Oncolytic viruses for cancer treatment

Interdisciplinary Technical Journal Club: Special Series on Laboratory Animal Science

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Concept of virotherapy for malignant tumors

Dates back more than a century!

Pasteur's attenuated rabies vaccine

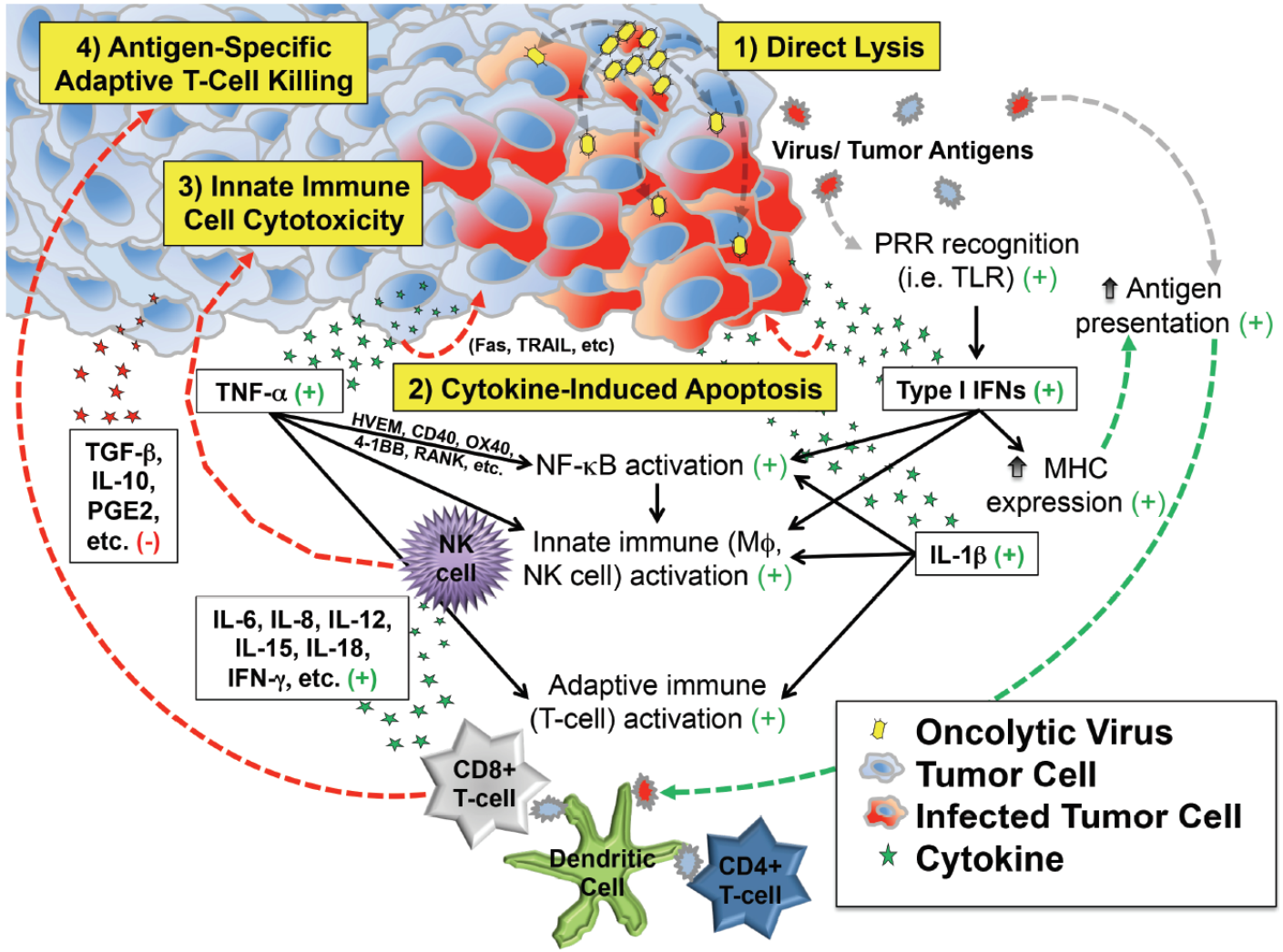
- Regression of cervical cancer after vaccination with Pasteur's attenuated rabies vaccine (following a dog bite) *(De Pace, Ginecologia (France) 1912:82-88)*
- 8/30 patients with melanomatosis with regressive changes *(Higgins and Pack 1951; Pack 1950)*

Measles infection (naturally occurring)

- regression in cases of Burkitt's lymphoma and Hodgkin's disease *(Bluming and Ziegler 1971; Taqi et al. 1981)*

Concern of serious adverse events and the rise of chemotherapy halted early progress

Concept of virotherapy for malignant tumors



Engineering viruses: a diversity of platforms

Differences:

- DNA or RNA
- single or double stranded
- positive or negative sense
- 2-300kb
- 1-300 genes
- 20-1000 nm
- icosahedral to helical
- with or without lipid envelope, etc.

Naturally occurring viruses: *vast diversity of life cycles, cell entry, replication mechanisms, cell and species tropism, cycle times, burst sizes, innate immune evasion, apoptosis, antiviral state prevention, immune combat strategies, modes of transmission, pathogenic mechanisms*

Similarities:

- **Dependence on the host cell** to provide a suitable environment for genome amplification, gene expression and progeny virus production
- **Adaptation to a specific set of host cell conditions and factors** such that propagation is precluded in cells that fail to provide the necessary environment.

→*allow viruses to be targeted to cancer cells as a self-replicating antineoplastic therapy.*

Choice of platform by features that may lead to superior oncolysis:

- replication kinetics
- genome plasticity
- Targetability
- seroprevalence and stability

Engineering viruses: a diversity of platforms

Advancements in molecular virology and genetics → modification of viruses for therapy

Viral therapy divided into two groups:

1) **Replication-competent oncolytic viruses (OVs)** → Specifically infect a tumor cell and induce tumor lysis through release of viral progeny and subsequent infection of surrounding tumor cells

2) **Replication-deficient viral vectors** → delivery mechanism for therapeutic genes

Table 1. Summary of viruses that have been developed as oncolytic vectors with a brief overview of some strategies implemented for tumor-specific targeting, increasing efficacy and immune evasion.

Genome	Family	Virus	Natural host	Targeting properties	Arming/immune evasion	Example malignancies targeted	Ref.
RNA	Coronaviridae	Mouse Hepatitis Feline Infectious Peritonitis	Mice Felines	Bispecific adapter	None	Glioma, EGFR(+) cancers, etc.	[14,15]
	Orthomyxoviridae	Influenza A	Birds, swine, humans, etc.	Deletion of NS1, IFN defects, α-2,3-linked glycan receptor	IL-15/ multiple HA, NA configurations	Melanoma, pancreatic adenocarcinoma, etc.	[16,17]
	Paramyxoviridae	Measles Mumps New Castle disease	Humans Humans Birds	scFy, DARPins ligands, protease-dependent activation, miRNA targetsCD46/SLAM/Nectin-4/ sialic acid expression, IFN defects, apoptosis defects	NIS, GM-CSF, IL-2. TNFα, NAP, PNP, anti-PDL1, anti-CTLA4, IFNβ/ pseudotyping, glycan shield, coating	Multiple myeloma, lymphoma, acute myeloid leukemia, ovarian, breast, glioblastoma, prostate, mesothelioma, etc.	[11,18–24]
	Picornaviridae	Coxsackie A21 Mengo Polio Seneca Valley	Humans Rodents Humans Swine, cattle	miRNA targets, IRES translational control ICAM1 and CD155 expression	None/serotype switching, capsid psuedotyping	Multiple myeloma, melanoma, glioma, neuroendocrine tumors, etc.	[25–27]
	Reoviridae	Reovirus	Humans	Constitutive Ras signaling	None/multiple serotypes	Pancreatic adenocarcinoma, glioma, prostate, multiple myeloma, melanoma, etc.	[28]
	Retroviridae	Moloney Murine Leukemia	Mice	S-phase dependent Integration, Tissue-specific promoter, Antibody targeted	Cytosine deaminase/ Nonlytic	Glioma, prostate, breast cancer, etc.	[29–32]
	Rhabdoviridae	Vesicular stomatitis	Horse, cattle, swine, rodents, arthropods	M protein mutants, miRNA targets, tumor targeting ligands IFN defects	IFNβ, IFNγ Tumor-associated antigen, NIS, TK, cytosine deaminase, IL-4, IL-12, IL-23/anti-Fab aptamers, pseudotyping, PEGylation	Acute myeloid leukemia, multiple myeloma, melanoma, various solid tumors, etc.	[8,33–38]
	Togaviridae	Semliki forest Sindbis	Rodents, Arthropod Birds, Arthropod	miRNA targets, laminin expression, IFN defects	IL-12, tumor-associated antigen	Cervical, colon, glioma, osteosarcoma, neuroblastoma, etc.	[39–42]
DNA	Adenoviridae	Adenovirus C	Humans	Deletion of E1b-55kDa or E1a, tumor-specific promotor, tumor targeting ligands, scFy	HSP, TK, NIS, IL-4, IL12-, IL-18, GM-CSF/serotype switching, polymer shielding	Head and neck, pancreatic, prostate, lung, osteosarcoma, ovarian, bladder, etc.	[43–47]
	Herpesviridae	Herpes simplex 1 Bovine herpes	Human Cattle	Deletion of ICP6, γ34.5 and UL39 glycoprotein modification, nestin promotor, miRNA targets, scFy	GM-CSF, ICP47 deletion, IL-4, IL-10, IL-12, TK, rat CYP450	Glioma, melanoma, breast, ovarian, prostate, colon pediatric solid tumors, etc.	[48–54]

AML: Acute myeloid leukemia; IRES: Internal ribosome entry site.

Delivery of OVs

- Drug administration: should be extremely controlled to produce a reliable, consistent and predictable pharmacokinetic profile (absorption, biodistribution, metabolism and excretion) and bioavailability.
- **Natural viral infections are not controllable!** (variable size of inoculum; host resistance varies from person to person; kinetics of the adaptive immune response differ greatly between individuals. → **range from asymptomatic seroconversion to full blown disease**.
- **Delivery of OVs as traditional drugs**: introducing a highly concentrated virus inoculum into the body via oral, intravenous (IV), intranasal, transdermal, subcutaneous or intramuscular. The dispersion of the inoculated virus, or its progeny, takes it to the targeted cancerous tissues.
- self-amplification and spreading after delivery; peak concentration may not be reached until sometime after the treatment is administered.

viruses

MDPI

Review

Stem Cell-Based Cell Carrier for Targeted Oncolytic Virotherapy: Translational Opportunity and Open Questions

Janice Kim, Robert R. Hall III, Maciej S. Lesniak † and Atique U. Ahmed *,†

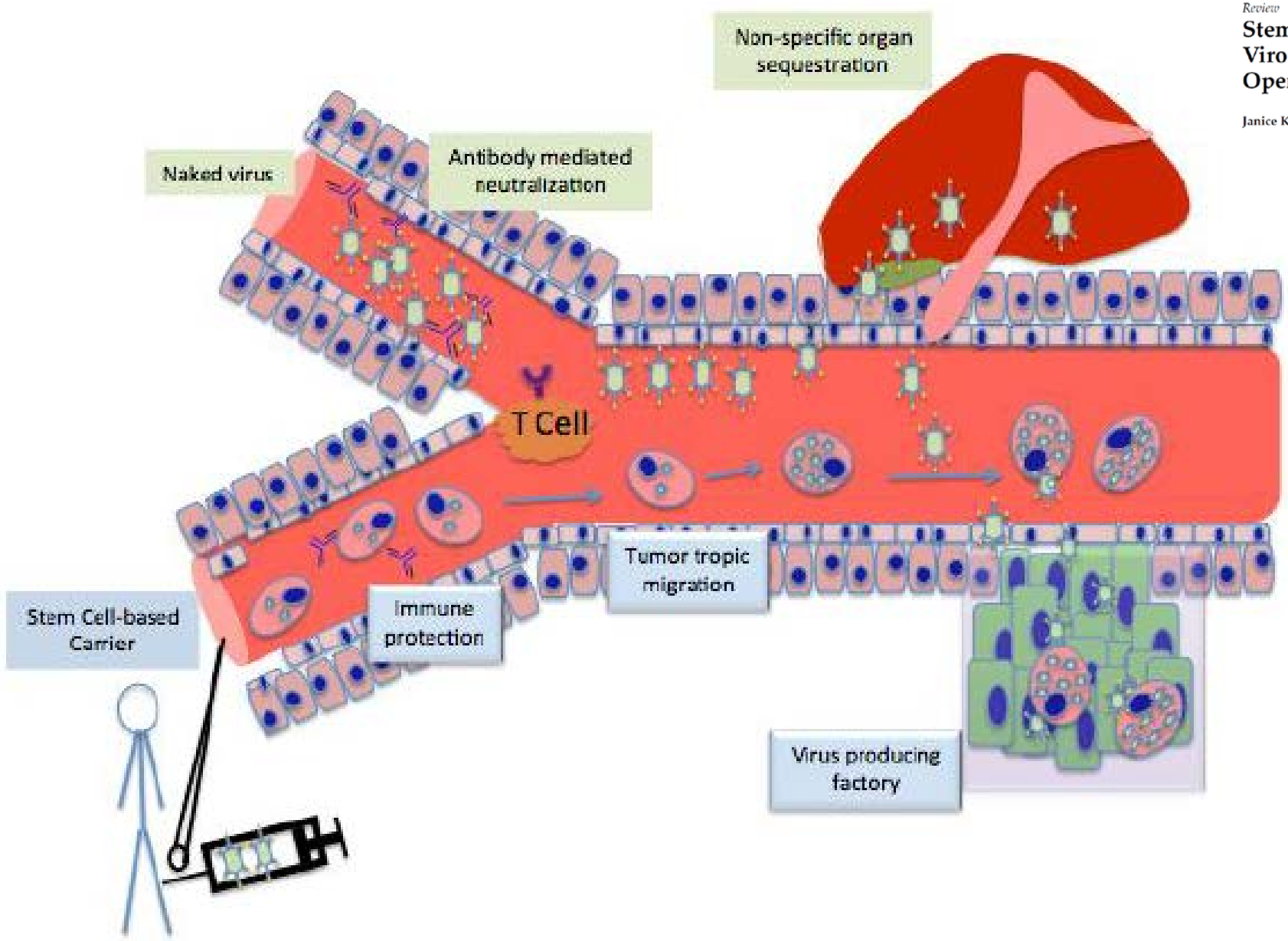


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Table 1 Selected examples of shielding the OV from host barriers

