CHARLOTTE LOZIER INSTITUTE

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To the Distinguished Chair and Honored Members of the Committees.

Thank you for the opportunity to provide testimony to your committee IN SUPPORT of SB 1474, regarding human fetal tissue trafficking.

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, a 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, cell and tissue culture, molecular biology and biochemistry for over 35 years to medical and nursing students, as well as undergraduate and graduate students. I am testifying in my capacity as a scientist and on behalf of the Charlotte Lozier Institute.

There is no sound scientific reason for the continued trafficking of fetal tissue, organs, and body parts. Moreover, the practice of using fetal tissue from induced abortion raises significant ethical problems, not least of which is the nebulous interpretation of valuable consideration or compensation for expenses in the harvest and processing of fetal organs and tissues.

We should first address some history on this research area.[1] While human fetal tissue research has gone on for decades, the success of fetal tissue research and especially fetal tissue transplants has been meager at best, and modern, ethically-derived alternatives exist and are coming to dominate the field.

Proponents of using fetal tissue from induced abortion point to three areas in claims of the need for harvesting tissue:

-Transplantation to treat diseases and injuries
-Vaccine development
-Basic biology research

[1] A downloadable version of the fetal tissue history and scientific information can be accessed at: https://www.lozierinstitute.org/history-of-fetal-tissue-research-and-transplants/

Fetal Tissue Transplantation: The first recorded fetal tissue transplants were in 1921 in the UK, in a failed attempt to treat Addison's disease,[2] and in 1928 in Italy, in a failed attempt to treat cancer.[3] The first fetal tissue transplant in the U.S. was in 1939, using fetal pancreatic tissue in an attempt to treat diabetes. That attempt also failed, as did subsequent similar fetal tissue transplants in 1959. Between 1970 and 1991 approximately 1,500 people received fetal pancreatic tissue transplants in attempts to treat diabetes, mostly in the former Soviet Union and the People's Republic of China. Up to 24 fetuses were used per transplant, but less than 2% of patients responded.[4] Today, patients take insulin shots and pharmaceuticals to control their diabetes, and adult stem cell transplants have shown success at ameliorating the condition.[5]

Between 1960 and 1990, numerous attempts were made to transplant fetal liver and thymus for various conditions. According to one review, "the clinical results and patient survival rates were largely dismal."[6] By contrast, conditions such as anemias and immunodeficiencies, for which fetal tissue attempts largely failed, are now treated routinely with adult stem cells, including umbilical cord blood stem cells,[7] even while the patient is still in the womb.[8]

Between 1988 and 1994, roughly 140 Parkinson's disease patients received fetal tissue (up to six fetuses per patient), with varying results.[9] Subsequent reports showed that severe problems developed from fetal tissue transplants. One patient who received transplant of fetal brain tissue (from a total of 3 fetuses) died subsequently, and at autopsy was found to have various non-brain tissues (*e.g*, skin-like tissue, hair, cartilage, and other tissue nodules) growing in his brain.[10]

In 2001, the first report of a full clinical trial[11] (funded by NIH) using fetal tissue for Parkinson's patients was prominently featured in the *New York Times*,[12] with doctors' descriptions of patients writhing, twisting, and jerking with uncontrollable movements; the doctors called the results "absolutely devastating", "tragic, catastrophic", and labeled the results "a real nightmare."

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[2] Hurst AF *et al.*, Addison's disease with severe anemia treated by suprarenal grafting, *Proc R Soc Med* 15, 19, 1922
[3] Fichera G, Impianti omoplastici feto-umani nel cancro e nel diabete, *Tumoi* 14, 434, 1928
[4] Federlin K *et al.*, Recent achievements in experimental and clinical islet transplantation. *Diabet Med* 8, 5, 1991
[5] See, *e.g.*, Voltarelli JC, Couri CEB, Stem cell transplantation for type 1 diabetes mellitus, *Diabetology & Metabolic Syndrome* 1, 4, 2009; doi:10.1186/1758-5996-1-4; Couri CEB *et al.*, C-Peptide Levels and Insulin Independence Following Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus, *JAMA* 301, 1573-1579, 2009; Voltarelli JC *et al.*, Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus, *JAMA* 297, 1568-1576, 2007
[6] Ishii T, Eto K, Fetal stem cell transplantation: Past, present, and future, *World J Stem Cells* 26, 404, 2014
[7] See, *e.g.*, Bernaudin F et al., Long-term results of related myeloablative stem cell transplantation to cure sickle cell disease, Blood 110, 2749-2756, 2007 AND de Heredia CD *et al.*, Unrelated cord blood transplantation for severe combined immunodeficiency and other primary immunodeficiencies, *Bone Marrow Transplantation* 41, 627, 2008
[8] Loukogeorgakis SP, Flake AW. In utero stem cell and gene therapy: Current status and future perspectives, *Eur J Pediatr Surg* 24, 237, 2014
[9] Reviewed in: Fine A, Transplantation of fetal cells and tissue: an overview, *Can Med Assoc J* 151, 1261, 1994
[10] Folkerth RD, Durso R, Survival and proliferation of nonneural tissues, with obstruction of cerebral ventricles, in a parkinsonian patient treated with fetal allografts, *Neurology* 46, 1219, 1996
[11] Freed CR *et al.*, Transplantation of embryonic dopamine neurons for severe parkinson's disease, *N Engl J Med* 344, 710, 2001
[12] Gina Kolata, "Parkinson's Research Is Set Back by Failure of Fetal Cell Implants," *New York Times* March 8, 2001; accessed at: http://www.nytimes.com/2001/03/08/health/08PARK.html

