

Viral vector systems in molecular biology – risk assessment and literature survey

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Summary

Importance of viral vector systems	Viral vector systems (VVS) are widely used in molecular biology for the transfection of DNA or RNA in eukaryotic cells, or for the genetic modification of eukaryotic cells. These transfection systems are extremely complex and serve <i>inter alia</i> to study the function of genes or their regulation at the level of individual cells or also of multicellular organisms.
Content and Objective	This document focuses on safety in the use of viral vector systems in molecular biology laboratories and considers the assessment of biological risks from the viewpoint of human health when working with these systems. The aim of this document is to put together a matrix for the required information in order to optimise the responsible identification and assessment of risks when handling viral vector systems. The electronic links to a great number of information sources, including a number of official guidelines and recommendations, which are regularly adapted to the current issues of viral vector systems, are organised by key topics in a tabular overview. This information from various universities, state and private databanks enable data to be completed for the notification of an activity with viral vector systems in a closed system.
Target groups	This document is intended to support the public authorities as well as researchers. The public authorities should be supported in their task of reviewing the project proposals with viral vector systems in regard to their risk as well as in the correct assignment to the corresponding activity class and safety level. Project leaders in research are responsible for risk identification and risk assessment, work safety and health protection of their employees and have to take the adapted safety measures.
Components of a viral vector system	Viral vector systems can be subdivided into two parts (that themselves consist of various components): A) the viral vector and B) the components, such as helper plasmids and packaging cells, required for the production of the viral vector. The interactions between all of these subsystems in the VVS are of importance for biological safety.
Separating essential genes and eliminating non-essential sequences	A central aspect of the safety of VVS is firstly the attenuation of the viral vector and secondly, for its production, the physical division of the essential genes on helper plasmids and/or helper sequences in the packaging cells. In addition to this, the homologies between the sequence of the viral vector (incl. insert) and the helper plasmids and helper sequences in the packaging cells are to be limited to a minimum.
Narrow host spectrum increases safety	The host spectrum of VVS can either be chosen to be specifically narrow (ecotropic, in particular when human cells cannot be infected) or deliberately broad (amphotropic, e.g. human and other cells): a narrow host spectrum is safer because the probability of accidental laboratory infection is lower.

Risk identification/assessment and classification of the activity	The risk of the activity with a VVS can be determined in particular on the basis of the following characteristics: 1.) original virus 2.) host spectrum 3.) cell tropism 4.) replication capacity 5.) ability to integrate into the host genome 6.) extent of the deletions of the viral gene 7.) capacity for self-inactivation 8.) packaging cells and number of helper plasmids 9.) risk potential of the insert 10.) transfection of cells <i>in vitro</i> or <i>in vivo</i> .
Responsibility of the project leaders	Pursuant to ContainO, project leaders of research are responsible for recognising health risks, for taking adapted security measures and consequently to determine the classification of the activity.

Note

Abstract of study	The present document is an extract from a study by the KÜNG Biotech & Umwelt Company from 2011. The study is 68 pages long.
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1 Objective

This document is concerned with the risk identification and risk assessment of viral vector systems (VVS) from the viewpoint of biological safety, and focuses on human health. Pursuant to the Ordinance on the Contained Use of Organisms (Containment Ordinance ContainO, SR 814.912), the project leaders have to determine and assess the health risks in order to then decide under their own responsibility on the safety measures to be taken and therefore the classification of the activity. In this connection, the Ordinance on Protection of Employees from Dangerous Microorganisms (PEMO, SR 832.321) is also significant.

The aim of the document is to put together the fundamentals in order to facilitate and optimise competent risk identification and risk assessment of VVS.

2 Importance and use of viral vector systems

VVS serve to introduce genetic information (DNA or RNA) into eukaryotic cells. This allows gene functions or their regulations to be studied and for example novel therapeutic products or therapies to be developed in connection with gene therapy, cancer therapy and vaccination. This is possible at the level of individual cells or also multicellular organisms.

The original viruses for VVS originate from few families. The most important representatives belong to the family of the *Retroviridae* (e.g. Lentiviruses) and the *Adenoviridae*. Further representatives originate from the family of the *Parvoviridae*, the *Herpesviridae* (e.g. Herpes-Simplex viruses), *Poxviridae* (e.g. NYVAC, ALVAC), *Paramyxoviridae* and *Togaviridae* (e.g. Semliki-Forest virus).

Besides the VVS there are also non-viral, chemical and physical methods for inserting DNA into a cell or into a cell nucleus. These will not be discussed here.

VVS can be divided into at least two groups:

1. New VVS that are developed in research groups with extensive knowledge in virology, immunology and pathology.
2. Systems from VVS produced in-house or from commercial kits which are already established in research and for which, extensive information on risks and safety are available, but in which, the risk identification and risk assessment must nevertheless not be neglected in the practical application.

3 Components of a VVS

Viral vector systems can be subdivided into the following components: A) the viral vector: 1.) an attenuated virus, generally for various functions and derived from a specific wild type or vaccine strain (depending on the virus consisting of DNA or RNA genome, viral enzymes and various matrix and/or envelope proteins, and 2.) the insert/s in the viral genome with specifically selected functions from a donor organism, B) the components needed to produce the viral vector: 3.) helper plasmids with functions for the production of the VVS which were deleted on the vector plasmid, 4.) packaging cells for the production of the VVS and based on the genetic information on the plasmids and at best on genetic information in the cell genome.

4 Biological risks

4.1 Pathogenic viruses as the starting system for viral vectors

Human or animal pathogenic wild type viruses or viruses that serve as vaccines are preferably selected as the starting vectors for the development of VVS, because these are naturally capable of infecting or transfecting human or animal cells.

In order to be able to use pathogenic viruses as the VVS, one has to remove their pathogenic characteristics to the greatest possible extent. The aim is to attenuate (deactivate) these viruses in such a way that they can transfect cells as efficiently as possible without causing negative effects such as cell death, cell malfunction, cell proliferation or the like.

