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Oncolytic viruses targeting CD47: a new road to success?

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ABSTRACT

Clinical success in the therapeutic targeting of the CD47 signaling pathway has thus far remained elusive despite a promising scientific rationale. Use of oncolytic viruses to deliver CD47 targeting agents represents a novel approach to modulate the immunological landscape of the tumor microenvironment and to generate a systemic antitumor immune response. In recent preclinical studies, an oncolytic herpes simplex virus-1 engineered to express an inhibitory CD47-binding nanobody demonstrated promising antitumor activity. Several other oncolytic viruses engineered to express CD47 inhibitory molecules are also in preclinical development. Oncolytic viruses have the potential to mitigate drug delivery issues and may avoid systemic toxicities that have limited conventional CD47 targeting therapeutics. These novel therapeutics warrant further evaluation in clinical trials. The potential advantages, limitations, and remaining critical questions regarding this strategic approach are discussed here.

In 2009, the Weissman Laboratory at Stanford identified the cell surface protein CD47 as a compelling anticancer target.[1 2] In an elegant series of mechanistic studies, the interaction of CD47 with its cognate receptor, signal regulatory protein-alpha (SIRPα) triggered a potent "don't eat me signal" to phagocytic immune effector cells including macrophages. Blocking the CD47-SIRPα interaction in the presence of secondary prophagocytic signals activated the destruction of target malignant cells by tumor-associated macrophages. This potent innate immune response results in the direct killing of tumor cells while simultaneously enhancing antigen presentation by dendritic cells and macrophages leading to an augmentation of the adaptive immune response.[3] Although CD47 is ubiquitously expressed in a broad range of tissues, malignant cells frequently overexpress CD47 relative to their normal tissue counterparts.[3] These seminal observations led to the clinical development in 2014 of the first anti-CD47 therapeutic, magrolimab (hu5F9-G4), a chimeric humanized IgG4 monoclonal antibody (mAb).[4]

Early clinical results with magrolimab were promising, with an acceptable safety profile and preliminary signals of antitumor activity.[4] Antitumor activity was enhanced when magrolimab was combined with agents that augmented prophagocytic signals on cancer cells. This included combinations in non-Hodgkin's lymphoma with rituximab, an anti-CD20 mAb with an active Fc domain that interacts with macrophage Fc receptors to stimulate phagocytosis.[5] Clinical activity was also seen in combination with azacitidine in high-risk myelodysplastic syndrome (hrMDS) and acute myeloid leukemia (AML).[6] Azacitidine can enhance the expression on target cells of calreticulin, which is known to have potent prophagocytic signaling properties.[7] These findings prompted the rapid entry of many additional CD47 inhibitors into clinical development.[8] However, despite the early clinical promise, subsequent randomized Phase 3 trials of magrolimab combinations in hrMDS and AML did not yield positive results.[9] Full study details have yet to be published, but safety concerns possibly including cytopenias and infections did lead to these studies being placed on temporary clinical hold.[9] The safety issues that emerged in these larger randomized global trials were not as prominent in the initial early phase studies.[8] Consequently, the enthusiasm for the therapeutic targeting of the CD47 pathway has diminished. Thus, despite compelling scientific rationale and promising early activity, the ultimate therapeutic success of agents targeting the CD47-SIRPa signaling pathway remains uncertain.

Recently, Li *et al* developed an oncolytic vaccinia virus (OVV) engineered with a transgene encoding for a CD47 blocking nanobody (OVV-αCD47nb) to inhibit tumorous CD47-SIRPα signaling.[10] This therapeutic strategy combines direct viral oncolytic effects with the selective delivery of an anti-CD47 molecule to the tumor microenvironment (TME). The αCD47nb construct lacks an active Fc domain, but it is an effective inhibitor of CD47 signaling. Successful delivery of immune response modulators using engineered oncolytic viruses is supported by the prior clinical approval of talimogene laherparepvec, which is an oncolytic herpes virus

Table 1 CD47 targeting oncolytic viruses

Agent	Oncolytic virus	CD47 inhibitor	Preclinical in vivo efficacy	Reference
OVV-αCD47nb	Vaccinia	αCD47nb	4T1 Breast, CT26 colon cancers	Li *et al*[10]
SG635-SF	Adenovirus	(SIRPα)-IgG1 Fc fusion protein	SK-OV3 and HO8919 ovarian cancer	Huang *et al*[15]
OV-αCD47-G1	HSV-1	αCD47-IgG1 antibody	Glioblastoma, breast cancer brain metastases, ovarian cancers	Xu *et al*[12] Tian *et al*[13] Wang *et al*[14]
SIRPα-Fc-VV	Vaccinia	(SIRPα)-IgG4 Fc fusion protein	Osteosarcoma	Cao *et al*[16]

Fc, fragment crystallizable; HSV-1, herpes simplex virus-1; IgG1, immunoglobulin G1; IgG4, immunoglobulin G4; OVV, oncolytic vaccinia virus; SIRPα, signal-receptor protein alpha; VV, vaccinia virus; αCD47, anti-CD47; αD47nb, anti-CD47 nanobody.

