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Addendum COGEM report: Assessment of preclinical gene therapy studies worldwide *General information on oncolytic viruses*

Table of Contents

1 Order Caudovirales (bacteriophages)

1.1 General information

Bacteriophages represent a unique heterogeneous class of viruses that can infect bacteria and are the most abundant entities on earth. Their structure consists of a polyhedral or filamentous capsid protein encapsulating either DNA or RNA. This viral capsid is attached to a fiber tail, which is used to attach to bacterial cell surface receptors and to initiate translocation of the viral DNA into the host bacterium. Phages replicate in bacteria through a lytic (vigorous replication) or lysogenic (vegetative/integrating replication) life cycle. Bacteriophages are non-pathogenic for humans, due to the fact that cells of more complex organisms have major differences in cell-surface and intracellular machinery that do not support phage replication, even when artificially introduced into these eukaryotic cells [1]. Bacteriophages have been studied extensively, and initial molecular genetic discoveries regarding DNA, genetic codes, mRNA and gene regulation have been made in bacteriophages.

1.2 Preclinical research

Since bacteriophages cause lysis of bacterial cells, a lot of scientific research has focused on the use of these viruses as an alternative for antibiotic therapy to combat bacterial infections (phage therapy) [2-4], which is beyond the scope of this report.
Most phages possess a large packaging capacity, e.g. lambda vectors up to 53 kb and M13 vectors even undefined larger [5-7]. This not only allows for the insertion of large transgenes, but also of plasmid maintenance sequences like EBNA1/*oriP* and endogenous promoters for transgenes. Coat proteins of phages can be engineered or selected using phage display (see below) to incorporate targeting and cell internalization enhancing ligands, which is needed for efficient gene transfer to eukaryotic cells [8-11]. Using phage display libraries, bacteriophages can be genetically modified to express specific peptides or proteins fused to their capsid [12]. This technique can be useful to identify and produce large numbers of (new) tumor-targeting molecules, which might have anticancer activity by inhibiting angiogenesis, metastasis or tumor progression [13]. Also, phage display can be used to create new vaccines to apply to cancer or infectious diseases [14, 15].

Phagemid vectors are plasmids with a bacteriophage origin of replication that are packaged into phage particles upon addition of helper phages, making the genetic modification of bacteriophages easier, and allowing for the development of phage-like particles [16, 17]. A theoretical advantage of the use of phage vectors is that the capsid protects the DNA from degradation, both in the extracellular environment and when taken up into the cell [18]. A disadvantage of systemically administered (untargeted) phages, is the rapid clearance by the reticuloendothelial system [19]. Phage VLPs have been used to package exogenous RNA, nanoparticles, chemotherapeutic drugs and protein cocktails [11, 20-22]. By inserting a eukaryotic gene cassette from AAV in an intergenomic region of a phage clone displaying RGD-4C, a chimeric AAV/Phage virus has also been created, improving transduction rates significantly [23-26].

The φC31 integrase enzyme from *Streptomyces* phage φC31 is normally responsible for the integration of the phage genome into the host bacterial genome using *attP* and *attB*

recombination sites, respectively [27]. In mammalian cells, pseudo-*attP* sites exist, and site specific genomic integration occurs *in vitro* and *in vivo* in mice, although random integration events also occur. Using a negative selection strategy, random integration during φC31-mediated transfection can be avoided [28].

Attempts have also been made to evaluate bacteriophages for oncolytic activity [29]. Phages have been shown to (weakly) bind to cancer cells by interaction between the KGD-motif of the phage capsid protein and integrin receptors on target cells, and high-affinity mutants have been described [30]. When administered to immune-competent mice bearing B16 melanoma tumors, a small reduction in metastasis load was observed, but no tumor regression. Interestingly, this only applied to purified bacteriophage preparations, as raw phage lysates containing bacterial debris actually accelerated tumor growth [31]. Furthermore, phages have been shown to support anti-tumor responses in DC-based vaccine therapy in a colon carcinoma mouse model [32].

More recently, genetically engineered bacteriophages have also been evaluated for efficacy in mouse models for melanoma and were shown to induce tumor regression by activating local antitumor immune responses [33, 34]. Also, phage based lambda nanobioparticles were successful in transfecting tumor cells with the apoptin gene from chicken anemia virus, which induced cytotoxicity *in vitro* and tumor regression in a mouse xenograft model for breast cancer [35].

1.3 Clinical trials

No information is available regarding phage gene therapy vectors or oncolytic bacteriophages. Clinical trials employing phages as bactericidal agents have shown reasonable safety of (par)enteral administration [3].

1.4 Safety

Patient

The use of bacteriophages as gene therapy vector or oncolytic agent treatment is still in its early stages, and it is questionable if this modality will ever reach clinical application. If further research points to useful efficacy in several immune competent models, an effort should also be made to evaluate the safety of these viruses. Especially when thinking about systemic high dose i.v. administration, off-target activity, pharmacokinetics, pharmacodynamics of and immunologic response to these large viruses should be addressed. Also, the preparation of phages in bacteria will demand special measures to purify viral stocks from any bacterial remnants, as these can not only influence treatment efficacy, but also potentially cause significant side effects.

Germline

Using ‘normal’ retargeted phages, no integration of DNA has been observed. However, when packaging AAV sequences in hybrid AAV/Ph vectors, integration does occur, as is reviewed later for AAVs. Also, the use of phage derived integrases of course leads to genomic integration with the risk of germline transmission.

Transmission

No information available.

Mutagenesis/reversion

As exemplified by phage display, bacteriophages can easily adapt to passaging *in vitro* and *in vivo* [36, 37]. This has strangely not been perceived as a potential safety issue.

2 Order Herpesvirales

2.1 Family Herpesviridae / Subfamily Alphaherpesvirinae

2.1.1 Genus Simplexvirus - Human herpesvirus 1/2 (herpes simplex virus 1/2; HSV-1/2)

2.1.1.1 General information

HSV-1 is a contagious virus which causes herpes labialis (cold sores) in humans. Infected patients can spread virus through shedding in saliva, but asymptomatic shedding can also occur. Symptoms of HSV-1 infection include watery blisters on the perioral or genital skin or mucous membranes. HSV-2 is a sexually transmitted disease which causes genital herpes in humans. Most transmissions occur when a patient is asymptomatic. HSV-2 can cause symptoms on identical body sites as HSV-1 and vice versa. Both viruses can cause life-threatening disease in immunocompromised patients, like newborns, HIV patients or patients taking immunosuppressive medication [38].

HSV is neurotropic and neuroinvasive and can become latent after primary infection in the immune-privileged site of the neuronal body in the trigeminal or sacral ganglia. Here, it can be reactivated to cause lifelong sporadic outbreaks which lead to transportation of virions through the axon to the skin, where virus replication and shedding occur, causing new symptoms.
The common structure of herpes virions consists of a large double-stranded non-segmented DNA genome encased in an icosahedral capsid which is wrapped in a cell-derived lipid bilayer envelope containing virally encoded membrane proteins and a tegument [39]. HSV virions can bind heparin sulfate moieties on host cell surfaces, which triggers a cascade of molecular interactions between viral and cellular proteins and receptors leading to penetration of the viral capsid and tegument into the cytoplasm of the infected cell [40]. The capsid is then transported to the nucleus where the viral DNA is injected through the nuclear membrane into the nucleus. Once inside the nucleus the HSV genome circularizes in the presence of ICP0 and remains in an episomal form, where it can either undergo replication or establish latency [41, 42].

The dsDNA HSV genome consists of two unique covalently linked sequences, Unique Long (U_L) and Unique Short (U_S), is ~152 kb long and encodes for 84 different proteins. RNA polymerase II of the infected host cell is needed for transcription of HSV genes. Upon infection, immediate early genes are transcribed first, allowing control of expression of early and late viral genes. Early gene expression will lead to production of enzymes needed for DNA replication and certain envelope glycoproteins. To finish, late HSV genes mostly encode structural proteins which form the virion particle. Capsid formation and subsequent encapsidation of viral DNA occur in the nucleus, while final virion maturation takes place in the cytoplasm. Viral gene expression in latently infected cells is largely repressed except for latency-associated transcripts (LATs).

2.1.1.2 Preclinical research

Replication defective HSV (rdHSV) vectors

Deletion of viral genes essential for lytic replication, reactivation and immune evasion (i.e. ICP0, ICP4, ICP27, and/or ICP47), while leaving latency genes intact, has resulted in recombinant rdHSV particles with transgene expressing capacity of equal size as the viral genome deletions. Like HSV amplicons, the production of rdHSV particles depends on the use of

complementing cell lines or helper virus. Transduction with rdHSV vectors causes a latent-like infection in (non-) neural tissue, which leads to long lasting transgene expression. rdHSV vectors expressing (pre)opioid or anti-inflammatory peptides have been developed for treatment of pain syndromes [43-45].

Conditionally replicating: oncolytic HSV (oHSV)

HSV-1 was one of the first viruses to be developed into an oncolytic virotherapeutic vector. The large HSV genome is easy to manipulate and allows insertions of multiple additional transgenes if needed. Furthermore, oHSV infects and replicates in most tumor cell types and spreads throughout the tumor. If needed, HSV replication can be hampered with anti-HSV medication (acyclovir).

Because HSV is neurotropic and causes a latent infection, most genetic modifications of oHSV have first focused on this potential safety issue [46]. To generate tumor-specific oHSVs, three main strategies have been used (Figure 1):

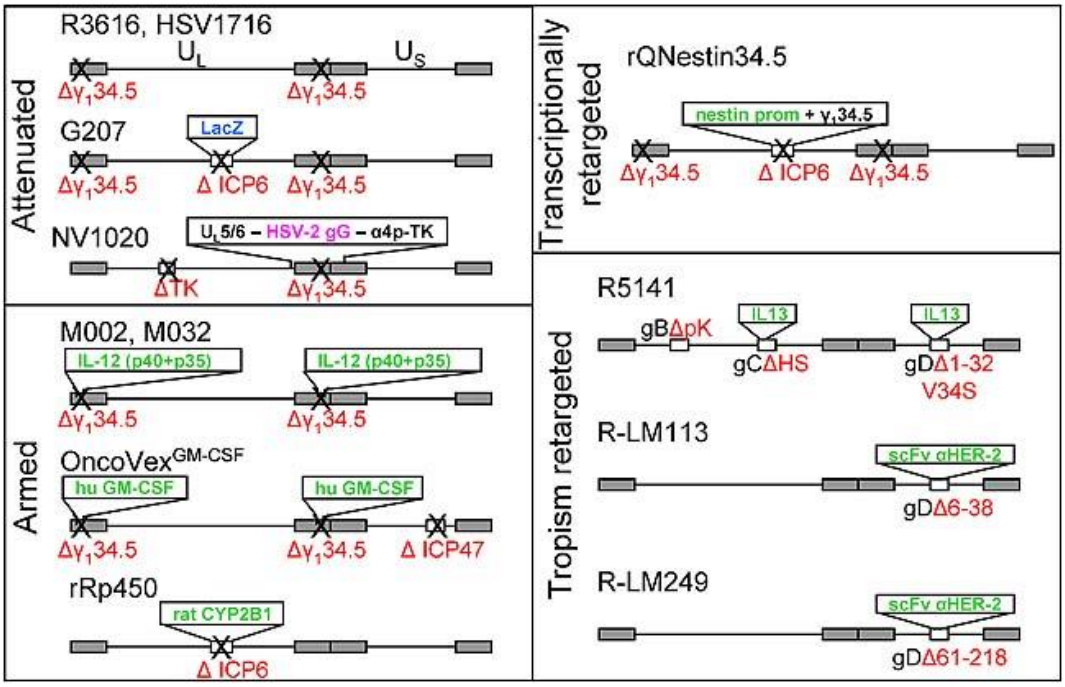

Figure 1: strategies for oHSV. From: Campadelli-Fiume G et al. *Reviews in medical virology* 2011; **21**(4)**:** 213-26 [46].

Attenuation by conditional replication in tumor cells

This first strategy consists mainly of deletion of viral genes that are essential for viral replication in non-dividing cells (UL23, UL39), counteract the PKR response (γ_1-34.5) or contribute to immune evasion (ICP47).

The UL23 gene encodes for the viral tk, normally responsible for processing nucleotides to facilitate DNA replication [47]. Deletion of UL23 leads to severe attenuation in normal cells, while rapidly dividing cancer cells still support replication [48]. However, UL23 deletion also renders HSV insensitive to first-line anti-herpes medication, thus losing a crucial safety feature for clinical application. As such, UL23 deletion has been abandoned in favor of other genetic mutations.

UL39 encodes for ICP6, the large subunit of ribonucleotide reductase. This enzyme is essential for viral DNA replication in quiescent cells. Inactivation of this gene leads to replication only in rapidly dividing cells, limiting viral replication to cancer cells [49].

The γ_1-34.5 gene encodes for the neurovirulence factor ICP34.5, which normally antagonizes PKR by de-phosphorylating eIF4a preventing a protein shutoff mechanism [50, 51]. Most cancer cells lose this mechanism so that viral replication can proceed in the absence of ICP34.5. However, the level of PKR activation and thus viral replication differs in tumor cells, which can be attributed to MEK activity, an inhibitor of PKR. Low MEK activity leads to high PKR activity and this prevents replication and oncolytic activity of $\Delta\gamma_1$-34.5 oHSV mutants. To improve oncolytic efficacy in tumor cells with low MEK activity, oHSVs have been developed that express anti-PKR genes or that alter the kinetics of US11 gene expression [52, 53]. Reversion to a neurotropic virulence has not been observed with these strategies. More recently, deletion of the Beclin-1 binding domain in the γ_1-34.5 gene was shown to increase oncolytic efficacy without causing neurotoxicity [54]. Replacement of γ_1-34.5 with GADD34, which also lacks the Beclin-1 binding domain resulted in similar findings [55].

HSV-1 gene α47 encodes for protein ICP47 that downregulates host cell expression of MHC-I [56]. The ICP47 protein inhibits the TAP machinery, which is involved in MHC-I antigen presentation to T-cells, thereby allowing HSV-infected cells to escape immune recognition. Deletion of this gene thus allows for efficient (viral) antigen presentation to circulating T cells and while this might seem counterintuitive for viral infection and replication efficacy, it actually exploits host immunity to elicit an anti-tumor response beyond conventional oncolysis [57]. Deletion of ICP47 also increases expression of US11, normally a blocker of PKR. Thus, a combination of ICP34.5 and ICP47 deletions leads to loss of immune evasion and more oncolytic selectivity of so-called third generation oHSVs [52].

There are some reports that HSV-2 might be a better oncolytic vector than HSV-1, and efforts have been made to evaluate oHSV-2 vectors with similar genetic safety alterations [58-61].

Arming with transgenes

To overcome the limitation of not reaching/infecting all tumor cells with oHSV, a boost in the local cytotoxic immune response is thought to contribute to oncolytic efficacy. Viral expression of immune stimulatory genes recruiting T-cells and/or macrophages have shown to be of value, including Flt3L [62], IL-4 [63], IL-12 [64-78], IL-15 [79], TNFα [80] and GM-CSF [66, 72, 81-84]. Most of these armed oHSVs have shown preclinical efficacy, and talimogene laherparepvec (OncoVex^{GM-CSF}) has recently undergone evaluation in a phase III clinical trial in patients with stage III/IV melanoma.

Another strategy encompasses the expression of therapy enhancing transgenes from oHSV, including direct oncolytic proteins [85-88], angiogenesis inhibition [76, 89-99], MMP expression [100, 101] or inhibition [102], tumor antigen expression [103], radiation therapy localizers [104-106], prodrug converting enzymes [107-115] and innate immune inhibition [116, 117]. These strategies can be combined with transcription targeting (see next paragraph).

Fusogenic glycoproteins have also been incorporated into oHSV vectors to circumvent the hostility of the extracellular environment by increasing cell-to-cell distribution [86, 108, 114, 118-128]. This strategy can also be combined with transcription targeting (see next paragraph) [129].

Targeting by tropism or transcription specificity

First generation oHSVs harboring genetic deletions are generally safe because they are attenuated for viral replication in normal cells. However, they are also attenuated in and thus less cytotoxic for cancer cells. Therefore, more recent strategies have focused on retargeting replicating oHSV to tumor cells by changing tropism or transcription specificity of so-called second generation oHSVs.

Glycoprotein D serves as the receptor binding protein, and fusing this glycoprotein with a heterologous ligand will retarget the virus to the tumor-specific receptor of choice, which is enhanced by detargeting of the normal receptor [130, 131]. Examples include IL-13Rα2 [132], HER2 [133-138], EGFR [101, 139, 140] and more tumor-specific receptors will probably be discovered and used for oHSV specific targeting.

Using transcriptional targeting, tumor specificity can be enhanced by placing viral genes under the control of tumor-specific promoters. A notable example is rQNestin34.5, which has the expression of the γ_1-34.5 under the control of the glioma-specific nestin promoter, which restores viral replication and cytotoxicity in glioma tumor cells [141]. Other promoters that have been investigated include AFP [142], ARR(2)PB [143], B-myb [144], CEA [145], HIF [146], midkine [147], Musashi1 [148], Ras [149], T-cell factor [150] and URR16 [151]. miRNA or siRNA targeting has also been attempted to limit viral replication to tumor tissue [101, 152-155].

Combination therapy

Since it is unlikely that single therapy with oHSV will be able to get durable treatment efficacy, efforts have also been made to evaluate combination therapies or other methods to optimize oHSV therapy: ionizing radiation [156-158], hyperthermia [159], chemotherapy [61, 75, 160-169], immunomodulating drugs [170], immune checkpoint modulating [171], PKR inhibition [172, 173], TAP inhibition [174], innate immune response inhibition [175-179], JAK/STAT inhibition [180], EGFR inhibition [122, 169, 181], VEGF blockade [182-184], mTOR inhibition [185], PI3K/Akt inhibition [186], caspase inhibition [187], collagen I synthesis inhibition [188], copper chelation [189], integrin inhibition [98], chemical compound screens [190] and carrier cell delivery [191-193].

2.1.1.3 Clinical trials

rdHSV vectors have been evaluated for safety of intradermal injection in patients who have intractable pain due to malignant disease located below the angle of the jaw, which showed some objective results without SAEs [194].

Several oHSVs (talimogene laherparepvec, HSV1716, NV1020, G207, M032, rRp450 and other) have already been used in clinical trials [46]. Most of these trials demonstrated a good safety profile of oHSV and treatment benefits were observed. A phase III clinical trial using talimogene laherparepvec has just been concluded in patients with advances melanoma, and indications are that this will be the first oncolytic virus to obtain FDA approval [195].

2.1.1.4 Safety

Patient

Existing rdHSV vectors and oHSVs have been shown to be safe to administer to patients. The use of newer oHSVs, especially vectors not fully attenuated but rather retargeted to tumors, will have to be evaluated in human-like models to exclude accidental neurotoxicity and

occurrence of latent infection. Given their promise of better oncolytic activity, it seems likely that these oHSVs will also proceed into clinical trials in the near future.

Germline

HSV and other *herpesviridae* maintain their genomes as extrachromosomal circular episomes in the nucleus of an infected cell without the need of integration for viral replication. However, there are several reports of chromosomal integrated viral DNA of other *herpesviridae* like Marek's disease virus and Epstein-Barr virus, and HHV-6 is found integrated into germ lines of approximately 1% of the general population [196]. Evidence for HSV-1/2 genomic integration is very scarce, and was mostly detected following infection with defective interfering particles or UV-inactivated viruses, or after transfection of sheared or subgenomic viral DNA, making the likelihood of HSV germline transmission very low [197-201].

Transmission

Preclinical evaluation employing intra-organ (brain or prostate) injection in non-human primates demonstrated no shedding of virus, which points to limitation of oHSV to injection sites [202-204]. This was confirmed by early clinical trials in patients injected intratumorally with oHSVs: sometimes shedding of HSV in saliva was noted, but this was shown to be wildtype virus as opposed to the injected oHSV [205, 206]. Other studies have observed limited leakage of oHSV from injection sites up to 2 weeks post treatment, without other excreta containing viable oHSV [207-211]. Intra-arterial hepatic injection did not result in detectable environmental shedding either [212].

Mutagenesis/reversion

The error rate of DNA viruses has been calculated to be 10^{-8} to 10^{-11} errors per nucleotide, making HSV a genetically very stable virus. A possible concern could be that a mutant oHSV recombines with a wt-endogenous virus. This however, is an unlikely event, given that the two viruses would then have to infect the same cell in (near) equal genome copy numbers. Also, if recombination would occur between mutants with deleted genes and wt-virus, this would yield the two starting viruses. If the oHSV carries heterologous genes, the recombinant would have to arise by illegitimate recombination – an extremely rare event that cannot be replicated *in vitro*. Furthermore, ganglia that are infected with one HSV virus, cannot be superinfected to yield a second one. Spontaneous reversion of deletion mutants is not possible, however mutants can acquire compensatory mutations, but are still highly attenuated [213]. Especially these compensatory mutations can be of concern when evaluating the safety of second and third generation oHSVs.

2.1.2 Genus Varicellovirus - Bovine herpesvirus 1 (BHV-1)

2.1.2.1 General information

Please refer to COGEM report '*Replication competent non-human viruses for use in clinical gene therapy: an inventory study'* (CGM 2010-10; page 39-40) [214].

2.1.2.2 Preclinical research

After having shown oncolytic efficacy in a set of immortalized and transformed cells *in vitro* [215], BHV-1 has been studied further for efficacy in breast cancer [216]. Also, efficacy has

been shown in 72% of the NCI panel of established human tumor cell lines, and susceptibility does not seem to correlate with type I IFN signaling, but more with kRAS mutations [217]. Genetic modifications of oncolytic BHV-1 have thus far been limited to the expression of GFP.

2.1.2.3 Clinical trials

No information available.

2.1.2.4 Safety

Since no effort has been made to change the tropism or virulence of BHV-1, no change can be reported since CGM 2010-10 (page 41-42) [214].

2.1.3 Genus Varicellovirus - Equid herpesvirus 1 (EHV-1)

2.1.3.1 General information

EHV-1 causes upper respiratory infection in horses and sometimes paralysis and abortion [218]. Like other herpesviruses, latent infection with periodic reactivation and transmission can occur. Human infection with EHV-1 has not been described, although human cells can be infected *in vitro* [219].