Viral vectors can be attenuated by just a few steps. Thus, for the majority of viral vectors on the viral genome, certain functions are removed first of all, such that after the first transfection with VVS, further infectious viral particles can no longer be formed (replication deficiency), for example for adenoviruses by removing the E1 region or for lentiviral vectors by the deletion of the sequences for envelope proteins (e.g. glycoprotein G120). *Gutless* vectors form particularly safe vectors. With adenoviruses for example, only the packaging and transcription signals of the viral DNA on the genome as well as a few non-coding sequences are fundamentally still found in a *gutless vector*.

In the development of VVS, the aims of the performed changes at the level of the virus genome in regard to biological safety are e.g.

- to specifically eliminate or control the ability to replicate and/or infect.
- to eliminate the pathogenicity factors and the non-essential vector characteristics.

4.2 Fragmentation of the functional units of the viral genome for the production of the VVS and elimination of non-essential viral sequences

For the production of VVS, the principle of physically splitting a virus genome into as many different plasmids as possible and if need be the packaging cell genome, reduces the probability that viral particles with a complete viral genome are produced by recombination. This increases the biological safety of the system. Simultaneously, as far as possible, all non-essential viral genes for the vector function are deleted (avoidance of homologous recombination events or cytotoxic effects).

In general, the following, important characteristics are physically separated from one another:

- function for the infection of a cell: this concerns the structural genes for packaging proteins or the envelope proteins and therefore their ability to insert themselves into a cell
- replication function: this concerns the genes for the DNA and/or RNA replication
- packaging signal (located on the vector plasmid)

For some lentiviral vector systems a differentiation is made for example between first, second and third generation systems. In the third generation systems the various functional virus sequences are distributed on three to four plasmids.

4.3 Self-inactivating VVS

In the so-called self-inactivating VVS (SIN) the U3 sequence in the *long terminal repeats* (LTR) which has transcriptional characteristics is deleted. In self-inactivating VVS, their reproductive capability is strongly reduced after the first transfection of cells.

Self-inactivating VVS have various positive effects in regard to biosafety:

1. The promoter activity is reduced to 10 % of the original activity and consequently also the transcription of neighbouring genes at the insertion point; the probability for *insertional oncogenesis* is diminished.
2. The probability of recombination between vector plasmid and packaging sequences is diminished.
3. The mobilisation of the vector insert sequences inserted in the genome is reduced.

4.4 Pseudotyping to restrict tropism

The host spectrum of VVS is determined by those surface proteins that have to dock onto the host cells.

The host spectrum of VVS can be specified by means of pseudotyping, i.e. restricted or enlarged. For that purpose, when producing the VVS, the vector genome is enveloped with packaging proteins that originate from another virus type. The resulting VVS thereby comprises a tropism adapted to the host cells being transfected.

The glycoproteins of the vesicular stomatitis virus (VSV-G) are used very frequently. If the vector plasmid DNA is packed into the VSV-G that is made available *in trans* by a packaging cell, then the VVS becomes amphotropic, i.e. it possesses a broad host spectrum.

4.5 Function of the insert DNA

The risk assessment of a VVS also concerns the evaluation of the insert, in particular also the gene products (proteins) with the possible effects on the cell regulation.

If DNA sequences (e.g. regulation sequence, regulation protein, toxin, epitope, enzyme, structural protein) are inserted as a functional and expressible unit into the genome of a viral vector, then they have to be more exactly considered by bearing in mind the involved components of the VVS in regard to the possible effects and risks. Two classes of inserts, for which it is reasonable to be particularly prudent, are cytokines and oncogenes (cf. Recommendations of the EFBS on "Risk assessment of activities using oncogenic and cytokine-encoding sequences")¹. The same applies to experiments with RNA interference, e.g. if the target gene is a tumour suppressor gene or if the interference can lead to severe metabolic defects.

4.6 Integration capacity

The characteristic that allows a viral vector genome to be integrated into the genome of the host cell means that retroviral vector systems (especially lentiviral vector systems) are attractive, because they also enable a continuous expression. However, the integration does not always occur randomly in the genome, rather preferably in transcriptionally active genes; this can increase the probability for an insertional mutagenesis (e.g. suppression of the expression of a tumour suppressor gene) and/or for a transactivation of the neighbouring gene.

¹ <http://www.efbs.admin.ch/de/dokumentation/empfehlungen/index.html>

5 Matrix for information on the risk assessment and classification of the activity

The following table 1 contains a summary of the required information for a VVS (incl. insert), in order to be able, based on this, to carry out the classification of the activity - and hence the risk assessment. This implicitly gives a list of relevant assessment aspects and criteria, which should be subsequently integrated in the notification procedure of the Containment Ordinance (notification form).

Table 1: Characteristics, Risk appraisal & Classification

Key: Host spectrum/tropism: M: human, P: primates, without human. N: rodent, *murin*, K: cats *feline*, V: bird *avian*, A: other, mammal; other.

Characteristics		host spectrum tropism						Notes
		M	P	N	K	V	A	
1	Wild type virus incl. risk group							Source is from human pathogen or zoonotic virus. This may increase the risk for humans (e.g. if attenuations can be complemented by contaminations/recombination).
2	Replication-competent VVS	yes / no						Replication competency generally increases the risk.
3	Replication-incompetent VVS	yes / no						Replication-incompetent VVS generally lower the risk. The degree of replication incompetency must be taken into account in the risk assessment.
4	Gutless VVS (residual viral DNA?)	yes / no						
5	Generation of ecotropic VVS							VVS can have various surface proteins that lead to different tropisms ("pseudotype viral vectors"). Ecotropic VVS have a narrow host spectrum. This is usually risk-mitigating.
6	Generation of amphotropic VVS							In contrast to ecotropic VVS, the amphotropic VVS has a broad host spectrum. This usually increases risk.
7	Pseudotyping (sequence and source?)	yes / no						
8	Characterised cell lines as target cells	yes / no						Characterised cell lines are well-defined and can mostly be classified into risk group 1. Exceptions are cells that contain pathogenic organisms (e.g. cell lines immortalised with EBV).
9	Primary cells	yes / no						If primary cells are used as target cells then the

