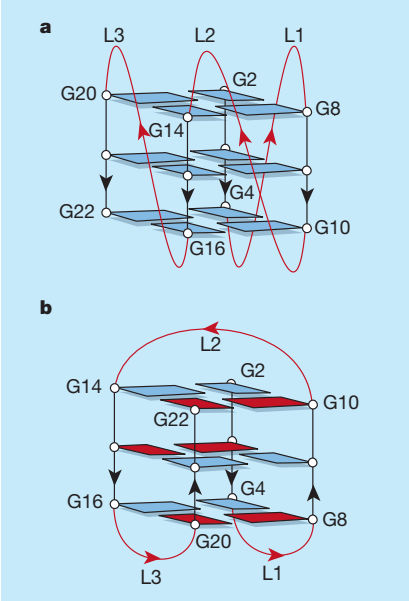

Figure 2 **Topology of the quadruplex formed by the four-repeat TTAGGG human telomere DNA sequence d[$AG_3(T_2AG_3)_3$]. a, The K^+-stabilized crystal structure described by Parkinson *et al.*[2]. b, The Na^+-stabilized solution structure[5]. The DNA backbone of the GGG columns and TTA connecting loops is shown by black and red lines, respectively. The guanine residues are shown as rectangles. Guanine can be aligned relative to its sugar in two orientations: *anti* (blue) when it is directed away from its sugar and *syn* (red) when it is positioned over the sugar. In a, the columns are all parallel to each other and all three loops (L1–L3) are of the double-chain-reversal type. In b, loops L1 and L3 are edgewise type and loop L2 is diagonal, and the opposing columns are antiparallel.**

The distinct topologies adopted by the K^+-coordinated and Na^+-coordinated four-repeat sequences could have implications for higher-order packing. The diagonal and edgewise loops on the top and bottom of the Na^+-coordinated structure[5], together with the fact that the two ends of the sequence are located on the same face, would stop quadruplexes from stacking up on top of each other.

But there is no such barrier to the stacking and subsequent packaging of the compact, disc-like quadruplexes in the K^+-coordinated structure[2]: the double-chain-reversal loops are directed outwards in a radial orientation and the chain ends are located on opposite faces of the quadruplex. Double-chain-reversal loops could also facilitate the necessary folding and unfolding of stacked quadruplexes during chromosome replication, without potential complications from the formation of knots in the structure.

Could the quadruplex structure that is described by Parkinson *et al.* help to protect chromosomes from fusing or recombining inappropriately, and stop telomeres from being mistakenly recognized by the cellular DNA-repair machinery as broken ends? In general terms such events are prevented by telomeres forming a complex with specific proteins[8], or by insertion of an overhanging single-strand telomeric sequence into an adjacent telomeric double-stranded segment through a process known as 't-loop' formation[9]. It remains to be seen whether quadruplex formation can contribute to this process.

Beyond fundamental chromosome organization, the new results[2] might also have clinical implications. The enzyme telomerase is needed for complete duplication of telomeric DNA during cell division[1]. In humans, it is highly expressed only in tumour cells, enabling them to carry on replicating their chromosomes almost indefinitely. (In non-tumour cells, by contrast, telomerase is not expressed and telomeres gradually erode to the point at which cells cannot duplicate their DNA safely, and so no longer divide.) So telomerase is a promising drug target. It binds to single-stranded telomere ends, and could potentially be inhibited by drugs that compete for these ends (in their quadruplex form). The structure-based design of such drugs[10] necessitates a molecular understanding of the range of quadruplex topologies. So the new structure[2], together with the previous Na^+-coordinated structure[5], is valuable in providing such information.

Finally, the quadruplex scaffold adopted by guanine-rich sequences has been observed in other contexts. For instance, quadruplexes have been associated with genomic regions that control gene transcription, and have been identified *in vivo* by antibody staining in the nuclei of certain protozoans[11]. Moreover, RNA quadruplexes have been identified in mammalian brain messenger RNAs that are recognized by the fragile X syndrome protein[12]. So the architecture of quadruplexes, and their interactions with proteins and other DNA and RNA sequences, should continue to be an active area of research with broad therapeutic implications. ■

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Daedalus

Cloud-chamber clouds

In the old 'Star Wars' Project, one scheme was to launch particle beams from Earth at the orbiting weaponry in space. The snag, of course, is that such beams are easily absorbed by the atmosphere, especially by clouds. The answer was to launch the beam as a series of pulses. The first beam would travel a certain distance before being absorbed and scattered; the next would ride in the expanded and clarified tunnel driven by the first, and would go further; ultimately the last pulse would break through into clear aerospace and would deliver its deadly energy to the space-borne threat. The whole process would take much less than a second.

Daedalus now connects this idea with the sad fact, bemoaned by every farmer, that endless clouds scud merrily over his fields but deposit no rain on his parched land. Many attempts have been made to make such annoying clouds rain, by seeding them from aircraft or even by firing cannon at them from the ground. Daedalus's scheme recalls the latter. He plans to fire a carbon dioxide laser at the clouds, followed by an electron beam or one of alpha particles. Unlike the Star Wars scheme, these co-linear beams will not reach space. They are intended to be broken up in the clouds, ideally near the tops of the most promising ones.

Wilson's cloud chamber is the crucial experiment here. In this device, the tiny racing fundamental particles precipitate enormously larger droplets along their track, revealing the particles to watchers or cameras. Daedalus reckons that the disruption of a cloud top by his beam system should release enormous numbers of wilsonian droplets, which will fall slowly through the cloud. As in ordinary rainfall, they will be further amplified by collision. Each droplet will collide with those beneath. It will grow in the process, fall faster, and collide more frequently with more cloud droplets. Ultimately, full-sized raindrops will fall out of the base of the cloud.

The beam gadget, though smaller and cheaper than the Star Wars device, will still be costly. Farmers will probably hire it by the day, and use it to wet all their land for that day. But it should then transform farming. It should make it a far more predictable business, less dependent on chance water. A cloud is just a mass of small water droplets: it ought to rain, and any device that encourages this process is going with the grain of atmospheric physics.

David Jones