OvirusTdb: A database of oncolytic viruses for the advancement of therapeutics in cancer

Anjali Lathwala, Rajesh Kumar, Gajendra P.S. Raghava

ARTICLE INFO

Keywords:
- Oncolytic virus
- Cancer therapy
- Immunotherapy
- Apoptosis
- Interleukins
- Database

ABSTRACT

One of the emerging technologies to fight against cancer is oncolytic virus-based immunotherapy. Recently, the FDA approved an oncolytic virus T-vec for the treatment of melanoma. To facilitate the scientific community, we build a manually-curated repository of oncolytic viruses called OvirusTdb (https://webs.iiitd.edu.in/raghava/ovirusTdb/). The repository maintains comprehensive information on therapeutically important oncolytic viruses with 5927 records where each record has 25 fields such as the virus species, cancer cell line, synergism with anti-cancer drugs, and many more. It stores information on 09 types of DNA, 15 types of RNA; 300 recombinant and 09 wild-type viral strains; tested against 124 cancer types and 427 cancer cell lines. Approximately, 1047 records suggest improved anti-cancer response using the combinatorial approach with chemotherapeutic agents. Nearly, 3243 and 1506 records indicate cancer cell death via apoptosis induction and immune activation, respectively. OvirusTdb may facilitate researchers in designing and discovering new oncolytic viruses for effective cancer treatment.

1. Introduction

Cancer is one of the leading causes of death worldwide. According to the GLOBOCAN database of the World Health Organization (WHO) report 2018, the global cancer burden rose to 18.1 million new cases and 9.6 million deaths are due to cancer (Siegel et al., 2019). In this scenario, cancer is the second prominent cause of deaths after cardiovascular diseases (Nagai and Kim, 2017). Scientists and researchers worldwide are trying to discover new molecules and treatment strategies to combat this deadly disease. Drugs such as Paclitaxel, Vincristine, Vinblastine, Docetaxel, NT-219, and several treatment strategies such as kinase inhibitor, mitotic disruptor, HDAC inhibitors, radiotherapy in combination with others approaches are currently being used to treat cancer (Nagai and Kim, 2017). The currently used cancer treatment approaches have several limitations such as increased resistance towards chemotherapeutic agents, delayed anti-cancer response time, and several other cytotoxic effects (Hanusova et al., 2015). An ideal anti-cancer therapeutic strategy is one that selectively kills cancer cells without harming normal cells and can also boost anti-tumor immune response.

Recently, several immunotherapeutic strategies were approved for the treatment of cancer with some of them being in clinical trials (Davola and Mossman, 2019). Among various immunotherapy-based strategies, oncolytic viruses (OV) are gaining much more importance as modern age therapeutics for generating anti-cancer response (Kaufman et al., 2015; Schirrmacher, 2019). OV can specifically spread in tumor cells without affecting normal cells (Bai et al., 2019). Coxsackie, measles, and vaccinia virus have the natural tendency towards specifically targeting cancer cells whereas viruses such as adenovirus and herpes simplex virus (HSV) are genetically modified to selectively replicate in cancer cells (Howells et al., 2017). Also, cancer cells have some intrinsic properties such as resistance to apoptosis, growth suppression, and defects in signalling pathways like interferon pathways (IFN) which makes them more susceptible to viral infection. By utilizing such differences, OVs can selectively infect cancer cells and initiate their lysis. Oncolysis of cancer cells further releases damage-associated molecular patterns (DAMP) and tumor-associated antigens (TAAs), which serve the basis of generation of anti-tumor immunity (Schalper et al., 2018). A schematic mechanism of the killing of cancer cells by the OVs is shown in Fig. 1.

* Corresponding author. Department of Computational Biology, Indraprastha Institute of Information Technology, Delhi, Okhla Industrial Estate, Phase III, (Near Govind Puri Metro Station), New Delhi, 110020, India.

E-mail addresses: anjalil@iiitd.ac.in (A. Lathwal), rajesh@imtech.res.in (R. Kumar), raghava@iiitd.ac.in (G.P.S. Raghava).


