chameleon' compounds that are influenced by dipolar aromatic resonance structures in both the ground and lowest excited states[14]. Being aromatic chameleon compounds, they can adapt to the opposite electron-counting rules for aromaticity in different states (Hückel's rule in the ground state versus Baird's rule in the lowest excited states). As a consequence, their dipole moments have opposite directions in the ground and lowest excited states, respectively.

These selected examples show that excited-state (anti)aromaticity influences excited-state geometries, reactivites and dipole moments, yet it also impacts excited-state energies, photoacidities and photobasicities, and possibly several other photophysical and photochemical properties and processes, similar to how Hückel aromaticity influences the ground state. Clearly, Baird's rules on excited-state (anti)aromaticity are awaiting applications in a variety of areas ranging from, for example, synthetic organic photochemistry to solar energy research. The concept has enormous potential and the future will hopefully bring many wonderful developments based on its applications. ❐

Henrik Ottosson is in the Department of Chemistry – BMC, Uppsala University, Box 576, 751 23 Uppsala, Sweden.
e-mail: henrik.ottosson@kemi.uu.se

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ANTICANCER AGENTS

Unleash the forces within

Liposomes are a leading drug-delivery platform in cancer chemotherapy. Now they can be used to destroy cancer cells through a method that converts chemical energy to mechanical force. These localized disruptions can cause cell death while minimizing the collateral damage to neighbouring cells.

Weiwei Gao and Liangfang Zhang

Chemotherapy inhibits the growth and division of cancer cells through chemical interference with molecular targets. It is an important clinical treatment option; however, drawbacks such as the emergence of cancer drug resistance and intolerable side effects can significantly limit its efficacy and suitability for some patients[1]. Applying localized, mechanical disruptions to cancerous cells is an appealing alternative for cancer treatment. Such an approach can be likened to minimally invasive surgical interventions that rely on physical rather than chemical interactions with the cellular targets.

A number of strategies have been proposed to induce physical damage to cancer cells[2,3], but their lack of specificity creates a challenge in translating them into a clinical treatment. If the treatment cannot be delivered solely to malignant cells, the applied energy may spread to the surrounding healthy cells and vital tissues, causing collateral damage. To circumvent this limitation, nanotechnology has provided a variety of solutions to enhance the spatial resolution of treatments and ensure that the external energy is directed to the site of interest[4].

Now, writing in *Angewandte Chemie International Edition*, Chung and colleagues report an innovative approach to destroying cancer cells through physical damage that is generated by a chemical reaction[5]. Central to their approach is a unique liposome system containing a thermally decomposable compound. On uptake by cancer cells and intracellular trafficking to lysosomes, the liposomes can be triggered to explode by mild external heating, generating powerful disruptive forces inside the cells, and eventually inducing cell death (Fig. 1). What is particularly interesting about this work is its creative use of liposomes — a leading drug-delivery