	as target cells ²		risk is increased, because the biological safety system of the vector can perhaps be complemented by the presence of a wild-type virus.
10	Target cell types (cell tropism)		The risk is increased in activities with VVS that can infect human cells. In addition, the considerations analogous to those under point 7 apply.
11	Additional components		Those additional sequences that increase the probability of recombination in the host genome are of importance.
12	System for the production of the VVS (helper viruses, number of plasmids, complementing by packaging cell lines)		At the level of the virus genome the biological safety measures aim to enhance 1.) to control or to eliminate the ability to replicate and/or infect and 2.) to eliminate the pathogenicity factors and the non-essential vector characteristics.
13	Integration of the viral genome into the target cell genome.	yes / no	Are possible effects expected from insertional mutagenesis? (e.g. increased expression of neighbouring host genes, deactivation of host genes)
14	Inserts (origin and function)		Cytokine-, toxin- or oncogene-coding sequences can increase the risk.
15	Sensitive/resistant against vaccines, antiviral agents	yes / no which	Sequences from (other) human pathogenic organisms can increase the risk (for example by transferring resistance to antibiotics).
Risk assessment of the VVS			
Group:			
Classification of the activity			
Class:			

² SECB Recommendation on the safe handling of human and animal cells and cell cultures; May 2010; <http://www.efbs.admin.ch/de/dokumentation/empfehlungen/index.html>

6 Information sources, Guidelines and Databanks

This chapter references various information sources and databanks that serve to complement and extend the documentation of a project proposal.

Incorporating the information databases enables data to be completed and critical aspects to be checked in a project notification or in an application for authorisation.

Table 2: Information sources and databanks on vectors, selected inserts and cell lines

External Information sources			
Components of the VVS	Specifics	Link	Source
Vector	<i>Map, host spectrum source</i>	Vector-Databank http://apps2.bvl.bund.de/vectorwww/protected/main/vector.do	ZKBS*
		The Vector Core http://www.med.umich.edu/vcore/	University of Michigan
		Lentiviral Vectors http://tronolab.epfl.ch/	EPFL, Trono's Lab, Lausanne
		Retroviral Vectors https://web.stanford.edu/group/nolan/_OldWebsite/retroviral_systems/retsys.html	Stanford University
Insert	<i>Oncogenes, tumour genes potential</i>	Genes in cancer http://atlasgeneticsoncology.org/Genes/Geneliste.html	University Hospital Poitiers, France
		Oncogene-Databank http://apps2.bvl.bund.de/oncogene/protected/main/index.do	ZKBS*
Packaging cell lines (factors <i>in trans</i>)	<i>Host spectrum of the virions</i>	New England Biolabs	commercial suppliers, search by vector name
Virion		Aldevron Clontech ThermoFisher Nolan Lab	
		Novagen (Merck) Pharmingen (BD Bioscience) Promega MP biomedical (Qbiogene) Agilent technologies (Stratagene)	
Cell lines (target cells or donor cells)	<i>Characterisation, classification and inserted viral sequences</i>	Cell line-Databank http://apps2.bvl.bund.de/cellswww/protected/main/cell.do	ZKBS*
		ATCC: http://www.lgcpromochem-atcc.com ECACC: http://www.phe-culturecollections.org.uk/ DSMZ: http://www.dsmz.de ICLC: http://www.iclc.it/indexpi.html	Culture collections
		*Zentrale Kommission für die Biologische Sicherheit	

National and international guidelines and recommendations

There are a number of guidelines and recommendations that are regularly updated for the essential issues of VVS. These documents are generally concerned with the standardised classifications of risk groups, classes of activities and safety levels.

Table 3: Guidelines and recommendations

Guidelines and Recommendations			
Institution, country	Key Aspect	Title	Year
Switzerland EFBS; Link	Activity class and safety level	SECB Recommendation on the safe handling of human and animal cells and cell cultures	May 2010
	Activity class and safety level	Recommendation of the SECB on the classification of work with genetically modified viral vectors	December, 2009
	Oncogenes and cytokines	Risk assessment of activities with oncogenic and cytokine-encoding sequences	1 June 2005
ZKBS Link			
Switzerland: swissmedic; Link	Environmental data; gene therapy	Guidance on how to prepare documentation on the possible risks for humans and the environment (environmental data) in the context of authorisation applications for clinical testing of somatic gene therapy and with medicaments that comprise genetically modified microorganisms.	27.11.09
EUROPEAN MEDICINES AGENCY; EMA	Live recombinant viral vectored vaccine, heterologous antigen (with keyword links)	Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines	valid from 1.1.2011
Great Britain: Health and Safety Executive, HSE	Activity class, safety level and detailed information on wild type viruses and vectors derived therefrom	Part 1: Introduction to the legislation and general health and safety issues	01/07
		Part 2: Risk assessment of genetically modified microorganisms (other than those associated with plants)	01/07
Belgian Biosafety Server; BBS	Activity class, safety level and information on VVS, role of the insert; cell cultures	Risks associated with the use of viral vectors, inserts or cellular cultures	4 June 2004
Australia: Office of Gene Technology Regulator, DHA; Link	Activity class and safety level; detailed risk assessment	Review of the Gene Technology Regulations 2001; Discussion Paper No. 3 (2010); Review of the Classification of Dealings with Viral Vectors	2010
		Guidance on classification of contained dealings with viral vectors	2007

Guidelines and Recommendations			
Institution, country	Key Aspect	Title	Year
Germany: Federal Office for Consumer protection and Food safety BVL; Link	Risk assessment	Recommendation by the ZKBS for the risk assessment of paramyxo viruses, adenoviruses, reoviruses, iridoviruses and herpes viruses from reptiles as the donor or recipient organism for genetic engineering work pursuant to § 5 para 1 GenTSV	October 2009
	Background, grouping and safety level	General opinion of the ZKBS on frequently carried out genetic engineering work with the basic criteria of comparability: Gene transfer with the help of retroviral vectors	October 2007
Germany: Federal Office for Consumer protection and Food safety BVL; Link	Safety measures	General opinion of the ZKBS on safety measures when handling retroviruses of the risk group 3**	1. mod. text of September 2007
	Risk group	Opinion of the ZKBS on the risk assessment of human adeno-associated viruses and AAV-derived vectors	December 2005
	Safety level and particular measures for work safety	Recommendation of the ZKBS on adenoviral and AAV-derived replication-defective vectors with cell cycle regulating genes	December 2004
		Safety measures for genetic engineering work with adenoviral vectors that transfer cell cycle activating genes	December 2003
CA: University of Western Ontario UWO; Link	Classes of activity, safety measures and particular measures for work safety	Policy on Research Utilizing Virus Vector Transduced Cells or Virus Infection of Animals (Version 5)	June 2009
USA: RAC-NIH; Link	Lentiviral Vectors	Biosafety Considerations for Research with Lentiviral Vectors <i>Recombinant DNA Advisory Committee (RAC) Guidance Document</i>	2006
USA: Stanford University; Link	Detailed info on the source viruses of the vectors and recommendations for safety levels (keyword links)	Working with Viral Vectors	?
USA: University of Washington, EHS; Link	Safety levels, disinfection and tests for replication capability	Viral Vectors for Gene Transfer	September 2009

