Non-Ad5 adenoviral vectors and methods and uses related thereto

Field of the invention

The present invention relates to the field of medicine. Specifically, the invention relates to cancer therapies. More specifically, the present invention relates to oncolytic human adenoviral vectors and cells and pharmaceutical compositions comprising said vectors. The present invention also relates to a use of said vectors in the manufacture of a medicament for treating cancer in a subject and to a method of treating cancer in a subject. Furthermore, the present invention relates to a method of producing an adenoviral vector.

Background of the invention

Cancer can be treated with surgery, hormonal therapies, chemotherapies and/or radiotherapies but in many cases, cancers, which are often characterized by an advanced stage, cannot be cured with present therapeutics. Therefore, novel cancer cell targeted approaches such as gene therapies are needed.

During the last twenty years gene transfer technology has been under intensive examination. The aim of cancer gene therapies is to introduce a therapeutic gene into a tumor cell. These therapeutic genes introduced to a target cell may for example correct mutated genes, suppress active oncogenes or generate additional properties to the cell. Suitable exogenous therapeutic genes include but are not limited to immunotherapeutic, anti-angiogenic, chemoprotective and "suicide" genes, and they can be introduced to a cell by utilizing modified virus vectors or non-viral methods including electroporation, gene gun and lipid or polymer coatings.

Requirements of optimal viral vectors include an efficient capability to find specific target cells and express the viral genome in the target cells. Furthermore, optimal vectors have to stay active in the target tissues or cells. All these properties of viral vectors have been developed during the last decades and for example retroviral, adenoviral and adeno-associated viral vectors have been widely studied in biomedicine.

To further improve tumor penetration and local amplification of the anti-tumor effect, selectively oncolytic agents, e.g. conditionally replicating adenoviruses, have been constructed. Oncolytic adenoviruses are a promising

tool for treatment of cancers. Tumor cells are killed by oncolytic adenoviruses due to a replication of the virus in a tumor cell, the last phase of the replication resulting in a release of thousands of virions into the surrounding tumor tissues for effective tumor penetration and vascular re-infection. Treatment approaches take advantage of molecular differences between the normal and tumor cells. Tumor cells allow replication of the virus while normal cells are spared due to engineered changes in the virus genome, which prevent replication in non-tumor cells. An optimal oncolytic adenovirus would infect and replicate only in cancer cells and would be potent enough to kill all cancer cells before the immunological response neutralizes the virus.

Making certain deletions or adding tissue specific promoters can make the virus more selective while adding transgenes can make the approach more potent. Indeed, in addition to replication mediated cell killing, oncolytic adenoviruses can also be armed with different therapeutic transgenes. This approach combines the advantages of conventional gene delivery with the potency of replication competent agents. One goal of arming viruses is induction of an immune reaction towards the cells that allow virus replication. Virus replication alone, although immunogenic, is normally not enough to induce effective anti-tumor immunity. To strengthen induction of therapeutic immunity, viruses can be armed with stimulatory proteins such as cytokines and by facilitating the introduction of tumor antigens to dendritic cells. Introduction of immunotherapeutic genes into tumor cells and furthermore, translation of the proteins, leads to activation of the immune response and efficient destruction of tumor cells.

Adenoviruses are medium-sized (90–100nm), nonenveloped icosahedral viruses, which have double stranded linear DNA of about 36 kilo base pairs in a protein capsid. The viral capsid has fiber structures, which participate in attachment of the virus to the target cell. First, the knob domain of the fiber protein binds to the receptor of the target cell (e.g. CD46 or coxsackievirus adenovirus receptor (CAR)), secondly, the virus interacts with an integrin molecule and thirdly, the virus is endocytosed into the target cell. Next, the viral genome is transported from endosomes into the nucleus and the replication machinery of the target cell is utilized also for viral purposes (Russell, W.C. 2000, J General Virol 81, 2573-2604).

The adenoviral genome has early (E1-E4), intermediate (IX and IVa2) and late genes (L1-L5), which are transcribed in sequential order. Early

gene products affect defense mechanisms, cell cycle and cellular metabolism of the host cell. Intermediate and late genes encode structural viral proteins for production of new virions (Wu and Nemerow, 2004, Trends Microbiol 12: 162-168; Russell, W.C. 2000, J General Virol 81, 2573-2604; Volpers, C. and Kochanek, S. 2004, J Gene Med 6 suppl 1, S164-71; Kootstra, N.A. and Verma, I.M. 2003, Annu Rev Pharmacol Toxicol 43, 413-439).

More than 50 different serotypes of adenoviruses have been found in humans. Serotypes are classified into six subgroups A-F and different serotypes are known to be associated with different conditions i.e. respiratory diseases, conjunctivitis and gastroenteritis. Nevertheless, all cancer trials utilizing recombinant adenoviruses have featured subgroup C viruses, which in most cases has been Ad5. Advantages of serotype chimeric capsids in the context of an otherwise serotype 5 virus have also been recognised. Even though serotype chimerism allows partial escape from neutralizing antibodies (Nab) existing against Ad5, the fact that most of the virus capsid is still from Ad5 renders the escape incomplete (Särkioja, M. *et al.* 2008, Gene Ther 15: 921-929).

Thus, there is a need for a fully non-Ad5 oncolytic virus, which is able to escape from Nab existing against Ad5. These viruses are useful especially in the context of pre-existing NAb against Ad5. This situation might arise as a result of natural infection or subsequent to treatment with an Ad5 based oncolytic virus.

Currently, little has been published on serotype 3 adenoviruses in the context of gene therapy. Wild type Ad3 is known to cause mainly respiratory infections and conjuctivitis in humans. The complete DNA sequence was reported in 2005 and it has only 62.75% identity with serotype 5. The genomic organisation is similar to other human adenoviruses having early and delayed early transcription units, including late and major late units (Sirena D *et al.* 2005, Virology 343: 283-298). A few years ago a wild type Ad3 virus was studied under normoxic and hypoxic conditions (Shen, B.H. *et al.* 2006, Gene Ther 13: 986-990). Recently, the same group published ColoAd1, a complex Ad3/Ad11p chimeric virus (Kuhn I *et al.* 2008, PLoS ONE 3: e2409). ColoAd1 was made by pooling an array of serotypes, then passaging the pools under conditions that invite recombination between serotypes. The authors call this method "Directed Evolution". These highly diverse viral pools were then placed under stringent directed selection to generate and identify potent

agents. In their experiments they found out that the Ad3/Ad11p chimeric virus was 2-3 orders of magnitude more potent and selective than the parent serotypes or the most clinically advanced oncolytic Ad, ONYX-015, *in vitro*. These results were further supported by *in vivo* and *ex vivo* studies. ColoAd1, however, given the approach utilized to develop it, lacks a rational basis for tumor selectivity. Also, its activity and safety *in vivo* is poorly understood as it has only been studied in one animal model, featuring colon cancer xenografts in mice.

Therefore, more efficient and accurate gene transfer based on non-Ad5 vectors as well as increased specificity and sufficient tumor killing ability of non-Ad5 gene therapies are warranted. Safety records of therapeutic vectors must also be excellent. The present invention provides a cancer therapeutic tool with the aforementioned properties by utilizing oncolytic human non-Ad5 viruses.

Summary

The object of the disclosure is to provide novel methods and means for achieving the above-mentioned properties of adenoviruses and thus, solving the problems of current cancer therapies. More specifically, the disclosure provides novel methods and means for gene therapy.

The present application describes construction of oncolytic human Ad3 vectors and their use in tumor cells lines and animal models, and it provides an alternative for oncolytic serotype 5 adenoviral vectors in virotherapies. The vector of the disclosure is the first selectively oncolytic human adenovirus based only on serotype 3. The vector is also the first non-Ad5 based oncolytic adenovirus controlled by a tumor specific promoter.

In a first aspect, there is provided an oncolytic human adenoviral vector, characterized by comprising a fully serotype 3 backbone and a tumor specific hTERT promoter controlling the Ad3 E1A region.

In a second aspect, there is provided a cell, characterized by comprising the adenoviral vector as defined above.

In a third aspect, there is provided a pharmaceutical composition, characterized by comprising the adenoviral vector as defined above.

In a fourth aspect, there is provided the use of the adenoviral vector as defined above in the manufacture of a medicament for treating cancer in a subject.

In a fifth aspect, there is provided a method of producing an adenoviral vector as defined above, characterized by comprising:

i) providing a DNA vector comprising at least partial Ad3 DNA and one or several tumor or tissue specific promoters and/or optionally one or several transgenes, and

ii) inserting the remainder of the Ad3 genome and optionally one or several tumor or tissue promoters and/or optionally one or several transgenes to the vector.

The present disclosure relates to a fully serotype 3 oncolytic human adenoviral vector.

The present disclosure further relates to a cell comprising the adenoviral vector of the disclosure.

The present disclosure also relates to a pharmaceutical composition comprising the adenoviral vector of the disclosure.

Furthermore, the present disclosure relates to a use of the adenoviral vector of the disclosure in the manufacture of a medicament for treating cancer in a subject.

Also, the present disclosure relates to a method of treating cancer in a subject, wherein the method comprises administration of the vector or pharmaceutical composition of the disclosure to a subject.

Still, the present disclosure relates to a method of producing an adenoviral vector of the disclosure comprising:

i) providing a DNA vector comprising at least partial Ad3 DNA and optionally one or several promoters and/or optionally one or several transgenes, and

ii) inserting the remainder of the Ad3 genome and optionally one or several promoters and/or optionally one or several transgenes to the vector.

The present disclosure provides a tool for treatment of cancers, which are refractory to current approaches. Also, restrictions regarding tumor types suitable for treatment remain few in the present disclosure compared to many other treatments. In fact, all solid tumors may be treated with the proposed disclosure. The treatment can be given intratumorally, intracavitary, intra-arterially, intravenously and in a combination of these.

Ad3 based viruses are able to enter cancer stem cell type cells better than Ad5 viruses. Efficacy of the virus of the present disclosure was shown in tumor cell lines and the virus was at least as potent as Ad5 or Ad5/3 based controls in several murine models of human cancer.

Besides enabling the transport of the vector to the site of interest the vector of the disclosure may also assure the expression and persistence of a transgene(s). Induction of an immune reaction towards cells that allow replication of unarmed viruses is normally not strong enough to lead to development of therapeutic tumor immunity. In order to overcome this weakness, the present disclosure provides armed viruses with a potent inducer of anti-tumor immunity (e.g. GM-CSF).

In the present disclosure, also human sodium iodide symporter (hNIS) transgene is utilized in targeting radioiodide to the target cell. This approach allows tumor cells to be killed due to the oncolytic effect of the virus and due to radiation induced cell death. The approach also takes advantage of synergy between radiation and oncolytic adenovirus replication. By introducing hNIS as a transgene, radioiodide therapy can be used to treat cancers of non-thyroid origin. An additional useful aspect of hNIS is non-invasive imaging of transgene expression, which allows monitoring viral spread and persistence.

The present disclosure also solves a problem related to therapeutic resistance of conventional treatments as well as other adenoviral therapies. A highly potential subject group of the present disclosure is a group of patients with high anti-Ad5 Nab titers or previously treated with Ad5 agents.

Furthermore, the present disclosure provides tools and methods for selective treatments, without toxicity or damages in healthy tissues. Also, advantages of the present disclosure may include different and reduced side effects in comparison to other therapeutics. Importantly, the approach is synergistic with many other forms of therapy including chemotherapy and radiation therapy, and can therefore be used in combination regimens.

