explored by comparing the rate of a process — such as the rate at which a particle will decay into other, lighter particles — with the rate of its CP-related process, in which all the initial and final particles are replaced with the corresponding antiparticles. If these rates are measured to be different, then a 'CP asymmetry' has been observed. Measurements of CP asymmetries are interesting for two reasons. First, they provide stringent tests of the standard model of particle physics. Second, they may provide hints that could point scientists in the direction of a solution to the mystery of the Universe's matter–antimatter imbalance.

Among the four known forces of nature — the standard model's weak, strong and electromagnetic forces, and the gravitational force — the weak force is the only one that distinguishes between matter and antimatter. But even the weak force would not do so if it were not that three quark particles exist for each of two charge types: the down, strange and bottom quarks, which have a charge that is minus one-third of the proton's charge; and the up, charm and top quarks, which have a charge that is two-thirds of the proton's charge. With three quarks of either charge, the weak force has a single coupling constant (a parameter that quantifies the force's strength), which is different for particles and antiparticles[2,3]. If, as the standard model predicts, all CP asymmetries are proportional to this single coupling constant, then the sizes of these asymmetries are correlated. By contrast, most theories that go beyond the standard model have many independent coupling constants that distinguish particles from antiparticles, and thus predict deviations from the standard-model correlations.

Mesons are bound states of one quark and one antiquark. Until the LHCb measurement was made, CP asymmetries had been observed in the decays of three types of meson: K^0 mesons, B^0 mesons, and $B^{\pm}$ mesons. The LHCb experiment is the first to measure CP asymmetry in the decay of a fourth type of meson, the B_s^0 meson. The fact that, within the standard model, the difference in the laws of physics followed by matter and antimatter is encoded in a single parameter provides a particularly strong correlation between this asymmetry and an asymmetry in B^0 decay that has been measured by several experiments with high accuracy. Although neither of these asymmetries, nor the corresponding decay rates, can be theoretically predicted with any accuracy, the product of the CP asymmetry with the decay rate should, according to the standard model, be equal (to a good approximation) between the B_s^0 decay and the B^0 decay[4,5]. The LHCb measurement is consistent with the predicted equality at the level of a few per cent, implying yet another triumph of the standard model.

In many extensions of the standard model, new particles are predicted to interact more strongly with the heavier quarks (strange, bottom, charm and top) than with the lighter ones (up and down). The K^0 mesons, the B^0 mesons and the $B^{\pm}$ mesons all have either a down (anti)quark or an up (anti)quark. But the B_s^0 mesons are different: they are made up of a strange quark and a bottom antiquark. Their antiparticles are composed of a bottom quark and a strange antiquark. Thus, scientists had hoped that although the effects of new physics were negligibly small in all previously measured CP asymmetries, they would be large enough to be observed in B_s^0 decays. Frustratingly, this seems not to be the case.

"The LHCb measurement reinforces the standard model's explanation of how the weak force distinguishes matter from antimatter."

The standard-model prediction[2] of how the weak force distinguishes between matter and antimatter therefore continues to successfully describe all measurements of CP asymmetries in meson decays. However, the standard model fails to explain the Universe's matter–antimatter imbalance. All structures in the Universe, from clusters of galaxies to human cells, are made of matter: protons, neutrons and electrons. Their antiparticles — the antiprotons, antineutrons and positrons — are not found in the Universe at large. If the laws of nature were identical for matter and antimatter, then particles and antiparticles would have been created in equal amounts and would then have annihilated each other, leaving only pure radiation and no matter structures in the Universe. Our very existence is possible only because of CP asymmetries. The standard model allows all antimatter to disappear from the Universe, but it predicts that the amount of surviving matter is many orders of magnitude smaller than observed.

