

**Defective viral genomes for antiviral therapeutics, vector control, spillover prevention, and vaccine development**

*Running title:* DVGs in disease control and prevention

**Supplementary File**

**Table S1. Defective viral genomes found in viruses**

<b>Family</b>	<b>Virus</b>	<b>Host</b>	<b>DVG types</b>	<b>DVG effect(s)</b>	<b>Model</b>
RNA viruses					
<i>Arenaviridae</i>	Lymphocytic choriomeningitis virus	Rodents, humans	Deletion	Persistence <sup>1</sup>	<i>In vivo</i>
			Unknown	Competes for replication resources <sup>2-8</sup>	<i>In vitro, in vivo</i>
	Pichinde virus	Rodents, humans	Deletion	Persistence <sup>4-6</sup>	<i>In vitro, in vivo</i>
				Competes for replication resources <sup>9</sup>	<i>In vitro</i>
	Tacaribe virus	Bats, rodents, and ticks	Unknown	Persistence <sup>9</sup>	<i>In vitro</i>
				Competes for replication resources <sup>10-12</sup>	<i>In vitro</i>
Equine arteritis virus	Horses, donkeys, mules, zebras	Deletion	Persistence <sup>12</sup>	<i>In vitro</i>	
			Unknown <sup>13</sup>	<i>In vitro</i>	

	Porcine reproductive and respiratory syndrome virus	Pigs	Deletion	Unknown <sup>14</sup>	Clinical sample, <i>in vitro</i>	
<i>Birnaviridae</i>	Infectious pancreatic necrosis virus	Salmonid fish	Unknown	Persistence <sup>15</sup>	<i>In vitro</i>	
<i>Bunyaviridae</i>	Bunyamwera virus	Humans, ruminants, horses, rodents (vector: mosquitoes)	Deletion	Competes for replication resources <sup>16,17</sup>	<i>In vitro</i>	
			Unknown		<i>In vitro</i>	
	Rift Valley fever virus	Ruminants, humans (vector: mosquito)	Deletion	Persistence <sup>18</sup>	<i>In vitro</i>	
<i>Coronaviridae</i>	Coronavirus	Mammals, birds	Deletion	Competes for replication resources <sup>19</sup>	<i>In vitro</i>	
				Elicit innate immune responses <sup>19</sup>		
				Deletion / mosaic / copy-back	Unknown <sup>20</sup>	<i>In vitro</i>
	Mouse hepatitis virus	Mice	Deletion	Unknown <sup>21-23</sup>	<i>In vitro</i>	
			Mosaic	Unknown <sup>24</sup>	<i>In vitro</i>	
			Unknown	Competes for replication resources <sup>25,26</sup>	<i>In vitro, in vivo</i>	
					Persistence <sup>26</sup>	<i>In vivo</i>
	Severe acute respiratory syndrome coronavirus 2	Humans	Deletion		Elicit innate immune responses <sup>27</sup>	<i>In vitro</i>
					Competes for replication resources <sup>27,28</sup>	<i>In vitro</i>
					Unknown <sup>29,30</sup>	Clinical sample
Transmissible gastroenteritis virus	Pigs, foxes, dogs, cats	Deletion	Unknown <sup>31</sup>	<i>In vitro</i>		
<i>Filoviridae</i>	Ebola virus	Humans, bats, primates	Copy-back	Unknown <sup>32</sup>	<i>In vitro, in vivo</i>	
			Deletion	Competes for replication resources <sup>33</sup>	<i>In vitro</i>	

