components. The authors found that nuclear-envelope components that incorporated efficiently into micronuclei were those components known[8] to localize to the core regions of reassembling nuclei. The nuclear-envelope components that were inefficiently incorporated or absent from micronuclei were those that are found on the non-core regions of reassembling nuclei.

Liu and colleagues investigated whether the failure of lagging chromosomes to recruit non-core nuclear-envelope components depends on the presence of the spindle. The authors treated cells undergoing cell division with drugs that dismantled the spindle. This treatment enabled both core and non-core nuclear-envelope components to assemble on lagging chromosomes that were forming micronuclei. The authors also conducted experiments in which they manipulated cells to displace some chromosomes away from the spindle to peripheral regions of a dividing cell. These displaced chromosomes formed micronuclei that had both core and non-core nuclear-envelope components. Such micronuclei did not rupture, revealing that non-core components are needed to prevent micronuclear fragility. The authors' results are consistent with a model in which the micronuclear assembly of nuclear-envelope material is perturbed in regions of the cell that have a high density of microtubules.

Cell division is a highly regulated process, and there are mechanisms to ensure its quality control. This raises the question of whether any such checkpoints exist in human cells to deal with lagging chromosomes.

In the fruit fly *Drosophila melanogaster*, there is a gradient of activity of the kinase enzyme Aurora B that is highest near the spindle in the centre of a dividing cell[9]. This enzymatic activity inhibits nuclear-envelope reassembly on lagging chromosomes that are within the region of high Aurora B activity. This mechanism for inhibiting nuclear-envelope reassembly might facilitate the reintegration of a lagging chromosome with the rest of the chromosomes that will form the new nucleus[9]. Indeed, when Aurora B is mislocalized away from the spindle in *Drosophila* cells[9], nuclear-envelope material, such as the non-core, nuclear-pore-complex protein Nup107, binds to lagging chromosomes with the same kinetics as to the main chromosome group.

However, when Liu *et al.* caused similar perturbations of Aurora B in human cells, this did not restore the recruitment of a non-core, nuclear-pore-complex protein (in this case, Nup133) to lagging chromosomes. The contrasting outcomes might reflect species-specific differences in sensitivity to Aurora B perturbations. Liu and colleagues found that core nuclear-envelope components accumulated on lagging chromosomes with normal kinetics and that drug-mediated inhibition of Aurora B at a late stage of cell division just before nuclear-envelope reassembly did not result in the recruitment of non-core, nuclear-envelope components to lagging chromosomes. These findings suggest that a dedicated chromosome-separation checkpoint is unlikely to exist in human cells. Instead, chromosome segregation to the daughter cells and nuclear-envelope assembly are not closely coordinated events. This could explain why lagging chromosomes often form micronuclei with deficient nuclear envelopes, rather than being incorporated into the nucleus.

How microtubules might limit the access of non-core, nuclear-envelope components to lagging chromosomes is unknown. The non-core and core components of the nuclear envelope both include membrane-bound proteins that redistribute during cell division to an organelle called the endoplasmic reticulum. One possibility is that these core and non-core proteins localize to different parts of the endoplasmic reticulum. Perhaps sheet-like domains of the organelle that are too large to enter spindle regions that have high microtubule density might contain non-core proteins, whereas the smaller tubular structures of the endoplasmic reticulum that might be able to enter the spindle regions could contain the core proteins. Alternatively, perhaps the localization of core and non-core nuclear-envelope proteins might be regulated by the microtubule-associated proteins that remove nuclear-envelope lipid membranes from chromosomes during an early stage of cell division[10]. It will be exciting to learn the outcome of studies to test these and other possible mechanisms, because the results might provide insights into general principles of how microtubules and other filament-like networks in the cell regulate the membrane-bound outer layer of organelles. ■

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1. Stephens, P. J. *et al. Cell* **144**, 27–40 (2011).
2. Ly, P. & Cleveland, D. W. *Trends Cell Biol.* **27**, 917–930 (2017).
3. Crasta, K. *et al. Nature* **482**, 53–58 (2012).
4. Zhang, C.-Z. *et al. Nature* **522**, 179–184 (2015).
5. Liu, S. *et al. Nature* **561**, 551–555 (2018).
6. Ungricht, R. & Kutay, U. *Nature Rev. Mol. Cell Biol.* **18**, 229–245 (2017).
7. Hatch, E. M., Fischer, A. H., Deerinck, T. J. & Hetzer, M. W. *Cell* **154**, 47–60 (2013).
8. Dechat, T. *et al. J. Cell Sci.* **117**, 6117–6128 (2004).
9. Afonso, O. *et al. Science* **345**, 332–336 (2014).
10. Schlaitz, A.-L., Thompson, J., Wong, C. C. L., Yates, J. R. & Heald, R. *Dev. Cell* **26**, 315–323 (2013).

