Anti-tumour Effective Paramyxovirus

The present invention relates to the treatment of tumours by administration of live animal paramyxovirus. The virus has a selectivity to kill human tumour cells but not human normal differentiated and human normal proliferating cells at the same dose. By genetic engineering the virus can be modified in such a way that one or more genes are replaced by the homologous genes of a related paramyxovirus. Alternatively these homologous genes are inserted as additional transgenes into the virus genome. By that method the anti-tumour activity of the resulting chimeric virus is enhanced compared to the parental virus.

The method of genetic engineering also allows the modification of the F protein cleavage site to be recognized by an enzyme that is expressed in tumour cells.

From the state of the art it is known that oncolytic viruses can be used as cancer therapeutics. Oncolytic viruses in general for the treatment of tumours are reviewed in (Chiocca, 2002). An actual list of oncolytic viruses is published in (Vaha-Koskela, Heikkila, and Hinkkanen, 2007). These viruses belong to various virus classes and families.

Viruses from the family *paramyxoviridae* that have been tested as oncolytic agents include measles virus (eg. (Peng et al., 2001), Newcastle disease virus (eg. (Sinkovics and Horvath, 2000), Tupaia paramyxovirus (Springfeld et al., 2005), mumps virus (eg. (Myers et al., 2005), simian virus 5 (eg. (Parks et al., 2002) and sendai virus (eg. (Kinoh et al., 2004).

In (Stojdl et al., 2003) it is describe that in the range of 80% of all tested tumour cell lines, there is a defect in the interferon response following infection with Vesicular Stomatitis Virus (VSV). It may be assumed that a similar percentage of tumour cell lines will be susceptible to infection with NDV because both VSV and NDV are members of the order mononegavirales. It has also been shown that the mechanism of selective replication of NDV in tumour cells is based on a defect in the cellular interferon response against the virus (see for example WO 99/18799).

What concerns recombinant paramyxoviruses, in EP-A-0702085 the genetically manipulated infectious replicating non-segmented negative-stranded RNA virus mutants, comprising an insertion and/or deletion in an open reading frame, a pseudogen region or an intergenic region of the virus genome is described.

Further, in WO99/66045 genetically modified NDV viruses obtained from full-length cDNA molecules of the virus genome are described.

In WO 00/62735 a method of tumour treatment comprising administering an interferon-sensitive, replication-competent clonal RNA virus, such as NDV is described. Further descried is the use of avian paramyxovirus 2. However, no supporting data are available with regard that APMV2 has oncolytic activity.

In WO 01/20989 (PCT/US00/26116) a method for treating patients having tumour with recombinant oncolytic paramyxoviruses is described. The tumour is reduced by administering a replication competent *paramyxoviridae* virus. Various methods are described that can be used to engineer the virus genome in order to improve the oncolytic properties.

Further, in WO 03/005964 recombinant VSV comprising a nucleic acid encoding a cytokine is described.

In US 6,699,479 NDV mutants are described which express the V-protein at a reduced level and comprising nucleotide substitutions in an editing locus.

In US 2004/0170607 the treatment of melanoma by administering a virus which is not a common human pathogen is described.

In WO2006/50984 recombinant NDV virus is described together with gene coding for anti tumour proteins. Especially a recombinant RNA-virus, preferably a paramyxovirus, preferably Newcastle disease virus (NDV) for treatment of diseases, especially for oncolytic tumor treatment is described. It is further described that recombinant viruses are produced that encode binding proteins (antibodies, ankyrin repeat molecules, peptides etc.), prodrug-converting enzymes and/or proteases and which lead to the selective expression of these molecules in virus-infected tumor cells. The activity of these binding proteins, prodrug-converting enzymes and/or proteases increases the anti-tumor effect of the virus. In WO2006/50984 the manufacture and the use of such modified viruses for treatment of cancer is described.

NDV can be genetically manipulated using the reverse genetics technology as described e.g. in EP-A-0702 085. For example, it is known to make recombinant NDV constructs comprising additional nucleic acids coding for secreted alkaline phosphatase (Zhao and Peeters, 2003), green fluorescent protein (Engel-Herbert et al., 2003), VP2 protein of infectious bursal disease virus (Huang et al., 2004), influenza virus hemagglutinin (Nakaya et al., 2001) and chloramphenicol acetyl transferase
(Huang et al., 2001) (Krishnamurthy, Huang, and Samal, 2000). None of these recombinant NDV has been constructed for use in the treatment of human disease. The recombinant NDVs were made to study either basic virology of NDV or to develop vaccine strains for poultry. As parental virus strains served lentogenic strains of NDV. These strains do not have significant oncolytic properties.

