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Oncolytic Viruses and Its Commercialization: A mini-review

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Oncolytic virus immunotherapy represents a new class of therapeutic approach that target the cancer cells selectively and it is emerging as supportive or alternative treatment to the standard of care such as surgery, chemotherapy and radiotherapy. Its unique advantages stems from its tumor cell specific lysis along with host immune stimulation. To date, a wide variety of oncolytic viruses are evaluated for this purpose and several of them demonstrated promising clinical results. Recently, it is used in combination with other anti-cancer modalities showing more enhanced results. This article briefly describes past, current and future perspectives of oncolytic virus immunotherapy focusing on the virus type and combination agents and discusses consideration in developing oncolytic viruses as commercial therapeutic agents in field of cancer treatment.

Keywords: oncolytic virus, immunotherapy, commercialization

INTRODUCTION

Cancer still remained one of the leading causes of death in spite of the medical advance. It is known to cause around one in every seven death worldwide. Only in United States, about 1.6 million of new case developed and 580 thousands deaths was reported in 2015[1]. The cardinal features of the devastating disease are summarized as uncontrolled cell division and its metastasis.

Various types of cancer treatments have been introduced including surgery, chemotherapy, radiotherapy and immune therapy[2]. The combination of them, surgery followed by chemotherapy or radiotherapy is generally considered most effective until now. The main disadvantages entailed with the current strategies with regard to the quality of life are permanent loss of organ or tissue and accompanying pain. Another issue of classical cancer therapy is the incomplete eradication of the cancer cells leading to the disease recurrence [3].

Tremendous efforts have been made to develop new approaches or improve preexisting cancer treatment to minimize these adverse effects, while the primary objective has been focused to increase patients' survival rate. Recently introduced targeted therapy can be stated as the most advanced, since it aimed at delivering therapeutic agents to and tar-

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geted tumorous tissue with minimal harm to normal tissues[4]. Among the agents used, viral elements with specific functional features have become of a great interest nowadays[5].

Oncolytic virus (OV) is a new promising agent of cancer treatment immunotherapy using OV has been recognized a one of possible next major breakthrough. OV immunotherapy utilizes native or genetically modified virus replicating selectively within cancer cells[6]. Its anti-tumor effects are thought to be mediated from direct lysis of cancer cells as well as the preferential infection. In 2015, the first OV immunotherapeutic biologics, T-VEC (talimogene laherparepvec) was approved by US Food and Drug Administration (FDA). With the success of T-VEC and enhanced understanding of virology, it can be easily anticipated that further development of new OV drug is highly encouraged. Interestingly, the virus in OV immunotherapy is used as an active reagent, whereas other gene therapies use virus as a carrier for gene delivery, although OV immunotherapy is also categorized as one of gene therapy.

This mini review provides brief overviews of the history of OV immunotherapy, the current status of OV immunotherapy according to the virus type incorporated and additional substances used in combination strategies. The review also covers a few examples of commercialized pharmaceuticals as well as future perspectives.

History of Oncolytic Virus Immunotherapy Development

It has been known for more than 100 years that viruses are able to kill cancer cells. The idea of using virus in cancer treatment was originally hit upon from an accidental incident in 1912. One cervical cancer patient bitten by a dog developed extensive tumor necrosis following administration of a live attenuated rabies virus for post-exposure prophylaxis[7]. Subsequently, similar observations of tumor regressions have been numerously reported in situations of naturally acquired viral infections [8]. Scientists believed that virus can be possibly used for tumor cell lysis.

Unexpectedly however, only over the past decade have clinical trials shown a therapeutic benefit in cancer treatment. In fact, there were many clinical trials performed for cancer treatment with wild type or naturally attenuated viruses between 1950 and 1980. Adenovirus received attention greatly in cervical cancer clinical trials demonstrating only mild flu-like adverse effect[9] as a safety feature as well as clear efficacy in tumor necrosis. Nonetheless, it didn't took much time for this enthusiasm to be cooled down, since the antitumor response lasted only few months and overall survival rate was not prolonged compared with conventional surgery [10-13].

Other viruses such as West Nile fever, dengue fever, yellow fever, and hepatitis were also investigated for their availability[8,14]. Despite these efforts, none of them have shown outstanding result compare to surgery and these viruses didn't seemed useful because biotechnology in those days was not so sufficiently developed as today's genetic engineering [8]. Clinical trials in those days did not elucidate the promising features, rather reveal inherent obstacles to overcome for OV immunotherapy to be used successfully [15,16].

