

World Journal of *Clinical Cases*

World J Clin Cases 2019 August 26; 7(16): 2134-2412



Contents

Semimonthly Volume 7 Number 16 August 26, 2019

REVIEW

- 2134 Role of infrapatellar fat pad in pathological process of knee osteoarthritis: Future applications in treatment
Jiang LF, Fang JH, Wu LD

MINIREVIEWS

- 2143 Application of Newcastle disease virus in the treatment of colorectal cancer
Song H, Zhong LP, He J, Huang Y, Zhao YX

ORIGINAL ARTICLE**Basic Study**

- 2155 Reduced microRNA-451 expression in eutopic endometrium contributes to the pathogenesis of endometriosis
Gao S, Liu S, Gao ZM, Deng P, Wang DB

Case Control Study

- 2165 Application of self-care based on full-course individualized health education in patients with chronic heart failure and its influencing factors
Sun J, Zhang ZW, Ma YX, Liu W, Wang CY

Retrospective Study

- 2176 Predicting surgical site infections using a novel nomogram in patients with hepatocellular carcinoma undergoing hepatectomy
Tang TY, Zong Y, Shen YN, Guo CX, Zhang XZ, Zou XW, Yao WY, Liang TB, Bai XL
- 2189 Serological investigation of IgG and IgE antibodies against food antigens in patients with inflammatory bowel disease
Wang HY, Li Y, Li JJ, Jiao CH, Zhao XJ, Li XT, Lu MJ, Mao XQ, Zhang HJ

- 2204 Incidence of infectious complications is associated with a high mortality in patients with hepatitis B virus-related acute-on-chronic liver failure
Wang C, Ma DQ, Luo S, Wang CM, Ding DP, Tian YY, Ao KJ, Zhang YH, Chen Y, Meng ZJ

Clinical Trials Study

- 2217 R/S ratio in lead II, and the prognostic significance of red cell distribution width in acute coronary syndrome
Coşkun A, Eren SH

- 2227 Comparative analysis of APACHE-II and P-POSSUM scoring systems in predicting postoperative mortality in patients undergoing emergency laparotomy
Nag DS, Dembla A, Mahanty PR, Kant S, Chatterjee A, Samaddar DP, Chugh P

Observational Study

- 2238 TAZ and myostatin involved in muscle atrophy of congenital neurogenic clubfoot
Sun JX, Yang ZY, Xie LM, Wang B, Bai N, Cai AL

Prospective Study

- 2247 Effects of dual sofosbuvir/daclatasvir therapy on, chronic hepatitis C infected, survivors of childhood malignancy
El-Shabrawi MH, Sherief LM, Yakoot M, Kamal NM, Almalky MA, AbdElgawad MM, Mahfouz AA, Helmy S, Kamal EM, Attia D, El-Khayat HR

Randomized Controlled Trial

- 2256 Hypoallergenicity of a thickened hydrolyzed formula in children with cow's milk allergy
Rossetti D, Cucchiara S, Morace A, Leter B, Oliva S

SYSTEMATIC REVIEWS

- 2269 Surveillance and diagnosis of hepatocellular carcinoma: A systematic review
Pascual S, Miralles C, Bernabé JM, Irurzun J, Planells M

META-ANALYSIS

- 2287 Neuraxial adjuvants for prevention of perioperative shivering during cesarean section: A network meta-analysis following the PRISMA guidelines
Zhang YW, Zhang J, Hu JQ, Wen CL, Dai SY, Yang DF, Li LF, Wu QB

CASE REPORT

- 2302 Primary malignant melanoma of the biliary tract: A case report and literature review
Cameselle-García S, Pérez JLF, Areses MC, Castro JDFD, Mosquera-Reboredo J, García-Mata J
- 2309 Successful treatment of tubulointerstitial nephritis in immunoglobulin G4-related disease with rituximab: A case report
Eroglu E, Sipahioğlu MH, Senel S, Ertas SK, Savas S, Ozturk F, Kocyigit I, Tokgoz B, Oymak O
- 2316 Effectiveness of vedolizumab treatment in two different anti-tumor necrosis factor alpha refractory pouchitis: A case report
Cakir OO
- 2322 Clinical outcomes and safety of high-resolution manometry guided superficial partial circular muscle myotomy in per-oral endoscopic myotomy for Jackhammer esophagus: Two cases report
Choi YI, Kim KO, Park DK, Chung JW, Kim YJ, Kwon KA

- 2330** Cardiac arrhythmias and cardiac arrest related to mushroom poisoning: A case report
Li S, Ma QB, Tian C, Ge HX, Liang Y, Guo ZG, Zhang CD, Yao B, Geng JN, Riley F
- 2336** Role of abdominal drainage in bariatric surgery: Report of six cases
Liu Y, Li MY, Zhang ZT
- 2341** A patient misdiagnosed with central serous chorioretinopathy: A case report
Wang TY, Wan ZQ, Peng Q
- 2346** Large carotid body tumor successfully resected in hybrid operating theatre: A case report
Li MQ, Zhao Y, Sun HY, Yang XY
- 2352** A huge pancreatic lipoma mimicking a well-differentiated liposarcoma: A case report and systematic literature review
Xiao RY, Yao X, Wang WL
- 2360** Ulcerative colitis complicated with colonic necrosis, septic shock and venous thromboembolism: A case report
Zhu MY, Sun LQ
- 2367** Acute pancreatitis connected with hypercalcemia crisis in hyperparathyroidism: A case report
Ma YB, Hu J, Duan YF
- 2374** Treatment of invasive fungal disease: A case report
Xiao XF, Wu JX, Xu YC
- 2384** Hepatocellular carcinoma successfully treated with ALPPS and apatinib: A case report
Liu L, Li NF, Zhang Q, Lin L
- 2393** Pseudothrombus deposition accompanied with minimal change nephrotic syndrome and chronic kidney disease in a patient with Waldenström's macroglobulinemia: A case report
Mwamunyi MJ, Zhu HY, Zhang C, Yuan YP, Yao LJ
- 2401** *Ex vivo* revascularization of renal artery aneurysms in a patient with solitary kidney: A case report
Chen XY, Zhao JC, Huang B, Yuan D, Yang Y
- 2406** Malignant syphilis accompanied with neurosyphilis in a malnourished patient: A case report
Ge G, Li DM, Qiu Y, Fu HJ, Zhang XY, Shi DM

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Manabu Watanabe, MD, PhD, Full Professor, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Toho University Medical Center, Ohashi Hospital, Tokyo 153-8515, Japan

AIMS AND SCOPE

World Journal of Clinical Cases (*World J Clin Cases*, *WJCC*, online ISSN 2307-8960, DOI: 10.12998) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The primary task of *WJCC* is to rapidly publish high-quality Case Report, Clinical Management, Editorial, Field of Vision, Frontier, Medical Ethics, Original Articles, Meta-Analysis, Minireviews, and Review, in the fields of allergy, anesthesiology, cardiac medicine, clinical genetics, clinical neurology, critical care, dentistry, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology and hepatology, etc.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2019 Edition of Journal Citation Reports cites the 2018 impact factor for *WJCC* as 1.153 (5-year impact factor: N/A), ranking *WJCC* as 99 among 160 journals in Medicine, General and Internal (quartile in category Q3).

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Ji-Hong Liu*
 Proofing Production Department Director: *Yun-Xiaojuan Wu*

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Semimonthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

August 26, 2019

COPYRIGHT

© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Application of Newcastle disease virus in the treatment of colorectal cancer

Hui Song, Li-Ping Zhong, Jian He, Yong Huang, Yong-Xiang Zhao

ORCID number: Hui Song (0000-0002-8063-6812); Li-Ping Zhong (0000-0003-1532-4107); Jian He (0000-0002-0626-3958); Yong Huang (0000-0003-4843-2788); Yong-Xiang Zhao (0000-0003-1219-0908).

Author contributions: Song H, Zhong LP, He J and Huang Y wrote the paper; Zhao YX approved the final version.

Conflict-of-interest statement: All the authors have no conflict of interest related to the manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: May 18, 2019

Peer-review started: May 18, 2019

First decision: June 11, 2019

Revised: June 21, 2019

Accepted: July 20, 2019

Article in press: July 20, 2019

Published online: August 26, 2019

P-Reviewer: Aykan NF, Katuchova J

Hui Song, Li-Ping Zhong, Jian He, Yong Huang, Yong-Xiang Zhao, National Center for International Research of Bio-targeting Theranostics, Guangxi Key Laboratory of Bio-targeting Theranostics, Collaborative Innovation Center for Targeting Tumor Diagnosis and Therapy, Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Corresponding author: Yong-Xiang Zhao, MD, PhD, Professor, National Center for International Research of Bio-targeting Theranostics, Guangxi Key Laboratory of Bio-targeting Theranostics, Collaborative Innovation Center for Targeting Tumor Diagnosis and Therapy, Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China. yongxiang_zhao@126.com

Telephone: +86-15177120015

Fax: +86-771-5317061

Abstract

Colorectal cancer (CRC) is one of the main reasons of tumor-related deaths worldwide. At present, the main treatment is surgery, but the results are unsatisfactory, and the prognosis is poor. The majority of patients die due to liver or lung metastasis or recurrence. In recent years, great progress has been made in the field of tumor gene therapy, providing a new treatment for combating CRC. As oncolytic viruses selectively replicate almost exclusively in the cytoplasm of tumor cells and do not require integration into the host genome, they are safer, more effective and more attractive as oncolytic agents. Newcastle disease virus (NDV) is a natural RNA oncolytic virus. After NDV selectively infects tumor cells, the immune response induced by NDV's envelope protein and intracellular factors can effectively kill the tumor without affecting normal cells. Reverse genetic techniques make NDV a vector for gene therapy. Arming the virus by inserting various exogenous genes or using NDV in combination with immunotherapy can also improve the anti-CRC capacity of NDV, and good results have been achieved in animal models and clinical treatment trials. This article reviews the molecular biological characteristics and oncolytic mechanism of NDV and discusses *in vitro* and *in vivo* experiments on NDV anti-CRC capacity and clinical treatment. In conclusion, NDV is an excellent candidate for cancer treatment, but more preclinical studies and clinical trials are needed to ensure its safety and efficacy.

