CHARLOTTE LOZIER INSTITUTE

Midwest Stem Cell Therapy Center—Kansas' Unique Initiative

Written Testimony of David A. Prentice, Ph.D.
Vice President and Research Director, Charlotte Lozier Institute
Adjunct Professor of Molecular Genetics, John Paul II Institute, Catholic University of America
Founding Member, Do No Harm: The Coalition of Americans for Research Ethics

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The Distinguished Chairs and Honored Members of the Committees.

I am a cell and developmental biologist, currently working for the Charlotte Lozier Institute in Washington, D.C. as Vice President and Research Director; I also serve as an adjunct professor at a Washington, D.C. university, and as an Advisory Board Member for the Midwest Stem Cell Therapy Center, the unique comprehensive stem cell center in Kansas. Previously I spent 10 years as Senior Fellow for Life Sciences at another policy think tank in Washington, D.C., and prior to that almost 20 years as Professor of Life Sciences at Indiana State University, and Adjunct Professor of Medical and Molecular Genetics, Indiana University School of Medicine. Before that I was a faculty member in the Department of Obstetrics, Gynecology and Reproductive Sciences, University of Texas Medical School at Houston. My post-doctoral work was done at Los Alamos National Laboratory. I have done federally-funded laboratory research, lectured, and advised on these subjects extensively in the U.S. and internationally. I've taught embryology, developmental biology, molecular biology and biochemistry for over 35 years to medical and nursing students, as well as undergraduate and graduate students. I am proud to be a native Kansan, born in La Crosse, Kansas, raised near Parker, Kansas, with my degrees (B.S. and Ph.D.) from the University of Kansas.

Thank you for the opportunity to testify on the progress of the Midwest Stem Cell Therapy Center, the unique Kansas stem cell initiative. I was honored to assist with development of the Kansas stem cell center, and testified in support of the bill, SB199, that made the Center a reality. Thank you for your support of this unique and successful idea. Currently I serve as a member of the Center's Advisory Board.

Stem cell treatments using adult stem cells from bone marrow, umbilical cord blood, and other tissue sources continue to be a cutting-edge medical technology. And Kansas continues to show leadership in bringing non-controversial stem cell therapies to patients, and information to physicians and the public. The Kansas stem cell center is focused on patients, with an emphasis on therapy, dissemination of information, and comprehensive view to fulfilling its mission. The MSCTC only works with non-controversial stem cell sources—adult stem cells and induced pluripotent stem (iPS) cells; embryonic and fetal sources are not used, in keeping the focus on the patient and deliverable therapies. You've already heard from other witnesses about the current progress of the MSCTC, in the less than three years it has existed, ongoing clinical trials, and development toward new applications of adult stem cells. I'd like to give you a glimpse of future possibilities as the Kansas adult stem cell center continues its growth.

There are at present **3,300 ongoing or completed clinical trials using adult stem cells**, listed in the NIH/FDA-approved database,[1] with over 70,000 people around the globe receiving adult stem cell transplants each year, for **dozens of different conditions**. There have now been **well over one million adult stem cell transplants** total.[2] The applications of adult and cord blood stem cells in clinical therapy are growing rapidly, and Kansas continues to position itself as one of the leaders in these therapies. Although the MSCTC has been in existence for less than three years, in a very real sense many other states and stem cell programs are rushing to catch up with the Kansas center.

There are an estimated 53 programs nationwide doing research in the stem cell field. In contrast to the MSCTC, most "stem cell centers" around the United States focus on basic research with little or no clinical component. Furthermore, most "stem cell treatment centers" emphasize only specific clinical treatments but do not educate the public or physicians. None of the identified stem cell centers provide a comprehensive program of treatment, research, training and education as does the MSCTC. This is also true in terms of patient focus. For example, California has the largest state-funded stem cell program in the country, and started its program with a focus on embryonic stem cells; yet it is turning to adult stem cells for a chance at success with patients.[3] Likewise the state of Maryland has switched its emphasis on research grants to adult stem cells.[4]

There has also been a surge of interest at the federal level. The GAO documents that seven different federal agencies invested a total of $2.89 billion in regenerative medicine from 2012-2014.[5] The agencies are focusing on numerous areas of investigation but a number of them overlap with existing priorities of the MSCTC, including stroke, traumatic brain injuries, limb repair. And again, in comparing various other state and collaborative initiatives, even though the Kansas adult stem cell center has been in existence less than three years, it already surpasses many other longer-standing initiatives, and the others are working to catch up with the Kansas MSCTC.

