cell Therapy Center to potential third parties seeking adult stem cell manufacturing.
  - Continued to deepen the relationship with Monsignor Tomasz Trafny, the Head of Science and Faith Department in the Pontifical Council for Culture at The Vatican and Executive Director of STOQ Project at The Vatican.
    - Msgr. Trafny returned to the MSCTC in 2017 and gave a Keynote Address at the 5th Annual Midwest Conference on Cell Therapy and Regenerative Medicine
- **Plans**:
  - Continue outreach efforts with potential clients seeking adult stem cell manufacturing locations
  - Continue periodic updates of the MSCTC website
  - Advertise at Kansas universities and other locations in the Midwest regarding stem cell collaborations and GMP manufacturing
  - Actively engage officials from The Vatican as well as the KC Archdiocese

I. Expense and income Report

State appropriations

FY17 – Total amount received: $771,697.00

Expenses		*% of FY total*
Salary	*$402,845.05*	*52.20%*
Annual Conference and Education	*$67,557.35*	*8.75%*
Research lab supplies	*$118,206.99*	*15.31%*
Insurance to cover production	*$21,200.00*	*2.74%*
Equipment validation and warranty, service agreements	*$34,437.87*	*4.46%*
Mandatory State reductions	*$29,033.00*	*3.76%*
Cardinal Health Consulting	*$40,484.95*	*5.27%*
Office supplies and other professional services (BG checks, etc.)	*$39,865.86*	*5.17%*
Telecom and Facilities Fees	*$3,847.95*	*0.50%*
Cleaning and testing supplies	*$10,895.80*	*1.41%*
Flow lab billing	*$292.13*	*0.03%*
Gowning- Clean room sterile and guest	*$2,876.73*	*0.37%*
Travel	*$153.32*	*0.03%*
FY17 Final Expenses Total	*$771,697.00*	*100.00%*



FY18 Year to Date Sources and Spends

Total amount received: $723,673.00

Table 1

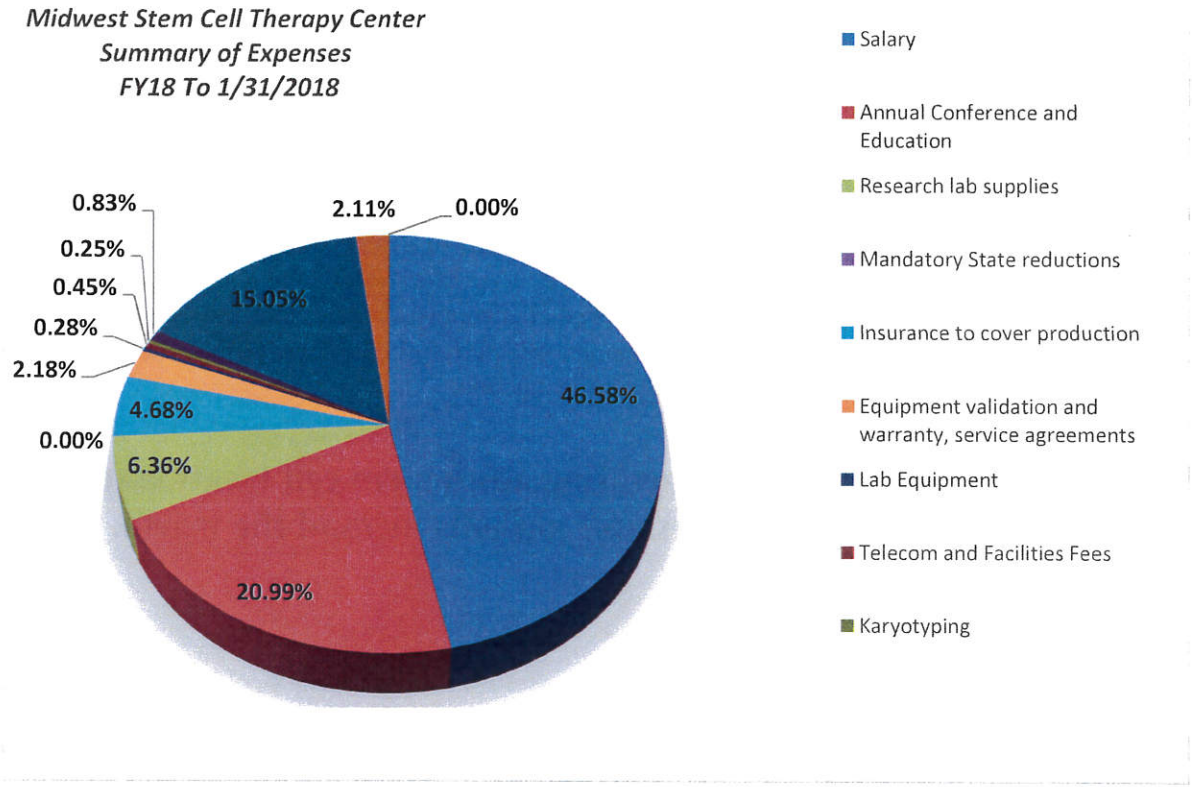
Actual Expenses through 1/31/18		*% of FY Total*
Salary	*210,828.89*	*29.13%*
Annual Conference and Education	*94,984.19*	*13.13%*
Research lab supplies	*28,795.47*	*3.98%*
Mandatory State reductions	*0*	*0.00%*
Insurance to cover production	*21,200.00*	*2.93%*
Equipment validation and warranty, service agreements	*9,849.22*	*1.36%*
Lab Equipment	*1,263.36*	*0.17%*
Telecom and Facilities Fees	*2,032.94*	*0.28%*
Karyotyping	*1,134.00*	*0.16%*
Gowning- Clean room sterile and guest	*3,740.55*	*0.52%*
Office supplies and other professional services (BG checks, etc.)	*68,099.19*	*9.41%*
Cleaning and testing supplies	*9,544.19*	*1.32%*
Travel	*15.62*	*0.00%*
Flow lab billing	*1,102.52*	*0.15%*
Total Fiscal Year expenses through 1/31/18	*452,590.14*	*62.54%*

