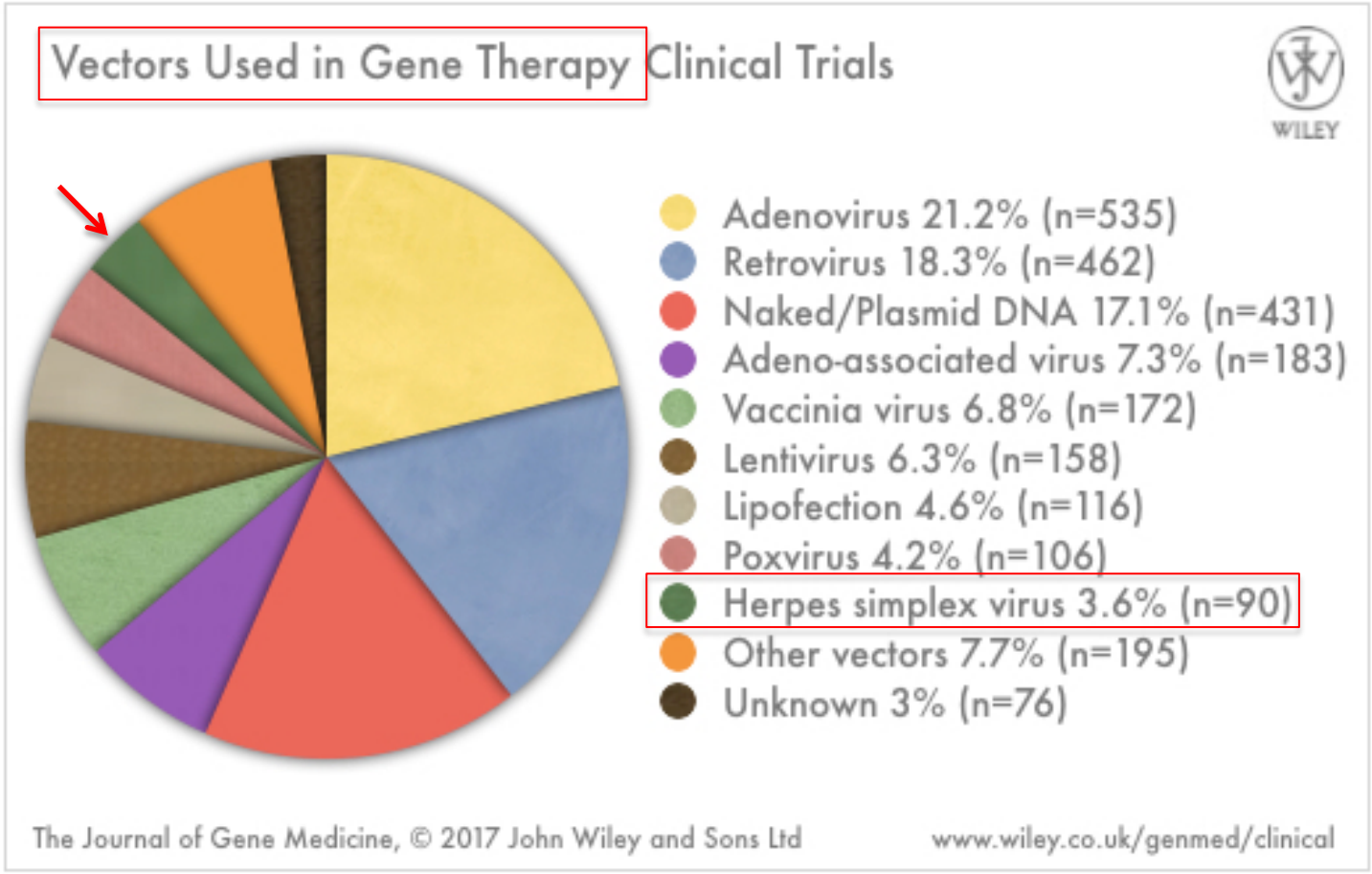
Risk considerations of the growing biomedical use of herpevirus vectors

8th Meeting of the European Advisory Committees on Biosafety,
Liege, 24/11/2017

Summary

- *Herpesvirus Vectors*
- *Use in Humans*
- *Biosafety Risks*

Herpesvirus vectors in Humans



Vaccines:

- Emery VC (2013) Human Herpesvirus Vaccines and Future Directions *American Journal of Transplantation* 13: 79–86 doi: 10.1111/ajt.12007
- Johnston C et al (2016) Status of vaccine research and development of vaccines for herpes simplex virus *Vaccine* 34: 2948-52 doi org/10.1016/j.vaccine.2015.12.076