2.1.3.2 Preclinical research

EHV-1 has been studied as a vaccine vector for different infectious diseases [220, 221]. Deletion of the sole essential tegument protein ETIF leads to severe attenuation with limited effect on transgene expression *in vivo* [222]. Deletion of the internal repeat sequence also leads to attenuation *in vivo* [223].

EHV-1 has been shown to be oncolytic for glioma cells *in vitro*, and susceptibility is based on the level of expression of MHC-I on these cells [224]. Oncolytic efficacy can be augmented with HDAC inhibitors [225].

Wildtype EHV-1 leads to severe toxicity when inoculated intranasally in mice. Attenuation does improve the safety, however, mice still experience significant weight loss [223]. No information is available for tumor models or human-like animal models.

2.1.3.3 Clinical trials

No information available.

2.1.3.4 Safety

Patient

Since EHV-1 is able to cause disease in horses and mice, and seems to infect multiple cell types through the abundantly expressed MHC-I receptor, future studies should also focus on attenuation of EHV-1 or changing tropism.

Germline

Similar to HSV, there is one report of genomic integration of EHV-1 DNA into hamster embryonic cell lines. [226]

Transmission
No information available.

Mutagenesis/reversion
No information available.

2.1.4 Genus Varicellovirus - Human herpesvirus 3 (Varicella Zoster virus; VZV)

2.1.4.1 General information

VZV is a ubiquitous virus which causes varicella (chicken-pox) as primary infection and can cause herpes zoster upon reactivation from latency.

2.1.4.2 Preclinical research

Recently, VZV has been evaluated as an oncolytic virus for malignant glioma *in vitro* and shown to be effective [227]. Wildtype and attenuated mutants rOKA/ORF63rev[T171], rOKA/47ΔC and pOKA66S were tested on several human glioma cell lines. It was concluded that rOKA/ORF63rev[T171] was the most effective oncolytic agent, and probably safer to use in humans due to attenuation.

2.1.4.3 Clinical trials

No information available.

2.1.4.4 Safety

No information available.

Since VZV is neurotropic and can not only cause herpes zoster, but also severe meningitis and encephalitis (in immune-compromised subjects), efforts should be made to evaluate (attenuated) VZVs for safety in a human-like model if further development is to be undertaken.

2.1.5 Genus Varicellovirus - Suid herpesvirus 1 (SuHV-1; pseudorabies; Aujeszky's disease virus)

2.1.5.1 General information

Please refer to CGM 2010-10 (page 42) [214].

2.1.5.2 Preclinical research

No additional information since CGM 2010-10 (page 43) [214].

2.1.5.3 Clinical trials

No information available.

2.1.5.4 Safety

Please refer to CGM 2010-10 (page 43-44) [214].

2.2 Family Herpesviridae / Subfamily Betaherpesvirinae

2.2.1 Genus Roseolovirus - Human herpesvirus 6B (HHV-6B)

2.2.1.1 General information

HHV-6B is the causative agent of the common childhood illness exanthema subitum (roseola infantum, sixth disease) [228]. Reactivation of HHV-6B is commonly seen in solid organ and hematopoietic cell transplant recipients, and can cause severe complications like encephalitis, bone marrow suppression and pneumonitis [229].

2.2.1.2 Preclinical research

One study has been reported using recombinant HHV-6B vectors with deleted US22 family genes to change virulent tropism to stimulated umbilical cord blood cells, while maintaining transduction efficiency in T-cells [230].

2.2.1.3 Clinical trials

No information available.

2.2.1.4 Safety

Germline

HHV-6 is capable of genomic integration and is found integrated into germ lines of approximately 1% of the general population [196].

No information available on patient safety, transmission or mutagenesis/reversion.

2.3 Family Herpesviridae / Subfamily Gammaherpesvirinae

2.3.1 Genus Rhadinovirus - Bovine herpesvirus 4 (BHV-4)

2.3.1.1 General information

Please refer to CGM 2010-10 (page 48-49) [214].

2.3.1.2 Preclinical research

After the initial publication that BHV-4 is oncolytic for A549 lung carcinoma cells *in vitro* and in nude mouse tumor xenografts *in vivo*, two more publications focusing on oncolytic BHV-4 have been published. One study evaluated BHV-4 as a treatment modality for malignant glioma, and showed that the virus was oncolytic *in vitro* and also effective and safe in an immunocompetent rat model [231]. The other study used a BHV-4 vector expressing the HSV-1 tk gene combined with gancyclovir which was evaluated *in vitro* and in immunocompetent orthotopic syngeneic mouse and rat glioma models with similar positive results.[232] Please also refer to CGM 2010-10 (page 49-50) [214].

2.3.1.3 Clinical trials

No information available.

2.3.1.4 Safety

Please refer to CGM 2010-10 (page 50-51) [214].

2.3.2 Genus Rhadinovirus - Saimiriine herpesvirus 2 (HVS-2)

2.3.2.1 General information

Please refer to CGM 2010-10 (page 45-46) [214].

2.3.2.2 Preclinical research

HVS-2 has been used in recent years as a gene therapy vector to stably transduce tumor cells or PSCs with therapeutic or reprogramming transgenes [233-237]. Although shown to be a good vector to establish non-integrating stable episomal transgene expression *in vitro*, there is only limited evidence for efficacy or safety *in vivo* [238]. Please also refer to CGM 2010-10 (page 46-47) [214].

2.3.2.3 Clinical trials

No information available.

2.3.2.4 Safety

Please refer to CGM 2010-10 (page 47-48) [214].

3 Order Mononegavirales

3.1 Family Bornaviridae

3.1.1 Genus Bornavirus - Borna disease virus (BDV)

3.1.1.1 General information

BDV can infect a wide variety of mammalian species, including humans, and has the unique ability to introduce cDNA of its RNA transcripts into host genomes. Infection with BDV can lead to severe neurobehavioral diseases, such as chronic progressive meningoencephalomyelitis in horses and sheep [239]. The possible role of zoonotic BDV in neuropsychiatric diseases is still very controversial [240, 241].

The virus is highly neutropic and chronically infects neurons and glial cells without causing cytotoxicity and with an extremely low number of infectious virus particles per cell. As an exception to other negative stranded RNA viruses, it replicates its genome in the nucleus, and the virus can spread from cell to cell in mitosis.

3.1.1.2 Preclinical research

Only one publication has reported the use of BDV as a vector to express foreign genes [242]. The unique feature of intranuclear parasitism could make BDV a candidate for gene delivery to the CNS, as was shown by GFP expression in rat brains. Deletion of the G envelop protein did not result in loss of infectivity, but probably did prevent cell-to-cell spread.

Several groups have focused on the evaluation of natural or experimental BDV infection in different species, including cats, ponies, horses, sheep, rabbits, guinea pigs, rats, bank voles and hens. Intracerebral injection of BDV in tree shrews also led to a persistent infection of the limbic system that sometimes resulted in clinical symptoms, including alterations in behavior [243]. Similar experiments with rhesus monkeys resulted in severe encephalomyelitis accompanied by retinopathy [244].

3.1.1.3 Clinical trials

No information available.

3.1.1.4 Safety

No information available.

Before BDV can progress towards further (pre)clinical studies, a serious effort should be made to reduce possible pathogenesis. Given the theoretical potential of BDV to cause neurologic or neuropsychiatric disease, BDV vectors do not seem a very promising candidate for future clinical use.

3.2 Family Paramyxoviridae / Subfamily Paramyxovirinae

3.2.1 Genus Avulavirus - Newcastle disease virus (NDV)

3.2.1.1 General information

Please refer to CGM 2010-10 (page 76-77) [214].

3.2.1.2 Preclinical research

Please refer to CGM 2010-10 (pages 77-80 and 82-84) for an overview of research activities with wildtype oncolytic NDV strains performed up until 5 years ago [214].

In more recent years, the interest in oncolytic NDV has revived with the advent of recombinant viruses (rNDV). Several approaches have been used to improve oncolytic efficacy of rNDV, including increasing virulence [245-252], expression of immunomodulating [245-247, 252-254] or apoptotic [255] transgenes, targeting of tumor cells with modified attachment proteins [256, 257] and combinations with other treatment modalities [258], most recently immune checkpoint blockade [259]. NDV has been shown to be very safe in tumor models using mice or rats, even when used in high dose and injected intravenously.

3.2.1.3 Clinical trials

Early clinical trials in humans also have demonstrated wildtype NDV to be a safe oncolytic agent with minimal side effects upon administration. Please also refer to CGM 2010-10 (page 80-82) [214].

3.2.1.4 Safety

Patient

NDV appears to be safe for administration in high dose to humans. The information on human-like models however is very scarce, with the exception of studies in non-human primates focusing on NDV as vaccine vector [260-265]. Of note, the authors of this report have carried out a preclinical study evaluating oncolytic rNDV injected intravenously in non-human primates, which was shown to be safe [266].

Germline

NDV's replication cycle is confined to the cytoplasm and does not have an intermediate DNA step, which means no integration and/or subsequent germline transmission can occur.

Transmission

Virulent strains pose an environmental risk. Relevant shedding of live virus was observed in non-human primates and early clinical trials [266]. Future research should focus on either limiting virulence for susceptible hosts [267], targeting NDV to human (tumor) cells, or optimizing non-virulent rNDV for oncolytic activity. Please also refer to CGM 2010-10 (page 85-88) [214].

Mutagenesis/reversion

Although NDV is an RNA virus with an inherent higher viral polymerase error rate due to the lack of proofreading, recombinant viruses with or without transgene(s) have shown to be genetically very stable upon passaging. Spontaneous reversion of PPMV-1 (which already possesses a multibasic cleavage site in the fusion protein) to virulent NDV has been observed when artificially passaged in susceptible chickens [268, 269]. Only passaging of non-virulent NDV in 1-day-old chicken brains has thus far been shown to lead to the isolation of virulent NDV [270-272].

3.2.2 Genus Morbillivirus - Canine distemper virus (CDV)

3.2.2.1 General information

Canine distemper virus is closely related to other morbilliviruses like MeV and rinderpest virus and causes systemic and/or nervous infection in all families of the order *Carnivora* like dogs and ferrets and some other mammals, most notably seals. General symptoms of CDV infection include respiratory and gastrointestinal problems, cutaneous rash, impaired immune function due to depletion of lymphocytes, and demyelinating leukoencephalomyelitis (DL) [273]. Immune suppression can persist after clearance of virus and in combination with DL mostly leads to death. Also in countries of the Western world, epidemics in dogs have occurred recently, highlighting the importance of regular vaccination.

3.2.2.2 Preclinical research

Two publications have focused on the use of CDV as an oncolytic vector. An attenuated CDV expressing GFP was shown to infect and kill neoplastic lymphocytes isolated from dogs with spontaneous lymphoma as well as induce apoptosis in cervical cancer cells [274, 275].

3.2.2.3 Clinical trials

No information available.

3.2.2.4 Safety

No information available.

Clearly, the work to date using CDV as oncolytic vector is still very limited and it is unlikely that this will change in the near future. When using attenuated strains, CDV should not pose an environmental risk. Human infection has not been described, however CDV should be evaluated in a human-like model before moving towards potential future clinical trials.

3.2.3 Genus Morbillivirus - Measles virus (MeV)

3.2.3.1 General information

Like other morbilliviruses, MeV is highly contagious (R_0 = 12-18) via the respiratory route and it can cause large outbreaks with high morbidity and mortality among all age classes in immune naive subjects. After initial infection via aerosol inhalation, MeV replicates in the lymphoid tissue of the upper respiratory tract. After a relatively long incubation phase, a prodromal phase with fever and respiratory tract symptoms develops. A few days later, pathognomonic Koplik's spots on the buccal mucosa appear, followed by a maculopapular rash after around 14 days post infection. If no complications occur, symptoms usually start to subside within a few days, and patients with normal cellular immunity recover rapidly. However, MeV infection is also associated with immune suppression due to lymphotropic infection, causing lymphopenia. This leads to an increased susceptibility to opportunistic infections which can be lethal, especially bacterial pneumonia. Mortality rates can reach up to 25% in situations with poor health care access, like overcrowded refugee camps in developing countries, while industrialized countries can keep this number below 0,1%. Rare but severe CNS complications are also associated with MeV infection, including acute post-infection measles encephalitis, measles inclusion body encephalitis and sub-acute sclerosing panencephalitis. Large-scale vaccination programs with live-attenuated MeV since the 1960s have been very successful, although recently

vaccination rates in Western countries have started to fall. An extensive safety record has been established for the use of vaccine strains of MeV in humans [276].

The MeV genome consists of a non-segmented negative sense ssRNA, typically 15.5-16 kb long, which obeys the 'rule-of-six' like most paramyxoviruses [277]. Six genes encode for 8 proteins, with genes closest to the 3' end of the genome being transcribed in greater abundance due to a transcription gradient [278]. Tissue culture adapted MeV strains use CD46 as cellular receptor to infect [279], while wildtype virulent MeV strains predominantly use SLAM/CD150 and nectin 4/PVRL4 [280-282].

3.2.3.2 Preclinical research

Most (pre)clinical research with oncolytic MeVs has been done using recombinant MeV of the attenuated vaccine Edmonston strain [283, 284]. Infection of cells with MeV leads to viral replication and expression of glycoproteins on the cell surface, which results in a typical cytopathic effect called syncytia formation. Cancer selectivity stems from CD46 overexpression on malignant cells, which also explains the choice for a lab adapted strain to be used as oncolytic vector [285]. Tumor selectivity may also be facilitated by defects in innate immune response in cancer cells. Oncolytic MeV has been shown to be a potent antitumor agent in a wide array of malignancies including Non-Hodgkin lymphoma, multiple myeloma, ovarian cancer, glioblastoma multiforme, T-cell leukemia, erythroleukemia, cutaneous T-cell lymphoma, breast cancer, hepatocellular carcinoma, colon cancer, prostate cancer, pancreatic cancer, mesothelioma, fibrosarcoma, rhabdomyosarcoma, renal cell carcinoma and medulloblastoma [284].

Recombinant MeV can accommodate and maintain large sizes of foreign genetic material with good genetic stability *in vitro* and *in vivo* [286-289]. Like with other oncolytic vectors that have been under extensive study, efforts have been made to express transgenes from MeV, including marker peptides [290-294], reporter proteins [293, 295-298], prodrug converting enzymes [299-309], radiation therapy localizers [295, 296, 310-316], innate immunity inhibitors [317, 318] or stimulators [319-321], angiogenesis inhibitors [322], immune checkpoint blockers [323] and tumor associated antigens [324].

Also, alternative strategies to improve oncolytic effect and selectivity have been evaluated, including receptor retargeting [287, 288, 299-303, 305, 309, 321, 325-345], selective F protein cleavage [346, 347], miRNA based selectivity [348-350], carrier cell delivery [351-359], exchanging envelope glycoproteins [360, 361] and combination therapy with immunosuppressors [300, 301, 362], HSP-90 inhibitors [363], chemotherapy [364], ionizing radiation [365], checkpoint kinase 1 inhibition [316], Rho kinase inhibition [366] or mononuclear phagocytic system blockade [367]. Recently, a new strategy has been described by making a chimeric oncolytic MeV/VSV vector, which was shown to outperform both parental viruses [368].

3.2.3.3 Clinical trials

Completed and ongoing clinical trials have first used non-recombinant MeV and later recombinant MeV-CEA and MeV-NIS [283, 369-371]. Intratumoral, intraperitoneal and intravenous administration have been done using doses up to 10^9 infectious viral particles without dose limiting toxicity or immunosuppression, despite low or absent neutralizing antibodies in some patients.

3.2.3.4 Safety

Patient

Although wildtype MeV can cause potentially serious disease, attenuated MeV vaccine strains like Edmonston have an excellent safety record.

Germline

MeV's replication cycle is confined to the cytoplasm and does not have an intermediate DNA step, which means no integration and/or subsequent germline transmission can occur.

Transmission

Spread of oncolytic MeV in the general population is highly unlikely since most individuals living in industrialized countries are immune to measles, although herd immunity is waning with declining vaccination percentages. There was no evidence of shedding in mouth gargle and urine samples in patients injected intraperitoneally with MeV-CEA [370].

Mutagenesis/reversion

MeV is an RNA virus with an inherent higher viral polymerase error rate due to the lack of proofreading, resulting in quasispecies populations. Reversion of MeV vaccine strains to virulent pathogenic strains has never been observed. Recombinant MeV expressing transgene(s) have shown good genetic stability upon passaging.

Generally, the use of MeV as an oncolytic agent is safe. However, strategies that revert an attenuated MeV vaccine strain to more virulent forms by e.g. blocking innate immunity - combined with retargeting to cancer cells to increase safety - should be evaluated properly to exclude higher pathogenicity of these oncolytic MeVs [317, 318, 343]. This also applies to the newly described MeV/VSV chimeric viruses [368].

3.2.4 Genus Respirovirus - Sendai virus (SeV; Hemagglutinating virus of Japan)

3.2.4.1 General information

Please refer to CGM 2010-10 (page 88-89) [214].

3.2.4.2 Preclinical research

Most research thus far has focused on the use of SeV as virosome vector or as non-replicating oncolytic gene therapy vector [372-377].

SeV-based virosomes can incorporate exogenous plasmid DNA or other (therapeutic) substances, and can fuse with target cell membranes by means of their HN and F glycoproteins to release their contents into target cells [378]. If needed, induction of antiviral cytokines can be abolished by pre-treatment with Triton-X100 [379]. SeV virosomes loaded with siRNA, tumor antigens, immune stimulatory cytokines or cytotoxic drugs have demonstrated antitumor efficacy *in vitro* and *in vivo* [380-390].

UV-inactivated SeV particles have shown oncolytic efficacy in syngeneic mouse models of colon carcinoma, renal carcinoma and melanoma, by inducing immune responses against tumor antigens [391-394], and also in immune deficient mouse models for prostate carcinoma and neuroblastoma by direct oncolysis [395-397]. These inactivated particles have also been

armed with therapeutic transgenes like IL-2 [388], or retargeted to tumor cells [398-400].

By deleting M and/or F genes from the viral genome, SeV also becomes non-transmissible [401-404]. These non-transmissible SeV vectors have also been armed with IL-2 [405], GM-CSF [406], IFN-β [407] or c-Myc suppressors [408, 409] and retargeted to tumors [407, 410-412]. More recently, a new strategy has been applied where attenuated recombinant SeV vectors were created by deleting accessory interferon-antagonizing viral proteins, in combination with broad tumor cell retargeting [413].

Finally, SeV has been used to activate DCs for cancer immunotherapy [414-421], which can be enhanced by expressing immune stimulatory transgenes [422].

3.2.4.3 Clinical trials

Previous clinical studies have demonstrated safety of a wildtype SeV vaccine administered intranasally and a non-transmissible SeV vector expressing FGF2 injected intramuscular in patients with critical limb ischemia [423, 424]. A phase I/IIa clinical trial using UV-inactivated SeV vector is currently in progress in patients with advanced melanoma [425].

3.2.4.4 Safety

Please refer to CGM 2010-10 (page 92-93) [214].

3.2.5 Genus Rubulavirus - Mumps virus (MuV)

3.2.5.1 General information

Mumps is a human infectious disease which results in (bi)lateral nonsuppurative swelling of the parotid glands. Severe cases of mumps can also lead to orchitis in post puberty males, possibly leading to infertility, and CNS damage, sometimes leading to deafness. Before the implementation of mumps vaccination programs, MuV was one of the most common causes of aseptic meningitis.

In the last ten years, several large mumps outbreaks have occurred in populations that have been vaccinated with the live attenuated Jeryl-Lynn vaccine strain (MuV-JL), which could be due to primary/secondary vaccination failure or antigenic differences between vaccine and wildtype infectious strains [426-432]. As a result, new and more efficient vaccines are sought after, also by means of recombinant strategies [433].

3.2.5.2 Preclinical research

After early Japanese reports of the successful use of vaccine strain Urabe in cancer patients as an oncolytic or immunotherapeutic agent [434, 435], only two additional preclinical studies have been reported. One used the commercially available MuV-JL strain, which was shown to have oncolytic efficacy *in vitro* and *in vivo* in a immune deficient mouse model of peritoneal ovarian cancer [436]. The other reported on live attenuated vaccine strain MuV-S_{79}, which showed oncolytic efficacy in an immune deficient mouse model of fibrosarcoma [437]. No further reports on oncolytic MuV have been published since these early ones.

3.2.5.3 Clinical trials

No information available.

3.2.5.4 Safety

Patient

Like for MeV, there is an extensive safety record for vaccine strains of MuV, with e.g. more than 300 million doses distributed in the US as part of the MMR vaccine or as monovalent form (Mumpsvax). No information is available for virulent or recombinant strains.

Germline

MuV's replication cycle is confined to the cytoplasm and does not have an intermediate DNA step, which means no integration and/or subsequent germline transmission can occur.

Transmission

Generally, the environmental risks of attenuated vaccine strain MuV are comparable to those of MeV, even with the recent outbreaks of mumps in vaccinated populations, since these are due to wildtype infectious strains. Although no study has been reported using recombinant oncolytic MuV, we would not exclude the possibility of this virus getting more attention in the (near) future.

Mutagenesis/reversion

MuV is an RNA virus with an inherent higher viral polymerase error rate due to the lack of proofreading, resulting in quasispecies populations. Reversion to wildtype of vaccine strains has never been observed.

3.3 Family Paramyxoviridae / Subfamily Pneumovirinae

3.3.1 Genus Pneumovirus - Human respiratory syncytial virus (HRSV)

3.3.1.1 General information

HRSV is the most common cause of lower respiratory tract infection in infants, and can lead to serious respiratory symptoms like bronchiolitis and pneumonia, requiring mechanical ventilation. Similarly, it can cause respiratory related mortality in immune compromised adults [438].

3.3.1.2 Preclinical research

Because of its targeting of ciliated cells of the airway epithelium, HRSV has been evaluated briefly as a gene therapy vector to deliver the CFTR gene to CF-patient derived primary airway epithelium cultures [439].

Recombinant HRSV has demonstrated oncolytic efficacy *in vitro* and in immune deficient and competent mouse models for prostate cancer [440, 441]. Also, a recent study reported *in vitro* oncolytic activity of a wildtype strain in skin carcinoma cells [442].

3.3.1.3 Clinical trials

No information available.

3.3.1.4 Safety

Patient

Given the fact that HRSV can cause severe disease in infants and immunocompromised adults, care should be given to avoid these populations. Other than that, most adults will have HRSV immunity which will protect them from accidental infection.