			Deletion / copy-back	Persistence <sup>34</sup>	<i>In vitro</i>
<i>Flaviviridae</i>	Bovine viral diarrhea virus	Cattle	Deletion	Competes for replication resources <sup>35</sup>	<i>In vitro</i>
			Deletion	Unknown <sup>36,37</sup>	<i>In vitro, in vivo</i>
	Classical swine fever virus	Pigs	Deletion	Competes for replication resources <sup>38-40</sup>	Clinical sample, <i>in vitro</i>
			Unknown	Competes for replication resources <sup>41</sup>	<i>In vitro, in vivo</i>
	Dengue virus	Humans (vector: mosquitoes)	Deletion	Competes for replication resources <sup>42-44</sup>	Clinical sample, <i>in vitro</i>
				Elicit innate immune responses <sup>43</sup>	<i>In vitro</i>
			Deletion / substitution	Persistence <sup>45</sup>	<i>In vitro</i>
			Unknown	Competes for replication resources <sup>46</sup>	<i>In vitro</i>
	Hepatitis C virus	Humans	Deletion	Unknown <sup>47,48</sup>	Clinical sample
			Unknown	Unknown <sup>49</sup>	
	Japanese encephalitis virus	Humans, pigs, birds (vector: mosquitoes)	Deletion	Competes for replication resources <sup>50,51</sup>	<i>In vitro</i>
				Persistence <sup>50,51</sup>	<i>In vitro</i>
			Unknown	Competes for replication resources <sup>52</sup>	<i>In vitro</i>
				Persistence <sup>52</sup>	<i>In vitro</i>
	Murray Valley encephalitis virus	Birds, humans (vector: mosquitoes)	Deletion	Competes for replication resources <sup>53</sup>	<i>In vitro</i>
				Persistence <sup>53</sup>	
Unknown			Competes for replication resources <sup>54</sup>	<i>In vitro</i>	
			Persistence <sup>54</sup>		
Langkat virus	Rodents, ticks, small mammals, primates, humans	Unknown	Competes for replication resources <sup>55</sup>	<i>In vitro</i>	
			Persistence <sup>55</sup>		

		(vector: mosquitoes)			
	Usutu virus	Birds, humans (vector: mosquitoes)	Deletion	Persistence <sup>56</sup>	<i>In vitro</i>
	West Nile virus	Birds, humans, horses (vector: mosquitoes)	Deletion	Competes for replication resources <sup>57</sup>	<i>In vitro, in vivo</i>
			Unknown	Competes for replication resources <sup>57-59</sup>	<i>In vitro</i>
	Zika virus	Humans, non-human primates (vector: mosquitoes)	Deletion	Competes for replication resources <sup>60</sup>	<i>In vitro</i>
			Unknown	Unknown <sup>61</sup>	<i>In vivo</i>
<i>Matonaviridae</i>	Rubella virus	Humans	Deletion	Competes for replication resources <sup>62</sup>	<i>In vitro</i>
				Persistence <sup>62,63</sup>	<i>In vitro</i>
			Unknown	Competes for replication resources <sup>64</sup>	<i>In vitro</i>
<i>Nodaviridae</i>	Flock House virus	Insects	Mosaic / deletion	Unknown <sup>65</sup>	<i>In vitro</i>
<i>Orthomyxoviridae</i>	Avian influenza virus	Wild aquatic birds, poultry, mammals, humans	Deletion	Unknown <sup>66</sup>	<i>In vitro</i>
	Low pathogenic avian influenza virus	Wild aquatic birds, poultry, mammals, humans	Deletion	Competes for replication resources <sup>67</sup>	<i>In vivo</i>
	Influenza A virus	Humans, birds, mammals	Deletion	Competes for replication resources <sup>68-88</sup>	<i>In ovo, in vitro, in vivo</i>
Elicit innate immune responses <sup>69,70,72,75,83,89-96</sup>				Clinical sample, <i>in vitro, in vivo</i>	

				Unknown <sup>97-104</sup>	Clinical sample, <i>in vitro</i> , <i>in vivo</i>
			Deletion / mosaic	Unknown <sup>105</sup>	<i>In ovo</i>
			Substitution	Competes for replication resources <sup>106</sup>	<i>In vitro</i>
			Unknown	Competes for replication resources <sup>107-115</sup>	<i>In ovo, in vitro, in vivo</i>
				Elicit innate immune responses <sup>110,116-119</sup>	<i>In ovo, in vitro, in vivo</i>
				Persistence <sup>107,108,120</sup>	<i>In vitro</i>
				Unknown <sup>121</sup>	<i>In vivo</i>
<i>Paramyxoviridae</i>	Canine distemper virus	Dogs, wild carnivores	Copy-back / deletion	Competes for replication resources <sup>122</sup>	<i>In vitro, in vivo</i>
	Measles virus	Humans	Copy-back	Competes for replication resources <sup>123-125</sup>	<i>In vitro</i>
				Elicit innate immune responses <sup>125-127</sup>	<i>In vitro</i>
				Unknown <sup>128</sup>	Clinical sample
			Unknown	Competes for replication resources <sup>129-132</sup>	<i>In vitro</i>
				Persistence <sup>130</sup>	<i>In vitro</i>
	Mumps virus	Humans	Copy-back	Competes for replication resources <sup>133</sup>	<i>In vitro, in vivo</i>
				Elicit innate immune responses <sup>133</sup>	
			Unknown	Competes for replication resources <sup>134,135</sup>	<i>In vitro</i>
				Persistence <sup>135</sup>	<i>In vitro</i>
	Newcastle disease virus	Birds	Deletion	Competes for replication resources <sup>136</sup>	<i>In vitro</i>
			Unknown	Competes for replication resources <sup>137</sup>	<i>In vitro</i>
	Nipah virus	Bats, pigs, humans	Copy-back / deletion	Competes for replication resources <sup>138</sup>	<i>In vivo</i>
Parainfluenza virus	Humans, primates	Copy-back	Competes for replication resources <sup>139</sup>	<i>In vitro</i>	
			Elicit innate immune responses <sup>139,140</sup>	<i>In vitro</i>	

