Cryopreservation breaks the organ transplant time barrier

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In a ground-breaking development, rat kidneys have been cryopreserved for an unprecedented duration of 100 days and subsequently transplanted successfully after nano-rewarming. This extraordinary achievement opens new possibilities for the field of organ banking.

Refers to Han, Z. et al. Vitrification and nanowarming enable long-term organ cryopreservation and life-sustaining kidney transplantation in a rat model. *Nat. Commun.* **14**, 3407 (2023).

The pressing issue of organ shortages for transplantation is fuelled by the rising incidence of kidney failure and the declining quality of organs from an ageing donor pool. However, the main bottleneck in organ transplantation is time; indeed, the current clinical standard for kidney preservation necessitates immediate transplantation following organ recovery[1]. This urgency often results in suboptimal matches between donors and recipients. Cryopreservation has emerged as a potential solution to this challenge. Such an approach would enable organs to be preserved in a suspended state for extended periods and ready for transplantation on demand. The prospect of long-term banking of cryopreserved organs holds promise for transforming organ transplantation into an elective procedure, thereby enhancing donor–recipient matching, improving equity in access, optimizing patient preparation, refining transplant tolerance protocols, increasing organ utilization and improving graft and patient survival. However, even though cryopreservation has successfully been used to store human embryos, extending the process to preserve whole organs has remained a scientific aspiration — until now. A study by Han et al. introduces an approach to cryopreservation that seemingly extends the shelf life of organs indefinitely[2].

> "The prospect of long-term banking of cryopreserved organs holds promise for transforming organ transplantation into an elective procedure"

By rapidly cooling rat kidneys to −150°C, Han et al. were able to halt the biological clock of the organs, effectively inducing a glass-like state — a process known as vitrification[2] (Fig. 1). Specifically, the researchers perfused a cocktail of cryoprotective agents (CPAs) and iron oxide nanoparticles into the organ's vasculature, which they followed by rapid cooling to ultralow temperatures to achieve a state of vitrification. This vitrified kidney, with its hard, smooth, glasslike appearance, was then transferred to a −150°C freezer for long-term banking. When these kidneys were later rewarmed and transplanted into nephrectomized recipients, they regained life-sustaining renal function. The rewarming stage poses more challenges to the process of cryopreservation: it requires both speed to avoid ice formation during devitrification and uniformity to prevent thermal stresses and mechanical cracks. Here, the iron oxide nanoparticles had a crucial role. Placing the vitrified kidney in a coil that generates electromagnetic fields activates these nanoparticles, generating heat. This innovative approach enabled rapid rewarming at an impressive rate of approximately 72 °C per minute throughout the entire organ, ensuring uniform warming rather than limiting warming to the organs' surface. This ground-breaking milestone marks an extraordinary achievement in 'reviving' a complex organ like the kidney and is the culmination of decades of research into methods to prevent the destructive formation of ice during the cooling process, minimize toxicity from CPAs, and enable fast and uniform rewarming[3].

> "The ability to scale up nanowarming techniques to human-scale organs remains uncharted territory"

Previous studies had demonstrated success in nanowarming vitrified organs, including kidneys, albeit without subsequent transplantation[4,5]. However, Han et al. identified the toxicity of CPAs, rather than injury resulting from vitrification and nanowarming, as the critical hurdle for achieving functional recovery. By improving the CPA cocktail, the researchers successfully reduced its nephrotoxicity, enabling recovery of viable organs after cryobanking and demonstration of renal function after transplantation.

Nonetheless, several questions and challenges remain to be addressed. Vitrified and nanowarmed kidneys from healthy donor rats still displayed a temporary period of graft dysfunction lasting for 2–3 weeks after transplantation. The underlying mechanisms of this dysfunction remain unknown, but residual CPA toxicity is a potential explanation. The consequences of CPA toxicity may be more severe in kidneys from deceased human donors, particularly those that meet extended criteria. Furthermore, the ability to scale up nanowarming techniques to human-scale organs remains uncharted territory, as the current success was limited to small model systems.