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IMMUNOLOGY

Antibodies pose a double threat to HIV

Drug treatments for HIV infection require the long-term use of daily medication that can have toxic side effects. A pair of HIV-targeting antibodies might offer an alternative therapeutic approach. SEE ARTICLE P.479

NANCY L. HAIGWOOD

It is estimated that 36.9 million people worldwide are infected with HIV (go.nature.com/2pugvhd). Drug treatment can prevent this infection from developing into AIDS and becoming lethal, by controlling the level of virus in the bloodstream. However, this therapy doesn't eradicate HIV, and is associated with toxicity and conditions such as metabolic disorders[1]. As part of ongoing efforts to improve the treatment options available, clinical-trial results are now reported in two papers from the same research group — one in *Nature* by Mendoza *et al.*[2] (page 479) and the other by Bar-On *et al.*[3] in *Nature Medicine*. The studies assess the effects of a treatment for HIV that uses two antibodies to target a viral protein.

The current standard treatment for HIV infection is long-term use of antiretroviral therapy (ART), a daily regime of drugs that block steps needed for viral replication. If ART treatment ceases, virus becomes detectable in the bloodstream within days, a phenomenon termed viral rebound that can lead to progression towards AIDS. ART does not provide a cure because the drugs do not kill infected cells in the viral reservoir[4], which is established when virus inserts its genome into the genome of a host immune cell (Fig. 1).

ART drugs can prevent viral production from the part of the reservoir termed the active viral reservoir, in which viral replication occurs. However, these drugs cannot target the viral reservoir that exists in a 'dormant' state, termed the latent viral reservoir. A latent viral reservoir can exist in certain tissues[5]; here, virus production occurs at an extremely low level and might increase in the future. This 'hidden' reservoir can evade destruction by

