interfaces, designed to be semipermeable to topological charge, thus leading to sophisticated forms of control over mobile, quantized information carriers. Artificial spin ice could be explored as a platform for neuromorphic 'memcomputing', in which the material functions as an interacting, collective memory storage unit capable of computation within the memory in absence of a logical unit[9]. Reprogrammable band structures for magnons[10], manipulation of superconductive vortices by pinning to magnetic monopoles[4], and coupling of the magnetic ensemble to transport[11] are other promising directions for applications. And the functionality for all these potential technological developments is strongly dependent on the capability to manipulate the microstate directly.

A complex system is defined by structure and ensemble. Much of the appeal of artificial spin ices has, since the beginning, relied on the control of the structure[2]. While not quite the dynamic Maxwell's demon of our dinner of pioneers, the technique demonstrated by Gartside and co-workers finally opens the way to a much-needed capability for static, local, reliable and accurate manipulation of the ensemble. ❐

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References

1. Gartside, J. C. et al. *Nat. Nanotech.* https://doi.org/10.1038/s41565-017-0002-1 (2017).
2. Nisoli, C., Kapaklis, V. & Schiffer, P. *Nat. Phys.* **13**, 200–203 (2017).
3. Farhan, A. et al. *Nat. Phys.* **9**, 375–382 (2013).
4. Wang, Y.-L. et al. *Science* **352**, 962–966 (2016).
5. Möller, G. & Moessner, R. *Phys. Rev. B* **80**, 140409(R) (2009).
6. Zhang, S. et al. *Nature* **500**, 553–557 (2013).
7. Anghinolfi, L. et al. *Nat. Commun.* **6**, 8278 (2015).
8. Nisoli, C. et al. *Phys. Rev. Lett.* **105**, 047205 (2010).
9. Di Ventra, M. & Pershin, Y. V. *Nat. Phys.* **9**, 200–202 (2013).
10. Iacocca, E. et al. *Phys. Rev. B* **93**, 134420 (2016).
11. Le, B. L. et al. *Phys. Rev. B* **95**, 060405 (2017).

CANCER NANOMEDICINE

A synthetic lethal bullet

Nanoparticles loaded with paclitaxel and nintedanib induce synthetic lethality in endometrial cancer cells.

Christian Rolfo and Elisa Giovannetti

Conventional chemotherapeutic drugs like paclitaxel and doxorubicin cause cell death by affecting cellular processes that are more active in tumours but that exist in normal cells as well: because of this, they are highly toxic, imposing limits to their doses. For more than twenty years, nanomedicine has focused on developing nanoparticles as simple drug-delivery vehicles that can drive chemotherapy drugs towards tumours. Now, the new frontier in the field is represented by the so-called molecularly targeted cancer therapies. These are potentially more effective and less harmful to normal cells than conventional chemotherapies since they are designed to specifically interact with receptors and signalling molecules that play a pivotal role in cancer cell proliferation, and to target key tumour-promoting micro-environmental factors. The latest formulations exploit synthetic lethal interactions between tumour-specific aberrations and additional molecular processes. Yet, the efficacy of these therapeutic molecules remains affected by limited targeted delivery. Now, reporting in *Nature Nanotechnology*, Ebeid and co-authors propose an innovative approach to generate 'synthetic lethal bullets' with high tumour-delivery efficiency, which combines conventional and molecularly targeted anticancer agents with an innovative nanoparticle technology aimed at shrinking endometrial tumours[1].

