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PRINCIPAL INVESTIGATOR: David T. Curiel

CONTRACTING ORGANIZATION: The Washington University, St. Louis, MO

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Owing to their exciting potential, virotherapy agents have been rapidly applied as experimental therapy for cancer of the ovary. In addition to addressing safety and efficacy, these recent human trials have also define the barriers to optimized virotherapy effectiveness. Specifically, these human trials have highlighted two key barriers limiting the full effectiveness of current virotherapy approaches for cancer of the ovary. First, pre-formed immunity to the virotherapy viral agent, in the form of antibodies, could neutralize the administered agent. This is highly relevant as many virotherapy agents are based on viruses to which humans have commonly been exposed. For example, the common "cold" virus, termed "adenovirus", has been highly useful as a virotherapy agent, however its use would be potentially impacted by the presence of antibodies to human adenovirus in treated subjects. We were able to construct an ovarian cancer CRAd with a SPARC promoter for tumor selective replication. Initially, we proposed a gorilla adenovirus "base" but found that a human adenovirus 5 base provided some technical advantages. In addition, we were able to show the SPARC-controlled CRAd replication in human and murine ovarian cancer cells selectively and induced direct tumor cell oncolysis. We were also able to show that the targeted CRAd could accomplish tumor cell oncolysis in an orthotopic challenge model. However, in pilot studies to this point, we have not been able to exploit this latter capacity to induce systemic immunity. After establishing proof-of-principle, we will shift to simian 36 base which can be modified as readily as human adenoviruses.

15. SUBJECT TERMS

Adenovirus, ovarian cancer, virotherapy, anti-tumor immunization

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TABLE OF CONTENTS

1. INTRODUCTION

We proposed the development of an adenovirus (Ad)-based virotherapy agent (CRAd) for ovarian cancer (OvCa). Our design intent embodied the use of a non-human primate Ad that was tumor-targeted via viral capsid-incorporated single domain camelid antibodies (sdAb). The ability of the CRAd to accomplish an anti-tumor immunization would be evaluated in an immunocompetent murine model of cancer of the ovary.

2. KEYWORDS

adenovirus, conditionally replicative adenovirus (CRAd), virotherapy, single domain antibody (sdAb), ovarian cancer, anti-tumor immunization, immunotherapy, oncolysis, SPARC

3. ACCOMPLISHMENTS

What were the major goals of the project?

1. To construct an ovarian cancer CRAd based upon gorilla adenovirus.
2. To characterize the tumor selectivity of the gorilla CRAd *in vitro* and *in vivo*.
3. To evaluate the ability of CRAd-based virotherapy to induce anti-tumor immunity in a syngeneic immunocompetent murine model of carcinoma of the ovary.

What was accomplished under these goals?

<u>To construct an ovarian cancer CRAd based upon gorilla adenovirus.</u>

We sought to construct a CRAd utilizing gorilla adenovirus as a “backbone”. This was proposed as GAd embodies the capacity to traverse pre-formed antibodies to the major human adenovirus, human adenovirus serotype 5 (huAd5). It was thus hypothesized that a GAd-based CRAd would be effective even in the setting of women with previous exposure to huAd5. To this end we established a collaboration with GenVec, Inc., who developed the GAd technology. Incurrent to early work, GenVec, Inc. was acquired by Intrexon, Inc. This latter corporation elected to not continue collaborations outside their more narrow focus on vaccines. We thus could not continue with our original aim of using GAd as the base for our ovarian cancer targeted CRAd. We thus developed an alternative strategy exploiting huAd5 as the CRAd base that explored novel targeting methods. To this end, we sought to exploit novel tumor selective promoters (TSPs) to achieve tumor selective oncolysis, in combination with the novel tumor targeting methods proposed in Specific Aim #2. This “double targeted” CRAd thus represented a highly novel virotherapy approach for ovarian cancer. These studies, reported in the Annual Progress Report, established the utility of the promoter element of the osteonectin (SPARC) gene. This promoter embodied the capacity for inductivity in tumor, and tumor stroma, potentially providing an efficacy advantage. We initially evaluated SPARC-promoter CRAds in *in vitro* and *in vivo* models of OvCa. These studies confirmed the utility of the OvCa CRAd design based on SPARC and thereby provided rationale for our proposed double targeting approach.

To characterize the tumor selectivity of the gorilla CRAd *in vitro* and *in vivo*.

As an adjunctive method to achieve tumor selectivity we explored the utility of camelid single domain antibodies (sdAb). Our group was the first to show that Ad could be retargeted based on capsid incorporated ligands[1] and sdAb[2]. For this current DOD proposal we derived sdAb with specificity against the OvCa tumor marker CD276. Our successful derivation of this sdAb represents the first realization of this useful OvCa targeting moiety. Our studies confirmed the precise OvCa tumor selectivity of the anti-CD276 sdAb. Molecular engineering of Ad allowed capsid incorporation of the anti-CD276 sdAb. We were able to show that this virus could retarget to CD276-positive OvCa tumor cells. Of note, evaluation of our targeted Ad in a murine orthotopic xenograft model of OvCa demonstrated precise tumor targeting (see *Appendix*). Of further note, our studies were the first to demonstrate successful vector targeting *in vivo* utilizing this emerging antibody class.

To evaluate the ability of CRAd-based virotherapy to induce anti-tumor immunity in a syngeneic immunocompetent murine model of carcinoma of the ovary.

There are a limited repertoire of syngeneic murine models of cancer of the ovary. In this regard, all previous studies of Ad-based virotherapy for ovarian cancer had exploited orthotopic xenograft models. The syngeneic murine model of OvCa based on “ID8” had recently been employed for a range of immunotherapy studies. On this basis, we considered its candidacy for the evaluation of CRAd induction of anti-tumor immunization. Unfortunately, none of our efforts realized induction of immunity for ID8. Based upon this consideration, we could not evaluate CRAd-induced anti-tumor immunization utilizing this model.

What opportunities for training and professional development has the project provided?

Postdoctoral fellows engaged in this project obtained foundational scientific training. This traineeship embodied attending national and international scientific meetings as well as publication of primary scientific findings and relevant subject reviews.