Strategy	Approach	Viral platform	Tumor type	Outcome
Cell-based delivery	Mesenchymal stem cell (bone marrow derived)	MV	Liver cancer	Evasion of host immunity in setting of systemic delivery
	Mesenchymal stromal cell	Ad	Pancreatic tumor	Decreased expression of CD24 and Ki67 and enhanced activity of caspase-3
	Neural stem cell	Ad	GBM	Single administration of oncolytic virus-loaded NSCs allows for up to 31% coverage of intracranial tumors
	Activated T-cells	VSV	Ovarian cancer	Increased efficiency compared to nonactivated T-cells
	Immortalized cell line from solid tumor HeLa (cervical carcinoma) A549 (lung carcinoma) MCF-7 (breast carcinoma) CT26 (colorectal carcinoma) SF268 (glioblastoma)	VSV	Murine model metastatic tumors	Ease of manipulation and propagation in vitro, but has a tendency to arrest in the small capillary beds of the lungs and fail to recirculate in animal (mice) model
	Dendritic cells	MV	Breast cancer	Prevention of pleural exudate in a xenograft model
	Sickle cell	Reovirus VSV	Melanoma	Absorption and transfection despite presence of neutralizing antibodies
	Macrophages	Ad	Prostate cancer	Abolishment of tumor regrowth
	Myeloid-derived suppressor cells	VSV	Metastatic colon tumor	Robust immunosuppressive activity, preferential migration to tumor and decreased toxicity
	Monocytes	Ad	Syrian hamster models of cancer	Antitumoral effect after multiple dosing
	Ghost erythrocytes	VSV-G	In vitro transfection	Improved transfection efficiency

Type of Carrier	Advantages	Disadvantages
	Transformed Cancer Cells	
Solid Tumors	Often stimulate antitumor immunity. Support rapid replication of the viruses they carry. Easy to inject.	Large size limits which tumor forms they can treat. Can cause new metastases. Administer low amounts of virus because of immediate immune responses upon injection.
Hematopoietic and lymphoid tumors	Kinesis via the circulatory system.	Rapid proliferation rate can lead to *de novo* tumors. Elicit immune response, reducing amount of virus delivered.
Xenogeneic/allogeneic	Injected cells are destroyed, preventing *de novo* metastases.	Immune response is profound, limits delivery because or side effects and rejection of injected cells.
	Immune Cells	
T cells	Home to metastases. Activated at tumor cite, release virus specifically into tumor. Do not elicit immune response.	Strong preference to be loaded with reoviruses. Usually refractory to viral infection *in vivo*.
Activated T Cells	Increased ability to take up viruses. Efficacy of viral treatments increases.	Activation is lengthy and tedious. Do not support all viruses.
CIKs	Home to tumors. Release high amounts of viruses upon reaching the tumor. Can affect a variety of tumor types.	Requires expansion of primary leukocytes using cytokines *in vivo*.
	Progenitor Cells	
Blood outgrowth endothelial cells	Very targeted delivery because of ability to become incorporated into tumor neovasculature Divide successfully and rapidly *in vivo*.	Cells are not immortal, new cells must be isolated from clinical samples. Currently unknown if they can support infection with replicating therapeutics.
Mesenchymal Stem Cells	Migrate to the tumor tissue. Allow viral replication. Release virus upon interaction with tumor. Evade the immune system.	High amount of non-specific migration in some cancers. Must be harvested from bone marrow.
Neural Stem Cells	Specifically migrate to brain tumors. Allow viral replication. Evade the immune system.	Require stereotactical extraction of cells from the subventricular zone.

viruses

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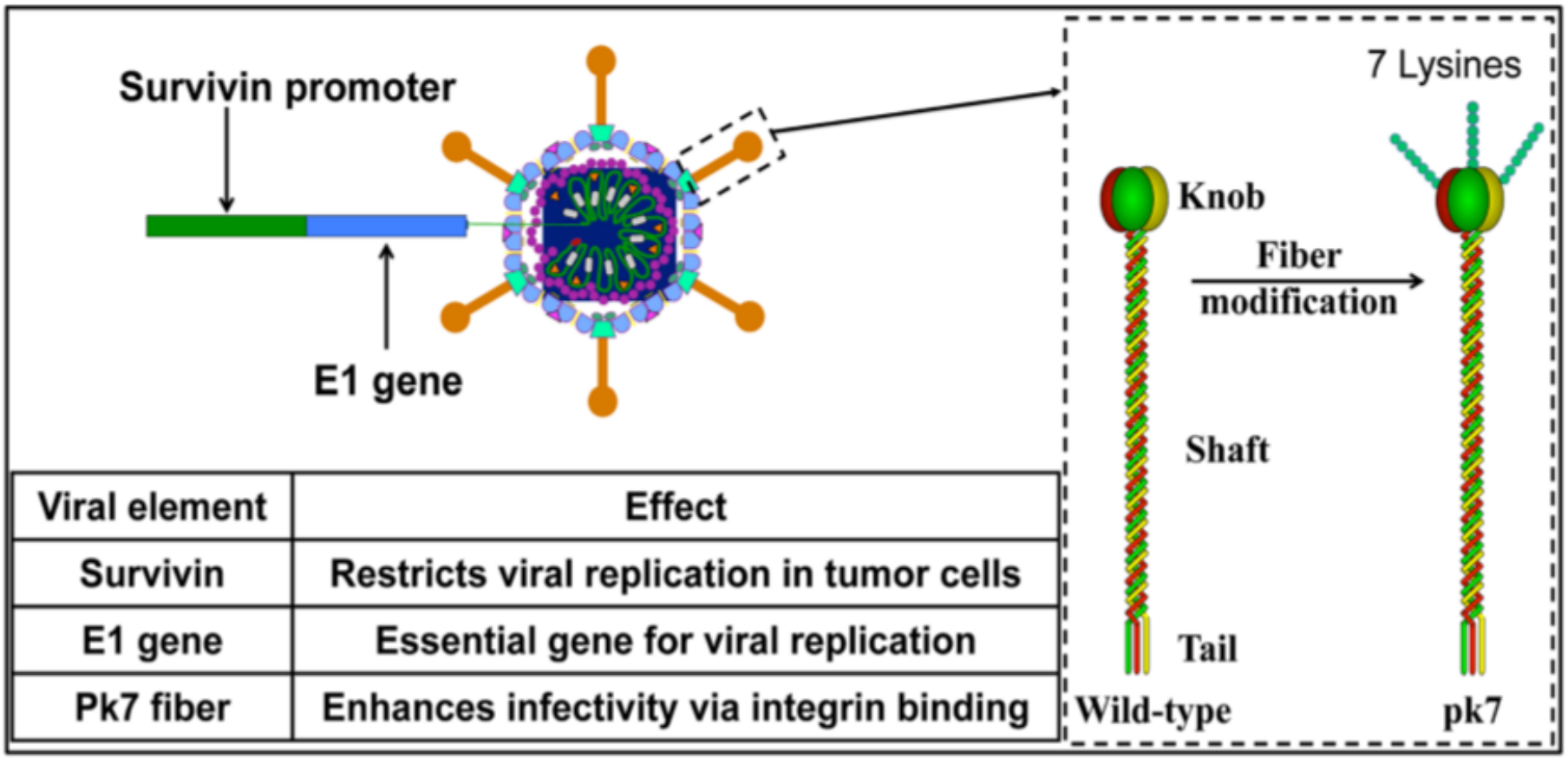
Stem Cell-Based Cell Carrier for Targeted Oncolytic Virotherapy: Translational Opportunity and Open Questions

Janice Kim, Robert R. Hall III, Maciej S. Lesniak † and Atique U. Ahmed *,†

Physical interface with biomaterials	Encapsulation (within biomaterial) alginate	Ad	Model for shielding the adenoviruses	Enhanced transgene expression and reduced immune response
	Encapsulation (within biomaterial) PLGA	Ad	Model for shielding the adenoviruses	Enhanced transgene expression and reduced immune response
	Surface modification coating with biodegradable nanoparticles (PNLG)	Ad	Model for shielding the adenoviruses	Improved efficacy and safety
Chemical modification with biomaterials	PAMAM dendrimer-coated	Ad	EGFR+ cells	Increased transduction efficiency, especially in low-to-medium CAR-expressing cancer cell lines
	Cationic polymers* (form electrostatic interactions with anionic Ad, can also be classified as physical interface)	Ad	Model for shielding the adenoviruses	Permitted ligand attachment and manipulation of molecular weight
	PLL (cationic polymer*)	Ad	Model for shielding the adenoviruses	Caused Ad to bind and infect cells through a pathway other than classic CAR-mediated entry PEG-PLL-Ad had gene expression ~4× compared to naked Ad
	Cationic lipids*	Ad	Model for shielding the adenoviruses	Increased delivery ~80× compared to naked Ad
	Liposomes			Resulted in effective immune shielding
	PEGylation (covalent chemical modification)	Ad VSV	Model for shielding the adenoviruses	Increased circulation half-life Protected from neutralization
	Poly-HPMA	Ad	Model for shielding the adenoviruses	Increased half-life by diminishing hepatic transgene expression

Table 1 (*Continued*)

Strategy	Approach	Viral platform	Tumor type	Outcome
	Polysaccharides	Ad	Model for shielding the adenoviruses	Unable to evade neutralizing antibodies
Substrate-mediated viral gene delivery	Hydrogel	Ad	Model for shielding the adenoviruses	Minimized sequestration by the mononuclear phagocytic system
	Silk-elastin-like polymer	Ad	Model for shielding the adenoviruses	Increased viral gene expression but demonstrated some acute toxicity
	Chitosan	Ad	Model for shielding the adenoviruses	Infectivity was observed in cells that do not express CAR
	Biogels: fibrin and collagen micelle based	Ad	Model for shielding the adenoviruses	Sustained release of viral particles by fibrin
	Microporous scaffolds (could be considered as physical interface given that coaxial electrospinning is used to encapsulate vectors)	Ad	Model for shielding the adenoviruses	Reduced macrophage activation



Viral element	Effect
Survivin	Restricts viral replication in tumor cells
E1 gene	Essential gene for viral replication
Pk7 fiber	Enhances infectivity via integrin binding

Fig. 1 Schematic of genome of CRAd-S-pk7. The fiber knob domain has seven lysine residues added to the C-terminal end to enhance the infectivity of the virus. The essential early replication gene (E1) is under the transcriptional control of the tumor-specific promoter survivin (S) to restrict viral replication to tumor cells (oncolysis)

Viral spread

Targeting viral spread to tumor cells can be accomplished by

- **transductional targeting** (modifying receptor tropism)
- **transcriptional targeting** (controlling virus gene expression with **tumor-specific promoters**)
- **physiologic targeting** (disrupting viral immune combat proteins)
- **apoptosis targeting** (disrupting viral antiapoptotic proteins)
- **miRNA targeting**.

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Table 4 Selected examples of tumor-specific promoters

Tumor target	Virus-encoded promoter	Viral platform	References
Bladder cancer	Uroplakin II	Ad	131
Brain tumors	Nestin	HSV-1	132
	Musashi-1	HSV-1	133
Breast cancer	Estrogen response element	Ad	134
Gastroenteropancreatic neuroendocrine tumors	Chromogranin-A	Ad	135
Glioma	Glial fibrillary acidic protein	Ad	136
Hepatocellular carcinoma	Alpha-fetoprotein	Ad, HSV-1	137
Melanoma	Tyrosinase	Ad	138
Mesothelioma	Mesothelin	Ad	139
Ovarian cancer and breast cancer	Mucin-1	Ad	140

Abbreviations: Ad, adenovirus; HSV-1, herpes simplex virus-1.

Arming viruses with transgenes

The addition of transgenes allows tumor cells that escape viral infection to be killed by bystander effects or be better targeted by the immune system.

Incorporation of

- secreted toxins
- prodrug convertases
- immunostimulatory proteins

→ increase of treatment efficacy

Safety

Careful steps must be taken to avoid the creation of OVs that might evolve to become serious pathogens.

Contingency plans to terminate the spread and/or transmission of an infection can increase clinical confidence in viral therapy.

Ideally, OVs should be nontransmissible!

