

## Reference Summary for Ebola Therapeutics and Vaccines

This summary is compiled by the Infectious Disease Clinical Research Program (IDCRP) at the Uniformed Services University (USU) for the Armed Forces Infectious Disease Society (AFIDS). This summary was initially built from the 5 November 2014 World Health Organization (WHO) Paper on Potential Ebola Therapies and Vaccines.

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### THERAPEUTICS

#### 1. ANTIBODY THERAPIES

##### ▪ Convalescent Plasma

###### a. Human

- Sadek RF, Khan AS, Stevens G, Peters CJ, Ksiazek TG. Ebola hemorrhagic fever, Democratic Republic of the Congo, 1995: determinants of survival. J Infect Dis. 1999 Feb;179 Suppl 1:S24-7. **Follow-up to Mupapa et al. 1999** [http://jid.oxfordjournals.org/content/179/Supplement\\_1/S24.short](http://jid.oxfordjournals.org/content/179/Supplement_1/S24.short)
- Mupapa K, Massamba M, Kibadi K, et al. Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. International Scientific and Technical Committee. J Infect Dis. 1999 Feb;179 Suppl 1:S18-23. [http://jid.oxfordjournals.org/content/179/Supplement\\_1/S18.full](http://jid.oxfordjournals.org/content/179/Supplement_1/S18.full)
- Emond RT, Evans B, Bowen ET, Lloyd G. A case of Ebola virus infection. Br Med J. 1977 Aug 27;2(6086):541-4. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1631428/pdf/brmedj00478-0011.pdf>

###### b. Non-Human Primates

- Jahrling PB, Geisbert JB, Swearingen JR, Larsen T, Geisbert TW. Ebola hemorrhagic fever: evaluation of passive immunotherapy in nonhuman primates. J Infect Dis 196(Suppl 2):S400-3, 2007 **(Negative results)** [http://jid.oxfordjournals.org/content/196/Supplement\\_2/S400.long](http://jid.oxfordjournals.org/content/196/Supplement_2/S400.long)

###### c. Small Animals

###### d. Convalescent Plasma Summaries

- WHO Blood Regulators Network (BRN) **Position Paper** on Collection and Use of Convalescent Plasma or Serum as an Element in Filovirus Outbreak Response. 14 August 2014 [http://www.who.int/bloodproducts/brn/brn\\_positionpaperconvplasmafiloviruses\\_finalweb14august2014.pdf](http://www.who.int/bloodproducts/brn/brn_positionpaperconvplasmafiloviruses_finalweb14august2014.pdf)

##### ▪ Immunoglobulin

###### a. Human

- Kudoyarova-Zubavichene NM, Sergeev NN, Chepurnov AA, Netesov SV. Preparation and use of hyperimmune serum for prophylaxis and therapy of ebola virus infection. J Infect Dis 179 (Supplement 1):S218-S223, 1999 [http://jid.oxfordjournals.org/content/179/Supplement\\_1/S218.full](http://jid.oxfordjournals.org/content/179/Supplement_1/S218.full)

###### b. Non-Human Primates

- Dye JM, Herbert AS, Kuehne AI, et al. 2012. Postexposure antibody prophylaxis protects nonhuman primates from filovirus disease. Proc Natl Acad Sci U S A 109:5034-5039. <http://www.pnas.org/content/109/13/5034.full.pdf>
- Jahrling PB, Geisbert J, Swearingen JR, et al. Passive immunization of Ebola virus-infected cynomolgus monkeys with immunoglobulin from hyperimmune horses. Arch Virol 11(Suppl):135-40, 1996 **(Negative results)**
- Borisevich IV, Mikhaïlov VV, Krasnianskiï VP, et al. Development and study of the properties of immunoglobulin against Ebola fever. Vopr Virusol 40(6):270-3,

1995 (only abstract available, article in Russian)

