other set consisted of stem-cell-like T cells that Jansen *et al.* demonstrate give rise to cytotoxic CD8 T cells that help to promote an effective antitumour immune response. Stem-cell-like T cells were present only at very low levels in tumours with low levels of T-cell infiltration, whereas tumours with high levels of T-cell infiltration had high levels of the stem-cell-like T cells.

To gain further insight, the authors assessed cellular gene-expression profiles, and analysed epigenetic modifications — types of modification to DNA and its associated proteins that can affect gene expression. They found that, compared with the exhausted cytotoxic CD8 T cells, the stem-cell-like T cells express distinctive immune-signalling molecules called chemokines that are correlated with better patient survival, along with higher levels of key co-stimulatory molecules (which are essential for T-cell differentiation into cytotoxic T cells). Previous analyses[9,10] of T cells revealed a pattern of progressive steps in epigenetic modification as stem-cell-like T cells give rise to cytotoxic CD8 T cells and then eventually become exhausted.

The epigenetic-modification profile of T cells in tumours can be profoundly influenced by factors in the tumour microenvironment, which can affect the ability of T cells to function as stem cells[11,12]. For example, the concentration of potassium ions in a tumour modulates epigenetic modifications that influence whether T cells are in the stem-cell-like state that is needed for them to give rise to cytotoxic CD8 T cells[11,12]. The effect of the tumour microenvironment on the development of cancer-targeting T cells is unclear, and should be a subject for future studies.

Jansen and colleagues noted that the higher than normal expression of chemokines and chemokine-binding receptors in the stem-cell-like T cells is similar to that seen in cells in the microenvironment of lymph vessels — structures through which immune cells move and which support T-cell activation and survival. The authors' analyses demonstrate that stem-cell-like T cells are located in niches in tumours near lymph vessels (Fig. 1), and are confined to dense zones of antigen-presenting cells, which can prime T cells to target tumours. The discovery of these niches by Jansen and colleagues now reveal how stem-cell-like T cells can be maintained in tumours in a functional state capable of generating cytotoxic T cells.

The authors observed a correlation between the presence of protein markers of stem-cell-like T-cell niches and longer, progression-free survival of the people assessed in the study. By contrast, other common ways of assessing an immune response in tumours, such as the expression of the immune-checkpoint protein PD-L1, did not reveal a correlation with progression-free cancer survival.

Previous research[13] identified stem-cell-like T cells that express rising levels of immune-checkpoint molecules as they progress towards forming cytotoxic CD8 T cells that eventually become exhausted[14]. In one example[13], approaches to block the immune-checkpoint protein PD-1 caused a burst of proliferation in stem-cell-like T cells that express the TCF7 protein. Similarly, in a skin cancer called melanoma, people whose CD8 T cells express TCF7 have a better clinical outcome if they receive immunotherapy to block immune-checkpoint proteins[15]. These results suggest that people whose tumours cannot be removed by surgery might benefit from therapy that blocks immune-checkpoint molecules, if their tumours contain stem-cell-like T cells.

Jansen and colleagues' work raises questions about how the stem-cell niches are generated and maintained, and whether tumours might act on them to evade destruction by the immune system. The discovery that resident stem-cell-like T cells exist in specialized niches in tumours suggests that clinical leveraging of such cells to increase the immune infiltration of tumours, together with immunotherapy to boost exhausted T cells, might unleash T-cell responses to aid the success of anticancer treatment.

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In Retrospect

Superconductivity mystery turns 25

N. Peter Armitage

In 1994, an unconventional form of superconductivity was detected in strontium ruthenate. The discovery has shed light on the mechanism of unconventional superconductivity at high temperatures.

Superconductivity is an effect in which a material's electrical resistance vanishes and any magnetic field is expelled below a transition temperature. Despite the remarkable phenomenology, this behaviour is actually quite common: almost half the elements in the periodic table are superconductors[1], albeit at temperatures near or below the extremely low one at which helium gas liquefies (about 4 kelvin). Since Nobel-prizewinning work in the late 1950s, we have had a successful theory[2] of superconductivity in these conventional systems. Electrons bind into 'Cooper pairs' that have isotropic (direction-independent) properties through an interaction with vibrations of surrounding ions. Over the past 40 years, researchers have looked for unconventional superconductors that involve different pairing interactions, such as magnetic ones. In 1994, Maeno *et al.*[3] reported one of the clearest examples of unconventional superconductivity, in strontium ruthenate near 1 K.

Understanding unconventional superconductors requires identifying both the pairing interaction and the order parameter — a quantity that reflects the interaction and the macroscopic, typically anisotropic, properties of the unconventional superconductivity. The most substantial development in this area of study was the discovery of superconductivity in layered copper-oxide compounds (known as cuprates) in the mid-to-late 1980s. The phenomenon was detected[4] at the unprecedentedly high temperature (for that time) of 30 K, which led to a worldwide effort to understand the mechanism of cuprate superconductivity.