Contributed equally to the work.
Currently, Talimogene Laherparepvec (T-vec) is the only modified OV-based drug approved by the food and drug administration (FDA) for the treatment of malignant melanoma (Bommareddy et al., 2017). Several OVs in wild-type or in modified forms completed the clinical trials for the treatment of various cancer types, while some others are in the completion phase. Modification in OV offers several advantages in terms of increased infectivity to a broad range of cancer cells, improved replication efficiency, and safety. For example, deletion in ICP and E1B gene of HSV enables its selective replication in cancer cells (Hummel et al., 2005). By expressing immune genes such as TNF related apoptosis-inducing ligand (TRAIL) and interleukin (IL) gene within the viral genome, one can increase the oncolytic potency of viruses as observed in both In-vivo and In-vitro experimental studies (Sova et al., 2004). All these evidence suggests that OVs can serve as an ideal anti-cancer molecule because of their multifunctional properties such as selective tumor replication, boosting anti-tumor immune response, allowing genetic modification for improved potency and tumor targeting.

There are numerous studies on the oncolytic potential of viruses with promising results in various clinical and preclinical studies, but this information is scattered in the literature is difficult to access. This gap in the literature and the immense therapeutic potential of OVs motivated us to make a single repository - OvirusTdb (webs.iiitd.edu.in/raghava/ovirusdb), which is an homage to numerous OVs that exhibits huge therapeutic potential to induce death in the cancer cells.

The information from this database could be used for designing and building new virus-based cancer therapeutics.

2. Materials and methods

2.1. Data acquisition

To ensure high-quality data collection, we adopted the same methodology as found in the literature for other manually curated databases such as ENdb, AntiTbPdb, CPPsite 2.0. PubMed was used to query and retrieve information regarding OVs. PubMed search was performed using the keywords - “oncolytic virus” and “oncolytic virotherapy”. A total of 4514 hits were found in PubMed. We downloaded all the PubMed indexed abstracts against our search keywords that were available in native English language. Since OVs hold great promise in cancer therapeutics; the relevant data can also be stored in the patents. We also searched the United States Patents and Trademark Office (USPTO) site using the above-mentioned keywords that resulted in 1100 patent records.

2.2. Data reviewing and inclusion criteria

The following strategy was adopted carefully for review and data extraction from the downloaded papers and patents. Firstly, we excluded all the review articles, hypothesis articles, and perspectives from the downloaded PubMed abstracts. Now, the filtered PubMed papers were manually reviewed for the presence of experimental details of OV and their efficacy in the treatment of cancer. This initial filtering of abstract leads to the inclusion of 1604 PubMed papers. Patents that are not freely available in native English language were discarded; this will lead to 644 patents. Since OVs are considered as an ideal candidate for cancer immunotherapy. The therapeutic effect of OVs can be measured either in in-vivo or in-vitro conditions along with a combination of other modalities. To ensure quality data extraction, each downloaded PubMed article and the patent were manually screened for relevant experimental details. The inclusion criteria for article and patents can be broadly classified into following major categories – (i) virus related information such as virus name, strain, family; (ii) in-vitro assay information that includes – cell line, origin, the concentration used, the method to measure effectiveness and results; (iii) in-vivo activity – includes toxicity, mode of delivery, model organism, etc. (iv) OV in combination with drugs and immunogenic effects were also checked. The articles that primarily contain this information were taken into consideration. Final complete records in the database were manually obtained from 166 research articles and 27 patents.

2.3. Literature curation for database creation

The downloaded PubMed and patent articles were manually screened for information and catalogued with following fields in a tabular form: Virus name: Name of the OV species e.g. Adenovirus, Herpes simplex virus; Strain/Serotype: The genetic variant or subtype of the virus used in the study e.g. M1, AR339; Genome: The type of genetic material of virus e.g. DNA or RNA; Family: The family to which virus belongs e.g. Adenoviridae, Herpesviridae; Genomic alteration: Any genomic modification in virus genome e.g. Deletion of E1A promoter gene, Insertion of IL-2 gene; Chemo-virotherapy: Virus in combination with anti-cancer drugs e.g. Paclitaxel, Cisplatin; Name of cell line: The name of cancer cell line used in the study e.g. M1, AR339; Origin of cell line: The cancer type from which cell line is derived e.g. Human pancreatic, Human glioblastoma cancer type; Source: The source of cell line from where it is obtained e.g. ATCC, NCI; In-vitro experimental details: Includes fields such as concentration of cell line, virus concentration, toxicity and assay information used to measure oncolysis by virus; In-vivo experimental details: Includes fields such as model or organism, virus concentration, toxicity, mode of delivery and results of the experiments; Pathway: Pathway induced or associated with oncolysis caused by virus e.g. Apoptosis induction by activation of caspases, Necroptosis; Immunogenic effect: Viral oncolysis based immune activation by secreting cytokines e.g. IL-2, TNF-alpha; PubMed ID: The PMID of the article and patent application number from where the information was retrieved.
2.4. Database architecture and web interface

