to inhibit the isoprenoid pathway, and thereby block a source of crucial microbial molecules, with the stimulation of an immune response due to the resulting accumulation of HMBPP, which is a highly potent signal that drives the activation of Vγ9Vδ2 T cells.

The authors took a structure-directed, *in silico* screening approach to identify possible IspH inhibitors, and tested around ten million compounds. Strikingly, 2 of the 24 most promising compounds inhibited IspH with high potency (at nanomolar concentrations) when tested *in vitro*. Further optimization of the molecular structures of these compounds improved their affinity for IspH compared with the affinity of IspH for its natural substrate, HMBPP.

However, the physical characteristics of the inhibitors were expected to limit their entry into bacteria. To circumvent this, Singh *et al.* adopted a strategy previously used to enable drugs to pass through membranes. This method generates what is called a prodrug – an inactive version of the drug (in this case, an ester derivative of the inhibitor) that can be taken up easily by cells and then metabolized into the active version. Crucially, unlike previous work[3,6] that described IspH inhibitors, this prodrug approach allowed such inhibitors to successfully enter bacteria. The authors confirmed that the drugs inhibited enzyme breakdown of HMBPP, hindering essential microbial processes, and that this resulted in the killing of a range of different bacteria, including *Escherichia coli*, without notable signs of drug toxicity to mammalian cells.

In keeping with the ability to inhibit HMBPP breakdown by IspH, prodrug use also led to the *in vitro* activation and proliferation of HMBPP-responsive Vγ9Vδ2 T cells during bacterial infection of samples of human peripheral blood mononuclear cells. This result indicates the potential of such prodrugs to act as dual-action immunoantibiotics. When tested *in vivo* in mice, the prodrugs induced direct antimicrobial effects and controlled bacterial infection through a process mediated by γδ T cells.

Singh *et al.* explored two key aspects of the potential of these new compounds to combat antimicrobial resistance. First, the researchers present *in vitro* and *in vivo* data indicating direct bactericidal effects on a variety of clinically isolated harmful bacteria that are resistant to current antibiotics, including multidrug-resistant microbes. The authors observed that the IspH inhibitors had greater ability to kill multidrug-resistant microbes than do the current best-in-class antibiotics. Second, using an *in vitro* model system, Singh and colleagues showed that bacteria did not acquire resistance to the IspH inhibitors in the presence of γδ T cells. But in the absence of these T cells, drug resistance occurred over a similar timescale to that observed for conventional antibiotics. These results emphasize the potential advantage that immunoantibiotics might have for tackling the emergence of drug resistance.

Singh and colleagues' study is a highly promising proof-of-concept that a new class of antimicrobial can be developed with a dual mechanism of action. Leveraging Vγ9Vδ2 T cells is appealing because of the therapeutic advantages offered by harnessing this approach. These cells, present in humans from early in life, are capable of highly potent defence functions[10], and, unlike many other types of T cell, don't depend on the recognition of major histocompatibility complex (MHC) molecules, which differ between individuals. Encouragingly, the pathway containing IspH is shared by a diverse range of clinically relevant disease-causing microorganisms, suggesting that such antimicrobial drugs could have broad applicability.

Antibiotic approaches using monotherapy (a single type of drug) have often resulted in the emergence of drug resistance, whereas combination therapies using multiple drugs, operating through different mechanisms of action, have been more fruitful and have met with relatively fewer resistance problems. This 'two-in-one' mechanism underpinning Singh and colleagues' strategy might, therefore, allow the targeting of existing multidrug-resistant microbes, as well as decrease the chances of resistance emerging. Although the subsequent steps on the road to drug development can often be challenging, the progress of this exciting class of compound towards clinical application will undoubtedly be followed with interest.