What makes the matter worse, conspicuous new chemotherapeutic agents was introduced for cancer

treatment in the 1970s and demonstrated the result of increasing survival rate. Compared to this competitor, OV immunotherapy for cancer treatment seemed to have no significant advantages. Naturally, people's interest faded away for a while.

As advanced knowledge in medical bioscience and biotechnology piled up, genetic engineering of virus becomes possible, which made the OV immunotherapy regain its spotlight. Currently, design and manipulation of viral genome has become the standard approach for oncolytic virus development. Typically, DNA viruses are used for this strategy. One of them is T-VEC, the first FDA approved OV biologics. A search of clinicaltrials.gov performed as of April 1, 2016, listed approximately 40 clinical trials recruiting patients for OV therapy[17].

Types of Viral Vectors

Most OVs are known to directly kill host tumor cells although the precise mechanisms are still incompletely understood. The direct killing functions are affected by targeting efficiency, replication rate and host cell antiviral response elements [10,12] On the other hand, OV's lytic potential is up to the type of virus, dose, viral tropism, cancer cell susceptibility to cell death. Furthermore, each OV has its own way of cellular entry. Most of OVs are engineered to improve the oncolytic selectivity in these days.

A variety of viruses are under clinical investigation ranging from linear single stranded (ss) tiny parvovirus H1 of 5 kb[18] to large double stranded (ds) vaccinia virus of 190 kb[19]. In addition to the 2 viruses, adenovirus (Ad), poxvirus[20], type I herpes simplex virus (HSV-1), coxsackievirus[21], retrovirus[22], poliovirus[23], measles virus[24], vesicular stomatitis virus[25], Newcastle disease virus[26] (NDV), reovirus have been evaluated.

Most of clinical trials are in early-phase, but several viruses entered into Phase III stage. As matter stands today, it can be said that Ad and HSV-1 are the most extensively studied. The discussion of this part will be restricted to these 2 OVs with reovirus worthy of recent note.

1. Adenovirus

In humans, approximately 50 different serotypes of Ad have been found [27]. Adenoviridae are a family of icosahedral, non-enveloped viruses with an approximately 30-40 kb linear dsDNA genome [28]. The capsid proteins disassemble inside the cell, resulting in the subsequent nuclear import of the viral genome [29] for initiation of viral transcription.

The oncolytic Ad has several biological properties including ease of production, oncolytic ability and a large packaging capacity. As a result, it became one of the most customizable vectors in clinical and preclinical studies for cancer therapy. Deletion of viral genes necessary for replicating in tumor cells but not in normal cells is a main strategy to induce a tumor-specific viral replicative lysis [30].

The host cell transcription factor, E2F, which is involved in cell cycle regulation, can activate the transcription of the Ad E2 gene and this induces p53-dependent apoptosis [31]. To avoid its induction of p53-dependent apoptosis, Ads produce a 55KE1b protein which binds to p53[32] and exports it to the cytoplasm for degradation, thereby keeping the host cell alive long enough for productive infection [33].

Several oncolytic Ad utilizes E1B-55k-deletion tactics including ONYX-015[34], which was once con-

sidered as a representative of this kind. E1B protein is capable of binding to p53 and inactivating it. Interestingly, McCormick[35] reported that ONYX-015[34] replicates efficiently even in $p53^+$ tumor cells[36], because of the tumor inhibiting p53 activity through other mechanisms such as overexpression of the endogenous p53 inhibitor, Mdm2, or the loss of $p14^{ARF}$, which downregulates Mdm2. Later, several clinical trials showed that the antitumor effect of single application of ONYX-015 was not ideal [37,38].

Recently, several clinical trials investigated Δ24RGD(DNX2401), an integrin-binding retargeted Ad[39,40]. Another noteworthy new Ad is enadenotucirev, which is fabricated on the Ad11/3 serotype , not the common serotype Ad5. It is anticipated less susceptible to rapid neutralization than preexisting Ad[41].