A second large, controlled study published in 2003 showed similar results (funded by NIH), with over half of the patients developing potentially disabling tremors caused by the fetal brain tissue transplants.[13] The results of these two large studies led to a moratorium on fetal tissue transplants for Parkinson's. Long-term follow-up of a few of the patients in these large studies showed that even in fetal tissue that grew in patients' brains, the grafted tissue took on signs of the disease and were not effective.[14] In contrast, adult stem cells have shown initial success in alleviating Parkinson's symptoms.[15]

A recent 2009 report emphasizes the instability and danger of fetal tissue transplants. A patient with Huntington's disease was recruited into a study (funded by NIH) in which she had fetal brain cells injected into her brain. She did not improve, and instead developed in her brain a growing mass of tissue, euphemistically termed "graft overgrowth" by the researchers.[16]

Note that fetal tissue has been taken in a number of cases from fetuses at developmental ages where fetal surgery is now used to correct problems in the womb and save lives. Note also that at these stages, science now demonstrates that the unborn fetus can feel pain.

Disastrous results for patients are seen not only with fetal tissue but also with fetal stem cells. In a recent example, a young boy developed tumors on his spine, resulting from fetal stem cells injected into his body.[17]

SUCCESSFUL ALTERNATIVE—Adult Stem Cell Transplants: In contrast, a recent review found that as of December 2012, over one million patients had been treated with adult stem cells.[18] The review only addressed hematopoietic (blood-forming) adult stem cells, not other adult stem cell types, so this is a significant underestimate of the patients who have benefitted from adult stem cell therapies. A public face for such patients can be found at the educational website stemcellresearchfacts.org, where patients successfully treated with noncontroversial adult stem cells tell their stories in short video vignettes.

There are at present over 3,300 ongoing or completed clinical trials using adult stem cells listed in the NIH/FDA-approved database,[19] with over 70,000 people around the globe receiving adult stem cell transplants each year for dozens of different conditions. Use of adult and cord blood stem cells in clinical therapy is growing rapidly.

A substantial amount of previous work with adult stem cells has been the successful application for treatment and recovery from various cancers. A number of these therapies have moved into standard medical practice, but there is still much to be done to increase the efficacy of adult stem cell transplants for cancer and to treat even more cancer types. For example, recently a French group found that they

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[13] Olanow CW *et al.*, A Double-blind Controlled Trial of Bilateral Fetal Nigral Transplantation in Parkinson's Disease, *Ann Neurol* 54, 403, 2003

[14] Braak H, Del Tredici K, Assessing fetal nerve cell grafts in Parkinson's disease, *Nature Medicine* 14, 483, 2008

[15] See, *e.g.*, Lévesque MF *et al.*, , Therapeutic microinjection of autologous adult human neural stem cells and differentiated neurons for Parkinson's disease: Five-year post-operative outcome, *The Open Stem Cell Journal* 1, 20, 2009

[16] Keene CD *et al.*, A patient with Huntington's disease and long-surviving fetal neural transplants that developed mass lesions, *Acta Neuropathol* 117, 329, 2009

[17] Amariglio N *et al.*, Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient, *PLoS Med* 6(2): e1000029. doi:10.1371/journal.pmed.1000029, 2009; BBC News, "Stem cell 'cure' boy gets tumour", 18 February 2009, accessed at: http://news.bbc.co.uk/2/hi/health/7894486.stm

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

[19] Search term: http://www.clinicaltrials.gov/ct2/results?term=adult+stem+cell+transplants&type=Intr accessed February 11, 2016.

could improve prognostic targeting of adult patients who would benefit from stem cell transplants for acute lymphoblastic leukemia, following a protocol previously successful in treating childhood leukemia.[20] Likewise a new review paper notes that bone marrow adult stem cell transplant remains a curative option for chronic myelogenous leukemia.[21] Other cell therapies known as adoptive cell transfer (ACT) and chimeric antigen receptors-T cell (CAR-T) are being developed, to rejuvenate the immune system and to attack cancer directly.[22] And a groundbreaking study has advanced a promising therapy to manage graft-versus-host disease, a problem sometimes seen with transplants for cancer.[23]