Youcef Mehellou is in the School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff CF10 3NB, UK. **Benjamin E. Willcox** is at the Institute of Immunology and Immunotherapy, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.
e-mails: mehellouy1@cardiff.ac.uk; b.willcox@bham.ac.uk

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Experimental physics

Helium nucleus measured with record precision

Wilfried Nörtershäuser

The size of the helium nucleus has been determined using exotic helium atoms in which one electron has been replaced with its heavier cousin, a muon. The result sheds light on a decade-old puzzle regarding the proton radius. **See p.527**

Helium is the second most abundant element in the Universe, after hydrogen. The nucleus of its most common isotope, helium-4, consists of two protons and two neutrons and is called the α-particle. This particle is more compact than other light nuclei – for instance, it is about 20% smaller than the nucleus of the hydrogen isotope deuterium[1], which contains only one proton and one neutron. The exact size of the α-particle is of particular interest because of a decade-old experiment that suggested the radius of the proton is considerably smaller than had been thought[2]. This result led to much speculation about possible missing pieces in the standard model of particle physics[3]. On page 527, Krauth *et al.*[4] report a determination of the α-particle size that strongly restricts such explanations and provides a benchmark for nuclear-structure theory.

The authors measured the α-particle size using a technique known as laser spectroscopy. This approach is based on the fact that atoms can emit and absorb light only at discrete frequencies, which are determined by the details of the atomic structure – namely, the interaction of the negatively charged electrons with the positively charged nucleus and with each other. Protons make up the charged component of the nucleus. The number of protons dictates the element, and their spatial extent is characterized by a property called the nuclear charge radius, which defines the size of the nucleus.

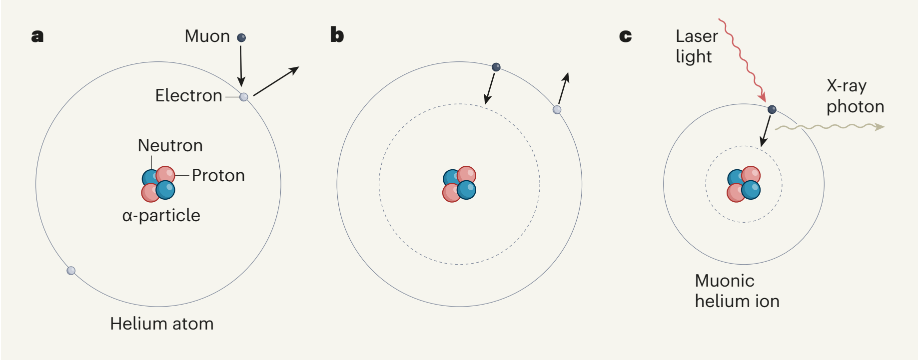

Figure 1 | Measuring the size of the helium nucleus. a, The nucleus of the helium atom, also known as the α-particle, comprises two protons and two neutrons, surrounded by two electrons. Krauth *et al.*[4] carried out an experiment in which a muon (a heavier cousin of the electron) ejected and replaced one electron in a helium atom. **b**, This muon gradually moved closer to the nucleus, and ejected the second electron from the atom. **c**, The result of this process was a muonic helium ion — a positively charged ion composed of an α-particle and a muon. The authors fired laser light at this ion shortly after its formation. In some cases, the muon then moved even closer to the nucleus and produced a single X-ray photon. By analysing this X-ray emission, the authors determined the size of the helium nucleus with unprecedented precision.

The exact frequencies of absorption and emission depend slightly on the charge radius. Therefore, this property can be determined if the atomic structure is understood well enough for a sufficiently accurate calculation of all other factors that affect the frequencies. Although there has been substantial progress in this field, such determinations are currently possible only for two-body systems — namely, a single electron or similar particle bound to a nucleus. Adding another particle leads to an enormous increase in complexity, and the quantum-mechanical calculations are currently unmanageable. Consequently, laser spectroscopy has previously been used to directly extract the sizes of only the proton[2] and the deuterium nucleus[5].

Krauth and colleagues used a clever method to apply this approach to the α-particle. They injected negatively charged muons — heavier cousins of electrons — into a low-density helium gas. Collisions between the muons and the gas caused the muons to lose energy, and allowed a given muon to replace one of the two electrons in a helium atom (Fig. 1). This muon then lost more energy and moved closer to the atomic nucleus. During this process, the second electron was ejected from the atom, generating a positively charged ion composed of an α-particle and a muon.