2. Herpes Simplex Virus

HSV-1 belongs to a member of the α herpes virus family. HSV-1 is a dsDNA virus with a 152kb genome and it replicates inside of the host nucleus. The attractive property of this virus as OV candidates is that it doesn't cause insertional mutagenesis. In wild type infections to normal cells, protein kinase R is stimulated by ds viral RNA productions and block protein synthesis by phosphorylation of eukaryotic initiation factor 2 alpha (eIF-2*a*). This virus contains gamma34.5 gene which codes proteins for de-phosphorylation and reactivation of eIF-2*a* to reverse this situation. Consequently, gamma 34.5-deleted HSVs are safe in normal cells due to the inefficient replication[42].

Several studies use OV derived from genetically engineered HSV (oHSV) strains, R3659 and G207, with deletions in diploid γ34.5 gene (Δγ34.5 oHSV)[43]. The oHSV is another widely tested OV in patients next to Ad. In fact, a major contemporary focus of OV immunotherapy pharmaceuticals has now moved to this virus since the commercial release of T-VEC. T-VEC are made from a JS1 HSV1 strain deleted for ICP34.5 and γ47, which is known to block HSV1 major histocompatibility complex class 1 antigen presentation[44]. It is engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF)[44]. According to phase III clinical trials, T-VEC injection into tumor tissue demonstrated great efficacy in durable response rate in malignant melanoma patients[45] .

3. Reovirus

Reovirus is a non-enveloped dsRNA virus that has inner core with icosahedral capsid in outer surface. It replicates inside of the host cytoplasm. It is known to activate protein kinase R pathways in normal cells, but not in RAS-transformed cancer cells[46]. Therefore, it has demonstrated oncolytic activity against a range of malignancies in clinical studies, including melanoma, glioma and ovarian cancers [47]. Most people are commonly exposed to this virus. It has critical advantages that it produces only mild symptoms and enters human cells easily to activate immune system[48,49].

To date, reovirus is one of the most clinically advanced oncolytic viruses (OV), showing modest efficacy in phase II clinical trials as a monotherapy as well as a combination therapy across diverse solid malignancies[50,51]. According to one clinical study of prostate cancer, a significant number of tumor-infiltrating $CD8^+$ T cells were found after reovirus injection, which means the reovirus has an immunothera-

peutic feature in addition to direct oncolytic effect [52].

Oncolytic reovirus is marketed under the name of Reolysin[53]. In 2015, it was designated as orphan drug for the malignant glioma by the FDA.

Combination Therapies with Oncolytic Viruses

OVs can be combined readily with nearly all kinds other cancer therapies due to its tolerable safety profiles and modulating ability of tumor microenvironment[3,54,55]. The supporting rationale was based on the anticipation that OVs can target residual cancer unaffectedly after conventional treatments. This part introduces several promising strategies in combination with OV immunotherapy.

1. Sunitinib

Sunitinib is an oral administered small-molecule, multi targeted receptor tyrosine kinase (RTK) inhibitor. FDA approved Sunitinib for treatment of renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumor. It is reported to inhibit cellular signaling by targeting multiple RTKs.

In combination therapy studies, sunitinib was administered prior to reovirus. The study demonstrated the improved immunotherapeutic efficacy of reovirus by allowing sunitinib to precondition the tumor microenvironment through downregulation of immune suppressor cells [56]. Although reovirus given as a monotherapy reduced tumor burden substantially, the simultaneous use of Sunitinib led to a significantly increased reduction in tumor volume [47].

2. Polymer-Coating

According to a recent study, Ad coated by layer-by-layer deposition of ionic polymers (polyethyleneimine (PEI) and hyaluronic acid) was evaluated whether the coating enhanced efficacy [57]. They reported that the infectivity of the virus increased after multilayer coating in spite of the presence of an anti-adenovirus antibody.

3. miRNA-143

MicroRNAs (miRNAs) are endogenous non-coding regulatory RNAs that inhibit gene expression at the post-transcriptional level [58]. Several studies reported miRNA-143 was frequently down-regulated and acted as a tumor suppressor in colorectal cancer [59,60]. The Kirsten rat sarcoma viral oncogene homolog (KRAS) is known as a frequently mutated gene in colorectal carcinogenesis [61]. Recent computer sequence analysis exhibited that the 3'-UTR of KRAS mRNA might represent a target of miRNA-143. The recombinant virus using Ad and miRNA-143 was constructed for tumor treatment [62,63].