Therefore, there must exist a force, as yet unknown to us, that distinguishes matter from antimatter in a way that is much stronger than that of the weak force. Theorists have made various suggestions as to what this new force might be. To disclose the nature of this force, further hints from experiments are needed. Searching for CP asymmetries in neutrino 'oscillations' of one type into another and for the electric-dipole moments of the neutron and the electron, in addition to measuring CP asymmetries in B_s^0-meson decays, seem the most promising avenues through which to obtain such hints. The consistency of the LHCb measurement with the standard model provides further motivation to pursue the other searches even more vigorously. ■

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CANCER

Calculated treatment

Mathematical modelling linked with patient data suggests that combination therapy is more effective than sequential treatment at preventing drug resistance in cancer. This predictive approach may pave the way for personalized therapies.

NATALIA L. KOMAROVA & C. RICHARD BOLAND

In a study published in *eLIFE*, Bozic *et al.*[1] use a mathematical approach to examine tumour evolution and response to chemotherapy. In one example, they describe a patient who had the skin cancer melanoma characterized by an estimated tumour burden of 9.8×10^{10} cells and 8 metastatic lesions. Their modelling predicts a 0% chance of disease control using a single drug, but that the likelihood of successful treatment could rise to 88% during combined therapy with two drugs. The approach offers a brave, quantitative look at designing targeted therapy for cancer.

The search for cancer treatments has traversed a long and thorny path, with more failures and disappointments than glimpses of success. A major breakthrough was achieved with the development of a drug called imatinib in the 1990s. This inhibitor of tyrosine kinase enzymes showed breathtaking success for treating chronic myelogenous leukaemia (CML). Imatinib and other small-molecule inhibitors 'recognize' and attack cancer cells, but spare normal cells, thereby reducing side effects compared with conventional chemotherapy. Since the discovery of imatinib, dozens of other such inhibitors have been developed for treating different cancers. However, the initial excitement surrounding these drugs was tempered by the appearance of drug resistance — the phenomenon in which disease returns a few months after initial treatment success[2].

Cancer is a process of Darwinian evolution played out in a particular organ. Normal cells divide and die, and each division brings a small chance of genetic change. Most such mutations are deleterious, and the cells die without leaving offspring, but some confer new properties that promote growth or survival and can lead to cancer. The greatest challenge for drugs targeted at such cells is the further evolution of mutations that confer drug resistance. Combining multiple drugs that have distinct mechanisms of action might provide a solution to this problem. The concept of a 'drug cocktail' was introduced in 1996 in the context of treating AIDS. There, the emergence of viral strains resistant to single drug treatments rendered all previous attempts to control the disease unsuccessful. Viral evolution in a patient is conceptually similar to the evolution of cancer cells, so similar treatment strategies might work well for both diseases.

Current common practice for treating cancers with small-molecule inhibitors is to administer the agents sequentially, starting with a 'first-line' drug and switching to 'second-line' therapies if the tumour relapses. Bozic *et al.* assessed the effectiveness of this approach using sophisticated mathematical techniques and data from patients with melanoma or with pancreatic or colorectal cancers. They convincingly demonstrate that a sequential strategy "precludes any chance for cure", even in the best-case scenario in which no single mutants confer resistance to both drugs. However, they show that simultaneously combining two or more drugs can provide much-needed hope for patients.

As demonstrated last year[3], drug-resistant mutants typically exist at low levels in tumours before the beginning of treatment. Treatment with a single drug gives a competitive advantage to mutants resistant to that drug, such that by the time of the switch to a second-line therapy, there is a high chance that a mutant that is also resistant to the second drug (a doubly resistant mutant) has already emerged (Fig. 1). But combination therapy eliminates cells that are singly resistant to either drug and therefore — because the likelihood of a doubly mutated cell emerging in such a population is low — greatly increases the chance of success.

The greatest obstacle for combination treatments is the phenomenon of cross-resistance, in which a single mutation confers resistance to more than one drug. But even if such mutants are generated, the authors estimate that combination treatment can be beneficial in some cases, whereas single-drug and sequential strategies offer no hope.

