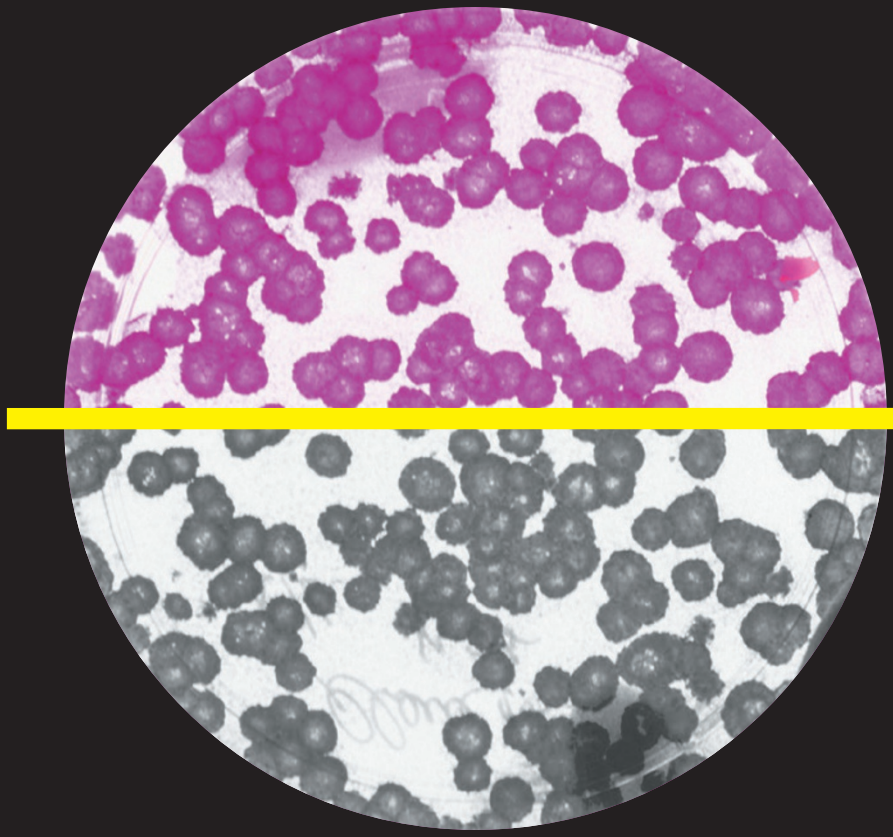


THE TRUTH ABOUT FETAL TISSUE RESEARCH

The use of aborted fetal tissue has sparked controversy in the United States, but many scientists say it is essential for studies of HIV, development and more.

BY MEREDITH WADMAN

Every month, Lishan Su receives a small test tube on ice from a company in California. In it is a piece of liver from a human fetus aborted at between 14 and 19 weeks of pregnancy.

Su and his staff at the University of North Carolina at Chapel Hill carefully grind the liver, centrifuge it and then extract and purify liver- and blood-forming stem cells. They inject the cells into the livers of newborn mice, and allow those mice to mature. The resulting animals are the only 'humanized' mice with both functioning human liver and immune cells and, for Su, they are invaluable in his work on hepatitis B and C, allowing him to probe how the viruses evade the human immune system and cause chronic liver diseases.

"Using fetal tissue is not an easy choice, but so far there is no better choice," says Su, who has tried, and failed, to make a humanized mouse with other techniques. "Many, many biomedical researchers depend on fetal tissue research to really save human lives," he says. "And I think many of them feel the same way."

MASSIMO BERGE/LIGHTHOUSE/SPL

An explosive climate has surrounded US research with fetal tissues since July, when an anti-abortion group called the Center for Medical Progress in Irvine, California, released covertly filmed videos in which senior physicians from the Planned Parenthood Federation of America bluntly and dispassionately discussed their harvesting of fetal organs from abortions for use in research. Planned Parenthood is a non-profit women's health provider that received US$528 million of government money in 2014, much of it in reimbursements for services ranging from contraception to cancer screenings, which it provides largely to poor women. Abortions, which are performed at about half of Planned Parenthood's 700 clinics, constitute 3% of its services. A handful of clinics in two states supply fetal tissue for research.