Administration of oncolytic viral therapy

Nonstandardized

- **Simple injections** (direct intratumoral/resection bed): bypassing BBB (+), high local concentration of virus (+), invasive nature (-), single dose delivery (-), limited total volume (-), virus reflux out of the injection tract (-)
- **Convection-enhanced delivery**: continuous virus delivery (+), higher volumes/requires lower titers (+), greater volume of distribution (+), minimizing reflux and spill into CSF spaces (+), need for invasive and complex surgical procedure (-)
- **Systemic vascular delivery** (intra-arterial and i.v.): BBB (-), high dose of virus (-), innate immune response (-), no need for invasive procedures (+)

Article

Cell

Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy

Antoni Ribas,[1,18,*] Reinhard Dummer,[2] Igor Puzanov,[3] Ari VanderWalde,[4] Robert H.I. Andtbacka,[5] Olivier Michielin,[6] Anthony J. Olszanski,[7] Josep Malvehy,[8] Jonathan Cebon,[9] Eugenio Fernandez,[10] John M. Kirkwood,[11] Thomas F. Gajewski,[12] Lisa Chen,[13] Kevin S. Gorski,[14] Abraham A. Anderson,[13] Scott J. Diede,[15] Michael E. Lassman,[15] Jennifer Gansert,[13] F. Stephen Hodi,[16] and Georgina V. Long[17]

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PD-1 (Programmed death protein 1; CD279)
PD-L1 (PD-1 ligand; CD274)

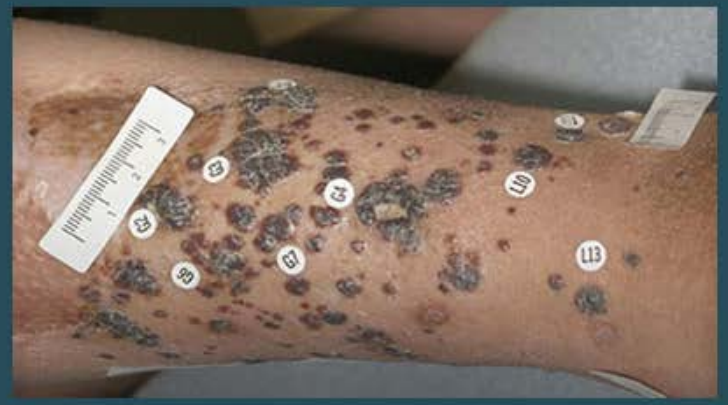
- PD-1: down-regulating the immune system and promoting self tolerance by suppressing T cell inflammatory activity

- PD-L1: is upregulated on macrophages and dendritic cells (DC) in response to LPS and GM-CSF treatment, and on T cells and B cells upon TCR and B cell receptor signaling,
- Several human cancer cells expressed high levels

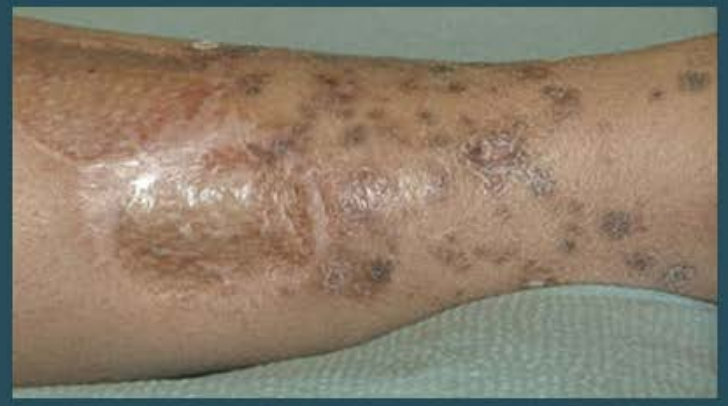
- Blockade of PD-1:PD-L1 interaction reduced the growth of tumors in the presence of immune cells (Pembrolizumab)

- Treatment with anti-programmed death protein 1 (PD-1) or anti-PD ligand 1 (PD-L1) antibodies results in long-lasting antitumor responses in patients with a variety of cancers → standard of care treatment for patients with metastatic melanoma, carcinomas of the head and neck, lung, kidney, and bladder, Merkel cell carcinoma, and Hodgkin disease

Patient with Complete Response[8,†]

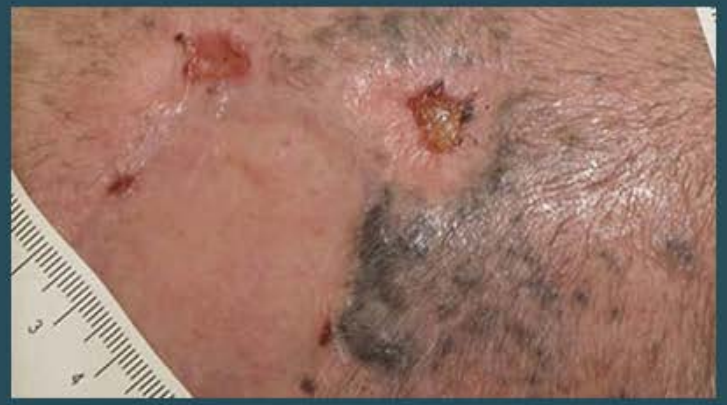


Before: Cycle 1



After: Cycle 13

Patient with Partial Response[8]



Before: Cycle 1

After: Cycle 10

vely replicate in
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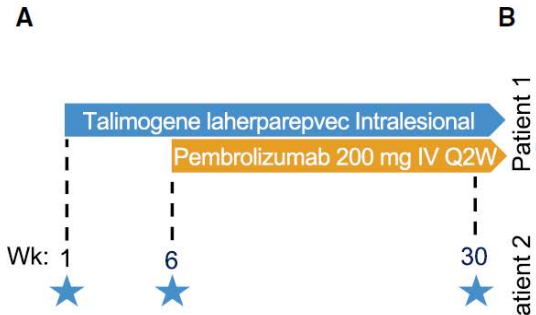
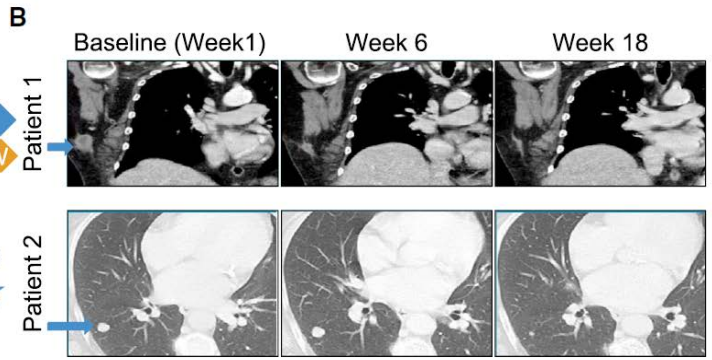
Hypothesis

- Intratumoral administration of an oncolytic virus optimized to attract immune cells might favorably change the tumor microenvironment in the injected lesions and increase CD8+ T cell infiltration.

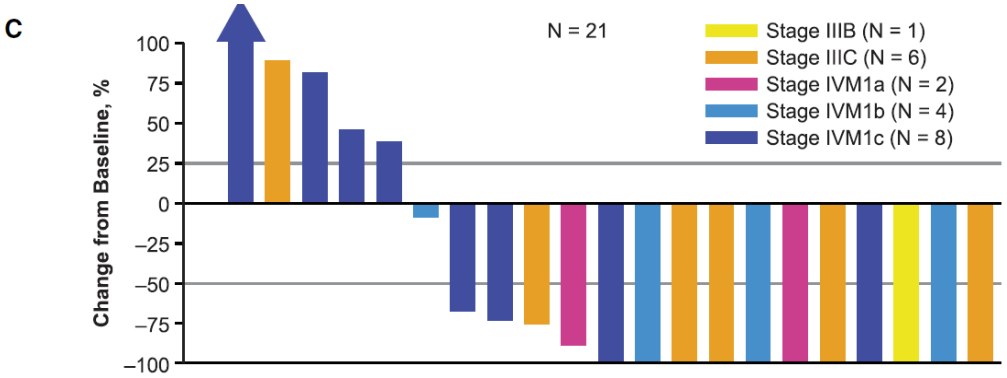
Melanoma Study Design and Clinical Response to Combination of Talimogene Laherparepvec and Pembrolizumab



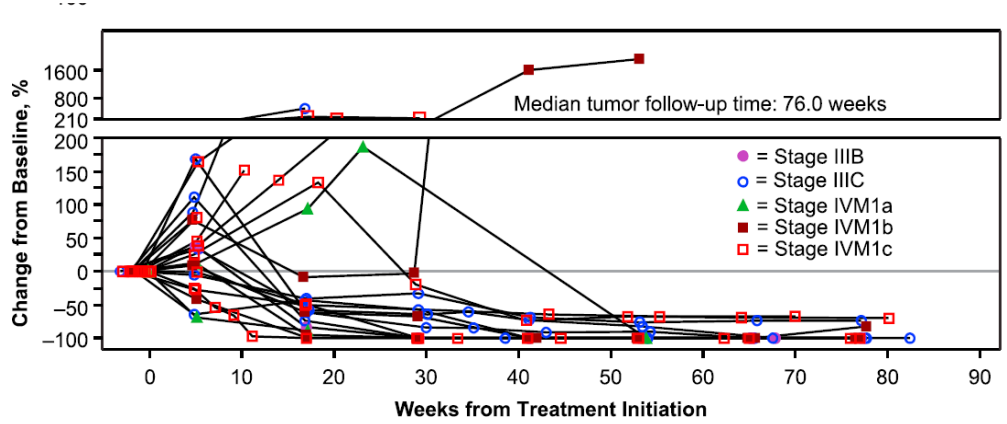
Phase 1b study design schema. Stars indicate the time of scheduled tumor biopsies



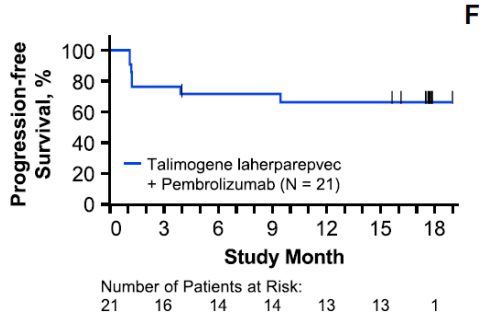
CT-scans of two patients with response to the combination therapy. Melanoma metastases are marked with a blue arrow at baseline.



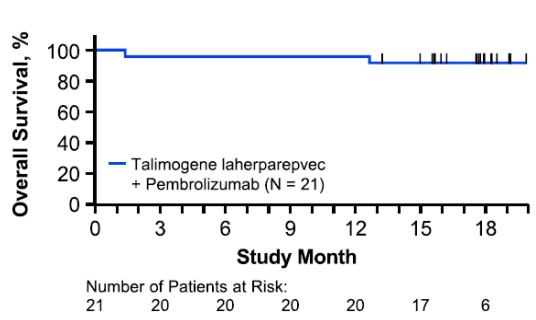
Waterfall plot of best response change in tumor burden from baseline.



Change in tumor burden over time.

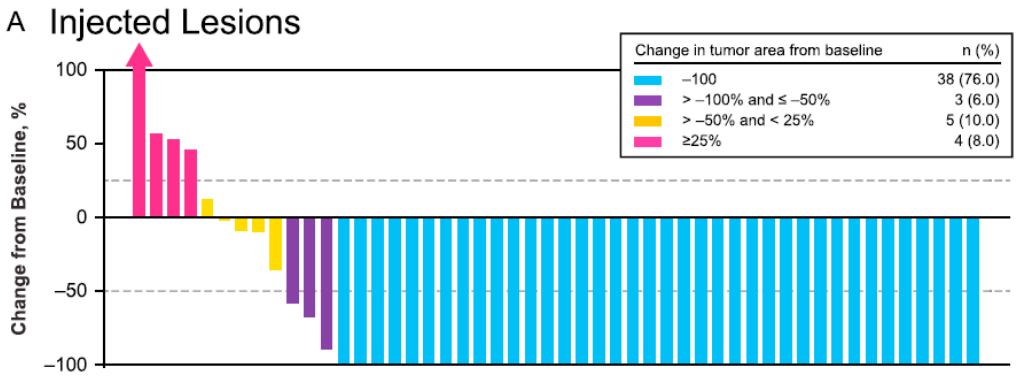


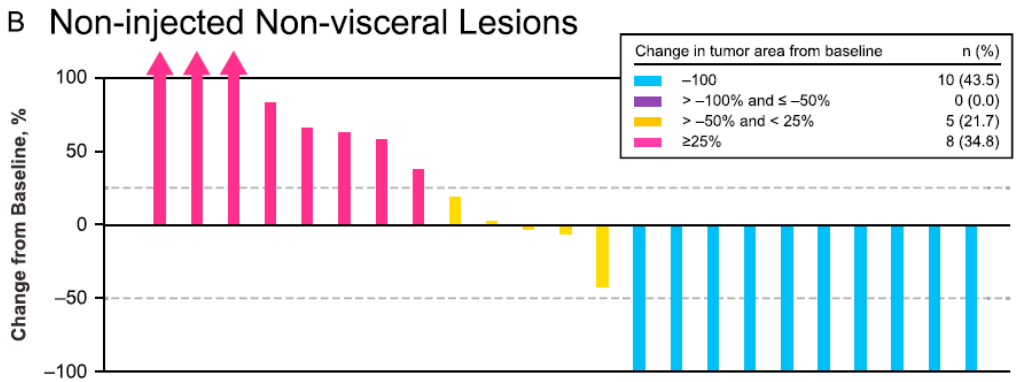
Kaplan-Meier analysis of progression-free survival.

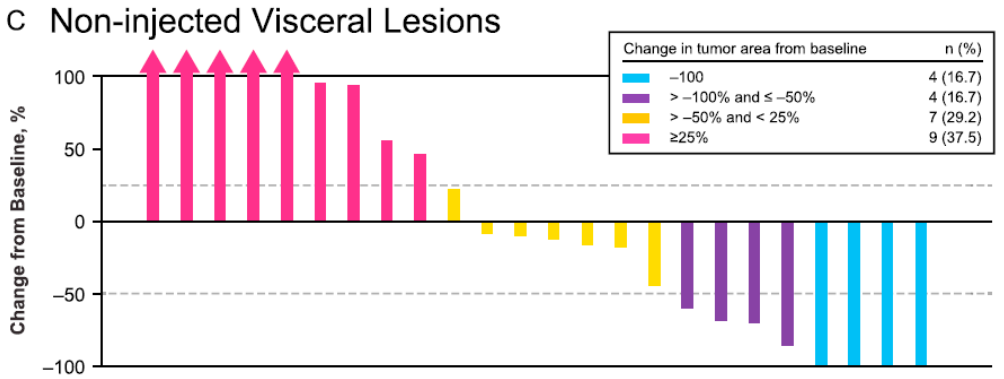


Kaplan-Meier analysis of overall survival.