9 Human Herpesviruses have been identified

Lysis / Latency switch

1 Herpes Simplex Virus – 1 (HSV-1)
2 Herpes Simplex Virus – 2 (HSV-2)
3 Varicella Zoster Virus (VZV)

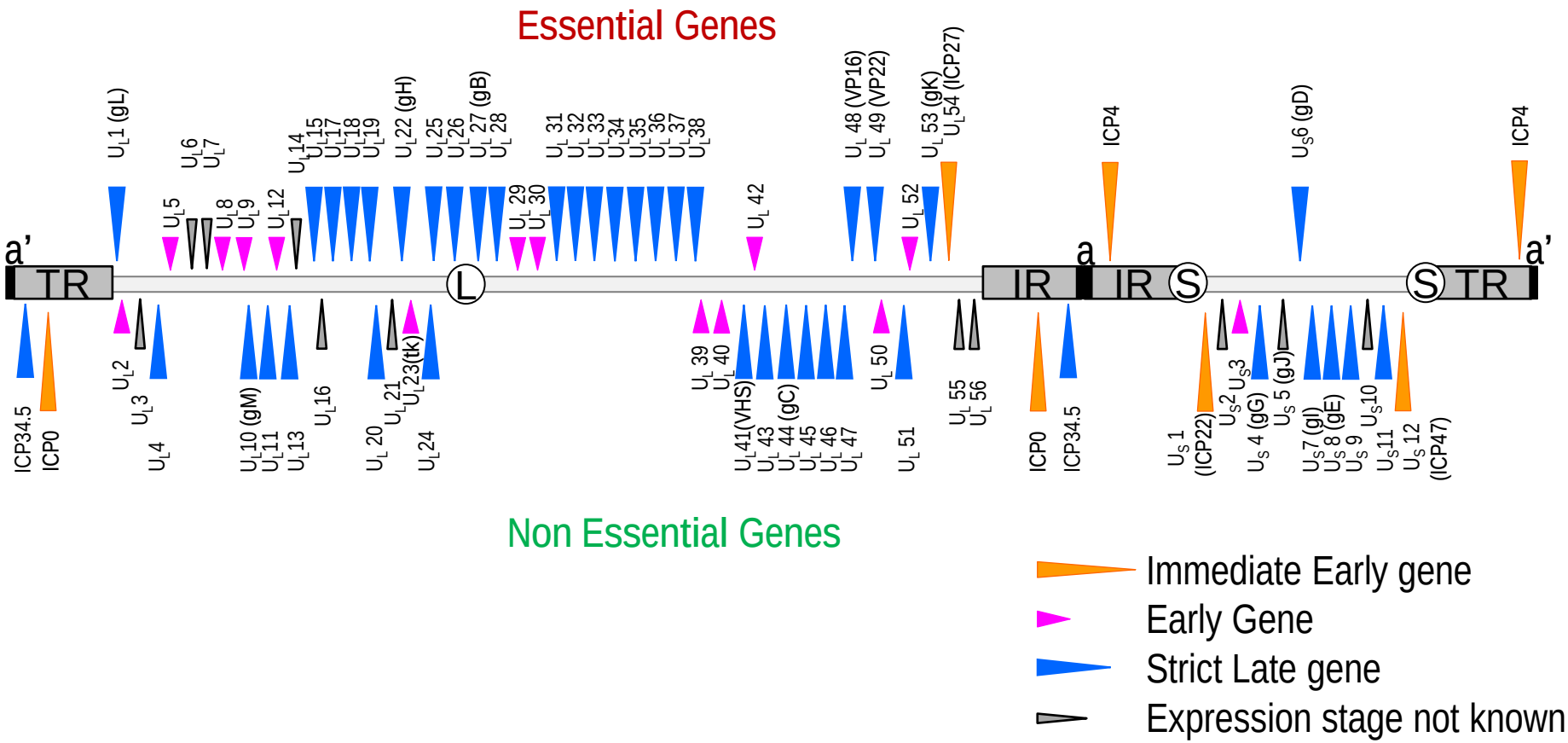
neurons

4 Epstein Barr Virus (EBV)
5 Cytomegalovirus (CMV)
6A Human B Lymphotrophic Virus
6B Human B Lymphotrophic Virus
7 Roseolovirus
8 Karposi's sarcoma herpesvirus (KSHV)

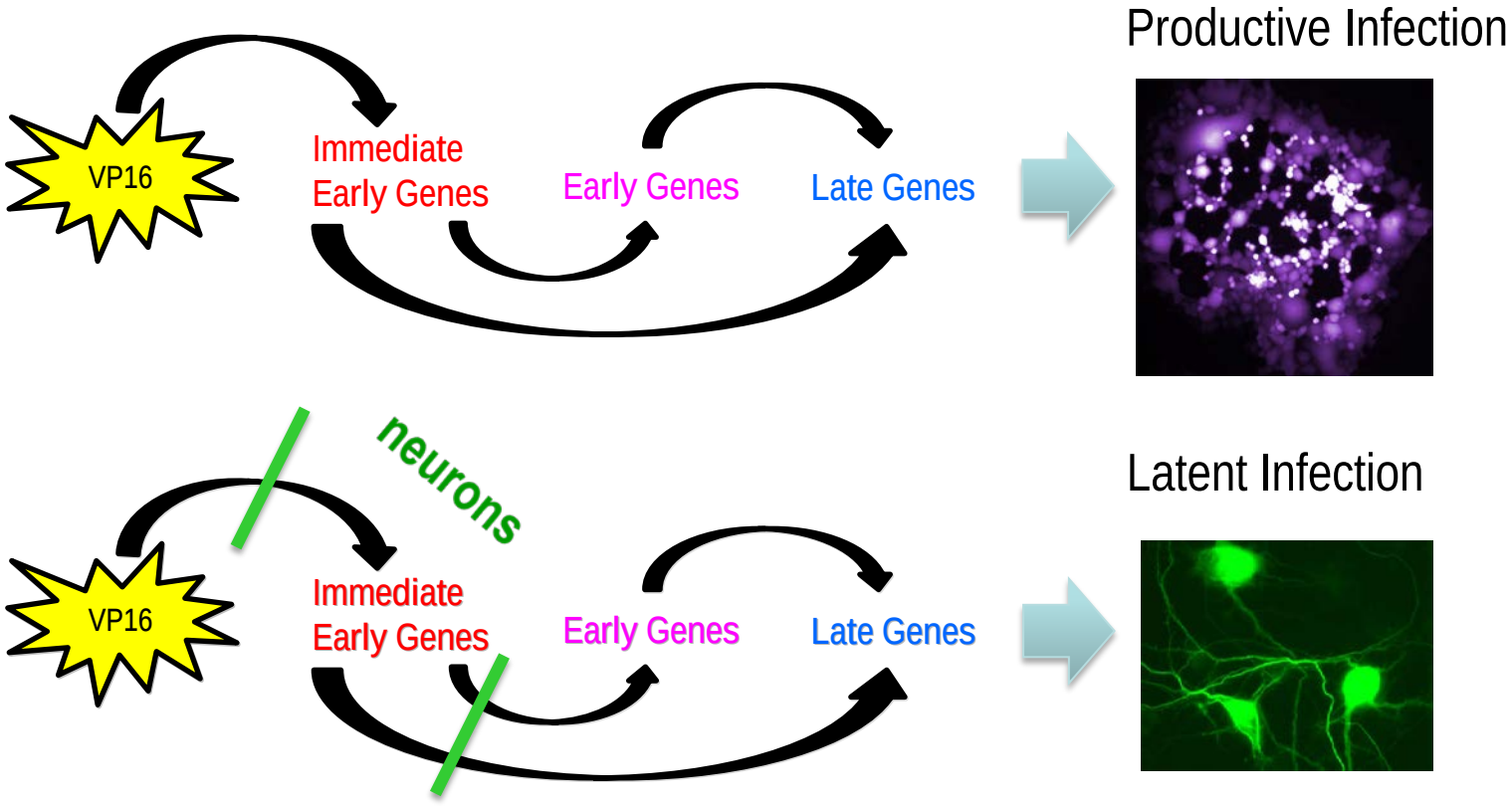
leukocytes

HSV-1 ds DNA genome

encodes ~80 genes (152 kb!)



