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## Resolving the Shortage of Organs for Transplantation: Ethics, Science, and Technology

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### **Introduction**

Organ transplantation in patients with end-organ failure improves quality of life and saves thousands of lives each year. However, the supply of human organs is insufficient to treat all patients who qualify for transplantation, so approximately 6,000-7,000 patients die each year while registered on organ transplant waiting lists. In an attempt to reduce the gap between the supply and the need for transplantable organs, the Rutland Institute for Ethics and the South Carolina Clinical and Translational Research Institute convened a one-day conference at the Medical University of South Carolina on November 20, 2009, with the goal of developing a consensus report on strategies for resolving the critical shortage of organs for transplantation. The topics proposed by the organizers to represent the most productive areas for likely new sources of organs were organ donation,

xenotransplantation, and regenerative medicine.

Using a variety of sources, the organizers of the conference identified organizations and individuals with special interest in resolving the organ gap, and invited them to participate in the conference. Several weeks in advance of the meeting, participants were provided publications chosen by the organizers and speakers to enrich the participants' understanding of the meeting topics.

Forty-five individuals attended the conference, including representatives of a variety of disciplines, such as science and technology research, transplant medicine and surgery, organ procurement organization administration, nursing, health law, university administration, philosophy, ethics, theology, and commercial development. Five speakers with expertise in specific areas—organ donation, xenotransplantation, regenerative medicine, and health law—opened the conference, providing baseline information about these areas of focus.

The participants were divided into three working groups, each comprising individuals from a broad range of organizations and disciplines, led by one or two experienced moderators. Each group was charged with the following:

Considering the need to resolve the shortage of organs for transplantation and human organ donation, xenotransplantation, and regenerative approaches:

- What are the most pressing and

- near-term legal and ethical issues?
- What are critical health care and economic issues?
  - What are the key regulatory and political challenges?

They were then asked to create a set of “Recommendations for Action”:

Considering each of the three organ supply approaches—donation, xenotransplantation, and regenerative medicine—what actions should be taken by government, industry, health care organizations, donor agencies, and relevant science and technology organizations to deal with the issues and challenges?

When the working groups completed their work over a period of several hours, the conference was reconvened in plenary session, each group presented its findings and recommendations, and after considerable discussion, developed a consensus set of recommendations for action, concluding the conference. The group had not finished its work, however. After the conference, the recommendations were refined further (including assignment of specific entities for carrying out the recommendations), the refinements were circulated to the groups’ moderators for comments and suggestions for change, and finally were circulated to all participants for their comments and suggestions. This report summarizes the conference proceedings and consensus recommendations.

### **Organ Donation**

Of the three major topics, organ donation provides perhaps the easiest objectives to achieve in the short term, because it has been an ongoing activity for decades, while both xenotransplantation and regenerative medicine are not yet ready for human application. In deliberating on ethical, legal, and social issues related to organ donation, the groups considered a broad range of basic ethical principles, such as establishing a proper balance between individual rights and

obligations and the rights and obligations of society. Discussion highlighted the need for better public education, including publicizing the number of health care practitioners who have consented to be organ donors (if the number is sufficiently large). To improve organ donation statewide, the possibility of establishing a standard policy for determination of brain death was raised by members of LifePoint, South Carolina’s organ procurement organization.

The idea of increasing the number of health care practitioners consenting to be donors and, if favorable, publicizing the fact was enthusiastically received. LifePoint has one of the highest organ donation rates in the US due to innovative restructuring of procurement personnel functions.<sup>1</sup> LifePoint is well placed to assess new strategies for increasing organ procurement that could have national benefits.

Evidence indicating that there is a good possibility of improving organ retrieval systems through the use of procedures, devices, or pharmaceutical agents to support organ viability and limit tissue degradation during organ procurement was thoroughly discussed. Active participation by hospital organizations, organ procurement groups and companies developing devices and pharmaceutical agents is needed.

Special attention was paid to the possibility of establishing pilot programs to study the effects of financial incentives aimed at increasing organ donation. The necessity of obtaining a Congressional waiver of the National Organ Transplantation Act clause that prohibits “valuable considerations” in exchange for human organs was discussed. In this regard, many cultural and religious objections would have to be answered. The consensus was that we should advocate for legal change to at least allow pilot studies to determine the potential impact of financial benefits on the organ supply. A concrete action that was proposed was to prepare a protocol for a financial incentive pilot study to serve as the basis for a legislative waiver of the “valuable con-

sideration” clause in the context of organ donation.

