Oncolytic virotherapy: Harnessing viruses for cancer treatment

Beata Halassy, Ph.D., M.Sc. in Biology.

University of Zagreb, Centre for Research and Knowledge Transfer in Biotechnology, Zagreb, Croatia

E-mail: bhalassy@unizg.hr

ORCID: 0000-0001-7370-0997

Summary

Oncolytic virotherapy (OVT) is an innovative form of immunotherapy that employs replication-competent viruses for the selective destruction of tumor cells and the induction of antitumor immune responses. Historically, viral infections were observed to induce tumor regression, and modern advances in molecular virology and genetic engineering have enabled the development of safer and more effective oncolytic viruses. To date, only four preparations (Rigvir, Oncorine, T-VEC, and Delytact) have been approved for clinical use, while many others show promising results in trials. The translation of OVT into routine practice faces several challenges, including demanding production processes, the lack of predictive preclinical models, and limited efficacy in terminal-stage patients. A recent case of successful experimental self-treatment of recurrent breast cancer in Croatia, using intratumoral application of measles virus and vesicular stomatitis virus, highlights the potential of lower-dose and more simply prepared formulations. This case opens new hypotheses for therapy optimization and emphasizes the importance of the Croatian Edmonston Zagreb measles virus strain as a promising platform for the development of domestic oncolytic therapies. In conclusion, OVT remains experimental but highly promising, and with adapted regulatory frameworks and increased investment in research, it may become an important contribution to cancer treatment.

Ključne riječi: cancer immunotherapy, oncolytic virotherapy, breast cancer, self-experimentation, self-treatment, measles virus, vesicular stomatitis virus

Onkolitička viroterapija ili liječenje raka virusima: etički izazovi u eksperimentalnom samoliječenjut

Sažetak

Onkolitička viroterapija (OVT) predstavlja inovativan oblik imunoterapije u kojem se za selektivnu destrukciju tumorskih stanica i poticanje antitumorskog imunosnog odgovora koriste virusi sa sposobnošću replikacije. Povijesno je uočeno da virusne infekcije mogu uzrokovati regresiju maligniteta, a suvremeni napredak u molekularnoj virologiji i genetskom inženjerstvu omogućio je razvoj sigurnijih i učinkovitijih onkolitičkih virusa. Danas su u kliničkoj primjeni odobrena tek četiri pripravka (Rigvir, Oncorine, T-VEC i Delytact), dok brojni drugi pokazuju obećavajuće rezultate u ispitivanjima. Translacija OVT-a u rutinsku praksu suočava se s izazovima, uključujući zahtjevnu proizvodnju, nedostatak prediktivnih pretkliničkih modela i ograničenu učinkovitost u terminalno oboljelih bolesnika. Prikaz uspješnog slučaja eksperimentalnog samoliječenja recidiva raka dojke u Hrvatskoj intratumorskom aplikacijom virusa ospica i virusa vezikularnog stomatitisa ukazuje na potencijal primjene ovakvih pristupa u nižim dozama i s jednostavnije pripremljenim pripravcima. Taj slučaj otvara nove hipoteze o optimizaciji terapije, a posebno naglašava važnost hrvatskog Edmonston Zagreb soja virusa ospica kao potencijalne platforme za razvoj domaće onkolitičke terapije. Zaključno, OVT je još uvijek eksperimentalna, ali iznimno perspektivna terapija koja bi, uz

prilagodbu regulatornih okvira i ulaganje u istraživanje, mogla postati značajan doprinos liječenju malignih bolesti.

Ključne riječi: imunoterapija za rak, onkolitička viroterapija, rak dojke, samoeksperimentiranje, samoliječenje, virus ospica, virus vezikularnog stomatitisa

1. Introduction

The use of viruses that have the ability to replicate for the treatment of cancer is called oncolytic virotherapy (OVT) and today represents a promising oncological therapy that is in rapid development (1-4). It is included in immunotherapy procedures, together with already advanced methods of "immune-checkpoint" blockade and adaptive cell therapy, because it acts by involving the patient's own immune system. In the later one, T lymphocytes are genetically modified *ex vivo* and then returned to the patient's bloodstream in order to recognize and destroy tumor cells (e.g. CAR-T, from chimeric antigen receptor T-cell).