All the information available in the literature related to OVs was stored in the SQL table and presented in the form of a user-friendly and interactive web interface named OvirusTdb. OvirusTdb is built on a Linux based Apache server (LAMP).

The responsive front-end web interface of OvirusTdb was developed using bootstrap, a popular responsive development framework that includes HTML, CSS, and JavaScript. MySQL client program was used to create the back-end database and all the data handling/manipulation was done using the structured query language (SQL). The complete architecture of the OvirusTdb is presented in Fig. 2. The manually retrieved information from the research articles and the patents is provided in tabular form under 25 different fields in the database. We carefully explored the articles for each detail of the experiments and whichever information is available is included in the database. We gave special attention to the information on immune activation mechanism towards cancer cells within each record of OvirusTdb which captures the immense potential of OVs for developing immune-therapeutic strategies to eliminate cancer.

3. Implementation of web tools

3.1. Data search

This facility allows the users to search within the database in a time-efficient manner using a query against any field of OvirusTdb such as name, strain, type, cytotoxicity, cell line, PMID, and the patent number. The simple search tool allows users to customize their search criteria by selecting the desired fields. Advanced search criteria provide users with the additional facility of multiple querying using numerous fields available for selection at a single time.

3.2. Data browsing

A user-friendly browsing facility is provided on the website to retrieve information from the database in an effortless manner. Users can browse major fields which include: 1) Name of virus species 2) Cancer type 3) Cell line source 4) Model organism 5) Assay information 6) Baltimore classification. One of the key advantages of browsing over data search is that users can retrieve information even if they do not have the appropriate keyword to search against the desired fields.

4. Results

4.1. Data statistics of the OvirusTdb

OvirusTdb is a unique storage place of experimentally tested OVs retrieved from the literature. It contains a total of 5927 records, out of which 5456 were collected from the research articles and 471 comes from the patents.

It provides information on 24 viral species, where the majority of viruses are modified and some are in their wild-type form. It also covers 124 and 427 different cancer types and cancer cell lines, respectively. It stores information on 300 viral strains that were genetically modified either to increase their targeting efficacy towards cancer cells or to make them evade the host immune response. One of the key advantages of using OV to treat cancer is that it also elicits an anti-tumor immune response which is evident from the data collected as in 25% of cases it triggers the immune response via increased interleukin secretion and T-cell activation. In nearly 55% of cases, OV induces apoptosis in the cancer cells. The complete statistics of the database are provided in Table 1. Table 1 clearly highlights the data depth and breadth used to build the OvirusTdb. Visualization of model organisms and assays utilized in the different in-vivo and in-vitro experimental studies of the database are shown in Fig. 3.

Fig. 3 clearly depicts the preference of BALB/c and MTT assays over other model organisms and assays, respectively. A frequently postulated scenario in literature is that the combination of chemotherapeutics with virotherapy would be more effective. These combination settings lead to a rapid reduction of proliferating tumor cells, thus providing enough time for the virus to successfully activate immune response towards cancer cells (Lauer and Binz, 2015). We have summarized the different chemotherapeutic drugs used in combination with OVs to enhance their efficacy towards tumor cell killing in Table 2. Data analysis revealed that chemo-virotherapy approaches using adenovirus and HSV...
represent the largest fraction of published studies.

Also, we have briefly summarized the preferred mode of administration of the OV in experimental models. It was found that the intratumoral mode of delivery was the most prominent one adopted for many OVs except for the vaccinia virus. In summary, the most widely studied OV for the treatment of cancer is the adenovirus followed by HSV and vaccinia virus.

