Exploring Alternatives to Fetal Tissue Research

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To the Distinguished Chairs and Honored Members of the Committee.
Thank you for the opportunity to provide testimony regarding this important subject.

I am a cell and developmental biologist, and am testifying on my own behalf and at the request of the Chairman; associations and positions noted are for identification purposes only. I have been a Professor and researcher for approximately 40 years. My scientific experience includes federally-funded laboratory research, including post-doctoral work at Los Alamos National Laboratory, and scientific research, teaching and mentoring graduate and undergraduate students, medical and nursing students, in the areas of cell biology, embryology and developmental biology, cell and tissue culture, molecular biology and biochemistry.

There is no scientific necessity for the continued taxpayer funding of fresh fetal tissue, organs, and body parts from induced abortion. Ample scientific alternatives exist, and modern alternatives have overtaken any need for fresh fetal tissue. Moreover, the practice of using fetal tissue from induced abortion raises significant ethical problems, not least of which is the nebulous interpretation of the term "valuable consideration" or compensation for expenses in the harvest and processing of fetal organs and tissues. Taxpayer funding, which is what this discussion is really about, should go to successful, patient-focused alternatives.

Adult Stem Cell Transplants-Successful Alternatives

A 2015 review found that as of December 2012, over one million patients had been treated with adult stem cells.[1] 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, backed by peer-reviewed publications.

There are at present at least 3,500 ongoing or completed clinical trials using adult stem cells listed in the NIH/FDA-approved database,[2] 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.

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

[2] Search term: http://www.clinicaltrials.gov/ct2/results?term=adult+stem+cell+transplants&type=Intr accessed March 29, 2016.

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, in the last few years a French group found that they 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.[3] Likewise a 2015 review paper notes that bone marrow adult stem cell transplant remains a curative option for chronic myelogenous leukemia.[4] 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.[5] And a groundbreaking study has advanced a promising therapy to manage graft-versus-host disease, a problem sometimes seen with transplants for cancer.[6] This has now launched a first-of-its-kind clinical trial at the University of Kansas Medical Center, with help from Kansas' Midwest Stem Cell Therapy Center.[7]

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 benefit 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.[8]

Studies have indicated that adult stem cells can have a protective,[9] and possibly even a reparative,[10] effect on individuals who have experienced neurological damage due to stroke, even years after the stroke event. The stroke study has now been expanded into a nationwide Phase 2b study for safety and efficacy. For traumatic brain injury (TBI) one research group has published a study indicating that TBI in adults is also amenable to treatment with adult stem cells.[11]

One 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

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

[4] 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

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

[6] 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

[7] Evaluation of Umbilical Cord-Derived Wharton's Jelly Stem Cells for the Treatment of Acute Graft Versus Host Disease; Clinical Trial NCT03158896.

[8] 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

[9] Sean I. Savitz *et al*., "Intravenous Autologous Bone Marrow Mononuclear Cells for Ischemic Stroke," *Annals of Neurology* 70.1 (2011): 59–69, doi: 10.1002/ana.22458

[10] Gary K. Steinberg *et al*., "Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study," *Stroke* 47.7 (2016): 1817-1824, doi: 10.1161/STROKEAHA.116.012995

[11] Charles S. Cox Jr. *et al.*, "Treatment of Severe Adult Traumatic Brain Injury Using Bone Marrow Mononuclear Cells," *Stem Cells* 35.4 (April 2017): 1065-1079, doi: 10.1002/stem.2538

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.[12] 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 previous intervention for multiple sclerosis had shown an improvement in neurological disability for patients. Treated patients also showed significant relapse-free survival (80%) and decreased neurological lesions.

Unlike current therapeutic methods such as drug and antibody-based treatments, which only stop or slow disease progression, cell-based therapies have shown the ability to put autoimmune patients into remission. A 2017 review outlined numerous cell-based methods for treatment of multiple sclerosis, including pre-conditioning followed by adult stem cell transplant, and point out that the field shows great promise as well as heartening early results for MS patients.[13]

Remission from MS was shown in another 2017 paper by a larger multicenter group, covering 25 centers in 13 countries and results for 281 multiple sclerosis patients.[14] In total, 78% of these patients had aggressive, progressive forms of multiple sclerosis. Transplant of the patient's own adult stem cells produced lasting remissions in most patients. Overall survival at five years was 93% of patients, with almost half of all patients still in remission from multiple sclerosis symptoms at the five-year mark.

