

## CANCER THERAPY

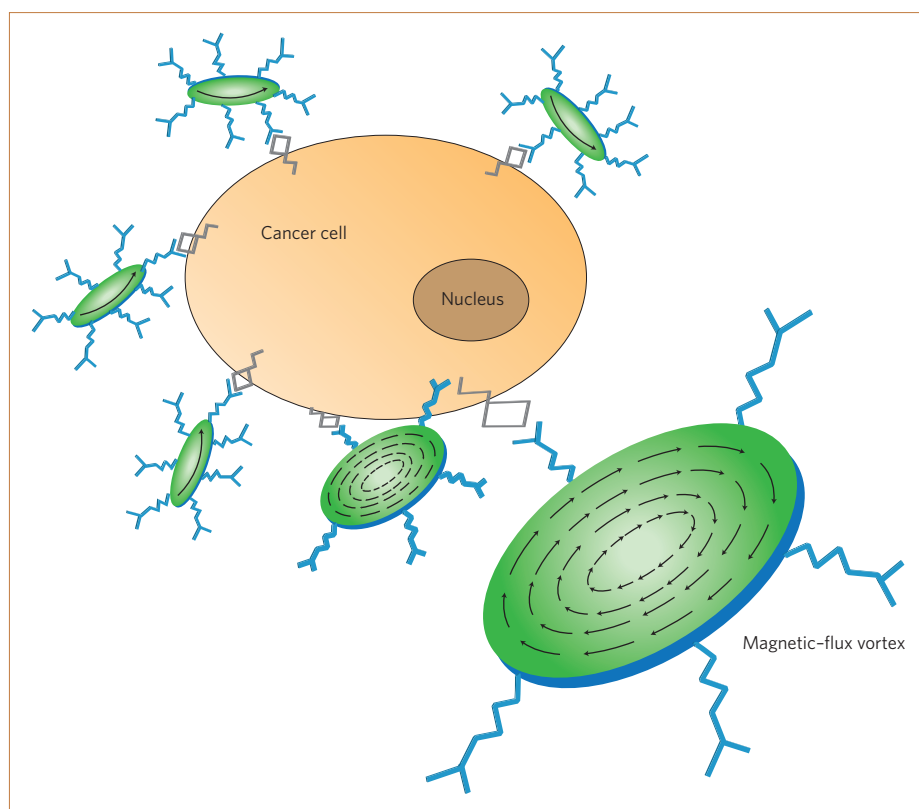
# A twist on tumour targeting

The concept of using magnetic micro- and nanoparticles for targeting solid tumours with drugs was first proposed over three decades ago, but has yet to translate into a clinical application. Rethinking the mechanistic approach could circumvent the difficulties that have stood in its way.

Jon Dobson

In the late-1970s, Widder, Senyi and others proposed using magnetic micro- and nanoparticles to carry drugs to specific sites within the body such as solid tumours<sup>1,2</sup>. The idea was that compounds intended to kill cells could be linked to the magnetic particles outside the body before being injected into the bloodstream. High-field magnets positioned outside the body over the target site would essentially pull these particle–drug complexes out of the bloodstream and into the tissue as they passed through the high-field region. Although in theory this revolutionary idea could be used to concentrate drugs at the site of the tumour, thereby reducing the side effects associated with systemic distribution of chemotherapy drugs, such as nausea, hair loss and compromised immune system, in practice the technique has yet to develop into a workable clinical application. A new twist on this technology that takes advantage of a different approach to using magnetic particles for treatment has the potential to overcome many of the challenges involved in translating magnetic targeting to the clinic. Now in *Nature Materials*, Kim *et al.* report their method for exploiting spin vortices in magnetic discs to mechanically trigger the destruction of cancer cells<sup>3</sup>. By using a mechanical mechanism rather than one reliant on targeted drugs or even tumour heating, cell death can also be induced at much lower magnetic fields and frequencies, thereby reducing potential side effects.