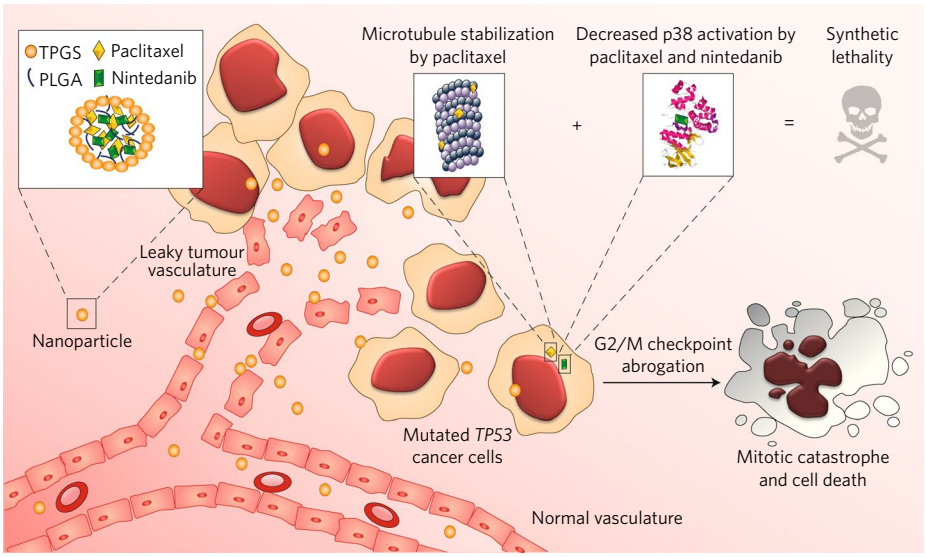

Fig. 1 | TPGS–PLGA nanoparticles loaded with nintedanib and paclitaxel extravasate through the leaky tumour vasculature and reach tumour cells. Paclitaxel induces microtubule stabilization. Cancer cells harbouring mutations in *TP53* could activate p38 to compensate p53 loss, leading to cell cycle arrest. p38 inhibition by nintedanib causes synthetic lethality by G2/M checkpoint abrogation, which triggers mitotic catastrophe in *TP53* mutated cancer cells and cell death. Structure of p38 retrieved from Protein Data Bank: 1WFC. The authors collaborated with J. Pinto Oblitas to create the figure.

Drug-delivery nanoparticles consist of macromolecular materials coupled with an active principle — a drug or a biologically active moiety — that is dissolved, entrapped, or encapsulated within the macromolecular shell or absorbed to its surface[2]. As an example, Abraxane, or nab-paclitaxel, is the first commercial-drug-loaded nanoparticle and consists of human serum albumin nanoparticles containing paclitaxel. It appeared on the market at the beginning of 2005, and it is now approved for different

tumour types, including breast, lung and pancreatic cancer.

Traditionally, the goal of nanoparticle-based chemotherapy has been to decrease normal tissue toxicity by improving drug specificity to tumours. The so-called EPR effect (enhanced permeability and retention) permits passive accumulation into the tumour interstitium thanks to its defective vasculature and ineffective lymphatic drainage. The heterogeneity of vascular permeability, however, limits nanoparticle penetration — most large-sized nanoparticles achieve only a suboptimal delivery and lack cytotoxic effects against cancer cells containing certain single-gene mutations that could be specifically targeted.

The elegant approach reported by Ebeid and co-authors pieces together this challenging puzzle. First, in choosing Food and Drug Administration-approved biocompatible poly(lactic-co-glycolic acid) (PLGA) at a monomer ratio of 75:25 and tocopherol polyethylene glycol succinate (TPGS) as surfactant, they synthesize a nanoparticle that allows better drug uptake and accumulation, while reducing drug efflux. TPGS acts as an inhibitor of the permeability glycoprotein (P-glycoprotein), which confers resistance by mediating the ATP-dependent efflux of a wide array of anticancer drugs[3]. Moreover, they encapsulate, for the first time, the conventional chemotherapeutic agent paclitaxel and the novel angiokinase inhibitor BIBF 1120, known as nintedanib. The latter is a potent triple receptor tyrosine kinase inhibitor that targets multiple tyrosine kinases and has already demonstrated relevant clinical activity in ovarian and lung cancer patients when combined with docetaxel or paclitaxel[4,5]. However, these initial trials highlighted the existence of adverse effects, suggesting the need for better criteria to select those patients who will take full advantage of the proposed treatment. With regard to this point, an additional strength of the work by Ebeid et al. is the choice of a combinatory nanoformulation that promotes synthetic lethality specifically in cells with mutations causing loss-of-function of the *TP53* gene. Synthetic lethality typically arises when a combination of deficiencies in the expression of two or more genes leads to cell death[6]. In this case, mechanistic insights obtained in vitro and in vivo indicate that combination of paclitaxel with nintedanib induces synergistic cell death. Cells with *TP53* loss-of-function rely on the p38 pathway to enter the G2/M checkpoint — a control step in the cell cycle that ensures DNA integrity before mitosis — and avoid cell death linked to the mitotic catastrophe. Treatment with paclitaxel stabilizes mitotic microtubules and its combination with nintedanib reduces p38 activation, which leads cells to bypass the G2/M checkpoint and induces a mitotic catastrophe.

