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(54) **ONCOLYTIC VIRAL VECTORS FOR USE IN THE TREATMENT OF RETINOBLASTOMA**

ONKOLYTISCHE VIRUSVEKTOREN ZUR VERWENDUNG BEI DER BEHANDLUNG VON
RETINOBLASTOM

VECTEURS VIRAUX ONCOLYTIQUES POUR UNE UTILISATION DANS LE TRAITEMENT D'UN
RÉTINOBLASTOME

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EP-A1- 2 428 229</p> <ul style="list-style-type: none">• JI X ET AL: "Oncolytic adenovirus delivering herpes simplex virus thymidine kinase suicide gene reduces the growth of human retinoblastoma in an in vivo mouse model", EXPERIMENTAL EYE RESEARCH, ACADEMIC PRESS LTD, LONDON, vol. 89, no. 2, 1 August 2009 (2009-08-01), pages 193-199, XP026336934, ISSN: 0014-4835, DOI: 10.1016/J.EXER.2009.03.007 [retrieved on 2009-03-28]• XIN SONG ET AL: "Combined Treatment with an Oncolytic Adenovirus and Antitumor Activity of Vincristine against Retinoblastoma Cells", INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES, vol. 13, no. 12, 27 August 2012 (2012-08-27), pages 10736-10749, XP055394331, DOI: 10.3390/ijms130910736 |
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- **GANESH S: "Intratumoral coadminisistration of hyaluronidase inzyme and oncolytic adenoviruses inhances virus potency in metastatic tumor models", CLINICAL CANCER RESE, THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 14, no. 12, 1 January 2008 (2008-01-01), pages 3933-3941, XP009153332, ISSN: 1078-0432**

Description

[0001] The present invention relates to the sector of medicine, more specifically the sector of oncology.

[0002] Retinoblastoma is the most common malignant intraocular tumour in children, with an incidence of 1/17,000 newborns. It develops in the retina, usually growing therebelow towards the vitreous cavity, from cells that have variants predisposed to cancer in both copies of the Rb1 gene, whether by inherited or acquired mutation. It is a disease that normally occurs before the age of five years and can be sporadic or hereditary, if there is a germ line mutation of the Rb1 gene.

[0003] Depending on its presentation, retinoblastoma can be unifocal or multifocal and unilateral (representing 65% of cases) or bilateral (representing the remaining 35% - with germ line mutation of the Rb1 gene). Unilateral retinoblastoma only occurs in one of the patient's eyes, and the average age at the time of diagnosis is 24 months, whereas bilateral retinoblastoma affects both eyes, with an average age at the time of diagnosis of 15 months.

[0004] Current treatment of retinoblastoma is aimed primarily at the patient's survival and secondly at preservation of sight. The optimum treatment is usually complex and involves experts from multiple disciplines of medicine, such as ophthalmologists, paediatric oncologists and radiation oncologists, amongst others. There are various therapeutic options, including especially: systemic or local ocular chemotherapy, radiotherapy, cryotherapy, laser therapy and surgery (enucleation of the affected eye). The choice of therapeutic regimen depends on many factors, such as the stage of tumour development, whether the tumour is unifocal or multifocal and unilateral or bilateral, the site and size of the tumour, amongst others. Because of the impact on the eye and its functions, the preferred therapy or treatment of choice is normally chemotherapy. There is, however, the problem that high-dose chemotherapy is highly toxic and in a percentage of cases the tumour develops resistance to said treatment. In these cases, the only therapeutically viable option to preserve the patient's life is currently enucleation.

[0005] In addition, although retinoblastoma as such is a very curable disease, there is a fundamental risk of the development of metastases, secondary malignancies or trilateral retinoblastoma. In these cases, the prognosis is less favourable because there are no clear and effective therapeutic options for treatment.

[0006] Gene therapy and virotherapy use viruses for therapeutic purposes against cancer. In gene therapy the virus is modified so as to prevent it from replicating and to serve as a vehicle or vector for therapeutic genetic material. In contrast, virotherapy uses viruses that replicate and propagate selectively in the tumour cells. In virotherapy the tumour cell dies through the cytopathic effect caused by the replication of the virus inside it rather than through the effect of a therapeutic gene. The preferential replication in a tumour cell is called oncotropism and tumour lysis is called oncolysis. Strictly speaking, viruses that replicate selectively in tumours are called oncolytic, although in a wider meaning the word oncolytic can be applied to any replicating virus that is able to lyse tumour cells, even non-selectively. In this description the term oncolytic is used with both meanings.

[0007] Cancer virotherapy far predates gene therapy. The first observations of tumours being cured with viruses date back to the beginning of the last century. As early as 1912 De Pace achieved tumour regression after inoculating the rabies virus into cervical carcinomas. Since then, many types of virus have been injected into tumours to treat them. There are viruses that have natural oncotropism, such as the autonomous parvovirus, the vesicular stomatitis virus and the reovirus. Other viruses can be genetically manipulated so that they replicate selectively in tumours. For example, the herpes simplex virus (HSV) has been made oncotropic by eliminating the ribonucleotide reductase gene, a dispensable enzymatic activity in actively proliferating cells such as tumour cells. Adenovirus, however, has been the virus most frequently used in both virotherapy and gene therapy for cancer because of its low pathogenicity and high ability to infect tumour cells.

[0008] Fifty-one serotypes of human adenoviruses have been identified, classified into six groups, differentiated from A to F.

[0009] Human adenovirus serotype 5 (Ad5), which belongs to group C, is a virus formed by an icosahedral protein capsid containing a 36-kilobase linear deoxyribonucleic acid (DNA). In adults, Ad5 infection is usually asymptomatic and in children it causes common cold and conjunctivitis. Ad5 generally infects epithelial cells - the cells of the bronchial epithelium during a natural infection. It enters the cell by means of the interaction of the fibre, a viral protein that extends like an antenna from the twelve vertices of the capsid, with a cell protein involved in intercellular adhesion, called the Coxsackie-Adenovirus Receptor (CAR). When viral DNA reaches the interior of the nucleus it starts systematically transcribing the early genes (E1 to E4) of the virus. The first viral genes to be expressed correspond to early region genes 1A (E1A). E1A binds to the cell protein of the retinoblastoma to release E2F and thus activate the transcription of other viral genes such as E2, E3 and E4 and the cellular genes that activate the cell cycle. E1B, for its part, binds to the p53 protein, to activate the cell cycle and prevent apoptosis of the infected cell. E2 encodes for virus replication proteins; E3 encodes proteins that inhibit the antiviral immune response; E4 encodes for proteins that transport viral RNA. Expression of the early genes leads to replication of the viral DNA, and once this is replicated, the major late promoter is activated, leading to expression of a messenger ribonucleic acid (RNA) transcript which, by cutting and differential splicing, generates all the RNAs that encode for the structural proteins that form the capsid.

[0010] There are two important aspects to be considered in relation to the design of oncolytic adenoviruses: selectivity and potency. To achieve selectivity towards the tumour cell, three strategies were used: elimination of viral functions necessary for replication in normal cells but dispensable in tumour cells; control of the viral genes that initiate replication by tumour-selective promoters; and modification of the viral capsid proteins involved in infection of the host cell. By means of these genetic modifications, a considerable level of selectivity has been achieved, with a tumour-cell replicative capacity some 10,000 times greater than the replicative capacity in the normal cell. In relation to oncolytic potency, various genetic modifications for increasing this have also been described. These modifications include: a) increased viral release, for example by deletion of E1B19K, overexpression of E3-11.6K (ADP), or relocation of the protein E3/19K in the plasma membrane; and b) the insertion of a therapeutic gene into the oncolytic adenovirus genome to generate an "armed oncolytic adenovirus". In this case, the therapeutic gene would have to mediate the death of the uninfected carcinogenic cells by activating a prodrug having a bystander effect (in other words, it kills the uninfected neighbouring cells), activating the immune system against the tumour, inducing apoptosis, inhibiting angiogenesis, or removing the extracellular matrix, among other things. In these cases, the form and time of therapeutic gene expression will be critical for the end result of the therapeutic approach.

[0011] However, the major obstacles encountered by adenoviral therapy in its clinical application are the immune response, whether pre-existing or generated by the first or subsequent injections of adenovirus, and the difficulty of adenoviruses being efficiently distributed throughout the tumour mass, i.e. not infecting solely the surface cells of the tumour but also reaching those located inside it. This latter difficulty has also been described for other anti-cancer drugs such as doxorubicin, Taxol [paclitaxel], vincristine and methotrexate and is thought to be related to the extracellular matrix of the tumour (involved in the resistance of tumour cells to chemotherapy drugs, BP Toole et al., "Hyaluronan: a constitutive regulator of chemoresistance and malignancy in cancer cells", *Seminars in Cancer Biology* 2008, vol. 18, pp. 244-50). Tumour cells and stromal cells in the tumour produce and assemble a matrix of collagens, proteoglycans and other molecules that hinder the transport of macromolecules within the tumour. Hyaluronic acid is one of the main components of said extracellular matrix involved in the resistance of tumour cells to therapeutic drugs. Hyaluronic acid is overexpressed in a wide variety of malignant tissues, and in many cases the levels of said acid are a prognostic factor for tumour progression. The interaction of hyaluronic acid with the receptors CD44 and RHAMM increases tumour survival and invasion. Moreover, hyaluronic acid can promote tumour metastases by inducing cell migration and adhesion, and protecting against the immune system.

[0012] On the other hand, the inhibition of interactions between hyaluronic acid and the tumour cells, reversing resistance to a large number of drugs, has been described. Various works have indicated that hyaluronidases, enzymes responsible for the degradation of hyaluronic acid, increase the activity of various types of chemotherapy in patients with melanoma, Kaposi's sarcoma, head and neck cancer and hepatic metastases from the colon. The mechanism of action of hyaluronidases is as yet unknown, but is generally attributed to a decrease in cell adhesion barriers, reduced interstitial pressure and improved penetration of the anticancer drug into the tumour, rather than its inhibitory effects on the signalling pathways related to cell survival.

