Human Fetal Tissue Regulation

Impact on Pediatric and Adult Respiratory-related Research

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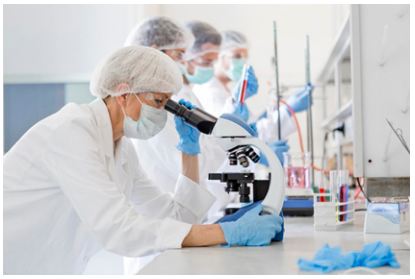

On June 13, 2019, the Trump Administration announced a new policy banning National Institute of Health (NIH)–supported intramural human fetal tissue research (approximately three projects). The ban also included a requirement for new ethics reviews of NIH extramural fetal tissue research (~200 ongoing projects). In response, the American Thoracic Society (ATS) issued a press release on June 5, 2019, expressing concern about this ban and its potential impact on research to advance cures for respiratory diseases, critical illnesses, and sleep disorders. The NIH subsequently issued new guidelines on July 26, 2019, regarding research using human fetal tissues obtained from elective abortions in extramural grant applications, stipulating the need to justify the use of these tissues and the establishment of a new ethics board to review and approve their use. The purpose of this article, an extension of a recently published article in the *ATS Research News Quarterly* (1) is to educate ATS members about the ban and its impact on intramural NIH fetal tissue research and about the new NIH guidelines for extramural grant applications, placing both in the context of past, current, and potential future benefits of human fetal tissue research.

Relationship to Restrictions on Human Embryonic Stem Cell Research

It is important to make a clear distinction between fetal tissues and embryonic stem cells (ESCs). ESCs are derived from blastocysts that represent fertilized eggs that have undergone several rounds of division in tissue culture settings (2). In the United States, these are generated and obtained from *in vitro* fertilization clinics and are specifically those that are not used clinically and that are donated for research purposes under strict regulatory guidelines. ESCs are not obtained from fetal tissues acquired from terminated pregnancies. In contrast, fetal tissue includes stem cells derived from placenta, amniotic fluid, and umbilical cord in addition to organ-specific tissues such as fetal lung and liver. Both ESCs and fetal tissues are powerful, yet different, complementary tools that have proven indispensable for major advances in understanding respiratory and other diseases, such as cystic fibrosis (CF), human immunodeficiency virus (HIV), Alzheimer's disease, spinal cord injury, and others (2). The use of human ESCs in biomedical research has also stimulated extensive ethical, moral, religious, and political discussions as well as a temporary ban on use of federal funding for the study of human ESCs during the administration of George W. Bush, a ban that was overturned by the Barack Obama administration. The ATS has previously published an official statement supporting study of ESCs (3).

The Policy/Ban and Related Legislation

The new policy states that intramural NIH researchers will not be permitted to obtain additional fetal tissues for research studies, effectively ceasing these and any future intramural studies. In addition, one large extramural study on HIV therapies at the University of California San Francisco has been halted, interrupting a 30-year partnership between the University of

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California San Francisco and the NIH. However, other current extramural studies using fetal tissues will apparently not be immediately affected or undergo additional review until renewal.

On July 29, 2019, the Trump Administration detailed additional justification and ethics review that, barring Congressional override, extramural researchers using fetal tissues will be required to include in grant applications submitted after September 25, 2019. Specifically, researchers will be required to add to the research plan section of grant proposals *1*) justification for use of fetal tissue; *2*) clarification as to lack of alternatives, including the methods and preexisting data used to determine this; *3*) plans for the use and disposal of human fetal tissue after completion of research; and *4*) details of how the tissue is obtained, including written informed consent and lack of enticements/benefits offered to patients to undergo abortion or donate the tissue. This information will be subject to application page limits, significantly decreasing the amount of space otherwise available in the research plan and will also be reviewed separately by an undefined newly established "ethics panel" before funding.