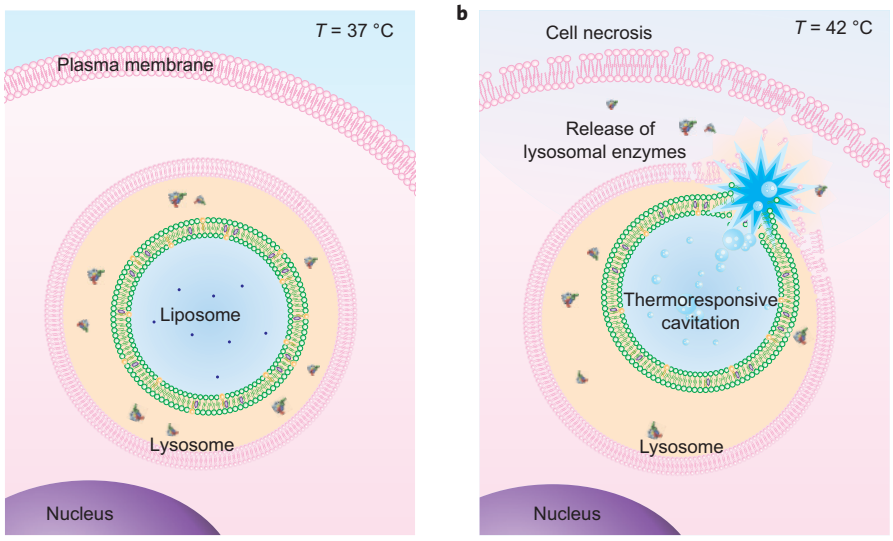

Figure 1 | A schematic showing the working mechanism of the thermoresponsive liposome system for destroying cancer cells. **a**, The liposomes containing ammonium bicarbonate reach lysosomes shortly after culturing with cancer cells. **b**, On heating up to 42 °C, the thermoresponsive liposomes generate transient cavitation, which disrupts lysosomal membranes, causes cells to lose their proteolytic contents, and ultimately leads to cell necrosis.

platform successful in chemotherapy — as a chemical nanoreactor to enable a physical-action-based anticancer strategy.

In this method liposomes play a critical role in converting chemical energy into mechanical forces, and the key step is the encapsulation of ammonium bicarbonate (NH_4HCO_3) within them. External heating causes the ammonium bicarbonate to decompose and generate bubbles of CO_2. Similar to the effects seen in sonochemistry — in which the bubbles are created using sound — the formation, growth and collapse of the CO_2 bubbles (known as 'transient cavitation') creates violent forces that can disrupt the membrane of the liposome. This sets off a chain of events that results in the death of the cell within which the liposomes reside.

Based on experiments *in vitro*, the researchers demonstrate that the liposomal NH_4HCO_3 is internalized within the lysosomes of cells. Lysosomes are membrane-bound vesicles that contain proteolytic enzymes. Heating the system to 42 °C results in the transient cavitation of CO_2 bubbles as described above. This disrupts the liposomal and lysosomal membranes, rupturing the lysosomes and releasing their enzymes into the cytosol, leading to cell death by necrosis.

Chung and colleagues' liposomal system has significant implications as it makes the disruptive mechanical forces 'deliverable'. The mechanical forces cause damage only at the spots where the liposomes are located. They demonstrate this by co-culturing cancer cells and normal cells in two neighbouring chambers that are separated by a membrane that allows the exchange of small biochemicals but not liposomes. The cancer cells are then exposed to the ammonium-bicarbonate-loaded liposomes and the normal cells are not. Chung and colleagues observe that only cells internalizing the liposomes undergo necrosis and the adjacent normal cells are not harmed.

Current developments using nanoparticles to improve on physical-action-based cancer therapies have been largely hindered by the low safety threshold of the inorganic materials that are commonly used for generating and focusing energy[6]. In contrast, the thermoresponsive liposome system developed by Chung and colleagues has fewer safety concerns given the vast numbers of liposomal systems approved for clinical use.

The CO_2-generating component, ammonium bicarbonate, is effectively non-toxic and widely used in food processing. Thermal decomposition of ammonium bicarbonate produces only small molecules that can be easily metabolized. Moreover, the liposomes are remarkably simple in composition, containing only a single type of compound for anticancer action, which means that the liposomal NH_4HCO_3 system leaves behind no harmful chemical agents after the treatment. These distinctive advantages, taken together, show that the liposome system developed by Chung and colleagues has a high potential for future clinical use.

The liposomes do not actively distinguish cancer cells from healthy cells. This is one aspect of the system that could be improved. For future development, the platform would benefit from the incorporation of additional mechanisms to specifically target cancer cells. Nanomedicine has already made significant progress and a rich knowledge has been accumulated of the principles required to engineer liposomes with precisely controlled physicochemical parameters and highly specific surface ligands designed to target tumours[7]. In addition to tumour targeting, the stability of the thermoresponsive liposomes needs to be reinforced under both storage and physiological conditions as liposomes typically have only moderate stability. This issue could potentially be solved by grafting the liposomal surfaces with established stealthy polymers such as polyethylene glycol or by other liposome stabilization approaches[8]. With continuing development, the thermoresponsive liposome system could become a valuable option for future cancer treatment. ❐

Weiwei Gao and Liangfang Zhang are in the Department of NanoEngineering and Moores Cancer Center, University of California, San Diego, La Jolla, California 92093, USA.
e-mail: zhang@ucsd.edu

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