HSV-1 genes are expressed in a hierarchical cascade



Why herpesvirus vectors?

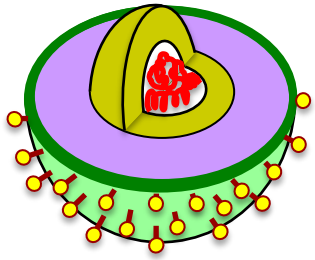
- *Preferential replication in tumor cells*
- *Large genome size for big or multiple transgenes*
- *Latency – proof of possibility to silence genome*
- *High infectivity in many cell types*
- *Neuronal transport – gene delivery to deep tissues*
- *Gene transfer in postmitotic cells, episomal persistence*

HSV-1 vector types

Replicative
(Conditional):

ONCOLYTICS, VACCINES

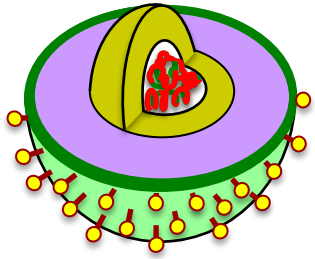
productive viral genome



Replication-incompetent:

CANCER IMMUNOTHERAPY, NEUROLOGICAL GENE THERAPY, VACCINES

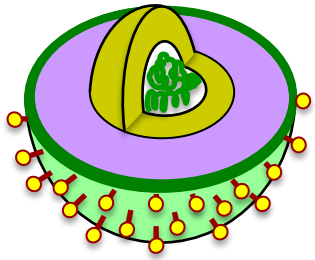
NON-productive viral genome



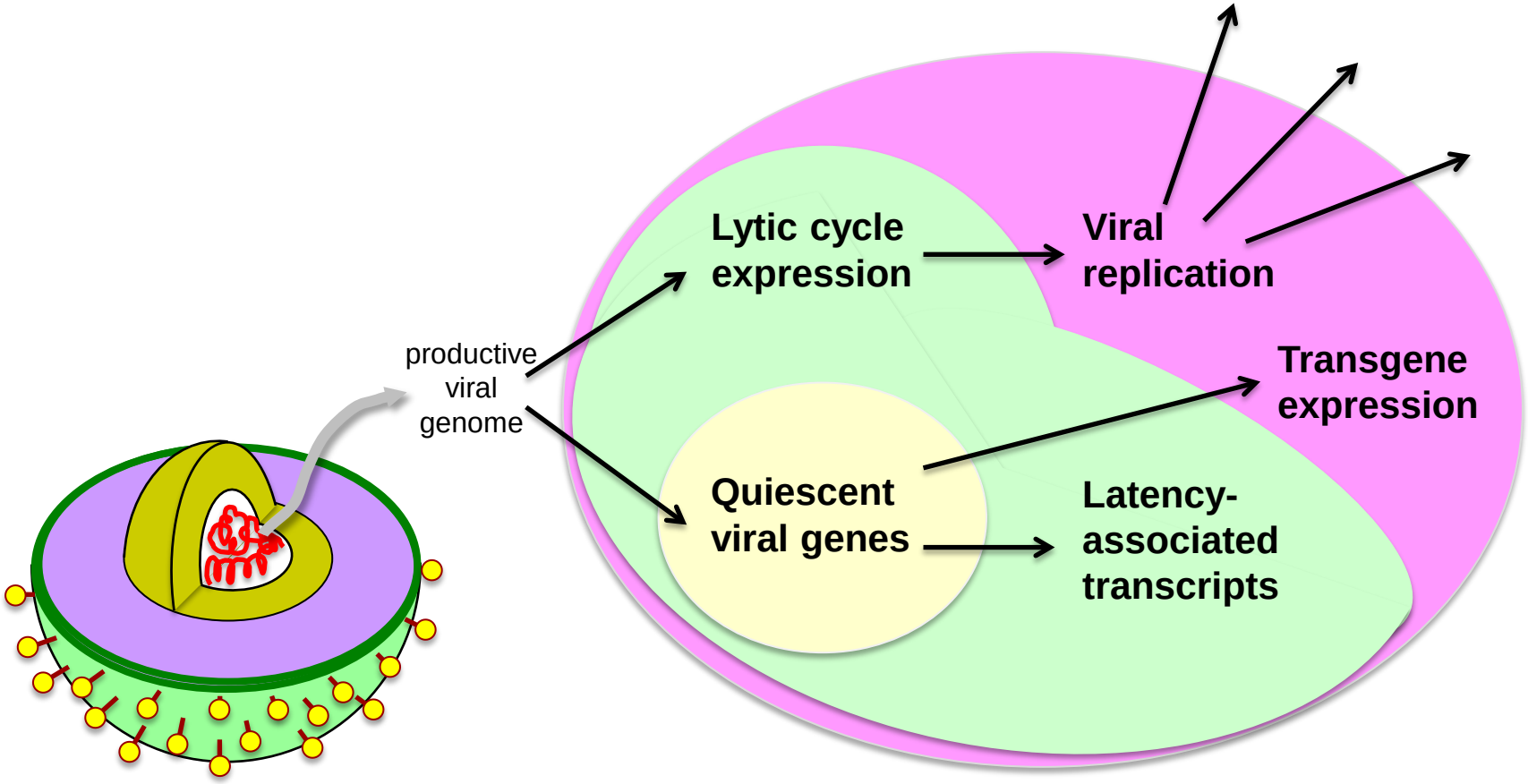
Amplicons
(Gutless):