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, adipose (fat) tissue, and even nasal tissue, and there is the promise of even more sources such as the solid portion of the umbilical cord (Wharton's jelly) and amniotic fluid. One published estimate is that here is a 1 in 200 chance that anyone living in the U.S. will undergo an adult stem cell transplant during our lifetime.[24]

There continues to be progress using adult stem cells, or stimulating the body's own adult stem cells, to treat diabetes. The NIH-FDA database lists over a dozen clinical trials using adult stem cells for diabetes at this point. Perhaps the best known is the collaboration between Dr. Richard Burt at Northwestern University and colleagues in Brazil; this group published results of two earlier studies on approximately two dozen Type I diabetes patients, where the patients were able to stop use of insulin after treatment.[25] Efforts continue to expand and improve this treatment. As another example, a small clinical trial at Massachusetts General Hospital found that treatment with a chemical adjuvant stopped the autoimmunity and transiently restored normal blood sugar levels in Type I diabetes patients.[26]

Another autoimmune disease that is showing significant strides in treatment using adult stem cells is multiple sclerosis. Two recent reports point to use of adult stem cells to induce remissions in multiple sclerosis. No standard interventions produce any significant reversal of disability. But 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

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[20] Dhedin N *et al.,* Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia, *Blood* 125, 2486, 2015

[21] Barrett AJ and Ito S, The role of stem cell transplantation for chronic myelogenous leukemia in the 21st century, *Blood* 125, 3230, 2015, doi: 10.1182/blood-2014-10-567784

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

[23] 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

[24] Nietfeld JJ *et al.*, Lifetime Probabilities of Hematopoietic Stem Cell Transplantation in the U.S., *Biology of Blood and Marrow Transplantation* 14, 316-322, 2008

[25] Voltarelli JC and Couri CEB, Stem cell transplantation for type 1 diabetes mellitus, *Diabetology & Metabolic Syndrome* 1, 4, 2009; doi:10.1186/1758-5996-1-4; Couri CEB *et al.*, C-Peptide Levels and Insulin Independence Following Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus, *JAMA* 301, 1573-1579, 2009; Voltarelli JC *et al.*, Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus, *JAMA* 297, 1568-1576, 2007

[26] Faustman DL *et al*., Proof-of-Concept, Randomized, Controlled Clinical Trial of Bacillus-Calmette-Guerin for Treatment of Long-Term Type 1 Diabetes, *PLOS One* 7, e41756, 2012

multiple sclerosis patients.[27] Patients were followed for up to five years after treatment and there was significant improvement after transplant, with 50% of patients showing improvement at two years after transplant, and 64% improved at four years after transplant. No other intervention for multiple sclerosis has shown an improvement in neurological disability for patients. Treated patients also showed significant relapse-free survival (80%) and decreased neurological lesions.

A separate publication from a group led by Dr. Richard Nash of the Colorado Blood Cancer Institute also showed evidence for adult stem cell transplants in remission of relapsing-remitting multiple sclerosis.[28] This group provided a three-year interim report on their five-year clinical study. With 24 patients enrolled in the study, at three years follow-up there were improvements in neurologic disability.

Other neurological conditions are also seeing advances. There continue to be promising signs for the use of adult stem cells in treatment of Parkinson's disease. A recent proof-of-principle experiment found that mesenchymal stem cells, a type of adult stem cell found in bone marrow as well as other tissues, could be transformed into dopamine-secreting cells and provide long-term relief from Parkinson's symptoms after transplant,[29] Another recent review shows almost a dozen current clinical trials in attempts to treat stroke using adult stem cells.[30] Furthermore, a commercial effort developing an adult stem cell treatment for ALS (Lou Gehrig's disease) has published evidence that their stem cell product is effective for neurodegenerative conditions. In a case study involving a patient with myasthenia gravis and motor-neuron disease, the treatment with adult stem cells provided significant relief from symptoms.[31] They have also announced, and presented at a recent meeting of the American Academy of Neurology, that preliminary results from their Phase 2a clinical trial with ALS patients have shown beneficial effects for the patients receiving the adult stem cell injections.[32]

Several published medical authors now note, "Hematopoietic stem cell transplantation (HSCT) is the only curative therapy for sickle cell disease."[33] Donor-derived adult stem cell transplants from bone marrow or umbilical cord blood are curative for children with sickle cell anemia, but adults often cannot tolerate the toxicity of similar transplants. Now, development of a lower-toxicity protocol shows that adults can not only tolerate the transplant but that many can stop taking anti-rejection drugs as well.[34] A total of 30 adult patients with severe sickle cell disease were treated with donor bone marrow stem cells after milder actions to open up their own bone marrow. Twenty-six patients showed long-term stable donor cell engraftment, with no graft-vs-host disease. Half of the patients (15) were able to stop immunosuppressive medication and maintain stable cell function without the drugs to prevent immune rejection of the transplant.