[0013] Hyaluronidase enzymes are a family of enzymes responsible for degrading hyaluronic acid. In the human species six genes that encode for hyaluronidase enzymes, having different properties and locations, have been located to date. The isoforms Hyal1 and Hyal2 are found in most tissues, Hyal1 being the predominant form in human plasma. Hyal3 is located in the bone marrow and testicles, but its function is not well characterised. The hyaluronidase enzyme PH20 is highly expressed in the testicles and is involved in the process by which the oocyte is fertilised by the spermatozoon. The hyaluronidase enzyme PH20 is anchored to the plasma membrane and the inner acrosomal membrane of the spermatozoa and gives the spermatozoon the ability to penetrate the extracellular matrix of the cumulus cells (which are rich in hyaluronic acid) and reach the zona pellucida of the oocyte. During the acrosome reaction, some of the hyaluronidase enzymes anchored in the spermatozoon membrane are processed enzymatically to give rise to a soluble form of the protein, which is released from the acrosomal membrane. The membrane protein PH20 is the only enzyme in the mammalian hyaluronidase family with activity at neutral pH.

[0014] In view of the above, there is a need to have alternative therapies, more effective than the current ones, to treat retinoblastoma. In addition, said alternative treatments are particularly necessary when the tumour develops resistance to chemotherapy at the maximum permitted doses and/or the doses to be used show excessively high levels of toxicity, to avoid enucleating one or both eyes (for cases when the various alternative treatments with chemotherapy do not have positive effects). New therapeutic alternatives are also required to allow the risk of the patient developing metastases, secondary malignancies or trilateral retinoblastoma to be eliminated or reduced.

[0015] After extensive and exhaustive experiments, the inventors of the present invention have discovered, surprisingly, that it is possible to use genetically modified oncolytic adenoviruses to treat retinoblastoma and that said oncolytic adenoviruses allow the risk of metastases, secondary malignancies and/or trilateral retinoblastoma to be eliminated or reduced. The results obtained by the inventors of the present invention prove surprising for various reasons, including the fact that the aforementioned modified oncolytic adenovirus is not effective in infecting cell lines derived from some tumours yet is so for cell lines derived from retinoblastoma; and, furthermore, in in-vivo treatments, even though the

adenovirus is injected into a theoretically semi-closed or isolated system (the vitreous cavity), the adenovirus manages to reduce the ability of the tumour cells to form metastases in comparison with the effect observed when using conventional chemotherapy. In other words, an effect is observed outside the eye which is totally unexpected and superior to that observed in conventional therapies of the prior art.

[0016] As used in the present document, "oncolytic adenovirus" and its plural refer to adenoviruses capable of replicating themselves or being replication-competent in the tumour cell. Said oncolytic adenoviruses are differentiated from non-replicating adenoviruses because the latter are unable to replicate themselves in the target cell.

[0017] According to a first aspect, the present invention discloses a composition comprising an oncolytic adenovirus for use for treating retinoblastoma, wherein the aforementioned oncolytic adenovirus comprises:

- a sequence encoding a hyaluronidase enzyme inserted into its genome; and
- replication machinery specific for tumour cells.

[0018] Said composition is injected by any route ensuring that the necessary amount of the adenovirus reaches the interior of the eyeball, preferably by intraocular injection, even more preferably intravitreal injection. Intraocular or intravitreal injections have the advantage that they are performed into an organ, the eye, which provides an immunoprivileged environment, facilitating a lower immune response, or no response, to the oncolytic adenovirus comprised in the composition. This situation makes it possible to ensure, to a large extent, that the action of the oncolytic adenovirus will remain confined to the eye, since if the adenovirus should ever leave said organ it could be neutralised by the immune system. Therefore, in a preferred embodiment, the aforementioned composition takes an appropriate form for intravitreal or intraocular administration or injection.

[0019] Another possible route of administration for the composition provided for in the present invention is intratumoral injection.

[0020] In a preferred embodiment, the treatment of retinoblastoma takes place in a mammal, preferably a human, more preferably a paediatric human patient.

[0021] In another preferred embodiment, the retinoblastoma treated is a retinoblastoma resistant to conventional chemotherapy and/or radiotherapy treatment; even more preferably said retinoblastoma is refractory or the result of a relapse and is resistant to conventional chemotherapy and/or radiotherapy treatment.

[0022] The oncolytic adenovirus used in the present invention is an oncolytic adenovirus with replication machinery and a capsid that allows infection and replication in human cancer cells. In a preferred embodiment, said oncolytic adenovirus is preferably generated from adenoviruses that infect humans, for example from an adenovirus of serotype 1 to 51, or combinations thereof (hybrid recombinant of two or more different serotypes of adenovirus) of human adenoviruses. In the most preferred embodiment, the oncolytic adenovirus used in the present invention is generated from a human adenovirus serotype 5.

[0023] It should be noted that the hyaluronidase enzyme contributes to ensuring greater or easier dispersion and penetration of the oncolytic adenovirus, thus ensuring that said adenovirus can reach and infect a larger number of retinoblastoma cells.

[0024] Furthermore, in one embodiment the hyaluronidase enzyme is a mammalian testicular hyaluronidase enzyme, more preferably a human one (GenBank Gene ID: 6677), also known as SPAM1 or spermatozoon adhesion molecule 1 or PH20. In one embodiment, the sequence of said enzyme has the sequence corresponding to the membrane-binding carboxy-terminal domain deleted from it, in order for the enzyme to be soluble. When this carboxy-terminal domain is deleted, the resulting enzyme is secreted into the extracellular environment.

[0025] In a preferred embodiment, the sequence encoding a hyaluronidase enzyme inserted into the oncolytic adenovirus genome is SEQ ID NO: 1, from which nucleotides 1471 to 1527, corresponding to the carboxy-terminal domain, have been deleted.

[0026] It is envisaged that the hyaluronidase enzyme sequence is inserted at any point in the oncolytic adenovirus genome as long as it allows said adenovirus to replicate selectively in tumour or cancer cells and as long as the hyaluronidase enzyme is expressed and produced effectively and functionally in the required quantities. Preferably, the hyaluronidase enzyme sequence is inserted into the genome of the oncolytic adenovirus after the nucleotide sequence of the adenovirus fibre.

[0027] Clearly, the expression of the hyaluronidase enzyme is controlled by a promoter operational in the retinoblastoma cells to be treated. Preferably, the expression of said enzyme is controlled by a promoter operational in animal cells. Preferably, the promoter is selected from the group consisting of the cytomegalovirus promoter, the adenovirus major late promoter, the SV40 promoter, the herpes simplex virus thymidine kinase promoter, the RSV promoter, the EF1- α promoter, the beta-actin promoter, the human IL-2 promoter, the human IL-4 promoter, the IFN promoter, the E2F promoter, the human GM-CSF promoter or combinations thereof. The promoter that regulates the expression of the enzyme can be present naturally in the adenovirus, as is the case with the adenovirus major late promoter. The promoter can also be inserted together with the sequence encoding the enzyme. In a preferred embodiment, the promoter is the

adenovirus major late promoter and this is already located in the oncolytic adenovirus genome. In this last embodiment it is not necessary to introduce the promoter together with the hyaluronidase enzyme sequence, but rather the latter is introduced into the oncolytic adenovirus genome in such a way that it remains under the control of said promoter.

[0028] It is envisaged that the oncolytic adenovirus comprises additional sequences that allow promotion or optimisation of the protein translation of the sequence encoding the hyaluronidase enzyme. Said sequences can be inside or outside the hyaluronidase enzyme gene. For example, said additional sequences are selected from the group consisting of a sequence of cutting and splicing that allows RNA to be processed, IRES (internal ribosome entry site) sequences, the picornavirus sequence 2A or combinations thereof.

[0029] The tumour cell-specific replication machinery comprised by the oncolytic virus used in the present invention is machinery that, as explained above, causes the oncolytic adenovirus to replicate itself in a specific form in tumour cells and not in healthy or normal cells. Said machinery can take different forms if, as a result, it provides oncolytic adenoviruses with a replicative capacity solely in the retinoblastoma (tumour) cells - in other words, adenoviruses with selective replication in which their replication machinery requires the virus to enter the cancer or tumour cells in order for the virus to replicate itself. In this respect, the oncolytic adenovirus used can have modifications in its genome sequence that give it selective replication in tumour cells.

[0030] In one embodiment this is achieved with the incorporation of a specific tissue promoter or a specific tumour promoter, where said promoter controls the expression of one or more genes in the group E1a, E1b, E2 and E4. In particular, the promoter is selected from the group consisting of the E2F promoter, the telomerase hTERT promoter, the tyrosinase promoter, the prostate-specific antigen (PSA) promoter, the alpha-fetoprotein promoter, the COX-2 promoter, as well as artificial promoters formed by various transcription factor binding sites such as binding sites for hypoxia-inducible factor (HIF-1), the ETS transcription factor, the tumour cytotoxic factor (TCF), the E2F transcription factor or the Sp1 transcription factor. Preferably, the promoter controls the expression of E1a.

[0031] In a preferred embodiment, the specific replication machinery for tumour cells is defective replication machinery that can be complemented in tumour cells with both defective copies of the Rb1 gene. In other words, this is replication machinery that is mutated or modified such that when it enters healthy (non-tumour) cells it is not expressed or is expressed in such a way that it does not lead to viral replication. Instead, when the oncolytic adenovirus enters a tumour cell with the characteristics mentioned above, the replication machinery acquires sufficient complementation (the tumour cell performs the functions lacking in the virus) for the virus to be able to be replicated (complete its cycle, producing viruses and leading to lysis of the tumour cell). In this embodiment, one option for achieving said selective replication in tumour cells with both defective copies of the Rb1 gene is the elimination of early functions of E1A that block the retinoblastoma (RB) pathway. Other viral genes that interact directly with the retinoblastoma protein, such as E4 and E4orf6/7 respectively, are candidates for deletion or truncation in order to achieve selective replication in tumour cells with both defective copies of the Rb1 gene. In the most preferred embodiment, the oncolytic adenovirus used in the present invention is characterised by the deletion $\Delta 24$, which affects the interaction of E1a with the retinoblastoma protein, and the insertion of four sites binding to E2F-1 and one site binding to Sp1 into the endogenous E1a promoter to control the expression of E1a. Said DNA sequence corresponds to SEQ ID NO: 2 in the attached list of sequences.

[0032] Other modifications that comply with the above, i.e. allow specific replication of oncolytic adenoviruses in retinoblastoma tumour cells, are also provided for and included in the present invention.

[0033] The two strategies explained for achieving selective replication in retinoblastoma are not mutually exclusive.

[0034] Furthermore, it is envisaged that the oncolytic adenovirus used in the present invention comprises one or more modifications in the capsid allowing increased affinity of said oncolytic adenovirus for the cancer or tumour cells (modifications in its capsid to increase its infectivity with regard to the cancer or tumour cells or to direct it to a receptor present in said cancer or tumour cells). In this way, the proportion of oncolytic adenoviruses infecting cancer or tumour cells is increased compared with those infecting healthy cells, and the latter adenoviruses can even reach a negligible amount compared with the former.

