Tracking down tissues

FDA inspections of tissue banks remain a work in progress, and no clear path yet exists for procuring human tissues for biomedicine or drug development. Emily Waltz investigates.

Last year's headlines about an underground trade in human body parts in New Jersey[1] prompted a public outcry and the formation of the Human Tissue Task Force (HTTF)—an internal US Food and Drug Administration (FDA) body with the specific mission of tightening the oversight of human tissue procurement. This summer, the HTTF released its first report, which identified several areas in need of improvement, such as tracking systems and more regular audits[2]. Two months later, FDA inspections of a few hundred (of several thousand) human tissue banking and procuring facilities revealed that the number of establishments with 'objectionable conditions' had more than doubled (http://www.fda.gov/cber/tissue/inspdata.htm). Although according to the FDA these situations pose little risk to human health, companies requiring human tissue for R&D still face a mélange of options in a supply system that is disorganized and scattered. And as the demand for human tissue grows, companies are having to find their own ways of collecting material and determining its quality.

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In the US, the demand for human tissues for drug R&D is growing.

Big demand

The HTTF was set up last year by the FDA after it discovered that a New Jersey tissue recovery company and several funeral homes were stealing body parts from the deceased, forging medical records and passing the tissues on to hospitals for transplant. The FDA closed down the company and the principals were indicted.

Experts say this kind of egregious abuse is driven largely by the great demand from the medical community for donated human tissue—a demand that has increased rapidly over the past two decades. As drug discovery becomes increasingly target driven, scientists are finding more applications for human tissue. Nearly any scientist who tests drug candidates, harvests regenerative cells, makes delivery devices or creates bioimplants will likely have a use for donated human tissues.

But with the unpredictability of death and the reluctance of the public to donate, there often isn't enough tissue to go around. "If supply wasn't a problem, human tissue would be used in every procedure out there," says Jamie Grooms, CEO of AxoGen in Alachua, Florida. The firm is developing peripheral nerve grafts from donated nerve tissue. "It always comes back to the question: What is the best material to use? Time and time again, the answer is human tissue," he says. "This industry has spent billions of dollars trying to duplicate what already exists [in nature]."

Yet in the United States, there is no central clearinghouse or resource center for these tissues. Instead, tissue providers have popped up all over the country to meet clinical needs, scattering the tissue supply. A mishmash of US state and federal oversight hasn't helped organize the system and, at the same time, has allowed some nefarious characters peddling dirty body parts to succeed in the industry. Scientists, especially those looking for specific or unusual tissue, are often forced to find their own way.

Do-it-yourself networks

When the founders of San Diego–based Cytori Therapeutics realized in 2004 that they needed enormous amounts of human fat to develop their technologies, they began collecting it the best way they knew how: they called the plastic surgeons in their address books and asked them to save the fat from their patients' liposuction procedures. The company sent its employees to personally pick up the samples from the surgeons' offices, eventually building a network of more than 18 surgeons who contribute an average of 50 liters of fat per month from consenting patients. Using that tissue, Cytori developed an automated system that separates stem and other regenerative cells from the fat, and the company is now developing cell-based therapies that treat cardiovascular disease and aid healing in reconstructive breast surgery.

Cytori researchers are not alone in concocting a patchwork method for gleaning human tissue. Companies frequently approach clinical colleagues, body donation programs, tissue banks, for-profit brokers and even their own employees to get samples for drug studies. Obtaining tissue using these methods is usually legal and ethical, say experts, as long as the proper consent is obtained and the tissues themselves are not sold for a profit.

Some of the most frequently studied tissues are biopsies and tumors from living donors. Like many companies, Bristol-Myers Squibb, based in Princeton, New Jersey, collects tissue samples from consenting cancer patients in its clinical trials to look for molecular corollaries and potential targets.

To help cut down on surprises when a compound goes from animal models to the clinic, companies sometimes use human tissue as an additional preclinical step. "We do a lot of weeding out in that process," says Mark Cockett, vice president of applied genomics at Bristol-Myers. "There have been a number of programs that we have stopped working on because we discovered that the human biology is different than the mouse biology."