The MSCTC has targeted four broad areas of investigation for development and multiplication of therapies.
Stroke and Neurodegenerative Diseases; Cancer and Immunotherapy; Cardiovascular Disease; Musculoskeletal, Trauma, Skin, Burns, Wounds, Autoimmune
Some of the specific projects are already underway, some others in pre-clinical research phase, and others in planning stages.

A substantial amount of previous work with adult stem cells has been the successful application of the cells for treatment and recovery from **various cancers**. The KU Cancer Center itself performed over 300 marrow and blood stem cell transplants for cancer treatments in 2015. While a number of these therapies have moved into standard medical practice, as seen by the numbers treated at the KU Cancer Center, one of the leaders in this field, there is still much work to be done to increase the efficacy of stem cell transplants for cancer and to treat even more cancer types.

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[1] Search term: http://www.clinicaltrials.gov/ct2/results?term=adult+stem+cell+transplants&type=Intr accessed February 6, 2016.

[2] Gratwohl A *et al.*, One million haemopoietic stem-cell transplants: a retrospective observational study, *Lancet Haematology* 2, e91, March 2015

[3] Gene Tarne, The Ethical Stems of Good Science, Charlotte Lozier Institute, https://lozierinstitute.org/the-ethical-stems-of-good-science/, October 1, 2012

[4] Gene Tarne and Andrew Mullins, Maryland Joins the Trend for Ethical Stem Cell Research, Charlotte Lozier Institute, https://lozierinstitute.org/maryland-joins-the-trend-for-ethical-stem-cell-research/, October 1, 2013

[5] U.S. Government Accountability Office. Regenerative Medicine. Federal Investment, Information Sharing, and Challenges in an Evolving Field. GAO-15-1553, June 2015.

Beyond cancer, adult stem cells are also showing therapeutic promise for other diseases and conditions where there has previously been no available treatment option. The published scientific literature now documents therapeutic success in trials of adult stem cells for patients with dozens of other conditions, including heart damage, stroke, sickle cell anemia, spinal cord injury, multiple sclerosis, and juvenile diabetes. Further, a growing number of adult stem cell transplants use cells from additional sources such as mesenchymal (connective) tissue and adipose (fat) tissue. Some of these were discussed in testimony last year.[6] Other examples are presented here.

One area of active work is the use of adult stem cells from the solid part of the umbilical cord to manage **graft-versus-host disease**, a significant problem sometimes seen with transplants for cancer.[7] A groundbreaking study by MSCTC faculty has advanced a promising therapy using adult stem cells to treat this condition.

Repair of heart damage is an ongoing area at the MSCTC. This includes current clinical trials,[8] as well as basic investigations into new potential cardiac repair technologies.[9] MSCTC members are also participating and publishing in areas of adult stem cell treatment for standardization of these repair techniques.[10]

While the MSCTC is not yet doing studies on treatments for autoimmune disease, this is an area of active investigation and one of the targeted areas for development. Adult stem cells are showing significant strides in treatment of multiple sclerosis. This recent report shows that use of adult stem cells can induce remissions in multiple sclerosis patients. [11] As the studies progress, they continue to show up in news stories, with patients who have made remarkable improvements. No standard interventions produce any significant reversal of disability. But in this study an international team led by Dr. Richard Burt of Northwestern University Feinberg School of Medicine has shown that adult stem cell transplants are associated with reversal of neurological disability for relapsing-remitting multiple sclerosis patients.