7 Selected literature grouped by search terms

Main keywords for the following literature survey

The following literature list is organised with each of the selected keywords. The preselection is generally based on:

- Selection with *viral vector system*
 - Publications *after 2005*
 - *Review* article
- ➔ **Based on this preselection, further searching was carried out with each of the keywords designated as the sub-heading.**

Significant Publications

- Progress and prospects: immune responses to viral vectors (2010) [5]
- Lentiviral vectors with measles virus glycoproteins - dream team for gene transfer? (2009) [6]
- State-of-the-art lentiviral vectors for research use: risk assessment and biosafety recommendations (2009) [7]
- Reassortment between avian H5N1 and human H3N2 influenza viruses in ferrets: a public health risk assessment (2009) [8]
- Design and production of retro- and lentiviral vectors for gene expression in hematopoietic cells (2009) [9]
- Oncolytic virus therapy using genetically engineered herpes simplex viruses (2008) [10]
- The design of vectors for RNAi delivery system (2008) [11]
- A natural human retrovirus efficiently complements vectors based on murine leukemia virus (2008) [12]
- Replicating and non-replicating viral vectors for vaccine development. (2007) [13]
- Lentivirus as a potent and mechanistically distinct vector for genetic immunization. (2007) [14]
- Gene delivery by lentivirus vectors (2007) [15]
- HSV-1 amplicon vectors: a promising and versatile tool for gene delivery (2007) [16]
- The state of the art of adeno-associated virus-based vectors in gene therapy. (2007) [17]
- Lentiviral vectors pseudotyped with murine ecotropic envelope: increased biosafety and convenience in preclinical research (2006) [18]
- Gene therapy progress and prospects: development of improved lentiviral and retroviral vectors-design, biosafety and production. (2005) [19]
- Toolbox for retrovectorologists (2004) [20]
- Biosafety of lentiviral vectors (2003) [21]
- Retroviral Vector Biosafety: Lessons from Sheep (2003) [22]

Biosafety / improvements in safety or improved safety

Biosafety

Study of Andes virus entry and neutralization using a pseudovirion system (2010) [23]

- Toward integrase defective lentiviral vectors for genetic immunization (2010) [24]
- Lentiviral vectors for immunization: an inflammatory field (2010) [25]
- State-of-the-art lentiviral vectors for research use: risk assessment and biosafety recommendations (2009) [7]
- Design and production of retro- and lentiviral vectors for gene expression in hematopoietic cells (2009) [9]
- In vivo biosafety model to assess the risk of adverse events from retroviral and lentiviral vectors (2008) [26]
- Oncolytic virotherapy (2008) [27]
- Lentivirus as a potent and mechanistically distinct vector for genetic immunization. (2007) [14]
- Lentiviral vectors pseudotyped with murine ecotropic envelope: increased biosafety and convenience in preclinical research (2006) [18]
- Intracellular trafficking of retroviral vectors: obstacles and advances (2005) [28]
- Genetic modification of hematopoietic stem cells with nonviral systems: past progress and future prospects. (2005) [29]
- Gene therapy progress and prospects: development of improved lentiviral and retroviral vectors--design, biosafety, and production. (2005) [19]
- Toolbox for retrovectorologists (2004) [20]
- Construction and isolation of recombinant MVA (2004) [30]
- Biosafety of lentiviral vectors (2003) [21]
- HIV-1 vectors: fulfillment of expectations, further advancements, and still a way to go. (2003) [31]
- Vaccinia vectors as candidate vaccines: the development of modified vaccinia virus Ankara for antigen delivery (2003) [32]
- Retroviral Vector Biosafety: Lessons from Sheep (2003) [22]
- Lentiviral vectors: turning a deadly foe into a therapeutic agent. (2000) [33]
- Two-helper RNA system for production of recombinant Semliki forest virus particles (1999) [34]

Improvements in safety or improved safety

- Self-inactivating alpharetroviral vectors with a split-packaging design (2010) [2]
- Recombinant baculovirus as a highly potent vector for gene therapy of human colorectal carcinoma: molecular cloning, expression, and in vitro characterization (2010) [35]
- Oncolytic virus therapy using genetically engineered herpes simplex viruses (2008) [10]
- Immunity to adeno-associated virus vectors in animals and humans: a continued challenge (2008) [36]
- The state of the art of adeno-associated virus-based vectors in gene therapy (2007) [37]
- Integrase defective, nonintegrating lentiviral vectors (2010) [38]

- Gene delivery by lentivirus vectors (2007) [15]

Guidelines + safety considerations

Regulatory requirement or guidelines or recommendation

- State-of-the-art lentiviral vectors for research use: risk assessment and biosafety recommendations (2009) [7]
- Release testing of retroviral vectors and gene-modified cells (2009) [39]
- The US and EU regulatory perspectives on the clinical use of hematopoietic stem/progenitor cells genetically modified ex vivo by retroviral vectors (2009) [40]
- Detection of replication competent retrovirus and lentivirus (2009) [41]
- Gene therapy: targeting the myocardium. (2008) [42]
- An inventory of shedding data from clinical gene therapy trials. (2007) [43]
- Lentiviral vectors pseudotyped with murine ecotropic envelope: increased biosafety and convenience in preclinical research (2006) [18]