Key words: Newcastle disease virus; Exogenous gene; Armed virus; Oncolytic therapy; Colorectal cancer

S-Editor: Gong ZM
L-Editor: Filipodia
E-Editor: Liu JH



©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: At present, the main treatment for colorectal cancer are surgical treatment and chemotherapy, but the majority of patients die due to liver or lung metastasis or recurrence. Therefore, there is an urgent need to find more effective treatment strategies to reduce mortality. Newcastle disease virus can selectively infect tumor cells and can also improve the ability of Newcastle disease virus to resist colorectal cancer by constructing an autologous tumor vaccine. Clinical treatment tests have shown a good therapeutic effect and its potential to become a new treatment for colorectal cancer.

Citation: Song H, Zhong LP, He J, Huang Y, Zhao YX. Application of Newcastle disease virus in the treatment of colorectal cancer. *World J Clin Cases* 2019; 7(16): 2143-2154

URL: <https://www.wjgnet.com/2307-8960/full/v7/i16/2143.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i16.2143>

INTRODUCTION

Colorectal cancer (CRC) is one of the main causes of global cancer death, and its incidence continues to rise^[1]. At present, surgery and chemotherapy are still the main treatments for CRC. About one-third of patients with CRC will have metastatic tumors of the liver or lung, making their 5-year overall survival rate only 50%^[2]. Similar to many other malignancies, CRC is a heterogeneous disease, therefore optimizing treatment and reducing related mortality is the main challenge. In the current treatment of tumors, in addition to traditional surgery, radiotherapy and chemotherapy, immunotherapy has become a very hot field, which mainly includes oncolytic virus^[3], tumor vaccine^[4], targeted therapy^[5], immune cell therapy^[6] and immunological checkpoint inhibitors^[7]. With the development of genetic engineering and the application of molecular biology, the treatment of CRC with oncolytic virus has been rapidly developed in recent decades, and genetically modified viruses have been used to evaluate the efficacy of anti-CRC *in vitro* and *in vivo*.

NEWCASTLE DISEASE VIRUS (NDV)

Molecular biological characteristics of NDV

NDV is a highly infectious avian pathogen^[8] that is an avian paramyxovirus type I virus, and a member of the genus *Avulavirus* in the family Paramyxoviridae^[9]. NDV is a bilayered, lipid-coated RNA virus of approximately 100-300 nm with a predominantly spherical morphology. The genome of NDV is a nonsegmented negative-sense, single-stranded RNA [ssRNA(-)] molecule consisting of 15186 nucleotides containing six open reading frames encoding six structural proteins: nuclear protein (NP), phosphoprotein (P), large polymerase protein (L), matrix protein (M), hemagglutinin-neuraminidase (HN) and fusion protein (F). Among its structural proteins, NP, P and L combine with the viral RNA to form the ribonucleoprotein complex, which is responsible for replication of the virus^[10] (Figure 1). M comprises a layer underneath the viral membrane that is involved in the assembly and budding of the virus. HN and F are present as oligomers, which together with the lipid bilayer membrane of the host constitute the outer envelope of the virus and are involved in entry of the virus into a cell. F is typically present as the inactive polypeptide F₀; cleavage produces the mature membrane-anchored F₁ and the membrane-distal F₂ domain, resulting in an infectious virus^[11].

The HN protein of NDV can trigger a conformational change in the F protein through receptor sialic acid-mediated endocytosis to release the fusion peptide and promote fusion of the virus with the cell membrane and allow the ribonucleoprotein complex to enter the cytoplasm of a host cell^[12]. The genome replicates in the cytoplasm^[13]: (1) The genomic ssRNA(-) is transcribed into messenger RNA in the cytoplasm for translation into different structural proteins; (2) The antigenome copy, or ssRNA(+), is used as the template for viral genome amplification, and subsequent budding releases virus progeny^[14]; and (3) HN can scavenge sialic acid residues and promote spread of the virus in infected tissues. Selective replication of the virus results in host cell lysis only in tumor cells^[15,16,17] with replication that is 10000 times

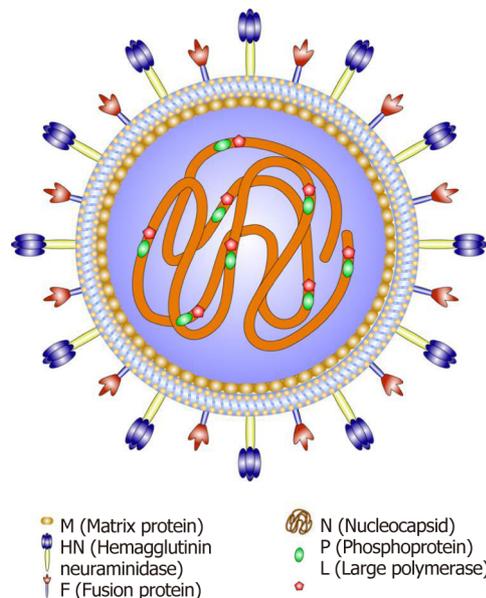


Figure 1 Molecular structure of Newcastle disease virus. Newcastle disease virus contains nuclear protein, P, L protein, M, HN and F. Among these proteins, NP, P and L combine with the viral RNA to form the ribonucleoprotein complex.

faster than that in most normal human cells. Viral replication is terminated *via* the defense mechanisms of interferon (IFN) in normal cells^[18]. In contrast, tumor cells usually have a weak type I IFN response and are also less sensitive to type I IFN receptor-mediated signaling; therefore, use of NDV in cancer patients is safe. The frameshift variant protein V is formed during transcription of the P gene. V participates in the antiviral reaction in avian cells, whereby the inhibition of IFN induction by NDV is suppressed by reduced stimulation of IFN- β through degradation of signal transduction and activator of transcription 1 *via* interactions with avian cell proteins^[19]. This response occurs because the immune escape mechanism functions only in birds and not in mammalian cells. Therefore, it appears that the V protein reduces the range of NDV hosts.

NDVs are usually divided into three types according to pathogenicity and virulence: Velogenic strains (virulent strains, strongly toxic), mesogenic strains (poisonous strains, moderately toxic), or lentogenic strains (attenuated strains, poorly toxic or nontoxic)^[20]. These viruses are also divided into two groups based on the degree of their influence on tumors: (1) Oncolytic strains that form syncytia in tumor cells and have viral oncolytic activity either *in vitro* or *in vivo*; and (2) Nononcolytic strains that inhibit tumor growth and can increase survival, though their killing effect on human tumor cells is still unclear. In general, the site of F protein cleavage mainly determines the virulence of NDV. The F-cleavage site of velogenic and mesogenic strains usually has the polybasic amino acid structure $_{112}R/G/KR-Q/KK/RR\downarrow F_{117}$, which is recognized and cut by Folin-like proteases (RXX/RR), inducing deadly respiratory diseases (such as chicken mites) in birds^[21]; examples include MTH-68/H, PV701 and Beaudette C. In contrast, lentogenic strains have the single amino acid motif $_{112}GR/KQGR\downarrow L_{117}$, which is cleaved by extracellular trypsin-like proteases; thus, replication is limited to specific tissues, and these strains are currently used. For the production of vaccines^[22], such as NDV-LaSota and NDV-HUJ, Heiden *et al*^[23] constructed a recombinant attenuated strain of NDV clone-30. When the F-cleavage site was altered, the intracerebral pathogenicity index was enhanced 1.2-fold. Overall, NDV virulence is related to the site of F cleavage and is regulated by multiple factors.

Although NDV is dangerous to many birds, its pathogenicity in humans is weak. Furthermore, most people are seropositive for NDV, and thus the immunogenicity that NDV may cause can be ignored. Under natural conditions, highly virulent NDV strains may infect humans but cause only mild fever, cough and other flu-like symptoms.

The oncolytic mechanism of NDV

The cells of various human tumors, such as liver cancer^[24], glioblastoma^[25] and lymphoma^[26], have been shown to be sensitive to NDV. In addition, because NDV RNA transcription and translation are not related to cell proliferation, the virus can target tumor stem cells, dormant tumor cells, and X-ray-irradiated vaccine tumor

cells^[27].