Table 2

Projected Expenses for remaining FY18		*% of FY Total*
Projected Salary and Fringe Total	*163,893.53*	*22.65%*
Projected Supplies and professional service	*102,046.23*	*14.10%*
Projected Equipment validation and calibration	*3,685.45*	*0.51%*
Projected Telecom	*1,457.65*	*0.20%*
Projected Expenses for remaining FY18	*271,082.86*	*37.46%*

Table 3

Center Income to date for FY18 (through 1/31/18)	
GMP Manufacturing income	*32,730.72*
Educational related income	*587.25*
Clinical Trial income	*345.60*
Total Center Income to date for FY18	*33,663.57*



VISION FOR THE FUTURE

Through support from the State of Kansas, establishing a solid donor base, third party adult stem cell manufacturing, and external grants, **establish the Midwest Stem Cell Therapy Center as the place to go to obtain adult stem cell therapy**. To this end, MSCTC staff and Advisory Board members along with KUMC Office of Organizational Development have developed a long-range strategic plan that incorporates the following elements:

- Achieve self-sustainability with a multipronged approach that includes developing and licensing novel adult stem cells for therapy, third-party manufacturing of adult stem cell products, processing and banking adult stem cells and marketing
- Advance cutting-edge adult stem cell therapy through increasing number of human clinical trials
- Develop a 'Service Line' model for enhanced delivery of regenerative medicine locally
- Increase the clinical trial/research workforce and build appropriate infrastructure
- Acquire state-of-the-art instrumentation for cell processing, outcome assessment, in vivo imaging, stem cell sorting, and devices for cell administration
- Recruit scientists and clinicians engaged in basic and translational stem cell research
- Perform cutting-edge bench-to-bedside adult stem cell translational trials in humans by collaborating with the FDA

As shown during the past five years, the MSCTC has consistently progressed in developing the required capability and capacity to address the goals developed by the Kansas Legislature as outlined in SB 199. During this "incubation" period, the progress shown in establishing the

Center and making it operational also uncovered significant opportunity for the Center to go beyond the original vision, most notably in the area of patient treatment. This potential along with clarification of the use of autologous stem cells by the US Food and Drug Administration in December, 2017, allows for continued support of the original goals of the Center and also provides a clear opportunity for the Center to become self-sustaining.

In order to further the missions of the Center, achieve greater public recognition, and realize its potential for patient therapy, a significant shift in organization and investment, and focus on aggressive growth is critically needed. Consideration by the Kansas Legislature to support such a change so that the Midwest Stem Cell Therapy Center can achieve its original goals and go beyond what was originally envisioned will be required. A proposal is being drafted for consideration for the 2019 KS Legislative agenda.

Kansas can be the leader in providing adult stem cell treatments and information to physicians and patients around the world.