How were results disseminated to communities of interest?

Our findings were shares within the scientific community in the context of meeting abstracts, scientific publications, and review articles. In addition, as project PI, I presented our data in the context of institutional seminars.

What do you plan to do during the next reporting period to accomplish the goals?

Not applicable.

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1 Belousova N, Korokhov N, Krendelshchikova V, Simonenko V, Mikheeva G, Triozzi PL, Aldrich WA, Banerjee PT, Gillies SD, Curiel DT, Krasnykh V. Genetically targeted adenovirus vector directed to CD40-expressing cells. J Virol. 2003;77(21):11367-77. PubMed PMID: 14557622; PMCID: 229360.

2 van Erp EA, Kaliberova LN, Kaliberov SA, Curiel DT. Retargeted oncolytic adenovirus displaying a single variable domain of camelid heavy-chain-only antibody in a fiber protein. Mol Ther Oncolytics. 2015;2:15001. doi: 10.1038/mto.2015.1. PubMed PMID: 27119101; PMCID: 4782946.

4. IMPACT

What was the impact on the development of the principle discipline(s) of the project?

The ability to retarget adenovirus with sdAbs represents a field milestone. This technology will now feasibilize the development of Ad-based virotherapy agents with an improved therapeutic index.

The demonstration of CRAd targeting to tumor plus tumor stroma represents a novel paradigm for traversing barriers to virotherapy efficacy.

What was the impact on other disciplines?

Targeted in vivo gene delivery has represented a field “Holy Grail” since the inception of gene therapy. Our demonstration of sdAb-based retargeting will impact the many applications whereby Ad is being presently employed – gene therapy, vaccinology, and oncolytic virotherapy.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change.

We had initially sought to use gorilla adenovirus as a “base” for CRAd design. Our cooperation with GenVec, Inc. to secure this expertise was terminated with GenVec, Inc. was acquired by Intrexon, Inc. This change required us to evaluate our design concepts in a human adenovirus background.

Actual or anticipated problems or delays and actions to resolve them.

We found that the ID8 syngeneic model of ovarian cancer did not allow anti-tumor immunization via CRAds. We tried to augment this response with checkpoint blockers without success.

Changes that had a significant impact on expenditures.

Not applicable.

Significant changes in use of human subjects, vertebrate animals, biohazards, and/or select agents.

We employed human adenovirus instead of gorilla adenovirus.

Significant changes in use or care of human subjects.

Not applicable.

Significant changes in use or care of vertebrate animals.

Not applicable.

Significant changes in use or care of biohazards and/or select agents.

Not applicable.

6. PRODUCTS

Publications, conference papers, and presentations

Journal Publications

Gonzalez-Pastor R, Goedegebuure PS, Curiel DT. **Understanding and addressing barriers to successful adenovirus-based virotherapy for ovarian cancer.** *Cancer Gene Ther*. 2020. Epub 2020/09/21. doi: 10.1038/s41417-020-00227-y. PubMed PMID: 32951021.

Gonzalez-Pastor R, Ashshi AM, El-Shemi AG, Dmitriev IP, Kashentseva EA, Lu ZH, Goedegebuure SP, Podhajcer OL, Curiel DT. **Defining a murine ovarian cancer model for the evaluation of conditionally-replicative adenovirus (CRAd) virotherapy agents.** *J Ovarian Res*. 2019;12(1):18. doi: 10.1186/s13048-019-0493-5. PubMed PMID: 30767772; PMCID: PMC6376676.

Other Publications, Conference Papers, and Presentations

Poster Presentation:

Gonzalez-Pastor R, Kashentseva EA, Dmitriev IP, Lu ZH, Goedegebuure SP, Podhajcer OL, Curiel DT: **Defining a murine ovarian cancer model for the evaluation of conditionallyreplicative adenovirus (CRAd)-based anti-tumor immunization**. *13th International Adenovirus Meeting* September 2019, **Mexico City, Mexico**.

Acknowledgement of Federal Support: YES

Website(s) or other Internet site(s)

Nothing to Report.

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other products

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	**David T. Curiel**
Project Role:	Principle Investigator
Nearest person month worked:	1
Contribution to Project:	Dr. Curiel oversaw vector design, construction, and closely interacts with all parties on overall project progress and on-going strategies.

Name:	**Igor Dmitriev**
Project Role:	Co-Investigator
Nearest person month worked:	1
Contribution to Project:	Dr. Dmitriev was closely involved in vector design and analysis of experimental data.

Name:	**Elena Kashentseva**
Project Role:	Senior Research Technician
Nearest person month worked:	3
Contribution to Project:	Ms. Kashentseva performed work in the areas of viral construction and validation.

Name:	**Zhi Hong Lu**
Project Role:	Senior Scientist
Nearest person month worked:	1
Contribution to Project:	Dr. Lu performed work in the areas of *in vivo* administration and imaging studies.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes, see *Appendix.*

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

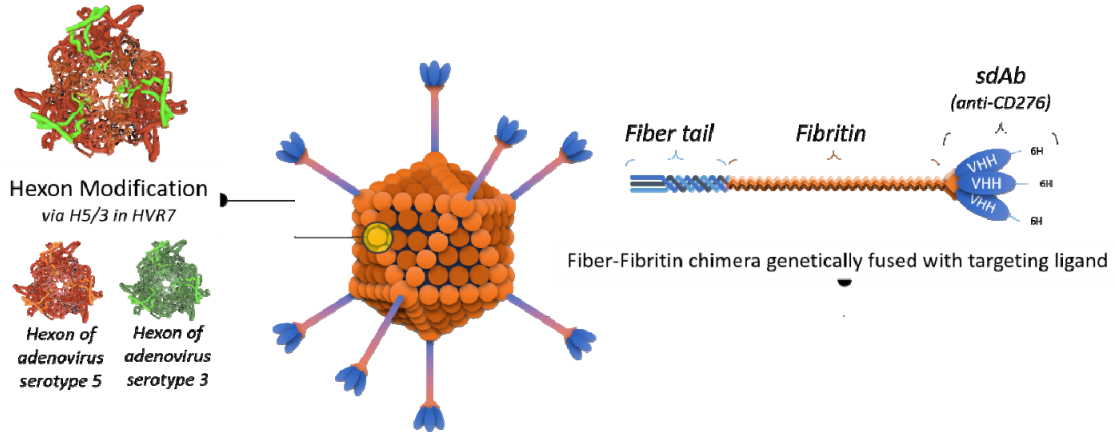
Not applicable.