[0035] In one embodiment, the oncolytic adenovirus used in the present invention has been modified genetically so as to include, in the adenovirus capsid proteins, ligands that increase infectivity or direct the virus to a receptor in the cancer or tumour cell. Directing the adenovirus to the tumour can also be achieved with bifunctional ligands that bind to the virus on one side and to the tumour receptor on the other. In a preferred embodiment, the oncolytic adenovirus used in the present invention has the capsid modified to increase its infectivity or to direct it better to the target tumour cell, such that the binding domain KKTK of the heparan sulfates present in the adenovirus fibre has been replaced by the domain RGDK. Said modification relates to positions 91 to 94 of the adenovirus fibre, taking the standard sequence of the adenovirus serotype 5 fibre as the reference. The sequence SEQ ID NO: 9 shows the complete sequence of the adenovirus type 5 fibre protein with the modified version in its heparan sulfate binding domain (modification RGDK).

[0036] Furthermore, it is also possible to modify the capsid of the viruses for other purposes, for example to increase the persistence of the oncolytic adenovirus in blood and thus increase the possibilities of said adenovirus reaching tumour nodules (particularly if said nodules or tumour foci are disseminated). For example, the capsid can be covered with polymers such as polyethylene glycol.

[0037] Therefore, in the most preferred embodiment, the oncolytic adenovirus used in the present invention is generated from a human adenovirus serotype 5 and comprises:

- a sequence encoding a hyaluronidase enzyme inserted into its genome, more preferably the human testicular hyaluronidase enzyme sequence (PH20, SEQ ID NO: 1) from which the sequence corresponding to the membrane-binding carboxy-terminal domain has been deleted in order for the enzyme to be soluble.
- deficient replication machinery that can be complemented in tumour cells by both defective copies of the Rb1 gene; more preferably said machinery comprises the deletion $\Delta 24$, which affects the interaction of E1a with the Rb protein, and the insertion of four binding sites to E2F-1 and one binding site to Sp1 into the endogenous E1a promoter to control the expression of E1a;
- modification of the adenovirus capsid to increase the infectivity of said virus or to direct said adenovirus better to the target tumour cell; more preferably the binding domain KKTK of the heparan sulfates present in the adenovirus fibre has been replaced by the domain RGDK.

[0038] Preferably, the oncolytic virus sequence of the present invention corresponds to SEQ ID NO: 3.

[0039] The oncolytic adenovirus used in the present invention can have inserted into its genome other genes in common use in the field of gene therapy for cancer to increase the cytotoxicity of oncolytic adenoviruses on tumour cells, for example the thymidine kinase gene, the cytosine deaminase gene, proapoptotic genes, immunostimulants, tumour suppressors or prodrug activators.

[0040] To construct the oncolytic adenovirus to be used in the present invention (i.e. as explained above), use is made of any of the methods of construction of genetically modified adenovirus known in the field of gene therapy and virotherapy using adenoviruses. The most commonly used method is based on first constructing the desired genetic modification in a plasmid containing the adenoviral region to be modified, and then carrying out homologous recombination in bacteria with a plasmid containing the rest of the viral genome.

[0041] The oncolytic adenovirus used in the present invention is propagated and amplified in cell lines normally used in the field of gene therapy and virotherapy such as the lines HEK-293 (Reference number: ATCC CRL-1573) and A549 (Reference number: ATCC CCL185). A preferred method of propagation of said adenovirus is by infection of a cell line permitting the replication of the adenovirus. The lung adenocarcinoma line A549 is an example of a line with such characteristics. Propagation takes place, for example, as follows: the A549 cells are grown on plastic cell culture plates and are infected using 100 virus particles per cell. Two days later, the cytopathic effect reflecting virus production can be observed as a clustering of the cells. The cells are collected and stored in tubes. After centrifuging at 1000 g for 5 minutes, the cell pellet is frozen and thawed three times, to lyse the cells. The resulting cell extract is centrifuged at 1000 g for 5 minutes and the supernatant, in which the viruses are located, is loaded over a caesium chloride gradient and centrifuged for 1 hour at 35,000 g. The virus band obtained from the gradient is loaded again over another caesium chloride gradient and centrifuged for 16 hours at 35,000 g. The virus band is collected and dialysed opposite PBS-10% glycerol. The virus dialysate is aliquoted and stored at -80°C . The number of plaque-forming units and particles is quantified following standard protocols known in the prior art. Phosphate-buffered saline (PBS) with 5% glycerol is a standard formulation for storing adenoviruses. However, new formulations improving virus stability have been described. The methods for purifying the adenovirus containing the hyaluronidase gene for use in cancer treatment are the same as those described for other adenoviruses and adenoviral vectors used in the prior art in virotherapy and gene therapy for cancer.

[0042] It will be understood that the composition used in the present invention is used in a pharmaceutically acceptable presentation. This means that said composition may additionally comprise pharmaceutically acceptable excipients.

[0043] The dose of oncolytic adenovirus required can be determined by the person skilled in the art, taking various parameters into account, for example the volume of the vitreous cavity, the volume of the retinoblastoma to be treated or the age and weight of the patient to be treated. It will be understood that the dose must be a therapeutically effective quantity of oncolytic adenovirus in order to produce a positive therapeutic effect on the retinoblastoma, "positive therapeutic effect" meaning the maintenance or reduction of retinoblastoma volume.

[0044] Obviously, the person skilled in the art will adapt the composition depending on the particular method of administration, taking particular account of the route of administration to be used.

[0045] The composition can also be administered in a therapeutic regimen that includes the administration of one or more other anti-tumour agents (such as one or more chemotherapy drugs) and/or one or more of the other aforementioned therapies conventionally used for treating retinoblastoma. The composition used in the present invention in relation to these other therapeutic agents and or therapies can be administered prior to, at the same time as or after the same. When the composition used in the present invention is administered at the same time as one or more other anti-tumour agents, said one or more other anti-tumour agents can be included in the composition used in the present invention or can be administered as separate compositions.

[0046] Alternatively, the composition used in the present invention, comprising the oncolytic adenovirus as explained

above, can be used alone in a therapeutic regimen for treating retinoblastoma, i.e. without using other anti-tumour agents and/or other conventional therapies.

[0047] According to a second aspect, the present invention discloses a composition comprising an oncolytic adenovirus for use for preventing, removing or reducing metastases, secondary malignancies and/or trilateral retinoblastoma associated with retinoblastoma, wherein the aforementioned oncolytic adenovirus comprises:

- a sequence encoding a hyaluronidase enzyme inserted into its genome; and
- replication machinery specific for tumour cells.

[0048] Said composition is injected by any route ensuring that the necessary amount of the adenovirus reaches the interior of the eyeball, preferably by intraocular injection, even more preferably intravitreal injection. Therefore, in a preferred embodiment, the aforementioned composition takes an appropriate form for intravitreal or intraocular administration or injection.

[0049] Another possible route of administration for the composition provided for in the present invention is intratumoral injection.

[0050] In a preferred embodiment, the prevention, removal or reduction of metastases, secondary malignancies and/or trilateral retinoblastoma associated with retinoblastoma takes place in a mammal, preferably a human, more preferably a paediatric human patient.

[0051] In another preferred embodiment, the retinoblastoma treated is a retinoblastoma resistant to conventional chemotherapy and/or radiotherapy treatment; even more preferably said retinoblastoma is refractory or the result of a relapse and is resistant to conventional chemotherapy and/or radiotherapy treatment.

[0052] The oncolytic adenovirus used is the same as has been explained previously.

[0053] The composition and the form in which said composition is used or can be administered is also the same as has been explained previously.

[0054] According to a third aspect, the present invention relates to a composition comprising an oncolytic adenovirus for use thereof in the treatment of retinoblastoma, wherein the aforementioned oncolytic adenovirus comprises:

- a sequence encoding a hyaluronidase enzyme inserted into its genome; and
- replication machinery specific for tumour cells.

[0055] Said composition is injected by any route ensuring that the necessary amount of the adenovirus reaches the interior of the eyeball, preferably by intraocular injection, even more preferably intravitreal injection. Therefore, in a preferred embodiment, the aforementioned composition takes an appropriate form for intravitreal or intraocular administration or injection.

[0056] Another possible route of administration for the composition provided for in the present invention is intratumoral injection.

[0057] In a preferred embodiment, the treatment of retinoblastoma takes place in a mammal, preferably a human, more preferably a paediatric human patient.

[0058] In another preferred embodiment, the retinoblastoma treated is a retinoblastoma resistant to conventional chemotherapy and/or radiotherapy treatment; even more preferably said retinoblastoma is refractory or the result of a relapse and is resistant to conventional chemotherapy and/or radiotherapy treatment.

[0059] The oncolytic adenovirus used is the same as has been explained previously.

[0060] The composition and the form in which said composition is used or can be administered is also the same as has been explained previously.

[0061] According to a fourth aspect, the present invention relates to a composition comprising an oncolytic adenovirus for use thereof in the prevention, removal or reduction of metastases, secondary malignancies and/or trilateral retinoblastoma associated with retinoblastoma, wherein the aforementioned oncolytic adenovirus comprises:

- a sequence encoding a hyaluronidase enzyme inserted into its genome; and
- replication machinery specific for tumour cells.

[0062] Said composition is injected by any route ensuring that the necessary amount of the adenovirus reaches the interior of the eyeball, preferably by intraocular injection, even more preferably intravitreal injection. Therefore, in a preferred embodiment, the aforementioned composition takes an appropriate form for intravitreal or intraocular administration or injection.

[0063] Another possible route of administration for the composition provided for in the present invention is intratumoral injection.

[0064] In a preferred embodiment, the prevention, removal or reduction of metastases, secondary malignancies and/or

trilateral retinoblastoma associated with retinoblastoma takes place in a mammal, preferably a human, more preferably a paediatric human patient.

[0065] In another preferred embodiment, the retinoblastoma treated is a retinoblastoma resistant to conventional chemotherapy and/or radiotherapy treatment; even more preferably said retinoblastoma is refractory or the result of a relapse and is resistant to conventional chemotherapy and/or radiotherapy treatment.

[0066] The oncolytic adenovirus used is the same as has been explained previously.

[0067] The composition and the form in which said composition is used or can be administered is also the same as has been explained previously.

