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Buying time for transplants

Funders need to pay more attention to research aimed at increasing the shelf life of human organs. Doing so could pay dividends for both transplantation and basic research.

There is currently a serious shortage of organs for transplant. In the United States, at least one in five patients on transplant waitlists dies awaiting an organ. Part of the problem is an insufficient number of donors. Part of the problem is the quality of the organs in the donor pool. But the real enemy is time. A meeting last month organized by the nonprofit Organ Preservation Alliance (OPA), the American Society of Mechanical Engineers and several partners brought together researchers, transplant surgeons, healthcare professionals and others to discuss means of extending organ 'lifetime' and encouraging more funds into the field.

The current gold standard for preserving organs, static cold storage (at 4–8 °C), quickly leads to chilling damage and ischemia/reperfusion injury; although kidneys can be stored for up to about 24 hours, hearts and lungs can barely be kept alive for more than 3–6 hours. This means that a huge proportion of donor organs are discarded.

According to the OPA, one-fifth of donated kidneys are never transplanted and almost two-thirds of donated hearts and lungs are wasted, sometimes because time runs out, sometimes because of damage. The ticking organ clock also means that those who receive grafts often get a suboptimal match (*Nat. Biotechnol.* **35**, 530–542, 2017).

This tragic waste could be avoided if organs could be preserved for more hours, days—or even weeks. The extra time would enable marginal organs to be rehabilitated by *ex vivo* treatments. It would allow comprehensive evaluations of donor tissues and better graft characterization. And organs could be transported farther, creating a larger catchment area for physiologically and immunologically matched/tolerized recipients.

At the fringes, basic research might also benefit: improved organ preservation would enhance the consistency and quality of human cell and tissue samples, thereby promoting reproducibility.

One promising approach to extend organ lifetime is continuous perfusion *ex vivo* using machine pumps at normothermic temperatures (35–37 °C). A combination of perfusion with hypothermic temperatures (4–10 °C) is now in routine use for kidney transplants and can extend lung survival times from 8 to 21 hours (*Lancet Respir. Med.* **5**, 119–124, 2017). The addition of cryoprotectants and staggered cooling and rewarming to suppress ice formation (supercooling) in rat livers enables perfusion technology to be pushed to even lower temperatures (–6 °C), extending storage times to 4 days (*Nat. Med.* **20**, 790–793, 2014).

The real game changer, though, would be the ability to chill below –100 °C. Slow freezing of tissues has been used for decades for research purposes and in reproductive medicine. But techniques for cryopreserving organs, such as 'vitrification' (which suppresses ice nucleation by suspending cells in a glassy state) and 'directional freezing' (controlling the direction of ice crystal propagation using a thermal gradient), remain works in progress. Vitrified samples are dogged by the toxicity of cryoprotectants; and rewarming often causes ice recrystallization and catastrophic chemical, osmotic and mechanical stress (fractures) within tissues.

This is where bioengineering can help. For example, radiofrequency-excited silica-coated iron oxide nanoparticles markedly enhance the uniformity of rewarming and viability of vitrified pig arteries (*Sci. Transl. Med.* **9**, eaah4586, 2017). Less toxic cryoprotectants are being engineered from ice-binding proteins and quantitative structure–activity relationship used to synthesize ice recrystallization inhibitors (*Sci. Rep.* **6**, 26403, 24 May 2016). 'Omic studies of amphibians, reptiles and mammals that are freeze tolerant and capable of sustained metabolic arrest are yielding clues about molecular pathways and cell-stress signals useful for designing cell-protective agents or to provide predictive markers of graft quality. Combining perfusion technology with miniaturized sensor technology for continuously monitoring physiology, serum proteins or small molecules can also improve organ quality assessment.

Between recovery and transplantation, *ex vivo* perfusion also opens up the possibility of acclimating donor organs to recipient physiology (for instance, adjusting heart blood pressure to more closely match that of a recipient). Perfused marginal organs can be therapeutically targeted using recombinant factors (such as tissue plasminogen activator to clear clots or interleukin 10 to dampen inflammation) and small molecules (such as β2-adrenergic receptor agonists to reduce edema), opening up the possibility of gene therapy, antisense treatment or RNA interference. For recipients, added organ shelf life would also allow better HLA matching and application of immune tolerance regimes to the recipient (for example, thymic and mixed hematopoietic chimerism).

The major problem though is not technology; it is galvanizing resources and funding behind the grand challenge of organ preservation. Cryobiology is a small field—the Society for Cryobiology claims only ~300 members. At the OPA meeting, many new biologists were invited, but there remains a chasm between basic and applied research—several clinicians mentioned a lack of crosstalk with basic researchers.

Funding also needs reviving. The European Union recently set aside $7.1 million for the Consortium for Organ Preservation in Europe (COPE). And the US Department of Defense (DoD) has announced $14.8 million in small-business grants for the field and the launch of a $300 million Advanced Tissue Biofabrication Manufacturing Innovation Institute, which will include a focus on tissue preservation. But in the context of other research, investment looks anemic. A search of NIH RO1 grants in the past year reveals a paltry $7 million spent on cryopreservation and *ex vivo* perfusion technology.

Organ preservation research thus remains in dire need of investment. At the very least, funding agencies should better coordinate grant programs to maximize the use of the available funding. In showcasing the substantial near-term clinical potential of *ex vivo* perfusion technology, the OPA meeting demonstrated how just a little funding could provide major benefits for the tens of thousands of people who die or are hospitalized each year waiting for a transplant.