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A Protocol for Recovery of Measles Virus from Intact/Recombinant Antigenomic DNA

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ABSTRACT

Measles virus (MV), a negative-strand RNA virus, has been known as an ideal candidate for oncolytic virotherapy. Recombinant MV could encode genes of interests to achieve several aims. Replication efficiency of oncolytic virus in tumor cells is a key parameter in efficient tumor eradication. Products of the P gene (P/V/C) support measles virus to circumvent IFN 1 as the main response of the innate immune system against viruses. But vaccine strains used in oncolytic virotherapy trials comprise several mutations in their P gene sequences. These mutations affect replication efficacy and cause the attenuation of measles strains applicable in vaccination. Thus, arming vaccine strains with a wild-type P gene is useful to achieve high viral titer. Here in this study, a fully detailed protocol was developed for efficient engineering and recovery of MV for different purposes.

Keywords: Measles virus, Reverse genetics, Viral rescue, Oncolytic virotherapy

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Introduction

Oncolytic virotherapy -using replicating viruses for cancer therapy- shows considerable potential in treating malignancies [1][2]. Introduction of nucleic acid or cDNA of some viruses in appropriate cells leads to the initiation of infectious cycles. Selectivity, self-amplification, potential of being armed with therapeutic transgenes, and cancer cell killing are the main advantages of these kind of cancer therapeutic agents [3].

Propagation of viruses in tumor cells leads to the interruption of cells machinery and signaling pathways. Inflammatory responses of infected tumor cells stimulate the innate immune system against tumor mass [1]. In addition, enhancement of viral oncolytic properties could be achieved by developing a revers genetic system [4]. Most oncolytic viruses follow similar mechanisms of action, and various platforms have been generated based on viruses with improved tumor specificity, intratumoral spread, therapeutic gene delivery, and especially targeted cancer immunotherapy [5]. Some of these biotherapeutics have advanced to clinical trials as well [10].

Among oncolytic viruses, measles virus (MV) vaccine strains have emerged as a promising oncolytic platform [6]. It has revealed potent antineoplastic activity against various human cancers, including lymphoma, ovarian cancer, mesothelioma, breast cancer, and hepatocellular carcinoma [7–9].

Measles virus is a non-segmented negative strand RNA virus (NNSV), belonging to the family *Paramyxoviridae*. MV full genome contains 15,894 nucleotides encoding six genes responsible for coding eight proteins in this order: 3'-N-P/V/C-M-F-H-L-5'. Viral polymerase is a RNA-dependent RNA polymerase (RdRp) composed of a large multifunctional catalytic protein (L) and a noncatalytic cofactor, mostly named phosphoprotein (P). During the replication cycle, RdRp not only converts complementary RNA to mRNA, but also plays a role in the replication of ribonucleoproteins (RNPs) for the synthesis of antigenomic positive-strand RNA [11]. Positive-strand RNA antigenome serves as a template for the amplification of negative-strand genomic RNAs, which are the templates for secondary transcription. RdRp transcribes the first gene (N) with higher processivity than other genes. The frequency of re-initiation is not 100%, resulting in a gradient of transcript levels: N is transcribed at the highest levels and L at the lowest levels [12, 13].

The P gene of MV uses overlapping reading frames to encode P, V, and C proteins as accessory proteins [14]. Vitaly, P/V/C proteins control innate intracellular immune defense by antagonizing type I interferon. These proteins inhibit IFN-induced STAT(signal transducer and activator of transcription) nuclear translocation and suppress STAT1 and STAT2 phosphorylation [15, 16]. Also, these proteins (P/V/C) may control tissue-specific viral gene expression [7, 11, 17–19]. Therefore, P/V/C proteins have been recognized as virulence factors [10, 15, 20–22].

Most importantly, in contrast to the N and L genes, the P gene and its derivatives (V and C genes) are much more variable than the other MV genes. Due to the differences in their viral phosphoprotein (P) gene, measles strains differ in their interferon antagonizing ability [23, 24].

