Stem Cell Reports
Voices

ISSCR

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Stem Cell Scientists Answer the Question, "Why Is It Important to You to Support Fetal Tissue Research?"

Invited "Voices" writers are an essential voice in the ISSCR's efforts to protect fetal tissue research and its crucial role in the understanding, prevention, and treatment of life-threatening diseases.

Sherry's Voice

R. Alta Charo
University of Wisconsin – Madison

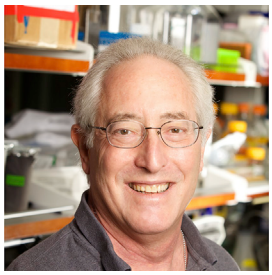
I still remember the last time I heard Sherry's voice. It was slurred by then, each word dragged slowly from lips and jaw no longer fully obeying commands. Many of her friends had stopped coming; it was just too difficult to watch the descent from a weakened leg whose cause was unknown, through the months of tests for diseases that might explain the inexorable advance of paralysis, to the growing horror of realization that it was Lou Gehrig's disease, a diagnosis of exclusion, a reluctant conclusion after ruling out any number of devastating but treatable alternatives.

Some of us, though, myself included, continued to visit. Because I lived 700 miles away, my stays would be over entire weekends, and through them I became part of the family. Over time, Sherry had moved to the ground floor of the rambling older house she and her husband occupied with their elementary-school-aged daughter. One particular weekend I remember clearly, she was too tired to deal with the difficulty of being helped to sit at the table to join her family for dinner. I sat beside her while she lay on the couch, and she slowly began talking about the future, the probable course of the disease, and the loss of her ability to breathe without a machine or eat without a tube. She talked about the absence of any kind of cure, and the hope for some development in the months and years to come, perhaps in time to save her. She dreaded the choices she would face about whether to try to survive, paralyzed and supported by machines, or to refuse these measures and allow nature to take its awful course. She worried about the loss of the ability to speak, and how she would be able to make her wishes known. And in that slow, slurred drawl, almost unrecognizable from the lively sounds she'd always made before, she said, "Be my voice."

In the 6 years that followed, as Sherry communicated first with a computer pad, and then with blinks, she and her family explored every possible treatment, from nutritional supplements to preclinical animal work with nerve growth factors treating spinal cord injuries. I sat by her bed, reading aloud from medical journals or, on one long afternoon, from a lengthy essay describing research that might link underlying causes of Parkinson's disease, Alzheimer's disease, and Lou Gehrig's disease. Fetal neurological tissue had already been under investigation for Parkinson's, and now there was preclinical research on embryonic stem cell treatment as well. Nothing yet had worked, but the possibility was there if the work continued without political or funding obstacles.

I never heard Sherry speak again. We held our last conversation with only the slightest of eye movements. She was on the verge of being locked in, forever unable to communicate, and she asked to discontinue further heroic measures. Thousands of people today still suffer from this pointlessly cruel disease, and I know Sherry would want every avenue investigated in the search for a cure. That's why I support fetal tissue research. For those thousands, I remain Sherry's voice.

Service to the Scientific Community



Lawrence S.B. Goldstein
UC San Diego School of Medicine; Sanford Consortium for Regenerative Medicine; Sanford Stem Cell Clinical Center

In addition to running an active biomedical research lab for the past 35 years, I have devoted some of my time and effort to educating members of the California and U.S. governments, and members of the local San Diego community, about the conduct and value of biomedical research. Important topics I have addressed have included therapy development, funding levels and practices, and research using controversial materials including embryonic stem cells and fetal tissue.

My education efforts are driven by the fact that as practicing scientists, and in particular stem cell scientists, we know that there are many areas in which government policy and community standards have a great impact

on our ability to pursue important research directions. Unless we as knowledgeable scientists participate in the development of policies and standards, non-scientists will be on their own to generate policies regarding funding and the regulation of research materials with which we work. For that reason, it is critically important for scientists to actively participate in decisions about funding levels and the development of rules and ethical standards for research using animals, human subjects, stem cells, fetal tissue, and other issues.

