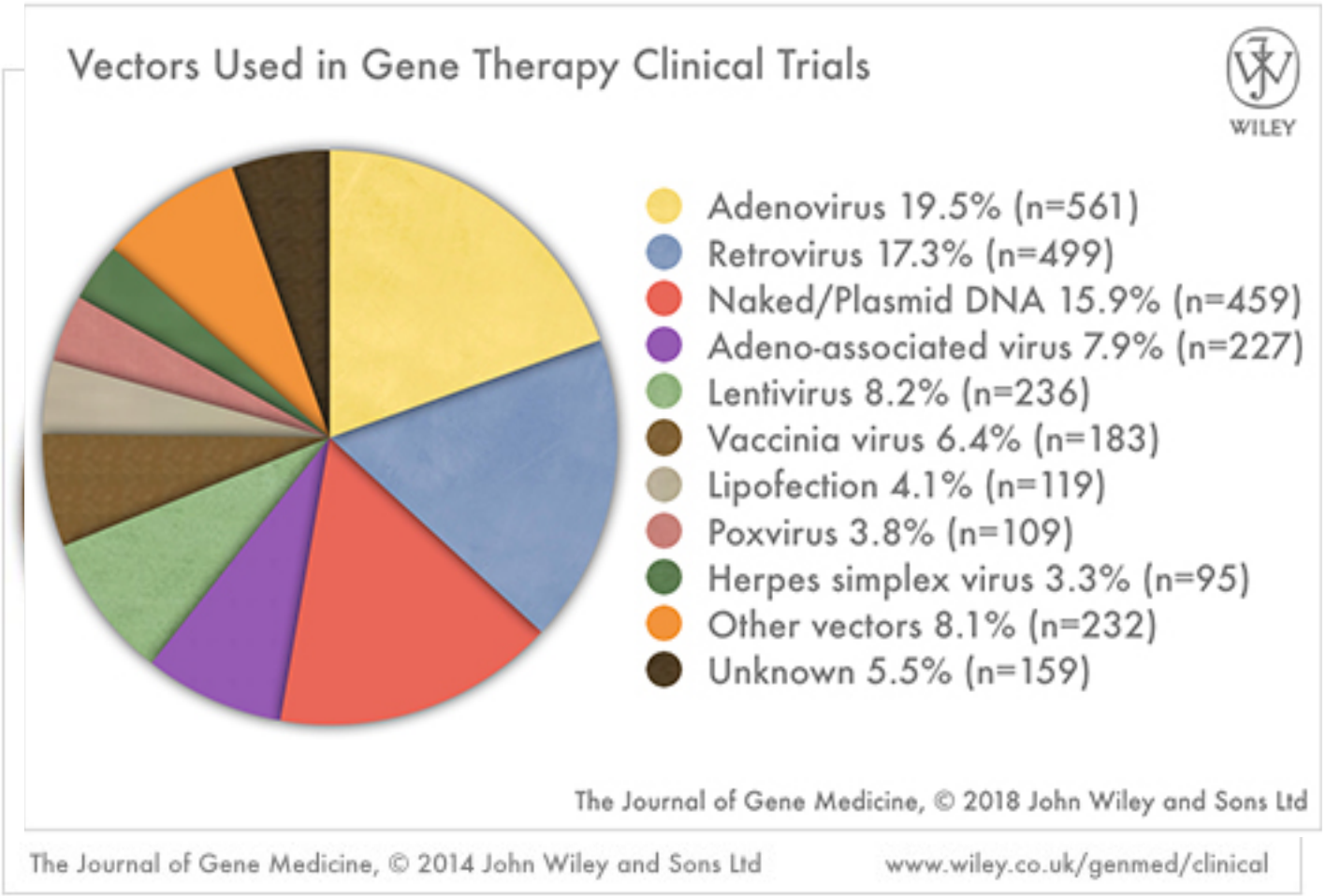
Ad &AAV application

adenovector accounts for 19,5 % of the trials (2018)



http://www.wiley.co.uk/genetherapy/clinical/

Cystic Fibrosis

- **CF is an autosomal recessive genetic disease caused by mutations in the CFTR gene**
- **1 in 20 Caucasians are carrier for mutations in CFTR; 1/2500 affected**
- **CF patients presents pancreatic insufficiency, increased NaCl sweat concentration, male infertility and airway disease (chronic infection and inflammation**

Gene therapy

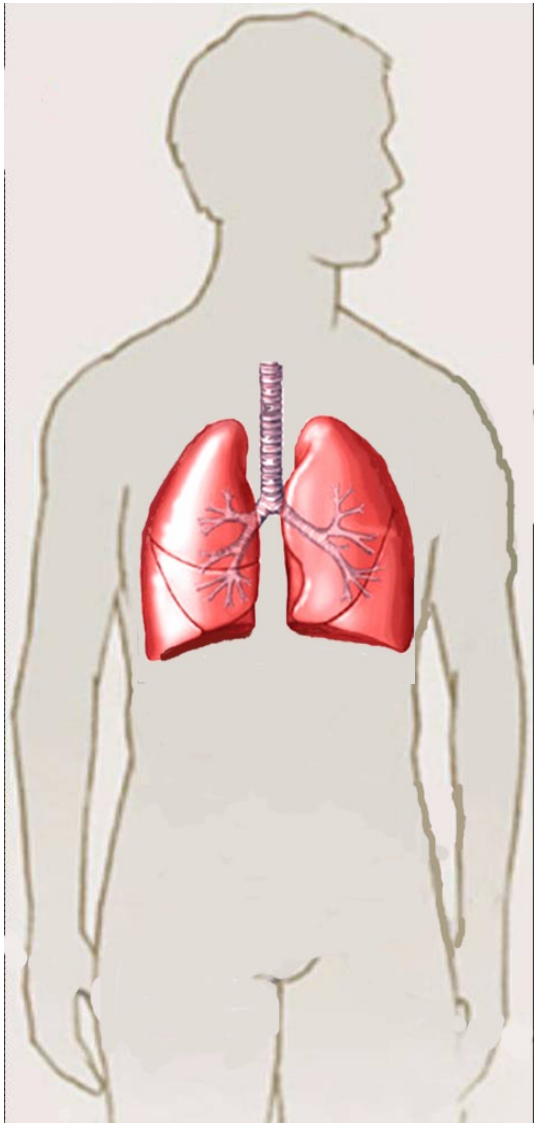
- **Correction of 5-10% of CF- cells restore some function in animal models (Dorin JR et al., 1997)**

Pharmacological approaches

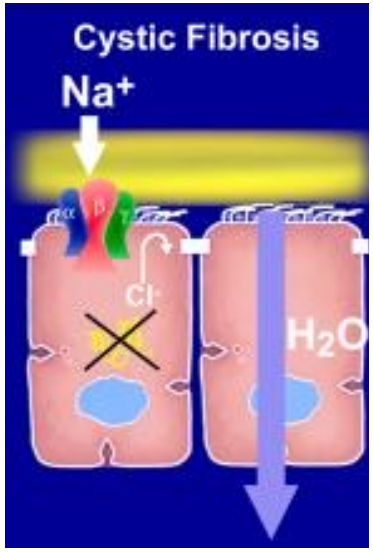
- **New anti-microbial strategies**
- **Anti-inflammatory**

New targets

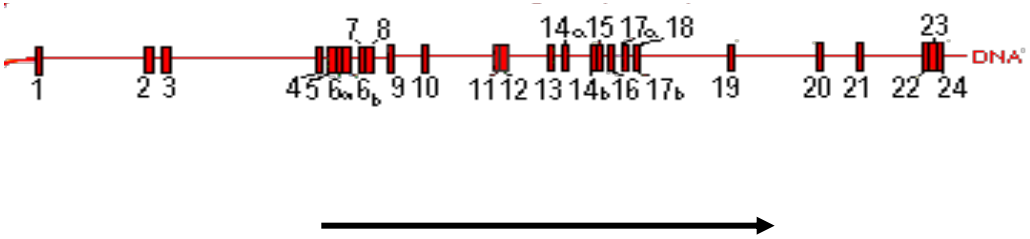
- **Suppressor genes**
- **Immune cells**



Cystic Fibrosis gene therapy: addition of a functional CFTR gene to target cells



Human CFTR locus (250 kb)



1992: Ad-CFTR in animal model

Recognizing that adenoviruses were trophic for the human airway epithelium, we realized that our in vivo gene transfer strategy would be ideal to transfer the human CFTR cDNA to the airway epithelium to treat cystic fibrosis. We quickly constructed an E1 - E3 - serotype 5 adenovirus gene transfer vector with an expression cassette that included the normal human CFTR cDNA under control of a constitutive promoter.

Cell. **1992** Jan 10;68(1):143-55.

In vivo transfer of the human cystic fibrosis transmembrane conductance regulator gene to the airway epithelium.

Rosenfeld MA[1], Yoshimura K, Trapnell BC, Yoneyama K, Rosenthal ER, Dalemans W, Fukayama M, Bargon J, Stier LE, Stratford-Perricaudet L, et al.

Author information

Abstract

Direct transfer of the normal cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene to airway epithelium was evaluated using a replication-deficient recombinant adenovirus (Ad) vector containing normal human CFTR cDNA (Ad-CFTR). In vitro Ad-CFTR-infected CFPAC-1 CF epithelial cells expressed human CFTR mRNA and protein and demonstrated correction of defective cAMP-mediated Cl- permeability. Two days after in vivo intratracheal introduction of Ad-CFTR in cotton rats, in situ analysis demonstrated human CFTR gene expression in lung epithelium. PCR amplification of reverse transcribed lung RNA demonstrated human CFTR transcripts derived from Ad-CFTR, and Northern analysis of lung RNA revealed human CFTR transcripts for up to 6 weeks. Human CFTR protein was detected in epithelial cells using anti-human CFTR antibody 11-14 days after infection. While the safety and effectiveness remain to be demonstrated, these observations suggest the feasibility of in vivo CFTR gene transfer as therapy for the pulmonary manifestations of CF.

The publication in Cell demonstrating **effective *in vivo* transfer of** the human cystic fibrosis transmembrane conductance regulator (CFTR) **cDNA to the epithelium of cotton rats**. The expression of the human CFTR protein in the airway epithelium was detected by an antibody 2 weeks after intratracheal administration of an E1 - E3 - serotype adenovirus vector expressing the human CFTR cDNA (Rosenfeld et al., 1992).