				Persistence <sup>139,141</sup>	<i>In vitro</i>
			Deletion / copy-back	Competes for replication resources <sup>142</sup>	<i>In vitro</i>
				Elicit innate immune responses <sup>142</sup>	
			Unknown	Competes for replication resources <sup>143</sup>	<i>In vitro</i>
	Persistence <sup>144</sup>	<i>In vitro</i>			
	Peste des petits ruminant virus	Sheep, goats	Unknown	Competes for replication resources <sup>145</sup>	<i>In vitro</i>
	Sendai virus	Rodents	Copy-back	Competes for replication resources <sup>146,147</sup>	<i>In vitro</i>
				Elicit innate immune responses <sup>146,148–150</sup>	<i>In vitro</i>
				Unknown <sup>151</sup>	<i>In vitro</i>
			Copy-back / deletion	Elicit innate immune responses <sup>152</sup>	<i>In ovo, in vitro</i>
				Unknown <sup>153</sup>	<i>In vitro</i>
			Deletion	Competes for replication resources <sup>154</sup>	<i>In vitro</i>
				Elicit innate immune responses <sup>155</sup>	<i>In vitro</i>
				Persistence <sup>154</sup>	<i>In vitro</i>
			Unknown	Competes for replication resources <sup>156</sup>	<i>In vitro</i>
Elicit innate immune responses <sup>157</sup>				<i>In vitro</i>	
Persistence <sup>156,158,159</sup>				<i>In vitro</i>	
Unknown <sup>160,161</sup>	<i>In ovo, in vitro</i>				
<i>Peribunyaviridae</i>	Marituba virus	Vertebrates (vector: mosquitoes)	Unknown	Competes for replication resources <sup>162</sup>	<i>In vitro</i>
<i>Phenuiviridae</i>	Toscana virus	Humans (vector: sandflies)	Deletion	Competes for replication resources <sup>163</sup>	<i>In vitro, in vivo</i>
<i>Picornaviridae</i>	Foot-and-mouth disease virus	Cloven-hoofed animals	Deletion / substitution	Unknown <sup>164</sup>	<i>In vitro</i>
	Poliovirus	Humans	Deletion	Competes for replication resources <sup>165</sup>	<i>In vitro</i>

