

## Viral Therapy for Bladder Cancer: Everything Old is New Again

A recent article on the use of viral therapy in the treatment of bladder cancer received much attention in the general media. The news headlines proclaimed how a common cold virus could be used to treat bladder cancer. This recent report was on a Phase I study using Coxsackievirus A21 (CVA21), a natural cold causing enterovirus, and their encouraging early results in bladder cancer.<sup>1</sup> News outlets indicated that this would ‘revolutionize’ the treatment of non-muscle invasive bladder cancer. While the press descriptions may be sensationalized, the concept of using virus based strategies to treat a variety of malignancies including bladder cancer is far from novel.

Viruses such as adenovirus, vaccinia virus and herpes viruses are just a few of the viral agents explored in the treatment of bladder cancer. These so called “oncolytic viruses” preferentially infect and kill tumor cells and induce significant immune responses. The bladder has been considered a useful target for experimental treatments such as a viral therapy for bladder cancer for a variety of reasons. Direct instillation of the experimental agents and relatively easy assessment of the anti-tumor effects are facilitated by the transurethral approach. As a relatively isolated organ, the histology of the bladder wall tends to limit systemic absorption allowing high titers of viral agents to be administered relatively safely. Since we have proof of principle that immune responses to agents such as intravesical BCG can treat cancer, inducing immune reactions with other agents such as viruses represent reasonable approaches to explore. In developing novel cancer therapies viruses are particularly useful in terms of being modifiable based on degrees of virulence and in the ability to insert genes that produce agents such as GM-CSF.

The only FDA approved viral therapy for any cancer thus far uses a modified herpes virus (HSV-1). This viral based therapy was approved in 2015 for the treatment of inoperable melanoma under the brand name T-VEC. There have been only a few limited studies using herpes virus to treat bladder cancer.

In 2001, my research team at Thomas Jefferson University’s Sidney Kimmel Cancer Center reported on what we believe was the first clinical trial using viral therapy in bladder cancer. This Phase I pre-cystectomy bladder cancer trial used the smallpox vaccine strain of vaccinia virus (also known as cow pox virus).<sup>2</sup> The vaccine was clinically available as Dryvax and was administered intravesically. While the initial results of intravesical vaccinia virus were promising, a concern for bioterrorism warfare in the Middle East ended our centers vaccinia virus research program. The concern was that the smallpox virus would be used against unvaccinated American troops. This resulted in the government restricting all non-military access to the smallpox vaccine.

Adenovirus is a double stranded DNA virus that is one of the most commonly tested vectors for viral cancer therapy. It is a virus also associated with the common cold. Several strains of genetically modified adenovirus have been tested in bladder cancer. Adstiladrin (rAd-IFN-alpha2b, nadofaragene firadenovec, previously known as Instiladrin) is an intravesical gene therapy consisting of a non-replicating adenovirus (rAd) containing the gene for interferon alpha (IFN-alpha2b). When combined with the excipient Syn3, intravesical administration of the rAd-IFN virus results in transduction of the virus into the cells lining the bladder. It is currently in a Phase III registration trial for use in high risk non-muscle invasive bladder cancer. This adenovirus based intravesical therapy may be the next viral agent approved in cancer (ClinicalTrials.gov Identifier: NCT02773849).

Newer treatments for non-muscle invasive bladder cancer are desperately needed. This is due to the recurring world-wide shortages of BCG and the fact that some patients with superficial bladder cancer do not respond to intravesical BCG. We commend our colleagues for their work in developing a new approach to bladder cancer using the cocksackie virus. Caution is needed when these preliminary but important scientific studies are widely promoted in the press and other media outlets. These reports may generate false hopes for patients and may not indicate that previous research studies do not qualify this new study as being “revolutionary”.

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### References

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2. Gomella LG, Mastrangelo MJ, MCCue PA et al. Phase I study of intravesical vaccinia virus as a vector for gene therapy of bladder cancer. *J Urol* 2001;166(4):1291-1295.