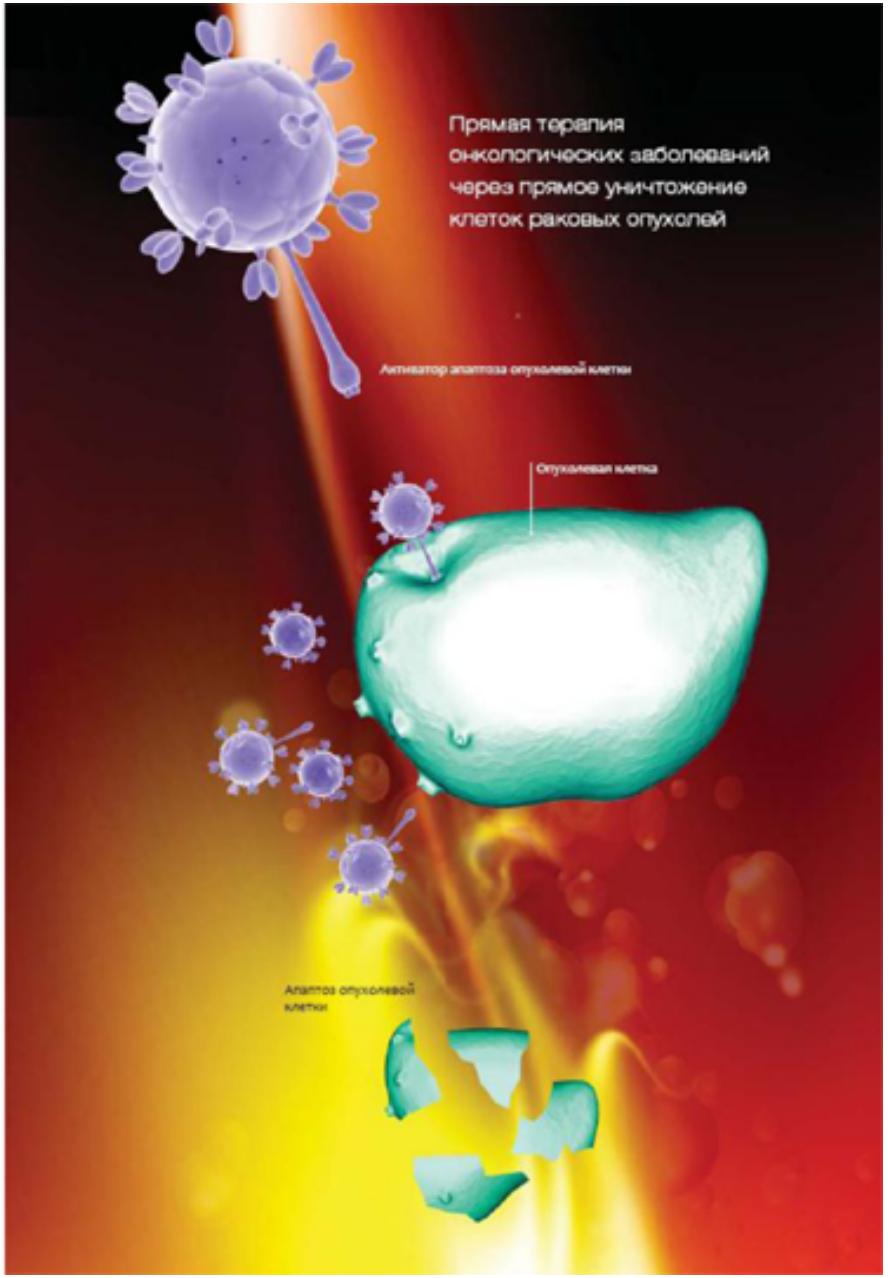
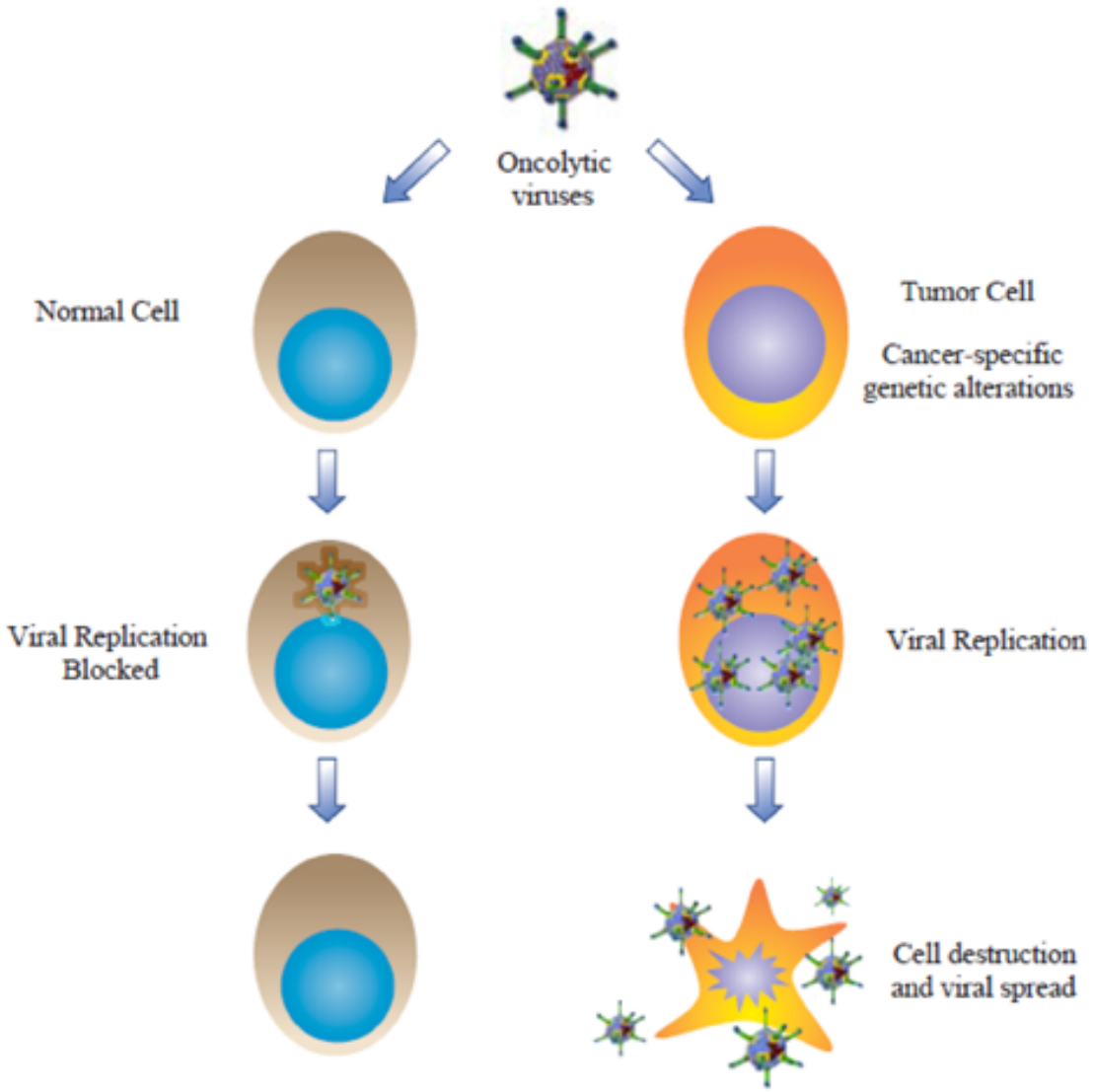
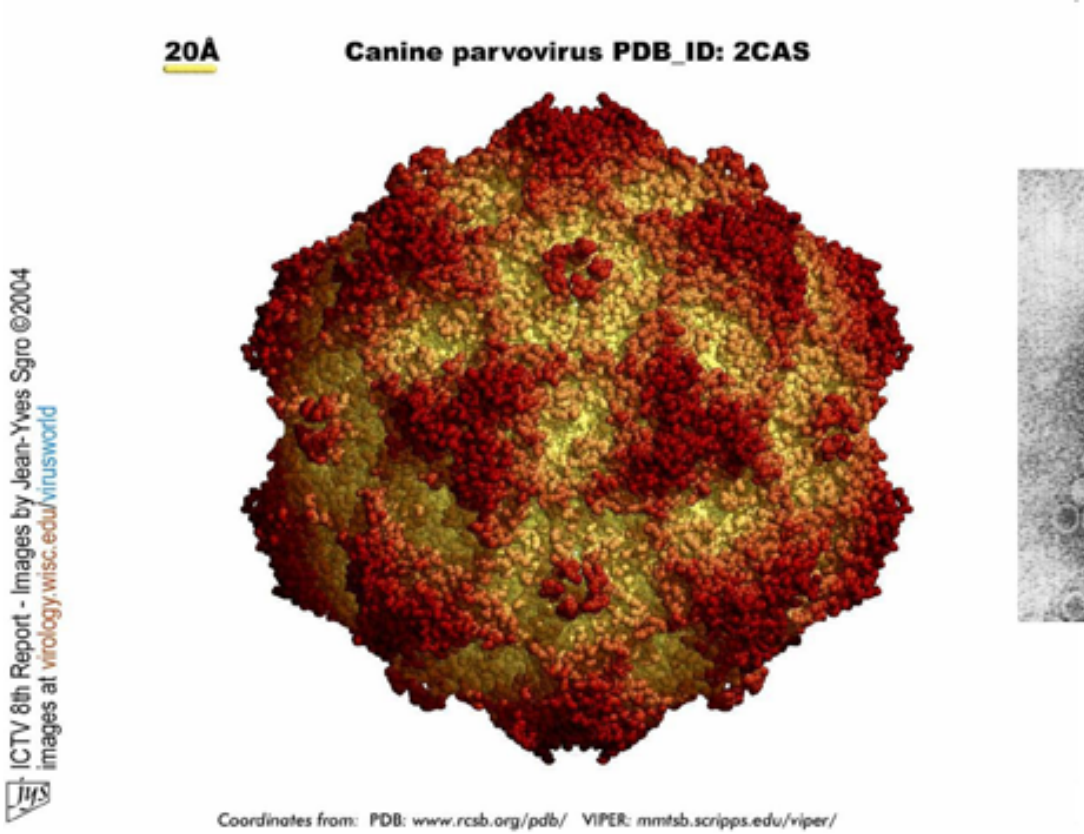
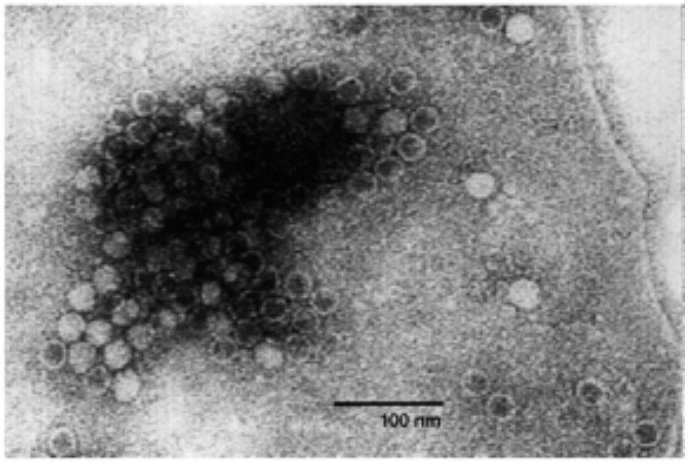
ПАРВОВИРУСЫ. НОВЫЕ ПОДХОДЫ К ЛЕЧЕНИЮ РАКОВЫХ ЗАБОЛЕВАНИЙ



СФУ, ноябрь 2012


Oncolytic viruses
Normal Cell
Tumor Cell
Cancer-specific genetic alterations
Viral Replication Blocked
Viral Replication
Cell destruction and viral spread



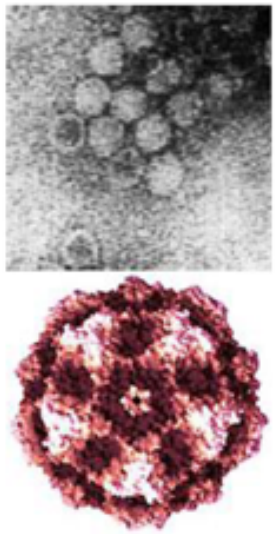


Парвовирусы *(Parvoviridae)* – семейство самых мелких ДНК–содержащих сферических вирусов, лишенных липопротеидной оболочки. Диаметр вирусных частиц 18-26 нм, капсид икосаэдрический Т1, количество капсомеров в вирионе – 60.

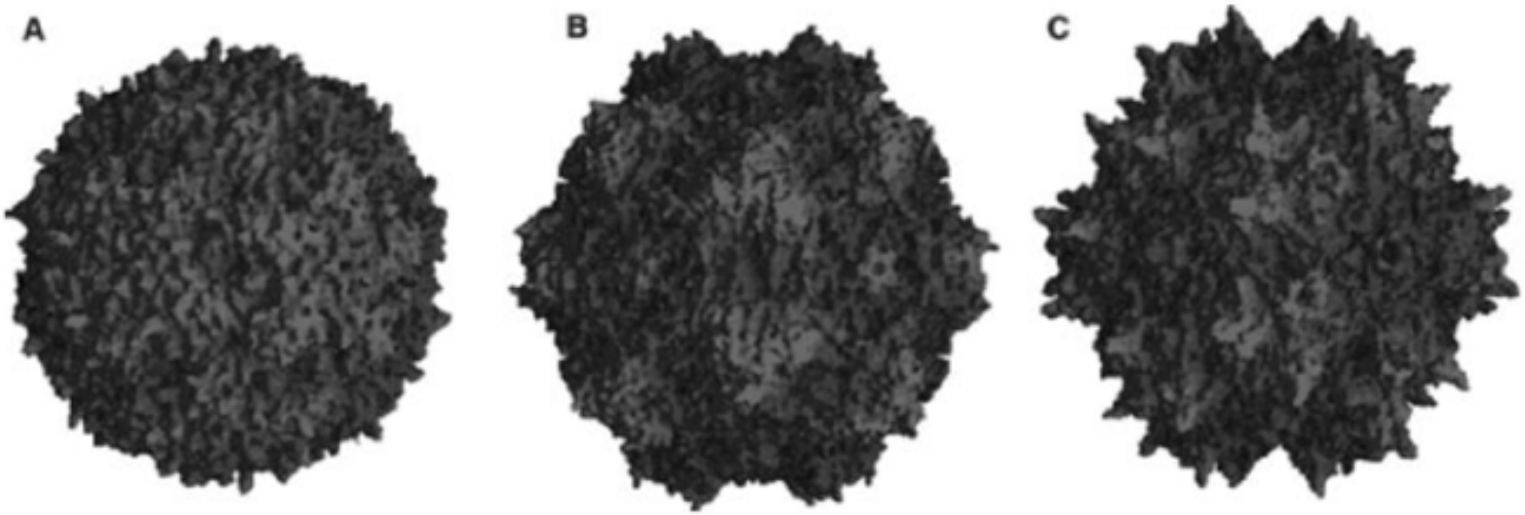
Family 00.050. *Parvoviridae*

Taxonomic Structure of the Family

Family	00.050. *Parvoviridae*
Subfamily	00.050.1. *Parvoririnae*
Genus	00.050.1.01. *Parvovirus*
Genus	00.050.1.02. *Erythrovirus*
Genus	00.050.1.03. *Dependovirus*
Genus	00.050.1.04. *Amdovirus*
Genus	00.050.1.05. *Bocavirus*
Subfamily	00.050.2. *Densovirinae*
Genus	00.050.2.01. *Densovirus*
Genus	00.050.2.02. *Iteravirus*
Genus	00.050.2.03. *Brevidensovirus*
Genus	00.050.2.04. *Pefudensovirus*
	00.050.2.00. Unassigned



