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CANCER A targeted treatment with off-target risks

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to react with each other. Several groups have reported the crystal-to-crystal transformation of monomers into layered polymers using this strategy. However, these polymers were not fully conjugated 2D polymers, and could be exfoliated only by applying heat or certain solvents, or both.

Enter Liu and colleagues. The basic building block of their 2D-CAP is a planar molecule that contains several aromatic rings — rings of atoms whose stability is enhanced by complete delocalization of their π-electrons. The authors judiciously designed this aromatic monomer so that it can form an ordered arrangement that, when heated, undergoes a crystal-to-crystal solid-state polymerization (Fig. 1).

Liu et al. first attempted the polymerization of their monomer on the surfaces of single crystals of gold, using a process in which the monomer lost its bromine atoms on heating and then formed covalent carbon–carbon bonds with its neighbours at the positions where its bromine atoms were detached. This yielded an undesirable mixture of 1D and 2D polymers. But when the authors pre-ordered the monomer by crystallizing it, the reaction yielded a monocrystalline polymer that was fully conjugated and formed of planar layers. The layers are stacked with a distinct lamellar structure that can be readily exfoliated into micrometre-sized sheets just 1 nm thick. The fact that individual layers could be exfoliated using adhesive tape suggests that 2D-CAP is a close analogue of graphene.

The building block’s shape and the stacking of the polymers result in the formation of uniform 1D channels (approximately 0.6 nm in diameter) through the 2D-CAP. Liu et al. demonstrated that these aligned channels can be used to store sodium ions in an energy-storage device that can be quickly charged and discharged at room temperature. In other words, the polymer can be used as an organic anode in a sodium-ion battery.

Less than a decade ago, extended, planar, fully conjugated polymers were considered to be just a dream. The exciting properties of Liu and colleagues’ 2D-CAP open up new horizons in the field of 2D materials and will inspire future efforts in this arena. A potential drawback of the authors’ approach, if applied to other monomers, is that, when heated, some monomers might decompose before polymerization occurs. A variety of monomers must therefore be designed that polymerize at temperatures low enough to prevent decomposition. Flexible synthetic routes are also needed that allow different monomers and polymers to be made easily, because this in turn will allow the properties of 2D polymers to be tuned. Another promising direction of research could be to choose two different monomers that can co-crystallize before reacting to form a single polymer.

The 2D-CAP reported by Liu et al. might have promising properties in addition to those described. For example, its electronic and optoelectronic properties are yet to be measured. Such measurements will require exfoliated polymer sheets to be overlaid onto different substrates, so that they can be used as the active layer in devices such as field-effect transistors.

Liu and colleagues’ approach paves the way for a general, controlled synthesis of extended crystalline 2D-conjugated materials, and might form the basis of a new branch of crystal engineering. Such organic analogues of graphene would constitute a class of material that might be useful in various technologies, thanks to the enhancement of electronic properties that arises from π-conjugation in two dimensions. Applications might include organic transistors faster than those available today, and highly efficient solar cells and sensors.

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**CANCER**

A targeted treatment with off–target risks

It emerges that blood–cancer–targeting drugs that block a tumour–survival pathway also activate a mutation–causing enzyme in mice and in human cells. This might have implications for the clinical use of these drugs. See Letter p.489

**DAVID A. FRUMAN AND SUSAN O’BRIEN**

Chemotherapy drugs cause DNA damage that triggers the death of rapidly dividing cancer cells, and are the standard treatment for many cancers. However, because these drugs also affect healthy dividing cells, chemotherapy can cause undesirable damage that results in short-term side effects such as nausea and hair loss. DNA damage from chemotherapy also risks increasing the number of mutations that might, in the longer term, result in other cancers or enable the original tumour to develop resistance to treatment. By contrast, targeted therapies are designed to block specific molecular pathways in cancer cells and induce tumour-cell death without causing DNA damage. On page 489, Compagno et al. report studies of mouse models and human cells showing that two targeted drugs that are commonly used instead of chemotherapy in the treatment of certain blood cancers unexpectedly increase DNA damage in both healthy cells and tumour cells.

The targeted drugs in question are ibrutinib (Imbruvica) and idelalisib (Zydelig). These two compounds are the first examples of an emerging class of targeted-therapy agent that has revolutionized the treatment of certain tumours arising from immune cells known as B cells, and both compounds have been approved for use in treatment by the US Food and Drug Administration (FDA). The drugs, often described as B-cell–receptor inhibitors, block the action of enzymes that transmit signals from receptor proteins on B cells (Fig. 1). These receptors sustain survival and maintain the tumour cells in anatomical sites that provide a nurturing environment. This B-cell–specific mechanism helps to explain both the drugs’ efficacy and their relatively innocuous side-effect profile.