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[27] 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

[28] Richard A. Nash *et al*., High-Dose Immunosuppressive Therapy and Autologous Hematopoietic Cell Transplantation for Relapsing-Remitting Multiple Sclerosis (HALT-MS), *JAMA Neurology* 72, 159, 2015

[29] Hayashi T *et al*., Autologous mesenchymal stem cell–derived dopaminergic neurons function in parkinsonian macaques, *J Clinical Investigation* 123, 272, 2013

[30] Doepner TR and Hermann DM, Stem cell-based treatments against stroke: observations from human proof-of-concept studies and considerations regarding clinical applicability, *Frontiers in Cell Neuroscience* 8, Article 357, October 2014

[31] Petrou P *et al.*, Rare combination of myasthenia and motor neuronopathy, responsive to Msc-Ntf stem cell therapy, *Muscle & Nerve* 49, 455, 2014

[32] Petrou P *et al.*, Autologous Transplantation of Mesenchymal Stem Cells Secreting Neurotrophic Factors (NurOwn®) In ALS: Results of a Phase 2 Clinical Trial, Abstract P2.059, AAN Annual Meeting 2015, Washington, DC

[33] Bernaudin F *et al.*, Long-term results of related myeloablative stem cell transplantation to cure sickle cell disease, *Blood* 110, 2749-2756, 2007

[34] Hsieh MM *et al.*, Nonmyeloablative HLA-Matched Sibling Allogeneic Hematopoietic Stem Cell Transplantation for Severe Sickle Cell Phenotype, *JAMA* 312, 48, 2014

Adult stem cells are also showing some promise at treating inherited conditions. A multicenter trial recently reported results of donor adult stem cell transplants for Hurler disease, a lethal genetic condition. The group found that it is imperative to diagnose and treat early, to achieve the best results.[35]

Adult stem cells are now being used to treat some conditions while still in the womb. There are now several cases where unborn children have been successfully treated with adult stem cells for severe immune deficiencies,[36] and another reported result where unborn children were successfully treated *in utero* for osteogenesis imperfecta,[37] a genetic condition that causes brittle bones that break very easily.

Adult limbal stem cells (taken from the edge of the eye) have been used in the past to grow new corneas for patients, replacing corneas damaged by chemical burns or other trauma.[38] The limbal stem cells can be taken from the patient's own damaged eye and used to grow new tissue *in vitro* for transplant, restoring sight to blind eyes. New research suggests that limbal stem cells could *prevent* corneal damage and scarring if applied in a timely manner, obviating the need to grow a completely new cornea.[39] Human limbal stem cells applied to corneal wounds in mice prevented the formation of fibrotic lesions, and induced regeneration of new corneal stroma. This represents a potential autologous source of cells to treat corneal damage directly.

Limbal stem cells are not the only cells that can form corneal tissue. A group in Pittsburgh has shown that stem cells from dental pulp can form corneal stroma cells, allowing repair of corneal damage.[40]

Scientists in Pittsburgh have shown that adding a biological protein matrix to a wound can attract and stimulate adult stem cells to restore muscle.[41] In their trial, three out of five patients showed significant muscle restoration in their legs.

Research continues to isolate tissue-specific adult stem cells from various organs, and to identify stem cells and progenitors that may facilitate tissue-specific repair. Three different groups recently reported on stem cells that participate in lung repair. Zuo *et al.* found specific airway stem cells that could grow and repair lung damage.[42] Vaughan *et al.* found that previously-unrecognized lung stem cells could regenerate lung tissue after injury.[43] And Pardo-Saganta *et al.* also found airway stem cells that

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[35] Aldenhoven M *et al.*, Long-term outcome of Hurler syndrome patients after hematopoietic cell transplantation: an international multicenter study, *Blood* 125, 2164, 2015

[36] Loukogeorgakis SP and Flake AW. In utero stem cell and gene therapy: Current status and future perspectives, *Eur J Pediatr Surg* 24, 237, 2014

[37] Chan JKY and Götherström C**.** Prenatal transplantation of mesenchymal stem cells to treat osteogenesis imperfecta, *Frontiers in Pharmacology* 5, 1, October 2014.

[38] Rama P *et al*., Limbal Stem-Cell Therapy and Long-Term Corneal Regeneration, *N. Engl. J. Med.* 363, 147, 2010

[39] Basu S *et al*., Human limbal biopsy-derived stromal stem cells prevent corneal scarring, *Science Translational Medicine* 6, 266ra172, 2014

[40] Syed-Picard FN *et al*., Dental Pulp Stem Cells: A New Cellular Resource for Corneal Stromal Regeneration, *Stem Cells Translational Medicine* 4, 276, 2015

[41] Sicari BM *et al.*, An Acellular Biologic Scaffold Promotes Skeletal Muscle Formation in Mice and Humans with Volumetric Muscle Loss, *Science Translational Medicine* 6, 234ra58, 2014

[42] Zuo W *et al.*, $p63^{+}Krt5^{+}$ distal airway stem cells are essential for lung regeneration, *Nature* 517, 616, 2015

[43] Vaughan AE *et al.*, Lineage-negative progenitors mobilize to regenerate lung epithelium after major injury, *Nature* 517, 621, 2015

responded after significant lung injury. [44] These discoveries open possibilities for specific therapies for lung diseases.