Germline

HRSV's replication cycle is confined to the cytoplasm and does not have an intermediate DNA step, which means no integration and/or subsequent germline transmission can occur.

No information available on transmission or mutagenesis/reversion.

3.4 Family Rhabdoviridae

3.4.1 Genus Vesiculovirus - Farmington virus (FarV)

3.4.1.1 General information

FarV was first isolated from an unidentified wild bird captured on a pheasant farm in central Connecticut in 1969 (CT-114) by injecting newborn mice intracerebrally, producing illness and death 24-48 hours post injection [443]. No further information on the origin tissue and natural host or pathogenicity of this virus is known, which is antigenically closest related to mosquito vectored viruses like Jurona and La Joya virus, but phylogenetically most closely related to plant rhabdoviruses [444].

3.4.1.2 Preclinical research

Using high-throughput screens of dozens (!) of novel rhabdoviruses to identify new oncolytic vectors, FarV was selected for its superior oncolytic efficacy in a panel of tumor cell lines [445]. FarV is non-neurotoxic in adult mice and demonstrated oncolytic efficacy in immune deficient and competent mouse models of GBM. Besides being restricted to IFN-defective cells, replication of FarV also appears to be restricted to dividing cells, adding to safety. Armed recombinant FarVs are being developed and systematically evaluated in syngeneic mouse models of GBM [446].

3.4.1.3 Clinical trials

No information available.

3.4.1.4 Safety

No information available.

Given the obscure origin and uncertain host range of FarV, a thorough evaluation is needed in different (human-like) animal models to gain more information on pathogenesis and environmental risks.

3.4.2 Genus Vesiculovirus - Maraba virus (MaV)

3.4.2.1 General information

Please refer to CGM 2010-10 (page 101) [214].

3.4.2.2 Preclinical research

After the initial report of oncolytic MaV [447], two more reports have been published using genetically altered MaV strain MG1. First, MG1 was reported to be a potential oncolytic vaccine boost vector for melanoma in a syngeneic mouse model [448], which was later demonstrated to depend on NK and dendritic cell activation [449]. In this latter study, single-cycle or non-replicating mutants were also evaluated, which were shown to be attenuated, also for oncolytic activity.

3.4.2.3 Clinical trials

Quite surprisingly, the results reported in aforementioned studies have prompted the planning of a phase I/IIa clinical trial employing heterologous prime-boost vaccination with AdMAGE3 and MaV-MAGE3 [450]. Before this planning, toxicology studies in non-human primates have demonstrated safety of MaV.

3.4.2.4 Safety

Please refer to CGM 2010-10 (page 103) [214].

3.4.3 Genus Vesiculovirus - Vesicular stomatitis virus (VSV)

3.4.3.1 General information

Please refer to CGM 2010-10 (page 98-99) [214].

3.4.3.2 Preclinical research

Compared with other oncolytic viruses, VSV has some distinct advantages: a well-studied biology, relative independency of cell cycle or a specific receptor, production of high virus yields in a wide range of cell types, intracytoplasmatic replication without risk of genomic integration, small and easy to manipulate genome, and lack of pre-existing immunity in humans. VSV oncoselectivity is based largely on defective or reduced type I IFN responses [451-454], although abnormal translation machinery and other cellular proteins have also been shown to play a role [455-458].

In the last decade, a great number of recombinant VSVs have been generated, aiming to optimize oncolytic potency and abolish neurotropism. For an excellent overview of strategies and resulting (recombinant) oncolytic VSVs, please also refer to Hastie & Grdzelishvili 2012 [459]. To summarize, VSVs have been generated that express reporter genes [460-468], have attenuating mutations [452, 462, 463, 469-475], express retargeting or fusogenic foreign glycoproteins [476-489], use miRNA retargeting [490, 491] and/or express cancer suppressor genes [474], prodrug converting enzymes [461, 492, 493], radiation therapy localizers [494, 495], tumor associated antigens [496-500], immunomodulating proteins [477, 496, 497, 501-516], or immune checkpoint blockade inhibitors [517].

Furthermore, combination therapy has been described with innate/adaptive immunity inhibitors [518-529], other oncolytic viruses [530], BCL-2/Mcl-1 inhibitors [531-534], tumor

embolization [535], adoptive T-cell transfer [499], anti-angiogenic compounds [536], or proteasome inhibitors [537].

Finally, optimizing delivery and distribution of oncolytic VSVs has been evaluated using cell-based carriers, aptamer coating or PEGylation of virions [538-541].

A relatively new strategy employed to increase the oncolytic activity of VSV consists of so-called semireplication-competent vectors. This is based on two *trans*-complementing propagation deficient VSV vectors [465]. Using this method, the genes that are essential for viral replication are divided between two separate viral genomes, so that only double-infected host cells will produce infectious progeny. This results in VSV vectors that are attenuated for neuropathology, but still maintain good oncolytic efficacy.

A recent study in purpose-bred beagle dogs showed that a dose up to 10^{10} $TCID_{50}$ of VSV-hIFNβ was well tolerated, with mild adverse events with the exception of one dog that received 10^{11} $TCID_{50}$ which developed severe hepatotoxicity and shock leading to euthanasia [542]. A following study testing VSV-hIFNβ on rhesus macaques via intrahepatic injection did not result in neurological signs and is considered to be safe enough to proceed into phase I clinical trials, which are currently ongoing in humans and pet dogs [509, 543].

3.4.3.3 Clinical trials

Currently ongoing in humans and pet dogs (see above).

3.4.3.4 Safety

Patient

VSV infection in humans is generally asymptomatic. When symptomatic, human VSV infection results in an acute, self-limiting disease with flu-like symptoms and occasionally vesicular lesions of the mouth or at the site of inoculation. A single case of VSV strain Indiana related encephalitis in humans has been reported [544]. Potential VSV neuropathogenesis is therefore of concern and as described earlier, several strategies have been applied to remove it.

Germline

VSV's replication cycle is confined to the cytoplasm and does not have an intermediate DNA step, which means no integration and/or subsequent germline transmission can occur.

Transmission

No VSV RNA was detected in buccal swabs taken from non-human primates after intrahepatic injection with VSV-hIFNβ [509].

Mutagenesis/reversion

VSV is an RNA virus with an inherent higher viral polymerase error rate due to the lack of proofreading, resulting in quasispecies populations [545]. Theoretically, VSV mutants harboring mutations in their M or G gene (making them oncoselective and abolishing neurotropism) could revert to wildtype VSV upon passaging, and recombinant VSVs expressing attenuating transgenes like hIFNβ can acquire mutations in this transgene, and these more wildtype-like mutants can also be selected for [546, 547]. Indeed, there is evidence present for reversion to wildtype VSV upon passaging of non-oncolytic mutants [548, 549], and loss of foreign gene expression has also been observed [550], which seems to depend on site of insertion [551].

Furthermore, recombinant oncolytic VSVs have been shown to optimize targeted glycoproteins upon passaging in tumor cells [552], and to mutate expressed transgenes to optimize replication [553]. These examples have strangely not been perceived as a safety problem. Of note, passaging of wildtype VSV in IFN stimulated cells did not lead to the emergence of IFN-insensitive mutants [554].

Please also refer to CGM 2010-10 (page 100-101) [214]. As with other heavily researched oncolytic viruses, more recent strategies for oncolytic VSV include reversion towards more wildtype-like retargeted viruses, and combination therapies that potentially alter the outcome of VSV infection dramatically. We would therefore strongly advise to evaluate these new strategies thoroughly before approval for future clinical trials.

4 Order Nidovirales

4.1 Family Coronaviridae / Subfamily Coronavirinae

4.1.1 Genus Alphacoronavirus - Alphacoronavirus 1 (aCoV-1; Feline enteric coronavirus / Feline infectious peritonitis virus)

4.1.1.1 General information

Please refer to CGM 2010-10 (page 109-110) [214].

4.1.1.2 Preclinical research

No progress has been reported on aCoV-1 since CGM 2010-10 (page 110-111) [214, 555].

4.1.1.3 Clinical trials

No information available.

4.1.1.4 Safety

Please refer to CGM 2010-10 (page 111-112) [214].

4.1.2 Genus Betacoronavirus - Murine coronavirus (mCoV; Mouse hepatitis virus)

4.1.2.1 General information

Please refer to CGM 2010-10 (page 106-107) [214].

4.1.2.2 Preclinical research

No progress has been reported on mCoV since CGM 2010-10 (page 107-108) [214, 555-558].

4.1.2.3 Clinical trials

No information available.

4.1.2.4 Safety

Please refer to CGM 2010-10 (page 108-109) [214].

5 Order Picornavirales

5.1 Family Picornaviridae

5.1.1 Genus Cardiovirus - Encephalomyocarditis virus (EMCV)

5.1.1.1 General information

Please refer to CGM 2010-10 (page 124-125) [214].

5.1.1.2 Preclinical research

No progress has been reported on EMCV since CGM 2010-10 (page 125) [214, 559-561].

5.1.1.3 Clinical trials

No information available.

5.1.1.4 Safety

Please refer to CGM 2010-10 (page 125-126) [214].

5.1.2 Genus Cardiovirus - Theilovirus (TMEV; Theiler's murine encephalomyelitis virus)

5.1.2.1 General information

Strains of TMEV fall into two subgroups based on differences in pathogenicity in mice. GDVII subgroup members cause an acute lytic neuronal disease and do not persist, while TO subgroup members cause subclinical neuronal disease followed by a chronic inflammatory demyelinating process, thought to be immune mediated [562]. As such, murine infections with TO subgroup TMEV serve as a model for multiple sclerosis (MS). TMEV can strongly drive CD8 T-cell immunity, even in a variety of immune deficient states. Therefore, TMEV has been evaluated as vaccine vector harboring tumor antigens.

5.1.2.2 Preclinical research

Two publications have described the use of TMEV as cancer vaccine vector. The first study showed that TMEV-OVA was capable of eliciting CD8 T-cell responses to tumors, which resulted in some growth delay of established B16-OVA melanoma allograft tumors [563]. A second study focused on the safety of TMEV vectors by inserting the vaccine epitope within the viral leader protein, which leads to dramatically increased type I IFN responses [564]. This attenuated TMEV vaccine vector maintained its ability to induce CD8 T-cell anti-tumor responses.

5.1.2.3 Clinical trials

No information available.

5.1.2.4 Safety

Patient

TMEV infections in humans are not associated with disease, although related cardioviruses like Saffold virus can lead to enteric, respiratory and possibly (severe) neurological symptoms in humans [565-568]. In combination with the pathogenicity in mice and close relation

to Saffold virus, TMEV seems like an illogical choice to pursue for further development.

Germline

TMEV's replication cycle is confined to the cytoplasm and does not have an intermediate DNA step, which means no integration and/or subsequent germline transmission can occur.

Transmission

No information available.

Mutagenesis/reversion

TMEV, like other picornaviruses, possesses genomic instability and variability, most likely due to the use of short direct repeats that act as parting and anchoring sites and allow deletion of intervening genomic segments [569]. Indeed, this genomic instability could lead to deletion of attenuating insertions, and thus reversion to wildtype.

5.1.3 Genus Enterovirus - Bovine enterovirus (BEV)

5.1.3.1 General information

Please refer to CGM 2010-10 (page 115-116) [214].

5.1.3.2 Preclinical research

No progress has been reported for BEV since CGM 2010-10 (page 116-117) [214, 570].

5.1.3.3 Clinical trials

No information available.

5.1.3.4 Safety

Please refer to CGM 2010-10 (page 117-118) [214].

5.1.4 Genus Enterovirus - Coxsackievirus (CVA/CVB)

5.1.4.1 General information

Coxsackieviruses can be divided into two groups (A and B) based on their pathogenicity in mice. Group A coxsackieviruses (CVA; serotype 1-22 & 24) cause flaccid paralysis due to generalized myositis, while group B coxsackieviruses (CVB, serotype 1-6) cause spastic paralysis due to focal muscle injury and neuronal degeneration.

The best known example of Coxsackievirus-related human disease is Hand, foot and mouth disease, caused by CVA-16. Other human infectious diseases caused by coxsackieviruses include acute hemorrhagic conjunctivitis (CVA-24), herpangia (CVA/CVB), aseptic meningitis (CVA/CVB), pleurodynia (CVB), or sporadically polio-like permanent paralysis (CVA-7). CVB-induced myo-/pericarditis may account for half the cases of sudden cardiac death [571].

CVA-21 causes upper respiratory tract infections, and it is considered one of the 'common cold' viruses [572]. Similarly to rhinoviruses, CVA-21 binds to ICAM-1 and additionally needs DAF-attachment for productive viral infection [573].

CVA-13, CVA-15 and CVA-18 were originally isolated from stool samples of

asymptomatic subjects [574].

5.1.4.2 Preclinical research

Given that ICAM-1 and DAF are overexpressed in melanoma cells, efforts to evaluate the oncolytic potential of CVA-21 (and other coxsackieviruses) have mainly focused on this disease [575]. Preclinical studies have reported oncolytic efficacy in immune deficient xenograft mouse models for melanoma, prostate and breast cancer [575-578], as well as *in vitro* oncolytic efficacy for multiple myeloma and chronic lymphocytic leukemia [579, 580]. Also, recent studies reported benefits of combination therapy with doxorubicin for treatment of breast cancer xenografts [581], docetaxel for NSCLC [582], and combinations with radiotherapy or chemotherapy were also found to be synergistic for treatment of bladder cancer [583]. Recently, it was shown that *in vivo* CVA-21 virus rescue was feasible by injecting infectious RNA into myeloma xenografts [584].

CVA-13, CVA-15 and CVA-18 were also found to be effective in immune deficient xenograft mouse models for melanoma [574], which can be an attractive alternative option given the fact that a high percentage of people have neutralizing antibodies against CAV-21.

By screening 28 (!) enteroviral strains, wildtype CVB-3 was recently added to the arsenal of oncolytic coxsackieviruses and evaluated as an option to treat NSCLC [585]. However, given the fact that CVB-3 is associated with acute and chronic cardiomyositis and pancreatitis [586], wildtype CVB-3 seems unsafe for administration to patients. Other groups have evaluated attenuated CVB-3 vectors for gene transfer to cardiomyocytes [587].

5.1.4.3 Clinical trials

Currently ongoing phase I/II clinical trials employing intratumoral injection of CVA-21 (CAVATAK) in patients with advanced melanoma in Australia are showing promising results [588].

5.1.4.4 Safety

Patient

Currently ongoing clinical trials have not led to serious adverse events.

Germline

CVA/B's replication cycle is confined to the cytoplasm and does not have an intermediate DNA step, which means no integration and/or subsequent germline transmission can occur.

Transmission

No information is available regarding shedding. When considering non- or low-pathogenic coxsackieviruses for oncolytic virotherapy, environmental risks can also considered to be low. However, when using viruses that do cause (severe) disease in humans, care should be taken to evaluate and/or attenuate these new vectors.

Mutagenesis/reversion

CVA/B, like other picornaviruses, possesses genomic instability and variability. Serial passage of CVB vectors expressing HIV-epitopes resulted in the truncated expression of larger inserted transgenes, although smaller (<20 kDa) transgenes where stably expressed after passaging [589]. Similarly, expression of GFP from an attenuated CVB-3 vector was maintained

up to 10 passages, although 23 viral nucleotide changes resulting in 10 amino acid mutations where present after 5 passages, without reversion to wildtype virulence [590]. As with shedding, these findings are important to include into the evaluation of pathogenic CVA/B (oncolytic) vectors.

5.1.5 Genus Enterovirus - Echovirus (EV)

5.1.5.1 General information

Echoviruses were first isolated from stool samples of asymptomatic humans. They were named ECHO, an acronym for Enteric Cytopathogenic Human Orphan, the latter meaning unassociated with known clinical disease. Echoviruses do not generally cause disease in mice, but in humans different types can cause several diseases including upper respiratory tract infection, aseptic meningitis, paralysis, encephalitis, exanthema, diarrhea, peri-/myocarditis, acute hemorrhagic conjunctivitis and hepatic disturbance. Natural infection with EV-1 is usually asymptomatic, although isolation of virus has been made from patients with mild upper respiratory infections. EV-1 binds to the integrin VLA-2 as its receptor, which can also be overexpressed on cancer cells [591].

5.1.5.2 Preclinical research

Preclinical studies have shown oncolytic efficacy of EV-1 in immune deficient mouse xenograft models for (peritoneally disseminated) ovarian, prostate and gastric cancer [577, 592, 593]. Another study has evaluated *in vitro* oncolytic activity for EV types 12, 15, 17, 26 and 29, which were also originally isolated from healthy individuals [594].

5.1.5.3 Clinical trials

No information available.

5.1.5.4 Safety

When considering non- or low-pathogenic echoviruses for oncolytic virotherapy, environmental and biosafety risks can also considered to be low. However, when using viruses that are associated with (severe) disease in humans, care should be taken to evaluate and/or attenuate these new vectors.

5.1.6 Genus Enterovirus - Poliovirus (PV)

5.1.6.1 General information

The vast majority of PV infections remain asymptomatic, but in 1-2% of cases infection results in neurological complications. Clinical polio syndrome is dominated by flaccid paralysis, due to cell tropism of PV for lower motor neurons in the spinal cord and brainstem expressing CD155/Necl-5 [595, 596]. CD155 (over)expression has also been shown in (neuro)ectodermal tumors, and transcriptional upregulation has been linked to signaling pathways commonly affected in malignancy, including Raf-Erk-Mnk signaling [597-599]. The neuropathogenicity of PV is dependent on the neuronal cell-type-specific function of its IRES element, which assures initiation of translation in a 5' end- and cap-independent manner. Mutations in the IRES genomic region or exchange with other viral IRES counterparts result in markedly neuro-attenuation in CD155-transgenic mice and non-human primates, without reducing the cytopathogenicity in

malignant cell types that express CD155 [600, 601]. Furthermore, restriction of PV replication in many murine tissues has been shown to be due to host innate immune responses and inability of IRES to interact with PTB1 [602, 603].

5.1.6.2 Preclinical research

Most preclinical research has been performed with PVS-RIPO, a recombinant PV type 1 (Sabin vaccine) strain with the IRES element of human rhinovirus type 2. PVS-RIPO has shown oncolytic efficacy in immune-deficient xenograft rat and mouse models of malignant glioma [604, 605].

5.1.6.3 Clinical trials

A currently ongoing phase I clinical trial with intratumoral infusion of PVS-RIPO in patients with recurrent GBM is showing durable responses [606].

5.1.6.4 Safety

Patient

Extensive evaluation in non-human primates has shown PVS-RIPO to be safe for either intraspinal or intrathalamic injection [601, 607]. No serious adverse events have been observed so far in an ongoing phase I clinical trial [606].

Germline

PV's replication cycle is confined to the cytoplasm and does not have an intermediate DNA step, which means no integration and/or subsequent germline transmission can occur.

Transmission

No observations of extraneural replication or shedding have been made in preclinical evaluation employing intraspinal or intrathalamic injection in non-human primates [601, 607].

Mutagenesis/reversion

One of the biggest concerns with PV is the inherent genomic instability of picornaviruses and thus the possible reversion to wildtype pathogenicity. PVS-RIPO has been evaluated extensively by e.g. serial passaging *in vitro* and *in vivo* and it was shown that escape mutants reverting to neuropathogenic virulence in the CD155-transgenic mouse model do arise [608]. Similar mutants have not been observed in human-like systems, which makes it unclear what the importance of this preclinical finding is in relation to clinical trials in humans.

5.1.7 Genus Senecavirus - Seneca Valley virus (SVV)

5.1.7.1 General information

Please refer to CGM 2010-10 (page 118-120) [214].

5.1.7.2 Preclinical research

Since its introduction as oncolytic virus in 2007, SVV has shown preclinical efficacy in immune deficient mouse xenograft models for NSCLC, retinoblastoma, rhabdomyosarcoma, Wilms tumors, glioblastoma and medullablastoma [609-614]. Interestingly, in these studies SVV

has been shown to cross the blood-brain-barrier and is effective in cerebral tumor eradication when injected intravenously. More recently, a recombinant SVV expressing GFP has been generated [615]. Another recent approach has been the development of a prodrug that can be activated by specific cleavage of the SVV 3C protease [616].

5.1.7.3 Clinical trials

Published results from a phase I clinical trial employing an intravenous dose escalation in patients with neuroendocrine tumors show that SVV is safe to administer even in high dose (10^{11} viral particles/kg) [617]. Also, intratumoral replication was observed as well as (marginal) treatment benefits. A phase II RCT in patients with extensive stage NSCLC and a phase I dose escalation trial in pediatric patients with neuroblastoma, rhabdomyosarcoma or rare tumors with neuroendocrine features are currently underway.

5.1.7.4 Safety

Patient

More evidence has now been gathered that SVV, although its natural host is still uncertain, is a safe virus to use for oncolytic virotherapy in (pediatric) patients. Please also refer to CGM 2010-10 (page 123-124) [214].

Germline

SVV's replication cycle is confined to the cytoplasm and does not have an intermediate DNA step, which means no integration and/or subsequent germline transmission can occur.

Transmission

Analysis of researchers in close contact with phase I trial patients revealed no detectable neutralizing antibody titers, which points to lack of effective viral transmission [617]. However, detailed evaluation of shedding was not performed.

Mutagenesis/reversion

Like other picornaviruses, SVV has an inherent genomic instability. Variable loss of GFP expression after numerous passages of recombinant SVV-GFP in culture without plaque purification was noted due to partial deletion of inserted transgenes at common RNA break points [615].

6 Order unassigned

6.1 Family Adenoviridae / Human adenoviruses

6.1.1 Genus Mastadenovirus - Human mastadenovirus (HAdV)

6.1.1.1 General information

Currently, all HAdVs (serotypes 1-57 in species A-G) are classified in the genus *Mastadenovirus*. HAdVs are large non-enveloped viruses with attachment fibers protruding from the viral capsid, encasing a linear non-segmented dsDNA genome of 26-48 Kbp, which encodes for 22-40 genes. Viral attachment using the fiber knob occurs through interaction with CD46 (species B), CD80/CD86 (type 3), CD46 and sialic acids (type 37), desmoglein-2 (types 3, 7, 11 and 14) or CAR (all other species) [618-622]. Secondary attachment of RGD motifs at the penton base with αv integrin results in endocytosis [623]. Upon acidification of the endosome, HAdV topology alters resulting in the translocation of the virion into the cytoplasm. Cellular microtubules transport the virion to the nucleus, where the viral DNA is released into the nucleus through the nuclear pore. HAdV genome replication takes place in the nucleus in an episomal state using the host's replication machinery and can be divided into an early and a late phase. Early genes express mainly non-structural, regulatory proteins which alter expression of host proteins necessary for DNA synthesis, activate other viral genes, and block host immune responses. Replication of the viral genome can occur once the early genes have generated adequate amounts of viral protein, replication machinery and substrate. A 5' end bound terminal protein serves as a primer for replication using the viral DNA polymerase. The late phase of replication mainly involves the production of sufficient structural proteins to encase the generated viral genomes. Cell lysis results in the release of progeny virus.