The cystic fibrosis clinical trials started in 1993

The team:
Crystal NG at the National Heart, Lung, and Blood Institute, **Jim Wilson** (Pensilvania University), **Mike Welsh** at Iowa and his colleagues at Genzyme.

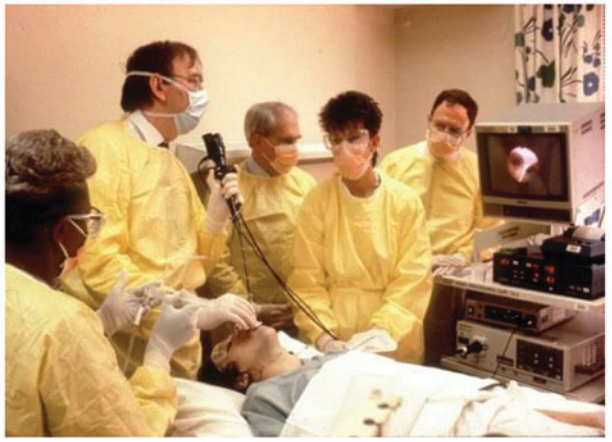
In a historic (for the gene therapy field) meeting at the NIH DNA Recombinant Advisory Committee meeting on December 4, 1992, with over 200 scientists, media, venture capitalists, and representatives from pharma in the audience, all three groups had protocols approved.

On April 16, 1993, a 23-year-old man with cystic fibrosis homozygous for the DF508 mutation of the CFTR gene was the first human to undergo *in vivo* gene therapy with administration of an E1- E3-minus recombinant adenovirus vector coding for the normal human CFTR cDNA to the nasal epithelium. One day later, using a fiberoptic bronchoscope, we administered 2 x 10^8 plaque-forming units of the same vector to the airway epithelium, an event that got worldwide media attention.

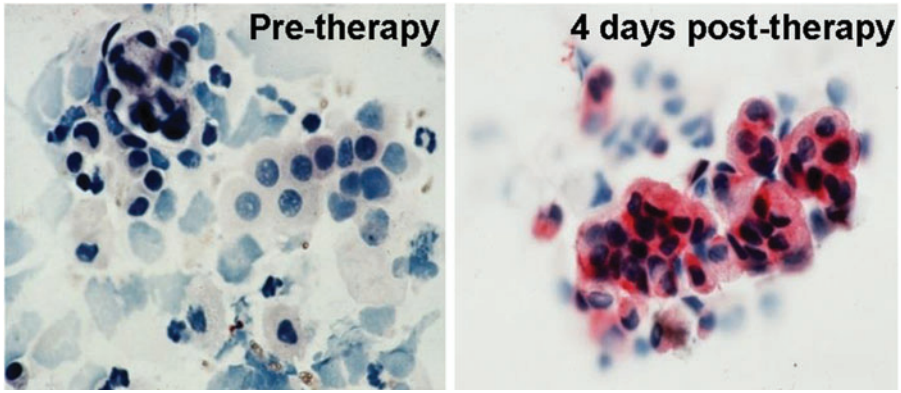
The Wilson and Welsh/Genzyme groups initiated their clinical studies soon afterward, with all three groups publishing their results within the next few years (Zabner et al., 1993; Crystal et al., 1994; Zuckerman et al., 1999).

the first human gene therapy with a recombinant virus

On April 16, 1993, at the Clinical Center, NIH, a 23-year-old man with cystic fibrosis received an adenovirus coding for the normal human CFTR cDNA to the nasal epithelium.
On the next day, the patient underwent fiberoptic bronchoscopy and 2 x10^8 plaque-forming units of the vector was delivered through a catheter to the bronchial epithelium.
The airways can be seen on the monitor. In the photo, left to right: staff nurse delivering the vector via a syringe, G. McElvaney, R. Crystal, staff nurse, and J. Hay.



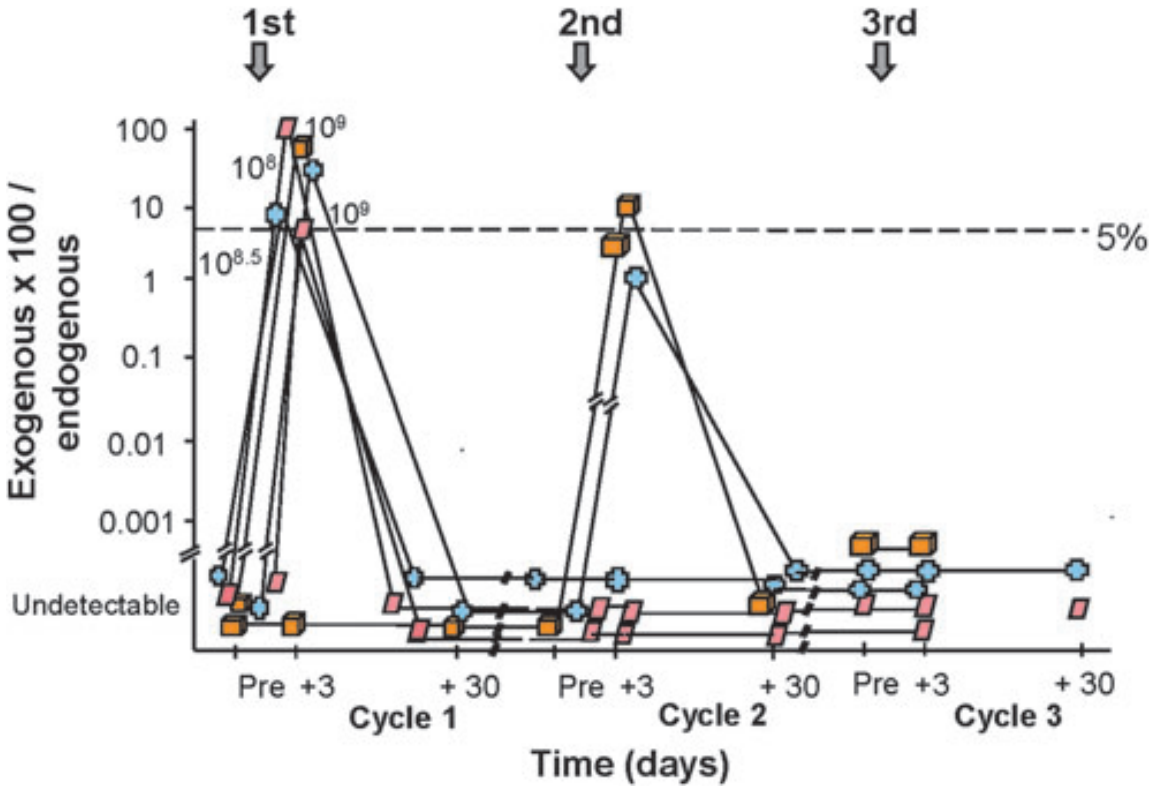
Successful gene transfer to the airway epithelium was demonstrated by anti-human CFTR antibody detection of CFTR before (left) and 4 days after (right) vector administration. The CFTR protein is stained red (Rosenfeld et al., 1992).



Repetive treatment

Harvey, B.G., Leopold, P.L., Hackett, N.R., et al. (1999). Airway epithelial CFTR mRNA expression in cystic fibrosis patients after **repetitive administration of a recombinant adenovirus**. J. Clin. Invest. 104, 1245–1255.

Therapeutic levels of CFTR mRNA in the airway epithelium of patients with cystic fibrosis could be achieved with the first administration.
This would quickly wane, and subsequent administrations were limited by immunity against the vector, with reduced yield of expression with each repeat of administration.



Quantitative assessment of the airway epithelium for the percentage of exogenous CFTR mRNA derived from the adenovirus vector compared with endogenous CFTR mRNA (individual's own CFTR gene expression) as a function of dose and time (baseline, days 3 and 30) after endobronchial spray of the first administration (cycle 1), second administration (cycle 2), and third administration (cycle 3) of the vector.
The dashed line represents the target 5% level of exogenous vector-derived CFTR mRNA, that is, the level above which there should be sufficient levels of normal CFTR mRNA to correct the defect.
Each symbol represents a different individual. Note that correction was achieved 3 days after the first administration (vector-derived mRNA levels all above the 5% level needed for correction), but this wanes by 30 days. Repeat administration (cycle 2) barely achieved this level, and the third administration resulted in no vector-derived CFTR mRNA expression. Adapted from Harvey et al. (1999).

Immune response

Ad vectors induced potent immune responses upon systemic application

Responses are directed against both the vector capsid and the low levels of Ad capsid proteins expressed from the vector

While gutless adenovirus vectors may be the answer, it is likely that the potent adenovirus capsid immunogens will outsmart the most clever vectorology.

This limits transgene expression and reduces the capacity for vector re-administration

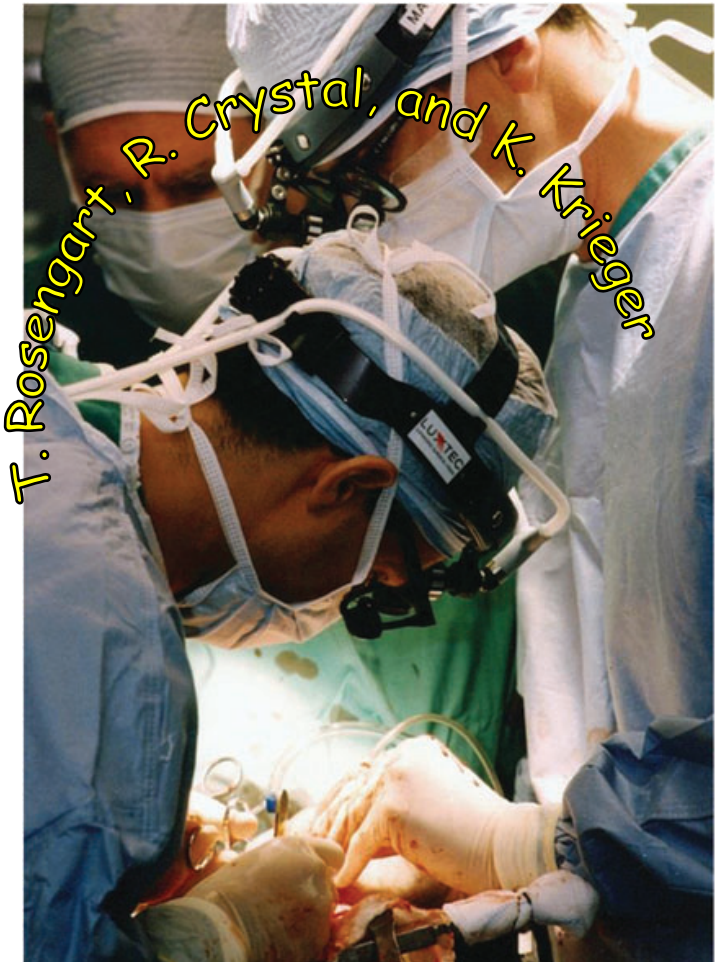
Such vectors induced potent immune responses upon systemic application.
Responses are directed against both the vector capsid and the low levels of Ad capsid proteins expressed from the vector. Induction of immune responses limits transgene expression and reduces the capacity for vector re-administration. While the immunogenicity of these vectors may be reduced by the deletion of additional genes, the immunogenic nature of Ad vectors means **that these viruses are better suited to applications for which prolonged transgene expression is not required**. The use of Ad vectors in vaccination to protect against a range of infectious pathogens has therefore proved to be a common strategy.
A significant proportion of gene therapy studies have also been designed to target cancers, where only short-term gene expression is required.

