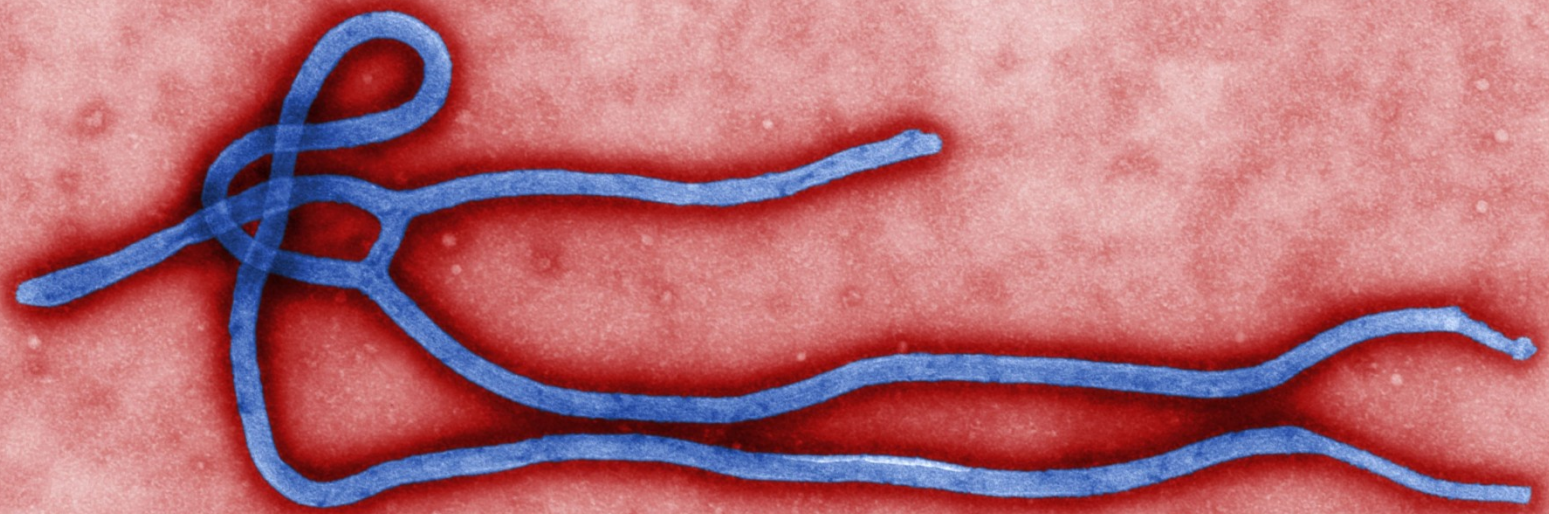
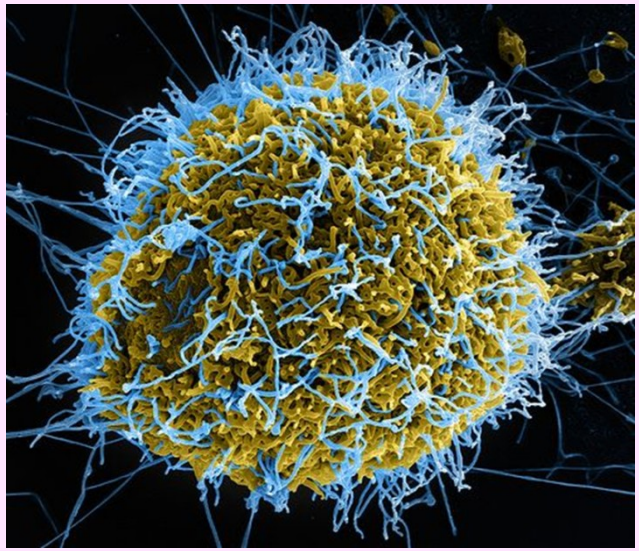
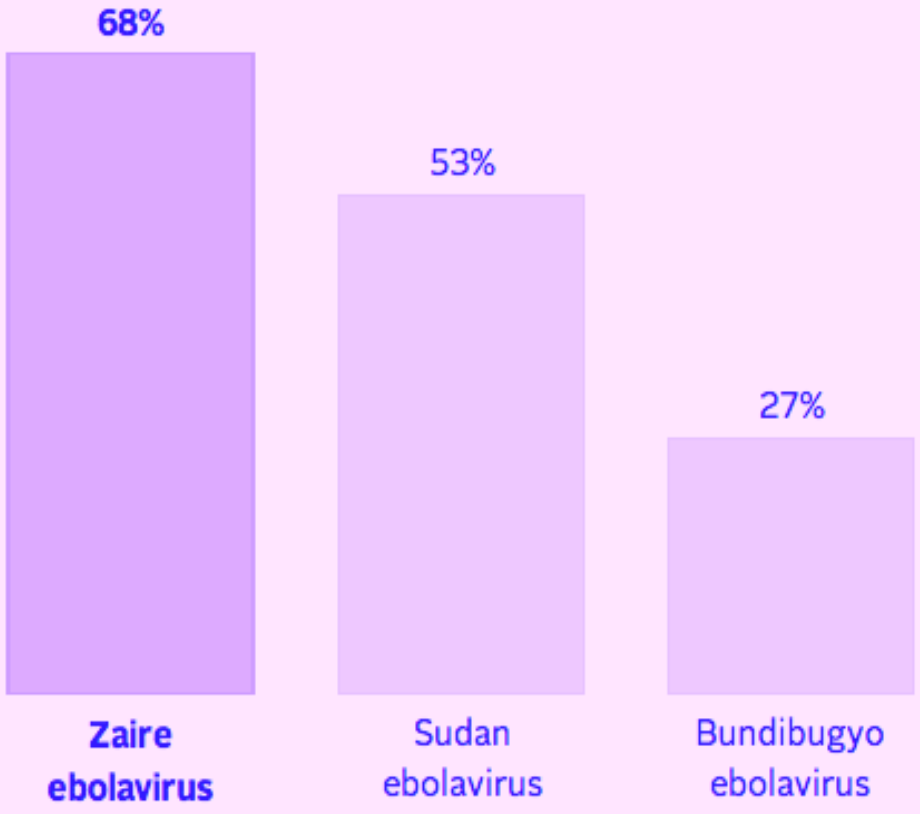
Therapeutic Strategy of Human Ebola Virus Infection Basing on Available Agents



Dr. Lai Kang Yiu

Average death rates from the 5 types of Ebola viruses



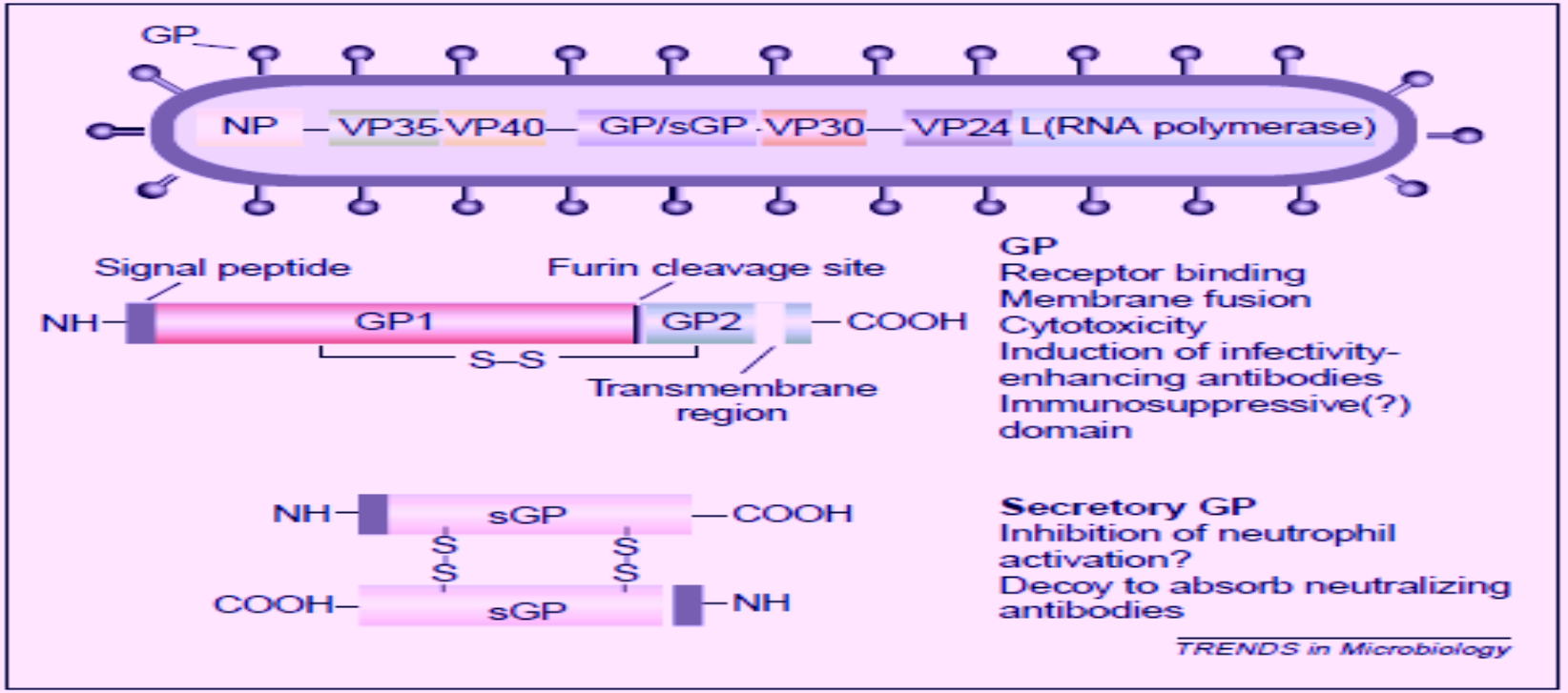


Source: CDC, WHO

Possible contributing factors to the disparate virulence of Ebola Zaire compared with Ebola Reston[a]

Factor	Ebola Zaire	Ebola Reston
GP cleavability by furin	Optimal	Suboptimal
GP epitopes for infectivity-enhancing antibody	+	–
GP endothelial cell toxicity[b]	+	±
VP35 function	IFN antagonist	?
sGP function	Inhibit neutrophil function; adsorb neutralizing antibodies	? ?

[a]Abbreviations: GP, glycoprotein; IFN, interferon; sGP, secretory glycoprotein.
[b]In organ culture, Zaire GP increased the permeability of endothelial cells derived from both human and non-human primates, whereas the Reston GP did so only in non-human cells[18].



Takada A, Kawaoka Y. The pathogenesis of Ebola hemorrhagic fever. Trends Microbiol. 2001 Oct;9(10):506-11.

Confirmed, probable, and suspect cases and deaths from Ebola virus disease in Guinea, Liberia, Nigeria, and Sierra Leone, as of 20 August 2014

	New (1)	Confirmed	Probable	Suspect	Totals
Guinea					
Cases	28	443	139	25	607
Deaths	10	264	139	3	406
Liberia					
Cases	110	269	554	259	1 082
Deaths	48	222	267	135	624
Nigeria					
Cases	1	12	0	4	16
Deaths	1	5	0	0	5
Sierra Leone					
Cases	3	804	40	66	910
Deaths	18	353	34	5	392
Totals					
Cases	142	1 528	733	354	2 615
Deaths	77	844	440	143	1 427

1. New cases were reported between 19 and 20 August 2014.

Patrick Sawyer

120 healthcare workers died in outbreak

How one funeral spread Ebola across Sierra Leone

Sierra Leone's 392 Ebola deaths traced back to one healer's claims to special powers

Travel Bans & Food Rations Loss of "Hope"

Liberian police in protective clothing address residents as they wait for food rations in Monrovia, part of the quarantine plan to curb the spread of the Ebola virus. (Ahmed Jallanzo / European Pressphoto Agency)

Why we need a treatment protocol for Ebola virus in Africa ?

The treatment could engender hope to encourage people with symptoms and their close contacts to come to hospital to limit spread of the disease.

This also could help in recruiting and maintaining adequate levels of hospital staffs who are at high risk of catching the dieases.

