Astronomy

The scattered ashes of an ancient star cluster

J. M. Diederik Kruijssen

Observations of a star system called the Phoenix stellar stream offer the first evidence of vanished star clusters that had extremely low levels of heavy elements. Their remnants might cast light on the early assembly of the Milky Way. **See p.768**

Globular clusters are among the most enigmatic objects in the Universe. They are systems of about 100,000 stars packed into regions of the order of just 10 parsecs (a few tens of light years) in diameter (Fig. 1), and most are almost as old as the Universe. Globular clusters orbit nearly all known galaxies that have more than one billion stars[1]. Their spheroidal distribution around these galaxies suggests that many of them formed in other, low-mass galaxies that once orbited the central galaxy but that have since been accreted by that galaxy and shredded by its tidal (gravitational) forces.

Astrophysicists have learnt to use globular clusters as 'fossils' to reconstruct this accretion process[2], which contributes to the assembly of large galaxies. However, globular clusters can also be destroyed by the host galaxy's tidal forces, erasing their secrets. On page 768, Wan *et al.*[3] report spectroscopic observations of a stellar stream — a thin and elongated group of stars — that they identify as the remnant of the most-metal-poor globular cluster discovered so far, providing a unique perspective on the earliest epochs of galaxy assembly.

The chemical composition of the stars in a globular cluster is a key observable property that links them to their natal galaxies. The stars in a cluster were born together, in the same parent molecular gas cloud, and have highly similar chemical compositions[4]. More specifically, all the stars in a cluster have the same iron content, which in turn reflects the iron content of the galaxy in which they formed.

Throughout cosmic history, iron has been produced in supernova explosions, which chemically enrich the gas around them; this gas is then used to make future generations of stars. The enrichment cycle proceeds more rapidly in galaxies that have higher masses and star formation rates, so that the metallicity (the abundance of elements that have atomic masses greater than that of helium, often measured simply as the iron content) increases not only with time, but also with galaxy mass[5]. This galaxy mass–metallicity relationship is predicted to have changed over time only very slowly during the early history of the Universe[6], when globular clusters formed. The metallicity of a globular cluster can, therefore, be used to determine the mass of the galaxy in which it formed.

The galaxy mass–metallicity relationship indicates that there must be a metallicity below which early-Universe galaxies contained fewer stars than typical globular clusters do, suggesting that those galaxies might not have been able to form such massive clusters. Theoretical models[7] predict that this limit corresponds to a metallicity of about 0.3% of the metallicity of the Sun (although this need not be a sharp limit, because the metallicities of individual galaxies are scattered around the median galaxy mass–metallicity relationship). At this metallicity, early-Universe galaxies should have contained just a few hundred thousand stars, similar to the number of stars in typical, present-day globular clusters.

Observations do indeed reveal a dearth of globular clusters with metallicities less than 0.3% of the solar value[8]. Such globular clusters are thought to have existed, but they were necessarily less massive and less well bound by gravity than were higher-metallicity clusters. As a result, these extremely metal-poor stellar clusters are thought to have been destroyed by tidal forces from their host galaxy over cosmic time[7]. If this hypothesis is correct, the remnants of extremely metal-poor globular clusters might still orbit the Milky Way.

Wan *et al.* used the observations of the Southern Stellar Streams Spectroscopic Survey to measure the metallicities of 11 stars in the Phoenix stellar stream, a group of stars that orbits the Galactic Centre at a distance of about 20,000 parsecs[9] (Fig. 1). Surprisingly, the researchers measured extremely weak absorption lines for calcium (which closely correlates with the iron content of stars) in the stellar spectra, indicating an average metallicity of just 0.20 ± 0.03% of that of the Sun. Moreover, the metallicities of the stars are uniformly low, with a star-to-star variability similar to the measurement uncertainty. This spread of metallicities is much lower than that of dwarf galaxies, implying that the Phoenix stream is not the remnant of such a system. Instead, it indicates that the stars in the Phoenix stream were born in the same stellar cluster. Their unusually low metallicities imply, excitingly, that the cluster must have formed at a time when its natal galaxy was one of the very lowest-mass galaxies.

Like all important discoveries, the measured metallicity of the Phoenix stream generates more questions than it provides answers. Although it is only a single object, it represents

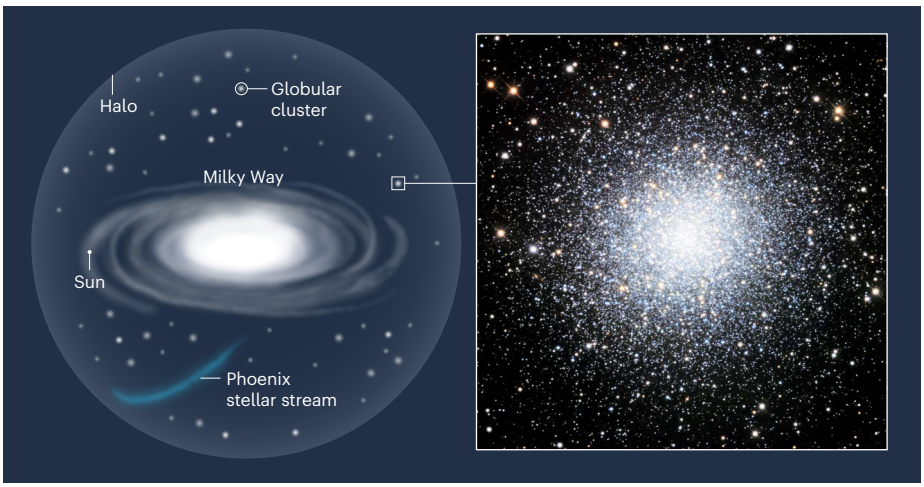

IMAGE: ROBERT GENDLER/SPL

Figure 1 | The Phoenix stream orbiting the Milky Way. Galaxies such as the Milky Way are surrounded by more than 100 globular clusters — systems of about 100,000 stars packed into regions of just 10 parsecs in diameter, in the galaxy's halo region. Wan *et al.*[3] report that a thin streak of stars known as the Phoenix stellar stream is a globular cluster that was disrupted by the Milky Way's gravity. The abundance of metals (elements heavier in atomic mass than helium) in the stream is significantly lower than that in any surviving globular cluster in our Galaxy. This discovery confirms theoretical predictions that the Milky Way hosts the debris of a vanished population of extremely metal-poor clusters, which formed early in the history of the Universe.

