Russian scientists develop hybrid molecules that evade cancer drug resistance

Russian scientists have created hybrid molecules that suppress tumour cell growth, including in cells that have become resistant to existing drugs. In cell culture experiments, these compounds proved 1.5 times more effective than one of the newest drugs used against resistant tumours. The findings could form the basis for a new generation of drugs for patients whose cancers no longer respond to standard therapy. The results were published in the journal Synthetic Communications.

Cancer claims nearly 10 million lives each year. Conventional chemotherapy is effective but causes severe side effects by destroying healthy cells along with tumours. Moreover, cancer cells can acquire drug resistance through genetic mutations. For example, many modern chemotherapeutics – such as erlotinib and gefitinib – block the epidermal growth factor receptor, a protein that is overactive in cancer cells and drives uncontrolled division. However, when this protein mutates, the drug stops working. Scientists are therefore searching for new molecules that can bypass the defence mechanisms of even resistant tumours.

Researchers from the Russian Presidential Academy of National Economy and Public Administration, together with colleagues, have synthesised hybrid molecules capable of blocking the epidermal growth factor receptor in cancer cells that are insensitive to existing drugs.

The building block for the assembly was oxadiazole – a ring compound of carbon, oxygen and nitrogen atoms. To this, the scientists attached a tetrazole ring, which forms strong hydrogen bonds with the active site of the target protein. Using a flexible molecular "bridge", the authors also introduced additional groups of various types, including one containing chlorine.

The key difference from existing analogues is that the new molecules, thanks to the bridge and the additional groups, find binding sites on the target protein not only in the active centre but also outside it – in regions that are not affected by mutation. This can be compared to a key with multiple notches that engage different parts of a lock. Even if one protrusion is missing, the remaining contact points still allow the door to open.

The researchers tested the new molecules on lung, liver, colon and breast cancer cell lines. The compound without chlorine killed cancer cells at concentrations comparable to those of osimertinib – one of the newest and most expensive drugs used against certain resistant tumours.

Using computer modelling, the scientists also assessed how the compounds would behave in the human body – their solubility and potential toxicity to healthy tissues.

"In medicinal chemistry, a drug molecule must fit its receptor like a key in a lock," said Olga Mikolaichuk, project leader and senior researcher at the Russian Presidential Academy of National Economy and Public Administration. "We have found just such an ideal key. It turned out that adding just one element – chlorine – to the molecular structure makes it most effective at stopping tumour cell division and triggering cell death. Next, we plan to combine the most active molecules with the protein albumin to reduce the risk of severe allergic reactions and improve treatment tolerability. This technology is already used in some modern anticancer drugs, such as Abraxane."

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