2. Mechanism of action of oncolytic viruses

Oncolytic viruses (OVs) selectively kill tumor cells that they are able to infect, namely, those prermissive to viral entry. They do this either directly, by exhausting the cells for the purpose of producing new viruses (the so-called cytopathic effect), or indirectly through the host immune system, thanks to the fact that a tumor cell infected with a virus presents viral antigens on its surface in addition to its own, and thus becomes visible to our immune system to which it was previously invisible. However, in addition to eliminating tumor cells, which occurs immediately after the application of the virus, oncolytic viruses also elicit an antitumor immune response that can act on tumor foci distant from the places of OV treatment. In other words, antitumour immunity that is generated can act systemically, long-term and after the oncolytic viruses are completely eliminated from the body. Namely, our immune system is designed to eliminate foreign and unknown, and to be inert towards the known and our own. Tumors are made up of our own cells, which contain our own proteins, and are therefore predominantly invisible to our immune system. Malignantly transformed cells sometimes express altered self-proteins, which, if sufficiently altered, become visible to our immune system and are called neoantigens. However, the amount of such altered proteins and the dense structure of solid tumors make neoantigens still poorly visible to the patient's immune system. After we apply oncolytic viruses and after the lysis of tumor cells occurs, an inflammatory environment is created within the treated tumor that contains all the participants and ingredients necessary for generating tumor-specific immunity - a large amount of tumor neoantigens is released and a large amount of antigen-presenting cells and T and B lymphocytes are recruited, and the probability of neoantigens meeting immune cells that can react against them increases drastically. Since OVs induce immunity to tumor neoantigens if they exist on tumors, and we do not even need to know what they look like, we say that OVs act as antigen-agnostic vaccines. In other words, OVs induce the formation of immunity to tumor neoantigens, even though tumor neoantigens are not included in the composition of the drug (oncolytic viral preparation), which is an important difference compared to other known preventive and therapeutic vaccines.

3. Historical development of oncolytic virotherapy

The use of viruses in cancer treatment originated from the observation that, occasionally, cancer patients who contracted a viral disease would experience a brief period of clinical remission. Since the mid-19th century, there have been consistent reports of cases in which tumor regression coincided with natural viral infection (5). This was most commonly observed in he-

matological malignancies, such as leukemia, Hodgkin's disease, and Burkitt's lymphoma, following infection with varicella, measles, influenza, and others (a review of reported cases and original references is available in Kelly and Russell 2007). Such cases demonstrated that: (i) under certain circumstances, certain viruses could destroy tumors without causing additional harm to the patient; (ii) this most often occurred in young patients with weakened immune systems; and (iii) all of these remissions were short-lived and incomplete (5). The development of OVT throughout history has occurred sporadically, in waves, simultaneously with advances in the development of virology and technical tools for studying viruses, such as the invention of cell and tissue culture systems in the mid-20th century, as a prerequisite for *ex vivo* virus multiplication; the emergence of animal models for studying the safety and preclinical efficacy of oncological therapy; genetic engineering and molecular virological methods at the turn of the 19th to 20th centuries, etc. Developments to date have shown that various human viruses have oncolytic and oncotropic potential. In fact, the innate property of viruses to destroy the cell they infect is far more pronounced in tumor cells than in normal cells, which represents a powerful natural mechanism of selection of viral activity towards tumor tissues. Today, the mechanisms behind this natural selectivity are also known, the most important of which are: (i) tumor cells often have a seriously impaired interferon signaling pathway (and others), which is an extremely powerful tool in defense against many viruses in healthy cells; (ii) tumor cells do not have the ability to stop the synthesis of their own proteins, unlike healthy cells, for which this is another mechanism of fighting viruses, because it blocks the creation of new viral proteins and the multiplication of the virus; (iii) tumor cells cannot initiate the process of programmed cell death, which is also one of the natural ways of healthy cells to fight viruses, because by its own "suicide", the infected cell prevents the multiplication of the virus and protects neighboring cells from viral infection. Due to the above differences between healthy and tumor cells, virus replication occurs abundantly and unhindered in tumor cells, while in healthy cells it is very quickly contained and limited.