Геном:	ДНК, одноцепочечная
Типы хозяина:	Vertebrates, Invertebrates
Морфология:	безоболочечный, изометрический
Репликация:	Автономная, S-фаза клеточного цикла, Не автономная, с вирусом помощником

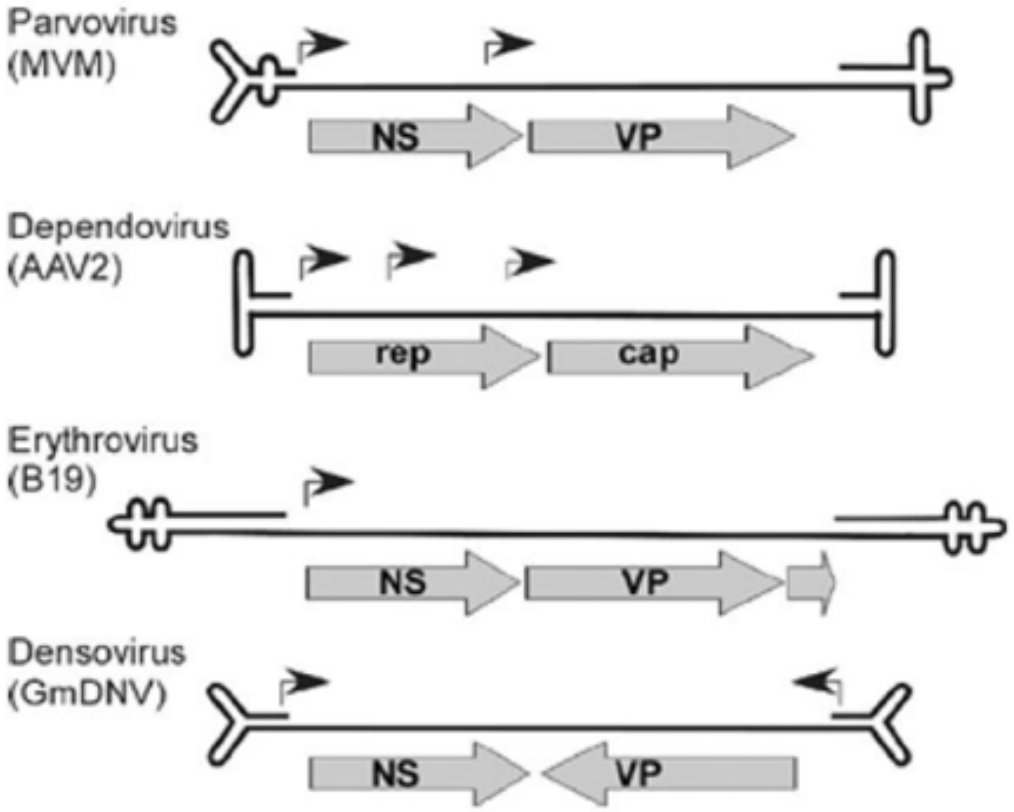


Surface topologies of the capsids of
various members of the family *Parvoviridae, calculated*
from the atomic structures of the viruses.
A: The insect infecting densonucleosis virus Galleria mellonella densovirus (GmDNV).
B: The autonomous parvovirus minute virus of mice.
C: The dependovirus adenoassociated virus 2 (AAV2).

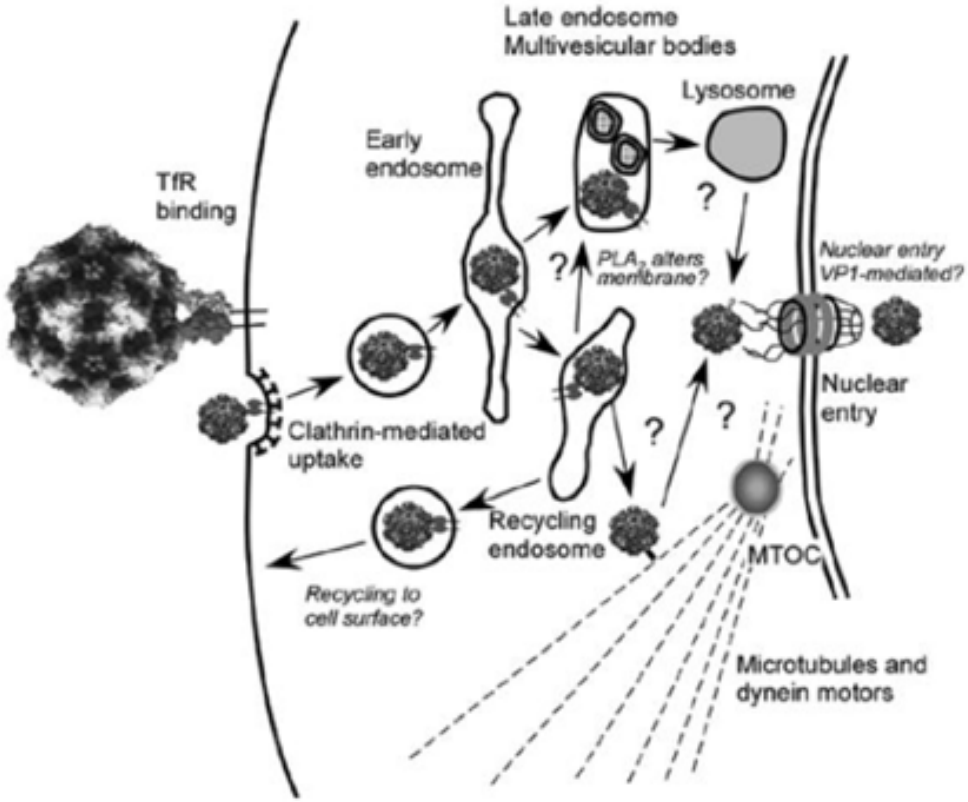
Геном вируса

- Несегментированный геном содержит одну молекулу ондоцепочечной линейной ДНК. В зрелых вирионах она может быть положительной или отрицательной, для некоторых членов семейства это соотношение может достигать пропорции в 50%.
- Длина генома около 5000 нуклеотидов.
- 5'-концевая последовательность содержит повторы и формирует шпильку, которая может достигать длины в 200-242 нуклеотида.
- После выделения геномная ДНК может формировать двухцепочечная форму ДНК.

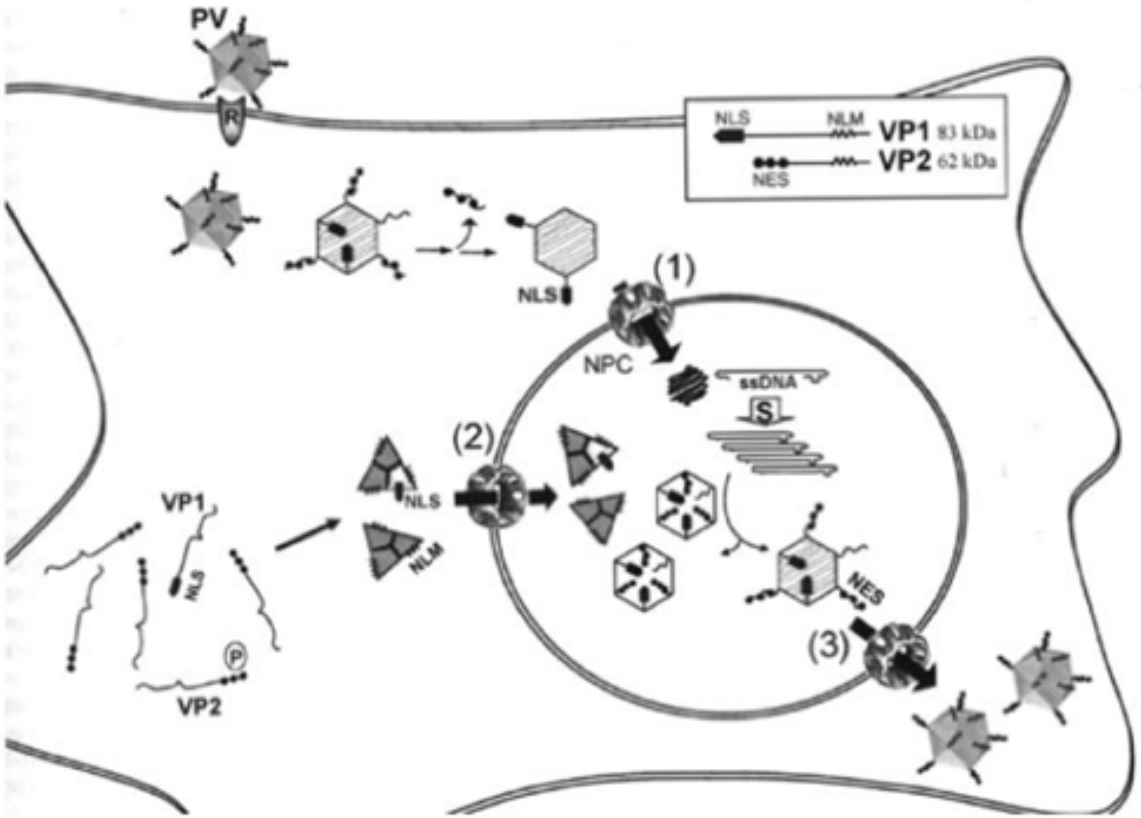
Схема организации генома парвовирусов



Предполагаемая схема проникновения парвовирусов в клетку



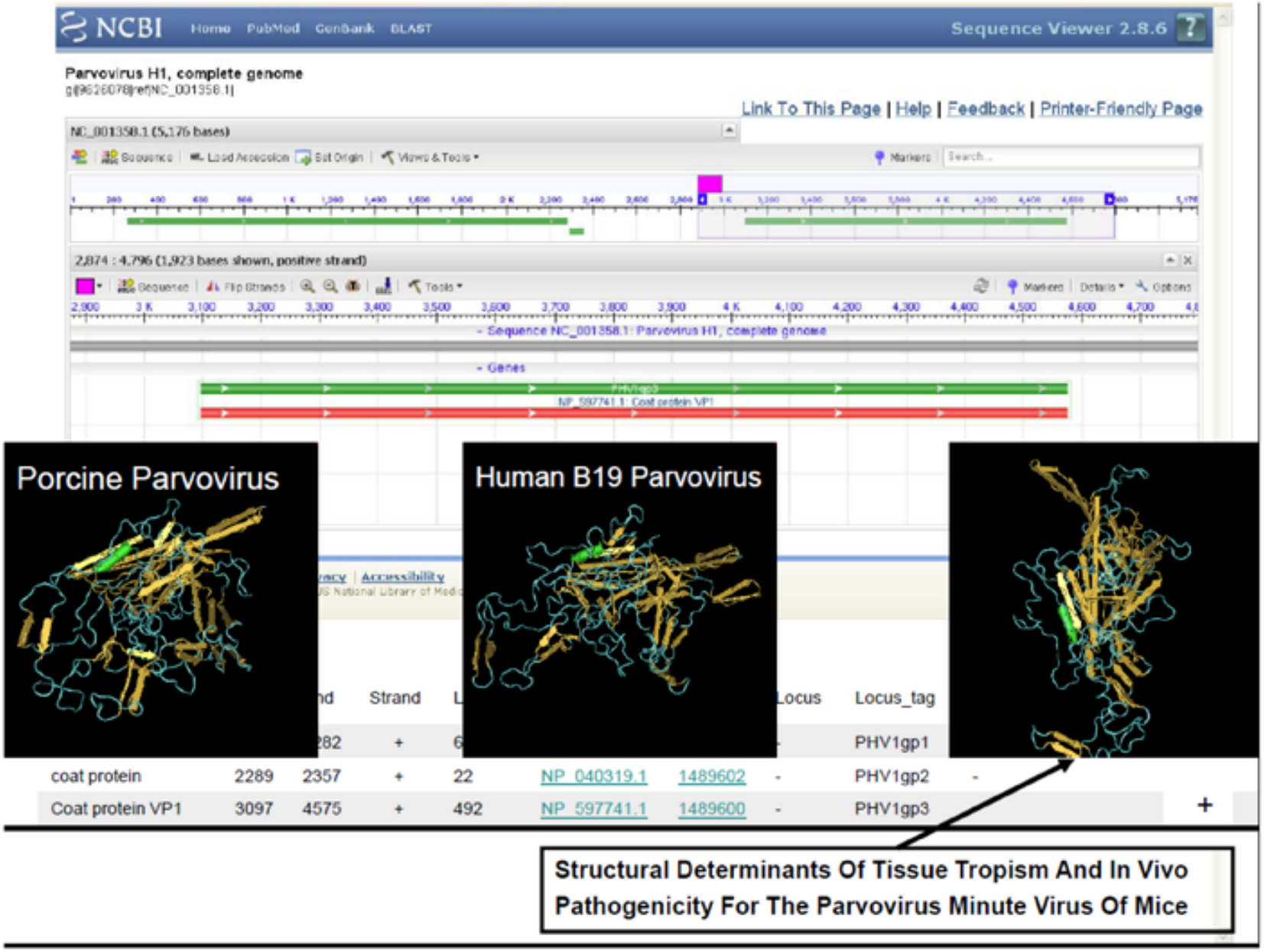
Репликация парвовирусов в клетке, схематично, для автономных парвовирусов