On February 20, 2020, the Department of Health and Human Services (DHHS) announced its intention to convene the existing NIH Human Fetal Tissue Research Ethics Advisory Board and to solicit new nominations to the Board. The Board is composed of 15 non–federal employee individuals, including at least one each of an attorney, ethicist, practicing physician, and theologian, and in addition, at least one-third of the members are scientists with substantial accomplishments in biomedical or behavioral research. The Board was charged with submitting a report to the DHHS Secretary and to Congress by August 30, 2020, describing the research grants reviewed and recommendations for whether the grants should be funded. The Board held its initial meeting on July 31, 2020, with Dr. Thomas Mariani presenting comments reflective of this *Perspectives* article on behalf of the ATS. A summary report of the meeting has been made available (https://osp.od.nih.gov/wp-content/uploads/HFT_EAB_FY2020_Report_08182020.pdf). The Board recommended to withhold funds for 13 of the 14 grants reviewed. The DHHS Secretary has not yet announced whether he will accept these recommendations.

In response to the administration's actions, the U.S. House of Representatives passed an amendment on June 13, 2019, sponsored by Representative Pocan (democrat [D]; Wisconsin) to the Fiscal Year 2020 Health Research and Services Spending Bill that would have prevented the Trump Administration from imposing new ethics reviews on all federally funded extramural research. However, the measure failed to pass the U.S. Senate. On April 1, 2020, Representatives Schakowsky (D; Illinois) and Pocan (D; Wisconsin) introduced subsequent legislation in the U.S. House of Representatives, the Protecting Cures Act of 2020, H.R.6417, which would eliminate the Trump Administration's restrictions on fetal tissue research, including a prohibition on the withholding of funds that support research and reaffirming the NIH's existing ethics framework. The ATS has endorsed the Protecting Cures Act. However, this Act has not moved in the House since its introduction in March, and a Senate bill has not been introduced. Additional resources provided by The National Conference of State Legislatures can be found at www.ncsl.org/research/health/embryonic-and-fetal-research-laws.aspx.

Past Contribution of Human Fetal Tissue Research

Despite some basic similarities, fundamental differences exist between developmental pathways in humans, rodents, and other animal models. Therefore, for many decades, human fetal tissue has been used in many areas of research to understand human organ development and human diseases (4). In 2014, the NIH spent ~$75 million on human fetal tissue research, about half of total spending on ESC research (5). A majority of these projects focused on HIV and other infectious diseases, including those with respiratory involvement. Historically, cell lines derived from human fetal tissues are a major resource for the development of viral vaccines, including those for hepatitis A, varicella, measles/mumps/rubella, herpes zoster, rabies, and more recently, for testing the effectiveness of the antibody therapy against coronavirus disease (COVID-19) from Regeneron Pharmaceuticals (6). In fact, these vaccines are typically derived from MRC-5 and WI-38 cells, both of which are lines originating from human fetal lung tissue. It is estimated that the ~6 billion doses of vaccines developed from these lines have prevented nearly 11 million deaths and 4.5 billion cases of disease (7). Fetal-derived tissues may also provide a powerful opportunity for developing vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other coronavirus infections.

Beyond vaccine development, there has been broad use of human fetal tissues and cells derived from these tissues in infectious disease and in developmental research. One prominent example is the generation of rodent models with humanized immune systems (4). These animals can be used to study uniquely human diseases, such as those resulting from infection with HIV, including respiratory and nonrespiratory (e.g., liver) complications. Participants in the 2018 National Institute of Allergy and Infectious Diseases Workshop on Humanized Mouse Models concluded that "human fetal tissue-derived humanized immune systems models remain the "gold standard" to which other model systems should be compared" (8). However, these are not heritable traits, and thus, ongoing generation of humanized mice requires continuous need for human fetal tissues.

Historically, the largest body of work in respiratory research using human fetal tissue aims to elucidate lung developmental processes. An important historical example is the discovery of pulmonary surfactant and its deficiency in the lungs of premature infants, leading to infant respiratory distress syndrome. Studies with fetal human lungs defined developmental changes and the maturational effects and mechanisms of glucocorticoid treatment, the current standard of care for prevention of respiratory distress syndrome in premature deliveries (9). The use of human fetal lung tissue has also helped elucidate genetic and congenital lung disorders associated with chromosomal anomalies, such as acinar dysplasia, alveolar dysplasia, trisomy 21, inherited surfactant protein deficiency, and CF (10). In many cases, there are no good alternatives to the use of human fetal tissue. For example, the mouse lacks chromosome 21, and hence, trisomy 21–associated lung anomalies cannot be accurately studied in a mouse model. Table 1 summarizes the use of various fetal tissues to study the pathogenesis and treatment of lung and other diseases.