Even with respect to the known virus systems and processes, there is still a huge demand for those virus species which can selectively be used for the treatment of cancer, respectively tumours, and which show a superiority over the known virus specimens.

Moreover, there are no data available in the art which show that APMV3-9 can be used for the production of a medicament for the treatment of cancer, respectively tumours.

It has now surprisingly be found that selective virus specimens of the instant invention, derived from the family of paramyxovirus, derived from the sub-class of APMV3-9 can be used in tumour therapy with a surprising effective reactivity in contrast to the state of the art specimens.

Paramyxovirus of the instant invention have not been described in the art to have an antitumour effect.

Those virus selected from the family of paramyxovirus are, for example,

Avian paramyxovirus 3 (APMV3), Avian paramyxovirus 4 (APMV4), Avian paramyxovirus 5 (APMV5), Avian paramyxovirus 6 (APMV6), Avian paramyxovirus 7 (APMV7), Avian paramyxovirus 8 (APMV8) and Avian

paramyxovirus 9 (APMV9), as well as Mapueravirus and Fer-de-Lance virus.

The viruses APMV3-9 are described in (Alexander, 2003).

The invention further comprises a process for the production of a chimeric virus by molecular biologically combining genetic elements of different viruses.

Especially the invention comprises the use of paramyxovirus from the group selected from APMV3, APMV4, APMV5, APMV6, APMV7, APMV8, APMV9, Mapueravirus and Fer-de-Lance virus for the production of a medicament for the treatment of cancer, respectively tumours.

Treatment of cancer and tumours means inhibition of tumor growth, preferably the killing of the tumor cells or the blocking of proliferation in a time gap by infection. The described paramyxovirus replicates selectively in tumor cells.

Especially the use comprises the production of a medicament for the treatment of proliferative disorders, in particular hyperproliferative disorders. Preferably neoplasms can be treated with the described virus, preferably cancers from the group consisting of lung, colon, prostate, breast and brain cancer can be treated.

More preferably the invention concerns the use of the inventive virus for the production of a medicament for the treatment of a solid tumour and metastatic tumour.

More preferably a tumor with low proliferation rate can be treated.

Examples of tumors with low proliferation rate are prostate cancer, breast cancer. lung cancer, ovarian cancer, melanoma, cervical cancer, bladder cancer, glioblastoma and fibrosarcoma.

In a further selected aspect the invention concerns the use of the virus for the production of a medicament for the treatment of brain tumours and glioblastoma.

A further aspect of the instant invention is a closely related paramyxovirus that has more than 80% sequence identity on RNA level. That virus can be a newly discovered paramyxovirus.

The inventive virus may further be recombinant and may further be modified to express one or more additional genes that originates from APMV1-9, preferably it

may be modified to express one or more additional gene(s) that originates from APMV1 (Newcastle disease virus).

The inventive virus may further be modified to comprise a gene encoding for a binding protein (see WO2006/050984).

The additional gene may encode for an enzyme, especially a prodrug converting enzyme, for an antibody or a fusion protein comprising at least one immunoglobulin domain with an antibody variable region (see WO2006/050984)

The modification results in a higher oncolytic potency as measured by the antitumour-effect when administered to tumour-bearing human or animal, for example a nude mice.

The inventive virus may further encode the gene(s) for the F and / or the HN protein of another paramyxovirus, whereby the F protein may have a multibasic cleavage site, and the virus may be modified in such a way that one gene is replaced by the homologous gene of a virus from the group APMV1-9.

The genetic modification may further result in an attenuation of the virus pathogenicity in birds.

The invention further comprises the use of the virus for the production of a medicament for the treatment of the above mentioned diseases together with pharmaceutically acceptable carrier and diluents. Such carrier and diluents are described in Remington's Pharmaceutical Science, 15^{th} ed. Mack Publishing Company, Easton Pennsylvania (1980). The used virus titers may be in the range of 10^9 to 10^{12} pfu per dose, in a range of 10^8 to 10^{11} pfu, in a range of 10^7 to 10^{10} pfu or in a range of 10^6 to 10^9 pfu dependent on the indication of treatment.