The Role of Treatment Protocol
Is to Generate "Hope"

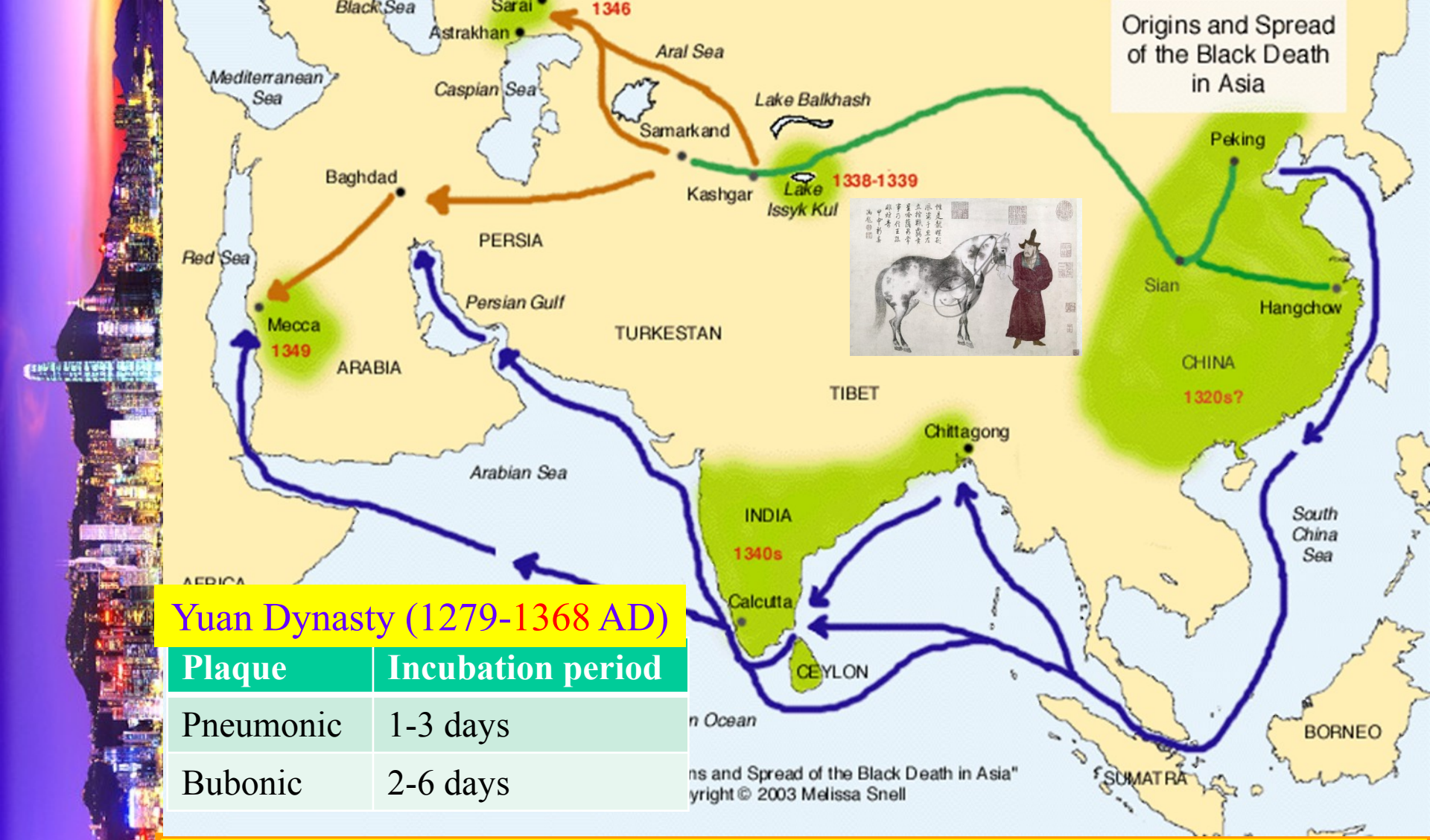
	Ebola	SARS
Total Infected	2615	1755
Death	1427	299
HCW death	120 (~240 infected)	6 (386)

Numbers of Probable Cases of SARS, Deaths, and Healthcare Workers Infected in Selected Countries and Globally

	Cumulative No. of Cases	Deaths No. (%)	Workers Infected No. (%)
Canada	251	41 (17)	108 (43)
China	5,327	349 (7)	1,002 (19)
Hong Kong	1,755	299 (17)	386 (22)
Taiwan	346	37 (11)	68 (20)
Philippines	14	2	4 (29)
Singapore	238	33	97 (41)
Thailand	9	2	1 (11)
Vietnam	63	5	36 (57)
Global	8,098	774	1,707 (21)

Unprecedented number of medical staff infected with Ebola W.H.O. 25/8/2014


Protection of our healthcare worker is paramount in winning this battle !
Ebola virus attack our defense system
the monocyte of our body and HCW of our medical system
TED ALJIBE/AFP/GETTY IMAGES



Yuan Dynasty (1279-1368 AD)

Plaque	Incubation period
Pneumonic	1-3 days
Bubonic	2-6 days

Black Death (1333-1369) killed 1/3 of the population of Europe and 2/3 of population of China

1755 SARS patients in 2003 and ~ 10% infected patient during the first wave of novel H1N1 with <0.1% mortality in 2009 has pushed our medical system to the limit

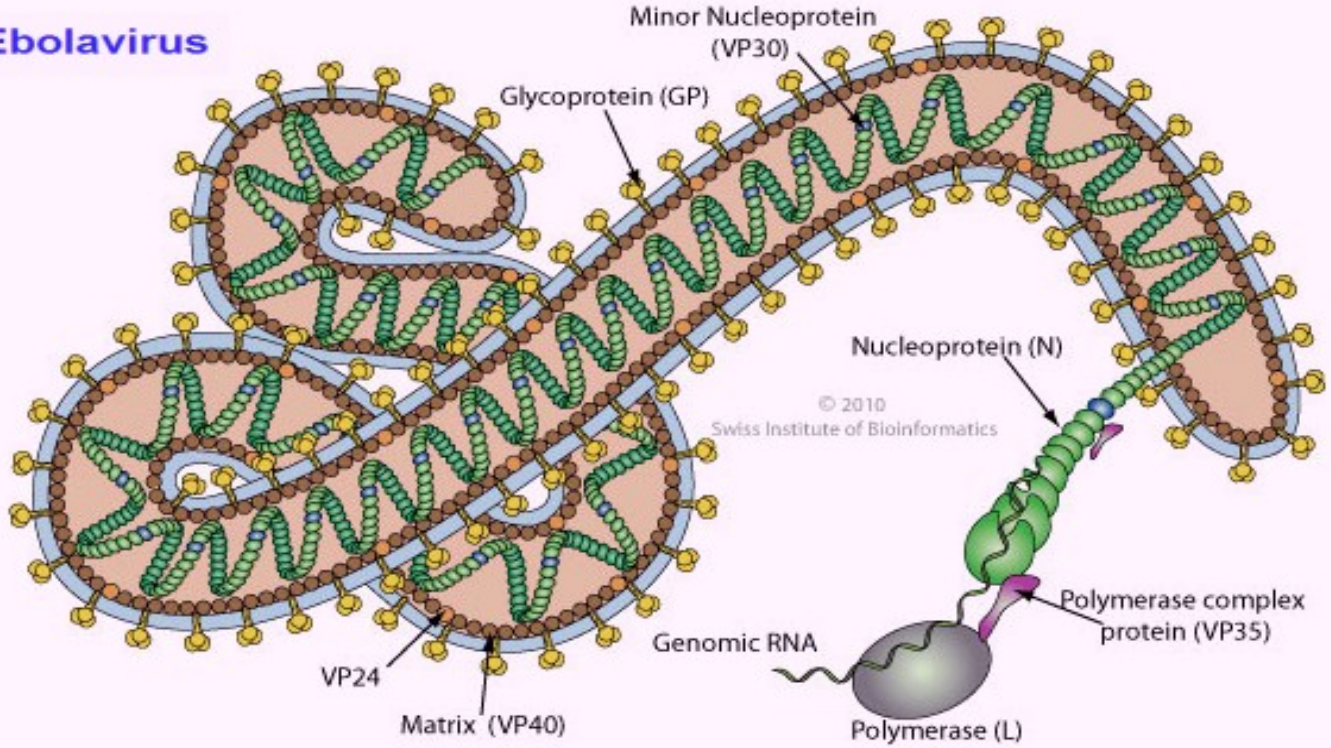
The Perspective of Ebola Virus outbreak in Hong Kong

The genome of Ebola virus is a linear, nonsegmented, single-stranded RNA of negative polarity

變幻原是永恆

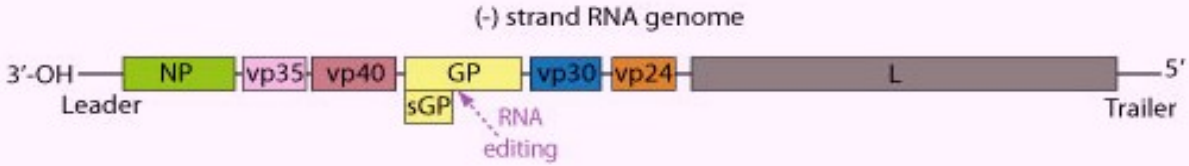
Being an RNA virus, the RNA polymerase of Ebola has no proofreading mechanism. ~1 error per replicated genome ➔ each cell can produce 10,000 new viral mutants to infect neighbouring cells. (300x than DNA virus)

Ebolavirus



Filamentous 970 nm long for Ebolavirus. Diameter is about 80nm.