[0068] According to a fifth aspect, the present disclosure relates to a method for treating retinoblastoma in a patient requiring the same, comprising the administration of a therapeutically effective amount of a composition comprising an oncolytic adenovirus, wherein the aforementioned oncolytic adenovirus comprises:

- a sequence encoding a hyaluronidase enzyme inserted into its genome; and
- replication machinery specific for tumour cells.

[0069] Said composition is injected by any route ensuring that the necessary amount of the adenovirus reaches the interior of the eyeball, preferably by intraocular injection, even more preferably intravitreal injection. Therefore, in a preferred embodiment, the aforementioned composition takes an appropriate form for intravitreal or intraocular administration or injection.

[0070] Another possible route of administration for the composition provided for in the present invention is intratumoral injection.

[0071] In a preferred embodiment, the patient requiring treatment of retinoblastoma is a mammal, preferably a human, more preferably a paediatric human patient.

[0072] In another preferred embodiment, the retinoblastoma treated is a retinoblastoma resistant to conventional chemotherapy and/or radiotherapy treatment; even more preferably said retinoblastoma is refractory or the result of a relapse and is resistant to conventional chemotherapy and/or radiotherapy treatment.

[0073] The oncolytic adenovirus used is the same as has been explained previously.

[0074] The composition and the form in which said composition is used or can be administered is also the same as has been explained previously.

[0075] According to a final aspect, the present disclosure relates to a method for preventing, removing or reducing metastases, secondary malignancies and/or trilateral retinoblastoma associated with retinoblastoma in a patient requiring the same, comprising the administration of a therapeutically effective amount of a composition comprising an oncolytic adenovirus, wherein the aforementioned oncolytic adenovirus comprises:

- a sequence encoding a hyaluronidase enzyme inserted into its genome; and
- replication machinery specific for tumour cells.

[0076] Said composition is injected by any route ensuring that the necessary amount of the adenovirus reaches the interior of the eyeball, preferably by intraocular injection, even more preferably intravitreal injection. Therefore, in a preferred embodiment, the aforementioned composition takes an appropriate form for intravitreal or intraocular administration or injection.

[0077] Another possible route of administration for the composition provided for in the present invention is intratumoral injection.

[0078] In a preferred embodiment, the patient requiring prevention, removal or reduction of metastases, secondary malignancies and/or trilateral retinoblastoma associated with retinoblastoma is a mammal, preferably a human, more preferably a paediatric human patient.

[0079] In another preferred embodiment, the retinoblastoma treated is a retinoblastoma resistant to conventional chemotherapy and/or radiotherapy treatment; even more preferably said retinoblastoma is refractory or the result of a relapse and is resistant to conventional chemotherapy and/or radiotherapy treatment.

[0080] The oncolytic adenovirus used is the same as has been explained previously.

[0081] The composition and the form in which said composition is used or can be administered is also the same as has been explained previously.

[0082] The inventors of the present invention have therefore managed to resolve the problems present in the prior art, since they have been able to ascertain that the use of oncolytic adenoviruses having the characteristics mentioned above makes it possible to provide an alternative therapeutic method to those currently available that allows enucleation of the eye to be avoided, and to provide a method that prevents, reduces or avoids the development of metastases, secondary malignancies or trilateral retinoblastoma associated with retinoblastoma.

[0083] For better understanding, the present invention is described in greater detail below with reference to the attached

figures, which are presented by way of example, and with reference to illustrative but nonlimiting examples. Said examples are carried out in cell cultures (in vitro) and in animal models (mouse and rabbit), both recognised and accepted as reliable models representative of retinoblastoma in the scientific world, on the basis of which a person skilled in the art will recognise the direct application of the methods and treatments of the present invention in humans.

Fig. 1 shows the results of the Western blot mentioned in example 2. In said Western blot the expression of the protein E1A is analysed in the various cell lines analysed. Retinal explants were used as a general control and, as a control of expression, the presence of tubulin was measured. In this figure, row 1 shows the expression of E1A and row 2 the expression of tubulin. With regard to the various columns, column A relates to the primary cell line HSJD-RBT1; column B relates to the primary cell line HSJD-RBVS1; column C relates to the primary cell line HSJD-RBT2; column D relates to the primary cell line HSJD-RBVS2, column E relates to the primary cell line HSJD-RBVS3; column F relates to the primary cell line HSJD-RBT5; column G relates to the primary cell line HSJD-RBT7; column H relates to the primary cell line HSJD-RBT8; column I relates to the primary cell line HSJD-RBVS8; column J relates to the cell line Y79; and column K relates to retinal explants.

Fig. 2 shows in graph form the survival of treated eyes and control eyes according to the Kaplan-Meier method for the study described in example 3. Fig. 2A relates to the results obtained by generating orthotopic tumours in mice using the cell line Y79; Fig. 2B relates to the results obtained by generating orthotopic tumours in mice using the primary cell line HSJD-RBT2; Fig. 2C relates to the results obtained by generating orthotopic tumours in mice using the primary cell line HSJD-RBT5; Fig. 2D relates to the results obtained by generating orthotopic tumours in mice using the primary cell line HSJD-RBVS1; Fig. 2E relates to the results obtained by generating orthotopic tumours in mice using the primary cell line HSJD-RBT7; and Fig. 2F relates to the results obtained by generating orthotopic tumours in mice using the primary cell line HSJD-RBVS8.

Fig. 3 shows in graph form the survival of treated eyes and control eyes according to the Kaplan-Meier method for the study described in example 4. Fig. 3A relates to the results obtained by generating orthotopic tumours in mice using the cell line Y79; Fig. 3B relates to the results obtained by generating orthotopic tumours in mice using the primary cell line HSJD-RBT-002; and Fig. 3C relates to the results obtained by generating orthotopic tumours in mice using the primary cell line HSJD-RBT-005.

Fig. 4 shows in graph form the survival of treated eyes and control eyes according to the Kaplan-Meier method for the study described in example 5.

Fig. 5 shows in graph form the survival of treated eyes and control eyes according to the Kaplan-Meier method for the study described in example 6.

Example 1. Generation of the oncolytic adenovirus VCN-01

[0084] The cDNA of hyaluronidase PH20 was obtained by PCR amplification (polymerase chain reaction amplification technique) of the various exons of the protein from the genome of the cell line A549 and subsequent binding of these exons with specific oligonucleotides that contain the target of the restriction enzyme MfeI. The resulting fragment was digested with MfeI and cloned by ligation in the shuttle plasmid, pNKFiberRGD (containing the sequence of the adenovirus fibre modified with RGD), to generate the plasmid pNKFiberPH20. The cDNA corresponding to the PH20 protein cloned in the plasmid pNKFiberPH20 is shown in SEQ ID NO: 1. SEQ ID NO: 1 shows the nucleotides coding for the PH20 protein from the start of its transcription (ATG) to position 1470. The nucleotide sequence of region 1471 to 1527 encodes for the hydrophobic tail of the protein, which is responsible for anchoring it to the membrane. Said sequence was deleted. After the position 1470 the translation stop codon TAA was added.

[0085] To generate the plasmid pAdwtRGD-PH20, the adenovirus fibre gene of the plasmid pVK50cau (which contains the complete Ad5 sequence with a Swal target in the fibre) was replaced by homologous recombination in yeast, according to procedures known in the prior art, by the fibre gene followed by the hyaluronidase PH20 gene of the plasmid pNKFiberPH20 digested with NotI/KpnI.

[0086] The adenoviral plasmid pICOVIR17 was used to generate the adenovirus ICOVIR17 (SEQ ID NO: 17). To generate this plasmid, the adenovirus fibre gene of the plasmid pICOVIR15 was replaced by homologous recombination in yeast by the fibre gene followed by the hyaluronidase PH20 gene of the plasmid pAdwtRGD-PH20 digested with SpeI/PacI.

[0087] The adenovirus ICOVIR15 (SEQ ID NO: 4) comes from the adenovirus Ad Δ 24RGD, characterised by containing the deletion Δ 24 in the sequence coding for the protein E1a. This deletion affects the interaction of E1a with the retinoblastoma protein. Ad Δ 24RGD also has the insertion of the RGD peptide in the adenovirus fibre, to increase the infectivity

of the virus. These two modifications were described in K. Suzuki et al., "A conditionally replicative adenovirus with enhanced infectivity shows improved oncolytic potency", Clin Cancer Res 2001, vol. 7, pp. 120-6. Starting from AdΔ24RGD, four binding sites to E2F-1 and one binding site to Sp1 were inserted into the endogenous E1a promoter to control the expression of E1a. In this way ICOVIR15 was obtained. This insertion was carried out by replacing the sequence 419-422 of the genome by the sequence with the four binding sites to E2F-1 and one binding site to Sp1, such that the final sequence is that shown in SEQ ID NO: 4. To do this, a single cleavage site BsiWI was created by mutagenesis directed to the E1A promoter of pEndK/Spe (J. E. Carette et al., "Conditionally replicating adenoviruses expressing short hairpin RNAs silence the expression of a target gene in cancer cells", Cancer Res 2004, vol. 64, pp. 2663-7). The binding site to Sp1 was introduced into the pEndK/Spe plasmid with the site BsiWI by ligation of said plasmid digested with BsiWI with the oligonucleotides Sp1F (SEQ ID NO: 5 - 5'-GTACGTCGACCACAAACCCCGCCAGCGTCTTGTTCATTGGCGTCGACGCT-3') and Sp1R (SEQ ID NO: 6 - 5'-GTACAGCGTCGACGCCAATGACAAGACGCTGGGCGGGGTTTGTGG TCGAC-3') paired together. The binding sites to E2F were introduced by means of binding the oligonucleotides E2FF2 (SEQ ID NO: 7 - 5'-GTACGTCGGCGGCTCGTGGC TCTTTCGCGGCAAAAAGGATTTGGCGCGTAAAAGTGGTTCGAA-3') and E2FR2 (SEQ ID NO: 8 - 5'-GTACTTCGAACCACTTTTACGCGCCAAATCCTTTTGGCGCGAAAGAGCCAC GAGCCGCCGAC-3') paired together, to create the plasmid pEndK415Sp1 E2F2. Next, the CAU sequence, which contains the elements required for plasmid replication in yeast - a centromere, the autonomous recombination sequence ARS and the selection marker URS3 - was introduced by homologous recombination in yeast, to create the plasmid pEndK415Sp1 E2F2CAU. Finally, homologous recombination in yeast of the plasmid pEndK415Sp1 E2F2CAU, digested with KpnI, with the adenoviral genome of the adenovirus AdΔ24RGD, was carried out to construct pICOVIR15cau. ICOVIR15 was obtained by transfection of PacI digestion of pICOVIR15cau to HEK293 cells (ATCC reference number CRL-1573).