Review + safety

- Viral vector-mediated gene transfer for CNS disease (2010) [44]
- Viral vector approaches to modify gene expression in the brain (2009) [45]
- Oncolytic virus therapy using genetically engineered herpes simplex viruses (2008) [10]
- State-of-the-art lentiviral vectors for research use: risk assessment and biosafety recommendations (2009) [7]
- Release testing of retroviral vectors and gene-modified cells (2009) [39]
- Use of HIV as a gene transfer vector (2009) [46]
- Retrovirus-induced oncogenesis and safety of retroviral vectors (2008) [47]
- rAAV vector-mediated gene therapy for experimental ischemic stroke. (2008) [48]
- The design of vectors for RNAi delivery system (2008) [11]
- Replicating and non-replicating viral vectors for vaccine development. (2007) [13]
- Lentivirus as a potent and mechanistically distinct vector for genetic immunization. (2007) [14]
- An inventory of shedding data from clinical gene therapy trials. (2007) [43]
- The continuing contribution of gene marking to cell and gene therapy. (2007) [49]
- The state of the art of adeno-associated virus-based vectors in gene therapy. (2007) [17]

Co-infection / Reassortment / Complementation

Coinfect or co-infect

- Efficient inhibition of hepatitis B virus replication by hepatitis delta virus ribozymes delivered by targeting retrovirus (2010) [50]
- Mixed infections of pandemic H1N1 and seasonal H3N2 viruses in 1 outbreak (2010) [51]
- Enhanced oncolytic activity of vesicular stomatitis virus encoding SV5-F protein against prostate cancer (2010) [52]
- AAV-directed muscular dystrophy gene therapy (2010) [53]

- Feline immunodeficiency virus vector as a tool for preventative strategies against human breast cancer (2010) [54]
- Adeno-associated viral vector serotypes 1 and 5 targeted to the neonatal rat and pig striatum induce widespread transgene expression in the forebrain (2010) [55]
- Secretory expression of porcine interferon-gamma in baculovirus using HBM signal peptide and its inhibition activity on the replication of porcine reproductive and respiratory syndrome virus (2009) [56]
- HSV as a vector in vaccine development and gene therapy (2009) [57]
- HIV-1 derived peptides fused to HBsAg affect its immunogenicity (2009) [58]
- Large-scale adeno-associated viral vector production using a herpesvirus-based system enables manufacturing for clinical studies (2009) [59]
- Insertional mutagenesis and development of malignancies induced by integrating gene delivery systems: implications for the design of safer gene-based interventions in patients (2009) [60]
- Immunity to adeno-associated virus vectors in animals and humans: a continued challenge (2008) [36]
- Reassortment between avian H5N1 and human H3N2 influenza viruses in ferrets: a public health risk assessment (2009) [8]
- Bluetongue virus: dissection of the polymerase complex (2008) [61]
- A natural human retrovirus efficiently complements vectors based on murine leukemia virus (2008) [12]
- Analysis of Venezuelan equine encephalitis replicon particles packaged in different coats (2008) [62]
- Development and preclinical evaluation of an alphavirus replicon particle vaccine for cytomegalovirus (2007) [63]
- Development and characterization of a recombinant cDNA-based hepatitis C virus system (2007) [64]
- Use of a Beet necrotic yellow vein virus RNA-5-derived replicon as a new tool for gene expression (2005) [65]
- An efficient and versatile mammalian viral vector system for major histocompatibility complex class I/peptide complexes. (2002) [66]

Recombination event

- Detection of replication competent retrovirus and lentivirus (2009) [41]
- Reactivation of an integrated disabled viral vector using a Cre-loxP recombination system in *Arabidopsis thaliana* (2007) [67]
- Plasmid-only rescue of influenza A virus vaccine candidates (2001) [68]

Reassortment

- Reassortment between avian H5N1 and human H3N2 influenza viruses in ferrets: a public health risk assessment (2009) [8]

Complement

- Enhanced oncolytic activity of vesicular stomatitis virus encoding SV5-F protein against prostate cancer (2010) [52]
- Antigen fusion with C3d3 augments or inhibits humoral immunity to AAV genetic vaccines in a transgene-dependent manner (2010) [69]
- Transient expression of herpes simplex virus type 1 ICP22 represses viral promoter activity and complements the replication of an ICP22 null virus (2009) [70]
- Bluetongue virus: dissection of the polymerase complex (2008) [61]
- A natural human retrovirus efficiently complements vectors based on murine leukemia virus (2008) [12]
- Development and characterization of a recombinant cDNA-based hepatitis C virus system (2007) [64]
- Construction and characterization of efficient, stable and safe replication-deficient foamy virus vectors (2007) [71]
- Production of recombinant adeno-associated viral vectors for in vitro and in vivo use (2007) [72]
- High-efficiency system for the construction of adenovirus vectors and its application to the generation of representative adenovirus-based cDNA expression libraries (2006) [73]
- Identification of 5' and 3' cis-acting elements of the porcine reproductive and respiratory syndrome virus: acquisition of novel 5' AU-rich sequences restored replication of a 5'-proximal 7-nucleotide deletion mutant (2006) [74]
- Replication-defective genomic HSV gene therapy vectors: design, production and CNS applications (2005) [75]
- Targeting specific neuronal populations using adeno- and lentiviral vectors: applications for imaging and studies of cell function (2005) [76]
- Lentivirus-mediated gene transfer to the respiratory epithelium: a promising approach to gene therapy of cystic fibrosis. (2004) [77]

Modifications in the Host Range

Tropism + Pseudotyping

- Different potential of C-type lectin-mediated entry between Marburg virus strains (2010) [78]
- Viral vector-mediated gene transfer for CNS disease (2010) [44]
- Capsid protein of cowpea chlorotic mottle virus is a determinant for vector transmission by a beetle (2010) [79]
- Study of Andes virus entry and neutralization using a pseudovirion system (2010) [23]
- Introduction of shRNAs into primary NK cells with lentivirus (2010) [80]
- Efficient inhibition of hepatitis B virus replication by hepatitis delta virus ribozymes delivered by targeting retrovirus (2010) [50]
- Targeting lentiviral vector to specific cell types through surface displayed single chain antibody and fusogenic molecule (2010) [81]
- Viral vector approaches to modify gene expression in the brain (2009) [45]