A brief article by Petrella *et al.* showed that another population of stem cells, mesenchymal stem cells from bone marrow, could close a bronchopleural fistula in a patient.[45] The cells were used essentially to plug a hole in a patient's lung that had developed after surgery. The doctors injected the patient's adult stem cells near the fistula, and bronchoscopy at 60 days showed complete healing.

In a paper published in late March, a Korean group reported complete healing in 80% of patients treated with adipose-derived adult stem cells for severe fistulae associated with Crohn's disease, a devastating condition of the digestive system.[46]

Researchers in Poland report significant improvement in a spinal cord injury patient, two years after the injury. The patient received multiple injections of his own bone marrow adult stem cells and found substantial recovery of movement and sensation over time.[47]

At present there is little that can be done to repair injured kidneys; a transplant is the usual solution. But there may be hope for the future from adult stem cells. Italian scientists have shown that they can turn human bone marrow stem cells into functional kidney cells in the laboratory. When transplanted into an animal model of kidney damage, the transformed cells started repair of the damaged kidneys and improved function.[48]

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. A national collaboration of several groups has published results showing that adult stem cells can repair knee joint injury, regenerating meniscus and improving knee pain following treatment.[49] While there is still a need for more 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.[50]

Vaccine development: Early attempts at growing viruses used cultures of mixed human fetal tissue, not individual cells, *e.g.*, for the initial example of growth of poliovirus in culture, 1949.[51] Later, poliovirus was produced in human fetal cell lines (WI-38, 1961,[52] fetal female lung; MRC-5, 1966, [53]fetal male

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[44] Pardo-Saganta A *et al.*, Injury Induces Direct Lineage Segregation of Functionally Distinct Airway Basal Stem/Progenitor Cell Subpopulations, *Cell Stem Cell* 16, 184, 2015

[45] Petrella F *et al.*, Airway Fistula Closure after Stem-Cell Infusion, *N. Engl. J. Med.* 372, 96, 2015

[46] Cho YB *et al.*, Long-Term Results of Adipose-Derived Stem Cell Therapy for the Treatment of Crohn's Fistula, *Stem Cells Translational Medicine* 4, 532, 2015, doi: 10.5966/sctm.2014-0199

[47] Jarocha D *et al.*, Continuous Improvement After Multiple Mesenchymal Stem Cell Transplantations in a Patient With Complete Spinal Cord Injury, *Cell Transplantation* 24, 661, 2015

[48] Papadimou E *et al.*, Direct Reprogramming of Human Bone Marrow Stromal Cells into Functional Renal Cells Using Cell-free Extracts, *Stem Cell Reports* 4, 685, 2015

[49] Vangsness CT *et al.*, Adult Human Mesenchymal Stem Cells Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy, *J Bone Joint Surg Am* 96, 90, 2014

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

[51] Enders JF *et al.*, Cultivation of the Lansing strain of poliomyelitis virus in cultures of various human embryonic tissues, *Science* 109, 85, 1949

[52] Original fetal cell cultivations 1961, original poliovirus growth 1962 in WI-1, standardized in WI-38; Hayflick L, Moorhead PS, The serial cultivation of human diploid cell strains, *Experimental Cell Research* 25, 585, 1961; Hayflick L *et*

lung). However, the production of poliovirus for the original Salk and Sabin vaccines was accomplished using cultured monkey tissue. Now most manufacturers of polio vaccine use other specific cell types including monkey cells, and most do not use any fetal cells; none use freshly aborted fetal tissue.

The first individual human cell (not tissue) grown in the lab was a tumor cell in 1951,[54] because the growth character of cancerous cells made them easiest to grow. In the 1960's and 1970's, cell culture work operated under an assumption that younger cells were better, grew faster, lived longer, so fetal cells obtained from abortion were used. These cells adapted to lab culture and continued to grow, becoming known as a "cell line" because they developed as a lineage from different, specific cells grown in the lab. A few human fetal cell lines (WI-38, MRC-5) are still in use for some vaccine production.[55] However, newer cell lines, e.g., A549 cells (adult human),[56] Sf9 cells (insect),[57] EB66 (duck),[58] and better culture techniques make this reliance on fetal cells an antiquated science. In addition, the CDC and other leading medical authorities have noted that "No new fetal tissue is needed to produce cell lines to make these vaccines, now or in the future."[59]

A clear example of the lack of necessity for further fetal tissue is development of the new vaccine -- rVSV-ZEBOV -- against Ebola virus. The successful results of the field trial, published July 31, 2015, were very welcome in the fight against this deadly disease.[60] This successful Ebola vaccine was not developed using fetal tissue or fetal cell lines, but rather with Vero, a monkey cell line, demonstrating again that medical science has moved beyond any need for fetal tissue in useful, lifesaving medical research.[61]