PRECLINICAL

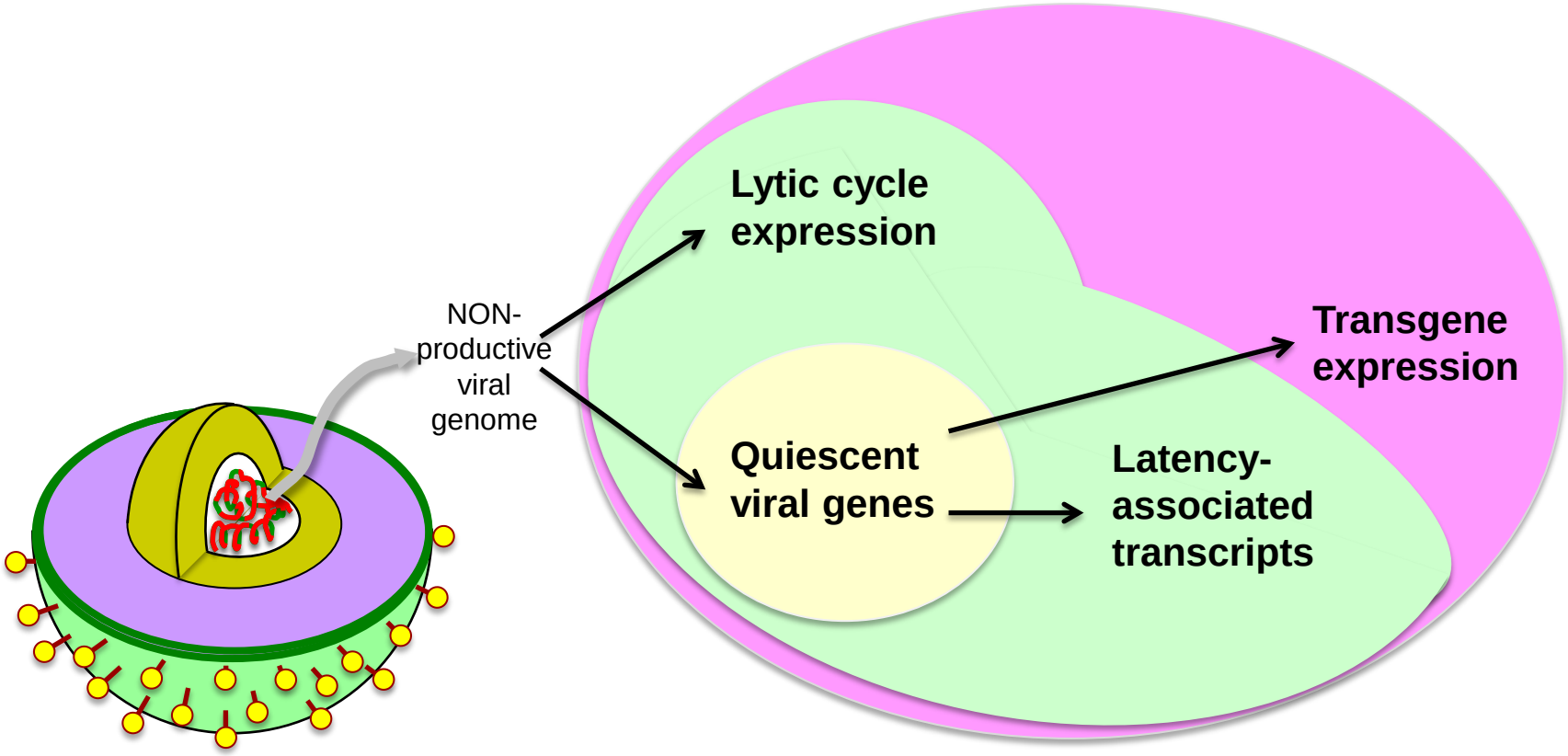
NON-viral genome



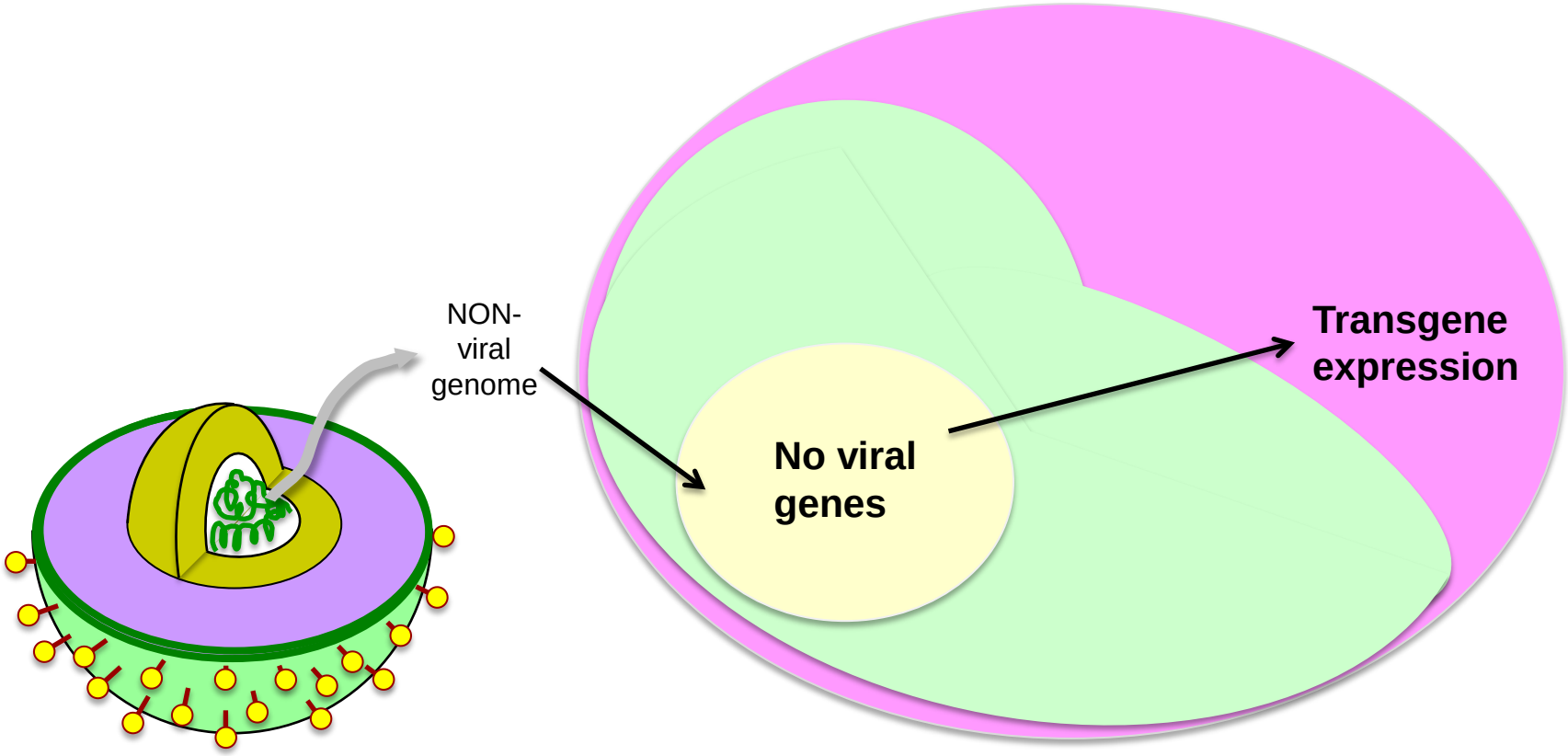
HSV-1 vector types
1 REPLICATIVE



HSV-1 vector types
2 REPLICATION-INCOMPETENT



HSV-1 vector types
3 AMPLICONS



Use in Humans

Viral vaccines against HHVs

Varicella zoster	Safe, efficacious live vaccine	Oxman MN et al (2005) A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults *N Engl J Med* 352: 2271-84
Herpes simplex (HSV1 & HSV2)	7 HSV candidates in clinical trials	Johnston C et al (2016) Status of vaccine research and development of vaccines for herpes simplex virus *Vaccine* 34: 2948-52 doi org/10.1016/j.vaccine.2015.12.076
Epstein Barr Virus	Modified vaccinia and adenovirus	Cohen JI (2015) Epstein–barr virus vaccines *Clinical & Translational Immunology* 4: e32 doi 10.1038/cti.2014.27
Cytomegalovirus	Modified Semliki virus	Bernstein DI et al (2009) Randomized, double-blind, Phase 1 trial of an alphavirus replicon vaccine for cytomegalovirus in CMV seronegative adult volunteers. *Vaccine* 28: 484–93 doi 10.1016/j.vaccine.2009.09.135

IMLYGIC, 1st of a kind

theguardian

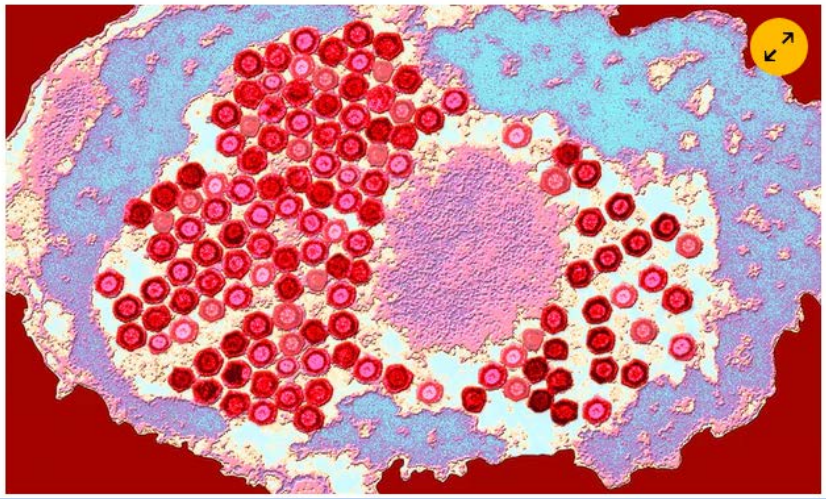
ball opinion culture business lifestyle fashion environment tech travel ≡ browse all sections

US approval for drug that turns herpes virus against cancer

REUTERS

Amgen wins EU green light for first virus-based cancer drug

Imlygic, which bursts melanoma cells open and triggers immune response, can shrink localised tumours but is not proven to extend life, says FDA



Amgen wins EU green light for first virus-based cancer drug

Corrigan PA et al (2017) Talimogene Laherparepvec: An Oncolytic Virus Therapy for Melanoma *Annals of Pharmacotherapy* **51**: 1-7 doi 10.1177/1060028017702654