9. APPENDICIES

Figures

Figure 1.

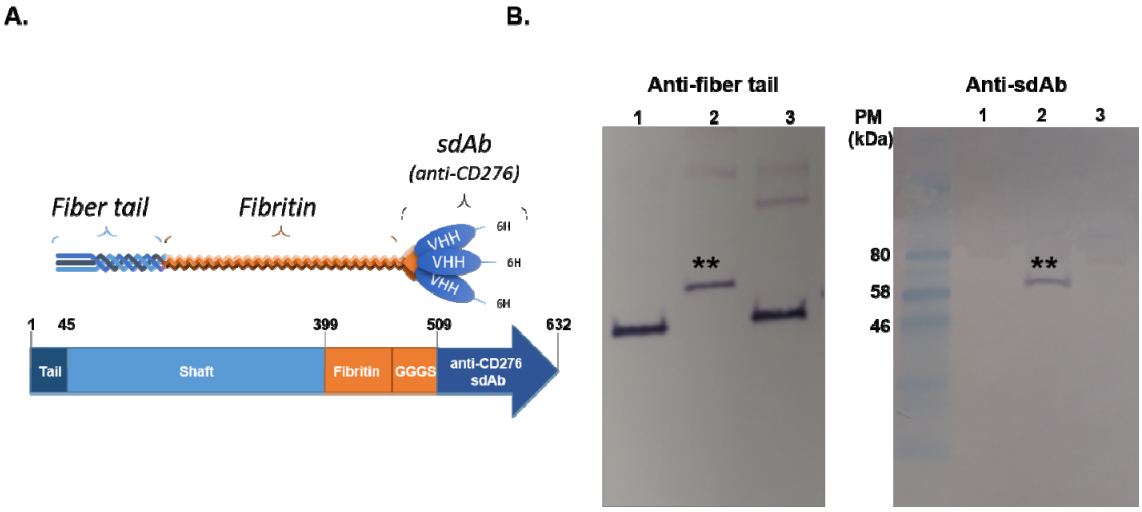
Schema to accomplish *in vivo* targeting via the CD276 axis exploiting camelid single domain antibody (sdAb) incorporated into the adenoviral vector capsid.



To achieve in vivo targeting for gene therapy, fiber-fibritin fused with camelid single domain antibody (sdAb) for fiber modification strategies were proposed into adenovirus. The Ad5 fiber knob was replaced to sdAb against CD276 (anti-CD276 sdAb), as a novel target binding moiety for tumor marker (B7-H3:CD276) targeting in vivo gene transduction.

Figure 2.

Confirmation of capsid incorporation of engineered fiber with anti-CD276 sdAb.

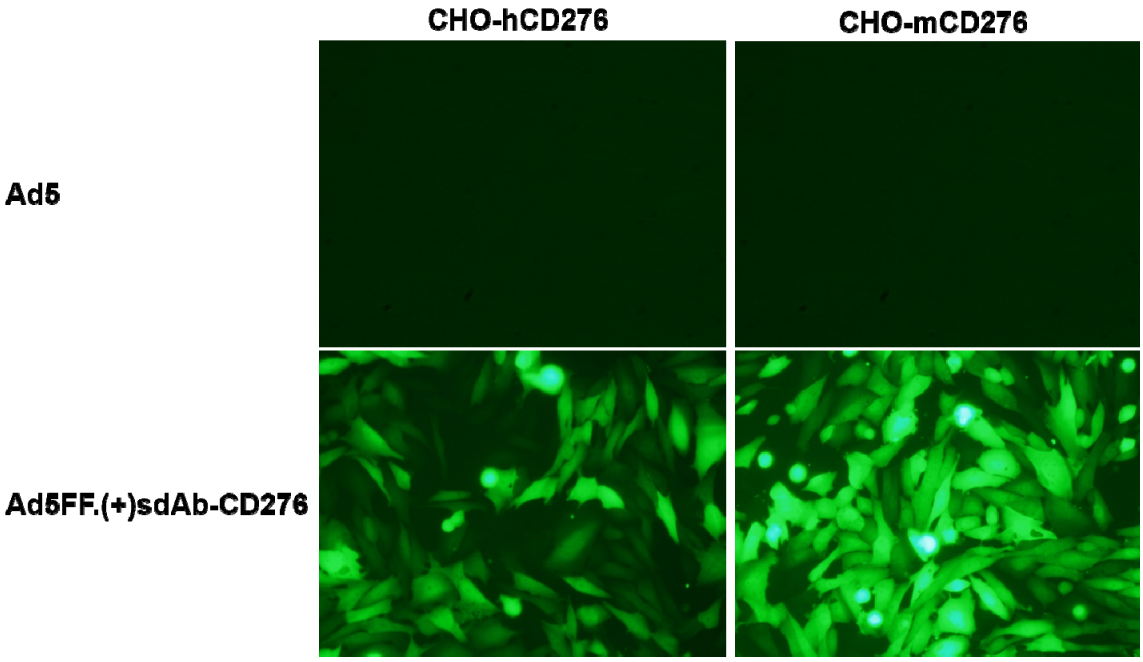


A, The schematic of fiber-fibritin (Ad5.ff) viral genomes with sdAb-CD276 were shown in arrow. The sdAb CD276 targeting moieties is fused to the entire fibritin protein with the trimerizing foldon domain of bacteriophage T4 followed by 4xGGGS peptide linker

connected to the sdAb open reading frame (ORF). And, the 6x-his tag protein was fused into C-terminal of sdAb-CD276 for evaluation the sdAb-CD276 incorporation. **B,** Evaluation of sdAb-CD276 incorporation into Ad5.ff proteins from purified engineered virion using western blotting analysis with specific antibodies (Abs). $5x10^9$ vp of each of purified engineered virions were subjected to SDS-PAGE followed by western blot analysis using anti-fiber tail (anti-4D2 Ab), or anti-sdAb (anti-tetra His Abs), respectively. The line number two band corresponding to Ad5 fiber tail proteins (shown in **left blot**) with expected MW and 6x-his tagged protein (shown in **right blot**), that means that the engineered virion has sdAb-CD276 into capsid viral particle (line 2), all bands detected using secondary anti-mouse Abs conjugated with alkaline phosphatase. Line 1; Ad5ff. (-) sdAb-CD276.H5/H3, Line 2; Ad5ff. (+) sdAb-CD276.H5/H3, and Line 3; Ad5

Figure 3.

