

IX. Biomedical
Research and Fetal
Tissue
Exhibits

Exhibit 9.1

FRED UPTON, MICHIGAN
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FOURTEENTH CONGRESS
Congress of the United States
House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115

Majority (202) 225-2927
Minority (202) 225-3641

February 16, 2016

Dr. David Brenner
Vice Chancellor & Dean
University of California San Diego School of Medicine
9500 Gilman Drive, Dept 0012
La Jolla, CA 92093-0012

Dear Dr. Brenner:

I am writing on behalf of the Democratic Members of the Select Investigative Panel of the Energy & Commerce Committee ("Select Panel"). On January 21, 2016, the Chair of the Select Panel, Marsha Blackburn, sent a letter requesting documents related to the Select Panel's investigation of "issues related to fetal tissue research."

Chair Blackburn's request asks for extensive documentation about how fetal tissue is obtained but appears not to seek information that would allow the Select Panel to explore why fetal tissue research is important or how it has helped advance our understanding and treatment of a range of diseases and conditions. The Democratic Members of the Select Panel believe that an objective and balanced inquiry must consider the past and potential future benefits of fetal tissue research.

I am therefore writing to request your assistance in providing the Panel with information that will further our understanding of the following:

- 1) Past benefits of fetal tissue research.
- 2) Potential future benefits that might be gained through continued fetal tissue research.
- 3) Unique aspects of fetal tissue in research, in comparison with adult cells, stem cells, or other cellular organisms that might be used for research purposes.

The Chair's document requests to you and others also ask for extremely sensitive information, including the identities of persons involved in fetal tissue research, such as the names of clinical and supervisory personnel at academic institutions and medical schools. Some

Letter to David Brenner
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of the information that has been requested is the type of information that is generally protected from disclosure by state and federal laws such as the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Family Educational Rights and Privacy Act (FERPA).

The Democratic Members of the Select Panel are concerned that some of the Chair's requests, including the request for names of certain clinical and supervisory personnel, seek information that puts people's privacy and safety at risk. As of now, this information is being sought without any rules in place to govern the Select Panel's handling of personally identifiable and other sensitive information. Without any formal rules on this subject, the Select Panel cannot provide the kind of assurances or protective measures that are often preconditions to disclosure under federal or state privacy laws.¹

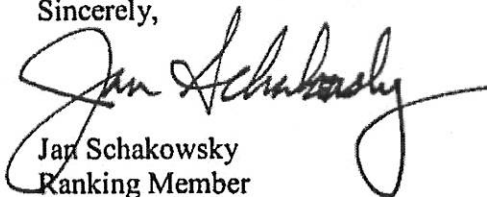
The Democratic Members have asked the Chair both to stop requesting certain types of personally identifiable information, and to work with us to have the Select Panel vote on formal rules that would protect information that we receive. To date, however, our requests to establish such rules have gone unanswered, leaving it to each individual recipient to negotiate the terms under which information might be withheld or provided. We have asked to be included in these discussions but the majority has refused.

The privacy and safety of individual researchers, healthcare providers, medical students, and patients requires much more than any potential ad hoc and unenforceable assurance of the Chair or her staff, and I want you to know that we will keep fighting to have clear rules put in place.

Please contact Jacquelyn Bolen on the Select Panel Democratic Staff at (202) 226-9471 or by email at jacquelyn.bolen@mail.house.gov to discuss a timeline for providing the additional information that we have requested.

We appreciate your cooperation in the Select Panel's work.

Sincerely,



Jan Schakowsky
Ranking Member
Select Investigative Panel

cc: The Honorable Marsha Blackburn, Chair
Select Investigative Panel

¹ See, e.g., 45 C.F.R. § 164.512(e)(1)(ii) (requiring notice of the request for protected health information to affected individuals and "reasonable efforts to secure a qualified protective order" for the information prior to any disclosure in response to a lawful subpoena issued as part of judicial or administrative proceedings).

Exhibit 9.2



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American Medical Colleges**
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Darrell G. Kirch, M.D.
President and Chief Executive Officer

April 22, 2016

The Honorable Marsha Blackburn
Chairman
Select Investigative Panel
Committee on Energy and Commerce
House of Representatives
Washington, DC 20515

Dear Chairman Blackburn:

I write on behalf of the Association of American Medical Colleges (AAMC) in response to your March 30 letter regarding the AAMC's support for human fetal tissue research. We would like to thank you personally, along with other members of the Energy and Commerce Committee, for your dedication to medical research as reflected in your support of the 21st Century Cures Act.

The Panel has requested information that will help it better understand assertions included in the joint statement organized by the AAMC expressing concerns over state legislative proposals that would restrict the use of human fetal tissue in research. We welcome the opportunity to provide the Panel with additional information on the importance of fetal tissue research in the context of biomedical research in general.

The AAMC believes where research pathways have been or can be discovered, such accomplishments reflect the strength of the research system as a whole. Research that looks promising today for one purpose may lead to discoveries in unexpected areas, provide insights about existing knowledge, or indicate that a new pathway should be explored. By closing the door on one type of research, we may never know what advances we might have attained. For every bit of knowledge or advance that has resulted from research using fetal tissue, alone or in combination with other research, there may be other questions and potential lines of inquiry that merit further exploration, using all available methods.

Scientists must consider and explore diverse paths, while leveraging available knowledge from the work and findings of previous research. When a particular approach appears successful, the research may illuminate other approaches that could lead to similar results or different outcomes. Similarly, researchers are unlikely to determine in hindsight whether their work could have been accomplished using another method. The testing of approaches in different scientific models, however, can be critical for understanding both the mechanisms of disease and the opportunities for translation and applicability of the knowledge for further clinical research.

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For example, Gelber and colleagues in a recent review in the *American Journal of Obstetrics and Gynecology* note that “fetal tissue benefits scientific research across many fields, including physicians and scientists who may not even realize its contribution to their work.”¹ Gelber et al. note, for example, that the HEK293 cell line useful in transfection and production and purification of human proteins, originated from the kidney cells of an aborted embryo. The cell line has been referenced in more than 28,000 articles, and has also been useful in the study of preeclampsia, fetal drug exposure, placental gene transfer, and development of therapeutics.²

The cell lines themselves have limitations, and access to fresh fetal tissue remains critically important. “[O]ff-the-shelf fetal cell lines are of limited use for scientists because they do not faithfully mimic native tissue and represent only a subset of cell types: WI-38 and MRC-5, for example, were derived from fetal lungs. The lines can also accumulate mutations after replicating in vitro over time...For all of these reasons, researchers turn to fresh tissue.”³

In parts of the letter to the AAMC, the Panel has requested “scientific information” on topics that are not readily addressed through the scientific process. For example, the Panel requests information describing any medical research using fetal tissue “that cannot or could not be conducted with other human tissue” (item 4); and a list of vaccines developed using fetal tissue “that could not have been developed using other human tissue, or cannot now be developed using other human tissue” (item 6). Where we stand today, it remains uncertain. Such questions could not be answered about most types of discoveries even with perfect hindsight. We support multiple approaches in continuing research to validate results in different models, which is especially important when moving new knowledge into clinical application.

In our quest to develop knowledge that can enhance health, lengthen life, and reduce illness, scientists need to understand such issues in human development, across all stages of life. Understanding the unique properties of human development at each stage is important to translate discovery from basic research to applications that enhance health. For example, primary human astrocytes derived from human fetal tissue and primary monocytes cells derived from blood donations are used to understand dysfunction of the blood-brain barrier, which is seen in neuroinflammation, and contributes to mortality and morbidity in multiple sclerosis, encephalitis, traumatic brain injury, and stroke. Fetal tissue cells also have been used to generate a 3-dimensional *organoid* model of the human stomach. The model helps characterize molecular signals and cell types present in the developing stomach, and of disease resulting from *Helicobacter pylori* infection.⁴ Human fetal and adult liver cells producing hepatitis B viral proteins in culture helped identify barriers to developing cell models of hepatitis B, such as cellular production of antiviral microRNAs.⁵

Fetal tissue has uniquely enabled the growth and study of viruses and ultimately, the development of vaccines. Research focused on the cultivation of poliovirus proved to be successful in aborted human embryo brain tissue after failure in chick, mouse, and monkey cells.⁶ Subsequent research demonstrated that this success was not linked to the use of neurons, and that the virus could be grown in cell lines from other embryonic tissues.⁷ The cell lines from this, and similar work, provided a host for cultivating adenovirus, MMR, varicella, rabies, and other viruses resulting in the development of

The Honorable Marsha Blackburn
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lifesaving vaccines (items 1 and 2).^{8,9} The AAMC stands by its statement, joined by more than 60 scientific and academic organizations, that restrictions on fetal tissue research "...would limit new research on vaccines not yet developed, for treatments not yet discovered, for causes of diseases not yet understood."¹⁰

Although cures for serious diseases and chronic conditions are the ultimate hope of health care providers, patients, families, and society, improvements in medical care that result from research are often incremental, adding new information to the body of knowledge about a disease to provide more effective treatments, slow disease progression, and improve quality of life. No one type of research is guaranteed to lead to a cure for a specific condition, and in no case do we ask scientists to prove that cures have been obtained or will be the outcome of the research before allowing the research to go forward (item 5).

In regard to AAMC's view on medical advancements that have been achieved using induced pluripotent stem cells (iPSCs) and other resources, and to information that addresses resources other than human tissue procured from aborted fetuses that can be used "when scientists need a cellular system that is less differentiated" (item 3), our response would be similar. The AAMC fully supports use of human tissue, including fetal and placental tissue, cell lines – including iPSCs, adult and embryonic stem cell lines, animal models, genetically modified or synthetic organisms, and other approaches to further knowledge to improve the health of all.

At the March 2 hearing of the Panel, Dr. Lawrence Goldstein of the University of California-San Diego Medical Center provided expert testimony on the properties of fresh fetal tissue distinct from other cell lines, as well as on differences between tissues from aborted fetuses and spontaneous abortion or miscarriage. To a question about research on the Zika virus and microcephaly, Dr. Goldstein responded that fetal tissue would be an efficient and important area of focus for this research. Two weeks later, the Panel noted in a press release a breakthrough in Zika research made by three academic medical centers, Johns Hopkins University, Florida State University, and Emory University, that was conducted with induced pluripotent stem cells. We believe this is an excellent illustration of our points above. The breakthrough using iPSC is not contrary to -- or undermining of any part of -- the importance of working directly with fetal tissue in Zika research. The AAMC celebrates advances in research and potential clinical applications for this devastating virus, from any avenue, and not knowing where the breakthroughs will come only supports the need to conduct many types of research.

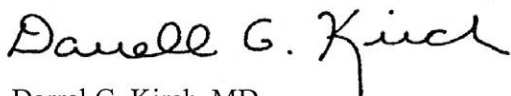
More recently, results reported in the journal *Nature* further indicate how the Zika virus may affect fetal development, using fetal tissue. The investigator at the University of Pittsburgh Medical Center is quoted, "It is absolutely essential to study Zika infection in human fetal tissue." This research does not suggest there is no role for iPSCs or other models. Nor does the research at Johns Hopkins suggest fetal tissue research should be abandoned because of an outcome in another area. We are cautiously encouraged at the pace of these discoveries on the Zika virus, and look forward to more progress in our understanding and development of an effective vaccine and treatment for microcephaly. Medical research must be both deliberate and responsive to urgent public health needs and new discoveries.

The Honorable Marsha Blackburn
April 22, 2016
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In closing, we note that a vital part of the United States research system's success is the diversity of approach and competition, as well as collaboration among investigators and laboratories. Research gives hope to those suffering and plants the seeds for our nation's future development and economic growth.

Please contact Heather Pierce, JD, MPH (hpierce@aamc.org) with any questions or further comments.

Sincerely,

A handwritten signature in black ink that reads "Darrel G. Kirch". The signature is written in a cursive style with a large, prominent "K".

Darrel G. Kirch, MD
President and Chief Executive Officer

cc: The Honorable Jan Schakowsky

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<http://www.ncbi.nlm.nih.gov/pubmed/25363776>
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- ⁷ Enders JF, Weller TH, Robbins FC. Cultivation of the Lansing strain of poliomyelitis virus in cultures of various human embryonic tissues. *Science* 1949;109:85-7.
- ⁸ Nobel Foundation. Presentation speech: Nobel Prize in Physiology or Medicine 1954. Nobel Lectures, Physiology or Medicine 1942-1962. Amsterdam (United Kingdom): Elsevier Publishing Company; 1954: 443-7.
- ⁹ Wadman M. *Nature*, 2015, op cit.
- ¹⁰ Association of American Medical Colleges. Statement in support of fetal tissue research. <https://www.aamc.org/download/444248/data/statementinsupportoffetaltissueresearch.pdf>. March 18, 2016. Accessed April 21, 2106.

American Academy of Pediatrics

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April 25, 2016

The Honorable Marsha Blackburn
Chairman, Select Investigative Panel of the Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Chairman Blackburn:

On behalf of the American Academy of Pediatrics (AAP), a non-profit professional organization of 64,000 primary care pediatricians, pediatric medical sub-specialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults, I write in response to your letter dated March 30, 2016 on fetal tissue research.

We appreciate your dedication to our shared goal of improving the health of America's children. In particular, we are pleased to continue to work with you to ensure that the National Institutes of Health (NIH) is appropriately including children in the clinical research it funds. We greatly appreciate your successful effort to include language in the 21st Century Cures Act that would require NIH to begin systematically collecting and reporting data on the actual numbers of children enrolled in NIH studies.

I am happy to provide further clarification to several points you addressed in your letter. Everyday there is a growing body of evidence regarding the detrimental effects associated with the Zika virus (ZIKV), including congenital microcephaly and Guillain-Barré syndrome, and yet there is a great deal that we do not know about Zika and how it may affect the health of women and children. It is essential that we aggressively expand medical research in this area to gain a greater understanding of this serious public health crisis. According to the Centers for Disease Control and Prevention (CDC), between January 1, 2015 and April 13, 2016 there had been 833 confirmed cases of Zika reported in the United States and its territories. Indeed, experts at the National Institute of Allergy and Infectious Diseases have confirmed that Zika infection in the United States will continue to grow. Further, a recent article in the *Lancet* estimates that approximately one percent of babies born to women infected with Zika during the first trimester of pregnancy will develop microcephaly.

It is essential to study the Zika virus in human tissue of different stages to learn how the virus is causing its damage so that we may be find out how to protect the brain as it develops. While this research can be performed in animal models, it is unclear how reliably the growth and development of such animal brains replicates the growth and development of the human brain. A recent report in the *New England Journal of Medicine* concludes that "(f)uture studies at various gestational ages will offer better insight into the role of ZIKV infection in abnormal brain development and provide markers for its detection."

The use of fetal tissue has been an important factor in the development of numerous lifesaving vaccines for children. The chicken pox, hepatitis A, polio, rabies, and rubella vaccines are grown in human cell cultures developed from two cell lines that were derived from fetal tissue in the 1960s. According to the CDC, it is estimated that for just the children born between 1994 and 2013, "vaccination will prevent an estimated 322 million illnesses, 21 million hospitalizations, and 732,000 deaths over the course of their lifetimes." While it is possible that these vaccines could have been developed using other human tissue, it would have no doubt delayed these lifesaving vaccines from reaching the children who needed them. Re-developing new vaccines without fetal tissue would expose children to unnecessary risk since the current vaccines are known to be safe and effective, and developing new vaccines would subject children to unnecessary clinical trials.

These established cell lines derived from fetal tissue are currently being used to develop an Ebola vaccine. According to data from the World Health Organization and the United Nations Children's Fund (UNICEF), in March 2015, the recent Ebola outbreak had killed over 5,000 children and "another 16,000 lost a primary caregiver." Akin to the research currently being conducted on the Zika virus, it is important that researchers have every resource at their disposal to develop new treatment breakthroughs given the uncertain and changing landscape of infectious disease research.

Given the historical and future potential benefits of this research, particularly in light of the Zika virus outbreak and its impact on child health, the AAP reaffirms its strong commitment to continued federal funding for fetal tissue research.

Sincerely,



Benard P. Dreyer, MD, FAAP
President

BPD/jdb

cc. The Honorable Janice Schakowsky, Ranking Member, Select Investigative Panel of the
Committee on Energy and Commerce

April 25, 2016

The Honorable Marsha Blackburn
Chair, Select Investigative Panel
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chairman Blackburn:

Thank you for your March 30, 2016 letter to the American Congress of Obstetricians and Gynecologists (ACOG) regarding fetal tissue research.

Representing more than 57,000 physicians and partners in women's health, ACOG is committed to fostering improvements in all aspects of the health care of women and establishing and maintaining the highest standards of practice. Although ACOG does not conduct fetal tissue research, we recognize the value of medical research in improving the lives of our patients and their families. As an organization of physicians and other women's health care practitioners who work every day to save and improve women's lives, ACOG strongly supports the continued practice of such research.

Fetal tissue research has played an integral role in the development of life-saving vaccines. For example, the polio vaccine was developed based on cultures derived from fetal cells. Vaccines for measles, rubella, and hepatitis A were also developed in cell lines initially derived from fetal tissue. Today, researchers are using fetal cells to help develop and test vaccines against Ebola, HIV, and hepatitis B and C.

Researchers are also currently working to develop a vaccine for the Zika virus, which causes severe birth defects, and has been linked to pregnancy loss and other serious complications. ACOG's members work with their patients every day to achieve healthy pregnancy outcomes. But, because there currently is no cure or vaccine for Zika and much remains unknown about the virus, diagnosis and care options will remain limited until more research is completed. As summer approaches, the virus is predicted to spread within the United States, and more American families will be affected. As a society, we must use the full potential of science, including fetal tissue research, if we hope to develop a vaccine that will prevent Zika-related birth defects and fetal and infant deaths. Fetal tissue analysis has already provided researchers with important information about the virus. Given the evidence that Zika causes birth defects, fetal tissue research is likely to continue to play a strong role in combating this disease.

The nature of scientific research is that it frequently yields unanticipated results. *See* April 6, 2016 Letter from Department of Health and Human Services, Assistant Secretary for Legislation

The Honorable Marsha Blackburn

April 25, 2016

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Jim R. Esquea to Hon. Jan Schakowsky. While much of the current research utilizing fetal tissue is aimed at examining certain diseases or developing specific vaccines, researchers cannot, today, identify which diseases may be cured or when. These studies could yield important discoveries with applications to myriad other sicknesses, helping countless individuals. Accordingly, closing the door on fetal tissue research would not only halt promising ongoing research but could negatively affect future medical research, and prevent development of future treatments and cures, in ways that are impossible to predict.

Again, thank you for your letter, and for soliciting our input on this important issue.

Sincerely,



Mark S. DeFrancesco, MD, MBA, FACOG
President

cc: The Honorable Jan Schakowsky

 The Children's Hospital of Philadelphia®

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[Via Email]

September 15, 2016

The Honorable Jan Schakowsky
Ranking Member
Select Panel on Infant Lives
2266 Rayburn House Office Building
Washington, D.C. 20515

Dear Representative Schakowsky:

I am writing on behalf of The Children's Hospital of Philadelphia (CHOP) in response to your letter of July 28, 2016.

The use of fetal tissue for medical research has led to many discoveries that have allowed scientists and physicians to better understand human development, fetal and newborn diseases, and to develop new treatments for adult and pediatric illnesses. Researchers who work on tissue regeneration with the hope that people who currently rely on organ transplants or need daily medications to replace hormones their sick organs no longer make, gain significant knowledge about normal tissue development that they try to mimic in the laboratory. Scientists who focus on preventing and treating newborn diseases such as infant leukemia can make faster progress because disease-causing mutations target fetal cells specifically. Fetal tissue has been used to seek treatments and cures for patients who suffer from devastating diseases, including diabetes, Down syndrome and rare blood disorders.