Important HAdV early genes and some of their known functions are:

- E1A: activates viral and cellular transcription; indispensable for replication and a potential oncogene
    - CR2 region: binds Rb
- E1B-19kDa: suppresses apoptosis by mimicking BCL-2; a potential oncogene
- E1B-55kDa: inactivates p53, mediates late viral RNA transport; a potential oncogene
- E1A+E1B: inhibition of inflammation [624]
- E2A & E2B: viral DNA replication machinery
- E3:
    - RIDα-10.4kDa: downregulates proapoptotic cell surface receptors, inhibits TNF-mediated cytolysis, inhibits NF-κB activation
    - CR1β-49kDa: modulates host immune responses
    - Gp-13kDa: inhibits MHC-I expression and peptide presentation
    - 14.7kDa: protect the virus from antiviral responses, inhibits cell death mediated by TNF-alpha and FasL receptors
- E4: regulation of viral DNA transcription

HAdVs can be associated with different diseases in humans: (upper) respiratory tract infection (mainly species B and C), conjunctivitis (species B and D) and gastroenteritis (species F and G). Rarely, HAdVs cause viral meningitis, encephalitis or hemorrhagic cystitis. Most patients

recover spontaneously, but immune compromised and sometimes healthy subjects can die of HAdV infection. HAdVs are spread by means of respiratory droplets or through the oral-fecal route, and virions are extremely stable outside of the human body, also in dry circumstances.

6.1.1.2 Preclinical research

Because of its association with mild disease and relatively easy to modify genome, most work on HAdV as vector for (cancer) gene therapy has been done with serotype 5 (HAdV-5) of species C. HAdVs have some distinct advantages as a gene transfer vector, including high transfection efficiency of cells irrespective of their growth status, easy to modify capsid and genome for retargeting and insertion of transgenes, and efficient production of high virus titers. Disadvantages are high immunogenicity of prevalent serotypes with pre-existing immunity, and transient expression of the transgene due to dilution of HAdV episomes upon cellular division.

Replication defective HAdV vectors (rdHAdV)

In the first generation rdHAdVs, the viral genome was modified by deleting E1A and/or parts of E1B and E3 genes (Figure 2A), and these viral genome deletions could be filled with transgenes (up to 8 kb) [625]. However, low-level viral replication still induced cellular immune responses against transduced cells, resulting in limited duration of gene expression *in vivo*. Second generation rdHAdVs therefore have been created which lack E2A and harbor mutations/deletions in E4, although controversy exist whether these vectors are more effective *in vivo* [626-628].

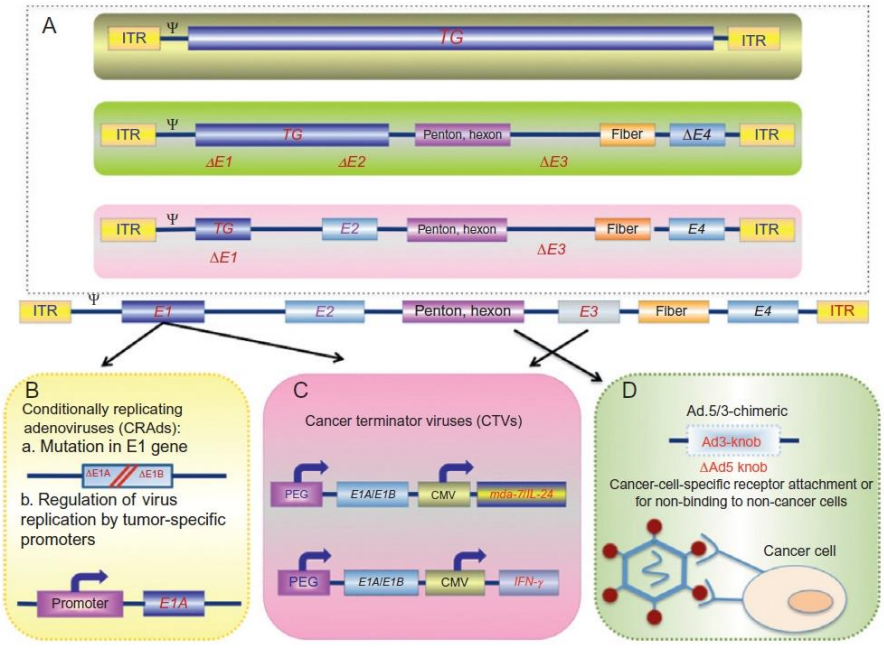

Figure 2. From: Das SK et al. *Advances in cancer research* 2012; **115:** 1-38 [629].

In another approach, third generation high-capacity 'gutless' or so-called helper-dependent HAdV vectors (hdHAdVs) have been created by removing the complete viral coding regions and leaving only the ITRs, permitting insertion of up to 37 kb of foreign sequences [628, 630]. The production of these hdHAdVs is dependent on a helper system, and the Cre*loxP* system is very successful in producing high titers virus stocks with very low amounts of

replicating helper virus contamination [631, 632]. This approach can also be used to create hybrid hdHAdV-retrovirus vectors, combining high infectivity with integration capacity [633].

In 1999, a dramatic fatal case of a systemic inflammatory response following intra-hepatic arterial administration of a second generation rdHAdV-5 in an 18-year-old patient enrolled in a phase I clinical trial put an abrupt stop to HAdV-5 procedures and led to a general rethinking of the approach [634]. More recent rdHAdV gene therapy vectors are being based on serotypes without pre-existing immunity in patients (most notably type 3), or modified capsids to prevent liver sequestration (see below) [635].

Conditionally replicating HAdV vectors (crHAdVs)

In the case of oncolytic HAdV vectors, replication is thought to be advantageous because of cancer cell killing by viral replication, reducing the number of administrations needed for effective treatment. As such, efforts have been made to develop crHAdVs (**Fig. 2B**), which specifically replicate (better) in cancer cells. Prime early examples are ONYX-015 (*dl1520*) and H101, which have a deletion of E1B-55kDa (and a deletion in E3 for H101), normally responsible for p53 binding and inactivation. Theoretically, deletion of this gene results in a crHAdV that is non-replicating in cells that express p53 (normal cells) and replicating in cells that lack p53 (cancer cells) [636]. Of note, later it was shown that the tumor specific replication of ONYX-015 was due to loss of E1B-55kDa-mediated late viral RNA export, rather than p53-inactivation [637].

In a similar approach, crHAdVs have been created exploiting the defects in Rb pathways in cancer cells by deleting the Rb-binding E1A-CR2 region (*dl922-947*; Delta24) [638, 639]. Additional modifications in Delta24 have also been created and evaluated for oncolytic efficacy [640-643]. Also, crHAdVs have been created targeting cells with an (over)active kRAS pathway [644] or with YB-1 overexpression [645-648]. More recently, crHAdVs harboring modifications in regulatory sequences upstream of E1A have also been shown to possess specific oncolytic efficacy [649, 650]. crHAdVs harboring mutations in E3 have also shown oncolytic efficacy [651-654]. Another crHAdV vector (AdDeltaDelta) has mutations in E1A-CR2 and E1B-19kDa with an intact E3 gene [655-657].

Promoter targeted crHAdVs

A different approach for creating crHAdVs is to use cancer or tissue specific promoters to limit expression of essential early HAdV genes to specific cells and/or tissues (**Fig. 2Bb**) [658, 659]. Examples of specific promoters include AFP [660-669], β-catenin [670], CAUT [671], CEA [672-675], CgA [676], COX-2 [677-681], CXCR4 [682-685], cyclin E [686], DD3 [687], E2F-1 [688-694], EH [690, 695, 696], eTie1 [697], G250 [698], hTERT [693, 699-765], hypoxia induced promoters [662, 691, 747, 749, 754-756, 763, 766-768], IAI.3B [769], Ki67 [770, 771], MDR1 [772, 773], melanocyte and melanoma-specific tyrosinase [705, 774-776], midkine [777-782], mortalin [783], MUC1 [731, 784-786], ODD [787], osteocalcin [788], p53 [717, 789, 790], PEG-3 [791-794], prostate specific promoters (e.g. PSES/PS(M)A) [795-808], S100A2 [809], SCCA1 [810], SCG3 [811], SLPI [812, 813], SPARC [768, 814], survivin [815-827], uPAR [828, 829], uroplakinII [803, 830], VEGFR-1 [831] and Wnt [832]. More recently, miRNA regulated expression of essential viral HAdV genes has also been evaluated [676, 738, 833-838]. Using FLP recombination target sites, a replication defective HAdV vector can be recombined into a replication competent HAdV, which might open new possibilities for retargeting [839, 840].

Expression of transgenes

Like other oncolytic viruses that have undergone extensive development, crHAdVs have also been armed with transgenes (**Fig. 2C**), often under the control of a tissue/cancer specific promoter as mentioned above. Examples include: marker genes [679, 805, 841], suicide/pro-apoptotic genes/siRNA/miRNA [168, 654, 664-668, 673, 675, 688, 691, 696, 698, 705, 709, 713, 718, 723, 726, 730, 734, 739, 743, 744, 748, 752-755, 761-763, 770, 771, 777, 794, 797, 801, 805, 818, 819, 821, 823, 825, 842-880], prodrug converting enzymes [671, 729, 872, 881-886], radiation localizers (radiovirotherapy) [639, 669, 746, 802, 807, 826, 832, 887-890], anti-angiogenic proteins [691, 715, 891-897], STAT3 inhibitors [898-900], ECM modulators [684, 728, 901-903], viral replication enhancers [904-906], fusogenic proteins [697, 764, 907], immune checkpoint blockers [908], osteoclastgenesis inhibitors [909] and of course immunomodulatory genes [663, 666, 674, 680, 681, 687, 707, 740, 745, 749, 756, 766, 767, 787, 791, 792, 794, 805, 817, 823, 827, 831, 837, 862, 863, 872, 910-947].

Optimizing biodistribution of crHAdVs

Despite the capacity to achieve tumor infection in animal models, the therapeutic efficacy of crHAdVs has been disappointing. The discrepancy between preclinical and clinical studies using crHAdV-5 could be explained by the differences in expression of CAR in primary tumors compared to established laboratory cell lines [948]. In addition, biodistribution of intravenous administered crHAdV is not solely determined by CAR expression in tissue [949]. Off-target toxicity by transduction of mainly the liver is a serious concern, even when crHAdVs are blinded for CAR [950-953]. This has been shown to be due to blood factors opsonization of crHAdV virions for Kupffer cell uptake, which can be counteracted by ablating the fiber region that interacts with these blood factors [954], although other studies have implicated the viral hexon to be a more potent binder of blood coagulation factor X [955, 956]. Hexon mutations or even complete exchange of hexons have been shown to reduce liver sequestration and transduction dramatically [957-959]. Other strategies used are PEGylation or polymer/dendrimer coating of crHAdV virions [888, 889, 935, 960-971], and cell-based or magnetic/liposomal nanoparticle delivery techniques [766, 769, 788, 799, 810, 824, 894, 972-992].

Retargeting crHAdV virions

To circumvent the limitation of low CAR expression in (tumor) cells, retargeting has also been applied to crHAdVs, permitting CAR-independent infection [993]. The strategy of retargeting can also circumvent existing humoral immunity for HAdV-5 in the general population, and aid in prevention of liver sequestration as described above. Examples include conjugation with anti-knob or anti-penton/hexon antibodies or adapters with retargeting ligands [678, 812, 964, 994-1024], pseudotyping or xenotyping with (chimeric) fiber knobs or capsids (**Fig. 2D**) [639, 682, 683, 685, 725, 740, 768, 772, 773, 776, 779-782, 814, 816, 822, 824, 837, 848, 851, 859, 867, 876, 890, 891, 908, 919-923, 928, 945, 947, 987, 1025-1051], peptide presentation (RGD or other) [682, 705, 785, 813, 820, 831, 846, 847, 909, 1010, 1026, 1027, 1037, 1038, 1050, 1052-1069], Affibody targeting [1070-1072], knob-less HAdVs [1073-1078] and genetically modified capsids and/or fiber knobs [778, 811, 837, 877, 1048, 1079-1100].

More recently, efforts have also been made to develop crHAdVs based fully on other serotypes, most notably HAdV-3 [742, 835, 986, 1101-1111], or even non-human AdVs (see next paragraphs). Using ‘directed evolution’ or ‘accelerated evolution’ strategies, other groups have reported the development of ColoAd1 and other crHAdVs which appear to be more potent than

parental HAdV-5 based vectors [849, 1112-1114]. Another interesting strategy is to develop genetically modified capsids incorporating marker proteins to visualize crHAdV infection and biodistribution [1115, 1116].

Combination therapies

Combination therapy with crHAdVs has also been evaluated in preclinical studies, including combination with radiotherapy [722, 804, 860, 864, 882, 936, 992, 1096, 1117-1121], chemotherapy [643, 647, 656, 657, 661, 686, 714, 721, 725, 727, 745, 747, 770, 773, 798, 820, 850, 856, 871, 875, 880, 899, 906, 917, 918, 920-923, 927, 933, 992, 999, 1000, 1046, 1096, 1122-1136], chemoembolization [1137], ECM degradation [1138, 1139], ultrasound guidance/induction [690, 966, 1140-1142], immunomodulation [719, 749, 750, 886, 1121, 1143-1148] and verapamil [1149, 1150].

Combinations of strategies for rdHAdV and crHAdV retargeting, expression of (multiple) viral and/or transgenes under control of specific promoters, delivery options and combination with other treatment modalities make for a virtually infinite number of treatment options to be evaluated for a large number of different types of cancer and models. However, studies describing direct comparisons between different prototype HAdV vectors are scarce, which makes it difficult to predict which HAdV will make it into clinical trials [879, 1151].

6.1.1.3 Clinical trials

458 clinical trials employing HAdV-mediated gene therapy have been reported to date. First and second generation rdHAdVs (mostly type 5, some type 2) have been evaluated in clinical trials for non-malignant diseases like CF [1152-1159], age-related macular degeneration [1160], coronary arterial disease [1161-1172], peripheral arterial disease [1173-1180], venous leg ulcers [1181], hip prosthesis loosening [1182], radiation-induced salivary hypofunction [1183], and choroideremia [1184]. Generally, gene transfer was transient and inefficient, and phase II/III trials including enough patients to evaluate treatment outcomes mostly did not show significant treatment benefits of rdHAdV mediated gene therapy [1166, 1171, 1176, 1180]. Dose limiting inflammation was sometimes observed, exemplified by an early lethal case report [634]. No clinical product based on rdHAdVs has been approved by the EMA or FDA thus far. Clinical trials employing third generation (hybrid) rdHAdVs or rdHAdVs based on other serotypes can be expected in the near future.

Similarly, rdHAdVs have also been evaluated extensively as (mostly locally administered) gene therapy vectors harboring anti-neoplastic proteins (most notably p53), suicide genes (e.g. HSV-tk) or immunomodulating genes (e.g. TNFα, IFN, IL-2, IL-12) in clinical trials for malignant diseases like lung cancer [1185-1194], mesothelioma [1195-1199], head and neck cancer [1191, 1200-1207], prostate cancer [1208-1215], breast cancer [1191, 1216, 1217], melanoma [915, 1191, 1216, 1218, 1219], ovarian cancer [1220-1225], brain tumors [1226-1233], leukemia [1234, 1235], colorectal cancer [1191, 1236, 1237], hepatic metastases from colorectal cancer [1238-1241], bladder cancer [1191, 1242-1245], pancreatic cancer [1191, 1236, 1246, 1247], sarcoma [1191], esophageal cancer [1191, 1248, 1249], biliary cancer [1191], HCC [1191, 1236, 1239, 1250-1252], adrenal cancer [1191], lymphoma [1253], and retinoblastoma [1254]. Also in these phase I/II trials for malignant diseases only transient gene transfer was observed with low efficiency and low tumor penetration, even with intratumoral injection, although most trials reported good safety profiles.

Evaluations of anti-tumor efficacy so far have been disappointing, leading the field

towards the use of retargeted rdHAdVs and crHAdVs [1233, 1247, 1255]. In China, Gendicine (rdHAdV-5 expressing p53) was approved for clinical use in patients with head and neck cancer in 2003 [1256]. However, its American and European alternative, Advexin, has never been approved for clinical application, due to insufficient safety and efficacy data [1257]. Similarly, the assessment of Cerepro (rdHAdV-5 expressing HSV-tk in combination with gancyclovir) for marketing authorization in patients with high-grade glioma resulted in a negative advise from EMA, after having failed to show improvement in overall survival [1233, 1258].

ONYX-015, H101 (Oncorine) and other first-generation crHAdVs have gone through several phase I/II trials without relevant signs of toxicity [1259]. However, the therapeutic effect was also disappointing, resulting in the discontinuation of further trials with these first generation oncolytic crHAdVs. Although Oncorine is registered for use in head and neck cancer patients in China, ONYX-015 was never approved by the FDA.

More recent clinical trials employing new generations of crHAdVs like RGD retargeted oncolytic crHAdVs [1260-1264], crHAdV-5/3 chimeric vectors [928, 945, 1265-1268], ColoAd1 [1269], hTERT-promoter driven crHAdV-5 vector Telomelysin [724], E2F-1-promoter driven CG0070 [937] and crHAdV vectors expressing immunomodulating genes [707, 925, 928, 937, 945, 1267, 1270] have shown safety with some promising preliminary results. Furthermore, combination therapy with low-dose cyclophosphamide, temozolomide or verapamil has been evaluated [1150, 1271, 1272], and cell-based carriers have also been used [692]. In 2011, the Finnish Advanced Therapy Access Program has concluded after running for 5 years, and the group of Akseli Hemminki will continue with 'normal' clinical phase I/II/III trials with their prime crHAdV candidate CGTG-102 [1273]. Also currently ongoing is a clinical trial using Rb-targeted crHAdV expressing hyaluronidase (VCN-01) [1274]. Clearly, there is a revival ongoing in the use of new generations of crHAdVs, and if these oncolytic HAdVs meet the expectations, more phase III trials can be expected.

6.1.1.4 Safety

Patient

In general, the use of first and second generation crHAdVs appears to be reasonably safe when administered locally and at lower doses systemically. However, the development of new crHAdVs expressing transgenes, with altered capsids, or different promoters can dramatically alter this perceived safety. Therefore, it is important to thoroughly evaluate newer crHAdVs for their patient safety in human-like animal models, since it is likely that these new agents will proceed into (more) phase I/II/III clinical trials.

Germline

While adenovirus vector DNA is perceived to remain as an episome following gene transfer, adenovirus vectors have been shown to integrate into host genomes at low efficiency (10^{-3}-10^{-6} per cell) through homologous and heterologous recombination [1275-1277]. Although this occurrence rate might seem low, it should be noted that clinical trials employing HAdV vectors use up to 10^{13} viral particles per dose. Preclinical experiments addressing germline transmission of HAdV vectors have mostly reported no evidence for this [1278-1285], although infection of oocytes, spermatozoa or embryos is possible and some reports have noted chromosomal integration after HAdV-mediated gene transfer into zona-free oocytes of mice [1286, 1287].

Transmission

Shedding of rdHAdVs and crHAdVs from injection sites and patient excretions, although certainly not always reported, has been observed in several (pre)clinical trials, and increases with dosage and systemic administration [796, 1193, 1202, 1216, 1231, 1250, 1257, 1260, 1288-1290].

Mutagenesis/reversion

HAdV vectors have been shown to be able to package up to 75-105% of their wild-type genome length as DNA. By introducing deletions in the parental genome, the inserted genes can of course be bigger. Bigger (>105%) or smaller (<75%) genomic DNA containing HAdV vectors grow very poorly and undergo rapid genome rearrangement which mostly results in the loss of the inserted gene(s) after only a few *in vitro* passages. In contrast, HAdV vectors with a genome length just below 105% grow very well and are relatively stable when passaged [625, 1291-1293]. It has also been shown that viral DNA contributes to capsid strength and integrity, meaning that HAdV vectors with smaller genomes are more sensitive to heat inactivation and have a lower infectivity [1294-1296].

Homologous recombination between AdVs of the same subgroup occurs with high efficiency during growth in co-infected cultured cells, and there is evidence of recombination events in humans too [1297-1302]. Theoretically, homologous recombination between wildtype AdVs and recombinant crHAdVs could lead to new wildtype AdVs that e.g. possess transgenes, or worse, have expanded tissue tropism due to retargeting strategies. Such recombination has never been detected in any clinical trial to date.

6.2 Family Adenoviridae / Non-human adenoviruses

6.2.1 Genus Mastadenovirus - Bovine mastadenovirus type 3 (BAdV-3)

6.2.1.1 General information

BAdV-3 (species B) was isolated from the conjunctiva of a healthy cow, and shares a high genomic similarity to HAdV-5 [1303, 1304]. Sialic acids serve as a primary receptor for BAdV-3, which results in a very broad cell tropism, and pre-existing anti-HAdV-5 humoral or cellular immunity does not neutralize BAdV-3 [1032, 1305-1308]. BAdV-3 causes mild disease in susceptible calves, leading to acute febrile respiratory disease and sometimes diarrhea, and serologic surveys have indicated the worldwide spread of BAdV-3 [1309-1311].

6.2.1.2 Preclinical research

BAdV-3's E3 gene is not essential for virus replication in tissue culture, although deletion does lead to a tenfold decrease in virus titers [1312]. To develop a replication defective BAdV-3 vector lacking the E1 gene, bovine helper cells transformed with HAdV-5 E1A were created [1313, 1314]. Like HAdVs, BAdV-3 keeps its genome in an episomal state in an infected cell [1315, 1316]. The packaging genome sequences have been identified, but this has not yet lead to development of 'gut-less' BAdV-3 vectors [1317]. Chimeric BAdV-3 with HAdV-5 fiber knobs or with RGD-enhanced capsids have shown increased transduction efficacy [1318-1320]. One study has shown that replication deficient BAdV-3 is capable of transducing tumor cells *in vivo*, even in

the presence of anti-HAdV-5 immunity [1321].