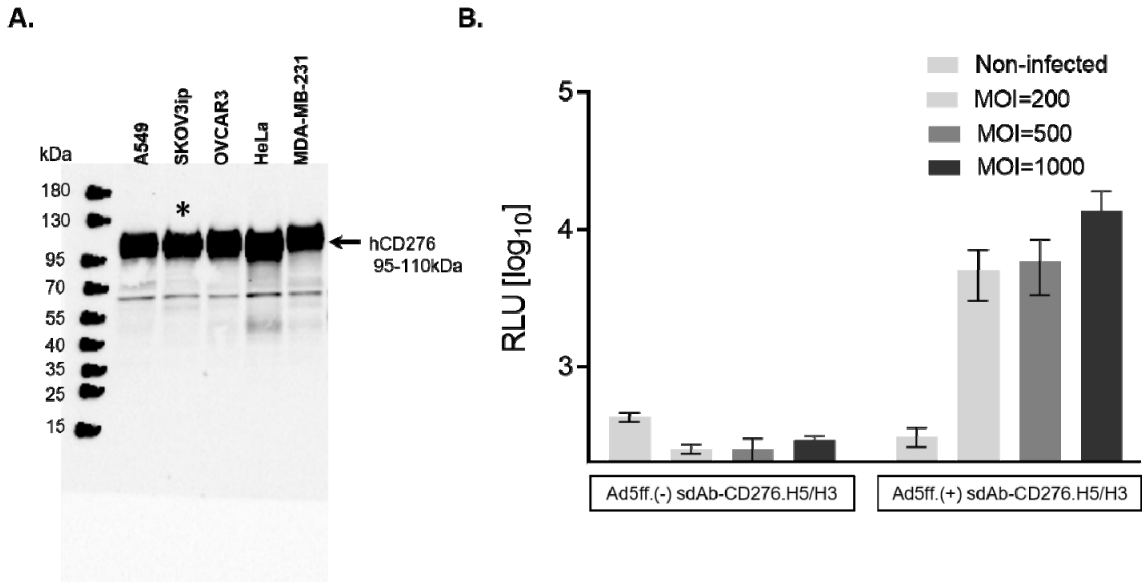
Targeted gene delivery *in vitro* via CD276 axis by adenoviral vector incorporating anti-CD276 sdAb to modified CHO cell lines.



The virus retargeting efficacy was evaluated in CHO (Chinese Hamster Ovary) cell lines (CHO-human CD276 over expressed and CHO-mouse CD276 over expressed cell line). These cell lines were kindly provided by Dr. Brad St. Croix]. The cells were infected with indicated virus [Ad5 or Ad5ff. (+) sdAb-CD276.H5/H3] at a multiplicity of infection (MOI) of 100, and EGFP expression were imaged on two days (48h) after virus infection using fluorescence microscopy.

Figure 4.

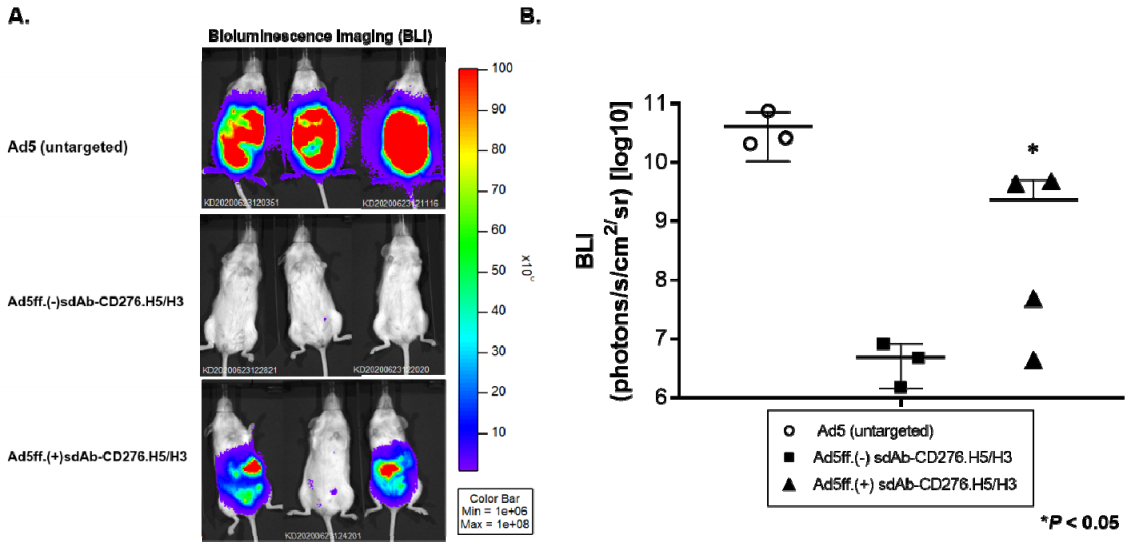
Targeted gene delivery to human tumor cells via CD276 axis by tropism modified adenovirus.