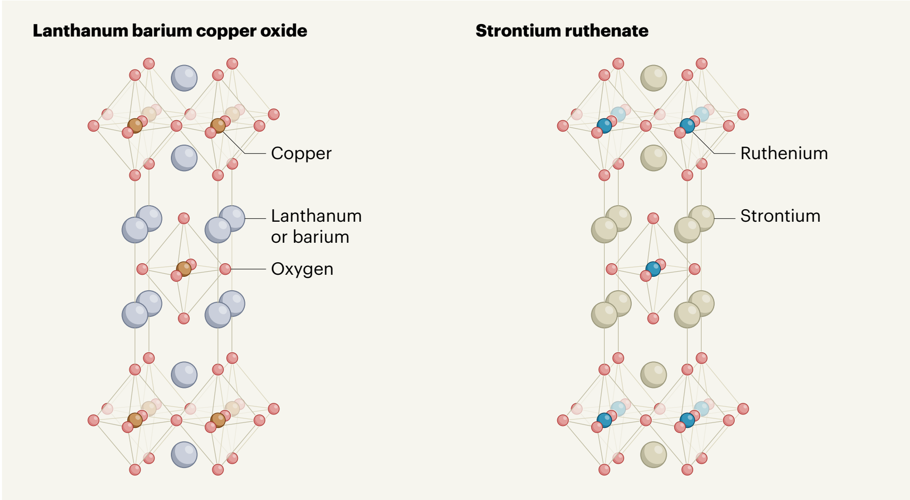

Figure 1 | Crystal structures of two superconductors. In 1986, lanthanum barium copper oxide was found[4] to superconduct (transport electricity without resistance) at the relatively high temperature of 30 kelvin. Eight years later, Maeno *et al.*[3] reported the discovery of superconductivity in strontium ruthenate at about 1 K. Although these two materials have the same crystal structures at high temperatures, their superconductivity mechanisms are likely to be markedly different.

The cuprates are now thought to have a highly anisotropic order parameter, and to have Cooper pairs made of electrons that have anti-aligned spins (intrinsic angular momenta). Such spins form non-magnetic states that have even parity, which means that the wavefunction of the state does not change sign if the signs of the spatial coordinates are flipped. Cuprate superconductivity has been proposed[5] to arise from an interaction of electrons with antiferromagnetic spin fluctuations (antiferromagnetism is a form of magnetism in which spins are anti-aligned with their neighbours). However, no theory has yet gained general acceptance.

One method that has been used to try to understand these compounds is to search for superconductivity in materials that are related in some way to the cuprates. In this way, it might be possible to identify the structural, electronic or magnetic features that are essential for the materials' high transition temperatures. In particular, the cuprate discovery led to a huge effort to investigate compounds that contain transition metals other than copper.

It was against this backdrop that Maeno and colleagues found superconductivity in strontium ruthenate, at about 1 K. This was decidedly not high-temperature superconductivity. But the work caused tremendous excitement because it described the detection of superconductivity in another layered transition-metal oxide – and in a material that has the same crystal structure as the original superconducting cuprate, lanthanum barium copper oxide[4] (Fig. 1). Almost immediately, it was realized that there were both similarities and differences between the cuprates and strontium ruthenate.

One main difference is that pure compounds of the cuprates (such as lanthanum copper oxide) are antiferromagnetic insulators and require the substitution of atoms (such as barium for lanthanum) to conduct electricity. By contrast, pure strontium ruthenate is strongly metallic. A striking aspect of the superconducting cuprates is that their metallic state at temperatures above the transition temperature seems to be even more unconventional than their superconducting state. The metallic state is thought to be the result of strong interactions between electrons. A radically new theory of 'strange metals' might be needed to understand the high-temperature metallic state and thereby also the superconducting state that forms from it[6]. In strontium ruthenate, electron interactions are also strong, but they do not change the fundamental character of the metallic state.

This aspect, and the fact that related materials in the larger ruthenate family exhibit ferromagnetism (a form of magnetism in which spins are aligned with their neighbours), led to the proposal[7] in 1995 that superconductivity in strontium ruthenate could be an analogue of the superfluid A phase in helium-3. In this phase, the compound exists as a superfluid (a zero-viscosity liquid) made from odd-parity Cooper pairs of neutral helium-3 atoms that have aligned spins[8]. The proposal gained much support, both for the compelling science that suggests it and for the beautiful idea that there could be an odd-parity superconductor driven by ferromagnetism in the same way that the cuprates might be even-parity superconductors driven by antiferromagnetism. Of course, the "great tragedy of Science [is] the slaying of a beautiful hypothesis" by experimental facts[9]. Experiments always have the final say.

The exciting science, the ability to grow large, extremely pure crystals and an exceedingly collaborative research community pushed superconducting strontium ruthenate forward as a highly active topic of investigation. Moreover, there was the abiding sense that it should be possible to unambiguously determine the nature of the material's unconventional order parameter, because its high-temperature metallic state – unlike that of the cuprates – seemed to obey the conventional theory of metals. This determination is an ongoing saga, with field-changing results coming even this year. Notable early work showed evidence for unconventional odd-parity pairing of electrons in nuclear magnetic resonance (NMR) spectroscopy[10], and for spontaneous generation of magnetism[11,12] consistent with the proposal outlined above.

In the past five years, sophisticated measurements of strontium ruthenate have failed to show an odd-parity superconducting transition splitting into two under mechanical strain, as had been predicted[13]. These measurements, along with a reinvestigation using NMR spectroscopy[14], have given compelling evidence that the superconductivity is likely to be even parity. But this even-parity state is inconsistent with the experiments that showed the presence of spontaneous magnetism. Therefore, the nature of unconventional superconductivity in strontium ruthenate must be considered unresolved.

This problem, together with that of the cuprates, has pushed theory, experiment and materials synthesis forward in directions that would have been unimaginable when superconductivity in these compounds was discovered. And as is so often the case, many of the ideas that scientists have grappled with in the context of a hard problem have turned out to be incredibly influential in areas well beyond their original scope. In this particular case, important cross-fertilizing connections can be made with topological insulators (bulk electrical insulators that have conducting surfaces) and quantum computation[15]. The research community is still hard at work on the mystery of strontium ruthenate. Experiments always have the final say.

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