Targeted delivery that can attack specifically cancer cells leaving healthy cells intact is one of the major obstacles in developing cancer therapeutics. The main advantage of using OV is its intrinsic tropism towards cancer cells and its permissiveness to accept genetic modifications. These modifications were done to increase its specificity towards cancer cells and to promote their evasion from the host immune response. Table 3 enlists the different genomic alterations found in the various experimental studies. It was observed that canine parvovirus, measles virus, Newcastle disease virus, semliki forest virus does not have any deletion mutants for them whereas reovirus and Sendai virus do not have any insertional mutants tested in experimental studies. As evident from the table, adenovirus is the preferred choice for genomic modifications owing to its capacity to induce strong innate and acquired immunity. It can adopt large size transgenic modifications which otherwise would be difficult to clone in other OV species (Yamamoto et al., 2017).

4.2. Application of the database

Curators of the OvirusTdb have developed this resource, keeping in mind the fact that the scientific community will get maximum information about OV at a single platform in a timeless and efficient manner. We foresee that this resource is highly informative for clinicians and genetic engineers. Firstly, a major potential application of this database can be seen from the analysis of Table 1, which provides the complete statistics of the OvirusTdb database. Table 1 indicates that OvirusTdb holds information on 300 genetically modified strains of OV. This information is crucial for researchers and genetic engineers who wish to design new OV with improved potency and efficacy. Secondly, OvirusTdb helps genetic engineers and clinicians in designing their experimental protocol as it stores the data on 22 model organisms, 124 cancer types and 427 cell lines at a single platform. Thirdly, another application of OvirusTdb can be seen from Table 2, which holds the information on the preferred mode of delivery and drug combination used with OV. This can help clinicians and researchers in choosing an optimal combination partner and route of administration of OVs for better outcomes. Fourthly, the OvirusTdb may guide genetic engineers to optimally design new OVs strain with improved efficacy and safety. Table 3 summarizes the different genetic modifications in OV that have been found in the literature for the cancer treatment.

### Table 1
The complete statistics of the database.

<table>
<thead>
<tr>
<th>Database Statistics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total records</td>
<td>5927 (Research articles = 5456 + Patents = 471)</td>
</tr>
<tr>
<td>Total viral species</td>
<td>24 (DNA genome = 9 + RNA genome = 15)</td>
</tr>
<tr>
<td>Wild-type viral strain</td>
<td>15</td>
</tr>
<tr>
<td>Genetically modified viral strain</td>
<td>300</td>
</tr>
<tr>
<td>Cancer studied</td>
<td>124</td>
</tr>
<tr>
<td>Cancer cell line tested</td>
<td>427</td>
</tr>
<tr>
<td>Assays</td>
<td>30</td>
</tr>
<tr>
<td>Mice/Rat species studies</td>
<td>22</td>
</tr>
<tr>
<td>In-vivo study</td>
<td>1</td>
</tr>
<tr>
<td>Viral strains with chemotherapeutic agents</td>
<td>1047 (records)</td>
</tr>
<tr>
<td>Apoptosis induction by viral strains</td>
<td>3243 (~55% of records)</td>
</tr>
<tr>
<td>Immune system activation by viral strains</td>
<td>1506 (~25% of records)</td>
</tr>
</tbody>
</table>

4.3. Comparison with other available resources on viruses

There are many resources available on the viruses such as VIPERdb - maintain information on 816 viral capsid structures, viruSITE - provides all genomic information on viruses and viroid published in NCBI, ViFi - a tool for detecting viral integration and fusion mRNA sequences from Next Generation Sequencing data, and ViPR - catalog information on immune epitopes, host factor and antiviral drugs for 19 virus families. None of the above mentioned available resources holds experimentally validated and detailed information on the oncolytic potential of viruses for cancer treatment. OvirusTdb, unlike other resources, provides users with comprehensive information on 24 viral species and their therapeutic efficacy on 427 cancer cell lines, including the information on any immune and apoptotic pathways it may activate.

4.4. Utility of the database

New strategies are emerging in the search for better therapy against cancer and OVs serve immense potential in this regard. We build OvirusTdb to provide its users with the huge advantage of getting extensive information on OVs at a single platform, which otherwise would be difficult to access. It provides user with vast knowledge on OVs that includes: i) the type of genomic modification that can improve the oncolytic potential of wild-type viruses, ii) chemotherapeutic drugs given in combination with OVs to improve their therapeutic potential, iii) the route of administration of virus to enhance its bioavailability, iv) the type of immune and cell death pathway it activates.