A, Expression of CD276 in human tumor cell lines. Different human cancer cell lines (including diverse of ovarian or breast cancer cells [e.g. SKOV3ip or MDA-MB-231]) were assessed to check the hCD276 gene expression using human CD276 primary antibody by western blotting analysis. **B,** Gene delivery to human ovarian cancer cell line via targeted and non-targeted adenoviral vectors. Further evaluating of the CD276 specific targeting transduction efficiency of the targeted adenoviral vector [Ad5ff. (+) sdAb-CD276.H5/H3 and non-targeted Ad as a control virus], indicated virus were infected in the human ovarian cancer cells (SKOV3ip)**.** The targeting transduction efficiency was evaluated with different MOI (MOI; 200, 500 or 1000) by measuring of firefly luciferase gene activity (RLU: relative light units) at 48h post infection. Of note, a control was consisted with CD276 untargeted Ad encoding firefly luciferase reporter gene [Ad5ff. (-) sdAb-CD276.H5/H3: CD276 sequence was inverted, non-functional activity of CD276]. The data was supported our targeted vector for in *vivo* study, as expected our specific targeting purposes.

Figure 5.

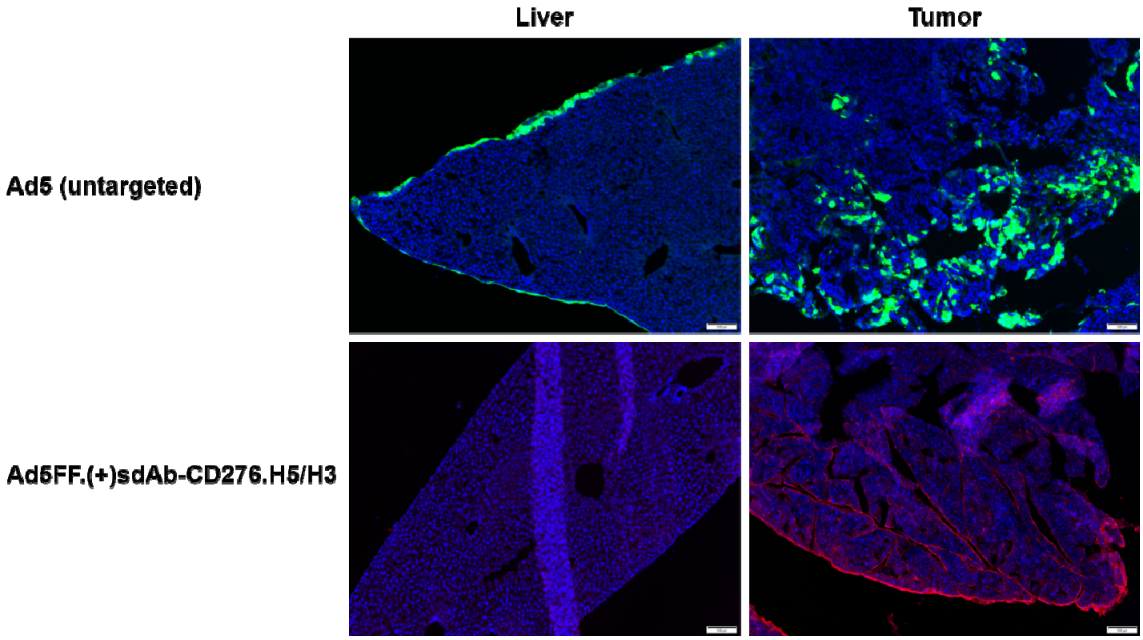
Evaluation of *in vivo* gene delivery of CD276-targeted adenoviral vector in orthotopic xenograft model of human ovarian cancer.



A, In *vivo* monitoring of firefly luciferase expression *via* the virus for gene transduction by bioluminescence (BLI) analysis under same scale in the indicated mice [untargeted Ad5, Ad5ff. (-) sdAb-CD276.H5/H3, and Ad5ff. (+) sdAb-CD276.H5/H3] were intraperitoneally injected (i.p) for 3 following days. The detail *In vivo* study schema with OvCa xenograft mouse model was described in Materials and Methods. The BLI images from individual mice from each groups shown in **A**. **B,** BLI images and corresponding signal quantification were analyzed. Quantification of total photon flux was measured from indicated mice body regions of interest (ROIs) via Living Image 2.6 software. Data are expressed as BLI bioluminescence (photon/s/cm^2/sr), mean ± SD (n = 3-4 animals per each of the groups). The non-targeted adenoviral vector [Ad5ff. (-) sdAb-CD276.H5/H3: CD276 sequence was inverted into virus, non-functional activity of CD276] was also assessed under the same conditions. Significant differences of among groups were analyzed by analysis of variance (ANOVA) using GraphPad Prism (La Jolla, CA, USA). Significance was established at the ***P* < 0.05**, as indicated in the figure.

Figure 6.