(HSV-1) engineered to express granulocyte-macrophage colony-stimulating factor. In 2015, the Food and Drug Administration (FDA) approved this agent for use in patients with advanced melanoma.[11]

In a series of preclinical studies by Li *et al*,[10] intratumoral injection of OVV-αCD47nb virus continually released αCD47nb in tumor tissues, ultimately resulting in superior growth inhibitory activity against breast and colon tumor cells and prolonging survival compared with control OVV alone. In the TME, treatment increased macrophage infiltration and polarized toward an antitumoral M1 macrophage phenotype. Broad systemic in vivo antitumor effects were also noted including the inhibition of lung metastases and the regression of distant tumors indicating an abscopal effect. Furthermore, the combination with a programmed cell death protein-1 (PD-1) immune checkpoint inhibitor further augmented OVV-αCD47nb antitumor activity consistent with an enhancement of both innate and adaptive antitumor immune responses.

The use of oncolytic viruses to deliver CD47 inhibitors is not entirely new (table 1). Previously, Xu *et al* engineered an oncolytic HSV-1 to express an anti-CD47 mAb.[12] This full-sized IgG1 anti-CD47 antibody contains an active Fc domain that can opsonize target cells thereby stimulating macrophage-induced antibody-dependent cellular phagocytosis and natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity. This virus induced the continuous release of CD47-blocking antibody in a glioblastoma mouse model resulting in intracranial macrophage infiltration and the subsequent phagocytosis of tumor cells. Intracranial injection of the virus limited anti-CD47 mAb systemic exposures and when combined with PD-1 checkpoint blockade it enhanced antitumor activity. Similar preclinical in vivo efficacy was seen in ovarian cancer models.[13] This viral construct was also active in combination with temozolomide in breast cancer brain metastases models.[14]

Huang *et al* developed an engineered oncolytic adenovirus with a transgene encoding for a SIRPα IgG1-Fc fusion protein.[15] The CD47 receptor SIRPα, when expressed as a trap fusion protein, is a potent CD47 binder that inhibits pathway signaling. Intratumoral injection of this viral construct resulted in improved tumor growth inhibition in vivo in a subcutaneous human ovarian cancer tumor relative to non-engineered viral controls. Immunohistochemical analyses demonstrated the recruitment of macrophages and NK cells into the TME after intratumoral injection. Cao *et al* developed a different SIRPα fusion protein engineered to be expressed by an OVV.[16] This viral construct expressed a chimeric SIRPα ectodomain fused to an IgG4 antibody Fc domain. This molecule increased survival in an in vivo subcutaneous osteosarcoma model relative to viral constructs that did not express the SIRPα fusion protein.

These preclinical studies conducted by Li *et al* and by others, demonstrate that intratumorally injected oncolytic viruses can deliver CD47-blocking signals to the TME with the potential for broad antitumor activity.[10] This may circumvent the limitations of traditionally administered anti-CD47 molecules that may be hampered by drug delivery and systemic toxicity issues. For example, the ubiquitous expression of CD47 on normal tissues creates a large pharmacokinetic sink that must be saturated before effective concentrations of anti-CD47 mAbs can access the TME. The need to administer high doses of CD47 blocking agents may incur greater safety risks due to potential adverse effects on normal cells. An engineered oncolytic virus that selectively targets the TME may obviate the safety risks encountered by conventional CD47 targeting agents such as magrolimab. Engineered oncolytic viruses are a promising therapeutic approach that deserves further evaluation in clinical trials.

However, there are still important concerns regarding this strategic approach. The vast majority of FDA-approved anticancer agents use an intravenous or oral route of administration rather than an intratumoral approach.[17] Furthermore, critical remaining questions include what is the optimal oncolytic viral vehicle and which CD47-targeting constructs are the most effective? The only FDA-approved oncolytic virus is an HSV-1 construct,[11] while the CD47-targeting viruses described here include HSV-1, adenovirus, and vaccinia viruses. In preclinical studies, all appear to effectively deliver CD47 inhibitory molecules to tumor tissues. However, the construct expressed by the OVV-αCD47nb virus developed by Li *et al*[10] lacks an

antibody Fc domain unlike the CD47-blocking constructs expressed by other CD47-targeting oncolytic viruses.[12 14 16] Thus, the αCD47nb protein cannot directly engage with Fc gamma receptors on macrophages to further enhance phagocytosis. In contrast, CD47 binders expressed by other oncolytic viruses that incorporate active IgG1 or IgG4 Fc domains can simultaneously add potent prophagocytic signals to target cells, thereby optimizing phagocytosis by effector macrophages.[3] Finally, the historical development of CD47 targeting molecules has focused on combination regimens due to this requirement for additional secondary prophagocytic signals on target cells.[8] Thus, the compelling antitumor activity of OVV-αCD47nb in preclinical studies may not fully translate to clinical efficacy unless combination strategies are employed. Potentially promising regimens for further clinical testing include combinations with mAbs containing active Fc domains, with programmed death-ligand 1 checkpoint inhibitors, or with other molecules that can augment prophagocytic signals on tumor cells. However, oncolytic viral constructs with active Fc domains may incur greater toxicity risks due to the increased potential to induce phagocytosis of normal cells expressing CD47. Effects on normal tissues may or may not be mitigated by the selective delivery mediated by oncolytic viruses. Further studies are needed to discern the clinical relevance of these different mechanisms of action.

In conclusion, these preclinical studies clearly demonstrate that engineered oncolytic viruses can inhibit CD47-SIRPα signaling in the TME and can augment in vivo antitumor immune effects. Consequently, clinical trials evaluating this novel approach are warranted. Until then, modulating CD47 signaling remains an anticancer strategy that has yet to demonstrate full therapeutic success.

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Competing interests CHT is a former employee and current stockholder of Johnson & Johnson, Gilead Sciences and IGM Biosciences. He sits on the Board of Directors for ALX Oncology, and he also holds patents for the therapeutic targeting CD47.

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