The oncolytic mechanism of NDV mainly include the following aspects. First, the virus selectively infects and replicates in tumor cells. Second, indirect effects of the innate and adaptive immune responses of the host immune system act against the virus, involving natural killer (NK) cells and cytotoxic T lymphocytes targeting the antigen^[28,29]. Third, the envelope protein also participates in the oncolytic effect. Fourth, the apoptotic pathway promotes the oncolytic effect. Fifth, the virus induces immunogenic death, necrosis and autophagy (Figure 2).

The NDV envelope protein participates in oncolytic effects

Studies have found that a variety of proteins of NDV can impact infected cells, and protein sequence characterization also revealed that M, L and F have a BH-3 domain that shows homology with the proapoptotic factor Bcl-2^[30]. Among these proteins, HN is an important immunogenic protein and virulence factor. Indeed, it has been reported that despite weaker efficacy than the parental NDV AF2240 strain, HN gene expression alone was able to induce apoptosis in human breast cancer MCF-7 cells^[31]. HN induces release of type I IFN from human peripheral blood mononuclear cells and up-regulates expression of tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)^[32]. He *et al*^[33] constructed a novel oncolytic adenovirus containing the human telomerase reverse transcriptase (hTERT) promoter and expressing the HN protein of NDV (Ad-hTERTp-E1a-HN) that selectively inhibits esophageal cancer EC-109 cells and inhibits tumor growth in mice. In addition, studies have indicated that the M protein of NDV AF2240 strain binds to Bax through its BH-3 domain to promote the transfer of Bax from the cytoplasm to the mitochondrial membrane, thereby activating the intrinsic apoptotic pathway^[34].

The IFN system affects oncolytic activity

NDV stimulates the body's immune system to produce a variety of cytokines with anti-tumor activity, such as various IFNs or TNF. Type I IFN exerts a direct antitumor effect by targeting tumor cells and tumor stem cells and can indirectly stimulate immune system activity to assist in tumor killing. The recombinant NDV obtained by inserting the influenza virus NS1 gene, which antagonizes the IFN system in mammalian cells, into the NDV Hitchner-B1 genome promoted apoptosis in human tumor cell lines and the B16 melanoma mouse model with enhanced oncolytic effects^[35].

An apoptotic pathway is involved in the NDV oncolytic effect

Some studies have shown that the oncolytic effect of NDV is related to the various apoptotic pathways of cells, and the apoptosis induced by NDV requires viral replication and expression of apoptotic proteins.

The exogenous apoptosis pathway is mainly mediated by the death receptor Fas and its ligands FasL and TRAIL. For example, due to overexpression of Fas, the recombinant attenuated strain rNDV-B1/Fas exhibited enhanced oncolytic ability *in vitro* and *in vivo*, which resulted in an earlier and stronger apoptotic response in infected cells^[36]. Compared to the wild-type virus, Bai's recombinant virus, LaSota-TRAIL^[37], increased expression of TRAIL by 3-fold. In a mouse experiment, the LaSota-TRAIL group displayed significantly increased survival and decreased tumor recurrence. Other studies have indicated that due to overexpression of the inhibitor of apoptosis protein Livin in tissues of stage III melanoma, advanced melanoma is more susceptible to the NDV-HUJ virus than is an early-stage tumor^[38]. Up-regulation of the apoptosis inhibitory protein survivin prolongs the viability of human breast cancer-resistant cells infected with the NDV AF2240 strain and increases viral protein synthesis as well as viral replication^[39].

NDV causes immunogenic cell death

One immunotherapy mechanism of oncolytic viruses is immunogenic cell death (ICD)^[40]. The manner in which NDV induces ICD in tumor cells includes immunogenic apoptosis, necrosis and pyroptosis, with termination of protein synthesis and subsequent exposure to calreticulin, heat shock proteins and the viral proteins HN and F.

Under endoplasmic reticulum stress, accumulation of unfolded proteins or misfolded proteins in the endoplasmic reticulum can cause the unfolded protein response, a specific response in NDV-infected cells. Activation of the unfolded protein response triggers caspase 12-induced cell death. Moreover, Cheng *et al*^[41] demonstrated that the structural proteins NP and P induce autophagy through the endoplasmic reticulum stress pathway.

The corresponding pattern recognition receptors of innate immune cells include cytoplasmic RIG-1, PKR, TLR and NKp46. The pathogen-associated molecular pattern

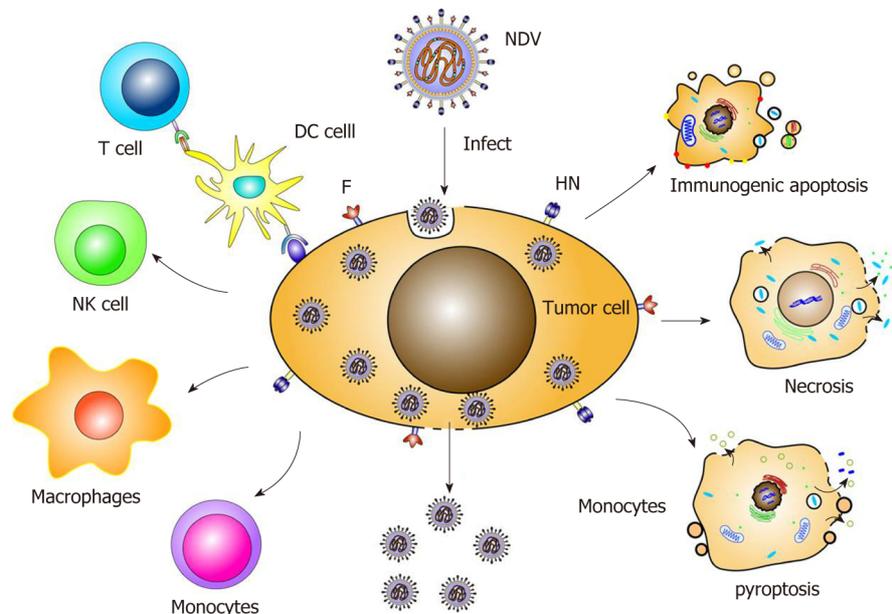


Figure 2 The main anti-tumor mechanisms and consequences of NDV infection of tumor cells. NDV enters the cytoplasm of tumor cells by endocytosis, stimulates the host's innate immune response, activates NK cells, monocytes and macrophages and promotes acquired immunity. The antigen presentation of tumor cells is enhanced. NDV can cause the immunogenic cell death of tumor cells via immunogenic apoptosis, necrosis and pyroptosis. HN: Hemagglutinin-neuraminidase; NDV: Newcastle disease virus; NK: Natural killer.

of NDV involves the virus 5'-adenosine triphosphate leader RNA, dsRNA and HN protein. Pattern recognition receptors trigger a variety of immune responses, including induction of type I IFN responses, promotion of immune cell activation and release of immune factors. In a mouse *in situ* glioma model, NDV virus therapy and molecules such as calreticulin, heat shock proteins and high mobility group protein-1 were found to induce ICD, stimulating specific immune T cells. Additionally, interaction between RIG-1 and RNA simultaneously activated type I IFN and induced IL-1 β production. The double-stranded RNA of NDV induces expression of TLR-3, FN- α and heat shock proteins, which promotes tumor cell apoptosis and inhibits tumor growth by enhancing the immune system response. NKp46 of NK cells recognizes viral HN proteins and transmits cytotoxicity-inducing signals, increasing production of IFN- α and TRAIL. After NDV infection of monocytes and NK cells, IL-2, IFN- γ , GM-CSF and TNF- α are produced to promote tumor-killing activity through TRAIL^[42,43].

Viral infection of tumors can promote an immunosuppressive environment by inducing immune cytokines and chemokines (RANTES and IP-10)^[44]. Although cytokines and chemokines recruit and activate neutrophils, NK cells, macrophages and CD4⁺ and CD8⁺ T lymphocytes, contributing to viral clearance, these molecules also alter immunosuppression. HN molecules on the surface of infected tumor cells increase the cell adhesion strength of lymphocytes and T cells for T cell costimulation. As the first responder of innate immunity, neutrophils cause the release of the chemokines CXCL1, CCL2 and CXCL10, thereby mediating immunogenic cell death^[45].

NDV induces programmed cell death, necrosis and autophagy

After NDV infection of cells, the accumulation of HN and F proteins on the host cell surface promotes the formation of cell syncytia and lead to cell-to-cell fusion, which ultimately triggers necrosis, syncytium disintegration, content release and an inflammatory response. Cell necrosis is also activated by caspase 8 through the cellular TLR and the TNF family.

The HN and F proteins of NDV rapidly induce syncytium formation and initiate stable autophagy fluxes in lung adenocarcinoma cells (A549), synergistically inducing autophagosome fusion with lysosomes for cell degradation^[46]. Autophagy is beneficial for viral replication in the early stages of NDV infection of tumor cells and lengthens the cell life cycle by regulating apoptosis. Mitochondrial autophagy has been reported to promote oncolytic NDV replication by breaking the intrinsic apoptosis regulation pathway in lung adenocarcinoma cells^[47]. Several ongoing trials are evaluating the impact of autophagy on human tumor therapy^[48]. For example, Hu *et al.*^[49] found that

NDV-infected U251 cells can promote autophagy to degrade lung cancer cells. The autophagy regulators chloroquine and rapamycin significantly enhanced the oncolytic effect of NDV on A549 cells in mice^[50]. This finding provides a new idea for exploring the antitumor strategy utilized by autophagy regulators and NDV.