It has been previously shown that wild-type MV IC-B strain significantly induces lower amount of IFN-α compared with attenuated MV isolates. Moreover, the P gene and its derivatives of wild-type MV strains block IFN-α signaling more than that of attenuated vaccine strains, which results in more efficient immune system evasion and faster MV genome replication [25]. Therefore, generating a chimeric MV based on attenuated vaccine strains, which carries wild-type P gene, may be a great idea to improve oncolytic efficiency by rapidly increasing the replication level while maintaining medical safety.

Though the design and construction of such a virus have been described elsewhere [23], here in, a detailed protocol was described for engineering a new MV by replacing its original P/V/C gene with that of a wild-type MV using a vaccine strain. This protocol is also applicable to rescue parental and recombinant MV (MV encoding the P/V/C gene of wild type strain) from DNA in HEK 293T and Vero cells. Recombinant MV (named MVbvwP) is expected to provide a substantial therapeutic advance over non-recombinant vaccine strains. Since obtaining a high viral titer is a crucial factor in all virotherapy procedures (because the titer determines the number of infected cells), this

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recombination could be used as an enhancer to increase the efficacy of virotherapy [10].

MV Reverse Genetics Procedure

The standard protocol for *Mononegavirales* rescue from DNA was established by Radecke et al. (1995) [26] and modified by Parks et al. (1999) [27]. Consecutive transcription of MV mRNAs from antigenomic sequence is necessary for in-vitro protein expression of MV. Therefore, co-transfection of a plasmid coding the full antigenomic sequence with three additional plasmids encoding helper virus proteins N, P, and L is fundamental in viral protein expression. Flanking the full antigenomic sequences of MV with autocatalytic ribozyme sequences results in the production of correct viral 5′- and 3′-ends after transcription of RNA by T7 RNA polymerase. In this system, co-transfection of a vector encoding T7 RNA polymerase gene supplies the enzyme which mediates the trimmed 5’ end of the antigenomic RNA. The 3’ end is usually trimmed with a ribozyme sequence [26]. Encapsulation of viral mRNA by N and P proteins is critical for the recognition of this complex by viral L polymerase and the construction of the L-P-N complex. Transcription of encapsulated viral genome by RdRp produces not only sub genomic, capped, and polyadenylated mRNAs but also encapsidated antigenomic and genomic RNAs [28]. After co-transfection of a plasmid coding full-length sequence of MV with helper plasmids, T7 polymerase encoded by a plasmid transcribes the full-length MV genome into antigenomic RNA. Then the N and P proteins expressed by the helper plasmids bind to it and form the RNP complex. The MV RdRp produced by pCA-L then binds to the RNP complex and replicates the MV genome. Transcription of the MV genome in a RNP complex leads to the generation and expression of viral mRNAs into viral proteins with a transcriptional gradient. This results in virion assembly and release in the infected host cell. In the next step, transfected cells will be picked up and overlaid on Vero cells. After about 4 days of overlaying, monitoring will be done to find the syncytia. By picking up a clone of syncytia and transferring it to a monolayer of Vero cells, a pure stock of virus will be produced.

Production Diagram

Schematic presentation of the procedures which end in viral production with improved titer and efficiency is shown in Fig. 1.

Fig 1. Protocol Diagram. In general, to produce measles virus from host cells, different steps could be considered. After introducing the desired gene in the MV genome, viral rescue, amplification, titration, and characterization are performed before making viral stocks.

Materials, Methods, and Equipment

Cells

HEK cell line (ATCC® CRL-1573), Vero cell line (ATCC® CCL-81), and MRC5 (ATCC® CCL-171) were obtained from ATCC. HeLa (human cervical epithelial carcinoma) and A549 (lung carcinoma) cell lines were obtained from Iranian Biological Resource Center. Except for MRC5 grown in MEM media (minimum essential **medium**), the other cell lines were grown at 37 ˚C in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal Bovine

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serum (FBS) (Gibco), L-glutamine, penicillin, and streptomycin in a 5% CO_2 humidified incubator.