Capitalizing on antiadenovirus immunity

Short-term expression is ideal for clinical applications in which the goal is to build new biologic structures.

Use of adenovirus to express angiogenic genes such as vascular endothelial growth factor (VEGF) in the myocardium **to generate new coronary vasculature**. In this application, the antivector immunity limits expression of the VEGF to 1–2 weeks, which is ideal for initiating angiogenesis and short enough to prevent excess blood vessels and hemangioma formation (Mack et al., 1998; Patel et al., 1999).

1997 - The first human studies with direct administration to the heart of individuals with diffuse coronary artery disease of an adenovirus vector coding for VEGF 121, one of the two isoforms of VEGF (Rosengart et al., 1999a,b, 2013



Noboru Sato, Philip L. Leopold, and Ronald G. Crystal. Induction of the hair growth phase in postnatal mice by localized transient expression of Sonic hedgehog. *J. Clin. Invest.* **104:855–864** (1999).

Abstract

Hair follicles form in prenatal skin and mature in the postnatal period, establishing a growth cycle in 3 phases: telogen (resting), anagen (growth), and catagen (regression). Based on the knowledge that Sonic hedgehog (Shh) expression is necessary for the embryonic development of hair follicles, and that anagen in the postnatal cycling follicle has morphologic similarities to the epithelial invagination process in embryonic skin, we hypothesized that localized, but transient, enhanced expression of the Shh gene in postnatal skin would accelerate initiation of anagen in the hair follicle cycle, with concomitant accelerated hair growth. To assess this concept, **an E1⁻ adenovirus vector, AdShh**, was used to transfer the murine Shh cDNA to skin of postnatal day 19 C57BL/6 mice. The treated skin showed increased mRNA expression of Shh, Patched (the Shh receptor), and Gli1 (a transcription factor in the Shh pathway). In mice receiving AdShh, but not in controls, acceleration into anagen was evident, since hair follicle size and melanogenesis increased and the hair-specific keratin ghHb-1 and the melanin synthesis–related tyrosinase mRNAs accumulated. Finally, C57BL/6 mice showed marked acceleration of the onset of new hair growth in the region of AdShh administration to skin 2 weeks after treatment, but not in control vector–treated or untreated areas. After 6 months, AdShh-treated skin showed normal hair and normal skin morphology. Together, these observations are consistent with the concept that upregulation of Shh activity in postnatal skin functions as a biologic switch that induces resting hair follicles to enter anagen with consequent hair growth.

inducing hair growth

Another good example of capitalizing on antivector immunity to limit gene expression was our demonstration that intradermal administration of an adenovirus coding for sonic hedgehog would provide a burst of sonic hedgehog (transcriptional activator) expression to resting hair follicles, with the resulting induction of hair growth (Sato et al., 1999).

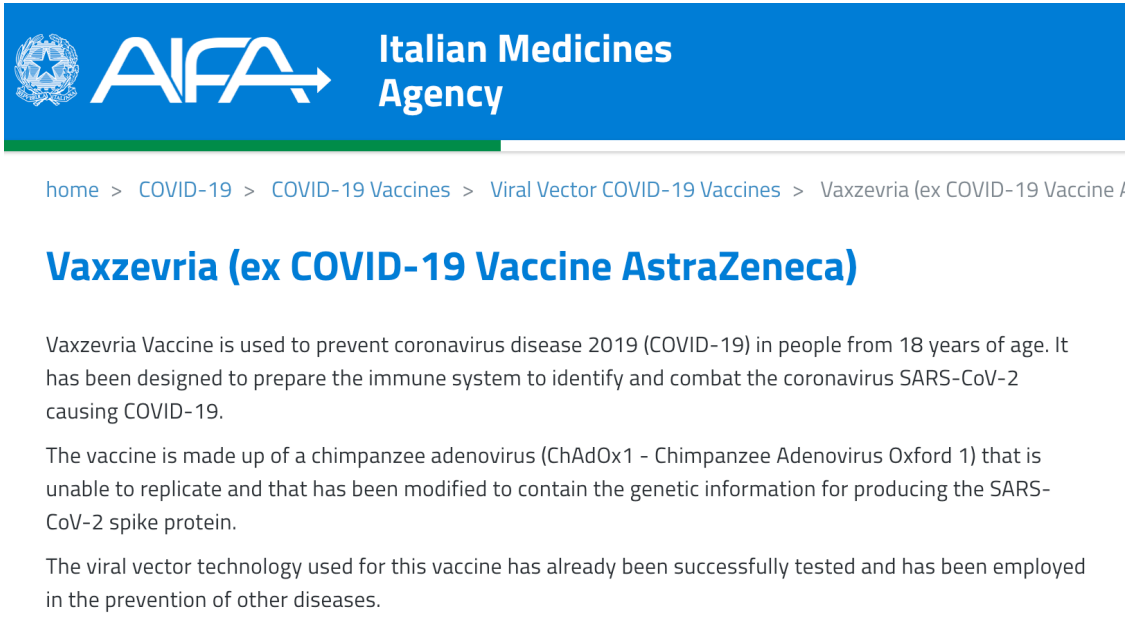
Induction of hair growth in a C57Bl/6 mouse 2 weeks after administration of an adenovirus vector coding for sonic hedgehog. To visualize hair growth, the hair of the mouse was bleached with blond hair dye to provide contrast for assessing new growth of the natural black hair of the mouse. The tuft of black hair is apparent (Sato et al., 1999).

other approaches

vaccine development

by taking advantage of the potent immunity against the adenovirus, vaccines have been created

- against the transgene (Krause and Worgall, 2011)
- or by inserting the antigen in the capsid (Lasaro and Ertl, 2009; Thacker et al., 2009; Matthews, 2011).



Ad vectors to target cancers: here only short-term gene expression is required

anti-cancer

Adenovirus vectors can also be used in therapies for cancer:

- inducing immunity against the cancer
- or directly killing the cancer cells

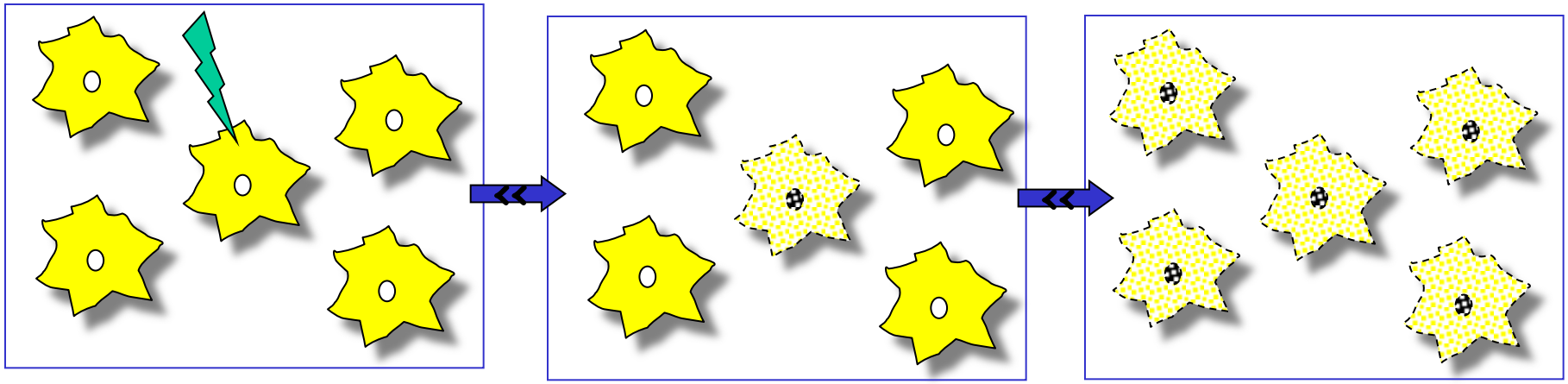
Ads against Cancer

Approach: inactivation of oncogenes and the addition of tumour suppressor genes or apoptosis-inducing genes.
***Limitation: require the successful transduction of each cell within the tumour, which is currently not feasible*.**