Changes in Tumor Burden at Lesion Level







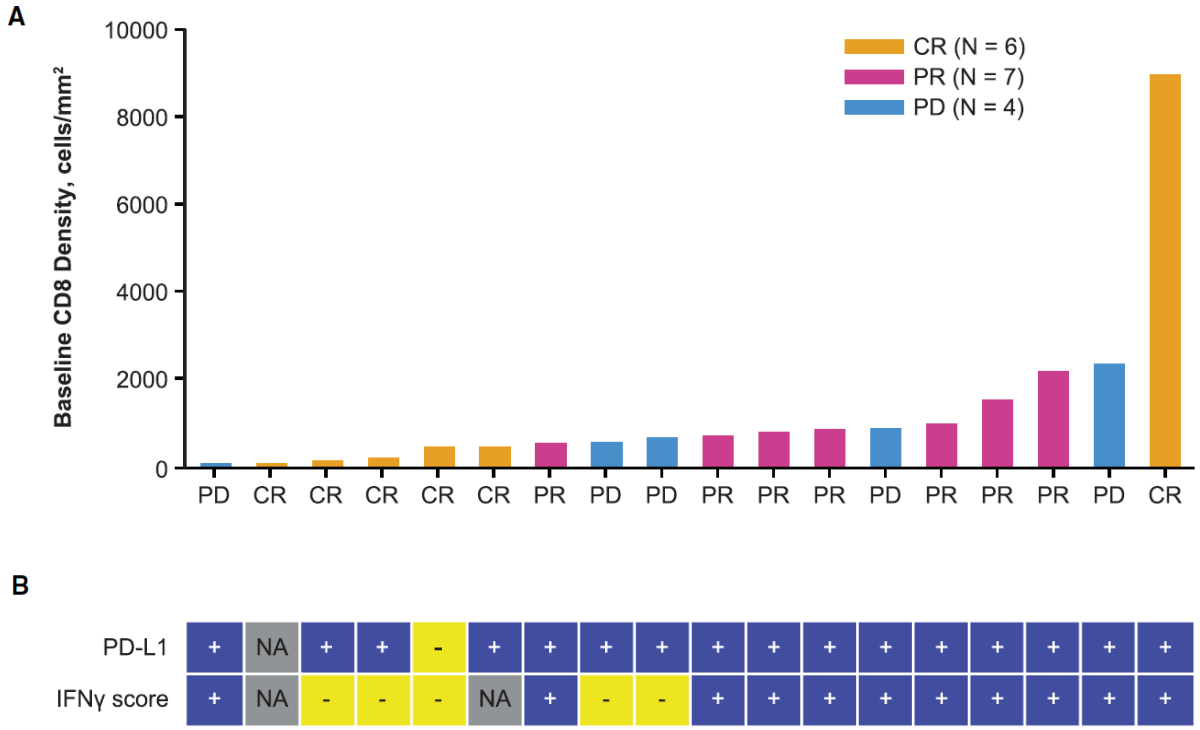
Includes index or new measurable lesion.
Evaluable indicates at least 2 assessments with bi-dimensional measurements.
Safety analysis set includes all subjects who received at least 1 dose of talimogene laherparepvec or pembrolizumab.

Combination of Talimogene Laherparepvec and Pembrolizumab Is Effective in Patients with Low Tumor CD8+ Density

CR = complete response

PR = partial response

PD = progressive disease



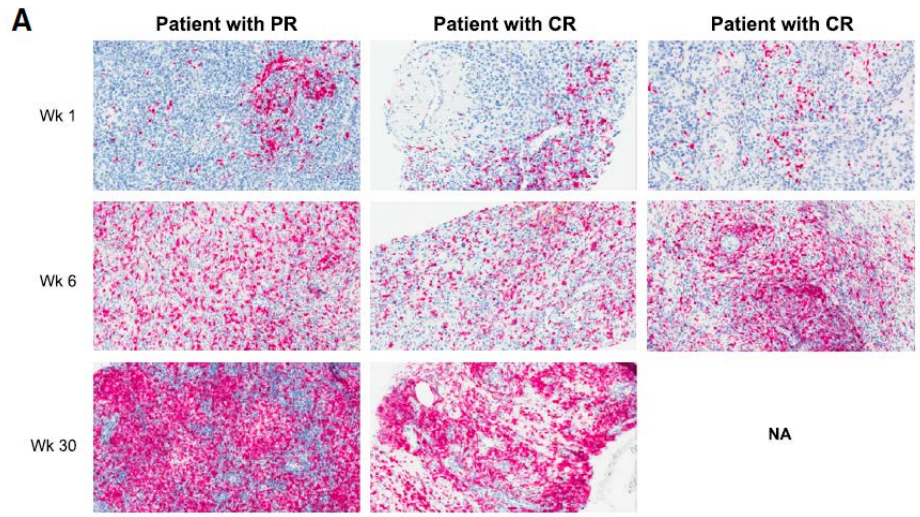
Baseline PD-L1 by IHC status (1% cutoff) and IFN-g signature score by NanoString analysis. Best overall response per investigator is shown as of cutoff date of August 2016.

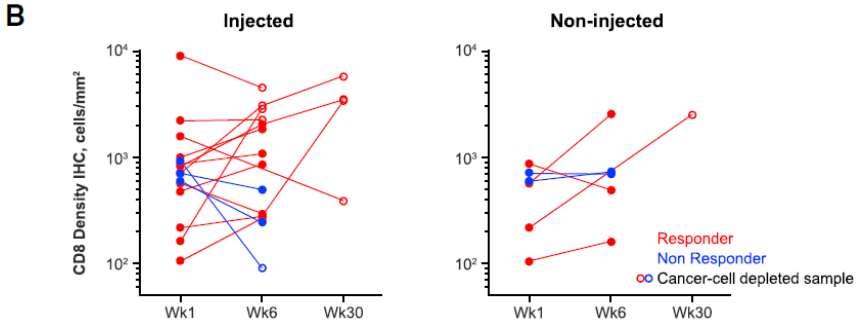
Table 1. Best Overall Response[a]

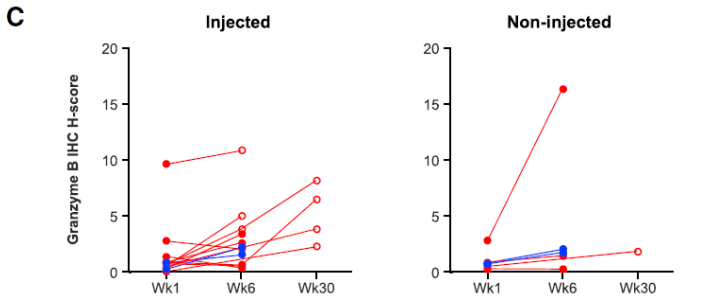
	Talimogene Laherparepvec Plus Pembrolizumab (N = 21)	
	Total[b]	Confirmed[b]
Patients with a response	15	13
Response rate, % (95% CI)	71 (48–89)	62 (38–82)
Best overall response, n (%)		
Complete response	8 (38)	7 (33)
Partial response	7 (33)	6 (29)
Stable disease[c]	1 (5)	3 (14)
Progressive disease	5 (24)	5 (24)
Disease control rate, n (%)	16 (76)	16 (76)

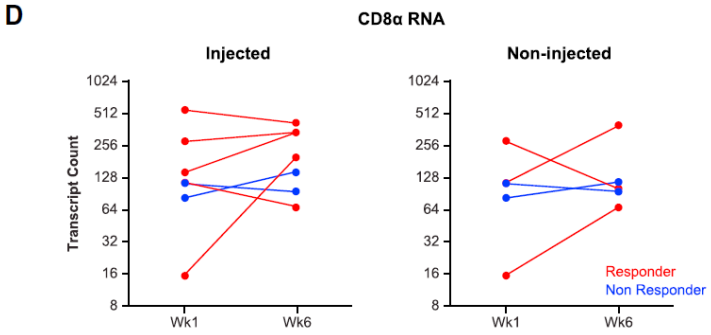
[a]Response was evaluated per immune-related response criteria by investigators; data cutoff was August 31, 2016.
[b]Responses were confirmed by a subsequent assessment at least 4 weeks later.
[c]A best overall response of stable disease required an evaluation of stable disease no earlier than 77 days after enrollment.

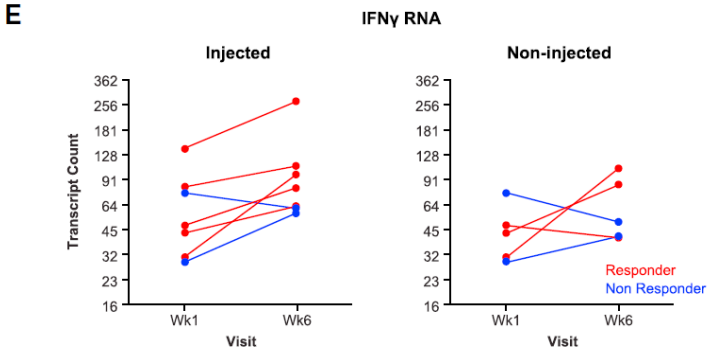
Talimogene Laherparepvec Increases Tumor CD8+ Density in Patients Responding to Combination of Talimogene Laherparepvec and Pembrolizumab





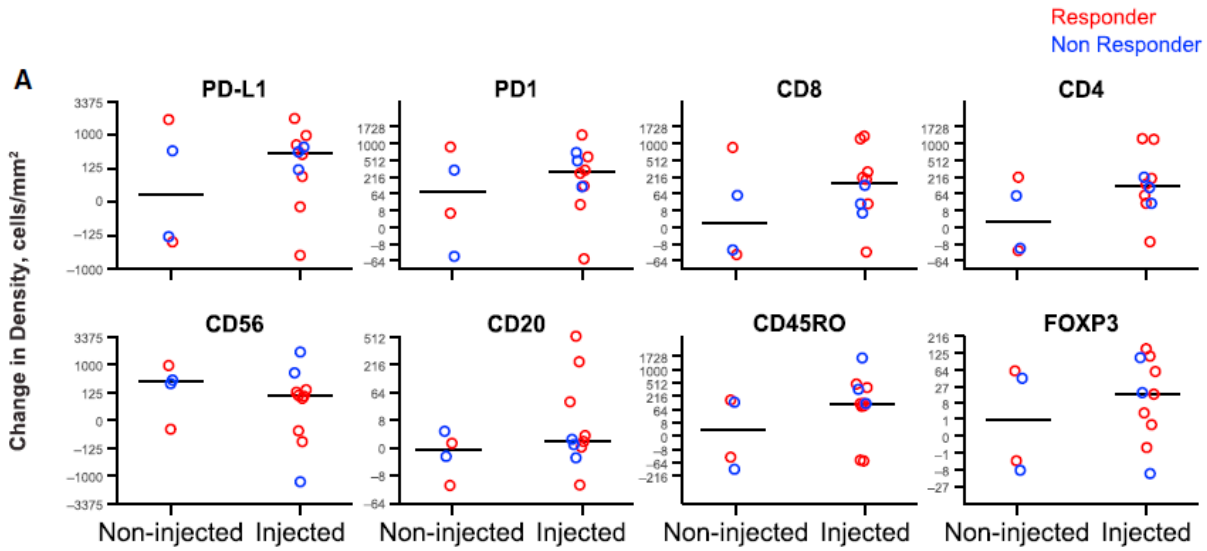


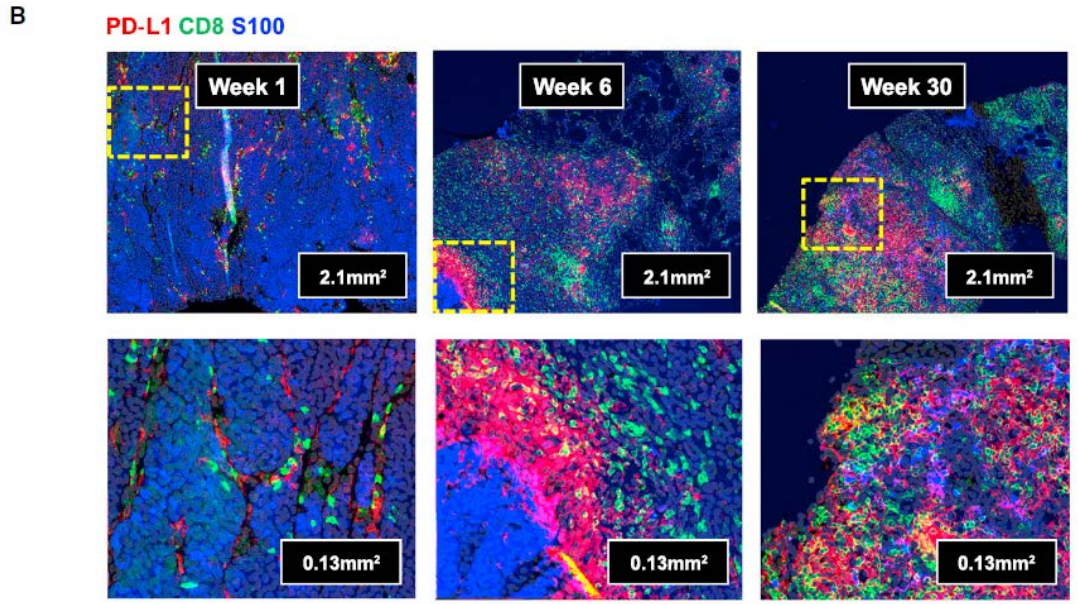




associated with the cytotoxic subset of CD8+ T cells and natural killer cells

Talimogene Laherparepvec Increases Tumor-Infiltrating Lymphocyte Density and PD-L1 Expression in Tumors