GENOME

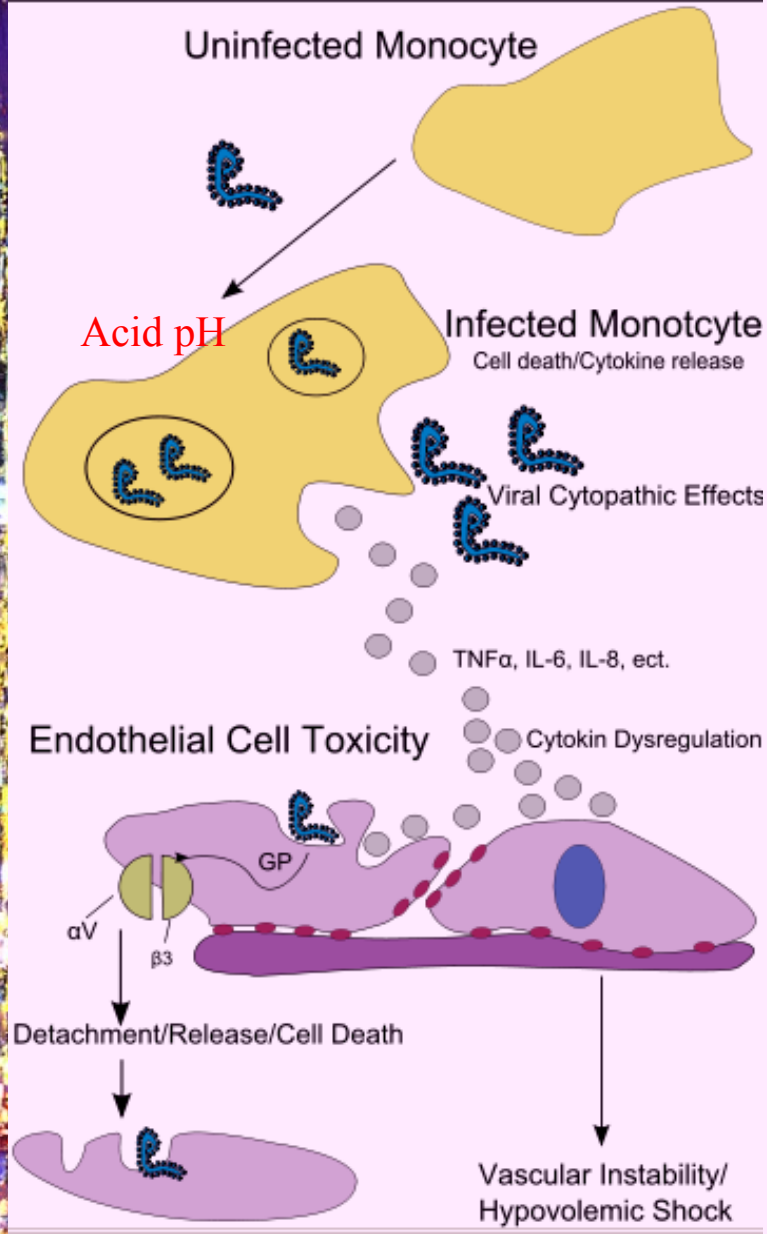


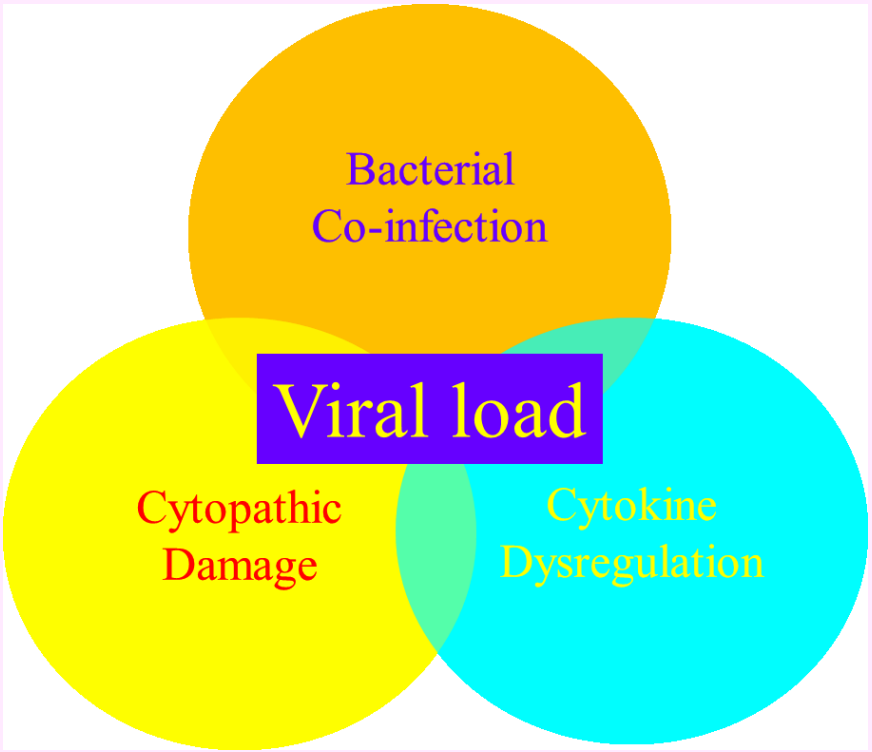
Negative-stranded RNA linear genome, about 18-19 kb in size. Encodes for seven proteins.

The 18.9-kb linear, non-segmented, negative-sense, single-stranded RNA genome of Ebola virus encodes seven structural proteins and one non-structural protein.

Ebola virus, protected from the host interferon response by its encoded VP35 and VP24 protein, has resulted a heavy viral load leading to cytopathic damage and cytokine dysregulation.

Ebola virus is a RNA virus with limited coding capacity. It has utilized the host metabolic pathway for its replication and propagation and during the process has led to apoptosis of the host cell with diffuse monocytic and endothelial damages and cytokine dysregulation.





Pathogenesis of Ebola Virus

Innate Immune Suppression

Broad cell tropism

Ebola virus is a small RNA virus with limited coding capacity

Rhesus Monkeys	1	2	3	4	5	6	7	8
Controls	<0.5	2.5	5;4.5	5.5	4.5	-		
	<0.5	2.5	54.5	6.5	5.5			
	<0.5	2.5	4.0	5.0	5.0			
- 2 Days	<0.5	<0.5	3.5	5.5	5.5	6.5		
	<0.5	<0.5	1.5	5.5	6.5		-	
Interferon +1 Hr	<0.5	<0.5	1.5	3.5	2.5	3.5	6.5	
	<0.5	2.5	3.5	6.5	2.5	3.5		-
+3 Days	<0.5	2.5	4.0	2.5	6.5			
	<0.5	1.5	5.0	6.5	6.0			

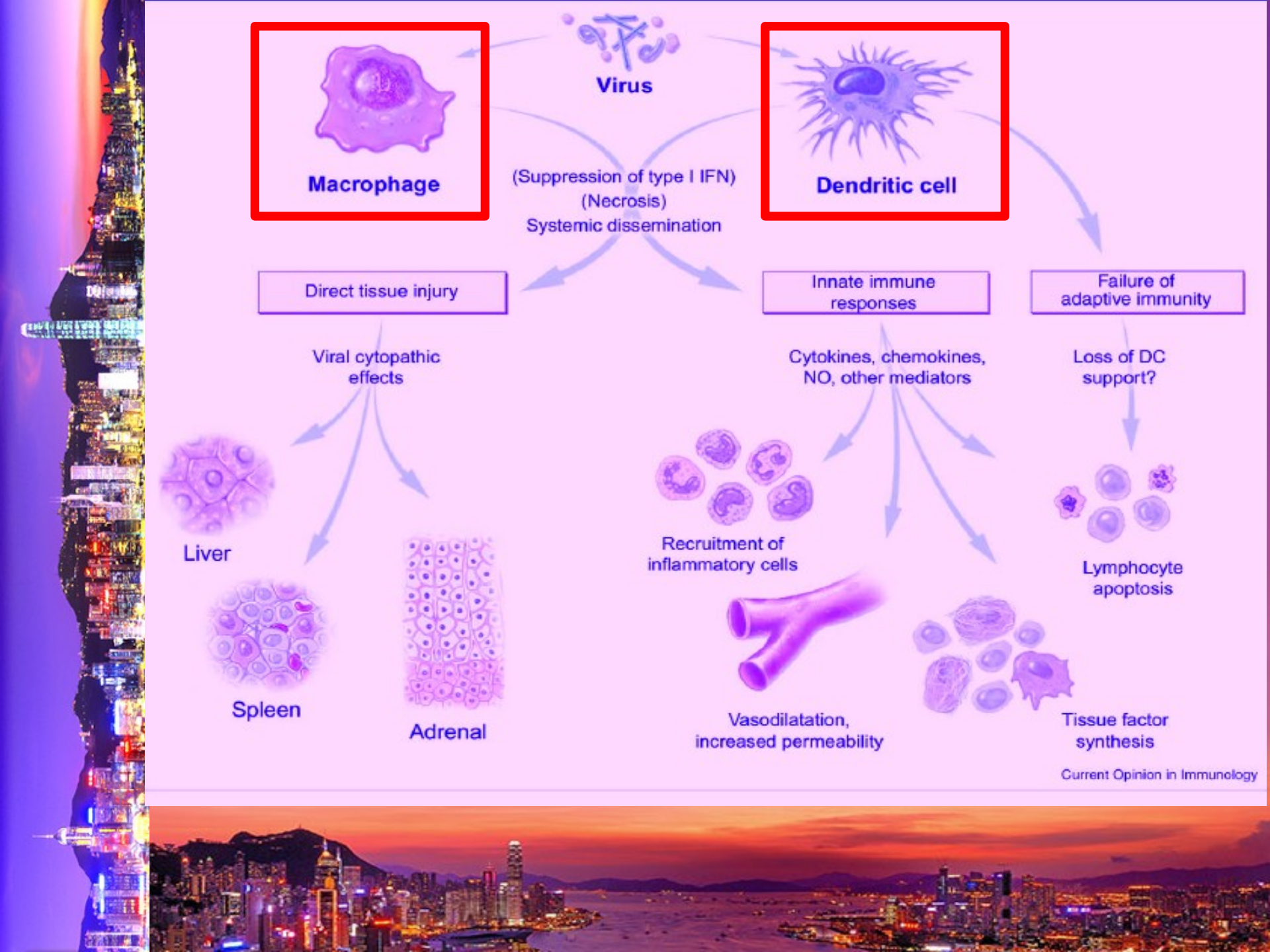
This demonstrate viral load contributes to mortality and the inability of IFN-α to suppress Ebola virus replication. Ebola virus infection is associated with robust IFN-α production, with plasma concentrations of IFN-α that greatly (60- to 100-fold) exceed those seen in other viral infections, but little IFN-β production.

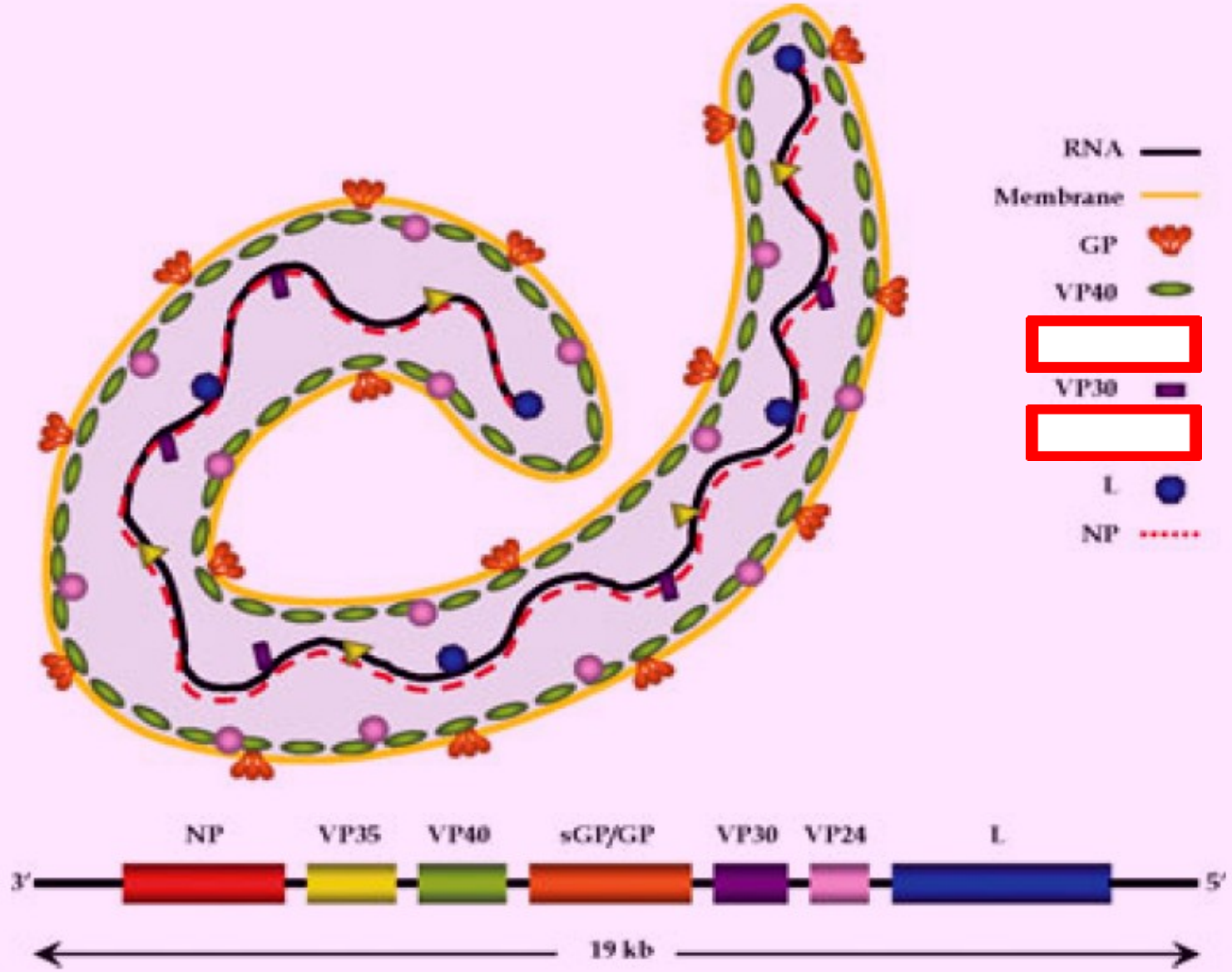
The effect of interferon on experimental Ebola virus infection in Rhesus monkey. E. T. W. Bowen
Interferon-β therapy prolongs survival in rhesus macaque models of Ebola and Marburg hemorrhagic fever. Smith LM et al. J Infect Dis. 2013;208:310-8

Correlative differences in patients who survive versus patients who succumb to Ebola virus infection

Nonlethal infection	Lethal infection
Prominent $CD8^+$ T cell activation	No $CD8^+$ T cell activation
Above-normal numbers of T cells	Below-normal numbers of T cells
10^7 viral genome copies/ml serum	10^{10} viral genome copies/ml serum
Detectable antibodies in blood at onset of symptoms	No detectable antibodies in blood at onset of symptoms
Low NO	High NO

Nat Immunol. 2007 Nov;8(11):1159-64.
Immunopathology of highly virulent pathogens: insights from Ebola virus.
Zampieri CA1, Sullivan NJ, Nabel GJ.