The pharmaceutical carrier and diluents may comprise an emulsion of the inventive virus, and may be administered by inhalation, intravenous infusion, subcutaneous injection, intraperitoneal injection or intratumoral injection.

Yet another aspect of the present invention is a method for the prevention or/and treatment of a proliferative disorder, in particular cancer, comprising administration to

a subject in need thereof a pharmaceutically effective amount of the pharmaceutical composition of the present invention. A pharmaceutically effective amount is a titre of the virus of the present invention, in particular the virus of the present invention which cures or suppresses the disease.

For the therapeutic effect the acceptable dosis is different and depends for example from the construct, the patient, the ways of administration and the type of cancer.

The invention further comprises the use of the inventive virus in combination with a chemotherapeutic agent.

The inventive virus may be used with any anti-tumor agents, alkylating agents, antimetabolites, plant-derived anti-tumor agents, hormonal therapy agents, topoisomerase inhibitors, camptothecin derivatives, kinase inhibitors, targeted drugs,. antibodies, interferons and/or biological response modifier and other anti-tumor-drugs. In this regard, the following is a non-limiting list of examples of secondary agents that may be used with the virus of the invention:

Alkylating agents include, but are not limited to, nitrogen mustard N-oxide, cyclophophamide, ifosfamide, thiotepa, ranimustine, nimustine, temozolomide, altretamine, apaziquone, brostallicin, bendamustine, carmustine, estramustine, fotemustine, glufosfamide, ifosfamide, mafosfamide, bendamustin and mitolactol; platinum-coodinated alkylating compounds include but are not limited to, cisplatin, carboplatin, eptaplatin, lobaplatin, nedaplatin, oxaliplatin or satrplatin;

Antimetabolites include but are not limited to, methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil alone or in combination with leucovorin, tegafur, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, gemcitabine, fludarabin, 5-azacitidine, capecitabine, cladribine, clofarabine, decitabine, eflornithine, ethynylcytidine, cytosine arabinoside, hydroxyurea, melphalan, nelarabine, nolatrexed, ocfosfite, disodium premetrexed, pentostatin, pelitrexol, raltitrexed, triapine, trimetrexate, vidarabine, vincristine, vinorelbine,

Hormonal therapy agents, e.g., exemestane, Lupron, anastrozole, doxercalciferol, fadrozole, formestane, 11 Beta-Hydroxysteroid Dehydrogenase 1 inhibitors, 17-Alpha Hydroxylase/17,20 Lyase Inhibitors such as abiraterone acetate, 5-Alpha

Reductase Inhibitors such as Bearfina (finasteride) and Epristeride, anti-estrogens such as tamoxifen citrate and fulvestrant, Trelstar, toremifene, raloxifene, lasofoxifene, letrozole, or anti-androgens such as bicalutamide, flutamide, mifepristone, nilutamide, Casodex, or anti-progesterones and combinations thereof;
Plant derived anti-tumor substances include for example those selected from mitotic inhibitors, for example epothilone such as sagopilone, Ixabepilone or epothilone B, vinblastine, vinflunine, docetaxel and paclitaxel;
Cytotoxic topoisomerase inhibiting agents include one or more agents selected from the group consisting of aclarubicin, amonafide, belotecan, camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, diflomotecan, irinotecan (Camptosar), edotecarin, epimbicin (Ellence), etoposide, exatecan, gimatecan, lurtotecan, mitoxantrone, pirambicin, pixantrone, rubitecan, sobuzoxane, tafluposide, and topotecan, and combinations thereof;
Immunologicals include interferons and numerous other immune enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon, alpha-2b, interferon beta, interferon gamma-1a or interferon gamma-n1. Other agents include L19-IL2 and other L19 derivatives, filgrastim, lentinan, sizofilan, TheraCys, ubenimex, aldesleukin, alemtuzumab, BAM-002, dacarbazine, daclizumab, denileukin, gemtuzumab ozogamicin, ibritumomab, imiquimod, lenograstim, lentinan, melanoma vaccine (Corixa), molgramostim, sargramostim, tasonermin, tecleukin, thymalasin, tositumomab, Vimlizin, epratuzumab, mitumomab, oregovomab, pemtumomab, Provenge,
Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth, or differentiation of tissue cells to direct them to have anti-tumor activity. Such agents include krestin, lentinan, sizofiran, picibanil, ProMune or ubenimex.
Pro-apoptotic agents are YM155, AMG 655, APO2L/TRAIL, CHR-2797.
Anti-angiogenic compounds include, acitretin, Aflibercept, angiostatin, aplidine, asentar, Axitinib, Recentin, Bevacizumab, brivanib alaninat, cilengtide, combretastatin, DAST, endostatin, fenretinide, halofuginone, pazopanib, Ranibizumab, rebimastat, removab, Revlimid, Sorafenib, Vatalanib, squalamine, Sunitinib, Telatinib, thalidomide, ukrain, Vitaxin,