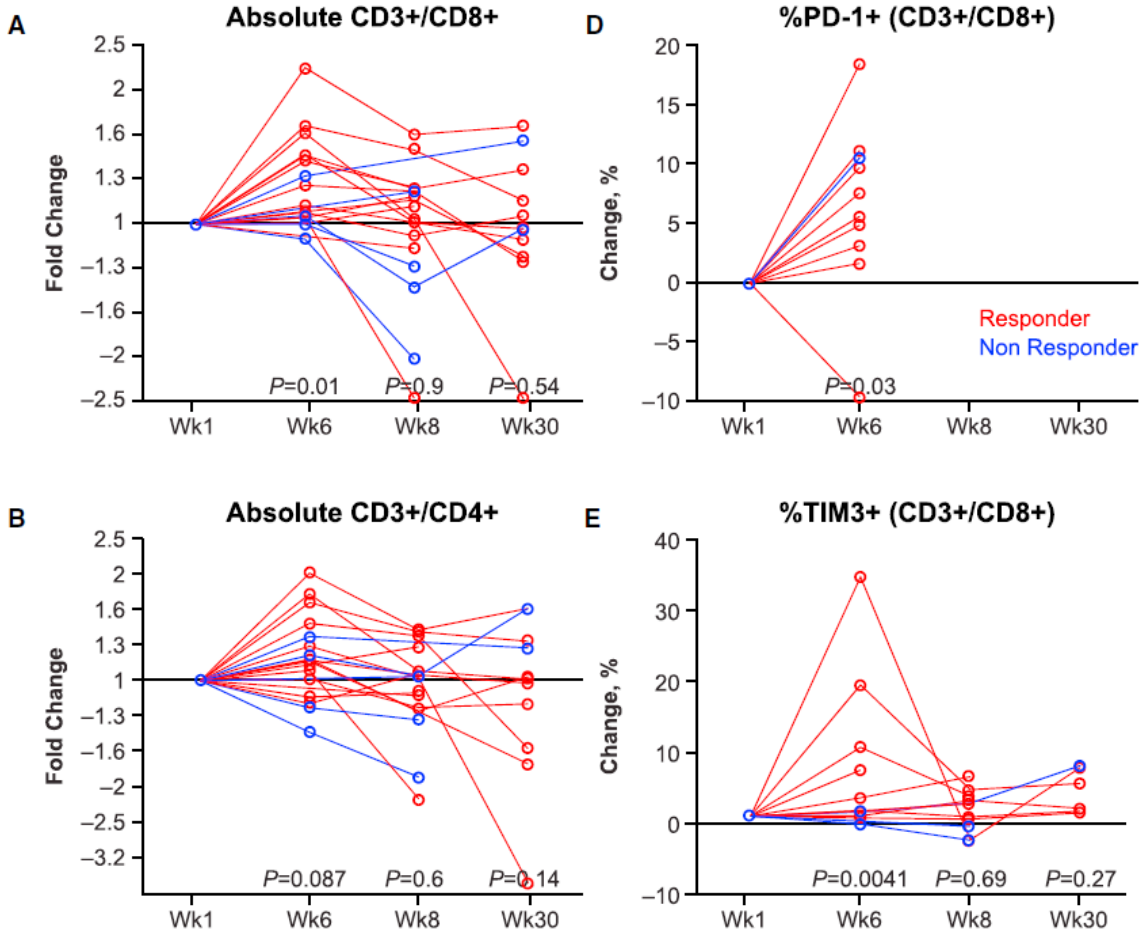




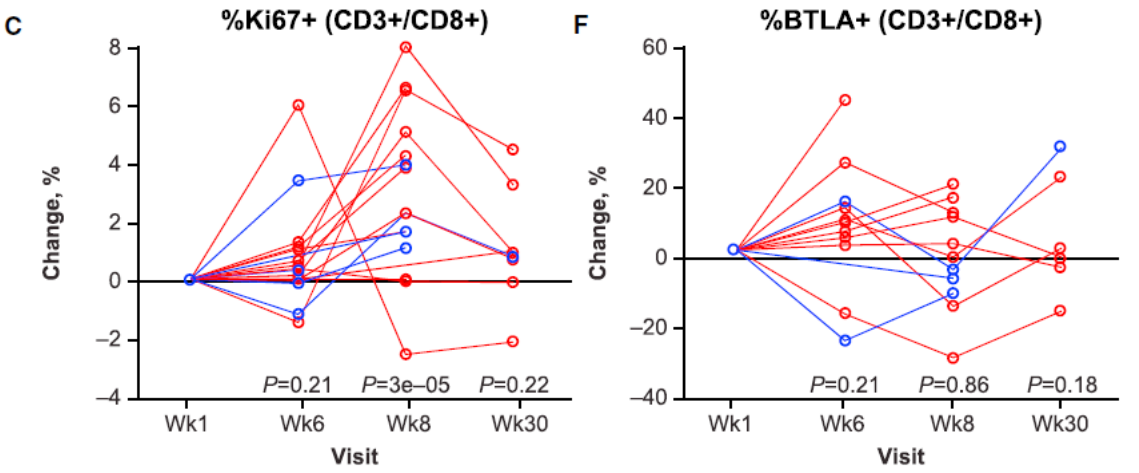
A subset of changes at week 6 from baseline in marker cell positive cell density for results with statistical significance

Twelve-color immunofluorescence staining was performed on a single slide from paired pre- and post-talimogene laherparepvec tumor biopsies from each of 13 patients. Markers evaluated included S100 (as melanoma segmentation marker), CD3, CD4, CD8, PD-1, PD-L1, CTLA-4, CD45RO, Foxp3, CD56, CD68, and CD20.

Circulating T Cell Subsets and Expression of Activation Markers

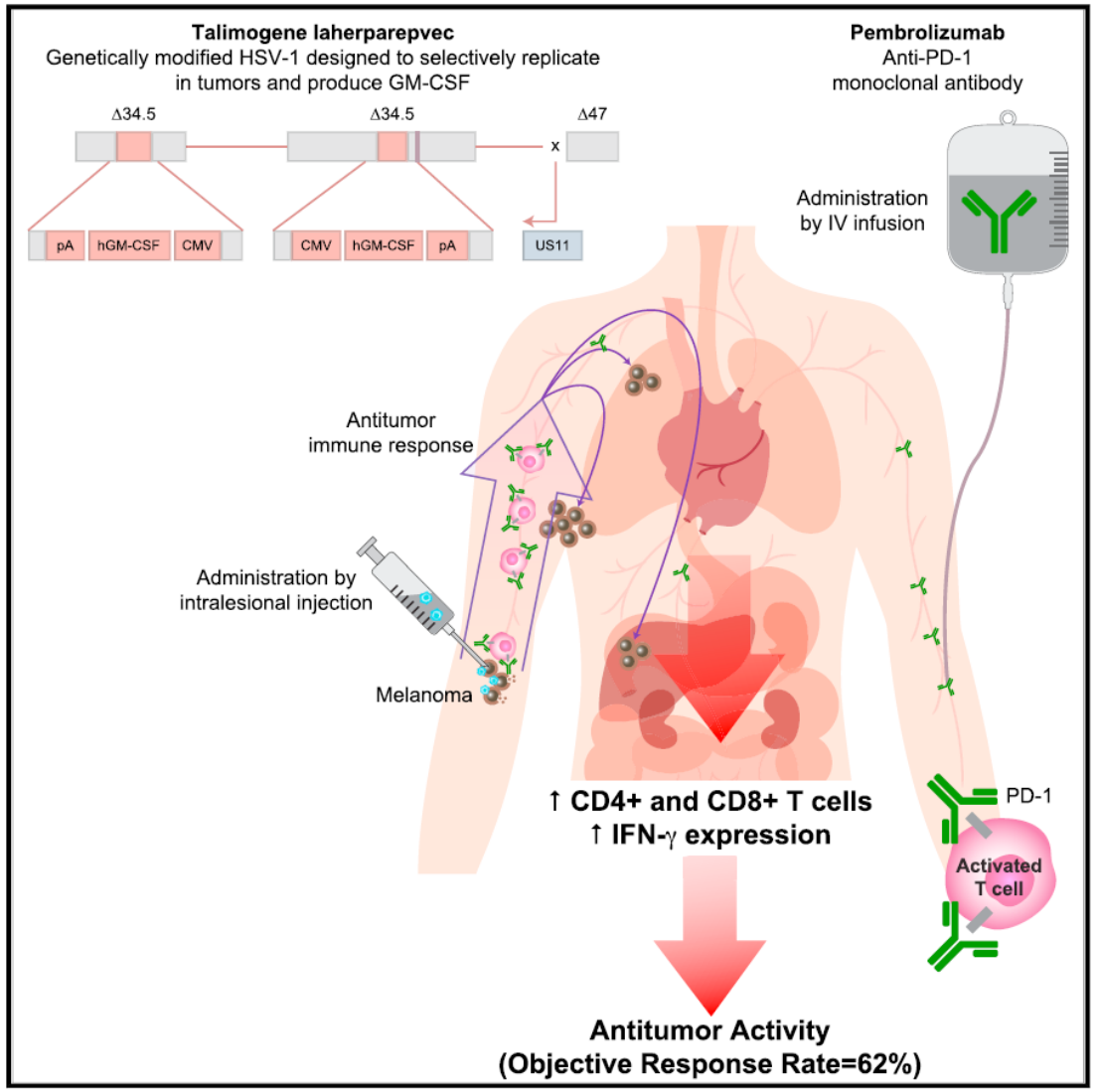


molecule expressed on IFN-g-producing CD8+



B- and T-lymphocyte attenuator protein

Conclusion



Highlights

- Oncolytic virus plus anti-PD-1 therapy favorably changed the tumor microenvironment
- A high overall response rate of 62% to the combination in metastatic melanoma
- A high complete response rate of 33% to the combination in metastatic melanoma
- Responses to this combination appeared independent of baseline $CD8^+$ infiltration

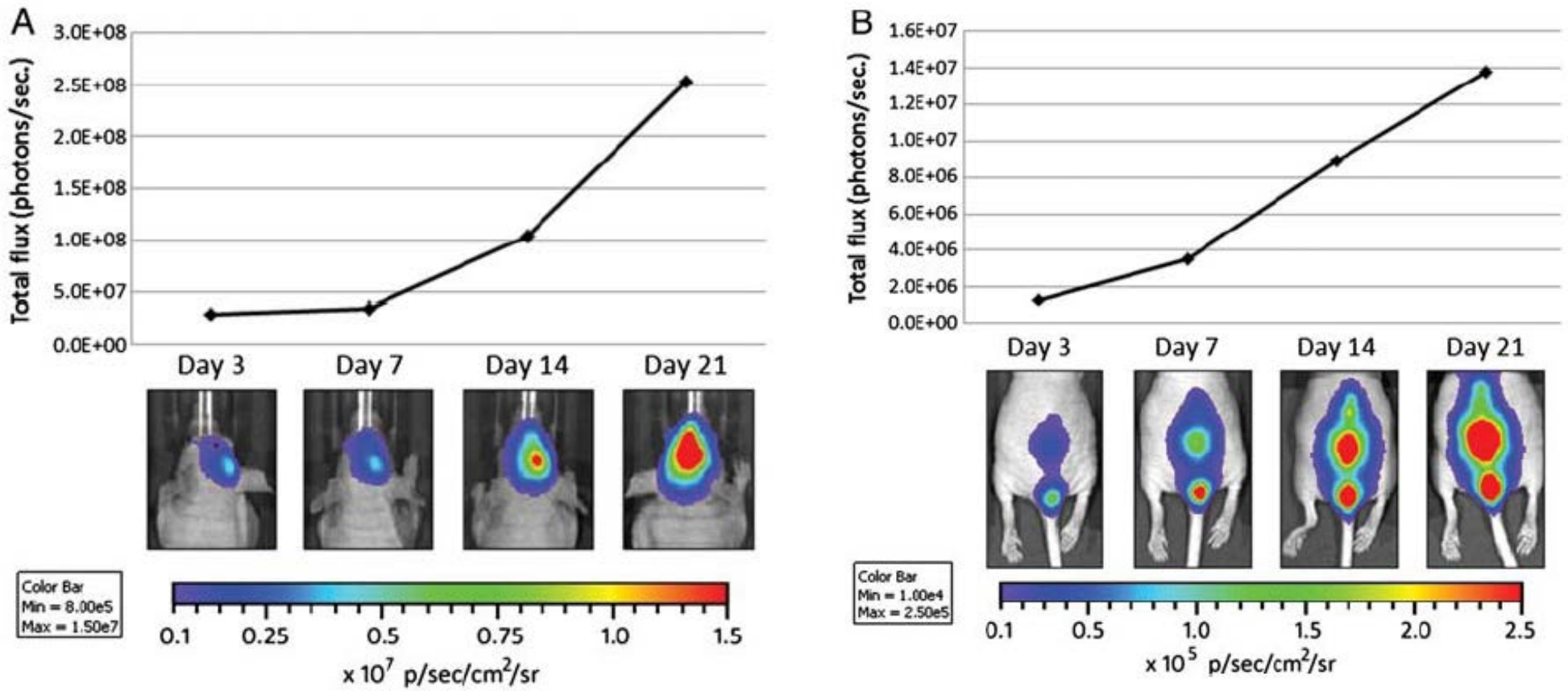
Neuro-Oncology 14(4):459–470, 2012.
doi:10.1093/neuonc/nor231
Advance Access publication February 3, 2012

NEURO-ONCOLOGY

Oncolytic measles virus prolongs survival in a murine model of cerebral spinal fluid–disseminated medulloblastoma

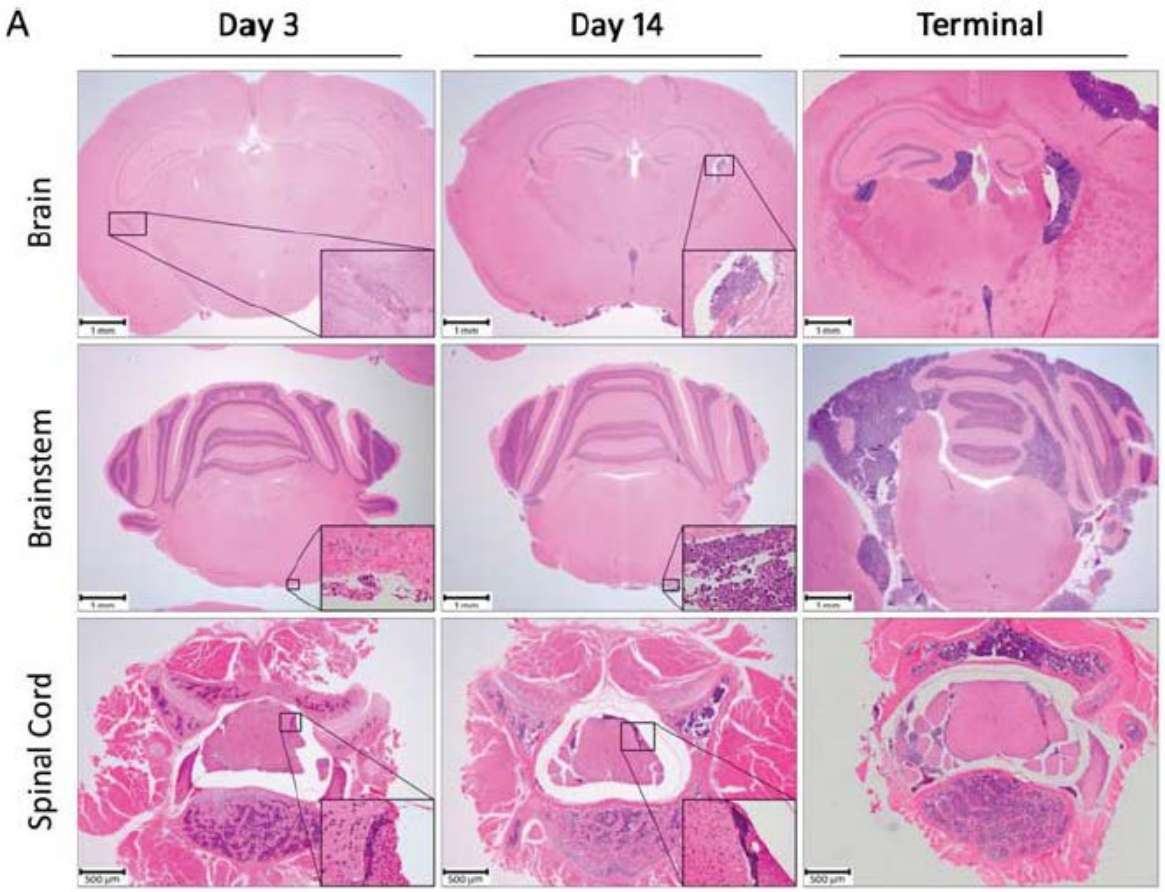
Adam W. Studebaker, Brian Hutzen, Christopher R. Pierson, Stephen J. Russell, Evanthia Galanis, and Corey Raffel