Previous mathematical analyses have also shown[4] that cyclic treatments are ineffective compared with combination treatments, and have led to the proposal[5] that a combination of three anticancer drugs would be needed to treat CML. It has also already been argued[6] that, even in the presence of cross-resistant mutations in CML, combination treatments give patients a better chance of cure than do single-drug treatments. And *in vitro* studies[7] that compared CML cells treated with one small-molecule inhibitor with those treated with a combination of two or three demonstrated that the combined therapy suppressed cell proliferation more effectively. But with Bozic and colleagues' success in synthesizing theoretical and experimental methods and applying the analysis to solid tumours, these modelling studies have taken a leap forward.

Even more significantly, the authors' paper outlines a roadmap for future personalized therapies, by showing that specific parameters for a patient can be measured and used in a mathematical model to calculate the probability of treatment success and to design the best possible treatment strategy. The authors extracted tumour parameters — including its size at presentation, cell division and cell death rates, and changes in the associated kinetic parameters following treatment — from 20 patients with melanoma who were treated with the small-molecule inhibitor vemurafenib. With this information, they were able to predict the most likely outcome of single, dual and triple therapies for each patient.

There is a bright future for this approach. As new drugs and more information on the exact mechanisms of drug action become available, the model can be iteratively improved. For example, there is currently a strong research focus on cellular plasticity, the heterogeneity of cells within a tumour and the role of cancer stem cells. But it is not known how the presence of cancer cells with differing properties affects a tumour's susceptibility to targeted treatments. Moreover, the evolutionary costs of resistance for a cell have not been quantified in most cases, nor have mutation rates for molecular changes of various kinds, although estimates have been made for the number of mutations conferring resistance to certain drugs in CML[7,8]. The potential complications of drug cocktails — including toxicity and undesirable drug interactions — must also be taken into account. But the overall message is loud and clear: mathematics can help to calculate treatment strategies, and the best hope so far lies in combination therapies. ■

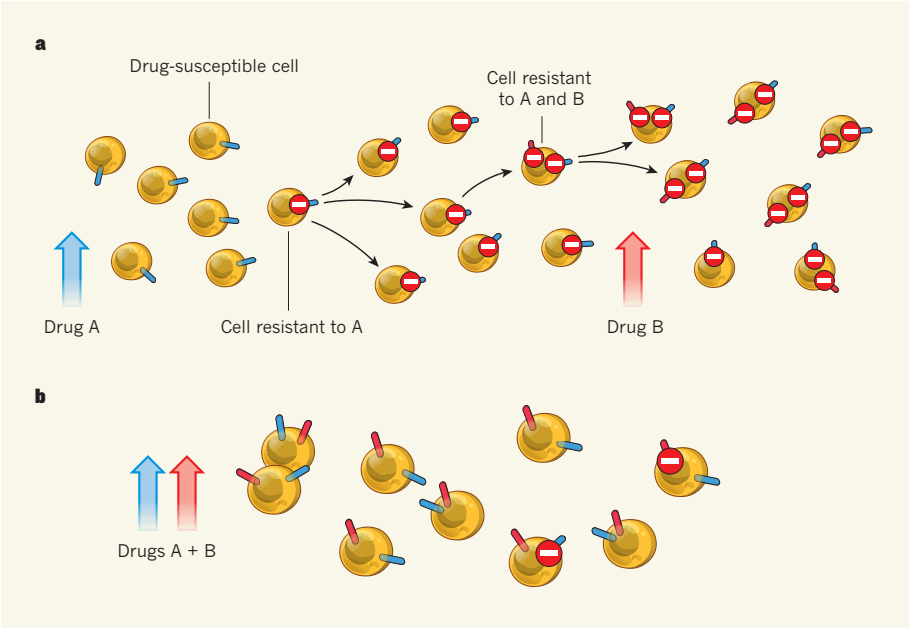

Figure 1 | Single-drug versus combination therapy. **a**, During therapy with one drug alone, a cell that acquires a mutation that confers resistance to the drug will be at a proliferative advantage. By the time this is recognized and treatment with a second drug is started, it is likely that a cell resistant to both drugs will already have emerged. **b**, Starting therapy with both drugs simultaneously means that cells acquiring single resistance will be immediately eliminated by the other drug. Bozic *et al.*[1] use mathematical modelling to show that this approach increases the chance of effective treatment.

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