Compared to adenoviral tools of the prior art, the present disclosure provides a more simple, more effective, inexpensive, non-toxic and/or safer tool for cancer therapy. Furthermore, helper viruses are not needed.

The novel products of the disclosure enable further improvements in cancer therapy.

Brief description of the figures

Figures 1a-e show schemas of Ad3-hTERT-hNIS-E1A (SEQ ID NO. 14); hNIS (SEQ ID NO. 15), Ad3-hTERT-GMCSF-E1A (SEQ ID NO. 16); GM-CSF (SEQ ID NO. 17), Ad3-hTERT-E1A-E3-hNIS, Ad3-hTERT-E1A-E3-GMCSF, and Ad3-hTERT-CD40L-E1A (SEQ ID NO. 20) partial; CD40L (SEQ ID NO 21).

Figures 2a-k show the cloning of viruses described in Figures 1a-e. The cloning of viruses with the transgenes in E1A is demonstrated in Figures 2a and 2c-g, the cloning of viruses with transgenes in the deleted Ad3 E3gp19k locus is demonstrated in Figures 2b and 2h-k.

Figure 3 shows a) the structure of Ad3-hTERT-E1A (SEQ ID NO. 18); hTERT (SEQ ID NO. 19). The hTERT promoter (295bp) was inserted to replace the TATA-box in front of the E1A region of the adenovirus 3. Arrows indicate the places of PCR primers used in Figure 3b. b) PCR of Ad3-hTERT-E1A. The PCR confirms that the hTERT promoter is on the right place and that the backbone is serotype 3. On the left we can see a band of 270bps and on the right 210bps from both sides of the hTERT promoter insertion area. These fragments have been sequenced and they gave the expected sequence. As negative controls Ad3wt, Ad5/3-hTERT-Δgp and MilliQ water were used. The presence of wild type adenovirus serotype 3 and 5, and Ad5/3 capsid modified viruses was excluded in other PCR experiments. c) Progressive infectivity

assay with Ad3-hTERT-E1A. The cells were plated on 96-well plates and the rows infected using 10-fold dilutions from 10^{-5} to 10^{-12} of Ad3-hTERT-E1A, each dilution in ten duplicates. Plates were observed by microscope and virus wells were compared to the mock wells. From the observations pfu/ml was calculated in the similar way as in $TCID_{50}$ (Adeasy manual, Agilent Technologies, Inc. 2008). The media (DMEM, 5% FBS) were changed every 4 to 7 days. The pfu/ml titer plateaus after 30 days, suggesting slow *in vitro* replication kinetics for Ad3-hTERT-E1A.

Figures 4A-D show cell killing assays with cancer cell lines. PC3-MM2 (prostate cancer) (A), A549 (lung cancer) (B), HTC116 (colon cancer) (C) and SKOV3.ip1 (ovarian cancer) (D) cells were used. Ad3-hTERT-E1A showed cell killing in all cell lines ($P<0.05$ versus Ad5/3luc1, the replication deficient control, at 10 VP/cell). Ad300wt, Ad5/3-hTERT-Δgp and Ad5/3-Δ24 killed cells faster than Ad3-based viruses. Bars indicate SE.

Figures 5A-C show cell killing assays with non-malignant and Ad3 receptor deficient cells. HUVEC (human umbilical vein endothelial cells) (A) and FSH173WE (fibroblasts) (B) were used to represent non-tumor cells. Ad3-hTERT-E1A did not differ from replication deficient Ad5/3-luc1 at low doses and killed significantly less cells than positive controls Ad3wt, Ad300wt, Ad5/3-Δ24 at 0.1, 1 and 10 VP/cell ($P<0.05$). It was known that LNM-35 (lung cancer) (C) cells lack the Ad3 receptor (Särkioja, M. *et al.* 2006, Cancer 107: 1578-1588). Ad3wt and Ad3-hTERT-E1A did not show any cytotoxicity on these cells. Bars indicate SE.

Figure 6 shows the *in vivo* efficacy of Ad3-hTERT-E1A in (A) PC3-MM2 (highly metastatic hormone refractory prostate carcinoma) tumors in nude mice. 10^9 VP was injected into each tumor weekly for a total of three injections and tumors were measured every 2-3 days. Tumors treated with Ad3-hTERT-E1A grew more slowly than PBS treated tumors ($P=0.0035$). (B) Similar data were seen in mice with A549 (lung cancer) tumors, although the PBS group had to be terminated early due to large tumor size. On day 17 a difference bordering on significance ($P=0.051$) was seen between PBS and Ad3-hTERT-E1A. Also, on day 30 Ad3-hTERT-E1A was found significantly ($P=0.01$) better than Ad5/3-hTERT-E1A suggesting the utility of Ad3-hTERT-E1A in this model. (C) Luciferase expressing SKOV3-luc ovarian cancer cells were grown intraperitoneally in SCID mice. A single intraperitoneal 10^9 VP virus injection was performed and the number of tumor cells as a function of

time was estimated with repeated luciferase imaging of live animals. A significant difference in the luciferase signal was seen between all virus treated groups and the PBS group (P<0.0001), and there were no differences between virus groups. Please note that the Ad300wt virus (wild type Ad5) could only be included in C-D. Bars indicate SE. (D) In survival analysis, all virus treated groups survived longer than the PBS group (P≤0.01). The only long term survivor from the experiment was one out of 7 mice from the Ad3-hTERT-E1A group. It was healthy and tumor free in imaging and autopsy at 100 days, when the experiment was ended.

Figures 7A-C show cell killing assays with CAMA-1 (breast cancer) (A), PANC-1 (pancreas cancer) (B) and ACHN (renal cancer) (C) cells. Ad3-hTERT-E1A showed cell killing in all of these cancer types. In all experiments Ad3-hTERT-E1A was significally more efficient than the replication deficient control Ad5/3-luc1 in 100VP/cell (P<0.05).

Figure 8 shows in vivo antitumor efficacy of Ad3-hTERT. A bioluminescence picture was taken on day 28.

Figure 9 shows an electron microscope picture of the Ad3-hTERT-E1A.

Figure 10 shows partial sequence of Ad3-hTERT-E1. The **sequenced DNA is marked in bold.** Underlined is the sequence of hTERT from pubmed. (Bases missing from the sequenced Ad3-hTERT-E1 compared to Ad3 backbone from pubmed are marked in brackets). BIG LETTERS IS THE hTERT INSERTION. *Primers used are marked in cursive.*

Figure 11 shows Ad5/3-Δ24-hNIS mediated iodide uptake in prostate cancer cells. Cells were infected with 10 VP/cell of Ad5/3-Δ24-hNIS or Ad5/3-Δ24-Δgp19K and exposed to ^{125}I 24 and 48 h post infection. The cells were analysed with gamma spectrometer to determine the radioactive iodide content of the cells. Non-infected cells were used as a negative control. Error bars present SEM. * p<0.05; ** p<0.01 and *** p<0.001.

Figure 12 shows Ad5/3-Δ24-hNIS replication and oncolysis in prostate cancer cells without radioiodide. The cells were infected with various viral doses (0-100 VP/cell) and the cell viability was determined 6-9 days later by MTS assay. A replication deficient Ad5/3luc1 and oncolytic Ad5/3-Δ24 were used as controls. Error bars present SEM.

Figure 13 shows Ad5/3-Δ24-hNIS mediated iodide uptake *in vivo*. Mice bearing subcutaneous prostate tumors received Ad5/3-Δ24-hNIS intratu-

morally (lower flank tumors), Ad5/3-Δ24-Δgp19K (upper right tumor) or saline (upper left tumor) followed by an intravenous ^{123}I injection (1.85 MBq/mouse). The iodide uptake was imaged A) 2 h and B) 13 h after the intravenous ^{123}I-injection with gamma camera. The pixel size was 1.08 mm x 1.08 mm. C) Biodistribution of ^{123}I 13 h after the ^{123}I injection. Bars present SEM, n=3, except n=6 in hNIS tumors.

Figure 14 shows Ad5/3-Δ24-hNIS anti-tumor efficacy *in vivo*. Subcutaneous prostate tumor bearing mice (6 mice/group, 12 tumors/group) received Ad5/3-Δ24-hNIS or growth medium intratumorally on two consecutive days followed by a 50 MBq intraperitoneal injection of ^{131}I or saline. The tumor size was measured every other day. The tumor growth rate was significantly slower in the combination treated group (Ad5/3-Δ24-hNIS + ^{131}I) when compared to all the other groups (*** $p < 0.001$). The experiment had to be ended at a predetermined time point of 17 days after the iodide injection due to animal husbandry constraints.

Figures 15a-d show that the GMCSF expression does not impair the virus replication and cell killing effect. Figure 15a represents results of a MTS assay showing the lung cancer derived (A549) cell killing efficiency of the new generated virus Ad5-D24-GMCSF. Figure 15b represents results of a MTS assay showing killing of JIMT-1 cancer initiating cells ("cancer stem cells") with Ad5-D24-GMCSF. Figure 15c represents results of a MTS assay showing the breast cancer cells (MDA-MB-436) killing efficiency with the new generated virus Ad5-D24-GMCSF. Figure 15d represents the results of a MTS assay showing the MDA-MB-436 killing efficiency with the new generated viruses Ad5-D24-GMCSF, Ad5-RGD-D24-GMCSF and Ad5/3-D24-GMCSF.

Figure 16a shows the adenovirus-coupled expression of human GMCSF. The A549 cell line was infected with Ad5D24 or Ad5D24-GMCSF, media were collected over time and analyzed for the expression of GMCSF by FACSARRAY. Figure 16b shows that the adenovirus-expressed GMCSF retains its biological activity in human lymphocytes. TF1 cells, which require human GMCSF for staying alive, were cultured in the presence of human recombinant GMCSF (E. coli-produced, purchased from Sigma) or supernatant from Ad5-D24-GMCSF infected cells.

Figure 17a shows the *in vivo* efficiency of Ad5-D24-GMCSF in Syrian Hamsters (permissive for human adenovirus replication) bearing pancreatic cancer tumors. Both Ad5D24 and Ad5-D24-GMCSF eradicate the

tumors within 16 days following the treatments. 1 x 10^9 VP of virus were administered on days 0, 2 and 4.

Figure 17b shows that an intratumoral injection of Ad5-D24-GMCSF resulted in high levels of hGMCSF in the serum of Syrian Hamsters. The animals treated with Ad5D24E3 or Ad5-D24-GMCSF were sampled on day 4 and the concentration of human GMCSF in the serum was assessed by FACSARRAY. Figure 17c shows that curing of HapT1 tumors with Ad5-D24-GMCSF (but not Ad5D24) protected Syrian hamsters from a subsequent re-challenge with HapT1. This demonstrates that Ad5-D24-GMCSF can induce a tumor specific immune response. The animals previously treated with Ad5D24 or Ad5D24-GMCSF (Figure 17a) were re-challenged with the same tumor and the tumor growth was measured over time.

Figure 17d shows induction of a tumor specific immune response by Ad5-D24-GMCSF; curation of HapT1 tumors with Ad5-D24-GMCSF did not protect Syrian hamsters from HaK tumors. The animals with HapT1 tumors previously treated with Ad5D24, or Ad5D24-GMCSF (Figure 17a) were re-challenged with a different tumor and the tumor growth was measured over time.

