goals of the collaboration is to determine the intrinsic magnetic moment of the antiproton. This quantity can be calculated to extremely high precision using the standard model of particle physics — the current explanation of the Universe's particles and forces.

In 2017, Smorra *et al.* made an ultraprecise measurement of the antiproton's magnetic moment (to one part in a billion)[9], constraining many theories of physics beyond the standard model. The key to their method was the simultaneous measurement of the spin precession and a quantity called the cyclotron frequency, which describes the cyclical motion of an antiproton in a trap. This task was challenging, because it required meticulous control of a device known as a magnetic bottle to non-destructively determine the spin state of the antiproton. The group's measurement required hundreds of experiments, each of which lasted for almost an hour, taking place over several months.

In the current paper, Smorra and colleagues, who include members of the BASE collaboration, analysed the data from these experiments. They proposed that waves corresponding to axion dark matter that oscillated at frequencies between $10^{-8}$ and $10^{-2}$ hertz would shift the spin-precession frequency in a small but measurable way if the axion coupling to antiprotons was sufficiently strong. Although no axion signal was detected, Smorra *et al.* constrained the parameter that quantifies axion–antiproton interactions to values greater than 0.1–0.6 gigaelectronvolts in the axion mass range from $2 \times 10^{-23}$ eV to $4 \times 10^{-17}$ eV (Fig. 1). These limits are as much as $10^5$ times stronger than astrophysical constraints (as estimated by the authors), which consider how axions might have been produced by antiprotons in the supernova 1987A.

Future work should aim to further constrain the axion–antiproton coupling and to look for evidence of interactions between axion dark matter and other forms of antimatter, such as positrons (the antiparticles of electrons). One key finding from these studies could be the observation that dark matter couples to antimatter in different ways from its couplings to ordinary matter — a result that might help to explain why there is a predominance of matter over antimatter in the Universe.

Smorra and colleagues have highlighted a growing trend in high-energy physics, whereby exquisitely precise measurements are used to nail down fundamental particle parameters and to look for evidence of physics beyond that of the standard model. Axion dark matter, which has a vast potential mass range and extraordinarily weak predicted couplings, has gone through a renaissance in terms of innovative detection techniques. The search for a preferred coupling of axion dark matter to antimatter (as opposed to ordinary matter) is an exciting prospect, and could prove to be the key to unlocking several mysteries in cosmology as technology improves.

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Medical research

# 'Undruggable' cancer protein targeted

**Roy S. Herbst & Joseph Schlessinger**

A molecule has now been characterized that acts to inhibit a cancer-causing form of KRAS protein and stimulate the immune system. The inhibitor is one of the first of its kind to show anticancer activity in the clinic.

Mutations in the gene *KRAS* are the most frequent drivers of tumour development across the spectrum of human cancers[1]. Despite this prevalence, mutant KRAS protein has remained an intractable therapeutic target. Writing in *Nature*, Canon *et al.*[2] describe a small molecule that binds one form of mutant KRAS with high specificity and sensitivity, inhibiting the protein. The authors use animal models to analyse how the inhibitor works, and show that it can shrink tumours in patients. This is among the first evidence of a clinical response to a specific KRAS inhibitor.

KRAS is an enzyme that controls a signalling pathway crucial for cell growth, differentiation and survival. The inactive protein is bound by a guanosine diphosphate (GDP) molecule — replacement of GDP by guanosine triphosphate (GTP) facilitates conformational changes in KRAS that allow the enzyme to bind and activate downstream effector molecules (Fig. 1a). Nearly all cancer-promoting KRAS mutations prevent GTP breakdown, leaving KRAS in a permanently active state[3] (Fig. 1b). One such mutation involves substitution of a glycine amino-acid residue for a cysteine residue. The resulting mutant protein, $KRAS^{G12C}$, is found infrequently in various cancers. It is most prevalent in lung cancer, and is responsible for approximately 12% of non-small cell lung cancers[4,5].

