transplants can survive for 3 months, with at least 10 animals surviving for this time frame, and with some indication that longer survival is possible[12]. The current study goes some way to meeting these criteria. However, it seems likely that regulatory authorities such as the US Food and Drug Administration will require a longer period of follow-up and a greater percentage of successful experiments before permitting human trials.

In addition, other issues should be given attention before pig-to-human transplants become a reality. One such issue is the potential for pig viruses such as porcine endogenous retroviruses (PERVs) to be transmitted to humans. The risk of PERV-related complications is considered to be small[13], but regulatory authorities worldwide still view the possibility with some caution. However, the genome-editing technology CRISPR–Cas has increased the speed with which pigs harbouring multiple genetic mutations can be generated, enabling researchers to produce live, healthy piglets in which PERVs have been deactivated[14]. This indicates one way of circumventing the risk of PERV transmission.

Another consideration is the fact that, in the past two decades, technology to improve blood circulation using mechanical support devices has evolved dramatically. These devices are used as a temporary fix while patients wait for a donor organ, but they can also be a permanent therapy for those with end-stage heart failure. The progress of this technology raises ethical questions regarding the use of pig hearts. For each patient, a case will have to be made for why a pig-heart transplant should be selected over mechanical support.

Regardless of the issues surrounding pig-to-human xenotransplantation, the blood-perfusion protocol exploited by Längin and colleagues could have a beneficial impact on human-to-human transplants. Cold static storage is still the standard for human organ transplants, but a blood-based solution could help to improve both short- and long-term results in the clinic. Moreover, it might allow the pool of donor hearts to be extended to include organs that are currently considered suboptimal because the donors are old or have an underlying condition that reduces the heart's ability to withstand the lack of a normal blood supply. ■

Christoph Knosalla *is in the Department of Cardiothoracic and Vascular Surgery, German Heart Center Berlin, 13353 Berlin, Germany, and at the DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin.*
e-mail: knosalla@dhzb.de

1. Benjamin, E. J. *et al. Circulation* **137**, e67–e492 (2018).
2. Colvin, M. *et al. Am. J. Transplant.* **18** (Suppl. 1), 291–362 (2018).
3. Branger, P. & Samuel, U. (eds) *Annual Report 2017: Eurotransplant International Foundation*; available at https://go.nature.com/2deatzh (2017).
4. Längin, M. *et al. Nature* **564**, 430–433 (2018).
5. Adams, A. B. *et al. Ann. Surg.* **268**, 564–573 (2018).
6. Mohiuddin, M. M. *et al. Nature Commun.* **7**, 11138 (2016).
7. Byrne, G. W., Du, Z., Sun, Z., Asmann, Y. W. & McGregor, C. G. A. *Xenotransplantation* **18**, 14–27 (2011).
8. Paoletti, E. *Transplantation* **102** (2S), S41–S43 (2018).
9. Lesnik, J. J., Singh, G. K., Balfour, I. C. & Wall, D. A. *Bone Marrow Transplant.* **27,** 1105–1108 (2001).
10. Kuwaki, K. *et al. Am. J. Transplant.* **4**, 363–372 (2004).
11. Kuwaki, K. *et al. Nature Med.* **11**, 29–31 (2005).
12. Cooper, D. K. C. *et al. J. Heart Lung Transplant.* **19**, 1125–1165 (2000).
13. Denner, J. *Science* **357**, 1238–1239 (2017).
14. Niu, D. *et al. Science* **357**, 1303–1307 (2017).

This article was published online on 5 December 2018.

ASTRONOMY

Abundant rare isotopes in a planetary nebula

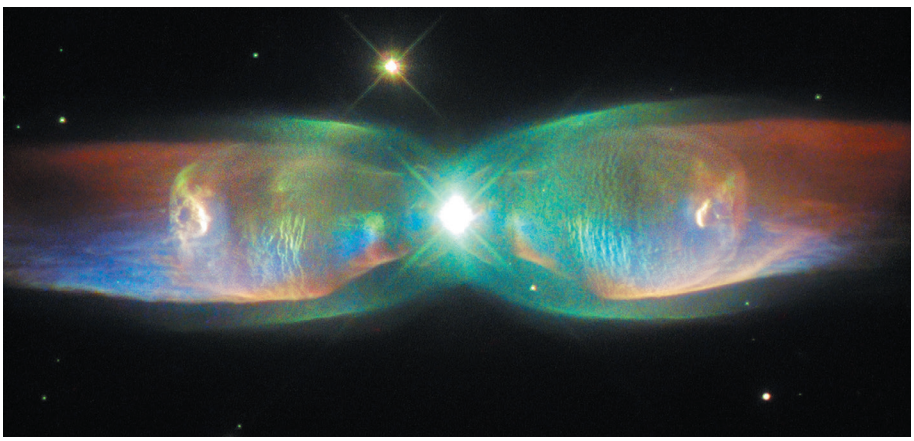
Observations reveal that a particular planetary nebula — the ejected envelope of an old star — is unusually enriched in rare carbon, nitrogen and oxygen isotopes. The finding could help to explain the origins of these isotopes. SEE LETTER P.378