4. Oncolytic viruses must not be pathogenic to patients

However, in order for human viruses to be used as a cancer treatment, their pathogenicity must be eliminated. Perhaps rare exceptions among human viruses in this regard are Coxsackievirus A21, an oncolytic human picornavirus whose pathogenicity is limited to mild upper respiratory tract infection and is currently being developed for oncolytic use under the name V937 (6,7), then reovirus, which does not cause disease in humans and is being developed for oncolytic use under the name pelareorep (8), and ECHO-virus 7 from the enterovirus genus, a nonpathogenic virus isolated from the digestive tract of a healthy boy, which has been used as an oncolytic virus for years in Latvia (9,10). The pathogenicity of human viruses can be circumvented by using animal viruses to treat cancer in humans, because some animal viruses replicate successfully in human tissue, especially tumor tissue, and do not cause disease in humans. However, due to the ever-present concern (which is difficult to quantify) that a virus that is currently non-pathogenic to humans could, through replication in human tissue, acquire and enhance its virulence in the human host, this concept has not been extensively investigated. Two animal viruses are exceptions: vesicular stomatitis virus (VSV) and Newcastle disease virus (NDV). NDV is pathogenic to birds, but its various forms have been so frequently administered to humans without any side effects that it is considered a safe platform for the development of oncolytic drugs for humans (11). VSV is pathogenic to cattle, and has a strong oncolytic effect in human tumors with impaired interferon pathways. Centuries of human exposure to this virus through work with infected livestock prove that the virus is safe for humans, as it has, at worst, caused sporadic cases of mild flu-like symptoms in humans.

5. Oncolytic viruses approved for clinical use

The entire field of oncolytic virus development has significantly accelerated in the last 30 years thanks to the development of technologies that enable genetic engineering of viruses and detailed virological research at the molecular level. Researchers are beginning to use genetic engineering to weaken (attenuate) the pathogenicity of the virus and strengthen the oncolytic potential and selectivity for tumor tissues. Today, there is no doubt, based on data from preclinical research and clinical trials, that many natural and genetically modified viruses possess oncolytic and oncotropic properties, that they are capable of infecting tumor tissue and destroying it, as well as inducing the reduction of metastases. Despite all this, only a few of them have been approved on the market in the form of medicines. The first OV approved for use in humans by any regulatory agency, and also the only natural virus in clinical use in humans, was Rigvir. It was developed and manufactured in Riga, Latvia, and was approved by the Latvian regulatory agency for the treatment of metastatic melanoma in 2004 (9,10). Its active substance is the oncolytic and oncotropic ECHO virus type 7 (from the family Picornaviridae, genus Enterovirus). Shortly thereafter, in another part of the world, Oncorine (H101) was introduced for the treatment of head and neck tumors (12). It was approved by the CFDA (Chinese Food and Drug Administration), the Chinese drug agency, in 2005, and has been used exclusively in China since 2006. Oncorine is a genetically modified adenovirus of serotype 5, with deletion of the E1B gene for attenuation. The first OV to receive broad regulatory approval outside of China is Talimogene laherparepvec (abbreviated T-VEC) or Imlygic for the treatment of inoperable malignant melanoma (13). It was approved in 2015 by the American (FDA, from the English Food and Drug Administration) and soon after by the European (EMA, from the English European Medicine Agency) and the Australian (TGA, from the English Therapeutic Good Agency) drug agency. It is herpes simplex virus type 1 (HSV1) on the one hand attenuated by genetic modifications, and on the other hand "armed" to induce the secretion of granulocyte and macrophage colony growth stimulating factor (GM-CSF), which stimulates the formation of antitumor immunity. After intratumoral application in one or more accessible (usually skin) lesions every two weeks for a period of up to 18 months, the virus induced a permanent systemic effect in 16% of treated patients, and particularly promising activity for the same indication was observed in combination with immune checkpoint inhibitors ipilimumab or pembrolizumab (14). Today, its effect on the entire spectrum of different types of tumors is being investigated. And the latest in the series approved for use in humans is Delytact, another genetically modified HSV1 that was developed within the academic and medical community in Japan, and under the special, accelerated regulatory pathway SAKIGAKE. It was approved in Japan in 2021 for the treatment of malignant gliomas (15,16).

