December 21, 2018

The Honorable Alex Azar
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Azar:

On behalf of the millions of patients throughout the nation and around the world, as well as the scientific and medical communities dedicated to advancing human health, the undersigned organizations and institutions write to express our collective and strong support for the Department's continued investment in important fetal tissue research. This research is critical for the development of new treatments for a wide range of serious diseases.

Public policy that facilitates ethically responsible research is in the best interest of patients worldwide. Decades of thoughtful deliberation on the conduct of fetal tissue research has provided an ethical and policy framework for valuable medical research to progress, leading to the discovery of new treatments. At this time, the ethical considerations strongly confirm the need to continue federally supported fetal tissue research, in accordance with current federal rules. Additional restrictions on this lifesaving research would be disruptive to biomedical research and devastating to patients.

Given the Department's current review of this vital research, we take this opportunity to offer you some essential scientific facts and information for your consideration.

Fetal tissue research cannot be replaced with existing alternative research models

Claims that other cells can be used to replace fetal tissue in biomedical research are patently incorrect. In fact, cells in fetal tissue have unique and valuable properties that often cannot be replaced by other cell types. Cells from fetal tissue are more flexible and less specialized than cells from adult tissue and can be more readily grown in culture. The study of human fetal tissue provides researchers with incomparable insights into how birth defects arise and how they can be prevented as well as an unparalleled window into the complexity of human tissue development, including why serious congenital defects sometimes arise. While there have been some advances in recent years that have reduced the need for fetal tissue in certain areas of research, it remains critically important in many other areas. As representatives of the scientific and medical communities we are obligated to correct the record.

<u>Induced pluripotent stem cells (iPSCs) and organoids cannot replace fetal tissue research</u>

Assertions that iPSCs and organoid models can replace fetal tissue research are simply false. These cells and model systems may reduce the need for fetal tissue to address certain questions, but they cannot replace it. Organoids can only be used to model certain aspects of human development that can be studied in culture (growing in laboratory dishes).

There are many disease processes or therapies for which studies in tissue culture are not sufficient - in vivo studies are required. This is particularly true of diseases that involve interactions between different tissues or complex combinations of cell types.

- Organoids lack immune cells and tend to mimic early fetal development, making them inadequate for modeling immune responses to infection, inflammation, or later stages of fetal development.
- There is a general inability to form a functional human immune system with organoids or with iPSCs, or to model the complex interactions between different kinds of immune cells and supporting cells in lymphoid organs. For this reason, diseases that affect the immune system, such as HIV, are studied by transplanting human hematopoietic and lymphoid tissues into mice, creating a functional human immune system in vivo.
- iPSCs are an inadequate substitute for fetal tissue because the cells generated from iPSCs lack the complex environment and signaling between different cell types that leads to complete tissues and organs. For this reason, we are unable to generate human organs from these cells, making it impossible to study disease processes that involve the interaction of different cell types within human organs.
- The cells derived from iPSCs or organoids grown from adult tissues do not replicate cells that can be obtained from fetal tissue. The cells derived from iPSCs are too developmentally immature and the cells derived from adult tissues are too developmentally mature. This makes it impossible to study congenital diseases, like zika virus, that affect fetal tissues in the latter half of gestation.

There are some cases in which diseases can be studied with cells derived from iPSCs or organoids. However, in those cases, the results still have to be validated using fetal tissue as the “gold standard” reference material. As a result, fetal tissue remains critically important to understand human development and to validate iPSCs or organoid models.

<u>Established fetal cell lines are not adequate substitutes for fetal tissue research</u>

While we support the continuation of research using established fetal cell lines, these cell lines are not a substitute for fetal tissue research. The existing fetal cell lines are limited to a small number of fetal cell types and stages. These cell lines cannot obviate the need to study fetal tissue for the same reason that organoids and iPSCs cannot completely replace fetal tissue: some diseases can only be studied in vivo where there are complex interactions among different cell types. At this time, researchers cannot study the entire fetal development period or complex tissues without access to fetal tissue.

<u>The NeoThy mouse model cannot replace the BLT mouse model</u>

The NeoThy mouse model (in which neonatal human thymic tissue and cord blood cells are transplanted into mice to form human blood and immune cells) cannot replace the BLT mouse model (in which fetal human bone marrow, liver, and thymic tissue are transplanted into mice to form human blood-forming and immune systems). BLT mice have human blood-forming stem cells that are maintained and give rise to diverse types of human blood and immune system cells within human blood-forming tissues (liver and bone marrow). In contrast, NeoThy miceonly have human thymic tissue in which one component of the

human immune system can develop. Cord blood cells can be transplanted into NeoThy mice to transiently form other components of the blood forming system but in the NeoThy mouse this occurs in mouse blood-forming tissues, not in human tissues. Consequently, the NeoThy mouse does not fully model human blood cell production within human tissues. The NeoThy mouse may be adequate for some applications, but the BLT mouse more fully and accurately models the formation of human blood and immune system cells in human tissues and therefore is a more realistic model for many diseases. The NeoThy mouse is also still a new model that has yet to be fully vetted by the scientific community.