Additionally, many vaccines that are now used to prevent devastating infections in children and adults were discovered because scientists had access to fetal tissues. It is clear that fetal tissue research has been instrumental in countless discoveries and scientific advances. These have translated to improving the health of people globally, and currently, giving hope to countless others who are waiting for new scientific breakthroughs to help them overcome their specific diseases.

Sincerely,



Peter M. Grollman
Senior Vice President, Public Affairs
The Children's Hospital of Philadelphia

cc: The Honorable Marsha Blackburn, Chair
Select Panel on Infant Lives

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November 10, 2016

By E-mail

The Honorable Jan Schakowsky
2367 Rayburn House Office Building
Washington, DC 20515

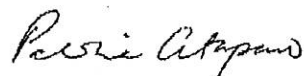
Dear Congresswoman Schakowsky:

I am responding to your letter of July 28th, 2016 to Lee C. Bollinger, President of Columbia University. I apologize for the delay in getting back to you.

Dr. Hans Snoeck, Professor of Medicine in Microbiology and Immunology at Columbia University Medical Center (CUMC), prepared the attached response to the questions you posed in your letter. I believe you and the other members of the Select Committee will find this information useful.

Please let me know if Dr. Snoeck, I, or any other member of the CUMC faculty can be of any further assistance on this or any other matter. Thank you.

Very truly yours,



Patricia Sachs Catapano
Associate General Counsel

cc: The Honorable Marsha Blackburn
Dr. Hans Snoeck
Lee Bollinger
Ms. Jacquelyn Bolen

Columbia University Medical Center Response to Congresswoman Schakowsky's Letter of July 28th, 2016. Prepared by Dr. Hans-Willem Snoeck.

1. Past benefits of fetal tissue research

Scientists have used fetal tissue in biomedical research for over sixty years. While not used as widely today, fetal tissue research (FTR) has played a significant role in the discovery of several treatments that are commonplace today. Vaccines are the prime example. Developing a vaccine requires being able to grow a virus. Viruses grow in cells. Early on fetal cells were much easier to grow than adult cells. Hence many vaccines currently used (such as rubella and rabies) were developed and are still produced using cell lines generated previously from fetal lung tissue.

Ender, Weller and Robbins, whose work was a crucial step in the eventual discovery of the polio vaccine, used fetal cells for some of their work. While the polio vaccine was not developed using fetal cells, the research leading to its identification and to the understanding of its biology was built upon FTR conducted a decade earlier. A final example is aging research. A fetal cell line was used in the 1960s to show that all cells, even those free of viruses and prior environmental exposures, have a limited capacity to keep dividing. This concept, known as the Hayflick limit, is the subject of one of the most cited papers of all time and is the foundation of human aging research.

This observation led to the discovery of telomeres by Blackburn, Greider and Szostak, who were awarded the Nobel Prize in 2009 for this work. Equally important, and perhaps somewhat ironically, FTR has played a crucial role in the development of several new and improved research and cell generation techniques that has obviated some, but by no means all of the need for FTR. In other words, if not for FTR, scientists would not have many of the research tools at their disposal that they do today. A perfect example of this are induced pluripotent stem (IPS) cells. These cells are similar to embryonic stem cells (ESCs), which are isolated and grown from early embryos, but, in contrast to the latter, have been generated by reprogramming adult cells to an 'embryonic' state. IPS cells would never have been developed if ESCs had not been discovered first. In essence, the fact that ESC generation required embryos was one of the driving forces behind reprogramming research.

There is no doubt that IPS cells may hold the key to unlocking the mysteries on many diseases and may lead to treatment and cures, but it is also true that were it not for FTR and research involving ESCs, IPS cells would not exist. Furthermore, although there are many similarities between IPS cells and ESCs, they are not identical. There are many instances where FTR are still very much irreplaceable. This is because, while IPS cells are very similar to ESCs, they are genetically manipulated cells that do show molecular differences compared to ESCs. The question how reliably they model human development and disease

compared to ESCs has not been fully resolved yet, and ESCs remain the 'gold standard' for the field for now.

2. Potential future benefits

The list below is just a few examples of how FTR may lead to a better understanding of disease and possible future treatments and cures.

A. Diseases that affect the fetus

Congenital abnormalities can be genetic or acquired. Acquired abnormalities are often caused by a virus, such as Zika, cytomegaly virus or rubella, which affect the brain of a developing fetus. To study any type of congenital abnormality, access to 'normal' control tissue for comparison is essential, but for obvious reasons, it is very difficult, and would be in many cases unethical, to conduct research experiments on the brains of normally developing fetuses. Research using fetal tissue makes it possible to examine how viruses and other ailments affect a developing brain. Using FTR, scientists can study brain tissue in the petri dish and better understand how viruses and other diseases progress and how best to stop them. Zika is a perfect example. Zika can prevent the full development of the fetal brain – microcephaly. By using FTR, researchers can gain much better knowledge of how and where the virus attacks the brain. Scientists are currently working with three dimensional structures known as organoids. Brain organoids, which are grown from ESCs and IPS cells, have shown strong promise in being able to model the disease; however, the validity of these models cannot be confirmed without the use of FTR.

B. Disease modeling and regenerative medicine

As mentioned in the response to question 1, without FTR, we would never have had access to many of the research tools, such as IPS cells, upon which we rely today, tools which are slowly but surely leading to advances in the field of regenerative medicine. Whether it is generating new cells and potentially organ systems, or perhaps more importantly, generating better and more precise disease models upon which researchers can more safely and more efficiently conduct their experiments, FTR has played a crucial role in getting us to where we are today. Will they play as large a role going forward? With the development of IPS and ES cells, perhaps not, but it is important to remember that (a) we would never have made the advances we have without FTR, and (b) nobody knows for sure where will be the next steps forward. Don't we want science to have at its disposal as many tools as possible? FTR is no doubt one of those tools.

Humanized mice are an example of this. These are mice with a human immune system. In the fetus, the blood and therefore the cells of the immune system are made in the liver, not in the bone marrow as in adults. Studies in the mouse have

shown fetal liver blood stem cells engraft much better in another individual than adult bone marrow blood stem cells. While this was an interesting finding, no one would conclude from this that human fetal liver transplantation should replace bone marrow transplantation for leukemia. However, the last fifteen years have seen a renewed interest in fetal liver blood stem cells. It was found that human fetal liver blood stem cells could easily engraft the bone marrow of severely immunodeficient mice, thus creating mice with human blood cells and a human immune system. Furthermore, T cells, the cells infected by HIV, are made from blood stem cells in an organ called the thymus during fetal life. Hence, humanized mice with human blood stem cells, human blood cells and a human thymus that recapitulate many features of the human immune system can now be made. This is critical in many fields, but one good example is HIV. HIV does not infect mouse cells, but does infect human immune cells in humanized mice. This has therefore become an important tool in HIV research.

C. Understanding human biology

Looking beyond the need to assist in the development of stem cell-based approaches to disease modeling and regenerative medicine, judicious use of fetal material will be required to perform biomedical research that is specifically relevant to humans. This research is not limited to disease, but also to normal and abnormal human development.

3. Unique aspects of fetal tissue research

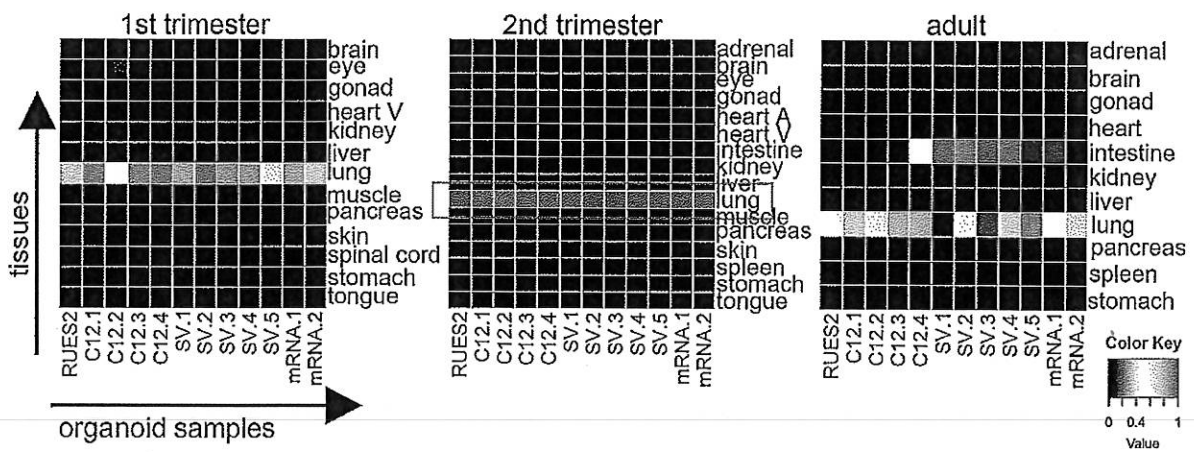
Fetal tissue has characteristics in terms of cell types present, cell proliferation, migration, gene expression, organization and architecture that are specific to a given stage of development. While some types of somatic stem cells can indeed be procured from non-fetal sources such as blood stem cells from cord blood, other types of cells, such as Mesenchymal stem cells, which can differentiate into fat, bone and other connective tissues, can only be generated from fetal. Access to human fetal tissue is still essential. The brain is an example. The human cortex is much more complex than that of a mouse, and is built layer by layer during development from dividing cells in the brain, called radial glia. While we have learned a lot from the mouse, and while novel technologies such as brain organoids derived from ES and IPS cells are extremely promising, fetal brain tissue is a unique resource in this field because scientists can study how specifically the human cortical architecture develops.

4. Fetal tissue research at CUMC

Dr. Megan Sykes, Professor of Medicine, directs the Columbia Center for Translational Immunology (CCTI). This Center has developed methods for generating human immune systems in mice that lack immune systems of their own. This model, which requires fetal human bone marrow stem cells and thymus tissue, allows new insights into the workings of the human immune

system and, most importantly, the testing of new treatments such as transplantation tolerance induction and cancer immunotherapies. This mouse model, which is available to the entire Columbia research community as a core service, is of great importance for studies of human immunology throughout the medical center. More recently, the CCTI extended the technology into a "personalized immune" mouse model, in which patients' bone marrow stem cells are used in combination with fetal thymus tissue to generate and thereby recapitulate the patient's own immune system in a cohort of mice. This model is being used to obtain a new understanding of human autoimmune disease, such as type 1 diabetes, and develop new treatments for these diseases as well as cancer.

Dr. Hans Snoeck, Professor of Medicine, has pioneered the differentiation of embryonic stem cells and iPS cells into lung organoids, which are now used to gain insight into idiopathic pulmonary fibrosis, a lethal disease for which there is currently no treatment. They may also be of use in developing ways to replace diseased lung tissue. A critical question in these studies is to what extent the organoids are identical to human lung, and exactly at which stage of development are they. To answer this question, a genome-wide comparison with human fetal and adult lung is required. As an example of this type of studies, the Snoeck lab determined the expression level of all the genes expressed in the organoids, and compared, using sophisticated bioinformatics approaches, with publicly available databases on gene expression in human organs in the first and second trimester of gestation, and of adult organs. The data are illustrated in the figure below --the brighter green the box, the higher the similarity. The data show that the thirteen organoids used in these experiments are the most similar to second trimester human fetal lung (green rectangle). This is extremely important information, as it indicates that the organoids still represent mid-gestation fetal, and not adult human lung. In this context, the broader field of human development and regenerative medicine needs more detailed gene expression profiles of a larger set of fetal tissues and cells.



5. Obtaining fetal tissue for research

It is becoming more difficult to obtain human fetal tissue for these important studies. We are very concerned because all of the above work depends on the availability of fetal human tissues. For the generation of humanized mice, post-natal surgical thymus specimens cannot substitute, as these do not grow in the immunodeficient mice, and there is currently no method available for making these tissues from stem cells, though there is an effort underway in the CCTI to meet this difficult challenge. This effort, of course, again requires human tissue to gauge our in vitro differentiated cells against. Similarly, the work on generation of lung organoids is not possible without the information gained from studying human fetal lung. The unavailability fetal tissue cells threatens the continuation of the important studies of human immune and lung disease as well as the development of novel therapies in these areas.



Dartmouth College

Office of the Provost

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Martin N. Wybourne
Senior Vice Provost for Research
Francis and Mildred Sears Professor of Physics

martin.n.wybourne@Dartmouth.edu

September 12, 2016

The Honorable Jan Schakowsky
United States House of Representatives
Ranking Member
Select Investigative Panel

Dear Representative Schakowsky,

I write in response your letter to Dartmouth's President Philip Hanlon dated July 28th, 2016. Your letter posed several questions regarding the benefits of fetal tissue research.

Much has been written about the importance and distinctiveness of fetal tissue research. In response to your questions, we have provided a sample of this literature:

Wadman, Meredith. "The Truth about Fetal Tissue Research." *Nature* 528 (December 10, 2015): 178–81. See article here: <http://www.nature.com/news/the-truth-about-fetal-tissue-research-1.18960>.

"FAQs on Fetal Tissue Research." The American Society for Cell Biology, April 2016. <http://www.ascb.org/wp-content/uploads/2015/12/fetal-tissue.pdf>.

Chapman, Audrey, Mark Frankel, and Michele Garfinkel. "Stem Cell Research and Applications Monitoring the Frontiers of Biomedical Research." American Association for the Advancement of Science and Institute for Civil Society, November 1999. https://www.aaas.org/sites/default/files/content_files/Stem%20Cell%20Research%20and%20Applications%20Report.pdf. (see The Science of Stem Cell Research and Potential Therapies)

You should also know that Dartmouth has not experienced any recent changes related to the availability of fetal tissue, although Dartmouth has historically used very little of this material.

Please let me know if you have any additional questions.

Sincerely,

Martin Wybourne

Why is human fetal material needed for research?

University-based biomedical research aims to improve human health and the United States has made an enormous investment in this enterprise, largely through research grants provided by the National Institutes of Health (NIH). Despite innumerable breakthroughs in medical research and practice arising directly from this support, many diseases, whether common like diabetes, sickle cell disease, Parkinson's, and cancer or rare like amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) and Fanconi anemia, remain "lost causes" of medicine. Though in certain cases maintenance therapies provide a degree of relief, such as insulin injections for diabetes or hydroxyurea therapy for sickle cell anemia, they nevertheless entirely fail to correct the underlying problem. In the worst of cases, comfort care is all that can be offered. The field of regenerative medicine seeks to do more than ease pain and slow decline; the goal is to cure by better understanding the mechanisms of how diseases develop and how to repair or replace the very cells and tissues impaired or lost due to disease, damage, and decay.

Scientists working in these fields are investigating ways to repair or create the cells, tissues or organs that have been damaged by disease. But, how does a researcher know that the tissue they have repaired or engineered will actually function as it should once transplanted into a patient? For that matter, by what method does an investigator actually learn *how* to repair or engineer a type of cell or tissue? It does not take a trained scientist to understand that an effective approach to this problem is to compare the engineered cells or tissue to their healthy counterparts prior to transplantation. From where is this "comparison" tissue obtained?

Despite various ethical and moral tensions expressed by individuals throughout the ages, the use of human biopsies, excess surgical or pathology specimens, and cadaveric tissues has enabled physicians and scientists to better understand the form and function of our own bodies and more recently, to obtain the very cells and tissue to which rudimentary repaired or engineered versions might be functionally compared. Healthy donors, patients, and others whose tissues and sometimes entire bodies have been donated to research via their own decision or by that of a legally-recognized surrogate, literally give of themselves to improve the world for all of us. In this way, many people working in the field of biomedical research take tragedy and turn it into knowledge that benefits humankind.

Human fetal material falls within this spectrum of tissue donation and research. The field of vaccine R&D is probably the best known example of how fetal material provides an invaluable resource to scientific and medical progress; most recently in work seeking to better understand and combat the spread of Zika virus, just as it did chicken pox and polio, among others. But, there are many avenues of active biomedical research beyond vaccine development and a number of those areas likewise benefit significantly from the use of fetal material; in many cases the use of fetal material is the *only* effective approach. Why, despite the availability of modern tools and methods, including the use of embryonic and "reprogrammed" stem cells, does fetal tissue remain needed? The most obvious answer is rather straightforward: nature is far better at making tissues and organs than scientists are.

Every field of human endeavor leading to ground-breaking technologies began simply but then built upon itself through a series of transitional technologies and approaches until goals were reached. Here, one might trace the path from tin cans connected via a length of string, through Bell's telephone, to the wall-mounted rotary, to the cordless, to the "brick" mobile, to the latest smart phone. Though the field of regenerative medicine seeks to replace defective cells and tissues, it must first understand how they are made, why they may fail, how to repair them, how to mimic or engineer them in the laboratory and how they can be protected from a patient's immune response when used in transplantation. The best clues to these processes come from nature itself and one must go the anatomic place and time during development to find those answers.

For example, if a researcher seeks to better understand the heart and post-heart attack tissue damage, it is relatively simple to obtain human heart tissue from various adult sources including from victims of heart attack. However, if one wants to understand how to generate new or replacement heart tissue, one must understand the *formation* of the heart, what types of cells during development first make the heart, what genes are "on" and "off" in those cells relative to non-heart cells, and how do those genetic "switches" change over time as the heart forms? Such information might then be used to engineer or "coax" non-heart cells to form cardiac tissues in the laboratory for use in transplantation. Scientists investigate these questions by obtaining and studying the "pre-heart" cells from the only time in development when they are present: the fetal period. This same principle holds true for many other types of cells during development that are present for only a short period of time and then disappear as organs grow and mature. We obtain various types of cells from critical developmental timepoints in nature and use them to teach us how to mimic or engineer their cognates in the laboratory for use in regenerative therapy.

Another example of this includes research to provide insulin-producing cells for transplantation into diabetics, including juvenile diabetics. Children suffering from Type I or juvenile diabetes lack the capacity to make the hormone insulin because their insulin-producing cells (pancreatic beta cells) have been destroyed by what is likely an immune system attack launched by their own body; an "autoimmune" disease. One goal of such research is to use stem cells to make human pancreatic beta cells for transplantation into diabetics, thereby relieving them of the daily finger pricks and insulin injections they need to stay alive.

Pancreatic beta cells are made during the early stages of human development. From a fertilized egg to a newborn, the development of different cells and tissues is a stepwise process involving many genes and different types of cells. We need to understand the normal or "natural" process of pancreatic beta cell formation, in order to learn how to direct the maturation or "differentiation" of human stem cells into functional beta cells. We use human fetal material to understand how pancreatic beta cells are normally made and then use that information to design experiments that direct the differentiation of stem cells.

In addition, we use fetal blood- and immune system-forming tissue to study the human immune response. This involves replacing the mouse immune system with a human immune

system. Mice that have human immune systems are an invaluable scientific resource, but these mice are engineered to this condition only by means of the use of human fetal material. These mice allow us to model and better understand the auto-immune attack that leads to type I diabetes, among other diseases. This works by combining human immune and insulin-producing cells in a living system (the mouse). Similar approaches are being used to learn how to make other transplantable cells and tissue “invisible” to immune system attack so that they might serve as “universal donor” stem cells for use in a wide variety of different transplantation strategies. Here, the use of fetal blood- and immune system-forming cells transplanted into mice allows the “universal donor” cells and tissues to be tested for their ability to resist rejection by a human immune system. In these experiments the use of fetal blood-forming material is far superior to other sources such as adult bone marrow or even cord blood. Better research leads to better therapies.

If human fetal tissue is needed, why can it not be obtained from miscarriages instead of abortion? Here, timing is very important. Almost all miscarriages happen at home or in locations in which fetal material is not recovered and, importantly, preserved in a usable state. Just as obtaining tissue during a scheduled surgery or an in-hospital autopsy soon after death provides tissue that is untainted by decay relative to obtaining those same tissues from the morgue or a funeral home, obtaining fetal material from elective pregnancy termination is far superior to obtaining whatever material might be recoverable following spontaneous miscarriage, even assuming a mechanism existed for the collection of such material.