				Unknown <sup>166-170</sup>	<i>In vitro</i>
			Unknown	Unknown <sup>171</sup>	<i>In vitro</i>
<i>Pneumoviridae</i>	Human metapneumovirus	Humans	Snapback	Elicit innate immune responses <sup>172</sup>	<i>In vitro</i>
	Respiratory syncytial virus	Humans	Copy-back	Competes for replication resources <sup>173</sup>	<i>In vitro</i>
				Elicit innate immune responses <sup>173</sup>	<i>In vitro</i>
				Unknown <sup>174</sup>	<i>In vivo</i>
	Unknown	Competes for replication resources <sup>175,176</sup>	<i>In vitro</i>		
Persistence <sup>176</sup>	<i>In vitro</i>				
<i>Reoviridae</i>	Reovirus	Vertebrates, invertebrates	Deletion / substitution	Unknown <sup>177</sup>	<i>In vitro</i>
	Rotavirus	Humans	Unknown	Competes for replication resources <sup>178</sup>	<i>In vitro</i>
<i>Retroviridae</i>	Human immunodeficiency virus	Human	Deletion	Unknown <sup>179</sup>	Clinical sample
			Deletion / mosaic	Unknown <sup>180</sup>	Clinical sample
			Substitution	Unknown <sup>181</sup>	Clinical sample
			Unknown	Genetic barriers to viral resistance <sup>182</sup>	<i>In vivo</i>
	Murine immunodeficiency virus	Mice	Unknown	Unknown <sup>183</sup>	<i>In vivo</i>
	Murine leukemia virus	Mice	Deletion	Unknown <sup>184</sup>	<i>In vitro</i>
	Retrovirus	Vertebrates	Unknown	Unknown <sup>185</sup>	<i>In vitro</i>
<i>Rhabdoviridae</i>	Bovine ephemeral fever virus	Cattle, water buffalo	Deletion	Competes for replication resources <sup>186</sup>	<i>In vitro</i>
	Rabies virus	Mammals	Unknown	Competes for replication resources <sup>187</sup>	<i>In vitro, in vivo</i>
	Vesicular stomatitis virus	Livestock, humans	Substitution	Persistence <sup>188</sup>	<i>In vitro</i>
			Copy-back	Competes for replication resources <sup>189,190</sup>	<i>In vitro</i>

		(vectors: sandflies, mosquitoes)		Elicit innate immune responses <sup>191</sup>	<i>In vitro</i>
				Unknown <sup>192,193</sup>	<i>In vitro</i>
			Copy-back / snapback	Unknown <sup>194</sup>	<i>In vitro</i>
			Deletion	Competes for replication resources <sup>195–198</sup>	<i>In vitro</i>
				Elicit innate immune responses <sup>199</sup>	<i>In vivo</i>
				Unknown <sup>200–202</sup>	<i>In vitro</i>
			Deletion / copy-back	Unknown <sup>203–205</sup>	<i>In vitro</i>
			Mosaic / copy- back / mutations	Persistence <sup>206</sup>	<i>In vitro</i>
			Snapback	Competes for replication resources <sup>207</sup>	<i>In vitro</i>
				Elicit innate immune responses <sup>208–210</sup>	<i>In vitro</i>
				Persistence <sup>209,210</sup>	<i>In vitro</i>
				Unknown <sup>194,211</sup>	<i>In vitro</i>
			Unknown	Competes for replication resources <sup>212–234</sup>	<i>In vitro, in vivo</i>
				Elicit innate immune responses <sup>229,235,236</sup>	<i>In vitro, in vivo</i>
				Persistence <sup>221,222,237</sup>	<i>In vitro</i>
Unknown <sup>238–240</sup>	<i>In vitro, in vivo</i>				
<i>Togaviridae</i>	Chikungunya virus	Humans (vector: mosquitoes)	Deletion	Unknown <sup>241</sup>	<i>In vitro</i>
				Competes for replication resources <sup>242</sup>	<i>In vitro, in vivo</i>
	Eastern equine encephalitis virus	Birds, humans, mammals (vector: mosquitoes)	Unknown	Unknown <sup>243</sup>	<i>In vitro</i>
	Semliki Forest virus		Deletion	Competes for replication resources <sup>244,245</sup>	<i>In vitro, in vivo</i>

		Rodents, humans, wild birds, non-human primates, domestic animals, mammals (vector: mosquitoes)	Deletion / mosaic	Persistence <sup>246</sup>	<i>In vitro</i>
				Unknown <sup>247-250</sup>	<i>In vitro</i>
				Unknown <sup>251</sup>	<i>In vitro</i>
			Unknown	Competes for replication resources <sup>252-265</sup>	<i>In vitro, in vivo</i>
				Elicit innate immune responses <sup>266</sup>	<i>In vitro, in vivo</i>
				Persistence <sup>267</sup>	<i>In vivo</i>
	Sindbis virus	Birds, humans (vector: mosquitoes)	Deletion	Competes for replication resources <sup>268,269</sup>	<i>In vitro</i>
				Elicit innate immune responses <sup>270</sup>	<i>In vitro</i>
				Unknown <sup>271-276</sup>	<i>In vitro</i>
			Unknown	Competes for replication resources <sup>277-283</sup>	<i>In vitro</i>
				Elicit innate immune responses <sup>284,285</sup>	<i>In vitro, in vivo</i>
				Persistence <sup>285</sup>	<i>In vivo</i>
			Unknown <sup>286-289</sup>	<i>In vitro</i>	
<i>Tornidovirineae</i>	Berne virus	Horses	Deletion	Competes for replication resources <sup>290</sup>	<i>In vitro</i>
DNA viruses					
<i>Baculoviridae</i>	<i>Autographa californica</i> multiple nucleopolyhedrovirus	Insects (moths)	Deletion	Unknown <sup>291</sup>	<i>In vitro</i>
<i>Hepadnaviridae</i>	Hepatitis B virus	Humans	Deletion	Competes for replication resources <sup>292</sup>	<i>In vitro</i>
				Unknown <sup>293,294</sup>	Clinical sample
<i>Herpesviridae</i>	Epstein-Barr virus	Humans	Rearrangement	Unknown <sup>295</sup>	Clinical sample
	Equine herpesvirus 1	Horses	Deletion	Unknown <sup>296</sup>	<i>In vitro</i>
			Deletion / mosaic	Unknown <sup>297,298</sup>	<i>In vitro</i>
			Mosaic	Unknown <sup>299,300</sup>	<i>In vitro</i>