Plasmids

P (+) MVbv encoding the full-length antigenomic sequence of Berna strain, P (+) MVbvwP encoding the full antigenomic sequence of recombinant MV coding the wild-type P gene, as well as pCA-P, pCA-N, pCA-L, and pCA-T7 polymerase as helper plasmids were used in this study [26].

Buffers and Reagent

Phosphate-buffered saline (PBS), 0.05% trypsin (Gibco, Gibco, cat. no. 25300), DMEM high glucose (GIBCO, GIBCO, cat. no. 11995), FBS (Hyclone), antibiotic antimycotic (100×) (Gibco), lipofectamine 3000 (Invitrogen), Opti-MEM I (Gibco) dilution medium for lipofectamine 3000, and dimethyl sulfoxide (DMSO) were used in this protocol.

Equipment

The following tools and equipment are needed for the procedure, including 96-well tissue culture plates, sterile reagent reservoirs for use with multichannel pipettors (a variety of multichannel and repeat pipettors) (pipette tips with filters are used for pipetting virus), biosafety cabinet, class II biosafety cabinet Type A2, humidified CO_2 incubator, cell culture, microscope (inverted with fluorescence lamp and appropriate filters for the fluorophore used, e.g. EGFP), gloves (disposable), water bath (set to 37 °C for thawing frozen cells and virus), tabletop centrifuge for pelleting cells, measuring pipettes (2, 5, 10, and 25 mL), T175-cm^2 tissue culture flasks, 1.5 mL tubes, autoclave, vortex mixer, cryogenic tubes (for aliquoting concentrated virus), micro-centrifuge (for spinning down virus aliquots before freezing), –80 °C freezer (for virus storage), 24-well tissue culture plates, 10-cm tissue culture plates, 15-cm tissue culture plates, cryogenic tubes, liquid nitrogen tank, sterile cryogenic tubes (5 mL for un-concentrated supernatants), storage boxes for 0.5 or 1.2 mL cryogenic tubes, storage boxes for 5 mL cryogenic tubes, pipetters (2–10, 20, 200, and 1,000 µL), and pipette tips (0.1–2.5, 2–20, 10–100, 100–1,000) with sterile filters (10, 20, 200, and 1,000 µL).

Development of the Recombinant Measles Construct: *Molecular cloning:*

P (+) MVbv coding the full antigenomic sequence of MV (Berna strain) was used as backbone for generating recombinant plasmid coding the wild-type strain. P (+) MD18T coding the sequence of P gene of wild type IC-B intended strain was synthetized by Biomatic Company. Both plasmids were cut with *Sfi*I and *Tth*111I. *Sfi*I / *Tth*111I fragment of p (+) MVbv was cloned at the corresponding sites of pMD18T. *Aau*I fragment of pMD18T was replaced with that of p (+) MVbv in backbone of pMD18T. Finally, *Sfi*I/*Tth*111i fragment was cloned back to p (+) MVbv (-Fig. 2A). This plasmid in combination with helper plasmids was used in the protocol of rescue procedure which was described in this study.

Protocol

Rescue from DNA: Day 1

About 2 mL of diluted 1x trypsin is placed into a T-75 flask and incubated at 37 °C for 3 minutes and aspirated completely. Then 7×10^5 HEK-293T cells are split into a 6-well plate, and the medium is added to a total of 2 mL.

Transfection of plasmids: Day 2

- Plasmid encoding full genome is co-transfected with appropriate amount of helper plasmids (given below) in HEK 293T cells, lipofectamine 3000 could be used as a transfection reagent for improving the transfection efficiency (with about 60% confluency). According to our experience, the optimum ratio of lipofectamine 3000 to total DNA for HEK 293T cells is about 1:3; for each microgram of DNA plasmids, 3 microliters of lipofectamine 3000 is used in this procedure. A mixture of plasmids encoding helper proteins is diluted in Opti-MEM as a serum free media. Then cells are transfected with high-quality plasmids. For a

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good transfection, following quantities are recommended: genome vector, 2600 ng; pCA-T7 polymerase, 685 ng; pCA-N, 350 ng; pCA-L, 350 ng, and pCA-P, 65 ng.