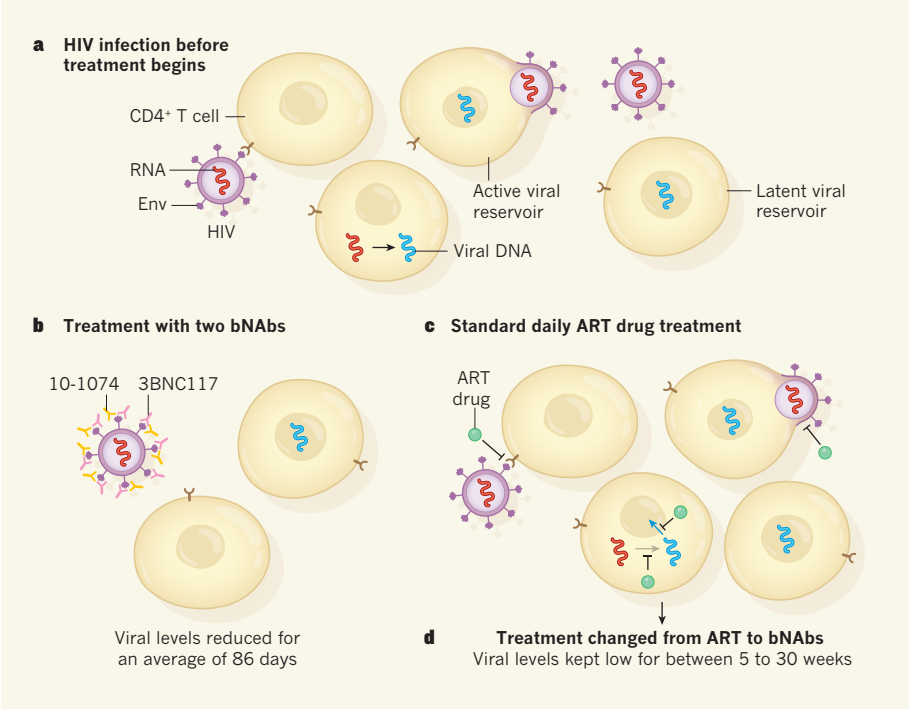

Figure 1 | Targeting HIV. **a**, When a person is infected with HIV, the protein Env on the viral surface can bind to receptors on immune cells called CD4+ T cells. This interaction enables the virus to enter the cell, undergo DNA synthesis using the viral RNA template, and become inserted into the host-cell genome. Cells that are actively making virus using these inserted copies of viral DNA are called the active viral reservoir, and virus particles are released from such cells after viral replication. However, some cells that have viral DNA insertions might be in a 'dormant' state that does not actively produce virus and instead forms what is known as the latent viral reservoir; these cells might give rise to virus production in the future. **b**, Bar-On *et al.*[3] report the results of a clinical trial that tested whether the introduction of two antibodies, 3BNC117 and 10-1074, which are a type of antibody known as a broadly neutralizing antibody (bNAb), can lower the blood levels of HIV in people who haven't received HIV treatment. The two antibodies bind to separate sites on Env, and prevent the virus from binding and infecting immune cells. **c**, The standard treatment for HIV infection is known as antiretroviral therapy (ART), and consists of a daily dose of drugs that block steps in viral replication. **d**, Mendoza *et al.*[2] report a clinical trial that tested whether 3BNC117 and 10-1074 can lower virus levels in the bloodstream of people who temporarily stop receiving ART. The results of both studies are encouraging, indicating that the use of two bNAbs can lower virus levels for a time.

the immune system. If these cells could be targeted, more-effective treatments might be possible.

There has been interest in the potential use of HIV-targeting antibodies to control the viral level in the bloodstream. Such antibodies can bind to and block a protein on the viral surface called Env, which is needed for HIV entry into host immune cells called CD4+ T cells. The discovery[6] of highly potent antibodies, termed broadly neutralizing antibodies (bNAbs), boosted this idea. These antibodies target regions of the Env molecule that are present in nearly all HIV strains. Individual bNAbs have already been tested[6–9] for use as clinical treatments for HIV. They are safe and well tolerated[10,11], and, in contrast to the daily dosage necessary for ART, administration is needed only every few weeks to maintain constant bNAb levels in the bloodstream and potentially in tissues.

Previous clinical studies[7–9] testing the individual effects of two bNAbs[12,13] — either 3BNC117 or VRC01 — found that the level of HIV in the bloodstream was initially suppressed for 6–10 weeks, but then viral rebound occurred, and the studies[7–9] reported the presence of antibody-resistant viral variants.

Mendoza *et al.* and Bar-On *et al.* carried out phase Ib clinical trials (small-scale trials to test the safety of a treatment) to investigate whether combining two bNAbs (3BNC117 and 10-1074) that target distinct sites on Env might decrease the probability of virus resistance occurring, and might control virus levels in HIV-infected people who did not receive ART during the trial period. Mendoza and colleagues assessed the effect of giving the two antibodies to 11 people who were temporarily stopping ART. Bar-On and colleagues analysed the effect of these two bNAbs on seven people who hadn't yet received ART.

Both studies reported an impressive reduction in bloodstream HIV levels compared with levels at the start of the trial. Viral rebound took many weeks to occur, and when it did, there was little or no evidence that viruses were resistant to both bNAbs. This suggests that using two antibodies might offer an alternative treatment option to ART, pending further studies.

Mendoza and colleagues observed that resistance to 10-1074 developed more rapidly than that to 3BNC117. This could be explained if there was a more rapid natural decline in the blood levels of 3BNC117, which had a shorter half-life than 10-1074. It effectively resulted in periods of treatment with a single type of bNAb rather than with the intended two. If the antibody dosage could be adjusted so that the half-lives of the two bNAbs were more closely matched, the development of treatment-resistant viral variants might be avoided. However, triple antibody combinations might be necessary to tackle the emergence of antibody resistance.

Maintained viral suppression from antibody treatment was evident in Mendoza and colleagues' study. The authors found that when the bNAbs were introduced 2 days before ART was stopped, and further doses given 3 and 6 weeks later, virus in the bloodstream was suppressed to undetectable levels for a median time of 21 weeks before viral rebound. The rebound timeframe ranged from 5 to 30 weeks, and 9 of the 11 trial participants maintained viral suppression without rebound for more than 15 weeks.