Extracellular matrix molecules in solid tumor tissues affect cell migration and invasion

NDV treatment in different metastatic tumor models has revealed a blockade effect on tumor migration and invasion. Studies have shown that the NDV strain AF2240 can reduce the migration ability of breast cancer cells by directly inducing a decrease in cell proliferation^[51]. In addition, oral squamous cell carcinoma was infected with the NDV D90 strain, and a correlation between apoptosis induction and cell migration was observed^[52]. Studies have shown that simultaneous injection of NDV, extracellular matrix-degrading enzymes, collagenase and heparanase into a tumor can increase spread of the virus in tumor tissue, thereby enhancing the oncolytic effect^[53]. However, because proteolytic enzymes are involved in tumor metastasis and their inhibitors have been used to suppress metastatic tumors, it is not known whether application of virus loading of a matrix metalloproteinase is feasible in the clinic.

NDV IN THE TREATMENT OF CRC *IN VITRO* AND IN MICE

The NDV strains currently used in mouse experimental models and clinical tests include pathogenic (MTH-68/H, Ulster and PV701) and nonpathogenic (Hitchner-B1, LaSota, 73-T and HUJ) strains^[54]. NDV has been shown to have potent anti-tumor effects against colon tumors^[55], hepatocellular carcinoma^[56] and melanoma^[57].

The appeal of viral vectors is related to their broad host cell range and high expression levels of foreign genes. Typically, viral vectors with a DNA or RNA genome can be loaded with foreign genes of different lengths; for example, most vectors allow insertion of 6-8 kb, including extensive therapeutic genes^[58]. Recently, reverse genetics technology has been applied to help produce recombinant NDV (rNDV) from nonsegmented negative-strand RNA-cloned cDNA to enhance oncolysis^[59], as follows: Mutating the F gene^[60]; inserting a gene encoding a cytokine, such as IL-2^[61], IL-15^[62] or IL-7^[63], to enhance the immunostimulatory effect; simultaneous insertion of two cytokines synergistically to increase antitumor effects^[64]; and inserting a bispecific antibody consisting of a single-chain variable region that can simultaneously target virus and immune cells. Concerning T cells, the targets can be CD3, CD25 and CD28, whereas the target of NDV can be F or HN^[65] (Figure 3).

Chia *et al*^[66] incubated with human NDV strain AF2240 *in vitro* with human CRC cell lines (SW620, ddd-1, Dks8, HCT116p53+/+, HCT116p53-/- and HT29). Cell death occurred in 70-90% of cells after 96 hours of culture, providing a basis for *in vivo* experiments. In one study, a nude mouse model of human colon cancer SW620 cells was established, and the anti-tumor effect was studied by intratumoral and intravenous injection using NDV Mukteshwar strain. The results showed that tumor growth in mice was inhibited by 43% and 40%, respectively, and the survival time was prolonged^[55].

In the subcutaneous model of BALB/c mice bearing CT26 colon cancer, NDV Ulster strain was injected in and around the tumor after tumor inoculation, and the tumor was completely relieved by the 40th day. The long-term survival rate was 70%^[67]. When NDV was used for local treatment of liver metastases of MTH-68/HCT26 colon cancer cells, it was observed that tumor growth was significantly inhibited, the survival time of mice was prolonged, and there was no toxic side effect on mice^[68]. Ockert *et al*^[69] constructed a tumor-bearing mouse model of human colon cancer (SW620, HT29 and MM17387) and injected intratumoral and intraperitoneal injections with NDV 73-T strain. The results showed that multi-dose NDV injection significantly inhibited tumor growth in mice compared with single dose, and the inhibition rate reached 77-96%.

Vigil *et al*^[70] treated the constructed CT26 colon cancer mouse model with the NDV recombinant strain rNDV/F3aa-IL-2 expressing IL-2. Compared with the wild-type control virus, the recombinant virus can significantly reduce the tumor growth of the tumor-bearing mice and prolong the survival time, so that the condition of most mice is sustained. Yamaki *et al*^[71] established CRC multifocal liver metastasis model of rats or multifocal lung metastasis model using the expression of mutant (L289A) new town of fusion protein of soluble tumor cystic stomatitis virus carrier (types) [rVSV NDV/F (L289A)]^[72] for hepatic artery and local drug delivery. The pulmonary metastasis models did not show long-term survival. However, in the mice liver

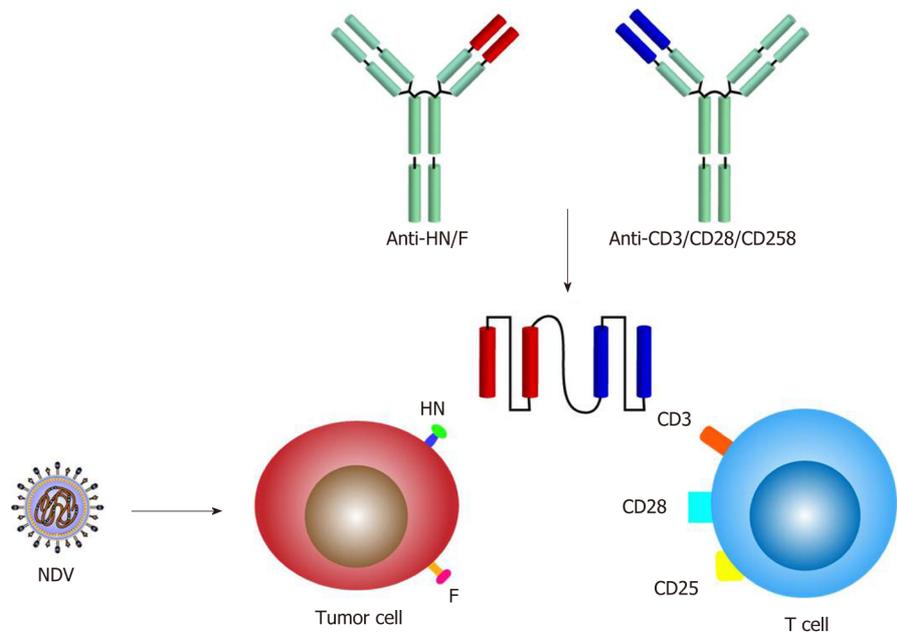


Figure 3 Bispecific antibodies consisting of single-chain variable regions can be simultaneously targeted to viruses and immune cells. When NDV infects tumor cells, bispecific antibodies can target F or HN on the surface of tumor cells and can simultaneously target CD3, CD25 or CD28 on the surface of immune T cells. F: Fusion protein; HN: Hemagglutinin-neuraminidase; NDV: Newcastle disease virus.

metastasis model, four of the seven rats survived for more than 100 d. This result provided an effective basis for the follow-up clinical trials.

CLINICAL APPLICATION OF NDV AGAINST CRC

The application of NDV tumor therapy has entered the clinical phase (phases I, II and III)^[73], and three methods are generally used in clinical trials: (1) Injection of infectious virus alone; (2) Injection of intact tumor cells infected with NDV; (3) Injection of the protein lysate of NDV-infected tumor cells; and (4) Combined use. As NDV infection of tumor cells can lead to enhanced immunogenicity, an autologous tumor vaccine (ATV-NDV) can be constructed using the tumor cells of a patient^[74], and clinically postoperative activity-specific immunotherapy has been performed for patients with CRC (Table 1).

Some phase I-IV clinical trials based on NDV vectors have yielded encouraging results. For the first time, Bohle *et al*^[75] treated 16 patients with colon cancer after tumor resection with a live, nontoxic NDV-modified tumor cell vaccine. Of the 16 patients, 12 patients had an enhanced specific anti-tumor response. In a phase I clinical trial, 20 patients with CRC were treated with ATV-NDV-specific immunotherapy, with the exception of four patients with mild fever and no serious side effects. Among them, 16 patients produced an active specific immune response to the vaccine, which provided effectiveness for subsequent clinical trials^[76].

Liebrich *et al*^[77] isolated tumor cells from human primary CRC and mixed vaccine with NDV nonlytic strain Ulster and used it for vaccination in 23 patients with colorectal liver metastasis. The results showed the active immune response in the patient is increased and can be further used in related tests. In a phase II clinical trial, 23 patients with liver metastases from CRC were completely resected after a consecutive 3 mo of ATV-NDV vaccination. At least 18 mo follow-up showed a 61% tumor recurrence in vaccinated patients compared with 87% of patients who underwent surgery alone^[78]. In a prospective randomized phase III trial, 50 patients with CRC hepatic metastases were randomized into an experimental group and a control group. The experimental group received six doses of ATV-NDV. After approximately 10 years of follow-up, no differences in primary and secondary endpoints were detected in the total patient group. However, the experimental subgroup (13 patients with colon cancer) showed significant advantages in terms of overall survival. The vaccination appeared to help prolong overall survival and metastasis-free survival^[79].

