indicating that ILC3 cells promoted the survival of RORγt-expressing $T_{\mathrm{reg}}$ cells by expressing a different integrin, called integrin $\alpha_v\beta_3$, which hasn't previously been linked to the induction of $\mathrm{pT_{reg}}$ cells. Integrin $\alpha_v\beta_3$ can bind to and activate TGF-β, but also engages several other proteins. Therefore, more work is needed to identify the RORγt-expressing cells that promote RORγt-expressing $T_{\mathrm{reg}}$ cells through integrin $\alpha_v\beta_8$, and to investigate the *in vivo* contribution of ILC3 cells to the promotion of RORγt-expressing $T_{\mathrm{reg}}$ cells through integrin $\alpha_v\beta_3$.

A key question is which RORγt-expressing antigen-presenting cell population – if any – has an essential (non-redundant) role in promoting the generation of $\mathrm{pT_{reg}}$ cells that express RORγt and FOXP3 and that enable tolerance to the microbiota. Different approaches to abolish the expression of MHCII in ILC3 cells gave opposing results in two studies: the work by Lyu and colleagues indicates that this deficiency caused a reduction in intestinal RORγt-expressing $\mathrm{pT_{reg}}$ cells, whereas Akagbosu and co-workers found no effect. These results leave open the question of whether ILC3 cells have key roles in promoting RORγt-expressing $\mathrm{pT_{reg}}$ cells. A genetic system to specifically remove Thetis cells is still lacking.

Analyses of mice lacking MHCII in AIRE-expressing cells, or ones that lack AIRE in RORγt-expressing cells, showed no decreases in gut RORγt-expressing $\mathrm{pT_{reg}}$ cells compared with control animals. However, these results might not be completely conclusive regarding the role of Thetis cells and AIRE, because it seems that AIRE is deleted in only a fraction of Thetis cells by the currently available genetic tools in mice. Furthermore, AIRE might be dispensable for the generation of microbiota-specific $T_{\mathrm{reg}}$ cells. Alternatively, peripheral expression of AIRE by Thetis cells or dendritic cells could have a role in peripheral tolerance to other antigens not related to the microbiota or by promoting functions not associated with the induction of $\mathrm{pT_{reg}}$ cells, as suggested by other work[15].

These cellular interactions that have a crucial role in the regulation of tolerance to the microbiota in mice might be evolutionarily conserved in humans. A population of dendritic cells that express AIRE in human tonsils was described previously[16]. Interestingly, by analysing previously published single-cell data for samples from fetal, child and adult human intestines and gut-draining lymph nodes[17], Akagbosu and colleagues identified a gene-expression signature comparable to that of TC III and TC IV in a group of cells previously defined as dendritic cells in human fetal samples. Whether ILC3, dendritic or Thetis-cell-like cells might have an antigen-presenting role in promoting the formation of $\mathrm{pT_{reg}}$ cells in humans needs to be assessed.

Immunologists are only beginning to understand how the host and its microbiota learn to live together. Answering the remaining questions might set the stage for new opportunities to boost gut health and prevent the onset of immune-mediated disorders.

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## Nuclear astrophysics

# Underground route to grasping the oldest stars

### Marco Pignatari & Athanasios Psaltis

Nuclear-fusion experiments performed deep under Earth's surface reveal one possible scenario that could have resulted in the chemical abundances found in an ancient star in the Milky Way. **See p.656**

When the first stars in the Milky Way formed around 13 billion years ago, they consisted mainly of hydrogen and helium. But other chemical elements – the heaviest being calcium – have been detected in the atmosphere of one of the oldest-known stars, an amazing object known as SMSS0313-6708 that lies just 1,800 parsecs from Earth[1]. Astronomers and astrophysicists were puzzled, and started to look for ways in which calcium and the other elements could have been made. The solution, it seems, might be found under Earth's surface. On page 656, Zhang *et al.*[2] report nuclear-physics experiments that could support one explanation for the chemical abundances found in SMSS0313-6708 – with implications for our understanding of other stars in the Universe.

Stars are giant nuclear-fusion reactors that initially generate energy by burning hydrogen in their cores and converting it to helium. Depending on the initial size of the star, the helium nuclei can then fuse to produce carbon and oxygen, followed by more fusion stages that produce heavier elements as the star evolves[3]. Stars that are around eight to ten times more massive than the Sun[4] end this cycle with powerful explosions called supernovae[5], ejecting the new chemical elements at high velocities into the interstellar space, and seeding the surrounding area with gas that will form the next generation of stars. The oldest stars in the Galaxy today therefore retain the chemical fingerprints of these first supernovae.

Finding these stars and measuring their tiny elemental abundances are key goals for astronomy, because such measurements reveal the main properties of the first generation of stars[6]. But computational experiments can also be informative about stellar properties by simulating the generation and evolution of stars. And as in real stars, nuclear reactions provide the fundamental ingredients for the production of elements in simulated stars. For this reason, understanding the rates at which these reactions occur can improve the precision with which stellar simulations can predict the abundances expected in stars such as SMSS0313-6708.