			Unknown	Competes for replication resources <sup>301</sup>	<i>In vitro, in vivo</i>
			Persistence <sup>300-303</sup>	<i>In vitro, in vivo</i>	
			Unknown <sup>304</sup>	<i>In vitro</i>	
	Herpes simplex virus	Humans	Deletion / mosaic	Competes for replication resources <sup>305</sup>	<i>In vitro</i>
			Unknown	Competes for replication resources <sup>306,307</sup>	<i>In vitro</i>
	Pseudorabies virus	Mammals	Mosaic	Competes for replication resources <sup>308</sup>	<i>In vitro</i>
Unknown			Competes for replication resources <sup>309,310</sup>	<i>In vitro</i>	
<i>Parvoviridae</i>	Adeno-associated virus	Humans (helper virus needed)	Deletions / snap back	Competes for replication resources <sup>311</sup>	<i>In vitro</i>
	Densonucleosis virus	Insects	Deletion / mosaic	Unknown <sup>312</sup>	<i>In vivo</i>
	Parvovirus	Mammals	Deletion	Competes for replication resources <sup>313</sup>	<i>In vitro</i>
<i>Polyomaviridae</i>	BK and JC Polyomavirus	Humans	Deletions / mosaic	Persistence <sup>314</sup>	Clinical sample
	Simian virus	Non-human primates	Unknown	Persistence <sup>315</sup>	<i>In vitro</i>

Notes: Clinical sample: DVGs identified from patient-derived clinical specimens; *In ovo*: Experiments conducted in embryonated eggs; *In vitro*: Experiments conducted in cell culture; *In vivo*: Experiments conducted in live animals.

Abbreviation: DVG: defective viral genome.

**Table S2. Applications of defective viral genome and defective interfering particles**

<b>Virus</b>	<b>DVG type</b>	<b>Model</b>	<b>Mechanism</b>
Antiviral therapeutics			
Chikungunya virus	Deletion	<i>In vitro,</i> <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Broad-spectrum antiviral activity across the alphavirus family.<sup>242</sup></li> </ul>
Dengue virus	Deletion, unknown	<i>In vitro,</i> <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Inhibit viral replication and reduce viral titers in cells<sup>43,46,316</sup> and in a mouse model.<sup>317</sup> <ul style="list-style-type: none"> <li>• Exhibit pan-serotype antiviral activity.<sup>46, 316</sup></li> <li>• Broad-spectrum antiviral effects against other viruses.<sup>317</sup></li> </ul> </li> </ul>
Human immunodeficiency virus	Unknown	<i>In vitro,</i> <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Reduce viral titers and inhibit replication <i>in vitro</i> and in mice.<sup>318</sup></li> </ul>
Influenza A virus	Deletion, substitution, unknown	<i>In vitro,</i> <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Inhibit viral replication in mice infected with homologous and heterologous subtypes.<sup>75,112</sup></li> <li>• Broad-spectrum antiviral activity against severe acute respiratory syndrome coronavirus 2<sup>69</sup> and other viruses.<sup>92,319</sup> <ul style="list-style-type: none"> <li>• Protect mice from lethal standard virus infection.<sup>320,321</sup></li> </ul> </li> </ul>
Nipah virus	Copy-back, deletion	<i>In vitro,</i> <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Reduce viral titers in cells<sup>138</sup> and in the hamster model.<sup>138,322</sup> <ul style="list-style-type: none"> <li>• Protect hamsters from lethal challenges.<sup>322</sup></li> </ul> </li> </ul>
Poliovirus	Deletion	<i>In vitro,</i> <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Reduce viral titers in cells and protect mice from lethal challenges.<sup>323</sup></li> </ul>
Severe acute respiratory syndrome coronavirus 2	Deletion, unknown	<i>In vitro,</i> <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Reduce viral titers in cells<sup>324,325</sup> and in a hamster model.<sup>326</sup></li> <li>• Reduce transmission and disease severity in a hamster model.<sup>326</sup> <ul style="list-style-type: none"> <li>• Protect hamsters from lethal challenges.<sup>327</sup></li> </ul> </li> </ul>
Vesicular stomatitis virus	Copy-back	<i>In vitro</i>	<ul style="list-style-type: none"> <li>• Reduce viral titers in both homotypic and heterotypic viral interference assays by inhibiting viral replication.<sup>190</sup></li> </ul>
Zika virus	Deletion	<i>In vitro,</i> <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Inhibit viral replication in vertebrate cells.</li> <li>• Reduce infection and virulence in a mouse model.<sup>328</sup></li> </ul>