Figures 18a-c show toxicology in mice. In toxicity studies, Ad3-hTERT-E1A was found less toxic than the Ad5 and Ad5/3 control viruses in an immune competent murine model. The histology of all major organs and basic blood values were analyzed. 72h after $8x10^{10}$ VP given intravenously, significant differences were seen in liver histology and in liver enzymes. With serotype 3 only minor liver inflammation close to nonportal veins was seen in some mice. At the same time point and dose serotype 5 and 5/3 groups displayed features of acute liver toxicity and elevated liver enzymes. Other organs and blood values showed no signs of toxicity. Graph of blood samples and liver histology pictures are attached (Fig 18c). Here is the full histopathological report: PBS: 5/5 Normal. No mitoses. No inflammation. Ad3wt: Mostly normal. Mitoses in 5/5 samples. Minor inflammation near (nonportal)veins in the parenchyme 5/5. Ad3-hTERT-E1A: Mostly normal. No mitoses. Borderline inflammation near (nonportal) veins in the parenchyme were seen in 3/5 samples. Ad5wt: 5/5: Many apoptotic hepatocytes throughout the parenchyme, endothelitis and damage in central veins (at the portal area same can not be seen), no pericentral hepatocyte destruction, steatosis, nekrosis, no lymfocytes in the portal area, acute liver damage, damage

throughout the parenchyme. Ad5/3-hTERT-deltagp19k: 5/5: Almost normal, some point necrosis (not as much as in Ad5wt), some apoptotic cells, mitosis of hepatocytes, (lobular) inflammation in the parenchyme, inflammation (as with Ad3) around the veins. Ad5/3-Δ24: 5/5: Acute fulminant liver failure, 50% of tissue in necrosis, damage stronger near the portal area where all cells are dead, possible fatty generation, some mitoses.

Figure 19 shows virus kinetics in 2 human patients with advanced solid tumors, refractory to standard therapies, which were treated with Ad3-hTERT-E1A. The blood cells were separated using Percoll gradients and the DNA was extracted. The samples were analyzed by qPCR. With patient 1 the virus seems to be cleared from the platelets and peripheral blood mononuclear cells (PBMC) in an hour. With patient 2 much of the virus seems to go to the PBMCs and plasma before rapid clearance from blood. With both patients no virus was detected from the red blood cells (RBC). Results suggest that treatment of cancer patients with Ad3-hTERT-E1A might be safe. Patient 1 gave two virus free urine samples suggesting that the virus is not secreted to the urine.

Figures 20a-b show biodistribution in mice. Murine biodistribution at 6h after $5x10^{10}$ VP intravenously suggested that much of the serotype 3 virus stays still in the blood and blood rich organs such as spleen, lung and the liver. All major organs were analyzed by qPCR (Figure 20b). Entry to other organs was found attenuated. In this assay blood clots β-actin was used for the serum values. Due to the lack of β-actin in blood compartments, blood values are best compared with absolute values as done in Fig 20a. The results suggest that Ad3 virus does not associate with RBCs or serum but is abundantly present in blood clots and plasma. Thus WBCs and platelets are possible Ad3 virus carriers in mice.

Detailed description of the invention

Adenoviral vector

In the present invention, it is shown that an oncolytic human adenovirus vector based on serotype 3 can be constructed and it allows tumor cell killing.

In Ad3, as well as in other adenoviruses, an icosahedral capsid consists of at least three major proteins: hexon, penton base, and fiber, along

with minor proteins such as VI, VIII, IX, IIIa, and IVa2 (Russell W.C. 2000, J General Virol 81, 2573-2604; Sirena D *et al.* 2005, Virology 343: 283-298).

Sirena *et al.* (2005, Virology 343: 283-298) have reported the complete nucleotide sequence of a wild type Ad3 (GeneBank accession no. DQ086466). The Ad3 genome contains early (E1-4), intermediate (IX and IVa2) and the major late unit (MLTU) regions flanked by left and right inverted terminal repeats (LITR and RITR, respectively), which contain the sequences required for the DNA replication.

In one embodiment of the invention, a fully serotype 3 oncolytic human adenoviral vector comprises one or more regions selected from the group consisting of E1, E2, E3, E4, intermediate and late regions.

In one embodiment of the invention, an oncolytic human adenoviral vector comprises the following regions: a left ITR, E1, pIX, pIVa2, E2, VA1, VA2, late region, E3 or partial E3, E4, and a right ITR.

The regions may be in any order in the vector, but in one embodiment of the invention, the regions are in a sequential order in the 5' to 3' direction. Open reading frames (ORFs) may be in the same DNA strand or in different DNA strands.

As used herein, the expression "adenovirus serotype 3 (Ad3)" refers to the genome or partial genome of human Ad3, which comprises one or several regions selected from the group consisting of E1, pIX, pIVa2, E2, VA1, VA2, late region, E3 or partial E3, and E4 of Ad3 origin.

As used herein, the expression "partial" region refers to a region, which lacks any part compared to a corresponding wild type region. "Partial E3" refers to the E3 region lacking gp19k.

As used herein, the expressions "VA1" and "VA2" refer to virus associated RNAs 1 and 2, which are transcribed by the adenovirus but are not translated. VA1 and VA2 have a role in combating cellular defence mechanisms.

The insertion of endogenous or exogenous elements may enhance effects of the vectors in target cells. The use of exogenous tissue or tumor-specific promoters is common in recombinant adenoviral vectors and they can also be utilized in the present invention. For example, viral replication can be restricted to target cells for example by promoters, which include but are not limited to hTERT, variants of hTERT, CEA, SLP, Cox-2, Midkine, E2F, variants of E2F, CXCR4, SCCA2 and TTS. They are usually added to control the E1A

region, but in addition to or alternatively, other genes, such as E1B or E4, can also be regulated.

In one embodiment of the invention, an oncolytic human adenoviral vector comprises the Ad3 E1A region under an hTERT promoter. Ad3-hTERT-E1A contains the human telomerase catalytic domain promoter up-stream of the E1A transcription site for tumor specific replication.

In recent decades research on telomeres and telomerases has progressed rapidly. Telomerase activation is a critical step in human carcinogenesis, and most human tumors feature activity of telomerase. This feature is closely linked with activity of hTERT promoter, which has been suggested to be active in most human tumors and therefore represents a useful tumor specific promoter. In one embodiment of the invention, an oncolytic human adenoviral vector is capable of replicating only in cells with telomerase activity.

In one embodiment of the invention, an oncolytic adenoviral vector comprises the Ad3 E3 region under a replication activated Ad3 E3 promoter. In one specific embodiment of the present invention, the transgene is placed into a gp19k deleted E3 region, under the E3 promoter. This restricts the transgene expression to tumor cells that allow replication of the virus and subsequent activation of the E3 promoter. The E3 promoter may be any exogenous or endogenous promoter known in the art, preferably an endogenous promoter.

Exogenous insulators i.e. blocking elements against unspecific enhancers, the left ITR, the native E1A promoter or chromatin proteins may also be included in recombinant adenoviral vectors. Any additional components or modifications may optionally be used but are not obligatory in the vectors of the present invention.

The E3 region is nonessential for viral replication *in vitro*, but the E3 proteins have an important role in the regulation of the host immune response i.e. in the inhibition of both innate and specific immune responses. The vector of the invention may have deletion in the gp19k region in the E3. The gp19k gene product is known to bind and sequester major histocompatibility complex 1 (MHC1) molecules in the endoplasmic reticulum, and to prevent the recognition of infected cells by cytotoxic T-lymphocytes. Since many tumors are deficient in MHC1, deletion of gp19k increases the tumor selectivity of viruses (the virus is cleared faster than the wild type virus from normal cells but there is no difference in tumor cells).

In one embodiment of the invention, an oncolytic adenoviral vector comprises one or more transgenes. In one embodiment of the invention, the transgene is placed in E1 under the hTERT promoter and/or in E3 under the replication activated Ad3 E3 promoter. In one embodiment of the invention, an oncolytic human adenoviral vector comprises the transgene in the place of the deleted gp19k in the E3 region.

In one embodiment of the invention, an oncolytic adenoviral vector comprises an internal ribosomal entry site (IRES) between the transgene and the E1A region. IRES refers to a nucleotide sequence that enables the initiation of the translation in the middle of a messenger RNA sequence in the protein synthesis. In one embodiment of the invention IRES is from encephalomyocarditis virus (EMCV), which is obtained from Clontech vector pIRES2-DsRed2. In one embodiment of the invention, an oncolytic adenoviral vector comprises the hTERT promoter, transgene, IRES and E1A.

In one embodiment of the invention, the transgene is selected from the group consisting of a granulocyte-macrophage colony-stimulating factor (GM-CSF), human sodium iodide symporter (hNIS), interferon alpha, interferon beta, interferon gamma, tumor necrosis factor alpha, CD40L, trastuzumab and other monoclonal antibodies.

GM-CSF participates in the immune response by acting through various mechanisms including the recruitment of natural killer (NK) cell and the stimulation of antigen presenting cells (APC). APC can then recruit, activate and target T-cells towards the tumor. The nucleotide sequence encoding GM-CSF may be from any animal, such as a human, ape, rat, mouse, hamster, dog or cat, but preferably GM-CSF is encoded by a human sequence. The nucleotide sequence encoding GM-CSF may be modified in order to improve the effects of GM-CSF, or unmodified, i.e. of a wild type. In a preferred embodiment of the invention, the nucleic acid sequence encoding GM-CSF is of a wild type.

In one embodiment of the invention, an oncolytic human adenoviral vector comprises hNIS (SEQ ID NO. 15), which targets radioiodide to the target cell. The expression of the sodium iodide symporter (hNIS) as a transgene is a strategy for targeting systemically applicable radioisotopes, e.g., radioiodide to tumors. This approach allows tumor cells to be killed due to the oncolytic effect of the virus and due to radiation induced cell death, and the approach also takes advantage of synergy between radiation and oncolytic

adenovirus replication. An additional useful aspect of hNIS is non-invasive imaging of transgene expression, which allows monitoring viral spread and persistence.

hNIS is an integral plasma membrane glycoprotein mainly expressed in thyroid follicular cells (Dohan O *et al.* 2003, Endocr Rev. 24: 48-77). The biological function of hNIS is to mediate active transport of iodine, which is a crucial component for thyroid hormone biosynthesis. This transporting ability of hNIS has been used for half a century in radioiodide therapy of thyroid carcinoma, where radioactive iodide molecules (^{131}I) are used to internally radiate cancer cells of thyroid origin.

In the present invention, interferon alpha, interferon beta, interferon gamma, tumor necrosis factor, CD40L, trastuzumab and/or other monoclonal antibodies may also be utilized as transgenes for inducing the immune system of the patient against tumor cells, e.g., by activating natural killer cells, T-cells and/or macrophages.

The vector of the invention may also comprise other modifications than partial deletions of E3 and insertion of transgenes and/or promoters as mentioned above. Any capsid modification, i.e. modification of hexon, fibre and/or penton base proteins known in the art, which improves delivery of the virus to the tumor cell, may also be utilized in the present invention. As used herein "capsid" refers to the protein shell of the virus, which includes hexon, fiber and penton base proteins. Modifications may be genetic and/or physical modifications and include but are not limited to modifications for incorporating ligands, which recognize specific cellular receptors and/or block native receptor binding, for replacing the fiber or knob domain of an adenoviral vector with a knob of other adenovirus (chimerism) and for adding specific molecules (e.g. FGF2) to adenoviruses. Therefore, capsid modifications include but are not limited to incorporation of small peptide motif(s), peptide(s), chimerism(s) or mutation(s) into the fiber (e.g. into the knob, tail or shaft part), hexon and/or penton base.