Other Approaches

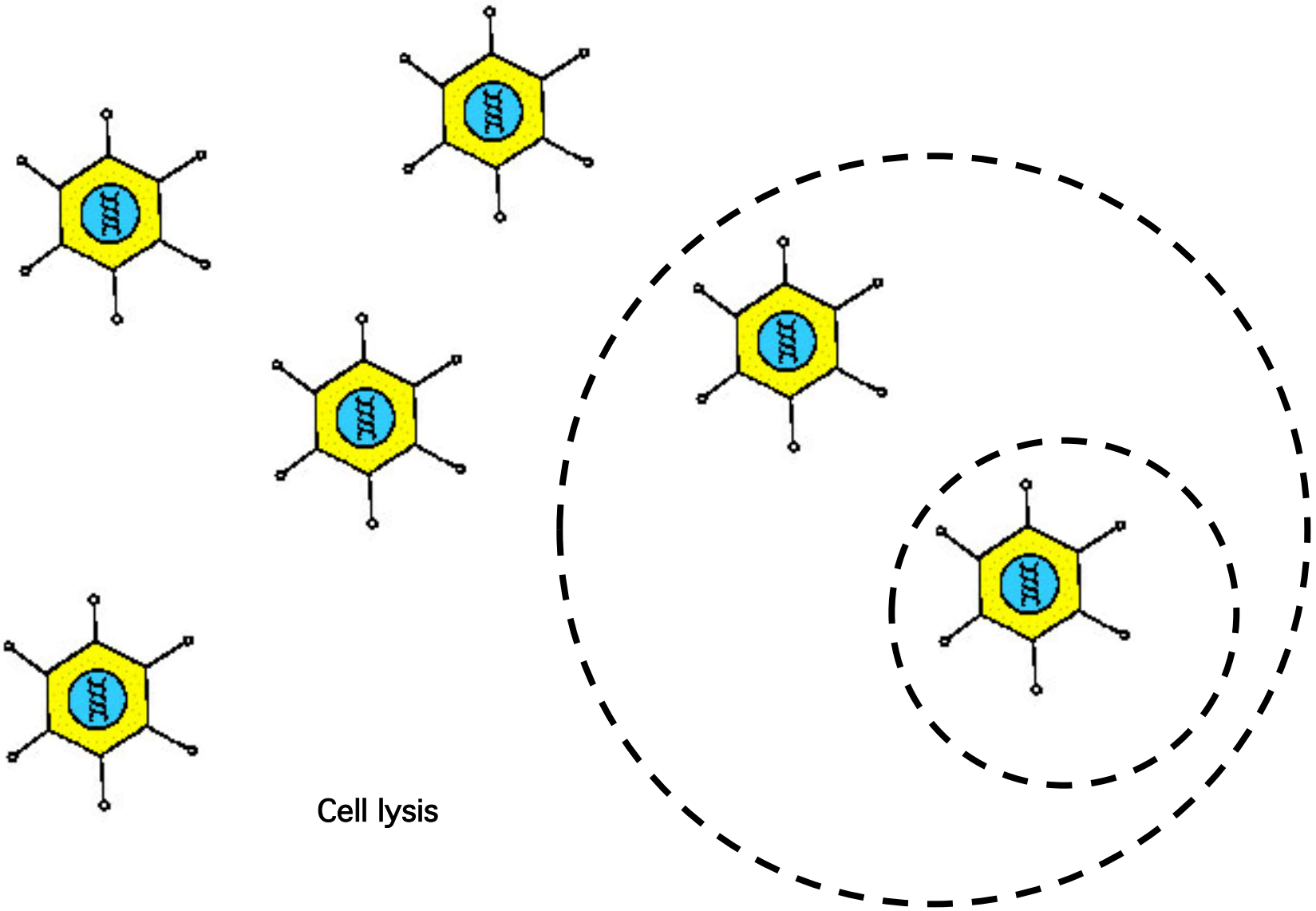
- Replication-deficient Ads with genes encoding secreted factors such as GM-CSF (granulocyte macrophage colony-stimulating factor) and IL-12 (interleukin-12) to stimulate cytotoxic effects towards the tumor.
- Activation of apoptosis in non-transduced cells by soluble TRAIL (tumor-necrosis-factor-related apoptosis inducin ligand) encoded by an Ad5 vector (bystander effect)

Effetto astante (bystander)

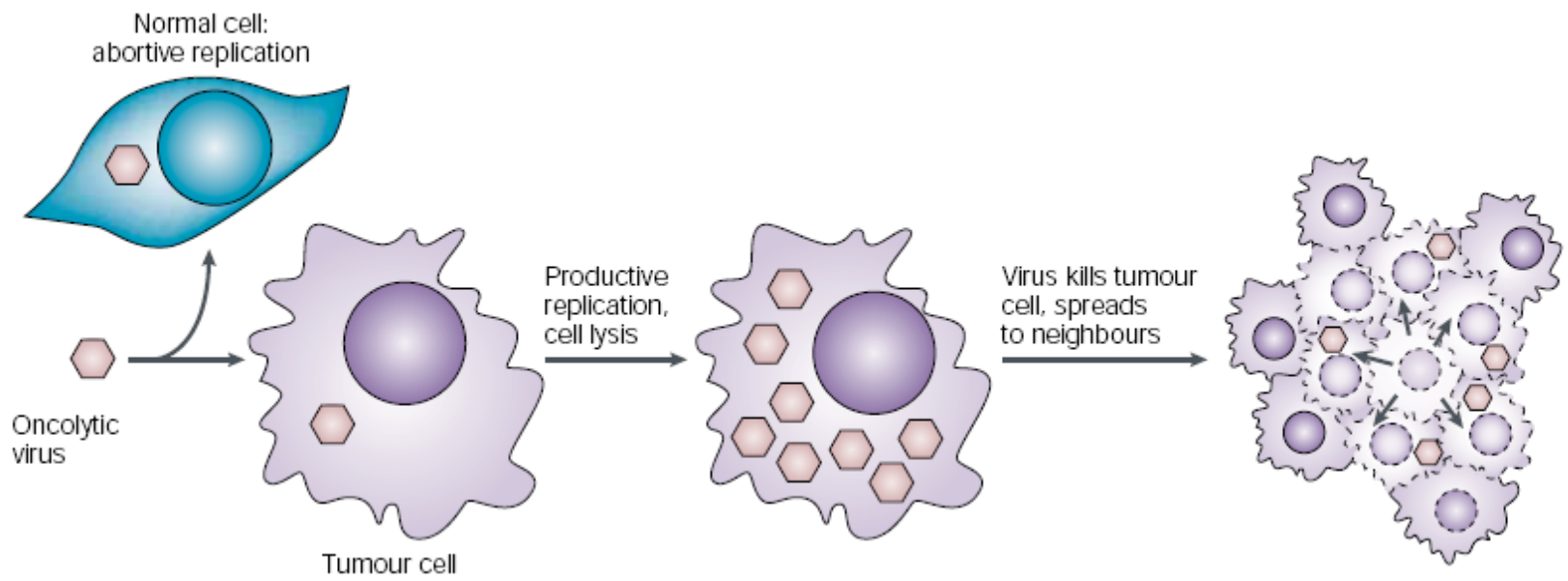


The bystander effect would improve the effect of the medicinal treatment by transmission to other cells.
some example of bystander effect include: diffusion of cytotoxic drugs produced in cells transduced with suicide transgene

Oncolytic virotherapy


Cell lysis

Strategia IV: virus oncolitici



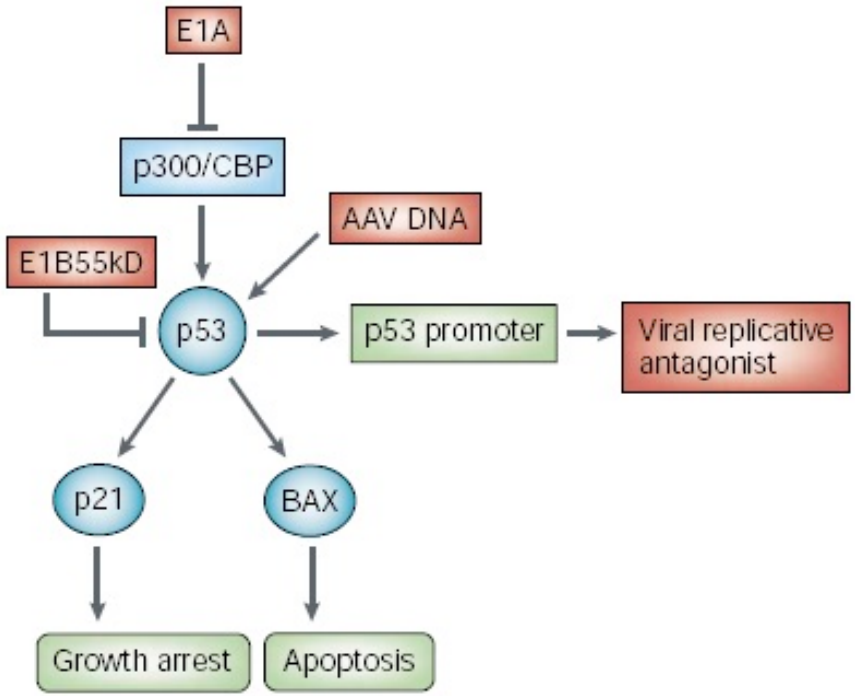
The oncolytic virotherapy is based on the concept that the viral life cycle is aborptive in normal cells but successfull in tumor cells. If this occurs, cancer cells are lysed whereas non-cancer cells survive

Table 1 | **Advantages and disadvantages of different oncolytic viruses**

Virus	Oncolytic strain occurrence	Advantages	Disadvantages
HSV1	Laboratory engineered	Can be easily manipulated genetically; clinical trial experience; drugs exist to shut-off unwanted viral replication	Side effects include serious or potentially fatal disease; unknown action of many HSV1 genes
Adenovirus	Laboratory engineered	Can be manipulated genetically; clinical trial experience; good knowledge of viral protein function; associated with relatively mild diseases	Replication cannot be easily shut-off
Reovirus	Naturally occurring	Associated with relatively mild diseases; good knowledge of viral gene function	Cannot be easily manipulated genetically; no clinical trial experience; undesirable viral replication cannot be easily shut-off
Vaccinia virus	Laboratory engineered	Can be easily manipulated genetically; clinical trial experience	Undesired viral replication cannot be easily shut-off; unknown action of many genes; side effects might include potentially fatal or seriously morbid disease
Vesiculostomatitis virus	Naturally occurring	Associated with relatively mild disease; good knowledge of viral gene functions	Cannot be easily manipulated genetically; no clinical trial experience; undesirable viral replication cannot be easily shut-off
Poliovirus	Laboratory engineered	Good knowledge of viral gene functions	Cannot be easily manipulated genetically; no clinical trial experience; undesirable viral replication cannot be easily shut-off; associated with fatality or serious disease