- Molecular evolution of adeno-associated virus for enhanced glial gene delivery (2009) [82]
- Lentiviral vectors with measles virus glycoproteins - dream team for gene transfer? (2009) [6]
- How HIV changes its tropism: evolution and adaptation? (2009) [83]
- Analysis of human immunodeficiency virus type 1 vector cis- and trans-acting elements production by means of Semliki Forest virus (2009) [84]
- Rafts, anchors and viruses--a role for glycosylphosphatidylinositol anchored proteins in the modification of enveloped viruses and viral vectors (2008) [85]
- Analysis of Venezuelan equine encephalitis replicon particles packaged in different coats (2008) [62]
- Core protein domains involved in hepatitis C virus-like particle assembly and budding at the endoplasmic reticulum membrane (2007) [86]
- Lentiviral vectors pseudotyped with murine ecotropic envelope: increased biosafety and convenience in preclinical research (2006) [18]
- Altering the tropism of lentiviral vectors through pseudotyping (2005) [3]
- Gene therapy progress and prospects: development of improved lentiviral and retroviral vectors--design, biosafety, and production. (2005) [19]
- Targeting specific neuronal populations using adeno- and lentiviral vectors: applications for imaging and studies of cell function (2005) [76]

Chimeric Vector

- Feline leukemia virus integrase and capsid packaging functions do not change the insertion profile of standard Moloney retroviral vectors (2010) [87]
- Capsid protein of cowpea chlorotic mottle virus is a determinant for vector transmission by a beetle (2010) [79]
- Recovery of infectious foot-and-mouth disease virus from full-length genomic cDNA clones using an RNA polymerase I system (2009) [88]
- Sleeping beauty transposition from nonintegrating lentivirus (2009) [89]
- Long-term protection in hamsters against human parainfluenza virus type 3 following mucosal or combinations of mucosal and systemic immunizations with chimeric alphavirus-based replicon particles (2007) [90]
- Chimeric herpes simplex virus/adeno-associated virus amplicon vectors (2006) [91]
- Therapy of cancer by cytokines mediated by gene therapy approach (2006) [92]
- Herpesvirus/retrovirus chimeric vectors (2004) [93]

Biologically active Inserts / Cytokine / DNA-Vaccine

(Cancer) Immunotherapy

- Feline immunodeficiency virus vector as a tool for preventative strategies against human breast cancer (2010) [54]
- HVJ envelope vector, a versatile delivery system: its development, application, and perspectives (2008) [94]
- HSV-1 amplicon vectors: a promising and versatile tool for gene delivery (2007) [16]

- [mRNA-transfected dendritic cells: a promising strategy in immunotherapy] (2007) [95]
- Amplicons as vaccine vectors (2006) [96]
- Recombinant alphaviruses as vectors for anti-tumour and anti-microbial immunotherapy (2006) [97]
- Genetically modified dendritic cells for cancer immunotherapy (2005) [98]
- A novel viral system for generating antigen-specific T cells (2005) [99]
- Boosting with recombinant vaccinia increases HPV-16 E7-Specific T cell precursor frequencies and antitumor effects of HPV-16 E7-expressing Sindbis virus replicon particles (2003) [100]
- An efficient and versatile mammalian viral vector system for major histocompatibility complex class I/peptide complexes. (2002) [66]

Oncolytic (virotherapy)

- Enhanced oncolytic activity of vesicular stomatitis virus encoding SV5-F protein against prostate cancer (2010) [52]
- Crossing the boundaries: stem cells and gene therapy (2010) [101]
- Enhanced cytotoxicity with a novel system combining the paclitaxel-2'-ethylcarbonate prodrug and an HSV amplicon with an attenuated replication-competent virus, HF10 as a helper virus (2010) [102]
- Medical application of herpes simplex virus (2010) [103]
- Adenoviral oncolytic suicide gene therapy for a peritoneal dissemination model of gastric cancer in mice (2010) [104]
- A three-plasmid system for construction of armed oncolytic adenovirus (2009) [105]
- A three-plasmid system for construction of armed oncolytic adenovirus (2009) [105]
- Oncolytic virus therapy using genetically engineered herpes simplex viruses (2008) [10]
- Therapy of cancer by cytokines mediated by gene therapy approach (2006) [92]
- Oncolytic virotherapy (2008) [27]
- Replication-competent retrovirus vectors for cancer gene therapy (2008) [106]
- The design of vectors for RNAi delivery system (2008) [11]
- A new recombinant vaccinia with targeted deletion of three viral genes: its safety and efficacy as an oncolytic virus (2007) [107]
- p53-expressing conditionally replicative adenovirus CNHK500-p53 against hepatocellular carcinoma in vitro. (2007) [108]
- Therapy of cancer by cytokines mediated by gene therapy approach (2006) [92]

Cancer + cytokin

- Amplicons as vaccine vectors (2006) [96]
- Therapy of cancer by cytokines mediated by gene therapy approach (2006) [92]

Immune response or DNA vaccine

- Toward integrase defective lentiviral vectors for genetic immunization (2010) [24]
- Antigen fusion with C3d3 augments or inhibits humoral immunity to AAV genetic vaccines in a transgene-dependent manner (2010) [69]