This strategy combined the advantages of both gene therapy and OV therapy by using virus vectors to harbor anti-cancer genes. Endogenous miRNAs was employed to control viral replication [64]. Several studies constructed Ads could replicate specifically in tumor cells therefore infect and kill more tumor cells while avoiding damage to normal cells [30,65].

4. Gold nanorod

It was demonstrated that gold nanorod (GNR)-mediated mild hyperthermia enhances the cellular uptake and consequent gene expression of oncolytic Ad to head and neck tumor cells[66]. The combination of oncolytic Ad expressing vascular endothelial growth factor promoter-targeted zinc-finger protein and GNR to enhance the antitumor effects.

Considerations in development OVs as commercial drug.

Currently, most studied OVs are ONYX-015 from Ad and T-VEC from HSV-1 and the latter is approved by FDA [6,67,68]. It will not be long before next commercial OV biologics will be released in the market. The designing strategy for OVs should be focused on selective tumor targeting and attenuating virulence since OVs are live viral particles in nature. At the same time, effort should be made to limit the immunogenicity of virus while increasing oncolytic efficacy. In order for OVs to stand as a commercial drug, a number of sophisticated strategies could be applied with the aid of today's state-of-the-art molecular biotechnology[17].

First, specific engineering of OVs is necessary to target unique cancer cell surface receptors[69]. Utilization of aberrant signaling pathways of cancer is also important since a number of molecules are known to be involved in virus accumulation and replication in cancer cells[70]. The tumor clearance by anti-tumor immunity is another available feature of OVs[71]. The suicide gene could be incorporated into OVs, which facilitates direct killing activity[72]. Needless to say, minimizing the antiviral immune neutralization is essential because rapid clearance of OV limit the drug's effective duration[73]. Finally, bioavailability of OVs should be enhanced[5].

There are many adversities to overcome to develop OVs as commercial drugs. Since OVs is a kind of a new class of drugs as a biologics, they are very different from chemically manufactured drugs. For example, they are live viruses of proliferating nature and it is very hard to find an effective dosage. In other words, conventional pharmacokinetics and pharmacodynamics cannot be applied to the OVs. Clinical trial designs should be modified for this kind of new drugs. All the difference from standard drugs may provoke regulatory issues regarding approval, manufacture and commercialization.

More specifically, there are no universally accepted standards for biosafety considerations. OV pharmaceuticals are mostly acquired by tissue culture method and there are several requirements in this type of manufacturing regarding high titer, pathogenicity, purity. Although FDA published guidelines on those general issues, they are often unable to cover all the unprecedented and upcoming issues practically.

Future Perspectives

The advent of T-VEC and its clinical success ignited the enthusiasm in the OV immunotherapy. There are numerous ongoing trials to overcome or avoid known weakness of OVs. However, the development of OVs as therapeutic agents is never easy to achieve. Special attention should be paid to where there is no need in case of conventional drugs. In addition, the ability of tumor cells to evade host immune surveillance is quite challenging.

New technologies are on our side to surmount these adversities. The clustered regularly interspaced short palindromic repeat (CRISPR)-Cas9 was proposed as an efficient tool especially for new OVs with large genomes[74,75]. Big data from microarrays, next-generation sequencing as well as omics technologies, are expected to provide various aspects of the immune response to viral infection. Mapping immune changes over the course of OV immunotherapy has the possibility to suggest important therapeutic insights[76]. The recently introduced checkpoint inhib-

itors are suggested that they have potency in wide variety of cancers. The combination therapy with T cell checkpoint inhibitor cast a promising prospect[77].

CONCLUSIONS

OVs represent a feasible source of biopharmaceuticals for cancer treatments and several of them already proved their efficacy and safety in clinical use. It is not only decrease tumor burden, but also can prolong patient's survival rate. It also showed favorable risk to benefit ratio. Ad and HSV-1 are the most studied ones and inhibitory effects are main concern. Their application is expected to expand along with the technological advances, particularly in the combination approaches, although our current knowledge and experience are not enough. Given the multitude of development array of OVs, OV immunotherapy could be the most effective way to cure this formidable disease.

The unique nature of these OVs can destroy cancer cells selectively without harming normal cells. At the level of tissue or organs, it can be said that OVs reverse tumorous tissues/organs to normal ones. [78]. Interestingly, it complies well enough to the paradigm of regenerative medicine. Hopefully, maximum number of patients could be benefited from this new OV immunotherapy without permanent loss of function and morphology.