4.5. Case study: Information retrieval and analysis on adenovirus from OvirusTdb

Here, we have shown a step-by-step procedure to retrieve desired information from OvirusTdb. For example, if a user is interested in adenovirus, type adenovirus in the search box under the simple search tab and then click check the name box. A number of fields are provided on the simple search page for selective retrieval of information as shown in Fig. 4. Users can get all the selected information on adenovirus stored in the database by clicking on the search option. In the example shown in Fig. 4, a total of 1716 records were found on the selected fields.

Detailed information about the individual record can be obtained by clicking the respective ID. PubMed papers can be retrieved simply by clicking on the PMID thus providing users of the database with the additional facility of having detailed information of the respective study. We have also provided the functional hyperlinking of OvirusTdb with viruSITE in order to provide users with further genomic information on selected OV species under the detailed information section.

4.6. Data submission, limitation, and update of OvirusTdb

We aim to make OvirusTdb - a single platform of all the available information related to the OVs used in cancer therapeutics. The online data submission platform under sources drop-down menu enables the user of the database to submit information in OvirusTdb. Nonetheless, curators of the database will ensure the legitimacy of the new entry before including it in the OvirusTdb.

The data stored in OvirusTdb was manually curated and thoroughly checked to mitigate the mistake, but it would be unfair to claim absolute consistency due to human mistakes that may have arisen. In order to have the latest information on the OVs used in cancer therapeutics, we will update the OvirusTdb, preferably after every year.

5. Discussion

Viruses that have the ability to infect and kill cancer cells are termed...
Fig. 3. Visual representation of data statistics using tree map for a) Model organisms used in the experimental setups to analyze the effect of oncolytic viruses b) Different assays used in the studies to analyze the oncolytic effects of viruses on different cancer types.
as “Oncolytic viruses”. Some OVs have the natural tendency to infect cancer cells while others have to be genetically modified to induce their desired oncolytic effect. The importance of using OV to treat cancer is seen in terms that not only does it kill cancer cells but also generate an anti-tumor immune response, which inhibits the remission after withdrawal of therapy.

The therapeutic potential of OVs for various cancers has been experimentally tested in several animal/tumor models and many such OVs are already in their late phases of clinical trials (Cervera-Carrascon et al., 2017). There are several challenges associated with OV therapy where one such challenge is the replication of the virus and its clearance from the system as host immune cells are competent enough to control virus replication (Campion et al., 2016). Another major factor that needs to be considered for successful OV therapy is the induction of the right immune response. Several studies are trying to elucidate the activation of selective DAMP which can induce the right cytokine to activate immunogenic cell death (ICD) (Garg et al., 2017; Showalter et al., 2017) of cancer.

Despite such limitations, T-vec is the only OV, approved by the FDA for the treatment of advanced skin melanoma. T-vec is a genetically modified virus that kills cancer cells while also activating an immune response against them. There are also other OVs in clinical trials that show promise in treating various cancers. For example, T-vec is currently being tested in clinical trials for the treatment of melanoma, prostate cancer, and glioblastoma.