- Plasmids are combined in a separate micro-tube and diluted using 125 µL of Opti-MEM.
- Lipofectamine is diluted in 125 µL of Opti-MEM as well. After 5 min, the contents of the DNA and lipofectamine tubes are combined, and then Step 3 begins while allowing the mixture to be incubated for 20 min. After 20 min of incubation, DNA–lipofectamine mixture is added to the plate and gently agitated to distribute, and the plate is returned into the incubator until the next day.

Plating Vero cells: Day 5

In this step, 1×10^{6} Vero cells/10 cm from the cell culture dish are seeded in 10 mL of complete DMEM.

Overlaying transfected cells on Vero cells: Day 6

Transfected cells are scraped 4 days after transfection, overlaid on plated Vero cells in a 100 mm plate, incubated for 6 days, and examined for syncytia formation every day during the incubation.

Virus Harvest and Titration

When 80% of cells are involved in Cytopathic Effect (CPE), cells are scraped and collected, then cells and cell soup are stocked at -70 °C after clarification with a centrifuge (4000 g, 4 °C, 10 min).

The virus is titrated with TCID50 method (as described later).

Virus Propagation

- Viral stocks for MV and recombinant MV should be prepared after propagation. Vero or MRC5 monolayer cells are infected with a multiplicity of infection (MOI) of 0.03 (found from titration step) and incubated at 35 °C and monitored for cytopathic effect every day.

If acceptable CPE could not be observed, Vero cell monolayer is infected in a 100-mm plate with a MOI of 0.03 of newly generated viruses (attenuated vaccine strain of MV (AIK-C), MVbv, and recombinant MVbvwP) and incubated at 37 °C.

- Supernatant is harvested in sterile tubes when cells reach ~80% cytopathic effect.
- Scraped cells and cell soup are centrifuged to make them clear and remove debris.
- Small aliquots of clarified supernatant are prepared.
- Infected cells are collected in serum free media.
- Lysate of cells are made by two cycles of freeze and thaw.
- The lysate is centrifuged at 4000 g and 4 °C for 5 min.
- Small aliquots of the supernatant are prepared in micro-tubes.
- Aliquots are stored at -80 °C.
- The viral sample is titrated by TCID50 method (as described later).

The schematic representation of the procedure is shown in Figure 2.

Determination of MV Infectious Titer: TCID50 Method

- About $1x10^{4}$ Vero cells are seeded into 96-well plates with 100 µL of DMEM, 5% FBS, and penicillin/streptomycin per well.
- The plates are incubated at 37 °C for 24 hours.
- A ten-fold serial dilution of the virus is prepared in 1.5 mL micro-tubes.
- Then 100 µL of each dilution is transferred into eight rows of a 96-well plate.
- The plate is incubated at 37 °C and examined 5 days later.
- TCID50 is calculated using Spearman-Kärber end-point dilution method [29].