6. Challenges in translating oncolytic virotherapy into clinical practice

Despite the wealth of scientific literature from almost a century of research history, which unequivocally demonstrates the preclinical efficacy of OVT, given the number of approved drugs and the spatial limitations of their application, oncolytic virotherapy has still not entered clinical practice with its full potential.

There are several reasons for the slow translation of this form of treatment, and I will highlight a few of the most important ones below. Effective doses of oncolytic viruses (more than 10^8 $CCID_{50}$/mL) are many times higher than those required in attenuated viral vaccines (about 10^3 $CCID_{50}$/mL), and the requirements of regulatory authorities for the purity and complete definition of all drug ingredients are higher than ever. The production of such preparations is an exceptional biotechnological challenge, because viruses, especially those with a lipid envelope, are very sensitive to any manipulation in the purification, concentration and storage processes. Preclinical (mouse) models of testing the effectiveness of this form of treatment are not reliable, predictive, and

are actually irrelevant. Many OV preparations, after promising results in mouse models, have shown much weaker effects than expected in the first clinical studies, which then discourages researchers, regulatory bodies, and investors. Clinical studies in oncology always begin by testing a new drug in patients with advanced disease, in the terminal stage, and when all other forms of treatment have been tried and are ineffective. Such patients have an exhausted and incompletely functional immune system, and the poor effectiveness of oncolytic virotherapy can be attributed precisely to the absence of the contribution of their own immunity. The immune response directed at the oncolytic virus, which is created during therapy or already exists due to previous exposure to the virus, represents an obstacle to the action of the virus, which is especially pronounced with intravenous administration, and is not so influential with direct intratumoral administration.

7. A case of successful experimental treatment of breast cancer recurrence with oncolytic viruses in Croatia

SThe case of my successful experimental self-treatment of breast cancer recurrence with viruses, recently conducted in Croatia (17), showed that it is possible to overcome all this and has once again raised the visibility and interest (18) in the development of this form of cancer treatment. The main outcomes of the treatment are summarized schematically in Figure 1. In the described case, I was a patient (but also an experienced virologist and self-experimenter) and, with the third occurrence (second recurrence) of breast cancer at the site of a previous mastectomy, classified as stage 3b, I decided to try to suppress this local recurrence with viral therapy. With the intratumor and repeated application of two viruses (first one, then the other) for a total duration of only two months, the size of the recurrent tumor tissue was reduced more than 2.5 times (from 2.5 cm^3 to less than 1 cm^3), and the structure of the tumor tissue was significantly changed from a solid, dense mass fixed to the muscle, to a movable, soft and loose formation, which was simply removed by surgery. Histopathological and immunochemical analysis of the removed tumor tissue showed significant changes compared to the material collected by biopsy before the experimental treatment (Figure 1).

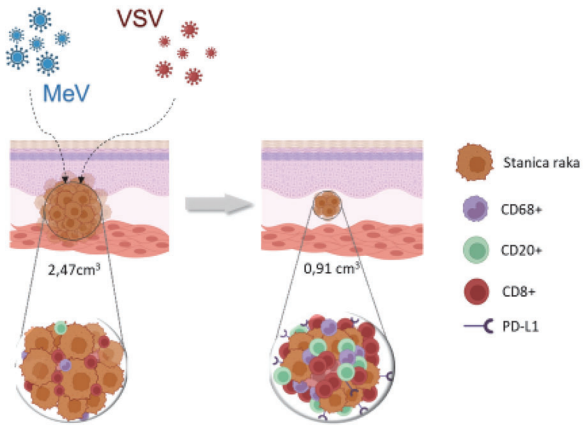

Figure 1. Schematic representation of the main outcomes of experimental self-treatment of local recurrence of breast cancer with oncolytic viruses. After 7 intratumoral applications of measles virus (MeV) and then 3 applications of vesicular stomatitis virus (VSV), the dense, hard, solid and fixed mass that infiltrated both the pectoral muscle underneath and the skin above it, transformed into a small, soft, loose and mobile nodule, located exclusively in the subcutaneous tissue. The size was reduced by more than 2.5 times. Histopathological analysis of the removed tumor demonstrated a picture of abundant fibrosis. The tumor showed areas devoid of tumor cells and infiltrated by numerous immune cells, among which B lymphocytes (CD20+), cytotoxic T lymphocytes (CD8+) and macrophages (CD68+) dominated. The expression of the PD-L1 receptor, which belongs to the group of proteins involved in the regulation of immune reactions, was observed.