Basic biology research: Broad, undefined claims continue to be made that fetal tissue and fetal cells are needed to study basic biology, development, disease production, or other broad study areas. However, this still relies on antiquated science and cell cultures. Current, progressive alternatives such as induced pluripotent stem (iPS) cells provide an unlimited source of cells, which can be produced from tissue of any human being, without harm to the individual donor, and with the ability to form virtually

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al., Preparation of poliovirus vaccines in a human fetal diploid cell strain, *Am. J. Hyg.* 75, 240, 1962; Hayflick L, The limited in vitro lifetime of human diploid cell strains, *Exp. Cell Res.* 37, 614, 1965.

[53] Jacobs JP *et al.*, Characteristics of a Human Diploid Cell Designated MRC-5, *Nature* 227, 168, 1970

[54] Gey GO *et al.*, Tissue culture studies of the proliferative capacity of cervical carcinoma and normal epithelium, *Cancer Res.* 12, 264, 1952

[55] CDC, Appendix B: Vaccine Excipient & Media Summary, Epidemiology and Prevention of Vaccine-Preventable Diseases, The Pink Book: Course Textbook - 13th Edition, 2015; accessed at: http://www.cdc.gov/vaccines/pubs/pinkbook/index.html

[56] See e.g., Shabram P and Kolman JL, Evaluation of A549 as a New Vaccine Cell Substrate: Digging Deeper with Massively Parallel Sequencing, *PDA J Pharm Sci Technol* 68, 639, 2014

[57] See e.g., Glenn GM et al., Safety and immunogenicity of a Sf9 insect cell-derived respiratory syncytial virus fusion protein nanoparticle vaccine, *Vaccine* 31, 524, 2013; AND Khan AS, FDA Memo: Cell Substrate Review for STN 125285, January 14, 2013; accessed at:
http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM339125.pdf

[58] See e.g., Brown SW, Mehtali M, The Avian EB66(R) Cell Line, Application to Vaccines, and Therapeutic Protein Production, *PDA J Pharm Sci Technol*. 64, 419, 2010

[59] See, *e.g.*, "Vaccine Ingredients – Fetal Tissues," The Children's Hospital of Philadelphia, 2014; accessed July 21, 2015 at www.chop.edu/centers-programs/vaccine-education-center/vaccine-ingredients/fetal-tissues; CDC quote accessed at: http://www.ascb.org/newsfiles/fetaltissue.pdf

[60] Butler D *et al.*, Ebola on trial, *Nature* 524, 13, 6 August 2015; Henao-Restrepo AM *et al.*, Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial, Lancet published online July 31, 2015; doi: 10.1016/S0140-6736(15)61117-5

[61] Agnandji ST et al., Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe — Preliminary Report, NEJM published on April 1, 2015; doi: 10.1056/NEJMoa1502924; originally developed by the Public Health Agency of Canada, which patented it in 2003, http://www.google.com/patents/WO2004011488A2?cl=en

any cell type for study and modeling,[62] or potential clinical application.[63] A new published report convincingly documents that iPS cells are molecularly and functionally equivalent.[64]

Stem cells from umbilical cord blood also show significant potential not only as laboratory models, but also have unique advantages for clinical applications and are already treating patients for numerous conditions.[65] Indeed, studies using "humanized mice", where the immune system is reconstituted with human cells for studies of viral (including HIV) and other infections, immune rejection, and basic immunity, need not use fetal tissue but rather have shown success using human umbilical cord blood stem cells[66] as well as adult peripheral blood stem cells and immune cells, as well as with mice genetically engineered to express human immune system genes.[67]

In regards to the study of normal or abnormal human development, there is no need either for abortion, or for the use of normal human fetal tissue or human fetal cadavers from abortion, to meet these aims. In fact, the proposed bill (SB 1474) clearly allows (parts A.1 and A.2) both for diagnostic procedures (to determine and investigate normal or abnormal development), and for pathology in the event of a deceased unborn or stillborn child. This amply allows for embryological study. Moreover, the prohibitions for use of fetal tissue are clearly articulated as resulting from abortion in parts C., D., E., and definition F.2; this means that embryological study is not prohibited regarding miscarriage or stillbirth (assuming the proper consenting is carried out).