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REFERENCES

1. Langenberg MH, Witteveen PO, Roodhart J, et al. Phase I evaluation of telatinib, a VEGF receptor tyrosine kinase inhibitor, in combination with bevacizumab in subjects with advanced solid tumors. *Ann Oncol.* 2011;22:2508-2515.
2. Tan KX, Danquah MK, Sidhu A, et al. Towards targeted cancer therapy: Aptamer or oncolytic virus? *Eur J Pharm Sci.* 2016;96:8-19.
3. Lolkema MP, Arkenau HT, Harrington K, et al. A phase I study of the combination of intravenous reovirus type 3 Dearing and gemcitabine in patients with advanced cancer. *Clin Cancer Res.* 2011;17:581-588.
4. Singh PK, Doley J, Kumar GR, et al. Oncolytic viruses & their specific targeting to tumour cells. *Indian J Med Res.* 2012;136:571-584.
5. Kaufman HL, Kohlhapp FJ, Zloza A. Oncolytic viruses: a new class of immunotherapy drugs. *Nat Rev Drug Discov.* 2015;14:642-662.
6. Fukuhara H, Ino Y, Todo T. Oncolytic virus therapy: A new era of cancer treatment at dawn. *Cancer Sci.* 2016;107:1373-1379.
7. Pack GT. Note on the experimental use of rabies vaccine for melanomatosis. *AMA archives of dermatology and syphilology.* 1950;62:694-695.
8. Kelly E, Russell SJ. History of oncolytic viruses: genesis to genetic engineering. *Mol Ther.* 2007;15:651-659.
9. Huebner RJ, Bell JA, Rowe WP, et al. Studies of adenoidal-pharyngeal-conjunctival vaccines in volunteers. *J Am Med Assoc.* 1955;159:986-989.
10. Rowe WP, Huebner RJ, Gilmore LK, et al. Isolation of a cytopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture. *Proc Soc Exp Biol Med.* 1953;84:570-573.
11. Huebner RJ, Rowe WP, Schatten WE, et al. Studies on the use of viruses in the treatment of carcinoma of the cervix. *Cancer.* 1956;9:1211-1218.