IMLYGIC, 1st of a kind

- *Phases I - III*
- *Safe, no deaths, no serious AEs*
- *Priming dose 10^6 particles → 10^8 particles x ~15*
- *Detectable in blood, urine (1/5), not in tears, nasal mucosa, feces*
- *Little at injection site*

Corrigan PA et al (2017) Talimogene Laherparepvec: An Oncolytic Virus Therapy for Melanoma *Annals of Pharmacotherapy* **51**: 1-7 doi 10.1177/1060028017702654

Oncolytic Herpesvirus Clinical Trials

IMLYGIC (T-VEC, Oncovex, Talimogene Laherparevec)	Amgen	ΔICP34.5, ΔICP47, expresses GM-CSF	melanoma, liver tumor, head & neck carcinoma
OrienX010	OrienGene Biotechnology	ΔICP34.5, ΔICP47, expresses GM-CSF	glioblastoma
SEPREHVIR (1716)	Virttu Biologics	ΔICP34.5	Hepatocellular carcinoma, glioblastoma, mesothelioma, neuroblastoma
G207	Medigene	ΔICP34.5, disrupted ICP6	glioblastoma
HF10	Takara Bio	Inactivated UL43, UL49.5, UL55, UL56	breast cancer, melanoma, pancreatic cancer
G47Δ	Medigene	ΔICP34.5, ΔICP47, disrupted ICP6	prostate cancer
NV1020	Medigene	Haploid ICP4, ICP0, ICP34.5, ΔTK, inactive UL24	Liver metastatic colorectal cancer

Kaufman HL et al (2015) Oncolytic viruses: a new class of immunotherapy drugs *Nat Rev Drug Discov* 14: 642-62 doi 10.1038/nrd4663

J Gene Med Gene Therapy Clinical Trials Worldwide http://www.abedia.com/wiley/

Nonreplicative Herpesvector Clinical Trials

DISC-GMCSF	Xenova	ΔgH (HSV-2), expresses GM-CSF	melanoma
NUREL-C2	Uni Pittsburgh	Inactive ICP4, ICP27, ICP22, expresses TNF & Connexin43	glioblastoma
NP2	Periphagen	ΔICP4, ΔICP27, expresses proenkephalin	intractable pain in cancer

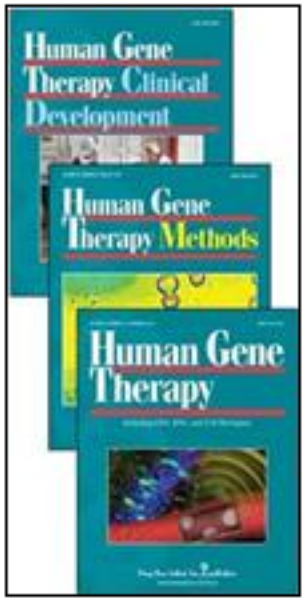
J Gene Med Gene Therapy Clinical Trials Worldwide http://www.abedia.com/wiley/

