carp-like cyprinoids and cichlids from the tilapia group, but these populations contain few species, and they tend to be found in shallow marginal habitats near the water's edge (Fig. 1).

Lake Victoria is thought to have been mainly dry before it started to refill with water around 17,000 years ago. Ngoepe and colleagues studied a series of sediment cores taken from Lake Victoria and extracted fish fossils that were dated by using radiocarbon evidence from other organic material in the cores. The authors were then able to reconstruct when various groups of fish species arrived in the habitat by using evidence painstakingly gathered from thousands of fossil teeth that were individually assigned to species groups.

Ngoepe and colleagues discovered that as the lake started to refill, it was initially colonized by species including haplochromine cichlids, catfishes, cyprinoids and cichlids from the tilapia group. The fauna of fish populations resembled those of the inshore swampy habitats of present-day Lake Victoria. However, as the lake continued to fill over millennia, only the haplochromine cichlids occupied the deep waters; the other species groups remained around the margins of the lake. This study clearly deflates the idea that haplochromine cichlids monopolized resources just because they were the first species group to arrive in the new habitat. Instead, only this group had sufficient versatility to thrive and radiate into the new ecological space.

Previous work shows that Lake Victoria's haplochromine cichlids have genetic and physical characteristics that might predispose them to diversification — including three key attributes[7]. First, sexual selection is prominent in populations of haplochromine cichlids, and is driven both by competition between males and by female mate choice. When there is strong sexual selection, it might mean that those individuals with the best ability to exploit the ecological niche also have the most success in breeding, and such populations would then become optimized for their environments in a relatively small number of generations compared with populations with random mating. Second, haplochromine cichlids have highly evolvable jaw structures that enable the fish to capitalize on the most rewarding prey in the local environment; other fish lineages are more constrained in their capacity for jaw evolution.

Third, haplochromine cichlids are known to share genetic material across species boundaries through a process called interspecific hybridization. The hybrid offspring are often viable, fertile and capable of breeding with both parental species. The ability of hybrids to act as conduits of genetic variation between species might mean that these cichlid populations are genetically primed for adaptive radiation when the opportunity arises[7,11]. But none of these attributes is unique to haplochromine cichlids — and some non-radiating cichlid lineages have all these characteristics, too, making it hard to identify a single cause of expansive cichlid diversification. Nevertheless, this combination of three attributes might be sufficient to enable radiation when ecological opportunity presents itself.

By digging deep into the past of Lake Victoria, Ngoepe and colleagues have tracked the evolution of an adaptive radiation that is comparatively modern. Although providing unprecedented historical insight, the work is necessarily limited to inferences from fish material that is well represented in sediment cores, such as teeth. It will be challenging to undertake a detailed reconstruction of the evolution of the full diversity of shapes and forms of cichlids known from the modern lake, which hosts species that are highly specialized for eating fish, molluscs and plankton[7]. Perhaps insights into the timeline and ecological conditions favouring the evolution of specific characteristics and lifestyles might one day be gleaned by linking knowledge of the genetic basis of these characteristics in modern fish with that from ancient DNA extracted from sediment-core fossils[12].

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Organ transplants

Pig genes changed for longer organ survival

Muhammad M. Mohiuddin

A raft of alterations to the pig genome — removing three antigen-encoding genes, adding seven human genes and eliminating a retrovirus — allows kidneys to be transplanted into monkeys, with implications for clinical trials. **See p.393**

On page 393, Anand and colleagues[1] describe the successful transplant of kidneys from genetically engineered miniature pigs (*Sus domesticus*) into cynomolgus monkeys (*Macaca fascicularis*). Highlighting the numerous modifications made to the pig genome, the authors show *in vivo* and *in vitro* that these alterations are justified, and that they might help to overcome the immunological hurdles of transplanting pig organs into people and to prolong the survival of the organs.

The transplant of human organs from a donor to a recipient became an accepted therapy for organ failure in the 1970s and 1980s. But the availability of organs for such 'allotransplantation' has not changed much since then, and some individuals with end-stage organ disease still die waiting for a suitable donor organ, despite improvements in alternative procedures (such as mechanical circulatory devices for hearts). Xenotransplants — transplanting animal organs (xenografts) into people — could overcome this deficit, and save many human lives.