One way to determine whether the characteristics of viral infection change after bNAb therapy is to compare the diversity of the nucleotide sequences that encode the Env protein before and after treatment. Mendoza and colleagues found that the rebounding viruses after antibody treatment had low sequence diversity, whereas a high degree of diversity has been observed in viral rebound after ART treatment[14,15]. It is possible that this difference arises because the antibodies restrict the growth of viruses from the tissue viral reservoir, in addition to targeting actively replicating viruses in the bloodsteam, leading to a low level of sequence diversity.

How effectively might antibodies control virus levels without pretreatment with ART? In Bar-On and colleagues' study, the treatment suppressed virus levels in the bloodstream for an average of 86 days, about 60 days longer than previously observed[7] after treatment with just one HIV-targeting bNAb. This dual treatment approach in people who already had detectable levels of HIV in their bloodstream clearly limited the emergence of resistant viral variants, providing a notable advance on treatment with a single type of antibody. However, suppression was complete only in people who had low levels of virus in their bloodstream at the beginning of the trial.

The results provide cause for optimism that a cocktail of antibodies might provide substantial and durable viral control in the absence of ART. However, such enthusiasm must be tempered with caution. Bar-On and colleagues initially conducted laboratory tests to determine whether their study participants had a viral strain that would be sensitive to the bNAbs. In three individuals in whom the virus level rebounded most quickly, these antibody-sensitivity tests failed to detect viruses that had partial or complete pre-existing resistance to one or

both bNAbs. This suggests that a more-sensitive test than that used by the authors will be needed to assess whether people are likely to respond to a particular bNAb combination.

In the war against HIV, there has been some controversy regarding the use of bNAbs as a treatment approach. Antibodies have been thought of as providing defences equivalent to a naval blockade, stopping HIV from initially infecting or preventing the infection from spreading. But once this barrier is breached and infection takes hold, it is assumed that T cells are the front line of immune defence against infected cells, with antibodies relegated to bystander status. However, models of infection with a simian–human chimaeric virus called SHIV in primates suggest that antibodies might have an active role in tackling infected cells.

In these primate models, human antibodies become widely distributed in tissues[16], and could be acting in a manner equivalent to minesweepers, by limiting the spread of infection. Not only are such antibodies distributed efficiently to tissues far from the site of antibody administration, but they can also help to destroy infected cells, at least in the early stages of an infection, and to prevent the establishment of the viral reservoir[16,17]. Once viral infection is established, the introduction of bNAbs that target Env can suppress the virus to undetectable levels in the bloodstream, as long as the antibodies persist there[18,19]. The role of these antibodies in tissues is not fully understood. When the antibody levels decay, viral rebound occurs and immune defences are mediated mainly by T cells[20].

Given the results in primates, is there any evidence that bNAbs can tackle the viral reservoir in human HIV infection? Mendoza and colleagues used an *in vitro* quantitative virus-outgrowth test to assess the viral-reservoir size. They found no significant differences in reservoir size before and after bNAb treatment. However, longer and more-effective bNAb treatment and larger study groups might be needed to establish definitively whether bNAbs affect the viral reservoir.

As strategies are sought to target the reservoir, it is encouraging to know that bNAbs might provide a useful weapon in the arsenal of viral-control tools. Moreover, if it turns out that a cocktail of bNAbs could act as a potential temporary replacement for ART, this type of 'drug holiday' might give people time to recover from ART-induced toxicity. ■