[0088] The adenovirus ICOVIR17, which contains the same modifications as ICOVIR15, plus the insertion of the hyaluronidase gene after the adenovirus fibre gene, was generated by digestion with PacI of the pICOVIR17 plasmid and transfection into HEK293 cells.

[0089] The adenovirus VCN-01 was generated using the adenoviral plasmid pICOVIR17RGDK. In this plasmid the native adenovirus serotype 5 fibre gene has been replaced by a modified version in its heparan sulfate binding domain (amino acids ⁹¹KKTK⁹⁴ of the polypeptide sequence replaced by ⁹¹RGDK⁹⁴). The plasmid pICOVIR17RGDK was constructed by homologous recombination in yeast between the partial digestion product of pICOVIR17 with NdeI and digestion with EcoRI of the plasmid pBSattKKT (containing the modified version of the adenovirus fibre described in N. Bayó-Puxan et al. "Replacement of adenovirus type 5 fiber shaft heparan sulfate proteoglycan-binding domain with RGD for improved tumor infectivity and targeting". Human Gene Therapy 2009, vol. 20, pp 1214-21).

[0090] The sequence SEQ ID NO: 9 shows the complete sequence of the adenovirus serotype 5 fibre protein with the modified version in its heparan sulfate binding domain (modification RGDK). The adenovirus ICOVIR17 contains a version of the adenovirus fibre gene into which the peptide RGD-4C has been inserted (Cys-Asp-Cys-Arg-Gly-Asp-Cys-Phe-Cys; CDCRGDCFC; SEQ ID NO: 10) into the HI region of the knob domain of the protein (hypervariable loop of the adenovirus capsid, evolutionarily non-conserved and highly exposed). VCN-01 is completely analogous to ICOVIR17 apart from the fibre gene, since in this case the VCN-01 fibre differs only from the native form of human adenovirus serotype 5 in that the amino acids ⁹¹KKTK⁹⁴ have been replaced by the peptide with a high affinity for integrins ⁹¹RGDK⁹⁴, in the shaft domain of the protein.

Example 2. Cytotoxicity in primary cultures of retinoblastoma refractory to conventional treatment with chemotherapy and/or radiotherapy.

[0091] First, IC₅₀ was studied in various primary cultures obtained from retinoblastomas showing resistance to conventional chemotherapy and/or radiotherapy treatment. The cell line Y79 (ATCC reference number HTB-18) was also analysed.

[0092] To obtain the various primary cultures, tumour samples were first taken from enucleated eyes of patients with retinoblastoma at the Sant Joan de Deu Hospital (HSJD, Barcelona), under a protocol approved by the corresponding Ethics Committee and with an Informed Consent. The specimens were collected from two possible sources: solid tumour tissue in the retina (retinoblastoma tumour; RBT) or from the tumour seeds in the vitreous body (retinoblastoma vitreous seedings; RBVS). To obtain cell suspensions of the RBT specimens, these were disaggregated using a mixture of collagenase (5 mg/mL) and DNase (40 Kunitz units/mL) (Sigma, St Louis, MO) at 37°C for 5 min; cells from RBVS samples were collected by centrifugation. After two washes with PBS, the tumour cells were cultured as tumour-spheres floating in a serum-free neural stem cell medium.

[0093] To determine the IC₅₀ values of VCN-01, tests were carried out with each line on 96-well plates seeded with 5000 cells per well. After being cultured for 24 hours, the cells were exposed to increasing doses of VCN-01 for 11-14 days in triplicate. At this point the metabolic activity of each well was determined using the reagent MTS (Promega, Fitchburg, WI, USA) and according to procedures known in the prior art. Based on these values and using Graphpad

Prism 5 software (La Jolla, CA, USA), the concentration of VCN-01 that was causing a 50% decrease in cell proliferation (IC_{50} value) was calculated.

Table 1. IC_{50} results obtained in primary cultures of retinoblastoma refractory to conventional chemotherapy and/or radiotherapy treatment; and in the cell line Y79.

Cell model	IC_{50} (TU/cell) (95% confidence interval)
HSJD-RBT-1	5.47 (4.81-6.21)
HSJD-RBVS-1	>100 (not sensitive)
HSJD-RBT-2	8.01 (5.69-11.29)
HSJD-RBVS-3	2.97 (1.60-5.50)
HSJD-RBT-5	0.0825 (0.0489-0.139)
HSJD-RBT-7	8.82 (4.29-18.14)
HSJD-RBT-8	27.29 (21.73-34.03)
Y79	0.0809 (0.0662-0.0988)

[0094] As can be seen in Table 1, VCN-01 demonstrated great cytotoxicity in all the cell lines tested except for one (HSJD-RBVS1), from which it can be deduced that not only can said oncolytic adenovirus correctly infect a large number of primary cell lines derived from retinoblastoma but that it also has high cytotoxic activity in them.

[0095] Furthermore, expression of the adenoviral protein E1A was analysed 24 hours from infection of the cell lines by Western blotting (said expression indicated that the defective replication machinery of VCN-01 was correctly complemented by the machinery of the corresponding tumour cell). As can be seen in Fig. 1, expression of the protein E1A was observed in all the cell lines mentioned above apart from the cell line HSJD-RBVS1, which agrees or correlates with the IC_{50} results obtained and shown in Table 1.

Example 3. Anti-tumour activity in various orthotopic models of human retinoblastoma in mice treated with an injection of VCN-01 or vehicle.

[0096] Female athymic mice (Hsd:Athymic Nude-Foxn1nu) aged 6 weeks were injected with 200,000 cells of the corresponding primary cell line or the cell line Y79 in 2 μ L Matrigel, into the vitreous cavity of both eyes. On the eighth day, an intravitreal injection of the 100x dose of VCN-01 (2 μ L with a total content of 3×10^9 virus particles per eye) was applied to the right eyes of each animal. The contralateral (left) eyes were injected by the intravitreal route with the vehicle in which VCN-01 (20 mM Tris pH 8.0 25 mM NaCl, 2.5% glycerol) had been diluted.

[0097] The distribution of mice in each of the experimental groups was as indicated in Table 2.

Table 2. Experimental groups and number of mice per study group in example 3.

Group (cell line with which the orthotopic tumour is generated in the eyes of the mice)	Number of mice in the treated group
Cell line Y79	17
HSJD-RBT2	6
HSJD-RBT5	6
HSJD-RBVS1	6
HSJD-RBT7	6
HSJD-RBVS8	5

[0098] In this case, what was studied was the survival of the treated and control eyes, i.e. the number of days until the size of the retinoblastoma required enucleation of said eye.

[0099] As can be seen in Fig. 2, eyes treated with the adenovirus VCN-01 survive in greater numbers and for a longer time in all the groups analysed (that is to say, irrespective of the cell line used for implanting the orthotopic tumour in the mouse eye, a significant improvement was observed when applying treatment with the adenovirus VCN-01).

Example 4. Anti-tumour activity in various orthotopic models of human retinoblastoma in mice treated with two injections of VCN-01 or vehicle.

[0100] Female athymic mice (Hsd:Athymic Nude-Foxn1nu) aged 6 weeks were injected with 200,000 cells of the corresponding primary cell line or the cell line Y79 in 2 μ L Matrigel, into the vitreous cavity of each eye. On the eighth day, an intravitreal injection of the 100x dose of VCN-01 (2 μ L with a total content of 3×10^9 virus particles) was applied to both eyes of the mice in the treated group, and the mice of the other group (control group) were given an intravitreal injection of vehicle (20 mM Tris pH 8.0, 25 mM NaCl, 2.5% glycerol) into each eye. On the twenty-second day, the therapeutic procedure was repeated, i.e. an intravitreal injection of the 100x dose of VCN-01 (2 μ L with a total content of 3×10^9 virus particles) was applied to both eyes of the mice in the treated group, and the mice of the other group (control group) were given an intravitreal injection of the same vehicle also into both eyes.

[0101] The distribution of mice in each of the experimental groups was as indicated in Table 3.

Table 3. Experimental groups and number of mice per study group in example 4.

Group (cell line with which the orthotopic tumour is generated in the eyes of the mice)	Number of mice in the control group	Number of mice in the treated group
Cell line Y79	6	6
HSJD-RBT2	6	6
HSJD-RBT5	6	6

[0102] In this case too, the survival of the treated and control eyes was studied, i.e. the number of days until the size of the retinoblastoma required enucleation of said eye.

[0103] As can be seen in Fig. 3, eyes treated with the adenovirus VCN-01 survive in greater numbers and for a longer time in all the groups analysed (that is to say, irrespective of the cell line used for implanting the orthotopic tumour in the mouse eye, a significant improvement was observed when applying treatment with the adenovirus VCN-01).

Example 5. Dose escalation study of VCN-01 in mice.

[0104] Female athymic mice (Hsd:Athymic Nude-Foxn1nu) aged 6 weeks were injected with 200,000 cells of the primary cell line HSJD-RBT2 (day 0) in 2 μ L Matrigel. Next, said mice were treated according to the following groups and the following regimen:

Table 4. Groups and treatment days in the study in example 5. The days are indicated by taking day 0 to be the day when the cells of the primary line of retinoblastoma are injected or implanted to generate the orthotopic tumours.

Group (treatment applied)	Number of mice in the group	Injection days (for VCN-01 and vehicle) / Chemotherapy days
Vehicle (control group; 20 mM Tris pH 8.0 25 mM NaCl, 2.5% glycerol)	7	8 and 22
Systemic chemotherapy (Carboplatin/ Etoposide) (6 mg/kg etoposide and 34 mg/kg carboplatin)	7	8, 29 and 50
VCN-01 dose 100x (3×10^9 virus particles per eye)	6	8 and 22
VCN-01 dose 10x (3×10^8 virus particles per eye)	7	8 and 22
VCN-01 dose 3x (1×10^8 virus particles per eye)	7	8 and 22
VCN-01 dose 1x (3×10^7 virus particles per eye)	7	8 and 22

[0105] The parameter analysed was the survival of the treated and control eyes, i.e. the number of days until the size of the retinoblastoma required enucleation of said eye.

[0106] The results obtained are summarised in Fig. 4. As can be seen in said figure, all the tested doses of VCN-01 gave significantly better results for eye survival than the control or chemotherapy treatment groups. In addition, it was possible to ascertain, surprisingly, that the dose that offered greatest survival of the eye for a longer time was 10x.