6.2.1.3 Clinical trials

No information available.

6.2.1.4 Safety

Patient

No information available.

Although BAdV-3 is not as much sequestrated by the liver, it does induce higher innate immune responses and spreads systemically in mice, making it essential to evaluate the safety of this vector in a human-like model [1321, 1322].

Germline

Similar to HAdVs, BAdV-3 keeps its genome in an episomal form, and genomic integration has not been observed [1315, 1316].

Transmission

No information available.

Mutagenesis/reversion

Although genomically similar to HAdV-5, due to lack of homology, recombination between BAdV-3 vectors and wildtype HAdV is very unlikely.

6.2.2 Genus Mastadenovirus - Canine mastadenovirus type 2 (CAdV-2)

6.2.2.1 General information

CAdV-2 causes respiratory (tracheobronchitis; kennel cough) and enteric disease in dogs, and is sometimes found in their CNS. Modified live vaccines are very effective in immunizing against infection [1323, 1324]. CAdV-2 infects cells through CAR and αvβ5 integrins [1325].

6.2.2.2 Preclinical research

CAdV-2 E1-deleted vectors have been evaluated for gene transfer [1326-1328]. To circumvent the cellular immune responses to these first generation CAdV-2 vectors, the more recent focus of research has been on ‘gut-less’ helper-dependent CDaV-2 vectors (hdCDAdV-2), which can achieve long lasting (>1 year) transgene expression in neuronal tissue with high cloning capacity (30 kb) [1329, 1330].

Cell tropism of (hd)CAdV-2 is remarkably strong for neurons, inducing retrograde axonal transport, and transduction of the respiratory tract in mice was also successful and long lasting [1331-1334]. Human plasma, memory T-cells and DCs have a notably lower immune response to CAdV-2 as compared to HAdV-5 [1327, 1335-1337].

A conditionally (osteocalcin promoter) replicating CAdV-2 was evaluated preclinically for canine osteosarcoma, and was also shown to be safe when injected into healthy dogs [1338, 1339]. More recently, a conditionally (E2F promoter controlling E1A + Delta24) replicating, tissue tropism expanded (RGD), hyaluronidase expressing CAdV-2 (ICOVIR17) was evaluated

preclinically for canine osteosarcoma and melanoma and subsequently used for treatment of 6 dogs with different tumor types [1340].

6.2.2.3 Clinical trials

No information available.

6.2.2.4 Safety

Patient

No information available.

When thinking of veterinary use, with 'canine patients', CAdV-2 seems safe to use. However, when applied to human use, the same consideration apply as for BAdV-3 (see above), although CAdV-2 seems to have a more favorable immune response profile.

Germline

No information available.

Transmission

No information available.

Mutagenesis/reversion

Due to lack of homology, recombination between CAdV-2 vectors and wildtype HAdV is very unlikely.

6.2.3 Genus Mastadenovirus - Porcine mastadenovirus type 3 (PAdV-3)

6.2.3.1 General information

PAdV-3 is not associated with any clinical disease in pigs, and neutralizing antibodies are present in >90% pigs. In the human population, neutralizing antibodies for PAdV-3 do not exist and HAdV-5 humoral or cellular immunity does not cross-react [1032, 1307, 1308, 1341]. PAdV-3 shares structural and genomic similarities with HAdV-5 with E1-E4 genes, and its E3 gene is dispensable for virus replication and can be used to replace with foreign genes [1342]. The cellular receptor for PAdV-3 has not yet been determined, but viral entry is independent of CAR and integrins.

6.2.3.2 Preclinical research

Replication defective PAdV-3 vectors lacking the E1A and/or E3 gene have been evaluated and found to be of similar potency as HAdV-5 in transducing human and murine cell lines, undergoing abortive infection in these cells [1032, 1341, 1343-1345]. Biodistribution of intravenously injected PAdV-3 was comparable to HAdV-5, with more rapid vector clearance [1316]. Also, administration of PAdV-3 lead to more immune activation and depletion of Kupffer cells in the liver [1322].

6.2.3.3 Clinical trials

No information available.

6.2.3.4 Safety

Patient

No information available.

PAdV-3 induce higher innate immune responses and spreads systemically in mice while depleting Kupffer cells, making it essential to evaluate the safety of this vector in a human-like model [1322]. So far, other non-human AdVs look like a more attractive choice for further development.

Germline

Similar to HAdVs and BAdV-3, PAdV-3 keeps its genome in an episomal form, and genomic integration has not been observed [1315, 1316].

Transmission

No information available.

Mutagenesis/reversion

Due to lack of homology, recombination between PAdV-3 vectors and wildtype HAdV is very unlikely.

6.2.4 Genus Mastadenovirus - Simian mastadenovirus (SAdV; chimpanzee AdV, ChAdV)

6.2.4.1 General information

SAdV-25 (ChAdV-68; Pan9) does not cause any apparent clinical symptoms in chimpanzees, while >80% of them have neutralizing antibodies, as opposed to only 2% in the general human population [1346-1348]. SAdV-25 was originally isolated from a mesenteric lymph node of a chimpanzee, and has high sequence identity with HAdV-4, with a less similar hexon hypervariable domain [1347, 1349]. SAdV-25 uses CAR as its target cellular receptor [1350].

SAdV-22 (Pan5), SAdV-23 (Pan6) and SAdV-24 (Pan7) have been isolated from chimpanzee lymph nodes in the same study as SAdV-25, and are genetically similar to it [1348, 1351]. No neutralizing antibodies for these SAdVs are present in human serum samples [1352].

6.2.4.2 Preclinical research

SAdV vectors have been evaluated extensively as vaccine vector, most notably for HIV, which is beyond the scope of this report [1353-1357].

Like with other non-human AdV vectors, the rescue of recombinant E1-deleted replication defective SAdV in cell lines that complement HAdV-5 E1 is not associated with any potential risk of generating replication competent vectors, and the non-essential E3 gene can be replaced with transgenes [1347, 1352]. SAdV-22, SAdV-23 and SAdV-24 were also developed into E1-deleted gene transfer vectors, with cross-neutralizing antibodies being generated between SAdV-22, SAdV-24 and SAdV-25, but not SAdV-23 [1352]. SAdV transduction capacity is generally comparable to that of HAdV-5, with lower hepatic sequestration [1350, 1352, 1358]. SAdV-24 targeting using Her2-targeted fiber protein has also been described [1358].

6.2.4.3 Clinical trials

No information available.

6.2.4.4 Safety

Patient
No information available.

Clinical trials using replication defective SAdV-25 vaccine vectors have reported good safety upon intramuscular administration [1359-1362].

Germline
No information available.

Transmission
No information available.

Mutagenesis/reversion

Although genomically similar to HAdV-4, due to lack of homology, recombination between SAdV-vectors and wildtype HAdV is very unlikely.

6.2.5 Genus Atadenovirus - Ovine atadenovirus type 7 (OAdV-7)

6.2.5.1 General information

OAdV-7 (type D) is the only sheep isolated ovine AdV assigned to the genus *Atadenovirus*, because it has a distinct genome organization with a high AT content and the lack of a clearly defined E1 region [1363-1365]. It causes no apparent disease in sheep or any other mammals it has been tested in so far [1366]. The receptor for OAdV-7 is still unknown, and the fiber and capsid lack a recognizable integrin-binding motif [1367]. OAdV-7 does not possess transforming ability, probably due to the lack of E1 genes [1368].

OAdV-7 neutralizing antibodies are not present in the general population and HAdV-5 immunity does not neutralize OAdV-7 in mice [1369].

6.2.5.2 Preclinical research

OAdV-7 has three non-essential genomic regions that can be used for insertion of transgenes: sites I, II and III [1364, 1366, 1370-1372], with III resulting in the most stable vectors [1373]. A range of human cell lines can be infected, leading to abortive replication without evident cytopathic effect, except in primary fibroblasts [1371, 1374]. Liver sequestration is less for OAdV-7 vectors compared to HAdV-5 [1369].

OAdV-7 vectors have been evaluated expressing transgenes like α1-antitrypsin [1369, 1375], factor IX [1373] and it was noted that high doses of OAdV-7 lead to immune responses, resulting in transient gene expression. Expression of pro-drug converting enzyme PNP was effective in reducing syngeneic murine or human xenograft prostate tumor sizes [1376-1379]. Even though this vector was described as highly potent and systems were developed for clinical grade production [1380], no results on a phase I clinical trial has been reported thus far (NCT00625430). More recently, OAdV-7 was used as a tumor vaccination vector [1381]. Chimeric OAdV-7 with HAdV-5 fiber knobs has been shown to have expanded human tissue tropism due to CAR-targeted infection [1367].

6.2.5.3 Clinical trials

No information available.

6.2.5.4 Safety

Patient

No information available.

Germline

No information available.

Transmission

No information available.

Mutagenesis/reversion

Due to lack of homology, recombination between OAdV-7 vectors and wildtype HAdV is very unlikely [1382].

6.2.6 Genus Aviadenovirus - Fowl aviadenovirus type 1 (FAdV-1; chicken embryo lethal orphan virus, CELO)

6.2.6.1 General information

FAdV-1 exists as a latent virus in eggs and can produce subclinical infections in chickens and (fatal) upper respiratory tract infection in quail and sparrows [1383, 1384]. Furthermore, FAdV-1 has been described as an oncogenic virus, causing tumors in hamsters and capable of *in vitro* transformation of mammalian cell lines [1385, 1386]. This stems from the HAdV-5 E1B homologue GAM-1 and Orf22, which interact with Rb leading to E2F-regulated transcription activation [1387, 1388]. FAdV-1 is clearly different from HAdVs, since it has only low sequence homology, a larger genome (~44kb) and two fibers of different length at each vertex [1389]. It does use the CAR as entry receptor [1390].

6.2.6.2 Preclinical research

FAdV-1 has been developed as a replication deficient gene therapy vector, and can transduce human lung, liver and kidney cells [1390-1392]. Russian groups have developed FAdV-1 vectors harboring GFP, IL-2, angiogenine, p53 and HSV-tk, although it sometimes remains unclear which FAdV-1 backbone was used in these studies, especially regarding deletions of GAM-1 and/or Orf22 [1393-1396]. In these studies, anti-tumor activity was shown in isograft mouse models of melanoma and xenografts of epidermoid carcinoma. Also, RGD was incorporated into fiber 1, which resulted in expanded tissue tropism [1397]. Packaging signals for FAdV-1 have also been described, although this has not yet lead to the development of a 'gut-less' helper-dependent FAdV-1 vector [1398].

6.2.6.3 Clinical trials

No information available.

6.2.6.4 Safety

Patient
No information available.

Given the oncogenic nature of FAdV-1 in hamsters, only GAM-1/Orf22 deleted vectors should be considered for clinical use.

Germline
No information available.

Transmission
No information available.

Mutagenesis/reversion

Due to lack of homology, recombination between FAdV-1 vectors and wildtype HAdV is very unlikely.

6.3 Family Baculoviridae

6.3.1 Genus Alphabaculovirus - Autographa californica multiple nucleopolyhedrovirus (AcMNPV)

6.3.1.1 General information

AcMNPV is considered the prototypic baculovirus, with a circular dsDNA genome (~134 kb) inside a rod-shaped nucleocapsid. The virus is a strictly insect pathogen and does not cause disease in vertebrates [1399]. Budded AcMNPV virions have an envelope derived from the host cell membrane, and enter subsequent host cells by endocytosis/phagocytosis, although the specific receptor and exact endocytotic pathways are unknown [1400-1403].

6.3.1.2 Preclinical research

Virtually all cell types (including stem cells), both nondividing and dividing, from several species can be transduced by baculoviruses [1404-1408]. Adding transgenes into the AcMNPV genome is theoretically without limit, given that the viral capsid extends to accommodate its (larger) genome. AcMNPV infects human cells and expresses transgenes under control of mammalian (BacMam) or constitutionally active viral promoters, but does not replicate or cause cytotoxicity in these cells [1409-1411].

Immunoprivileged sites like the CNS, eye and testis have been shown to be good targets for *in vivo* gene delivery by AcMNPV, while systemic application is hampered by inactivation by serum complement [1412-1414]. Ample research has been devoted to counteracting this problem [1415-1417], while direct injection of target tissue (including tumors) circumvents complement inactivation [1418-1426]. Modification of the virus surface through capsid modification, xenotyping (e.g. with VSV-G) or coating can further augment the infectivity of AcMNPV, while simultaneously overcoming the limitation of complement inactivation [1412, 1415, 1427-1432].

Incorporating WPRE boosts AcMNPV mediated transgene expression significantly [1433]. AcMNPV-mediated transient high-level transgene expression has been used in the

transduction of stem cells [1434]. By incorporating AAV's integrating sequences into AcMNPV vectors, stem cells can also be stably transduced [1435, 1436].

Baculovirus hybrid viruses have been developed to apply episomal or transposon systems, such as SB or PB [1437] and ZFN [1438].

AcMNPV cancer gene therapy has been shown effective in mouse models for epidermal tumors [1439], glioma [1440], prostate cancer [1441] and other solid tumors [1442]. Also, AcMNPV-infected DCs can induce antitumor immunity [1443] and systemic administration of wildtype virus leads to NK cell stimulation with anti-tumor effects [1426]. Somatic gene therapy using AcMNPV vectors has mainly focused on tissue engineering, like cartilage and bone regeneration [1444].

AcMNPV vectors have also been developed as a vaccine vector and as production 'factories' for recombinant proteins and other viruses, which is beyond the scope of this report [1434, 1445].

6.3.1.3 Clinical trials

No information available.

6.3.1.4 Safety

Patient

No information available.

Germline

Transduction of human mesenchymal stem cells with AcMNPV did not result in chromosomal integration [1446].

Transmission

No information available.

Mutagenesis/reversion

Since AcMNPV does not replicate in human cells, mutagenesis upon administration is also unlikely.

6.4 Family Birnaviridae

6.4.1 Genus Avibirnavirus - Infectious bursal disease virus (IBDV)

6.4.1.1 General information

Please refer to CGM 2010-10 (page 67-68) [214].

6.4.1.2 Preclinical research

Recently, only one publication has described the use of IBDV as vaccination vector for hepatitis C [1447]. Please also refer to CGM 2010-10 (page 68) [214].

6.4.1.3 Clinical trials

Please refer to CGM 2010-10 (page 68-69) [214].

6.4.1.4 Safety

Please refer to CGM 2010-10 (page 69-71) [214].

6.5 Family Flaviviridae

6.5.1 Genus Flavivirus - West Nile virus Kunjin (WNV-KUN)

6.5.1.1 General information

WNV-KUN is endemic in northern Australia and usually causes asymptomatic infection in humans, although rare cases of mild fever and/or mild encephalitis have been described [1448, 1449]. Outside of this region, most people in the general population do not have neutralizing antibodies directed at WNV-KUN. Following extensive flooding in Eastern Australia in 2011, mosquito vectored virulent WNV-KUN caused a major outbreak of equine encephalitis, although only one mild human case was reported [1450].

6.5.1.2 Preclinical research

Most research has focused on the use of WNV-KUN RNA replicon-based gene delivery systems [1451-1453]. The basic principle of such a system is the packaging of transgenes into the genome of WNV-KUN virus-like particles (VLPs), which lack structural genes in their genome. These VLPs can be used to infect/transfect cells where the replicon RNA is continually amplified by replicon encoded RNA replicases, resulting in high levels of gene expression without viral replication [1454]. dsRNA replication intermediates serve as innate immune stimulators, although WNV-KUN replicons do not induce apoptosis or cytopathic effects. Interestingly, dividing WNV-KUN replicon-transfected cells retain replicon RNA and continue to produce its corresponding recombinant protein [1455].

A WNV-KUN replicon vector encoding for GM-CSF with increased type I IFN induction was shown effective in clearing syngeneic colon carcinoma and melanoma tumors in mice [1456]. WNV-KUN replicon vectors have also been developed as (tumor) vaccine vectors, which is beyond the scope of this report [1457-1460].

6.5.1.3 Clinical trials

No information available.

6.5.1.4 Safety

Patient

No information available.

Germline

WNV-KUN based replicon vectors only deliver RNA without a DNA step in their replication, so there is no risk of genomic integration.

Transmission

No information available.

Mutagenesis/reversion

RNA recombination in flavivirus systems appears to be very rare, making the risk of generating potentially infectious recombinant viruses very low.

6.6 Family Orthomyxoviridae

6.6.1 Genus Influenzavirus A - Influenza A virus (IAV)

6.6.1.1 General information

IAVs are classified according to their antigenic properties based on the glycoproteins HA (17 subtypes) and NA (10 subtypes) [1461]. All subtypes (except H17N10) circulate in aquatic birds, causing asymptomatic gastrointestinal or respiratory infection [1462]. IAV is a (-)ssRNA virus with 8 gene segments, coding for up to 16 proteins. HA protein is initially synthesized as a polypeptide precursor (HA0), which has to be cleaved by cellular proteases to active HA1 and HA2 subunits, in order to produce infectious virus particles [1463]. The sequence of the HA cleavage site defines by which type of proteases HA0 can be cleaved, resulting in LP and HP strains, the latter of which the HA0 can be cleaved by more abundant proteases [1464, 1465]. HP avian IAV therefore causes systemic disease with high mortality in birds [1461]. NS1 protein is a non-structural protein that has potent antagonistic effects on PKR mediated cellular innate immunity and apoptosis [1466, 1467].

Zoonotic events of avian IAV transmission to humans are rare due to decreased polymerase activity and difference in cellular receptors [1468]. However, severe pandemics in the human population have occurred in 1918, 1957, 1968 and most recently in 2009 with a triple (including swine IAV) reassortant virus [1469-1471]. Subsequently, these pandemic viruses become established in the human population and cause seasonal epidemics. These epidemics still result in 3-5 million cases of severe illness yearly worldwide, with 250.000-500.000 lethal cases, mostly in older and/or immune-compromised patients. Prophylactic vaccination is applied on a large scale, although antigenic drift makes that the vaccine composition has to be updated almost annually [1472]. Clinical symptoms associated with human IAV infection include high fever, headache, nonproductive cough and muscle aches. Uncomplicated disease resolves spontaneously within several days. However, complications of IAV infection include viral pneumonia and secondary bacterial pneumonia, which can lead to death.

6.6.1.2 Preclinical research

IAV infection induces apoptosis or necrosis in cultured (tumor) cells [1473, 1474]. This observation has led several groups to evaluate IAV as an oncolytic virus. Deletion or truncation of NS1 from IAV (ΔNS1-IAV) leads to a virus that is non-replicating in cells that express normal PKR. However, tumor cells can either have defective PKR or overexpression of kRAS that leads to inhibition of PKR. These tumor cells are susceptible to ΔNS1-IAV oncolysis, as shown in xenograft mouse models of melanoma and colon carcinoma [1475-1478]. Expression of IL-15 from this ΔNS1-IAV resulted in more oncolysis *in vitro* [1479]. A panel of IAVs from several host species (including HP strains) was evaluated for their ability to infect pancreatic adenocarcinoma cells *in vitro* and *in vivo*, with H7N3 IAV causing tumor regression in tumor xenografts of melanoma [1480].

A recent study showed that IAVs with alteration in NS1 and PB1-F2 are also conditionally replicating in IFN-deficient cells, with increased apoptosis and efficacy in an immune-deficient mouse xenograft model for pancreatic cancer [1481]. Also, expression of IL-15 from a stable ΔNS1 chimeric IAV vector was shown effective in a syngeneic mouse model for melanoma [1482].

6.6.1.3 Clinical trials

No information available.

6.6.1.4 Safety

Patient

No information available.

Germline

IAV's replication cycle is confined to the cytoplasm and does not have an intermediate DNA step, which means no integration and/or subsequent germline transmission can occur.

Transmission

Seasonal IAV viruses spread very efficient from human to human. No information is available for ΔNS1-IAV viruses.

Mutagenesis/reversion

Although IAV is an RNA virus with an inherent higher viral polymerase error rate due to the lack of proofreading, spontaneous reversion of ΔNS1-IAV to wildtype IAV seems unlikely. However, recombination with other wildtype IAVs could theoretically lead to reassortant chimeric IAVs with wildtype-like properties expressing transgenes.

6.7 Family Parvoviridae / Subfamily Parvovirinae

6.7.1 Genus Dependoparvovirus - Adeno-associated dependoparvovirus (AAV)

6.7.1.1 General information

AAVs were first discovered as small (22µm) non-enveloped virus-like particles in preparations of human and simian adenoviruses [1483]. These AAV serotype 2 (AAV-2) particles were found to be infective, but only replication competent in the presence of adenovirus replication (and later also of HSV-1/2), hence the name 'adeno-associated virus' [1484-1486]. No disease has been associated with AAV in either human or animal populations.

The genome of AAV is composed of linear ssDNA with two open reading frames (rep and cap) of 4675 nucleotides, flanked by ITRs of 145 bases [1487-1490]. The ITR is the origin of DNA replication and serves as a primer for second strand synthesis by the cellular DNA polymerase, in addition to being essential for AAV genome packaging and site-specific integration into the host genome. The rep gene encodes for 4 non-structural proteins (Rep78, Rep68, Rep52 and Rep40) that have a role in viral genome replication, control of transcription and packaging [1491, 1492]. The cap gene encodes for 3 structural capsid proteins (VP1, VP2 and VP3) in a 1:1:10 ratio [1493]. Differences in the structure of these capsid proteins result in the subtyping of AAV into at least 12 serotypes, which can have a very different tissue tropism [1494].

AAV attaches to mammalian cells via the cellular receptor HSPG, while internalization is through endocytosis with interaction with co-receptors like integrins, HGFR, FGFR-1 and laminin [1495]. Using cytoskeletal components, the virion is then transported to the nucleus, where it escapes endosomal degradation and releases its genome into the nucleus [1496]. When no

helper virus is present, AAV can persist as genomic integrated provirus through Rep78 dependent recombination of AAV termini and host cell sequences in genome region AAVS-1 (19q13.3), or in episomal form, and can be reactivated upon helper virus re-infection [1497-1502].