The atomic structure of this muonic helium ion can be determined theoretically with extremely high precision. Moreover, because the muon has approximately 200 times the mass of an electron (go.nature.com/3twyjba), it is bound roughly 200 times closer to the helium nucleus than an electron would be. As a result, laser spectroscopy is about eight million times more sensitive to the α-particle size when a muonic helium ion, rather than an ordinary, singly charged helium ion, is used. This remarkable sensitivity justifies the huge experimental effort that was required for the current work.

A muon exists for only two microseconds before it decays into an electron and elusive particles called neutrinos (go.nature.com/3twyjba). Therefore, Krauth *et al.* had to detect each individual muon that entered their experimental chamber and could potentially lead to the formation of a muonic helium ion. They then needed to fire a laser that had a well-defined frequency within one microsecond of this muonic-helium-ion formation (Fig. 1). Finally, they had to detect a single X-ray photon that was emitted from the ion after successful laser excitation, as well as the electron generated by the decay of the muon. At the correct laser frequency, about 8 of these events were detected per hour, and needed to be distinguished from roughly 50,000 events associated with other atomic processes.

The result of this heroic effort is a determination of the α-particle radius with a precision of just one attometre (10^{-18} m), which is roughly 1,000th the size of the proton radius. The value is about five times more precise than measurements based on electron–helium scattering[6]. Although this finding might sound rather academic, it is important for several areas of fundamental physics. In particular, for the first time, the results from laser spectroscopy of muonic atoms and electron scattering are in excellent agreement, which was not the case for the proton or the deuterium nucleus.

For the proton radius, the value obtained[2] from muonic hydrogen was about 4% smaller than the previously accepted value obtained from other approaches, including electron scattering and laser spectroscopy of ordinary hydrogen. This proton-radius puzzle led to many theories about processes involved in the interaction between muons and other particles that are not contained in the standard model[3]. However, the agreement in the case of helium rules out several of these speculative processes because there is no reason why they should not occur in muonic helium, as well as in muonic hydrogen and muonic deuterium.

Krauth and colleagues' measurement can also be used to improve *ab initio* nuclear-structure models. Whereas atomic structure is determined by the well-understood electromagnetic interaction, nuclear structure is governed by the strong nuclear force, which is much more complex. The protons and uncharged neutrons in the nucleus, known collectively as nucleons, have a complicated internal structure. Each nucleon is made up of three fundamental particles, called quarks, that are tied together by the strong force. The nucleus itself is bound by the residual strong force that persists beyond the borders of the nucleons and acts only within distances of less than one femtometre (10^{-15} m).

Physicists do not yet have a theory that can explain nuclear structure on the basis of a description at the quark level. Instead, they rely on *ab initio* nuclear-structure models that consider 'effective' forces between individual nucleons. The formulation of these models requires knowledge of some key parameters that describe light nuclear systems. The charge radius of the α-particle that has now been obtained can serve as such a parameter.

The authors' result also provides a benchmark for planned experiments that will enable precise measurements of nuclear charge radii of elements heavier than helium. This goal will be achievable once required quantum-mechanical calculations for two-electron (helium-like) systems are available. Theoretical[7] and experimental[8] efforts in this direction are under way. The measured charge radius of helium will serve as an ideal test case for such calculations. If agreement is obtained, it should then be possible to determine the charge radii of at least all the stable isotopes from lithium to nitrogen by carrying out laser spectroscopy on their respective helium-like ions. Such ions can be produced in small laboratory experiments with much less effort than is required for studies of the corresponding muonic systems at large particle-accelerator facilities.

Wilfried Nörtershäuser is at the Institute for Nuclear Physics, Technical University of Darmstadt, 64289 Darmstadt, Germany.
e-mail: wnoertershaeuser@ikp.tu-darmstadt.de

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