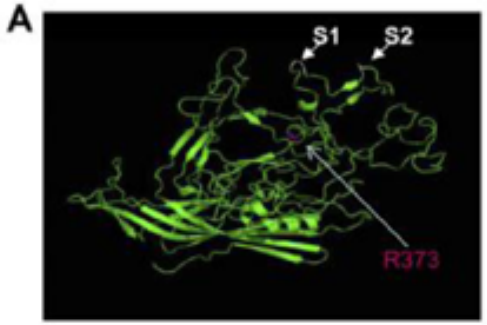


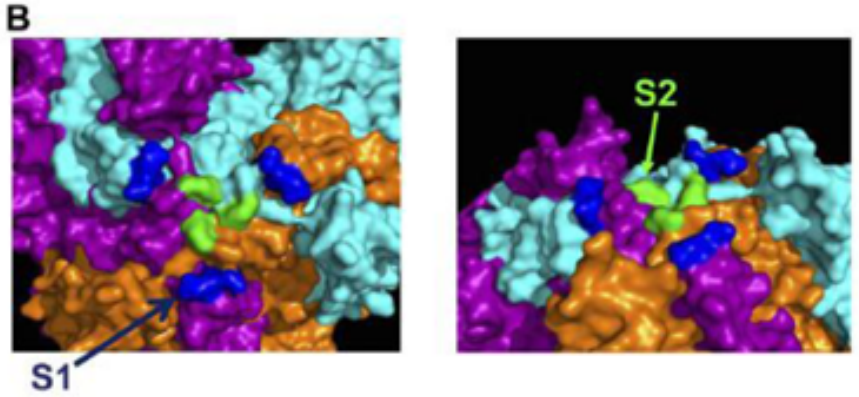
Product Name	Start	End	Strand	Length	Accession	GeneID	Locus	Locus_tag	COG(s)	Protein Clusters	Structure
Non-capsid protein	264	2282	+	672	NP_040318.1	1489601	-	PHV1gp1	-		
coat protein	2289	2357	+	22	NP_040319.1	1489602	-	PHV1gp2	-		
Coat protein VP1	3097	4575	+	492	NP_597741.1	1489600	-	PHV1gp3	-		

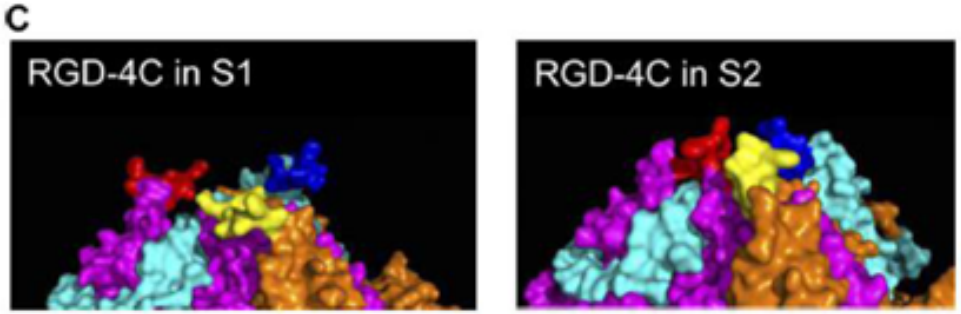
Некоторые лабораторные особенности парвовирусов

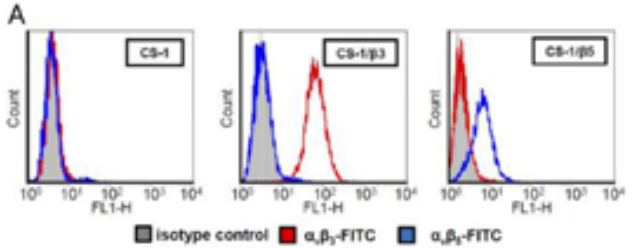
- Репликация только в клетках на S-фазе клеточного цикла (вирус не имеет ДНК полимеразы)
- Очень строгая хозяйская специфичность.
- Возможное отсутствие ЦПД на культуре клеток.
- Косвенные методы титрования, например РТГА с эритроцитами обезьян.
- Высокая стойкость в окружающей среде.
- Не относится к микроорганизмам 3-4 групп ПБА по классификации Роспотребнадзора.

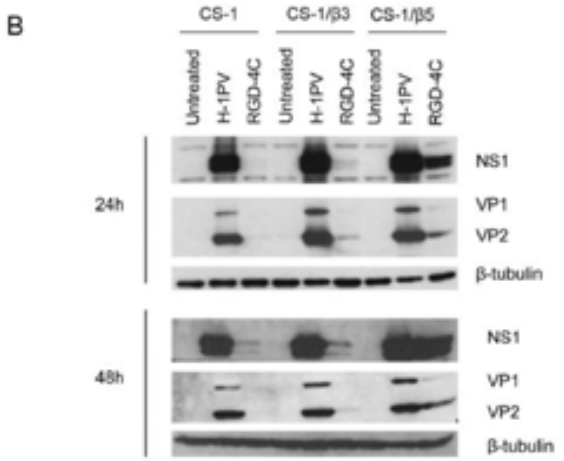

NCBI
Home
PubMed
GenBank
BLAST
Sequence Viewer 2.8.6
Parvovirus H1, complete genome
Link To This Page | Help | Feedback | Printer-Friendly Page
Porcine Parvovirus
Human B19 Parvovirus
Strand
Locus
Locus_tag
PHV1gp1
coat protein 2289 2357 + 22 NP_040319.1 1489602 - PHV1gp2 -
Coat protein VP1 3097 4575 + 492 NP_597741.1 1489600 - PHV1gp3 +
Structural Determinants Of Tissue Tropism And In Vivo Pathogenicity For The Parvovirus Minute Virus Of Mice


A
S1
S2
R373


B
S2
S1


C
RGD-4C in S1
RGD-4C in S2


A
CS-1
CS-1/β3
CS-1/β5
Count
FL1-H
isotype control
αvβ3-FITC
αvβ5-FITC


B
CS-1
CS-1/β3
CS-1/β5
Untreated
H-1PV
RGD-4C
24h
48h
NS1
VP1
VP2
β-tubulin

Основные механизмы онколитического действия парвовирусов

- Прямой лизис раковых клеток
- Индукция апоптоза раковых клеток
- Иммуномодуляция и формирование противоракового иммунитета

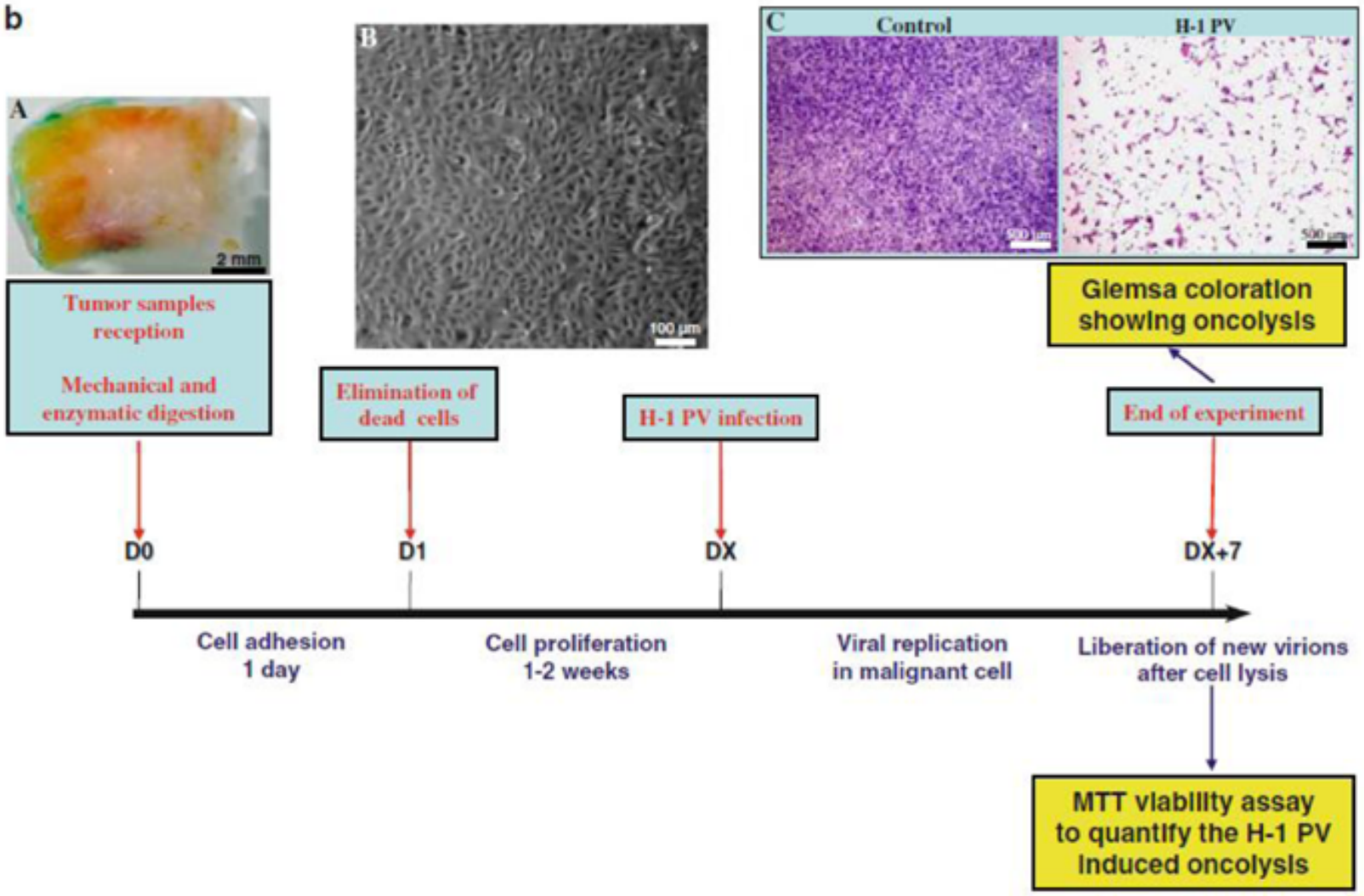

b
A
2 mm
B
100 µm
C
Control
H-1 PV
500 µm
500 µm
Tumor samples reception
Mechanical and enzymatic digestion
Elimination of dead cells
H-1 PV infection
End of experiment
Giemsa coloration showing oncolysis
D0
D1
DX
DX+7
Cell adhesion 1 day
Cell proliferation 1-2 weeks
Viral replication in malignant cell
Liberation of new virions after cell lysis
MTT viability assay to quantify the H-1 PV induced oncolysis

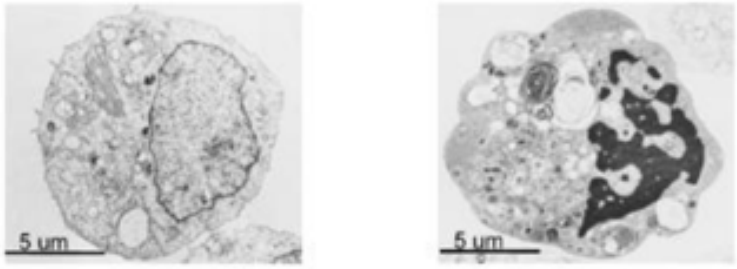
Table 1. Advantages and Drawbacks of Autonomou Parvovirus Vectors

Advantages
Oncolytic/Oncotropic properties
S-phase dependence
Lack of integration in host genome
Weak inflammatory and CTL responses
Low pre-immunity for H-1 virus in the human population
Safety in pre-clinical and Phase I studies
Disadvantages
Limited size of accommodated transgenes
High neutralizing antibody response
Relatively low titers of recombinant viruses

Некоторые характеристики белка NS1парвовируса H-1, индуцирующего апоптоз, в сравнении с апоптином и белком E4orf4

Characteristics	Apoptin	E4orf4	NS1	References
p53-independent apoptosis	Yes	Yes	Yes	(Backendorf et al., 2008; Lavoie et al., 2000; Di Piazza et al., 2007)
Blocked by Bcl-2	No	No	No	(Backendorf et al., 2008; Landry et al., 2006; Di Piazza et al., 2007)
Acts via caspase pathways	Yes	No	Yes	(Danen-van Oorschot et al., 2000; Landry et al., 2006; Di Piazza et al., 2007)
Cytochrome *c* release	Yes	No	Yes	(Danen-van Oorschot et al., 2000; Li et al., 2009; Di Piazza et al., 2007)
Interference with APC/C	Yes	Yes	–	(Heilman et al., 2005, 2006)
Interference with CKIIα	–	–	Yes	(Nuesch and Rommelaere, 2007)
Nuclear localization	Yes	Yes	Yes	(Backendorf et al., 2008)
Phosphorylated to be active	Yes	Yes	Yes	(Rohn et al., 2002; Gingras et al., 2002; Lachmann et al., 2008)
Degradation of cytoskeleton	–	Yes	Yes	(Li et al., 2009; Bär et al., 2008)
Interaction with PP2A	–	Yes	–	(Shtrichman et al., 1999)
Ceramide elevation	Yes	–	–	(Liu et al., 2006b)
Mitotic catastrophe	–	Yes	–	(Li et al., 2009)

D



293-NS1 non-induced

293-NS1 induced (72h)

Journal of Virology, June 2010, p. 5909–5922
0022-538X/10/$12.00 doi:10.1128/JVI.01797-09

Vol. 84, No. 12

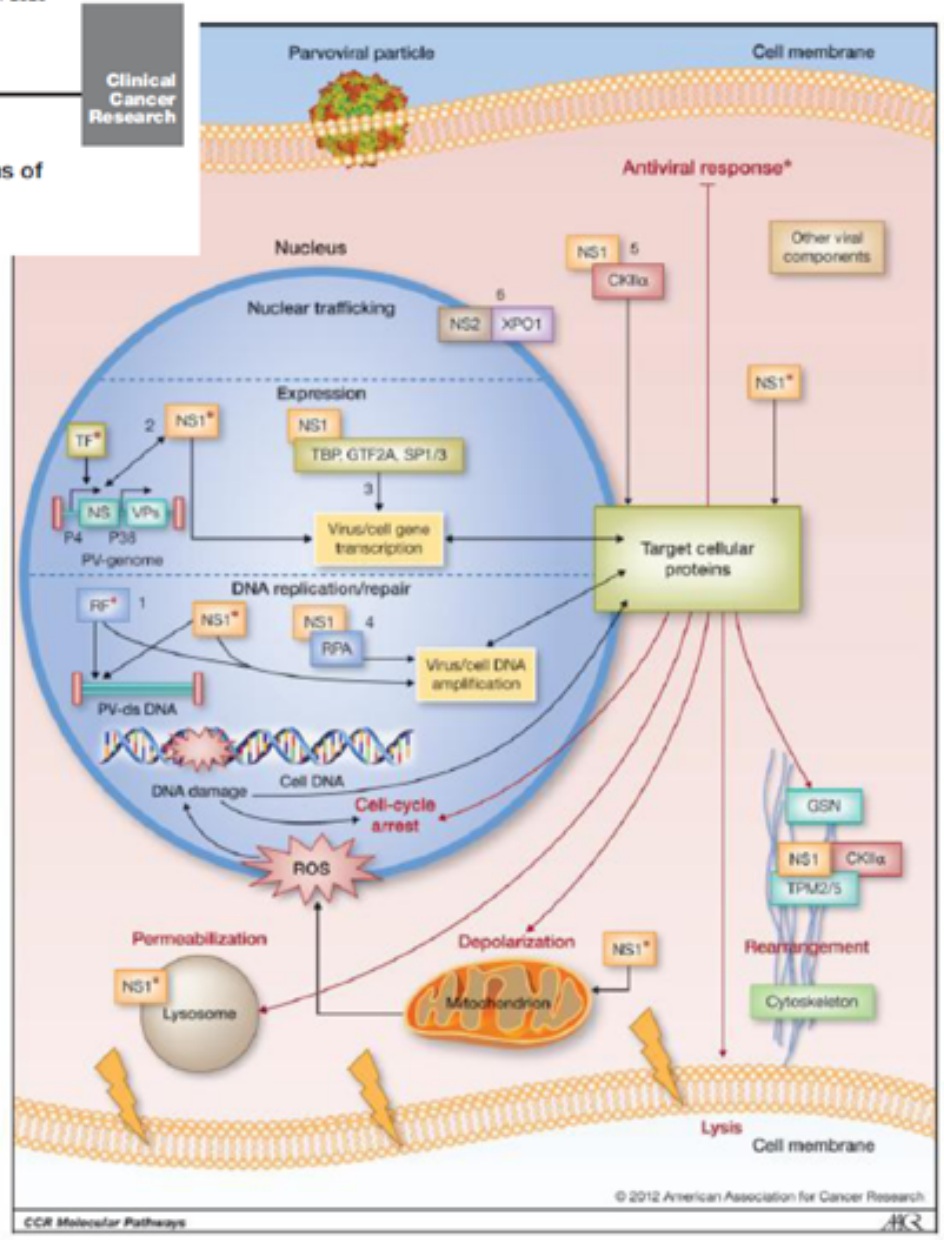
Published OnlineFirst May 7, 2012; DOI:10.1158/1078-0432.CCR-11-2325