Endometrial cancer is one of the only two common cancers with increasing incidence and mortality and thus urgently needs more effective treatments such as rationally designed multi-drug regimens, similar to the one proposed in this study. Of the different types of endometrial cancers, one of the most aggressive is uterine serous carcinoma, where *TP53* is mutated in 93% of the cases. However, the clinical relevance of this study reaches beyond the applicability of these findings to endometrial cancer. In fact, *TP53* is the most frequently mutated gene in all cancers, and a recent study demonstrated that its mutations are clonal, meaning that they occur early in tumourigenesis and are present in the majority of cancer cells[7]. Future studies on ovarian and lung cancers selected for *TP53* driver mutations could indeed pave the way to the development of personalized medicine strategies for different tumour types.

Nanoparticles present hope for improving cancer treatments by acting at least at two main levels: conferring new properties to a pharmaceutical agent (increased stability, modified pharmacokinetics and decreased toxicity) and driving the agent directly to the tumour, harnessing synthetic lethal interactions with targeted nanoparticles. The nanoparticles developed by Ebeid and co-authors have great potential for anticancer drug delivery and tumour targeting in *TP53*-mutated endometrial cancer, because they can exploit all the above-mentioned effects, as illustrated in Fig. 1. Of course, only new experiments and clinical trials will tell us whether, a century after Paul Ehrlich's seminal hypothesis on chemotherapeutic magic bullets[8] and the first description of the synthetic lethality phenomenon by Calvin Bridges[9], we can finally begin to use successful nanoparticle-based synthetic lethal bullets. ❐

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References

1. Ebeid, K. et al. *Nat. Nanotech.* https://doi.org/10.1038/s41565-017-0009-7 (2017).
2. Kreuter, J. in *Encyclopedia of Pharmaceutical Technology* (eds Swarbrick, J. & Boylan, J. C.) 165–190 (Dekker, New York, 1994).
3. Gottesman, M. M., Fojo, T. & Bates, S. E. *Nat. Rev. Cancer* **2**, 48–58 (2002).
4. du Bois, A. et al. *Lancet Oncol.* **17**, 78–89 (2016).
5. Reck, M. et al. *Lancet Oncol.* **15**, 143–155 (2014).
6. O'Neil, N. J., Bailey, M. L. & Hieter, P. *Nat. Rev. Genet.* **18**, 613–623 (2017).
7. Jamal-Hanjani, M. et al. *N. Engl. J. Med.* **376**, 2109–2121 (2017).
8. Strebhardt, K. & Ullrich, A. *Nat. Rev. Cancer* **8**, 473–480 (2008).
9. Bridges, C. B. *Amer. Nat.* **56**, 51–63 (1922).

TWO-DIMENSIONAL MATERIALS

Negative capacitance gives a positive boost

Negative capacitance effect in a ferroelectric-based gate stack provides an effective solution for hysteresis-free steep-slope operation in a MoS_2 field-effect transistor.

Adrian M. Ionescu

Nanoelectronics is facing many challenges at present in addition to aggressive scaling of complementary metal–oxide–semiconductor (CMOS) technology nodes (that is, the specific manufacturing processes and their design rules), driven by Moore's Law. For gate lengths of less than 10 nm, making metal–oxide–semiconductor field-effect transistors (MOSFETs) is no longer satisfactory, as the operation voltage scaling saturates at 0.7 V owing to exponentially increasing