Example 6. Dose escalation study of VCN-01 in mice.

[0107] Female athymic mice (Hsd:Athymic Nude-Foxn1nu) aged 6 weeks were injected with 200,000 cells of the primary cell line HSJD-RBT2 (day 0) in 2 μ L Matrigel. Next, said mice were treated according to the following groups and the following regimen:

Table 5. Groups and treatment days in the study in example 5. The days are indicated by taking day 0 to be the day when the cells of the primary line of retinoblastoma are injected or implanted to generate the orthotopic tumours.

Group (treatment applied)	Number of mice in the group	Injection days (for VCN-01 and vehicle) / Chemotherapy days
Vehicle (control group; 20 mM Tris pH 8.0 25 mM NaCl, 2.5% glycerol)	8	8 and 22
Intravitreal chemotherapy (Melphalan; 0.033 μ g in 2 μ L per eye)	5	8 and 22
VCN-01 HIGH dose (3×10^8 virus particles per eye) (10x VCN-01)	7	8 and 22
VCN-01 LOW dose (3×10^7 virus particles per eye) (1x VCN-01)	8	8 and 22
VCN-01 VERY LOW dose (3×10^8 virus particles per eye) (1x/10 VCN-01)	8	8 and 22
VCN-01 ULTRA LOW dose (3×10^5 virus particles per eye) (1x/100 VCN-01)	8	8 and 22

[0108] The parameter analysed was the survival of the treated and control eyes, i.e. the number of days until the size of the retinoblastoma required enucleation of said eye.

[0109] The results obtained are summarised in Fig. 5. As can be seen in said figure, all the doses revealed a superior result compared with the control group. Furthermore, the HIGH and LOW doses also demonstrated a superior effect at the end of treatment than the group treated with intravitreal chemotherapy.

[0110] Although the invention has been described in relation to preferred embodiments, these should not be considered to limit the invention, which is to be defined by the broadest interpretation of the following claims.

Example 7. Analysis of the influence of VCN-01 on brain metastases in retinoblastoma in mice.

[0111] Extraocular extension of retinoblastoma to the central nervous system (CNS) is fatal for patients.

[0112] To carry out this study an orthotopic model of retinoblastoma was used. Use was made of brains from the mice in Examples 5 and 6, female athymic nude mice (Hsd:Athymic Nude-Foxn1^{nu} strain - Harlan Laboratories, Gannat, France), aged 6 weeks, which received an injection into the posterior segment of each eye, of 2×10^5 cells HSJD-RBT2 (primary culture of cells mentioned above and obtained from the eye of a retinoblastoma patient resistant to chemotherapy).

Table 6. Brains analysed in the study in Example 7, with details of the treatment applied to each of the mice from which the brains were extracted.

Group	Treatment	Dose	Route of administration	Number of brains
1	Vehicle (negative control)	2 μ L per eye	Intravitreal	14
2	Systemic chemotherapy (positive control)	6 mg/kg etoposide and 34 mg/kg carboplatin	Intraperitoneal	5

(continued)

Group	Treatment	Dose	Route of administration	Number of brains
3	Reference dose of VCN-01 (100x VCN-01)	3×10^9 virus particles in 2 μ L per eye (5.7×10^8 TU)	Intravitreal	6
4	High dose of VCN-01 (10x VCN-01)	3×10^8 virus particles in 2 μ L per eye (5.7×10^7 TU)	Intravitreal	11
5	Intermediate dose of VCN-01 (3x VCN-01)	1×10^8 virus particles in 2 μ L per eye (1.9×10^7 TU)	Intravitreal	7
6	Low dose of VCN-01 (1x VCN-01)	3×10^7 virus particles in 2 μ L per eye (5.7×10^6 TU)	Intravitreal	14
7	Very low dose of VCN-01 (1x/10 VCN-01)	3×10^8 virus particles in 2 μ L per eye (5.7×10^5 TU)	Intravitreal	6
8	Ultra-low dose of VCN-01 (1x/100 VCN-01)	3×10^8 virus particles in 2 μ L per eye (5.7×10^4 TU)	Intravitreal	5

[0113] The therapeutic regimen applied to each of the groups mentioned in Table 6 (by way of reference, the cell injection day was -7) was:

- Group 1 (Vehicle): injection on days 1 and 15.
- Group 2 (Systemic chemotherapy): injection of etoposide on days 1, 2 and 3 and injection of carboplatin on day 1. The same administration regimen was repeated on days 22, 23 and 24; and 43, 44 and 45.
- Groups 3 to 8 (administration of different doses of VCN-01). Injection on days 1 and 15.

[0114] The presence of human retinoblastoma cells in the brains mentioned in Table 6 was evaluated. Said evaluation was performed by measuring the amount of CRX messenger ribonucleic acid (mRNA) by means of real-time polymerase chain reaction. For this, total ribonucleic acid (RNA) from the brains of the mice was extracted using TRIzol (Life Technologies, Waltham, MA, USA). Next, complementary deoxyribonucleic acid (cDNA) was synthesised with the M-MLV reverse transcriptase system (Life Technologies, Waltham, MA, USA) using 1 μ g of the RNA extracted. The amount of CRX mRNA was measured using the common protocol known in the prior art for the real-time polymerase chain reaction; specifically, a reaction was prepared with a volume of 10 μ L, using the SYBR® Green PCR Master Mix (Life Technologies, Waltham, MA, USA); the primers and probe shown in Table 7 were used; and the 7500 Sequence Detection System (Applied Biosystems, Foster City, CA, USA) was used to detect the signals in the various cycles of the real-time polymerase chain reaction (first stage of 10 min at 95°C, followed by 40 cycles of 15 s at 95°C and 1 min at 60°C).

[0115] As a control, for normalisation of CRX gene expression, the mRNA of the TATA box binding protein (TBP) was used. Its expression was measured in accordance with the protocol indicated above and known in the prior art, and using the primers and probe indicated in Table 7 for that purpose.

Table 7. Primers and probe used in the real-time polymerase chain reaction to measure the expression of CRX and TBP.

Type	Gene	Sequence	SEQ ID NO:
Forward primer	CRX	5'-AGGTGGCTCTGAAGATCAATCTG-3'	11
Reverse primer	CRX	5'-TTAGCCCTCCGGTTCTTGAA-3'	12
Probe	CRX	5'-FAM-CTGAGTCCAGGGTTC-MGB-3'	13
Forward primer	TBP	5'-GAACATCATGGATCAGAACAACAG-3'	14
Reverse primer	TBP	5'-ATTGGTGTCTGAATAGGCTGTG-3'	15
Probe	TBP	5'-FAM-CTGCCACCTTACGCTCAGGGCTTGG-TAMRA-3'	16

[0116] The signals obtained were processed by the $2^{-\Delta\Delta C_t}$ method, in order to determine the positive brain samples and the negative brain samples. The results obtained are summarised in table 8

Table 8. Results obtained in the analysis of retinoblastoma brain metastases for the various groups of mice analysed in Example 7.

Group	Treatment	Number of available brains analysed	Number of brains with metastasis
1	Vehicle (negative control)	14	6
2	Systemic chemotherapy (positive control)	5	4
3	Reference dose of VCN-01	6	0
4	High dose of VCN-01	11	0
5	Intermediate dose of VCN-01	7	0
6	Low dose of VCN-01	14	3
7	Very low dose of VCN-01	6	1
8	Ultra-low dose of VCN-01	5	0

[0117] As can be deduced from Table 8, only four of the 49 mice treated with the various doses of VCN-01 (8%) showed signs of metastasis in the CNS (i.e. human retinoblastoma cells could be detected in the brains of said mice), while 43% of the negative controls and 80% of the mice treated with systemic chemotherapy had metastases in the CNS. None of the mice treated with an intermediate, high and reference dose of VCN-01 developed metastases.

[0118] It can therefore be concluded that, in a surprising manner, VCN-01 prevented the spread of retinoblastoma to the CNS.

SEQUENCE LISTING

[0119]

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<120> Use of viral vectors in the treatment of retinoblastoma

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<170> PatentIn version 3.5

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<210> 2

<211> 1406

<212> DNA

<213> Artificial Sequence

<220>

<223> Sequence of the modified endogenous promoter of E1a + encoding Ela-Delta24 region in VCN-01 (comprising the four binding sites to E2F-1, the binding site to Sp1 and the encoding region of Ela-Delta24)

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<400> 2

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<210> 3

50 <211> 37607

<212> DNA

<213> Artificial Sequence

<220>

55 <223> Complete sequence of VCN-01 (ICOVIR-17K)

<400> 3

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45

50

55

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55	acaacattac	agcccccata	ggagggtataa	caaaattaat	aggagagaaa	aacacataaa	37140
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 15 tattattgat gatg 37634

Claims

- 20 1. Composition comprising an oncolytic adenovirus for use in the treatment of retinoblastoma in the prevention, removal or reduction of metastases, secondary malignancies and/or trilateral retinoblastoma associated with retinoblastoma, **characterised in that** said oncolytic adenovirus comprises:
 - 25 - a sequence encoding a hyaluronidase enzyme inserted into its genome; and
 - replication machinery specific for tumour cells.
2. Composition comprising an oncolytic adenovirus for use according to claim 1, **characterised in that** the composition is administered by intraocular or intravitreal injection.
- 30 3. Composition comprising an oncolytic adenovirus for use according to either claim 1 or claim 2, **characterised in that** the retinoblastoma is a retinoblastoma resistant to conventional chemotherapy and/or radiotherapy treatment.
4. Composition comprising an oncolytic adenovirus for use according to claim 3, **characterised in that** the retinoblastoma resistant to conventional chemotherapy and/or radiotherapy treatment is refractory or the result of a relapse.
- 35 5. Composition comprising an oncolytic adenovirus for use according to any one of claims 1 to 4, **characterised in that** the oncolytic adenovirus is generated from a human adenovirus serotype 5.
6. Composition comprising an oncolytic adenovirus for use according to any one of claims 1 to 5, **characterised in that** the hyaluronidase enzyme is the human hyaluronidase enzyme PH20.
- 40 7. Composition comprising an oncolytic adenovirus for use according to claim 6, **characterised in that** the aforementioned sequence that encodes a hyaluronidase enzyme is SEQ ID NO: 1, from which nucleotides 1471 to 1527, corresponding to the carboxy-terminal domain, have been deleted.
- 45 8. Composition comprising an oncolytic adenovirus for use according to any one of claims 1 to 7, **characterised in that** the replication machinery specific for tumour cells is defective replication machinery that can be complemented in tumour cells by both defective copies of the Rb1 gene.
- 50 9. Composition comprising an oncolytic adenovirus for use according to claim 8, **characterised in that** the defective replication machinery that can be complemented in tumour cells by both defective copies of the Rb1 gene comprises the deletion $\Delta 24$ in the sequence coding for the E1a protein and the insertion of four binding sites to E2F-1 and one binding site to Sp1 into the endogenous promoter of E1a to control the expression of E1a.
- 55 10. Composition comprising an oncolytic adenovirus for use according to any one of claims 2 to 9, **characterised in that** the oncolytic adenovirus used in the present invention has the capsid modified such that the binding domain ⁹¹KKTK⁹⁴ of the heparan sulfates present in the adenovirus fibre has been replaced by the domain ⁹¹RGDK⁹⁴.