Expression cassettes are used for expressing transgenes in a target, such as a cell, by utilizing vectors. As used herein, the term "expression cassette" refers to a DNA vector or a part thereof comprising nucleotide sequences, which encode cDNAs or genes, and nucleotide sequences, which control and/or regulate the expression of said cDNAs or genes. Similar or different expression cassettes may be inserted to one vector or to several

different vectors. Ad3 vectors of the present invention may comprise either one or several expression cassettes. However, only one expression cassette is adequate. In one embodiment of the invention, the oncolytic human adenoviral vector comprises at least one expression cassette. In another embodiment of the invention, the oncolytic human adenoviral vector comprises only one expression cassette.

A cell comprising the adenoviral vector of the invention may be any cell, such as a eukaryotic cell, bacterial cell, animal cell, human cell, mouse cell etc. For example, the cell may be used for producing the adenoviral vector *in vitro* or *in vivo*, or the cell may be a target, such as a tumor cell, which has been infected with the adenoviral vector.

Cancer

Any cancers or tumors, including both malignant and benign tumors as well as primary tumors and metastasis may be targets of gene therapies. In a specific embodiment of the invention, the cancer is any solid tumor. In one embodiment of the invention, the cancer is selected from a group consisting of nasopharyngeal cancer, synovial cancer, hepatocellular cancer, renal cancer, cancer of connective tissues, melanoma, lung cancer, bowel cancer, colon cancer, rectal cancer, colorectal cancer, brain cancer, throat cancer, oral cancer, liver cancer, bone cancer, pancreatic cancer, choriocarcinoma, gastrinoma, pheochromocytoma, prolactinoma, T-cell leukemia/lymphoma, neuroma, von Hippel-Lindau disease, Zollinger-Ellison syndrome, adrenal cancer, anal cancer, bile duct cancer, bladder cancer, ureter cancer, brain cancer, oligodendroglioma, neuroblastoma, meningioma, spinal cord tumor, bone cancer, osteochondroma, chondrosarcoma, Ewing's sarcoma, cancer of unknown primary site, carcinoid, carcinoid of gastrointestinal tract, fibrosarcoma, breast cancer, Paget's disease, cervical cancer, colorectal cancer, rectal cancer, esophagus cancer, gall bladder cancer, head cancer, eye cancer, neck cancer, kidney cancer, Wilms' tumor, liver cancer, Kaposi's sarcoma, prostate cancer, lung cancer, testicular cancer, Hodgkin's disease, non-Hodgkin's lymphoma, oral cancer, skin cancer, mesothelioma, multiple myeloma, ovarian cancer, endocrine pancreatic cancer, glucagonoma, pancreatic cancer, parathyroid cancer, penis cancer, pituitary cancer, soft tissue sarcoma, retinoblastoma, small intestine cancer, stomach cancer, thymus cancer, thyroid cancer, trophoblastic cancer, hydatidiform mole, uterine cancer, endometrial cancer, vagina cancer, vulva cancer, acoustic neuroma,

mycosis fungoides, insulinoma, carcinoid syndrome, somatostatinoma, gum cancer, heart cancer, lip cancer, meninges cancer, mouth cancer, nerve cancer, palate cancer, parotid gland cancer, peritoneum cancer, pharynx cancer, pleural cancer, salivary gland cancer, tongue cancer and tonsil cancer.

Pharmaceutical composition

A pharmaceutical composition of the invention comprises at least one type of the vectors of the invention. Furthermore, the composition may comprise at least two, three or four different vectors of the invention. In addition to the vector of the invention, a pharmaceutical composition may also comprise any other vectors, such as other adenoviral vectors, other therapeutically effective agents, any other agents, such as pharmaceutically acceptable carriers, buffers, excipients, adjuvants, antiseptics, filling, stabilising or thickening agents, and/or any components normally found in corresponding products.

The pharmaceutical composition may be in any form, such as solid, semisolid or liquid form, suitable for administration. A formulation can be selected from a group consisting of, but not limited to, solutions, emulsions, suspensions, tablets, pellets and capsules.

In one embodiment of the invention, the oncolytic adenoviral vector or pharmaceutical composition acts as an *in situ* cancer vaccine. As used herein an "*in situ* cancer vaccine" refers to a cancer vaccine, which both kills tumor cells and also increases the immune response against tumor cells. Virus replication is a strong danger signal to the immune system (=needed for a TH1 type response), and thus acts as a powerful costimulatory phenomenon to the GM-CSF mediated maturation and activation of APCs, and the recruitment of NK cells. Tumor cell lysis also helps to present tumor fragments and epitopes to APCs and furthermore, costimulation is produced by inflammation. Thus, an epitope independent (i.e. not HLA restricted) response is produced in the context of each tumor and therefore takes place *in situ*. A tumor specific immune response is activated in the target cell as well as the surrounding cells, e.g. in the target tissue.

The effective dose of vectors depends on at least the subject in need of the treatment, the tumor type, the location of the tumor and the stage of the tumor. The dose may vary for example from about 10^8 viral particles (VP) to about 10^{14} VP, preferably from about $5x10^9$ VP to about 10^{13} VP and more preferably from about $8x10^9$ VP to about 10^{12} VP.

The pharmaceutical compositions may be produced by any conventional processes known in the art, for example by utilizing any one of the following: batch, fed-batch and perfusion culture modes, column-chromatography purification, CsCl gradient purification and perfusion modes with low-shear cell retention devices.

Administration

The vector or pharmaceutical composition of the invention may be administered to any eukaryotic subject selected from a group consisting of plants, animals and human beings. In a preferred embodiment of the invention, the subject is a human or an animal. An animal may be selected from a group consisting of pets, domestic animals and production animals.

Most adults have been exposed to the most widely used adenovirus serotype Ad5 and therefore, the immune system can rapidly produce neutralizing antibodies (NAb) against them. In fact, the prevalence of anti-Ad5 NAb may be up to 50%. It has been shown that NAb can be induced against most of the multiple immunogenic proteins of the adenoviral capsid. In one embodiment of the invention, the subject has high amounts of anti-Ad5 neutralizing antibodies. In one embodiment of the invention, the subject has previously been treated with Ad5.

Any conventional method may be used for administration of the vector or composition to a subject. The route of administration depends on the formulation or the form of the composition, the disease, the location of tumors, the patient, comorbidities and other factors. In one embodiment of the invention, the administration is conducted through an intratumoral, intramuscular, intra-arterial, intravenous, intrapleural, intravesicular, intracavitary or peritoneal injection, or an oral administration.

Only one administration of oncolytic human adenoviral vectors of the invention may have therapeutic effects. However, in one embodiment of the invention, oncolytic adenoviral vectors or pharmaceutical compositions are administered several times during the treatment period. Oncolytic human adenoviral vectors or pharmaceutical compositions may be administered for example from 1 to 10 times in the first 2 weeks, 4 weeks, monthly or during the treatment period. In one embodiment of the invention, administration is done three to seven times in the first 2 weeks, then at 4 weeks and then monthly. The length of the treatment period may vary, and may, for example, last from two to 12 months or more.

Nevertheless, in the context of advanced tumor masses, a single round of treatment may not eradicate the tumor. Therefore, re-administration of the virus is likely to be required for increasing efficacy. A key factor limiting systemic re-administration is the neutralizing antibody (NAb) response induced by the virus. In order to avoid neutralizing antibodies in a subject, the vectors of the invention may vary between treatments.

The gene therapy of the invention is effective alone, but combination of adenoviral gene therapy with any other therapies, such as traditional therapy, may be more effective than either one alone. For example, each agent of the combination therapy may work independently in the tumor tissue, the adenoviral vectors may sensitize cells to chemotherapy or radiotherapy and/or chemotherapeutic agents may enhance the level of virus replication or effect the receptor status of the target cells. The agents of combination therapy may be administered simultaneously or sequentially.

In one embodiment of the invention, the method or use further comprises administration of concurrent radiotherapy or radioiodide to a subject. In another embodiment of the invention, the method or use further comprises administration of concurrent chemotherapy to a subject. As used herein "concurrent" refers to a therapy, which has been administered before, after or simultaneously with the gene therapy of the invention. The period for a concurrent therapy may vary from minutes to several weeks. Preferably the concurrent therapy lasts for some hours.

Agents suitable for combination therapy include but are not limited to All-trans retinoic acid, Azacitidine, Azathioprine, Bleomycin, Carboplatin, Capecitabine, Cisplatin, Chlorambucil, Cyclophosphamide, Cytarabine, Daunorubicin, Docetaxel, Doxifluridine, Doxorubicin, Epirubicin, Epothilone, Etoposide, Fluorouracil, Gemcitabine, Hydroxyurea, Idarubicin, Imatinib, Mechlorethamine, Mercaptopurine, Methotrexate, Mitoxantrone, Oxaliplatin, Paclitaxel, Pemetrexed, Temozolomide, Teniposide, Tioguanine, Valrubicin, Vinblastine, Vincristine, Vindesine and Vinorelbine.

Methods of producing adenoviral vectors include any conventional methods known in the art. Usually a transgene(s) is inserted into a shuttle plasmid and then homologous recombination is performed between the shuttle plasmid and a plasmid containing the remainder of the viral genome ("rescue plasmid"). The new genome can then be cut from the plasmid and transfected

to virus production cells. Alternatively, the rescue plasmid can be co-transfected into producer cells for recombination in those cells.

In one embodiment of the present invention, a plasmid construct is used for placing a transgene(s) to the adenoviral vector.

In one embodiment of the invention, the adenoviral vector is produced in a cell line. Usually, eukaryotic cells are transfected with the adenoviral vector and thereafter virus-producing cells are selected, expanded and tested. The viral vectors of the present invention also need extensive purification before administration to animals or human beings.

The present invention is illustrated by the following examples, which are not intended to be limiting in any way.

Examples

Cell culture

293 cells were purchased from Microbix (Toronto, Canada). 293-2v6-11 cells contain a ponasteron-inducible E4orf6 region (Mohammadi E.S. *et al.* 2004, Nucleic Acids Res 32: 2652-2659). 911-1c11 cells were kept in 1mg/ml G418 (Sirena, D. *et al.* 2005, Virology 343: 283-298). SKOV3.ip1 ovarian adenocarcinoma cell line was obtained from Dr. Price (M. D. Anderson Cancer Center, Houston, TX). Firefly luciferin-expressing ovarian adenocarcinoma cell line SKOV3-luc was kindly provided by Dr. Negrin (Stanford Medical School, Stanford, CA). PC-3MM2 highly metastatic hormone refractory subline of prostate carcinoma was a kind gift of Isaiah J. Findler (MD Anderson Cancer Center, Houston, TX). LNM35/EGFP, a highly lympho-genous metastatic subline of a human large cell carcinoma of the lung, was provided by Takashi Takahashi (The Honda Research Institute, Japan). The human umbilical vein endothelial cells known as the HUVEC were bought from Lonza (Basel, Switzerland). The following cell lines were obtained from ATCC (Manassas, VA): ACHN kidney cell carcinoma, A549 lung adenocarcinoma, FHS173WE human fibroblast cell line, HTC116 colorectal carcinoma, CAMA-1 breast adenocarcinoma, PANC-1 pancreatic epithelioid carcinoma. All cell lines were cultured under recommended conditions.