the first direct evidence that the Milky Way once hosted a population of extremely metal-poor globular clusters. How numerous were those clusters? The discovery of more such remnants would herald a new and exciting way of reconstructing the demographics of the lowest-mass galaxy population that contributed to the assembly of the Milky Way.

By estimating the initial masses of such extremely metal-poor globular clusters, future studies could potentially determine what fraction of their natal galaxy's mass these clusters constituted, thereby revealing how the lowest-mass galaxies formed and evolved in the early Universe. Direct observations of star-forming proto-galaxies in the early Universe could be made using NASA's James Webb Space Telescope, due to launch in 2021, and would independently test the results of such studies[10]. Finally, by comparing the orbital kinematics of fossil stellar streams with those of groups of globular clusters thought to have arrived in the Milky Way during the same accretion event[11], it might be possible to assign the streams to specific progenitor galaxies of the Milky Way.

Thanks to all-sky surveys that can detect stars with extremely low surface brightness and obtain exquisite stellar kinematics, there has been a surge in the discovery of fossil stellar streams[12], many of which probably represent the remnants of tidally disrupted globular clusters. Wan and colleagues' discovery makes it a priority to obtain accurate metallicities for all of these streams. Who knows how many relics like the Phoenix stream might be hiding in the Milky Way's halo. Now that the first one has been found, the hunt is on.

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Medical research

An umbrella approach to test lung cancer therapies

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A clinical trial has tested the use of gene-sequencing results for lung cancer to match patients to targeted therapies. Some paired treatments were a good fit, but others did not succeed, for reasons that will require further exploration. **See p.807**

Genomic complexity is a hallmark of many cancers. Within this complexity, the identification of specific DNA alterations for which targeted therapeutic options are available has opened the door to a new era of genome-driven cancer treatment. Approved targeted therapies are in clinical use for a long list of cancer-related genomic alterations, on the basis of evidence that matched treatments lead to improvements in survival times and response (a decrease in tumour size). However, there is an ongoing need to find therapeutic matches for other, unvetted, genomic changes associated with cancer. On page 807, Middleton *et al.*[1] report a clinical trial undertaken using a framework termed an umbrella trial[2] to search for such treatment pairings. In this sort of trial, under the 'umbrella' of a single type of cancer investigated — lung cancer, in this case — the effectiveness of different targeted therapies is investigated in 'arms' of the trial, each corresponding to a tumour subset that harbours specific genomic alterations of interest.

Middleton and colleagues' research is part of the National Lung Matrix Trial. For this study, the authors focused on non-small cell lung cancers from 5,467 people in the United Kingdom. Cancer samples were tested for tumour-associated genomic alterations that could be assigned to one of the 22 trial arms. If an alteration was identified, people could be matched to a specific targeted therapy. Each alteration–therapy pairing was chosen on the basis of preclinical data from laboratory studies supporting the match. Data were reported from 288 patients (14% of the eligible population who were matched to a therapy), representing 19 of the 22 arms. The authors used a statistical method called Bayesian analysis to assess the clinical outcomes. This separated the trial results into two groups, depending on how successful the treatment outcomes were.

Those in the first group were successful matches. Certain paired treatments resulted in high response rates (more than 60% of the people treated had substantial tumour shrinkage) and durable progression-free survival (no signs of tumour growth for more than 12 months). For example, the drug osimertinib, which inhibits the receptor protein EGFR, successfully treated lung cancers associated with an alteration of a threonine to a methionine amino-acid residue (T790M) in EGFR. The drug crizotinib, which inhibits particular receptor proteins including ROS1 and MET, provided effective treatment (Fig. 1) for tumours with abnormalities in either of the genes *ROS1* or *MET*. These results are consistent with previous clinical data[3–5], which has led to the approval or recommendation of these molecularly targeted therapies in national treatment guidelines. Middleton and colleagues' results confirm the power of these mutations to predict treatment outcomes, and also highlight the transformative effect of genome-based personalized medicine in anticancer health care. The success of some personalized approaches has driven the increased adoption of DNA sequencing to identify genomic changes that then direct precision treatments in routine practice.

By comparison, outcomes were less successful in the second group. Response rates of less than 10% and short progression-free survival times were observed for most types of the paired treatments tested. Several testing arms were abandoned because they were ineffective. In cancers with mutations associated with alterations in the progression of the cell cycle, treatment with a drug that inhibits the key cell-cycle enzymes CDK4 and CDK6 achieved only a 1% response rate. The response rate was 3% in cancers with alterations in the PI3K signalling pathway that were treated with inhibitors of the proteins mTOR or AKT, which act in this pathway. A low response rate, of 7%, was found in cancers with alterations in another signalling pathway, the RAS pathway, that were treated with inhibitors of proteins that are activated by RAS (MEK, mTOR or CDK4/6).

The highest response rate in this second