Patentansprüche

1. Zusammensetzung, umfassend ein onkolytisches Adenovirus zur Verwendung bei der Behandlung von Retinoblastom bei der Prävention, dem Entfernen oder der Verringerung von Metastasen, sekundären bösartigen Tumoren und/oder einem trilateralen Retinoblastom, das mit dem Retinoblastom assoziiert ist, **dadurch gekennzeichnet, dass** das onkolytische Adenovirus das Folgende umfasst:
 - eine Sequenz, die für ein Hyaluronidase-Enzym kodiert, das in sein Genom inseriert ist; und
 - eine Replikationsmaschinerie, die für Tumorzellen spezifisch ist.
2. Zusammensetzung, umfassend ein onkolytisches Adenovirus, zur Verwendung nach Anspruch 1, **dadurch gekennzeichnet, dass** die Zusammensetzung durch intraokuläre oder intravitreale Injektion verabreicht wird.
3. Zusammensetzung, umfassend ein onkolytisches Adenovirus, zur Verwendung nach Anspruch 1 oder Anspruch 2, **dadurch gekennzeichnet, dass** das Retinoblastom ein Retinoblastom ist, das gegen konventionelle Chemotherapie- und/oder Strahlentherapiebehandlung resistent ist.
4. Zusammensetzung, umfassend ein onkolytisches Adenovirus, zur Verwendung nach Anspruch 3, **dadurch gekennzeichnet, dass** das Retinoblastom, das gegen konventionelle Chemotherapie- und/oder Strahlentherapiebehandlung resistent ist, refraktär oder das Ergebnis eines Rückfalls ist.
5. Zusammensetzung, umfassend ein onkolytisches Adenovirus, zur Verwendung nach einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet, dass** das onkolytische Adenovirus aus einem menschlichen Adenovirus vom Serotyp 5 hergestellt ist.
6. Zusammensetzung, umfassend ein onkolytisches Adenovirus, zur Verwendung nach einem der Ansprüche 1 bis 5, **dadurch gekennzeichnet, dass** das Hyaluronidase-Enzym das menschliche Hyaluronidase-Enzym PH20 ist.
7. Zusammensetzung, umfassend ein onkolytisches Adenovirus, zur Verwendung nach Anspruch 6, **dadurch gekennzeichnet, dass** die vorgenannte Sequenz, die für ein Hyaluronidase-Enzym kodiert, SEQ ID NO: 1 ist, aus der die Nukleotide 1471 bis 1527, die der carboxyterminalen Domäne entsprechen, deletiert wurden.
8. Zusammensetzung, umfassend ein onkolytisches Adenovirus, zur Verwendung nach einem der Ansprüche 1 bis 7, **dadurch gekennzeichnet, dass** die Replikationsmaschinerie, die für Tumorzellen spezifisch ist, eine defekte Replikationsmaschinerie ist, die in Tumorzellen durch beide defekten Kopien des Rb1-Gens komplementiert werden kann.
9. Zusammensetzung, umfassend ein onkolytisches Adenovirus, zur Verwendung nach Anspruch 8, **dadurch gekennzeichnet, dass** die defekte Replikationsmaschinerie, die in Tumorzellen durch die beiden defekten Kopien des Rb1-Gens komplementiert werden kann, die Deletion $\Delta 24$ in der Sequenz, die für das E1a-Protein kodiert, und die Insertion von vier Bindungsstellen für E2F-1 und einer Bindungsstelle für Sp1 in den endogenen Promotor von E1a umfasst, um die Expression von E1a zu regulieren.
10. Zusammensetzung, umfassend ein onkolytisches Adenovirus, zur Verwendung nach einem der Ansprüche 2 bis 9, **dadurch gekennzeichnet, dass** bei dem in der vorliegenden Erfindung verwendeten onkolytischen Adenovirus das Kapsid so modifiziert ist, dass die Bindungsdomäne ⁹¹KKTK⁹⁴ der Heparansulfate, die in der Adenovirusfaser vorliegt, durch die Domäne ⁹¹RGDK⁹⁴ ersetzt worden ist.

Revendications

1. Composition comprenant un adénovirus oncolytique pour une utilisation dans le traitement d'un rétinoblastome lors de la prévention, de l'enlèvement ou de la réduction de métastases, de malignités secondaires et/ou de rétinoblastome trilatéral associé avec un rétinoblastome, **caractérisée en ce que** ledit adénovirus comprend :
 - une séquence encodant un enzyme de hyaluronidase insérée dans son génome, et
 - un mécanisme de répllication spécifique pour les cellules tumorales.

2. Composition comprenant un adénovirus oncolytique pour une utilisation selon la revendication 1, **caractérisée en ce que** la composition est administrée par injection intraoculaire ou intravitréenne.
3. Composition comprenant un adénovirus oncolytique pour une utilisation selon l'une ou l'autre de la revendication 1 ou de la revendication 2, **caractérisée en ce que** le rétinoblastome est un rétinoblastome résistant à la chimiothérapie conventionnelle et/ou au traitement de radiothérapie.
4. Composition comprenant un adénovirus oncolytique pour une utilisation selon la revendication 3, **caractérisée en ce que** le rétinoblastome résistant à la chimiothérapie conventionnelle et/ou au traitement de radiothérapie est réfractaire ou le résultat d'une récurrence.
5. Composition comprenant un adénovirus oncolytique pour une utilisation selon l'une quelconque des revendications 1 à 4, **caractérisée en ce que** l'adénovirus est généré à partir d'un adénovirus humain de sérotype 5.
6. Composition comprenant un adénovirus oncolytique pour une utilisation selon l'une quelconque des revendications 1 à 5, **caractérisée en ce que** l'enzyme de hyaluronidase est l'enzyme de hyaluronidase humain PH20.
7. Composition comprenant un adénovirus oncolytique pour une utilisation selon la revendication 6, **caractérisée en ce que** la séquence mentionnée précédemment qui encode un enzyme de hyaluronidase est SEQ ID NO :1, de laquelle les nucléotides 1471 à 1527, correspondant au domaine carboxy-terminal, ont été supprimés.
8. Composition comprenant un adénovirus oncolytique pour une utilisation selon l'une quelconque des revendications 1 à 7, **caractérisée en ce que** le mécanisme de réplication pour des cellules tumorales est un mécanisme incapable de se répliquer qui peut être complété dans les cellules tumorales par les deux copies défectueuses du gène Rb1.
9. Composition comprenant un adénovirus oncolytique pour une utilisation selon la revendication 8, **caractérisée en ce que** le mécanisme incapable de se répliquer qui peut être complété dans des cellules tumorales par les deux copies défectueuses du gène Rb1 comprend la suppression $\Delta 24$ dans la séquence codant pour la protéine E1a et l'insertion de quatre sites de liaison à E2F-1 et d'un site de liaison à Sp1 dans le promoteur endogène de E1a pour contrôler l'expression de E1a.
10. Composition comprenant un adénovirus oncolytique pour une utilisation selon l'une quelconque des revendications 2 à 9, **caractérisée en ce que** l'adénovirus oncolytique utilisé dans la présente invention comprend une modification du capsid de telle sorte que le domaine de liaison ⁹¹KKTK⁹⁴ des sulfates d'héparine présent dans la fibre de l'adénovirus a été remplacé par le domaine ⁹¹RGDK⁹⁴.