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1. Paula, A. A., Falcão, M. C. N. & Pacheco, A. G. *AIDS Res. Ther.* **10**, 32 (2013).
2. Mendoza, P. *et al. Nature* **561**, 479–484 (2018).
3. Bar-On, Y. *et al. Nature Med.* https://doi.org/10.1038/s41591-018-0186-4 (2018).
4. Sengupta, S. & Siliciano R. F. *Immunity* **48**, 872–895 (2018).
5. Boritz, E. A. *et al. Cell* **166**, 1004–1015 (2016).
6. Pegu, A., Hessell, A. J., Mascola, J. R. & Haigwood, N. L. *Immunol. Rev.* **275**, 296–312 (2017).
7. Caskey, M. et al. *Nature* **522**, 487–491 (2015).
8. Bar, K. J. *et al. N. Engl. J. Med.* **375**, 2037–2050 (2016).
9. Scheid, J. F. *et al. Nature* **535**, 556–560 (2016).
10. Ledgerwood, J. E. *et al. Clin. Exp. Immunol.* **182**, 289–301 (2015).
11. Mayer, K. H. *et al. PLoS Med.* **14**, e1002435 (2017).
12. Scheid, J. F. *et al. Science* **333**, 1633–1637 (2011).
13. Zhou, T. *et al. Science* **329**, 811–817 (2010).
14. Rothenberger, M. K. *et al. Proc. Natl Acad. Sci. USA* **112**, E1126–E1134 (2015).
15. Kearney, M. F. *et al. PLoS Pathog.* **10**, e1004010 (2014).
16. Hessell, A. J. *et al. Nature Med.* **22**, 362–368 (2016).
17. Liu, J. *et al. Science* **353**, 1045–1049 (2016).
18. Shingai, M. *et al. Nature* **503**, 277–280 (2013).
19. Barouch, D. H. *et al. Nature* **503**, 224–228 (2013).
20. Nishimura, Y. *et al. Nature* **543**, 559–563 (2017).

ENGINEERING

Complex motion guided without external control

Mechanical structures have been made that exhibit self-guided, multi-step sequences of shape changes in response to an applied force. Such structures could have applications in flexible electronics and soft robotics. SEE LETTER P.512

LARRY L. HOWELL

It is reasonable to expect that to guide a mechanical structure through a complex, predetermined series of shape changes, electronic controls would be needed. In many cases, motors move the structure, sensors detect position and electronic devices called microcontrollers execute algorithms to provide external control. Achieving complex motion using only the structure's geometry might seem unrealistic, but, if possible, it would have many advantages. In particular, it would simplify the manufacture of mechanical structures and enable them to be readily produced in various sizes. On page 512, Coulais *et al.*[1] report an approach for designing materials that follow a prescribed motion and that then reconfigure at specified points to enter another phase of motion. This movement is guided only by the material's geometry, which eliminates the need for external sensing and control.

Engineered structures known as mechanical metamaterials are designed to behave in ways not common in nature[2–4]. They are usually made by combining building blocks (unit cells) into patterns, to produce a combined structure that can behave in ways not possible using a solid material. Advances in materials, manufacturing, computational capabilities and mechanical-design approaches are enabling designs that were not previously possible, such as the mechanical metamaterials described by Coulais and colleagues.

The authors used thin, flexible parts, strategically combined with thick, stiff parts, to achieve the desired structural motion. They refer to the movement of these parts as soft deformation, because it is caused by the bending of the flexible parts, rather than by mechanical hinges. This type of motion is not new, of course, because it can be seen extensively in nature. Consider, for example, the movement of an elephant's trunk, your beating heart or a butterfly's flapping wings — in each case, motion results from the bending of flexible parts.

Designs in which a combination of flexible and stiff components enables a specified motion are often referred to as compliant mechanisms[5]. The use of these mechanisms in engineered materials offers several advantages over conventional design methods, such as the ability to achieve complex motion from a single part rather than from an assembly of pieces connected by hinges. Coulais *et al.* used compliant mechanisms to realize surprisingly sophisticated multi-step motions (Fig. 1). One clever aspect of their approach is the use of parts that have different degrees of flexibility, so that, in response to an external force, some parts deform before others do.

Coulais and colleagues also used what they call self-contact, whereby a stiff part is intentionally brought into contact with another stiff part to prevent further motion between the two. This 'contact-aided' mechanism[6,7] is similar to a door-stop that prevents a door from colliding with a wall. In the authors' approach, bending of the most flexible part results in self-contact, which ends the first step of a multi-step pathway (Fig. 1a). The most flexible part then becomes inactive, and the second step begins (Fig. 1b). The next-most flexible part becomes the main source of deformation, and this part bends until the next occurrence of self-contact.

The authors produced unit cells from these flexible and stiff components, and combined the unit cells into patterns to achieve the desired motions. In one demonstration, they considered unit cells consisting of a cross-shaped arrangement of five equally sized squares, which were