Clinical Cancer Research

Molecular Pathways

Molecular Pathways: Rodent Parvoviruses—Mechanisms of Oncolysis and Prospects for Clinical Cancer Treatment

Jürg P.F. Nüesch, Jeannine Lacroix, Antonio Marchini, and Jean Rommelaere



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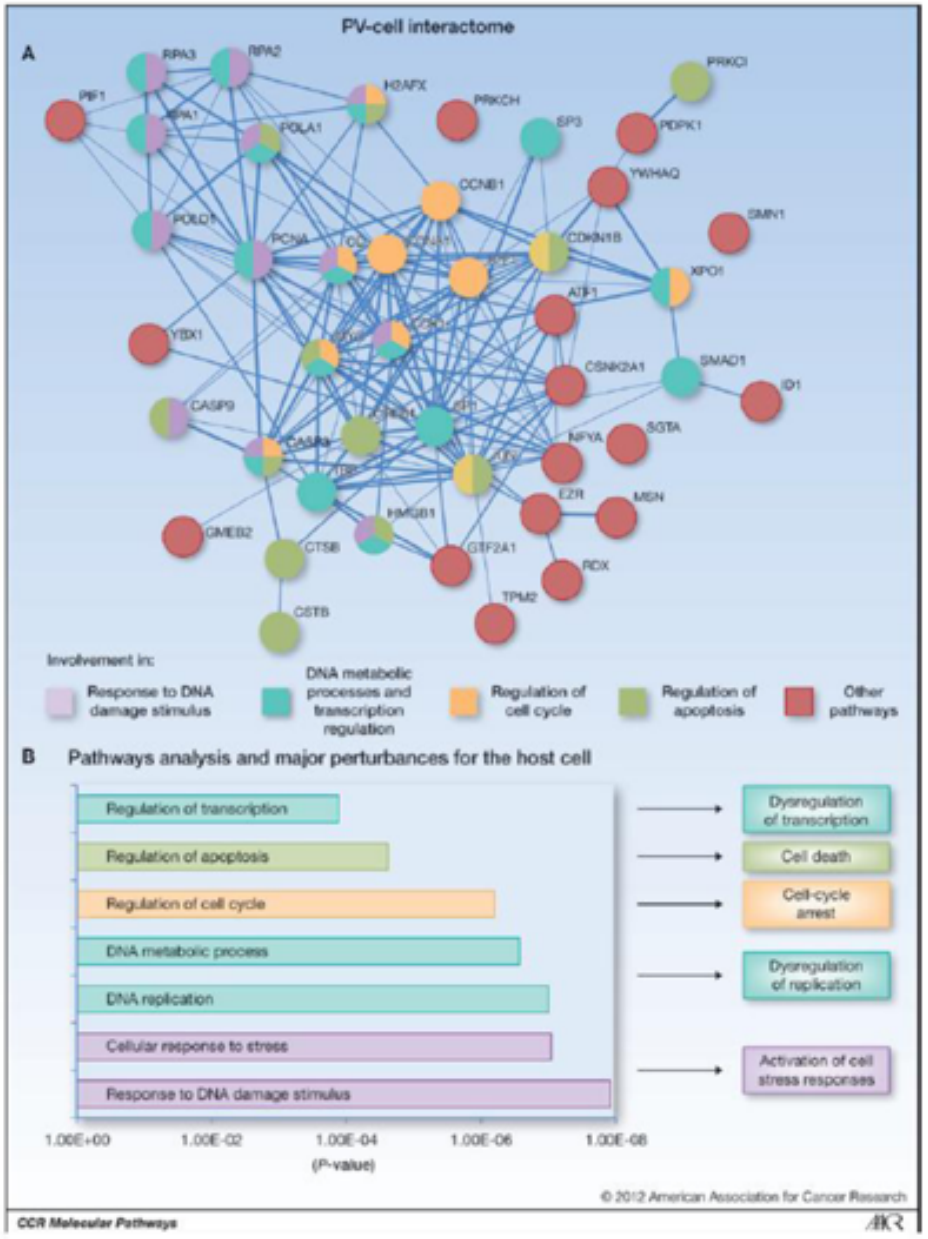
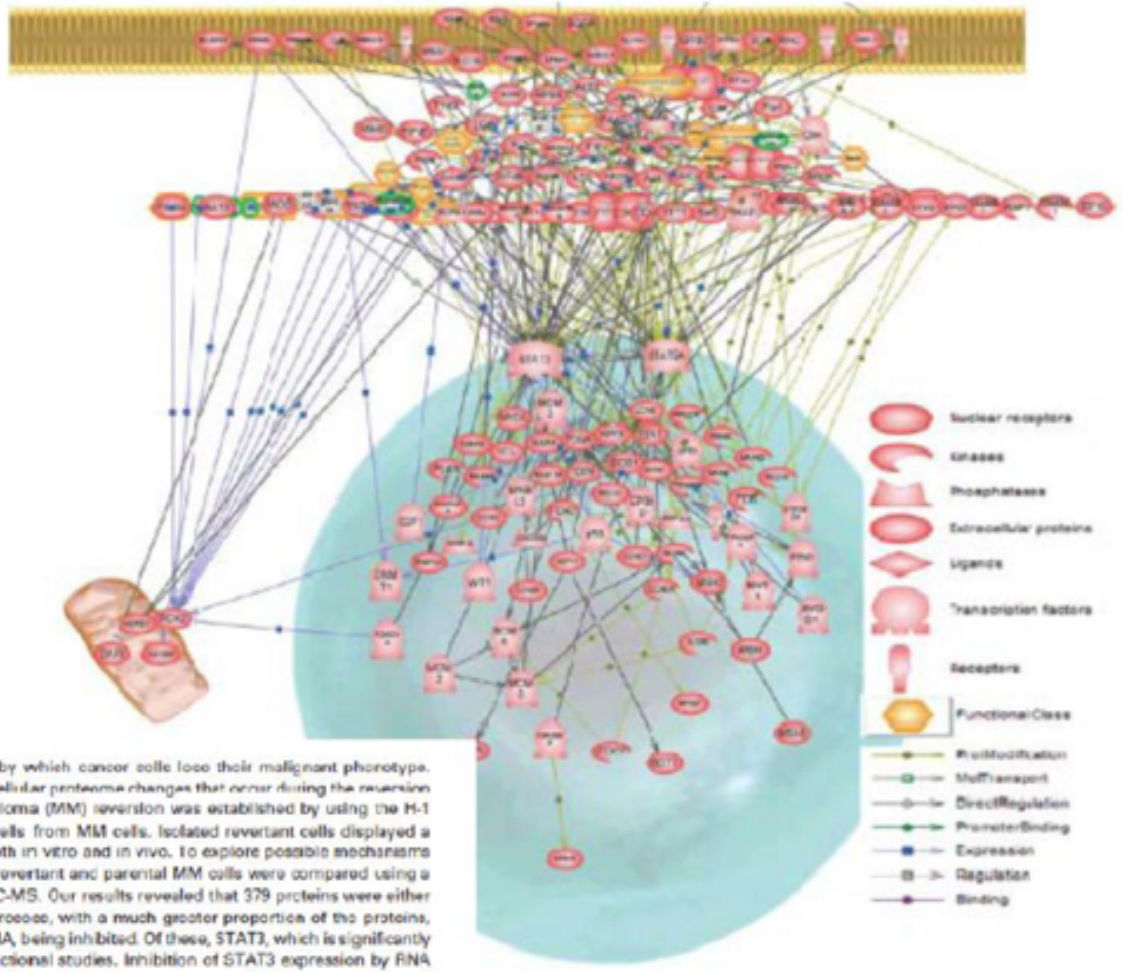


Quantitative Proteomic Analysis of Tumor Reversion in Multiple Myeloma Cells



Tumor reversion is defined as the process by which cancer cells lose their malignant phenotype. However, relatively little is known about the cellular proteome changes that occur during the reversion process. A biological model of multiple myeloma (MM) reversion was established by using the H-1 parvovirus as a tool to select for revertant cells from MM cells. Isolated revertant cells displayed a strongly suppressed malignant phenotype both in vitro and in vivo. To explore possible mechanisms of MM reversion, the protein profiles of the revertant and parental MM cells were compared using a quantitative proteomic strategy termed SILAC-MS. Our results revealed that 379 proteins were either activated or inhibited during the reversion process, with a much greater proportion of the proteins, including STAT3, TCTP, CDC2, EAG2, and PCNA, being inhibited. Of these, STAT3, which is significantly down regulated, was selected for further functional studies. Inhibition of STAT3 expression by RNA interference resulted in suppression of the malignant phenotype and concomitant down regulation of TCTP expression, suggesting that myeloma reversion operates, at least in part, through inhibition of STAT3. Our results provide novel insights into the mechanisms of tumor reversion and suggest new alternative approaches for MM treatment.

Journal of Digestive Diseases

Journal of Digestive Diseases 2012; 13; 366–373

Table 2. Tumor formation from implanted gastric cancer cells

Cell line	Group	Mean volume (mm^3)†
MKN28	Empty vector	461.04 ± 18.09
	pcDNA3.1-NS1	457.40 ± 20.11
SGC7901	Empty vector	446.84 ± 30.98
	pcDNA3.1-NS1	No‡
MKN45	Empty vector	596.36 ± 20.39
	pcDNA3.1-NS1	No‡

†Mean ± standard deviation.
‡No, no tumor was observed ($P < 0.05$ *versus* empty vector group).

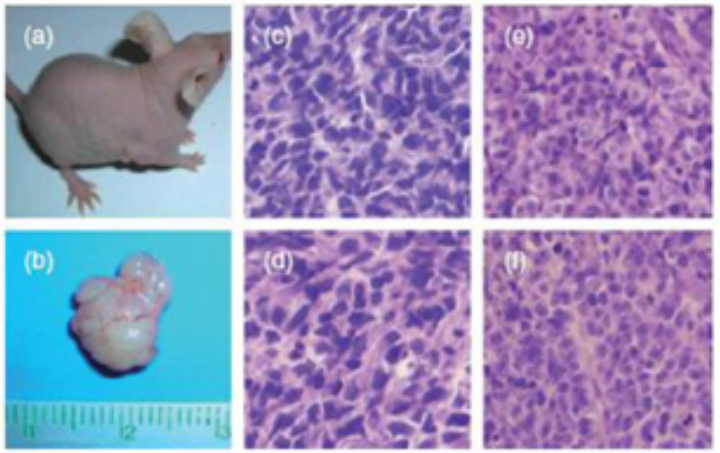
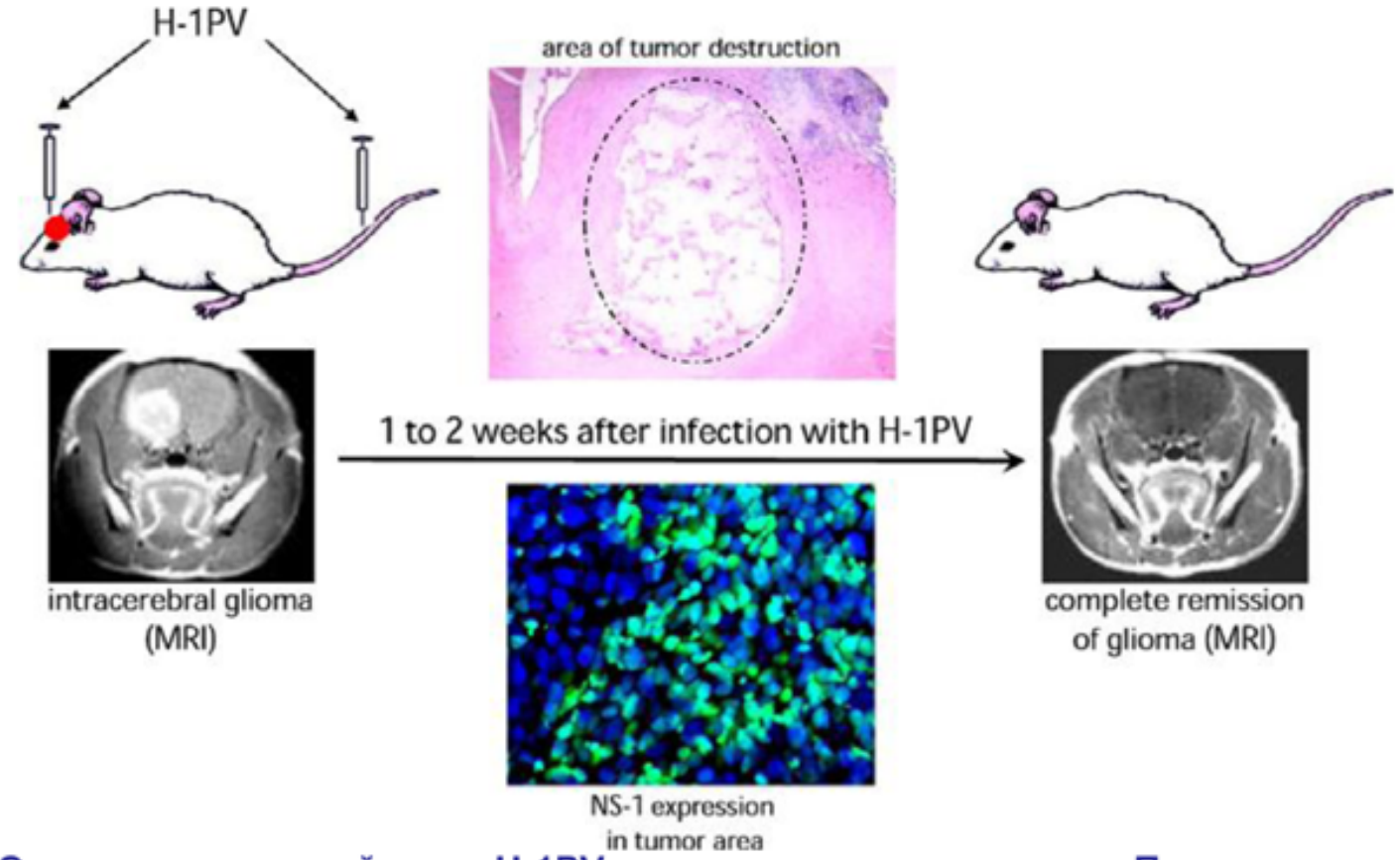


Figure 5. Tumor formation from xenografts of transfected gastric cancer cells. (a, b) MKN45 cells transfected with empty vector were implanted in the right flank of nude mice, producing a tumor of 1 cm in diameter after 3 weeks. Sections of tumor xenografts were stained with hematoxylin and eosin and examined microscopically. Tumors derived from MKN28 cells transfected with (c) empty vector or (d) recombinant plasmid pcDNA3.1-NS1 and from (e) SGC7901 or (f) MKN45 cells transfected with empty vector.