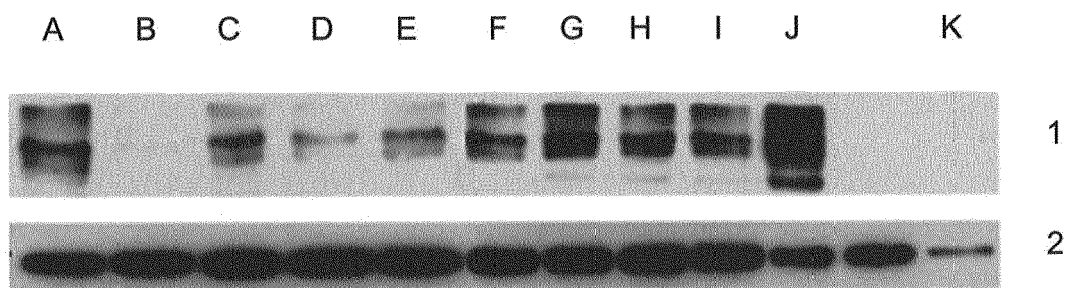


Figure 1

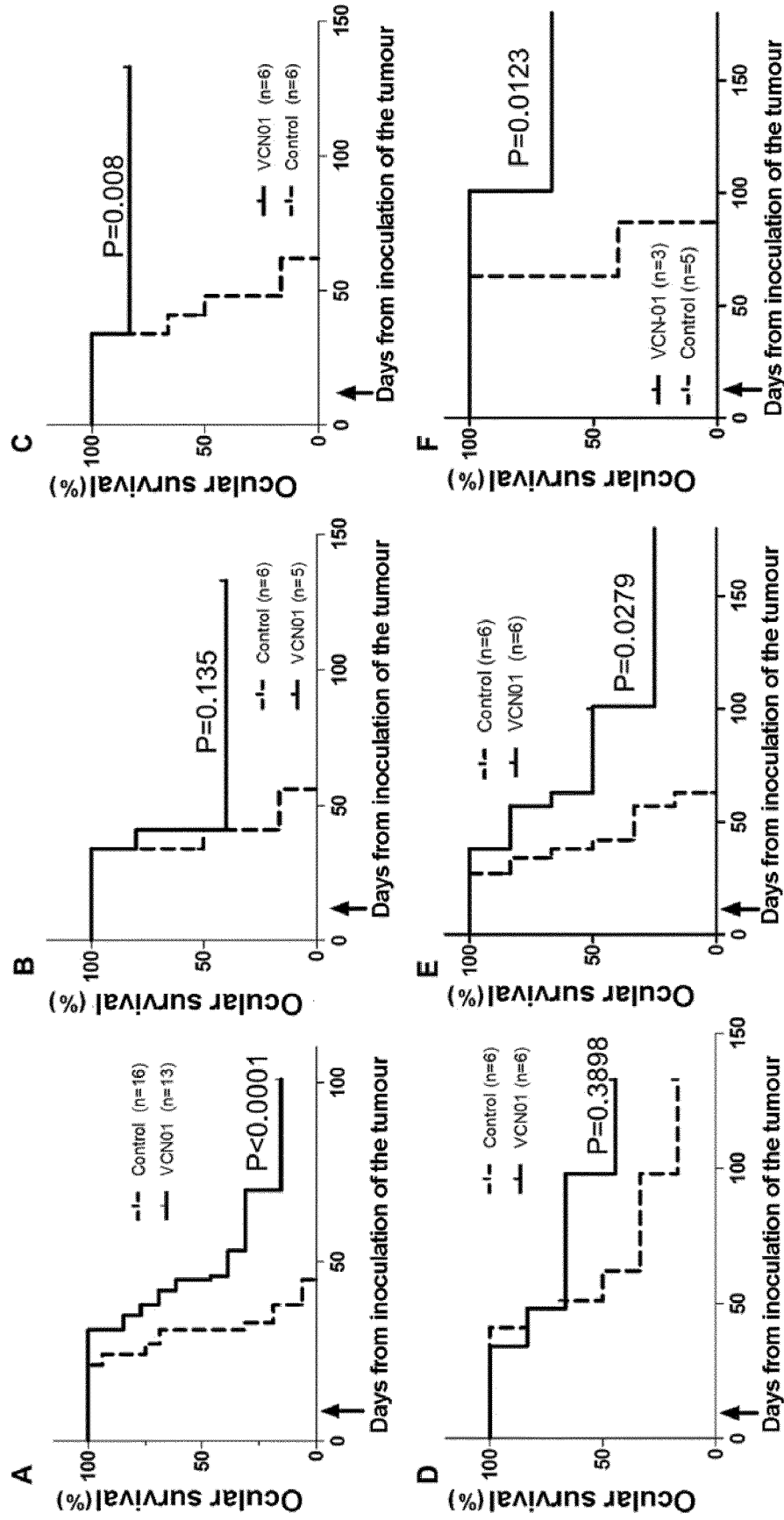


Figure 2

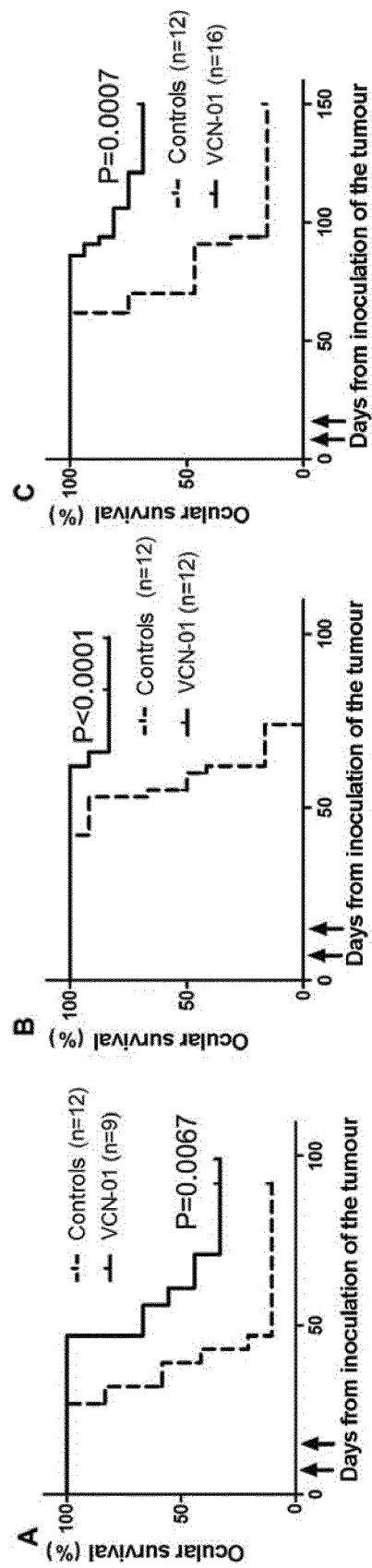


Figure 3

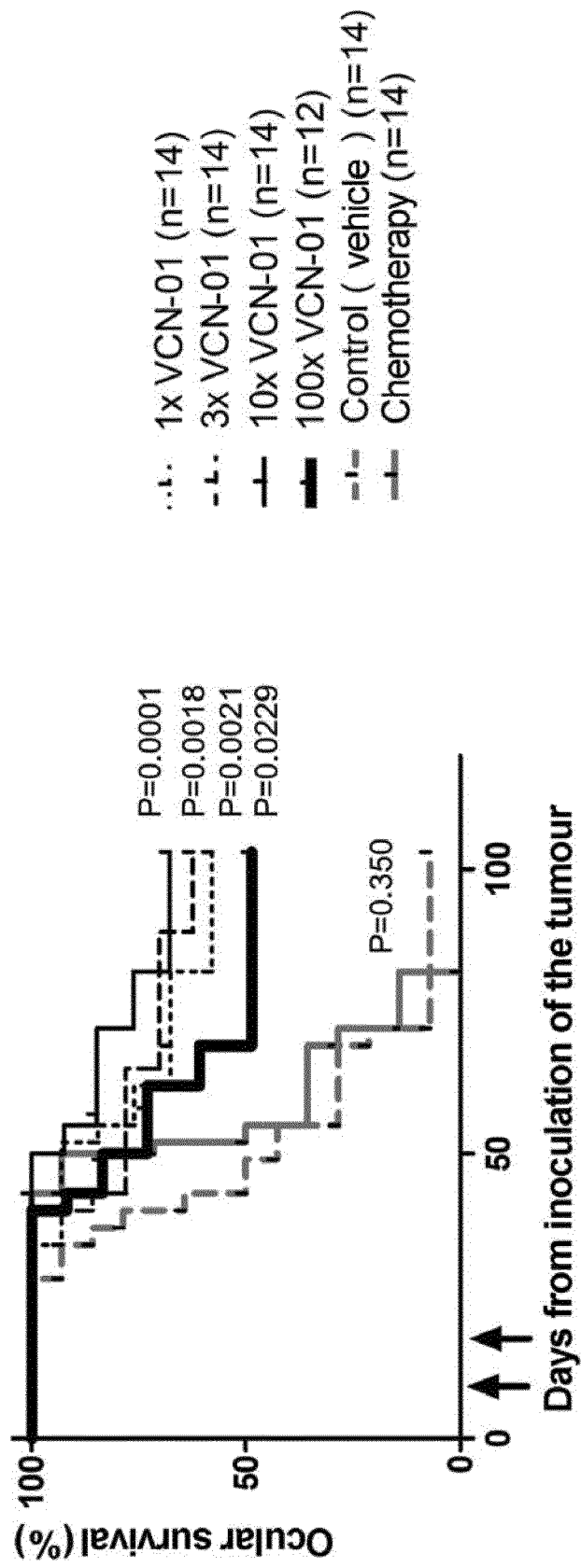


Figure 4

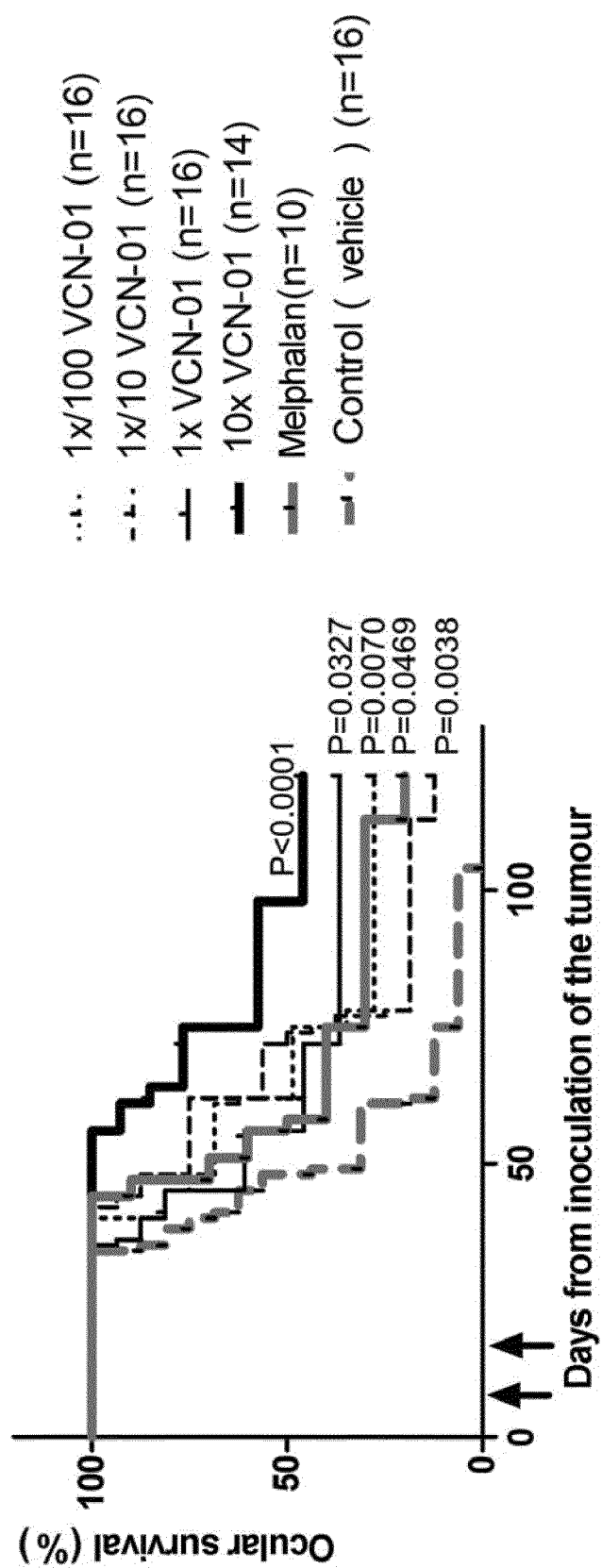


Figure 5

REFERENCES CITED IN THE DESCRIPTION

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