Some have pointed out that despite the scarcity of tissue available from miscarriages, that even a small amount of this rare material could be used to generate cell lines capable of additional growth/expansion in the laboratory to the potential benefit of hundreds of other laboratories. While it is true that cell lines are invaluable resources in biomedical research, cell lines cannot teach us about the operation of cells that are organized into systems that perform bodily functions, such as integrated organs and tissues. In other words, as an organ, the heart (for example), is more than a collection of cardiac cells. There are multiple different types of heart cells along with other organ-specific supporting cell types and structures that form/combine at specific times during development. Simply put, an organ’s cell lines do not tell the story of how that organ develops or works.

What is more, there are many types of cells in nature, including almost all neurons, that scientists have not been able to make grow or multiply as cell lines. Neurons, heart cells, and certain kidney cells, to name but three types critical to our understanding of human disease and cellular therapies, appear never to divide again once they are formed in nature; yet continued cellular division is an absolute requirement for the formation of a cell line. Non-dividing cells are termed “post-mitotic” and the only way to generate a cell line from them is to genetically engineer and/or damage them such that they ignore their own regulatory signals and continue to grow unchecked in a manner that is quite similar to what occurs in advanced stages of cancer. While such so-called “immortalized” cell lines remain of value to certain avenues of research, they are completely unsuitable for many areas of research designed to understand how cells normally grow and develop. For studies such as these, as well as research designed to better

understand complex tissue organization and function, the use of formed tissue, not cells, is the only effective approach.

Why not study animal tissues instead? While humans and lower animals share an amazing amount of biology in common, and have similarities that contribute enormously to ideas relevant to human health, not everything is the same between us. There are many conditions, diseases, and basic biological features of our species that are uniquely human. To understand human-specific differences, one must use human tissue. A case in point is the human fovea within the eye. We possess high acuity color vision due to a specialized area of the human retina, the fovea. Such a high-acuity area does not exist in most mammals or other experimental model organisms. Tragically, this is the very area that is prone to degenerate as we age. Age-related macular degeneration, which occurs in approximately 25% of people over age 75, leads to loss of high-acuity vision. All of the activities of daily living, even those as simple as face recognition, are lost in macular degeneration. To understand the vulnerability of this area, or to regenerate it someday, we need to understand its development and function. Although some retinal stem cells exist, including those from humans, they do not form a fovea in the lab. Our lack of knowledge of the normal development of the fovea stymies attempts to generate this tissue in the lab. Because the fovea develops during gestation, and is almost unique to humans, human fetal tissue provides the required starting point for such studies.

Science is a tool for methodically exploring the world and improving the human condition. It can proceed most rapidly and efficiently when investigators have the best available resources. The advancement of science is not, however, an unqualified objective. Scientists must take into account societal and ethical concerns. The use of human fetal tissue in research can be conducted in a fair and responsible manner. Abortions occur in this country because they are a legal medical procedure. Fetal remains from this procedure can simply be discarded as medical waste. Or, adult women can donate those remains to research, in much the way other human tissue and organs, following surgery or death, is donated to research. The process requires attention to issues of informed consent and other ethical considerations (no financial or other inducements, a separation between the decision to undergo the procedure and a decision to donate, no change in treatment afforded whether a donation is made or not). With these issues taken into consideration and properly conducted, the important and unique resource of human fetal tissue can be used responsibly in research.

Select resources for further reading:

An authoritative overview describing the use of mice containing a human immune system to study infectious disease and vaccine development - Table 4 therein describes many infectious diseases studies using this system:

<http://www.nature.com/nri/journal/v12/n11/full/nri3311.html>

A fundamental understanding of many biological processes relevant to human health and disease has stemmed from experimental studies in similar “humanized” animal models, particularly in rodents. A few examples of these include:

Hepatitis C

<http://www.nature.com/nprot/journal/v7/n9/abs/nprot.2012.083.html>

HIV

<http://www.nature.com/cmi/journal/v9/n3/full/cmi20127a.html>

Malaria

[http://www.cell.com/trends/parasitology/fulltext/S1471-4922\(15\)00145-2](http://www.cell.com/trends/parasitology/fulltext/S1471-4922(15)00145-2)

Graft-versus-host disease (GvHD)

<http://www.ncbi.nlm.nih.gov/pubmed/26588186>

<http://www.nature.com/cmi/journal/v9/n3/full/cmi20122a.html>

Cancer

<http://www.ncbi.nlm.nih.gov/pubmed/25185190>

<https://www.ncbi.nlm.nih.gov/pubmed/26479923>

<http://www.nature.com/onc/journal/v35/n3/full/onc201594a.html>

<http://www.humouse.org/images/publications/vatakis2011.pdf>

HARVARD
UNIVERSITY



July 7, 2016

Ms. Jacquelyn Bolen
Investigative Counsel, Democratic Staff
Select Investigative Panel of Energy & Commerce
2367 Rayburn House Office Building
Washington, DC 20515

Dear Jacquelyn:

I am responding on behalf of Dean Jeffrey Flier to Representative Schakowsky's February 16, 2016 letter seeking information on the past and future benefits of fetal tissue research and the unique role fetal tissue continues to play in critical areas of biomedical research. In response to your letter and other inquiries regarding the importance of fetal tissue research, we have prepared the attached background paper that we offer in response to your questions.

I hope you find the document helpful in regards to your inquiry and will remain available to facilitate answers to any additional questions you may have as your review continues.

Sincerely,

A handwritten signature in black ink, appearing to read "Kevin Casey".

Kevin Casey
Associate Vice President for Public Affairs & Communications
Harvard University

cc: The Honorable Marsha Blackburn, Chair
Select Investigative Panel



JOHNS HOPKINS
M E D I C I N E

Paul B. Rothman, M.D.

The Frances Watt Baker, M.D. and Lenox D. Baker, Jr., M.D.

Dean of the Medical Faculty

Chief Executive Officer

September 20, 2016

The Honorable Jan Schakowsky
Ranking Member, Select Panel on Infant Lives
U.S. House of Representatives
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Dear Representative Schakowsky:

In response to your request dated July 28, 2016, Johns Hopkins is pleased to provide additional information on the use of human fetal tissue in biomedical research. As a leading recipient of federal research funds, we appreciate the opportunity to inform the Select Panel on Infant Lives about the unique importance of this material and applaud your interest in its value.

It is critical that human fetal tissue continue to be available to academic researchers as it exhibits unique characteristics that thus far have not been replicated in any other systems. Human fetal cells enable our researchers to develop laboratory models of diseases that can be investigated in ways not possible in patients. A number of our researchers are working in areas that already have, or we anticipate will benefit from the use of fetal tissue to better understand disease progression, test potential therapies and ultimately relieve human suffering.

1) Past benefits of fetal tissue research.

Through the use of human fetal cells acquired from collaborators in Germany, one of our research teams has developed new and genetically accurate models of medulloblastoma, glioblastoma, uveal melanoma and other tumors of the brain and eye—and some other rare cancers for which no good treatments or laboratory models exist. This team also discovered that a key molecule, BRAF, can activate cells to transform to cancer. More study is needed to understand how to stop BRAF or possibly even prevent it from transforming these cells in the first place.

The hallmark of amyotrophic lateral sclerosis, or ALS, is gradual degeneration of nerve cells in the brain and spinal cord that normally control muscles. As the nerve cells degenerate, the muscles they control grow weak and ultimately stop working and ALS patients typically die by suffocation. Although biomedical research often requires decades to get basic discovery to the bedside, one of our research teams has been working with human fetal cells for more than 10 years in hopes of developing a way to use these cells as a treatment to slow or stop the progression of ALS. They originally discovered that injecting a certain type of fetal cell into mouse ALS models appears to protect the existing cells from degenerating. This finding was so promising for a potential ALS treatment that the FDA has approved an investigational new drug application for early stage clinical trials.

degenerating. This finding was so promising for a potential ALS treatment that the FDA has approved an investigational new drug application for early stage clinical trials.

Normal eye development and our ability to see requires significant blood flow: characterized by growth of blood vessels in the developing eye that then disappear once the retina is formed. Using fetal eye tissue, our researchers were the first to show the location of two forms of the VEGF protein, which are responsible for the growth and disappearance of these blood vessels, are located. In that study, they found that although it is difficult to know where VEGF is in the blood vessels of fully developed eyes, in human fetal eye tissue, they were able to see that VEGF is clearly associated with two specific cell types. This discovery can be used to learn more about how tumors and diabetic retinopathy progress.

2) Potential future benefits that might be gained through continued fetal tissue research.

Because of the unique nature of fetal tissue, a wide array of neurological conditions likely could benefit from the use of human fetal cells in research. Unlike some other adult tissues, the human brain cannot be regenerated in the laboratory. Moreover, brain cells are difficult to remove from live patients without significantly invasive procedures and adult brain cells grow slowly in the lab.

One leading cause of death in malaria patients is a complication known as cerebral malaria. In these cases, although the parasite does not infect the brain directly (because it cannot cross the blood brain barrier), it still can lead to abnormal behavior, loss of consciousness, seizures and coma. One of our research teams uses human fetal cells to induce adult brain cells to grow better in culture, in order to understand how microbes and parasites activate the blood brain barrier and cause inflammation. Knowing this will help us get certain drugs across the blood brain barrier to better treat countless brain infections, disorders and diseases.

Cell-based therapies, treatments that involve transplanting cells that can grow to repair or replace diseased tissue like that in ALS, will only come to fruition with access to human fetal cells.

3) Unique aspects of fetal tissue in research, in comparison with adult cells or other cellular organisms that might be used for research purposes.

Human fetal tissue is unique because we are not yet able to replicate *the development* of human tissues using any other methods. In order to develop new therapies to treat disease, we need to understand how normal tissue transforms to disease to identify the best “entry” points to stop the process. This is why it is so important to be able to model diseases in the lab. Due to limited access to all human tissues, most research has been performed in mouse models or more recently, with the use of induced pluripotent stem cells (iPSCs). While both are easier to access and work with, both are limited in their abilities to fully mimic human disease.

Many researchers have shown that cells from mice or other animals do not transform into cancer or respond to certain drugs the same way as human cells. Others have found that iPSCs are not a useful model.

Representative Schakowsky:

Recipient Name

Page 3

Our researchers have shown that human fetal cells hold unique properties that are not shared even with human iPSCs: human fetal cells survive, mature and migrate more reliably. They also have found that human fetal cells behave more reliably than human embryonic or iPSC-derived neural stem cells, and they do not appear to form tumors as these other cells do. These properties make human fetal cells important for developing cell-based therapies.

For example, our researchers who study pilocytic astrocytoma, the most common pediatric brain tumor, need to look at regional effects in the brain, which cannot be modeled by iPSCs. In addition, benign prostatic hyperplasia and prostate cancer together affect more than 90 percent of all men during their lifetime. Although our researchers have tried and failed at developing models of these conditions with adult cells from the prostate or bone marrow, they have successfully generated models using human fetal prostate cells.

4) Summary of any research conducted since 2010 that Johns Hopkins University has been involved in that used fetal tissue or relied upon other studies that used fetal tissue.

Since 2010, our researchers have used human fetal cells to:

- Develop new brain tumor models to treat brain cancer
- Confirm that certain discoveries made in mice hold true in humans, whereas others do not
- Show that, unlike other types of cells, human fetal cells do not develop tumors when transplanted into mice
- Demonstrate that human fetal cell transplants in mice are not toxic
- Successfully transplant into mouse spinal cord human fetal cells that survived, migrated and grew as hoped
- Discover that as prostate cancer progresses, cells from the bone marrow are recruited to the tumor and these cells could be exploited to deliver drugs directly to the tumor to avoid exposing the rest of the body to aggressive cancer drugs. At least one clinical trial testing this is now underway.
- Discover where specific proteins are located in blood vessels to promote or inhibit vessel growth

5) Description of any recent changes experienced by Johns Hopkins University in the availability of fetal tissue for research and the related impact of these changes, including whether or not there have been interruptions and/or delays in research as a result.

One research team reported that adverse publicity led a private funder to request that they alter their research approach to use mouse instead of human fetal cells. Some researchers have not experienced much change to date. However, we are generally concerned that changes in the availability of human fetal tissue will result in major setbacks in the understanding of devastating diseases and development of future treatments and cures for patients. We also are concerned that, due to the sensational nature of linking fetal tissue research to broader concerns about abortion, faculty will be discouraged from pursuing important scientific questions due to difficulty in acquiring needed material or out of fear of personal reprisal.

Representative Schakowsky:
Recipient Name
Page 4

Sincerely,

A handwritten signature in black ink, appearing to read "P. Rothman". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Paul B. Rothman, M.D.
Dean of the Medical Faculty
CEO, Johns Hopkins Medicine



May 25, 2016

Jan Schakowsky
Ranking Member
Select Investigative Panel
House Energy and Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

Office of the Senior
Vice President for Research

tel 503 494-1085
fax 503 494-1099

Daniel Dorsa, PhD
Senior Vice President for Research

dorsad@ohsu.edu
www.ohsu.edu/research

Mail code: L335
3181 S.W. Sam Jackson Park Rd.
Portland, OR 97239-3098

Dear Ranking Member Schakowsky,

On behalf of Oregon Health & Science University (OHSU), thank you for your letter inquiring about the overall benefits of research that include the use of fetal tissue.

OHSU is pleased to join with over 61 academic medical centers, scientific and medical societies in Association of American Medical Colleges-organized letter in support of current federal policies governing research that includes fetal tissue.

The AAMC letter highlights the many benefits of research using fetal tissue, including past lifesaving discoveries, such as the development of vaccines for diseases such as polio, hepatitis A, measles, mumps, rubella, chickenpox, and rabies.

Research using fetal tissue helps researchers replicates human systems and is also used when scientists need a cellular system that is less differentiated than adult cells. This type of research has helped improve our understanding of numerous health issues including early brain development, neurocognitive disorders, maternal and fetal health conditions, congenital heart defects, Down syndrome, and other infectious diseases such as HIV/AIDS and influenza.

For example, in HIV/AIDS research, the use of fetal tissue has been critical to advancing animal models that can mimic the human immune system. Having an animal model that can generate a human immune response is crucial to developing much needed vaccines for this terrible disease and others, such as Hepatitis C Virus, Dengue Virus, Epstein Barr Virus and Cytomegalovirus.

“Research that looks promising today for one purpose may lead to discoveries in unexpected areas, provide insights about existing knowledge, or indicate that a new pathway should be explored” stated AAMC President Darryl Kirsch in his April 22 letter to Chairman Blackburn. “By closing the door on one type of research, we may never know what advances we might have attained.”

While we can only guess what future benefits lie in store as a result of research using fetal tissue, we know that research using fetal tissue has saved millions of lives and we hope it will continue to save millions more.

Thank you for your interest in the benefits of research using fetal tissue.
Should you have additional questions, don't hesitate to contact Lynne Boyle,
Director, Federal Relations.

Sincerely,

A handwritten signature in black ink, appearing to read "Daniel Dorsa". The signature is written in a cursive style with a large initial "D".

Daniel Dorsa, Ph.D.
Senior Vice President for Research

HARRIET S. RABB

VICE PRESIDENT and
GENERAL COUNSEL

PHONE: 212-327-8070

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September 21, 2016

Honorable Jan Schakowsky
Ranking Member
Select Investigative Panel
House of Representatives
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Dear Congresswoman Schakowsky,

The Rockefeller University offers our response to your request for information regarding the importance and availability of fetal tissue as a critical resource in aspects of our scientific research. We set forth below your concerns and our responses.

Past benefits of fetal tissue research

Human fetal cells and tissues have had a decisive and major impact on our current understanding of the molecular and cellular origins of human organs and tissues. Human fetal tissues have allowed researchers to explore and understand the biology and uniqueness of human development. This knowledge has translated into the rational design of both treatment and prevention of numerous human diseases and has saved innumerable human lives.

Fetal tissue has contributed directly to the improvement of child and adult human health. In the 1960s, cell lines derived from fetal tissue were used to manufacture vaccines including those that counter measles, rubella, rabies, chicken pox, shingles and hepatitis A, cumulatively saving millions of lives. The rubella vaccine alone eliminates 5000 miscarriages each year.

Fetal tissue has been used to uncover disease pathways that overlap with natural developmental processes and may guide development of therapeutic treatments for heart disease. Fetal cell lines have been used in medical advances for the production of pharmaceuticals, including an arthritis drug and therapeutic proteins that fight cystic fibrosis and hemophilia. Every indication emphatically supports the notion that further understanding of degenerative diseases such as Alzheimer's, Huntington's, and a host of other devastating and as yet incurable conditions, depend specifically on access to fetal tissue.

Ongoing fetal tissue research is critical for continued advances in regenerative medicine, including organ/tissue regeneration of heart, liver, pancreas, lung, muscle, skin, and more, holding out hope for a wide variety of therapeutic discoveries.

Human tissue-based models for studying uniquely human viral diseases are important for understanding mechanisms of disease progression and developing preventive measures and therapies. Fetal tissue has been used to build increasingly complex models of human disease. A single human fetal liver yields material sufficient to produce dozens of humanized mice. Certain human viruses are severely host-range restricted, meaning they infect humans and no other animals. Fetal tissues are essential for production of humanized mice that can be used in learning about such uniquely human conditions.

Potential future benefits that might be gained through continued fetal tissue research

Future benefits of fetal tissue research will include the enhancement of our basic knowledge of human development. It will inevitably impact clinical approaches and provide new means to address currently incurable diseases by providing new technological platforms. Scientists have used information gleaned from studies of motor neuron development to guide stem cells to become neurons and establish stem cell-derived models of Amyotrophic Lateral Sclerosis, a currently untreatable and fatal disease. These models have allowed researchers to develop new drugs that already are being used in clinical trials to treat ALS. Another of the most promising novel technical platforms in regenerative medicine is using cell-based therapy strategies to replace defective organs rather than attempting to repair the diseased tissue.

For some conditions, potential future benefits must be gained by human fetal tissue research. Certain humanized mice can be produced best with human fetal tissues. Such mice are unique in their ability to support long term infection, thus allowing evaluation of therapies aimed at finding cures.

It is increasingly important to study infection, disease mechanisms and antiviral interventions in human cells. Fetal tissue provides a rich source of stem cells for studies in cell culture and also engraftment into small animals that can then be used to model infection, disease progression and test therapies. These provide valuable preclinical models that increase the chances of success before progressing to human clinical trials.

Investigators continue to mine existing gene expression information from fetal tissue samples in order to understand gene function and growth-regulating pathways encountered in normal versus tumor samples. Much that applies to cancer can be learned from gene expression analysis in organ development.

Wide ranges of adult diseases and disorders have their origin during very early human development. Examples include types 1 and 2 diabetes, schizophrenia, and Huntington's disease. Knowledge of how the human fetus generates discrete organs will provide the blueprint for applying human embryonic stem cells for the generation of specific organs used for supportive and regenerative medicine.

Unique aspects of fetal tissue in research

Neither adult stem cells, nor reprogrammed somatic cells approach the versatility and quality of the natural stem cells derived from the fetus which remains the best resource for regenerative medicine. Model organisms, from the fruit fly to rodents, unfortunately cannot fully model human diseases.

We are aware of how many times promising solutions for diabetes, cancer, and neurodegenerative diseases have been shown to cure the mouse or rat but fail when tested in humans. The human neocortex, for example, contains cells and anatomy that are specifically human, and not found even in other primates. Fetal tissue provides a unique source of human cells that have the potential to be used directly or engrafted into immunodeficient animals. Human fetal tissue offers an important and unique resource for basic and medical research. There is no comparable substitute for fetal tissue for the accurate understanding of human development.

The adult immune system is “educated” to reject animal hosts, complicating the creation and production of animal models with humanized immune systems. In contrast to the adult, fetal immune cells have not yet been educated and therefore do not recognize the host as foreign. As a result, fetal tissues do not reject the host but rather are engrafted, leading to a chimera that is composed of mouse tissues and human immune cells. These mice are uniquely suited to finding cures through research.