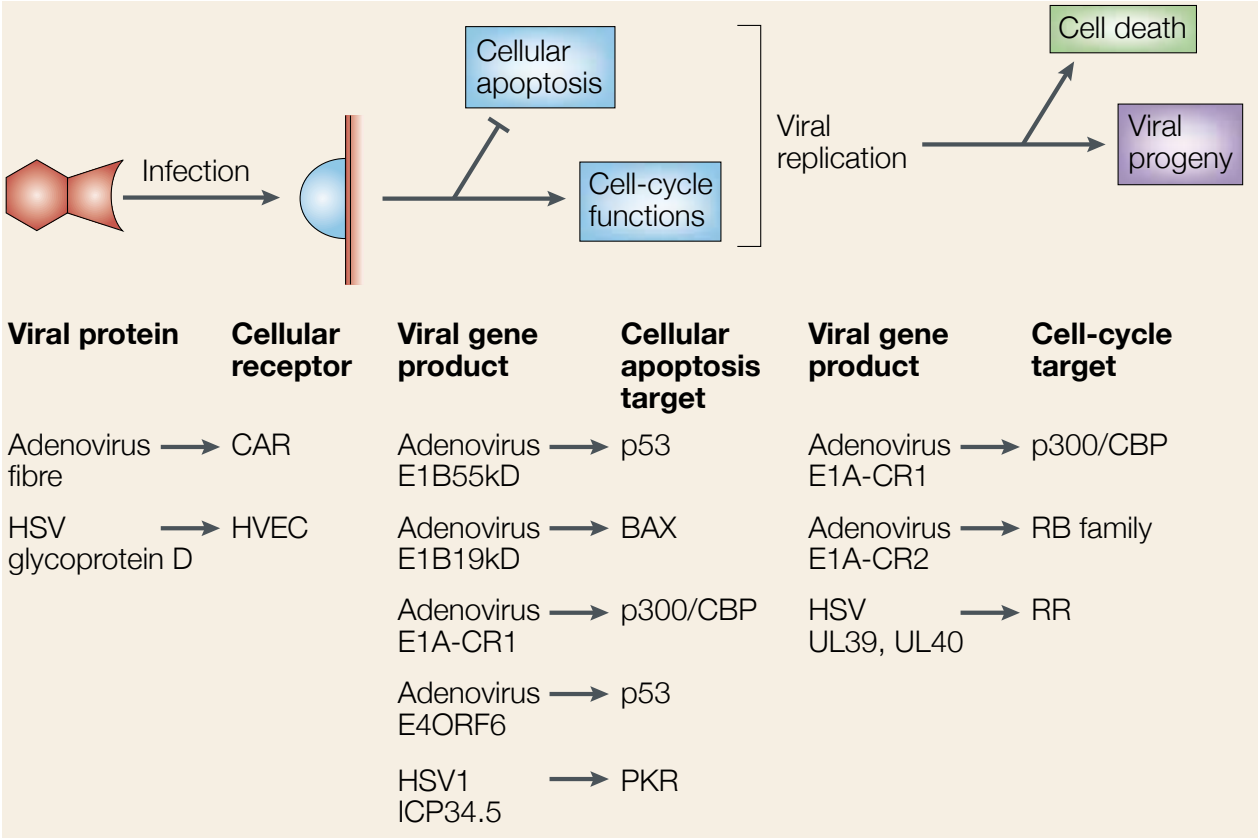
HSV1, herpes simplex virus type 1.

Virus oncolitici e p53



- **p53 induce arresto della crescita cellulare e apoptosi in risposta al danno al DNA**
- **p53 induce apoptosi anche in risposta all'infezione virale, così da impedire la propagazione del virus ai tessuti circostanti**
- **la proteina virale E1B-55kD blocca l'attività di p53, consentendo al virus di replicarsi**
- **Virus difettivi per E1B non riescono quindi a replicarsi nelle cellule normali perché è attiva p53, ma riescono a replicarsi selettivamente nelle cellule tumorali con p53 inattivata**

Cocchia 2002



The life cycle of Ad or herpes simplex virus (HSV)-1 can be divided into several stages.
During the infection stage, viral surface proteins, such as the adenovirus fibre or HSV glycoprotein D, mediate attachment to cellular receptors, such as coxsackie and adenovirus receptor (CAR) or HSV entry mediator C (HVEC), also known as nectin 1.
Once inside the cell, viruses express several gene products that target cellular proteins and modulate various cellular processes, such as preventing apoptosis or inducing cell-cycle entry.
These promote viral replication and production of viral proteins that eventually lead to cell lysis and release of viral progeny. Each step is mediated by a diverse group of proteins. Examples of viral proteins and their cellular targets are provided. PKR, double-stranded, RNA-dependent protein kinase; RR, ribonucleotide reductase.

Ad oncolitici la cui replicazione è limitata a cellule con p53 e Rb mutate

Ad Deleti per E1B (target p53 ricontrolla) or
Ad con mutazioni in E1A (target co-activator of p53- oppure Rb

tropismo ristretto ai tumori
Si replicano in maniera selettiva nelle cellule tumorali

Improving tumor selectivity: 1) tumor specific promoters driving expression of E1; 2) changing the receptor specificity restricting the infection to tumor-cells only

One approach to achieving tumour selective replication involves linking viral genes to promoters that are only functional in tumour cells.

One tumour-specific promoter is derived from the gene that encodes alpha-fetoprotein (AFP). AFP is expressed in several tissues during development, but in adult tissues its expression is limited to tumors of hepatic and intestinal origin.

In an adenoviral vector, this promoter can be used to regulate the expression of E1A. There is a 10 thousand-fold increase in the replication of this virus in AFP-expressing cells, compared with AFP-negative cells

Intravenous administration in mice causes regression of AFP-positive tumours, such as hepatocellular carcinomas.

La selettività dei virus oncolitici per le cellule tumorali può essere incrementata agendo sulla specificità di infezione

I virus sono ingegnerizzati modificando le proteine virali di superficie che riconoscono recettori cellulari specifici, permettendo al virus di entrare in maniera selettiva solo nelle cellule tumorali.

Table 2 | **Tumour-selective viral infection**

Virus	Redirected viral ligand	Cellular target	Effect	References
Dual adenovirus system*: AdsCAR-EGF + Δ24	Bispecific-antibody that binds adenovirus fibre to EGFR	EGFR	Redirects viral infection to EGFR-expressing cells	138
Adenovirus: Ad5-Δ24RGD	H1-loop in fibre of Ad modified by incorporation of RGD	Integrin	Redirects viral infection to integrin-expressing cells	139
Δ24 or ONYX-015‡	Infusion of bispecific antibodies to fibre and EGFR	EGFR	Redirects viral infection to EGFR-expressing cells	140
Ad5/35	Fibre of adenovirus serotype 35 substituted into adenovirus serotype 5	Unknown	Redirects virus away from CAR and towards an unidentified cellular receptor expressed by human breast cancer cells	141

adaptor

fiber modification

adaptor

fiber modification

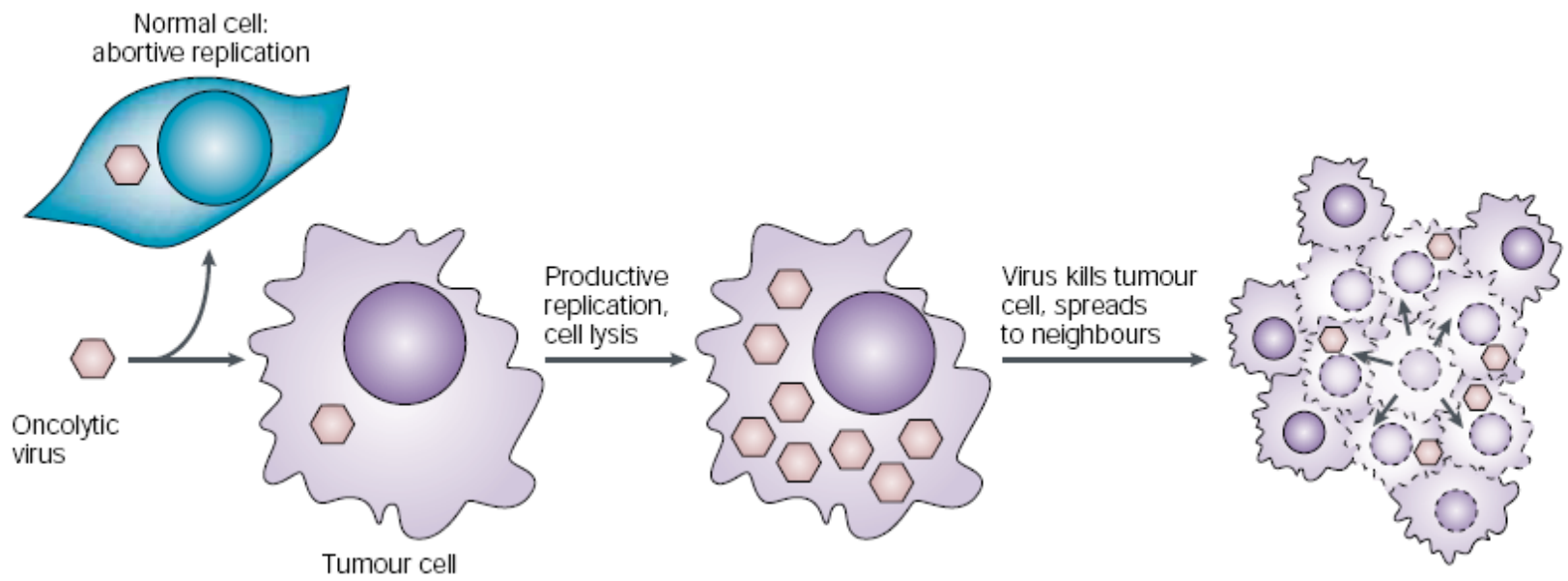
*Consists of a 1:1 mix of replication-defective, sCAR–EGFR-secreting adenovirus and the OV, AdΔ24 (REF. 47; also shown in FIG. 3). ‡Also shown in FIG. 1. Ad, adenovirus; CAR, coxsackie and adenovirus receptor; EGF, epidermal growth factor; EGFR, epidermal growth-factor receptor; OV, oncolytic virus.