First clinical trial of gene therapy for pain shows substantial pain relief for patients

Date: April 12, 2011

Source: University of Michigan Health System

Joseph Glorioso, PhD, Receives Pioneer Award for Engineering Herpes Simplex Virus Gene Delivery Systems



New Rochelle, NY, February 19, 2014—Joseph C. Glorioso, III, PhD (University of Pittsburgh School of Medicine, PA) devoted much of his research career to de
cel
Pio
An
an
an
Per
ava

As
Pot
use
the
represents the most imp
opportunity to study com
acquired diseases, includ

UMHS HEADLINES
UNIVERSITY OF MICHIGAN HEALTH SYSTEM

Search

Home | Announcements | Submit an item | Calendar of Events | Help and Frequently Ask

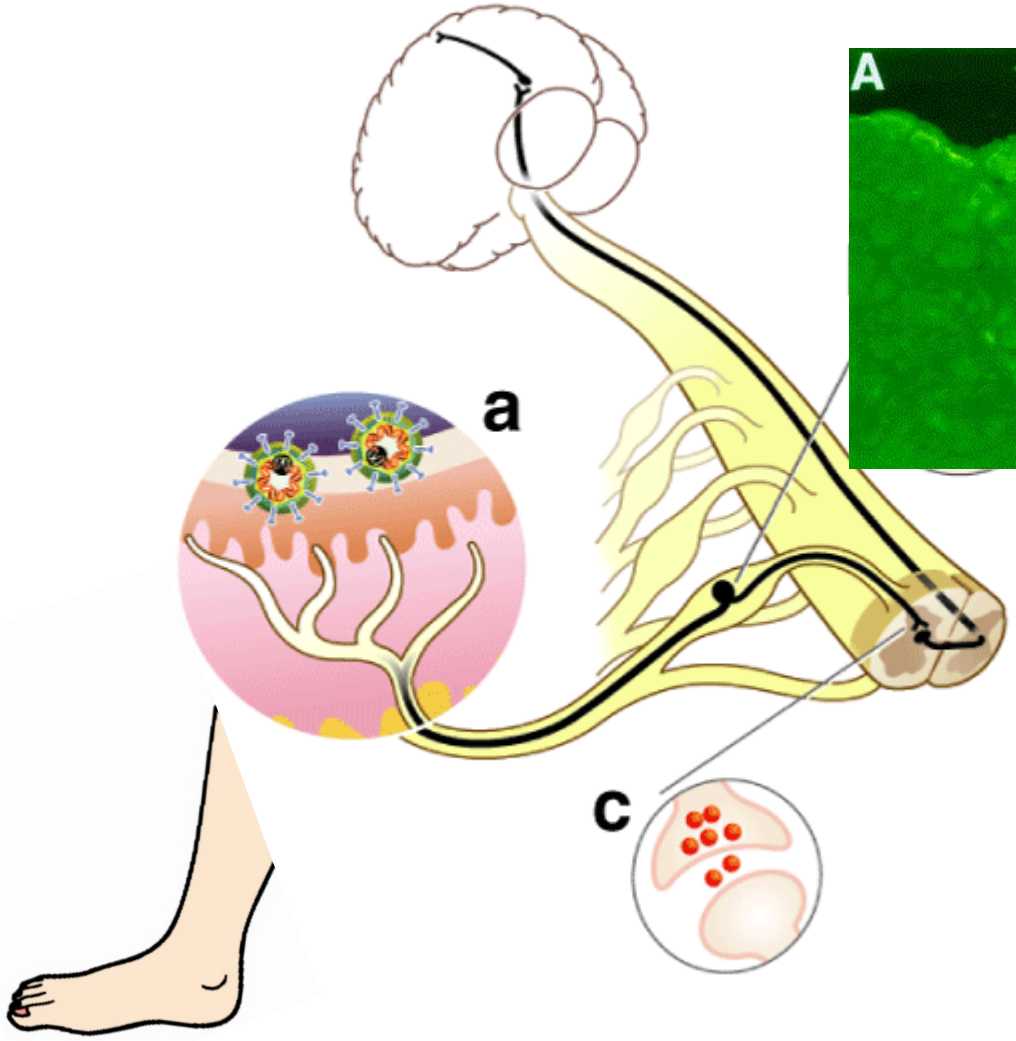
Dr. David Fink receives national VA research award from top officials in surprise ceremony

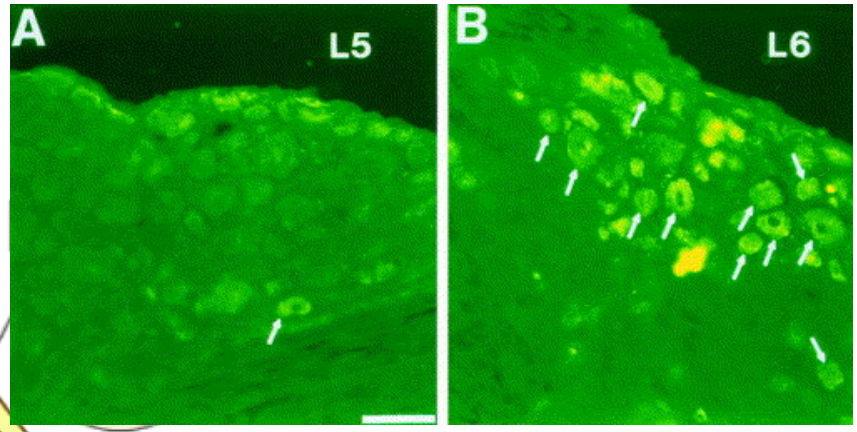
Posted on December 16, 2014

Gene therapy pioneer, U-M Medical School Department of Neurology chair and longtime Veterans Affairs researcher David Fink, M.D., received the 2014 Paul B. Magnuson Award from VA in a surprise ceremony at the VA Ann Arbor Healthcare System on Monday.