As working scientists, we all have an obligation to contribute service to our communities. Some of us do this by participating as grant reviewers, journal reviewers, and editorial board members; less commonly, scientists also provide community service as advocates and defenders of research.

I have chosen to contribute a significant portion of my service work in the form of explaining the value of science to local and national governments and defending research that is valuable but that may impinge on controversial social issues.

Research with embryonic stem cells and fetal tissue brings substantial value to the study of intractable diseases and the development of novel therapies. Embryonic stem cell research and fetal tissue research are similar in that they use cells and tissues derived from controversial but legal practices such as *in vitro* fertilization (IVF) and elective abortion. In fact, fetal tissue from elective abortion and excess frozen embryos from IVF would be discarded as medical waste if not used in biomedical research. Thus, I think that research with these cells and tissues is ethical and scientifically and medically valuable.

Opponents of this research often argue, incorrectly, that research using embryonic stem cells or fetal tissue is not valuable and thus important research with these cells and tissues derived from the destruction of embryos or elective abortion should be prohibited. As professional scientists, we must rebut these inaccurate claims and bring professional knowledge and experience to the debate. While we must respect those who argue that IVF or elective abortion should be curtailed based on ethical criteria, these arguments are not strictly about scientific and medical value.

The question of whether embryonic stem cells or fetal tissue should be used in valuable research as opposed to routinely destroyed requires an understanding of scientific and medical value that we as professional scientists must provide.

The ISSCR Supports Fetal Tissue Research

Douglas Melton
Harvard Stem Cell Institute, Harvard University

As president of the ISSCR, I cannot overstate the society's mission to support stem cell science and the field around the world. Often that involves advocating for policy and regulatory reform that allows our work to continue and thrive.

Federal funding for fetal tissue research in the U.S. came under scrutiny last year, after groups ideologically opposed to the use of this tissue lobbied Congress and federal agencies. In September we wrote a letter to Congressional leadership outlining the benefits of fetal tissue research, noting the long-standing public and bipartisan support it has enjoyed. We had co-signatures from 64 medical, scientific, and patient groups, which helped amplify our message that this research is essential to saving lives.

The Department of Health and Human Services (HHS), which funds much of the nation's biomedical research, later announced the launch of a "comprehensive review" of human fetal tissue research. Their action came after a letter from anti-abortion groups and conservative lawmakers opposed to a contract to supply fetal tissue for research. The contract was terminated as a result, and federal funds attached to all fetal tissue research became subject to a broad review that continues today.

The ISSCR expressed concern about the review and its negative effect on current and planned research. The HHS then invited us to a "listening session" on the merits of fetal tissue research and any alternatives that might replace it. Martin Pera represented the ISSCR, describing the critical role of fetal tissue research in development of therapies to treat disease. In December, we wrote a letter to the HHS co-signed by 70 organizations to explain the scientific importance of fetal tissue research and the limitations of existing alternative models.

On another front, Larry Goldstein's article in *The Hill* (read widely by policy makers), "Fetal tissue research is the victim of special interest politics," reiterated that use of this tissue has been bipartisan and relies on agreed-upon regulatory and ethical principles.

A committee in the U.S. Congress called a hearing on "Exploring Alternatives to Fetal Tissue Research" and invited the ISSCR to testify. Former president Sally Temple delivered oral remarks and written testimony clearly explaining how alternatives mentioned in the hearing, "may be useful at times but cannot fully replace fetal tissue." Her testimony was a powerful counter to claims of anti-abortion groups that fetal tissue research is outdated and no longer necessary.

Our thanks go out to Sally Temple, Martin Pera, Larry Goldstein, Alta Charo, Alan Trounson, and other

members who have been terrific advocates for science and speak with policy makers about important issues facing the field.

It isn't always an easy choice to advocate for science, but it is an important one. Through our members speaking out, we have established the ISSCR as a reputable voice in the field and in policy venues around the world. When our voice is heard, we make a difference in how our science is perceived and we help advance the enterprise of stem cell science. There is no more important mission for the ISSCR.

To get involved in advocating for stem cell science, please contact Eric Anthony at eanthony@isscr.org.