In the past few years, several irreversible small-molecule inhibitors have been developed[6–8] that bind covalently to a pocket in GDP-bound $KRAS^{G12C}$ to inhibit GTP binding. These inhibitors successfully prevent activation of the protein in animal models, but none has had any effect on tumours in patients. Canon *et al.* characterized another small-molecule inhibitor, AMG 510, that forms a covalent bond with GDP-bound $KRAS^{G12C}$ (Fig. 1c). AMG 510 has similar structural properties to one of the previous inhibitors, ARS-1620, but has one key difference — it binds a structure called a cryptic surface groove that forms in $KRAS^{G12C}$, and so recognizes the mutant protein with high specificity.

The authors showed that AMG 510 inhibits the exchange of GDP for GTP more potently than does ARS-1620. Moreover, AMG 510 strongly inhibits phosphorylation of the protein ERK (a known effector of KRAS activity) in cells harbouring $KRAS^{G12C}$, and impairs cell proliferation.

Next, Canon and colleagues turned to mice carrying $KRAS^{G12C}$ tumour cells taken from patients. Treatment with AMG 510 at a concentration of 100 milligrams per kilogram of body weight resulted in tumour regression, but the cancer subsequently returned. At 200 mg $kg^{-1}$, however, AMG 510 triggered permanent tumour regression in eight out of ten mice. Of note, the robust potency with which AMG 510 triggers cell death raises the possibility that it becomes covalently attached to other cysteine-containing proteins, in addition to $KRAS^{G12C}$ — something that should be investigated in future, if the molecule is to be regularly used in patients.

Interestingly, mice showed a durable

response to the 200 mg kg$^{-1}$ AMG 510 treatment only if they had a functioning immune system (known as immune competence). In mice lacking the immune cells called T cells, tumours returned. This led the authors to ask whether it would be possible to combine AMG 510 with an immunotherapy called anti-PD-1 therapy, which harnesses the immune system to combat cancer. Indeed, treatment with AMG 510 at 100 mg kg$^{-1}$ combined with anti-PD-1 therapy resulted in complete tumour regression in nine out of ten immune-competent mice.

Canon and colleagues found that AMG 510 treatment boosted the expression of inflammatory molecules called chemokines in the animals' tumours. This was associated with an increase in infiltration of the tumours by T cells and dendritic cells, both of which are involved in the immune system's response to cancer. Furthermore, when the authors reintroduced KRAS$^{G12C}$ cancer cells to mice that had been cured by the combination treatment, no tumours grew. This suggests that the combination treatment established a long-term T-cell response to KRAS$^{G12C}$ tumour cells. The researchers could also improve the cure rate and efficacy of AMG 510 treatment by combining it with a standard chemotherapy drug or with a drug that inhibits the protein MEK, which acts downstream of KRAS.

These data served as the cornerstone for AMG 510 trials in the clinic. Canon *et al.* describe clinical results for four people who have non-small cell lung cancer. All four harbour the KRAS$^{G12C}$ mutation and were treated with AMG 510. This is a very small number of patients, but the results are promising. In two of the four patients, the cancer stopped growing. The other two showed a partial response — their tumours shrank by 34% and 67% after six weeks. At the point at which the authors stopped collecting data, these patients had been receiving AMG 510 for 39 and 26 weeks, respectively, and were still taking the drug.

Canon and colleagues' findings are supported by more clinical results from their group, presented at conferences earlier this year[9,10]. The conference proceedings suggest that AMG 510 has broad activity in lung cancer, with tumour shrinkage observed in four patients, and cessation of tumour growth in several more. Of note, however, these data were reported at an early stage of the trial, and the results for people treated for colon cancer look less promising at this early stage. It will be interesting to discover the long-term outcomes of the patients treated by Canon and colleagues. It will also be important to investigate whether combination strategies might be effective if these patients develop resistance to AMG 510 treatment.