Dr. Fink is a staff neurologist, and an investigator with the Geriatric Research, Education and Clinical Center, at the Ann Arbor VA. He is also the Robert Brear Professor of Neurology at U-M. He has been

HSV-1 vectors are transported from skin to spinal cord





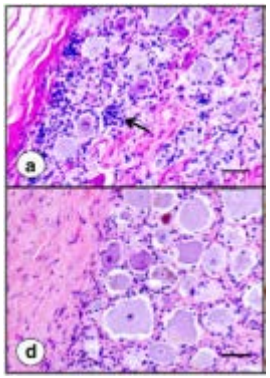
Minimally invasive delivery into poorly accesible tissues

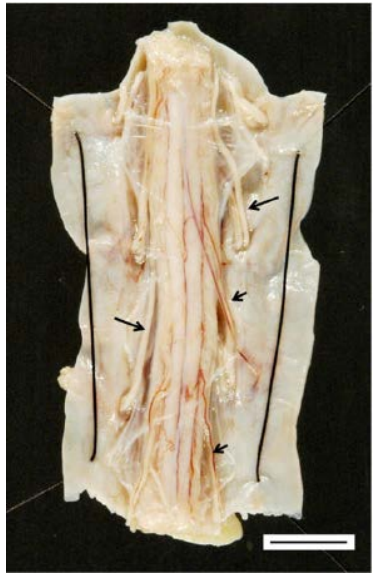
Other neurological applications: Friedreich's Ataxia

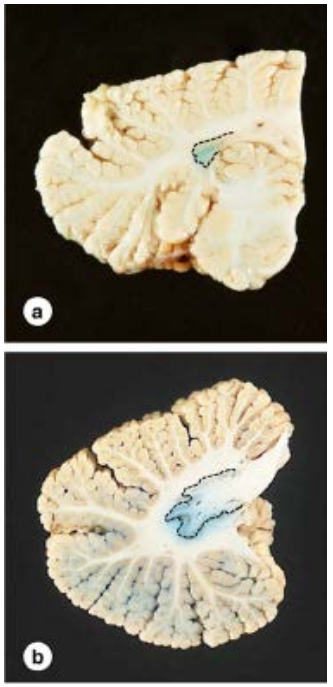
Recessive: mutations in FXN reduce expression of frataxin, an essential protein which is especially vital in certain neurons of the CNS:

PROGRESSIVE DEGENERATION OF:

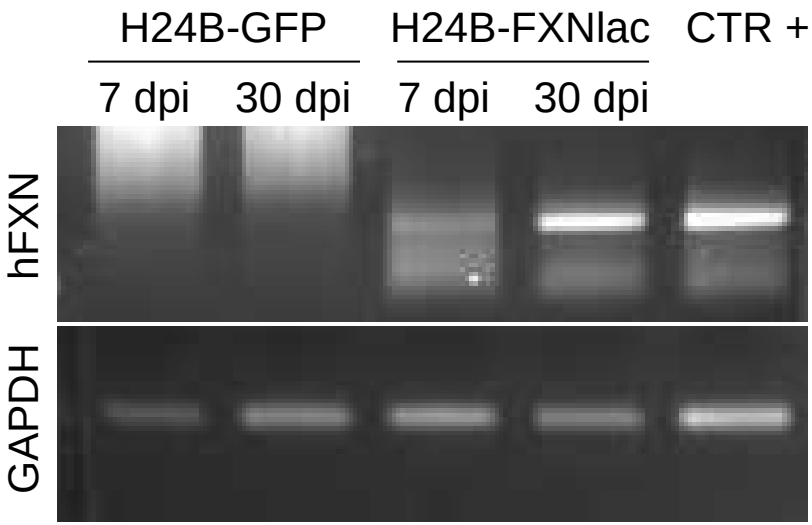
- Dorsal Root Ganglion neurons
- Sensory tracts of spinal cord
- Dentate nuclei of the cerebellum



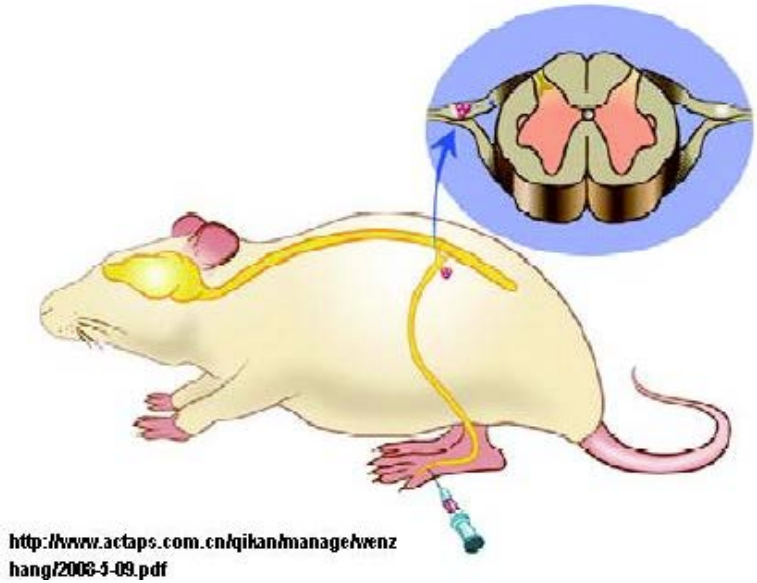




Preliminary biodistribution of HSV-FXN vector



SPECIFIC transgene targeting into DRGs



- HSV-FXN vector injected into footpad: 8.75×10^5 PFU/mouse footpad
- 5 days after injection: 50-400 genomes per DRG detected and one animal that had 270,000 genomes

Other neurological applications: enhancing HSV-1 to silence sensory afferents in the bladder

ERANET JTC-2016

Emergence of a spinal micturition reflex after SCI: abolition by silencing of hyperexcited C-fiber bladder afferents by gene therapy to restore continence and micturition, (ELPIS)

Biosafety Risks

Shedding

- Replication competence: ability to multiply and amplify in human host affects dissemination in the body and may increase shedding. Possibility of recombination with wildtype virus.
- Immunogenicity: vectors that elicit a strong immune response are cleared from circulation more rapidly than weakly immunogenic vectors → shorter duration shedding. In multiple administrations, shedding may be for a shorter duration in the later dose cycles than early doses (immune-priming).
- Persistence and latency: duration may be longer due to persistence or latency (eg neurons, leukocytes) followed by reactivation. Shedding may be intermittent and unpredictable (reactivation stimuli)
- Tropism: may affect what samples should be collected to assess shedding. Modifications of tropism may alter shedding profile because of retargeting of the product to different tissues or organs.