AMANDA KARAKAS

The origin of the chemical elements in the Universe is one of the most fascinating and enduring mysteries in astronomy. Progress so far has come from studies of stars, but here only elemental abundances can be determined reliably. Isotopic ratios are more difficult to obtain. On page 378, Schmidt *et al.*[1] study the composition of the young planetary nebula K4-47 — a glowing shell of gas and dust that formed from the outer layer of a Sun-like star and that was thrown off during the final stages of the star's evolution. The authors find that the nebula is unusually enriched in rare isotopes of carbon (^{13}C), nitrogen (^{15}N) and oxygen (^{17}O). The measured composition of K4-47 shows that this object is more enriched in these isotopes than is almost any other nebula or star examined so far.

Why is Schmidt and colleagues' finding such a big deal? For one thing, it seems to suggest that stars similar to the Sun can make these rare isotopes — a result that was not expected. Computer simulations[2] of Sun-like stars have shown that they can be factories for carbon and nitrogen, but only in the form of the dominant isotopes ^{12}C and ^{14}N. Furthermore, theory[2] predicts that the rarer isotopes are not made inside stars that become planetary nebulae. What about direct observations of ageing Sun-like stars, as opposed to planetary nebulae? Such observations are difficult, but the available data[3,4] mostly agree with theory, making K4-47 a particularly unusual object.

The only instance in which the isotopes ^{13}C, ^{15}N and ^{17}O are synthesized at the same time is in explosions. CNO cycles are a collection of thermonuclear reactions that involve the capture of protons by isotopes of carbon, nitrogen



ESA/HUBBLE & NASA/JUDY SCHMIDT

Figure 1 | A bipolar planetary nebula. A planetary nebula is a glowing shell of gas and dust that is ejected from a Sun-like star during the final stages of the star's evolution. Shown here is the planetary nebula M2-9 (also known as the Twin Jet nebula). Schmidt *et al.*[1] report observations of the planetary nebula K4-47 that, like M2-9, has an hourglass (bipolar) shape and highly collimated outflows of material. The authors find that K4-47 contains an unexpectedly high abundance of rare isotopes of carbon, nitrogen and oxygen.

and oxygen. These reactions are the workhorse of stellar energy production but do not make much ^{13}C, ^{15}N and ^{17}O. Generating these isotopes requires conditions of high temperature and density, as well as plenty of protons. Such a mechanism is known as the hot CNO cycle. So far, the products of the hot CNO cycle have been found only in classical novae[5] — nuclear explosions that occur in certain binary star systems.

So how can the presence of the rare isotopes in K4-47 be explained? One mechanism proposed by Schmidt *et al.* is that the progenitor of K4-47 underwent an explosive event called a helium-shell flash immediately before it became a planetary nebula. This is, in essence, a mixing event that causes hot material from the core of a star, rich in ^{12}C, to be moved to a cooler region, where hydrogen-fusion reactions are occurring. The mixing elevates the temperature of the cooler region, enabling reactions of the hot CNO cycle to proceed before the material is expelled to space.

Although the explosive nature of this scenario is unusual, similar mixing has previously been proposed to explain the composition of other chemically peculiar stars, such as Sakurai's object[6] (also known as V4334 Sagittarii). Detailed computer simulations are needed to test this mechanism. If it can be verified, it will be evidence of previously unknown stellar behaviour that provides insight into how rare isotopes of common elements are generated.

But there are other possible explanations. The isotopic composition of K4-47 is similar to that of J-type carbon stars[4], which have ratios of ^{12}C to ^{13}C of less than 15. The sequence of events that lead to a J-type star is unknown, and their existence is not predicted by the theory that describes the evolution of single stars. It has been suggested that J-type stars instead result from binary evolution[7], in which two stars orbit each other and interact.

Such interactions have been proposed for all planetary nebulae that, like K4-47, have an hourglass (bipolar) shape and highly collimated outflows of material[8,9] (Fig. 1). Observations show that the central stars of planetary nebulae are more likely to be binary stars than was previously thought, giving further credence to this idea. K4-47 could therefore be the product of an interaction or merger between two stars.

Alternatively, K4-47 might not be a planetary nebula at all. It has been speculated that it could be a planetary-nebula mimic, in which the extended nebula was ejected by a pair of interacting binary stars during an explosion[10]. The isotopic composition of K4-47 could be explained if the interaction of these stars resulted in an explosion akin to a classical nova that would allow for the hot CNO cycle. One prediction of this scenario is that gas would be ejected at high velocities. Has such ejection been observed?