In vivo evaluation of medulloblastoma dissemination and disease progression

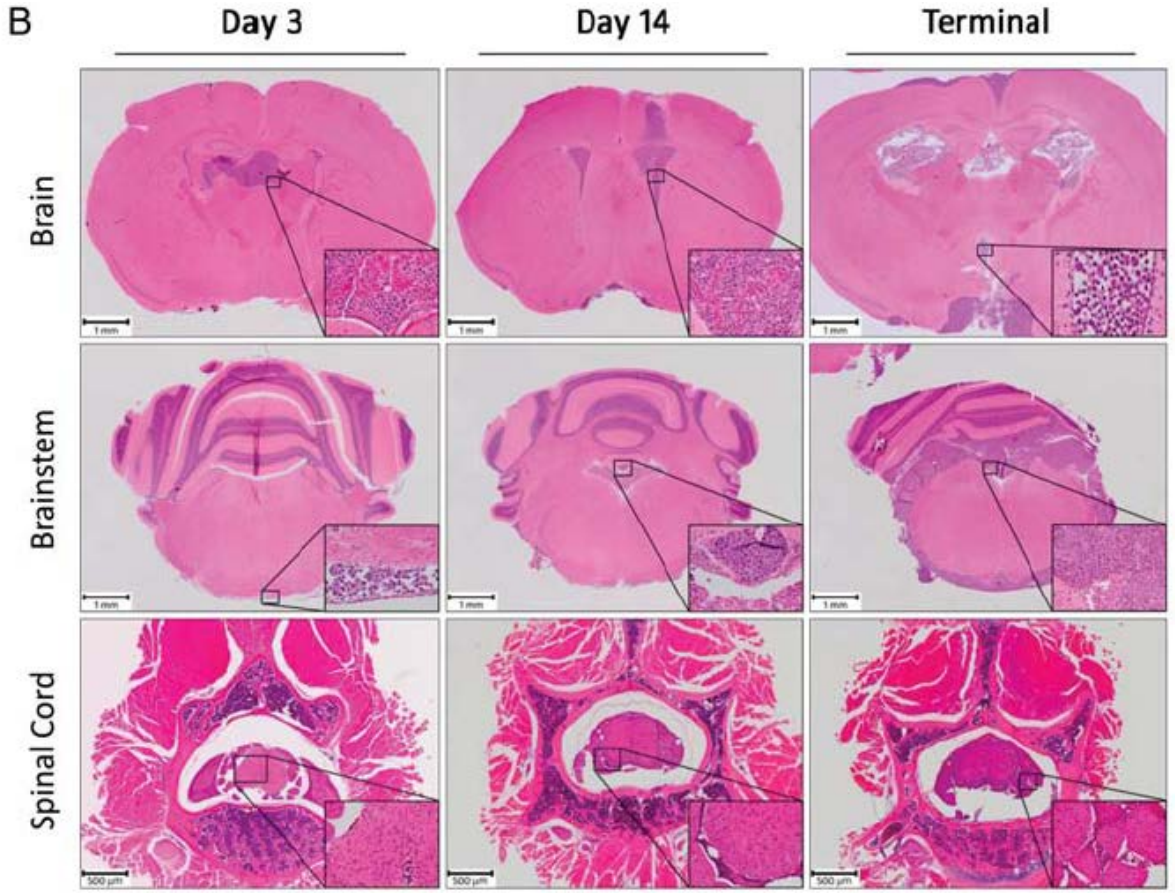


D283luc ($1 \times 10_6$ cells) or D425luc ($5 \times 10_5$ cells) were injected into the right lateral ventricle of 5-week-old Hsd:Athymic Nude-Foxn1nu mice

Mouse brain following injection of medulloblastoma cells

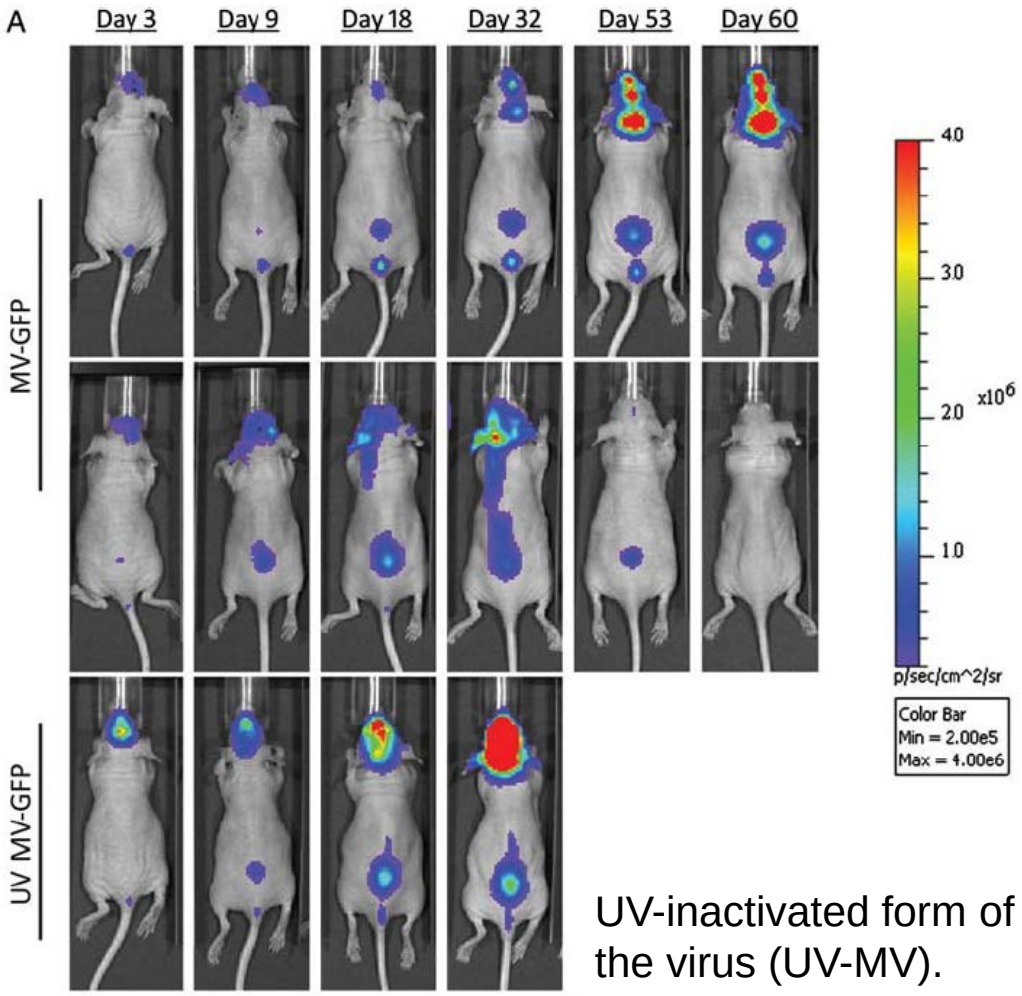


D283luc

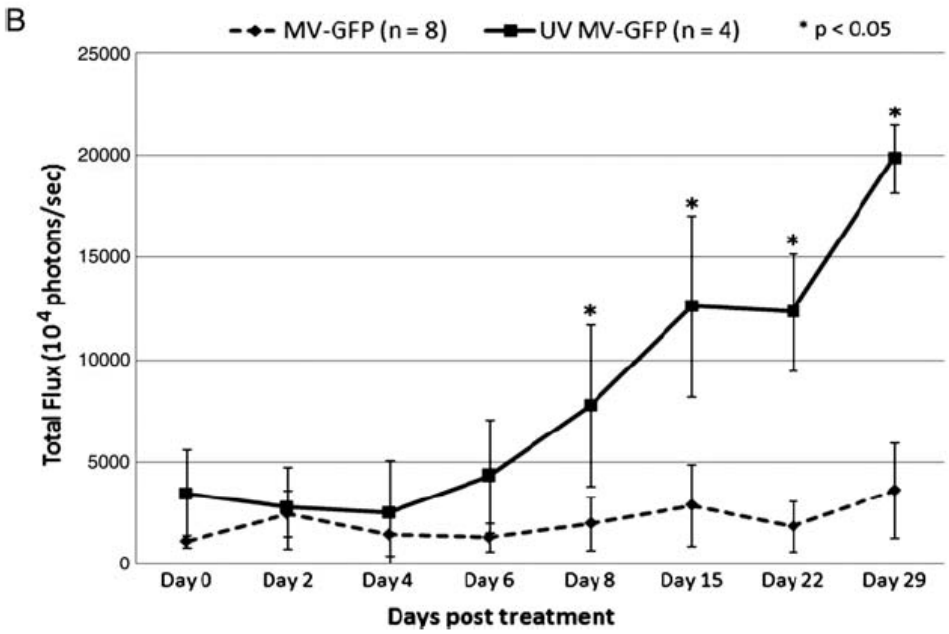


D425luc

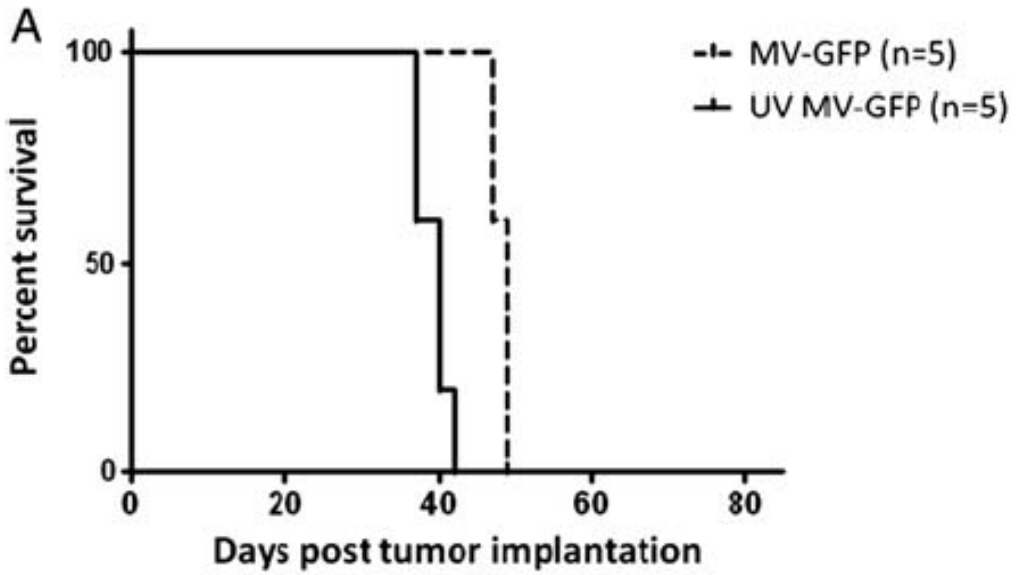
In vivo evaluation of antitumor activity of measles virus (MV)



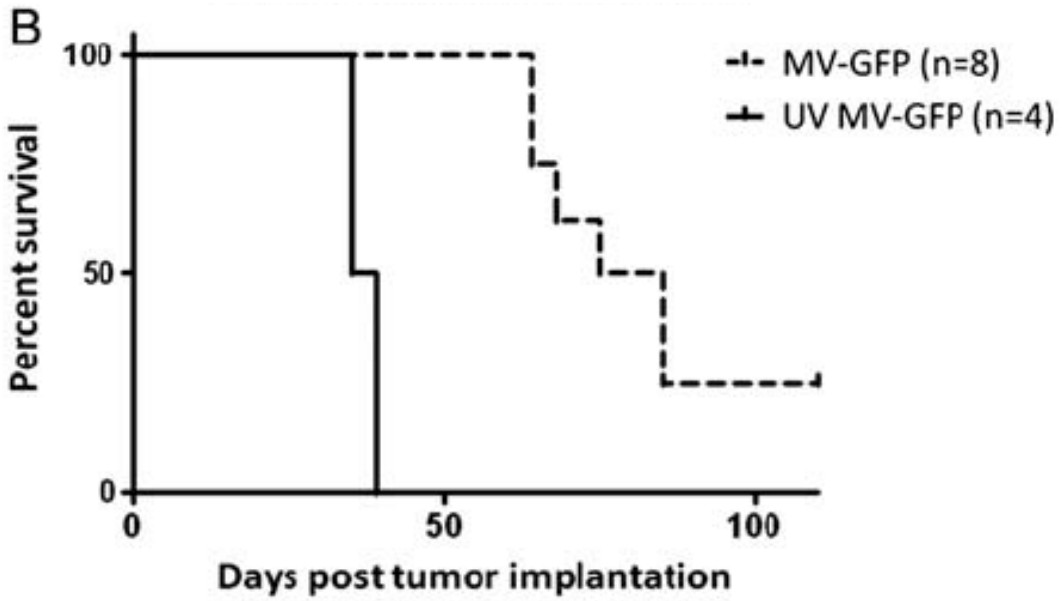
UV-inactivated form of the virus (UV-MV).