Further, in terms of modeling human tissues and cells, including during development, scientists have now developed methods to form 3-dimensional cellular structures that faithfully form tissue structure and function as that from normal organs. Termed "organoids", the constructs provide superior models to study tissue organization and disease, as well as starting points for potential transplantation. One example is aggregation of hepatocytes into "mini-livers", actually just 3-D monocultures in suspension that are small enough to survive by diffusion of nutrients. Such mini-livers can potentially serve as laboratory models for liver function, as bioartificial livers for toxicity testing, and may even be useful for transplantation for liver regeneration. The laboratory of McGuckin and Forraz has shown that hepatocytes can be produced in culture from umbilical cord blood stem cells, a readily-available source of multipotent stem cells, and have recently reviewed the field of hepatocyte production and liver repair.[68]

Some of the more complex organoid structures are also self-assembling, given the right mix of cells and substrates. In 2009, Sato *et al.* showed that adult intestinal stem cells could recreate the crypt and villus

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[62] See, *e.g.,* Marchetto MC *et al.*, Induced pluripotent stem cells (iPSCs) and neurological disease modeling: progress and promises, *Human Molecular Genetics* 20, R109, 2011

[63] See *e.g.,* Li HL *et al.*, Precise Correction of the Dystrophin Gene in Duchenne Muscular Dystrophy Patient Induced Pluripotent Stem Cells by TALEN and CRISPR-Cas9, *Stem Cell Reports* 4, 143, 2015

[64] Choi J *et al*., A comparison of genetically matched cell lines reveals the equivalence of human iPSCs and ESCs, *Nature Biotechnology* 33, 1173, November 2015

[65] See, *e.g*., Ballen KK *et al.*, Umbilical cord blood transplantation: the first 25 years and beyond, *Blood* 122, 491, 2013; AND, Roura S *et al.*, The role and potential of umbilical cord blood in an era of new therapies: a review, *Stem Cell Research & Therapy* 6, 123, 2015

[66] See, *e.g.,* McDermott SP et al., Comparison of human cord blood engraftment between immunocompromised mouse strains, *Blood* 116, 193, 2010

[67] Shultz LD et al., Humanized mice in translational biomedical research, *Nature Reviews Immunology* 7, 118, 2007

[68] Saba Habibollah, Nico Forraz, and Colin P. McGuckin, "Application of Umbilical Cord and Cord Blood as Alternative Modes for Liver Therapy," *in*: N. Bhattacharya, P.G. Stubblefi eld (eds.), Regenerative Medicine: Using Non-Fetal Sources of Stem Cells (Springer-Verlag, London, 2015), 223-241, doi: 10.1007/978-1-4471-6542-2_22

structure seen in normal small intestine.[69] Likewise, Takebe *et al.* were able to generate self-assembling liver buds, starting first with iPS cells.[70] The cells were differentiated into endodermal cells (precursors to liver), and then cultured with a mixture of additional cell types normally found in mature liver. The endodermal cells differentiated into hepatocytes, and aggregated with the other cells types to form vascularized liver organoids. When transplanted into mice with drug-induced liver damage, these metabolically-active liver organoids were able to link up with the host circulation and rescue the lethal condition.

Recently, even more complex organoids with specific architectures have been constructed. One example is development of a tissue-engineered colon which is also innervated similar to normal colon tissue.[71] Proper innervation is important for colon function. Individuals without properly developed nerve integration in colon tissue (*e.g.*, Hirschsprung disease) develop blockages that can be life-threatening. Both epithelial and mesenchymal cells from colon tissue were isolated and combined in the laboratory onto a scaffold formed of organic molecules designed for cell attachment. The cells assembled into colon organoids with the proper architecture and function found in normal colon, including musculature. Inclusion of neural progenitor cells from normal colon resulted in normal, innervated tissue structures equivalent to native colon.

An Australian team has used various small molecules (retinoic acid and a retinoic acid receptor antagonist) in association with fibroblast growth factor 9 to mimic the normal developmental signals seen during kidney formation.[72] Starting with human iPS cells, they were able to generate kidney organoids that contain 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.)

A Japanese group that previously had developed functional human kidney organoids that secrete urine[73] and also secrete the kidney-derived hormone erythropoietin[74] has now advanced their constructs such that a functional ureter has been grown from the developing kidney.[75]

Several groups have now constructed neural organoids, sometimes called "mini-brains". A group at the University of California-San Diego School of Medicine used iPS cells created from the skin cells of patients with MECP2 duplication syndrome,[76] a genetic condition that leads to various symptoms of neural disorders. Besides modeling in the laboratory the abnormal neuronal development seen with this

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[69] Toshiro Sato *et al*., "Single Lgr5 stem cells build crypt–villus structures in vitro without a mesenchymal niche," *Nature* 459 (14 May 2009): 262- 265, doi: 10.1038/nature07935

[70] Takanori Takebe *et al.*, "Vascularized and functional human liver from an iPSC-derived organ bud transplant," *Nature* 499 (25 July 2013): 481-484, doi:10.1038/nature12271

[71] Minna M. Wieck *et al.*, "Human and murine tissue-engineered colon exhibit diverse neuronal subtypes and can be populated by enteric nervous system progenitor cells when donor colon is aganglionic," *Tissue Engineering Part A* (2015): in press, doi: 10.1089/ten.TEA.2015.0120