It was confirmed that viruses influenced tumor regression, because the tumor infiltrated both the pectoral muscle and the skin before treatment (diagnosed by imaging techniques – ultrasound, magnetic resonance imaging and PET-CT analysis), while the surgically removed tumor was located exclusively in the subcutaneous tissue, without contact with the muscle or skin. Parts of the tumor were completely devoid of tumor cells, i.e. the histopathological picture of abundant fibrosis was reminiscent of those encountered in successful neoadjuvant chemotherapy. Finally, the remaining tumor was filled with immune cells – B lymphocytes, cytotoxic T lymphocytes and macrophages, indi-

cating that the immune system was activated in the fight against the tumor. All this was achieved without any significant and lasting side effects. Partially purified preparations of the vaccine strain of measles virus Edmonston Zagreb and the wild strain of vesicular stomatitis virus were used for the experimental therapy. The first is an attenuated and human virus that has been used for decades in measles vaccines and is considered an effective and safe vaccine strain for measles prevention (19,20). The second is an animal pathogen that causes an economically important disease in livestock, but is not pathogenic in humans. All indicators pointed to the effectiveness of the experimental self-treatment with oncolytic viruses, which over time has also been confirmed by the durability of the achieved remission. After two previous relapses that occurred at intervals shorter than two years from the previous onset of the disease, the achieved remission has now lasted for five years.

Although this is an isolated case (n=1) that cannot, by itself, provide definitive evidence, this instance of experimental self-treatment (17) suggests some potentially interesting avenues for further investigation and has therefore attracted great interest in the scientific and professional community throughout the world. It may be possible to replace the need for high concentrations of infectious virus in an oncolytic virus preparation, which are challenging and expensive to produce, with repeated applications of preparations of lower viral concentrations, which are relatively simple to prepare. Absolute purity and definition of the composition of oncolytic virus preparations, which are challenging and expensive to achieve, may not be necessary because the use of partially purified preparations in this isolated case was without any significant side effects, especially compared to the side effects brought about by existing forms of treatment. It may not be necessary to use genetically modified viruses, the use of which always arouses fear, suspicion and resistance, if an effective effect can be achieved with viruses that are already present in nature, if only they are administered in an appropriate manner. It may be possible to circumvent the OVT-inhibiting effect of patient's immunity to the oncolytic virus, generated during the therapy, by the use of different viruses in sequence. All these hypotheses need to be investigated and proven in real clinical studies.

Some reviewers, journal editors, and experts in the field have questioned the ethics of the case of self-experimentation presented here. Self-experimentation is a form of experiment in which the experimenter (physician, researcher) and the subject (patient) are the same person. Today, experiments on humans are only permitted with the prior positive opinion of a competent ethics committee, which does not exist in this case, which has given rise to debates about ethics. In order to assess the ethics of this case, it is necessary to recall the reasons for the adoption of laws and regulations that regulate experiments on humans. The formalization of the code of ethics into today's regulations was carried out only at the end of the 20th century, after the misuse of people for experiments during that same century (21). Before that, throughout the history of mankind, starting with Hippocrates, the actions of doctors were based on ethical codes that did not have the force of law, but were more a matter of culture and practice. The Nuremberg Principles, adopted after World War II (1947), represent the starting point of modern medical ethics. Among these principles, two are worth highlighting: the principle that requires the patient's consent to participate in experiments (after prior information about the potential benefits) and the principle that prohibits conducting experiments on humans that may cause death or permanent injury to them, except in cases where the experimenter himself serves as the research subject. This is the only article in the history of medical ethics that directly mentions self-experimentation and has not been repealed by any subsequent document. Since it defines that self-experimentation is permitted even in the case of expectation of harm, then this indirectly extends to situations when there is no harm. In simpler terms, the conduct of experiments on humans is regulated by today's