CONCLUSIONS: NS1 expression in poorly differentiated gastric cancer cells prevents them from forming tumors, perhaps by impairing the stem-like phenotype. The parvoviral NS1 protein warrants further investigation for its therapeutic potential against cancer.



Онколитическое действие H-1PV в отношении глиомы крыс. После стереотаксической интракраниальный имплантации клеток глиомы и роста опухоли, как было показано ЯМР , вирус H-1PV вводился внутриопухолево и/или внутривенно . Последующее исследование ЯМР и гистологические анализы выявили онколитическое разрушение опухоли в обработанных животных и экспрессию цитотоксического парвовирусного белка NS-1 (данные иммунофлюоресцентного анализа) в регрессирующих опухолях. (Rommelaere et al., 2010)

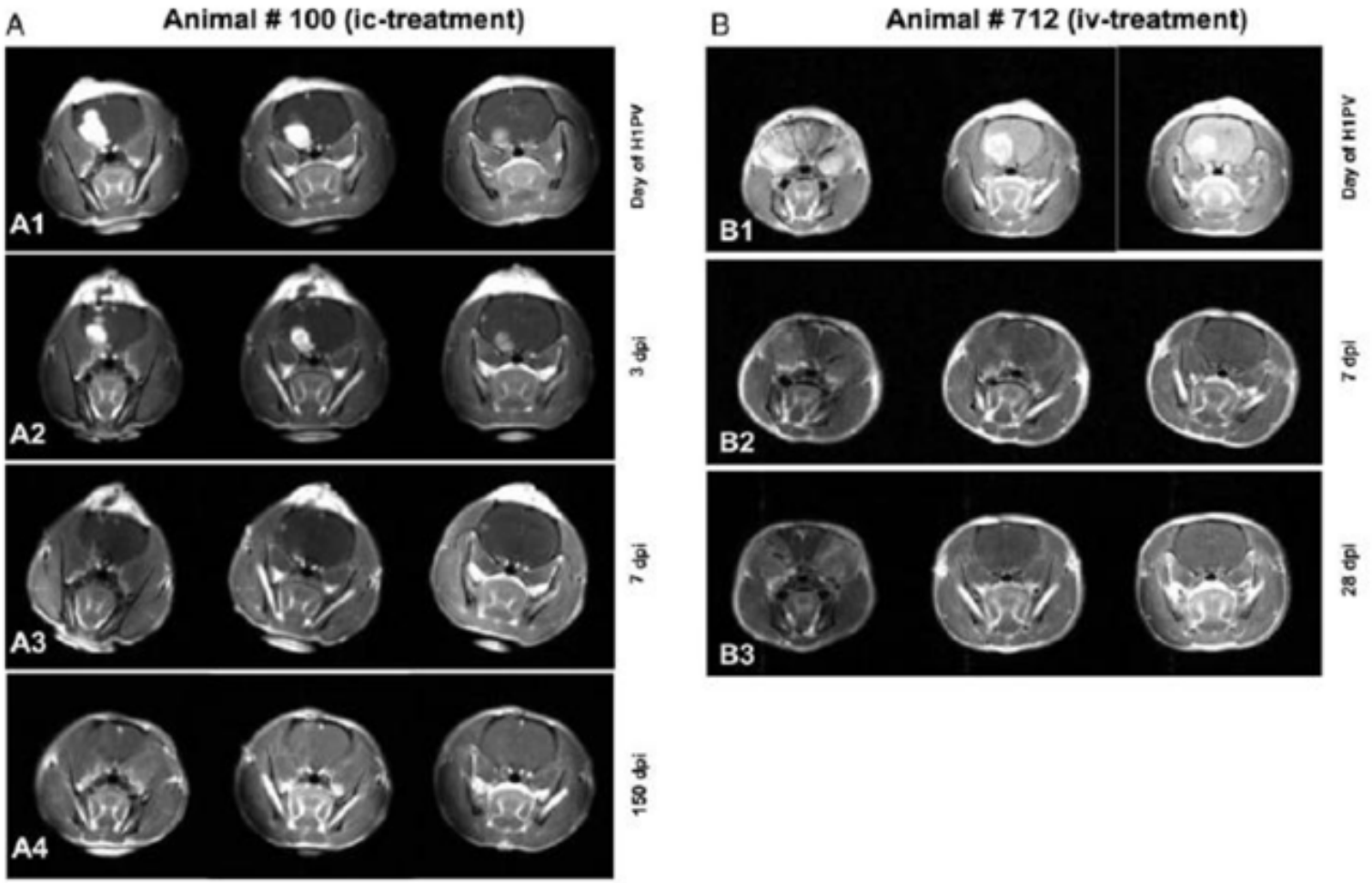


Fig. 1. Complete remission of RG-2 gliomas after H-1PV treatment MR images of animal #100 (A1 to A4) and #712 (B1 to B3) at different time points. For each examination, 3 coronary sections are shown. Tumor volumes defined by the area of contrast enhancement progressively decreased after H-1PV injection. Animal #100 was infected with H-1PV intratumorally (A1) and examined on days 3, 7, and 150 p.i. (A2, A3, and A4, respectively). Examination dates for animal #712, which was infected intravenously (B1), were days 7 and 28 p.i. (B2 and B3). Both animals have survived for more than 6 months and without tumor recurrence.

Парвовирусы и ксенотрансплантанты

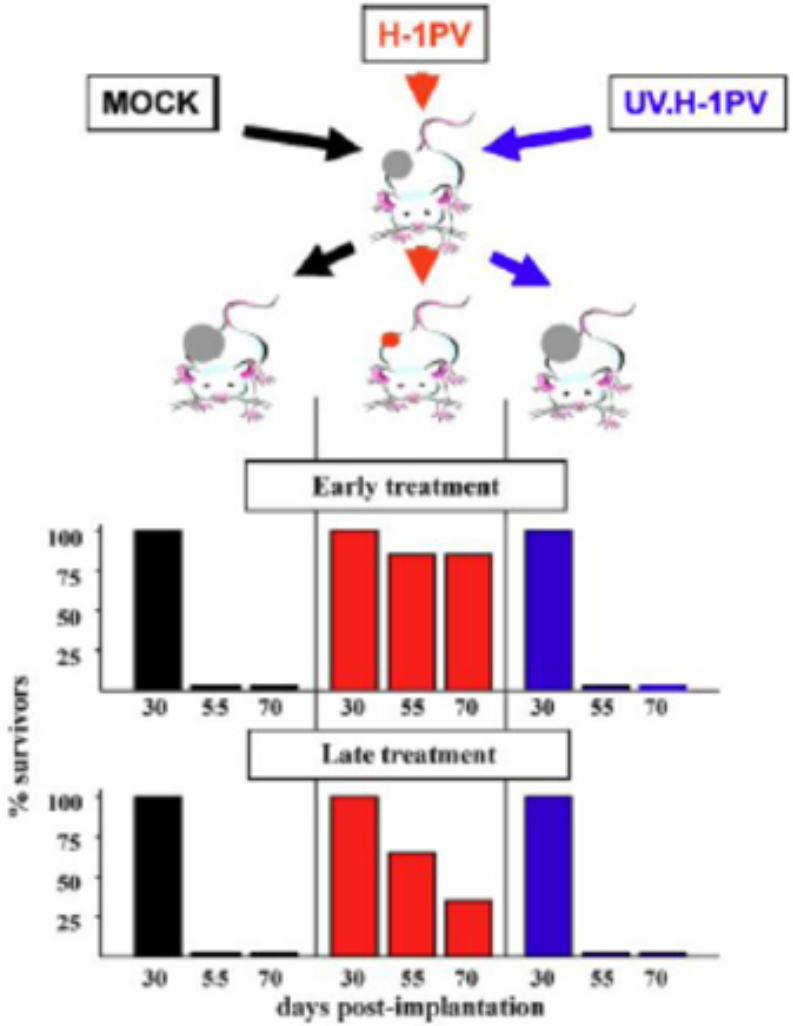
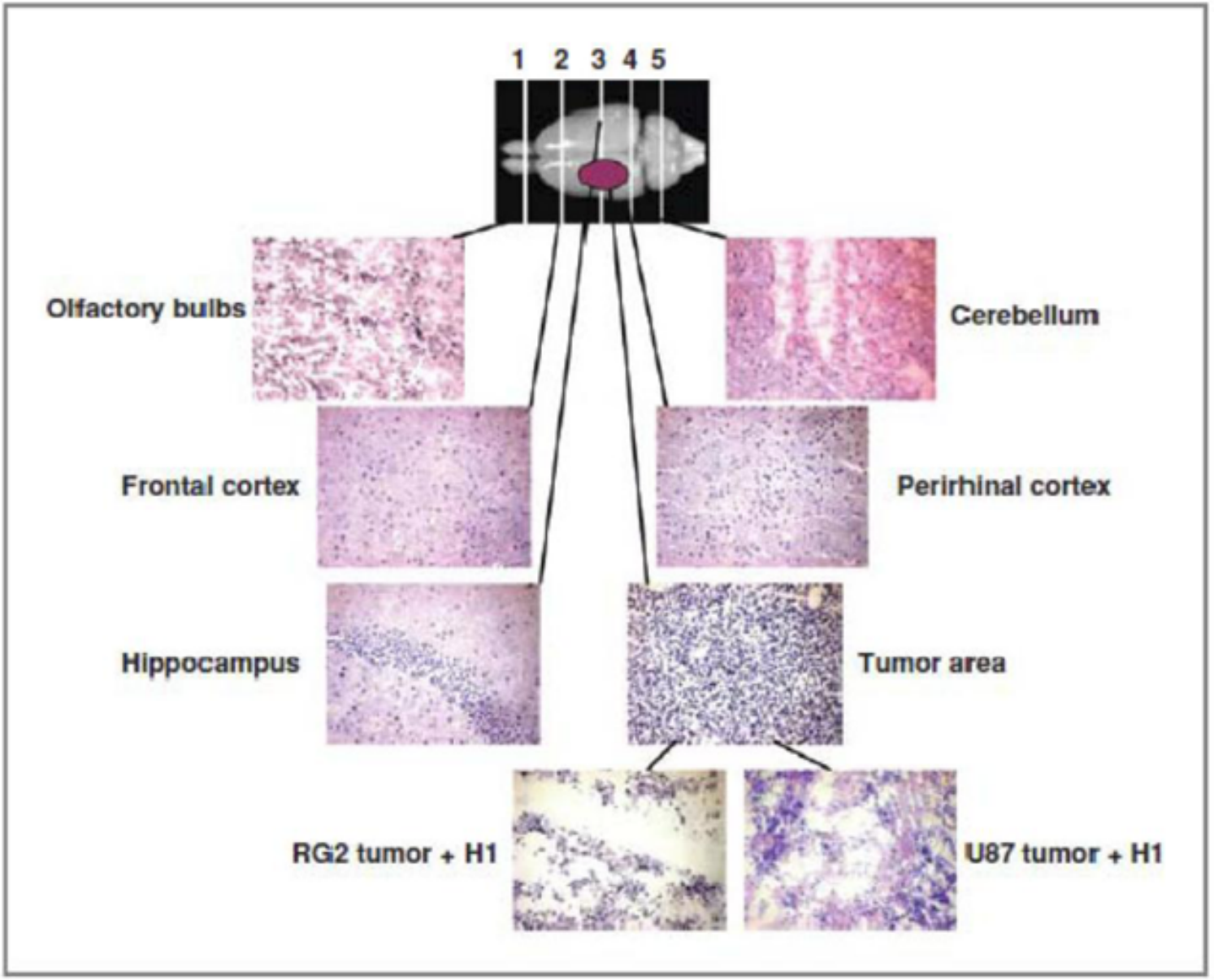


Fig. 3. Therapeutic effect of parvovirus H-1PV on human lymphoma xenografts in immunodeficient mice.. Infectious (H-1PV) or inactivated (UV.H-1PV) virus particles were injected into established subcutaneous Burkitt's lymphomas in SCID mice, either early (14 days) or late (28 days) after cell implantation. Bars give the percentages of mice surviving at the indicated times after tumor implantation upon early or late parvoviral treatment.