Cancer gene therapy and CAR down regulation

In molti tumori si osserva una down regolazione del recettore CAR rendendo le cellule resistenti all'infezione da adenovirus

Pseudotyping con proteine delle fibre di Ad che non utilizzano CAR (Ad35-CD46 che è upregolato in molti tumori)

Strategia IV: virus oncolitici



The oncolytic virotherapy is based on the concept that the viral life cycle is aborptive in normal cells but successfull in tumor cells. If this occurs, cancer cells are lysed whereas non-cancer cells survive

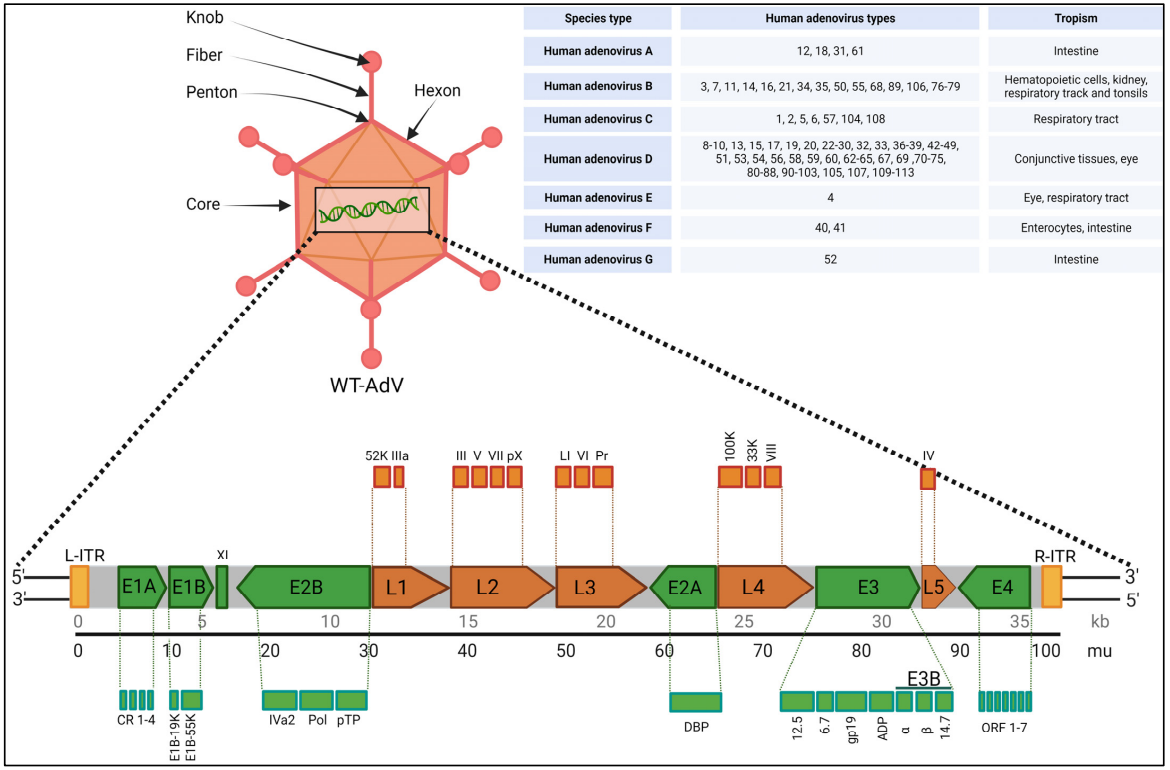
La selettività dei virus oncolitici per le cellule tumorali può essere incrementata agendo sulla replicazione

La selettività per la replicazione può essere ottenuta :

•utilizzando promotori specifici

•modificando i geni virali richiesti per una efficiente replicazione

The Adenovirus



Species type	Human adenovirus types	Tropism
Human adenovirus A	12, 18, 31, 61	Intestine
Human adenovirus B	3, 7, 11, 14, 16, 21, 34, 35, 50, 55, 68, 89, 106, 76-79	Hematopoietic cells, kidney, respiratory track and tonsils
Human adenovirus C	1, 2, 5, 6, 57, 104, 108	Respiratory tract
Human adenovirus D	8-10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, 42-49, 51, 53, 54, 56, 58, 59, 60, 62-65, 67, 69 ,70-75, 80-88, 90-103, 105, 107, 109-113	Conjunctive tissues, eye
Human adenovirus E	4	Eye, respiratory tract
Human adenovirus F	40, 41	Enterocytes, intestine
Human adenovirus G	52	Intestine

Figure 1. Highlights of adenovirus capsid features with overview of viral genome. In the top right corner, the species (A–G) of AdVs with their known tropism are indicated. The schematic representation of the gene map is for understanding purposes only and is not normalized for actual gene size. Kb: kilobases; mu: map unit. Created with BioRender.com (accessed on 1 December 2023).

Trivedi et al 2023

Adenoviral vectors

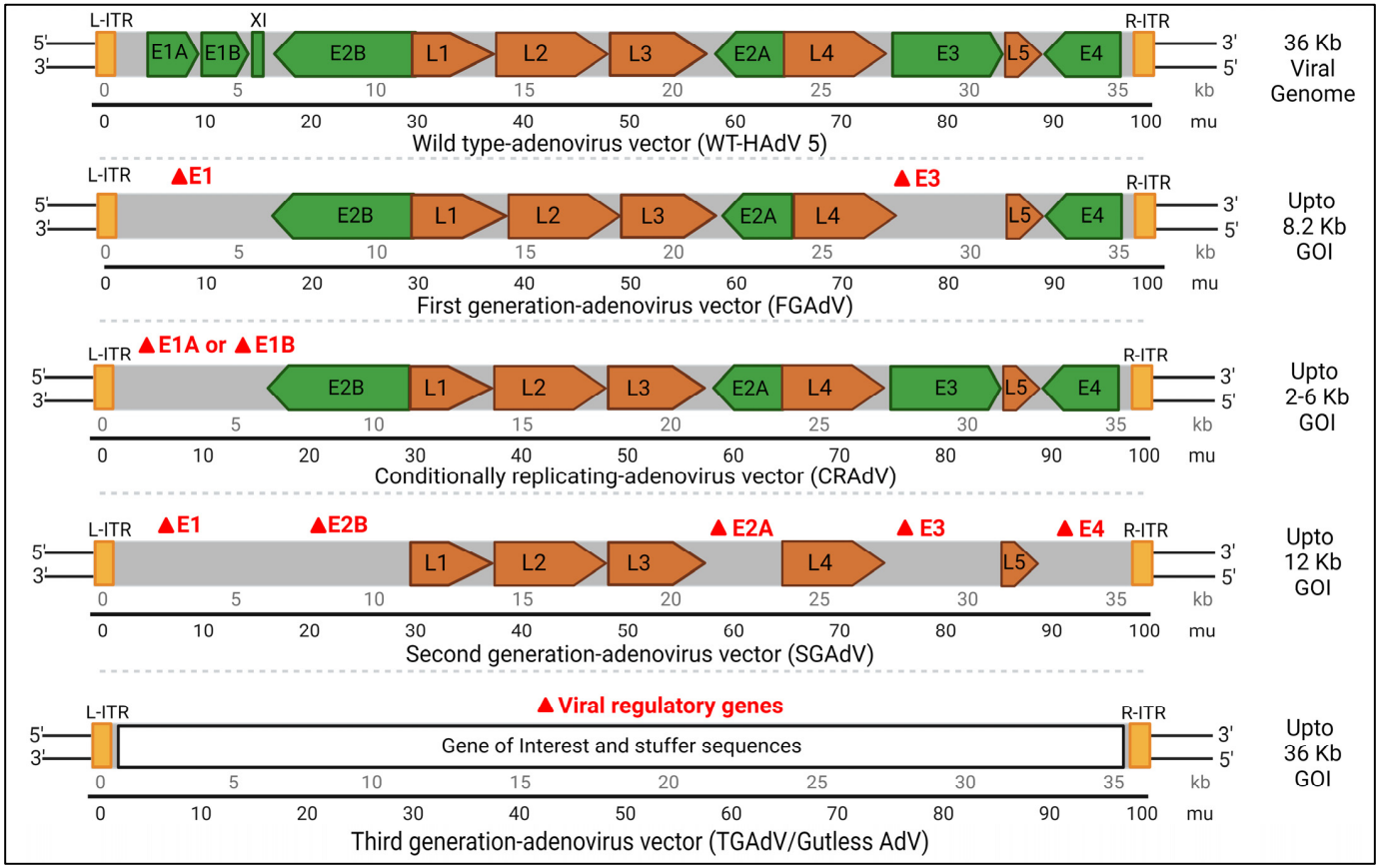
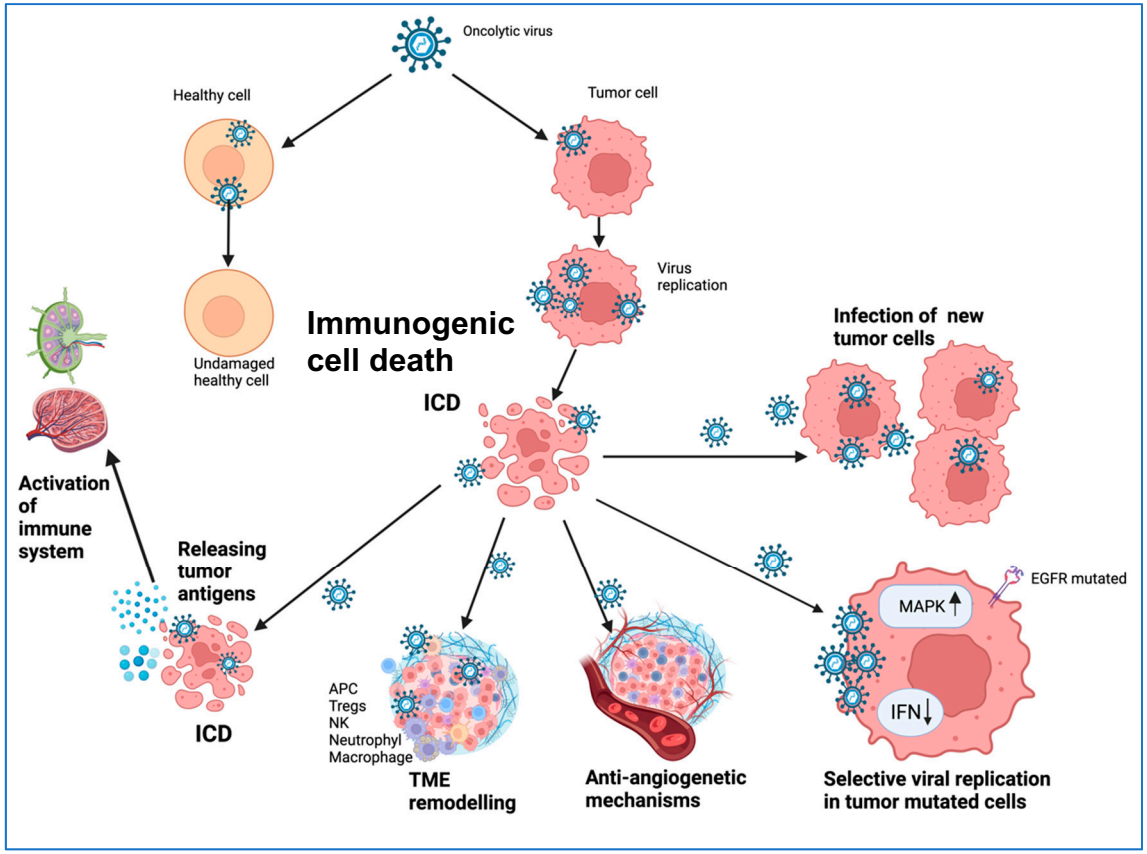


Figure 2. Represents an overview of the scope of the modifications and packaging capacity of rAdV vectors. Red delta signifies the possibility of gene deletion for creating multi-generational rAdVs. The suggested approximate insert size of the gene of interest (GOI) depends on the specific application. Early and late genes are explained in previous sections. The schematic representation of the gene map is for understanding purposes only and is not normalized for actual gene size. Kb: kilobases; mu: map unit Created with BioRender.com (accessed on 1 December 2023).