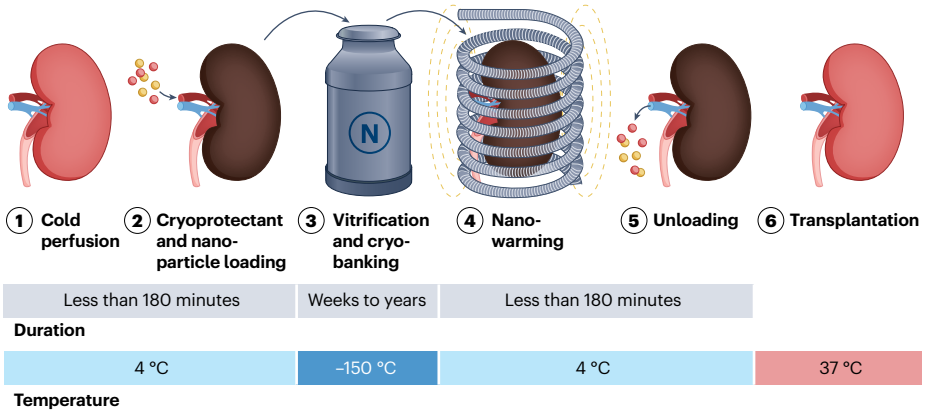

Fig. 1 | Process for the vitrification and nanowarming of donor kidneys. After procurement, the kidney undergoes hypothermic perfusion, during which it is perfused with cold preservation solutions (1). Subsequently, a solution containing cryoprotective agents (CPAs) and iron oxide nanoparticles (IONPs) is introduced into the blood vessels, ensuring an even distribution throughout the organ (2). The kidney, now loaded with CPAs and IONPs, is rapidly cooled to −150 °C, causing it to enter a glasslike state suitable for long-term storage (3). When the kidney is needed for transplantation, it is removed from storage and 'revived' by placing it in a magnetic coil. An alternating magnetic field activates the nanoparticles, generating heat and allowing rapid and uniform rewarming of the kidney (4). The CPAs and IONPs are flushed out during hypothermic perfusion (5), after which the kidney is ready for transplantation (6).

Although cryobanking offers the potential for long-term organ preservation on the shelf, researchers are also exploring various other technologies to enhance and extend the ex vivo preservation of kidneys and other organs. The current clinical standard for kidney preservation involves hypothermic perfusion at temperatures ranging from 4 °C to 8 °C, allowing preservation for up to 24–36 h (refs. 1,6). In the past decade, normothermic preservation, maintaining temperatures of 34–37 °C, has garnered interest for its ability to provide a near-physiological platform for interventions. This approach has shown promise in extending liver preservation for up to 7 days[7]. However, red blood cell-based kidney perfusion remains limited to hours[8], likely due to the occurrence of hemolysis and subsequent acute kidney injury. Alternatively, perfusion at subnormothermic temperatures between 20 and 32 °C circumvents the need for red blood cells, allowing multi-day ex vivo perfusion while maintaining sufficient oxidative metabolism to support cellular repair processes[9].

Lowering temperatures below 0 °C ceases metabolism and effectively halts biological time, theoretically enabling indefinite organ storage. Although ultra-low temperatures require high concentrations of CPAs and present challenges during rewarming, some studies have explored temperatures closer to 0 °C. These efforts include supercooling human livers at −4 °C for 27 h or partially freezing rodent livers at −15 °C for up to 5 days[10]. However, the durations achieved with these methods fall markedly short of the nearly unlimited storage window that may be achieved with vitrified organs.

Organ cryobanking represents a remarkable opportunity to store organs for extended periods, ranging from days to weeks or even years, thereby revolutionizing the field of transplantation. Specialized facilities may emerge to handle the banking, resuscitation and transplantation of organs. The ability to store organs long-term, either frozen in time or in a metabolically active state for shorter durations, will facilitate the development of innovative interventions that have the potential to reshape transplantation practices. Examples include the induction of immune tolerance in recipients of deceased donor organs and modulation of immune responses during organ perfusion. Ultimately, the goal is to develop platforms that enable the transportation, repair, assessment, banking and even functional enhancement of organs from deceased donors, leading to increased availability and quality of organs and thus benefiting the tens of thousands of individuals who die or are hospitalized each year while waiting for a transplant.

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Competing interests

The authors declare no competing interests.