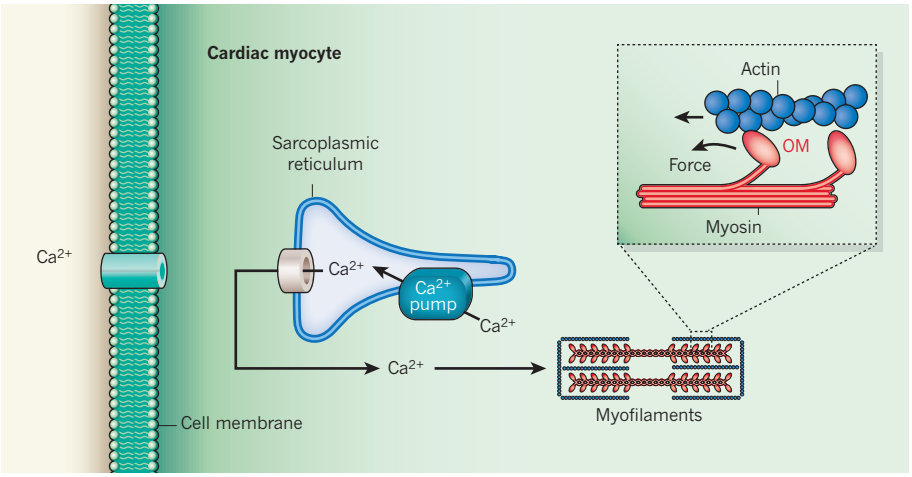

Figure 1 | How omecamtiv mecarbil functions. In heart muscle cells, Ca^{2+} influx from outside the cell triggers Ca^{2+} release from the sarcoplasmic reticulum. This in turn activates contraction by enabling myosin molecules to grab and pull on the actin filament. Reuptake of Ca^{2+} by the Ca^{2+} pump allows heart relaxation between beats. Increasing either the amount of Ca^{2+} released or the myofilaments' response to Ca^{2+} — as induced by the drug omecamtiv mecarbil (OM)[2] — can enhance contractility.

more precisely focused on molecular targets with the aim of enhancing sarcoplasmic-reticulum function while minimizing the energetic disadvantage and arrhythmia risk of the older drugs. For instance, gene therapy aims to increase expression in the sarcoplasmic reticulum of the Ca^{2+} pumps, which are downregulated in heart failure[4]. Other examples are drugs that either block pathological Ca^{2+} leak from the sarcoplasmic reticulum or stimulate Ca^{2+} uptake by this organelle[5]. These drugs might more selectively boost the transient increase in cytoplasmic Ca^{2+} levels without causing arrhythmia and with limited energetic consequences. So there is also hope for refinement of this strategy.

Malik *et al.*[2] find that omecamtiv mecarbil — also an inotropic drug — increases heartbeat strength by selectively enhancing the ability of the myosin molecule to generate force (Fig. 1). However, rather than boosting Ca^{2+} release, it jumps downstream and allows generation of greater force for the same Ca^{2+} signal. Targeting the final step of force production is a big advantage of this approach, because it potentially avoids unintended side effects typical of other upstream modulators of Ca^{2+} handling or neurohumoral signalling.

Indeed, the authors report that omecamtiv mecarbil enhances cardiac output without appreciably altering consumption of oxygen and ATP by the heart. This is presumably because any extra ATP is used right at the force-generating step, rather than being also used to transport Ca^{2+} into the sarcoplasmic reticulum or out of the cell, or via altered metabolism. As the heart weakens, it receives less nutritive, oxygen-rich blood (that is, the heart pumps blood through its own coronary arteries), which further limits cardiac contraction. By augmenting force while avoiding extra energetic costs, omecamtiv mecarbil increases the apparent efficiency of cardiac contraction and preserves the energy supply–demand balance.

Omecamtiv mecarbil belongs to the class of drug that enhances contractile protein responses to Ca^{2+} — such as levosimendan[6] — by increasing the force produced for a given level of Ca^{2+} release. But two aspects of Malik and co-workers' study are particularly noteworthy.

First, cardiac myosin is a new drug target and, although quite promising, the drug might have unintended side effects. Between beats, the heart must relax completely (the diastolic phase) to allow refilling with blood and to provide adequate oxygen flow to the heart muscle (most coronary blood flow is between beats). Because omecamtiv mecarbil prolongs contraction time, diastolic filling may be compromised, especially at higher heart rates. Drugs that allow significant force generation by myofilaments at diastolic Ca^{2+} levels can also impede ventricular refilling, and elevate cardiac stiffness and diastolic energy consumption. This potential limitation of omecamtiv mecarbil should be further assessed.

Second, although this drug is highly specific for cardiac myosin, slow skeletal-muscle fibres also use the same myosin isoform as in cardiac muscle. Consequently, omecamtiv mecarbil may cause stronger, more sustained contractions in slow-twitch muscles too. If so, it is tempting to speculate that the drug could find additional therapeutic or performance-related applications — for instance, in strengthening diaphragm muscles of patients on ventilators. The prospect of developing other small-molecule activators that specifically target fast skeletal myosins could hold similar promise for augmenting force in the muscle wasting that occurs in cancer or ageing.

Agents such as omecamtiv mecarbil could certainly contribute to future therapy for those who have heart failure. Complex and pervasive as heart failure is, so, fortunately, is the range of

50 Years Ago

P. M. Borisov has outlined a project, in the … *Literaturnaya Gazeta*, of a 90 km. long dam across the Bering Strait equipped with powerful pumps pumping cold Arctic Ocean water into the Pacific Ocean at the rate of 500 km.^{3} in 24 hours. Such a project ... would increase the flow of warm Atlantic Ocean water into the Arctic Ocean and change the climate of the Arctic regions. This project is criticized by D. A. Drogaitzev…[who] argues that such a project would displace the locus of Atlantic Ocean cyclones to the region of the Barentz Sea. Such a displacement would certainly change the climate of Northern Europe and Western Siberia, but this change will produce colder winters and hotter summers and will lead to the displacement of the desert belt from the region of North Africa and Central Asia to the north of Europe.
From *Nature* 6 May 1961

100 Years Ago

Three letters have recently appeared in *The Times* … relating to a mysterious heraldic animal known as the "jall" or "eall," of which the effigy has been recognised in St. George's Chapel, Westminster … Although described as having horns, tusks, and a short fluffy tail, the jall has been identified with the goat … In an old document … the eall is stated to be as large as a horse, with a tail like that of an elephant, goat-like jaws, and horns capable of movement, its colour being black. Other accounts state, however, that it has jaws like a wild boar and cloven hoofs. It may be suggested, if the beast ever had corporeal existence, that the African wart-hog may have formed the original type, that animal having a black hide, cloven hoofs, an elephant-like tail, large tusks, and big face-warts which might perhaps be regarded as elastic horns.
From *Nature* 4 May 1911