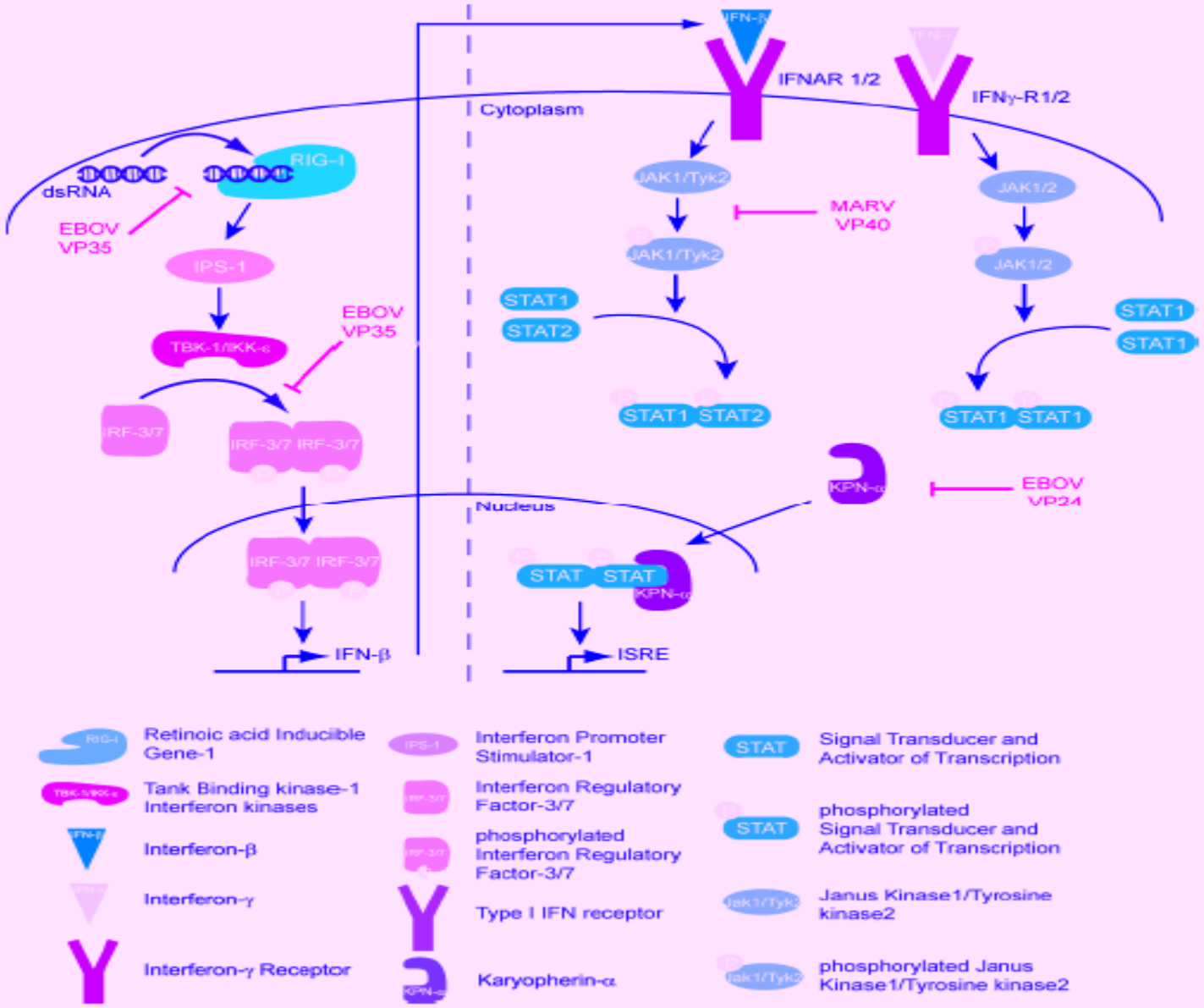

Virus
Macrophage
Dendritic cell
(Suppression of type I IFN)
(Necrosis)
Systemic dissemination
Direct tissue injury
Innate immune responses
Failure of adaptive immunity
Viral cytopathic effects
Cytokines, chemokines, NO, other mediators
Loss of DC support?
Liver
Spleen
Adrenal
Recruitment of inflammatory cells
Lymphocyte apoptosis
Vasodilatation, increased permeability
Tissue factor synthesis
Current Opinion in Immunology



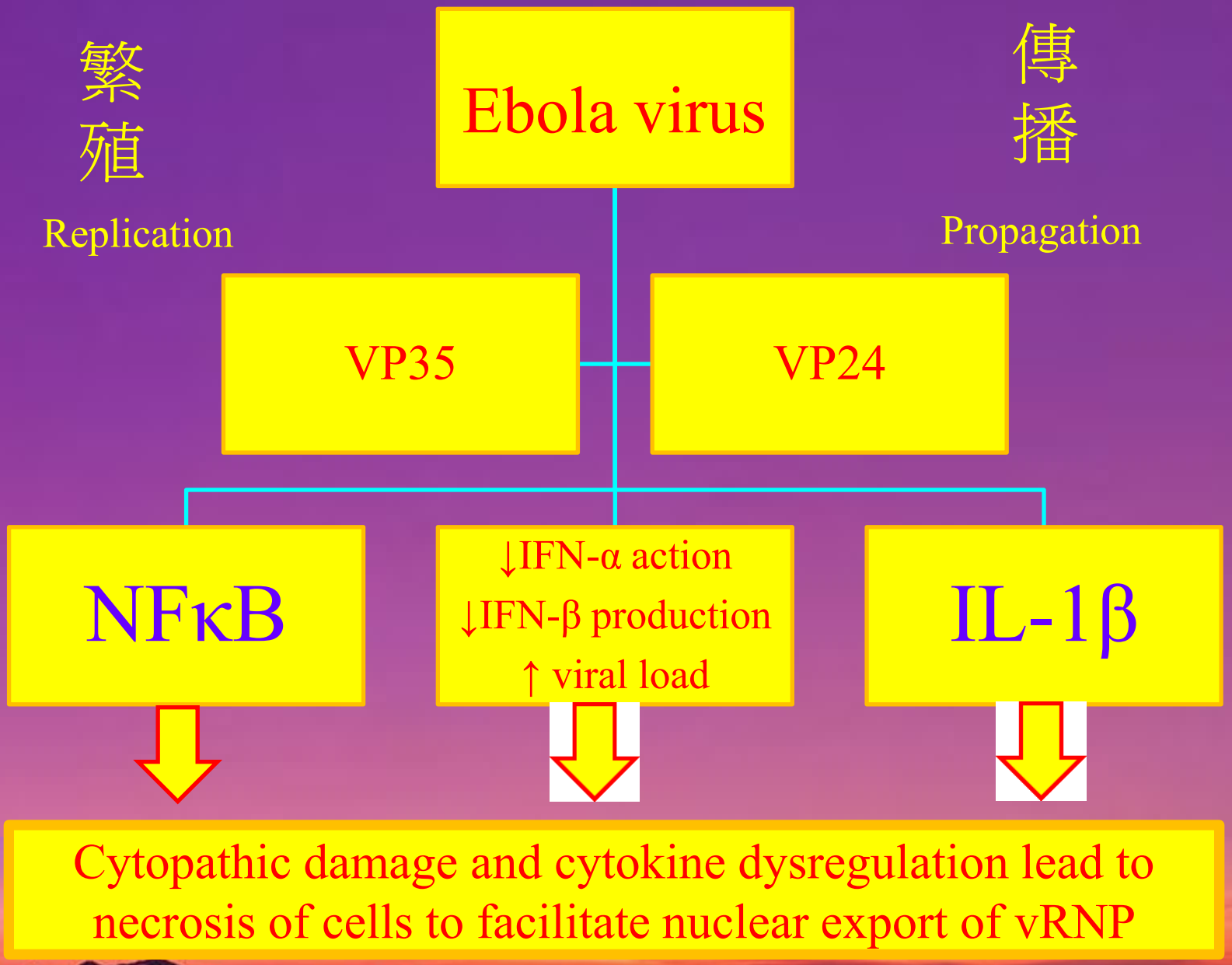
How Ebola virus counters the interferon system.

Kühl A, Pöhlmann S. Zoonoses Public Health. 2012;59 Suppl 2:116-31.

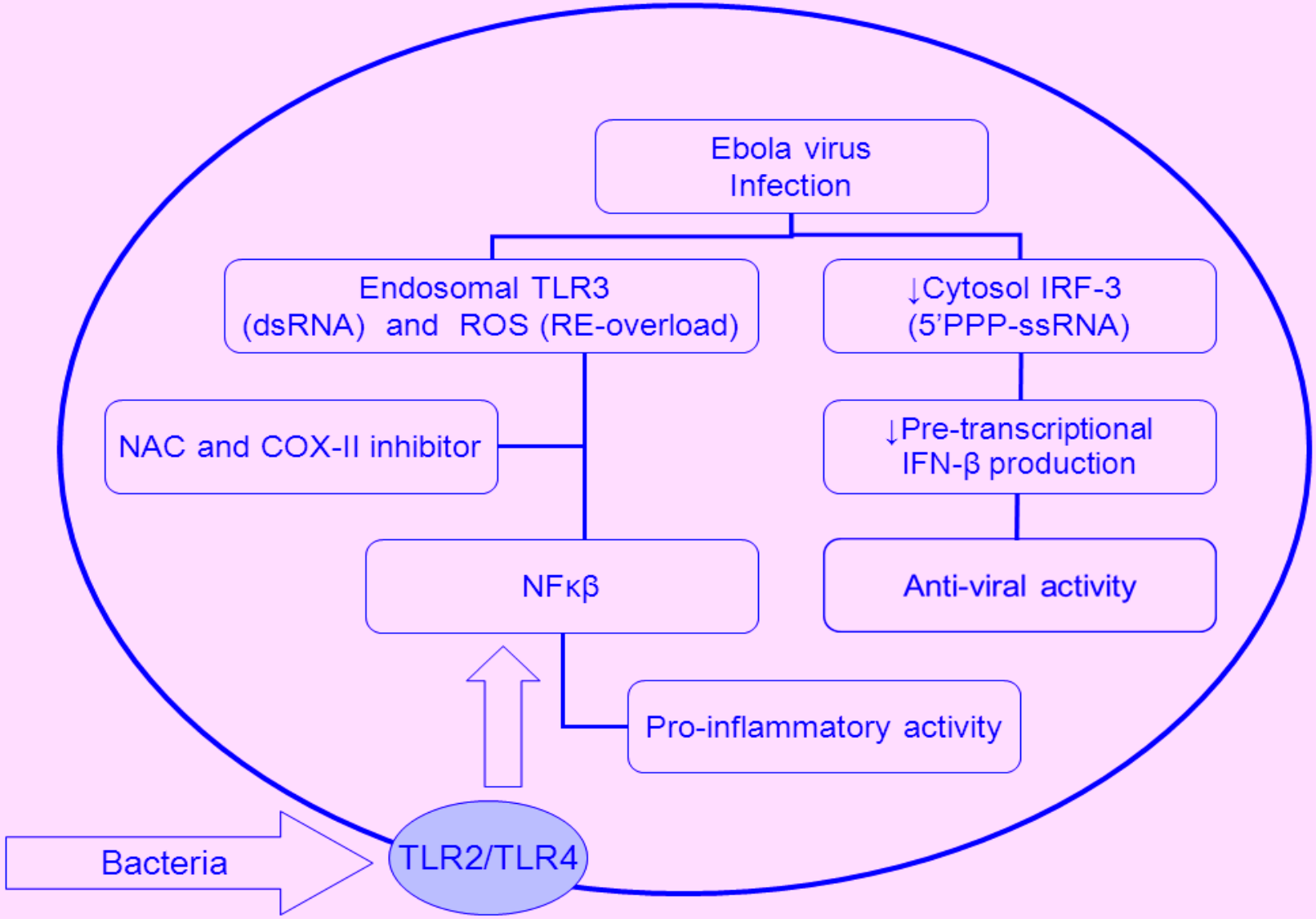
Filoviral proteins counter the host IFN response through multiple mechanisms in order to limit host antiviral responses.