6.7.1.2 Preclinical research

The main advantages of AAV-based vectors are that they are non-replicating and cause no apparent pathology, can infect cells (both dividing and non-dividing) of different tissues and that they elicit a low immune response. Disadvantages are their small size with limited transgene capacity and the presence of neutralizing antibodies (>90%) and cellular immunity in the general human population against AAV-2 [1503].

Since the first description of AAV-mediated transduction of human and mouse cells [1504], the field of AAV gene therapy has undergone extensive evolution towards successful clinical trials [1505, 1506]. Recombinant AAV vectors (rAAVs) can be produced in helper cell lines by supplying *in trans* rep, cap and helper genes in addition to a plasmid with a transgene cassette incorporated between the ITRs, without the need for replication competent helper or AAV virus in 2- or 3-plasmid systems [1507].

Sc-rAAVs were developed to circumvent rate-limiting second-strand DNA synthesis [1508-1510]. Sc-rAAVs display enhanced transduction in comparison with conventional rAAV vectors, although it limits the transgene size by half [1511-1513].

The host immune response to AAV-2 hinders the efficient systemic delivery and persistence of rAAV-vectored transgenes, mainly due to cellular and humoral immunity [1514-1516]. Efforts have been made to overcome this immunity by restricting transgene expression to the target tissue, codon-optimization, manipulating the rAAV capsid by (directed) mutagenesis, peptide display and chemical conjugation [1494, 1517-1520]. The discovery of novel AAV serotypes has led to the use of tissue specific AAVs, that also can evade pre-existing AAV-2 immunity [1521-1526]. For a summarized overview of current and emerging AAV vectors, please refer to table 1.

Organs	Disease targets	AAV serotypes and isolates	Emerging vector candidates
Liver	Hemophilia, α-1 antitrypsin deficiency, ornithine transcarbamylase deficiency	AAV8	AAV2 (Y→F), AAV7, AAV-HSC15/17
Heart	Congenital heart failure, cardiomyopathies	AAV1, AAV6, AAV9	AAVM41, AAV2i8, AAV9.45
Skeletal Muscle	Muscular dystrophies, α-1 antitrypsin deficiency, lipoprotein lipase deficiency, lysosomal storage disorders	AAV1, AAV6, AAV9	AAV7, AAV2.5, AAV6 (Y445F/Y731F), AAV2i8, AAV9.45
Lung	Cystic fibrosis, α-1 antitrypsin deficiency	AAV5	AAV6.2, AAV2.5T, AAV-HAE1/2
CNS	Parkinson's, Alzheimer's, Batten's, Canavan's, epilepsy, amyotrophic lateral sclerosis, spinal muscular atrophy, Rett syndrome, lysosomal storage disorders	Intracranial: AAV1, AAV5, AAV8 Systemic: AAV9	For systemic use: AAVrh.10, AAV Clone 32/83
Eye	Leber's congenital amaurosis, macular degeneration	AAV4, AAV8	AAVShH10, AAV2 (Y→F), AAV8(Y733F)

Table 1: current and emerging AAV vectors. From: Asokan A et al. *Molecular Therapy* 2012; **20**(4)**: 699**-708

rAAV delivery in immune-privileged sites (e.g. eye, CNS) and transient immune suppression have been largely without induction of relevant immune responses [1519]. However, immune activation and circumventing strategies for rAAV vectors are difficult to test preclinically, since no good animal model exists to date [1527].

rAAV-2 vector gene transfer related genotoxicity has been associated with hepatic tumor formation in mice [1528-1530]. rAAV proviral genomes preferentially integrate near or within transcriptionally active genes, although it is still under debate whether these integrations

significantly enhance the chance of oncogenic transformation [1531-1537].

6.7.1.3 Clinical trials

To date, 109 registered clinical trials in humans have been conducted or are underway, mainly for somatic diseases like hemophilia B, cystic fibrosis, Parkinson's, Batten's or Canavan's disease, rheumatoid arthritis, Leber's congenital amaurosis, age-related macular degeneration, heart failure, Pompe and Duchenne disease [1538-1541]. rAAVs have shown efficacy of transgene expression in tissues such as liver, retina and brain, although host and vector-related immunity not seen in animal models have limited duration and strength of transgene expression when administered systemically [1542-1546]. Therefore, more recent clinical trials are evaluating several other serotypes besides AAV-2 as gene transfer vectors [1538].

Glybera (alipogene tiparvovec; an AAV-1 vector expressing LPL) has been approved for treatment of LPL deficiency by the EMA and FDA, being the first (and only) gene therapy product to date in Europe and the USA. Of note, intramuscular injection of Glybera has not led to systemic or local immune responses limiting transgene expression [1547].

6.7.1.4 Safety

Patient

Generally, rAAV administration appears to be safe. Sometimes, dose limiting toxicity is encountered, but this mainly relates to rAAV-2 vectors or other vectors with pre-existing immunity. Also, random integration events have thus far not resulted in oncogenic transformations in patients. New and generated rAAV serotypes should be evaluated in a human-like model for off-target toxicity, although no good animal model exists for predicting safety.

Germline

Since rAAV is capable of genomic integration, germline transmission is a possible safety concern. A preclinical trial in rats found transgene expression of an AAV-2 vector in Sertoli and spermatogonia like cells, and subsequent studies have shown that *in vitro* incubation of murine, porcine and goat germline stem cells with rAAV vectors lead to germline transmission [1548-1550].

Also, one clinical trial has reported the presence of AAV DNA in semen samples up to 12 weeks after administration, although no vector sequences were detected in motile sperm [1543]. The risk of germline transmission thus appears to be very low and transient.

Transmission

rAAV is replication defective, and as such not directly transmissible. Shedding of rAAV however, can occur around the time of high dose administrations [1290].

Mutagenesis/reversion

In theory, replication of rAAV vectors can only occur during a unique condition of co-infections with adenovirus, wild-type AAV and the rAAV vector. rAAV vectors only retain about 300 nucleotides of viral sequence (2x ITR), which makes the likelihood of recombination with wildtype AAV very low.

6.7.2 Genus Protoparvovirus - Carnivore protoparvovirus 1: feline panleukopenia virus (FPaV)

6.7.2.1 General information

Please refer to CGM 2010-10 (page 63) [214].

6.7.2.2 Preclinical research

No additional information since CGM 2010-10 (page 63-64) [214].

6.7.2.3 Clinical trials

No information available.

6.7.2.4 Safety

Please refer to CGM 2010-10 (page 63-64) [214].

6.7.3 Genus Protoparvovirus - Rodent protoparvovirus 1: LuIII parvovirus (LPaV)

6.7.3.1 General information

Autonomous rodent protoparvoviruses (like LPaV, MVM and RPaV-H1) can only infect cells that undergo spontaneous transition through S phase, which makes that only dividing cells are susceptible, while replication is further enhanced in oncogenically transformed cells [1551, 1552]. They contain a ssDNA genome of ~5.1 kb which is packaged by capsid proteins VP1 and VP2 [1553]. VP2 is capable of virion formation and DNA packaging by itself, but VP1 is required for infectivity and delivers the viral genome into the host cell nucleus [1554-1557]. Please also refer to CGM 2010-10 (page 58-60) [214].

LPaV was originally isolated from a human tumor [1558]. No human disease is associated with protoparvovirus (including LPaV) infection [1559].

6.7.3.2 Preclinical research

Early research has focused on the development of LPaV-based gene transfer vectors/nanoparticles, but these have undergone no recent development [1560-1563].

In a recent study, a panel of 12 wild-type and 2 recombinant protoparvoviruses was tested *in vitro* and *in vivo* for oncolytic potential for glioblastoma [1564]. In this panel, LPaV showed best efficacy *in vitro* and was also effective in clearing xenograft tumors in mice, without relevant off-target toxicity.

6.7.3.3 Clinical trials

No information available.

6.7.3.4 Safety

No information available.

6.7.4 Genus Protoparvovirus - Rodent protoparvovirus 1: minute virus of mice (MVM)

6.7.4.1 General information

Please refer to LPV (above) and CGM 2010-10 (page 58-60) [214].

6.7.4.2 Preclinical research

Please refer to CGM 2010-10 (page 60-62) for preclinical research up to 2010 [214].

Interestingly, recent preclinical work on MVM as oncolytic or gene therapy vector is limited, probably because RPaV-H1 has taken the lead into a clinical trial (see next). It was shown that Raf-1 overexpression in cancer cells leads to VP trimer phosphorylation and translocation into the nucleus, needed for MVM replication [1565]. Also, PKR-mediated antiviral responses were shown effective against MVM, which could present another mechanism for oncoselectivity [1566]. Finally, MVM resulted in protection against tumor formation in immune competent mice, but this effect was lost in immune deficient mice, pointing to the importance of the immune system in oncolytic efficacy [1567].

6.7.4.3 Clinical trials

No information available.

6.7.4.4 Safety

Please refer to CGM 2010-10 (page 62-63) [214].

6.7.5 Genus Protoparvovirus - Rodent protoparvovirus 1: rodent parvovirus H1 (RPaV-H1)

6.7.5.1 General information

Please refer to LPaV (above) and CGM 2010-10 (page 58-60) [214].

6.7.5.2 Preclinical research

Please refer to CGM 2010-10 (page 60-62) and an excellent review by Rommelaere et al for preclinical research up to 2010 [214, 1568].

Recent research has focused on the importance of the immune system in oncolytic activity [1569-1571], combination with other therapies like radiotherapy [1572, 1573], chemotherapy or targeted agents [1574-1576], retargeting by modifications of the viral capsid [1577] and also arming with anti-angiogenic chemokines [1578] or pro-drug converting enzymes [1579].

6.7.5.3 Clinical trials

Currently, one clinical trial is active in patients with progressive or recurrent GBM (NCT01301430) [1580]. Also, a case has been reported of compassionate use in an 8 year old patient with metastatic neuroblastoma [1581].

6.7.5.4 Safety

Please refer to CGM 2010-10 (page 62-63) [214].

As with other oncolytic viruses, strategies that include retargeting and expression of immunomodulating or therapeutic transgenes can alter the safety of RPaV-H1, and should be evaluated accordingly.

6.8 Family Poxviridae / Subfamily Chordopoxvirinae

6.8.1 Genus Avipoxvirus - Canarypox virus (CPoV)

6.8.1.1 General information

For a general introduction into (non-human) poxviruses and a specific introduction into canarypox virus, please refer to CGM 2010-10 (page 24-25 & 34-35) [214].

6.8.1.2 Preclinical research

Most research on CPoV based vaccine vectors (ALVAC [1582]) has focused on infectious diseases [1583]. In the field of oncology, CPoV has been evaluated as cancer-antigen directed vaccine [1584-1586], or as immune stimulatory [1584, 1587-1592] and anti-tumor gene transducer [1593, 1594].

6.8.1.3 Clinical trials

Clinical trials have been conducted with CPoV vectors expressing tumor antigens, like CEA [1595-1598], MAGE [1599], p53 [1600], EpCAM [1601, 1602], gp100 [1603], or immune-stimulatory proteins [1604-1606]. Mostly, significant tumor responses were seen only in a minority of patients, with transient tumor-antigen specific T-cell responses. As evidenced by a lack of research papers from the last 5 years, the use of CPoV in cancer (vaccine) therapy seems to have lost its popularity.

6.8.1.4 Safety

Please refer to CGM 2010-10 (page 35) [214].

6.8.2 Genus Avipoxvirus - Fowlpox virus (FPoV)

6.8.2.1 General information

FPoV is a large (270x350 nm) and complex virus, with a dsDNA genome of 288 kb with 260 ORFs [1607]. Infectious virions can exist in two forms: intracellular mature virus (IMV) and extracellular enveloped virus (EEV). The central region of the genome is flanked by two identical ITRs and contains relatively conserved genes involved in viral replication and structure, as opposed to the more variable terminal genes, which are involved in host range restriction. FPoV replicates in the cytoplasm and infected avian cells display characteristic CPE 4-6 days post infection [1608]. Fusion of the virion –a poorly understood mechanism- with the host cell membrane releases the virion core into the cytoplasm [1609]. Within this core, viral RNA polymerases and transcription factors are present, which can start with early viral gene transcription. Next, uncoating of the viral DNA allows for viral DNA replication and intermediate and late viral gene transcription. Accumulation of viral proteins in so-called inclusion bodies or ‘viral factories’ results in the formation of IMVs. These can be released from the host cell by either cytolysis, virus-induced exocytosis or budding, the latter of which results in EEVs [1610]. In human cells, these last maturation steps of virions do not occur, leading to abortive infection [1611].

Avipoxviruses are transmitted via biting insects or aerosols and are usually named after the species of first isolation, in the case of FPoV, chickens. FPoV infections can result in disease in chickens and associated mortality is usually low, although in flocks under stress (including

commercial poultry) mortality can reach up to 50%. The disease is characterized by proliferative pox-lesions on the skin and/or diphtheritic membranes in the respiratory tract, mouth and esophagus. Vaccines are available, and commercial poultry is usually vaccinated with a pigeonpox virus. FPoV does not cause disease in mammals, likely because it does not replicate in mammalian cells due to host range restriction.

6.8.2.2 Preclinical research

Like CPoV, FPoV has been extensively evaluated as a (cancer) vaccine vector. FPoV boosts immune responses against foreign transgenes encoded by the virus and induces a strong T-cell immune response. FPoV vectors can accommodate large amounts of foreign DNA [1612].

Also, antisera against orthopoxviruses (like vaccinia) do not neutralize APV, and FPoV itself does not elicit high levels of neutralizing antibodies, making it possible to administer boost vaccines without losing potency.

FPoV cancer vaccines expressing tumor antigens like survivin [1613], mucin-1 and CEA [1614], sometimes combined with immune co-stimulatory molecules like TRICOM [1615], have been evaluated in several immune competent animal models for different types of cancer. Direct injection of FPoVs expressing anti-tumoral or immune-stimulatory genes has also been proposed in immune competent models for osteosarcoma, hepatoma or renal cell carcinoma [1616-1618].

6.8.2.3 Clinical trials

Most recent clinical trials have employed prime boost tumor-antigen vaccination schemes using vaccinia virus prime and multiple FPoV boosts [1614, 1619-1630]. A phase III trial with Prostvac +/- GM-CSF for metastatic castration-resistant prostate cancer is currently recruiting patients (NCT01322490) [1631].

Trials employing intratumoral injection of FPoV vectors harboring immune-stimulatory molecules have also been conducted, with limited T-cell responses [1632].

6.8.2.4 Safety

Patient

FPoV has been very well tolerated in (cancer) patients.

Germline

FPoV replication takes place in the cytoplasm, which makes the risk of genomic integration very low [1633].

Transmission

No information available. Theoretically, no replication of FPoV in humans is expected and thus no shedding can occur beyond the administration site.

Mutagenesis/reversion

Spontaneous recombination between FPoV vectors and wild-type viruses or mutation events could theoretically lead to restoration of replication competence. During the design of FPoV vectors, the aim was to introduce at least two gene deletions critical for viral replication, limiting this risk. Reversion to wild-type virus has not been observed in clinical trials of FPoV vectors.

6.8.3 Genus Leporipoxvirus - Myxoma virus (MyxV)

6.8.3.1 General information

Please refer to CGM 2010-10 (page 28-29) [214].

6.8.3.2 Preclinical research

Please refer to CGM 2010-10 (page 29-30) for preclinical trials up to 2010 [214].

As reviewed by Chan et al [1634], recent research has added more evidence for oncolytic activity of wild-type MyxV in mouse models for leukemia, multiple myeloma, pancreatic cancer, brain tumors and ovarian cancer.

Genetic modification of MyxV has mainly been used to study host range restriction, although oncolytic efficacy of deletion mutants has also been evaluated [1635-1637]. Recombinant MyxV producing vaccinia virus F11L gene, which is related to virus exit and spread, was shown to produce bigger and faster growing plaques, resulting in higher viral titers and better oncolytic activity [1638, 1639].

6.8.3.3 Clinical trials

No information available.

6.8.3.4 Safety

Please refer to CGM 2010-10 (page 30-32) [214].

6.8.4 Genus Orthopoxvirus - Raccoonpox virus (RPoV)

6.8.4.1 General information

Please refer to CGM 2010-10 (page 25-26) [214].

6.8.4.2 Preclinical research

Except development of RPoV as vaccine vector (which is beyond the scope of this report), there is no progress to report since CGM 2010-10 (page 26-27) [214].

6.8.4.3 Clinical trials

No information available.

6.8.4.4 Safety

Please refer to CGM 2010-10 (page 27-28) [214].

6.8.5 Genus Orthopoxvirus - Vaccinia virus (VV)

6.8.5.1 General information

In 1796, Dr. Edward Jenner discovered that inoculation of a person with material from a cowpox lesion (‘vaccine’, from the Latin word vacca for cow) could induced immunity to smallpox (variola). In the 19th century, VV was used to replace the cowpox vaccine, and smallpox has been eradicated worldwide in 1977, the most successful vaccination/eradication campaign to date [1640].

The origin of VV is unknown, but there are several hypotheses: evolution from variola

virus through continual passage in the skin of cows or humans; derivation from cowpox virus through continual repeated passage in the skins of animals; hybrid virus between cowpox and variola virus; and/or extinct natural host [1641]. VV has been isolated from buffalos, even up to 5 years after VV vaccination campaigns, and this strain is considered a subspecies.

6.8.5.2 Preclinical research

VV infection is highly immunogenic and produces a strong CTL response and neutralizing antibodies [1642, 1643]. As such VV vaccine vectors have been evaluated for infectious diseases (beyond the scope of this report) and cancer [1644-1650].

As an oncolytic virus, VV has the advantage of fast replication and cell lysis [1651], broad cell/tumor tropism [1652], lack of genomic integration, shielding from host immunity of EEV VV virions resulting in capability of (systemic) spreading between tumors [1652-1656], and a large genome packaging accommodation [1657].

Several strategies have been described to target oncolytic VV to tumor cells:

- Vaccinia growth factor (VGF) is homologous to cellular growth factor EGF and TGFα and can stimulate the cell for enhanced viral replication through EGFR [1658-1660]. Deletion of the VGF gene will result in a VV that is targeted to cells with inherent EGFR pathway activity, which is often observed in cancer cells [1652, 1661, 1662].
- J2R gene - encoding for viral tk - deletion similarly results in a VV that is dependent on overexpression of cellular tk, which is also often observed in cancer cells [1663-1666].
- The combination of VGF and TK gene deletion is known as vvDD and results in an even more selective oncolytic VV [1652, 1653].
- B18R binds to IFNARs and can thereby inhibit the cellular antiviral innate immune response [1667, 1668]. Deletion of B18R thus leads to a selectivity for IFN-deficient cells [1669].
- A56R gene encodes for HA and deletion results in severe (neuro)-attenuation [1670].
- Deletion of genes that inhibit apoptosis [1671, 1672].
- Other viral genes important for attenuation/oncoselectivity are being evaluated, and functional genomics can be of value for this effort [1673, 1674].

Arming of VV has also been described, e.g. with immune stimulators [1652, 1669, 1675-1682], apoptotic proteins [1683-1685], anti-angiogenic antibodies/proteins [1686-1689], ECM proteases [1690] and prodrug-converting enzymes [1691, 1692]. Furthermore, different imaging modalities can be used with VVs expressing imaging transgenes [1677, 1693-1702].

GLV-1h68 (GL-ONC1) was created by inserting three reporter proteins, RUC-GFP, lacZ and gusA into the F14.5L, J2R and A56R loci of the VV genome, respectively, while harboring several other attenuating mutations [1703, 1704]. GLV-1h68 has undergone extensive preclinical testing in models for breast cancer [1703, 1705, 1706], thyroid cancer [1707, 1708], mesothelioma [1709], pancreatic cancer [1710], prostate cancer [1711, 1712], HCC [1713, 1714], sarcoma [1715], glioma [1716], salivary gland carcinoma [1717], colorectal cancer [1718], sometimes in combination with radiation therapy [1719, 1720].

Although VV can travel systemically through the blood, efforts have also been made to enhance the ability of VV to evade the premature removal by the host innate (complement) and adaptive immune reponses after first delivery. As such, increasing EEV virion production [1656,

1721], complement inhibition [1722, 1723], macrophage phagocytosis inhibition [1724] and carrier cell delivery [1725] have been evaluated in preclinical studies.

Interestingly, different strains can be used as backbone for oncolytic VV, which can differ in their efficacy, although direct comparison between strains has not been described often [1726].

6.8.5.3 Clinical trials

Early clinical trials employing non-recombinant vaccine strains of VV have shown safety when injected superficially into melanoma tumors, while local treatment of bladder cancer was also evaluated [1727-1729].

JX-594 (TK gene deleted, GM-CSF expressing VV Wyeth; Pexa-Vec) [1675, 1730, 1731] has been evaluated in phase I-II clinical trials for patients with metastatic melanoma [1732, 1733], (primary) liver tumors [1734-1737], lung, colorectal and various other solid cancer types [1738]. A phase II clinical trial for patients with peritoneal carcinomatosis of ovarian origin is not yet recruiting patients (NCT02017678).

GLV-1h68 (GL-ONC1) is currently active in several phase I clinical trials [1739, 1740].

6.8.5.4 Safety

Patient

Vaccinia based vaccination for variola has been given as a skin inoculation to tens of millions of healthy children during the smallpox eradication campaigns. Safety of VV has been good, with major side effects like progressive/generalized VV infection, eczema vaccinatum or encephalitis occurring in ~1:800 cases, leading to 1 in a million lethality [1741, 1742]. Risk populations like immunocompromised patients or patients with eczema should be avoided.

Clinical trials with oncolytic VV thus far have reported good safety with minor side effects like transient low-grade fever and local pain, although reactive tumor swelling did result in dose-limiting hyperbilirubinaemia in patients with injected liver tumors [1735].

Germline

VV replication takes place in the cytoplasm, which makes the risk of genomic integration very low [1633].

Transmission

Commonly, live vaccinia virus is shed from skin injection after vaccination [1742, 1743]. Also, in clinical trials, live JX-594 was detected in throat swabs and skin pustules of patients up to one week after administration [1738].

Mutagenesis/reversion

Theoretically, recombination between oncolytic recombinant VV and wildtype VV is possible, however, since VV vaccination is not practiced on a large scale anymore, highly unlikely. Spontaneous mutation rates for VV have been shown to be very low [1744].