One of the primary reasons that magnetic drug targeting has failed to deliver on its early promise is that the magnetic fields generated either by permanent magnets or electromagnets reduce rapidly with distance to the target tissue. Although this rapid reduction in field strength is necessary to produce a field gradient, and hence exert a force on the particle, it seriously restricts the targeting ability in the body<sup>4</sup>. More recently, research groups have been investigating the use of magnetized stents, natural tumour-homing cells loaded with magnetic nanoparticles, and magnetic nanoparticles functionalized with



**Figure 1** | Magnetic spin-vortex discs (shown in green) are coated with antibodies (shown in blue) that bind to membrane receptors expressed by the cancer cells. The application of an alternating magnetic field spins the discs, disrupting the cell membrane and initiating apoptosis (programmed cell death) by means of cell-signalling cascades.

tumour-targeting antibodies for magnetic fluid hyperthermia (MFH) applications as a way to overcome this<sup>5–7</sup>. Magnetic fluid hyperthermia involves injecting a magnetic-nanoparticle-containing fluid to target tumours; the nanoparticles' surfaces may be functionalized with cancer-cell antibodies that are attracted to receptors on the cancer cells. When an alternating magnetic field is applied it preferentially heats the nanoparticles, either killing the cancer cells or making them more susceptible to other treatments. Although these techniques have met with some success in animal

models, there are also inherent problems with translating MFH to a clinical setting, including coil/power supply requirements, the relatively high concentrations of magnetic nanoparticles needed for heat-induced programmed cell death — apoptosis — in the tumour, non-specific heating and undesirable physiological side effects. Despite the fact that clinical trials are now in progress, to a large extent, these problems have not been adequately solved<sup>8</sup>.

Kim *et al.* have addressed these issues by using the unusual magnetic properties of minute iron–nickel magnetic discs.

These spin-vortex discs, in which the diameter ( $\sim 1 \mu\text{m}$ ) is much larger than the thickness ( $\sim 60 \text{ nm}$ ), show interesting magnetic properties. The electron spins in the plane of the disc, each of which generates a tiny magnetic field of its own, are oriented in such a way as to form a magnetic-flux vortex — essentially closing the magnetic flux in on itself (Fig. 1). This gives these discs two properties that are highly desirable for biomedical applications: zero remanence, that is, no magnetization without an applied magnetic field, and the ability to respond mechanically to an applied field by spinning.

The lack of magnetic remanence means the spin-vortex discs are not prone to self-aggregation when in suspension, unlike the case of permanent magnetic materials. This prevents them blocking the blood vessels when the particles are injected into the bloodstream. Furthermore, when subjected to a magnetic field, the discs experience a torque and, in an alternating field of relatively low frequency and strength, they begin to spin.

Although the ability to make the discs spin is interesting, even more important is the fact that the effect is accomplished at much lower frequencies and field strengths than those required to induce MFH. This

means that the potential for targeting the discs to tumours, spinning them on cue and initiating cancer-cell destruction through the disruption of the cell membrane, can be accomplished at fields and frequencies that do not result in non-specific heating, will not interfere with normal physiological function and are easily achievable in terms of electromagnetic-coil design. By functionalizing the discs with tumour-specific antibodies to direct them and focusing the fields to the site of the tumour, only those discs exposed to the field will be actuated. This provides an elegant and rapid technique for targeting tumour destruction without the side effects associated with systemic treatments such as chemotherapy.

Although this technique overcomes many obstacles and holds great promise for the long-awaited translation of magnetic targeting to a clinical application, there are issues that will need to be addressed before this can occur. The size of the particles used in this study means that they would be rapidly taken up by the reticuloendothelial system — scavenger cells — when injected into the bloodstream, and most would never make it to their target<sup>9</sup>. Particles this large are also excluded from the brain by the blood/brain barrier<sup>10</sup>. However, Kim *et al.* point out that the disc geometry can be

scaled down to roughly 100 nm diameter while still preserving the spin-vortex state. In addition, more biocompatible discs that do not use nickel may need to be developed. However, compared to the hurdles faced in magnetic targeting and MFH up to this point, these problems seem imminently surmountable. □

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