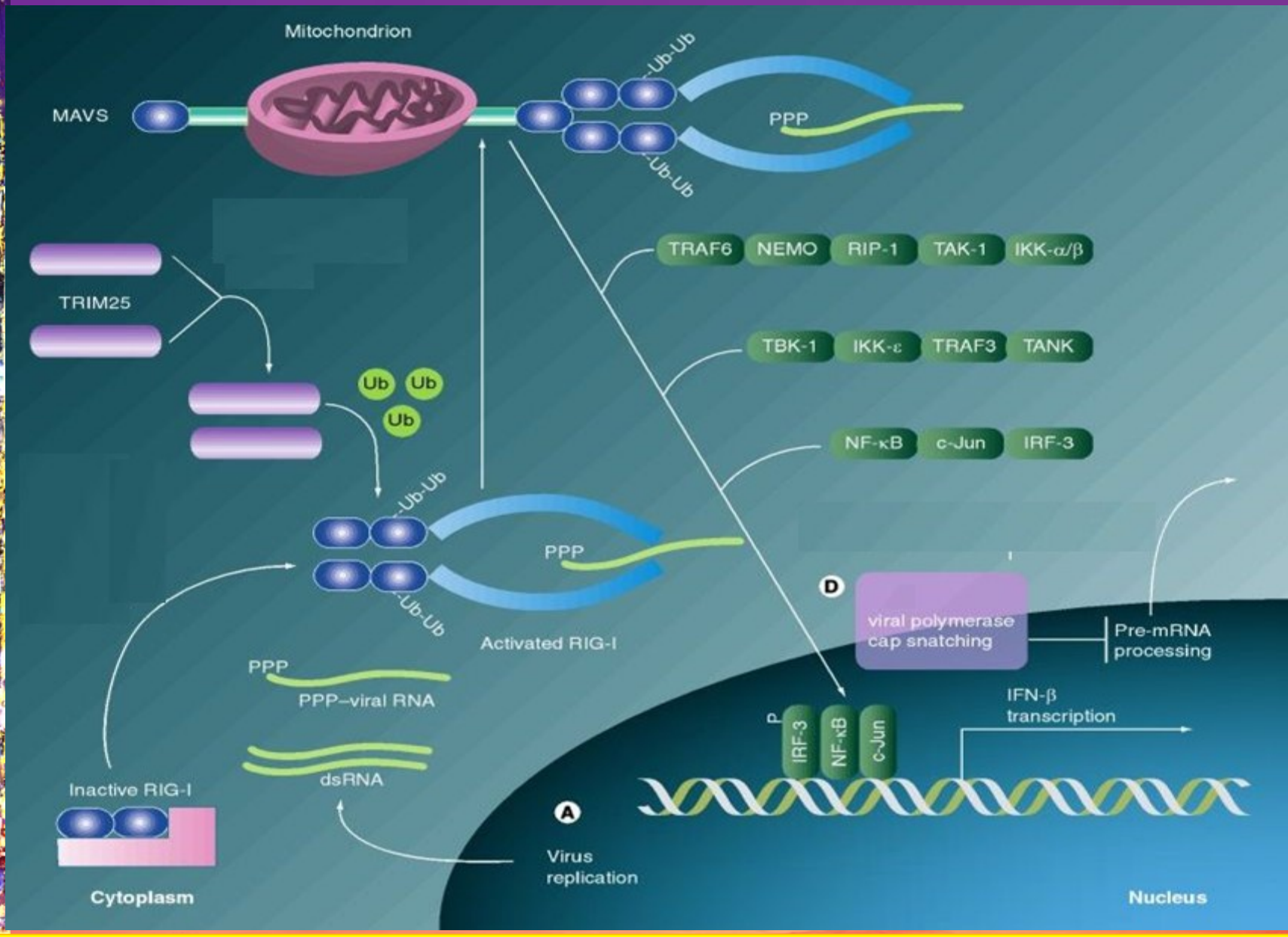
Ramanan P, Shabman RS, Brown CS, Amarasinghe GK, Basler CF, Leung DW. Filoviral immune evasion mechanisms. Viruses. 2011 Sep;3(9):1634-49.



Ebola virus selectively inhibits responses to interferons, but not to interleukin-1beta, in endothelial cells. Harcourt BH et al. J Virol. 1999 Apr;73(4):3491-6.



Viral stress-inducible genes. Sen GC et al. Adv Virus Res. 2007;70:233-63.
Pahl, H.L. *et al.* Activation of NF-kappa B by-ER stress requires both Ca2+ and reactive oxygen intermediates as messengers. *FEBS .Lett.* **392**, 129-36 (1996). Pahl HL, Baeuerle PA. The ER-overload response: activation of NF-kappa B. Trends Biochem Sci. 1997; 22: 63-7.
Pahl, H.L. Signal transduction from the endoplasmic reticulum to the cell nucleus. *Physiol. Rev.* **79**, 683-701 (1999).
Koarai, A. *et al.* Oxidative stress enhances toll-like receptor 3 response to double-stranded RNA in airway epithelial cells. Am J Respir *Cell. Mol. Biol.* **42**, 651-60 (2010).



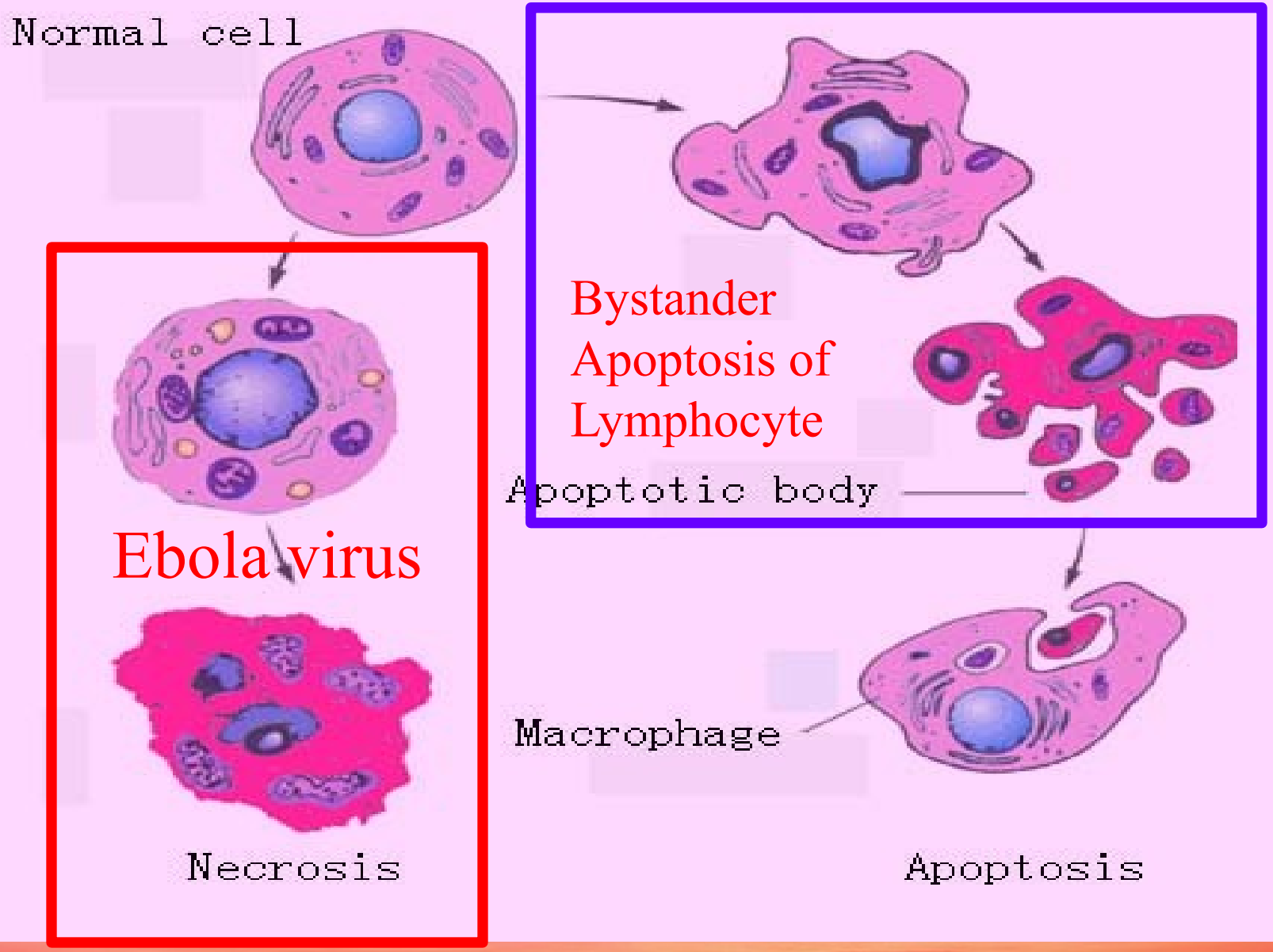
Interferon Dysregulation is the last attempt of the body to control viral infection. **Heavy viral load (dsRNA)** might lead to profound TLR3, NFκB and IRF-3 activation and interferon dysregulation. Ebola virus can induce massive dose of IFN –alpha.

IFN-β	Constitutive IFN-β inhibition	Inducible IFN-β inhibition		Mortality
		Pre-transcriptional	Post-transcriptional (Optimal human CPSF30 binding)	
H2N2 or H3N2	×	×	✓	<0.1%
2009PV	?	✓	×	<0.1%
1918PV	?	✓	✓	~2.5%
H5N1 (1997)	✓	✓	×	33%
H7N9 (2013)	?	✓	×	33%
H5N1 (2003-	✓	✓	✓	~60%

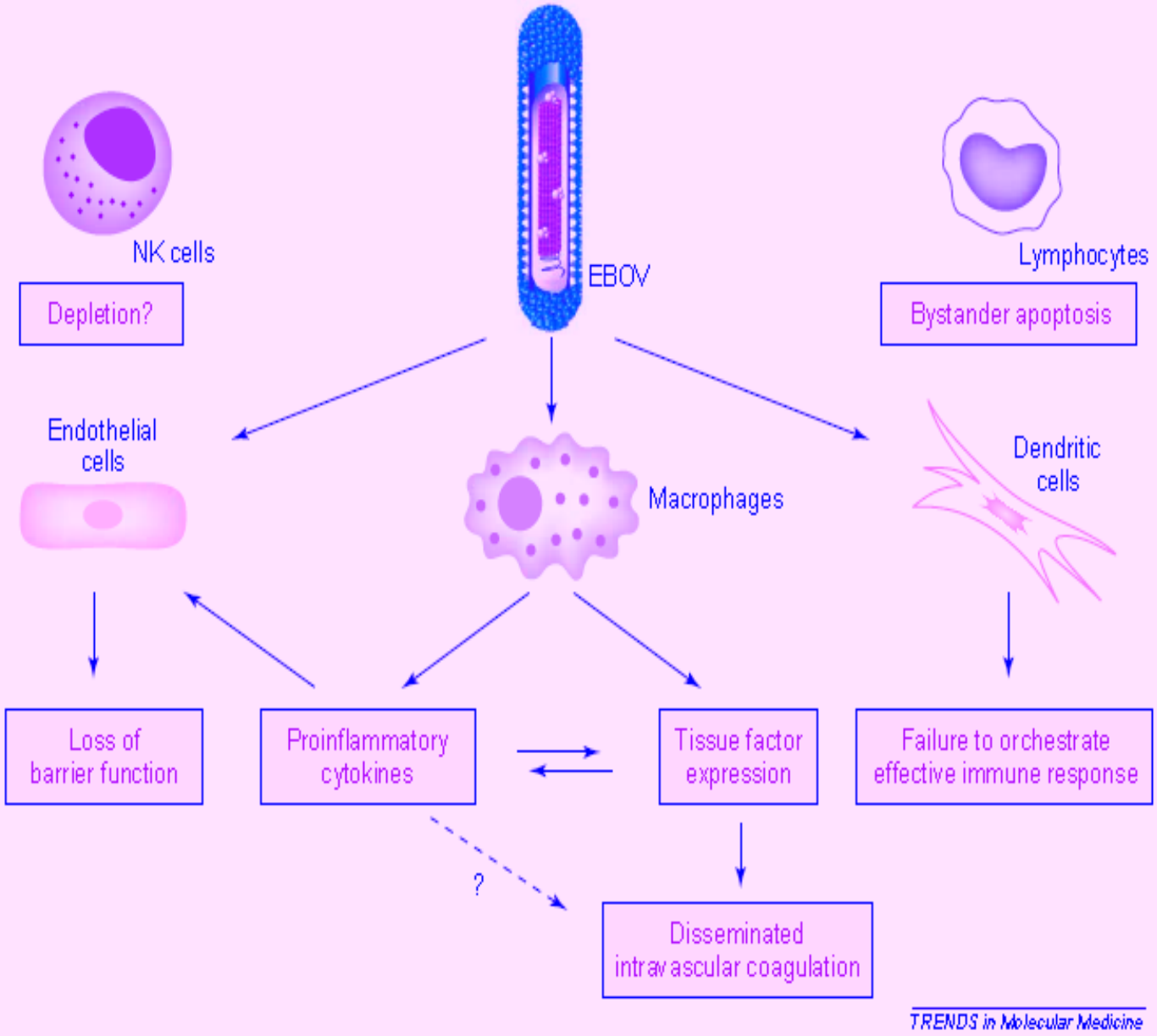
IFN-β is encoded by a single gene, while both the human and mouse genomes contain 13 functional IFN-α genes