Clinical trials of both ibrutinib and idelalisib revealed unprecedented rates of leukaemia tumour regression, specifically in the most common adult leukaemia, chronic lymphocytic leukaemia (CLL), including in high-risk groups of people with CLL who tend not to respond to other classes of therapy. Ibrutinib is also approved for the treatment of other cancers, such as relapsed mantle-cell
Ibrutinib and idelalisib do not damage DNA directly or interfere with DNA-repair enzymes. However, idelalisib targets a signalling enzyme known as PI3Kδ that suppresses expression of the enzyme AID (refs 10, 11), which has a potentially dangerous capacity to affect DNA integrity. AID normally converts cytosine bases to uracil bases in the DNA sequence of antibody-forming immunoglobulin genes, leading to mutations and recombination (DNA-sequence-exchange events) that are essential to the production of diverse antibodies when fighting infection12. AID is expressed only in activated B cells in which an immune response is occurring, and the enzyme’s action is tightly controlled to preferentially target the immunoglobulin genes, because changes to other DNA sequences might cause cancer. Rare ‘off-target’ effects of AID on non-immunoglobulin genes can contribute to the development of certain human B-cell tumours9.

Compagno and colleagues observed that idelalisib or the PI3Kδ inhibitor duvelisib (an investigational drug) augment AID expression in activated B cells. As would be expected, this increase was accompanied by a higher frequency of on-target mutations and recombination events for immunoglobulin genes. This outcome might alter antibody responses, but would probably not affect patients’ health. However, of greater concern was an increase in off-target DNA recombination observed in activated B cells, leading to some DNA changes often found in B-cell cancers. Idelalisib and duvelisib treatment increased genomic instability when tested in human mantle-cell lymphoma cells in vitro. Using B cells from AID-deficient mice and genome-edited human B cells lacking AID, the authors show that the DNA damage triggered by PI3Kδ inhibitors depends on AID.

Ibrutinib inhibits an enzyme known as BTK. In most proposed B-cell-receptor signalling pathways, BTK acts downstream of PI3Kδ and is not thought to be involved in the pathway that regulates AID expression. However, some studies suggest that PI3Kδ and BTK work together in a large multiprotein complex and support each other’s activity13. Compagno and colleagues observed that inhibiting BTK with ibrutinib reduced PI3Kδ activity (monitored by phosphorylation of the protein AKT) and increased AID expression in B cells. In comparison to treatment with PI3Kδ inhibitors, ibrutinib also resulted in increases in genomic DNA mutation and recombination events, although to a lesser extent.

Two key experiments support the in vivo relevance of these findings. First, Compagno and colleagues report that idelalisib, duvelisib and ibrutinib all increase the development of AID-dependent tumours of B-cell origin in a mouse model. Second, the authors’ analysis of DNA from blood cells of people with CLL before and after treatment with idelalisib demonstrated a significant increase in off-target mutations by AID.

As the authors note, longer-term follow-up of patients treated with B-cell-receptor inhibitors will be needed to evaluate whether the events demonstrated in mice, such as an increase in the formation of AID-dependent tumours, occur in humans. Both ibrutinib and idelalisib were approved by the FDA less than five years ago. These agents are given indefinitely, and treatment is generally continued until the disease becomes resistant or the patient encounters an unacceptably high level of toxicity. In the phase II clinical trial of ibrutinib, one cohort group received ibrutinib after failure of chemotherapy and the other cohort group received it as their initial treatment. In the five-year follow-up of this trial, about one-third of people receiving ibrutinib after failure of chemotherapy were still on ibrutinib treatment, whereas two-thirds of people who received ibrutinib as their initial therapy were still responding to treatment and receiving the drug14.

Because complete remissions with B-cell-receptor inhibitors are uncommon, there is little enthusiasm for stopping therapy — the presumption is that if treatment were to cease, the disease would recur. Recent strategies have explored small-molecule combination approaches, such as the use of two B-cell-receptor inhibitors, in an attempt to increase complete remission rates and enable discontinuation of therapy. Given that Compagno and colleagues’ results demonstrate that drugs considered to be non-DNA-damaging might, in fact, induce genomic instability, the ability to discontinue therapy might become an even more attractive concept to address in clinical trials in the future.

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**Figure 1** Inhibition of a B-cell-receptor signalling pathway might increase the number of harmful mutations. Certain blood cancers, such as chronic lymphocytic leukaemia, require activation of a B-cell-receptor signalling pathway to survive. In a signalling pathway downstream of the B-cell receptor, the kinase enzymes PI3Kδ and BTK have been proposed to promote each other’s activity10. When an immune response occurs, PI3Kδ maintains low expression of the enzyme AID, which mutates the DNA of immunoglobulin genes to facilitate the formation of diverse antibodies. The drugs idelalisib and ibrutinib target a B-cell-receptor signalling pathway and are used for cancer treatment; idelalisib and duvelisib (an investigational drug) both inhibit PI3Kδ, and ibrutinib inhibits BTK. Using mouse models and human cells, Compagno et al.11 observed that drug-mediated inhibition of the B-cell-receptor signalling pathway can increase the expression of AID, causing DNA mutations in non-immunoglobulin off-target genes — potentially increasing the incidence of tumour-promoting mutations. Effects of drug use are shown in red.