Trivedi et al 2023

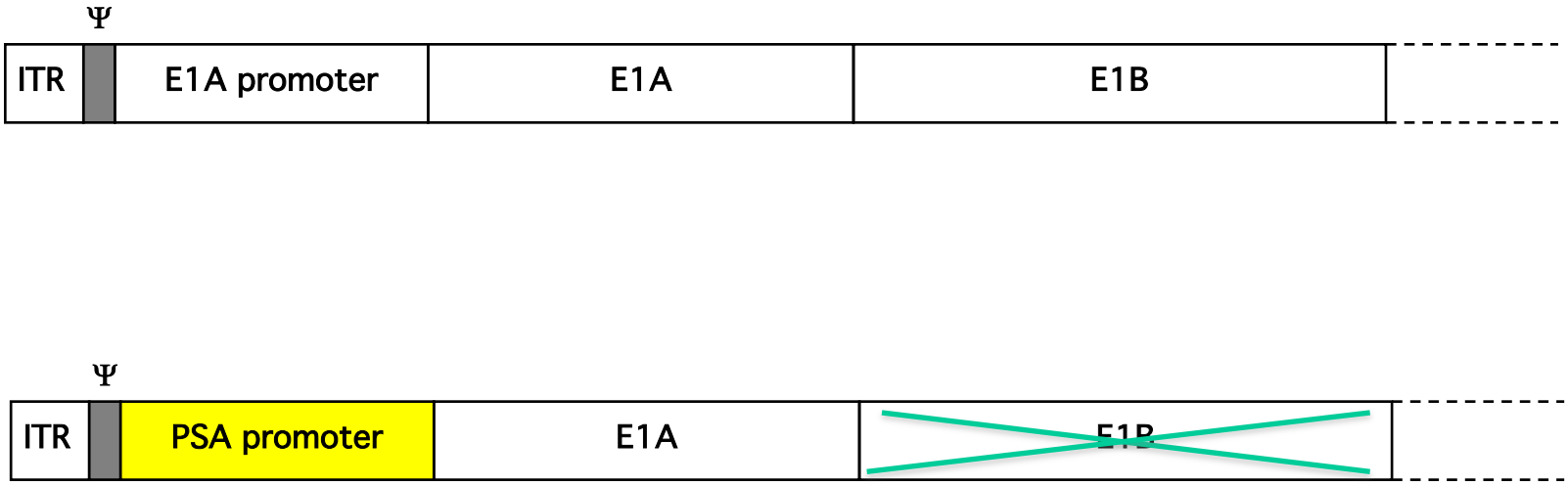
Oncolytic viruses



TME, complex network leading to tumor cells proliferation. Oncolytic viruses induce TME remodelling leading to antitumor systematic immune response.

Figure 1. Mechanisms of action of oncolytic viruses. The replication of virus inside the tumor cell triggers immunogenic cell death (ICD), followed by release of tumor antigens that activate the immune system, remodeling of TME, activation of the antiangiogenic mechanisms, increase in viral replication in tumor-mutated cells, and spread of the viral infection to other tumor cells [9,55–58] (BioRender.com).

Oncolytic adenoviral vector



Promotore prostata-specifico: tropismo ristretto a cellule prostatiche, l'assenza di E1B rende il virus capace di innescare il ciclo litico solo in cellule tumorali prive di attività Rb

The ONYX 015

The first oncolytic virus, ONYX-015 aka DL1520, was developed as a defective AdV with deletion in E1B55k subunit. It selectively targeted and destroyed human cancer cells with non-functional p53 genes. Clinical trials for head and neck cancer treatment were conducted, but ONYX-015 had to be directly injected into tumors due to its high intravenous toxicity, limiting its use to large tumors only.

ONYX-015, an E1B gene-attenuated adenovirus, causes tumor-specific cytolysis and antitumoral efficacy that can be augmented by standard chemotherapeutic agents

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Correspondence should be addressed to D.H.K.

The 55-kilodalton (kDa) protein from the E1B-region of adenovirus binds to and inactivates the p53 gene, which is mutated in half of human cancers. We have previously shown that the replication and cytopathogenicity of an E1B, 55-kDa gene-attenuated adenovirus, ONYX-015, is blocked by functional p53 in RKO and U2OS carcinoma lines. We now report that normal human cells were highly resistant to ONYX-015-mediated, replication-dependent cytolysis. In contrast, a wide range of human tumor cells, including numerous carcinoma lines with either mutant or normal *p53* gene sequences (exons 5–9), were efficiently destroyed. Antitumoral efficacy was documented following intratumoral or intravenous administration of ONYX-015 to nude mouse-human tumor xenografts; efficacy with ONYX-015 plus chemotherapy (cisplatin, 5-fluorouracil) was significantly greater than with either agent alone.

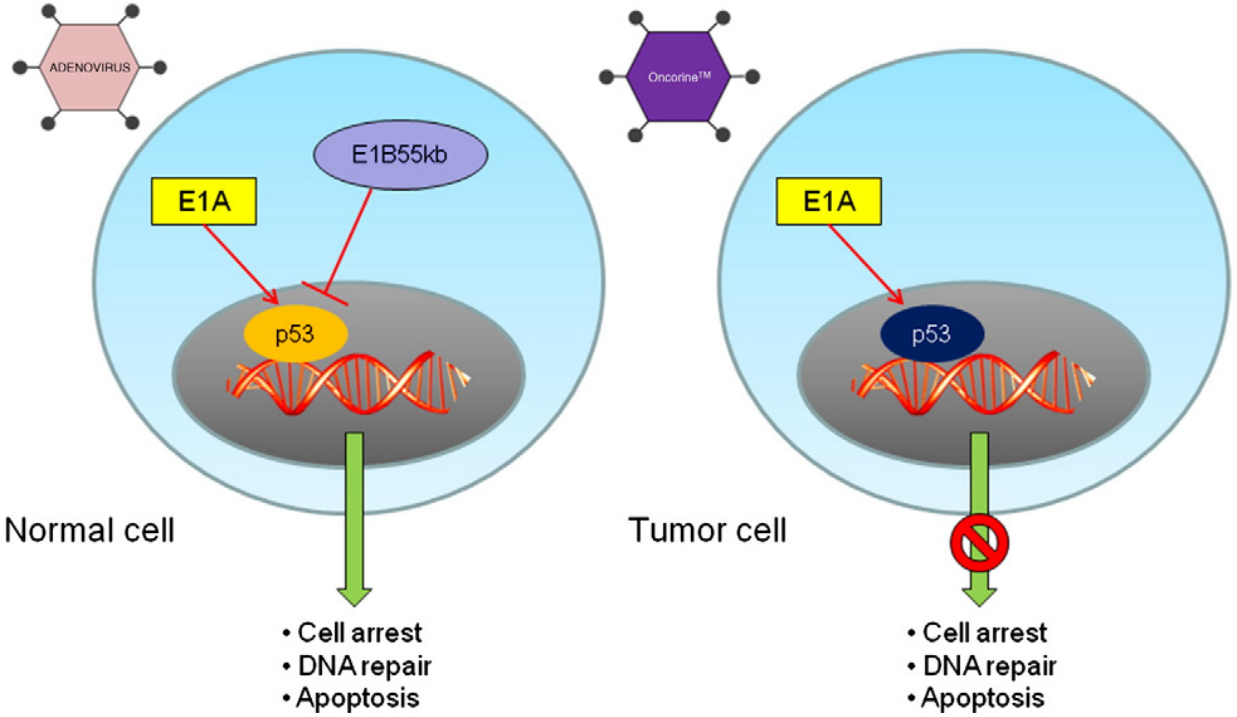
Heise C, Sampson-Johannes A, Williams A, McCormick F, Von Hoff DD, Kirn DH. ONYX-015, an E1B gene-attenuated adenovirus, causes tumor-specific cytolysis and antitumoral efficacy that can be augmented by standard chemotherapeutic agents. Nat Med. 1997 Jun;3(6):639-45. doi: 10.1038/nm0697-639. PMID: 9176490.

Studi clinici di terapia dei tumori con adenovirus oncolitici (ONYX-015)

Fase	Tumore	Adenovirus	Chemiot.	Risposte (anche parziali)	Progressione tumorale
I	Testa e collo	ONYX-015	-	5/22 (23%)	9/22 (41%)
II	Testa e collo	ONYX-015	-	8/24 (33%)	7/24 (29%)
II	Testa e collo	ONYX-015	-	8/36 (22%)	15/36 (42%)
I	Pancreas	ONYX-015	-	6/22 (27%)	5/22 (23%)
I	Glioblastoma multiforme	ONYX-015	-	0/24	23/24 (96%)
II	Carcinoma orale	ONYX-015	-	N/S	N/S
II	Hepatobiliary	ONYX-015	-	8/16 AFP ↓ (50%)	3/16 (19%)
I	Ovarian	ONYX-015	-	1/16 CA125 ↓	14/16 (88%)
II	Carcinoma epatocellulare	ONYX-015	-	1/5 AFP ↓	4/5 (80%)
II	Cancro del colon metastatico	ONYX-015	-	4/18 CEA ↓	11/18 (61%)
II	Testa e collo	ONYX-015	+	19/37 (53%)	5/30 at 6 months (17%)

Modificata da Aghi e Martuza, Oncogene 24:7802:7816, 2005

OncorineTM is a conditionally replicative adenovirus. It was developed by Sunway Biotech Co. Ltd and gained marketing approval in China in 2005 in combination with chemotherapy for the treatment of late-stage refractory nasopharyngeal cancer. OncorineTM contains a deletion in E1B 55K region, which restricts the virus to bind and inactivate wild-type p53 protein



The only difference between the Chinese and American viruses is a slightly larger deletion in H101's E3 gene, which affects immune response.