Table 2

<table>
<thead>
<tr>
<th>Oncolytic Virus Species</th>
<th>Drug in Combination</th>
<th>Mode of Delivery of Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>Cisplatin; 5-Fluorouracil (5-FU); Vinristine; Paclitaxel; Docetaxel; 5-Fluorouracil; Gemcitabine; Sorafenib</td>
<td>Intratumoral; Intravenous; Tail Vein Injection</td>
</tr>
<tr>
<td>Alphavirus</td>
<td>Bucladesine (dabcAMP); Cytosine arabinoside (ara-C); Camptothecin (CPT); H-89 protein kinase inhibitor</td>
<td>Intratumoral; Intravenous; Subcutaneous</td>
</tr>
<tr>
<td>Bovine Herpesvirus</td>
<td>Vaccinia virus; Flucytosine (5-FC); Nab paclitaxel; Gemcitabine; Cisplatin; Cidofovir; 5-Fluorouracil</td>
<td>Intratumoral; Intravenous</td>
</tr>
<tr>
<td>Herpes Simplex Virus</td>
<td>SN-38; Fluorouracil (5-FU); Tubastatin; Tubacin; Rapamycin; Mitomycin; Tacedine (C994); ATN-22; Z-YVAD-FMK; SP600125; 3-Methyladenine (3 MA)</td>
<td>Intratumoral; Intravenous; Subcutaneous</td>
</tr>
<tr>
<td>Maraba Virus</td>
<td>Paclitaxel</td>
<td>Intratumoral; Intravenous; Subcutaneous</td>
</tr>
<tr>
<td>Measles Virus</td>
<td>Camptothecin (CPT); Alisertib</td>
<td>Intratumoral; Intravenous; Subcutaneous</td>
</tr>
<tr>
<td>Newcastle Disease Virus</td>
<td>Camptothecin (CPT)</td>
<td>Intratumoral; Intravenous</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Resveratrol; Norflaxacin</td>
<td>Intratumoral</td>
</tr>
<tr>
<td>Poxvirus</td>
<td>I-131</td>
<td>Intratumoral; Intravenous</td>
</tr>
<tr>
<td>Reovirus</td>
<td>Paclitaxel; Docetaxel; Cisplatin; Gemcitabine; Vinblastine</td>
<td>Intratumoral</td>
</tr>
<tr>
<td>Sendai Virus</td>
<td>Serpin (PAI-1)</td>
<td>Intratumoral; Intravenous</td>
</tr>
<tr>
<td>Vaccinia Virus</td>
<td>Flucytosine (5-FC); Nab paclitaxel; Gemcitabine; Cidofovir; 5-Fluorouracil (5-FU)</td>
<td>Intratumoral; Intravenous</td>
</tr>
<tr>
<td>Vesicular Stomatitis</td>
<td>Cisplatxin; Ruxolinitib</td>
<td>Intratumoral; Intravenous</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Oncolytic Virus Species</th>
<th>Different Insertion Modifications in Viral Genome</th>
<th>Different Deletion Modifications in Viral Genome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>Insertion of DCN and LRP genes; CMVp-driven ING4 gene; hTERT promoter; CCL21 and IL-15 genes with TERTp; APOB promoter-driven E1A gene; miR-122; miR-143; VST1 and filovirus gene; TSPy and E24 gene; EGFP gene; E1A and apoptin before hTERT promoter; p53 gene and 11R CPP; MCMV gene; Fovirus pol; dnc gene and V1 and 24 genes; E24 gene and E24 promoter; DCN, shMet and Erbitux-conjugated PEGylated at PAMAM; TRAIL and MnsOD genes; IL-21 and CCL21 genes; TRAIL and smac gene via IETD linker; IL-18 gene, Relaxin gene, ipocalin2 gene</td>
<td>E1 gene deletion; E1B gene with 827 bp deletion; E1B55K-deleted mutant driven by the MDR1 promoter; E1/E3-deleted mutant; 245bp deletion between E1A and E1B; 24 bp deletion in hTERT promoter; Deletion of E1A, E1B and E1ACR2 promoters;</td>
</tr>
<tr>
<td>Canine parvovirus</td>
<td>CPV genome expressing non-structural protein (NS1); Fusogen membrane ligated with GALV.fus protein; Double fusogen expressing EGFP and GALV.fus protein; Insertion of SNORD44 and GASS genes; Anti-angiogenic Vst120 gene</td>
<td>NA</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Δβ134.5 attenuated virus; Non-fusogenic ligated with EGFP protein; Fusigen membrane ligated with GALV.fus protein; Double fusogenic expressing EGFP and GALV.fus protein; Insertion of SNORD44 and GASS genes; Anti-angiogenic Vst120 gene</td>
<td>R1 domain poorly functional; Deletion of ICP34.5 and ICP6 genes; ICP34.5, ICP4 genes and ICP46 nucleotide reductase deletion; ICP46; ICP47 and ICP47 genes deletion</td>
</tr>
<tr>
<td>Measles virus</td>
<td>Addition of Etag; Insertion of P gene; Insertion of P, N and L genes; Genetically engineered for expressing H-852 plasmid neutralizing activating protein; Genetically engineered for expressing human lambda immunoglobulin chain; RS33A gene insertion in pMV-HLV(7+)</td>
<td>NA</td>
</tr>
<tr>
<td>Newcastle disease virus</td>
<td>rl gene insertion; Insertion of HNKMRS sequence in fusogenic site between 111 and 116 nucleotide; Insertion of HNRTKR sequence in fusogenic site between 111 and 116 nucleotide; Insertion of IL-2 gene between HN and L gene of pAnh-wt; Insertion of TRAIL gene; Insertion of NS1 promoter</td>
<td>NA</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Insertion of hNIS and VEGF genes</td>
<td>ICP34.5, ICP4 and ICP47 genes deletion</td>
</tr>
<tr>
<td>Reovirus</td>
<td>NA</td>
<td>Deletion of T3 gene</td>
</tr>
<tr>
<td>Semliki forest virus</td>
<td>Insertion of IL-2 gene between HN and L gene of pAnh-wt</td>
<td>Deletion of M, F gene at cytoplasmic location</td>
</tr>
<tr>
<td>Sendai virus</td>
<td>NA</td>
<td>Deletion of 66R, 2L, 15L, TK genes</td>
</tr>
<tr>
<td>Tanapoxvirus</td>
<td>Insertion of fic and MCP-1 genes</td>
<td>Defective in I4L, F4L and J2R genes; Deletion of TK gene</td>
</tr>
<tr>
<td>Vaccinia virus</td>
<td>Insertional inactivation of TK gene; beta-gamma-carboxylic acid, galactosidase and GPP genes insertion; smac and gtp genes insertion; glaf-2 gene into 2J2 focus; IL-2 gene; G1PF gene; Yuc-52 gene at FI4.5L; TK and HA gene locus; Insertion of human DAL; insertion of FCU1 gene</td>
<td>Deletion of envelope protein G; M51 gene deletion</td>
</tr>
</tbody>
</table>

