# Rotavirus vaccine: A potential new role as an anticancer agent

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Numerous vaccines, from flu shots to those those that help thwart chickenpox and measles, are widely used to guard against contagion, but researchers in France are proposing a breakthrough role for rotavirus vaccines: deploying them in cancer treatment.

Scientists from throughout France—Paris, Lyon, Villejuif and beyond—are part of a large research team that has asked a tantalizing question: Can rotavirus vaccines be repurposed to overcome resistance in cancer immunotherapy? The team is focusing on resistance that emerges to the form of cancer treatment known as checkpoint blockade immunotherapy.

So far, their investigation suggests the question about repurposing can be answered with a resounding "yes."

"We have found that rotavirus vaccines, Rotateq and Rotarix, have both immunostimulatory and oncolytic properties," Dr. Tala Shekarian of Centre de Recherche en Cancérologie de Lyon told Medical Xpress.

"Moreover, they can directly kill cancer cells with features of immunogenic cell death. In vivo, intra-tumoral rotavirus therapy has anti-tumor effects, which are mainly immune-mediated," she said.

To date, the research has been conducted in cell lines and animal models with results that have surprised seasoned scientists.

"Interestingly, in several immunocompetent murine tumor models, intra-tumoral rotavirus overcame resistance to and synergized with immune checkpoint-targeted therapy," Shekarian said.

Checkpoint blockade immunotherapy is an innovative form of treatment that relies on medications known as immune checkpoint inhibitors to address multiple forms of cancer. These medications engage the body's immune system to recognize and attack malignant cells. Keytruda, a medication that helped revolutionize the treatment of non-small-cell lung cancer is a checkpoint inhibitor drug.

All checkpoint inhibitors are based on a deceptively simple principle:

Cancer cells possess a protein dubbed PD-L1. T cells, key soldiers in the immune system's army, have a surface protein called PD1. Tricky cancer cells use their PD-L1 proteins to help them elude T cells, to get past the guards—the checkpoints—activities that allow them to proliferate and spread. Checkpoint inhibitor medications prevent cancer cells from eluding and hiding.

A problem with these drugs, which are used to treat multiple cancers ranging from Hodgkins lymphoma to lung, bladder, ovarian and kidney cancers, is that they simply stop working. Cancer cells develop resistance to them in a way that is vaguely similar to the stubborn resistance of superbugs to antibiotics. Once resistance emerges, tumor cells can resume exploiting the vast armies of "good guys," the T cells, which are again unable to keep lethal, malignant invaders at bay.

Enter the rotavirus vaccines.

They are already approved, possess a high safety profile and complement checkpoint inhibitor treatments, scientists in France say.

Reporting in *Science Translational Medicine*, Shekarian is the first author in an investigation that demonstrates how off-the-shelf rotavirus vaccines can double as anticancer agents. The discovery suggests that viruses, but not just rotavirus, possess potent anticancer properties. The pathogens can deactivate properties of cancer cells whether they are live agents or attenuated—weakened—as vaccines.

The oncolytic properties of common viruses can be exploited to prime antitumor immunity, the team wrote in the journal.

Shekarian and her colleagues underscored in their report that while many "viruses are currently in active clinical development in combination with immune checkpoint–targeted therapies … the implementation of these

therapies is limited by their manufacturing constraints [and] the risk of exposure of clinical staff."

A more expeditious approach, the French team reported in the journal, was to test already approved agents.

"Rotavirus vaccines are pediatric and adult clinical grade products. Therefore, in situ immunization strategies with intra-tumoral attenuated rotavirus could be implemented quickly in the clinic," Shekarian told Medical Xpress.

The research was led by Dr. Aurélien Marabelle of Centre de Lutte contre le Cancer Léon Bérard in Lyon. Marabelle, who is traveling and unable to comment on the team's laboratory investigations, is also associated with INSERM, or Institut national de la santé et de la recherche médicale. INSERM is the French national institute of health and research, the only public health research institution in France.

The researchers tested several vaccines in vitro and found that rotavirus vaccines activated NF-κB, which stands for nuclear factor kappa light chain enhancer of activated B cells. This is a family of transcription factors that regulate important cellular activities such inflammatory responses, cell growth and apoptosis, or programmed cell death.

In a human cell line, NF-κB was protective in a tumor model that was resistant to an immune checkpoint blockade, Shekarian, Marabelle and the team found.

Additional research involving live or inactivated rotavirus vaccines in multiple tumor models showed durable immunity, especially when combined with other immunotherapies.

These studies indicate that rotavirus vaccines already in production and

circulation could double as anticancer agents, the scientists said.

"The development in clinic of such approaches was the driver of the work, using commercially available vaccines," Shekarian said, noting that they are safe for children, they're inexpensive and easily available worldwide, including underdeveloped countries.

**More information:** Tala Shekarian, et al. Repurposing rotavirus vaccines for intratumoral immunotherapy can overcome resistance to immune checkpoint blockade, *Science Translational Medicine* (2019) DOI: 10.1126/scitranslmed.aat5025