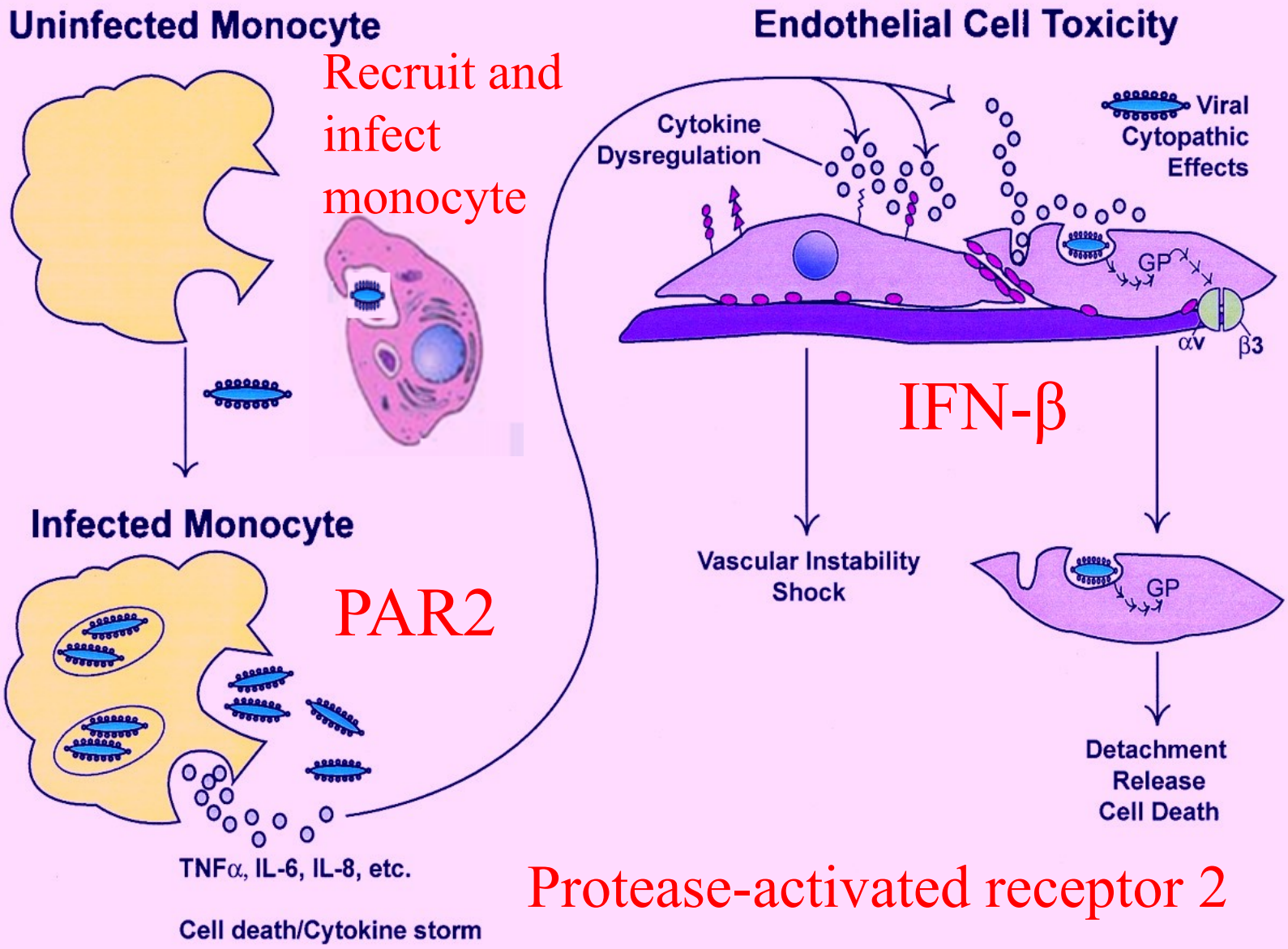
In influenza infection, the mortality is related to the degree of interferon suppression, in particular interferon-beta. Ebola virus lead to profound suppression of interferon- beta.

Kuo, R.L. et al. Influenza A virus strains that circulate in humans differ in the ability of their NS1 proteins to block the activation of IRF3 and interferon-β transcription. *Virology*. 408. 146-58 (2010).

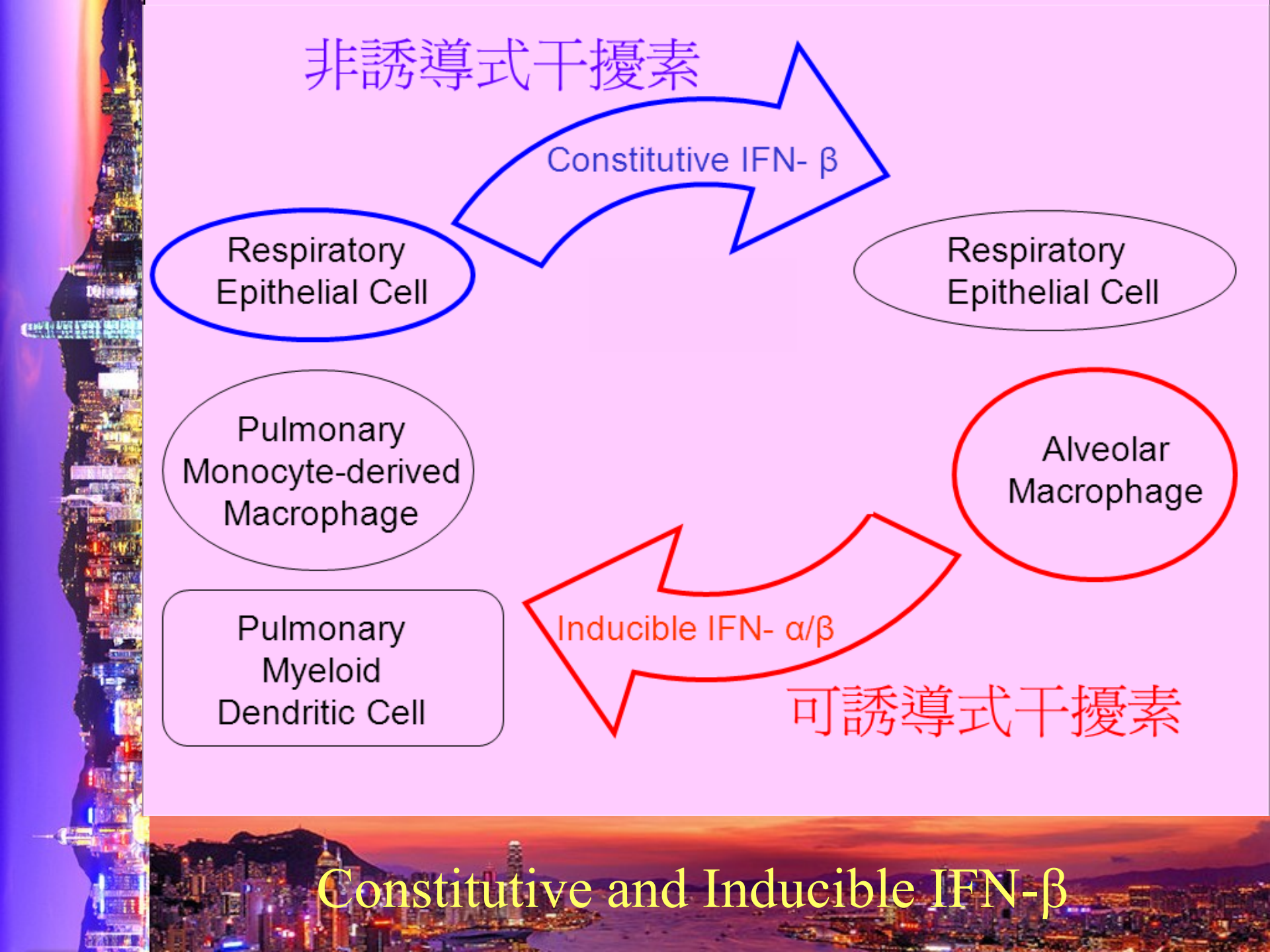


Olejnik J, Alonso J, Schmidt KM, Yan Z, Wang W, Marzi A, Ebihara H, Yang J, Patterson JL, Ryabchikova E, Mühlberger E. Ebola virus does not block apoptotic signaling pathways. J Virol. 2013 May;87(10):5384-96.


NK cells
EBOV
Lymphocytes
Depletion?
Bystander apoptosis
Endothelial cells
Macrophages
Dendritic cells
Loss of barrier function
Proinflammatory cytokines
Tissue factor expression
Failure to orchestrate effective immune response
?
Disseminated intravascular coagulation
TRENDS in Molecular Medicine

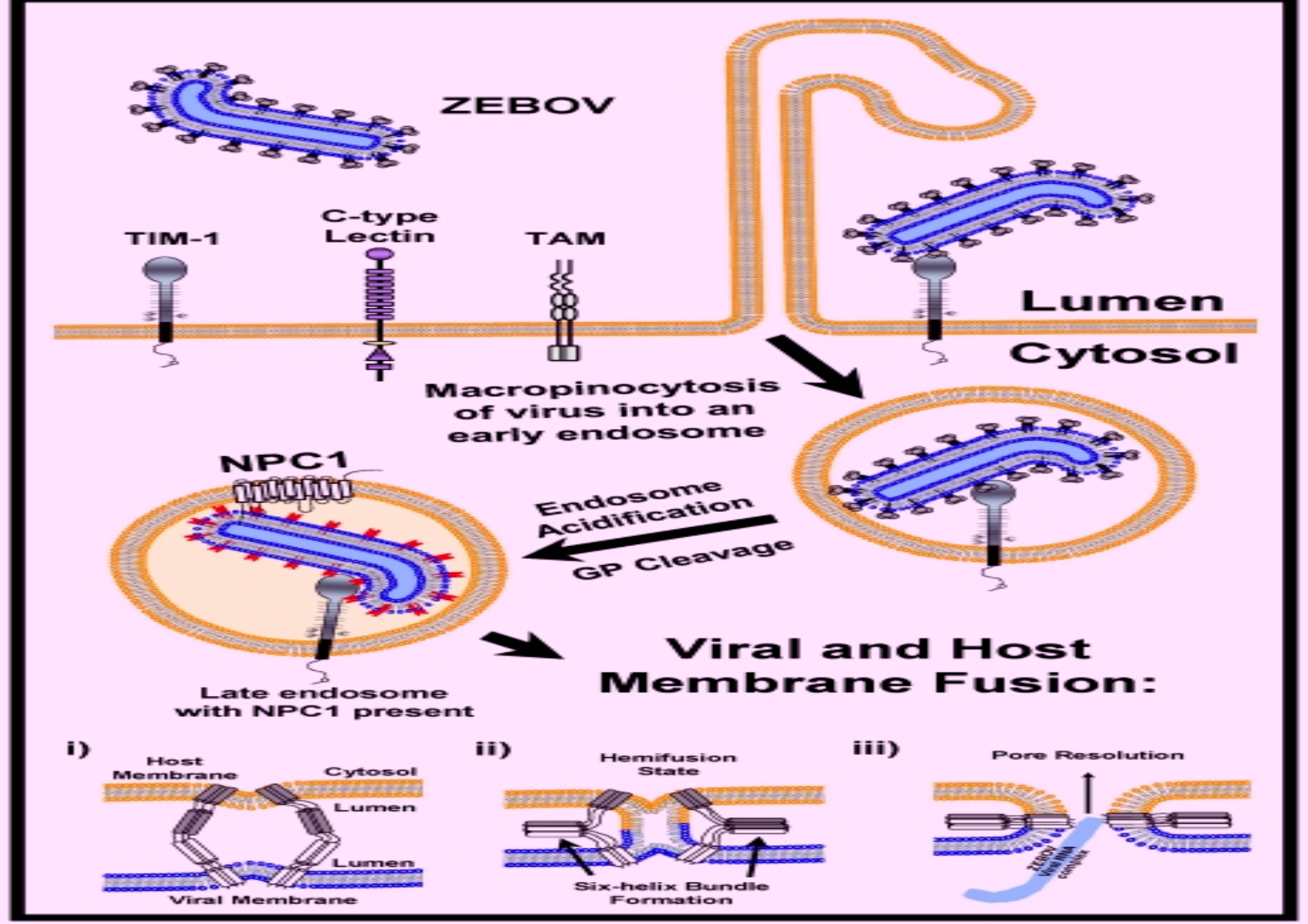


What can we learn from the productive replication of macrophage monocytes and endothelial cells in the pathogenesis of Ebola virus ?


