Substance tackles skin cancer from two sides

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By playing it safe and using a two-pronged attack, a novel designer molecule fights malignant melanoma. It was created and tested by an international team of researchers led by the University of Bonn. On the one hand, the substance is similar to components of viruses and in this way alerts the immune system. The body's own defences are also strengthened against cancer cells in this process. At the same time, the novel molecule also puts pressure on the tumour in a different way. It switches off a specific gene in the malignant cells, thus driving them to suicide. With mice suffering from cancer, the researchers have thus been able to fight metastases in the lung. In *Nature Medicine*'s November issue they report about this promising strategy.

For their research project, the scientists drew on the latest insights into biology's box of tricks. A close relative of the nuclear DNA, known as RNA, served them as therapy. It has only been known for a few years that small RNA molecules can basically be used to target certain genes and switch them off. This effect is called RNA interference; the Americans Craig Mellow and Andrew Fire were awarded the Nobel Prize in 2006 for its discovery.

'We used this method in order to drive the tumour cells to suicide,' the Bonn dermatology researcher Professor Thomas Tüting explains. Every single body cell is equipped with a corresponding suicide programme. It is activated, for example, if the cell becomes malignant. It dies before it can do any more harm. 'But in tumours a gene is active that suppresses this suicide programme,' Professor Tüting, who is head of the Experimental Dermatology Laboratory, explains. 'We have pinpointed

this gene and switched it off by using RNA interference.'

At the same time the researchers also crept up on cancer by another route: 'We basically "disguised" our RNA,' Professor Gunther Hartmann, director of the Institute of Clinical Chemistry and Pharmacology says. 'That is why the immune system took it for the genetic makeup of a virus.' Many viruses actually do use RNA to store information. So if the body discovers RNA fragments which it takes to be the genetic makeup of a virus, it mounts an attack on them. By means of this trick the body's defences were prompted to tackle the tumour cells far more aggressively than normal.

RNA is also present in the body's own cells. For a long time it was not known how the immune system distinguishes between 'harmful' and 'harmless' RNA. Only two years ago, Professor Hartmann was able to shed light on the problem in a sensational article in the journal 'Science'. The scientists used this knowledge in order to modify the RNA substance in such a way that it was able to alert the immune system.

'The beauty of this method is that we can attack the cancer with one designer molecule along two completely different routes,' Professor Hartmann says. 'This way the tumour is deprived of opportunities of sidestepping the attack that make successful therapy so difficult in other cases.' Initial experiments in mouse models have shown that growth of metastases in the lungs is inhibited significantly by the new molecule. The therapy even led to the secondary tumours becoming smaller or even disappearing entirely.

Despite this, the research team warns against excessive optimism: 'What works in mice does not necessarily prove successful in humans as well,' Professor Tüting warns. 'Apart from that, many issues need to be addressed before a trial with cancer patients can even be thought of.' Still, the approach appears very promising, especially as the therapeutic

RNA molecule can be easily customised to suit different kinds of cancer.

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