Antitumor effect of measles virus (MV)

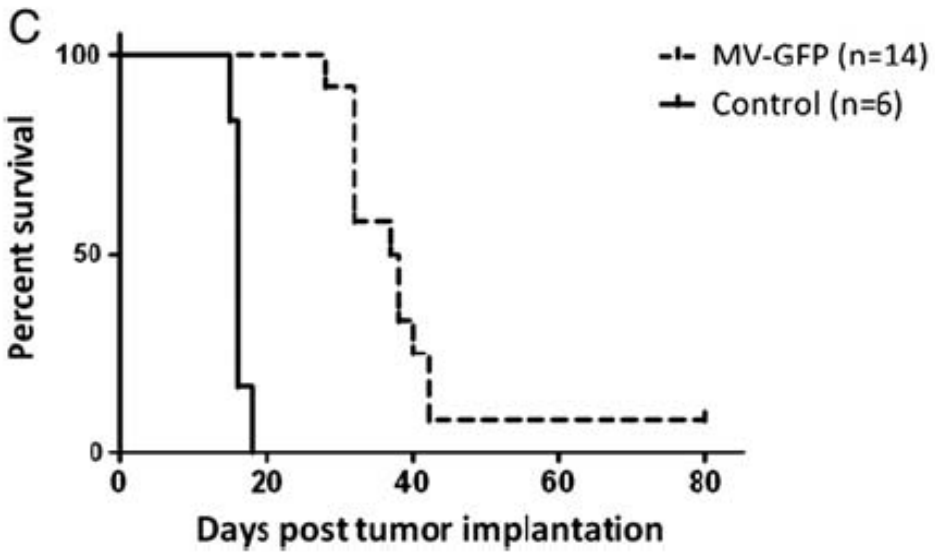


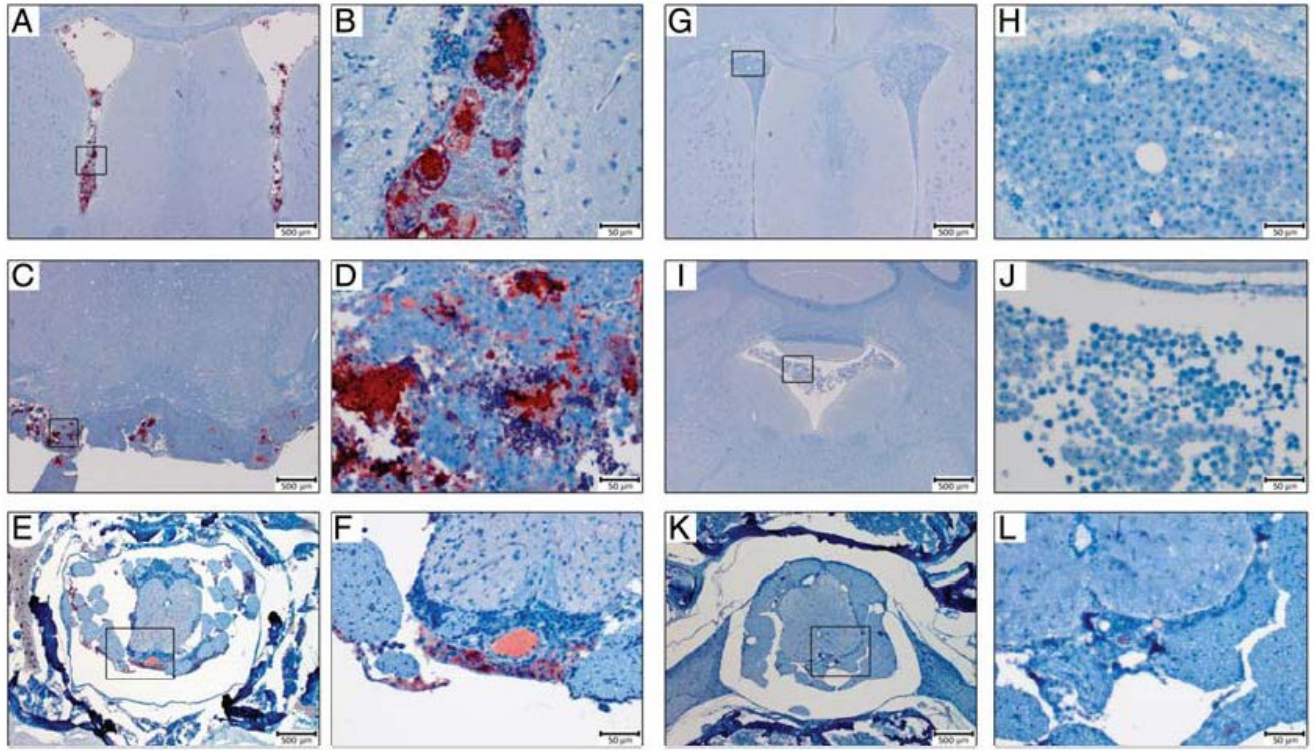
1 × 106 pfu of MV or the same dose of UV-MV
Fourteen days post tumor implantation



1 × 106 pfu of MV or the same dose of UV-MV
Three days post tumor implantation

Antitumor effect of measles virus (MV)





medulloblastoma luciferase-expressing cell line, D425luc

Conclusion

- Inoculation of MV directly into the CSF via the lateral ventricle significantly increased the survival of animals presenting with disseminated medulloblastoma.
- Intravital bioluminescent imaging provided a means by which disseminated medulloblastoma could be evaluated and a method to monitor tumor response to MV therapy.
- Evidence of MV infection at tumor deposits distant from the site of MV inoculation, concomitant with an increase in animal survival, demonstrated that modified MV has therapeutic potential for disseminated medulloblastoma.
- Additional studies, including evaluating the toxicity of MV injection directly into the CSF of previously immunized, immunocompetent, nonhuman primates will need to be completed prior to using the virus in a clinical trial for the treatment of disseminated medulloblastoma.

Taken together…

Delivery of OVs

- OVs do not obey conventional pharmacological principles due to their ability to be biologically amplified after administration.
- Intravenous delivery allows a virus to reach distant sites of metastasis via the circulation, but extravasation into the tumor parenchyma is inefficient.
- Intratumoral injection can concentrate virus at a site of tumor growth, but regression of distant tumors requires that the virus spread systemically or induce a systemic antitumor immune response.
- Neutralizing antibodies, hepatosplenic sequestration of the virus by macrophages and dilution of the virus in blood or tissue may limit the effectiveness of treatment.

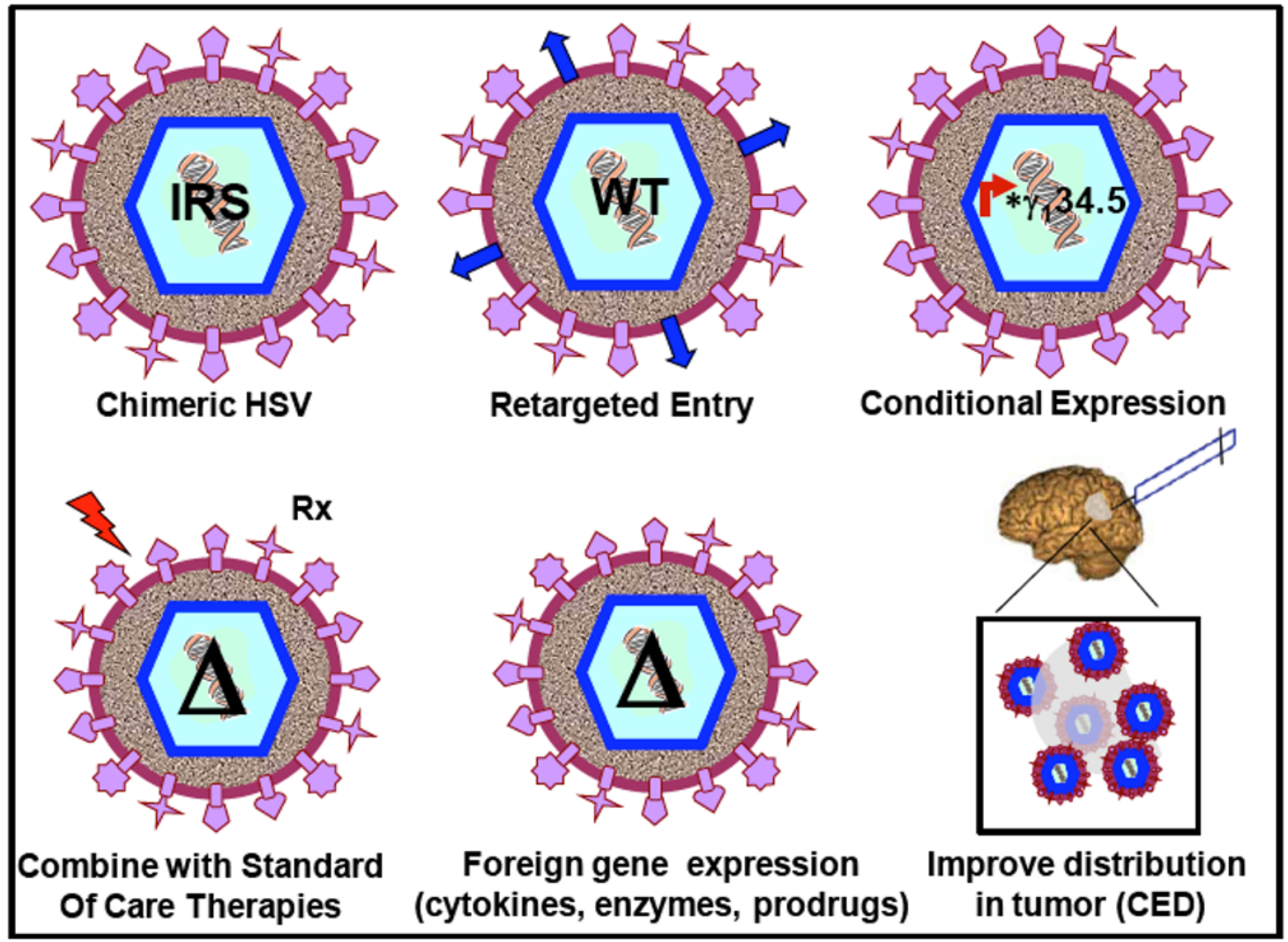


Fig. (1). Strategies to improve oHSV therapy of malignant glioma. Each of the different strategies discussed in detail in the text are shown schematically. IRS= C134 chimeric HSV expressing IRS gene from HCMV; WT= retargeted viruses that have wildtype ICP34.5 but can only infect cells with upregulated tumor-specific receptors; *$\gamma_1$34.5= ICP34.5 expressed from tumor-specific promoters; Δ= $\gamma_1$34.5 deleted viruses.

Critical factors for succsessful oncolytic viro-therapy

- distinct and well-defined mechanism of tumor selectivity,
- strong cytolytic potential with low nontumor toxicity,
- potential for systemic application,
- rapid replication cycle with swift intratumoral spread,
- accessibility to genetic engineering,
- easy manufacturing and high-titer stock production,
- availability of antiviral agents to control unwanted viral spread,
- genetic stability,
- no preexisting immunity/bypass preexisting immunity
- stimulation of anti-tumor immunity.
- Safety!

Malignant glioma

Most common primary brain tumor

- WHO Grade III and IV
- standard of care: maximal safe surgical resection followed by radiotherapy with concomitant and adjuvant temozolomide

Features of malignant gliomas

- physiologic isolation of the tumor due to the blood–brain barrier
- infiltrative nature
- relative immune privileged status of the brain
- relative resistance to traditional radiation and chemotherapies
- cancer stem cells with the ability for self-renewal and resistance to conventional therapy

GBM and oncolytic virotherapy

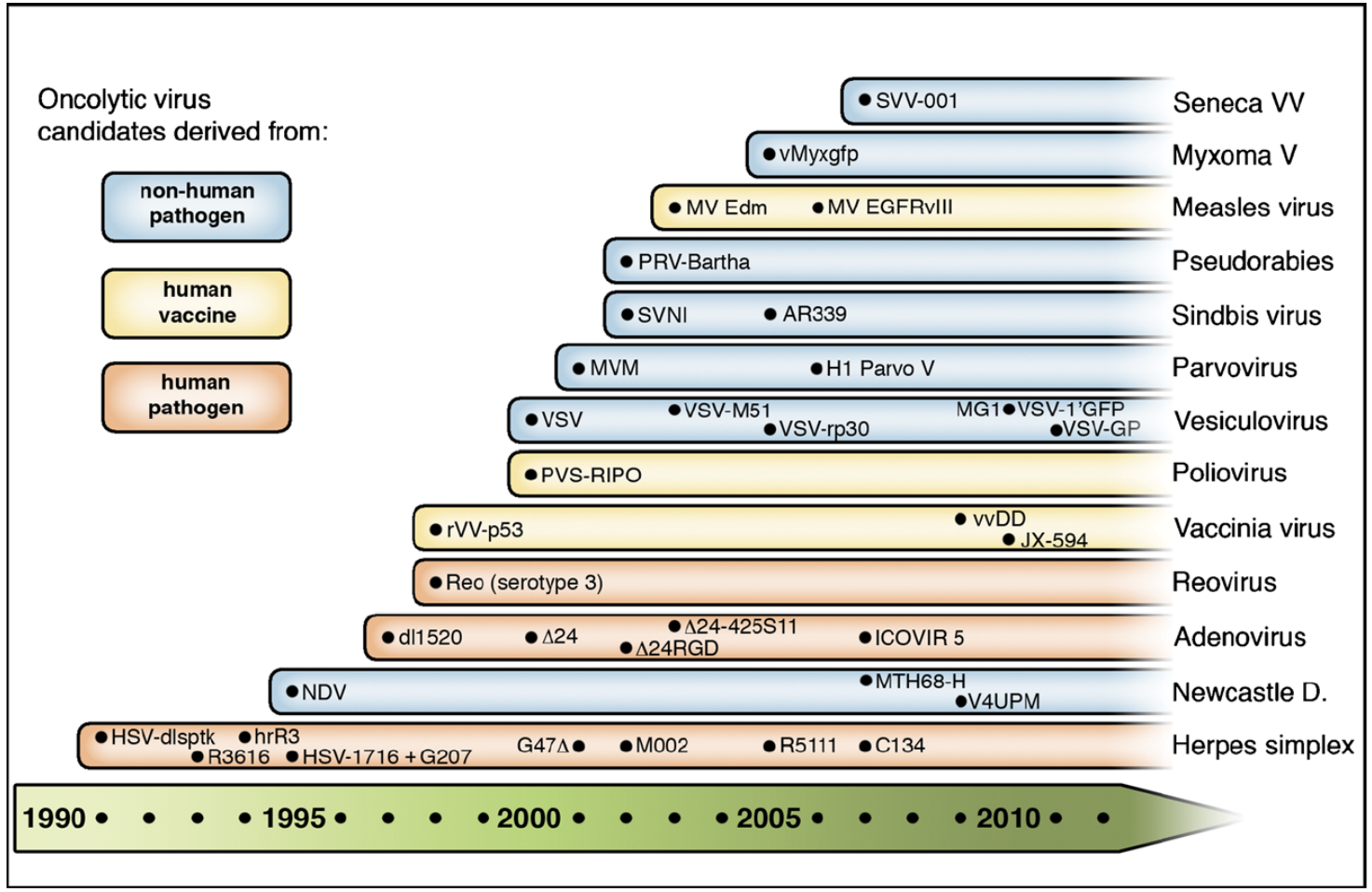
1. GBM nearly exclusively confined to 1 organ compartment, distant metastases not characteristic of the disease (OVs: potential local replication and intratumoral spread).
2. GBM grow surrounded by mostly postmitotic cells (attractive for viruses that require active cell cycles for replication).