For personal use only. No other uses without permission. Copyright ©2020. Elsevier Inc. All rights reserved.
modified type – 1 HSV currently being evaluated in several countries for combination therapy with chemo and radiotherapy agents (Kanai et al., 2010).

Although the strategy of using OV to treat cancer seems to be fascinating, still there is much more to be explored in this area (Kanai et al., 2010). As mentioned, the approval of T-vec by the FDA further promoted and strengthened the research in oncolytic virus-based therapy (OVT). There is a need for critical monitoring of patients treated with OV for the presence of immune biomarkers, a type of cancer cell death induced by DAMP, to understand how OVT works in the population.

Despite such a huge therapeutic application, there is no database that collectively provides information on all the experimentally tested OV s present in literature to treat cancer. Therefore, to catalog all the available data on OV s used in cancer therapeutics, we developed a database “OvirusTdb” that stores this information in the form of a total of 5924 records. To the best of the author’s knowledge, there is no such database present in literature that covers almost all the aspects of virus-based cancer therapy. We believe that this database is useful for virologists, immunologists, oncologists, and biotechnologists who wish to design and use OV s with/without a combination approach for the treatment of cancer.

Funding

There is no funding available to support publishing this article as an open access.

CRediT authorship contribution statement

Anjali Lathwal: Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. Rajesh Kumar: Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. Gajendra P.S. Raghava: Conceptualization, Methodology, Investigation, Resources, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

Authors are thankful to funding agencies University Grant Commission (UGC) and Council of Scientific and Industrial Research (CSIR), Indraprastha Institute of Information Technology, New Delhi (IIIT-D), and Govt. of India for financial support and fellowships.

Abbreviations

WHO World Health Organization
IL Interleukin
OV Oncolytic Virus
Ad Adenovirus
HSV Herpes Simplex Virus
IFN Interferon
DAMP Damage Associated Molecular Patterns
TAA Tumor-Associated Antigens
T-VEC Talimogene Laherparepvec
TRAIL TNF related apoptosis-inducing ligand
USPTO United States Patents and Trademark Office
LAMP Linux based Apache server

Fig. 4. Visual representation of the utility of the database.
OVT Oncolytic Virus Therapy
ICD Immunogenic Cell Death

References

Kanai, R., Wakimoto, H., Cheema, T., Rabkin, S.D., 2010. Oncolytic herpes simplex virus vectors and chemotherapy: are combinatorial strategies more effective for cancer? Future Oncol. 6, 619–634.