非誘導式干擾素
Constitutive IFN- β
Respiratory Epithelial Cell
Respiratory Epithelial Cell
Pulmonary Monocyte-derived Macrophage
Alveolar Macrophage
Pulmonary Myeloid Dendritic Cell
Inducible IFN- α/β
可誘導式干擾素
Constitutive and Inducible IFN-β

WHO has advised that the use of experimental medications and vaccines under the exceptional circumstances of this outbreak is ethically justifiable. However, existing supplies of all these experimental medications are either extremely limited or exhausted.

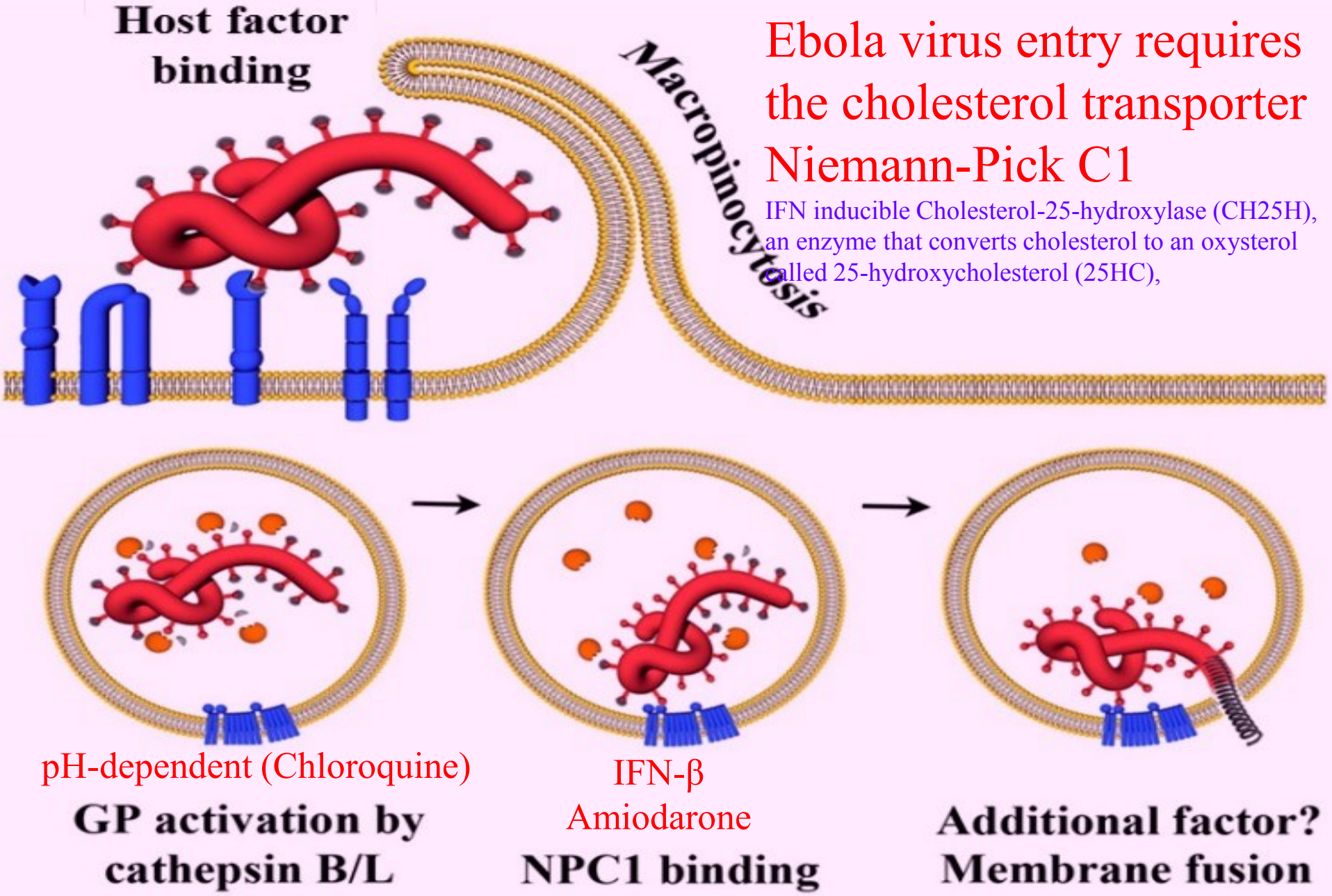
Before all these agents are available, in combating such unprecedented global public-health crisis, alternative intervention that might be effective against Ebola virus, are affordable, can be stockpiled and would be available on the first pandemic day should be explored to complement conventional therapy.



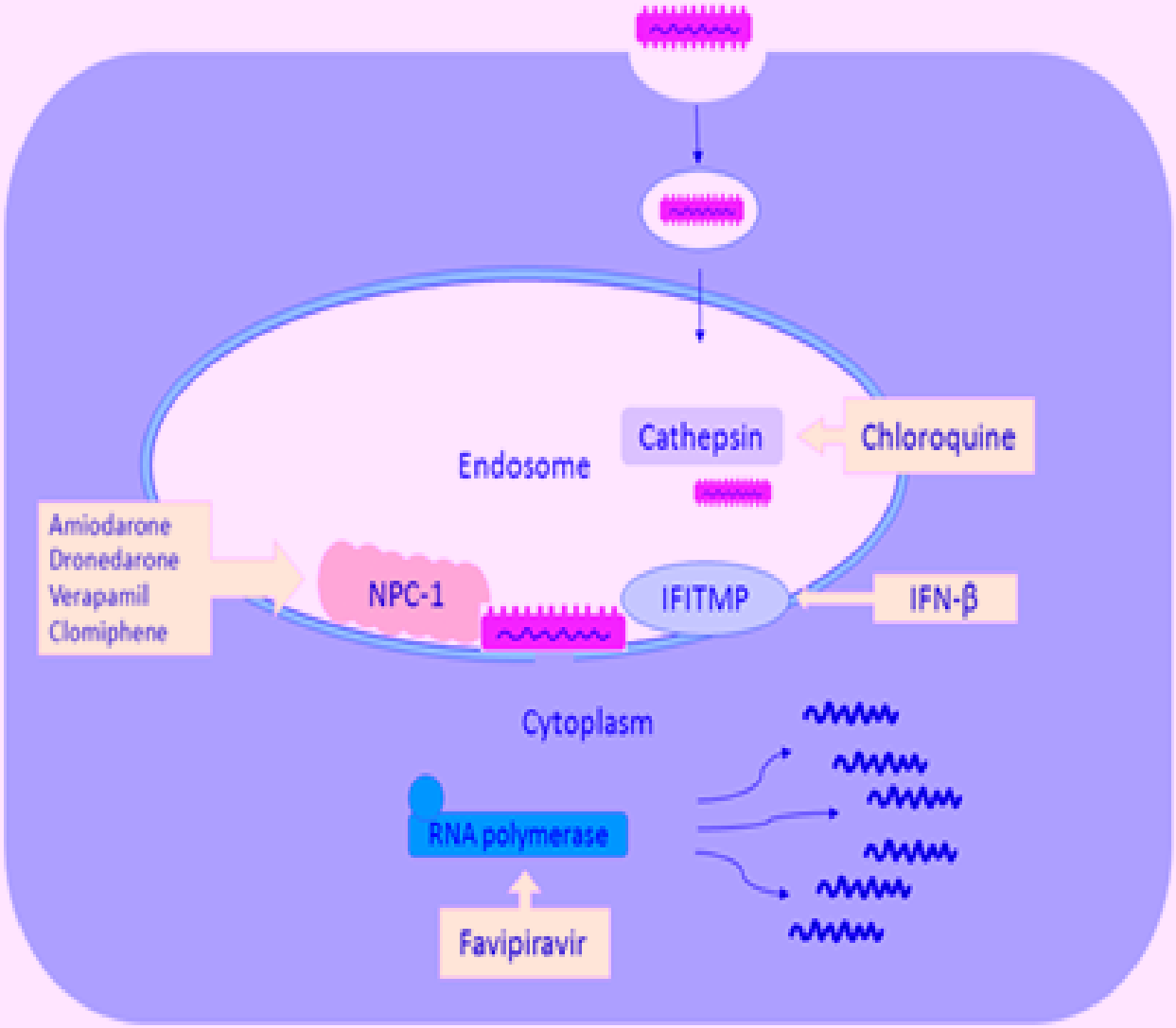
Filovirus entry: a novelty in the viral fusion world. Hunt CL et al. Viruses. 2012;4(2):258-75.

Ebola virus entry requires the cholesterol transporter Niemann-Pick C1

IFN inducible Cholesterol-25-hydroxylase (CH25H), an enzyme that converts cholesterol to an oxysterol called 25-hydroxycholesterol (25HC),



Host cell factors in filovirus entry: novel players, new insights. Hofmann-Winkler H et al. Viruses. 2012 Dec;4(12):3336-62.
The clinically approved drugs amiodarone, dronedarone and verapamil inhibit filovirus cell entry. Gehring G et al. J Antimicrob Chemother. 2014 Aug;69(8):2123-31.
Su-Yang Liu et al. 2012. Interferon-Inducible Cholesterol-25-Hydroxylase Broadly Inhibits Viral Entry by Production of 25-Hydroxycholesterol. *Immunity*, volume 38, issue 1, 92-105;