As noted last year, there continues to be progress using adult stem cells in development of a successful treatment for **diabetes**. These are not just new, fancier insulin pumps, but actual treatments for the disease. The NIH-FDA database lists over a dozen clinical trials at this point. A Chinese group recently published results of a study using adult stem cells from bone marrow and umbilical cord blood, showing that their technique could improve the conditions of Type I diabetes patients.[12]

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[6] David A. Prentice. Written testimony: Progress on Kansas' Midwest Stem Cell Therapy Center Research, April 30, 2015; accessed at: https://lozierinstitute.org/written-testimony-of-david-a-prentice-ph-d-progress-on-kansas-midwest-stem-cell-therapy-center-research/

[7] McGuirk JP *et al.*, Wharton's Jelly-Derived Mesenchymal Stromal Cells as a Promising Cellular Therapeutic Strategy for the Management of Graft-versus-Host Disease, *Pharmaceuticals* 8, 196, 2015

[8] Afzal MR *et al.*, Adult Bone Marrow Cell Therapy for Ischemic Heart Disease. Evidence and Insights From Randomized Controlled Trials, *Circulation Research* 117, 558, 2015

[9] Rajasingh S et al., Generation of Functional Cardiomyocytes from Efficiently Generated Human iPSCs and a Novel Method of Measuring Contractility, PLoS ONE 10(8):e0134093, 2015. doi:10.1371/journal.pone.0134093

[10] Golpanian S et al., Concise Review: Review and Perspective of Cell Dosage and Routes of Administration From Preclinical and Clinical Studies of Stem Cell Therapy for Heart Disease, Stem Cells Translational Medicine 5, 186, 2016

[11] Burt RK *et al.*, Association of Nonmyeloablative Hematopoietic Stem Cell Transplantation With Neurological Disability in Patients With Relapsing-Remitting Multiple Sclerosis, *JAMA* 313, 275, 2015

[12] Cai J et al., Umbilical Cord Mesenchymal Stromal Cell With Autologous Bone Marrow Cell Transplantation in Established Type 1 Diabetes: A Pilot Randomized Controlled Open-Label Clinical Study to Assess Safety and Impact on Insulin Secretion, Diabetes Care 39, 149, 2016

Faculty at the MSCTC are actively investigating the potential of adult stem cells for treatment of various liver diseases. Recently, an international research team published results showing that a specific type of adult stem cell (CD133) showed positive results for treatment of a small group of patients with liver cirrhosis.[13]

A breath of fresh air is not always easy to obtain, especially if your lungs have been damaged through a chronic pulmonary disease. While lung transplants can address this problem, long-term complications can ensue due to immunosuppression, and the availability of transplantable lungs is insufficient to meet current needs. Harvard researchers have shown the potential of bioengineered lungs to meet these needs.[14] Their method to construct replacement lungs relies on decellularized cadaveric lungs and adult bone marrow mesenchymal stem cells and human umbilical vein endothelial cells (to reconstruct blood vessels in the re-cellularized lungs.) A second test system used endothelial and perivascular cells derived from human iPS cells. Benam et al. took a different route for constructing bioengineered lung tissue. They used human cells to construct a human "small airway-on-a-chip".[15] This organ-on-a-chip will be a valuable model to investigate human lung inflammatory diseases.

While it may get some chuckles and seem a non-serious application, an Italian group has shown that injections of platelet-rich plasma (PRP), often associated with stem cell stimulatory schemes, could restore hair follicle stem cell growth and remediate some hair growth in male pattern baldness patients.[16] This or similar applications to stimulate stem cell growth could potentially be a strong commercial product.

As mentioned last year, a number of doctors are attempting to treat joint problems with adult stem cells, usually from adipose-derived cells from the patient. Others are looking at the possibility of using donor adult stem cells that could be matched to many patients. There is still a lack of many published peer-reviewed studies in the area of orthopedic surgery use of adult stem cells, this is an area of significant growth for regenerative medicine.[17] This also highlights an area of opportunity for the MSCTC, because the Kansas center could help advance the frontier of research and therapies to help even more people, providing clinical-grade stem cells for treatments and trials done by other research groups, and by providing the **coordination for clinical trials** among clinics and centers doing patient treatments. This would foster more safe and validated patient treatments, improve collaboration, and increase the knowledge base on best practice for specific adult stem cell applications.