1 2 3 4 5
Olfactory bulbs
Cerebellum
Frontal cortex
Perirhinal cortex
Hippocampus
Tumor area
RG2 tumor + H1
U87 tumor + H1

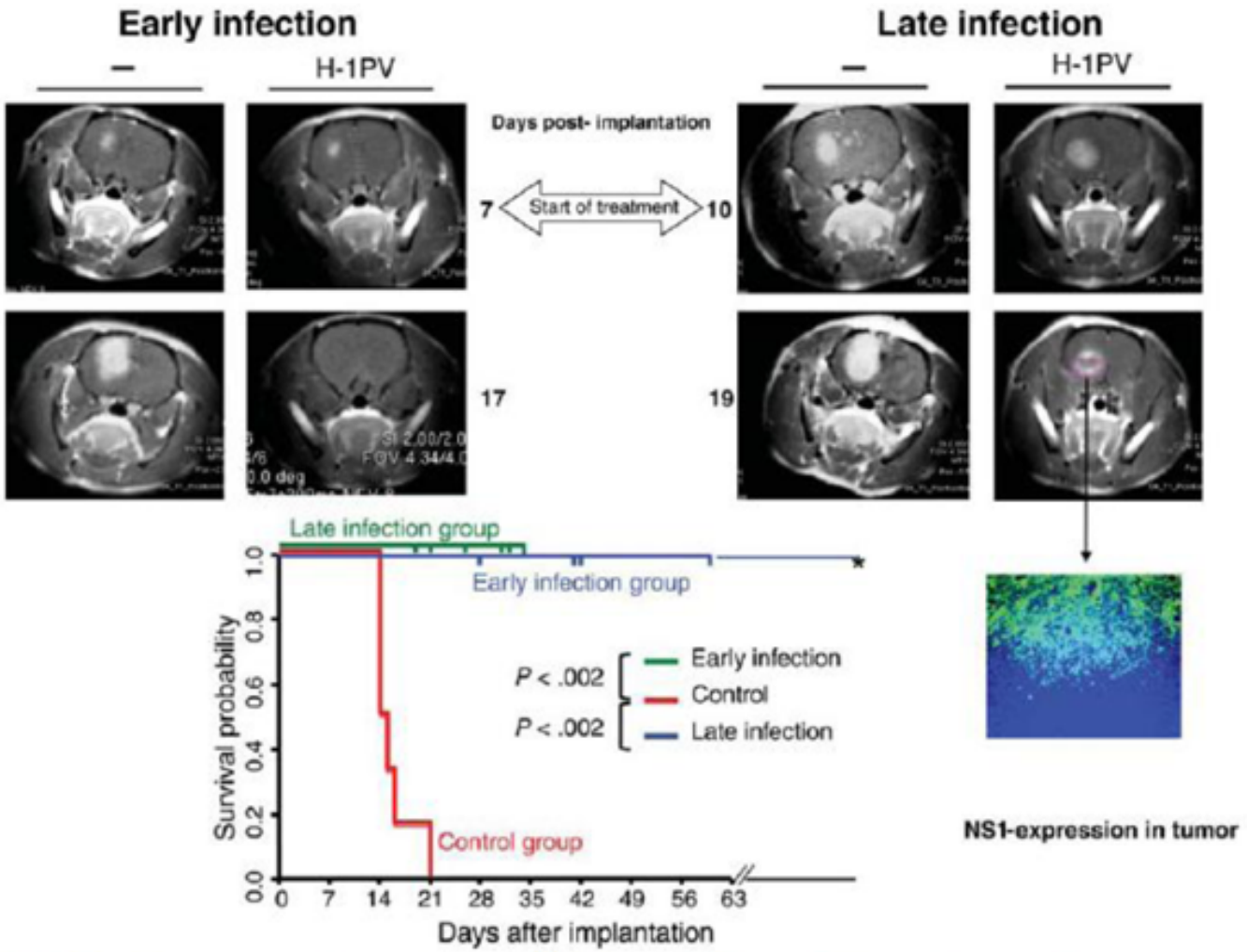


Fig. 5. H-1PV-induced suppression of human gliomas (established from U87 cells) in RNU rats. (Upper panel) Demonstration of tumor

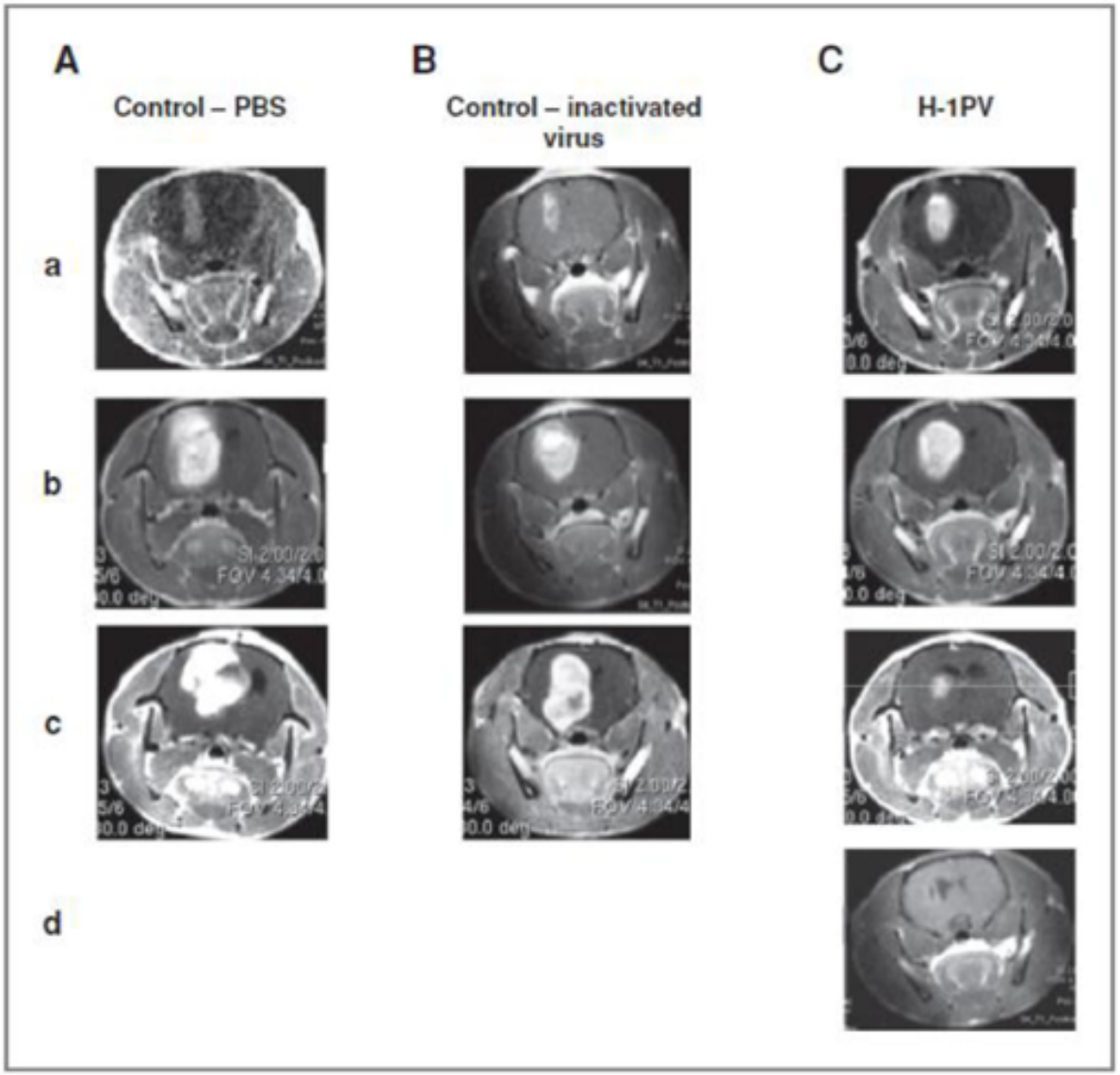
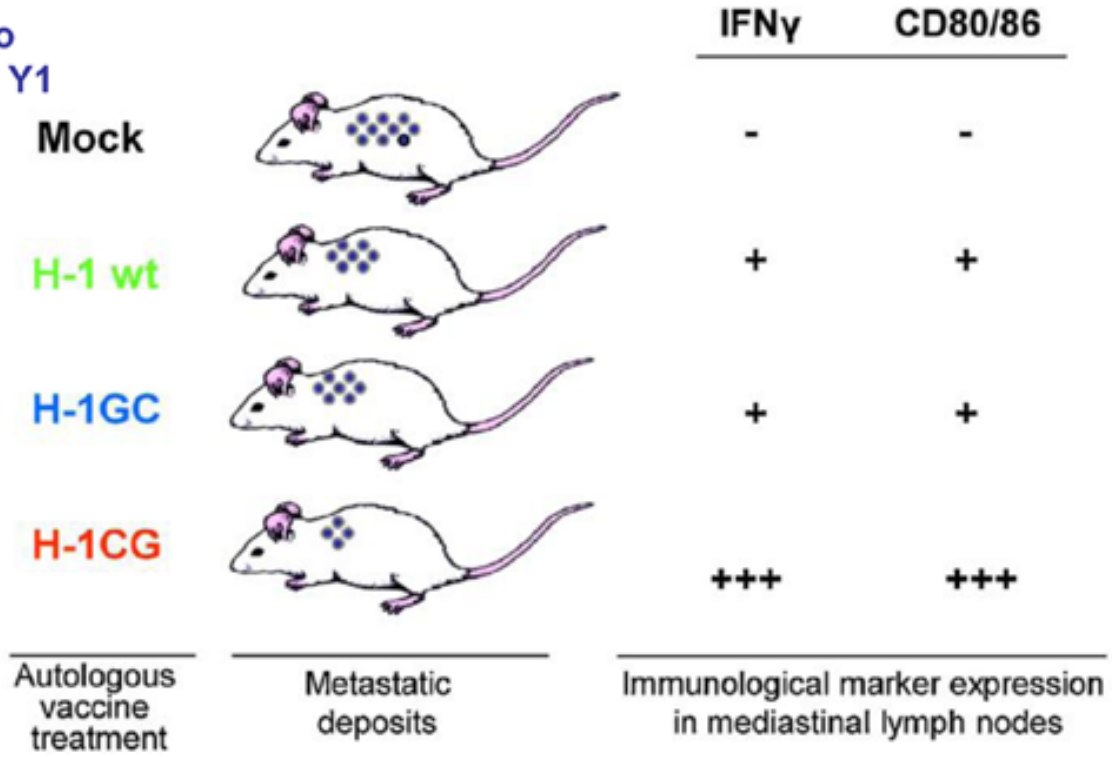


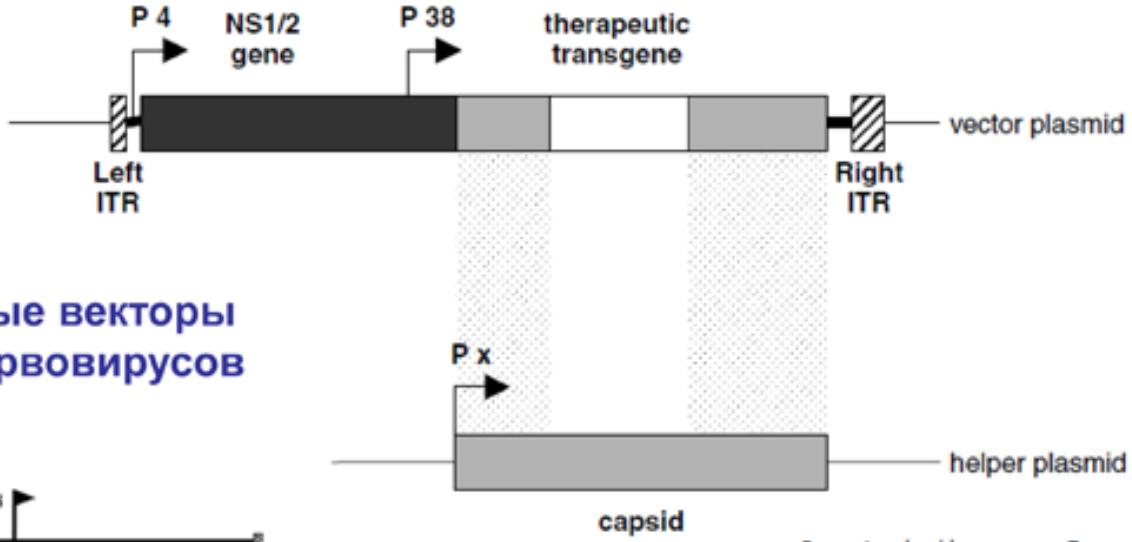
Figure 1. Glioma regression by intranasally administered H-1PV. MR images of 3 animals, each from 1 experimental group, are given as representative examples. Rats bearing an intracranial RG-2 glioma were intranasally treated with (A) PBS, (B) noninfectious H-1PV capsids (UV-irradiated empty capsids equivalent to 1×10^{10} particles), (C) infectious H-1PV (1×10^{8} pfu) 7 days after tumor cell implantation. MRI was done 7 (a), 12 (b), 17 (c), or 22 (d) days after tumor cell implantation. There are no images at day 22 (d) for the control groups because no PBS- or empty virus-treated rats survived for so long. MR image for group B (empty capsids) had to be done at day 16 due to the lack of survivors at later times. The group C animals survived symptom free for more than 80 days after tumor cell implantation. NB: Probably due to regression of the tumor, MRI shape of brains changed slightly (C, d).

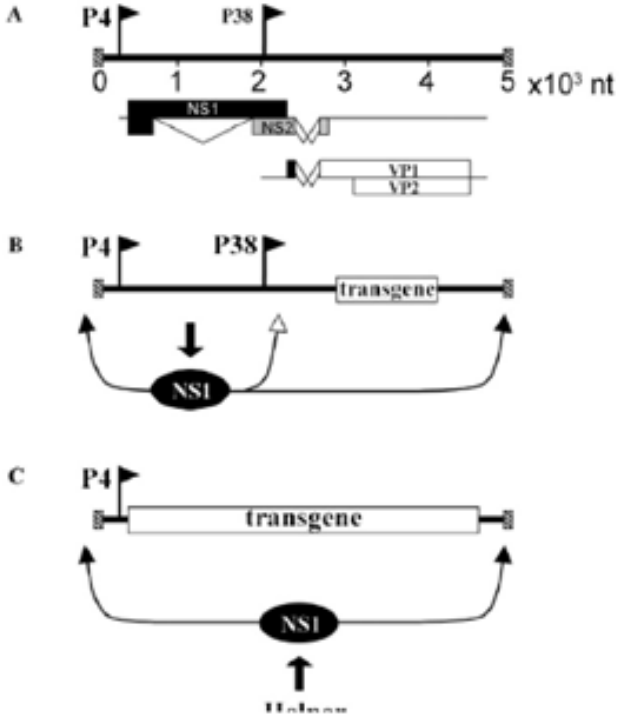
Immunomodulation by CpG-enriched parvoviruses

Иммуностимулирующий мотив R1R2CGY1Y2, где R1 пурин предпочтительно G), R2 — пурин или T, а Y1 и Y2 — пиримидины



Автономные векторы на базе парвовирусов





Parvovirus backbone	Transgene product
	Markers
MVMp	chloramphenicol acetyltransferase
MVMp, MVMi, H-1	(enhanced) green fluorescent protein
H-1	luciferase
	Cyto/chemokines
MVMp, MVMi	murine B7-1 (CD80)
MVMp	murine B7-2 (CD86)
MVMp, H-1	human interleukin-2
MVMp	murine interleukin-4
MVMp	human interferon gamma-inducible protein 10
H-1	human monocyte chemotactic protein 1
H-1	human monocyte chemotactic protein 3
	Toxins
MVMp	HSV-1 thymidine kinase
H-1	Apoptin
	Vaccine target
MVMi	Borrelia burgdorferi outer surface protein A

Table 3. Anti-Neoplastic Effects of Recombinant Parvoviruses[1]

Virus/Transgene[2]	Infection[3]	Tumor cells	Mice[4]	Antitumor Effect[1]	Ref
H-1/IL-2	*in vitro*	carcinoma	nude	yes	Haag *et al.*, 2000
H-1/MCP-1	*in vitro*	carcinoma	nude	no	Haag *et al.*, 2000
H-1/MCP-3	*in vitro*	carcinoma	nude	yes	Wetzel *et al.*, 2001
MVMp/IL-2	*in vitro*	melanoma	syn	yes	El Bakkouri *et al.*, 2000 b
MVMp/IP-10	*in vivo*	endothelioma	syn	yes	Giese *et al.*, 2002
MVMp/MCP-3	*in vivo*	melanoma	syn	yes	Wetzel, 2000
MVMp/MCP-3	*in vitro*	melanoma	syn	yes	Wetzel, 2000
MVMi/B7.1	*in vivo*	thymoma	syn	yes	Palmer and Tattersall, 2000 b

[1]Antitumor effects of recombinant viruses include longer life expectancy of treated animals, inhibition of tumor growth, prevention of tumor appearance and regression of established tumors. Yes: enhanced effect of the recombinant compared with an appropriate control virus (wild-type, empty vector or vector harboring a marker transgene). No: no improvement of the antineoplastic effect of recombinant over control virus.