**c. Small Animals**

▪ **Monoclonal Antibodies**

**a. Human**

**b. Non-Human Primates**

- Qiu X, Wong G, Audet J, et al. Reversion of advanced Ebola virus disease in nonhuman primates with **ZMapp**. *Nature*. 2014 Oct 2;514(7520):47-53.
- Qiu X, Audet J, Wong G, et al. Sustained protection against Ebola virus infection following treatment of infected nonhuman primates with **ZMAb**. *Sci Rep*. 2013 Nov 28;3:3365. <http://www.nature.com/srep/2013/131128/srep03365/full/srep03365.html>
- Pettitt J, Zeitlin L, Kim DH, et al. Therapeutic Intervention of Ebola Virus Infection in Rhesus Macaques with the **MB-003** Monoclonal Antibody Cocktail. *Science Transl Med* 5(199):199ra113, 2013 <http://stm.sciencemag.org/content/5/199/199ra113.full>
- Qiu X, Audet J, Wong G, et al. Successful treatment of Ebola virus–infected cynomolgus macaques with monoclonal antibodies. *Sci Transl Med*. 2012 Jun 13;4(138):138ra81. **ZMAb** <http://stm.sciencemag.org/content/4/138/138ra81.long>
- Olinger GG Jr, Pettitt J, Kim D, et al. Delayed treatment of Ebola virus infection with plant-derived monoclonal antibodies provides protection in rhesus macaques. *Proc. Natl. Acad. Sci. U.S.A.* 109: 18030–18035, 2012. **MB-003** <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3497800/>
- Oswald WB, Geisbert TW, Davis KJ, et al. Neutralizing antibody fails to impact the course of Ebola virus infection in monkeys. *PLoS Pathog*. 2007 Jan;3(1):e9. **KZ52 (Negative results)** <http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.0030009#ppat-0030009-g002>

**c. Small Animals**

- Parren PW, Geisbert TW, Maruyama T, Jahrling PB, Burton DR. Pre- and postexposure prophylaxis of Ebola virus infection in an animal model by passive transfer of a neutralizing human antibody. *J Virol* 2002;76:6408-12. **KZ52** <http://jvi.asm.org/content/76/12/6408.full>

▪ **Antibody Therapy Review**

- Qiu X, Kobinger GP. Antibody therapy for Ebola: Is the tide turning around? *Hum Vaccin Immunother*. 2014 Apr;10(4):964-7.

**2. ANTI-VIRALS**

▪ **Polymerase inhibitors**

**a. Human**

**b. Non-Human Primates**

- Warren TK, Wells J, Panchal RG, et al. Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue **BCX4430**. *Nature*. 2014 Apr 17;508(7496):402-5.

**c. Small Animals**

- Smither SJ, Eastaugh LS, Steward JA, et al. Post-exposure efficacy of Oral **T-705 (Favipiravir)** against inhalational Ebola virus infection in a mouse model. *Antiviral Research* 104:153–155, 2014
- Oestereich L, Lüdtke A, Wurr S, et al. Successful treatment of advanced Ebola virus infection with **T-705 (favipiravir)** in a small animal model. *Antiviral Research* 105:17–21, 2014 <http://www.sciencedirect.com/science/article/pii/S0166354214000576>

**d. Polymerase Inhibitor Summaries**

- Furuta Y, Gowen BB, Takahashi K, et al. **Favipiravir (T-705)**, a novel viral RNA

polymerase inhibitor. Antiviral Res. 2013 Nov;100(2):446-54. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3880838/>

▪ **Lipid nanoparticle/small interfering RNA (LNP/siRNA)**

**a. Human**

- Tekmira. TKM-Ebola in development <http://www.tekmira.com/pipeline/tkm-ebola.php>

**b. Non-Human Primates**

- Thi EP, Mire CE, Ursic-Bedoya R, et al. Marburg virus infection in nonhuman primates: Therapeutic treatment by lipid-encapsulated siRNA. Sci Transl Med. 2014 Aug 20;6(250):250ra116. **NP-718m** <http://stm.sciencemag.org/content/6/250/250ra116.short>
- Geisbert TW, Lee AC, Robbins M, et al. Postexposure protection of non-human primates against a lethal Ebola virus challenge with RNA interference: a proof-of-concept study. Lancet 375:1896-1905, 2010 <http://download.thelancet.com/pdfs/journals/lancet/PIIS0140673610603571.pdf?id=gaa79G73ifyidcewDbMMu>