Vocal impairment, known as dysphonia, affects approximately 20 million people in the United States. A majority of these have some damage to their vocal folds which is very difficult to repair. A research group now reports that they have constructed a bioengineered vocal fold using adult human tissue that shows normal morphology and function.[18] After two weeks in culture the cells had organized and grown into structures resembling native vocal folks. Vocal folds grafted into canine hosts showed normal morphology

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[13] Mohamadnejad M et al., Intraportal Infusion of Bone Marrow Mononuclear or CD133+ Cells in Patients With Decompensated Cirrhosis: A Double-Blind Randomized Controlled Trial, Stem Cells Translational Medicine 5, 87, 2016

[14] Xi Ren *et al*., "Engineering pulmonary vasculature in decellularized rat and human lungs," *Nature Biotechnology* 33.10 (October 2015): 1097-1102, doi: 10.1038/nbt.3354

[15] Kambez H. Benam *et al*., "Small airway-on-a-chip enables analysis of human lung inflammation and drug responses in vitro," *Nature Methods* (published online December 21, 2015): *in press*, doi: 10.1038/nmeth.3697

[16] Gentile P et al., The Effect of Platelet-Rich Plasma in Hair Regrowth: A Randomized Placebo-Controlled Trial, Stem Cells Translational Medicine 4, 1317, 2015

[17] Murrell WD *et al.*, Regenerative Treatments to Enhance Orthopedic Surgical Outcome, *PM&R* 7, S41, 2015

[18] Changying Ling *et al*., "Bioengineered vocal fold mucosa for voice restoration," *Sci. Transl. Med.* 7.314ra187 (November 18, 2015): 1-11, doi: 10.1126/scitranslmed.aab4014

and generated vibrations and acoustic output. When grafted into humanized mice (mice with a human immune system, in this case constructed using human adult stem cells), the vocal folds were tolerated and not rejected. These bioengineered vocal folds show promise for treatment of human patients.

Humanized mice, as mentioned above, can be used to study transplantation and the immune system. They can also be used to study infection diseases such as the recent Zika virus or Ebola virus infections, or HIV infection and pathology, or as models for cancer and other conditions. Adult stem cells from umbilical cord blood have been shown to be the most effective stem cells for construction of these humanized mice, and could potentially be used for individualized study.[19]

In terms of modeling human tissues and cells, including during development, scientists have now developed methods to form 3-dimensional cellular structures that resemble tissue from normal organs. Termed organoids, the constructs provide superior models to study tissue organization and disease, as well as starting points for potential transplantation. There are many recent examples, including an Australian team using human iPS cells to generate kidney organoids.[20] The kidney organoids contained kidney-specific cell types and structures – nephrons associated with a collecting duct network. The individual nephrons showed differentiated structural organization into tubules and glomeruli, similar to that observed in adult kidneys. Organoids grew to a size containing 500 nephrons (compared to approximately 1-2 million nephrons per adult kidney.)

Another area showing significant potential, and in which the MSCTC is looking at collaborative ventures, are cell therapies known as adoptive cell transfer (ACT) and chimeric antigen receptors-T cell (CAR-T). These cell-based therapeutic techniques are designed to assist a patient's immune system in attacking and resisting cancer.[21] A version of this system was used recently to treat a young girl in the U.K. who had leukemia.[22] Immune cells underwent genetic engineering to make them resistant to chemotherapy and so that they would not cause a GVHD reaction. The girl could then be treated with high-dose chemotherapy yet maintain her "borrowed" immune system. Once the leukemia was eradicated, she received an adult stem cell transplant to generate her own new immune and blood system.

Kansas' Midwest Stem Cell Therapy Center is unique, comprehensive, and focused on the patients first. It encompasses clinical treatments, basic and translational research, education and training, a valuable resource for cell processing, and a center for stem cell information including development of a one-of-a-kind clinical database. It is already on the path to becoming a focal point for adult stem cell therapies, trials, and collaborations, as well as for education and training.

Kansas is at the forefront in adult stem cell therapies and information for physicians and patients around the world.

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[19] Drake AC et al., Human CD34+ CD133+ Hematopoietic Stem Cells Cultured with Growth Factors Including Angptl5 Efficiently Engraft Adult NOD-SCID Il2rc2/2 (NSG) Mice, PLoS ONE 6(4): e18382, 2011. doi:10.1371/journal.pone.0018382

[20] Minoru Takasato *et al*., "Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis," *Nature* (October 2015): in press, doi:10.1038/nature15695

[21] Rosenberg SA and Restifo NP, Adoptive cell transfer as personalized immunotherapy for human cancer, *Science* 348, 62, 2015

[22] Jennifer Couzin-Frankel, Baby's leukemia recedes after novel cell therapy, Science 350, 731, November 15, 2015