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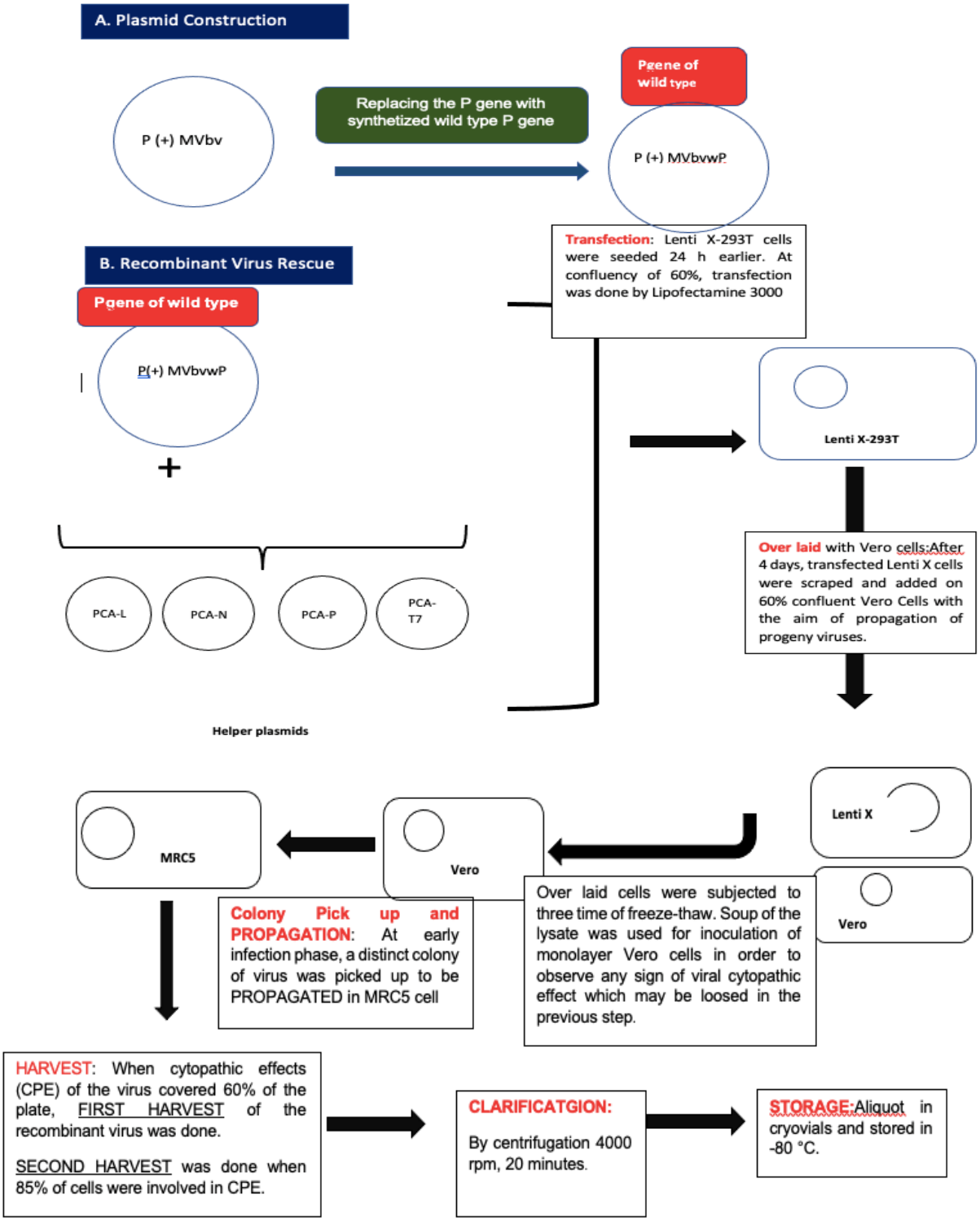

Fig. 2. Different steps of the MV rescue procedure are described in this diagram.

Virus Characterization by Western Blot

The produced viruses are characterized by sequencing the viral genome and western blotting against viral P and N proteins.

Multi-step Growth Kinetic Analysis of Recombinant MVs for more characterization.

Multiple-step growth kinetic analysis is performed to document the replication fitness of

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recombinant MV (MVbvwP) as well as MVbv and AIK-C vaccine strains.

1. About $5x10^5$ Vero cells/well are plated in a 6-well plate and incubated at 37 °C.
2. In the next day, cells are inoculated with a MOI of 0.03.
3. Cells are scraped in 1 mL of Opti-MEM or FBS free medium for the intracellular sample.
4. Supernatant is collected for the extracellular sample 12, 24, 36, 48, 72, and 96 hours post-infection.
5. Cells are scraped at each time point after collecting the supernatant and subjected to two- or three-time freeze-thaw cycle for determining cell-associated viral titer.
6. Viral titer is assessed at 50% tissue culture infectious dose ($TCID_{50}$) in Vero cells.
7. TCID50 is calculated using the Spearman-Kärber end-point dilution method to verify the efficiency of the production of MV recombinant particles.