legal regulations primarily to protect patients from overly enthusiastic experimenters, and to ensure that patients are maximally informed about the procedures in the experiment and the expected benefits. It is obvious that there is no better informed and more willing patient to have an experiment conducted on them than the self-experimenter. Therefore, the described experimental self-treatment is unequivocally within the limits of ethical acceptability (18,22). It should not be forgotten that the history of self-experimentation is long, rich and fruitful - it has brought many discoveries to the world and society. To date, around 480 described cases of self-experimentation have been identified, of which as many as 7 resulted in discoveries for which Nobel Prizes were later awarded (e.g. Barry Marshall won the Nobel Prize in 2005 for the discovery of the connection between stomach ulcers and Helicobacter pylori infection, which he proved by drinking a culture of the bacteria and causing himself symptoms of the disease).

8. Prospects for the development of oncolytic virotherapy in Croatia

For Croatia, the contribution of the described successful self-treatment of recurrent breast cancer is particularly valuable in the fact that the vaccine strain of the measles virus Edmonston Zagreb, which is the property of the Republic of Croatia, was used for the therapy. This indicates that in Zagreb, in the stored working and master banks of this virus, there is enormous potential for the development of its application for a new therapeutic indication - cancer treatment. Croatia has a strong and internationally recognized scientific community of virologists and immunologists, and we also have a tradition of producing biological drugs with viruses as the active substance (animal and human prophylactic vaccines). There is no doubt that Croatia could also become a place for the development of this type of therapy for its citizens, and possibly the production of a viral oncolytic vaccine, if the leadership of the health and scientific system recognized this potential and provided active support.

9. Conclusion

In conclusion, oncolytic virotherapy is today an experimental therapy in intensive development. There are only a few approved drugs, for only a few indications, most of which (with the exception of T-Vec intended for the treatment of melanoma) are approved for use in the territory of the country where they were developed. The main challenge in development is to find a compromise between the high regulatory requirements for purity and definition of the composition with the biotechnological challenges to produce such preparations and the absence of a predictive preclinical model, which makes development through the classic regulatory path almost impossible. The recent approval of Delytact in Japan shows that this can be overcome with special regulatory models that facilitate and accelerate the path of a new product towards clinical application. I am sure that the time of tumor treatment with oncolytic viruses is upon us.

References

1. Harrington K, Freeman DJ, Kelly B, Harper J, Soria JC. Optimizing oncolytic virotherapy in cancer treatment. Nat Rev Drug Discov. 2019;18:689–706. doi: 10.1038/s41573-019-0029-0.
2. Russell SJ, Peng KW, Bell JC. Oncolytic virotherapy. Nat Biotechnol. 2014;30:658–670. doi: 10.1038/nbt.2287.
3. Russell SJ, Bell JC, Engeland CE, McFadden G. Advances in oncolytic virotherapy. Commun Med. 2022;2(1):4–6. doi: 10.1038/s43856-022-00098-4.
4. Russell SJ, Peng KW. Oncolytic Virotherapy: A Contest between Apples and Oranges. Mol Ther. 2017;25(5):1107–1116. doi: 10.1016/j.ymthe.2017.03.026.
5. Kelly E, Russell SJ. History of oncolytic viruses: Genesis to genetic engineering. Mol Ther. 2007;15(4):651–659. doi: 10.1038/sj.mt.6300108.
6. Bradley S, Jakes A, Harrington K, Pandha H, Melcher A, Errington-Mais F. Applications of coxsackievirus A21 in oncology. Oncolytic Virother. 2014;3:47–55. doi: 10.2147/ov.s56322.
7. Andtbacka RH, Curti B, Daniels GA, Hallmeyer S, Whitman ED, Lutzky J et al. Clinical responses of oncolytic coxsackievirus A21 (V937) in patients with unresectable melanoma. J Clin Oncol. 2021;39(34):3829–3838. doi: 10.1200/JCO.20.03246.