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.[15] 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.

Several published medical authors now note, "Hematopoietic stem cell transplantation (HSCT) is the only curative therapy for sickle cell disease."[16] 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.[17] 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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[12] 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
[13] Scolding NJ *et al.*, Cell-based therapeutic strategies for multiple sclerosis, *Brain* 140, 2776–2796, 1 November 2017
[14] Paolo A. Muraro *et al.*, "Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis," *JAMA Neurol*. (Published online February 20, 2017): doi: 10.1001/jamaneurol.2016.5867
[15] 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
[16] Bernaudin F *et al.*, Long-term results of related myeloablative stem cell transplantation to cure sickle cell disease, *Blood* 110, 2749-2756, 2007
[17] 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.[18]

Another possible route is to use genetic engineering of autologous cells to repair the genetic problem; use of autologous cells avoids the need for tissue matching of a donor. Genetic correction of autologous epidermal stem cells has been used successfully to replace all of the skin for a young boy in Germany suffering from a genetic condition called junctional epidermolysis bullosa (JEB).[19]

As was mentioned previously, adult stem cells are now being used to treat some conditions while still in the womb. Besides the ongoing trial for thalassemia, there are now several cases where unborn children have been successfully treated with adult stem cells for severe immune deficiencies,[20] and another reported result where unborn children were successfully treated *in utero* for osteogenesis imperfecta,[21] a genetic condition that causes brittle bones that break very easily.

Adult stem cells have also shown their ability to regrow the lens of the eye. Lin et al. reported that by using a new, cautious surgical technique for removal of a clouded, cataract lens, they could also preserve and stimulate lens endogenous stem cells in the eye. These adult stem cells would then re-grow a new lens and restore vision. The group demonstrated the efficacy of this technique in a clinical trial with 12 infants, successfully restoring visual function to these patients who had previously had cataracts.[22]

Scientists in Pittsburgh have shown that adding a biological protein matrix to a wound can attract and stimulate adult stem cells to restore muscle.[23] In their trial, three out of five patients showed significant muscle restoration in their legs.

Inaccurate Claims for Fetal Tissue

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

-Vaccines
-Humanized mice to study infectious diseases
-Basic biology observations
-Transplantation to treat disease conditions and injuries

Distinction between fresh fetal tissue and historic fetal cell lines

Before addressing the history of these areas of fetal tissue research and modern alternatives, it is important for the Committee to understand the distinction between fresh aborted fetal tissue (which is

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

[19] Tobias Hirsch *et al*., "Regeneration of the entire human epidermis using transgenic stem cells," *Nature* 551.7680 (16 November 2017): 327–332, doi:10.1038/nature24487

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

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

[22] Lin H *et al.*, Lens regeneration using endogenous stem cells with gain of visual function, *Nature* 531, 323, 17 March 2016

[23] 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

the topic under discussion) and historic fetal cell lines derived from an abortion. Historically, cell and tissue culture was begun in the early 1900's to provide physicochemical, physiological and biochemical control over the cellular environment in experiments. This allows significantly more complete characterization of the cells, their growth and their responses to stimuli, especially when a homogeneous culture of cells is used. Moreover, cell culture provides identical experimental replicates; reproducibility is a cornerstone of science. The use of fresh tissues introduces genetic, cellular and physiological variability into experiments which prevents accurate replicates. Establishment of a cell line involves placing small pieces of tissue, or tissue that has been dissociated mechanically or enzymatically, into a cell culture dish. After a period of time (hours or days depending on the tissue and protocol), some of the cells in the tissue source will attach to the surface of the culture dish, and continue to grow and divide on the culture surface; this is termed a "primary culture." Unattached tissue and cells will be washed from the culture dish, and the still-attached cells will be subcultured into other dishes. This subculture is termed a "secondary culture" and also a "cell line", as the cells, which are the progeny of the original cells and not a part of the source tissue, serve as the progenitors for any subsequent cell cultures (their lineage). Cell lines can be maintained in laboratory culture for days to years and decades. The first human cell line grown in the lab—HeLa—was derived from cervical carcinoma in 1951,[24] and this cell line continues to be grown in labs and used in experiments.