Vector control strategy			
Chikungunya virus	Deletion	<i>In vivo</i>	<ul style="list-style-type: none"> <li>• Prevent viral dissemination of chikungunya virus in mosquitoes.<sup>242</sup></li> </ul>
Sindbis virus	Unknown	<i>In vivo</i>	<ul style="list-style-type: none"> <li>• Enhance siRNA-mediated antiviral immunity in insects.<sup>285</sup></li> </ul>
Zika virus	Deletion	<i>In vivo</i>	<ul style="list-style-type: none"> <li>• Impair viral dissemination and transmission in mosquitoes.<sup>328</sup></li> </ul>
Zoonotic diseases and spillover			
Bunyamwera virus	Deletion, unknown	<i>In vitro</i>	<ul style="list-style-type: none"> <li>• Inhibit viral replication in cells.<sup>16,17</sup></li> </ul>
Canine distemper virus	Copy-back, deletion	<i>In vitro</i> , <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Inhibit viral replication in a dose-dependent manner in cells.<sup>122</sup></li> <li>• Replicate and persist in the blood and lymph nodes of ferrets.<sup>122</sup></li> </ul>
Lymphocytic choriomeningitis virus	Deletion, unknown	<i>In vitro</i> , <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Inhibit expression of surface viral antigens and viral synthesis in cells and mice.<sup>2</sup> <ul style="list-style-type: none"> <li>• Replicate and persistent in cells<sup>3,4</sup> and in mice.<sup>5,6</sup></li> </ul> </li> </ul>
Vaccine development			
Dengue virus	Deletion	<i>In vitro</i> , <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Induce IFN responses in the cells<sup>43</sup> and in a mouse model.<sup>317</sup> <ul style="list-style-type: none"> <li>• Trigger innate immune responses.<sup>316</sup></li> </ul> </li> </ul>
Human immunodeficiency virus	Unknown	<i>In vivo</i>	<ul style="list-style-type: none"> <li>• Trigger immune responses without increasing inflammation in rhesus macaques.<sup>318</sup></li> </ul>
Influenza A virus	Deletion, substitution	<i>In vitro</i> , <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Enhance IFN-I and -III responses.<sup>69</sup></li> <li>• Trigger IFN induction against other viruses (e.g., respiratory syncytial virus, yellow fever virus, and Zika virus).<sup>319</sup> <ul style="list-style-type: none"> <li>• Induce IFN-I in the mouse model.<sup>92</sup></li> </ul> </li> <li>• Increase surface expression of human leukocyte antigen.<sup>329</sup></li> <li>• Provide protection when prophylactic DIPs are administered up to 7 days before lethal challenge.<sup>77</sup> <ul style="list-style-type: none"> <li>• Trigger adaptive immune response in mice.<sup>77,93,330</sup></li> </ul> </li> <li>• Induce high serum titers of neutralizing antibodies against hemagglutinin in mice.<sup>330</sup> <ul style="list-style-type: none"> <li>• Enable resistance to reinfection in ferrets.<sup>93</sup></li> </ul> </li> <li>• Promote IgG2c-biased antibody responses and T-cells linked to type-I immunity in mice.<sup>331</sup></li> </ul>