"Using human cells allows an early read on safety," adds Neil Warma, CEO of Viron Therapeutics in London, Canada. "It gives you the advantage of stopping development early, and the cost savings associated with that are enormous." Viron is developing viral protein–based anti-inflammatory therapeutics and often demonstrates efficacy using human tissues, such as endothelial cells and hepatocytes, that are configured into customized cell-interaction assays.

Hepatocytes, isolated from whole donated livers and liver resections, are a frequent request from scientists who study toxicology and drug–drug interaction of compounds. The cells, which act as a filter through which drugs must pass and do a majority of the detoxification and metabolism in the body, are important indicators of whether a drug might change or become inactive. The FDA requires metabolism and toxicology data for every new drug before it is approved and sometimes specifically recommends that a company test its candidate on human tissue before it reaches clinical stages.

Table 1 Selected vendors of human whole tissues and cells

Institute/Company	Tissues
National Disease Research Interchange (NDRI)	Frozen tissue inventory and fresh tissue liaison; big selection, including rare diseases, HIV, cord blood, stem cells, tissue microarrays, pancreatic islets, arteries and whole organs
International Institute for the Advancement of Medicine (IIAM) (Jessup, Pennsylvania)	Fresh tissue liaison; frozen tissue inventory; whole body donation program; normal and diseased tissue; whole organs
Lonza Walkersville	Isolated cells from fresh, normal tissue; inventory of frozen cells; custom procurement of non-normal tissue
AllCells (Emeryville, California)	Primary cells from normal and diseased tissue, including hematopoietic, endothelial, leukemia and dendritic cells
Asterand (Detroit, Michigan)	Fresh, frozen and formalin-fixed paraffin-embedded samples; primary cells; tissue microarrays; custom procurement

In addition, a host of firms incorporate human tissue into implant products and regenerative therapies. For example, Organogenesis, based in Canton, Massachusetts, makes a circular piece of bioengineered skin the size of a hockey puck that integrates into wounds, such as venous leg ulcers, and helps them heal. The bilayered product is made by incorporating collagen with fibroblasts and keratinocytes from newborns' circumcised foreskin, which the company gets from local hospitals where parents have consented to donate, according to Geoff MacKay, Organogenesis' CEO. Now that they've honed their technique, they can make about 100,000 final products from one piece of discarded foreskin.

Although researchers often need only a few cells to conduct their studies, finding just the right kind can be tricky. "If I didn't know a dozen plastic surgeons, this would be very difficult," says Eric Daniels, senior director of business development at Cytori.

Even the National Institutes of Health (NIH), in Bethesda, Maryland, is struggling to track down samples for its $100 million cancer genome atlas project. The project aims to identify all the genetic mutations associated with cancer and requires thousands of tumor samples. So far, despite access to major tissue banks, the agency has only a fraction of the particular tumors it needs[3].

Scattered supply

The supply of tissue starts with formal donations, mostly through hospitals where staff are required by federal regulation to report deaths to their local organ procurement organization, or OPO. The OPO acts as a liaison to find recipients for transplantable organs and homes for the rest of the tissues.

Organ donation for transplant is one of the few areas in which there are highly organized networks for tissue distribution. The OPO checks the computerized national waiting list operated by the United Network of Organ Sharing (UNOS; http://www.unos.org) to find a recipient and helps coordinate the transfer of the organ. In 2006, nearly 15,000 people donated an organ, but at any given time nearly 100,000 people are awaiting an organ transplant, according to statistics kept by UNOS.

Viable organs, particularly the kidneys, liver, heart, lungs and pancreas, get priority over research needs when there is a potential recipient waiting for a transplant. For organs that cannot be used for transplantation, some OPOs, such as the New York Organ Donor Network, in New York City, have established relationships with researchers and connect them directly with the fresh tissue.

In addition to hospital staff, many others, including medical examiners, funeral homes, hospice caretakers and law enforcement officials, also have first-line access to bodies, although the usefulness of this tissue is limited by time and competing interests. A medical examiner's top priority is to determine the cause and manner of death, says Kristin Roman, medical examiner for Staten Island, New York. Certain tissues may not be removed if they interfere with the autopsy. For instance, a drug called papaverine, which is sometimes used to cut street drugs, is also used to preserve blood vessels for donation and could be misleading on a toxicology report, according to Roman.