In a phase III trial, Liang *et al*^[80] used ATV-NDV to treat 335 patients with stage I-IV

Table 1 Summary of clinical studies using NDV in CRC

Ref.	Type of NDV	Aim of the study	Tumor type	Number of subjects	Outcomes
Bohle <i>et al</i> ^[75]	ATV-NDV	Phase I clinical trial	Colon cancer	16 patients	2 patients exhibited an enhanced specific anti-tumor response
Lehner <i>et al</i> ^[76]	ATV-NDV	Phase I clinical trial	CRC	20 patients	16 patients produced an active, specific immune response
Liebrich <i>et al</i> ^[77]	ATV-NDV	Phase II clinical trial	CRC	23 patients	The active immune response in the patients was increased
Schlag <i>et al</i> ^[78]	ATV-NDV	Phase II clinical trial	CRC	23 patients	A 61% tumor recurrence rate was observed in vaccinated patients compared with 87% of patients treated with surgery alone
Schulze <i>et al</i> ^[79]	ATV-NDV	Phase III clinical trial	CRC	50 patients	Advantages in terms of overall survival in subgroup; ATV-NDV appears to be beneficial prolonging overall survival and metastasis-free survival
Liang <i>et al</i> ^[80]	ATV-NDV	Phase III clinical trial	CRC	567 patients	Average survival and median survival of the immunotherapy group (310 patients) were higher than those of the control group (257 patients)
Schirmacher <i>et al</i> ^[82]	ATV-NDV and bsHN-CD28	Phase I clinical trial	CRC	14 patients	4 patients experienced a partial diminishment of metastases

ATV: Autologous tumor vaccine; CRC: Colorectal cancer; NDV: Newcastle disease virus.

CRC. The average survival and median survival of the immunotherapy group (310 patients) were higher than those of the control group. The other 25 patients with advanced disease had a 1-year survival rate of 96%. The total effective rate of immunotherapy was 24%. After NDV vaccine immunotherapy, the number of NK cells increased, and the immune function improved significantly. In patients with stage IV colon cancer, tumor memory T cells (MTCs) may induce tumor-associated antigens either spontaneously or upon vaccination with an antitumor vaccine, which may constitute a potential mechanism in those patients with long-term survival^[81].

Multiple immunizations of colon cancer patients with ATV-NDV using CD3 or CD28 on HN or F and T cells simultaneously targeting the virus have been shown to be clinically effective and improve long-term survival^[82]. Attachment of the NDV-specific single-chain antibody anti-HN \times anti-CD28 (bsHN-CD28) to ATV-NDV enhances T cell costimulatory signals. After using ATV-NDV-bsHN-CD28 to treat 14 cases of advanced CRC not surgically treatable in the phase I clinical trial, no tumor-reactive blood circulation MTCs were detected in any of the patients before vaccination; however, all patients exhibited the immune response of tumor-reactive MTCs at least once during five vaccinations. Among them, four patients experienced partial diminishment of metastases^[83].

NDV-based treatment causes only mild pus-like symptoms, and these side effects are temporary and well tolerated; even high doses *via* intravenous administration did not cause significant toxicity. Although rNDV treatment may lead to some side effects, the response is negligible when compared to the therapeutic effect. When a patient is initially desensitized with a lower dose, the subsequent maximum tolerated dose may be increased by a factor of ten^[84].

DISCUSSION

The multiple preclinical data and clinical trials with oncolytic NDV clearly demonstrate its efficacy for CRC. However, there are several questions that need to be

resolved. One of the key issues in oncolytic therapy is targeted delivery^[85]. Moreover, the extracellular matrix and other barriers in solid tumors may interfere with and slow viral transmission, thereby reducing oncolysis.

In addition, due to the induction of neutralizing antibodies, the oncolysis effect of the virus after repeated viral administration may decrease over time^[86]. To overcome the potential neutralizing effect of the antibody on the virus, an aptamer was used to block the antibody, thereby preventing neutralization of the virus. Furthermore, treatment with a paramyxovirus mesenchymal stem cell vector protects the virus against neutralizing antibodies with efficient transfer of the virus to the tumor.

In terms of safety and treatment outcomes, improvement is needed for the application of NDV. For example, NDV 73T damages normal cells while killing tumor cells. In clinical use, NDV may also pose safety problems for medical personnel and the environment because NDV virulent strains and poisonous strains can cause fatal respiratory and neurological diseases in poultry. Furthermore, insertion of an exogenous gene into the NDV genome has pros and cons: On the one hand, exogenous genes may enhance the anti-tumor effect of NDV; on the other hand, insertion of foreign genes may affect replication of the virus.

CONCLUSION

In 2005, the Chinese government approved the first transgenic oncolytic type 5 adenovirus (Adeno-5; H101) virus for the treatment of tumors; in 2013, the United States Food and Drug Administration affirmed the use of herpes simplex virus type 1 (HSV1; T-Vec). Thus, oncolytic viruses have become a new generation of biosafety agents. Among these agents, NDV meets many conditions for new drugs used in the human body: Selective potent oncolytic activity; a strong type I IFN reaction and a wide range of immunostimulatory effects. NDV directly destroys cancer cells, induces ICD and activates DC1- and Th1-directed antitumor immune responses, resulting in effective destruction of cancer cells and the development of tumor-associated MTCs after onset, which provides long-term protective activity to prolong survival.

Driven by successful animal experiments and clinical trials, the strategy of introducing, integrating and improving NDV anti-CRC therapy has been widely explored. The development of reverse genetics technology allows NDV to be employed as a vector for the integration of therapeutic genes. In the future, we envision multimodal combination therapy as the ideal option for treating complex diseases, such as tumors. Indeed, by combining oncolytic NDV with hyperthermia, therapeutic transgenes, dendritic cells, T cells, bispecific antibodies or NDV-based vaccines (*e.g.*, ATV-NDV), multimodal combination therapy is expected to be a good application prospect. However, more research is needed to determine the preclinical and clinical effects of NDV to verify its safety and efficacy in CRC therapy.

REFERENCES

- 1 Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; **67**: 7-30 [PMID: 28055103 DOI: 10.3322/caac.21387]
- 2 Wang W, Kandimalla R, Huang H, Zhu L, Li Y, Gao F, Goel A, Wang X. Molecular subtyping of colorectal cancer: Recent progress, new challenges and emerging opportunities. *Semin Cancer Biol* 2019; **55**: 37-52 [PMID: 29775690 DOI: 10.1016/j.semcancer.2018.05.002]
- 3 Geevarghese SK, Geller DA, de Haan HA, Hörer M, Knoll AE, Mescheder A, Nemunaitis J, Reid TR, Sze DY, Tanabe KK, Tawfik H. Phase I/II study of oncolytic herpes simplex virus NV1020 in patients with extensively pretreated refractory colorectal cancer metastatic to the liver. *Hum Gene Ther* 2010; **21**: 1119-1128 [PMID: 20486770 DOI: 10.1089/hum.2010.020]
- 4 Inoda S, Morita R, Hirohashi Y, Torigoe T, Asanuma H, Nakazawa E, Nakatsugawa M, Tamura Y, Kamiguchi K, Tsuruma T, Terui T, Ishitani K, Hashino S, Wang Q, Greene MI, Hasegawa T, Hirata K, Asaka M, Sato N. The feasibility of Cep55/c10orf3 derived peptide vaccine therapy for colorectal carcinoma. *Exp Mol Pathol* 2011; **90**: 55-60 [PMID: 20950610 DOI: 10.1016/j.yexmp.2010.10.001]
- 5 Hu Z, He J, Gong W, Zhou N, Zhou S, Lai Z, Zheng R, Wang Y, Yang X, Yang W, Zhong L, Lu X, Zhao Y. TLS11a Aptamer/CD3 Antibody Anti-Tumor System for Liver Cancer. *J Biomed Nanotechnol* 2018; **14**: 1645-1653 [PMID: 29958558 DOI: 10.1166/jbn.2018.2619]
- 6 Huang Y, Mao Q, He J, Su J, Peng Y, Liang W, Hu Z, Zhou S, Lu X, Zhao Y. Fusions of Tumor-derived Endothelial Cells with Dendritic Cells Induces Antitumor Immunity. *Sci Rep* 2017; **7**: 46544 [PMID: 28436481 DOI: 10.1038/srep46544]
- 7 Xu-Monette ZY, Zhang M, Li J, Young KH. PD-1/PD-L1 Blockade: Have We Found the Key to Unleash the Antitumor Immune Response? *Front Immunol* 2017; **8**: 1597 [PMID: 29255458 DOI: 10.3389/fimmu.2017.01597]
- 8 Ganar K, Das M, Sinha S, Kumar S. Newcastle disease virus: current status and our understanding. *Virus Res* 2014; **184**: 71-81 [PMID: 24589707 DOI: 10.1016/j.virusres.2014.02.016]
- 9 Afonso CL, Amarasinghe GK, Bányai K, Bao Y, Basler CF, Bavari S, Bejerman N, Blasdel KR, Briand FX, Briese T, Bukreyev A, Calisher CH, Chandran K, Cheng J, Clawson AN, Collins PL, Dietzgen RG,