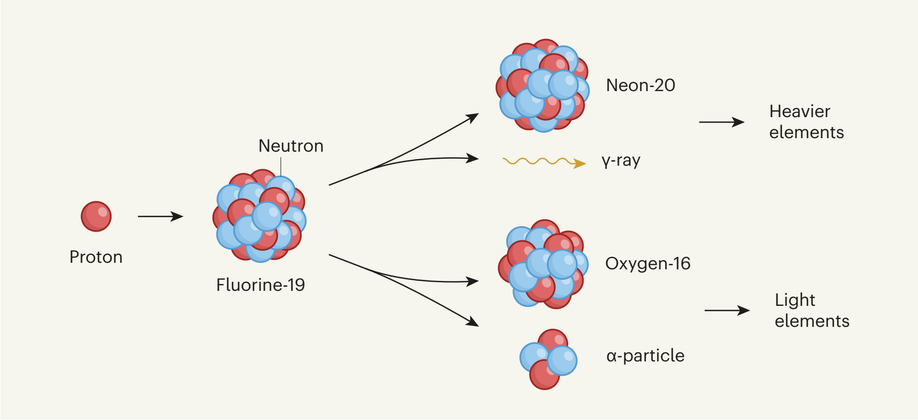

**Figure 1 | Two ways in which a proton can fuse with a fluorine-19 nucleus.** When an intense beam of protons hits a solid target comprising the isotope fluorine-19, the protons fuse with the fluorine nuclei, resulting in two possible reactions: the production of a neon-20 isotope and a γ-ray, or the production of an oxygen-16 isotope and an α-particle (containing two protons and two neutrons). When oxygen-16 is produced, subsequent reactions do not result in the production of elements heavier than fluorine-19. The generation of neon-20, which is heavier than fluorine-19, is therefore known as a breakout reaction, because it breaks the cycle of proton captures that produce light elements only. Zhang *et al.*[2] performed experiments showing that this breakout reaction occurs at a rate that is 7.4 times higher than previously thought, making it a likely candidate to explain the abundance of elements as heavy as calcium in one of the Milky Way's oldest stars.

Zhang and collaborators studied one such reaction, in which a fluorine-19 isotope fuses with a proton to produce a neon-20 isotope and a γ-ray. To determine the rate at which this occurs with high precision, the researchers needed to induce the reaction at an unprecedentedly low energy, similar to the conditions found in stars. They achieved this by using a particle accelerator that is buried deep below Earth's surface.

Overcoming the effects of natural radioactivity is one of the biggest challenges for physicists trying to recreate the nuclear-fusion reactions that occur in stars. This radioactivity is a constant flux of electrons, protons, neutrons, γ-rays and muons that come either from Earth's surface or from outer space. Our bodies have evolved over the eons to handle this amount of radiation without incurring damage to our genetic code. But when these particles interact with air molecules, they produce unwanted noise, known as background, in the sensitive detectors used by nuclear physicists. This background has the effect of overshadowing the signal from the reactions physicists are trying to measure.

One way to reduce background is to perform the experiments deep underground. A handful of laboratories across the world can provide such conditions — one under the Gran Sasso mountains in Italy[7], another in the Black Hills of South Dakota in the United States[8] and a third in an underground cave in Dresden, Germany, that was previously used as storage by a local brewery[9]. But China Jinping Underground Laboratory[10] (CJUL) in Sichuan province is currently the deepest laboratory in the world. Lying 2.4 kilometres below the peaks of the Jinping Mountains, CJUL hosts the Jinping Underground Nuclear Astrophysics experiment (JUNA). This experiment is exposed to a tiny fraction of the natural radioactivity that would pass through a laboratory on Earth's surface — one-millionth of the cosmic muons and one-ten-thousandth of the neutrons.

The reaction that Zhang *et al.* studied in this laboratory is relevant to SMSS0313-6708 because it is implicated in one of the mechanisms proposed to explain the chemical abundances measured in the star. In this mechanism, after light metals such as carbon and oxygen were made, early in the star's evolution, a subsequent sequence of proton-capture reactions generated abundances of heavier elements, all the way up to calcium[1].

Along this nuclear-reaction path, the fluorine-19 isotope has a key role. The quantity of material made that is heavier than fluorine-19 depends on the relative rates of the two competing proton-capture reactions, the one studied by Zhang *et al.* and another reaction that produces an oxygen isotope instead (Fig. 1). In this latter reaction, the fusion of a fluorine-19 nucleus and a proton produces an α-particle (also known as a helium-4 nucleus, consisting of two protons and two neutrons) and oxygen-16. Heavier elements are not made, and the production flow 'cycles' back to lighter nuclei. For this reason, the reaction involving neon-20 is called a breakout reaction, because it allows material to escape the cycle of proton captures that produces light elements only[11].

Zhang *et al.* investigated this breakout reaction by firing an intense beam of protons at solid fluorine-19 targets. On the basis of previous evaluations[12], the rate of this reaction was expected to be around 4,000 times smaller than the one generating oxygen-16. By using the ultralow background environment of CJUL and a sensitive detection system for the γ-rays emitted in the reaction, the authors substantially reduced the uncertainty associated with measurement of the reaction rate compared with that of earlier studies[13,14]. They discovered that, at the relevant stellar temperatures, the rate of the reaction producing neon-20 through fusion of fluorine-19 and a proton was 7.4 times larger than previous estimates, making it easier than expected for a plausible proton-capture mechanism to generate the calcium abundance found in SMSS0313-6708.

The rate reported in the study provides a key ingredient for the next generation of stellar simulations, which will aim to understand the nature of the star that exploded as a supernova immediately after the formation of the Milky Way. These studies could also shed light on which chemical products spread through the gas that formed SMSS0313-6708 shortly after this explosion.

Zhang and colleagues' work was one of the first experiments planned for JUNA[15]. Such underground nuclear laboratories are already producing invaluable information for researchers simulating stars in the cosmos. The fact that these experiments can now achieve the precision necessary to improve the simulations and compare them with astronomical observations shows that this is an exciting era indeed for probing the evolution of stars in the Universe.

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