Construction of Ad3-hTERT-E1

For cloning of Ad3-hTERT-E1 three different PCR were performed on Ad3-wt plasmid pKSB2Ad3wt (Sirena, D. *et al.* 2005, Virology 343: 283-298), two of them to exclude the original TATA-box from the Ad3wt sequence

(Figures 1-3). The first PCR product included LITR with a MluI digestion site until the TATA-box (forward primer: 5'-CAT GGT ACC CAA GTG TGT CGC TGT CGA GT-3' (SEQ ID NO: 1), reverse primer 5'-CAT GAT ATC AGC GAT CAG CTG ACA CCT AC-3' (SEQ ID NO: 2); adding KpnI site in front and EcoRV site at the end), the second started directly after the TATA-box until the first half of the E1A region (forward primer: 5'-CAT GAT ATC GTG CCA GCG AGA AGA GTT TT-3' (SEQ ID NO: 3), reverse primer 5'-CAT TCT AGA GCG AGC ACA ATA GTT CTT TCA-3' (SEQ ID NO: 4); adding EcoRV site at front and XbaI at the end). The third PCR amplified 1600 bp of the end of adenovirus type 3 including RITR. The respectively digested first two PCR products around the TATA-box were cloned into KpnI/XbaI digested pUC19 cloning vector resulting in pGBAd3E1, including a TATA-box excluded start of the Ad3 sequence. The hTERT promoter derived from pBT255 was digested with KpnI/XhoI, blunted, and cloned in front of the E1 region by a EcoRV digestion of pGBAd3E1 resulting in pGBAd-3hTERT-E1.

The third PCR product with the end of the Ad3 sequence was now cloned into NotI/blunted pShuttle, followed by digestion with HindIII, and subsequently cloned into HindIII digested pGBAd3-hTERT-E1 resulting in pSGBAd3-hTERT-E1 as shuttle vector with end and modified start of the adenovirus 3 genome. Finally pSGBAd3-hTERT-E1 was digested with XhoI/MscI, resulting in the plasmid being opened up in between the modified start and preserved end of the adenovirus 3 sequence, and homologous recombined with MluI digested and thus backbone-free pKSB2Ad3wt, to reduce background due to same resistance gene and to achieve a plasmid with Ad3-hTERT-E1 sequence (pKGB-Ad3-hTERT-E1).

The recombinant Ad3-hTERT-E1A virus was rescued by transfecting 911-1c11 cells with MluI-digested pKGB-Ad3-hTERT-E1. Subsequent amplification of a first large Ad3-hTERT-E1A virus stock was done in 293-2v6-11 cells, followed by 2nd amplification in A549 cells. After amplification the viruses were purified on double cesium chloride gradients. The stocks were confirmed not to have serotype 5 contamination by PCR (for the standard method, see Kanerva, A. *et al.* 2003, Mol Ther 8: 449-458). Then the presence of the hTERT promoter in front of the E1A was confirmed (Fig. 3b). The primers used to get the 270bp band were 5'-GGT TAT GCC AGG GTG GAG TA-3' forward (SEQ ID NO: 5) and 5'-AAG GTG AAG GGG CAG GAC-3' reverse (SEQ ID NO: 6). For the 210bp band, the primers used were 5'-AGC

CCC TCC CCT TCC TTT-3' forward (SEQ ID NO: 7) and 5'-CCC GGT CTC ACT GGA GAT AA-3' reverse (SEQ ID NO: 8). The PCR bands were then sequenced and the expected sequence was obtained (see SEQ ID NO: 9 and Figure 10).

Finally the Ad3-hTERT-E1A was observed by electron microscope (see Figure 9).

Other adenoviruses

Please see Table 1 for adenoviruses relevant to this invention.

Table 1. Adenoviruses

Virus name	Back-bone sero-type	Fiber knob sero-type	E1A	Ratio (VP/pfu)	Reference
Ad5 wt	5	5	Wild type	19	ATCC (Ad300 wt strain)
Ad5/3-hTERT-E1A	5	3	Controlled by hTERT promoter (mediates selectivity to telomerase active cells)	10	Bauerschmitz, G.J. *et al.* 2008, Cancer Res 68: 5533-5539 (Named here Ad5/3-hTERT-Δgp)
Ad5/3-Δ24	5	3	24bp deletion (mediates selctivity to p16/Rb pathway mutant tumor cells)	22	Kanerva, A. *et al.* 2003, Mol Ther 8: 449-458.
Ad5/3luc1	5	3	Deleted (makes virus replication deficient)	5	Kanerva, A. *et al.* 2002, Clin Cancer Res 8: 275-280.
Ad3 wt	3	3	Wild type	9	Sirena, D. *et al.* 2005, Virology 343: 283-298.
Ad3-hTERT-E1A	3	3	Controlled by hTERT promoter (mediates selectivity to telomerase active cells)	9	This application

Progressive infectivity assay

The methodology established for Ad5 based viruses had to be optimized to account for the slower replication of Ad3 wild type and Ad3-hTERT-E1A. To estimate a functional titer, the usual 10-day cytopathic effect

assay was not sufficient and therefore we developed a more dynamic progressive infectivity assay (Fig. 3c), where the cytopathic effect was allowed to develop until the titer plateaued. This represents the actual functional titer of the virus.

The cells were plated on 96-well plates, 10 000 cells/well and rows were infected the next day with decreasing 10-fold dilutions from 10^{-5} to 10^{-12} of Ad3-hTERT-E1A, each dilution in ten duplicates. The infection was done in DMEM, 2% FBS. The plates were observed by microscope and the virus wells were compared to the mock wells. From the observations pfu/ml was calculated in the similar way as in $TCID_{50}$ (Adeasy manual, Agilent Technologies, Inc. 2008). The media (DMEM, 5% FBS) was changed every 4 to 7 days.

In vitro, the virus was slower in reaching the maximum titer and the functional infectivity assay required 35 days.

***In vitro* cytotoxicity assays**

The cells were plated at 10 000 cells/well on 96 well plates. The next day, the cells in triplicates or quadruplicates were infected with the viruses at 0.1 to 100 VP/well. The infection was done in 2% fetal bovine serum (FBS). The plates were regularly observed and the growth media was changed every 3-5 days. Six to twenty days later, as optimal for each line, the cell viability was analyzed with MTS assay (Cell Titer 96 AQueous One Solution Cell Proliferation Assay, Promega). MTS analyzes were performed on the following days: PC-3MM2 on day 8, A549 on day 17, HTC116 on day 6, SKOV3.ip1 on day 18, HUVEC on day 11, FSH174WE on day 13, LNM-35/EGFP on day 10, CAMA-1 on day 11, PANC-1 on day 20 and ACHN on day 11. The results are shown in Figures 4A-D.

Although both fully Ad3 viruses eventually killed all cancer cells in a cytotoxicity assay, they seemed slower than Ad5 based oncolytic agents, including a 5/3 serotype chimera. In non-cancer cells, Ad3-hTERT-E1A was less toxic than the control viruses, including wild type Ad3. Ad3-hTERT-E1A was not able to kill cells that lack the Ad3 receptor.

Oncolytic potency of Ad3-hTERT-E1A on cancer cell lines *in vitro*

The ability of Ad3-hTERT-E1A to kill cancer cells *in vitro* was analyzed by infecting monolayers representing seven different tumor types (Figures 4A-D and Figures 7A-C). In all malignant cell lines Ad3-hTERT-E1A

showed complete oncolysis, while the non-replicative Ad5/3luc1 virus showed no cell killing ($p<0.05$). However, as anticipated based on experience from growing and titering the virus, Ad3-hTERT-E1A was somewhat slower than the serotype 5 viruses.

Tumor selectivity of Ad3-hTERT-E1A

For analyzing the tumor selectivity, we infected HUVEC (human umbilical vein endothelial cells) and FSH173WE (fibroblasts) with the same viruses and performed cell killing assays (Fig. 5). No cell killing was seen at low virus concentrations and at higher doses Ad3-hTERT-E1A was less toxic than the control viruses Ad3wt, Ad5wt, Ad5/3-hTERT-E1A, Ad5/3-Δ24 (0.1, 1 and 10 VP/cell $P<0.05$). From the previous work with Ad5/3 chimeras, we knew that LNM-35/EGFP cannot be infected with Ad5/3 and thus may lack the Ad3 receptor (Särkioja, M. *et al.* 2006, Cancer 107: 1578-1588). Fittingly, no cell killing was seen with Ad3-hTERT-E1A or Ad3 wild type.

Animal experiments

All animal experiments were approved by the Experimental Animal Committee of the University of Helsinki and the Provincial Government of Southern Finland. Mice where frequently monitored for their health status and euthanized as soon as signs for pain or distress was noticed. For the subcutaneus model female NMRI nude mice were used (Charles River, Germany). They were ordered at the age of 3-4 weeks and quarantined for 2 weeks. For the intraperitoneal model female fox chase SCID mice (Charles River, Germany) were used. They were ordered at the age of 6-7 weeks and quarantined for 4 months.

Oncolytic potency *in vivo*

We tested the efficacy of Ad3-hTERT-E1A in mice bearing PC-3MM2 prostate cancer xenografts (Fig. 6A). Ad3-hTERT-E1A was able to reduce tumor growth significantly in comparison to PBS injections ($P=0.0035$). Interestingly, even though the virus was slower than positive controls *in vitro*, there was no difference in efficacy *in vivo*. Ad3-hTERT-E1A was at least as oncolytic as Ad5 and Ad5/3 based controls *in vivo*. In mice with A549 xenografts (Figure 6B), the Ad3-hTERT-E1A group had the smallest tumors from day 17 onwards, but because of rapid tumor growth in the PBS group, and termination of that group at day 17, the experiment lost much statistical

power. At day 17 a borderline difference (P=0.051) could be seen comparing Ad3-hTERT-E1A and the PBS. At day 30 Ad3-hTERT-E1A had reduced tumor growth significantly (P=0.01) better than Ad5/3-hTERT-E1A, which is known to be a highly potent oncolytic adenovirus (Bauerschmitz, G. J. *et al.* 2008, Cancer Res 68: 5533-5539).

Subcutaneous tumors may not be optimal surrogates of human cancers and therefore we proceeded to utilize an orthotopic model featuring intraperitoneally disseminated carcinomatosis induced with luciferase expressing SKOV3Luc cells (Figures 6C, D). Ad3-hTERT-E1A significantly reduced the luciferase signal as compared to PBS treated mice ($p<0.0001$). There was no difference in efficacy between the different replication competent viruses. Ad3-hTERT-E1A extended the median survival of mice from 34 to 46 days (PBS *versus* Ad3-hTERT-E1A), which resulted in a significant difference in Kaplan-Meier survival analysis (p=0.01). One out of the 7 mice treated with Ad3-hTERT-E1A survived until the end of the experiment (day 120) and may have been cured as no evidence of tumor could be detected in luciferase imaging or autopsy and its behavior was normal.

Subcutaneous animal experiment

Mice where injected subcutaneously to both flanks with 2 x 10^6 PC-3MM2 or 5 x 10^6A549 cells. After 13 and 11 days, respectively, the tumors had developed to measurable sizes and the mice were treated intratumoral by 10^9VP in PBS or only PBS. Injection volume per tumor was 50 µl. The injection was repeated after one and two weeks. The tumors were measured frequently and the volume was calculated $V = L \times H^2 \times 0.52$. The measured volume before the first treatment was regarded as 100% and the tumor growth was compared to this. With the A549 group some of the tumors treated with PBS grew aggressively and the mice had to be euthanized after two and a half weeks.