- Dolnik O, Domier LL, Dürrwald R, Dye JM, Easton AJ, Ebihara H, Farkas SL, Freitas-Astúa J, Formenty P, Fouchier RA, Fù Y, Ghedin E, Goodin MM, Hewson R, Horie M, Hyndman TH, Jiāng D, Kitajima EW, Kobinger GP, Kondo H, Kurath G, Lamb RA, Lenardon S, Leroy EM, Li CX, Lin XD, Liú L, Longdon B, Marton S, Maisner A, Mühlberger E, Netesov SV, Nowotny N, Patterson JL, Payne SL, Paweska JT, Randall RE, Rima BK, Rota P, Rubbenstroth D, Schwemmler M, Shi M, Smither SJ, Stenglein MD, Stone DM, Takada A, Terregino C, Tesh RB, Tian JH, Tomonaga K, Tordo N, Townser JS, Vasilakis N, Verbeek M, Volchkov VE, Wahl-Jensen V, Walsh JA, Walker PJ, Wang D, Wang LF, Wetzel T, Whitfield AE, Xie JT, Yuen KY, Zhang YZ, Kuhn JH. Taxonomy of the order Mononegavirales: update 2016. *Arch Virol* 2016; **161**: 2351-2360 [PMID: 27216929 DOI: 10.1007/s00705-016-2880-1]
- 10 Liu T, Song Y, Yang Y, Bu Y, Cheng J, Zhang G, Xue J. Hemagglutinin-Neuraminidase and fusion genes are determinants of NDV thermostability. *Vet Microbiol* 2019; **228**: 53-60 [PMID: 30593380 DOI: 10.1016/j.vetmic.2018.11.013]
- 11 Yaacov B, Eliaho E, Lazar I, Ben-Shlomo M, Greenbaum I, Panet A, Zakay-Rones Z. Selective oncolytic effect of an attenuated Newcastle disease virus (NDV-HUJ) in lung tumors. *Cancer Gene Ther* 2008; **15**: 795-807 [PMID: 18535620 DOI: 10.1038/cgt.2008.31]
- 12 Lamb RA, Jardetzky TS. Structural basis of viral invasion: lessons from paramyxovirus F. *Curr Opin Struct Biol* 2007; **17**: 427-436 [PMID: 17870467 DOI: 10.1016/j.sbi.2007.08.016]
- 13 Fournier P, Schirmacher V. Oncolytic Newcastle Disease Virus as Cutting Edge between Tumor and Host. *Biology (Basel)* 2013; **2**: 936-975 [PMID: 24833054 DOI: 10.3390/biology2030936]
- 14 Molouki A, Peeters B. Rescue of recombinant Newcastle disease virus: current cloning strategies and RNA polymerase provision systems. *Arch Virol* 2017; **162**: 1-12 [PMID: 27695950 DOI: 10.1007/s00705-016-3065-7]
- 15 Fountzilias C, Patel S, Mahalingam D. Review: Oncolytic virotherapy, updates and future directions. *Oncotarget* 2017; **8**: 102617-102639 [PMID: 29254276 DOI: 10.18632/oncotarget.18309]
- 16 Tayeb S, Zakay-Rones Z, Panet A. Therapeutic potential of oncolytic Newcastle disease virus: a critical review. *Oncolytic Virother* 2015; **4**: 49-62 [PMID: 27512670 DOI: 10.2147/OV.S78600]
- 17 Yurchenko KS, Zhou P, Kovner AV, Zavjalov EL, Shestopalova LV, Shestopalov AM. Oncolytic effect of wild-type Newcastle disease virus isolates in cancer cell lines in vitro and in vivo on xenograft model. *PLoS One* 2018; **13**: e0195425 [PMID: 29621357 DOI: 10.1371/journal.pone.0195425]
- 18 Zhang S, Sun Y, Chen H, Dai Y, Zhan Y, Yu S, Qiu X, Tan L, Song C, Ding C. Activation of the PKR/eIF2 α signaling cascade inhibits replication of Newcastle disease virus. *Viral J* 2014; **11**: 62 [PMID: 24684861 DOI: 10.1186/1743-422X-11-62]
- 19 Wang X, Dang R, Yang Z. The interferon antagonistic activities of the V proteins of NDV correlated with their virulence. *Virus Genes* 2019; **55**: 233-237 [PMID: 30706195 DOI: 10.1007/s11262-019-01637-3]
- 20 Liu L. Fields Virology, 6th Edition. *Clin Infect Dis* 2014; **59**: 613 [DOI: 10.1093/cid/ciu346]
- 21 Kumar R, Tiwari AK, Chaturvedi U, Kumar GR, Sahoo AP, Rajmani RS, Saxena L, Saxena S, Tiwari S, Kumar S. Velogenic newcastle disease virus as an oncolytic virotherapeutics: in vitro characterization. *Appl Biochem Biotechnol* 2012; **167**: 2005-2022 [PMID: 22644640 DOI: 10.1007/s12010-012-9700-1]
- 22 Spalatin J, Turner AJ, Hanson RP. Observations on the transmissibility of lentogenic strains of Newcastle disease virus: significance of variables. *Avian Dis* 1976; **20**: 361-368 [PMID: 938383 DOI: 10.2307/1589274]
- 23 Heiden S, Grund C, Röder A, Granzow H, Kühnel D, Mettenleiter TC, Römer-Oberdörfer A. Different regions of the newcastle disease virus fusion protein modulate pathogenicity. *PLoS One* 2014; **9**: e113344 [PMID: 25437176 DOI: 10.1371/journal.pone.0113344]
- 24 An Y, Liu T, He J, Wu H, Chen R, Liu Y, Wu Y, Bai Y, Guo X, Zheng Q, Liu C, Yin J, Li D, Ren G. Recombinant Newcastle disease virus expressing P53 demonstrates promising antitumor efficiency in hepatoma model. *J Biomed Sci* 2016; **23**: 55 [PMID: 27465066 DOI: 10.1186/s12929-016-0273-0]
- 25 Abdullah JM, Mustafa Z, Ideris A. Newcastle disease virus interaction in targeted therapy against proliferation and invasion pathways of glioblastoma multiforme. *Biomed Res Int* 2014; **2014**: 386470 [PMID: 25243137 DOI: 10.1155/2014/386470]
- 26 Al-Shammari AM, Rameez H, Al-Taei MF. Newcastle disease virus, rituximab, and doxorubicin combination as anti-hematological malignancy therapy. *Oncolytic Virother* 2016; **5**: 27-34 [PMID: 27579294 DOI: 10.2147/OV.S95250]
- 27 Schirmacher V. Fifty Years of Clinical Application of Newcastle Disease Virus: Time to Celebrate! *Biomedicines* 2016; **4**: pii: E16 [PMID: 28536382 DOI: 10.3390/biomedicines4030016]
- 28 Ricca JM, Oseledchik A, Walther T, Liu C, Mangarin L, Merghoub T, Wolchok JD, Zamarin D. Pre-existing Immunity to Oncolytic Virus Potentiates Its Immunotherapeutic Efficacy. *Mol Ther* 2018; **26**: 1008-1019 [PMID: 29478729 DOI: 10.1016/j.ymthe.2018.01.019]
- 29 Chaurasiya S, Chen NG, Fong Y. Oncolytic viruses and immunity. *Curr Opin Immunol* 2018; **51**: 83-90 [PMID: 29550660 DOI: 10.1016/j.coi.2018.03.008]
- 30 Liu B, Ji Y, Lin Z, Fu Y, Muhammad Dafallah R, Zhu Q. Two single amino acid substitutions in the intervening region of Newcastle disease virus HN protein attenuate viral replication and pathogenicity. *Sci Rep* 2015; **5**: 13038 [PMID: 26267791 DOI: 10.1038/srep13038]
- 31 Ghrici M, El Zowalaty M, Omar AR, Ideris A. Induction of apoptosis in MCF-7 cells by the hemagglutinin-neuraminidase glycoprotein of Newcastle disease virus Malaysian strain AF2240. *Oncol Rep* 2013; **30**: 1035-1044 [PMID: 23807159 DOI: 10.3892/or.2013.2573]
- 32 Liao Y, Wang HX, Mao X, Fang H, Wang H, Li Y, Sun Y, Meng C, Tan L, Song C, Qiu X, Ding C. RIP1 is a central signaling protein in regulation of TNF- α /TRAIL mediated apoptosis and necroptosis during Newcastle disease virus infection. *Oncotarget* 2017; **8**: 43201-43217 [PMID: 28591723 DOI: 10.18632/oncotarget.17970]
- 33 He D, Sun L, Li C, Hu N, Sheng Y, Chen Z, Li X, Chi B, Jin N. Anti-tumor effects of an oncolytic adenovirus expressing hemagglutinin-neuraminidase of Newcastle disease virus in vitro and in vivo. *Viruses* 2014; **6**: 856-874 [PMID: 24553109 DOI: 10.3390/v6020856]
- 34 Molouki A, Hsu YT, Jahanshiri F, Abdullah S, Rosli R, Yusoff K. The matrix (M) protein of Newcastle disease virus binds to human bax through its BH3 domain. *Viral J* 2011; **8**: 385 [PMID: 21810274 DOI: 10.1186/1743-422X-8-385]
- 35 García-Sastre A, Egorov A, Matassov D, Brandt S, Levy DE, Durbin JE, Palese P, Muster T. Influenza A virus lacking the NS1 gene replicates in interferon-deficient systems. *Virology* 1998; **252**: 324-330 [PMID: 9878611 DOI: 10.1006/viro.1998.9508]
- 36 Cuadrado-Castano S, Ayllon J, Mansour M, de la Iglesia-Vicente J, Jordan S, Tripathi S, García-Sastre A, Villar E. Enhancement of the proapoptotic properties of newcastle disease virus promotes tumor