Understanding Human Development

Martin Pera
The Jackson Laboratory

In the early days of research on human embryonic stem cells, there was great controversy over the use of embryos to derive the cell lines. I was deeply involved in the public discussions in Australia around that topic. One of the arguments we made back then was that the system might be used to gain novel insights into human development and its disorders. Today, prospects for achieving that goal have never been better.

Improved methods for growing and differentiating human pluripotent stem cells, alongside new advances in three-dimensional culture systems that enable researchers to build realistic models of peri-implantation embryos and developing organs like brain and kidney, are providing experimental windows into critical phases of human embryonic and fetal life. The availability of facile and precise methodology for gene targeting in human pluripotent stem cells means that the wealth of new data on the genetic basis of developmental disorders can now be subjected to high-throughput functional assessment *in vitro*.

Some have suggested that these exciting advances have rendered any requirement for the use of human fetal tissue in research redundant. However, these stem cell models are still a work in progress, and research on both human embryonic and fetal tissue is essential to guide their refinement and to establish their validity.

The key to modeling human development with *in vitro* systems is the fidelity issue—the extent to which *in vitro* models represent robust replicas of their *in vivo* counterparts. Though human pluripotent stem cells have probably been examined with multi-omics technology in more detail than most any other human cell type, we still are working out where they lie in the context of the peri-implantation stages of embryo development, and if they represent an optimal state of pluripotency. Single-cell gene expression data on normal embryos is helping to resolve this issue. Efforts to differentiate human pluripotent stem cells into multiple cell types have met with considerable success, but in many cases the differentiated cells do not reach functional maturity *in vitro*, and we often lack rigorous global evidence that these cells are bioequivalent to their normal tissue counterparts in their transcriptome, their epigenome, and their functional capabilities. Moreover, for accurate modeling of human development, there is an additional requirement to establish that the pathway to reaching a given stage *in vitro* faithfully captures the chain of events that occurs in the embryo. We have learned much from model systems, but only through careful analytical comparison of *in vitro* phenotypes with normal human embryonic and fetal cells can we be confident that we have followed the right road and reached the correct destination.

Precision models of human development could help us to improve infertility treatment and achieve healthy pregnancies, avoid or repair the often drastic consequences of developmental disorders, and make better tissues from stem cells for use in transplantation therapy. There is much evidence from human studies that events in peri-implantation development can profoundly influence lifelong health; stem cell models can help us understand the implications of errors in the massive epigenetic programming that takes place in this critical stage. Embryonic and fetal tissue is crucial to achieving all of these goals.

Research on human embryos remains essential, and the controversy around it has not gone away; however, the issue is not at the forefront of concerns in my laboratory and throughout our field in the way that it was a decade ago. As *in vitro* systems are refined, fetal tissue research may become less necessary once our models retrace with fidelity the remarkable journey of human development.

A Mother's Vision

Sally Temple
Neural Stem Cell Institute

My mother lost her vision to age-related macular degeneration (AMD). It robbed her of her favorite pastimes, including reading, enjoying art, and baking for family and friends, and it took away her independence.

Witnessing her struggles, I decided to work on combating this devastating, blinding neurodegenerative disease that afflicts many elderly people.

The macula is an exquisite structure, one that is not present in mice or rats, but is restricted to a few species, such as primates and birds of prey. I learned how the normal human macula forms by reading the textbook based on Ida Mann's thesis, published in 1924, which is a foundational work on fetal human retina development that led her to identify congenital abnormalities contributing to loss of sight. By examining fetal eyes, even with century-old technology, Mann was able to illuminate the causes of childhood eye disease to an unprecedented degree.

Since Mann's pioneering work, we have continued to learn about the human retina by studying donated fetal tissue and using ever more sophisticated technologies. Breakthroughs in cell culture are being combined with improved biochemical and molecular analyses to produce *in vitro* models of the retinal pigment epithelium and neural retinal cells. Through new studies, we have been able to define the characteristics of retinal cells and uncover the complex cellular and molecular mechanisms underlying human vision.