Tissue from spontaneous abortions cannot replace tissue from elective abortions

Tissue from spontaneous abortions is not a suitable or reliable substitute for tissue from elective abortions. Spontaneous abortions, commonly called miscarriages, often result from profound genetic defects, developmental abnormalities, or other conditions that undermine the usefulness of the tissue for research. Additionally, spontaneous abortions generally do not occur in settings where the tissue can be adequately preserved for research.

Fetal tissue research is critical for researching early human development

Fetal tissue allows researchers to more fully understand congenital defects such as those of the heart or nervous system and to understand how viruses like the Zika virus impact fetal development. The use of donated fetal tissue has been critical for understanding how Zika virus crosses the placenta and impacts human brain development. The insights gained through studies of Zika virus in human fetal tissue are already guiding the development of therapies to prevent transmission of the virus. This prominent and contemporary example illustrates the need for continued federal support of fetal tissue research. Further limitations would hinder the development of critical new treatments and potentially cost lives.

There are well-established and rigorous regulatory frameworks for fetal tissue research

Rigorous legal and ethical oversight of fetal tissue research has been in place for decades. This research has garnered bipartisan support in the U.S. Congress and has been funded by the National Institutes of Health (NIH). Numerous federal panels and reviews, conducted under both Republican and Democratic congressional majorities and presidential administrations, have evaluated human fetal tissue research and have concluded it is critical for lifesaving biomedical research. This research has long been viewed as good public policy to improve human health and has proceeded with public support. Legal and ethical frameworks that are already in place ensure rigorous and appropriate oversight, including that the tissue is obtained legally and with donor consent. Unreasonably and unconscionably, the fetal tissue that is used for research otherwise would be discarded if not donated for research.

Fetal tissue research improves human health and saves lives

Historically, fetal tissue research has been critical for scientific and medical advances that have saved the lives of millions of people, including the development of vaccines against polio, rubella, measles, chickenpox, adenovirus, rabies, and treatments for debilitating

diseases such as rheumatoid arthritis, cystic fibrosis, and hemophilia. Fetal tissue was also essential for the development of a therapy to prevent the transmission of HIV (Truvada). It remains critical for on-going clinical research for Amyotrophic Lateral Sclerosis (ALS), spinal cord injury, and Parkinson's disease. Fetal tissue is medically necessary to best understand human development. It is vitally important for testing new therapies and as a source of cells for new cell therapies that offer the potential to improve the treatment of major public health problems.

As you conclude your review of fetal tissue research, we urge you to allow this important research to continue to support the families who are relying on biomedical research to develop new treatments for diseases that affect their loved ones and millions of other people around the world. Thank you for your consideration.

Sincerely,

AIDS Foundation of Chicago
AIDS Treatment Activist Coalition
Alliance for Aging Research
American Academy of HIV Medicine
American Academy of Neurology
American Association for the Advancement of Science
American Association of Anatomists
American Association of Colleges of Pharmacy
American Association of Immunologists
American Physiological Society
American Society for Cell Biology
American Society for Investigative Pathology
American Society for Reproductive Medicine
American Society of Hematology
American Thoracic Society
Americans for Cures
Association of American Medical Colleges
Association of American Universities
Association of Independent Research Institutes
Association of Public and Land-grant Universities
AVAC
Axis Advocacy
Bailey House, Inc.
Christopher and Dana Reeve Foundation
Coalition for the Life Sciences
Columbia University Irving Medical Center
Council on Governmental Relations
Endocrine Society
Federation of American Societies for Experimental Biology
Global Healthy Living Foundation

Harvard University
HIV Medicine Association
HIV+Aging Research Project-Palm Springs
Housing Works
Infectious Diseases Society of America
International Foundation for Autoimmune & Autoinflammatory Arthritis
International Rectal Microbicide Advocates
International Society for Cell & Gene Therapy
International Society for Stem Cell Research
Johns Hopkins University
Lupus and Allied Diseases Association
Massachusetts General Hospital
Nashville CARES
NASTAD
National Multiple Sclerosis Society
New York University
NMAC (Formerly known as the National Minority AIDS Council)
Project Inform
Research!America
Rutgers Biomedical and Health Sciences
Society for Neuroscience
Society of Family Planning
Stanford University School of Medicine
Stony Brook University
Texans for Cures
The Michael J. Fox Foundation for Parkinson's Research
The Nebraska Coalition for Lifesaving Cures
The State University of New York System
Treatment Action Group
Tuberous Sclerosis Alliance
University at Buffalo- The State University of New York
University of California System
University of Michigan
University of Minnesota
University of Pittsburgh
University of Washington
University of Wisconsin – Madison
Washington State University
Weill Cornell Medicine
Yale University