[2]Transgene products: MCP-1 and MCP-3, monocyte chemotactic protein 1 and 3; IL-2, Interleukin 2; IP-10, Interferon γ-inducible protein 10; B7.1, costimulatory molecule B7.1. :

[3]In vitro: tumor cells infected in culture prior to their subcutaneous grafting. *In vivo*: established tumors infected in animals.

[4]H-1 virus-derived vectors were used against human tumors grafted in immunodeficient (nude) mice, while MVM-derived vectors were used against mouse tumor cells implanted in syngeneic (syn) mice.

J Neurooncol
DOI 10.1007/s11060-011-0506-5

LABORATORY INVESTIGATION - HUMAN/ANIMAL TISSUE

The combined effects of oncolytic reovirus plus Newcastle disease virus and reovirus plus parvovirus on U87 and U373 cells in vitro and in vivo

Abstract Previous results had documented oncolytic capacity of reovirus, parvovirus and Newcastle disease virus (NDV) on several tumor cell types. To test whether combinations of these viruses may increase this capacity, human U87- and U373-glioblastoma cells, in vitro or xenografted into immuno-compromised mice, were subjected to simultaneous double infections and analyzed. Our results show that reovirus (serotype-3) plus NDV (Hitcher-B1) and reovirus plus parvovirus-H1 lead to a significant increase in tumor cell killing in vitro in both cell lines (Kruskal–Wallis test, $P < 0.01$) and in vivo. Immunofluorescence and flow cytometry analyses demonstrated the simultaneous replication of the viruses in nearly all cells (>95%) after combined infection. These data thus indicate that a synergistic anti-tumor effect can be achieved by the combined infection with oncolytic viruses.

J Neurooncol
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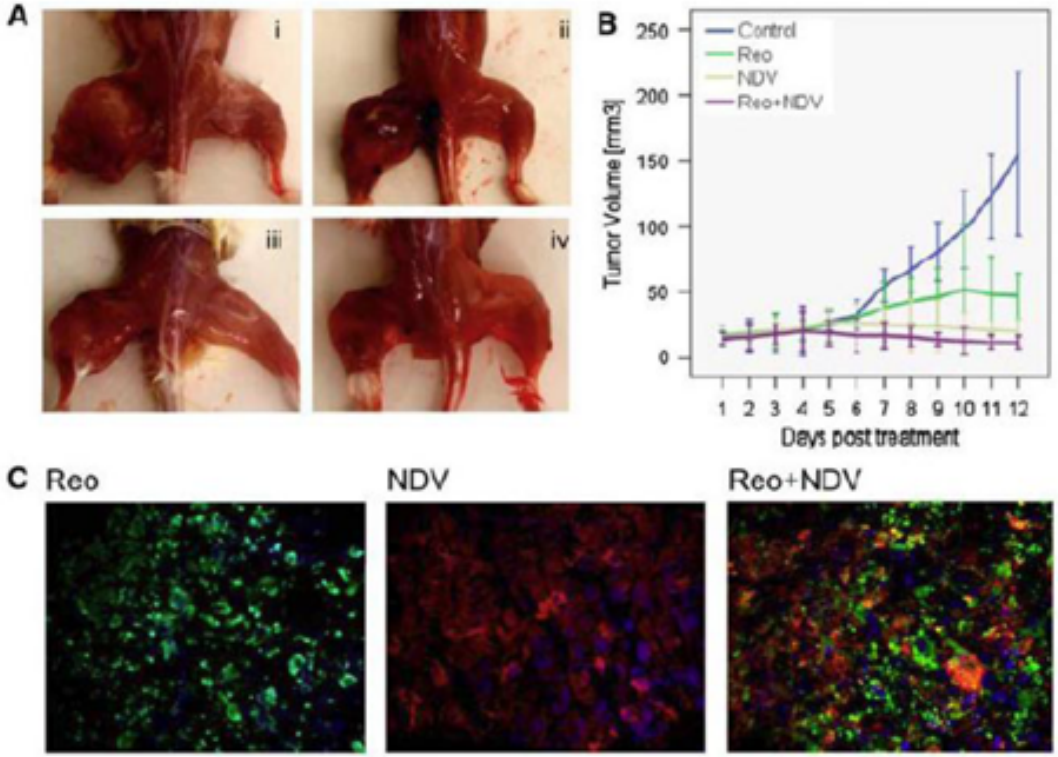

Fig. 6 Effects of reovirus or NDV alone or in combination on U87 human malignant glioma tumor xenografts grown subcutaneously in SCID/NOD mice. U87 cells was introduced as a tumor xenograft subcutaneously in SCID/NOD mice and approximately 2 weeks later animals were treated with reovirus (*green line*, the plotted values represent the mean of the measurements, $n = 4$) or NDV (*red line*, the plotted values represent the mean of the measurements, $n = 4$) as single or combined therapy. Control animals were treated with PBS (*blue line*, the plotted values represent the mean of the measurements, $n = 4$). **a** Tumors were measured daily to calculate tumor volume and animals were euthanized day 12 post infection. (*i*) control-mice, (*ii*) Reo, (*iii*) NDV, (*iv*) Reo plus NDV. **b** Development of tumor size. *Error bars* SEM. **c** Immunofluorescence staining of tumor mass 12 days post-infection (reovirus is colored *red*, NDV *green* and nucleus *blue*)

Generation of an Adenovirus-Parvovirus Chimera with Enhanced Oncolytic Potential

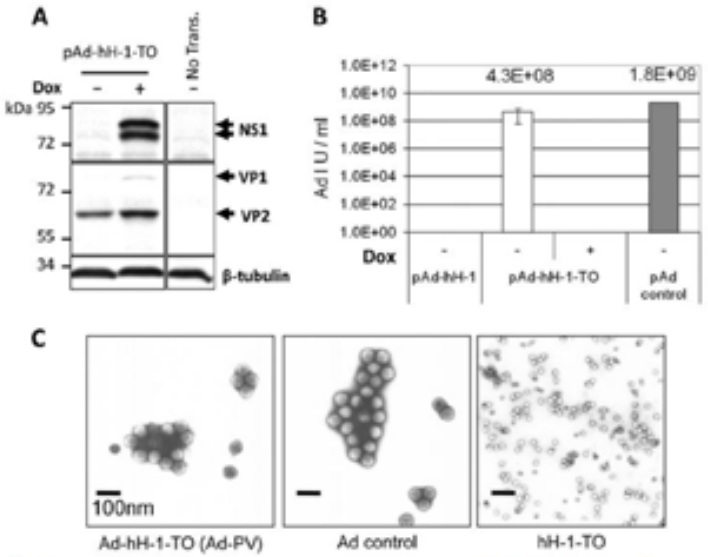

FIG 3 Generation of Ad-PV chimeras. (A) Inducible gene expression from the chimeric pAd-hH-1-TO plasmid. T-REx-293 cells were transfected with pAd-hH-1-TO plasmid and further grown in medium with or without DOX for 5 days. Cells were then lysed and total protein extracts analyzed by Western blotting for the presence of parvovirus NS1 and VP proteins and β-tubulin (loading control). No Trans., no transfection. (B) Ad-PV chimera production. In a first round of production, T-REx-293 cells were transfected with the chimeric pAd-hH-1-TO plasmid or either of the parental pAd (pAd5ΔE1ΔE3) and pAd-hH-1 plasmids and grown in medium supplemented with DOX or without supplementation. Cell lysates from these cultures were used for infection of fresh T-REx-293 cells in a second round of production, and the procedure was repeated a third time by scaling up the volume of the culture flasks as described in Materials and Methods. Viral stocks were purified twice through CsCl gradient ultracentrifugation and titrated using an Adeno-X Rapid Titer kit (Clontech), and yields were expressed as Ad infectious units/milliliter (IU/ml). (C) Electron microscopy (EM) analysis of produced virions. EM images of the purified Ad-hH-1-TO (Ad-PV), Ad, and hH-1-TO viruses are shown. Bars, 100 nm.

In this study, the goal was to generate a chimeric adenovirus-parvovirus (Ad-PV) vector that combines the high-titer and efficient gene transfer of adenovirus with the anticancer potential of rodent parvovirus.

To this end, the entire oncolytic PV genome was inserted into a replication-defective E1- and E3-deleted Ad5 vector genome. The chimera effectively delivered the PV genome into cancer cells, from which fully infectious replication-competent parvovirus particles were generated. Remarkably, the Ad-PV chimera exerted stronger cytotoxic activities against various cancer cell lines, compared with the PV and Ad parental viruses, while being still innocuous to a panel of tested healthy primary human cells.

This Ad-PV chimera represents a novel versatile anticancer agent which can be subjected to further genetic manipulations in order to reinforce its enhanced oncolytic capacity through arming with transgenes or retargeting into tumor cells.

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Generation of an Adenovirus-Parvovirus Chimera with Enhanced Oncolytic Potential

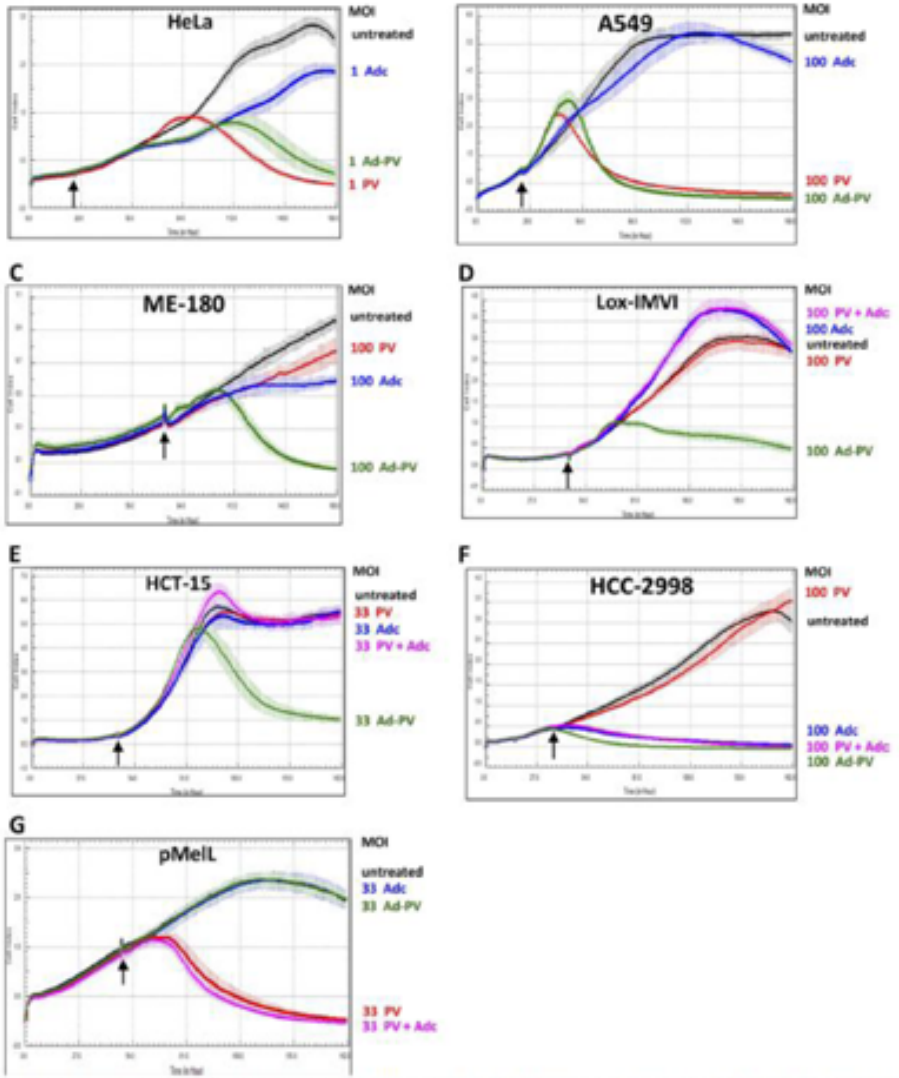


FIG 7 Enhanced toxicity of the Ad-PV chimera for cancer cell lines. HeLa (A), A549 (B), ME-180 (C), Lox-IMVI (D), HCT-15 (E), HCC 2998 (F), and pMelL (G) human cancer cells were seeded in 96-well E-plates (xCelligence Roche) and infected at the indicated MOIs with Ad-hH-1-TO chimera (Ad-PV). Ad control