Intraperitoneal animal experiment

An orthotopic model of peritoneally disseminated ovarian cancer was developed by injecting 5 x 10^6 SKOV3-luc cells intraperitoneally in 300 µl of pure DMEM into SCID mice. After three days the mice (n=7) were imagined noninvasively and treated intraperitoneally by injecting PBS or 10^9VP in PBS per mouse. The mice were imaged on day 3, 7, 14, 21, 28, 35 and 42 using IVIS 100 (Xenogen, Alameda, CA, USA) to estimate the number of tumor cells

is the mice (Fig. 8). For bioluminescence imaging, 150 mg/kg D-luciferin (Promega, Madison, WI, USA) was injected intraperitoneal and captured 10min later with 10s expousure time, 1f/stop, medium binning and open filter. During imaging the mice were in isoflurane gas anesthesia. The images were overlaid with Living Image 2.50 (Xenogen). Total flux (photons/s) was measured by drawing regions of interest (ROI) around the peritoneal area of the mice. Background was subtracted.

Toxicology in mice.

In toxicity studies (Figures 18a-c), Ad3-hTERT-E1A was found less toxic than the Ad5 and Ad5/3 control viruses in an immune competent murine model. The histology of all major organs and basic blood values were analyzed. 72h after $8x10^{10}$ VP given intravenously, significant differences were seen in liver histology and in liver enzymes. With serotype 3 only minor liver inflammation close to nonportal veins was seen in some mice. At the same time point and dose serotype 5 and 5/3 groups displayed features of acute liver toxicity and elevated liver enzymes. Other organs and blood values showed no signs of toxicity. Graph of blood samples and liver histology pictures are attached (Fig 18c). Here is the full histopathological report: PBS: 5/5 Normal. No mitoses. No inflammation. Ad3wt: Mostly normal. Mitoses in 5/5 samples. Minor inflammation near (nonportal)veins in the parenchyme 5/5. Ad3-hTERT-E1A: Mostly normal. No mitoses. Borderline inflammation near (nonportal) veins in the parenchyme were seen in 3/5 samples. Ad5wt: 5/5: Many apoptotic hepatocytes throughout the parenchyme, endothelitis and damage in central veins (at the portal area same can not be seen), no pericentral hepatocyte destruction, steatosis, nekrosis, no lymfocytes in the portal area, acute liver damage, damage througout the parenchyme. Ad5/3-hTERT-deltagp19k: 5/5: Almost normal, some point necrosis (not as much as in Ad5wt), some apoptotic cells, mitosis of hepatocytes, (lobular) inflammation in the parenchyme, inflammation (as with Ad3) around the veins. Ad5/3-Δ24: 5/5: Acute fulminant liver failure, 50% of tissue in necrosis, damage stronger near the portal area where all cells are dead, possible fatty generation, some mitoses.

Virus kinetics in human patients.

So far 8 patients with advanced solid tumors, refractory to standard therapies, have been treated with Ad3-hTERT-E1A. The safety has been good

with doses of $5x10^{10}$ up to $5x10^{11}$ virus particles and dose escalation continues. Overall, all patients have experienced grade 1-2 adverse events, typically fever, nausea and tiredness. No grade 3 or higher adverse events have been seen so far. Complete analyses, including efficacy and immunological data are being processed.

From the first two patients blood samples were taken, as shown in Figure 19. The blood cells were separated using Percoll gradients and the DNA was extracted. The samples were analyzed by qPCR. With patient 1 the virus seems to be cleared from the platelets and peripheral blood mononuclear cells (PBMC) in an hour. With patient 2 much of the virus seems to go to the PBMCs and plasma before rapid clearance from blood. With both patients no virus was detected from the red blood cells (RBC). Results suggest that treatment of cancer patients with Ad3-hTERT-E1A might be safe. Patient 1 gave two virus free urine samples suggesting that the virus is not secreted to the urine.

Statistical analysis

Nonparametric Man-Whitney test (SPSS 15.0 for Windows) was used to compare two independent samples for all the *in vitro* and some of the *in vivo* data. The analysis of tumor size was performed using a repeated measures model with PROC MIXED (SAS Ver. 9.1). Models were run with the tumor size measurements in the natural metric and log transformed. The effects of the treatment group, time in days and the interaction of the treatment group and time were evaluated by F tests. Curvature in the models was tested for by a quadratic term for time. The a priori planned comparisons of specific differences in predicted treatment means averaged over time and at the last timepoint were computed by t-statistics. For the A549 experiment we compared the groups at 17 and 30 days and the PC-3MM2 at 30 days and time-averaged. Survival was evaluated using the Kaplan-Meier survival plot with log rank regression (SPSS 15.0 for Windows). For all analyses a two-sided P value of <0.05 was deemed statistically significant.

Viral constructs comprising hNIS and/or GMCSF and/or CD40L

hNIS and/or GMCSF transgene is (are) added to the human Ad3 based vector of the invention by utilizing methods known in the art or as described in the above examples or in the examples below, wherein a non-Ad5 adenoviral vector of the present invention, for example Ad3-hTERT-E1A, can be used instead of the Ad5/3-Δ24 backbone (see also Figures 1 and 2):

I. hNIS transgene

MATERIALS AND METHODS

Cell culture

Andorgen independent prostate cancer cell lines 22Rv1, PC-3, DU-145 and lung adenocarcinoma cell line A549 were purchased from ATCC (Manassas, VA). PC-3MM2 cells are a metastatic hormone refractory sub line of PC-3 (courtesy of Isaiah J. Fidler, MD Anderson Cancer Center, Houston, TX). Human embryonic kidney epithelial 293 cells were purchased from Microbix (Toronto, Canada). Cell line 911 was obtained from Dr Alex J. van der Eb (University of Leiden, The Netherlands). All cell lines were cultured in the recommended conditions.

Viral constructs

To create Ad5/3-Δ24-hNIS, EcoRI-digested and blunted hNIS fragment (from pcDNA3-hNIS, courtesy of Steve Russell, Mayo Clinic, Rochester, MN) was inserted into BsiWI-MfeI-digested and blunted pTHSN (Kanerva A. *et al.* Gene Ther 12: 87-94) to obtain pTHSN-hNIS. To make the control virus Ad5/3-Δ24-Δgp19K, BsiWI-MfeI-digested and blunted pTHSN was self-ligated resulting in pTHSN-Δgp19K. In order to obtain pAd5/3-Δ24-hNIS and pAd5/3-Δ24Δgp19K, PmeI-linearized pShuttle-Δ24 (Suzuki, K. *et al.* 2002, Clin Cancer Res 8: 3348-59) and pAd5/3- E1-hNIS or pAd5/3-E1-Δgp19K were electroporated into BJ5183 cells.

Adenoviral plasmids were linearized and transfected into 911 cells with Superfect (Qiagen, Valencia, CA) following the manufacturer's instructions. Adenovirus colonies were picked and viruses were propagated in A549 cells and purified using standard techniques. Ad5/3-Δ24 and Ad5/3luc1 viruses were constructed previously (Kanerva, A. *et al.* 2003, Mol Ther 8: 449-58; Kanerva, A, *et al.* 2002, Clin Cancer Res 8: 275-80). Viral particles (VP) were determined with spectrophotometry and plaque forming units (pfu) with TCID50 assay. Titers were Ad5/3-Δ24- hNIS: 1.1×10^{12} VP/ml; 9.0×10^{10}pfu/ml, Ad5/3-Δ24-Δgp19K: 1.5×10^{12} VP/ml; 2.8×10^{11} pfu/ml, Ad5/3-Δ24: 1.7×10^{12} VP/ml and Ad5/3luc1: 6.9×10^{11} VP/ml.

RT-PCR

Prostate cancer cells were infected with Ad5/3-Δ24-hNIS and Ad5/3-Δ24-Δgp19K (10 VP/cell) for 2 h at +37°C. Cells were harvested 24 and

48 h after infection. Total RNA was isolated using the RNeasy Kit (Qiagen) and treated with DNase before RT-PCR. 350 ng of total RNA was used for each reaction. Amplification (35 cycles, annealing at +54°C) was carried out with the OneStep RTPCR Kit (Qiagen) using hNIS-specific primers (Forward 5'-CTT CTG AAC TCG GTC CTC AC-3' (SEQ ID NO: 10); Reverse 5'-TCC AGA ATG TAT AGC GGC TC-3' (SEQ ID NO: 11) and β-actin-specific primers (Forward 5'- CGA GGC CCA GAG CAA GAC A -3' (SEQ ID NO: 12); Reverse 5'-CAC AGC TTC TCC TTA ATG TCA CG -3' (SEQ ID NO: 13). PCR product size for hNIS and β-actin was 453 bp and 482 bp, respectively.

Iodide uptake

Prostate cancer cells were infected with Ad5/3-Δ24-hNIS and Ad5/3-Δ24-Δgp19K (10 VP/cell) for 2 h at +37°C. Cells were washed with 1 x PBS 24 and 48 h post infections and incubated with 7.4 kBq of sodium iodide [^{125}I]NaI (MAP Medical Technologies Oy, Tikkakoski, Finland) for 20 min at room temperature. Cells were washed twice with 1 x PBS followed by lysis using 300 µl of Cell Culture Lysis Reagent for each sample (Promega, Madison, WI). Radioactivity was quantified with a well counter connected with a multi-channel analyzer Atomlab 950 (Biodex Medical System, Shirley, NY).

Cell killing assays

Prostate cancer cells were infected with Ad5/3-Δ24-hNIS, Ad5/3-Δ24-Δgp19K, Ad5/3-Δ24 and Ad5/3luc1 using 0.01, 0.1, 1, 10 and 100 VP/cell. Growth medium was replaced every other day. Cell viability was determined 6 days post infection (p.i.) for PC-3MM2, 7 days p.i. for DU-145 and PC-3 and 9 days p.i. for 22Rv1 cells.

-9 days post infection with CellTiter 96 AQueous One Solution cell proliferation assay [also called the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxy-methoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium [MTS] assay; Promega, Madison, WI).

Tissue culture infectious dose (TCID50) assay

Cell line samples: 5 x 10^4 prostate cancer cells/well were plated in triplicates in 1 ml of 5% GM on 24-well plates, incubated overnight and infected with Ad5/3-Δ24-hNIS (5 vp/cell) for 2 h at +37°C. At 8, 24, 48 and 72 h post infection cells and growth media were collected, frozen at -80°C and freeze-

thawn three times. For TCID50, the cells were spun down and the supernatant was added to 293 cells.

Tissue samples: Organs collected from mice treated with Ad5/3-Δ24-hNIS and ^{131}I were collected, weighed, manually homogenized and diluted into 800 µl of DMEM. They were freeze-thawed at -80°C three times. For TCID50, the tissue samples were spun down and the supernatant was added to 293 cells.

For both experiments, $10^4$4 293 cells were plated in 100 µl of 5% DMEM into 96-well plates, incubated overnight, and infected with the supernantants of aboce experiments. After 10 days, the development of CPE was assessed to estimate the titer.

***In vivo* studies**

Male NMRI/nude mice were purchased from Taconic (Ejby, Denmark). Tumors were established in eight-week old mice by subcutaneous injection of 5 x 10^6 PC-3MM2 cells under medetomidineketamine- 0.9% saline (1:2:7) anesthesia. In the imaging experiment, 3 mice received intratumorally saline (upper left tumor), 7 x 10^8 VP Ad5/3-Δ24-Δgp19K (upper right tumor) and 7 x 10^8 VP Ad5/3-Δ24-hNIS (lower right and left tumors) 11 and 12 days after tumor cell inoculation. A day after the last viral injection mice received intravenously 1.85 MBq of sodium iodide [^{123}I]NaI (MAP Medical Technologies Oy, Tikkakoski, Finland) followed by imaging with gamma camera Toshiba 7200A/UI (Toshiba, Tokyo, Japan) 0.5 h, 1 h, 1.5 h, 2h, 4h and 13h after iodide exposure. Animal regulation did not allow analysis of later time points. The gamma energy peak 159 keV was recorded using 20% window, and 150 kilocounts were collected per image. The used matrix size was 256 x 256 x 16, this made the pixel size 1.08 mm x 1.08 mm. At 13 h, various organs (heart, lung, liver, spleen, kidney, thyroid, stomach, muscle, blood and bone) and tumors were collected, weighed and analysed with a well counter connected with a multi-channel analyzer Atomlab 950 (Biodex Medical System, Shirley, NY). Results are expressed as percentage from initial iodide dose per gram of tissue (ID%/g).