[72] 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

[73] Takashi Yokoo *et al*., "Xenobiotic Kidney Organogenesis from Human Mesenchymal Stem Cells Using a Growing Rodent Embryo," *J Am Soc Nephrol* 17 (2006): 1026–1034, doi: 10.1681/ASN.2005101043

[74] Takashi Yokoo *et al*., "Generation of a Transplantable Erythropoietin-Producer Derived From Human Mesenchymal Stem Cells," *Transplantation* 85.11 (June 15, 2008): 1654–1658, doi: 10.1097/TP.0b013e318173a35d

[75] Shinya Yokote *et al*., "Urine excretion strategy for stem cell-generated embryonic kidneys," *Proc. Natl. Acad. Sci. USA* (September 2015): Published online before print, doi: 10.1073/pnas.1507803112

[76] S Nageshappa *et al*., "Altered neuronal network and rescue in a human MECP2 duplication model," *Molecular Psychiatry* (8 September 2015): advance online publication, doi: 10.1038/mp.2015.128

condition, the group took the experiment an additional step and used the organoids to screen for potential drugs to treat the condition. They were able to find one drug candidate that reversed the neuronal alterations seen with the mutation, without harming the cells, and hope to move into clinical trials soon.

Separately, a group at Brown University recently developed their own brain organoids. The mini-brains they developed look like globular collections of cells, but form synapses similar to normal brain tissue.[77] The technique they have developed produces large numbers of organoids, efficiently and cheaply. The technique uses only postnatal cells, harvested from brain tissue.

Another research team recently claimed in a news story that they had created "a nearly complete human brain in a dish that equals the brain maturity of a 5-week-old fetus."[78]

Fetal Tissue Funding, Statutes, and Trafficking:

Use of fresh harvested human fetal tissue is an antiquated and dying scientific practice. One indication of this is the fact that NIH allocated only $76 million for this area in FY2014, out of a total NIH budget of over $30 billion. [79] While there are undoubtedly additional projects funded through other sources, the indications are that fetal tissue research is not advancing, but rather is being replaced by newer, more progressive and successful research areas.

Federal statutes applicable to fetal tissue research are primarily 42 U.S.C. 289g-1 and 289g-2, as well as 42 U.S.C. 274e. §289g–1 pertains to "Research on transplantation of fetal tissue", §289g–2 specifically pertains to "Prohibitions regarding human fetal tissue", and §274e pertains to "Prohibition of organ purchases". Both §289g–2 and §274e prohibit "valuable consideration" for fetal tissue or organs. The meaning of valuable consideration generally includes any profit, but excludes "reasonable payments" for storage, transportation, etc. However, without more rigorous definition, including a pre-set listing of fixed costs, there is uncertainty as to the legality of any payments or goods exchanged for fetal tissue or organs. §289g–1 discusses informed consent provisions for the woman, as well as the physician and any researcher who receives fetal tissue. There are significant questions as to whether adequate informed consent has been given regarding fetal tissue donation nationally. For example, one Planned Parenthood consent form states:

> "Research using the blood from pregnant women and tissue that has been aborted has been used to treat and find a cure for such diseases as diabetes, Parkinson's disease, Alzheimer's disease, cancer, and AIDS."[80]

Obviously these diseases have not been cured, and most certainly not using fetal tissue. The statement is very misleading and seems designed to sway decisions of any women seeking additional justification for abortion, as well as encouraging trafficking of fetal tissue.

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[77] Yu-Ting L. Dingle *et al*., "3D Neural Spheroid Culture: An In Vitro Model for Cortical Studies," *Tissue Engineering Part C: Methods* (October 2015) in press, doi: 10.1089/ten.tec.2015.0135

[78] Emily Caldwell, "Scientist: Most complete human brain model to date is a 'brain changer'," The Ohio State University News Room (August 18, 2015): accessed at https://news.osu.edu/news/2015/08/18/human-brain-model/

[79] NIH Fetal Tissue Research funding, accessed 6 November 2015 at: http://report.nih.gov/categorical_spending_project_listing.aspx?FY=2014&ARRA=N&DCat=Human+Fetal+Tissue

[80] See e.g., Kimberly Leonard, "Is it time to regulate fetal tissue donations?" US News and World Report, Sept. 4, 2015, accessed at: http://www.usnews.com/news/articles/2015/09/04/beyond-abortion-and-planned-parenthood-regulating-fetal-tissue; informed consent form at: http://www.usnews.com/cmsmedia/ce/71/6e9b40d548bdb7147eb94f9b27ab/150902-consentform-graphic.jpg or at: http://www.centerformedicalprogress.org/human-capital/document-vault/

There is also concern that the physician assertion in §289g–1 -- "no alteration of the timing, method, or procedures used to terminate the pregnancy was made solely for the purposes of obtaining the tissue" -- may be contravened.

In summary, continued use of fetal tissue is an outdated science, presents no advantage to medical research, and raises grave ethical concerns. Noncontroversial, successful alternatives exist to the use of fetal tissue in research.