8. Müller L, Berkeley R, Barr T, Ilett E, Errington-Mais F. Past, present and future of oncolytic reovirus. Cancers (Basel). 2020;12(11):3219. doi: 10.3390/cancers12113219.
9. Donina S, Strele I, Proboka G, Auzinš J, Alberts P, Jonsson B et al. Adapted ECHO-7 virus Rigvir immunotherapy (oncolytic virotherapy) prolongs survival in melanoma patients after surgical excision of the tumour in a retrospective study. Melanoma Res. 2015;25(5):421–426. doi: 10.1097/CMR.0000000000000180.
10. Alberts P, Olmane E, Brokane L, Krastina Z, Romanovska M, Kupcs K et al. Long-term treatment with the oncolytic ECHO-7 virus Rigvir of a melanoma stage IV M1c patient, a small cell lung cancer stage IIIA patient, and a histiocytic sarcoma stage IV patient-three case reports. Acta Pathol Microbiol Immunol Scand. 2016;124:896–904. doi: 10.1111/apm.12576.
11. Tayeb S, Zakay-Rones Z, Panet A. Therapeutic potential of oncolytic Newcastle disease virus a critical review. Oncolytic Virother. 2015 Mar 27;4:49–62. doi: 10.2147/OV.S78600.
12. Liang M. Oncorine, the world first oncolytic virus medicine and its update in China. Curr Cancer Drug Targets. 2018;18:171–176. doi: 10.2174/1568009618666171129221503.
13. Rehman H, Silk AW, Kane MP, Kaufman HL. Into the clinic: Talimogene laherparepvec (T-VEC), a first-in-class intratumoral oncolytic viral therapy. J Immunother Cancer. 2016;4(1):1–8. doi: 10.1186/s40425-016-0158-5.
14. Puzanov I, Milhem MM, Minor D, Hamid O, Li A, Chen L et al. Talimogene laherparepvec in combination with ipilimumab in previously untreated, unresectable stage IIIB-IV melanoma. J Clin Oncol. 2016;34(22):2619–2626. doi: 10.1200/JCO.2016.67.1529.
15. Maruyama Y, Sakurai A, Noda S, Fujiwara Y, Okura N, Takagi T et al. Regulatory issues: PMDA – Review of Sakigake designation products: Oncolytic virus therapy with delytact injection (Teserpaturev) for malignant glioma. Oncologist. 2023;28(8):664–670. doi: 10.1093/oncolo/oyad041-
16. Todo T, Ito H, Ino Y, Ohtsu H, Ota Y, Shibahara J et al. Intratumoral oncolytic herpes virus G47Δ for residual or recurrent glioblastoma: a phase 2 trial. Nat Med. 2022;28(8):1630–1639. doi: 10.1038/s41591-022-01897-x.
17. Forčić D, Mršić K, Perić-Balja M, Kurtović T, Ramić S, Silovski T et al. An unconventional case study of neoadjuvant oncolytic virotherapy for recurrent breast cancer. Vaccines. 2024;12(9):958. doi: 10.3390/vaccines12090958.
18. Corbyn Z. This scientist treated her own cancer with viruses she grew in the lab. Nature. 2024;635(8039):529–530. doi: 10.1038/d41586-024-03647-0.
19. Beck M, Smerdel S, Dedic I, Delimar N, Rajninger-Miholic M, Juzbasić M et al. Immune response to Edmonston-Zagreb measles virus strain in monovalent and combined MMR vaccine. Dev Biol Stand. 1986;65:95–100.
20. Markovitz LE, Sepulveda J, Diaz-Ortega JL, Valdespino JL, Albrecht P, Zell ER et al. Immunization of six-month-old infants with different doses of Edmonston-Zagreb and Schwartz measles vaccines. N Engl J Med. 1990;322(9):580–587. doi: 10.1056/NEJM199003013220903.
21. Hanley BP, Bains W, Church G. Review of scientific self-experimentation: ethics history, regulation, scenarios, and views among ethics committees and prominent scientists. Rejuvenation Res. 2019;22(1):31–42. doi: 10.1089/rej.2018.2059.
22. Pugh J, Wilkinson D, Savulescu J. Self-censorship: should scientific journals decline to publish self-experimentation? J Med Ethics. 2025:jme-2025-110730. doi: 10.1136/jme-2025-110730.