Some ethical rules for collecting tissue limit donations as well, often for good reason. Aborted fetuses offer a wealth of important tools for scientists, but a federal law prohibits medical staff from requesting consent from parents who are considering abortions, as it may sway their decision[4].

There are a host of tissue banks in the United States that store the tissue once it is procured. Some of these banks specialize in tissues such as eyes or bones. A few organizations specialize in getting tissue from primary sources to researchers (**Table 1**). One of the largest, the Philadelphia-based National Disease Research Interchange (NDRI), is the closest thing to a clearinghouse for research tissue. It keeps an inventory of frozen samples of everything from arteries to uteri and also places fresh tissue directly with researchers.

Nonorgan tissue destined for implantation is sent to processing companies that specialize in cleaning and shaping it. Allosource, of Centennial, Colorado, specializes in musculoskeletal tissue and sells everything from patella wedges to Achilles tendons. They obtain the tissue through four large OPOs, screen it for diseases, eradicate bacteria and then cut and shape it. Tissue distributors, such as Medtronic's spinal division in Memphis, Tennessee, often connect processing companies with implant surgeons.

Other companies specialize in isolating cells from donated tissues. Lonza Corporation has a division called Lonza Walkersville, based in Walkersville, Maryland, that specializes in this area and will set up customized donation programs to meet specific requests. Columbia, Maryland–based Osiris Therapeutics goes to Lonza for bone marrow. Osiris is developing therapies using mesenchymal cells separated from bone marrow for graft-versus-host disease, Crohn's disease, acute myocardial infarction and arthritis of the knee.

Living donations—such as biopsies, amniotic fluid and tumors—that would otherwise be disposed of as hazardous waste, are fairly plentiful and more likely to end up with researchers. For instance, Ervin Wheeler, a plastic surgeon in La Mesa, California, who collects fat for Cytori, says none of his liposuction patients have ever chosen not to donate to the company's research efforts.

Clinical trials are a good place to collect living donor samples accompanied by follow-up health data. The National Surgical Adjuvant Breast and Bowel Project (NSABP), in Pittsburgh, is a clinical trials cooperative group that requires its member institutes to send tissue samples from trials. Over the past 40 years, the group has collected samples and clinical follow-up from more than 100,000 people, according to Soon Paik, director of the division of pathology at NSABP. The method for preserving the tissue long-term requires fixing it in formalin and then encasing it in paraffin, or wax, which limits what can be done with the tissue. But companies such as Genomic Health, of Redwood City, California, which makes a breast cancer assay and other molecular diagnostic services, have been able to harness information from the NSABP samples to create their products, according to Steve Shak, chief medical officer at Genomic Health.

But with such a decentralized system, many industrial researchers are choosing to forfeit the hunt and start their own collections. Pfizer, of New York City, has a biobank where it stores both animal and human tissue. When Bristol

Myers needs blood samples to study platelet targets for thrombotic disease, the company often turns to its own employees for volunteers. Like many universities, Indiana University (IU), in Bloomington, Indiana, has several tissue banks set up by various schools or collected by individual investigators. Indianapolis-based Eli Lilly recently set up a deal with IU that gives its scientists access to many of those tissues.

Messy laws

The multiple layers of rules that govern the tissue trade certainly haven't helped solidify the industry. On the federal level, the FDA requires every establishment that handles tissue for transplant to register with the agency, and it audits several of these establishments each year (**Box 1**). Anyone donating tissue for transplant must be tested for infectious diseases, and donors must be screened for risk factors such as drug abuse, according to FDA guidelines. Most nonorgan transplant tissue, such as meniscus or bone, must be processed to rid it of bacteria, but the standards vary from processor to processor. Tissue used solely for research or education is almost completely unregulated.

In addition to FDA regulations, four states license and inspect tissue establishments on their own. Accreditation of tissue banks is left up to the nonprofit American Association of Tissue Banks (AATB) of McLean, Virginia, but most states don't require accreditation. States require consent for every tissue donated, but it's up to internal review boards to approve the specifics, such as consent forms. The Uniform Anatomical Gift Act of 1987 provides guidelines for states on how to govern donated tissue for transplant, and every state has adopted the act, but in various forms. It was revised in late 2006 with language that makes the donation process easier for donors and families, and as of October, 19 states had adopted it. On top of the federal regulations, suppliers tend to get audited by their customers, which means inspections can happen on a weekly basis, says Kevin Cmunt, executive vice president at Allosource.