Pigs are the most promising donor animals, owing to the availability of the technology required to modify their genome, their short gestation period, their rapid growth to a human-compatible size and the anatomical similarity of their organs to those of humans. But overcoming the complex rejection of porcine organs by the human immune system has presented a challenge for more than 40 years. In the past few years, improved gene-editing technology (the CRISPR technique) and modified immunosuppressive approaches have led to encouraging preclinical xenograft survival experiments, and in January 2022, the first transplant of a genetically modified pig heart to a human recipient was conducted[2,3], invigorating the field.

Anand *et al.*[1] now describe the fruits of

several years of research that have highlighted the importance of stopping pre-existing primate – either human or non-human primate (NHP) – antibodies from interacting with the pig molecules that cause xenograft rejection. Previous work involving the efforts of many research groups revealed the roles of three major immunogenic carbohydrate molecules in pigs by removing these antigens individually[4–6]. The antigens in question are galactose α-1,3- galactose, SDa and Neu5Gc, and they were removed by knocking out the genes encoding the enzymes that produce them (α-1,3-galactosyl transferase, B4 galactosidase and CMAH) from the pig genome.

The *CMAH* gene is of questionable importance in the preclinical NHP model, but removing it seems to be essential for transplants into humans. NHPs express *CMAH*, but humans do not; it is thought that removing this gene from pigs exposes new antigens in pig organs that might elicit immune rejection in NHP recipients[7]. These antigens have not been characterized, but doing so would probably be clinically irrelevant, given that humans lack *CMAH*.

In their work, Anand *et al*. remove all three carbohydrate antigens, and overcome various other molecular disparities between pigs and primates by engineering the pigs to express seven human genes. These genes encode proteins involved in: protecting the cells that line blood vessels (the CD46 and CD55 proteins, which are part of a pathway called the complement cascade); preventing unwanted blood clots (endothelial protein C receptor and thrombomodulin); and generating an inflammatory response to xenografts (the anti-phagocytic protein CD47, haem oxygenase 1 and the anti-cell-death protein A20). These modifications are similar to those previously reported individually and collectively, except that other groups also knocked out a growth-hormone receptor[2,3,8], and did not remove A20. Knocking out this receptor is one solution to the problem posed by the fast growth rate of pigs: although such rapid growth will be useful for the xenograft supply chain, pig organs might outgrow their primate recipients. Another solution is to use minipig donors (Fig. 1), as Anand *et al*. have done.

In total, Anand *et al*. made 69 gene modifications to the pigs' genome to overcome organ rejection. One set of modifications unique to their study is the removal of all 59 copies of the porcine endogenous retrovirus (PERV) gene, constituting 86% of the 69 alterations. This might not be truly necessary, but, as the authors indicate, it does safeguard against activation of this virus.

PERV does not cause disease in pigs, but there is (limited) *in vitro* evidence that it can infect human cells[9]. So far, however, there is no *in vivo* evidence of disease transmission in human transplant recipients, whether decedent or living. Workers from the same research group as Anand *et al*. have previously described[10] the knockout of all copies of PERV genes and the resulting benefits, but do not address the topic further now. Long-term screening of people who receive xenografts and their immediate contacts will be crucial, to ensure that viruses found in porcine genes are not activated later on, and that transmission to humans does not occur.

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Figure 1 | Yucatan miniature pigs. Anand *et al*.[1] have made 69 modifications to the genome of Yucatan minipigs to increase the success of transplants of pig kidneys to primates.

Despite such extensive genetic modifications of donor pigs, all studies have found that immunosuppression of the recipient is still necessary, requiring new drugs to block the pathways involved (such as the CD40–CD40-ligand pathway). In an ideal scenario, genetic modifications alone would prevent xenograft rejection, and some form of tolerance for the donor organ would be induced in the recipient. Anand *et al*. conclude, however, that adding human genes to pigs does provide an extra layer of protection (beyond that afforded by the immunogenic gene knockouts), and helps to prolong xenograft survival in cynomolgus monkeys – complementing other reports.

"The authors show that it is time for clinical translation of this vital technology."

Anand and colleagues' paper – together with other reports of successful xenotransplants in preclinical NHP models and in humans – shows that it is time for clinical translation of this vital technology, which has the potential to save lives that would otherwise be lost to the shortage of human organs. There is still much to be learnt from NHP preclinical models. But it will be clinical trials, enrolling people who have been excluded from all other hope of treatment, that will truly further our understanding of this remarkable procedure, and help to realize the potential of this technology.

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Clarification

The original version of the News & Views article 'Pig genes changed for longer organ survival' (*Nature* **622**, 244–245; 2023) did not specify that the pig-to-human heart transplant in 2022 involved a genetically modified heart.