The videos provoked a furore that has intensified over the past few weeks. On 3 December, the Republican-led US Senate voted to strip Planned Parenthood of government funding. This is despite the fact that fetal tissue research is legal, the US National Institutes of Health (NIH) has been funding it for decades and President Obama is sure to veto the bill, should it reach his desk. A few days earlier, on 27 November, a gunman shot dead three people at a Planned Parenthood clinic in Colorado Springs, Colorado. In a post-arrest interview, the suspect is reported to have said "no more baby parts".

The episode has shone a spotlight on a little-discussed arm of biomedical research, raising the questions of why, how and how widely fetal tissue is used. To find out, *Nature* turned to an NIH database of research grants funded in 2014 to find those using fresh human fetal tissue, and in October contacted 18 researchers working with it. Su was one of only two who were willing to be interviewed. Most requests were declined or went unanswered; a public-affairs officer at one major Texas university refused to have a researcher speak to *Nature* to keep that person "safe".

The figures show that in 2014, the NIH funded 164 projects using the tissue, at a cost of $76 million. This is slightly less than half of what the agency spent on work with human embryonic stem cells (ES cells), which has also been highly controversial, and 0.27% of the $27.9 billion it spent on all research. (By comparison, the UK Medical Research Council spent 0.16% — £1.24 million ($1.9 million) — of its total spending on research on five projects involving fetal tissue in the 12 months up to 31 March 2015.) Analysis of the NIH projects shows that the tissue is used most heavily for research on infectious diseases, especially HIV/AIDS; in the study of retinal function and disease; and in studies of normal and anomalous fetal development (see 'Fetal tissue research by discipline').

> "USING FETAL TISSUE IS NOT AN EASY CHOICE, BUT SO FAR THERE IS NO BETTER CHOICE."

Opponents argue that the work is not necessary because other model systems and techniques can be used. "This is antiquated science," says David Prentice, the vice-president and research director at the Charlotte Lozier Institute, the research arm of the Susan B. Anthony List, which is an anti-abortion organization in Washington DC. "There are better and, frankly, more successful alternatives."

But supporters of the research counter that fetal tissue is legally obtained, that it would otherwise be destroyed, that such work has already led to major medical advances and that, if there were better alternatives, they would turn to them. "Fetal tissue is a flexible, less-differentiated tissue. It grows readily and adapts to new environments, allowing researchers to study basic biology or use it as a tool in a way that can't be replicated with adult tissue," says Carrie Wolinetz, the NIH's associate director for science policy.

"I get very frustrated when misinformed people go on about how it can all be done with computer models or cell cultures or stem cells or animals," says Paul Fowler, a reproductive biologist at the University of Aberdeen Institute of Medical Sciences, UK, who in January published a study using livers from aborted fetuses to probe the impacts of maternal smoking on liver development[1]. "In some areas, the human is absolutely dramatically different than rodents."

Some argue that the entire episode represents a thinly cloaked attempt to attack and limit access to abortion by eroding support and funding for Planned Parenthood. "People are talking about fetal tissue, but really what this discussion is about is abortion," says Shari Gelber, a specialist in maternal–fetal medicine at Weill-Cornell Medical College in New York City, who has argued for the value of the research.

LABORATORY LINES

Cell lines derived from aborted fetal tissue have been fairly commonplace in research and medicine since the creation in the 1960s of the WI-38 cell strain, which was derived at the Wistar Institute in Philadelphia, Pennsylvania, and MRC-5, which came from a Medical Research Council laboratory in London (see *Nature* **498,** 422–426; 2013). Viruses multiply readily in these cells, and they are used to manufacture many globally important vaccines, including those against measles, rubella, rabies, chicken pox, shingles and hepatitis A.