Result

Virus rescue and propagation

MVbv and MVbvwP were recovered as described in the Materials and Methods section. Due to the lytic nature of MV during replication, formation of cytopathic effects represents the formation of progeny viruses. In the case of MVbvwP, cytopathic effects appeared 3 days post-transfection, while the rescue of MVbv parental strain occurred on the third day of co-culturing with Vero cells (Fig. 3).

Phenotypic differences between MVbv and MVbvwP strains

In order to evaluate the effect of wild-type P gene on CPE formation in MCF7, Hela, and A549, these cells were plated with the same number and infected by recombinant MV (MVbvwP) and vaccine strains (MVbv or AIK-C) at a MOI of 0.5 PFU/cell under consistent conditions. The results showed visible differences in harshness of syncytia in cells infected with MVbvwP and the two other vaccine strains (MVbv and AIK-C). In the case of MVbvwP, more cells were involved in syncytia and detached rapidly, while in the case of MVbv and AIK-C vaccine strains, the observed syncytia was smaller and stayed attached longer before detachment (Fig. 4).

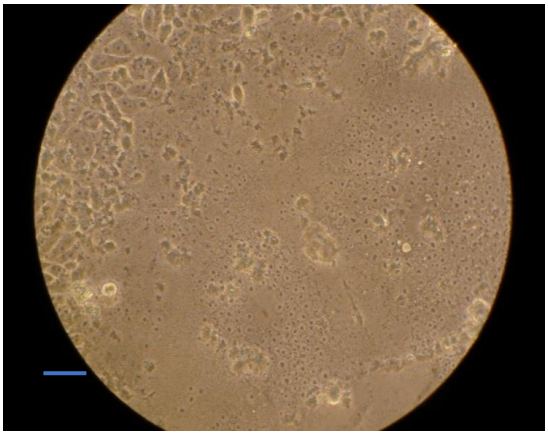

Fig. 3. Cytopathic effects due to cell-to-cell fusion in Vero cells (captured at 20X magnification). Following the transfection, cells were daily monitored by microscopy. Transfected cells were scraped 4 days after transfection and put on plated Vero cells in a 100 mm Petri dish. Upon the detection of a few fused cells, this region was marked and followed up in the second day to confirm a positive spread of fusion. As CPEs progressed, clones were collected, and further analysis and propagation of the virus were done. Scale bar is equal to 40μm

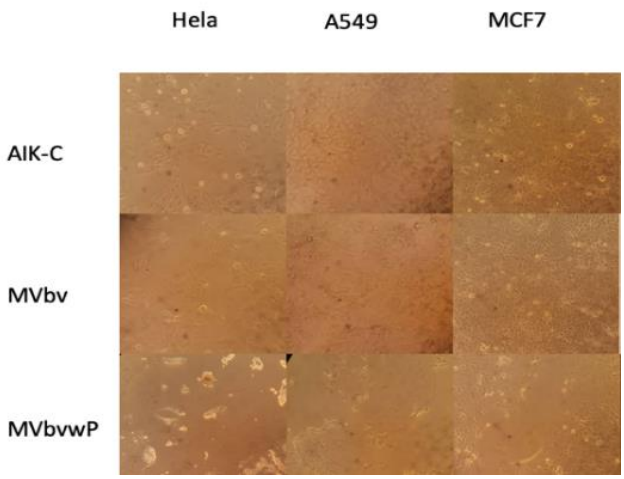

Fig. 4. Harshness of cytopathic effects by MVbvwP as an engineered strain in comparison with unmodified vaccine strains. Spread and cytopathic effect of three viruses were compared on the monolayer of three different cell lines. Monolayers of MCF7, A549, and HeLa were inoculated with the same MOI (0.5) by recombinant (MVbvwP) and vaccine strains (MVbv and AIK-C). Cells were photographed 48 h after infection at 10× magnification. Note that the recombinant virus showed more disseminated infection, while AIK-C and MVbv vaccine strains caused small foci.