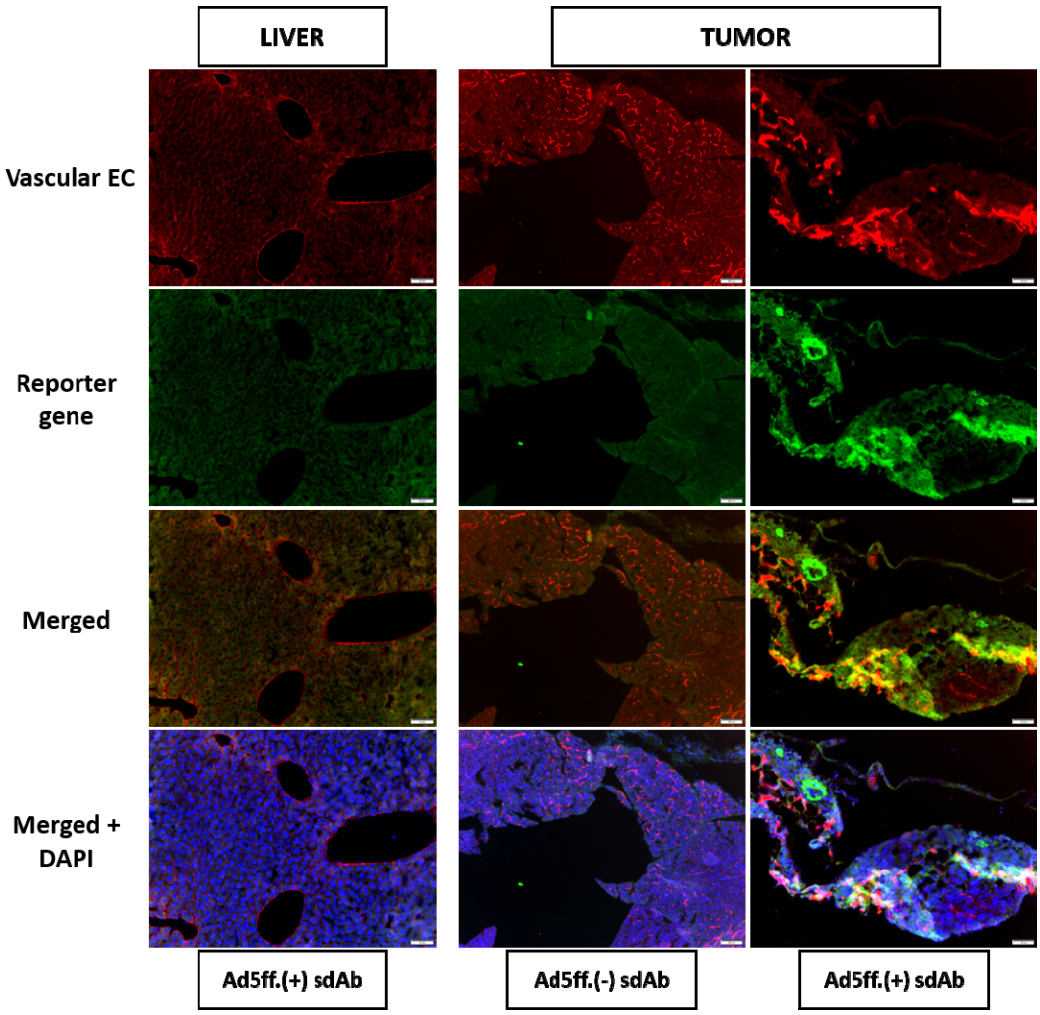
Analysis of targeted versus ectopic *in vivo* gene delivery of adenoviral vectors in human ovarian cancer model.



The ectopic gene transduction in *vivo* with sdAb-CD276 targeted adenoviral vector was analyzed in the tissues (liver and tumor) using histopathological image analysis. OvCa tumor (SKOV3ip) bearing mice were intraperitoneally injected with $1x10^{11}$ vp of viruses (each of untargeted Ad5 or CD276 targeted [Ad5ff. (±) sdAb-CD276.H5/H3]) *via* i.p injection, and liver and tumor (omentum tissues) were harvest at three days later for immunohistochemistry staining (IHC) analysis. Blue: nuclei (stained with Hoechst 33258), Green: GFP signal through untargeted Ad5-EGFP vector, and Red: RFP signal through targeted Ad vector [Ad5ff. (±) sdAb-CD276.H5/H3], the transgene was detected with anti-firefly luciferase (Luc) antibody.

Figure 7.

Evaluation of specificity of *in vivo* gene delivery accomplished by CD276 targeted adenoviral vector.



The targeting specificity of *in vivo* gene delivery was verified in the context of vascular ECs. The tissue slices were co- stained with vascular EC markers CD31 and endomucin (Red), combined with luciferase gene (Green) using each of specific primary antibodies for Immunohistochemistry fluorescence analysis. The images were taken using epifluorescence microscopy (Olympus America, Center Valley, PA). The transduced gene expression via CD276 targeting adenoviral vector was verified by reporter gene (firefly luciferase gene), that was evaluated the co-localization signal in the tumor vascular ECs with combined signal. Reporter gene has shown co-localized with vascular ECs in yellow (Merge). Blue: nuclei (stained with Hoechst 33258), red: vascular ECs (CD31/endomucin), green: reporter gene (acquisition of firefly luciferase gene with anti-firefly luc Abs), and yellow: merged (reporter gene expression in vascular ECs). The non-targeting adenoviral vector [Ad5ff. (-) sdAb-CD276] was compare as a control, both

adenoviral vectors were shown in liver un-targeting via H5/H3 hexon modification (liver data shown only in targeting Ad [Adff. (+) sdAb-CD276]).

Other Support for David T. Curiel

Active Support

R01 CA211096 (Curiel) 1.80
6/19/2017-5/31/2022 National Institutes of Health calendar
Novel targeted adenovirus
The goal of this project is to develop targeted adenoviral vectors and thereby address key proof-of-principle issues of field wide relevance.
Role: Principal Investigator

not assigned (Aboody, Karen) 0.12
7/1/2017-5/11/2021 The Ivy Foundation calendar
Neural Stem Cell -Oncolyric virotherapy for brain tumors
The overall objective of this application is to significantly advance NSC-mediated virotherapy as a novel treatment for newly diagnosed and recurrent glioma patients.
Role: Principal Investigator

UH3 HL141800 (George) 0.96
9/1/2017-7/31/2022 National Institutes of Health calendar
A 3D in vitro disease model of atrial conduction
The central objective of this proposal is to create and validate a robust 3D in vitro microphysiological model of human atrial conduction utilizing patient-derived induced pluripotent stem cells. The model can be used to test the safety and efficacy of drugs to treat atrial arrhythmias such as atrial fibrillation (AF) in a precision medicine format. In addition, we will create and test an adenoviral-based strategy to delivery CRISPRi technology to selectively and inducibly knockdown gene regulatory transcription factors as a novel strategy to intervene in atrial arrhythmias such as AF.
Role: Principal Investigator

R41 TR001869 (Curiel) 0.60
9/18/2018-8/31/2020 National Institutes of Health calendar
NOVEL PLATFORM TECHNOLOGY FOR HEMOPHILIA GENE THERAPY
We propose to develop a novel vector approach that addresses the key limitations to current methods and utilizes the unique capacity to target pulmonary endothelium for reconstituting deficient serum factors. We will accomplish this by combining technologies from Washington University and Precision Virologics, Inc. In Phase I we will demonstrate the feasibility of the new platform technology to efficiently deliver to pulmonary endothelium and achieve stable long-term correction of factor VIII deficient mice.
Role: Principal Investigator