### **Xenotransplantation**

Xenotransplantation (“xenos” is the Greek word for “foreign”) refers to the transplantation of living cells, tissues or organs from one species to another. The current status of xenotransplantation has been recently reviewed in detail.<sup>2</sup> The use of primates as sources of organs makes a good deal of sense, because, of all nonhuman species, they are the most closely related to human beings genetically. However, because such uses of primates have been intensely criticized on ethical and emotional grounds, it seems clear that primates are not a viable source of organs. Although many medical and ethical issues are associated with the use of porcine (pig) organs, since the controversy about their use is less intense than that associated with the use of primate organs, it seems likely that pigs will be the organ source of choice when clinical trials of xenotransplantation begin.

Several technical challenges have to be met before pig-to-human organ transplantation becomes a reality. One such challenge is that human beings have preformed antibodies that react against living pig cells, consequently more effective, less toxic approaches to control immune responses are needed. One major advance, which led to the 2005 prediction that the first clinical trials of pig-derived xenotransplants were likely to begin within five years, by 2010, was the development of genetically modified pigs (“knock-out” pigs) in which porcine antigens that are targets for human antibodies have been deleted. In fact, mechanisms have now been established to control porcine cell transplantation, and trials of porcine insulin-producing pancreatic islet  $\beta$ -cells—as a potential cure for diabetes—are expected to begin soon.

Transplantation of whole organs is not quite

so imminent. Indeed, transplantation of major organs may be decades away, depending in part on successful outcomes for pig islets in clinical trials.

Because of the possibility of xenogeneic infectious diseases (infectious agents in animals mutating into human pathogens, such as has occurred in the cases of human immunosuppression virus (HIV) and the hemorrhagic Ebola virus), making long-term surveillance of subjects in clinical trials of xenotransplantation mandatory should be seriously considered by the Public Health Service and US Food and Drug Administration.

No research is currently being performed in South Carolina with knock-out pigs, a shortcoming that generated much discussion among the conference participants. If South Carolina is to compete in the commercial development of this field, which is likely to have a huge medical and economic impact, seed funding is required to establish knock-out pig colonies in our state.

As in the case of organ donation, successful introduction of xenotransplantation in this state will require improved communication within health care professional communities and at all levels of society. Moreover, the complex issues associated with this promising field of investigation and its eventual clinical applications suggest the importance of funding for research on ethical, legal, and social issues in xenotransplantation.

#### Regenerative Medicine Technologies

Regenerative medicine is a part of bioengineering that combines principles and methods from the physical and engineering sciences, medicine, and biology to exploit living cells for therapeutic and diagnostic purposes. The goal of the field is to develop innovative technologies and approaches that will enable repair, replacement, or restoration of diseased cells, tissues, and organs. Regenerative medicine may permit damaged tissues and organs to regenerate inside the body by stimulating the patient's own cells. Another approach is to grow tissues and organs in the laboratory and safely implant them when the body can-

not heal itself. For the purposes of this conference, attention was focused on the potential of regenerative medicine to solve the problem of the organ shortage.

A strategic analysis of tissue and organ engineering identified four overarching goals for the field: understanding and controlling the cellular response; formulating biomaterial scaffolds and the tissue matrix environment; developing enabling tools; and promoting scale-up, translation, and commercialization. Regenerative medicine has already created commercial products such as artificial skin for treatment of burns and replacement cartilage for knee repairs. However, clinical application of regenerative medicine is in its infancy and it is likely to be at least 15 years before we will see engineered human organs in clinical trials.