- remission in syngeneic murine cancer models. *Mol Cancer Ther* 2015; **14**: 1247-1258 [PMID: 25761895 DOI: 10.1158/1535-7163.MCT-14-0913]
- 37 **Bai FL**, Tian H, Yu YH, Yin JC, Ren GP, Zhou B, Li DS. TNF-related Apoptosis-inducing Ligand Delivered by rNDV is a Novel Agent for Cancer Gene Therapy. *Technol Cancer Res Treat* 2015; **14**: 737-746 [PMID: 24988059 DOI: 10.7785/tcrt.2012.500446]
- 38 **Lazar I**, Perlman R, Lotem M, Peretz T, Ben-Yehuda D, Kadouri L. The clinical effect of the inhibitor of apoptosis protein livin in melanoma. *Oncology* 2012; **82**: 197-204 [PMID: 22441029 DOI: 10.1159/000334234]
- 39 **Altieri DC**. Survivin - The inconvenient IAP. *Semin Cell Dev Biol* 2015; **39**: 91-96 [PMID: 25591986 DOI: 10.1016/j.semedb.2014.12.007]
- 40 **Ye T**, Jiang K, Wei L, Barr MP, Xu Q, Zhang G, Ding C, Meng S, Piao H. Oncolytic Newcastle disease virus induces autophagy-dependent immunogenic cell death in lung cancer cells. *Am J Cancer Res* 2018; **8**: 1514-1527 [PMID: 30210920]
- 41 **Cheng JH**, Sun YJ, Zhang FQ, Zhang XR, Qiu XS, Yu LP, Wu YT, Ding C. Newcastle disease virus NP and P proteins induce autophagy via the endoplasmic reticulum stress-related unfolded protein response. *Sci Rep* 2016; **6**: 24721 [PMID: 27097866 DOI: 10.1038/srep24721]
- 42 **Schwaiger T**, Knittler MR, Grund C, Roemer-Oberdoerfer A, Kapp JF, Lerch MM, Mettenleiter TC, Mayerle J, Blohm U. Newcastle disease virus mediates pancreatic tumor rejection via NK cell activation and prevents cancer relapse by prompting adaptive immunity. *Int J Cancer* 2017; **141**: 2505-2516 [PMID: 28857157 DOI: 10.1002/ijc.31026]
- 43 **Tan L**, Zhang Y, Qiao C, Yuan Y, Sun Y, Qiu X, Meng C, Song C, Liao Y, Munir M, Nair V, Ding Z, Liu X, Ding C. NDV entry into dendritic cells through macropinocytosis and suppression of T lymphocyte proliferation. *Virology* 2018; **518**: 126-135 [PMID: 29481983 DOI: 10.1016/j.virol.2018.02.011]
- 44 **Cassady KA**, Haworth KB, Jackson J, Markert JM, Cripe TP. To Infection and Beyond: The Multi-Pronged Anti-Cancer Mechanisms of Oncolytic Viruses. *Viruses* 2016; **8**: pii: E43 [PMID: 26861381 DOI: 10.3390/v8020043]
- 45 **Garg AD**, Vandenberk L, Fang S, Fasche T, Van Eygen S, Maes J, Van Woensel M, Koks C, Vanthillo N, Graf N, de Witte P, Van Gool S, Salven P, Agostinis P. Pathogen response-like recruitment and activation of neutrophils by sterile immunogenic dying cells drives neutrophil-mediated residual cell killing. *Cell Death Differ* 2017; **24**: 832-843 [PMID: 28234357 DOI: 10.1038/cdd.2017.15]
- 46 **Sun Y**, Yu S, Ding N, Meng C, Meng S, Zhang S, Zhan Y, Qiu X, Tan L, Chen H, Song C, Ding C. Autophagy benefits the replication of Newcastle disease virus in chicken cells and tissues. *J Virol* 2014; **88**: 525-537 [PMID: 24173218 DOI: 10.1128/JVI.01849-13]
- 47 **Li Y**, Wang LX, Yang G, Hao F, Urba WJ, Hu HM. Efficient cross-presentation depends on autophagy in tumor cells. *Cancer Res* 2008; **68**: 6889-6895 [PMID: 18757401 DOI: 10.1158/0008-5472.CAN-08-0161]
- 48 **Kang Y**, Yuan R, Xiang B, Zhao X, Gao P, Dai X, Liao M, Ren T. Newcastle disease virus-induced autophagy mediates antiapoptotic signaling responses *in vitro* and *in vivo*. *Oncotarget* 2017; **8**: 73981-73993 [PMID: 29088762 DOI: 10.18632/oncotarget.18169]
- 49 **Hu L**, Sun S, Wang T, Li Y, Jiang K, Lin G, Ma Y, Barr MP, Song F, Zhang G, Meng S. Oncolytic newcastle disease virus triggers cell death of lung cancer spheroids and is enhanced by pharmacological inhibition of autophagy. *Am J Cancer Res* 2015; **5**: 3612-3623 [PMID: 26885450]
- 50 **Jiang K**, Li Y, Zhu Q, Xu J, Wang Y, Deng W, Liu Q, Zhang G, Meng S. Pharmacological modulation of autophagy enhances Newcastle disease virus-mediated oncolysis in drug-resistant lung cancer cells. *BMC Cancer* 2014; **14**: 551 [PMID: 25078870 DOI: 10.1186/1471-2407-14-551]
- 51 **Ahmad U**, Ahmed I, Keong YY, Abd Manan N, Othman F. Inhibitory and apoptosis-inducing effects of Newcastle disease virus strain AF2240 on mammary carcinoma cell line. *Biomed Res Int* 2015; **2015**: 127828 [PMID: 25821783 DOI: 10.1155/2015/127828]
- 52 **Zhang CX**, Ye LW, Liu Y, Xu XY, Li DR, Yang YQ, Sun LL, Yuan J. Antineoplastic activity of Newcastle disease virus strain D90 in oral squamous cell carcinoma. *Tumour Biol* 2015; **36**: 7121-7131 [PMID: 25877754 DOI: 10.1007/s13277-015-3433-z]
- 53 **Yaacov B**, Lazar I, Tayeb S, Frank S, Izhar U, Lotem M, Perlman R, Ben-Yehuda D, Zakay-Rones Z, Panet A. Extracellular matrix constituents interfere with Newcastle disease virus spread in solid tissue and diminish its potential oncolytic activity. *J Gen Virol* 2012; **93**: 1664-1672 [PMID: 22622327 DOI: 10.1099/vir.0.043281-0]
- 54 **Kim SH**, Samal SK. Newcastle Disease Virus as a Vaccine Vector for Development of Human and Veterinary Vaccines. *Viruses* 2016; **8**: 183 [PMID: 27384578 DOI: 10.3390/v8070183]
- 55 **Sharma KK**, Kalyani IH, Mohapatra J, Patel SD, Patel DR, Vihol PD, Chatterjee A, Patel DR, Vyas B. Evaluation of the oncolytic potential of R₂B Mukteshwar vaccine strain of Newcastle disease virus (NDV) in a colon cancer cell line (SW-620). *Arch Virol* 2017; **162**: 2705-2713 [PMID: 28578522 DOI: 10.1007/s00705-017-3411-4]
- 56 **Wu Y**, Yan S, Lv Z, Chen L, Geng J, He J, Yu Q, Yin J, Ren G, Li D. Recombinant Newcastle disease virus Anhinga strain (NDV/Anh-EGFP) for hepatoma therapy. *Technol Cancer Res Treat* 2014; **13**: 169-175 [PMID: 23819497 DOI: 10.7785/tcrt.2012.500356]
- 57 **Bommareddy PK**, Kaufman HL. Unleashing the therapeutic potential of oncolytic viruses. *J Clin Invest* 2018; **128**: 1258-1260 [PMID: 29504947 DOI: 10.1172/JCI120303]
- 58 **Lundstrom K**. New frontiers in oncolytic viruses: optimizing and selecting for virus strains with improved efficacy. *Biologics* 2018; **12**: 43-60 [PMID: 29445265 DOI: 10.2147/BTT.S140114]
- 59 **Cheng X**, Wang W, Xu Q, Harper J, Carroll D, Galinski MS, Suzich J, Jin H. Genetic Modification of Oncolytic Newcastle Disease Virus for Cancer Therapy. *J Virol* 2016; **90**: 5343-5352 [PMID: 27009956 DOI: 10.1128/JVI.00136-16]
- 60 **Wang W**, Cheng X, Buske PJ, Suzich JA, Jin H. Attenuate Newcastle disease virus by codon modification of the glycoproteins and phosphoprotein genes. *Virology* 2019; **528**: 144-151 [PMID: 30616204 DOI: 10.1016/j.virol.2018.12.017]
- 61 **Wu Y**, He J, An Y, Wang X, Liu Y, Yan S, Ye X, Qi J, Zhu S, Yu Q, Yin J, Li D, Wang W. Recombinant Newcastle disease virus (NDV/Anh-IL-2) expressing human IL-2 as a potential candidate for suppresses growth of hepatoma therapy. *J Pharmacol Sci* 2016; **132**: 24-30 [PMID: 27174862 DOI: 10.1016/j.jphs.2016.03.012]
- 62 **Niu Z**, Bai F, Sun T, Tian H, Yu D, Yin J, Li S, Li T, Cao H, Yu Q, Wu Y, Ren G, Li D. Recombinant Newcastle Disease virus Expressing IL15 Demonstrates Promising Antitumor Efficiency in Melanoma Model. *Technol Cancer Res Treat* 2015; **14**: 607-615 [PMID: 24645750 DOI: 10.7785/tcrt.2012.500414]
- 63 **Zhao L**, Mei Y, Sun Q, Guo L, Wu Y, Yu X, Hu B, Liu X, Liu H. Autologous tumor vaccine modified