			<ul style="list-style-type: none"> <li>• Induce long-term CD8+ T-cell protection in mice.<sup>331,332</sup></li> </ul>
Measles virus	Copy-back	<i>In vitro, in vivo</i>	<ul style="list-style-type: none"> <li>• Induce IFN-I signaling and specifically interact with RIG-I and LGP2.<sup>126</sup> <ul style="list-style-type: none"> <li>• Activate the innate immune system.<sup>126</sup></li> </ul> </li> <li>• Induce IFN-I and -III IFN production by monocyte-derived dendritic cells.<sup>125</sup> <ul style="list-style-type: none"> <li>• Stimulate production of IFN-<math>\beta</math> in mice.<sup>127</sup></li> </ul> </li> <li>• Demonstrate potential as a vaccine candidate or adjuvant.<sup>125,126</sup></li> </ul>
Parainfluenza virus	Copy-back	<i>In vitro</i>	<ul style="list-style-type: none"> <li>• Reduce complement-mediated lysis of standard virus-infected cells.<sup>139</sup> <ul style="list-style-type: none"> <li>• Trigger the IFN-induction cascade in cells.<sup>140</sup> <ul style="list-style-type: none"> <li>• Stimulate IFN in mice.<sup>323</sup></li> </ul> </li> </ul> </li> <li>• Generate neutralizing antibodies that fully protect mice from challenges.<sup>323</sup> <ul style="list-style-type: none"> <li>• Elicit protective adaptive immunity.<sup>323</sup></li> </ul> </li> </ul>
Poliovirus	Deletion	<i>In vitro, in vivo</i>	<ul style="list-style-type: none"> <li>• Reduce pro-inflammatory cytokine expression in hamsters.<sup>326</sup></li> </ul>
Severe acute respiratory syndrome coronavirus 2	Unknown	<i>In vivo</i>	
Sendai virus	Copy-back, unknown	<i>In vitro, in vivo</i>	<ul style="list-style-type: none"> <li>• Trigger robust, sustained IRF-3 and NF-<math>\kappa</math>B activation with strong immunostimulatory activity in cells.<sup>150</sup> <ul style="list-style-type: none"> <li>• Promote cytokine expression in mice.<sup>150</sup></li> <li>• Induce IFN-<math>\beta</math> and ISGs expression.<sup>333</sup></li> </ul> </li> <li>• Activate human T cells and induce specific adaptive immune responses in mice.<sup>155</sup></li> <li>• Induce pro-inflammatory cytokines and mobilize dendritic cells in mice.<sup>155</sup></li> <li>• Enhance IgG production and boost vaccine efficiency in mice.<sup>333</sup> <ul style="list-style-type: none"> <li>• Serves as a potent adjuvant for vaccination.<sup>155,333</sup></li> </ul> </li> </ul>
Vesicular stomatitis virus	Unknown	<i>In vitro</i>	<ul style="list-style-type: none"> <li>• Activate IFN signaling pathways.<sup>334</sup></li> </ul>

			<ul style="list-style-type: none"> <li>• Activate IFN-<math>\beta</math> promoter, IFN-stimulated response element promoter, and NF-<math>\kappa</math>B promoter.<sup>334</sup></li> </ul>
Oncolytic Virotherapy			
Sendai virus	Copy-back	<i>In vitro,</i> <i>in vivo</i>	<ul style="list-style-type: none"> <li>• Activate pro-apoptotic genes and induce cancer cell-selective apoptosis.<sup>149</sup></li> <li>• Trigger intratumoral apoptosis and tumor suppression in mice.<sup>149</sup></li> </ul>

Notes: *In vitro*: Experiments conducted in cell culture; *In vivo*: Experiments conducted in live animals.

Abbreviations: DIPs: Defective interfering particles; IFN: Interferon; IRF-3: Interferon regulatory factor 3; ISGs: Interferon-stimulated genes; LGP2: Laboratory of genetics and physiology 2; NF- $\kappa$ B: Nuclear factor kappa light chain enhancer of activated B cells; RIG-I: Retinoic acid-inducible gene I; siRNA: Small-interfering RNA.

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