Cells that have been grown in laboratory culture for decades are not a "tissue" or an "organ" or a "body part" in any sense of the terms. To conflate the two is unscientific, willfully confusing deception. Fetal tissue is derived from ongoing abortion to harvest more tissue. Fetal cell lines, though derived from an abortion in the 1960's or 1970's, and thus ethically disadvantaged, do not involve ongoing abortion to harvest fresh cells; instead, the cells are propagated in laboratory culture, sometimes cryopreserved (stored frozen) for future use.

Vaccines

I bring up this point precisely because some of the claims made regarding fetal tissue are inaccurate for this very reason. Some of the earliest attempts at growing viruses sometimes used cultures of mixed human fetal tissue. For example, the proof of principle experiment showing that polio virus could be grown in non-nervous tissue culture in 1949, used human fetal tissue. [25] But it is decidedly not true that the 1954 Nobel prize given to Enders et al. was for production of polio vaccine, as some have claimed, nor even for growth of enough virus used to produce the polio vaccine.

The fact is, the original Salk and Sabin vaccines were both produced using laboratory-cultured monkey tissue.[26] Later, some poliovirus was produced in human fetal cell lines (WI-38,[27] fetal female lung; MRC-5, [28]fetal male lung) and some continues to this day. [29] But it misrepresents the science to say that

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

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

[26] Salk JE, Recent Studies on Immunization against Poliomyelitis, *Pediatrics* 12, 471, 1953; and Salk JE *et al*., Formaldehyde Treatment and Safety Testing of Experimental Poliomyelitis Vaccines, *Am. J. Public Health* 44, 563, 1954; and Salk JE *et al*., Studies in Human Subjects on Active Immunization Against Poliomyelitis II. A Practical Means for Inducing and Maintaining Antibody Formation, *Am. J. Public Health* 44, 994, 1954; and Sabin AB, Present status of attenuated live-virus poliomyelitis vaccine, *JAMA* 162, 1589, 1956

[27] 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 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.

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

polio vaccine was produced in "fetal tissue." HeLa cells were also used in the past to make some polio vaccine,[30] but it would be likewise misleading to say that polio vaccine was produced in human cervical carcinoma tissue.

Nonetheless, even the American Society for Cell Biology has passed on mistaken information regarding use of fetal tissue vs. historic fetal cell lines for vaccines.

> "Fetal tissue already has proved its value in a wide range of life-saving vaccines against diseases that include measles, mumps, rubella, chickenpox, polio, hepatitis A, hepatitis B, rabies, and shingles, she said."
> Correction (4/22/2016, 2:57 p.m.): This article originally quoted Rep. Janice Schakowsky as naming diphtheria, tetanus, and whooping cough among a group of vaccines developed with the help of fetal tissue. She was relying on information provided by the American Society for Cell Biology, which has corrected its list to remove those vaccines. This article has been revised to reflect the correction.[31]

and

> According to the Centers for Disease Control and Prevention, "some vaccines such as rubella and varicella [were] made from human cell-line cultures, and some of these cell lines originated from aborted fetal tissue, obtained from legal abortions in the 1960s. No new fetal tissue is needed to produce cell lines to make these vaccines, now or in the future."[32]

Nonetheless, fresh fetal tissue has <u>never</u> been used for vaccine production, and currently most vaccines do not even use the historic fetal cell lines, e.g., much of the polio vaccine is made using the Vero (monkey) cell line.