12. Georgiades J, Zielinski T, Cicholska A, et al. Research on the oncolytic effect of APC viruses in cancer of the cervix uteri; preliminary report. *Biul Inst Med Morsk Gdansk.* 1959;10:49-57.
13. Zielinski T, Jordan E. [Remote results of clinical observation of the oncolytic action of adenoviruses on cervix cancer]. *Nowotwory.* 1969;19:217-221.
14. Southam CM, Moore AE. Induced virus infections in man by the Egypt isolates of West Nile virus. *Am J Trop Med Hyg.* 1954;3:19-50.
15. Ring CJ. Cytolytic viruses as potential anti-cancer agents. *J Gen Virol.* 2002;83:491-502.
16. Kreppel F, Kochanek S. Modification of adenovirus gene transfer vectors with synthetic polymers: a scientific review and technical guide. *Mol Ther.* 2008;16:16-29.
17. Lawler SE, Speranza MC, Cho CF, et al. Oncolytic Viruses in Cancer Treatment: A Review. *JAMA Oncol.* 2016.
18. Di Piazza M, Mader C, Geletneky K, et al. Cytosolic activation of cathepsins mediates parvovirus H-1-induced killing of cisplatin and TRAIL-resistant glioma cells. *J Virol.* 2007;81:4186-4198.
19. Guse K, Cerullo V, Hemminki A. Oncolytic vaccinia virus for the treatment of cancer. *Expert Opin Biol Ther.* 2011;11:595-608.
20. Kim JH, Oh JY, Park BH, et al. Systemic armed oncolytic and immunologic therapy for cancer with JX-594, a targeted poxvirus expressing GM-CSF. *Mol Ther.* 2006;14:361-370.
21. Dmitriev I, Krasnykh V, Miller CR, et al. An adenovirus vector with genetically modified fibers demonstrates expanded tropism via utilization of a coxsackievirus and adenovirus receptor-independent cell entry mechanism. *J Virol.* 1998;72:9706-9713.
22. Lu YC, Chen YJ, Yu YR, et al. Replicating retroviral vectors for oncolytic virotherapy of experimental hepatocellular carcinoma. *Oncol Rep.* 2012;28:21-26.
23. Merrill MK, Bernhardt G, Sampson JH, et al. Poliovirus receptor CD155-targeted oncolysis of glioma. *Neuro Oncol.* 2004;6:208-217.
24. Mader EK, Maeyama Y, Lin Y, et al. Mesenchymal stem cell carriers protect oncolytic measles viruses from antibody neutralization in an orthotopic ovarian cancer therapy model. *Clin Cancer Res.* 2009;15:7246-7255.
25. Tesfay MZ, Kirk AC, Hadac EM, et al. PEGylation of vesicular stomatitis virus extends virus persistence in blood circulation of passively immunized mice. *J Virol.* 2013;87:3752-3759.
26. Elankumaran S, Chavan V, Qiao D, et al. Type I interferon-sensitive recombinant newcastle disease virus for oncolytic virotherapy. *J Virol.* 2010;84:3835-3844.
27. Ghebremedhin B. Human adenovirus: Viral pathogen with increasing importance. *Eur J Microbiol Immunol (Bp).* 2014;4:26-33.
28. Williams PD, Ranjzad P, Kakar SJ, et al. Development of viral vectors for use in cardiovascular gene therapy. *Viruses.* 2010;2:334-371.
29. Trotman LC, Mosberger N, Fornerod M, et al. Import of adenovirus DNA involves the nuclear pore complex receptor CAN/Nup214 and histone H1. *Nat Cell Biol.* 2001;3:1092-1100.
30. Alemany R. Designing adenoviral vectors for tumor-specific targeting. *Methods Mol Biol.* 2009;542:57-74.
31. Dynlacht BD. E2F and p53 make a nice couple: converging pathways in apoptosis. *Cell Death and Differentiation.* 2005;12:313-314.
32. Berk AJ. Recent lessons in gene expression, cell cycle control, and cell biology from adenovirus. *Oncogene.* 2005;24:7673-7685.
33. Rao L, Debbas M, Sabbatini P, et al. The adenovirus E1A proteins induce apoptosis, which is inhibited by the E1B 19-kDa and Bcl-2 proteins. *Proc Natl Acad Sci U S A.* 1992;89:7742-7746.
34. Harada JN, Berk AJ. p53-Independent and -depen-

dent requirements for E1B-55K in adenovirus type 5 replication. *J Virol.* 1999;73:5333-5344.