18-06 (Curiel) 1/1/2019-12/31/2020 0.60
University of Missouri calendar
TARGETED GENE THERAPY FOR SPINAL TUMORS
The goal of this project is to advance targeting to tumor endothelial cells to realize vector technology that will make effective gene therapy for intramedullary glioma feasible. We hypothesize that our optimized targeting to tumor neoangiogenesis will feasibilize an effective gene therapy for glioma IMSCT, providing the basis of a novel translational approach for this intractable cancer.
Role: Principal Investigator

20-FY19-01 (Gillanders/Curiel) 1/1/2019-12/31/2020 1.20
Siteman Cancer Center calendar
Evaluation of a Novel Personalized Vaccine Strategy for Breast Cancer
The goal is to activate immune cells capable of recognizing and killing breast cancer using the "prime/boost" neoantigen vaccines, and then take the "brakes" off these immune cells using checkpoint blockade therapy. This combination has the potential to be a synergistic and highly effective strategy in TNBC, and in other cancers, particularly cancers resistant to checkpoint blockade therapy alone.
Role: Principal Investigator

PR182272 (Abate) 0.24
4/1/2019-9/30/2020 Department of Defense calendar
A novel approach to enhance TB lung immunity
A prime-pull approach using chemokines to recruit immune cells into the lungs will help control TB infection and disease.
Role: Co-Investigator

R01 EB026468 (Curiel) 1.20
7/1/2019-3/31/2023 National Institutes of Health calendar
Novel Vector Platform for Gene Therapy
The goal of this proposal is to develop a novel gene therapy approach for alpha 1-antitrypsin deficiency (AAT) lung disease by expressing AAT in the lower respiratory tract and to demonstrate the efficacy of this strategy in a new murine model of the disease.
Role: Principal Investigator

UG3 TR002851 (Curiel) 3.60
8/15/2019-7/31/2022 National Institutes of Health calendar
Endothelial-targeted adenovirus for organ-selective gene editing in vivo
The goal of this proposal is to develop adenoviral vectors targeted to endothelial subsets and to exploit this delivery technology to achieve gene editing at these cellular targets.
Role: Principal Investigator

R01 CA240983 (Gillanders/Schreiber) 0.30
9/1/2019-7/31/2023 National Institutes of Health calendar
Targeting Neoantigens in Triple Negative Breast Cancer
We propose both clinical and preclinical studies on neoantigen DNA vaccines +/- anti-PD-L1. We will conduct a randomized phase 1 clinical trial of neoantigen DNA vaccines +/- anti-PD-L1 (durvalumab) in patients with persistent triple negative breast cancer following neoadjuvant chemotherapy. Preclinical studies in breast cancer mouse models will focus on recombinant adenovirus-plasmid DNA neoantigen vaccine prime-boost strategies or targeting of macrophages in the tumor microenvironment. Combined, these studies will allow functional validation of our epitope prediction algorithms and inform the design of second generation neoantigen vaccine strategies.
Role: Co-Investigator

not assigned (Curiel) 0.60
1/1/2020-12/31/2020 CMMN-Cancer Center calendar
Bone marrow niche mobilization for metastatic disease
The major challenge to exploit metastatic niche endothelium for therapeutic intent is the issue of selective access to this site. We potentially have a solution to this barrier. We have developed adenoviral (Ad) vectors that are capable of selective gene delivery to EC. Now we are positioned to address the heretofore elusive hypothesis that malignant

cellular eviction from metastatic niches will control tumor growth and also function in combination with antineoplastic therapies.
Role: Principal Investigator

(Ornitz) 0.36
2/1/2020-1/31/2023 Children's Discovery Institute calendar
Targeting the FGF signaling pathway as a novel therapy for hypoxia-induced pulmonary hypertension
This proposal will investigate how FGF signaling regulates the pathogenesis of pulmonary hypertension, and how it can be used to prevent or treat pulmonary hypertension in premature infants and children with lung disease.
Role: Co-Investigator

not assigned (Curiel) 0.60
3/2/2020-3/1/2022 Emerson Collective Cancer Research Fund calendar
In vivo generation of CAR T-cells for cancer immunotherapy
We have developed adenovirus-based vectors capable of gene transfer to specific target cells in an intact human. This highly original approach will thus allow more facile local and worldwide implementation of CAR T-cell immunotherapy, thereby allowing application of this promising approach for the widest range of patients and cancers.
Role: Principal Investigator

UH3 HL141800 (Curiel/George/Rentschler) 0.60
5/15/2020-5/14/2021 National Institutes of Health calendar
A 3D IN VITRO DISEASE MODEL OF ATRIAL CONDUCTION
Mechanistic Studies and Model Development to Understand Cardiac Injury in SARS-CoV-2 Infection.
Specific Aim 1: Determine viral tropism in healthy and predisposed adult human cardiac tissue using human cardiac organotypic slices.
Specific Aim 2: Delineate the mechanistic relationship between Notch signaling and the IL-6 release on cardiac electrophysiology.
Specific Aim 3: Establishment of an in vivo murine model for testing SARS-CoV-2 cardiac effects.
Role: Principal Investigator

R01 AI130190 (Hoft) 0.30
4/1/2021-3/31/2026 National Institutes of Health calendar
Universal T cell targeted influenza vaccine
We will identify and evaluate vaccine targets relevant for human infection with highly diverse strains of influenza A virus which cause seasonal epidemics or more serious pandemics. We will prepare several novel vaccines focused on inducing relevant immune cell types, and test these vaccines in humanized mice with the ultimate goal of developing a “universally relevant” influenza vaccine.
Role: Principal Investigator

Completed Support

R21 AI131254 (Curiel) 3/20/2017-2/28/2020
National Institutes of Health
Gorilla Adenovirus Zika Vaccine for Humans
A key question that will be explored in this proposal is whether protective humoral responses will be greater when soluble E or the prM/M-E subviral particle (SVP) is the

immunogen in the context of Ad-based vaccines.
Role: Principal Investigator

PR172217 (Hoft) 5/1/2018-10/31/2019
Department of Defense
Universal Influenza T-Cell targeted Mucosal Vaccines
The goals of this project are to develop T-cell-based influenza vaccines which provide long term heterotypic immunity
Role: Principal Investigator