**c. Small Animals**

- Geisbert TW, Hensley LE, Kagan E, et al. Postexposure protection of guinea pigs against a lethal ebola virus challenge is conferred by RNA interference. J Infect Dis 193:1650-1657, 2007 <http://jid.oxfordjournals.org/content/193/12/1650.long>

▪ **Anti-sense phosphorodiamidate morpholino oligomers (PMOs)**

**a. Human**

- Sarepta Therapeutics in development <http://www.sarepta.com/pipeline/avi-7288-marburg>
- Heald AE, Iversen PL, Saoud JB, et al. Safety and Pharmacokinetic Profiles of Phosphorodiamidate Morpholino Oligomers with Activity against Ebola Virus and Marburg Virus: Results of Two Single-Ascending-Dose Studies. Antimicrob Agents Chemother. 2014 Nov;58(11):6639-47. <http://aac.asm.org/content/58/11/6639.full.pdf+html>

**b. Non-Human Primates**

- Warren TK, Warfield KL, Wells J, et al. Advanced antisense therapies for postexposure protection against lethal filovirus infections. Nat Med. 2010 Sep;16(9):991-4.
- Warfield KL, Swenson DL, Olinger GG, et al. Gene-specific countermeasures against Ebola virus based on antisense phosphorodiamidate morpholino oligomers. PLoS Pathog. 2006 Jan;2(1):e1. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1326218/>

**c. Small Animals**

- Iversen PL, Warren TK, Wells JB, et al. Discovery and Early Development of **AVI-7537** and **AVI-7288** for the Treatment of Ebola Virus and Marburg Virus Infections. Viruses. 2012 Nov 6;4(11):2806-30. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3509674/>

▪ **Selective Estrogen Receptor Modulators (SERMS)**

**a. Human**

**b. Non-Human Primates**

**c. Small Animals**

- Johansen LM, Brannan JM, Delos SE, et al. FDA-Approved Selective Estrogen Receptor Modulators Inhibit Ebola Virus Infection. Sci Transl Med 5(190):190ra79, 2013 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3955358/>

▪ **Anti-virals Reviews**

- Florescu DF, Keck MA. Development of **CMX001 (Brincidofovir)** for the treatment of

serious diseases or conditions caused by dsDNA viruses. *Expert Rev Anti Infect Ther.* 2014 Oct;12(10):1171-8.

- Huggins JW. Prospects for treatment of viral hemorrhagic fevers with **ribavirin**, a broad-spectrum antiviral drug. *Rev Infect Dis* 11 Suppl 4:S750-61, 1989

### 3. ANTI-INFLAMMATORIES

#### ▪ Interferons

##### a. Human

##### b. Non-Human Primates

- Smith LM, Hensley LE, Geisbert TW, et al. **Interferon- $\beta$**  Therapy Prolongs Survival in Rhesus Macaque Models of Ebola and Marburg. *J Infect Dis.* 2013 Jul 15;208(2):310-8 <http://jid.oxfordjournals.org/content/208/2/310.long>

##### c. Small Animals

### 4. ANTI-COAGULANTS

##### a. Human

##### b. Non-Human Primates

- Geisbert TW, Hensley LE, Jahrling PB, et al. Treatment of Ebola virus infection with a recombinant inhibitor of factor VIIa/tissue factor: a study in rhesus monkeys. *Lancet* 362:1953-1958, 2003 (**rhAPC [Xigris; Eli Lilly]**) [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(03\)15012-X/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(03)15012-X/fulltext)

##### c. Small Animals

### 5. SEPSIS-RELATED THERAPIES

##### a. Human

##### b. Non-Human Primates

- Hensley LE, Stevens EL, Yan SB, et al. Recombinant human activated protein C for the postexposure treatment of Ebola hemorrhagic fever. *J Infect Dis* 196 Suppl 2:S390-9, 2007 (**rNAPc2**) [http://jid.oxfordjournals.org/content/196/Supplement\\_2/S390.long](http://jid.oxfordjournals.org/content/196/Supplement_2/S390.long)