- Cell-penetrating DNA-binding protein as a safe and efficient naked DNA delivery carrier in vitro and in vivo (2010) [109]
- AAV-directed muscular dystrophy gene therapy (2010) [53]
- Viruses as vaccine vectors for infectious diseases and cancer (2010) [110]
- HIV-1 derived peptides fused to HBsAg affect its immunogenicity (2009) [58]
- Oncolytic virus therapy using genetically engineered herpes simplex viruses (2008) [10]
- Immunity to adeno-associated virus vectors in animals and humans: a continued challenge (2008) [36]
- The state of the art of adeno-associated virus-based vectors in gene therapy (2007) [37]
- Progress and prospects: immune responses to viral vectors (2010) [5]
- Integration-deficient lentiviral vectors: a slow coming of age (2009) [111]
- Current prospects for mRNA gene delivery (2009) [112]
- Genetic manipulation of corneal endothelial cells: transfection and viral transduction (2009) [113]
- DNA vaccines: developing new strategies to enhance immune responses (2008) [114]
- Analysis of Venezuelan equine encephalitis replicon particles packaged in different coats (2008) [62]
- Molecular engineering of viral gene delivery vehicles (2008) [115]
- Replicating and non-replicating viral vectors for vaccine development. (2007) [13]
- Development and preclinical evaluation of an alphavirus replicon vaccine for influenza (2007) [116]
- Lentivirus as a potent and mechanistically distinct vector for genetic immunization. (2007) [14]
- Immune responses to adenovirus and adeno-associated vectors used for gene therapy of brain diseases: the role of immunological synapses in understanding the cell biology of neuroimmune interactions (2007) [117]
- Cellular and humoral immune responses to alphavirus replicon vaccines expressing cytomegalovirus pp65, IE1, and gB proteins (2007) [118]
- [mRNA-transfected dendritic cells: a promising strategy in immunotherapy] (2007) [95]
- The state of the art of adeno-associated virus-based vectors in gene therapy. (2007) [17]
- Rational design of gene-based vaccines (2006) [119]

Insert expression or transgene expression

- Self-inactivating alpharetroviral vectors with a split-packaging design (2010) [2]
- Lentiviral vectors for immunization: an inflammatory field (2010) [25]
- Extending the transposable payload limit of Sleeping Beauty (SB) using the Herpes Simplex Virus (HSV)/SB amplicon-vector platform (2010) [120]
- Adeno-associated viral vector serotypes 1 and 5 targeted to the neonatal rat and pig striatum induce widespread transgene expression in the forebrain (2010) [55]
- Engineering multigene expression in vitro and in vivo with small terminators for T7 RNA polymerase (2009) [121]

- Insertional mutagenesis and development of malignancies induced by integrating gene delivery systems: implications for the design of safer gene-based interventions in patients (2009) [60]
- The state of the art of adeno-associated virus-based vectors in gene therapy (2007) [37]
- Stable expression of a foreign protein by a replication-competent rubella viral vector (2009) [122]
- Genetic manipulation of corneal endothelial cells: transfection and viral transduction (2009) [113]
- The expression of exogenous genes in macrophages: obstacles and opportunities (2009) [123]
- Retroviral gene transfer into primary human natural killer cells (2009) [124]
- Advances in high-capacity extrachromosomal vector technology: episomal maintenance, vector delivery, and transgene expression (2008) [125]
- Analysis of the effects of alterations in the tick-borne encephalitis virus 3'-noncoding region on translation and RNA replication using reporter replicons (2008) [126]
- Recombination-ready Sindbis replicon expression vectors for transgene expression (2007) [127]
- High-efficiency system for the construction of adenovirus vectors and its application to the generation of representative adenovirus-based cDNA expression libraries (2006) [73]
- Establishment and applications of Epstein-Barr virus-based episomal vectors in human embryonic stem cells (2006) [128]*
- Therapy of cancer by cytokines mediated by gene therapy approach (2006) [92]
- Use of herpes virus amplicon vectors to study brain disorders (2005) [129]

iRNA

- Lentiviral vector engineering for anti-HIV RNAi gene therapy (2010) [130]
- Cellular toxicity following application of adeno-associated viral vector-mediated RNA interference in the nervous system (2010) [131]
- Lentivirus production (2009) [132]
- The design of vectors for RNAi delivery system (2008) [11]
- Expression of short hairpin RNAs against the coxsackievirus B3 exerts potential antiviral effects in Cos-7 cells and in mice. (2007) [133]

Insertionsmutagenese

Insertional mutagenesis

- Hybrid lentiviral vectors (2010) [134]
- Integrase defective, nonintegrating lentiviral vectors (2010) [38]
- Insertional mutagenesis and development of malignancies induced by integrating gene delivery systems: implications for the design of safer gene-based interventions in patients (2009) [60]
- State-of-the-art lentiviral vectors for research use: risk assessment and biosafety recommendations (2009) [7]

- Insertional mutagenesis and development of malignancies induced by integrating gene delivery systems: implications for the design of safer gene-based interventions in patients. (2009) [135]
- Design and production of retro- and lentiviral vectors for gene expression in hematopoietic cells (2009) [9]
- In vivo biosafety model to assess the risk of adverse events from retroviral and lentiviral vectors (2008) [26]
- Gene delivery by lentivirus vectors (2007) [15]
- Gene therapy progress and prospects: development of improved lentiviral and retroviral vectors--design, biosafety, and production. (2005) [19]
- Safety concerns related to hematopoietic stem cell gene transfer using retroviral vectors. (2004) [136]

Retroviral integration site

- Detection of retroviral integration sites by linear amplification-mediated PCR and tracking of individual integration clones in different samples (2009) [137]
- Retrovirus-induced oncogenesis and safety of retroviral vectors (2008) [47]
- The continuing contribution of gene marking to cell and gene therapy. (2007) [49]
- Gene therapy progress and prospects: development of improved lentiviral and retroviral vectors--design, biosafety, and production. (2005) [19]
- Safety concerns related to hematopoietic stem cell gene transfer using retroviral vectors. (2004) [136]

Insertional oncogenesis

- The US and EU regulatory perspectives on the clinical use of hematopoietic stem/progenitor cells genetically modified ex vivo by retroviral vectors (2009) [40]
- Retrovirus-induced oncogenesis and safety of retroviral vectors (2008) [47]
- Retroviral gene therapy: safety issues and possible solutions. (2005) [138]

Reduced insertional mutagenesis

- Integration-deficient lentiviral vectors: a slow coming of age (2009) [111]
- Current prospects for mRNA gene delivery (2009) [112]
- Stem cell marking with promotor-deprived self-inactivating retroviral vectors does not lead to induced clonal imbalance (2009) [139]
- Recent advances in rational gene transfer vector design based on poly(ethylene imine) and its derivatives (2005) [140]

SIN (self inactivating vector)