Modern technologies have opened the door to studying the cellular interplay in complex human tissues during their development, normal, and disease states, as well as in aging. From single-cell expression analysis of fetal tissue, a great deal about intracellular communication can be learned that will increase our understanding of how normal as well as malignant growth is governed, and how therapeutic interventions may take advantage of these molecular programs.

Recent changes experienced in the availability of fetal tissue for research

Currently, there is a paucity of sources from which to obtain human fetal tissue, creating roadblocks to the conduct of important biomedical research. Entities that previously provided the sources of human fetal tissue have either closed, due to external pressure, or currently offer more limited options than previously proffered.

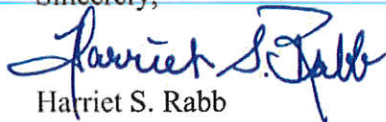
Laboratories have experienced significant difficulties in securing fetal tissue for research. One lab reported: We used to receive fetal tissue once or more every week. Over the past year, the supply of fetal tissue has dwindled and become increasingly unavailable and unreliable – to the point where we can no longer depend on this important resource for our studies.

Another lab despaired: In the past, our laboratory was able to obtain fetal tissues nearly every week. For the last several months, we have been unable to obtain any fetal tissue. Humanized mouse production has come to a standstill, and we are currently unable to perform research that we hope will lead to cures for human disease.

* * *

Thank you for your interest in our research and the challenges it faces. I hope you find the information provided here responsive to your questions.

Sincerely,



Harriet S. Rabb



UCLA HEALTH | DAVID GEFGEN SCHOOL OF MEDICINE AT UCLA
OFFICE OF GOVERNMENT RELATIONS
924 WESTWOOD BOULEVARD
SUITE 350
LOS ANGELES, CALIFORNIA 90024

September 19, 2016

VIA E-MAIL (Heather.Sawyer@mail.house.gov)

The Honorable Jan Schakowsky
Ranking Member
Select Investigative Panel on Infant Lives
Energy and Commerce Committee
United States House of Representatives
2367 Rayburn House Office Building
Washington, DC 20515-6115

Dear Representative Schakowsky:

On behalf of the University of California, Los Angeles ("UCLA"), I have attached UCLA's response to your letter of July 28, 2016, requesting that UCLA provide the Select Investigative Panel on Infant Lives with information to better understand the importance of and risk to fetal tissue research.

UCLA conducts research using fetal tissue that is vital to an understanding of human biology and to efforts directed toward new treatments for a wide variety of adult and childhood diseases and medical conditions. Our research is conducted in full compliance with federal and state law and in accordance with our tripartite mission of education, research, and public service. The information provided below answers the five specific requests made in your letter.

Please note that UCLA has omitted identifying information from the enclosed documents based on concerns for the safety and security of individuals conducting research. Should you have any questions regarding this response, please contact me at (310) 267-7064 or maltschule@mednet.ucla.edu.

Sincerely,

A handwritten signature in black ink, appearing to read "Michael Altschule".

Michael Altschule
Executive Director, Government Relations
UCLA Health / David Geffen School of Medicine

cc: Honorable Marsha Blackburn c/o Matthew Tallmer
(via e-mail, Matthew.Tallmer@mail.house.gov)

1. Past benefits of fetal tissue research.

Since the 1930's, fetal tissue has been used in a broad range of research that has led to lifesaving discoveries. The Association of American Medical Colleges (AAMC), of which UCLA is a member, has previously noted that human fetal tissue research has been critical in establishing permanent cell lines for use in vaccine research for diseases such as polio, hepatitis A, measles, mumps, rubella, chickenpox, and rabies. These established cell lines are currently being used to develop an Ebola vaccine¹.

Fetal tissue proved to be necessary for the production of consumer vaccines against measles, rubella, rabies, chicken pox, shingles and hepatitis A. According to the journal *Nature*, at least 5.8 billion vaccine doses have been derived from fetal tissue lines.²

2. Potential future benefits that might be gained through continued fetal research.

Biomedical research continues to benefit from the use of new fetal tissue. According to the U.S. Department of Health and Human Services, "fetal tissue continues to be a critical resource for important efforts such as research on degenerative eye disease, human development disorders such as Down syndrome, and infectious diseases, among a host of other diseases."³

As noted in the journal *Nature*, "In the past 25 years, fetal cell lines have been used in a roster of medical advances, including the production of a blockbuster arthritis drug and therapeutic proteins that fight cystic fibrosis and haemophilia." Yet, existing fetal material and cell lines "...are of limited use for scientists because they do not faithfully mimic native tissue and represent only a subset of cell types.... The lines can also accumulate mutations after replicating *in vitro* over time." New fetal material is critical if we are to continue to pursue vaccines for HIV and other diseases as well as create treatments and cures for devastating illnesses such as Parkinson's and Alzheimer's Disease, blinding eye disorders such as macular degeneration, diabetes, and schizophrenia.⁴

Our response to question 4 below cites a diverse range of diseases being studied by UCLA laboratories whose research requires the use of fetal tissues. These research activities are critical for the development of new therapies for the treatment of these diseases.

3. Unique aspects of fetal tissue in research, in comparison with adult cells or other cellular organisms that might be used for research purposes

As described in the following summary of research performed in UCLA laboratories (response to question 4), human fetal tissues are critical for current and future research activities for multiple

¹ AAMC Statement (March 18, 2016)

² <http://www.nature.com/news/the-truth-about-fetal-tissue-research-1.18960>

³ HHS Letter to Senators Joni Ernst and Roy Blunt, August 14, 2015.

⁴ <http://www.nature.com/news/the-truth-about-fetal-tissue-research-1.18960>

reasons. First, human fetal tissues exhibit biological properties that are distinct from those of tissues derived from children or adults, and these properties, often related to an enhanced capacity for growth and regeneration, can be highly desirable for the development of novel therapies. It therefore is critical to understand the unique properties of fetal tissues, which can be accomplished only through a direct analysis. Some therapies under development would require the direct use of fetal cells, such as recent clinical trials using fetal neural cells to treat patients with spinal cord injury or Parkinson's Disease. Most therapies, however, will emerge from the study of fetal tissues rather than directly including the cells in the ultimate drug product.

Second, the direct study of human fetal tissues is essential for an understanding of human development. This understanding is necessary for the advancement of fundamental biology, for the pursuit of therapies for the treatment of developmental diseases, such as Down syndrome and the microcephaly associated with Zika virus infection, and for the pursuit of therapies for the treatment of many other diseases that have been linked to developmental defects, including several cancers.

Third, human fetal tissues are critical for the establishment of mouse models for the study of human diseases and for the testing of potential new drugs and other therapies. For example, rodents are highly valuable for biomedical research, but they are inadequate for many studies of human disease and for the advanced testing of new therapies (e.g. HIV does not infect rodent cells). To circumvent the limitations of rodents, human fetal tissues can be implanted into immunocompromised mice, thereby generating an invaluable model system for studies that require the use of a living animal, such as the testing of new drugs. Importantly, human fetal tissues are essential for the establishment of these models due to their unique properties in comparison to tissues from children and adults.

4. Summary of any research conducted since 2010 that UCLA has been involved in that used fetal tissue or relied upon other studies that used fetal tissue

Research laboratories at UCLA studying a wide array of human diseases have used fetal tissues for their medical research projects since 2010. A survey of these researchers resulted in a consistent response that the use of fetal tissues has been, and will continue to be, essential for progress in their fields. While much remains to be learned about the specific properties of fetal tissues, it has been well-established that their properties are distinct from those of adult tissues. Fetal cells often differ from other cells because the fetal cells need to support the rapid growth and maturation of the tissue during fetal and neonatal development; in contrast, the functions of cells from children and adults are usually restricted to maintenance of the physiological functions of the tissue. An understanding of the unique properties of fetal cells and tissues is likely to be of great value for the development of new treatments for a number of devastating human diseases.

We provide here a summary of seven representative research efforts at UCLA that rely on fetal tissues and for which the research is strongly dependent on continued availability of fetal tissue

CANCER: One project focuses on an effort to improve the treatment of a form of lymphocyte leukemia in young children. Although the survival rate of these patients has improved dramatically, approximately 15% of pediatric patients with the most aggressive forms of the leukemia continue to die. A growing body of evidence suggests that these fatal leukemias may be unusually aggressive because they emerged from a unique type of B cell progenitor (B cells are white blood cells that secrete antibodies) generated only during fetal development. Research recently completed at UCLA has shown that the genetic regulation of fetal and adult B cell development is distinct. The aim of the ongoing research is to identify genes expressed only in fetal B-cell progenitors that contribute to the development of the aggressive forms of leukemia observed in young children.

IMMUNITY: Another UCLA research laboratory is immersed in an analysis of fetal T cells, another important type of white blood cell generated in the thymus. A primary goal of this laboratory is to develop improved strategies for rejuvenation of the immune system in cancer patients and in HIV patients whose immune systems have been compromised by chronic virus infection. Human fetal T cell progenitors have been found to be completely different from progenitors found in children and adults in their ability to rejuvenate the immune system. This laboratory has been performing detailed comparisons of the molecular properties of the fetal and adult cells in an effort to understand how to speed up immune system rejuvenation and make the immune system healthier.

As exemplified above, one general reason several UCLA laboratories rely on fetal tissues for their research is that an examination of the properties of the fetal tissues is needed to understand how they differ from older tissues and from tissues derived from induced pluripotent stem cells (iPSCs). iPSC are cells with embryonic stem cell like properties that can be generated from a patient's own skin cells (by a method developed less than 10 years ago), and then matured into any of a wide variety of human tissues; these cells hold great promise for the treatment of many degenerative and chronic diseases. One goal of the researchers is to engineer adult cells and iPSC to possess the unique, beneficial properties of fetal cells. This goal can be achieved only if the molecular features of the fetal cells have been clearly defined.

LUNG DISEASES: A UCLA laboratory is pursuing new treatments for a form of lung disease in infants. A long-term goal is to treat this disease by generating iPSC from a patient and then converting the iPSC into therapeutic lung cells. The ultimate therapy would not require the use of fetal cells. However, successful development of the therapy depends on an understanding of the unique properties of fetal lung cells, which have been found by the UCLA laboratory to grow and divide far more robustly than comparable cells from children or adults. The laboratory has developed a disease model that is being used to understand the unusual growth properties of the fetal cells and how these properties can be harnessed for therapeutic benefit.

GENETIC AND MUSCLE DISORDERS: Another UCLA laboratory studies diseases of muscle, including muscular dystrophy, toward the goal of regenerating functional muscle in patients. Similar to the findings with fetal lung, this laboratory has found that the regenerative capacity of human fetal muscle cells greatly exceeds that of older muscle satellite cells. Recent studies of the underlying mechanisms have revealed possible molecular explanations for the differences between the fetal cells and older cells. This professor considers fetal muscle cells to be the “gold standard” for all efforts to develop therapies for degenerative muscle diseases, due to the powerful and unique regenerative properties of these cells. Quite simply, for an understanding of the important differences between fetal muscle cells and older muscle cells, which are critical for the development of novel therapies, there is no alternative to the ability to analyze the fetal tissues themselves. It is also noteworthy that several of these studies are moving rapidly toward clinical trials, which necessitates the focus on human cells rather than rodent models.

HIV: Another reason several researchers rely on the availability of fetal tissues is that the fetal tissues can be used to create mice implanted with a specific human tissue, thereby providing an animal model in which potential therapies for the treatment of diseases of that human tissue can be tested. Such mice can eliminate the need for the testing of therapies in non-human primates, and are often preferable to studies of non-human primates because they allow the direct study of human cells.

Some UCLA laboratories use mice containing a human immune system for their studies of potential HIV therapies. These mice, which can be generated successfully only with the use of human fetal cells, are extremely important for progress of the HIV field, as HIV does not infect rodent cells. Currently, these mice are being used to study gene therapy approaches for the treatment of HIV infection, with the studies leading rapidly toward clinical trials.

BRAIN/SPINAL CORE INJURY: Human fetal tissues are also of great value for studies of the unique structure of the human brain, which is dramatically different from that of the mouse brain. UCLA research has used human embryonic stem cell lines to generate brain organoids (collections of neuronal cells that self-assemble into structures that resemble small portions of the brain). A comparison to fetal brain tissue is essential for the researchers to evaluate the validity of their organoid method, which is currently being used to understand developmental diseases of the brain, as well as the impact of Zika virus on brain development. The laboratory hopes to use this model to screen for drugs that may protect the fetal brain from the growth impairment caused by Zika virus infection. This same laboratory is also studying strategies for the generation of spinal cord neurons in the laboratory, for use in determining the underlying causes of neurodegenerative diseases, such as spinal muscular atrophy and amyotrophic lateral sclerosis, and for screening for drugs that could slow disease progression and extend patient lifespan.

INFERTILITY: The final UCLA laboratory discussed in this report uses fetal tissues for studies aimed at the diagnosis and treatment of human infertility. State-of-the-art genomics methods are being used to develop reference maps of germ cells and of fertilized eggs at the earliest stages of embryonic development. One goal of these studies is to better understand the reasons for spontaneous miscarriages. These studies are strongly dependent on human fetal tissues because early embryonic development in mice differs substantially from that in humans. The reference maps being developed by this laboratory are also of great importance for the study of germ cell cancers.

5. Description of any recent changes experienced by UCLA in the availability of fetal tissue for research and the related impact of these changes, including whether or not there have been interruptions and/or delays in research as a result.

Most UCLA researchers surveyed emphasized that recent national events have increased the challenge of obtaining the fetal tissues required for the research projects described above. One reputable company was forced to close due to legal expenses associated with challenges to its operations. This has delayed important studies and has forced laboratories to spend a considerable amount of time and resources searching for alternative suppliers. One laboratory has identified a reliable source of fetal tissues in Germany. Another laboratory has reduced their effort on studies that require fetal tissues, despite the importance of this research, due to concerns about personal safety. Of further note, recent publicity surrounding the procurement of fetal tissue delayed publication of a manuscript submitted by UCLA investigators to a renowned journal by more than seven months. The findings reported in that study have the potential to impact the development of therapies for HIV, cancer, multiple sclerosis, asthma, and organ transplant rejection.

UC San Diego Health

UC San Diego Health

Office of the Vice Chancellor Health Sciences

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David A. Brenner, M.D.

Vice Chancellor Health Sciences
Dean, School of Medicine

September 15, 2016

VIA E-MAIL (Heather.Sawyer@mail.house.gov)

The Honorable Jan Schakowsky
Ranking Member
Select Investigative Panel
U.S. House of Representatives
Committee on energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Dear Ranking Member Schakowsky:

On behalf of the University of California San Diego ("UC San Diego"), I have attached UC San Diego's response to your letter of February 16, 2016, requesting that UC San Diego provide the Select Investigative Panel on Infant Lives with information that will further your understanding of the importance of fetal tissue research to advance our understanding and treatment of a range of diseases and conditions.

UC San Diego conducts research using fetal tissue which is vital to our understanding of human biology and for accelerating innovative stem cell research into patient diagnostics and therapy. Our research is conducted in full compliance with federal and state laws and in accordance with our mission of education, research, and public service. The information provided below answers the three specific questions made in your letter. UC San Diego has omitted identifying information from the attached document based on concerns for the safety and security of individuals conducting research.

Should you have any questions regarding this response, please contact Angela Phillips Diaz, Executive Director, Government Research Relations, UC San Diego at (202) 974-6323 or apdiaz@ucsd.edu.

UC San Diego Health

I want to thank the Members of the Select Panel for their support of biomedical research and the opportunity to emphasize the importance of fetal tissue and cells to biomedical research.

Sincerely,



David A. Brenner, MD
Vice Chancellor, UC San Diego Health Sciences
Dean, UC San Diego School of Medicine

cc: Honorable Marsha Blackburn c/o Matthew Tallmer
(via email, Matthew.Tallmer@mail.house.gov)

Attachments

UC San Diego Responses to 2/16/16 Select Panel Questions

1. Past benefits of fetal tissue research

Cell lines derived from fetal tissue have been instrumental in the development of vaccines for the following diseases: measles, mumps, rubella, chicken pox, polio, hepatitis A, rabies, shingles, and adenovirus (for military personnel).¹

2. Potential future benefits that might be gained through continued fetal tissue research

Three examples of vital cutting edge, state-of-the-art medical research being conducted at UC San Diego that depends upon the use of fetal tissue and cells:

- a. Alzheimer's disease: Alzheimer's disease cells are used to understand why brain cells with Alzheimer's disease are abnormal and to try to develop drugs to mitigate the disease. A type of cell that is valuable in this work is an astrocyte, which is a support cell type in the brain. Fetal astrocytes, vital to these research investigations, are used. These fetal astrocytes provide growth factors that keep nerve cells healthy and other factors that are not yet defined that help the neurons establish connections and maintain long-term growth and viability. Although cells that are similar to astrocytes from stem cells can be made, the fetal astrocytes are the "gold standard". Astrocytes made from stem cells cannot be used to replace the fetal astrocytes because they are not identical in capacity to the best of our current knowledge. The fetal astrocytes are vital to these investigations and could be instrumental in treating and or curing Alzheimer's disease.
- b. Spinal cord injury: At the Sanford Stem Cell Clinical Center, fetal neural stem cells are being used in clinical trials for spinal cord injury in human patients. These fetal neural stem cells have previously been shown to yield remarkable results in animals that have spinal cord injury. These fetal stem cells, when implanted at the site of a spinal cord injury in animals develop into new neurons that appear to function as relays across the site of the injury rendering the animals able to function in a way that is superior to their performance before the injury. As a result of these investigations, the Center received FDA approval to test the fetal stem cells in human patients. Physicians and surgeons have initiated an FDA-approved phase 1 clinical trial of these cells and have implanted them in four patients to date. The trial has been successful to date. We have learned that at a minimum the surgery is safe and the fetal cells are safe. We will track the patients over the next few years to observe what we are hopeful

¹ The American Society for Cell Biology (ASCB), FAQs on Fetal Tissue Research, April 2016.

will be evidence of beneficial effect on the patients' paralysis. The next goal is to advance this trial to cervical spinal cord injuries soon. We hope to see evidence of positive impact on these patients as time progresses over the next 3-5 years. This trial and others like it are vital to advancing medical science attempts to cure spinal cord injury. These same fetal neural stem cells are also being used in NIH clinical trials at various sites nationwide for ALS also known as Lou Gehrig's disease.

- c. Kidney generation: A group of NIH-funded scientists are working together to try to learn whether it is possible to build new kidneys from stem cells. The hoped-for building of new kidneys is significant because 93,000 Americans are on waiting lists for kidney transplant. The goal of building a functional kidney is ambitious, but one that we believe can be obtained through hard work, determination, and time. Fetal tissue is vital to the future of this investigation as it is only by examining this fetal tissue that it will be possible to determine the earliest biochemical signals that cells use to tell some cells to make kidneys and other cells to make other organs.

Our ability to examine the earliest stages of human development are vital to our understanding and our ability to treat many diseases in the future including diseases of pregnancy, diseases of the placenta, and diseases of children and adults. Development of many of these new therapies will rely on our learning and understanding of the proper developmental signals that cells use at the earliest stages of development. Without fetal tissue, vital research such as these three examples will take longer and slow the development of therapies and vaccines in the future which could be life changing for individuals and their families.

3. Unique aspects of fetal tissue in research, in comparison with adult cells, stem cells, or other cellular organisms that might be used for research purposes.

Fetal tissue and cells play a vital role in modern cutting edge medical research. These fetal tissues and cells cannot be replaced by embryonic stem cells, reprogrammed stem cells, or adult stem cells. These other cell types do not make astrocytes with identical properties as those from fetal sources. These fetal astrocytes provide growth factors that keep nerve cells healthy and other factors that are not yet defined that help the neurons establish connections and maintain long-term growth and viability.