35. McCormick F. ONYX-015 selectivity and the p14ARF pathway. *Oncogene.* 2000;19:6670-6672.
36. Au T, Thorne S, Korn WM, et al. Minimal hepatic toxicity of Onyx-015: spatial restriction of coxsackie-adenoviral receptor in normal liver. *Cancer Gene Ther.* 2007;14:139-150.
37. Khuri FR, Nemunaitis J, Ganly I, et al. a controlled trial of intratumoral ONYX-015, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer. *Nat Med.* 2000;6:879-885.
38. Crompton AM, Kirn DH. From ONYX-015 to armed vaccinia viruses: the education and evolution of oncolytic virus development. *Curr Cancer Drug Targets.* 2007;7:133-139.
39. Kimball KJ, Preuss MA, Barnes MN, et al. A phase I study of a tropism-modified conditionally replicative adenovirus for recurrent malignant gynecologic diseases. *Clin Cancer Res.* 2010;16:5277-5287.
40. Jiang H, Clise-Dwyer K, Ruisaard KE, et al. Delta-24-RGD oncolytic adenovirus elicits anti-glioma immunity in an immunocompetent mouse model. *PLoS One.* 2014;9:e97407.
41. Kuhn I, Harden P, Bauzon M, et al. Directed evolution generates a novel oncolytic virus for the treatment of colon cancer. *PLoS One.* 2008;3:e2409.
42. Kaufman HL, Kim DW, DeRaffele G, et al. Local and distant immunity induced by intralesional vaccination with an oncolytic herpes virus encoding GM-CSF in patients with stage IIIc and IV melanoma. *Ann Surg Oncol.* 2010;17:718-730.
43. Roth JC, Cassady KA, Cody JJ, et al. Evaluation of the Safety and Biodistribution of M032, an Attenuated HSV-1 Virus Expressing hIL-12, After Intracerebral Administration to Aotus Non-Human Primates. *Hum Gene Ther Clin Dev.* 2014.
44. Liu BL, Robinson M, Han ZQ, et al. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties. *Gene Ther.* 2003;10:292-303.
45. Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. *J Clin Oncol.* 2015;33:2780-2788.
46. Strong JE, Coffey MC, Tang D, et al. The molecular basis of viral oncolysis: usurpation of the Ras signaling pathway by reovirus. *EMBO J.* 1998;17:3351-3362.
47. Lawson KA, Mostafa AA, Shi ZQ, et al. Repurposing Sunitinib with Oncolytic Reovirus as a Novel Immunotherapeutic Strategy for Renal Cell Carcinoma. *Clin Cancer Res.* 2016.
48. Danthi P, Guglielmi KM, Kirchner E, et al. From touchdown to transcription: the reovirus cell entry pathway. *Curr Top Microbiol Immunol.* 2010;343:91-119.
49. Errington F, Steele L, Prestwich R, et al. Reovirus activates human dendritic cells to promote innate antitumor immunity. *J Immunol.* 2008;180:6018-6026.
50. Harrington KJ, Vile RG, Melcher A, et al. Clinical trials with oncolytic reovirus: moving beyond phase I into combinations with standard therapeutics. *Cytokine Growth Factor Rev.* 2010;21:91-98.
51. Karapanagiotou EM, Roulstone V, Twigger K, et al. Phase I/II trial of carboplatin and paclitaxel chemotherapy in combination with intravenous oncolytic reovirus in patients with advanced malignancies. *Clin Cancer Res.* 2012;18:2080-2089.
52. Thirukkumaran CM, Nodwell MJ, Hirasawa K, et al. Oncolytic viral therapy for prostate cancer: efficacy of reovirus as a biological therapeutic. *Cancer Res.* 2010;70:2435-2444.
53. Gollamudi R, Ghalib MH, Desai KK, et al. Intravenous administration of Reolysin, a live replication competent RNA virus is safe in patients with advanced solid tumors. *Invest New Drugs.* 2010;28:641-649.

54. Harrow S, Papanastassiou V, Harland J, et al. HSV1716 injection into the brain adjacent to tumour following surgical resection of high-grade glioma: safety data and long-term survival. *Gene Ther.* 2004;11:1648-1658.

55. Herman JR, Adler HL, Aguilar-Cordova E, et al. In situ gene therapy for adenocarcinoma of the prostate: a phase I clinical trial. *Hum Gene Ther.* 1999;10:1239-1249.

56. Yu P, Lee Y, Liu W, et al. Intratumor depletion of CD4+ cells unmasks tumor immunogenicity leading to the rejection of late-stage tumors. *J Exp Med.* 2005;201:779-791.

57. Yoshihara C, Hamada K, Koyama Y. Preparation of a novel adenovirus formulation with artificial envelope of multilayer polymer-coatings: therapeutic effect on metastatic ovarian cancer. *Oncol Rep.* 2010;23:733-738.

58. Liu WH, Ren LN, Wang X, et al. Combination of exosomes and circulating microRNAs may serve as a promising tumor marker complementary to alpha-fetoprotein for early-stage hepatocellular carcinoma diagnosis in rats. *J Cancer Res Clin Oncol.* 2015;141:1767-1778.

59. Guo H, Chen Y, Hu X, et al. The regulation of Toll-like receptor 2 by miR-143 suppresses the invasion and migration of a subset of human colorectal carcinoma cells. *Mol Cancer.* 2013;12:77.

60. Chen X, Shi K, Wang Y, et al. Clinical value of integrated-signature miRNAs in colorectal cancer: miRNA expression profiling analysis and experimental validation. *Oncotarget.* 2015;6:37544-37556.

61. Worthley DL, Leggett BA. Colorectal cancer: molecular features and clinical opportunities. *Clin Biochem Rev.* 2010;31:31-38.

62. Ginn SL, Alexander IE, Edelstein ML, et al. Gene therapy clinical trials worldwide to 2012 - an update. *J Gene Med.* 2013;15:65-77.

63. Luo Q, Basnet S, Dai Z, et al. A novel E1B55k-Da-deleted oncolytic adenovirus carrying microRNA-143 exerts specific antitumor efficacy on colorectal cancer cells. *Am J Transl Res.* 2016;8:3822-3830.