Companies have shipped at least 5.8 billion vaccines made with these two cell lines which, with others, have become standard laboratory tools in studies of ageing and drug toxicity. (Research with such lines is not covered by US regulations governing the use of fresh fetal cells and tissue nor captured in the NIH database.) 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.

But off-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. And creating humanized mice such as Su's requires whole pieces of fetal organs to provide sufficient numbers of stem cells. For all of these reasons, researchers turn to fresh tissue.

In the United States, this is collected at medical centres and clinics that perform abortions under a patchwork of laws and regulations governing consent, tissue collection and transfer (see 'Fetal tissue and the law'). US law says that clinics can recover "reasonable payments" to offset the costs of providing the tissue, but it makes it a felony to profit from doing so. Planned Parenthood officials say that its clinics obtain full and informed consent from women choosing to donate fetal remains for research, and the organization announced in October that its clinics will no longer recover costs of $45–60 per specimen for collecting the tissue.

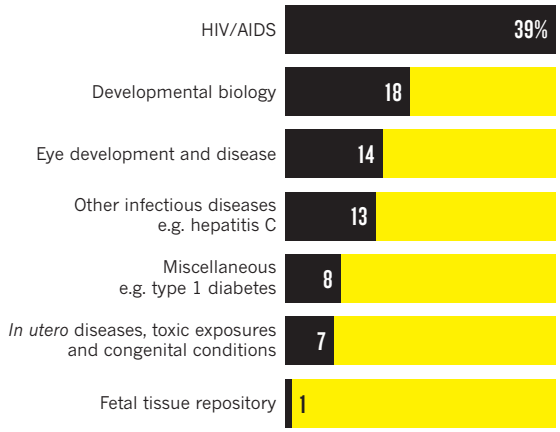
From the clinics, fetal tissue is then often passed to biological-research supply companies, which act as intermediaries and process the tissue before selling it to researchers. Su pays $830 for each sample of fetal liver tissue supplied to his lab by one of the most widely used suppliers, Advanced Bioscience Resources in Alameda, California.

HIV AND AIDS

The category of fetal tissue work that draws most NIH funding is the study of HIV and AIDS: it accounts for 64 of the 164 NIH grants. Researchers in this field have long struggled with the paucity of effective models for this uniquely human disease. The standard models, macaques, are expensive to breed, are infected with SIV instead of HIV and have immune responses that are different from those of people. The flexibility and adaptability of fetal tissue — and its richness as a

FETAL TISSUE RESEARCH BY DISCIPLINE

The US National Institutes of Health funded 164 projects using human fetal tissue in the 2014 fiscal year, in these research areas:



SOURCE: NIH

US REGULATION

Fetal tissue and the law

Regulations governing US-funded fetal tissue research, first issued in 1975, state that:

- The research must comply with all applicable US, state and local laws and regulations.
- If information associated with the fetal tissue allows it to be traced to a living individual, that person becomes a research subject and informed consent from the donor is required for its use.

(Laws in at least 40 states require informed consent from the woman even if the fetal tissue will be anonymized.)

Additional requirements from a 1993 US law:

- Providers may not transfer fetal tissue for profit, but can receive funds to cover 'reasonable payments', such as for processing, storage and transportation.
- Researchers may not acquire fetal tissue if they know that a pregnancy was initiated in order to provide that tissue for research.
- Violators of either provision above are subject to criminal penalties of up to ten years in prison, up to US$500,000 in fines, or both. These apply to both the tissue supplier and the tissue receiver in a transaction.

source of stem cells — has allowed the creation of a number of mice with humanized immune systems.

Prominent among these is the BLT (bone marrow–liver–thymus) mouse, which was created in 2006 (ref. 2). This model is made by destroying the animal's immune system and then surgically transplanting liver and thymus tissue fragments from a human fetus into the mouse. The immune system is further humanized with a bone-marrow transplant, using blood-forming stem cells from the same fetal liver. The animal enables studies of, for instance, immune responses that are key to developing an effective HIV vaccine. The mouse has "accelerated the study of HIV pathogenesis and novel approaches to harness anti-viral immunity to control HIV", reads a recent review by several NIH-funded scientists who are using the mouse[3].