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Analysis of growth kinetic of recombinant MVbvPw and vaccine strains

Replication kinetics of recombinant virus (MVbvwP) and vaccine strains (MVbv and AIK-C) were compared by titration of viruses after propagation in Vero cells. Cell-free viruses were released in the supernatant, and cell-associated viruses were tittered separately 24, 48, 72, 96, and 120 h post infection. This study results showed more efficient and faster replication kinetics for the recombinant MVbvPw than for the vaccine strains. Overall, the recombinant MVbvPw virus titer was about 1.5 times higher than that of the vaccine strains at all time points (Fig. 5).

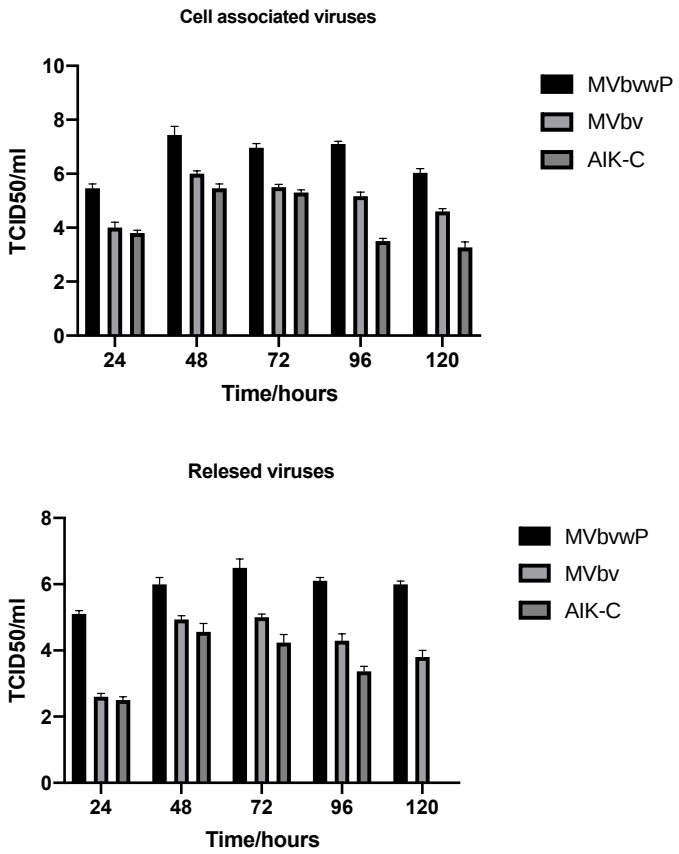

Fig. 5. Growth curve analysis. Vero cells were infected at a MOI of 0.03 PFU of AIK-C, MVbv, or recombinant MVbvwP and incubated at 37 °C. Titration test was done by TCID50 method on cell-associated viruses (A) and cell-free viruses (B) at different time points. The results were represented as the mean of three independent experiments.

Discussion and Conclusion

This protocol describes a valuable platform for generating new recombinant modalities with the aim of developing new oncolytic therapies or vaccines against a variety of infectious agents. The use of MV as an oncolytic agent makes the production and distribution of this recombinant agent to be efficient and cost effective. In addition, MV vaccine strains are a safe option for use in oncolytic virotherapy. This study findings showed that the wild-type P gene could dramatically enhance the rate of virus spread in different cell lines when used at the same multiplicity of infection.

In conclusion, this protocol could be successfully used to generate a recombinant MV equipped with wild-type P gene (or other transgenes) in order to increase the efficiency of replication and spread through the tumor cells. Our previous findings showed that the wild-type P gene could dramatically enhance the rate of virus spread in different cell lines when used at the same multiplicity of infection [23]. This modification successfully touches this goal and could result in the production of a potential candidate for use in further vivo studies.

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