In 2012, Yoshiki Sasai's research group described the remarkable formation of a human optic cup and retina from pluripotent stem cells. Testing the authenticity of the cell types produced in these organoids depends on comparing them with human fetal tissue as a key reference material; without this we would not know if the organoid model accurately creates human retinal cells. This approach helped pave the way for *ex vivo* production of a variety of retinal cells that are now part of a global effort to restore cells lost due to AMD and other blinding disorders.

Today we have research tools that were only imagined even a decade ago. Applications of cutting-edge single-cell analyses define cellular heterogeneity with precise granularity, and we are beginning to appreciate the unique variety of cell states in the human retina. Recent studies of the time course of fetal retinal development at epigenomic and transcriptomic levels and comparisons with tumor tissue have identified the molecular changes that occur as retinoblastoma, a cancer occurring in the infant retina, develops.

With each technological advance, we learn more about the human retina: the diverse cells, the emerging and dynamic cytoarchitecture, the development of vision, and, importantly, the cause of disease. By continuing to apply current technology to investigate donated fetal retina, we have the opportunity to make real-world advances that will forever benefit humanity—for example, to understand, prevent, and treat childhood eye cancers; to learn why albinism impairs macula development; and to learn why aging leads to macular degeneration.

How much does sight mean? How important is it to see our friends and loved ones, to read, or to use sight to work, to play, to create? Studying donated human fetal tissue, tissue that would otherwise be discarded, is essential for sight-saving and life-saving research.

Protecting Scientific Research

Alan Trounson
Hudson Institute of Medical Research

Science and politics have often clashed, and I've been involved in two important conflicts. The first was when policy makers interfered with the pursuit of science to advocate a ban on human IVF, and the other was when they did so again to advocate a ban research on embryonic stem cells.

In both cases, it was critical to gather support of the scientific community, and it wasn't an easy task. There are now millions of couples who benefit from IVF, and pluripotent stem cells are evolving in clinical trials to treat disease. However, at the time there was no guarantee that we would either prevail or submit to forces of anti-science opposition. Perhaps my experiences in weathering the storms of political and religious wrath about our IVF and stem cell science helped my appointment as president of the California Institute for Regenerative Medicine (CIRM), created in defiance to President George W. Bush's ban on funding human embryonic stem cell research.

I feel the political ground presently shifting around access to human fetal tissues and there are calls for banning it by state and national governments. Again, I believe this is driven by religious and ideological agendas that threaten medical advances. We should strongly oppose these efforts to pass draconian laws and regulations that prevent scientific access to fetal tissues.

Many important medical understandings have come from the use of fetal tissue in research. Notably, we may never have discovered induced pluripotent stem cells without having derived human embryonic stem cells from donated human IVF embryos. Similarly, the use of fetal brain tissue has paved the way for the potential therapeutic use of embryonic stem cells and induced pluripotent stem cells to treat Parkinson's disease. As we define the essential parameters of dopaminergic neurons in pluripotent stem cell derivatives, it is critical that we have access to fetal neural tissue.

We've seen the dramatic impact of transplanting fetal neural stem cells into brains of children suffering Batten's disease (BD) and Pelizaeus-Merzbacher disease (PMD), with patients now around 8 years after transplantation and many showing the benefits of receiving these cells. These fetal derived brain cells have unique properties of global migration within the central nervous system and make all three functional neural cell types. This may be the basis of expanding their use for other such rare diseases and brain injuries, including perhaps conditions such as cerebral palsy.

The human immune system is a unique, complicated, and unpredictable system and very difficult to model *in vitro* or in animal models. The "BLT humanized mouse model," using transplanted human fetal liver and thymus immune-compromised mice, enables the formation of human immune system cells, including cytotoxic T cells. This model is used widely for viral research, including research into HIV, dengue virus, and other dangerous pathogens, and it could be used to optimize immune cell therapies for cancer. Advances in immune cell therapies including chimeric antigen receptor technology also benefit from experiments using BLT mice, as advances in gene editing scopes and immune cancer killing cell types develop that avoid tumor inhibition and antigen escape and prevent cancer stem cell survival.

We simply cannot ignore the benefits of access to fetal tissue, when properly regulated procurement can be arranged from consenting donors after fetal loss.