Platinum-coordinated compounds include but are not limited to, cisplatin, carboplatin, nedaplatin, satraplatin or oxaliplatin;

Camptothecin derivatives include but are not limited to camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, irinotecan, edotecarin, and topotecan;

Antibodies include Trastuzumab, Cetuximab Bevacizumab, or Rituximab, ticilimumab, Ipilimumab, lumiliximab, catumaxomab, atacicept; oregovomab, alemtuzumab;

VEGF inhibitors can also be combined with the inventive virus. Examples of VEGF inhibitors are Sorafenib, DAST, Bevacizumab, Sunitinib, Recentin, Axitinib, Aflibercept, Telatinib, brivanib alaninate, Vatalanib, pazopanib and Ranibizumab.

EGFR (HER1) inhibitors can also be combined with the inventive virus. Examples of EGFR inhibitors are Cetuximab, Panitumumab, Vectibix, Gefitinib, Erlotinib, Zactima.

HER2 inhibitors can also be combined with the inventive virus. Examples of HER2 inhibitors are Lapatinib, Tratuzumab, Pertuzumab.

mTOR inhibitors can also be combined with the inventive virus. Examples of mTOR inhibitors are Temsirolimus, sirolimus/Rapamycin, everolimus.

cMet inhibitors can also be combined with the inventive virus.

PI3K- and AKT inhibitors can also be combined with the inventive virus.

CDK inhibitors can also be combined with the inventive virus. Examples of CDK inhibitors are roscovitine and flavopiridol.

Spindle assembly checkpoints inhibitors and targeted anti-mitotic can be combined with the inventive virus. Example for targeted anti-mitotic drug are the PLK inhibitors, the Aurora inhibitors such as Hesperadin, Checkpoint Kinase inhibitors and the KSP inhibitors.

HDAC inhibitors can be combined with the inventive virus. Example for HDAC inhibitors are panobinostat, vorinostat, MS275, belinostat and LBH589.

HSP90 inhibitors and HSP70 inhibitors can be combined with the inventive virus.

Proteasome inhibitors can be combined with the inventive virus. Examples for proteasome inhibitors are bortezomib and carfilzomib.

Serine/threonine kinase inhibitors can be combined with the inventive virus. Serine kinase inhibitors include MEK inhibitors and Raf inhibitors such as Sorafenib.

The inventive virus may be used with Farnesyl transferase inhibitors, e.g. tipifarnib.

The nventive virus may be used with tyrosine kinase inhibitors including Dasatinib, Nilotibib, DAST, Bosutinib, Sorafenib, Bevacizumab, Sunitinib, AZD2171, Axitinib, Aflibercept, Telatinib, imatinib mesylate, brivanib alaninate, pazopanib, Ranibizumab, Vatalanib, Cetuximab, Panitumumab, Vectibix, Gefitinib, Erlotinib, Lapatinib, Tratuzumab, Pertuzumab and c-Kit inhibitors.

Vitamin D receptor agonists can be combined with the inventive virus.

Bcl-2 protein inhibitors can be combined with the inventive virus. Example for Bcl-2 protein inhibitors are obatoclax, oblimersen sodium and gossypol.

Cluster of Differentiation 20 receptor antagonists can be combined with the inventive virus. An example for a Cluster of Differentiation 20 receptor antagonist is rituximab.

Ribonucleotide Reductase Inhibitors can be combined with the inventive virus. An example for a Ribonucleotide Reductase Inhibitor is Gemcitabine.

Topoisomerase I and II Inhibitors can be combined with the inventive virus. Example for a Topoisomerase I and II Inhibitor is Camptosar (Irinotecan) and doxorubicin.

Tumor Necrosis Apoptosis Inducing Ligand Receptor 1 Agonists can be combined with the inventive virus. Example for a Tumor Necrosis Apoptosis Inducing Ligand Receptor 1 Agonist is mapatumumab.