For the therapeutic experiment, tumor bearing mice were randomized into 4 groups (6 mice/group, 2 tumors/mouse): mock, 131I, Ad5/3-Δ24-hNIS and Ad5/3-Δ24-hNIS + ^{131}I. 6 and 7 days after tumor cell inoculation mice received intratumorally either growth medium or 7 x 108 VP of Ad5/3-Δ24-hNIS per tumor. A day after the last viral injection, mice received intraperitoneally 50

MBq of carrier-free sodium iodide ([^{131}I]NaI, MAP Medical Technologies Oy, Tikkakoski, Finland). Tumor size was measured every other day and the volume calculated using the formula (length x width2 x 0.5). When mice were killed due to the tumor size, the organs were collected, weighed and their radioactivity determined with a gamma counter (Wizard 3, PerkinElmer, Turku, Finland) for 180 seconds. The results are expressed as percentage from initial iodide dose per gram of tissue (ID%/g). The whole body emitted radioactivity was measured at days 9, 10, 11, 13, 14, 15, and 17. On days 9-11, measurements were performed on a dose calibrator (CRC-120, Capintec, Inc., Ramsey, NJ), and after day 11 on a whole-body measurement apparatus consisting of a lead measurement chamber and an UniSpec tube-base multichannel analyzer with sodium iodide scintillation crystal (Canberra Industries, Inc., Meridien, CT). The mice were weighed at day 14, and the same weight was used in calculations throughout the experiment.

In all experiments, mice were killed when the tumor size reached 15 mm in any diameter, as required by animal regulations. The therapeutic *in vivo* experiment had to be stopped on day 17 due to animal husbandry constraints. All the animal experiments were approved by the national committee for animal experimentation in Finland (State Provincial Office of Southern Finland, Hämeenlinna, Finland).

Statistical analysis

Analysis of the iodide uptake was performed by one-way analysis of variance (ANOVA) with Bonferroni's post-hoc test. The analysis of the tumor volume over time between experimental groups was performed using a repeated measures model with PROC MIXED (SAS Ver. 9.1, Cary, NC). The tumor volume measurements were log transformed for normality. The a priori planned comparisons of specific differences in predicted treatment means averaged over time and at each time point by t-statistics and Tukey-Kramer model was used for adjustments. For all analyses a two-sided p value of <0.05 was deemed statistically significant.

Results

hNIS specific mRNA is detected in Ad5/3-Δ24-hNIS infected prostate cancer cells

A new virus containing the Ad3 knob in the Ad5 fiber shaft, a 24 bp deletion in the *E1A* region and hNIS inserted in the *E3* was constructed. To

assess the expression of the transgene from the virus, hormone refractory prostate cancer cell lines PC-3MM2, 22Rv1, PC-3 and DU-145 were infected with Ad5/3-Δ24-hNIS or Ad5/3-Δ24-Δgp19K (a positive control without a transgene) and analysed with RT-PCR 24 and 48h after infection. All Ad5/3-Δ24-hNIS infected cell lines featured a 454 bp sized, hNIS specific amplification product, suggesting that hNIS is expressed from the virus genome. In contrast, Ad5/3-Δ24-Δgp19K infected cells or cells *per se* did not yield to an amplification product.

Ad5/3-Δ24-hNIS can mediate efficient iodide uptake into prostate cancer cells

In order to assess the functionality of the hNIS expressed from the virus, prostate cancer cells were infected with Ad5/3-Δ24-hNIS or Ad5/3-Δ24-Δgp19K followed by exposure to ^{125}I and quantification of the iodide accumulation (Fig. 11). When compared to non-infected or control virus treated cells, Ad5/3-Δ24-hNIS resulted in a significantly higher iodide uptake in all examined cell lines. In comparison to the mock infection, Ad5/3-Δ24-hNIS caused up to 2.5 ($p<0.001$) and 3 ($p<0.001$) times higher iodide accumulation in PC-3MM2 and 22Rv1 cells, respectively. In PC-3 and DU-145 cells a more modest, but still significantly enhanced accumulation was seen when compared to mock treated cells (up to 1.6 ($p<0.05$) and 1.3 ($p<0.001$) times higher levels, respectively). Ad5/3-Δ24-Δgp19K treatment did not result in iodide accumulation, suggesting that iodide uptake was mediated by hNIS expressed from Ad5/3-Δ24-hNIS rather than from viral infection or replication *per se*.

Ad5/3-Δ24-hNIS replicates in and causes oncolysis of prostate cancer cells

Prostate cancer cell lines were infected with Ad5/3-Δ24-hNIS, Ad5/3-Δ24-Δgp19K, Ad5/3-Δ24 and Ad5/3luc1 followed by determination of cell viability 6 (PC3-MM2), 7 (PC-3 and DU-145) or 9 (22Rv1) days post infection (Fig. 12). Ad5/3-Δ24-hNIS showed efficient cell killing in all examined prostate cancer cell lines. The most rapid and efficient oncolysis was seen in PC-3MM2 cells, where almost complete cell killing was achieved 6 days after infection using 1 VP/cell of Ad5/3-Δ24-hNIS. In addition, oncolysis was similar to that seen with Ad5/3-Δ24-Δgp19K. In other prostate cancer cell lines, the oncolytic potency of Ad5/3-Δ24-hNIS was slightly less than Ad5/3-Δ24-Δgp19K.

In fact, Ad5/3-Δ24-Δgp19K which has the partial deletion in E3, showed the highest oncolytic potency in all examined cell lines. It is possible that the larger genome size of Ad5/3-Δ24-hNIS may impact the speed of oncolysis as compared to Ad5/3-Δ24-Δgp19K. The hNIS transgene is ~2.2 kbp, which together with the 1 kbp Δgp19K keeps the genome size under 105%, which has been suggested important for retaining virus functionality. The replicativity of Ad5/3-Δ24-hNIS was assessed in PC-3 and 22Rv1 cells where the TCID50 assay showed the increase in infectious particles in function of time.

Ad5/3-Δ24-hNIS can mediate radioactive iodide uptake into prostate cancer tumors

Subcutaneous PC-3MM2 tumors were established in nude/NMRI male mice. The lower tumors were infected intratumorally on two consecutive days with 7 x 10^8 VP/tumor of Ad5/3-Δ24-hNIS and the upper right tumor with the same dose of Ad5/3-Δ24-Δgp19k (Figs. 13A and B). The upper left tumor was mock treated. A day after the last viral injection, 1.85 MBq of ^{123}I per mouse was administered intravenously and mice were imaged with a gamma camera from 0.5 to 13 h after the ^{123}I injection. Some iodide accumulation into Ad5/3-Δ24-hNIS treated tumors was seen already 0.5 h after the ^{123}I injection. Two hours after the iodide exposure, a strong iodide accumulation was seen throughout Ad5/3-Δ24-hNIS treated tumors, whereas tumors injected with a control virus or saline did not uptake iodide (Fig. 13A). After 2h, the iodide accumulation reached a plateau and remained relatively constant up to the last imaging time point of the experiment 13 h after the iodide injection (Fig. 13B). In addition, iodide was heavily accumulated into thyroid and stomach due to the endogenous NIS expression of these organs. A high stomach uptake is typically seen in mice but not in humans. In patients, it would be possible to protect the normal thyroid from radioiodide, but this was not done in this mouse study. Since clearance of the radioactive iodide occurs through the urine, iodide accumulation in the bladder was seen.

To quantify ^{123}I biodistribution *in vivo*, organs and tumors were collected after imaging and their radioactive content was determined (Fig. 13C). Because of the endogenous hNIS expression, the thyroid and stomach captured about 30% of the injected dose. Nevertheless, the Ad5/3-Δ24-hNIS treated tumors accumulated more than 6% of the total iodide dose. This correlated with large amounts of infectious virus present in tumors, while only trace amounts were seen in the thyroid and stomach. Since tumors were

collected more than 10 days after the virus injection and TCID50 measures infectious virus, high TCID50 values probably reflect virus replication. Adenoviruses lose their capsid when they enter cells and thus the input virus cannot be detected with TCID50; it requires production of new virions. The iodide uptake remained low in other organs including mock or Ad5/3-Δ24-Δgp19K treated tumors (<1% of the initial dose).

Ad5/3-Δ24-hNIS with ^{131}I inhibits tumor growth *in vivo*

To assess the efficacy of Ad5/3-Δ24-hNIS *in vivo*, prostate tumor bearing mice were treated with ^{131}I or Ad5/3-Δ24-hNIS alone, or with their combination (Fig. 14). When tumors were treated with Ad5/3-Δ24-hNIS without radioiodide, tumor growth was significantly slower than in the mock or ^{131}I alone groups (p<0.05 for both). When the mice received both Ad5/3-Δ24-hNIS and 131I, tumor sizes were significantly smaller than in any other group (all p <0.001). An adjusted pairwise analysis indicated a significant difference between Ad5/3-Δ24-hNIS + ^{131}I *versus* virus alone, ^{131}I alone or mock already on day 2 (all p <0.05). The adjusted pairwise p-values between Ad5/3-Δ24-hNIS + ^{131}I *versus* virus alone, ^{131}I alone or mock on days 4, 6 and 8 were also all <0.001. Due to animal husbandry constraints, it was predefined that the experiment would be ended on day 17, although some of the mice were still in good condition.

Whole body emitted radioactivity was measured starting from one day after the iodide injection. Radioactivity declined rapidly during the next 3 days as expected by clearance through kidneys.

When tumor size reached 15 mm in any diameter, mice were killed and organs were collected for radioactivity measurements. Radioactivity declined over time and most radioactivity was seen in the thyroid gland and stomach, and briefly in the heart probably due to propagation of ^{131}I by circulation. In other organs the radioactivity remained low. Importantly, the virus injection did not affect iodide biodistribution and therefore the safety profile of the approach resembles that of radioiodide therapy for thyroid cancer.

II. GM-CSF transgene

Cloning of three D24-GM-CSF type viruses

- PCR out hGM-CSF,
- create SunI/MunI sites => 445 bp (pORF-GM-CSF as a template)
- SunI/MunI digestion of PCR product and pTHSN

- Sticky-end ligation =>
- *Pme*I linearized pShuttle-D24 + pTG3602 => pAd5-D24
- Ad5-D24-GM-CSF

Homol recomb: *Srf*I linearized pAd5-D24 + *Fsp*I linearized pTHSN-GM-CSF => pAd5-D24-GM-CSF

PacI linearization & transfection => Ad5-D24-GM-CSF

All phases of the cloning were confirmed with PCR and multiple restriction digestions. The shuttle plasmid pTHSN-GMCSF was sequenced. Absence of wild type E1 was confirmed with PCR. The E1 region, transgene and fiber were checked in the final virus with sequencing and PCR, which was then taken to the clean lab for production. To this end, viral DNA was extracted by over night (ON) incubation with an appropriate buffer solution and after PCR and sequencing was performed to analyze the integrity of the fiber as well as the GMCSF cDNA. All phases of the virus production, including transfection, were done on A549 cells to avoid risk of wild type recombination as described before (Kanerva, A. *et al.* 2003, Mol Ther 8, 449-58; Baeurschmitz, G.J. *et al.* 2006, Mol Ther 14, 164-74). GM-CSF is under the E3 promoter, which results in replication associate transgene expression, which starts about 8h after infection. E3 is intact except for deletion of *6.7K/gp19K*. Ad5/3-D24-GM-CSF and Ad5-RGDD24-GM-CSF were constructed identically, except a rescue plasmid featuring either a knob from serotype 3, or RGD-4C in the Ad5 fiber HI-loop were used.

