

New cancer findings can give wider access to immunotherapy

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Researchers at Karolinska Institutet in Sweden have published new findings in the journal *Cancer Discovery* showing how pharmacological activation of the protein p53 boosts the immune response against tumours. The results can be of significance to the development of new combination therapies that will give more cancer patients access to

immunotherapy.

Given its ability to react to damage to cellular DNA, and the key role it is thought to play in preventing [tumour growth](#), the [protein p53](#) has been dubbed the "guardian of the genome." Half of all tumours have mutations in the gene that codes for the protein, and in many other tumours, p53 is disabled by another protein, MDM2.

It has long been known that p53 is able to silence certain sequences in our genome called endogenous retroviruses (i.e. DNA elements evolutionarily inherited from viruses), thus preventing genome instability. The researchers now show that the protein can also activate these sequences in cancer cells, leading to anti-tumour [immune response](#).

"This was an astonishing discovery. When we blocked the suppressor MDM2, p53 activated [endogenous retroviruses](#), which induced antiviral response and boosted the production of immune-activating interferons," says lead investigator Galina Selivanova, Professor at the Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet.

The results were obtained when the researchers blocked MDM2 in mouse models using a substance coded as ALRN-6924 from the US company Aileron Therapeutics. The increase of interferon response was also seen in tumour samples from two patients taking part in the company's clinical trials of ALRN-6924.

"This shows that there are synergies that should be exploited between substances that block MDM2 and modern immunotherapies," Professor Selivanova continues. "A combination of these can be particularly important for patients who don't respond to immunotherapy."

Immunotherapy, or immuno-oncology, is described as a revolution in modern cancer treatment in the way it triggers the body's immune

system to fight [cancer cells](#). However, it does not work with all patients, and the presence of interferons could be a biomarker for whether or not immunotherapy will prove efficacious.

"If we can increase the level of interferons, we can therefore increase the chances that the immunotherapy will succeed."

Professor Selivanova is a pioneer in research on how mutated p53 can be re-activated using special molecules, one of which, APR-246, is undergoing clinical studies under the name Eprentapopt at Aprea Therapeutics, a company that she co-founded.

"We now want to examine if Eprentapopt produces the same interferon boost and can have the same potential to increase access to immunotherapy for patients with severe forms of [cancer](#)," she says.

More information: Xiaolei Zhou et al, Pharmacological activation of p53 triggers viral mimicry response thereby abolishing tumor immune evasion and promoting anti-tumor immunity, *Cancer Discovery* (2021). [DOI: 10.1158/2159-8290.CD-20-1741](https://doi.org/10.1158/2159-8290.CD-20-1741)

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