##### c. Small Animals

### 6. COMBINATION THERAPIES

#### ▪ Interferons with Antibodies

##### a. Human

##### b. Non-Human Primates

- Qiu X, Wong G, Fernando L, et al. mAbs and Ad-vectored IFN- $\alpha$  therapy rescue Ebola-infected nonhuman primates when administered after the detection of viremia and symptoms. *Sci Transl Med.* 5(207):207ra143, 2013. <http://stm.sciencemag.org/content/5/207/207ra143.long>
- Jahrling PB, Geisbert TW, Geisbert JB, et al. Evaluation of immune globulin and recombinant interferon-alpha2b for treatment of experimental Ebola virus infections. *J Infect Dis* 179 Suppl 1:S224-34, 1999 (**Negative results**) [http://jid.oxfordjournals.org/content/179/Supplement\\_1/S224.long](http://jid.oxfordjournals.org/content/179/Supplement_1/S224.long)

##### c. Small Animals

- Qiu X, Wong G, Fernando L, et al. Monoclonal antibodies combined with adenovirus-vectored interferon significantly extend the treatment window in Ebola virus-infected guinea pigs. *J Virol* 87(13):7754-7, 2013 <http://jvi.asm.org/content/87/13/7754.long>
- Richardson JS, Wong G, Pillet S, et al. Evaluation of different strategies for post exposure treatment of ebola virus infection in rodents. *J Bioterr Biodef* S1:007, 2011 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3509938/>
- Ignatyev G, Steinkasserer A, Streltsova M, et al. Experimental study on the possibility of treatment of some haemorrhagic fevers. *J Biotechnol.* 2000 Sep 29;83(1-2):67-76.

## VACCINES

### 1. ADENOVIRAL VECTORS

#### a. Human

#### b. Non-Human Primates

- Choi JH, Jonsson-Schmunk K, Qiu X, et al. A Single Dose Respiratory Recombinant Adenovirus-Based Vaccine Provides Long-Term Protection for Non-Human Primates from Lethal Ebola Infection. *Mol Pharm.* 2014 Nov 1. **Ad-CAGoptZGP** <http://pubs.acs.org/doi/abs/10.1021/mp500646d>
- Stanley DA, Honko AN, Asiedu C, et al. Chimpanzee adenovirus vaccine generates acute and durable protective immunity against ebolavirus challenge. *Nat Med.* 2014 Oct;20(10):1126-9
- Sullivan NJ, Geisbert TW, Geisbert JB, et al. Immune protection of nonhuman primates against Ebola virus with single low-dose adenovirus vectors encoding modified GPs. *PLoS Med.* 2006 Jun;3(6):e177. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1459482/>
- Sullivan NJ, Geisbert TW, Geisbert JB, et al. Accelerated vaccination for Ebola virus haemorrhagic fever in non-human primates. *Nature.* 2003 Aug 7;424(6949):681-4. **ADV-GP/NP**

#### c. Small Animals

### 2. VESICULAR STOMATITIS VIRUS VECTORS

#### a. Human

- Günther S, Feldmann H, Geisbert TW, et al. Management of Accidental Exposure to Ebola Virus in the Biosafety Level 4 Laboratory, Hamburg, Germany. *J Infect Dis.* 2011 Nov;204 Suppl 3:S785-90. [http://jid.oxfordjournals.org/content/204/suppl\\_3/S785.long](http://jid.oxfordjournals.org/content/204/suppl_3/S785.long)