- Self-inactivating alpharetroviral vectors with a split-packaging design (2010) [2]
- Adenoviral oncolytic suicide gene therapy for a peritoneal dissemination model of gastric cancer in mice (2010) [104]
- Insertional mutagenesis and development of malignancies induced by integrating gene delivery systems: implications for the design of safer gene-based interventions in patients. (2009) [135]

- Stem cell marking with promotor-deprived self-inactivating retroviral vectors does not lead to induced clonal imbalance (2009) [139]
- Design and production of retro- and lentiviral vectors for gene expression in hematopoietic cells (2009) [9]
- Construction and characterization of efficient, stable and safe replication-deficient foamy virus vectors (2007) [71]
- Retroviral gene therapy: safety issues and possible solutions. (2005) [138]
- Self-inactivating retroviral vectors with improved RNA processing (2004) [141]

Defective and non-integrative vectors (amplicons)

- HSV-1-derived amplicon vectors: recent technological improvements and remaining difficulties--a review (2009) [142]
- HSV-1 amplicon vectors: a promising and versatile tool for gene delivery (2007) [16]
- Chimeric herpes simplex virus/adeno-associated virus amplicon vectors (2006) [91]
- Amplicons as vaccine vectors (2006) [96]
- HSV-1 based amplicon vectors as an alternative system for the expression of functional HCV proteins (2006) [143]
- HSV-1 amplicon vectors are an efficient gene transfer system for skeletal muscle cells (2006) [144]
- HSV-1-based amplicon vectors: design and applications (2005) [145]
- Use of herpes virus amplicon vectors to study brain disorders (2005) [129]
- Herpesvirus/retrovirus chimeric vectors (2004) [93]

Chronic fatigue syndrome

- Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome (2009) [146]
- Virology. A new virus for old diseases? (2009) [147]
- Replication-defective genomic HSV gene therapy vectors: design, production and CNS applications (2005) [75]

Vaccinia

Vaccinia

- Generation of recombinant coronaviruses using vaccinia virus as the cloning vector and stable cell lines containing coronaviral replicon RNAs (2008) [148]
- A new recombinant vaccinia with targeted deletion of three viral genes: its safety and efficacy as an oncolytic virus (2007) [107]
- Use of dual recombinant vaccinia virus vectors to assay viral glycoprotein-mediated fusion with transfection-resistant primary cell targets (2004) [149]
- Boosting with recombinant vaccinia increases HPV-16 E7-Specific T cell precursor frequencies and antitumor effects of HPV-16 E7-expressing Sindbis virus replicon particles (2003) [100]

Vaccinia + biosafety

- Construction and isolation of recombinant MVA (2004) [30]
- Vaccinia vectors as candidate vaccines: the development of modified vaccinia virus Ankara for antigen delivery (2003) [32]

Adeno-associated Virus

- Progress and prospects: immune responses to viral vectors (2010) [5]
- AAV-directed muscular dystrophy gene therapy (2010) [53]
- Adeno-associated viral vector serotypes 1 and 5 targeted to the neonatal rat and pig striatum induce widespread transgene expression in the forebrain (2010) [55]
- Cellular toxicity following application of adeno-associated viral vector-mediated RNA interference in the nervous system (2010) [131]
- Optimized adeno-associated viral vector-mediated striatal DOPA delivery restores sensorimotor function and prevents dyskinesias in a model of advanced Parkinson's disease (2010) [150]
- Molecular evolution of adeno-associated virus for enhanced glial gene delivery (2009) [82]
- Large-scale adeno-associated viral vector production using a herpesvirus-based system enables manufacturing for clinical studies (2009) [59]
- Insertional mutagenesis and development of malignancies induced by integrating gene delivery systems: implications for the design of safer gene-based interventions in patients (2009) [60]
- Immunity to adeno-associated virus vectors in animals and humans: a continued challenge (2008) [36]
- Insertional mutagenesis and development of malignancies induced by integrating gene delivery systems: implications for the design of safer gene-based interventions in patients. (2009) [135]
- Adeno-associated virus-mediated gene delivery approaches for the treatment of CNS disorders (2008) [151]
- rAAV vector-mediated gene therapy for experimental ischemic stroke. (2008) [48]
- Adeno-associated virus (AAV)-mediated transduction of male germ line stem cells results in transgene transmission after germ cell transplantation (2008) [152]
- The gene delivery system for rheumatoid synovium. (2008) [153]
- The design of vectors for RNAi delivery system (2008) [11]
- The state of the art of adeno-associated virus-based vectors in gene therapy (2007) [37]
- Gene therapy: the first two decades and the current state-of-the-art (2007) [154]
- Immune responses to adenovirus and adeno-associated vectors used for gene therapy of brain diseases: the role of immunological synapses in understanding the cell biology of neuroimmune interactions (2007) [117]
- Production of recombinant adeno-associated viral vectors for in vitro and in vivo use (2007) [72]
- Targeting the heart with gene therapy-optimized gene delivery methods (2007) [155]
- The state of the art of adeno-associated virus-based vectors in gene therapy. (2007) [17]

- Virus-mediated gene transfer to induce therapeutic angiogenesis: where do we stand? (2007) [156]
- Viral vectors for gene delivery in tissue engineering (2006) [157]
- Chimeric herpes simplex virus/adeno-associated virus amplicon vectors (2006) [91]
- Genetically modified dendritic cells for cancer immunotherapy (2005) [98]
- Current issues in adeno-associated viral vector production (2005) [158]
- Gene targeting with viral vectors (2005) [159]
- AAV hybrid serotypes: improved vectors for gene delivery (2005) [160]
- Adeno-associated viral vectors for clinical gene transfer studies (2005) [161]
- Recombinant adeno-associated virus vector expressing angiostatin inhibits preretinal neovascularization in adult rats. (2005) [162]

Baculoviridae

- Bioprocessing of baculovirus vectors: a review (2010) [163]
- Recombinant baculovirus as a highly potent vector for gene therapy of human colorectal carcinoma: molecular cloning, expression, and in vitro characterization (2010) [35]
- Secretory expression of porcine interferon-gamma in baculovirus using HBM signal peptide and its inhibition activity on the replication of porcine reproductive and respiratory syndrome virus (2009) [56]

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