Schmidt and colleagues say they have not seen these high-velocity outflows of material, so they rule out a nova-like explosion as an explanation. But this finding is in contrast to previous studies that have observed high-velocity bullets of material ploughing through the surrounding medium[11,12]. So who is right? Answering this question will require follow-up observations of K4-47 using astronomical instruments that can extract high-resolution spatial, dynamical and chemical information about the object.

Either way, K4-47, which is rich in the products normally associated with a nova but is embedded in something that looks like a planetary nebula, is one of the most isotopically unusual astronomical objects studied so far (along with CK Vulpeculae[13]). Detailed computer modelling and follow-up observations are required to tease out the true nature of the progenitor of K4-47. Such work could tell us something about how the rare isotopes of carbon, nitrogen and oxygen are made in stars. ■

Amanda Karakas *is at the Monash Centre for Astrophysics, School of Physics and Astronomy, Monash University, Victoria 3800, Australia.*
e-mail: amanda.karakas@monash.edu

1. Schmidt, D. R., Woolf, N. J., Zega, T. J. & Ziurys, L. M. *Nature* **564**, 378–381 (2018).
2. Karakas, A. I. & Lattanzio, J. C. *Publ. Astron. Soc. Aust.* **31**, e030 (2014).
3. Lambert, D. L., Gustafsson, B., Eriksson, K. & Hinkle, K. H. *Astrophys. J. Suppl. Ser.* **62**, 373–425 (1986).
4. Abia, C. & Isern, J. *Mon. Not. R. Astron. Soc.* **289**, L11–L15 (1997).
5. Gehrz, R. D., Truran, J. W., Williams, R. E. & Starrfield, S. *Publ. Astron. Soc. Pacif.* **110**, 3–26 (1998).
6. Herwig, F. *et al. Astrophys. J.* **727**, 89 (2011).
7. Zhang, X. & Jeffery, C. S. *Mon. Not. R. Astron. Soc.* **430**, 2113–2120 (2013).
8. De Marco, O. *Publ. Astron. Soc. Pacif.* **121**, 316–342 (2009).
9. Jones, D. & Boffin, H. M. J. *Nature Astron.* **1**, 0117 (2017).
10. Corradi, R. L. M. *et al. Astrophys. J.* **535**, 823–832 (2000).
11. Gonçalves, D. R. *et al. Mon. Not. R. Astron. Soc.* **355**, 37–43 (2004).
12. Akras, S., Gonçalves, D. R. & Ramos-Larios, G. *Mon. Not. R. Astron. Soc.* **465**, 1289–1296 (2017).
13. Kamiński, T. *et al. Astron. Astrophys.* **607**, A78 (2017).

NEURODEGENERATION

Amyloid-β 'seeds' in old growth-hormone vials

Some samples of human growth hormone used as therapy until the mid-1980s contain amyloid-β peptide and cause genetically modified mice to develop amyloid-β deposits in the brain. SEE LETTER P.415

TIEN-PHAT V. HUYNH & DAVID M. HOLTZMAN

In cerebral amyloid angiopathy (CAA) and Alzheimer's disease, insoluble aggregates of a peptide known as amyloid-β (Aβ) progressively build up in the spaces between cells, forming amyloid deposits. In Alzheimer's disease, these aggregates are found between neurons, whereas in CAA, a related but not always coexisting condition, they are found in the walls of brain blood vessels. Aβ aggregates are thought to be early drivers of the pathological processes of CAA and Alzheimer's disease that culminate in neurodegeneration. In 2015, researchers reported evidence of early Aβ pathology in the brains of some people with growth deficiency who had been treated with human growth hormone collected from pituitary glands at autopsy[1]. This finding raised the possibility that Aβ pathology might be transmissible between humans under certain conditions through contaminated brain-tissue derivatives. On page 415, Purro *et al.*[2] provide further support for this hypothesis.

From 1958 to 1985, approximately 30,000 children with growth deficiency were treated with cadaver-derived growth hormone (c-hGH) worldwide[3]. In 1985, three recipients were found to have developed Creutzfeldt–Jakob disease (CJD), which is fatal. CJD belongs to a group of diseases known as transmissible spongiform encephalopathies, which are characterized by progressive and irreversible brain damage resulting from the accumulation of a misfolded form of a brain protein called prion protein. These abnormal prion proteins can themselves cause normal prion proteins to misfold, and thus spread the disease. Given the evidence that contaminated c-hGH had caused CJD, this type of treatment was quickly stopped and synthetic recombinant human growth hormone (rhGH) became the standard of care.

Alzheimer's disease is not a classic prion disease, but shares characteristics with this type of disorder. Misfolded, aggregated Aβ peptides and tau proteins, which are toxic to neurons, are present in the brain as key components of Alzheimer's disease. Inoculation of minute amounts of misfolded Aβ (known as Aβ 'seeds') isolated from the brains of people with Alzheimer's disease can induce build-up of Aβ deposits (called Aβ plaques) in non-human primates[4], and brain extracts from people or