One clear example of the lack of necessity for fetal tissue or historic fetal cell lines in vaccine production is the new shingles vaccine, Shingrix.[33] The new vaccine, made using CHO (hamster) cells, is superior to the older vaccine. Another example of is the recent success of a field test of a vaccine against Dengue virus, a close relative of Zika.[34] The vaccine provided 100% protection,[35] but was developed using monkey cells and a mosquito cell line.[36] And another example is development of the vaccine rVSV-ZEBOV, against Ebola virus. This successful Ebola vaccine was not developed using

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[29] See, e.g., 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

[30] Scherer WF *et al*., Studies on the propagation in vitro of poliomyelitis viruses. IV. Viral multiplication in a stable strain of human malignant epithelial cells (strain HeLa) derived from an epidermoid carcinoma of the cervix, *J. Exp. Med*. 97, 695, 1953

[31] Paul Basken, The Chronicle of Higher Education

[32] from: "Talking Points", Fetal Tissue Research, Second in an occasional series of pocket-sized briefing papers from the American Society For Cell Biology, April 2001. NOTE: this talking point sheet was removed from ASCB website in 2015, and replaced with a new set of talking points that did not mention this CDC quote.

[33] Package insert, https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm581605.pdf

[34] Kirkpatrick BD *et al*., The live attenuated dengue vaccine TV003 elicits complete protection against dengue in a human challenge model, *Sci. Transl. Med*. 8, 330ra36, 2016.

[35] Check Hayden E, Dengue vaccine aces trailblazing trial, *Nature*, 16 March 2016, doi: 10.1038/nature.2016.19576

[36] Men R et al., Dengue Type 4 Virus Mutants Containing Deletions in the 39 Noncoding Region of the RNA Genome: Analysis of Growth Restriction in Cell Culture and Altered Viremia Pattern and Immunogenicity in Rhesus Monkeys, *J. Virology* 70, 3930, 1996; and Medina F et al., Dengue Virus: Isolation, Propagation, Quantification, and Storage, *Current Protocols in Microbiology* 15D.2.1-15D.2.24, November 2012

fetal tissue or historic 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.[37]

Basic biology observations

Numerous, progressive alternatives exist to provide models for basic biology and developmental work. One that I will mention is induced pluripotent stem (iPS) cells, which can provide an unlimited source of identical cells for experimental replicates, and which can be produced from tissue of almost any human being, without harm to the individual donor, and with the ability to form virtually any cell type for study and modeling,[38] or potential clinical application.[39]

One of the most significant uses of iPS cells as well as some adult stem cells has been in modeling growth and development of tissues and 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.[40]

More complex organoids with specific architectures have also been constructed. One example is development of a tissue-engineered colon which is also innervated similar to normal colon tissue.[41] An Australian team has generated 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.[42] Cerebral organoids have also been used to discern the mechanism of action of Zika virus on developing brains that results in microcephaly.[43]

Humanized mice

Mice constructed to contain a human immune system (termed "humanized mice") can be used for the study of immunity and immune development, vaccines, immunotherapies, and cancer. Construction of humanized mice starts with immunodeficient mice (made so by irradiation to destroy their bone marrow, or genetic mutation to make them deficient in immune cells). The mice receive transplants of human

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[37] 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

[38] 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

[39] 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

[40] 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

[41] 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

[42] 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

[43] Garcez PP, Loiola EC, da Costa RM, Higa LM, Trindade P, Delvecchio R, Nascimento JM, Brindeiro R, Tanuri A, Rehen SK. Zika virus impairs growth in human neurospheres and brain organoids. *Science* 2016;352:816-818

immune cells, which take up residence in the mouse bone marrow and create a human immune system within the mouse's body. Historically, humanized mice were constructed by transplant of aborted fetal tissue such as fetal liver, fetal bone marrow, or fetal liver with fetal thymus, because it was thought that the young fetal tissue would be more robust in growth.

Robust ethical alternatives exist that do not use fetal tissue. The majority of humanized mice are actually constructed using human umbilical cord blood stem cells[44] as well as adult peripheral blood stem cells and immune cells; another model involves mice genetically engineered to express human immune system genes.[45]. Another recent example is the "NeoThy" humanized mouse, using neonatal thymus tissue and umbilical cord blood stem cells.[46] Neonatal thymus, routinely excised during cardiac surgeries, is abundant and allows for construction of up to 50-fold more humanized mice per donor compared with aborted fetal tissue. Neonatal thymus tissue is also more developmentally mature than fetal tissue, which provides an advantage in constructing more clinically relevant humanized mouse models.