UC San Diego's researchers are leaders nationally and internationally in biomedical research and fetal tissue and cells are critical tools for their ground-breaking work.



University of Colorado
Anschutz Medical Campus

August 29, 2016

The Honorable Jan Schakowsky
Ranking Member, Select Investigative Panel
House Energy and Commerce Committee
Washington, D.C. 20515
Via Email Only To: Jacquelyn.Bolen@mail.house.gov

Dear Congresswoman Schakowsky,

I write in response to your previous letter regarding the scientific importance of fetal tissue research and the practices of the House Select Committee on Infant Lives. Thank you for your concern about the safety and privacy of our faculty and employees. Nowhere are those concerns more deeply felt than in Colorado, and they have been of paramount importance to me and my staff as we have determined responses to questions about fetal tissue research. In all instances, we have chosen to redact the names of faculty, students, staff or other individuals involved in fetal tissue research in documents disclosed outside the university. We made this decision to ensure those individuals are able to pursue their research without interference and in a manner consistent with the requirements promulgated by the National Institutes of Health and other federal and state authorities. We appreciate your strong support for our researchers in this matter. For that reason, we have also chosen not to publicly identify details of research involving fetal tissue conducted on our campus, because such specifics on that research would lead to the identification of individual researchers.

In 2014-2015, the CU Anschutz Medical Campus received about \$420 million in sponsored research funding and currently has about 5,600 active research protocols encompassing research involving basic science, clinical trials, human research, and animal trials and research. While research depending on fetal tissue is used in very few research projects on our campus, faculty members have relied on this type of research when they saw opportunities to advance science and alleviate human suffering.

The University of Colorado complies with the long-standing federal and state statutes that relate to the use of fetal tissue for research. Since 2012, CU Anschutz has also maintained a policy that requires all researchers to demonstrate the scientific necessity of using fetal tissue for research before initiating a research protocol that employs the tissue. That policy also requires researchers to demonstrate that the research is translational – meaning that it is likely to move the science towards real-world impact. Thus, all active research projects employing fetal tissue do so because of unique scientific properties that cannot be replicated with adult tissue, and are intended to lead towards improvements in human health.

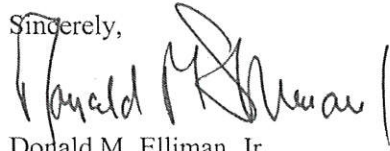
In September 2015, the University of Colorado School of Medicine signed the AAMC's open letter in support of fetal tissue research because we support the rights of our faculty members to pursue legal and ethical avenues of research to end human suffering and prevent disease. We continue to support the AAMC's further explanation of the scientific necessity of fetal tissue as detailed in its April 22nd letter to Chairwoman Blackburn. ~~As that letter states, "By closing the door on one type of research, we may never know what advances we might have attained."~~

OFFICE OF THE CHANCELLOR

Building 500 | Mail Stop F565 | 13001 East 17th Place | Aurora, Colorado 80045
Phone 303 724 8900 | www.ucdenver.edu

Thank you for your continued advocacy to preserve important lines of scientific inquiry and to protect the faculty, students, and staff who have chosen to conduct this research.

Sincerely,



Donald M. Elliman, Jr.
Chancellor, University of Colorado Anschutz Medical Campus



August 10, 2016

The Honorable Jan Schakowsky
Ranking Member, Select Panel on Infant Lives
Committee on Energy & Commerce
United States Congress
2367 Rayburn House Office Building
Washington, DC 20515

Dear Congresswoman Schakowsky:

I write to respond to your request for information dated July 28, 2016, and received in my office on July 29th. You indicated that the Select Panel 'are extremely concerned that increased restrictions...are having a chilling effect on research' and requested our assistance in addressing several aspects concerning research involving fetal tissues for the Panel. The responses to your inquiries are provided below and reflect feedback from the University of Illinois at Chicago (UIC) faculty working with fetal tissues or related cell types.

1) Past benefits of fetal tissue research.

Fetal tissue has played an indispensable role for over 50 years, in advancing biomedical research particularly in pioneering innovative approaches for vaccine development and regenerative medicine. Fetal tissue cultures were used to generate large quantity of poliomyelitis virus, which facilitated development of vaccines against polio [1]. Subsequently, fetal tissues aided in creating vaccines for measles, mumps, chicken pox, whooping cough, and a number of other diseases. Recent data from the U.S. Center for Disease Control and Prevention show the major impact that availability of these vaccines for childhood immunizations has had on the morbidity and mortality in children born between 1994 and 2013 in the U.S. (<http://www.cdc.gov/pdf/wk/mm6316.pdf#12>).

Transplantation of fetal tissues into patients with immunological, hematological and neurological diseases has stimulated progress in regenerative medicine. Successful transplantation of fetal liver in an infant with severe combined immunodeficiency occurred in 1975 [2]. Additionally, substantial evidence exists supporting the benefit of fetal tissue transplantation as a therapeutic option for Parkinson's disease (PD). Studies in this area began following a clinical trial in the late 1980s and showed a dramatic improvement in two PD patients who received transplantation of fetal mesencephalic substantia nigra tissue [3]. Subsequent trials of fetal brain transplantation to PD patients have been conducted in many countries.

2) Potential future benefits that might be gained through continued fetal tissue research.

As noted above, fetal tissue research holds great promise for providing cell-based approaches for treating diseases where currently no effective therapies exist.

The positive findings in PD have led to clinical trials evaluating fetal cell-based treatment for other neurodegenerative diseases such as Huntington's disease [4], Amyotrophic Lateral Sclerosis, and injuries to the spinal cord. Clinical trials with cells derived from fetal tissues are also ongoing for age-related macular degeneration and chronic liver disease.



The emergence of potentially devastating viral epidemics such as Zika or Ebola is a reminder of how important it is for us to continue developing vaccines, and the availability of fetal tissue cells are essential for these efforts [5]. Another valuable application of fetal tissues in the area of immunology is re-creation of the human immune system by using blood-forming cells from the fetus. This allows scientists to develop therapies that are compatible with the human immune system instead of relying on studies of animals whose immune system may have subtle but important differences from humans.

Finally, fetal tissue is essential for studying birth defects and the impact of premature birth on infant health and development. Knowledge from this research is needed to guide development of therapies to prevent or reduce the morbidity and mortality from birth defects and developmental disorders.

3) Unique aspects of fetal tissue in research, in comparison with adult cells or other cellular organisms that might be used for research purposes.

There are four kinds of stem or regenerative cells currently used in research:

Adult stem cells are obtained from an individual after birth. Examples of adult stem cells are bone marrow derived adult blood stem cells. They are routinely used in bone marrow transplants to help patients with leukemia. The main limitation with these adult cells is that they are not very pliable and cannot be kept alive in the laboratory for very long. For example, a blood forming adult stem cell cannot be converted into neurons to treat and study brain disorders. Researchers are therefore limited to studying very few diseases.

The second group of stem cells is that of human embryonic stem cells. They are obtained from excess in vitro fertilized eggs from fertility clinics that are no longer needed after a couple has become pregnant. As long as proper consent is obtained from the couple, the eggs are donated and used for the derivation of stem cells. Unlike fetal cells, these embryonic stem cells have never been in a human womb and thus are dependent on laboratory (i.e., artificial) manipulation for generating desired cell types.

A third group of stem cells is that of induced pluripotent stem cells which are created by forcing an adult skin cell to become like an embryonic stem cell by inserting certain genes. They are very similar to embryonic stem cells except for the fact that they undergo a “stress” as they are being forced to take on the new stem cell identity. The “stress” may potentially alter the expected functioning of the derived cell. The potential for deviation from “normal” behavior is why many researchers study embryonic stem cells and induced pluripotent stem cells side-by-side.

The fourth group of stem cells are **fetal tissue derived cells**. Fetal tissues are unique in that they contain stem or progenitor cells that can be readily expanded. The major advantage of using these cells is that they are further along in their maturity. Complex cell types such as neurons are not readily generated in a laboratory from embryonic stem cells or induced pluripotent stem cells. Nature has its own complex machinery of generating functioning neurons that we cannot yet fully emulate. Since neural progenitor cells in the fetal tissues are already regionally specified (for example, fetal ventral midbrain tissues for transplantation to PD patients), the transplantation of the fetal tissues to patients is safer as compared to pluripotent stem cells that have the potential to become any cell types in the body. Importantly, fetal tissue is not only a significant source of advanced regenerative cells such as fetal neurons, it also allows us to study actual events in human development that are essential to understanding human birth defects that could never be examined in laboratory derived cells.



Finally, fetal cells can be used to develop cell lines that are long lived, i.e., several years, and allow researchers to replicate, confirm and standardize research results.

4) Summary of any research conducted since 2010 at UIC that involved fetal tissue or relied upon other studies that used fetal tissue.

Fetal brain tissue obtained from a commercial vendor is being used for a laboratory-based study evaluating the neuroreplacement of degenerative dopaminergic neurons in PD by human stem cells. The hypothesis for this research is that mononuclear bone marrow (BM) cells can be converted into neural stem cell-like cells (NSC-like cells) that are similar to brain-derived NSCs (fetal tissue). This effort to establish an alternative effective neuroreplacement therapy for PD is to avoid possible immunological rejection.

HEK293 cells, a cell line derived from fetal tissue, are being used to express proteins to study the interaction of metabolic enzymes in order to develop new treatments for severe inflammation in the lung.

5) Description of any changes experienced by UIC in the availability of fetal tissue for research and the related impact of these changes, including whether or not there have been interruptions and/or delays in research as a result.

There are certain questions that can be asked and answered with the use of fetal tissues for research that cannot be addressed through other means including one investigator's research on the fetal basis of adult disease, focusing on prostate cancer. Early life exposures to certain toxicants are thought to increase susceptibility to prostate cancer with aging. The availability of human fetal prostate tissue to test this in the laboratory would allow this investigator to directly test whether the human prostate gland is similarly susceptible or responsive to these environmental factors. However, because of difficulty in obtaining fetal tissues and concerns about their continued availability, this researcher opted to use a less satisfactory alternative, human prostate organoids grown in vitro.

To conclude, our faculty support the statement from the International Society for Stem Cell Research regarding their opposition to the efforts to limit or prohibit biomedical research using fetal tissue <http://www.isscr.org/home/about-us/news-press-releases/2016/2016/02/26/isscr-endorses-fetal-tissue-research-as-essential>.

As your own website has demonstrated, the researchers, federal agencies and academic institutions who have confirmed the need for fetal tissue research are numerous <https://selectpaneldems-energycommerce.house.gov/our-work/benefits-fetal-tissue-research>. The Congressional Research Services (CRS) Report from 2015 provides a succinct overview of the regulations and use of fetal tissue [6] for those involved in this research.

We support our colleagues in the American Association for the Advancement of Science (AAAS), American Association of Medical Colleges (AAMC), the Association of American Universities (AAU) and the Association of Public and Land-Grant Universities (APLU) in their concern regarding the Select Panel's request for information which seem to go beyond the Panel's stated scope <https://www.aamc.org/download/457826/data/aamc-aau-apluletteronfetalissuesubpoenas.pdf>.



We trust that our open and honest feedback provided above can assist you and the other members of the Select Panel in continuing your important discussions with respect to the past and future vital need of fetal tissue research.

Sincerely,

A handwritten signature in black ink that reads "Michael Amiridis".

Michael D. Amiridis
Chancellor

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February 29, 2016

BY ELECTRONIC MAIL

Mr. Matthew Tallmer
United States House of Representatives
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Dear Mr. Tallmer:

Thank you for your January 21, 2016, letter to Dr. Marschall S. Runge, Executive Vice President of Medical Affairs and Dean of the Medical School, from the Select Panel on Infant Lives (“Select Panel”). I am pleased to respond on Dr. Runge’s behalf.

We very much appreciate the opportunity to provide the Select Panel with information on the conduct of fetal tissue research at the University of Michigan (“University”). The research enterprise at the University is substantial and is a critical component of the University’s mission. In order to demonstrate the size, scope, and productivity of the research enterprise at the University, certain data for FY 2015 are instructive. Illustratively, in FY 2015 the University’s research expenditures totaled \$1.3 billion, exceeding the billion-dollar mark for the seventh straight year; this remains one of the highest levels in the nation. In addition to federal funding of \$738 million, direct research contracts from industry increased almost 25 percent, to a record high of \$62 million in FY 2015. Finally, the Office of Technology Transfer reported record numbers of licensing agreements and startup companies for FY 2015, demonstrating the entrepreneurial and innovative spirit that is present at the University.

We have diligently sought to gather information responsive to the Select Panel’s request within the brief time period provided for a response. This review is ongoing, and the University will supplement this response as additional, responsive information becomes available.

As you know, the University is an extraordinarily complex, large organization. With an enterprise this size, it is important to note that, in providing the requested information, we have used our best efforts to gather accurate information. Thus, in preparing this response, we have sought information throughout the University. For example, we searched research protocols by the

keyword search function, using “fetal tissue,” and arrived at a lengthy list of studies that could potentially involve the use of fetal tissue. Many studies on this list were “false positives” that did not involve fetal tissue.

At this point in its review, for the time period for which the Select Panel has requested information, the University has located eight (8) studies that involved the use of fetal tissue. A brief description of each study follows:

1. **Blindness:** One researcher in the Department of Ophthalmology procured tissue from Advance Bioscience Resources, Inc. (“ABR”) to perform research that places the tissue in culture and expands it so that it can be used for certain experiments over the course of several months. The ultimate goal of this research is to study pathways potentially involved in age-related blindness. The research team uses cultures to screen compounds and perform other studies to find ways to therapeutically tackle age-related blindness and age-related macular degeneration.

Another researcher in the Department of Ophthalmology procured fetal tissue from ABR to understand macular degeneration, the leading cause of blindness. This research study involved establishing primary cultures for retinal pigment epithelium. Primary cultures are a category of growing cells that more realistically model actual tissues in the body, relative to cell lines. Cell lines lose many properties over time that make them less like the tissues from which they came. The goal of this research is to model age-related macular degeneration. At this time, therapies exist for only ten to fifteen percent of patients and animal models are not very good. Fetal human retinal pigment epithelium behaves more like the type of tissue that researchers are attempting to model.

2. **Pediatric Behavioral Disorders:** One researcher in the Department of Psychiatry procured fetal tissue from the University of Michigan Health System. This research study examined the impact of steroids given to children with membrane disease as part of their standard clinical care to determine whether there is an impact of the steroid treatment on the children’s behavior and brain structure.
3. **Prostate Cancer:** One researcher in the Department of Urology procured fetal tissue from University of Washington. This research seeks to better understand how prostate cancer spreads to bone.
4. **Cancer in Young Boys:** One researcher in the Department of Human Genetics procured fetal tissue from Novogenix. This research study was an attempt to confirm previously successful experiments that used fetal gonadal tissues isolated from mice. The work was undertaken with the goal of giving young boys treated for cancer the opportunity to have their own children and lead normal lives after radiation or chemical cancer therapy. Although a useful experimental system for understanding the development of the gonad, the

mouse fetal gonad is not an exact analog of human development. In order to apply preliminary mouse-based findings to improvements in human health, it is important to confirm the results in human cells. The goal of this research was to uncover the mechanisms that control germ cell development and may allow the growth of germ cells independent of the development of other tissues (i.e., in vitro germ cell development).

5. **Genetic Impacts of Environmental Toxins**: One researcher in the Department of Environmental Health Sciences procured fetal tissue from University of Washington to conduct research examining the impact of early environmental toxins on the epigenome with the goal of protecting people from disease that is environmentally-induced. This research examines how early exposure to toxins can change gene expression.
6. **Pediatric Eye Cancer and Congenital Blindness**: Another researcher in the Department of Ophthalmology procured fetal tissue from ABR to conduct research to establish whether a new children's eye cancer biomarker and therapeutic target is also required for human retinal development. The ultimate goal of this research study was to better understand childhood eye cancer, congenital blindness, and for comparison of cultured stem cell lines against proteins that are actually produced during development for treatment of blinding diseases and cancer.
7. **Cellular Development**: One researcher in the Department of Internal Medicine procured tissue from two (2) sources: Novogenix and ABR. This research generates tissue cultures. Over the last five (5) years, the research team has generated human organ-like tissue in culture ("organoid") as part of an effort to validate the understanding that the organoid operates like tissue derived from natural sources. This research uses the tissue culture system to study disease with the ultimate goal of understanding how organs and tissues develop in embryos.

We are proud of our faculty's efforts in the pursuit of new discoveries that will result in fewer deaths from cancer and other diseases and improved quality of life.

The University of Michigan very much appreciates the opportunity to provide additional information on the importance of fetal tissue in the pursuit of groundbreaking discoveries in the areas of cancer, ophthalmic disease, and brain development. The University will also provide a response to the inquiry received from Ranking Member Schakowsky, as requested.

Sincerely,


Cynthia H. Wilbanks
Vice President for Government Relations

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March 22, 2016

The Honorable Jan Schakowsky
Ranking Member
Select Investigative Committee
2367 Rayburn House Office Building
Washington, DC 20515

Dear Representative Schakowsky:

Thank you for the opportunity to comment on the past and potential benefits of fetal tissue research. I also appreciate your efforts to protect the privacy and safety of our faculty. As you understand, the inclusion of their names has been of concern to them, to me in my role as Dean/VP, and to other senior leaders at the University of Minnesota.

Your letter requests additional information about the past benefits of fetal tissue research. Many of these are well-known. Human fetal tissue has played a role in advancing breakthroughs that have saved countless lives, including vaccines for Polio, Hepatitis A, German measles, chickenpox, rabies, and rubella. Research using human fetal tissue has led to a widely used arthritis medication, as well as treatments that greatly improve the lives of people with Cystic Fibrosis and hemophilia. It was also critical in my research to develop an intervention to prevent mother-to-child transmission of HIV. That research alone has saved over 1 million infants in the last 10 years, while also reducing elective abortion in HIV positive women by more than half in this country.

There are also many potential future benefits of research using human fetal tissue. At the University of Minnesota, researchers are working on more effective treatments for diabetes, Parkinson's and other neurological disorders, HIV/AIDS, spinal cord injuries and efforts to counter the adverse effects of chemotherapy and bone marrow transplant for children.

Other researchers use fetal tissue to understand cell biology and human development, to do research on preventing birth defects or on eyesight-robbing macular degeneration.

Finally, you asked about the unique aspects of fetal tissue in research, in comparison with adult cells, stem cells, or other cellular sources that might be used for research purposes

Many have asked why fetal tissue has remained a necessity in biomedical research. The reason is that fetal tissue has vital properties that are not found in any other biological cell or tissue: rapid cell division and growth, specific immune properties and adaptation.

The Honorable Jan Schakowsky
March 22, 2016
Page 2 of 2

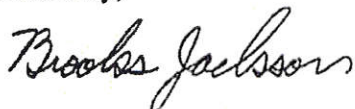
To provide just one example, those properties have established an important animal model for research into the HIV virus, which infects only humans and chimpanzees. A decade ago, with the use of fetal tissue, scientists at the University of Minnesota and elsewhere developed a mouse model that closely mimics a human immune system and, unlike ordinary mice, can be infected with HIV. The development of that mouse model was critical because before treatments can be tested on humans, they must be tested using animal models.

There is currently no substitute for the use of human fetal tissue in some areas of research. Where possible, researchers have looked for alternatives, such as using adult cells that have been "reprogrammed" to their earlier forms. But those techniques are still being refined, and some fields, such as the study of fetal development, are likely to remain reliant on fetal tissue. Although researchers seek answers in many different ways, there are some lines of inquiry--ones related to devastating diseases-- where scientists have not been able to develop alternatives to research using fetal tissue.

Neither can other suggested alternatives such as cell cultures, developed cell lines, computer modeling or umbilical or placental tissue substitute for fetal tissue at the present time, although they are potentially promising in the future.