6.8.6 Genus Orthopoxvirus - Modified vaccinia Ankara (MVA)

6.8.6.1 General information

MVA was produced by passaging VV strain Chorioallantois Vaccine Ankara 516 times in chicken embryo fibroblasts [1745]. The MVA genome has been sequenced at 178 kb length with ~177 ORFs, and harbors 6 major deletions relative to Chorioallantois Vaccine Ankara, as well as many shorter deletions, insertions and point mutations, resulting in gene fragmentation, truncation, or deletions of ORFs [1745-1747]. As a result, MVA no longer encodes for many of its original immune evasion and virulence factors, resulting in a replication defective virus in humans and laboratory animals. Several strains/isolates have been generated from the original MVA, and are designated with their own passage number. Although MVA-572 was said to be genetically stable, more recent studies have shown that this strain and other strains are actually not completely homogenous, resulting in replication in some human cells and immune deficient mouse models of genotypic variants [1748, 1749]. MVA induces only very moderate CPE as compared to VV [1750, 1751] .

6.8.6.2 Preclinical research

With its ability to induce strong DC cell immune responses, MVA has been developed primarily as a vaccine vector for either infectious diseases (beyond the scope of this report) or malignant diseases. MVA can also be used as a (transient) gene transfer vector [1752] .

6.8.6.3 Clinical trials

A multitude of clinical trials has been conducted with MVA as vaccine or gene vector, as summarized by Verheust et al [1745].

6.8.6.4 Safety

Patient

MVA-571 has been administered first as a pre-vaccine to >120.000 individuals, including high-risk subjects, without any serious adverse events reported [1753]. Subsequent studies with other MVAs have confirmed this safety record [1754, 1755].

Germline

MVA replication takes place in the cytoplasm, which makes the risk of genomic integration very low [1633].

Transmission

Since MVA is not replication competent, no isolation of replicating virus has been reported from (pre)clinical trials and transmission of well characterized MVA stocks is highly unlikely [1756].

Mutagenesis/reversion

Spontaneous reversion of MVA to wild-type CVA seems impossible, since ~15% of the genome was lost during passaging. Some of the disrupted or deleted genes could theoretically be rescued by recombination with a naturally occurring orthopoxvirus, which is considered an extremely rare event [1757].

6.8.7 Genus Parapoxvirus - Orf virus (OrfV)

6.8.7.1 General information

OrfV has a worldwide distribution causing acute dermal infection in goats and sheep (orf: contagious ecthyma or scabby mouth) [1758]. OrfV viral particles have been shown to be potent (cellular) immune stimulators, even when not replicating [1758-1763]. Interestingly, this immune stimulation hardly leads to the formation of neutralizing antibodies due to immune evasion of the virus [1764, 1765].

6.8.7.2 Preclinical research

One study has used inactivated OrfV to induce immune activation which resulted in tumor growth rate reduction of melanoma isografts and breast cancer xenografts, at least partly mediated by NK cell activation [1766]. Another study showed antifibrotic effects of inactivated OrfV in models of liver fibrosis [1767]. Furthermore, one recent study has evaluated OrfV as an oncolytic agent, which was shown to be largely dependent on cellular immune activation, and augmented by viral replication [1768].

6.8.7.3 Clinical trials

No information available.

6.8.7.4 Safety

Patient

Human infections with OrfV do not lead to serious disease [1764, 1769, 1770]. The striking immunomodulatory and immune evasive nature of OrfV could make it an interesting candidate for further development.

Germline

No information available.

Transmission

Wild-type OrfV can spread from infected animals to other animals' wounds by direct contact [1764].

Mutagenesis/reversion

No information available.

6.8.8 Genus Yatapoxvirus - Tanapox virus (TPoV)

6.8.8.1 General information

Following extensive flooding of the Tana River in Kenya, two consecutive outbreaks among the Wapakomo tribe were observed in 1957 and 1962, leading to the isolation of TPoV from pock-like skin lesions [1771]. YLDV shares over 98% genomic homology with TPoV and is considered a strain of TPoV [1772, 1773]. Outbreaks of YLDV occurred in several primate facilities in the US in 1965 and 1966, with infections spreading from different monkey species to their human caretakers [1774, 1775]. The host range of TPoV seems to be restricted to non-

human primates and humans [1776].

TPoV virions are very similar to VV virions. Replication *in vitro* is markedly slower than VV: 36-38 hours as compared to less than 24 hours [1777]. The TPoV genome is ~145 kb long [1778].

Please also refer to CGM 2010-10 (page 32-33) [214].

6.8.8.2 Preclinical research

Since CGM 2010-10 (page 33-34), only one study has reported on the evaluation of TPoV as an oncolytic virus in 14 different tumor cell lines *in vitro* [214, 1779].

6.8.8.3 Clinical trials

No information available.

6.8.8.4 Safety

Patient

TPoV causes low-grade fever, one or rarely more pock-like skin lesions with regional lymphadenopathy and subsequent ulceration of the pock-like lesion, with spontaneous resolution after 6 weeks [1779].

Germline

TPoV replication takes place in the cytoplasm, which makes the risk of genomic integration very low [1633].

Transmission

Zoonotic transmission of TPoV from monkeys to humans has been observed, without human-to-human transmission, although this cannot be excluded [1773].

Mutagenesis/reversion

No information available.

Please also refer to CGM 2010-10 (page 34-35) [214].

6.9 Family Reoviridae / Subfamily Sedoreovirinae

6.9.1 Genus Orbivirus - Bluetongue virus (BTV)

6.9.1.1 General information

Please refer to CGM 2010-10 (page 72-73) [214].

6.9.1.2 Preclinical research

No additional original studies have been published on BTV since CGM 2010-10 (page 73) [214].

6.9.1.3 Clinical trials

No information available.

6.9.1.4 Safety

Please refer to CGM 2010-10 (page 73-74) [214].

6.10 Family Reoviridae / Subfamily Spinareovirinae

6.10.1 Genus Orthoreovirus - Mammalian orthoreovirus (mORV)

6.10.1.1 General information

mORV is a ubiquitous pathogen with high seropositivity in humans, and has been isolated from sewage, stagnant and river water throughout the world [1780-1784]. Like echovirus, respiratory enteric 'orphan' virus means that mORV is not associated with a named disease in humans, although it can cause mild flu-like upper respiratory or gastrointestinal tract symptoms. Three serotypes of mORV can be distinguished: type 1 Lang, type 2 Jones and type 3 Abney or Dearing (mORV-T3D). mORV-T3D was isolated from the intestinal tract of a healthy human subject.

mORV virions have a 10-segmented dsRNA genome encased by a non-enveloped icosahedral capsid with a double protein shell [1785]. Each segment encodes for 1 or 2 proteins. Wild-type mORV-T3D can bind to sialic acids with low affinity [1786], while high affinity receptor JAM-A/1 is needed for mediation in infection, although recently it was shown that JAM-A/1 independent infection of tumor spheroids is also possible as opposed to monolayer cell culture [1787-1791].

Endocytotic internalization and subsequent acidification of the endosome releases partially uncoated 'infectious subviral particles' (ISVPs) into the cytoplasm [1792]. Proteolytic cleavage of the inner core protein releases the dsRNA genome into the cytoplasm, where the viral polymerase will first synthesize plus-strand transcripts, which are then translated into viral proteins in viral factories and also serve as a new template for genomic dsRNA [1793]. Newly formed viral cores are precisely assorted to include the 10 genomic segments, while minus-strand synthesis ensures dsRNA genome creation. Viral particles then mature and are released from the host cell after membrane breakdown [1794].

6.10.1.2 Preclinical research

mORV-T3D replicates in cells with dysfunctional cell signaling cascades, most importantly (but not exclusively) kRAS-overexpression and subsequent PKR inhibition, making it an inherent oncolytic virus [1795-1812]. A multitude of cancer types have been shown to respond to mORV-T3D treatment in (animal) models, including glioblastoma [1798, 1800, 1813-1815], breast cancer [1816-1818], colorectal cancer [1797, 1807, 1819-1822], melanoma [1823-1828], pancreatic cancer [1829, 1830], mantle cell lymphoma [1831], gastric cancer [1832, 1833], prostate cancer [1834-1837], sarcoma [1838], leukemia [1839], multiple myeloma [1840-1843], head and neck cancer [1844, 1845], HCC [1846] and ovarian cancer [1847].

Combination therapy with ionizing radiation [1848], chemotherapy [1822, 1825, 1827, 1836, 1845, 1849-1852], transient immune suppression [1853, 1854] and other oncolytic viruses [1814] have been evaluated, as well as carrier cell delivery [1821, 1855-1857].

Cellular immunity has been found to be important for anti-tumor efficacy [1828, 1835, 1839, 1847, 1858-1860]. Other mORV subtypes and attenuated strains have also been evaluated for oncolytic efficacy [1861, 1862].

The absence or inaccessibility of the JAM-A/1 receptor is perceived as a possible limitation for mORV-T3D infection of tumor cells [1818, 1820, 1863]. As such, bio-selection through passaging has been attempted to retarget mORV-T3D to other receptors, although this strategy is probably limited by the quasispecies presence in mORV-T3D isolates [1864-1868]. The segmented genome of mORV-T3D makes reverse genetics challenging, but several techniques have been described to overcome this challenge [1863, 1869-1874]. Only one study using recombinant oncolytic mORV-T3D has been described thus far, and more can be expected in the near future, probably focusing on receptor retargeting and expression of therapeutic or imaging transgenes [1875].

6.10.1.3 Clinical trials

At this time, 16 clinical trials employing intratumoral or intravenous injection of mORV-T3D (REOLYSIN®: pelareorep) have been conducted and more (n=15) are currently underway or planned to start in the near future. As excellently summarized by Harrington et al. and Maitra et al. [1876, 1877], these trials have shown safety of mORV-T3D administration to patients with various solid tumors without dose limiting toxicities, while having some appreciable anti-tumor effects in phase II/III trials.

6.10.1.4 Safety

Patient

High mORV titers injected i.v. have been shown reasonably safe, even in combination with standard therapies like chemo- or radiotherapy, and also when combined with transient immune suppression [1876, 1877].

Germline

mORV replication takes place in the cytoplasm without an intermediate DNA step, which makes the risk of genomic integration very low.

Transmission

Limited mORV shedding has been observed in clinical trials in patient samples of urine, saliva and feces, mostly with high i.v. administrations [1877].

Mutagenesis/reversion

As an RNA virus with a viral RNA polymerase, mORV genome replication is prone to errors. Furthermore, since wild-type isolates are in use, these probably represent several quasispecies [1878]. Even so, since mORV-T3D does not seem to cause disease in human subjects, the relevance of this mutation rate is low.

6.11 Family Retrovirinae / Subfamily Orthoretrovirinae

6.11.1 Genus Alpharetrovirus - Rous sarcoma virus (RouSV)

6.11.1.1 General information

RouSV is the only known naturally occurring replication-competent retrovirus that has acquired a cellular gene, the v-*src* oncogene [1879], and causes sarcomas in chickens [1880-1882].

6.11.1.2 Preclinical research

The oncogene is replaced by a transgene in early RouSV based vectors (called RCAS) [1883, 1884]. Similar to HIV-1 development (see below), SIN-RDR-RouSV vectors have been recently developed by eliminating enhancer and promoter elements from the LTRs, while using split packaging systems and removing additional viral-coding sequences and retroviral splice sites from the vector [1885, 1886]. This SIN-RDR-RouSV vector has been evaluated in preclinical (animal) models for X-CGD [1887]. Integration profiles of alpharetroviruses including RouSV are much more neutral than gamma- or HIV-1 based retroviruses [1885, 1888-1890].

6.11.1.3 Clinical trials

No information available.

6.11.1.4 Safety

No information available.

Given the favorable integration pattern of alpharetroviruses, it is possible that these retroviruses will receive more attention and development in the near future.

6.11.2 Genus Gammaretrovirus - Gibbon ape leukemia virus (GALV)

6.11.2.1 General information

GALV was found first in captive gibbon apes with leukemia and is closely related to another retrovirus found in wild koalas named koala retrovirus [1891-1893]. GALV can infect a wide variety of cells from different species through the SLC20A1 receptor, and causes leukemia when injected into juvenile monkeys [1894-1899].

6.11.2.2 Preclinical research

Similar to RCR-MuLV (see below), GALV has been evaluated as replication competent oncolytic virus expressing CD for the treatment of HCC and mesothelioma in preclinical (animal) models [1900, 1901]. GALV envelope glycoproteins are often used to pseudotype other viral vectors to optimize tropism.

6.11.2.3 Clinical trials

No information available.

6.11.2.4 Safety

No information available.

6.11.3 Genus Gammaretrovirus - Murine leukemia virus (MuLV)

6.11.3.1 General information

Please refer to CGM 2010-10 (page 139-142) [214].

6.11.3.2 Preclinical research

MuLV development has been focused on non-replicating as well as more recently replicating vectors (Figure 3). The capacity of MuLV and other retroviruses to integrate into the host genome of dividing cells carries the risk of insertional mutagenesis/oncogenesis. Reducing this risk was an important goal in designing the first (and more recent) retroviral vectors. To this end, replication-defective retroviral (RDR-)MuLV vectors lacking viral genes required for self-replication and incapable of cell-to-cell spread or general dissemination were developed [1902-1904]. RDR-MuLV vector genomes generally have a *cis* retroviral genome sequence driving transgene expression and packaging, and virions are produced by providing structural viral genes (i.e. Gag, Pol and Env) in *trans* in vector-producing cells [1905]. Recombination of RDR-MuLV vector genomes with vector-producing cell genomes could lead to emergence of replication-competent retroviral vectors (RCRs), which is why overlapping sequences of viral and cellular genomes were reduced to a minimum [1906-1908]. RDR-MuLV virions are capable of infecting and integrating their genomic transgene into host cells, while viral replication is not possible due to the lack of structural viral genes in the host cell. This results in a fairly limited gene transduction rate, which can be enough for correction of (mono)genetic diseases, but mostly will not result in proper anti-cancer activity [1909].

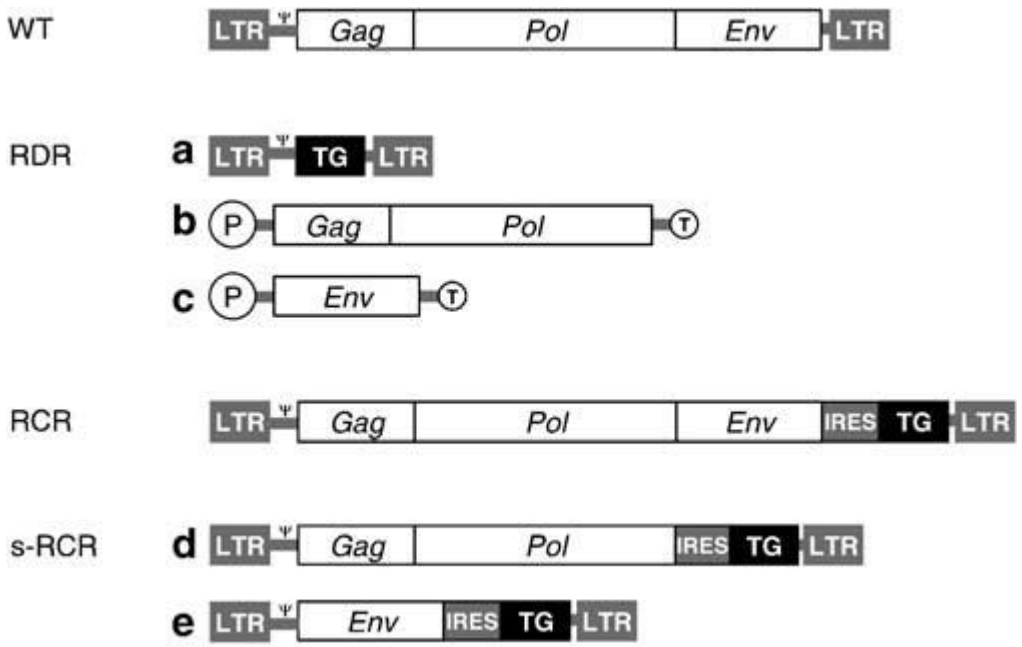

Figure 3: MuLV vectors. From: Dalba C et al. *Molecular Therapy* 2007; **15**(3)**:** 457-466 [1905].

Clinical trials using these first generation RDR-MuLV vectors to correct monogenic diseases like X-linked SCID (X-SCID) in children have been complicated by cases of acute leukemia due to proviral integration in (the proximity of) proto-oncogenic loci [1910-1913]. Although most patients responded well to chemotherapeutic treatment without loss of transduced cells, this is of course a serious complication of these first generation integrating RDR-MuLV vectors. Similar observations have been made in clinical trials for patients with X-chromosome linked chronic granulomatous disease (X-CGD) and Wiskott-Aldrich syndrome (WAS) [1914]. This has led to a general reconsideration of RDR-MuLV vector design.

LTR sequences of RDR-MuLV vectors exert strong promoter and enhancer activity driving transgene expression, but also expression of genes neighboring the insertion site, which is considered to be a contributing factor in the adverse events observed in the clinical trials described above. Therefore, modification of LTRs by deleting the enhancer regions was proposed to reduce this risk. So-called self-inactivating (SIN-)RDR-MuLV vectors lack enhancer regions and use an internal promoter and enhancer to drive transgene expression [1915-1917]. However, also these SIN-RDR-MuLV vectors have been shown to possess oncogenic activity (although considerably lower), and their integration profile does not differ from RDR-MuLV vectors [1916, 1918-1923]. Besides strong ubiquitously active viral promoters, other weaker (cellular) promoters can be used in SIN-RDR-MuLVs to achieve transcriptional targeting [1919, 1921, 1924-1926]. Incorporation of WPRE or codon optimization leads to increased transgene mRNA stability, export and translatability, needed to optimize transgene expression from these relatively weak (targeted) cellular promoters [1927-1929].

Integration of RDR-MuLV vectors favors promoter and enhancer regions [1930-1932]. Targeting of RDR-MuLV integration to pre-selected locations of the host genome by swapping integrases between other retroviruses or fusing the integrase with sequence specific DNA-binding domains has been evaluated with limited success [1933, 1934].

Another safety issue of (SIN-)RDR-MuLV vectors consists of an increased polyA signal read-through in the 3'-LTR, which may result in the activation of normally silent oncogenes upon integration [1935]. The deletions in SIN-RDR-MuLV LTRs actually increase this risk [1936, 1937].

To circumvent genotoxic events associated with integration, non-integrating (episomal) RDR-MuLV vectors have also been developed to achieve transient gene expression by mutating the viral integrase, leading to a marked reduction of viral (but not spontaneous) integration, which can be combined with strategies like ZFN or SB [1938-1942]. Chromatin insulators have also been described as means to dampen genotoxicity [1943].

Silencing of RDR-MuLV gene expression (in embryonic stem cells) was observed due to binding of a cellular protein complex to the primer binding site of the viral genome [1944-1946]. Substitution of the primer binding site with an endogenous retroviral sequence or an artificial sequence resulted in new RDR-MuLV vectors which are less prone to gene silencing [1947-1951].

Pseudotype	Abbreviation	Receptor	Modification	Target Species
Ecotropic MLV env	Eco	mCAT	not required	mouse and rat
Amphotropic MLV env	Ampho	PiT2	not required	multiple
Xenotropic MLV env	Xeno	XPR1	not required	human and others
Vesicular Stomatitis Virus glycoprotein	VSVg	not determined	not required	multiple
Simian Endogenous Retrovirus env	RD114	RDR/ASCT2	not required	human and others
Gibbon Ape Leukemia Virus env	GALV	PiT1	not required	human and ape
Measles Virus (vaccine strain) H and F proteins	MV	CD150, CD46	not determined	human
Human Immunodeficiency Virus gp120 env	HIV	CD4 and co-receptor	C-terminal truncation	human

Table 2: pseudotypes of lentiviral and RDR-MuLV vectors. From: Maetzig T et al. *Viruses* 2011; **3**: 677-713

There are at least three different naturally occurring strains of MuLV, which differ in their envelope proteins resulting in large differences in tropism. Similarly, retargeting through pseudotyping of the viral envelope or expression from heterologous vectors has been evaluated extensively to create MuLV vectors with specific tropisms (Table 2) [1952-1961].

Rexin-G is a RDR-MuLV with an engineered envelope to incorporate a high-affinity collagen-binding domain derived from von Willebrand factor, while expressing cytocidal cyclin G1 as therapeutic transgene [1962-1964]. Rexin-G has been shown to accumulate in sites of newly exposed collagen, including tumors, and was effective in preclinical (animal) models for various (metastatic) cancer types [1963, 1965]. Similarly, Reximmune-C expresses GM-CSF and is used to improve anti-tumor immune responses following Rexin-G treatment [1966].

Regarding the application of MuLV vectors in cancer patients, the replication capacity of RCR-MuLVs is considered to be beneficial to optimize gene expression in tumors. This stems from the fact that for oncolytic activity, gene expression does not have to be long lasting, but preferably strong. The first RCR-MuLVs were developed by insertion of either a transgene into the 3' LTR, or an additional splice acceptor site and transgene downstream of the *env* gene [1967-1970]. However, these viral genome configurations led to genetic instability. More recent RCR-MuLV vector genomes consist of an intact viral genome including an IRES-transgene immediately after the stop codon of the *env* gene, which results in more genetic stability, while retaining good replication capacity [1970-1972]. The fact that RCR-MuLVs can only infect and integrate in dividing cells results in an inherent onco-selectivity. In contrast to most other oncolytic viruses, the oncolytic activity of RCR-MuLVs depends solely on the transgene that is carried by the virus, since infection itself is not cytolytic. The transgene of choice to date has mostly been CD, which converts the antifungal drug 5-FC into the active chemotherapeutic agent 5-FU. Oncolytic activity of RCR-MuLV-CD (Toca 511) has been evaluated in preclinical (animal) models for breast cancer [1973], glioblastoma [1974-1978] and mesothelioma [1979]. Toca 511 has a modified backbone and a codon-optimized and heat-stabilized CD gene and has been shown to be genomically very stable while maintaining oncolytic efficacy upon passaging [1976, 1980].

To create RCR-MuLVs that have less risk of inadvertent spread, semi-replication

competent RCR-MuLVs (s-RCR-MuLVs) have also been devised. This strategy is based on two transcomplementing RDR-MuLV vectors, which can each transduce a transgene, in addition to viral genes *gag-pol* or *env*. Although considered to be safer than conventional RCR-MuLVs, the oncolytic efficacy is also attenuated, and no progress has been reported since first publication [1981].