***In vitro* analysis of D24-GM-CSF type viruses**

The in vitro efficacy of D24-GM-CSF type viruses was studied in lung cancer cells (A549), breast cancer stem cell derived explant cells (JIMT-1) and breast cancer cells (MDA-MB-436) utilizing MTS cell killing assays. The MTS assay is currently the standard method to assess cell viability in cancer gene therapy publications. Ad5Luc1 is a replication deficient virus and acts as a negative control. Ad5wt is a wild type Ad5 virus (strain Ad300wt) and was used as a positive control. Ad5-d24-E3 harbors an isogenic 24bp deletion in E1 but is intact in E3. VP indicates virus particles.

In summary, Ad5-D24-GMCSF had oncolytic activity similar to positive controls in vitro, and therefore transgene production did not compromise the oncolytic potency of the virus (Figures 15a-c). Similar data was shown for Ad5/3-D24-GM-CSF and Ad5-RGD-D24-GM-CSF (Figure 15d).

To test whether Ad5D24-GMCSF was able to express the transgene, A549 cell line was infected with 1000 VP/cell and media were collected over time. The concentration of GMCSF (Figure 16a) in the media was measured by FACSARRAY. In addition to that, we also analyzed whether the virus-expressed GMCSF retained its biological function. To this end, TF1 cell line, whose growth and survival is strictly dependent on human GMCSF, was treated with media collected from a A549 cell line previously infected with Ad5D24-GMCSF. The TF1 viability was assessed over time by the MTS assay. The result of this experiment was that the virus expressed-GMCSF was able to stimulate growth of such cell line, and no difference was found with the same cell line treated with human recombinant GMCSF (Sigma) (Figure 16b).

***In vivo* analysis of D24-GM-CSF type viruses in animals**

The *in vivo* efficacy of Ad5-D24-GM-CSF was tested in immune competent Syrian hamsters, which are semipermissive for human adenovirus replication (mice are non-permissive) (Ying B. *et al.* 2009, Cancer Gene Ther doi:10.1038/cgt.2009.6.). $7x10^6$ HapT1 pancreatic cancer cells were injected subcutaneously and $1x10^9$ virus particles (VP) of Ad5-D24-GM-CSF or Ad5D24E3 (which does not express GM-CSF) were injected intratumorally on day 0, 2 and 4. The mock group was injected with the same volume of growth media at the same indicated time points. Figure 17b shows that intratumoral injections of Ad5-D24-GMCSF resulted in high levels of hGM-CSF in the serum of Syrian hamsters. Human GM-CSF is known to be active in Syrian hamsters (Cho, Exp Toxicol Pathol 2006 vol. 57 (4) pp. 321-8). Interestingly, all animals were tumor-free by day sixteen except for mock group (Figure 17a). Tumor scars were still analyzed for two additional weeks to assess whether reappearance of the tumor might have occurred. However, on day 32 there was still no sign of tumor in these animals so that the first part of the experiment was terminated and animals of the Mock group were euthanized. The remaining treated animals were at this point challenged with the same tumor in the right side of the upper body by subcutaneous injection of $7x10^6$ HapT1 cells, while on the left side were challenged with a different tumor ($1x10^6$ of HaK tumor) for which the animals were naïve. Tumor growth was measured over time and is reported in Figures 17c-d. Interestingly, the animals that were previously treated with Ad5D24GMCSF completely rejected the HapT1 tumor challenge, while Hak tumors grew normally, whereas in the

animals that were previously treated with Ad5D24E3 HapT1 and HaK tumors grew independently (Figures 17c-d).

In summary, the data indicates that Ad5-D24-GM-CSF has an antitumor activity in immune competent tumor bearing animals, and it is able to elicit tumor-specific immunity to the degree of rejecting subsequent challenge of the same tumor.

III. CD40L transgene

Using methods similar to those described above Ad3-hTERT-CD40L-EIA was constructed and analyzed for biodistribution in mice (Figures 20a-b). Murine biodistribution at 6h after $5x10^{10}$ VP intravenously (Figure 20a) suggested that much of the serotype 3 virus stays still in the blood and blood rich organs, such as spleen, lung and the liver. All major organs were analyzed by qPCR (Figure 20b). Entry to other organs was found attenuated. In this assay blood clots β-actin was used for the serum values. Due to the lack of β-actin in blood compartments, blood values are best compared with absolute values as done in Fig 20a. The results suggest that Ad3 virus does not associate with RBCs or serum but is abundantly present in blood clots and plasma. Thus WBCs and platelets are possible Ad3 virus carriers in mice.

Claims

1. An oncolytic human adenoviral vector, characterized by comprising a fully serotype 3 backbone and a tumor specific hTERT promoter controlling the Ad3 E1A region.

2. An oncolytic human adenoviral vector according to claim 1, characterized by comprising one or more regions selected from the group consisting of E1, E2, E3, E4, intermediate and late regions.

3. An oncolytic human adenoviral vector according to claim 1 or 2, characterized by comprising the following regions: a left ITR, E1, pIX, pIVa2, E2, VA1, VA2, late region, E3 or partial E3, E4, and a right ITR.

4. An oncolytic human adenoviral vector according to any one of claims 1-3, characterized in that the regions are in a sequential order in the 5' to 3' direction.

5. An oncolytic human adenoviral vector according to any one of claims 1-4, characterized in that the promoter is a replication activated Ad3 E3 promoter controlling the Ad3 E3 region.

6. An oncolytic human adenoviral vector according to any one of claims 1-5, characterized by comprising one or more transgenes.

7. An oncolytic human adenoviral vector according to claim 6, characterized in that the transgene is selected from the group consisting of a granulocyte-macrophage colony-stimulating factor (GM-CSF), human sodium iodide symporter (hNIS), interferon alpha, interferon beta, interferon gamma, tumor necrosis factor, CD40L, trastuzumab and other monoclonal antibodies.

8. An oncolytic human adenoviral vector according to claim 6 or 7, characterized in that the transgene is placed in E1 under the hTERT promoter and/or in E3 under the replication activated Ad3 E3 promoter.

9. An oncolytic human adenoviral vector according to any one of claims 1-8, characterized by comprising internal ribosomal entry site (IRES) between the transgene and the E1A region.

10. An oncolytic human adenoviral vector according to any one of claims 1-9, characterized by comprising the hTERT promoter, transgene, IRES and E1A.

11. An oncolytic human adenoviral vector according to any one of claims 6-8, characterized by comprising the transgene in the place of the deleted gp19k in the E3 region.

12. An oncolytic human adenoviral vector according to any one of claims 1-11, characterized by comprising at least one expression cassette.

13. An oncolytic human adenoviral vector according to any one of claims 1-2, characterized by comprising only one expression cassette.

14. An oncolytic human adenoviral vector according to claim 1, characterized in that the vector is capable of replicating only in cells with telomerase activity.

15. An oncolytic human adenoviral vector according to any one of claims 1-14, characterized by comprising hNIS, which targets radioiodide to the target cell.

16. A cell, characterized by comprising the adenoviral vector according to any one of claims 1-15.

17. A pharmaceutical composition, characterized by comprising the adenoviral vector according to any one of claims 1-15.

18. An oncolytic human adenoviral vector or pharmaceutical composition according to any one of claims 1-15 and 17 as an *in situ* cancer vaccine.

19. A use of the adenoviral vector according to any one of claims 1-15 in the manufacture of a medicament for treating cancer in a subject.

20. The use according to claim 19, characterized in that the cancer is selected from a group consisting of nasopharyngeal cancer, synovial cancer, hepatocellular cancer, renal cancer, cancer of connective tissues, melanoma, lung cancer, bowel cancer, colon cancer, rectal cancer, colorectal cancer, brain cancer, throat cancer, oral cancer, liver cancer, bone cancer, pancreatic cancer, choriocarcinoma, gastrinoma, pheochromocytoma, prolactinoma, T-cell leukemia/lymphoma, neuroma, von Hippel-Lindau disease, Zollinger-Ellison syndrome, adrenal cancer, anal cancer, bile duct cancer, bladder cancer, ureter cancer, brain cancer, oligodendroglioma, neuroblastoma, meningioma, spinal cord tumor, bone cancer, osteochondroma, chondrosarcoma, Ewing's sarcoma, cancer of unknown primary site, carcinoid, carcinoid of gastrointestinal tract, fibrosarcoma, breast cancer, Paget's disease, cervical cancer, colorectal cancer, rectal cancer, esophagus cancer, gall bladder cancer, head cancer, eye cancer, neck cancer, kidney cancer, Wilms' tumor, liver cancer, Kaposi's sarcoma, prostate cancer, lung cancer, testicular cancer, Hodgkin's disease, non-Hodgkin's lymphoma, oral cancer, skin cancer, mesothelioma, multiple myeloma, ovarian cancer, endocrine pancreatic cancer, glucagonoma, pancreatic cancer, parathyroid cancer, penis cancer, pituitary cancer, soft tissue sarcoma, retinoblastoma, small intestine cancer, stomach cancer, thymus cancer, thyroid cancer, trophoblastic cancer, hydatidiform mole,

uterine cancer, endometrial cancer, vagina cancer, vulva cancer, acoustic neuroma, mycosis fungoides, insulinoma, carcinoid syndrome, somatostatinoma, gum cancer, heart cancer, lip cancer, meninges cancer, mouth cancer, nerve cancer, palate cancer, parotid gland cancer, peritoneum cancer, pharynx cancer, pleural cancer, salivary gland cancer, tongue cancer and tonsil cancer.

21. The use according to claim 19 or 20, characterized in that the subject is a human or an animal.

22. The use according to any one of claims 19-21, characterized in that the medicament is to be administrated through an intratumoral, intramuscular, intra-arterial, intravenous, intrapleural, intravesicular, intracavitary or peritoneal injection, or an oral administration.

23. The use according to any one of claims 19-22, characterized in that oncolytic human adenoviral vectors or pharmaceutical compositions are to be administered several times during the treatment period.

24. The use according to any one of claims 19-23, characterized in that the medicament is to be combined with administration of concurrent radiotherapy or radioiodide to a subject.

25. The use according to any one of claims 19-24, characterized in that the medicament is to be combined with administration of concurrent chemotherapy to a subject.

26. The use according to any one of claims 19-25, characterized in that the subject has high amounts of anti-Ad5 neutralizing antibodies.

27. The use according to any one of claims 19-26, characterized in that the subject has previously been treated with Ad5.

28. A method of producing an adenoviral vector according to any one of claims 1-15, characterized by comprising:

i) providing a DNA vector comprising at least partial Ad3 DNA and one or several tumor or tissue specific promoters and/or optionally one or several transgenes, and

ii) inserting the remainder of the Ad3 genome and optionally one or several tumor or tissue promoters and/or optionally one or several transgenes to the vector.

29. A method according to claim 28, characterized in that a plasmid construct is used for placing a transgene(s) to the adenoviral vector.

30. A method according to claim 28 or 29, characterized in that the adenoviral vector is produced in a cell line.

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