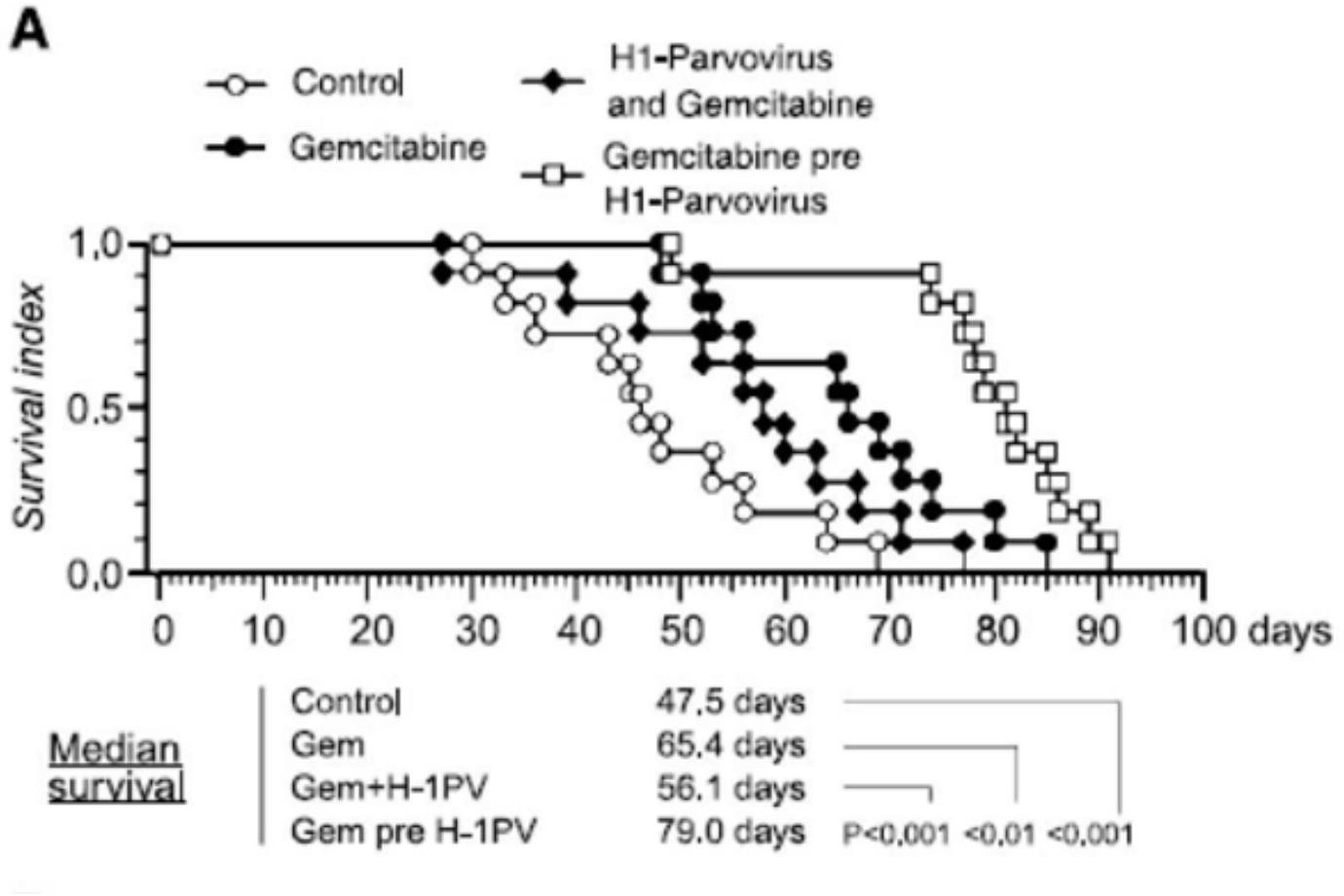
Journal of Virology October 2012 Volume 86 Number 19 p. 10418–10431

DOI:10.1158/1078-0432.CCR-08-1088

Cancer Therapy: Preclinical

Improvement of Gemcitabine-Based Therapy of Pancreatic Carcinoma by Means of Oncolytic Parvovirus H 1PV

Assia L. Angelova,[1] Marc Aprahamian,[3] Svitlana P. Grekova,[1] Amor Hajri,[3] Barbara Leuchs,[1] Nathalie A. Giese,[2] Christiane Dinsart,[1] Alexia Hermann,[1] Ginette Balboni,[3] Jean Rommelaere,[1] and Zahari Raykov[1]



Research Article

Improved Killing of Human High-Grade Glioma Cells by Combining Ionizing Radiation with Oncolytic Parvovirus H-1 Infection

Karsten Geletneky,[1,2] Andreas D. Hartkopf,[3] Robert Krempien,[4] Jean Rommelaere,[2] and Joerg R. Schlehofer[2]

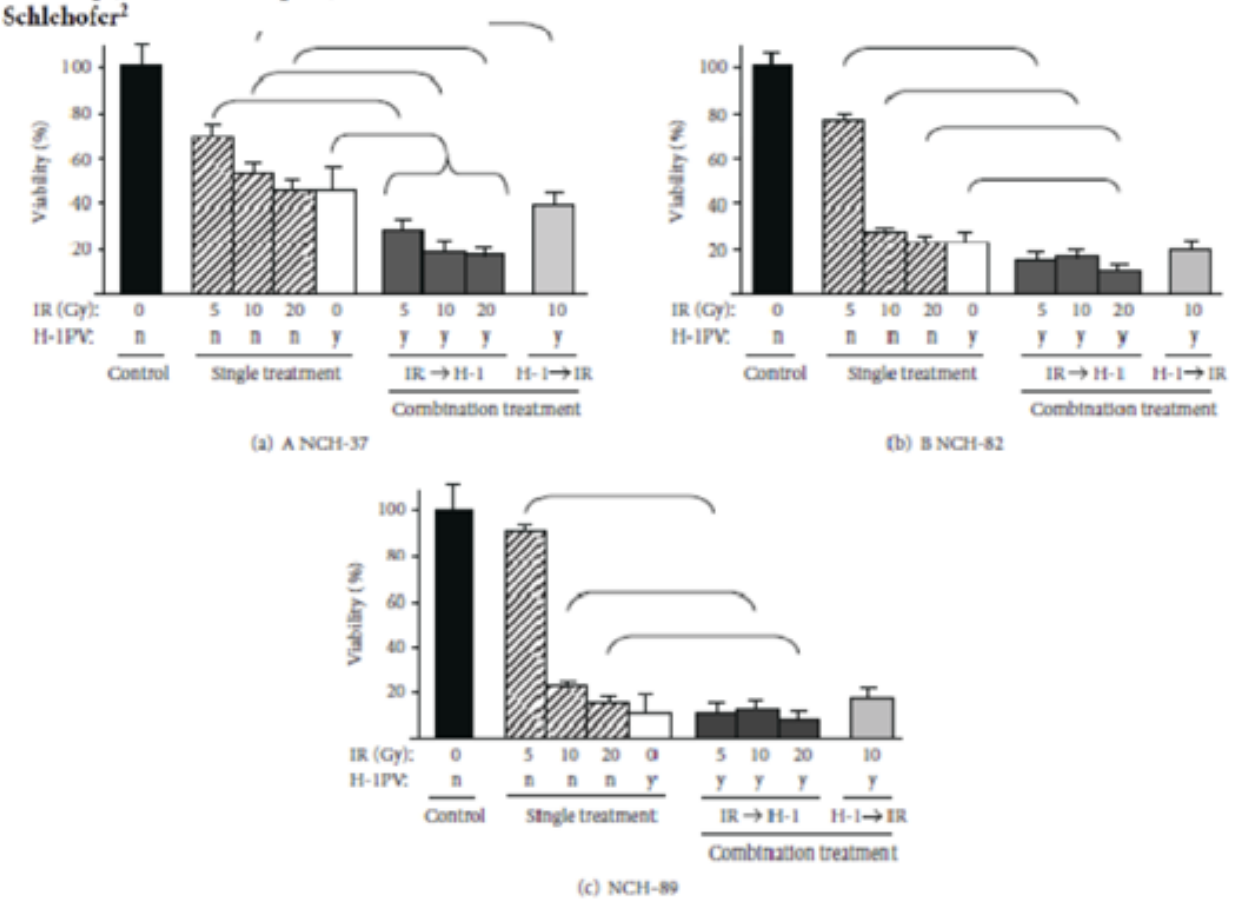


FIGURE 2: *Effects of ionizing radiation (IR), parvovirus H-1 (H-1PV) infection, and combination of IR and H-1PV infection on human high-grade glioma cells.* Short-term cultures of human gliosarcoma NCH-37 (a), human glioblastoma NCH-82 (b), and human glioblastoma

Клинические испытания препарата ParvOryx 01

Phase I/IIa study of intratumoral/intracerebral or intravenous/intracerebral administration of Parvovirus H-1 (ParvOryx) in patients with progressive primary or recurrent glioblastoma multiforme: ParvOryx01 protocol

Aim

This trial aims to investigate the safety, biodistribution, maximum tolerated dose and signs of anti-tumor activity of parvovirus H-1 in patients suffering from recurrent malignant gliomas. According to preclinical data and differing from previous oncolytic virus trials in GBM patients ParvOryx01 will not only include intratumoral virus application but also intravenous treatment.

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Клинические испытания препарата ParvOryx 01

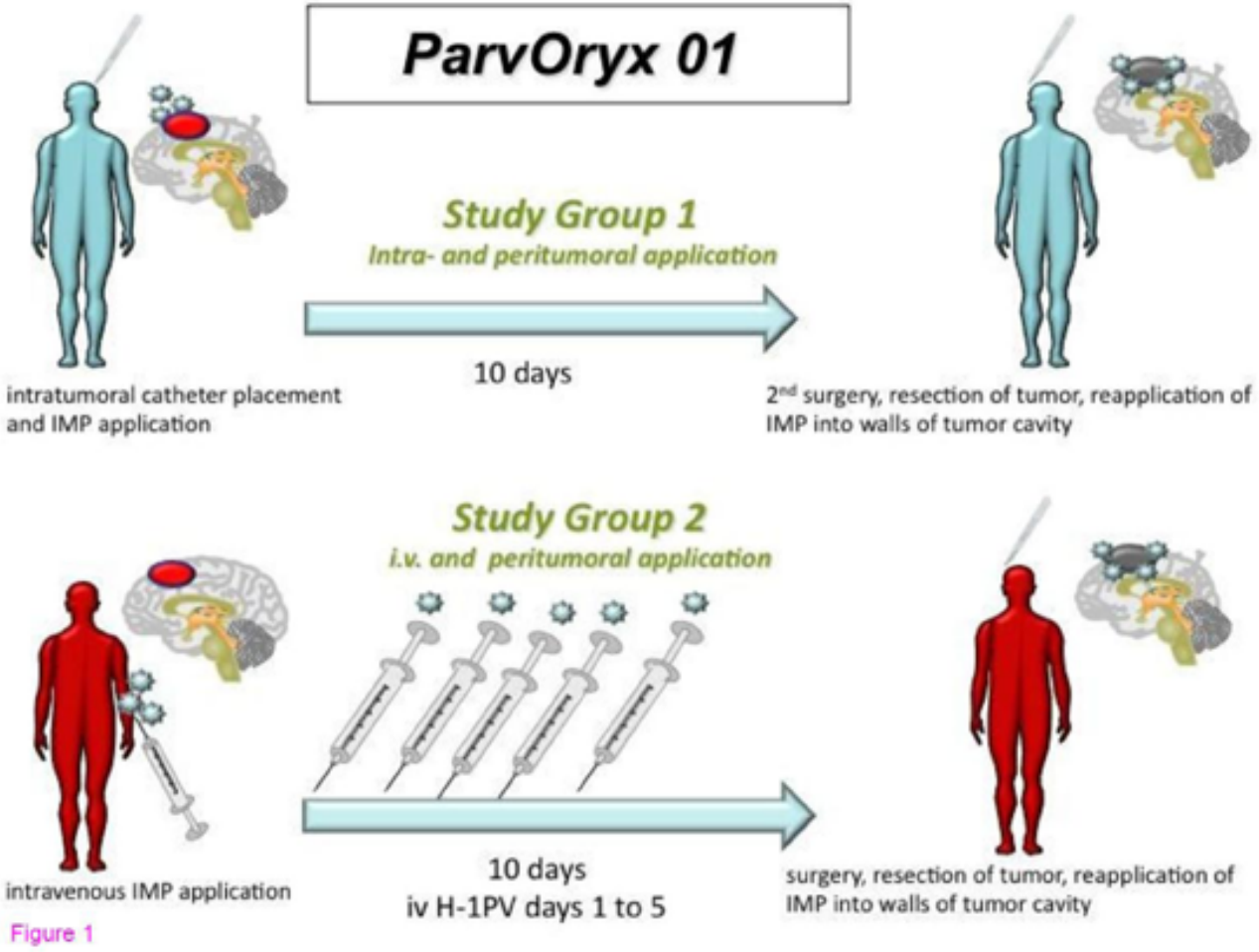

Figure 1

Клинические испытания препарата ParvOryx 01

Table 1 Dose schedule for both study groups

GROUP I			
Escalation Level	**Study Time**	**Dose and route of administration**	**Duration**
Level 1 Total dose: 1×10^6 pfu	Day 1	5×10^5 pfu, intratumoral (via catheter)	15 minutes
	Day 10	5×10^5 pfu, intracerebal (direct injection at multiple locations of resection wall)	15-30 minutes
Level 2 Total dose: 5×10^7 pfu	Day 1	2.5×10^7 pfu, intratumoral (via catheter)	15 minutes
	Day 10	2.5×10^7 pfu, intracerebal (direct injection at multiple locations of resection wall)	15-30 minutes
Level 3 Total dose: 1×10^9 pfu	Day 1	5×10^8 pfu, intratumoral (via catheter)	15 minutes
	Day 10	5×10^8 pfu, intracerebral (direct injection at multiple locations of resection wall)	15-30 minutes
GROUP II			
Escalation Level	**Study Time**	**Dose and Route of Administration**	**Duration**
Level 1 Total dose: 1×10^6 pfu	Day 1 - 5	1×10^5 pfu, intravenous infusion	2 hours
	Day 10	5×10^5 pfu, intracerebral (direct injection at multiple locations of resection wall)	15-30 minutes
Level 2 Total dose: 5×10^7	Day 1 - 5	0.5×10^7 pfu, intravenous infusion	2 hours
	Day 10	2.5×10^7 pfu, intracerebral (direct injection at multiple locations of resection wall)	15-30 minutes
Level 3 Total dose: 1×10^9 pfu	Day 1 - 5	1×10^8 pfu, intravenous infusion	2 hours
	Day 10	5×10^8 pfu, intracerebral (direct injection at multiple locations of resection wall)	15-30 minutes

Specification of virus application and dose escalation during the Parvoryx01 trial: dose group 2 will be treated after completion of group 1 and after interim analysis of safety and tolerability in group 1.

Заключение

- **Онколитические парвовирусы, и прежде всего парвовирус H-1PV, способны селективно инфицировать и лизировать клетки раковых опухолей.**
- **Парвовирусы вызывают иммуностимулирующий эффект, индуцируя элиминацию опухолевых клеток через формирование специфического противоракового иммунитета.**
- **Один из возможных механизмов противоопухолевого действия связан с индукцией апоптоза белками 11кДа и NS1 парвовирусов.**
- **Векторные системы на основе генома парвовирусов также перспективны для генной терапии различных онкологических и соматических заболеваний человека.**
- **Парвовирусы были весьма успешно использованы для экспериментального лечения глиомы, нейробластомы, лимфомы, гепатомы, карциномы поджелудочной железы и опухолей молочной железы.**
- **Создан первый онколитический препарат «ParvOryx» на основе парвовируса H-1PV и начаты клинические испытания фазы I/IIa на пациентах с мультиформной глиобластомой.**

Каждой опухоли – индивидуальный онколитический парвовирус

Спасибо за внимание!