Table 1. Contributions of human fetal tissue research to pathogenesis and treatment of diseases

Fetal Tissue	Experimental System	Disease	Contribution
Lung (9)	Tissue and BAL Explant culture	RDS	Define developmental gene expression patterns Association with low surfactant content and structural immaturity
	Parenchymal primary cell culture		Demonstrate maturational benefits of glucocorticoid therapy Identify molecular targets of glucocorticoids Optimize dose and time of antenatal glucocorticoid therapy to prevent RDS
(10, 11, 18)	—	Congenital anomalies: surfactant protein mutations Acinar dysplasia, alveolar dysplasia, and trisomy 21 Cystic fibrosis	Provide cell-specific data on molecules and pathways of embryonic and fetal tissue development and effects of mutations
(12–14)	Airway smooth muscle cells Explants	Bronchopulmonary dysplasia Asthma	Effects of hyperoxia and tobacco components on cell structure and function Dosing of corticosteroids for postnatal antiinflammatory effects
(15)	Cell lines	Cancer Drug cytotoxicity	Testing antitumor and cytoprotective agents Developing cancer risk biomarkers
(7)	Cell lines	Viral diseases: Hepatitis A Varicella Measles Mumps Rubella Rabies	Cell source for virus growth and development of clinically effective vaccines
Liver (19)	Isolated cells	Chronic liver disease	Stem cell source for transplantation and regeneration in liver failure
	Organoids Humanized mouse model	Hepatitis HIV	*In vitro* model for hepatobiliary organogenesis Investigate human immune response to liver pathogens and efficacy of antiviral drug therapies
Thymus (+liver) (20)	Isolated cells Humanized mouse model	Autoimmune diseases Viral diseases	Study autoimmune induction of type I diabetes Model for mechanistic studies of HIV and other viral infections and treatment
Pancreas (21, 22)	Tissue Isolated islets Immortalized cell lines	Type I/II diabetes	Source of hESC Gestational age and transplantation Investigate strategies for protection of β cell against autoimmune and metabolic insults
Kidney (23)	Tissue	Agenesis/failure	Provide developmental data for comparison with organoids/tissues generated from iPSCs
Brain	Tissue	Hypoxic-ischemic encephalopathy	Mechanism of arrested development of oligodendrocyte progenitor cells
	Isolated cells	Neurodegenerative diseases	Provide developmental data for comparison with organoids/tissues generated from iPSCs
		Stroke	Source of ESCs for transplantation
Heart (24)	Tissue Cardiomyocytes	Congenital heart disease	Genetic mutations Developmental data for comparison with iPSCs Radiologic microstructure and fluid mechanics studies with CHD
Prostate	Xenograph rodent model Organ culture Isolated fibroblasts	Prostate cancer	Mechanisms of estrogenic and androgenic influences
Testis	Tissue Xenograph rodent model	Testicular cancer	Control for cancer tissue Effects of hormones and gonadotoxins

Definition of abbreviations: BAL = bronchoalveolar lavage; CHD = congenital heart disease; ESC = embryonic stem cell; hESC = human embryonic stem cell; HIV = human immunodeficiency virus; iPSC = induced pluripotent stem cell; RDS = infant respiratory distress syndrome (hyaline membrane disease).

Potential Impact on Current Human Fetal Lung Tissue Research

The number of investigators and projects using fetal tissues is increasing, particularly with new analytical techniques such as gene mapping and single-cell sequencing. Recent studies from groups in the United States and Europe have highlighted novel cellular and molecular features in human fetal lungs (11). These advances would not have been possible without the use of fetal human tissue, as alternative models (mice, induced pluripotent stem cells, or organoids) have not provided comparable information.

In prominent examples of critical ongoing clinical need, severely premature (24–28 wk of gestation) infants remain at higher risk of developing respiratory disorders, including bronchopulmonary dysplasia, asthma, and airway hyperreactivity. Because there are no ideal animal models of any of these conditions that fully recapitulate human disease, human fetal tissues and cells remain invaluable for assessing environmental factor exposures as well as the effects of hormones, growth factors, and other agents (e.g., drugs) on lung development (12–14). Beyond lung development, human fetal lung tissue has been used in lung cancer studies and congenital diseases (15).