Shedding measurements

Viremia and virus shedding

No viral shedding was observed in any patient on this trial as all HSV-1 cultures including blood, buccal swab, and urine at all study visits through day 28 were negative. PCR for HSV-1 genomes were also negative in all buccal swab and urine samples. Blood PCR for HSV-1 genomes were negative at baseline, day 0, and day +1 following virus injection. In contrast, blood PCR for HSV-1 genomes at day +4 turned positive in 1 patient at dose level 1, 2 patients at dose level 2, and all 3 patients at dose level 3 (6 of 9 patients total). In 2 patients, PCR remained positive at day +7, and in one of those patients (HSV04), it remained positive through day 28. Unfortunately, this patient's disease rapidly progressed leading to hospice care so we were unable to confirm viral clearance at a later time point.

Streby KA et al (2017) Intratumoral Injection of HSV1716, an Oncolytic Herpes Virus, Is Safe and Shows Evidence of Immune Response and Viral Replication in Young Cancer Patients *Clin Cancer Res* 23: 3566-3574 doi: 10.1158/1078-0432.CCR-16-2900

Recombination/Reactivation

JOURNAL OF VIROLOGY, Oct. 1984, p. 300–305
0022-538X/84/100300-06$02.00/0

Vol. 52, No. 1

Detection of Multiple Strains of Latent Herpes Simplex Virus Type 1 Within Individual Human Hosts

MARCIA E. LEWIS,†* WAI-CHOI LEUNG, VERONA M. JEFFREY, AND KENNETH G. WARREN
Neurovirology Research Unit, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada T6G 2G3

Received 22 March 1984/Accepted 11 June 1984

One hundred and fifteen isolates of herpes simplex virus were recovered from parallel explant cultures of trigeminal and vagus ganglia and trigeminal nerve roots derived from 20 unselected human cadavers. Restriction enzyme patterns of strains recovered from 18 of 20 individuals could be differentiated from individual to individual, although all isolates from a single host were identical. Isolates from two individuals differed among themselves in the number and location of certain restriction enzyme sites.

Recombination/Reactivation

JOURNAL OF VIROLOGY, Apr. 2004, p. 3872–3879 Vol. 78, No. 8
0022-538X/04/$08.00+0 DOI: 10.1128/JVI.78.8.3872–3879.2004

Superinfection Prevents Recombination of the Alphaherpesvirus Bovine Herpesvirus 1

François Meurens,[1] Frédéric Schynts,[2] Günther M. Keil,[3] Benoît Muylkens,[1] Alain Vanderplasschen,[1] Pierre Gallego,[4] and Etienne Thiry[1]*

In vivo, the rise of recombinant viruses can be modulated by different factors, such as the dose of the inoculated viruses, the distance between inoculation sites, the time interval between inoculation of the first and the second virus, and the genes in which the mutations are located.

. The dramatic effect of the time interval on the rise of recombinant viruses is particularly important for the risk assessment of recombination

Recombination/Reactivation

Gene Therapy (1997) 4, 1300–1304

Intracerebral recombinant HSV-1 vector does not reactivate latent HSV-1

Q Wang[1], J Guo[1] and W Jia[1,2]
[1]*Departments of Surgery and Ophthalmology, University of British Columbia; and* [2]*British Columbia Cancer Agency, Vancouver, Canada*

Pharmacovigilance

- Route of administration: should be considered in the selection of sample types to collect in a shedding study. eg. in addition to routine samples (urine, feces, saliva): skin swabs at injection site for intradermal administration; nasopharyngeal washes for inhalation or intranasal delivery.
- Tests for adventitious agents introduced during manufacture (eg mycoplasma)
- Tests to distinguish between wildtype and vector
- Herpesvirus PCR and plaque assays offered by CROs

HSV vectors have an excellent safety profile

Preferential replication in tumor cells

Immune tolerance: prevalence >90% human population

Natural OFF state in neurons: potential for neurological therapy

Clinical Record: no deaths or serious adverse events

Future regulatory challenges…

More complex vectors:

1 Multiple, and/or really big transgenes

2 Cell-type retargeting
- cell entry
- innate defences
- transcription factors
- miRNA

3 Chimeras with other viruses

Lim F (2013) HSV-1 as a Model for Emerging Gene Delivery Vehicles
ISRN Virology Article ID 397243, 12 pages doi 10.5402/2013/397243

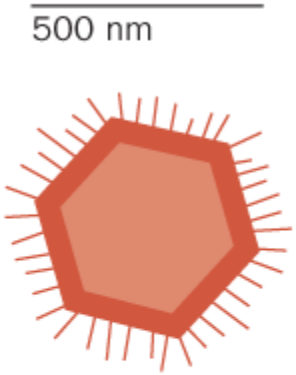
Megavirales

Pandoravirus salinus

Base pairs:
2.5 million

Length:
1,000 nm

Diameter:
500 nm



Megavirus chilensis

Base pairs:
1.26 million

Diameter:
500 nm

Influenza type A

Base pairs:
13,500

Diameter:
100 nm

The third biggest virus is ***Phycodnavirus.***
Infecting algae
Double stranded DNA
Size = 250-560 kbp
(Mimivirus = 1181 kbp)

A phycodnavirus at cell surface

Received 21 Mar 2014 | Accepted 30 May 2014 | Published 27 Jun 2014

DOI: 10.1038/ncomms5268

Plant genomes enclose footprints of past infections by giant virus relatives

Florian Maumus[1,*], Aline Epert[2], Fabien Nogué[2] & Guillaume Blanc[3,*]

nature COMMUNICATIONS

Chlorovirus ATCV-1 is part of the human oropharyngeal virome and is associated with changes in cognitive functions in humans and mice

www.pnas.org/cgi/doi/10.1073/pnas.1418895111

Robert H. Yolken[a,1], Lorraine Jones-Brando[a], David D. Dunigan[b], Geetha Kannan[c], Faith Dickerson[d], Emily Severance[a], Sarven Sabunciyan[a], C. Conover Talbot Jr.[e], Emese Prandovszky[a], James R. Gurnon[b], Irina V. Agarkova[b], Flora Leister[a], Kristin L. Gressitt[a], Ou Chen[a], Bryan Deuber[a], Fangrui Ma[b], Mikhail V. Pletnikov[c], and James L. Van Etten[b,1]

Thank you for your attention