Many questions remain. Could AMG 510 be more suitable as the first-line treatment for cancers involving KRAS$^{G12C}$ than the current standard treatments, which involve chemotherapy or immunotherapy? Could the new inhibitor be effective when cancers have spread to the brain (a major site for secondary tumours in KRAS-mutated cancer), which is associated with a high chance of death? The optimal dose of AMG 510 and any toxicity associated with that dose remain to be determined. In addition, it will be interesting to see how this molecule compares with other such inhibitors in the clinic, including a recently reported[11] small molecule called MRTX849.

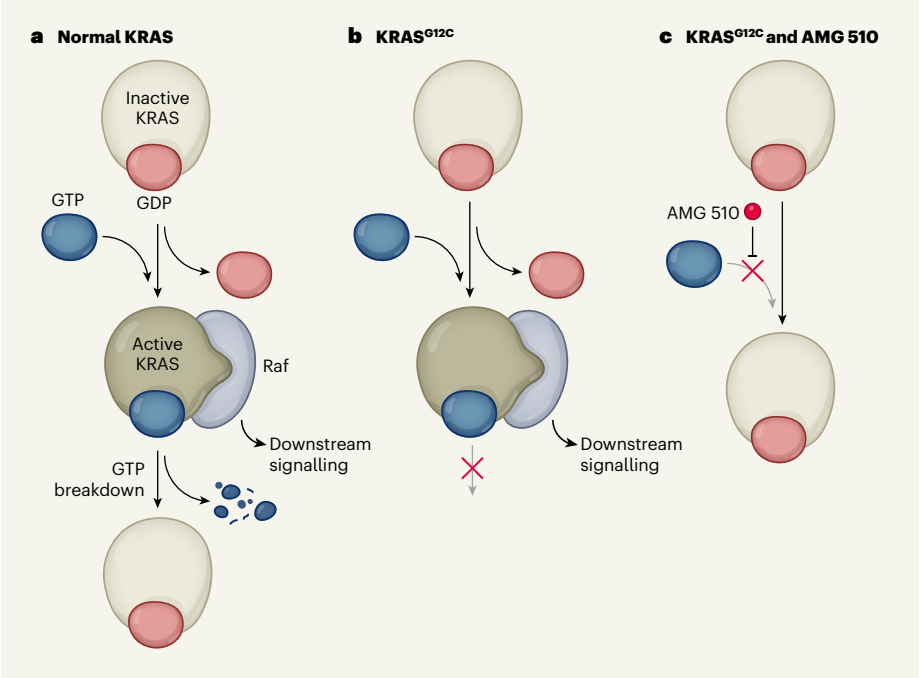


**Figure 1 | Inhibitor blocks the action of a mutant KRAS protein.** **a**, KRAS is activated in normal tissues by replacement of a bound guanosine diphosphate (GDP) molecule with guanosine triphosphate (GTP). This exchange leads to conformational changes in KRAS, to binding of the protein Raf and so to activation of downstream signalling pathways that control cell growth and differentiation. GTP is broken down to GDP to inactivate KRAS once more. **b**, A mutant form of KRAS, dubbed KRAS$^{G12C}$, prevents GTP breakdown, rendering the protein permanently active — this, in turn, can lead to cancer. **c**, Canon *et al.*[2] have characterized a small molecule, AMG 510, that interacts with KRAS$^{G12C}$ to prevent GTP binding in the first place, thus inhibiting the protein's cancer-promoting activity.

**"The combination treatment established a long-term T-cell response to tumour cells carrying the mutant protein."**

Nonetheless, Canon and colleagues' results provide a solid proof of concept that AMG 510 treatment results in cancer-cell death, and highlight a putative mechanism by which the molecule acts. Moreover, the work validates the assumption that it is KRAS$^{G12C}$ (rather than another unidentified mutant protein) that drives the cancers that carry this mutation. It also provides support for targeting KRAS therapeutically, and represents a major step towards bringing KRAS inhibition to the clinic. Finally, the authors have revealed an intriguing link between a targeted cancer therapy and immune responses. Further study of this relationship might lead to the discovery of new combination therapies for cancer.

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