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Gamechanger: how PsiVac is unleashing the full power of oncolytic viruses

Biotech company PsiVac is developing Ixovex-1, the first patented virus with a single base pair mutation able to replicate rapidly, opening potential new treatment options for solid tumors and beyond.

PsiVac is set to end decades of disappointing data on oncolytic viruses with a radical new approach that upends conventional wisdom about the modality. Rather than engineer the viral genome, PsiVac introduces a critical single base pair mutation to create viruses that are highly selective and replicate rapidly. The result is a virus, Ixovex-1, that delivers a step change in efficacy and enhanced safety.

Oncolytic viruses can be incredibly powerful. Selectively replicating oncolytic viruses infect tumor cells, make copies of themselves and lyse their hosts, releasing progeny that infect adjacent tumor cells and repeat the process. Oncolytic viruses thereby directly kill cancer cells and cause the release of tumor-associated antigens that enable the immune system to recognize a cancer type and develop long-term memory against it. The one-two punch of direct killing and the triggering of the immune system are potentially highly potent.

Yet, oncolytic viruses have so far failed to fully deliver on that promise. The problem stems from the deletion of part of the viral genome to achieve selectivity for tumor cells. Deletions enhance safety but reduce replication efficiency, significantly limiting efficacy.

Many companies are pitching armed oncolytic viruses as the solution to limited efficacy. By adding a gene encoding for an immunomodulatory cytokine, such as GM-CSF, researchers can create viruses that cause local expression of immune therapeutics and alter the tumor microenvironment.

> **PsiVac is the first company with a patented virus that has no insertion or deletion**

That approach fails to fix the reduced replication efficiency that is the fundamental weakness of engineered viruses, though, and is unlikely to work better than systemic administration of a cytokine. The amount of cytokine produced using armed oncolytic viruses is unknown, making the dosage and timing less controllable than systemic delivery. The uncertain benefits are offset by the demonstrated downside of weakening replication efficiency.

Efforts to develop drugs without that downside have been undermined by the refusal of patents on viruses without insertions or deletions. PsiVac, a UK-based biotech, overcame that barrier using a critical single base pair mutation, making it the first company with a patented virus that has no insertion or deletion. PsiVac will soon prove its hypothesis clinically. A phase 1 clinical trial will commence in late 2021, followed shortly by a phase 2 study.

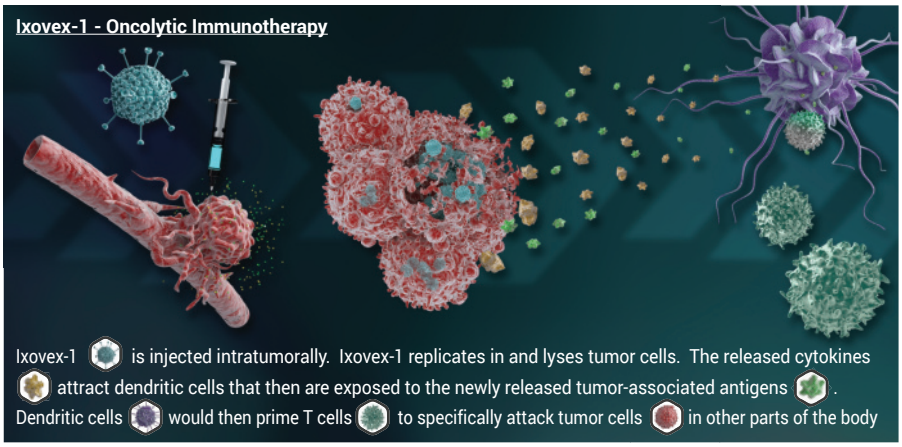

Fig. 1 | The mode of action of Ixovex-1 developed by PsiVac.

Validating a breakthrough concept

Ixovex-1 is almost identical to the wild-type form of the human adenovirus serotype 5. The only difference is a single base pair mutation at a specific splice site. That limited modification enables PsiVac to maintain the structural integrity of the virus while inhibiting replication in normal cells and enhancing efficacy (Fig. 1).

In preclinical tests, Ixovex-1 replication was significantly attenuated in healthy cells compared with wild-type virus and H101 virus; a gene-deleted adenovirus sold as Oncorine. PsiVac's findings suggest Ixovex-1 will be safer than an approved oncolytic virus.

PsiVac has generated compelling efficacy data, too. In large and non-small cell lung cancer (NSCLC) cells, Ixovex-1 replicated as well as the wild-type control and significantly better than H101 virus, validating PsiVac's hypothesis that its modification maintains replication efficiency. An evaluation of Ixovex-1 in 16 solid tumor cell lines provided further validation.

In a preclinical proof-of-concept study, Ixovex-1 was better at controlling NSCLC than H101 virus and as effective as the wild-type virus. Two of the seven mice treated with Ixovex-1 were cured, showing that the maintained replication efficiency translates into superior efficacy.

Advancing a life-saving medicine

Having shown that Ixovex-1 is safe, powerful and replication efficient in all tested solid tumor cell lines, PsiVac is planning human clinical trials. Lonza carried out successful small-scale feasibility production studies, paving the way for upscaling and current good manufacturing practice (cGMP) production. Lonza is a leader in contract manufacturing, and employs top cell and gene therapy experts, offering services ranging from process development to clinical and commercial supply. PsiVac has partnered with Lonza for the process development and GMP manufacture of Ixovex-1.

Kevin Harrington will oversee trials in London at the Royal Marsden and University College London hospitals. Harrington was lead investigator on the pivotal trial of T-Vec, the first oncolytic virus approved in the USA.

PsiVac plans to test Ixovex-1 in combination with another drug, possibly a checkpoint inhibitor, in phase 2 trials. That plan is informing PsiVac's criteria for selecting a partner. PsiVac is looking for a partner with immuno-oncology assets and expertise, and the capabilities and drive needed to quickly take Ixovex-1 to market. The biotech company may alternatively seek investment and advance Ixovex-1 itself.

Organizations that partner, license, or invest will gain exposure to a potentially game-changing asset in one of the hottest immuno-oncology subsectors and help PsiVac realize the full, life-saving potential of oncolytic viruses.

CONTACT
Imad Mardini
PsiVac Ltd
London, UK
Tel: +44 20 7971 1100
Email: i.mardini@ixogen.com