5-Hydroxytryptamine Receptor Antagonists can be combined with the inventive virus. Example for 5-Hydroxytryptamine Receptor Antagonists are rEV598, Xaliprode, Palonosetron hydrochloride, granisetron, Zindol, palonosetron hydrochlorid or AB-1001.

Integrin Inhibitors can be combined with the inventive virus. Example for Integrin Inhibitors are Alpha5Beta1 integrin inhibitors such as E7820, JSM 6425, volociximab or Endostatin.

Androgen receptor antagonists can be combined with the inventive virus. Examples for Androgen receptor antagonists are nandrolone decanoate, fluoxymesterone, fluoxymesterone, Android, Prost-aid, Andromustine, Bicalutamide, Flutamide, Apo-Cyproterone, Apo-Flutamide, chlormadinone acetate, bicalutamide, Androcur, Tabi, cyproterone acetate, Cyproterone Tablets, nilutamide.

Aromatase Inhibitors can be combined with the inventive virus. Examples for Aromatase Inhibitors are anastrozole, letrozole, testolactone, exemestane, Aminoglutethimide and formestane.

Matrix metalloproteinase inhibitors can be combined with the inventive virus.

Other anticancer agents include alitretinoin, ampligen, atrasentan bexarotene, bortezomib, bosentan, calcitriol, exisulind, finasteride, fotemustine, ibandronic acid, miltefosine, mitoxantrone, l-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, hydroxycarbamide, pegaspargase, pentostatin, tazarotne, velcade, gallium nitrate, Canfosfamide darinaparsin or tretinoin;

Examples

Tumour-selective replication

When incubated with human tumour cells such as HT29 colon carcinoma cells or HT1080 fibrosarcoma cells, the virus is able to replicate and produce progeny virus. The titer achieved in tumour cells is at least 100fold higher than the titer achieved in human primary normal cells.

When the cell-killing effect of the virus is examined the necessary MOI to kill primary normal cells is at least 100, more preferably 1000fold higher than the MOI that is sufficient to kill human tumour cells.

Production of the virus

The virus is grown either in embryonated bird eggs (preferably chicken eggs) or in human tumour cell lines or derivatives of human tumour cell lines.

The virus is harvested from the allantoic fluid of the eggs or from the supernatant of the cells or from the cell pellet (cell-associated virus).

The virus is concentrated and purified using a discontinuous sucrose gradient ultracentrifugation. Alternatively the virus is concentrated and purified using tangential flow filtration.

Anti-tumour effect

The anti-tumour effect of the virus is shown in murine tumour models. When administered intratumourally or intravenously, the virus results in the regression of established human xenograft-tumours in nude mice. The effective dose of virus is in the range of 10^5 to 10^9 pfu / injection. In some tumour models repeated

administration in intervals of 2-14 days (preferably 7 days) is necessary to be most effective.

Genetic engineering of the virus

The reverse genetic system is published for many paramyxoviruses. It is adapted analogously to the paramyxovirus of this invention.

The viral genome is sequenced. Based on the sequence, primers for cloning are designed that span unique restriction enzyme recognition sites within the viral genome. By RT-PCR several fragments of the viral genome are cloned as DNA in a plasmid vector like pX8δT.

With the genomic plasmid, mutations, exchange of genes and other types of genetic engineering are carried out on the DNA-level.

By transfection of the genomic plasmid-DNA into cells that express the T7-polymerase together with helper plasmids, recombinant virus can be rescued. An alternative method for the rescue of virus may be used. For example expression of the T7-polymerase may be accomplished by cotransfecting the cells with an expression plasmid encoding for T7-polymerase.

Additional transgenes are expressed in the virus as it is described for the related virus NDV (Puhler et al., 2008).

The additional transgenes are preferably inserted in the intergenic region between M-F or F-HN.

The F and HN transgenes may be derived from any APMV, preferably from a virus that has itself strong oncolytic potency. The F and H / HN transgenes may be derived from another paramyxovirus other than APMV.

It may be sufficient to express only the heterologous F or the HN protein individually in order to increase the oncolytic potency of the virus.

Chimeric viruses

In order to combine positive features of two different viruses or in order to get rid of negative features it is possible to substitute fragments of the genome with homologous fragments of another virus. That virus may be any related paramyxovirus and is not limited to APMV.

The endogenous genes for the F and HN proteins of APMV can be replaced by heterologous genes from related paramyxoviruses to alter the specificity and tumour-selectivity of the virus.