Part of H101's success may be due to not treating manageable patient fevers in the phase III trial. After observing a high rate of responses in such patientsin a phase II study, it was reasoned that higher body temperature should aid viral replication and enhance the anti-cancer immune response.

oncolytic virotherapy trials

Virus	Name	Modifications	Phase	Tumor	Route	Combination	Site	Status (PubMed reference)
Adenovirus	Oncorine (H101)	E1B-55k-	2	SCCHN	IT	Cisplatin	Multicenter	Completed, PMID: 14693057
		E3-	3	SCCHN	IT	Cisplatin	Multicenter	Completed, PMID: 15601557
	Onyx-015	E1B-55k-	1	Lung Mets	IV	–	Mutlicenter	Completed, PMID: 11420638
		E3B-	1	Glioma	Intracavity	–	Mutlicenter	Completed, PMID: 15509513
			1	Ovarian cancer	IP	–	Mutlicenter	Completed, PMID: 11896105
			1	SCCHN	IT	–	Multicenter	Completed, PMID: 10741699
			1	Solid tumors	IV	Enbrel	Mary Crowley	Completed, PMID: 17704755
			1	Sarcoma	IT	Mitomycin-C Dox, cisplatin	Mayo Clinic	Completed, PMID: 15647767
			1/2	PanCa	IT	Gemzar	UCLA	Completed, PMID: 12576418
			2	CRC	IV	–	Mutlicenter	Completed, PMID: 12697873
			2	Hepatobiliary	IT	–	Montefiore	Completed, PMID: 12576437
			2	CRC, PanCa	IA	–	Mutlicenter	Completed, PMID: 12414631
			2	SCCHN	IT	–	Multicenter	Completed, PMID: 11208818
			2	SCCHN	IT	Cisplatin, 5-FU	Multicenter	Completed, PMID: 10932224
			2	CRC	IV	5-FU/leucovorin	Stanford	Completed, PMID: 15803147
	CG7060	PSA control	1	Prostate cancer	IT	RT	Johns Hopkins	Completed, PMID: 11606381
	CG7870/CV787	Rat probasin-E1A	1/2	Prostate cancer	IV	–	Multicenter	Completed, PMID: 16690359
		hPSA-E1B E3+	1/2	Prostate cancer	IV	Docetaxel	Mary Crowley	Terminated, 2005
	CG0070	E2F-1, GM-CSF	2/3	Bladder cancer	Intracavity	–	UCSF	Not yet open, PMID: 16397056
	Telomelysin	hTERT	1	Solid tumors	IT	–	Mary Crowley	Completed, PMID: 19935775
	Ad5-CD/TKrep	CD/TK	1	Prostate cancer	IT	5-FC & GCV	Henry Ford, Detroit	Completed, PMID: 12208748
			1	Prostate cancer	IT	5-FC+GCV+RT	Henry Ford, Detroit	Completed, PMID: 14612551
	Ad5-D24-RGD	RGD, Delta-24	1	Ovarian cancer	IP	–	UAB	Completed, PMID: 20978148
			1	Glioma	IT	–	MD Andersen	Recruiting
			1/2	Glioma	IT	–	Erasmus Medical Center	Recruiting
	Ad5-SSTR/TK-RGD	SSTR, TK, RGD	1	Ovarian cancer	IP	GCV	UAB	Active, PMID: 16397056
	CGTG-102	Ad5/3, GM-CSF	1/2	Solid tumors	IT	–	Baylor	Not open, PMID: 20664527
		Delta-24	1	Solid tumors	IT/IV	Metronomic CTX	Docrates Hospital Helsinki	Recruiting
	INGN-007 (VRX-007)	wtE1a, ADP	1	Solid tumors	IT	–	Mary Crowley	Not open, PMID: 19197324
	ColoAd1	Ad3/11p	1/2	CRC, HCC		–	PsiOxus	Not open, PMID: 18560559

SCCHN: squamous cell carcinoma of the head and neck
PanCa: pancreatic cancer
IT, intratumor
IV, intravenus

Russel et al Nat. Biotech 2012

oncolytic virotherapy trials

legend to the previous table

5-FC: 5-fluorocytosine; 5-FU: 5-fluorouracil; ADP: Adenovirus death protein; β-gal: Beta galactosidase; Ca: Cancer; CBDCA: Carboplatin; CD: Cytosine deaminase; CEA: carcinoembryonic antigen; CNS: Central nervous system; CRC: colorectal cancer; CTX: Cyclophosphamide; Dox: Doxorubicin; FOLFIRI: 5-fluorouracil, leucovorin, irinotecan; GCV: Ganciclovir; Gemzar: Gemcitabine; GFP: green fluorescent protein; GM-CSF: granulocyte-macrophage colony-stimulating factor; HCC: hepatocellular carcinoma; HSV: herpes simplex virus; hTERT: human telomerase reverse transcriptase; ICP: infected cell protein; IFN: interferon; IP: intraperitoneal; IRES: internal ribosomal entry site; IT: intratumoral; IV: intravenous; Mets: metastases; MV: measles virus; NDV: Newcastle disease virus; NIS: sodium iodide symporter; PanCa: pancreatic cancer; PSA: prostate specific antigen; PTX: paclitaxel; RT: radiation; SCCHN: squamous cell carcinoma of the head and neck; Somatostatin R: stomatostatin receptor; SSTR: stomatostatin receptor; TK: thymidine kinase; UAB: University of Alabama Birmingham; UCSF: University of California, San Francisco; VGF: vaccinia growth factor; Wt: wild-type.

Oncolytic adenovirus limitations

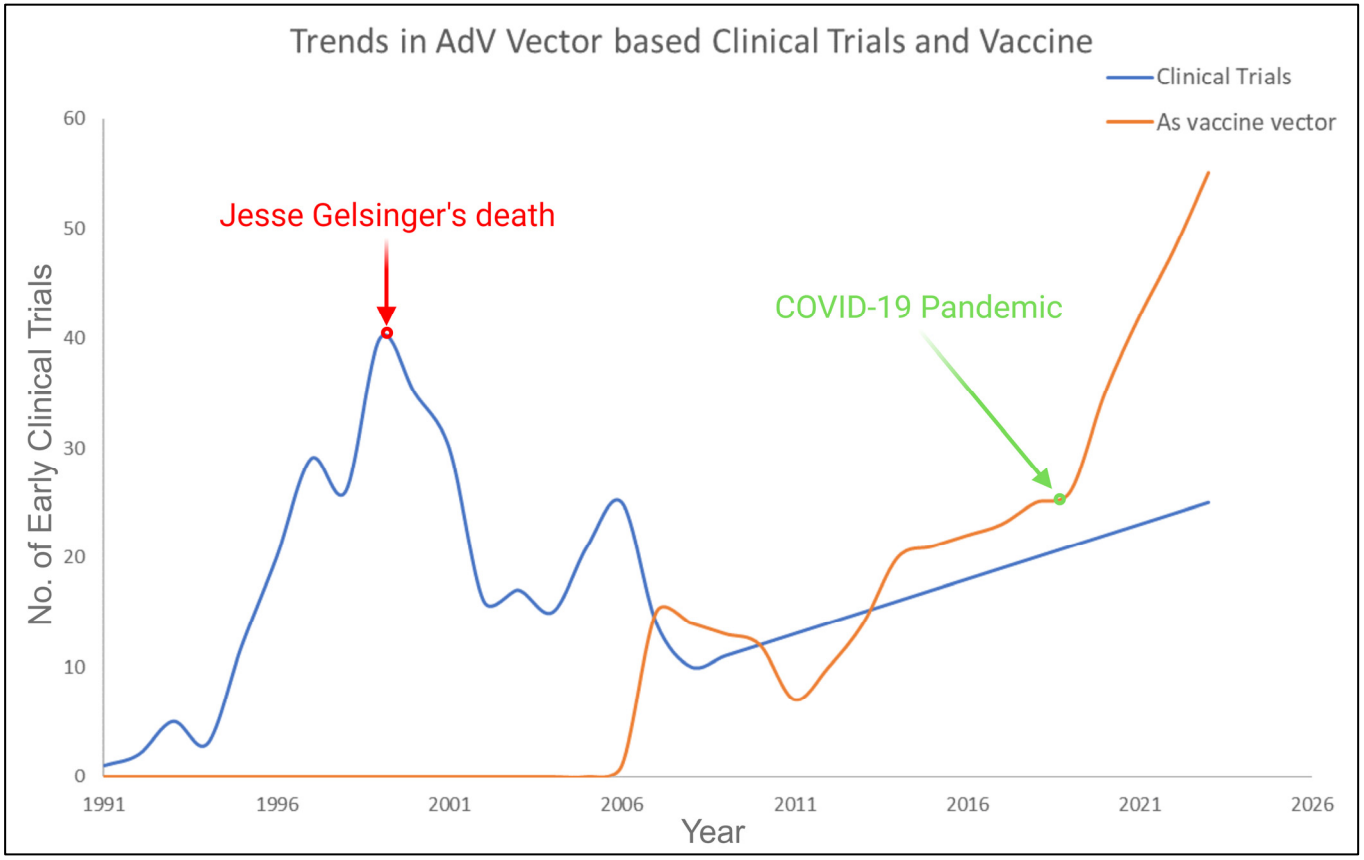
Onyx-15, in retrospect, was not the ideal oncolytic virus. For one thing, the E3 deletion probably hurt Onyx-15's potency. Onyx scientists chose an E3-deleted adenovirus mutant off the shelf, not realizing their mistake until years later. «It definitely leads to more rapid clearance of the virus».

Adenovirus, in retrospect, had a number of fundamental flaws:

- It spreads very slowly;
- the packaging capacity to express other genes is extremely limited;
- works poorly when given intravenously
- injecting the virus directly into primary tumors — the H101 and Onyx-15 approach — is unlikely to infect and eliminate distant metastases.

Onyx-15 oncolytic trials terminated in 2000

overview of the clinical trials trend



The red highlighted point on the graph indicates the decline in adenovirus vector application and the green highlighted indicates the decline in adenovirus vector application and the green highlighted section represents the recent pandemic, which points towards the upward trajectory of revamped interest in adenovirus vectors. (accessed on 1 December 2023).

Biblio

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Trivedi et al 2023 Evolving Horizons: Adenovirus Vectors’ Timeless Influence on Cancer, Gene Therapy and Vaccines

viruses

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Review

Evolving Horizons: Adenovirus Vectors’ Timeless Influence on Cancer, Gene Therapy and Vaccines

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