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Oncolytic adenovirus VCN-01 turns cold tumors hot

VCN Biosciences is developing a highly selective, advanced generation of oncolytic adenoviruses.

Intriguing historical observations that some viral infections can promote cancer remission have led to investigations of the therapeutic potential of oncolytic viruses that replicate, infect and selectively lyse tumor cells. This interest has increased dramatically in recent years with the recognition that such approaches may help tackle tumors that have thus far proved less responsive to immune checkpoint inhibitors, by turning immunologically 'cold' tumors 'hot'.

Clinical-stage immuno-oncology company VCN Biosciences is developing a portfolio of its own uniquely designed therapeutic oncolytic adenoviruses. The company's experienced team is currently pursuing four clinical trials of its lead candidate VCN-01, focusing on different tumor indications, that have shown promising results in refractory tumors such as pancreatic adenocarcinomas, retinoblastoma, and metastatic squamous cell carcinoma of the head and neck.

VCN's proprietary PH20 hyaluronidase expression technology is at the core of its oncolytic virus pipeline, including VCN-01. PH20 hyaluronidase breaks down hyaluronan, a component of the tumor extracellular matrix. In desmoplastic tumors, such as pancreatic cancer, this hyaluronan-rich matrix blocks the perfusion of anticancer therapeutics. The hyaluronidase expression technology thus enables unique tumor remodelling properties that improve intratumoral viral spreading, immune system infiltration, and tumor uptake of drugs. Importantly, the expression of PH20 requires an actively replicating virus; nontumor cells that may be infected with VCN-01 do not allow viral replication nor PH20 expression.

Furthermore, the resulting adenovirus candidates also exhibit a range of beneficial properties, including the possibility of systemic administration, incorporation of a variety of expression cassettes, and a good toxicity profile. This allows for the administration of extremely high doses of the virus, which disperse through the bloodstream toward the body's different metastatic sites. Once the virus reaches and infects the tumor cell, its highly cytopathic nature enables the efficient generation of tumor neoantigens that can boost the innate immune response (**Fig. 1**).

Unlike other companies in the fast-moving viral oncolytic field that have developed products to express immune-stimulatory transgenes, VCN believes its adenoviruses naturally contain sufficient immune-stimulatory elements, and that the expression of hyaluronidase by its candidates and remodelling of the matrix are crucial to the induction of effective immune responses.

VCN-01 leading the way in pancreatic cancer

VCN-01, VCN's lead candidate, is being developed to target a range of solid tumors, focusing initially on pancreatic cancer. Virus penetration within the tumor is improved through the expression of hyaluronidase by VCN-01, which simultaneously decreases intratumoral fluid pressure and facilitates the uptake of the chemotherapy or biologic drug. In addition, VCN's capsid has been engineered to ensure the virus evades liver tropism and selectively targets the tumor once administered intravenously.

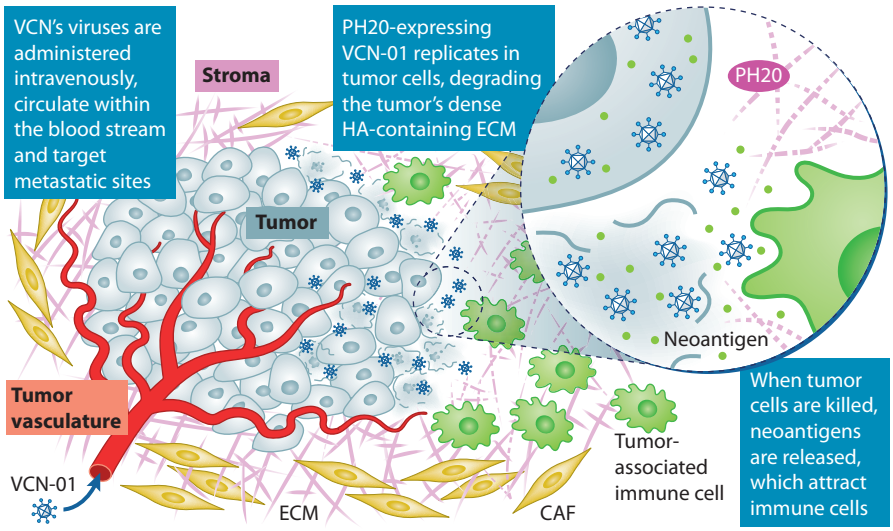

Fig. 1 | Expression and replication by VCN Biosciences' unique products. VCN-01 is designed to selectively target and replicate only in cancer cells, leading to the release of tumor neoantigens. CAF, cancer-associated fibroblast; ECM, extracellular matrix; HA, hyaluronan. Image modified from original source: Park, K., Han, B. & Korc, M. in *Cancer Nanotechnology Plan 2015* (ed. Hartshorn, C. M.) 25–28 (National Cancer Institute, 2015).

Clinical data from patients with pancreatic cancer demonstrated an extremely good safety profile, and also showed that VCN-01 induced $CD8^+$ T cell infiltration and activation of interferon-γ-mediated transcription, effectively converting a poorly immunogenic tumor into an inflamed tumor. In addition, in a subset of patients, the expression of programmed cell death 1/programmed cell death 1 ligand 1 was upregulated.

Additional data obtained to date in patients with pancreatic cancer have shown higher response rates and longer survival with VCN-01 than with the standard of care. More importantly, long-term survivors (more than 3.5 years) showed delayed significant responses that were indicative of immune-mediated activity.

To further confirm its antitumoral activity and to assess its potential, in addition to a trial investigating its use in combination with nab-paclitaxel and gemcitabine for pancreatic cancer, VCN-01 is currently being tested in combination with immune checkpoint inhibitors in metastatic squamous cell carcinoma of the head and neck refractory to checkpoint inhibitors. Results from these trials are expected soon.

Next steps and partnering

Having originated from the Virotherapy Group of the Catalan Institute of Oncology (ICO-IDIBELL), VCN still benefits from a tight collaboration with the institute, which has resulted in a very promising second candidate (VCN-11). VCN-11 has been specifically designed to overcome one of the theoretical limitations for adenovirus: the blocking of the virus by neutralizing antibodies. This candidate is currently in the late preclinical stage and is expected to enter the clinic soon.

Following the very strong data from its trials of VCN-01, the company is interested in further exploring the combination of this candidate with immune checkpoint inhibitors to target immunological cold tumors including pancreatic cancer. According to VCN's CEO Manel Cascalló, "VCN-01 is ready for combination trials and we are therefore interested in collaborating with interested parties in the field."

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