The mouse has also helped to demonstrate that prophylactic drugs may prevent vaginal HIV infection — a strategy that is now in late-stage human trials. The animal is currently being used to examine how genital infection with herpes simplex virus alters immunity at the vaginal mucosa, making it easier for HIV to infect. In a similar vein, Su is now using his humanized mouse to examine the mechanisms by which hepatitis C and HIV co-infection can hasten liver disease.

There are drawbacks: the BLT mouse's average lifespan is relatively short, at only around 8.5 months, because the animals tend to develop cancers of the thymus. And the humanized immune system is not inherited, so the model must be created again and again — leading to the constant demand for fetal tissue that so disturbs abortion opponents.

HUMAN DEVELOPMENT

In some research areas, fetal tissue may, in time, be replaced by other materials and methods: alternative, flexible cell types, including human ES cells and induced pluripotent stem (iPS) cells, and organoids, which are lab-created cellular structures that resemble tissue from normal organs (see *Nature* **523,** 520–522; 2015). But there is one area in which, scientists say, fetal tissue is needed by definition: studies of early human development, and why it sometimes goes wrong.

"Human fetal tissue is likely never going to be replaced in some areas of research, particularly relative to fetal development," says Wolinetz. And the application of such work goes far beyond understanding developmental disorders such as congenital heart disease or other malformations, says Neil Hanley, an endocrinologist at the University of Manchester, UK. "For a wide range, now, of adult diseases and disorders, we know that they have their origins during very early human development," he says — type 2 diabetes and schizophrenia are both cases in point. "And unless you understand normal you're not going to understand abnormal."

The 30 developmental-biology grants involving fetal tissue that were awarded by the NIH in 2014 range from a study of the differentiation of myoblasts, which are the embryonic precursors of muscle cells, to several examinations of development of the urogenital tract — studies with relevance, for instance, to hypospadias, a common condition in which the urethra fails to close and the underside of the penis is incompletely formed. One project is creating a three-dimensional atlas of gene expression in the genital tubercle, the precursor of the penis. Another is probing gene activity in cells lining the fetal intestine to help explain excessive intestinal inflammation in premature babies. Hanley says that such studies are important, particularly because gene regulation — the finely tuned symphony that controls when and where genes are active — can vary strikingly between species, so findings in other animals often do not hold true in humans.

More than half of the 30 grants are for studies of brain development, and many of these projects are seeking advances in combating maladies such as autism, schizophrenia and Alzheimer's disease. Larry Goldstein, a neurobiologist at the University of California San Diego School of Medicine in La Jolla, uses cells called astrocytes from the brains of aborted fetuses to nourish neurons that he has derived from iPS cells and that have mutations associated with Alzheimer's disease. The astrocytes are thought to secrete factors that keep the neurons healthy in culture, and he uses the system to study the pathogenesis of the disease and to test potential drugs.

Goldstein hopes eventually to derive the astrocytes, too, from iPS cells. But "the human fetal astrocytes that we get at present are the gold standard that we use, and will use, to compare astrocytes that we make by differentiation", he says. He has also used neurons from aborted fetal brains to compare with the neurons made from iPS cells[4]. "As long as fetal tissue is available, this is a very valuable use of it," he says.

Another 23 of the NIH grants using fetal tissue involve eye development and disease. Damage to the retinal pigment epithelium (RPE), a single layer of cells at the back of the eye, has a key role in a

ANDY KATZ/DEMOTIX/CORBIS; WIN MCNAMEE/GETTY

The collection of aborted fetal tissue for use in research has prompted demonstrations for and against US health provider Planned Parenthood.

number of eye diseases, including age-related macular degeneration, the most common cause of blindness in adults in the developed world. The 2000s saw advances in ways to create cell cultures with RPE dissected from the eyes of fetuses, allowing scientists to study the function of these cells in a dish. And although some scientists have turned to stem cells to generate RPE, like Goldstein they continue to use fetal tissue as a benchmark of normal development and function.