Thank you, again, for the opportunity to provide this information and for your strong support of biomedical research. If you have additional questions, please do not hesitate to contact me.

Sincerely,



Brooks Jackson, M.D., M.B.A.
Dean of the Medical School
Vice President for Health Sciences

cc: Dean Johnson, Chair of the Board of Regents
Eric Kaler, President
Brian Herman, Vice President for Research
William Donohue, General Counsel
Brian Steeves, Executive Director, Board of Regents' Office



Penn Medicine

Perelman School of Medicine
University of Pennsylvania Health System

August 10, 2016

The Honorable Jan Schakowsky
Ranking Member, Select Investigative Panel
Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515-6115

Dear Representative Schakowsky:

I am responding to your July 28, 2016 letter to Dr. Amy Gutmann, the President of the University of Pennsylvania. The University believes strongly that there have been very significant scientific benefits from past research using human fetal tissues, and that there will be tremendous future benefits through continued research using human fetal tissues, that could not, and cannot, be achieved, without using human fetal tissues. I have spoken with researchers at Penn, who have provided the following examples:

One of the most promising areas of research involving the use of human fetal tissue is the study of how and why congenital abnormalities develop in a fetus. Congenital anomalies occur in 3-4% of pregnancies and cost society billions of dollars per year in long term disability care, and cause incalculable emotional toll on patients and families. A major goal in human biology research is to understand what happens during human embryonic and fetal development that causes these anomalies. Human fetal tissue research enables scientists to learn what is normal development and how abnormalities arise, either those that are immediately apparent in the fetus or that can manifest themselves many years later, such as in the central nervous system. This understanding will lead to treatments that could decrease the frequency of the anomalies and to appropriate postpartum treatments that may improve the quality of life for the patients. Furthermore, researchers are now learning that the events during human embryonic and fetal development set the stage for many other conditions, such as autism, and some ailments that will not present until many decades later in life, such as degenerative diseases including Alzheimer's and Parkinson's.

Another important area of research involving the use of human fetal tissue is the emerging science of epigenetics – the study of environmental effects on the way genes are expressed. Scientists at Penn Medicine are in the forefront of this rapidly evolving field. Our knowledge of mammalian developmental biology over many years has come from studying model systems, mainly with the mouse. We have learned that developmental mechanisms have been conserved through evolution, that humans and mice share many protein-coding genes and that the differences between species are unlikely to be due to gene diversity (although these exist.) Instead, research shows that

differences between species largely result from modifications in regulatory programs that control gene expression; that is, when and where specific genes are expressed. In plain language, it is not necessarily our genes that separate us from our brethren in the animal kingdom and from each other, but also when these genes are 'turned on and off'. While humans share many similarities with the mouse and other mammalian models in developmental mechanisms, researchers have learned there are many differences in how genes are expressed. The reality of this finding has proved that it is problematic, misleading, frustrating and wrong to extrapolate what researchers have learned in other animals to humans, without direct studies on human tissues, including human fetal tissue. The clearest example of this is the human brain: the development of the brain has changed dramatically in the evolution of the human and with greater complexity than in any other species on earth. As other human organs and tissues are investigated, significant differences in gene expression are realized as well, reinforcing the need to study and use human fetal tissue directly. Only by studying human fetal tissue can we better understand how we are different from our animal brothers and develop treatments targeted to our particular genetic and epigenetic codes.

Opponents to human fetal tissue research argue that its use in research is unnecessary because they believe there are other model systems and techniques that can be used. But science has refuted that argument. As one example, opponents of fetal tissue research tout the use of human stem cells to recreate human embryogenesis in a dish as an alternative to fetal tissue. However, investigators learned quickly that human embryonic stem cells (those that can produce all tissues in our bodies) were very different from the mouse counterparts. These differences have been responsible for the general lack of cell-based interventions that have been promised and desperately sought since the introduction of human embryonic stem cell research in 1998 – a full 18 years ago. It has taken years to figure out how to grow the different cells we need to effect human therapies, because of the lack of information on human cells. Work with the stem cells cannot happen in a vacuum because any progress with these cells must be validated against the standard of normal tissues. What happens in a dish in a laboratory does not mean that is what is happening in the embryo – it must be confirmed. The study of human fetal tissue is, and will continue to be, needed to inform the studies with stem cells so that eventually these stem cells can generate safe and effective therapies. We now are beginning to see many publications on human 'organoids' – tissue-like structures that are being used to claim recapitulations of events in human embryogenesis. We must approach these claims with circumspection until they are confirmed with fetal tissues studies. Finally, fetal tissues continue to be the source of other types of stem cells that are involved in development of specific tissues within the embryo and are of important value as well for potential therapies, for diseases like HIV and AIDS, and vaccine production.

This work has the potential to save many lives from both genetic and non-genetic diseases. The University of Pennsylvania believes that responsible and ethical biomedical research involving human fetal tissue is a public health imperative. Investigators recognize that it is a privilege to work with this tissue, as it is with any human tissue. If there were effective alternatives, they would be used instead. So much

good can come from the study of fetal tissue, whereas its normal fate following abortion is to be discarded, sacrificing its potential to be useful in the advancement of biomedical science, as we race the clock to treat and cure a variety of devastating diseases.

Thank you for this opportunity to share with the Panel our University's experience conducting responsible and ethical biomedical research using human fetal tissue, and our belief why research with such tissues must continue.

Sincerely,

A handwritten signature in cursive script that reads "Susan E. Phillips". The signature is written in black ink and is positioned above the printed name and title.

Susan E. Phillips
Senior Vice President for Public Affairs

cc: The Honorable Marsha Blackburn, Chair



February 24, 2016

Select Investigative Panel, Minority Staff
Committee on Energy and Commerce
U.S. House of Representatives
Via email: heather.sawyer@mail.house.gov

Select Panel on Infant Lives, Majority Staff
Committee on Energy and Commerce
U.S. House of Representatives
Via email: matthew.tallmer@mail.house.gov

Re: Your letter dated February 11, 2016

To Whom it Concerns:

We are in receipt of your letter dated February 11, 2016, subsequently sent via email on February 16, 2016, seeking information related to the benefits of research using fetal tissue. Below, we both reiterate some of the information we included in our February 15, 2016, letter to the Select Panel on Infant Lives ("Panel"), and provide additional information.

1) Past benefits of fetal tissue research

As noted in our letter to the Panel dated February 15, 2016, the development of the human polio vaccine would not have been possible without cells of fetal origin. Other vaccines for rabies, chicken pox, German measles, and hepatitis A were all developed with the help of fetal-derived cells.

A search of *PubMedCentral* using four commonly used fetal cell lines as a search term yielded the information below:

- Cell line HEK-293 (also called 293T), derived in the Netherlands in the 1970s: 9,014 publications focusing on multiple types of cancer, stroke, Parkinson's disease, epilepsy, Alzheimer's disease, diabetes, cardiac and vision issues, and addiction.
- Cell line MRC-5, derived at the U.K. Medical Research Council in the 1970s: 1,424 published studies focusing on such diseases as conditions as multiple cancers, viruses, lung inflammation, polio vaccine, and the parasite that causes sleeping sickness.
- Cell line WI-38, derived at the Wistar Institute in the early 1960s: 1,387 published studies focusing on such diseases and conditions as multiple types of cancer, cell growth, cell aging, anti-cancer drugs, and gene expression.
- Cell line IMR-90, derived in the U.K. in the 1970s: 493 published studies focusing on such diseases and conditions as aging, lung injury, and other topics.

2) Potential future benefits that might be gained through continued fetal tissue research

Also noted in our letter to the Panel dated February 15, 2016, researchers around the country are using fetal tissue in research with the goal of understanding, mitigating the effects of, and discovering cures for a host of debilitating and deadly conditions. Such areas of research include:

- Preventing spontaneous pregnancy loss and recurrent spontaneous miscarriage.
- Preventing maternal diseases of pregnancy, including preeclampsia, and other such conditions which limit human fertility and reproductive success, and prevent couples from having healthy babies.
- Treating or curing many forms of cancer.
- Treating acute or chronic Graft-versus-Host-Disease (GVHD). Chronic GVHD arises in about 30-50% of patients who receive transplanted immune cells as a way of treating their cancer (acute GVHD treatments are only partially effective, and there is currently no effective treatment for chronic GVHD).
- Studying white blood cells that mediate transplant rejection or acceptance, so that ultimately transplants need not be accompanied by drugs that suppress the immune system globally, making the patient more vulnerable to infections and cancer.
- Using mouse models to provide a way for scientists to test human organ replacement therapies such as stem-cell derived heart or nerve transplants, before offering these approaches to a patient.
- Examining the responses of human immune cells to viral or bacterial infections. This could lead to the development of new vaccine or treatment strategies for viruses that are specific for humans and for major bacterial pathogens (e.g. tuberculosis or typhoid fever) or against multi-drug resistant bacteria (e.g. multi-drug resistant Staph aureus).
- Studying the involvement of white blood cells in atherosclerosis (a disease which results in heart attacks and sudden cardiac death).
- Studying how the maternal vascular system contributes to successful pregnancy and provides appropriate nutrient support for the growing fetus.
- Conducting research on how Trisomy 21 (Down's syndrome) affects fetal growth and development, which directly leads to physiological problems for Down's individuals postnatally and throughout their lifetime.

3) Unique aspects of fetal tissue in research, in comparison with adult cells, stem cells, or other cellular organisms that might be used for research purposes

Fetal tissues and cells are less specialized and more flexible, and can be grown in the lab in situations where adult cells and tissue do not survive. Many living tissues from adults are difficult or impossible to obtain for research purposes, such as brain, heart, and other vital tissues. In this way, tissue from legal abortions with proper consent of the patient providing the tissue is in some cases the only accessible source for many human tissues.

The human fetal thymus is the ultimate reference tissue for anti-tumor and anti-viral vaccine development, and for discovery of novel cell types involved in immune rejection or protection of tissue transplants. Cutting off access to this reference tissue will cripple basic research on the development of the human thymus, a critical organ for understanding and correcting inborn immunologic defects in children. While some valuable research can be done on the fetal thymus of other mammals, ultimately the human fetal thymus will be a key reference point for human clinical trials of transplants to correct inborn immune defects.

It is not possible to form fully functional, intact tissue or organs from stem cells in the laboratory at this point, but fetal tissue provides access to this human tissue. Additionally, interactions among various tissues and organ systems are typical of many disease processes which cannot be mimicked using stem cells in the laboratory.

And because fetal tissue is less likely to stimulate rejection, it is used for cell and tissue transplants, with the potential to treat diabetes, Parkinson's, and other illnesses. Stillbirths and spontaneous abortions are poor sources of material because the cells are typically severely damaged or dead.

I hope this information answers your questions. If you have additional questions related to this response, please do not hesitate to contact me.

Sincerely,



Robert N. Golden, MD
Robert Turell Professor in Medical Leadership
Dean, School of Medicine and Public Health
Vice Chancellor for Medical Affairs
University of Wisconsin-Madison

Yale SCHOOL OF MEDICINE

May 9, 2016

The Honorable Jan Schakowsky
Ranking Member
Select Investigative Panel
2367 Rayburn House Office Building
Washington, D.C. 20515

ROBERT J. ALPERN, MD
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Dear Congresswoman Schakowsky,

I am writing in response to your recent letter seeking information on the past and potential future benefits of research involving fetal tissue.

As a leading research institution, Yale has had a long history of contributions to the field of medicine that have had major impacts on the health and welfare of people around the world. Included among these were the first use of chemotherapy as a cancer treatment in the U.S., the development of the first artificial heart pump in the U.S., and the first insulin pump for diabetes. These discoveries were the result of years of basic, investigator-driven research and scientific collaboration that sought to make clear the mechanisms by which living organisms function and the operations by which drugs act.

Transformative medical and technological advances like these have been accompanied by national, institutional, and community-based conversations about the social and ethical issues raised by the participation of human subjects in novel experimental treatments and cures. These discussions have sought to address the impact of scientific innovation through the development of practical information, guidance, regulation, and, where necessary, the control of particular practices that have allowed potentially lifesaving research to continue and the public to benefit from the advances resulting from its historic investment in biomedical research.

In 1988, the Human Fetal Tissue Transplantation Research Panel, chaired by Judge Arlin Adams, provided an important public forum to consider the scientific value and ethical acceptability of fetal tissue research, hearing testimony from lawyers, ethicists, religious leaders, biomedical researchers, clinical physicians, and the general public, including families with children afflicted by disease and disability. At its conclusion, the panel determined that the research was in the public interest, with the potential to help millions, and that it would not increase the number of abortions, with the moral imperatives and research exigencies not incompatible. This in turn led to policy and regulation to ensure that fetal tissue would be made available for research purposes while establishing important safeguards to prevent the development of a market for such tissue



and to insulate the decision to obtain the medical procedure from any decision to donate the tissue to research.

Others have written extensively on the past benefits of fetal tissue research, including the vaccines for rubella and varicella, which effectively eradicated a major source of child mortality and mental retardation. Also, as widely discussed, research utilizing fetal kidney cells was crucial to the ultimate development of the polio vaccine. (Many types of tissue contributed to the discovery of the vaccine against polio, including human embryonic tissue, although the vaccine developed by Jonas Salk was cultured in monkey kidney tissue.) In addition, fetal tissue research has resulted in significant improvements in the care of the unborn threatened by premature delivery, death, or disease, as in the case of the development of amniocentesis as a tool to detect and, in some cases, to treat fetal abnormalities in utero.

Today, researchers use fetal tissue to investigate and understand the complex events that occur during normal human development and that cannot be studied in laboratory animals. Some of our most serious medical conditions are due to abnormal specification and differentiation of developing cells, and it is hoped that a better understanding of normal cell processes will allow us to identify – and correct – the abnormalities that cause deadly disease and illness. Researchers also use this tissue to study fetal pharmacology and the effects of chemical and other agents in the fetus and to improve techniques to save the lives of premature infants.

The field of neuroscience provides one particularly compelling example of how fetal tissue is used in research, permitting a detailed exploration of the questions raised in your letter. Neuronal production, neuronal migration and the regional patterning of the brain mostly occur in the first 2 – 5 months of gestation. More than 2/3 of human genes are expressed in this developing brain, and nearly all of the genetically-based developmental disorders are likely the result of structural and/or functional alteration occurring prenatally, even when the symptoms of disease may not appear until childhood, adolescence or adulthood. Without model systems based on the prenatal human brain, we would be unable to investigate the normal – and abnormal – forms and structures, functions, and genetic differences that are unique to the developing human brain and may be crucial for understanding and, eventually, treating major neurological and psychiatric disorders.

In the past, researchers have used animal models – primarily rodents – to explore brain structure and development. Although these models have led to important scientific insights, their broad application has been limited by the lack of complexity and sophistication in the rodent brain. When compared to a rodent brain, the human brain has a 1,000-fold expansion in the cortical surface area and gyrification of the surface as well as specific types of neurons that are not present in rodents. In addition, human brains develop entire areas of higher association not present in rodents or other animals that are important for logical thought, language, and abstraction. As a result, animal models for neuropsychiatric disorders are difficult to interpret, and research has confirmed that animal models in general are not a reliable tool for predicting neurological responses in humans, making them a poor guide for later research or clinical decision making. Consequently, virtually no therapeutics for neurological and psychiatric disorders have been developed based solely on experimental animal models. While comparisons

between animal and human brain specimens allow us to understand similarities and differences between human and rodent model system, thereby providing clues to the pathogenesis of neurological and psychiatric disorders, animals are not a substitute for experimental systems based on the developing human brain.

Similarly, adult brains are not an adequate model for studying prenatal brains and their development. Of critical importance, the expression of genes in the prenatal brain differs in fundamental ways from the expression of genes in an infant, child or adult brain. Researchers have discovered that the embryonic brain's genetic program draws to a close and new gene expression emerges around the time of birth. In demonstrating this effect, researchers have confirmed that the genes that guide the construction and assembly of the brain are quite different from those that must govern its function during maturation postnatally. In fact, the differences are so profound, with so many genes that are expressed differently, that the fetal brain at the molecular level is almost a different organ from the adult brain, making adult brain cells a poor proxy for fetal brain cells.

Over the past several years, researchers have identified the conditions that have allowed specialized adult cells to be genetically reprogrammed, coaxing them to assume a stem cell-like, or pluripotent, state. In this short span of time, and informed by investigations involving fetal tissue and embryonic stem cells (ESCs), researchers have made great strides in improving the techniques to generate these de-differentiated adult cells, known as induced pluripotent stem cells (iPSCs), whose developmental fates, until recently, had been assumed to be fixed. The idea that a patient's own cells, harvested from accessible areas like the skin, could provide a sufficient amount of immune-matched cells that could be reprogrammed into the cell types that have been compromised or destroyed by disease or injury is exciting and is being pursued by researchers worldwide.

As of this writing, however, there are significant technical challenges that must be overcome before iPSCs are used for these purposes – or before we can be confident that they are a reliable alternative to fetal tissue. Although there have been successes in reprogramming some adult cells, the technique needs to be refined and the process made more efficient. In order to serve as a good model for reenacting the trajectory of early brain development in normal and diseased states, iPSCs must be able to recapitulate the later stages of human brain development. Currently, both iPSCs and ESCs only recapitulate some of the fundamental mechanisms underlying neurodevelopment at the very earliest stages of the human brain.

Also, iPSCs and ESCs currently provide very simplified models of human brain development. In fact, the extent to which these cellular models are able to recapitulate true human brain development *at any stage* is still actively investigated and open to scientific debate. As researchers learn more about the molecular mechanisms that underlie reprogramming, they must seek to understand any alterations in DNA that would determine whether these cell types are truly clinically similar. For example, adult stem cells may contain more DNA abnormalities caused by environmental factors, such as exposures to sunlight and toxins and unexpected errors in DNA replication that inevitably occur during the course of a lifetime. Researchers must understand, minimize and fully characterize this variability between ESCs, iPSCs, and fetal cell

lines so they can fully appreciate how their results match to the biology of the disease being studied.

Whether the differences between human iPSCs, ESCs and fetal tissue cells will be consequential remains to be determined, but the most important uses for newly sourced fetal brain tissue is to validate these alternative model systems and provide tissue for those cellular and molecular processes that cannot be studied using human iPSCs or ESCs. In addition to understanding and accounting for any variation, researchers also need to compare fetal cells with the alternatives in terms of their ability to proliferate, differentiate, survive and function after transplant, and avoid immune rejection in an animal or human recipient. As noted above, researchers are actively developing new models that have the potential to substitute for fetal tissue. Yet, only time and further research will determine if alternative models will be viable replacements for fetal tissue in clinical settings.

Some have questioned the need for continued access to new sources of fetal tissue for comparison with adult cells, stem cells and other cellular organisms that might be used for research purposes. As in any field, progress toward scientific goals, be it understanding how the nervous system functions in health or disease or developing alternatives to existing models, is limited by experiments that are technically and conceptually possible. Although neuroscience is in a period of significant innovation, the vast complexity of the human brain makes it one of the greatest challenges in modern medicine. Recent advances, such as the sequencing of the human genome, the development of new tools to map neuronal connections, and higher fidelity imaging technologies, now allow researchers to observe how the human brain is structurally and functionally connected – moving them ever closer to understanding the timing and regulation of signaling pathways at the cellular, intercellular and intracellular levels.

So far, these new tools have advanced our understanding of the maturing adolescent and adult brain, but there is still much to understand about how and when brain systems come “on-line” and how fetal brain development may shape the trajectory for brain plasticity across development and adulthood. Moving forward, new sources of fetal tissue are key to understanding these basic neural developmental processes. In turn, understanding these foundational early brain developmental processes, including how neural systems emerge, lights the way to understanding how to reopen the brain’s own regeneration capacities and develop new therapeutic approaches to a host of degenerative neural diseases or even the sequelae of brain injury.