With a variety of US laws, and whole bodies fetching more than $200,000 on the market, some people with access to body parts have taken advantage of their unique situations. Several people involved in last year's scandal with Biomedical Tissue Services, the Fort Lee, New Jersey, tissue recovery company, face up to 25 years in prison for falsifying records. There have also been instances of ethical malpractice in tissue collection in the UK (**Box 2**).

Box 1 The regulations

The FDA, through its Center for Biologics Evaluation and Research (CBER), regulates tissue intended for transplant under 21 CFR Parts 1270 and 1271. The regulations focus on preventing the use of tissue contaminated with infectious disease and preventing tissue handlers from contaminating the tissue, says Paul Richards, a spokesperson for CBER. If the results of processing cannot be verified by inspection and tests, the processors must use established procedures (good tissue practices or GTPs) during all steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging and distribution. The regulations also focus on screening donors before tissues are released, says Richards. Manufacturers must screen and test donors for risk factors for, and clinical evidence of, a number of communicable disease agents including HIV, hepatitis B and hepatitis C. In addition, reproductive tissues and donors of leukocyte-rich cells must be screened for additional pathogens.

Tissue intended for research use only is not regulated by the FDA at present. However, the American Association of Tissue Banks is currently developing standards for research tissue and will require infectious disease testing of donors whose tissues may only be recovered for research use. This would be applicable only for those research banks that seek accreditation for research tissue banking (in development), according to Scott Brubaker, chief policy officer for the AATB.

Public attitudes

Since the 1800s, when the bodies of those who couldn't afford a burial were often donated to medical schools for dissection, the research community's access to cadaverous human tissue has been somewhat taboo. And although the benefits of life-saving transplants from tissue donations are becoming better known, high-profile scandals involving ethical malpractice and sensationalism about the 'body part trade' in novels, such as Michael Crichton's *Next* or Annie Cheney's *Body Brokers,* are not helping the battle for hearts and minds.

"The real issue is will the public be willing to give permission to use more and more identifiable material," says Eric Meslin, a bioethicist at IU. "If the public [says] 'no bloody way', then it would be good to know that in advance."

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1. Waltz, E. *Nat. Med.* **12**, 487–488 (2006).
2. Human Tissue Task Force. 2007 Report (Department of Health & Human Services, Public Health Service, Food and Drug Administration, Bethesda, Maryland, USA, 2007). <http://www.fda.gov/cber/tissue/httf07report.htm>.
3. Waltz, E. *Nat. Med.* **13**, 391 (2007).
4. National Institutes of Health Revitalization Act of 1993 <http://www.hhs.gov/ohrp/humansubjects/guidance/publiclaw103-43.htm>.
5. Anonymous. Taken without consent. *The Guardian* 31 January (2001) <http://society.guardian.co.uk/alderhey/comment/0,431159,00.html>.

Box 2 A global problem?

The US isn't alone in needing to hone its oversight of tissue procurement procedures. In the UK, it was discovered that doctors were collecting organs from deceased infants and children without discussing it with the parents. Although no one was prosecuted in the most highly publicized case[5], this incident raised awareness of the issue, which provided an impetus for tightened regulations surrounding human tissue donation. Last year, for the first time, the UK began requiring formal consent from all donors and set up the Human Tissue Authority in London to inspect tissue establishments and regulate the use of human tissue for both research and transplant.

This year, Germany is also centralizing its tissue banks. In the past, donated tissues were kept in various hospital and nonprofit tissue banks throughout the country. Under the new law, donated tissues must be at least reported to a central repository, if not kept there. In June, the bill was passed by the German parliament, or Deutche Bundestag, and was signed into law effective August 1.

In 2000, Singapore created a bioethics committee to build a basis for regulation of the country's relatively new biomedical sector, and nearly all of the regulatory documents since then have focused on donated tissue. "You can't get away from touching human tissue," says Edison Liu, who heads the committee. The reports are adopted by Singapore's regulatory agencies, such as the Ministry of Health, which oversee internal review boards at hospitals where tissues are collected. A national tissue repository stores a majority of the remaining tissues.