Transplantation

The first recorded fetal tissue transplants were in 1921 in the UK, in a failed attempt to treat Addison's disease,[47] and in 1928 in Italy, in a failed attempt to treat cancer.[48] 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.[49] Today, patients take insulin shots and pharmaceuticals to control their diabetes, and adult stem cell transplants have shown some success at ameliorating the condition.[50]

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."[51] 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,[52] even **while the patient is still in the womb**.[53]

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[44] See, e.g., McDermott SP *et al*., Comparison of human cord blood engraftment between immunocompromised mouse strains, *Blood* 116, 193, 2010. and Huey DD, Niewiesk S. Production of humanized mice through stem cell transfer, *Current Protocols in Mouse Biology 8*, 17–27, 2018.

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

[46] Brown ME *et al.*, A Humanized Mouse Model Generated Using Surplus Neonatal Tissue, *Stem Cell Reports* 10, 1175-1183, April 10, 2018 doi: 10.1016/j.stemcr.2018.02.011

[47] Hurst AF *et al.*, Addison's disease with severe anemia treated by suprarenal grafting, *Proc R Soc Med* 15, 19, 1922

[48] Fichera G, Impianti omoplastici feto-umani nel cancro e nel diabete, *Tumoi* 14, 434, 1928

[49] Federlin K *et al.*, Recent achievements in experimental and clinical islet transplantation. *Diabet Med* 8, 5, 1991

[50] 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

[51] Ishii T, Eto K, Fetal stem cell transplantation: Past, present, and future, *World J Stem Cells* 26, 404, 2014

[52] 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

[53] Krieger LM, "UCSF welcomes in-utero stem cell transplant baby" *The Mercury News* May 29, 2018; accessed at: https://www.mercurynews.com/2018/05/29/ucsf-performs-first-ever-transplant-in-a-fetus/; In Utero Hematopoietic Stem Cell

Between 1988 and 1994, roughly 140 Parkinson's disease patients received fetal tissue (up to six fetuses per patient), with varying results.[54] 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.[55]

In 2001, the first report of a full clinical trial[56] (funded by NIH) using fetal tissue for Parkinson's patients was prominently featured in the *New York Times*,[57] 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."

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.[58] 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.[59] In contrast, adult stem cells have shown initial success in alleviating Parkinson's symptoms.[60]

A 2009 report emphasized 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.[61]

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.

While NIH does not fund any fetal stem cell clinical trials, there is cause for concern here as well. In a recent example, a young boy developed tumors on his spine, resulting from fetal stem cells injected into his body.[62]

Transplantation for Alpha-thalassemia Major (ATM), Clinical Trial NCT02986698; clinicaltrials.gov; Loukogeorgakis SP, Flake AW. In utero stem cell and gene therapy: Current status and future perspectives, *Eur J Pediatr Surg* 24, 237, 2014

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[61] 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

[62] 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

Federal statute

I want to point out that the federal statute under discussion, pertaining to fresh aborted fetal tissue, only references "research on transplantation of human fetal tissue for therapeutic purposes." As it happens, NIH has not funded any transplantation experiments or clinical trials since at least 2007. All of the current funding for fetal tissue research is basic research; it is not for transplantation. Federal statute is silent on basic research using fetal tissue.

NIH Funding of Fetal Tissue Research

Research/Disease Areas (Dollars in millions and rounded)	FY 2014 Actual	FY 2015 Actual	FY 2016 Actual	FY 2017 Actual	FY 2018 Estimated (Enacted)	FY 2019 Estimated
Human Fetal Tissue	$76	$80	$103	$98	$103	$95

Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)
Table Published: May 18, 2018
Accessed 20 November 2018 at: https://report.nih.gov/categorical_spending.aspx

In conclusion, there is no scientific necessity for continued use of fetal tissue, and it presents no advantage to medical research. Taxpayer funds should be redirected to the numerous, modern, more productive scientific alternatives.