6.11.3.3 Clinical trials

RDR-MuLV vectors have been used in relatively successful clinical trials for monogenic diseases like X-SCID [1982, 1983], ADA-SCID [1984-1988], X-CGD [1989, 1990], WAS [1991], epidermolysis bullosa [1992], and melanoma [1993]. However, as noted, oncogenic integration has led to the redesign of RDR-MuLV vectors, and in the meantime lentiviral vectors have taken the lead due to their more favorable integration profiles and ability to transduce non-dividing cells. Even so, the clear clinical benefit of MuLV-vector treated patients with ADA-SCID and SCID-X1 outperforms the results obtained after allogenic stem cells transplantation with HLA-mismatched donors, which make risk-evaluation and patient education important in the possible continued application of this strategy.

Rexin-G has been evaluated in several phase I/II clinical trials in patients with pancreatic cancer, (osteo)sarcoma and other metastatic solid cancers [1994-2000]. Similarly, Reximmune-C has been tested in one phase I clinical trial [2001]. However, no further clinical trials have been reported for either vector since 2010, and it seems that development has stopped, although the therapy is supposedly available in Manila, the Philippines.

RCR-MuLV-CD Toca 511 (vocimagene amiretrorepvec) is being investigated in clinical trials in the United States in subjects with recurrent high-grade glioma (NCT01156584, NCT01985256 and NCT01470794). Up to now, over 70 patients have been treated without dose limiting toxicity and with evidence of clinical oncolytic efficacy [1980].

6.11.3.4 Safety

Please refer to CGM 2010-10 (page 145-147) [214].

6.11.4 Genus Lentivirus - Equine infectious anemia virus (EIAV)

6.11.4.1 General information

Wild-type EIAV causes a self-limiting anemia, with a clinical syndrome of fever, weight loss and ventral edema in horses, donkeys and mules, but is non-pathogenic to humans [2002, 2003]. Once infected, the horse remains infected for life.

6.11.4.2 Preclinical research

Oxford Biomedica uses SIN-RDR-EIAV vectors with transgenes under the control of a CMV promoter and pseudotyped with VSV-G for different indications (LentiVector):

- RetinoStat expresses angiostatic proteins endostatin and angiostatin for treatment of age-related macular degeneration [2004, 2005].
- StarGen expresses the normal ABCA4 gene for treatment of Stargardt disease [2006, 2007].
- UshStat expresses the normal MYO7A gene for treatment of Usher syndrome type 1B [2008, 2009].
- EncorStat expresses endostatin and angiostatin (similar to RetinoStat) to transduce

corneal transplants *ex vivo* to prevent graft rejection [2010, 2011].

- Glaucoma-GT expresses normal COX-2 and PGF-2a receptor genes for treatment of glaucoma [2012].
- ProSavin expresses the normal tyrosine hydroxylase, aromatic L-amino acid decarboxylase, and guanosine 5'-triphosphate cyclohydrolase 1, which are critical for dopamine synthesis for treatment of Parkinson's disease [2013].
- MoNuDin expresses the normal VEGF gene to neurons for treatment of motor neuron disease (ALS) [2014].

6.11.4.3 Clinical trials

Oxford BioMedica has several clinical trials ongoing/completed:

- RetinoStat: NCT01301443, NCT01678872
- StarGen: NCT01367444, NCT01736592
- UshStat: NCT01505062, NCT02065011
- ProSavin: NCT00627588, NCT01856439

The results of the first phase I/II trial of ProSavin injected into the putamen of Parkinson's disease patients have recently been reported and showed a very good safety profile with some improvement in motor behavior.

6.11.4.4 Safety

Patient

So far, SIN-RDR-EIAV vectors seem to be safe for application in patients.

Germline

EIAV vectors integrate into the host cell DNA, and have a theoretical small risk of germ line transmission when used as *in vivo* gene therapy agent, and the local injection strategy limits this risk even further.

Transmission

In the toxicity study of RetinoStat, very low amounts of vector particles were detected in a minority of non-human primates on day 2 in saliva and eye swabs [2005]. In a similar study evaluating StarGen, no shedding was observed [2006]. The clinical study of ProSavin noted only limited detection of viral sequences in urine samples [2015].

Mutagenesis/reversion

No information available.

6.11.5 Genus Lentivirus – Human immunodeficiency virus 1/2 (HIV-1/2)

6.11.5.1 General information

Due to the long period of time between initial infection and onset of disease, the name lentivirus was chosen for these pathogens (lenti = slow in Latin). HIV-1 and HIV-2 both are causative agents of acquired immunodeficiency syndrome in humans, although HIV-2 has slower disease kinetics and a distribution essentially restricted to West Africa [2016]. HIV-1 is closely

related to SIV-cpz and HIV-2 to SIV-sm (see below). Primary infection with HIV is characterized by an acute phase of transient viral replication, progressing into a chronic infection with low level replication, targeting CCR-5 positive myeloid cells, while hiding from the immune system [2017]. Upon migration and differentiation of infected monocytes, HIV-1 can reactivate and resume its replication cycle [2018, 2019].

Interaction of the viral envelope with the cellular receptor triggers membrane fusion, releasing viral nucleoprotein complexes into the cytoplasm. Integration into the nucleus most probably is preceded by active nuclear import, since lentiviruses can integrate into non-dividing cells efficiently [2020-2022].

6.11.5.2 Preclinical research

HIV-1 based vectors have been developed most extensively, and were the first retroviral vectors to transduce non-dividing neurons when injected into rat brains [2023]. Several generations have now been developed (Figure 4).

1. First generation HIV-1 vectors consist of three plasmids [2023]
    a. Transfer vector with transgene cassette flanked by two LTRs and RRE, packaging and RT sequences
    b. Pseudotyping plasmid expressing *env*
    c. Packaging plasmid expressing all other viral ORFs
2. Second generation HIV-1 vectors consist of three plasmids [2024-2027]
    a. Transfer vector as in first generation
    b. Pseudotyping plasmid as in first generation
    c. Packaging plasmid expressing *tat, rev*, *gag* and *pol*
3. Third generation SIN HIV-1 vectors consist of four plasmids [2028]
    a. Transfer vector as in first generation
    b. Pseudotyping plasmid as in first generation
    c. Packaging plasmid expressing *gag* and *pol*
    d. Separate plasmid expressing *rev* under the control of a RouSV promoter

Transfer vectors can be optimized by incorporation of HPRE [2027, 2029], heterologous polyA enhancer elements like SV40 or β-globulin [2030, 2031], or the use of different internal promoters. Three other major modifications include: firstly substitution of the 5' U3 viral promoter for a heterologous promoter, enabling Tat-independent transcription; secondly deletion of the enhancer/promoter sequence in the 3' U3, resulting in SIN vectors; and thirdly inclusion of the cPPT-CTS sequence exerting a positive effect on transduction efficiency [2024, 2025, 2028, 2030, 2032-2036].

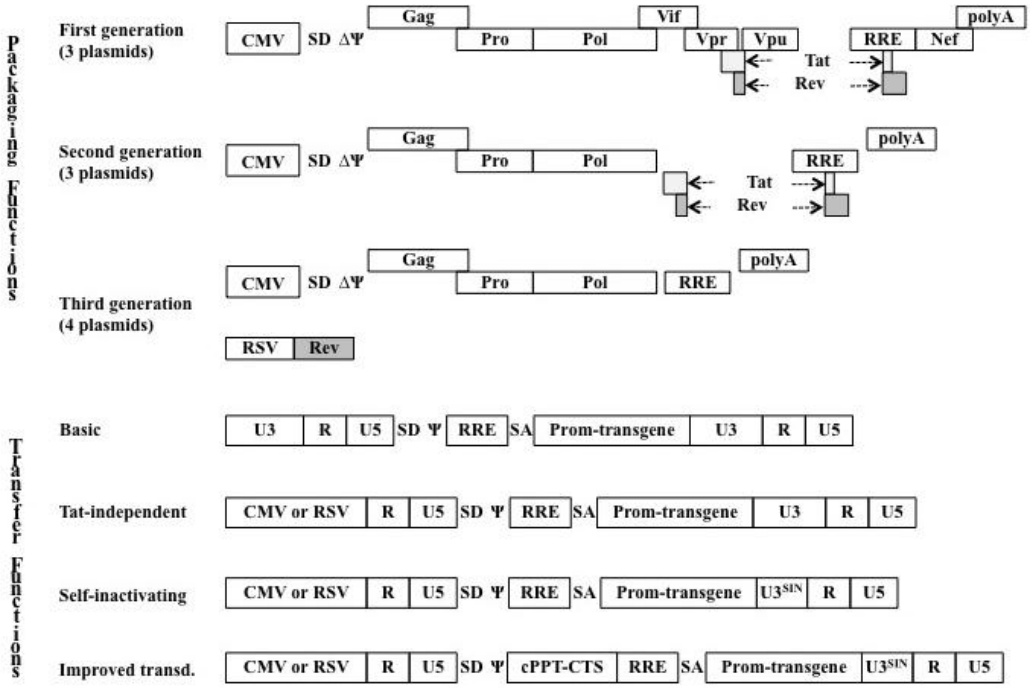

Figure 4: generations of HIV-1 packaging vectors and optimization of transfer vectors. From: Durand et al. *Viruses* 2011; **3**: 132-159

Pseudotyping of HIV-1 vectors has benefited to their tissue tropism, infectivity and selectivity [2037-2044]. SIV/HIV-2 Vpx protein enhances transduction of myeloid cells by HIV-1 vectors markedly [2045-2048].

HIV-1 vectors show a preferential integration into actively transcribed genes, and integrate through a largely stochastic process, driven by an active process targeting open chromatin regions in the host cell genome [1888, 2049-2053]. This lowers the risk of genotoxicity [1921, 2054-2056]. Modifications of HIV-1 vectors to more selectively target proviral integration are relatively new and results obtained so far are disappointing [2057-2060]. As an alternative strategy, non-integrating HIV-1 vectors have also been developed to produce transient episomal vectors [2061, 2062].

6.11.5.3 Clinical trials

Clinical trials using SIN HIV-1 based vectors have been performed for monogenic diseases like β-thalassaemia [2063], WAS [2064], X-ALD [2065], metachromatic leukodystrophy [2066]. To date, no oncogenic transformation has been reported in these clinical trials with good clinical benefits. An additional trial for ADA-SCID is currently underway (NCT01380990) [2067]. Also, multiple clinical trials have evaluated HIV-1 vectored chimeric antigen receptors expressed by T-cells targeted to CD19 as treatment for advanced leukemia [2068-2070].

6.11.5.4 Safety

Patient

Based on data from clinical trials so far, SIN HIV-1 vectors appear very safe with lower chances of insertional oncogenesis than MuLV based vectors.

Germline

HIV-1 vectors integrate into the host cell DNA, and have a theoretical risk of germ line transmission when used as *in vivo* gene therapy agent.

Transmission

So far, no transmission of SIN HIV-1 vectors has been reported in clinical trials, although this is mostly a theoretical risk [2071].

Mutagenesis/reversion

Since SIN HIV-1 based vectors are very stable genomically, and do not replicate, reversion to wild-type is theoretically impossible.

6.11.6 Genus Lentivirus - Simian immunodeficiency virus (SIV)

6.11.6.1 General information

SIVs are divided in 5 lineages according to their host species: sooty mangabey (SIV-sm), African green monkey (SIV-agm), chimpanzee (SIV-cpz), mandrill (SIV-mnd) and syke (SIV-syk) [2072, 2073]. SIV infections are non-pathogenic in their host species, but can become pathogenic when transmitted to a different species [2074]. SIV-agm strain TYO1 has been studied extensively and was found to be non-pathogenic for African green monkeys and experimentally infected Asian macaques [2075].

6.11.6.2 Preclinical research

Using similar strategies as HIV-1 vectors, several (SIN) SIV vectors have been created based on SIV-agm [2076, 2077] and SIV-mac [2078-2080]. Pseudotyping has been applied to change cell/tissue tropism [1957, 2081, 2082].

SIN SIV-agm based vectors have been evaluated for retinal gene transfer in (animal) models for retinitis pigmentosa [2083-2085], as well as for X-CGD [2086], hemophilia [2087, 2088] and cystic fibrosis [2082].

Transgenic rhesus monkeys have been created by transducing early-cleavage-stage embryos [2089].

6.11.6.3 Clinical trials

No information available.

6.11.6.4 Safety

Patient

Toxicity testing in non-human primates of intraocular administration of a SIV-agm based vector expressing hPEDF showed no dose limiting toxicity [2090].

Germline

SIV vectors integrate into the host cell DNA, and have a theoretical risk of germ line transmission when used as *in vivo* gene therapy agent.

Transmission

In the toxicity study in non-human primates, no shedding was observed upon intraocular administration [2090].

Mutagenesis/reversion

SIN SIV based vectors do not replicate, making reversion to wild-type theoretically impossible.

6.12 Family Retrovirinae / Subfamily Spumaretrovirinae

6.12.1 Genus Spumavirus - Feline foamy virus (FFoV)

6.12.1.1 General information

FFoV is endemic in cats and is considered apathogenic, although histopathological changes in lungs and kidneys have been noted in inoculated cats [2091].

6.12.1.2 Preclinical research

In general, most early studies using FFoV vectors have focused on the use of cats as a model for human disease, since FFoV does not readily infect human or murine cells. To improve this tropism, chimeric FFoV/SFoV have been devised [2092]. Replication-competent (RC-) FFoV vectors expressing GFP from their 3'-LTR have been reported, however with low genetic stability [2093]. Replication-deficient (RD-) FFoV vectors were developed using a similar strategy as RD-SFoV (see below). In short, structural viral genes are replaced with transgenes under the control of a CMV promoter [2094, 2095]. Several generations of SIN-FFoV vectors have also been described, of which most recent gutless FFoV vectors with minimized viral sequences [2096-2099]. Pseudotyping using a small-molecule controlled heterodimerization system has also been described recently, which could be used for FFoV pseudotyping [2100].

6.12.1.3 Clinical trials

No information available.

6.12.1.4 Safety

Patient

No information available.

Germline

FFoV integrates its genome/transgene into the host cell, thus having the theoretical risk of germ line transmission when used as *in vivo* gene therapy agent.

Transmission
Zoonotic transmission of FFoV into humans seems unlikely [2101, 2102].

Mutagenesis/reversion
Latest generation RD- and SIN-FFoV vectors have been shown to be genomically very stable.

6.12.2 Genus Spumavirus - Simian foamy virus (SFoV)

6.12.2.1 General information

SFoV is endemic to most non-human primates and is zoonotic for humans [2103-2107]. SFoV causes no apparent disease in its natural hosts or in humans, while the virus is highly cytopathic *in vitro* with syncytia formation and vacuolization. A human case of SFoV infection was first described in a patient with nasopharyngeal carcinoma [2108].
SFoV binds to the cell via cell membrane-associated heperan sulfate (co-)receptor leading to a broad cell and host tropism and is taken up by receptor-mediated endocytosis [2109-2111]. Subsequent intracellular transport is along microtubules towards the microtubule organizing center (MTOC), where capsidated virions accumulate. Further disassembly involves viral and cellular proteases and is cell cycle dependent. SFoV preintegration complexes enter the nucleus through nuclear membrane breakdown, and integrate into the host cell genome. Expression of integrated proviral genes is regulated by a viral transactivator promoter, and differentially spliced RNAs are exported out of the nucleus to be translated into viral proteins. Preassembly of SFoV capsids takes place in the MTOC where after capsid assembly the packaged RNA genome is reverse transcribed. Budding and release of virions mainly takes place at internal cellular membranes, and less at the plasma membrane.
Like other retroviruses, SFoV has three ORFs (gag, pol and env) flanked by two LTRs. In addition, SFoV possesses at least two additional ORFs, which encode for proteins with regulatory and immunomodulating functions.

6.12.2.2 Preclinical research

Please refer to CGM 2010-10 for preclinical research up to 2010 [214]. The most recent generation of SFoV vectors is self-inactivating (SIN), with transgene expression driven by chimeric 5'LTRs with CMV immediate early promoters, and harboring safety deletions in the 3' LTR [2112, 2113]. SFoV vectors have a much more random integration pattern than gammaretroviruses and lentiviruses, adding to their safety for insertional mutagenesis [2114, 2115]. In addition, polyA read-through is less as compared to these other retroviral vectors [2116]. Therefore, genotoxicity of SFoV vector integration seems to be limited [2117].

SFoV vectors have been shown to transduce a multitude of cell types, including neuronal, hematopoietic and embryonic stem cells [2118-2122]. In addition, efficacy for treatment of monogenic diseases like SCID, pyruvate kinase deficiency, WAS or Fanconi anemia has been shown in animal models [2123-2128]. *In vivo* gene therapy for canine SCID-X1 has recently also been described [2129]. Non-integrating SFoV vectors with mutations in their integrase have also been developed [2130].

6.12.2.3 Clinical trials

In dogs, SFoV vectors have been used to treat different monogenic diseases (see above). Currently, no clinical trials in humans have been performed or are in progress, although a protocol is active for transduction of blood stem cells of healthy volunteers (NCT00758992).

6.12.2.4 Safety

Patient

Zoonotic events do not cause apparent disease in humans. Insertional oncogenesis has not been observed in clinical trials in dogs, even though the vector was sometimes integrated in the vicinity of growth-promoting sites [2131-2133].

Germline

Since SFoV integrates its genome into host cells, germline transmission of integrated transgenes is a theoretical risk when used as *in vivo* gene therapy agent.

Please also refer to CGM 2010-10 [214].

6.13 Family Togaviridae

6.13.1 Genus Alphavirus - Semliki Forest virus (SFV)

6.13.1.1 General information

Please refer to CGM 2010-10 (page 129-130 & 133-134) [214].

6.13.1.2 Preclinical research

In addition to CGM 2010-10 (page 134-136), oncolytic SFV has been evaluated in (animal) models of HCC [2134, 2135], ovarian cancer [2136], melanoma [2137], (metastatic) colon cancer [2138, 2139]. Arming with immune stimulators [2134, 2135, 2137-2139] and TAAs [2136] has been described. Also, combination therapy with oncolytic VV and miRNA targeting has been attempted [2136, 2140, 2141].

In addition, non-replicating SFV gene therapy vectors (SFV RNA replicons) [2142] have been evaluated for stroke [2143], glioma [2144], breast cancer [2145], melanoma [2146]. VV/SFV and hAdV/SFV chimerics have been developed to produce non-replicating SFV replicon delivery systems [2147-2149].

6.13.1.3 Clinical trials

No information available.

6.13.1.4 Safety

Please refer to CGM 2010-10 (page 134-137) [214].

6.13.2 Genus Alphavirus - Sindbis virus (SBV)

6.13.2.1 General information

Please refer to CGM 2010-10 (page 129-131) [214].

6.13.2.2 Preclinical research

In addition to the studies reported in CGM 2010-10 (page 131-132), SBV has been evaluated as replicating oncolytic virus in (mouse) models for colorectal cancer [2150], ovarian cancer [2151, 2152], and hematopoietic malignancy [2153]. NK cells have been found to be important for antitumor effects, with improved efficacy of SBV-IL-12 vectors [2151, 2152], and there are clues that defective IFN pathways relate to SBV oncolytic susceptibility [2154]. Arming of an oncolytic SBV with TAAs and miRNA targeting have also been evaluated [2155, 2156].

Also, more studies have been published on SBV as a non-replicating (cancer) gene therapy vector [2157, 2158]. Of note, production of replication-incompetent SBV vectors also results in low-level production of replication-competent wild-type SBV through recombination [2159].

6.13.2.3 Clinical trials

No information available.

6.13.2.4 Safety

Please refer to CGM 2010-10 (page 132-133) [214].

6.13.3 Genus Alphavirus - Venezuelan equine encephalitis virus (VEEV)

6.13.3.1 General information

Epizootic strains of mosquito vectored VEEV can cause significant disease in horses [2160]. VEEV infection of horses causes a biphasic illness: a first phase with fever, viral replication in lymphoid tissue (DCs) and high serum viremia, and a second phase with invasion of the CNS leading to an often lethal encephalitis [2161, 2162]. VEEV infection of humans leads to a much milder disease ranging from asymptomatic to flu-like symptoms. Encephalitis is observed in only 0.1-0.7% of the human cases, most commonly in children and elderly patients [2163].

VEEV cDNA clones of attenuated strains have allowed the development of VEEV gene expression vectors by introducing transgenes in the viral genome [2164, 2165]. VEEV replicons are based on a viral genome in which the transgene is inserted to replace the viral structural genes [2166]. The viral replicase will be translated in host cells, and this replicase in turn synthesizes (-)RNA which will act as a template for vector amplification (including transgenes), without production of new virions due to the lack of structural genes. Expression levels of heterologous proteins from VEEV replicons are extremely high, although transient due to the induction of innate immune activated apoptosis in infected cells [2167]. Please also refer to CGM 2010-10 (page 129-130) [214].

6.13.3.2 Preclinical research

VEEV based replicons have been evaluated mostly for vaccination for infectious diseases (beyond the scope of this report), and also as tumor vaccines [2168-2179]. The apparent superiority of VEEV replicons over other alphavirus vectors in vaccination could be related to the inherent tropism of VEEV for DCs [2162]. Addition of VEEV vectored IL-12 augmented the anti-tumor efficacy of a VEEV-CEA replicon vaccine [2180].

6.13.3.3 Clinical trials

VEEV replicons have been evaluated in clinical trials mainly for infectious diseases, but also as tumor vaccine, although the cancer vaccine trials described in literature have reported relatively disappointing results [2181, 2182]. Subsequent clinical trials are currently ongoing.

6.13.3.4 Safety

Patient

Clinical trials thus far have shown excellent safety of VEEV replicons.

Germline

VEEV replication takes place in the cytoplasm, which makes the risk of genomic integration very low [2166].

Transmission

Human-to-human transmission has never been observed, and VEEV is a mosquito vectored virus, which adds to the safety in case of environmental shedding.

Mutagenesis/reversion

Since VEEV replicons lack structural viral genes, reversion to wild-type due to spontaneous mutation is impossible. Recombination with a wild-type virus could lead to a wild-type-like VEEV expressing additional transgenes. This event is however very unlikely, and the resulting VEEV would probably not be viable since additional transgenes cannot be incorporated as a surplus into the viral genome.

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