To allow proper assembly of virions all three proteins M, F and HN can be replaced by the homologous gene segment of a related virus.

In order to decrease the pathogenicity for birds, the gene for the P/V protein is either mutated or replaced by the gene from a related virus. The same procedure can also increase the specificity of the virus for killing of human tumour cells compared to normal cells.

The endogenous L, P and NP proteins can be exchanged. The exchange of these three proteins will have an effect on the replication properties of the virus.

Transgenes

In order to decrease the pathogenicity of the virus, the gene for avian interferon is inserted into the viral genome.

In order to increase the tumour-penetration of the virus, transgene(s) are inserted that encode for extracellular-matrix-resolving enzymes like relaxin, collagenase, MMP etc.

In order to increase the therapeutic potency, transgenes are inserted that encode for proteins that have an ant-tumour activity like toxins, prodrug-converting enzymes, proteases, antibodies etc. Examples are TRAIL and mutants thereof, MDA-7, IL2, TNF-a, IGF-BP-7.

For imaging purposes and as biomarkers, transgene(s) are inserted that encode for reporter-genes like GFP, luciferase, NIS or marker peptides like PSA, insulin C-peptide, common virus-antigens (peptides) etc.

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What is claimed is:

1. Use of paramyxovirus from the group APMV3, APMV4, APMV5, APMV6, APMV7, APMV8, APMV9, Mapueravirus and Fer-de-Lance virus for the production of a medicament for the tumour treatment.

2. Use according to claim 1, wherein the virus is a closely related paramyxovirus that has more than 80% sequence identity on RNA level.

3. Use according to claim 1, wherein the virus is recombinant.

4. Use according to claim 1, wherein the virus is modified to express one additional gene that originates from APMV1-9.

5. Use according to claim 1, wherein the virus is modified to express two or more additional genes that originate from APMV1-9

6. Use according to any one of claims 4 - 5, wherein the genes encode the F and / or the HN protein of another paramyxovirus.

7. Use according to claim 6, wherein the F protein has a multibasic cleavage site.

8. Use according to claim 3, wherein the virus is modified in such a way that one gene is replaced by the homologous gene of a virus from the group APMV1-9

9. Use according to claim 3, wherein the genetic modification results in an attenuation of pathogenicity in birds.

10. Use according to claim 3, wherein the genetic modification results in a higher selectivity of the virus to infect tumour cells compared to non-transformed normal cells.

11. Use according to claim 3, wherein the genetic modification results in a higher oncolytic potency as measured by the antitumour-effect when administered to tumour-bearing nude mice.

12. Use according to claim 1, wherein the virus is administered intratumourally.

13. Use according to claim 1, wherein the virus is administered intraperitoneally.

14. Use according to claim 1, wherein the virus is administered by inhalation.

15. Use according to claim 1, wherein the virus is administered intravenously.

16. Use according to claim 1, wherein the virus is purified by gradient ultracentrifugation.

17. Use according to claim 1, wherein the virus is purified by tangential flow filtration.

18. Use according to claim 1, wherein the tumour is selected out of the group consisting of colon carcinoma, breast carcinoma, lung carcinoma, prostate carcinoma, ovarian carcinoma, melanoma, cervical carcinoma, bladder carcinoma, glioblastoma and fibrosarcoma.

19. Use according to claim 1, wherein the pharmaceutical composition further comprises a chemotherapeutic agent.

20. Use according to claim 1, wherein the said pharmaceutical composition further comprises a recombinant therapeutic antibody.

21. Use according to claim 1, wherein the pharmaceutical composition further comprises a recombinant therapeutic protein.

22. Use according to claim 1, wherein the virus is modified to express at least one additional gene encoding for a binding protein.

23. Use according to claim 1, wherein the virus is modified to express at least one additional gene encoding for an enzyme.

24. Use according to claim 1, wherein the virus is modified to express at least one additional gene encoding for a prodrug converting enzyme.

25. Use according to claim 1, wherein the virus is modified to express at least one additional gene encoding for an antibody.

26. Use according to claim 3, wherein the virus is modified to express at least one additional gene encoding for a fusion protein comprising at least one immunoglobulin domain with an antibody variable region.

27. Use according to claim 1, wherein the tumour is metastatic.

28. Use according to claim 8, wherein two to five genes are replaced, resulting in a chimeric virus that has only one to four remaining genes of the originating virus.