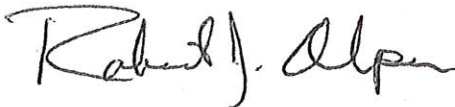
Currently, research involving fetal tissue represents a small proportion of the overall NIH budget, but this is a reflection of emphasis within existing budget constraints – not a lack of scientific opportunity offered by work with fetal tissue. NIH does an enviable job of balancing many competing priorities, but its research portfolio is, in fact, more heavily invested in understanding what goes wrong in adulthood, such as the development of cardiovascular disease, and less on understanding how early developmental processes and events shape the risk for later diseases across organ systems, especially the brain. As they should, conversations about priority-setting at NIH focus on both the burden of disease and the opportunity to support meaningful health benefits, but many diseases may have their origins in the earliest developmental processes.

Clues to innovative treatments may also lie in understanding how these early developmental processes, especially at the neural level, are regulated. Although neuroscience is a rapidly maturing field, research into epigenetics of neurological and neuropsychiatric disease and disorders, at the very earliest stages of human development, has not attracted significant support in the past. Yet, as new technological and conceptual approaches are developed, it is hoped that the share of the NIH budget dedicated to human neuroscience will increase.

The burden of major disorders, such as cancer, intellectual disabilities, Alzheimer's disease, and autism spectrum disorder, are enormous, exacting a great emotional and financial toll on families as well as health and social welfare agencies. We all want our children and grandchildren to live healthier lives, benefitting from more sophisticated medical approaches to treat and, ultimately, spare them from age-associated diseases and disorders. In fact, many researchers, including those who work with fetal tissue, enter their fields with the hope that they can make a difference for those with chronic or acute conditions that degrade quality of life. In too many cases, we do not fully understand the symptoms or causes of the different types of diseases and disorders that can affect the human condition, and, when we do, our efforts often fall short of finding a cure. The knowledge gained through research using fetal tissue has already provided critical insights into etiologies of certain human disorders and offers the possibility of hope for reducing this burden, either directly through the development of new targets for treatments or indirectly through a deep knowledge of individual cells and whole systems. To abandon this research would significantly impede progress toward scientific understanding and the alleviation of human suffering.

Thank you for your interest in continuing this important research.

Sincerely,

A handwritten signature in cursive script that reads "Robert J. Alpern". The signature is written in dark ink and is positioned above the typed name.

Robert J. Alpern, MD
Dean and Ensign Professor of Medicine
Yale School of Medicine



Rush D. Holt

Chief Executive Officer and
Executive Publisher, *Science*

April 25, 2016

To: Chairwoman Marsha Blackburn
Select Investigative Panel, House Energy and Commerce Committee

Dear Chairwoman Blackburn:

On behalf of the American Association for the Advancement of Science (AAAS), the world's largest general scientific society, I write in response to the March 30 letter from Chairwoman Blackburn of the Select Panel on Infant Lives. I appreciate the opportunity to present scientific information on the efficacy of fetal tissue research and to assist the committee in understanding its important role in addressing questions about medical research to promote human health.

As we indicated in our March 15 letter,¹ the decision to terminate a pregnancy does not bear on the decision to donate tissue. Scientific studies, such as one conducted by the University of California, San Francisco (UCSF),² reveal that reasons for this decision may relate to socioeconomic status, age, health, and marital status. Furthermore, the guidelines set forth in the National Institutes of Health Revitalization Act, PL 103-43, clearly stipulate that the option to donate tissue cannot be discussed with the woman until after she has made a decision to terminate a pregnancy.

Scientists who work with fetal tissue—many of whom are hesitant to be cited due to safety concerns—state that fetal tissue is unique and useful because it can offer information that other types of research, such as research using animal or adult tissue, do not always provide. Studies on animals may be predictive of results in humans, but not always. Fetal tissue is specific to early human development and may provide a level of assurance that may not be found solely utilizing adult or animal tissue.

It is used to study areas such as infectious diseases, eye development and disease, and to better understand fetal development.³ AAAS has long taken the position that research on cells derived from all sources, when conducted under strong ethical guidelines, should be conducted to answer questions about human health and development.⁴ This is in part because science is unpredictable. We do not know where the next medical advance will emerge, but we do know that sometimes, breakthroughs come from surprising places.

Regarding your inquiries about scientific information surrounding medical advances, vaccines, or cures achieved through the use of human fetal tissue research, fetal tissue research has been conducted since the

¹ http://www.aaas.org/sites/default/files/AAAS_FTR_March%202016.pdf

² <http://bmcwomenshealth.biomedcentral.com/articles/10.1186/1472-6874-13-29>

³ <http://www.nature.com/news/the-truth-about-fetal-tissue-research-1.18960#graphic>

⁴ http://www.aaas.org/sites/default/files/content_files/Stem%20Cell%20Research%20and%20Applications%20Report.pdf

1930's and was instrumental, for example, in discovering the vaccine for polio, where researchers infected fetal kidney cells in petri dishes to produce a large amount of virus that they could then harvest, purify and use to vaccinate people. This kind of discovery is made possible by allowing multiple lines of inquiry, and by utilizing a range of tools, which include fetal tissue research.

Perhaps the timeliest example to demonstrate the potential for scientific advancement from research that uses donated tissue involves the Zika virus. As you are aware, the Zika virus has been linked to fetal deaths and birth defects such as microcephaly, prompting the World Health Organization to declare it an international public health emergency. In order to understand the virus' effect on pregnant women and their fetus, scientists are using fetal tissue to test how the virus may cause these birth defects. Donated tissue gives unique insight as to the *in vivo* effects of the virus, and as stated by the Nowakowski study on Zika,⁵ it provides scientists a more comprehensive understanding of how the virus operates. Donated fetal tissue allows scientists to gain the necessary information on how the virus affects the fetus *in utero*, and to test a range of potential therapies and treatments for safety and efficacy.

To cite another recent example, there is a potential new prenatal stem-cell therapy to treat *osteogenesis imperfecta*, known as brittle bone disease, which was featured in a news article in *Science*.⁶ This debilitating disease is genetic, and researchers are preparing a clinical trial to test this therapy in pregnant women. The therapy involves the use of mesenchymal stem cells (MSCs) from donated fetal liver that is infused through an umbilical vein that directly treats bone development of the fetus before birth. Early tests overseas have shown sufficient promise to move to a clinical trial, and one of the promises of this therapy is that this specific type of stem cell has not demonstrated as strong of an immune reaction as blood stem cells.

Examples like these demonstrate the need to explore many different types of research, including research using donated tissue. By limiting the scope of research and restricting the scientific community's ability to follow the evidence, we thereby limit the possibility of discovering new medical advances, vaccines, or cures aimed at bettering society.

Finally, we want to reiterate our concern expressed in our March 15 letter over reports that the Select Panel plans to issue subpoenas that would risk making public the names of researchers, students, and others involved in fetal tissue research. There is, unfortunately, a history of scientists being harassed and threatened for conducting certain types of research, and AAAS has long sought to support and defend these researchers. Scientists do not choose their careers to court controversy. They do so because they want to answer important questions, and to advance science in service of society. As history has shown, answers to these questions can sometimes change the world for the better.

Sincerely,



Rush D. Holt, PhD
Chief Executive Officer and
Executive Publisher, *Science* Family of Journals

cc: Rep. Jan Schakowsky

⁵ <http://www.sciencedirect.com/science/article/pii/S1934590916001181>

⁶ <http://science.sciencemag.org/content/352/6283/284.full>

Exhibit 9.3

Vaccinations currently FDA-approved for use in the United States, based on:
<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm>

Product Name	Trade Name	Sponsor	FDA approval	Propagated in	Animal or other cells	Historic cell lines	Fetal tissue
Vaccines currently under development or recently approved							
1	Ebola virus	rVSV-ZEBOV-GP New Link Genetics	2016	Vero monkey kidney cells	X		
2	HIV	RV144 (ALVAC) HIV-1 Sanofi Pasteur GlaxoSmithKline	2016 HVTN 702 (Phase 11/111 trial)	Chicken embryo fibroblasts Chinese Hamster Ovary cells	XX		
3	Malaria	RTS,S and Pfs25-EPA GlaxoSmithKline Biologicals	n/a	Yeast cells	X		
4	Cancer	Sipuleucel-t (Provenge) Dendreon Corporation	2010	Patient's blood cells in culture	X		
		Tumor antigens	n/a	Patient's cancer cells in culture	X		
Vaccines produced using human fetal cell lines							
1	Adenovirus Type 4 and Type 7 Vaccine, Live, Oral	No Trade Name Barr Labs, Inc.	2011	WI-38	XXX	X	
2	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated	Quadracel Sanofi Pasteur Limited	2015	Corynebacterium diphtheriae, Clostridium tetani and Bordetella	XXX	X	

	<u>Poliovirus Vaccine</u>									
3	<u>Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine</u>	Pentacel	Sanofi Pasteur Limited	2008						
4	<u>Hepatitis A Vaccine, Inactivated</u>	Havrix	GlaxoSmithKline Biologicals	2005						X
5	<u>Hepatitis A Vaccine, Inactivated</u>	VAQTA	Merck & Co, Inc	1996						X
6	<u>Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine</u>	Twinrix	GlaxoSmithKline Biologicals	2007						X
7	<u>Measles, Mumps, and Rubella Virus Vaccine, Live</u>	M-M-R II	Merck & Co, Inc	2008						X

8	<u>Measles, Mumps, Rubella and Varicella Virus Vaccine Live</u>	ProQuad	Merck & Co, Inc	2005	Embryonated chicken eggs (Measles and Mumps); WI-38 for RA 23/7 (rubella); MRC-5 for Varicella	XX	XX
9	<u>Rabies Vaccine</u>	Imovax	Sanofi Pasteur, SA	2011	MRC-5	X	
10	<u>Varicella Virus Vaccine Live</u>	Varivax	Merck & Co, Inc	1995	WI-38 and MRC-5	X	
11	<u>Zoster Vaccine, Live, (Oka/Merck)</u>	Zostavax	Merck & Co., Inc.	2006	MRC-5	X	
Vaccines produced without human fetal tissue or fetal cell lines							
1	<u>Anthrax Vaccine Adsorbed</u>	Biothrax	Emergent BioDefense Operations Lansing Inc.	2010	Bacillus Anthracis culture	X	
2	<u>BCG Live</u>	BCG Vaccine	Organon Teknika Corp LLC	2010	Mycobacterium bovi culture	X	
3	<u>BCG Live</u>	TICE BCG	Organon Teknika Corp LLC	2010		X	
4	<u>Diphtheria & Tetanus Toxoids Adsorbed</u>	No Trade Name	Sanofi Pasteur, Inc	2003	Corynebacterium diphtheriae and Clostridium tetani cultures	XX	
5	<u>Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed</u>	Infanrix	GlaxoSmithKline Biologicals	1997	Corynebacterium diphtheriae, Clostridium tetani and	XXX	

9	<u>Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)</u>	PedvaxHIB	Merck & Co, Inc	2011			Haemophilus influenzae type b and Neisseria meningitidis serogroup B culture	XX					
10	<u>Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)</u>	ActHIB	Sanofi Pasteur, SA	1996			Haemophilus influenza type b and Clostridium tetani cultures	XX					
11	<u>Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)</u>	Hiberix	GlaxoSmithKline Biologicals, S.A.	2009			Haemophilus influenza type b and Clostridium tetani cultures	XX					
12	<u>Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) & Hepatitis B Vaccine (Recombinant)</u>	Comvax	Merck & Co, Inc	1996			Haemophilus influenza type b and Neisseria meningitidis serogroup B cultures; yeast cells (Hepatitis)	XX					
13	<u>Hepatitis B Vaccine (Recombinant)</u>	Recombivax HB	Merck & Co, Inc	1999			Genetically engineered yeast culture	X					
14	<u>Hepatitis B Vaccine (Recombinant)</u>	Engerix-B	GlaxoSmithKline Biologicals	1998			Genetically engineered yeast culture	X					

15	<u>Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant</u>	Gardasil	Merck & Co, Inc.	2006	Genetically engineered yeast culture	X	
16	<u>Human Papillomavirus 9-valent Vaccine, Recombinant</u>	Gardasil 9	Merck & Co., Inc	2014	Genetically engineered yeast culture	X	
17	<u>Human Papillomavirus Bivalent (Types 16, 18) Vaccine, Recombinant</u>	Cervarix	GlaxoSmithKline Biologicals	2009	Trichoplusia ni insect cell culture	X	
18	<u>Influenza A (H1N1) 2009 Monovalent Vaccine</u>	No Trade Name	CSL Limited	2009	Embryonated chicken eggs	X	
19	<u>Influenza A (H1N1) 2009 Monovalent Vaccine</u>	No Trade Name	MedImmune LLC	2009	Embryonated chicken eggs	X	
20	<u>Influenza A (H1N1) 2009 Monovalent Vaccine</u>	No Trade Name	ID Biomedical Corporation of Quebec	2009	Embryonated chicken eggs	X	
21	<u>Influenza A (H1N1) 2009 Monovalent Vaccine</u>	No Trade Name	Novartis Vaccines and Diagnostics Limited	2009	Embryonated chicken eggs	X	
22	<u>Influenza A (H1N1) 2009 Monovalent Vaccine</u>	No Trade Name	Sanofi Pasteur, Inc.	2009	Embryonated chicken eggs	X	

23	<u>Influenza Virus Vaccine, H5N1 (for National Stockpile)</u>	No Trade Name	Sanofi Pasteur, Inc.	2007	Embryonated chicken eggs	X		
24	<u>Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted</u>	No Trade Name	ID Biomedical Corporation of Quebec	2013	Embryonated chicken eggs	X		
25	<u>Influenza Vaccine, Adjuvanted</u>	FLUAD	Novartis Vaccines and Diagnostics Limited	2015	Embryonated chicken eggs	X		
26	<u>Influenza Virus Vaccine (Trivalent, Types A and B)</u>	Afluria	CSL Limited	2008	Embryonated chicken eggs	X		
27	<u>Influenza Virus Vaccine (Trivalent, Types A and B)</u>	FluLaval	ID Biomedical Corp of Quebec	2008	Embryonated chicken eggs	X		
28	<u>Influenza Vaccine, Live, Intranasal (Trivalent, Types A and B)</u>	FluMist	MedImmune, LLC	2007	Embryonated chicken eggs	X		
29	<u>Influenza Virus Vaccine (Trivalent, Types A and B)</u>	Fluarix	GlaxoSmithKline Biologicals	2005	Embryonated chicken eggs	X		
30	<u>Influenza Virus Vaccine (Trivalent, Types A and B)</u>	Fluvirin	Novartis Vaccines and Diagnostics Ltd	2005	Embryonated chicken eggs	X		
31	<u>Influenza Virus Vaccine (Trivalent, Types A and B)</u>	Agriflu	Novartis Vaccines and Diagnostics S.r.l.	2009	Embryonated chicken eggs	X		
32	<u>Influenza Virus</u>	Fluzone,	Sanofi Pasteur,	2002	Embryonated	X		

	<u>Vaccine (Trivalent, Types A and B)</u>	Fluzone High-Dose and Fluzone Intradermal	Inc		chicken eggs			
33	<u>Influenza Virus Vaccine (Trivalent, Types A and B)</u>	Flucelvax	Novartis Vaccines and Diagnostics, Inc.	2012	Madin Darby Canine Kidney (MDCK) cell culture	X		
34	<u>Influenza Vaccine (Trivalent)</u>	Flubluk	Protein Sciences Corporation	2013	Spodoptera frugiperda (Sf9) insect cell culture	X		
35	<u>Influenza Vaccine, Live, Intranasal (Quadrivalent, Types A and Types B)</u>	FluMist Quadrivalent	MedImmune, LLC	2012	Embryonated chicken eggs	X		
36	<u>Influenza Virus Vaccine (Quadrivalent, Types A and Types B)</u>	Fluarix Quadrivalent	GlaxoSmithKline Biologicals	2012	Embryonated chicken eggs	X		
37	<u>Influenza Virus Vaccine (Quadrivalent, Types A and Types B)</u>	Fluzone Quadrivalent	Sanofi Pasteur, Inc	2013	Embryonated chicken eggs	X		
38	<u>Influenza Virus Vaccine (Quadrivalent,</u>	FluLaval	ID Biomedical Corporation	2013	Embryonated chicken eggs	X		

	<u>Types A and Types B)</u>												
39	<u>Japanese Encephalitis Virus Vaccine, Inactivated, Adsorbed</u>	Ixiaro	InterCell Biomedical	2009	Vero monkey kidney cell culture	X							
40	<u>Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine</u>	Menveo	Novartis Vaccines and Diagnostics, Inc.	2010	N. meningitidis and Corynebacterium diphtheriae culture	XX							
41	<u>Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine</u>	MenHibrix	GlaxoSmithKline Biologicals	2012	Neisseria meningitidis, Haemophilus influenza and Clostridium tetani cultures	XXX							
42	<u>Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine</u>	Menactra	Sanofi Pasteur, Inc	2005	Neisseria meningitidis and Corynebacterium diphtheriae cultures	XX							
43	<u>Meningococcal Group B Vaccine</u>	BEXSERO	Novartis Vaccines and Diagnostics, Inc	2015	Neisseria meningitidis and recombinant Escherichia coli cultures	XX							
44	<u>Meningococcal Group B Vaccine</u>	TRUMENBA	Wyeth Pharmaceuticals,	2014	Recombinant Escherichia coli	X							

45	<u>Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined</u>	Menomune-A/C/Y/W-135	Sanofi Pasteur, Inc	2009	Neisseria meningitides culture	X							
46	<u>Pneumococcal Vaccine, Polyvalent</u>	Pneumovax 23	Merck & Co, Inc	2008	Streptococcus pneumoniae cultures	X							
47	<u>Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein)</u>	Prenar	Wyeth Pharmaceuticals Inc	2000	Streptococcus pneumoniae and Corynebacterium diphtheriae cultures	XX							
48	<u>Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)</u>	Prenar 13	Wyeth Pharmaceuticals Inc	2010	Streptococcus pneumoniae and Corynebacterium diphtheriae cultures	XX							
49	<u>Poliovirus Vaccine Inactivated (Monkey Kidney Cell)</u>	I POL	Sanofi Pasteur, SA	2012	Vero monkey kidney cell culture	X							
50	<u>Rabies Vaccine</u>	RabAvert	Novartis Vaccines and Diagnostics	1997	Primary chicken fibroblast culture	X							
51	<u>Rotavirus Vaccine, Live, Oral</u>	ROTARIX	GlaxoSmithKline Biologicals	2008	Vero monkey kidney cell culture	X							
52	<u>Rotavirus Vaccine, Live, Oral,</u>	RotaTeq	Merck & Co., Inc.	2006	Vero monkey kidney cell	X							

								tetani cultures			
60	<u>Typhoid Vaccine</u> <u>Live Oral Ty21a</u>	Vivotif	Berna Biotech, Ltd	2013	Salmonella typhi cultures	X					
61	<u>Typhoid Vi</u> <u>Polysaccharide</u> <u>Vaccine</u>	TYPHIM Vi	Sanofi Pasteur, SA	2014	Salmonella typhi cultures	X					
62	<u>Yellow Fever</u> <u>Vaccine</u>	YF-Vax	Sanofi Pasteur, Inc	2008	Embryonated chicken eggs	X					

References

<http://www.historyofvaccines.org/content/articles/human-cell-strains-vaccine-development>

<http://www.immunize.org/packageinserts/>

<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm>

<https://www.medicines.org.uk/emc/medicine/25927>

Exhibit 9.4

Table X: Clinical Trials using fetal tissue and/or cell lines derived originally from embryos or fetuses.