UG3 HL141800 (George/Rentschler/Curiel) 9/20/2018-7/31/2019
National Institutes of Health
A 3D in vitro disease model of atrial conduction
Impact of Opioids on Atrial and Ventricular Conduction
The primary goal of this project is toinvestigate the impact of opioids on the electrical conduction patterns in the heart (both atria and ventricles) using our novel in vitro and ex vivo model and viral vector drug delivery systems.
Role: Principal Investigator

Other Support for Igor Dmitriev

Active

R01 CA211096 (Curiel) 3.00
6/19/2017-5/31/2022 National Institutes of Health calendar
Novel targeted adenovirus
The goal of this project is to develop targeted adenoviral vectors and thereby address key proof-of-principle issues of field wide relevance.
Role: Co-Investigator

UH3 HL141800 (George) 2.00
9/1/2017-7/31/2022 National Institutes of Health calendar
A 3D in vitro disease model of atrial conduction
The central objective of this proposal is to create and validate a robust 3D in vitro microphysiological model of human atrial conduction utilizing patient-derived induced pluripotent stem cells. The model can be used to test the safety and efficacy of drugs to treat atrial arrhythmias such as atrial fibrillation (AF) in a precision medicine format. In addition, we will create and test an adenoviral-based strategy to delivery CRISPRi technology to selectively and inducibly knockdown gene regulatory transcription factors as a novel strategy to intervene in atrial arrhythmias such as AF.
Role: Co-Investigator

18-06 (Curiel) 1/1/2019-12/31/2020 2.16
University of Missouri calendar
TARGETED GENE THERAPY FOR SPINAL TUMORS
The goal of this project is to advance targeting to tumor endothelial cells to realize vector technology that will make effective gene therapy for intramedullary glioma feasible. We hypothesize that our optimized targeting to tumor neoangiogenesis will feasibilize an effective gene therapy for glioma IMSCT, providing the basis of a novel translational approach for this intractable cancer.
Role: Co-Investigator

20-FY19-01 (Gillanders/Curiel) 1/1/2019-12/31/2020 1.80
Siteman Cancer Center calendar

Evaluation of a Novel Personalized Vaccine Strategy for Breast Cancer
The goal is to activate immune cells capable of recognizing and killing breast cancer using the "prime/boost" neoantigen vaccines, and then take the "brakes" off these immune cells using checkpoint blockade therapy. This combination has the potential to be a synergistic and highly effective strategy in TNBC, and in other cancers, particularly cancers resistant to checkpoint blockade therapy alone.
Role: Co-Investigator

PR182272 (Abate) 1.80
4/1/2019-9/30/2020 Department of Defense calendar
A novel approach to enhance TB lung immunity
A prime-pull approach using chemokines to recruit immune cells into the lungs will help control TB infection
and disease.
Role: Co-Investigator

R01 EB026468 (Curiel) 3.00
7/1/2019-3/31/2023 National Institutes of Health calendar
Novel Vector Platform for Gene Therapy
The goal of this proposal is to develop a novel gene therapy approach for alpha 1-antitrypsin deficiency (AAT) lung disease by expressing AAT in the lower respiratory tract and to demonstrate the efficacy of this strategy in a new murine model of the disease.
Role: Co-Investigator

UG3 TR002851 (Curiel) 4.80
8/15/2019-7/31/2022 National Institutes of Health calendar
Endothelial-targeted adenovirus for organ-selective gene editing in vivo
The goal of this proposal is to develop adenoviral vectors targeted to endothelial subsets and to exploit this delivery technology to achieve gene editing at these cellular targets.
Role: Co-Investigator

(Ornitz) 0.60
2/1/2020-1/31/2023 Children's Discovery Institute calendar
Targeting the FGF signaling pathway as a novel therapy for hypoxia-induced pulmonary hypertension
This proposal will investigate how FGF signaling regulates the pathogenesis of pulmonary hypertension, and how it can be used to prevent or treat pulmonary hypertension in premature infants and children with lung disease.
Role: Co-Investigator

UH3 HL141800 (Curiel/George/Rentschler) 2.40
5/15/2020-5/14/2021 National Institutes of Health calendar
A 3D IN VITRO DISEASE MODEL OF ATRIAL CONDUCTION
Mechanistic Studies and Model Development to Understand Cardiac Injury in SARS-CoV-2 Infection.
Specific Aim 1: Determine viral tropism in healthy and predisposed adult human cardiac tissue using human cardiac organotypic slices.
Specific Aim 2: Delineate the mechanistic relationship between Notch signaling and the IL-6 release on cardiac electrophysiology.
Specific Aim 3: Establishment of an in vivo murine model for testing SARS-CoV-2 cardiac effects.
Role: Co-Investigator

R01 AI130190 (Hoft) 1.20
4/1/2021-3/31/2026 National Institutes of Health calendar
Universal T cell targeted influenza vaccine
We will identify and evaluate vaccine targets relevant for human infection with highly diverse strains of influenza A virus which cause seasonal epidemics or more serious pandemics. We will prepare several novel vaccines focused on inducing relevant immune cell types, and test these vaccines in humanized mice with the ultimate goal of developing a “universally relevant” influenza vaccine.
Role: Co-Investigator

Completed Support

PR172217 (Hoft) 5/1/2018-10/31/2019
Department of Defense
Universal Influenza T-Cell targeted Mucosal Vaccines
The goals of this project are to develop T-cell-based influenza vaccines which provide long term heterotypic
immunity
Role: Co-Investigator

UG3 HL141800 (George/Rentschler/Curiel) 9/20/2018-7/31/2019
National Institutes of Health
A 3D in vitro disease model of atrial conduction
Impact of Opioids on Atrial and Ventricular Conduction
The primary goal of this project is to
investigate the impact of opioids on the electrical conduction patterns in the heart (both atria and ventricles) using our novel in vitro and ex vivo model and viral vector drug delivery systems.
Role: Co-Investigator