- with recombinant new castle disease virus expressing IL-7 promotes antitumor immune response. *J Immunol* 2014; **193**: 735-745 [PMID: 24943214 DOI: 10.4049/jimmunol.1400004]
- 64 **Xu X**, Sun Q, Mei Y, Liu Y, Zhao L. Newcastle disease virus co-expressing interleukin 7 and interleukin 15 modified tumor cells as a vaccine for cancer immunotherapy. *Cancer Sci* 2018; **109**: 279-288 [PMID: 29224228 DOI: 10.1111/cas.13468]
- 65 **Fournier P**, Aigner M, Schirmmacher V. Transcriptome analysis and cytokine profiling of naive T cells stimulated by a tumor vaccine via CD3 and CD25. *Int J Oncol* 2010; **37**: 1439-1452 [PMID: 21042712 DOI: 10.3892/ijo_00000796]
- 66 **Chia SL**, Yusoff K, Shafee N. Viral persistence in colorectal cancer cells infected by Newcastle disease virus. *Viol J* 2014; **11**: 91 [PMID: 24886301 DOI: 10.1186/1743-422X-11-91]
- 67 **Schirmmacher V**, Griesbach A, Ahlert T. Antitumor effects of Newcastle Disease Virus in vivo: local versus systemic effects. *Int J Oncol* 2001; **18**: 945-952 [PMID: 11295039 DOI: 10.3892/ijo.18.5.945]
- 68 **Apostolidis L**, Schirmmacher V, Fournier P. Host mediated anti-tumor effect of oncolytic Newcastle disease virus after locoregional application. *Int J Oncol* 2007; **31**: 1009-1019 [PMID: 17912426]
- 69 **Ockert D**, Schirmmacher V, Beck N, Stoelben E, Ahlert T, Flechtenmacher J, Hagemüller E, Buchcik R, Nagel M, Saeger HD. Newcastle disease virus-infected intact autologous tumor cell vaccine for adjuvant active specific immunotherapy of resected colorectal carcinoma. *Clin Cancer Res* 1996; **2**: 21-28 [PMID: 9816085]
- 70 **Vigil A**, Park MS, Martinez O, Chua MA, Xiao S, Cros JF, Martínez-Sobrido L, Woo SL, García-Sastre A. Use of reverse genetics to enhance the oncolytic properties of Newcastle disease virus. *Cancer Res* 2007; **67**: 8285-8292 [PMID: 17804743 DOI: 10.1158/0008-5472.CAN-07-1025]
- 71 **Yamaki M**, Shinozaki K, Sakaguchi T, Meseck M, Ebert O, Ohdan H, Woo SL. The potential of recombinant vesicular stomatitis virus-mediated virotherapy against metastatic colon cancer. *Int J Mol Med* 2013; **31**: 299-306 [PMID: 23232984 DOI: 10.3892/ijmm.2012.1205]
- 72 **Ebert O**, Shinozaki K, Kourmioti C, Park MS, García-Sastre A, Woo SL. Syncytia induction enhances the oncolytic potential of vesicular stomatitis virus in virotherapy for cancer. *Cancer Res* 2004; **64**: 3265-3270 [PMID: 15126368 DOI: 10.1158/0008-5472.CAN-03-3753]
- 73 **Taguchi S**, Fukuhara H, Homma Y, Todo T. Current status of clinical trials assessing oncolytic virus therapy for urological cancers. *Int J Urol* 2017; **24**: 342-351 [PMID: 28326624 DOI: 10.1111/iju.13325]
- 74 **Takamura-Ishii M**, Nakaya T, Hagiwara K. Regulation of Constitutive Interferon-Stimulated Genes (ISGs) in Tumor Cells Contributes to Enhanced Antitumor Response of Newcastle Disease Virus-Infected Tumor Vaccines. *Cancers (Basel)* 2018; **10**: pii: E186 [PMID: 29882780 DOI: 10.3390/cancers10060186]
- 75 **Bohle W**, Schlag P, Liebrich W, Hohenberger P, Manasterski M, Möller P, Schirmmacher V. Postoperative active specific immunization in colorectal cancer patients with virus-modified autologous tumor-cell vaccine. First clinical results with tumor-cell vaccines modified with live but avirulent Newcastle disease virus. *Cancer* 1990; **66**: 1517-1523 [PMID: 2208003 DOI: 10.1002/1097-0142(19901001)66:7<1517::AID-CNCR2820660714>3.0.CO;2-I]
- 76 **Lehner B**, Schlag P, Liebrich W, Schirmmacher V. Postoperative active specific immunization in curatively resected colorectal cancer patients with a virus-modified autologous tumor cell vaccine. *Cancer Immunol Immunother* 1990; **32**: 173-178 [PMID: 2289211 DOI: 10.1007/BF01771453]
- 77 **Liebrich W**, Schlag P, Manasterski M, Lehner B, Stöhr M, Möller P, Schirmmacher V. In vitro and clinical characterisation of a Newcastle disease virus-modified autologous tumour cell vaccine for treatment of colorectal cancer patients. *Eur J Cancer* 1991; **27**: 703-710 [PMID: 1829908 DOI: 10.1016/0277-5379(91)90170-I]
- 78 **Schlag P**, Manasterski M, Gerneth T, Hohenberger P, Dueck M, Herfarth C, Liebrich W, Schirmmacher V. Active specific immunotherapy with Newcastle-disease-virus-modified autologous tumor cells following resection of liver metastases in colorectal cancer. First evaluation of clinical response of a phase II-trial. *Cancer Immunol Immunother* 1992; **35**: 325-330 [PMID: 1394336 DOI: 10.1007/BF01741145]
- 79 **Schulze T**, Kemmner W, Weitz J, Wernecke KD, Schirmmacher V, Schlag PM. Efficiency of adjuvant active specific immunization with Newcastle disease virus modified tumor cells in colorectal cancer patients following resection of liver metastases: results of a prospective randomized trial. *Cancer Immunol Immunother* 2009; **58**: 61-69 [PMID: 18488223 DOI: 10.1007/s00262-008-0526-1]
- 80 **Liang W**, Wang H, Sun TM, Yao WQ, Chen LL, Jin Y, Li CL, Meng FJ. Application of autologous tumor cell vaccine and NDV vaccine in treatment of tumors of digestive tract. *World J Gastroenterol* 2003; **9**: 495-498 [PMID: 12632504 DOI: 10.3748/wjg.v9.i3.495]
- 81 **Schirmmacher V**, Fournier P, Schlag P. Autologous tumor cell vaccines for post-operative active-specific immunotherapy of colorectal carcinoma: long-term patient survival and mechanism of function. *Expert Rev Vaccines* 2014; **13**: 117-130 [PMID: 24219122 DOI: 10.1586/14760584.2014.854169]
- 82 **Haas C**, Lulei M, Fournier P, Arnold A, Schirmmacher V. A tumor vaccine containing anti-CD3 and anti-CD28 bispecific antibodies triggers strong and durable antitumor activity in human lymphocytes. *Int J Cancer* 2006; **118**: 658-667 [PMID: 16108015 DOI: 10.1002/ijc.21390]
- 83 **Schirmmacher V**, Schlude C, Weitz J, Beckhove P. Strong T cell costimulation can reactivate tumor antigenspecific T cells in latestage metastasized colorectal carcinoma patients: results from a phase I clinical study. *Int J Oncol* 2015; **46**: 71-77 [PMID: 25354198 DOI: 10.3892/ijo.2014.2692]
- 84 **Hotte SJ**, Lorence RM, Hirte HW, Polawski SR, Bamat MK, O'Neil JD, Roberts MS, Groene WS, Major PP. An optimized clinical regimen for the oncolytic virus PV701. *Clin Cancer Res* 2007; **13**: 977-985 [PMID: 17289893 DOI: 10.1158/1078-0432.CCR-06-1817]
- 85 **Wang Y**, Deng W, Li N, Neri S, Sharma A, Jiang W, Lin SH. Combining Immunotherapy and Radiotherapy for Cancer Treatment: Current Challenges and Future Directions. *Front Pharmacol* 2018; **9**: 185 [PMID: 29556198 DOI: 10.3389/fphar.2018.00185]
- 86 **Chaurasiya S**, Warner S. Viroimmunotherapy for Colorectal Cancer: Clinical Studies. *Biomedicines* 2017; **5**: pii: E11 [PMID: 28536354 DOI: 10.3390/biomedicines5010011]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