Studies involving transplantation of human fetal tissue			
	Title	Clinical trial number	Status
1	Human Fetal Liver Cell Transplantation in Chronic Liver Failure	NCT01013194	completed
2	Using [18F]FDOPA PET/CT to Monitor the Effectiveness of Fetal Dopaminergic Grafts in Parkinson Disease Patients	NCT01013194	not yet recruiting
3	Human Neural Stem Cell Transplantation in Amyotrophic Lateral Sclerosis	NCT01640067	completed
4	Safety Study in Retinal Transplantation for Dry Age Related Macular Degeneration	NCT00346060	completed
5	Safety Study in Retinal Transplantation for Retinitis Pigmentosa	NCT00345917	completed
6	TRANSEURO Open Label Transplant Study in Parkinson's Disease (TRANSEURO)	NCT01898390	completed
7	Evaluation of Safety and Tolerability of Fetal Mesencephalic Dopamine Neuronal Precursor Cells for Parkinson's Disease	NCT01860794	recruiting
Studies involving transplantation of stem cell lines derived from embryonic or fetal tissue (huCNS-sc; MA09-hRPE; OPC1; PEC-01/VC-01 PF-05206388)			
	Title	Clinical trial number	Status
<i>Completed, no published results</i>			
1	Study of HuCNS-SC Cells in Patients With Infantile or Late Infantile Neuronal Ceroid Lipofuscinosis (NCL)	NCT00337636	completed
2	Study of Human Central Nervous System Stem Cells (HuCNS-SC) in Age-Related Macular Degeneration (AMD)	NCT01632527	completed
3	Study of Human Central Nervous System Stem Cells (HuCNS-SC) in Patients With Thoracic Spinal Cord Injury	NCT01321333	completed
4	Long-Term Follow-Up Study of Human Stem Cells Transplanted in Subjects With Connatal Pelizaeus-Merzbacher Disease (PMD)	NCT01391637	completed
5	Study of Human Central Nervous System (CNS) Stem Cells Transplantation in Pelizaeus-Merzbacher Disease (PMD) Subjects	NCT01005004	completed
6	Sub-retinal Transplantation of hESC Derived RPE(MA09-hRPE)Cells in Patients With Stargardt's Macular Dystrophy	NCT01345006	completed

7	Safety and Tolerability of Sub-retinal Transplantation of hESC Derived RPE (MA09-hRPE) Cells in Patients With Advanced Dry Age Related Macular Degeneration	NCT01344993	completed
8	Safety and Tolerability of Sub-retinal Transplantation of Human Embryonic Stem Cell Derived Retinal Pigmented Epithelial (hESC-RPE) Cells in Patients With Stargardt's Macular Dystrophy (SMD)	NCT01469832	completed
9	Safety Study of GRNOPC1 in Spinal Cord Injury	NCT01217008	completed
10	Observational Study of Ischaemic Stroke	NCT01859572	completed
11	A Pilot Feasibility Study of Oral 5-Fluorocytosine and Genetically-Modified Neural Stem Cells Expressing E.Coli Cytosine Deaminase for Treatment of Recurrent High Grade Gliomas	NCT01859572	completed
<i>Active and/or recruiting patients or "unknown"</i>			
12	A Phase I/IIa, Open-Label, Single-Center, Prospective Study to Determine the Safety and Tolerability of Sub-retinal Transplantation of Human Embryonic Stem Cell Derived Retinal Pigmented Epithelial (MA09-hRPE) Cells in Patients With Advanced Dry Age-related Macular Degeneration(AMD)	NCT01674829	recruiting
13	Safety and Tolerability of MA09-hRPE Cells in Patients With Stargardt's Macular Dystrophy (SMD)	NCT01625559	active, not recruiting
14	Long Term Follow Up of Sub-retinal Transplantation of hESC Derived RPE Cells in Stargardt Macular Dystrophy Patients	NCT02445612	active, not recruiting
15	Long Term Follow Up of Sub-retinal Transplantation of hESC Derived RPE Cells in Patients With AMD	NCT02463344	active, not recruiting
16	Dose Escalation Study of AST-OPC1 in Spinal Cord Injury	NCT02302157	recruiting
17	Three Year Follow-up Safety Study in Subjects Previously Implanted With VC-01™; []	NCT02939118	enrolling by invitation
18	A Safety, Tolerability, and Efficacy Study of VC-01™ Combination Product in Subjects With Type I Diabetes Mellitus	NCT02239354	recruiting
19	Safety Study of Human Spinal Cord-derived Neural Stem Cell Transplantation for the Treatment of Chronic SCI	NCT01772810	active, not recruiting

20	Dose Escalation and Safety Study of Human Spinal Cord Derived Neural Stem Cell Transplantation for the Treatment of Amyotrophic Lateral Sclerosis	NCT01730716	unknown
21	Human Spinal Cord Derived Neural Stem Cell Transplantation for the Treatment of Amyotrophic Lateral Sclerosis	NCT01348451	active, not recruiting
22	Safety and Tolerability of hRPC in Retinitis Pigmentosa	NCT02464436	recruiting
23	Pilot Investigation of Stem Cells in Stroke Phase II Efficacy	NCT02117635	active, not recruiting
24	Safety Trial of CTX Cells in Patients with Lower Limb Ischaemia	NCT01916369	recruiting
25	Pilot Investigation of Stem Cells in Stroke	NCT01151124	active, not recruiting
26	Genetically Modified Neural Stem Cells, Flucytosine, and Leucovorin for Treating Patients with Recurrent High-Grade Gliomas	NCT02015819	recruiting
27	A Study of Implantation of Retinal Pigment Epithelium in Subjects with Acute Wet Age Related Macular Degeneration	NCT01691261	active, not recruiting
28	Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure	NCT02057900	recruiting
<i>Terminated, Withdrawn or Suspended</i>			
29	Study of HUCNS-SC Subretinal Transplantation in Subjects With GA of AMD	NCT02467634	terminated
30	Study of Human Central Nervous System (CNS) Stem Cell Transplantation in Cervical Spinal Cord Injury	NCT02163876	terminated
31	Safety and Efficacy Study of HuCNS-SC in Subjects With Neuronal Ceroid Lipofuscinosis	NCT01238315	withdrawn
32	Long-Term Follow-Up of Transplanted Human Central Nervous System Stem Cells (HuCNS-SC) in Spinal Cord Trauma Subjects	NCT01725880	terminated
33	Long-Term Follow-up Safety Study of Human Central Nervous System Stem Cells in Subjects With Geographic Atrophy of Age-Related Macular Degeneration	NCT02137915	terminated
34	Research With Retinal Cells Derived From Stem Cells for Myopic Macular Degeneration	NCT02122159	withdrawn
35	Study to Evaluate Sub-retinal Transplantation of Retinal Pigmented Epithelial Cells in Patients With Dry AMD	NCT02563782	suspended

Exhibit 9.5

Class 1: Fetal tissue is required				
Area of Research		Use of human fetal tissue	Alternatives	Focus
1	Sudden infant death (SIDS) and brain development	To compare brains from infants who died of SIDS to normal brain tissue	N/A	Fetal development
2	Normal brain development and multiple sclerosis	To determine whether cells in the subventricular zone produce oligodendrocyte progenitor cells in development	N/A	Fetal development
3	Interaction of bacteria and intestinal cells in development	To study the maturation of intestinal tissue with respect to intestinal disease	N/A	Fetal development
4	The effects of breast milk on intestinal development	To study the maturation of intestinal tissue and the effects of breast milk	N/A	Fetal development
5	Development of the cerebral cortex	To study the cellular and molecular maturation of the human brain	N/A	Fetal development
6	The effects of human Cytomegalovirus (CMV) on brain development	To study the effects of CMV on cellular gene expression	N/A	Fetal development
7	Population cytogenetics	Human fetal oocytes	N/A	Meiotic errors in fetal development
8	The role of maternal antibodies in the development of neonatal lupus	To study the mechanism of disease in the fetus	N/A	Fetal development
Class 2: The value of fetal tissue is limited and alternatives are available				
Area of Research		Use of human fetal tissue	Alternatives	Focus
1	The effects of Varicella-Zoster-Virus (VZV) on neural function	Humanized mice and tissue distribution of molecules in fetal sensory neurons	Because VSV specifically infects human and primate cells, the use of human tissue to study VSV infection is justified, but not strictly required. Because this study examines changes in tissue structure and the tissue distribution of specific molecules, the use of intact tissue is justified. However, no element of the experimental design requires the tissue to be of fetal	Adult neural function in VZV infection

			<p>origin. Moreover, adult tissue would have more clinical relevance to VSV infection and human disease. Primate tissue or adult human sensory tissue could be used. Humanized mice can be produced using cord blood, PBMC, or adult thymic and liver tissue</p>	
2	The effects of Varicella-Zoster-Virus (VZV) skin and sensory neurons	Humanized mice and tissue distribution of molecules in fetal sensory neurons and tonsillar cells	<p>Because VSV specifically infects human and primate cells, the use of human tissue to study VSV infection is justified, but not strictly required. Because this study examines changes in tissue structure and the tissue distribution of specific molecules, the use of intact tissue is justified. However, no element of the experimental design requires the tissue to be of fetal origin. Moreover, adult tissue would have more clinical relevance to VSV infection and human disease. Primate tissue or adult human sensory tissue and tonsillar tissue could be used. Humanized mice can be produced using cord blood, PBMC, or adult thymic and liver tissue.</p>	Adult neural and skin function in VZV infection
3	Human Immunodeficiency Virus (HIV) pathogenesis	BLT humanized mice	<p>This project does not study HIV infection in fetal life, and no specific justification is given for the use of human fetal tissue. Humanized mice can be produced using cord</p>	Adult HIV infection

			blood, PBMC, or adult thymic and liver tissue	
4	HIV and Herpes Simplex Virus (HSV) interaction	BLT humanized mice	This project does not study HIV or Herpes infection in fetal life, and no specific justification is given for the use of human fetal tissue. Humanized mice can be produced using cord blood, PBMC, or adult thymic and liver tissue	Adult HIV and HSV infection
5	Study of Epstein-Barr (EBV), lymphocytic choriomeningitis (LCMV) and influenza A (IAV)	BLT humanized mice	This project does not study viral infection in fetal life, and no specific justification is given for the use of human fetal tissue for the study of basic cellular and molecular mechanisms of disease. Humanized mice can be produced using cord blood, PBMC, or adult thymic and liver tissue	Adult EBV, LCMV and IAV infection
Class 3: Fetal tissue is not required or advantageous; alternatives are available				
	Area of Research	Use of human fetal tissue	Alternatives	Focus
1	HSV transport in neurons	Fetal sensory neurons	The proposed studies do not specifically address the role of HSV infection during human neuronal development, but rather focus on basic cellular mechanisms of viral transport in neurons. No justification is provided for the use of human tissue, and there is no scientific advantage to fetal neurons, compared to the existing models, for this basic, cell culture research. The investigator proposes the use of animal neurons and human neural cell lines. In addition, human	Adult HSV infection

			neurons derived from iPSCs or primary adult human brain tissue derived from surgical or post-mortem donation could be used for neural cell culture.	
2	Role of lactate transporters in retinal survival	Fetal retinal cells	The proposed studies do not specifically address retinal development or the metabolic coupling of retinal cells during fetal life, but rather focus on basic cellular mechanisms of neuronal survival and function. No justification is provided for the use of human tissue, and there is no scientific advantage to fetal neurons, compared to the existing models, for this basic, cellular research. The majority of the prior studies from this laboratory and the studies proposed in this grant employ mouse model systems. In addition, human neurons derived from iPSCs or primary adult human retinal tissue derived from surgical or post-mortem donation could be used.	Basic mechanisms of retinal survival
3	Age-related macular degeneration (AMD)	Fetal retina for biochemical and electrophysiologic analysis	Because AMD causes structural degeneration of retinal tissue the use of intact tissue to study AMD is justified. However, no element of the experimental design requires the tissue to be of fetal or of human origin. Moreover, adult tissue would have more clinical relevance to	Adult onset AMD

			AMD. Finally, all of the proposed studies involving human fetal tissue are biochemical, and do not examine the unique structural aspects of intact fetal tissue. Use of mouse retina, human retinal cell lines (ARPE-19) and donated post-mortem human eyes are proposed by the investigator and would be superior scientific models.	
4	HIV, immunity and dementia	Fetal liver and brain to create humanized mice. Fetal neural cell cultures.	The grant proposes the use of cord-blood derived CD34+ cells as an alternative to the use of human fetal liver tissue, yet elects to use fetal tissue as the "primary cell source" largely for reasons of convenience and economics, stating, "Collections of blood are limited as one cord blood sample can reconstitute only 4-5 animals." Human neural cell lines, human neurons derived from iPSCs or primary adult human brain tissue derived from surgical or post-mortem donation could be used for neural cell culture.	Adult HIV infection
5	Mechanisms of neuron survival and growth in HIV	Fetal neuron culture	The proposed studies do not specifically address the role of HIV infection during human neuronal development, but rather focus on basic cellular mechanisms of neuronal survival and differentiation. No justification is provided for the use of human	Basic mechanisms of neuron survival in HIV

			<p>tissue, and there is no scientific advantage to fetal neurons, compared to the existing models, for this basic, cellular research. The majority of the prior studies from this laboratory and the studies proposed in this grant employ rat PC12 cells as a model system. In addition, human neurons derived from iPSCs or primary adult human brain tissue derived from surgical or post-mortem donation could be used for neural cell culture.</p>	
6	Effects of HIV on neural and vascular systems	Fetal neuron culture	<p>The proposed studies do not specifically address the role of HIV infection during human neuronal development, but rather focus on basic cellular mechanisms of neuronal survival and differentiation. No justification is provided for the use of human tissue, and there is no scientific advantage to fetal neurons, compared to the existing models, for this basic, cellular research. Adult neural progenitors as well as patient-specific NPCs obtained by reprogramming, and have been employed in studies of disease in similar models. Human neural cell lines, human neurons derived from iPSCs or primary adult human brain tissue derived from surgical or</p>	<p>Basic mechanisms of neural and vascular function in HIV</p>

			post-mortem donation could be used for neural cell culture.	
7	Down syndrome (DS)	Fetal neurons from aborted DS infants	DS alters the normal development of the brain, and therefore the use of human fetal tissue is relevant to the study of DS. However, this study does not directly address developmental changes in DS neural tissue, and primarily uses human fetal tissue to “validate” the iPSC model. Adult DS and normal brain tissue, as well rodent hippocampal neurons and neurons from a mouse model of DS (Ts65Dn) could be used.	Basic mechanisms of neural function in DS
8	Development of retinal vasculature	Fetal eyes	While human tissue is likely to exhibit distinct properties relative to animal models, the justification for the use of human tissue in these basic studies of cell-biology is not clear. The investigators have previously used animal models of retinal development, and will continue to employ both these models and iPSC derived tissue for the current studies.	Basic mechanisms of retinal vasculature formation
9	Shigella flexneri bacterial infection	Fetal intestinal epithelial cells (IEC) and human cell lines	Shigella is a human-specific pathogen and therefore only human cells can be used for this study. No specific justification is provided for the use of human fetal tissue. Human colon-cancer derived cell lines T-84 and HCT-8 or adult intestinal tissue could be used,	Basic mechanisms of Shigella infection

			and would be a more scientifically appropriate model.	
10	Genetic basis of hearing	Fetal cochlea	No justification is provided regarding significant differences between human and animal development that would require the use of human tissue for these basic, molecular and cellular studies. Studies from this group demonstrate a high degree of similarity in expression of cochlear transcripts between humans and mouse, indicating mouse models could be used.	Basic biology of hearing
11	HIV associated neurocognitive disorders	Fetal brains and astrocytes	This study does not address the effects of HIV infection during fetal stages, and no specific justification is given for the use of human fetal astrocytes. Human astrocyte cell lines (A735; hTERT; HASTR/ci35), adult human astrocytes from post-mortem donation or astrocytes derived from hESCs or hiPSCs are alternatives.	Adult cognitive disorders and HIV
12	Chron's disease	Fetal intestinal tissue for production of humanized mice	No justification is provided for the use of human fetal tissue for the study of the basic molecular mechanisms of immune regulation. The grant proposes the use of mouse iso-grafts for the same experimental series in which human tissue is also employed. Adult human intestinal tissue obtained from surgical procedures could also potentially be used for this analysis, and would	Adult onset bowel disease

			be a scientifically more appropriate model.	
13	Cellular and molecular mechanisms of retinal function	Fetal eyes and retinal pigment epithelium	This study does not directly examine the development of cell polarity in fetal stages, and no justification is given for the use of human fetal cells. The study proposes a number of alternatives, including a human RPE cell line (ARPE-19), adult bovine RPE, young porcine RPE, adult cow eye culture, and mouse RPE.	Basic mechanisms of retinal function
14	Treatment for HIV	Fetal liver for humanized mice	This study does not directly examine the HIV infection in fetal stages, and no justification is given for the use of human fetal cells. The investigator indicates that humanized mice can be made using Umbilical Cord Blood (UCB), but proposes using fetal tissue instead, due to "substantial increases in the cost of UCB from our current vendor."	Treatment of Adult HIV infection
15	The molecular and genetic mechanisms of oxidative stress in HIV infection	Fetal brain derived microglia and astrocytes	This study does not address the role of HIV infection in fetal life, and no specific justification is given for the use of fetal brain tissue. Human astrocyte cell lines (A735; hTERT; HASTR/ci35), adult human astrocytes from post-mortem donation astrocytes derived from hESCs or hiPSCs could be used for these studies. Tissue from adult HIV-infected patients has been used for similar studies,	Basic mechanisms of HIV infection

			including studies of oxidative stress, and would be a more scientifically appropriate model.	
16	Study of AKIP signaling pathways in the pancreas	Fetal pancreatic beta cells	This project does not study the role of PKA signaling in fetal life, and no specific justification is given for the use of human fetal tissue for the study of basic cellular and molecular mechanisms of PKA-signaling, other than its availability through the core associated with this project. The proposed studies use both fetal and adult islet cells. Preliminary data from this grant indicates that AKIP is strongly expressed by human adult islet cells.	Basic mechanisms of pancreas function
17	Inflammation in HIV infection	Fetal brain and liver for humanized mice	This project does not study HIV infection in fetal life, and no specific justification is given for the use of human fetal tissue for the study of basic cellular and molecular mechanisms of the disease. The study proposes several model systems, including CD34+/CD38+ cells from bone marrow, and peripheral blood as well as a number of cell types derived from Peripheral Blood Mononuclear Cells (PBMC). Humanized mice can be produced using non-fetal sources of CD34+ progenitors, including cells from cord blood.	Basic Mechanisms of HIV infection

18	Gene expression in myopia	Fetal eyes	This study does not examine eye disease that arises in fetal development, and provides no specific justification for the use of fetal tissue. The proposal lists adult eye and animal models of myopia as alternatives to the use of fetal tissue.	Basic mechanisms of myopia
19	HIV and neural progenitor Cells (NPC)	Fetal neural tissue	This study does not directly examine the role of HIV infection in fetal neurogenesis, and no specific justification is provided for the use of fetal NPCs. Adult neural progenitors as well as patient-specific NPCs obtained by reprogramming, and have been employed in similar disease models.	Basic mechanisms of HIV infection
20	Study of anti-retroviral therapy in NeuroAids	Fetal astrocytes to construct a model of the blood-brain barrier	This study does not directly examine the role of HIV infection in fetal neurogenesis, and no specific justification is provided for the use of fetal astrocytes. Adult astrocytes obtained by reprogramming, astrocyte cell lines (animal or human) and primary astrocytes from adult patients and have been employed in similar diseasemodels.	Adult HIV infection
21	Genes involved in neurotransmission	Cortical neurons from Down syndrome (DS) fetuses	DS alters the normal development of the brain, and therefore the use of human fetal tissue is relevant to the study of DS. However, this study does not directly address developmental changes in DS neural tissue, and	Basic mechanisms of neural transmission

			primarily uses human fetal tissue to “validate” results obtained from adult DS neurons and iPSC-derived neurons. The investigators proposed the use of adult DS and normal brain tissue, as well rodent hippocampal neurons and neurons from a mouse model of DS (Ts65Dn) as alternatives.	
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