About 15 viruses have been considered and examined for glioblastoma targeting!

→7 have advanced to clinical trials (HSV, adenovirus [AdV], Newcastle disease virus [NDV], reovirus, H1 parvovirus, measles virus [MV], and poliovirus [PV])

→several others are at advanced preclinical stages

Oncolytic virus therapy for glioblastoma



REVIEW ARTICLE

Oncolytic Virus Therapy for Glioblastoma Multiforme

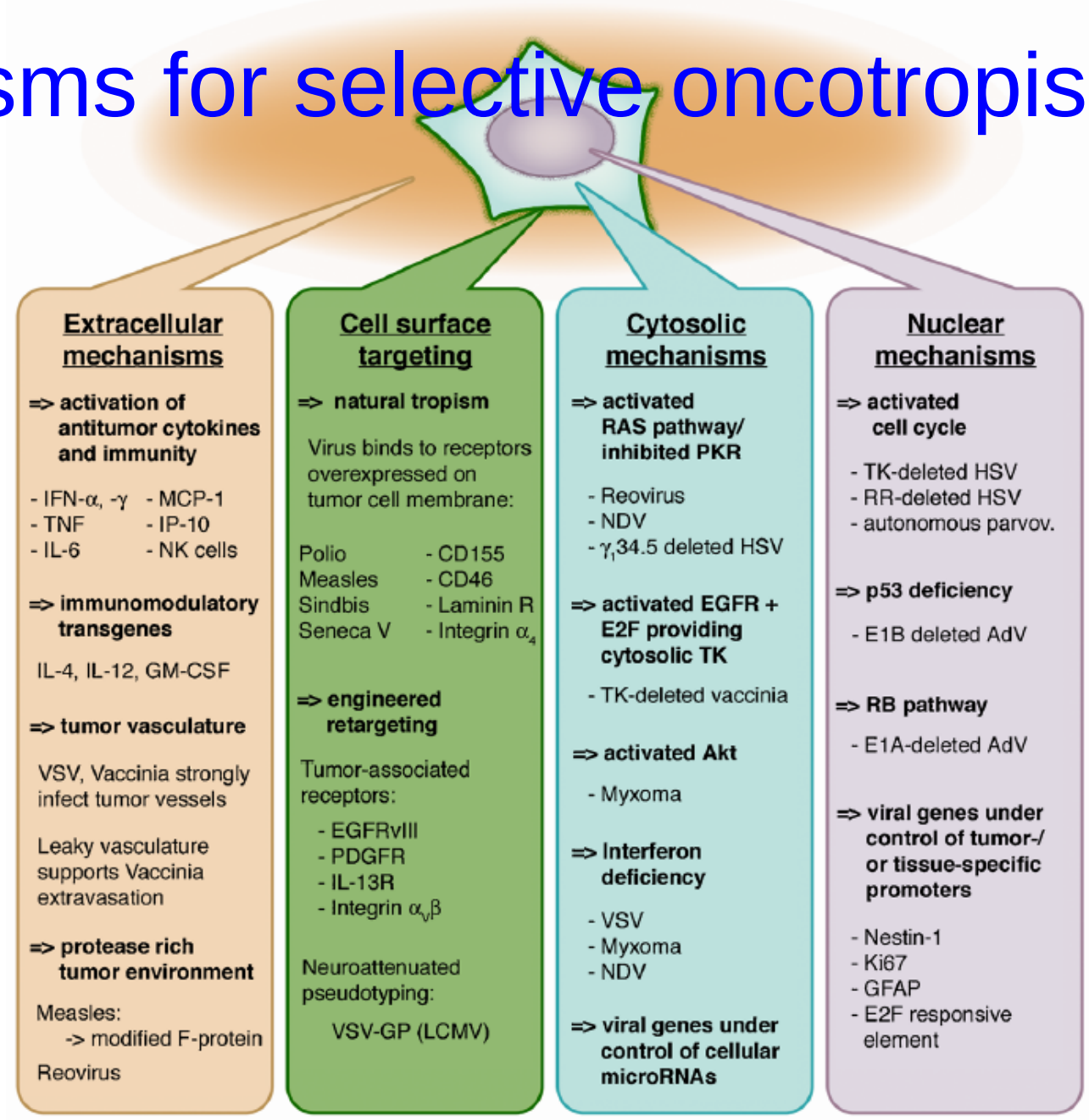
Concepts and Candidates

Guido Wollmann, MD, Koray Ozduman, MD,† and Anthony N. van den Pol, PhD**

The Cancer Journal • Volume 18, Number 1, January/February 2012

Timeline of OV development for glioblastoma therapy.

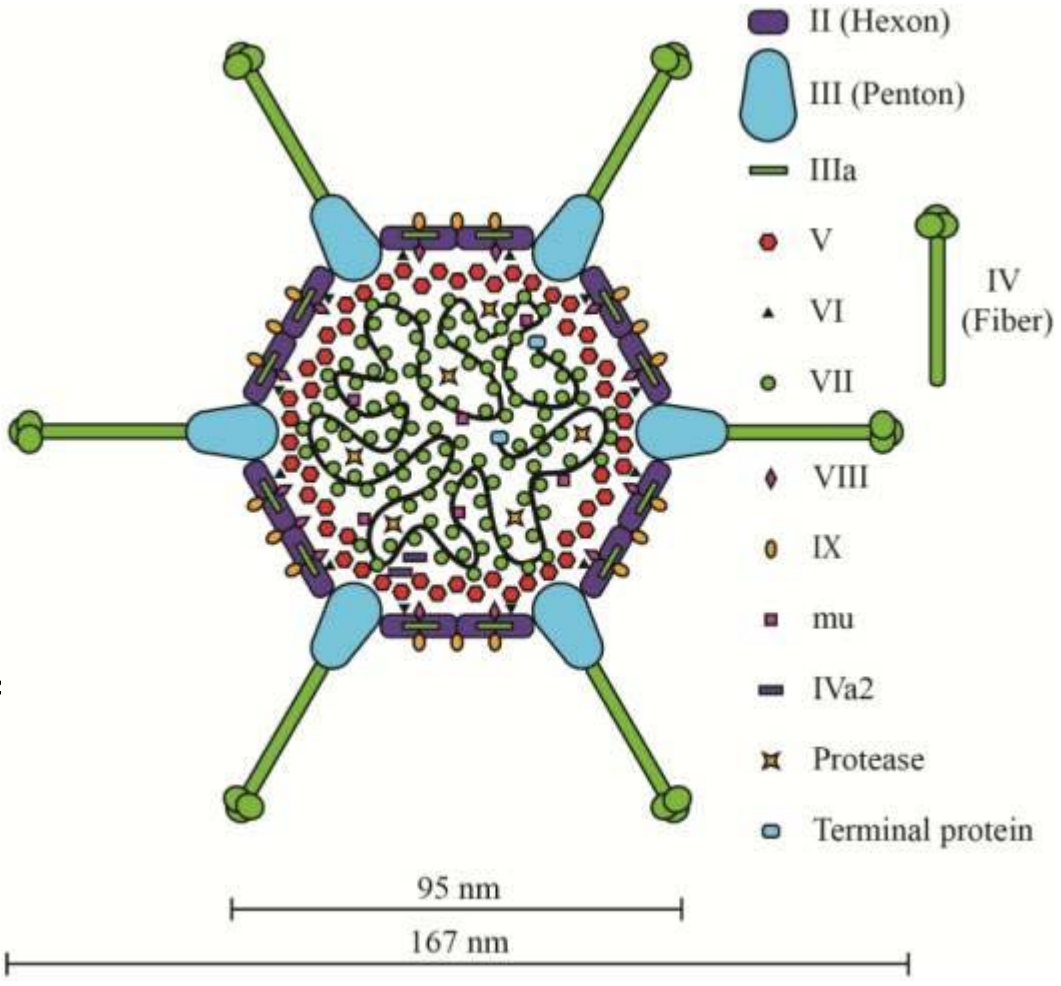
Mechanisms for selective oncotropism and oncolysis



The Cancer Journal • Volume 18, Number 1, January/February 2012

Conditionally Replicating Adenovirus

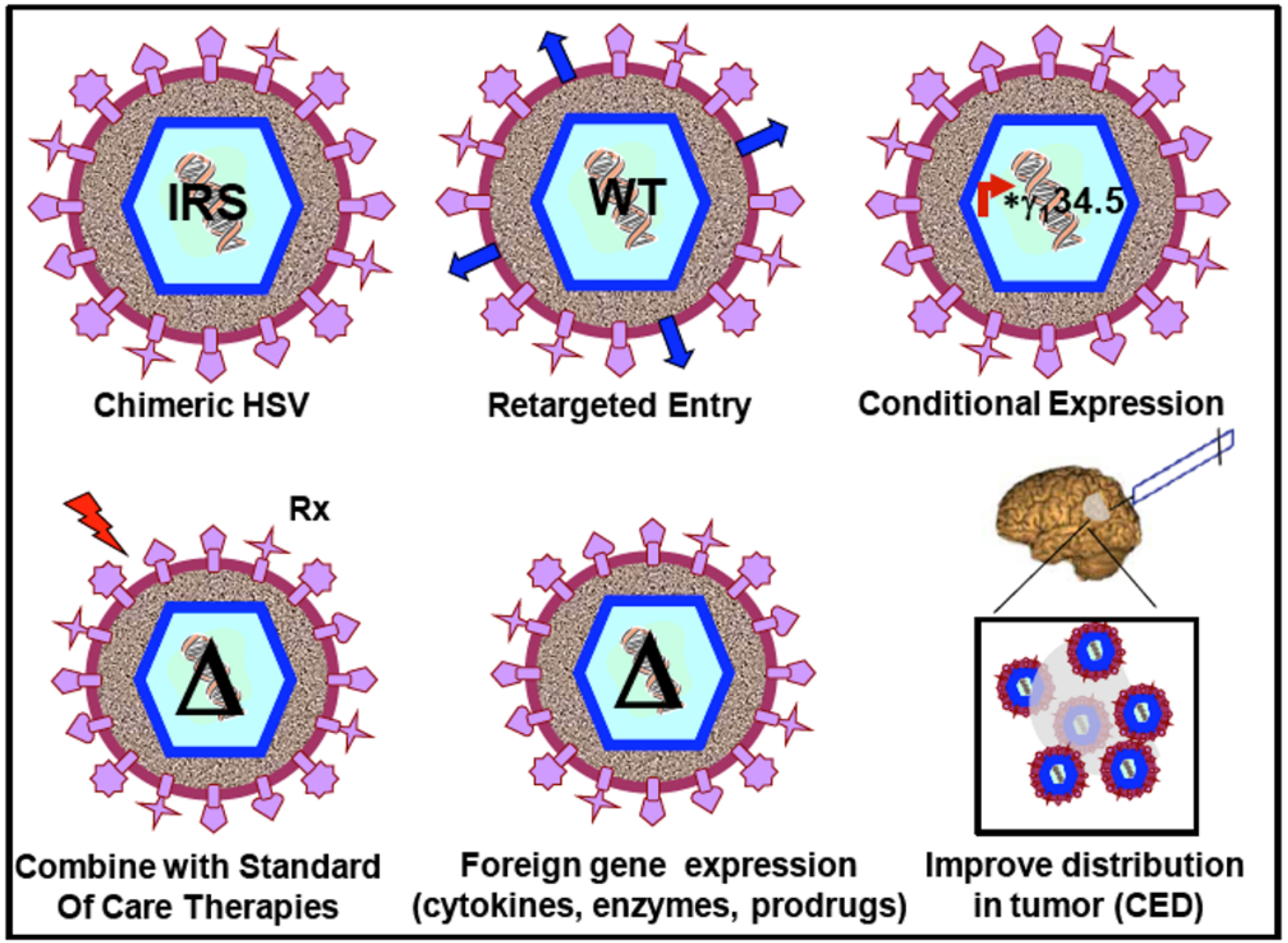
- Adenovirus: double-stranded, nondeveloped DNA virus, medium-sized (~70-100 nm), icosahedral nucleocapsid
- Common human pathogen, more than 50 adenovirus types (HAdV-1 to 57) in seven species (Human adenovirus A to G)
- The Ad5 capsid is composed of three major proteins (II, III, and IV) and five minor proteins
- Entry into host cells is initiated by the binding of fiber protein to the coxsackie and adenovirus receptor (CAR), which is expressed on the surface of many cell types
- mild respiratory infections, conjunctivitis, gastroenteritis, etc.



Viruses. 2014 Sep; 6(9): 3563–3583.
Published online 2014 Sep 24. doi: 10.3390/v6093563
The Adenovirus Genome Contributes to the Structural Stability of the Virion
Bratati Saha,[1,2,3] Carmen M. Wong,[1,2,3] and Robin J. Parks[1,2,3,4,*]

Thank you!

- Questions?



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