Notably, congenital diseases such as CF, thalassemia, and congenital heart disease are difficult to treat, let alone cure, and have each benefited from key fetal tissue research for which no or limited alternatives exist. For example, recombinant human deoxyribonuclease, or Pulmozyme, is a powerful mucolytic developed in human fetal kidney cells and has become an invaluable therapeutic for patients with CF (16).

Do Viable Alternatives Exist to Human Fetal Tissue in Biomedical Research?

In December 2018, the NIH issued a Notice of Intent to Publish Funding Opportunity Announcements for "research to develop, demonstrate and validate experimental human tissue models that do not rely on human fetal tissue" (NOT-OD-19–042). The notice stated that the "NIH is interested in investing up to $20M over the next two years in these scientific topic areas." Since then, individual institutes have published several Notices of Special Interest (NOT-CA-19–047, NOT-EY-19–011, NOT-AI-19–040, NOT-CA-19–028, NOT-CA-19–040, NOT-TR-19–019, and NOT-HD-19–011) announcing opportunities for administrative supplements to existing NIH grants or requests for applications (RFA-GM-19–001 and RFA-MH-20–140) related to the development of alternatives for specific uses of human fetal tissue. The NIH suggests several alternatives to human fetal tissue from elective abortions in biomedical research, including development and validation of models that use donated tissue from spontaneous abortions or deceased newborns (miscarriages or stillbirths), induced pluripotent stem cells, umbilical cord blood hematopoietic stem cells, organoids, microphysiologic (tissues-on-chips) systems, and humanized mouse models. Lung organoids in particular show promise for understanding cell–cell interactions in the developing lung or in preclinical pharmaceutical screening. RNA sequencing analysis reveals that their transcriptional profiles are highly similar to human fetal lung. In experimental designs, they exhibit organized airway structures with surrounding lung mesenchyme and alveolar epithelial cells. However, organoids only partly recapitulate certain aspects of human lung development or disease. As such, fetal tissue remains indispensable.

A coalition of biomedical research societies, including the ATS, wrote a letter to the DHHS in July 2019 to express their collective opinion that no viable alternatives currently exist for the use of human fetal tissue in a number of research areas (17). In particular, the letter stated that "Fetal cell lines are not a substitute for fetal tissue because the lines are limited to a small number of cell types and are inadequate for studying complex interactions between cells. Similarly, organoids and stem cell model systems are simplistic models that only mimic certain aspects of human development." Therefore, although alternatives do exist for use of human fetal tissue, these models remain limited, and no viable options to human fetal tissue exist for much research on human lung development and disease.

Conclusions

The ban on using human fetal tissues obtained from elective abortions for intramural NIH researchers will result in the abrupt ending of ongoing projects and promising research that has been funded for many years in some situations. For NIH-funded extramural scientists, the new regulation for additional justification and ethics committee review represents an unnecessary burden and may restrict the potential for beneficial research using human fetal tissues obtained from elective abortions. Although it is mandatory to ensure a high ethical standard in the use of all human tissues, this function is historically and adequately provided by local institutional ethics review boards. Also, this new policy appears designed to hinder the development of proposals with human fetal tissue research, considering the extensive required justification that now has to be included within the research plan page limit of grant proposals. Although these rules do not make human fetal research impossible for established investigators, they do represent significant obstacles.

Importantly, by prohibiting the proposed use of human fetal tissue obtained from elective abortions in research training awards and fellowships, including all training grants, predoctoral and postdoctoral fellowships, and career development awards, this new policy also makes it nearly impossible for trainees and early career investigators to include use of human fetal tissue in their NIH proposals. Furthermore, trainees working in the laboratories of established investigators will be significantly less able to implement novel ideas related to the study of human fetal tissues. Ultimately, some of the most valuable tools for lung development research will be off limits to arguably the most productive and innovative investigators in pulmonary, critical care, and sleep medicine. The ATS will continue to monitor policy developments in this area and advocate both for continued open access to human fetal tissue for all federally funded intramural and extramural scientific research. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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