Goldstein agreed to speak to *Nature*, he says, because "somebody has to speak up responsibly". He stressed that he and his colleagues think hard about the ethics of their work. "We are not happy about how the material became available, but we would not be willing to see it wasted and just thrown away."

Occasionally, fetal tissue is used for clinical work. Last year, a company called Neuralstem in Germantown, Maryland, in collaboration with scientists at the University of California, San Diego, launched a trial in which stem cells from fetal spinal cord were implanted to treat spinal-cord injuries. In May, researchers in the United Kingdom and Sweden launched a study in which dopaminergic neurons from aborted fetuses are transplanted into the brains of patients with Parkinson's disease (see *Nature* **510,** 195–196; 2014). Research with fetal tissue is less controversial in countries where abortion is more widely accepted.

UNCOMFORTABLE VIEWING

The Planned Parenthood videos caused even some supporters of fetal tissue research to feel uncomfortable. In one video, physician Deborah Nucatola, the group's senior director of medical services, describes how she crushes fetuses above and below key organs to preserve them intact for research. She also described turning a fetus into a breech presentation to deliver the head last, when the cervix is more dilated, thus preserving the brain.

This raised the question of whether physicians are altering abortion techniques to accommodate research requests, violating a widely held precept of research ethics. Arthur Caplan, a bioethicist at the New York University School of Medicine, dismisses the videos as "pure politics", but some of the footage "did get my eyebrow to arch", he says. "You can't use a different approach to the abortion to try to preserve something. Those are just no-no's."

Planned Parenthood spokeswoman Amanda Harrington says that the organization is not aware of any instances in which the method of an abortion has been changed to preserve organs. But, she adds, "if minor adjustments that have no bearing on the woman's health and safety are done when the woman has expressed a desire to donate tissue, that is entirely appropriate and ethical and legal". Women's health and safety, she says, "is always the number one priority".

The question for many scientists is what the fallout of the controversy will be. On the heels of the Colorado shootings, some Republicans in Congress backed off earlier attempts to defund Planned Parenthood, and President Obama is expected to veto any bill that does so. This means that the lasting damage of the videos may end up being inflicted not on Planned Parenthood's budget, but on science. Since July, four bills that would criminalize or otherwise restrict the research have been introduced in the US Congress, and lawmakers have launched similar efforts in a dozen state legislatures. (Missouri, Arizona and North Dakota already ban the research.)

Su felt the climate for his research grow colder when, on 1 October, a new North Carolina law was signed that makes it a felony to sell fetal tissue for any amount within the state. Su receives the tissue he uses from outside the state, but the message behind the new law concerns him. "I hope this current controversy, or possible congressional interventions, won't slow down biomedical research," he says. "The benefit is bigger than the drawback on this."

The controversy "absolutely puts fetal tissue research at risk", says Caplan. "Young scientists are unlikely to enter a field riven with controversy, where funding is uncertain and physical threats are a real possibility."

Caplan says that parallels could emerge with events in the early 2000s, when the use of human ES cells in US research became politically fraught. Then, tight federal regulations governing NIH funding of the research were adopted, but some states, including California and Massachusetts, responded by pouring money into the science all the same.

"To move ahead, the reality is that fetal tissue research need not be funded or permitted everywhere," Caplan says. "It needs to be allowed somewhere." ■

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3. Karpel, M. E., Boutwell, C. L. & Allen, T. M. *Curr. Opin. Virol.* **13,** 75–80 (2015).
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CORRECTION

The News Feature 'The truth about fetal tissue research' (*Nature* **528,** 178–181; 2015) incorrectly stated that around 5.8 billion people have received vaccines made with the WI-38 and MRC-5 cell lines. In fact, companies have shipped some 5.8 billion vaccines made with these two cell lines.