64. Ylosmaki E, Hakkarainen T, Hemminki A, et al. Generation of a conditionally replicating adenovirus based on targeted destruction of E1A mRNA by a cell type-specific MicroRNA. *J Virol.* 2008;82:11009-11015.

65. Russell SJ, Peng KW, Bell JC. Oncolytic virotherapy. *Nat Biotechnol.* 2012;30:658-670.

66. Jung BK, Lee YK, Hong J, et al. Mild Hyperthermia Induced by Gold Nanorod-Mediated Plasmonic Photothermal Therapy Enhances Transduction and Replication of Oncolytic Adenoviral Gene Delivery. *ACS Nano.* 2016.

67. Larson C, Oronsky B, Scicinski J, et al. Going viral: a review of replication-selective oncolytic adenoviruses. *Oncotarget.* 2015;6:19976-19989.

68. Rehman H, Silk AW, Kane MP, et al. Into the clinic: Talimogene laherparepvec (T-VEC), a first-in-class intratumoral oncolytic viral therapy. *J Immunother Cancer.* 2016;4:53.

69. Yu Z, Chan MK, P Oc, et al. Enhanced nectin-1 expression and herpes oncolytic sensitivity in highly migratory and invasive carcinoma. *Clin Cancer Res.* 2005;11:4889-4897.

70. Mansour M, Palese P, Zamarin D. Oncolytic specificity of Newcastle disease virus is mediated by selectivity for apoptosis-resistant cells. *J Virol.* 2011;85:6015-6023.

71. Bar S, Daeffler L, Rommelaere J, et al. Vesicular egress of non-enveloped lytic parvoviruses depends on gelsolin functioning. *PLoS Pathog.* 2008;4:e1000126.

72. Sova P, Ren XW, Ni S, et al. A tumor-targeted and conditionally replicating oncolytic adenovirus vector expressing TRAIL for treatment of liver metastases. *Mol Ther.* 2004;9:496-509.

73. Fulci G, Breymann L, Gianni D, et al. Cyclophos-

phamide enhances glioma virotherapy by inhibiting innate immune responses. *Proc Natl Acad Sci U S A.* 2006;103:12873-12878.

74. Yi L, Li J. CRISPR-Cas9 therapeutics in cancer: promising strategies and present challenges. *Biochim Biophys Acta.* 2016;1866:197-207.
75. Yuan M, Webb E, Lemoine NR, et al. CRISPR-Cas9 as a Powerful Tool for Efficient Creation of Oncolytic Viruses. *Viruses.* 2016;8:72.
76. Swift SL, Stojdl DF. Big Data Offers Novel Insights for Oncolytic Virus Immunotherapy. *Viruses.* 2016;8.
77. Zamarin D, Holmgaard RB, Subudhi SK, et al. Localized oncolytic virotherapy overcomes systemic tumor resistance to immune checkpoint blockade immunotherapy. *Sci Transl Med.* 2014;6:226ra232.
78. Park YJ, Cha S, Park YS. Regenerative Applications Using Tooth Derived Stem Cells in Other Than Tooth Regeneration: A Literature Review. *Stem Cells Int.* 2016;2016:9305986.

한글초록

종양용해성 바이러스와 그 상업화: 종설

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종양용해성 바이러스를 이용한 면역 치료는 새로운 치료 접근 방식으로서 암세포만을 선택적으로 표적화하여 작용하여 기존의 표준적인 치료법, 즉 수술적 적출법, 화학 요법, 방사선 요법의 보조치료나 대체치료법으로 떠오르고 있다. 이 치료법의 독특한 장점은 종양 세포에 특정된 세포 용해와 후속적인 숙주의 면역 반응 자극에서 기인한다. 현재까지 다양한 종류의 종양용해성 바이러스가 면역 치료 목적으로 시험되었으며 그 중 일부는 전도 유망한 결과를 보여주었다. 이 논문에서는 종양용해성 바이러스를 이용한 면역치료법의 과거, 현재 그리고 미래를 바이러스의 종류와 복합치료법 때 사용되는 제재에 초점을 맞추어 간단히 기술하였으며, 종양용해성 바이러스의 상업적 치료제화를 위한 고려 사항에 대해서 고찰해 보았다.

주제어: 종양용해성 바이러스, 면역 치료법, 상업화