South Carolina is already involved in basic regenerative medicine research and has achieved international recognition in vascular tissue biofabrication. Biofabrication may have broader commercial applications than other forms of regenerative medicine.<sup>3</sup> Creation of organs outside the body requires development of strategies for creating vascular beds, because without a vascular supply, tissues are limited to a few hundred microns in thickness. The huge clinical potential for biofabrication points to a critical issue: continued development of this field in South Carolina requires seed funding for translational research to bring this technology to the bedside. Translational research is expensive compared with basic research due to the need for large animal models and analytical procedures to secure future patient safety. This would be a worthwhile investment because of the potential multibillion-dollar market for emerging biofabrication industries.<sup>3</sup>

Information flow and communication are challenges at all levels of society. Scientists and engineers must communicate better both with one another and with the general public in terms they can understand. The South Carolina Bioengineering Alliance could play an important role in developing mechanisms for constructive and efficient communication among regenerative medicine researchers, as

is being done by the Tissue Engineering Society nationally and internationally. The many ethical, legal, and social issues associated with regenerative medicine and xenotransplantation require an active process for public debate and discussion. One way to achieve this would be to designate a small but specific portion of all federal funds for scientific and engineering research in regenerative medicine and xenotransplantation to the development and maintenance of the necessary mechanisms for constructive and effective communication about ethical, legal, and social issues.

#### Recommendations for Action

The gap between the rapidly increasing number of patients with end-stage organ failure who need a replacement organ and the much more slowly increasing number of medically suitable organs for transplantation has grown every year for the past 20 years, resulting in deaths of 6,000-7,000 patients a year for lack of a suitable replacement organ. Solving the problem of the inadequate supply of organs for transplantation has been daunting. With an eye to making genuine progress on this front the participants in the conference "Resolving the Shortage of Organs for Transplantation," offer the following consensus recommendations including specification of organizations within South Carolina that are best positioned to undertake the recommended actions.

#### Organ Donation

- Intensify public education by:
  1. developing culturally competent materials for educating the public, medical professionals, nurses, health care trainees, high-school students (focus on seniors), and church and other community leaders (Donate Life-SC and LifePoint)
  2. encouraging mass media to feature celebrity advocates for organ donation (Donate Life-SC through Donate Life America)
  3. advocating for creation of a National Donor day (American Hospital Association [AHA] through South Carolina Hospital Association [SCHA] & American Medical Association [AMA] through Resolution from

the South Carolina Medical Association [SCMA])

4. increasing the number of health care practitioners consenting to be organ donors and publicizing numbers, if favorable (Donate Life-SC and LifePoint)
- Determine the need for further assessment of barriers to organ donation (SCHA and LifePoint)
- Establish uniform standards for determination of brain death in all hospitals in SC (SCHA and LifePoint)
- Write protocol for financial incentive pilot study to serve as concrete basis for legislative waiver of “valuable consideration” clause (LifePoint & MUSC Transplant Program)
- Improve system to retrieve organs (LifePoint & device/pharmaceutical companies)
- Be more proactive using donation after cardiac death (DCD) for increasing organ donation (SCHA and LifePoint)

### **Xenotransplantation**

- Analyze efficacy of xenotransplantation from animal experimental data and from patient data (if it is used as a bridge to transplantation), in order to decide whether or not to carry out clinical trials of xenotransplantation as destination therapy and, if so, in order to inform their design (AMA through Resolution from SCMA)
- Advocate for increased research of zoonotic infectious diseases (AMA through Resolution from SCMA)
- Monitor xenotransplant recipients and close personal contacts during clinical trials per existing federal guidelines (AMA through Resolution from SCMA)
- Encourage the state of South Carolina to support and fund research in porcine gene knock-out technology and translational research (SCMA & SCHA)
- In planning clinical trials, include public and provider awareness strategies about risks and benefits of xenotransplantation (AMA through Resolution from SCMA)
- Advocate for a minimal amount of federal dollars for the study of ethical, legal,

and social issues in xenotransplantation (AMA through Resolution from SCMA)

### **Regenerative Technologies**

- Encourage the state of South Carolina to support, sustain, and stimulate translational research in regenerative medicine and biofabrication (SCMA & SCHA)
- Develop mechanisms for more constructive and efficient communication with the public and between regenerative medicine researchers. (South Carolina Bioengineering Alliance)
- Develop active process to study and debate ethical, legal, and social issues related to regenerative medicine (SCHA & SCMA)
- Advocate for a minimal amount of federal dollars for the study of ethical, legal, and social issues in regenerative medicine (AMA, through Resolution from SCMA)

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