#### b. Non-Human Primates

- Marzi A, Engelmann F, Feldmann H, et al. Antibodies are necessary for rVSV/ZEBOV-GP-mediated protection against lethal Ebola virus challenge in nonhuman primates. *Proc Natl Acad Sci U S A.* 2013 Jan 29;110(5):1893-8. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3562844/>
- Mire CE, Miller AD, Carville A, et al. Recombinant Vesicular Stomatitis Virus Vaccine Vectors Expressing Filovirus Glycoproteins Lack Neurovirulence in Nonhuman Primates. *PLoS Negl Trop Dis.* 2012;6(3) <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3308941/>
- Geisbert TW, Feldmann H. Recombinant Vesicular Stomatitis Virus-Based Vaccines Against Ebola and Marburg Virus Infections. *J Infect Dis.* 2011 Nov;204 Suppl 3:S1075-81. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3218670/>
- Geisbert TW, Daddario-DiCaprio KM, Lewis MG, et al. Vesicular Stomatitis Virus-Based Ebola Vaccine Is Well-Tolerated and Protects Immunocompromised Nonhuman Primates. *PLoS Pathog.* 2008 Nov;4(11) <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2582959/pdf/ppat.1000225.pdf>
- Feldmann H, Jones SM, Daddario-DiCaprio KM, et al. Effective post-exposure treatment of Ebola infection. *PLoS Pathog.* 2007 Jan;3(1):e2. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1779298/>
- Jones SM, Feldmann H, Ströher U, et al. Live attenuated recombinant vaccine protects nonhuman primates against Ebola and Marburg viruses. *Nat Med.* 2005 Jul;11(7):786-90.

#### c. Small Animals

### 3. Vaccine Reviews

- Galvani AP, Ndeffo-Mbah ML, Wenzel N, Childs JE. Ebola Vaccination: If Not Now, When? *Ann Intern Med.* 2014 Aug 21 <http://annals.org/article.aspx?articleid=1899514>
- Marzi A, Feldmann H. Ebola virus vaccines: an overview of current approaches.

### Natural History and General Review Literature

- WHO Potential Ebola Therapies and Vaccines. 5 November 2014 [http://apps.who.int/iris/bitstream/10665/137590/1/WHO\\_EVD\\_HIS\\_EMP\\_14.1\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/137590/1/WHO_EVD_HIS_EMP_14.1_eng.pdf?ua=1)
- Ansari AA. Clinical features and pathobiology of Ebolavirus infection. *J Autoimmun.* 2014 Sep 23. pii: S0896-8411(14)00130-9.
- Wong G, Qiu X, Olinger GG, Kobinger GP. Post-exposure therapy of filovirus infections. *Trends Microbiol.* 2014 Aug;22(8):456-63.
- Choi JH, Croyle MA. Emerging targets and novel approaches to Ebola virus prophylaxis and treatment. *BioDrugs.* 2013 Dec;27(6):565-83. <http://link.springer.com/article/10.1007%2Fs40259-013-0046-1>
- Kortepeter MG, Bausch DG, Bray M. Basic clinical and laboratory features of filoviral hemorrhagic fever. *J Infect Dis.* 2011 Nov;204 Suppl 3:S810-6 [http://jid.oxfordjournals.org/content/204/suppl\\_3/S810.long](http://jid.oxfordjournals.org/content/204/suppl_3/S810.long)
- Feldmann H, Geisbert TW. Ebola haemorrhagic fever. *Lancet.* 2011 Mar 5;377(9768):849-62. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3406178/>
- Rollin PE, Bausch DG, Sanchez A. Blood chemistry measurements and D-Dimer levels associated with fatal and nonfatal outcomes in humans infected with Sudan Ebola virus. *J Infect Dis.* 2007 Nov 15;196 Suppl 2:S364-71. [http://jid.oxfordjournals.org/content/196/Supplement\\_2/S364.long](http://jid.oxfordjournals.org/content/196/Supplement_2/S364.long)
- Gonzalez JP, Herbreteau V, Morvan J, Leroy EM. Ebola virus circulation in Africa: a balance between clinical expression and epidemiological silence. *Bull Soc Pathol Exot.* 2005 Sep;98(3):210-7.
- Baize S, Leroy EM, Georges AJ, et al. Inflammatory responses in Ebola virus-infected patients. *Clin Exp Immunol.* 2002 Apr;128(1):163-8 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1906357/>
- Leroy EM, Baize S, Debre P, Lansoud-Soukate J, and Mavoungou E. Early immune responses accompanying human asymptomatic Ebola infections. *Clin Exp Immunol.* 2001 Jun;124(3):453-60. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1906073/>
- Leroy EM, Baize S, Volchkov VE, et al. Human asymptomatic Ebola infection and strong inflammatory response. *Lancet.* 2000 Jun 24;355(9222):2210-5. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(00\)02405-3/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(00)02405-3/fulltext)