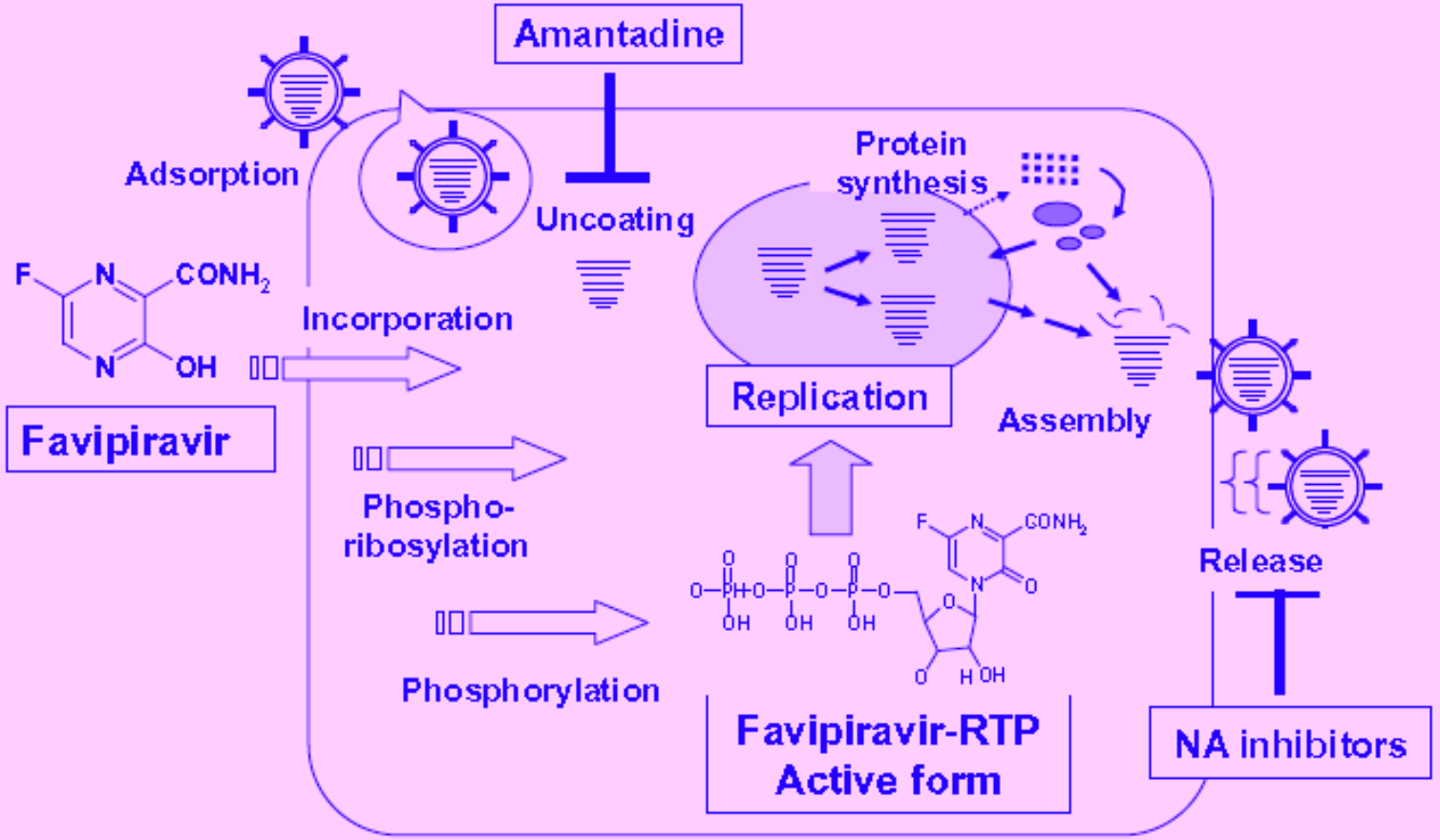
Schematic diagram showing the replication cycle of Ebola virus and the site of action of currently available therapeutic medications against Ebola virus infection.

Available Therapeutic Strategies For Ebola Virus Infection in Africa

Treatment	Mechanism
Chloroquine [1]	Increase the endosomal pH to prevent the pH-dependent activation of cysteine proteases cathepsin B/L essential for the cleavage of ZEBOV GP
Cationic amphiphiles • Amiodarone [1] • Dronedarone [1] • Verapamil [2] • Clomiphene [3] • Toremifene [1]	These agents induce a Niemann-Pick C-like phenotype and block the entry of Ebola virus through late endosomes.
Favipiravir	Favipiravir inhibit proliferation of Ebola virus through suppression of viral RNA polymerase.
Interferon- beta (IFN-β)	IFN-β is able to induce interferon-inducible transmembrane proteins (IFITMP) production to restrict entry of Ebola virus. IFN-β may reduce viral load and pro-inflammatory cytokine production.

1: Chloroquine, Amiodarone, Dronedarone and Toremifene administration is associated with an increased risk of QT prolongation and *Torsades de pointes*.
2: Verapamil should be avoided in patient with hypotension.
3. Therapeutic anti-Ebola activity cannot be achieved with oral clomiphene at 50-200mg daily.

Y. Furuta et al. / Antiviral Research 100 (2013) 446–454

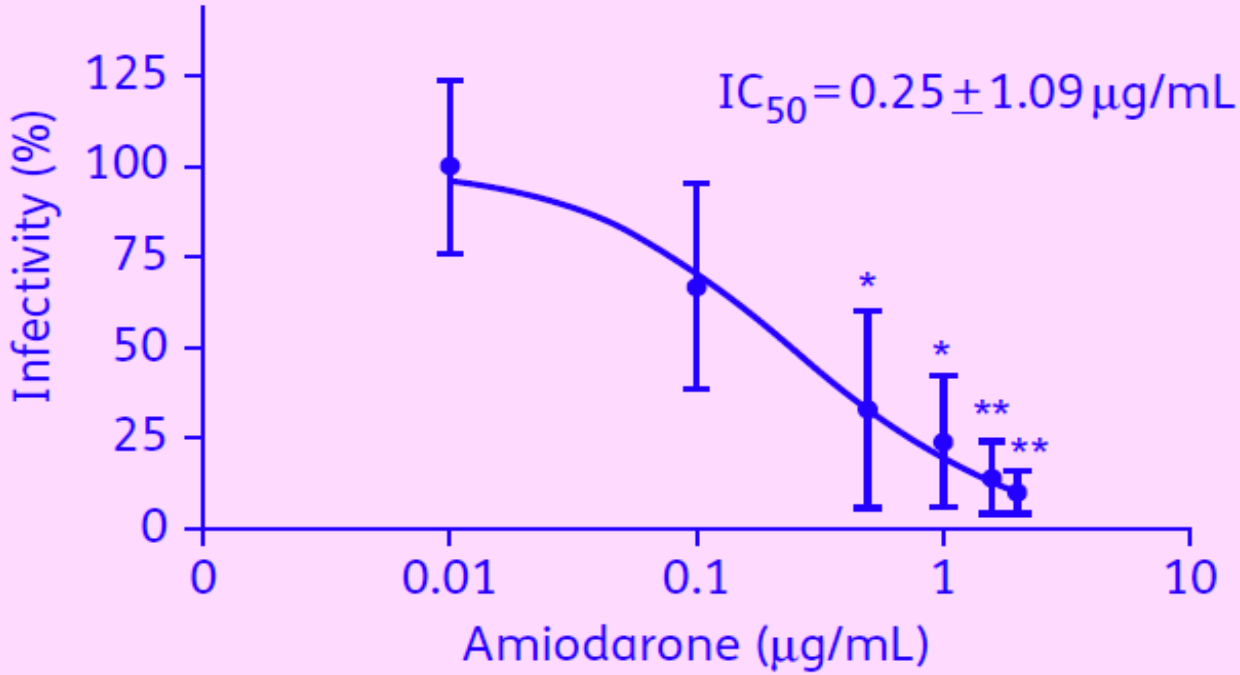


Favipiravir is able to suppress the replication of EBOV in cell culture. Favipiravir, initiated at day 6 post EBOV infection, induced rapid virus clearance, reduced biochemical parameters of disease severity, and prevented a lethal outcome in 100% of mice lacking the type I interferon receptor.

Oestereich L, Lüdtke A, Wurr S, Rieger T, Muñoz-Fontela C, Günther S. Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. Antiviral Res. 2014 May;105:17-21.
Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Furuta Y et al. Antiviral Res. 2013 Nov;100(2):446-54

Amiodarone

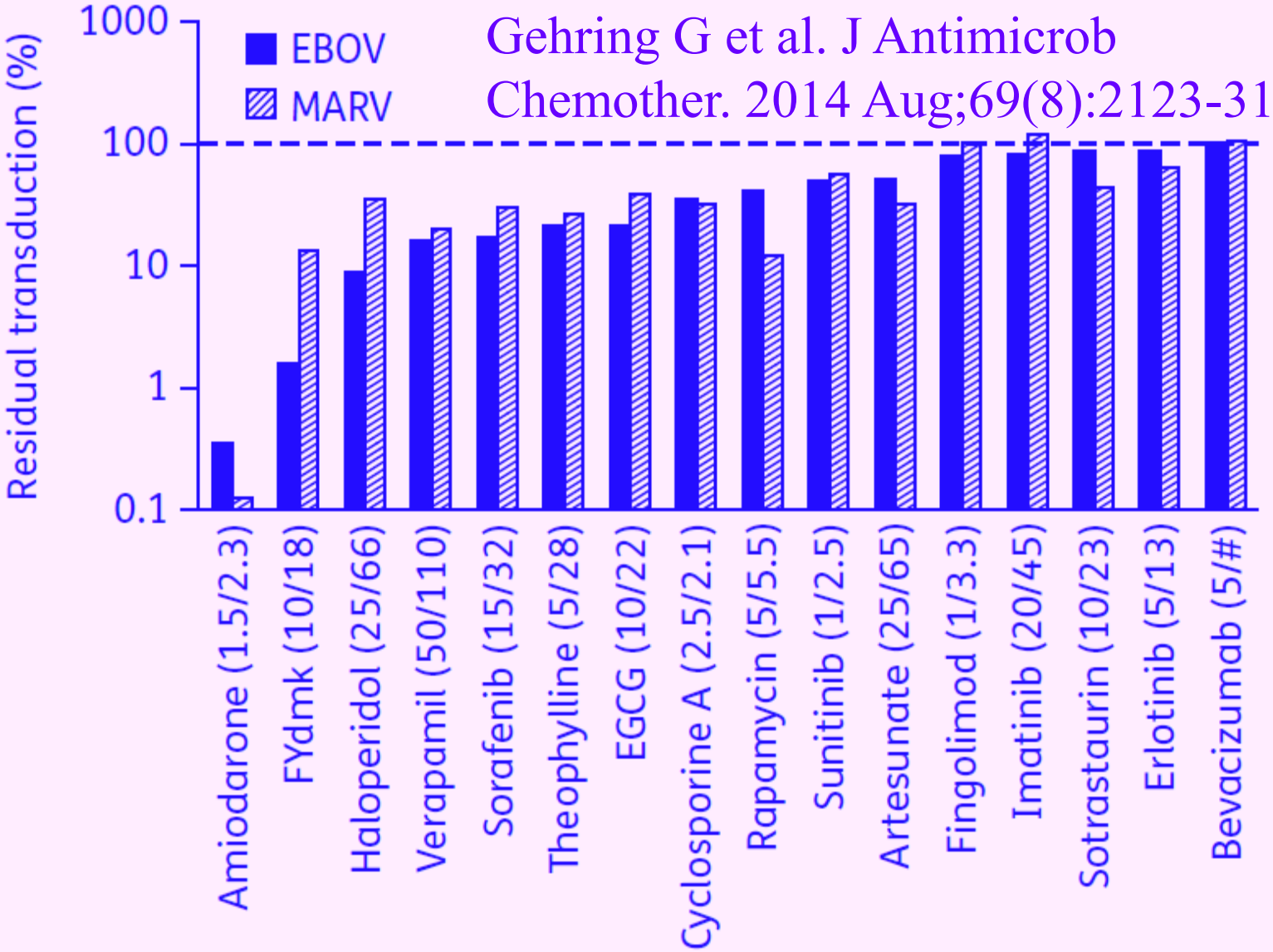
- Block Ebola viral entry (99% reduction) at late endosome phase by inducing a Niemann-Pick C-like phenotype. Significant inhibition seen in most endothelial and epithelial cells (macrophage, monocyte, endothelial cells) except primary hepatocyte and fibroblast.
- IC_{50} of amiodarone for EBOV is 0.25 ug/ml and serum level of amiodarone 1.5-2.5 ug/ml at dose for management of arrhythmia.
- Inhibitory effect on EBOV entry dose dependent and reversible upon removal of drug. Prolonged exposure to amiodarone will not lead to compensatory change in host cell.
- Available in both oral and intravenous preparation and both long term and short term side effect known. As a generic drug, its use would be feasible in both resource-rich and resource-poor setting.



Amiodarone inhibition of authentic EBOV infection. EAhy cells were exposed to purified Zaire Ebola virus in the presence or absence of amiodarone at the indicated concentrations. After 20 h cells were fixed and stained for Ebola NP protein. The percentage of cells infected with authentic EBOV in the absence of drug was set to 100%. Means $\pm$ SD from $n = 3$ independent experiments are shown. Significant inhibition is indicated by asterisks ($^*P < 0.05$, $^{**}P < 0.01$).

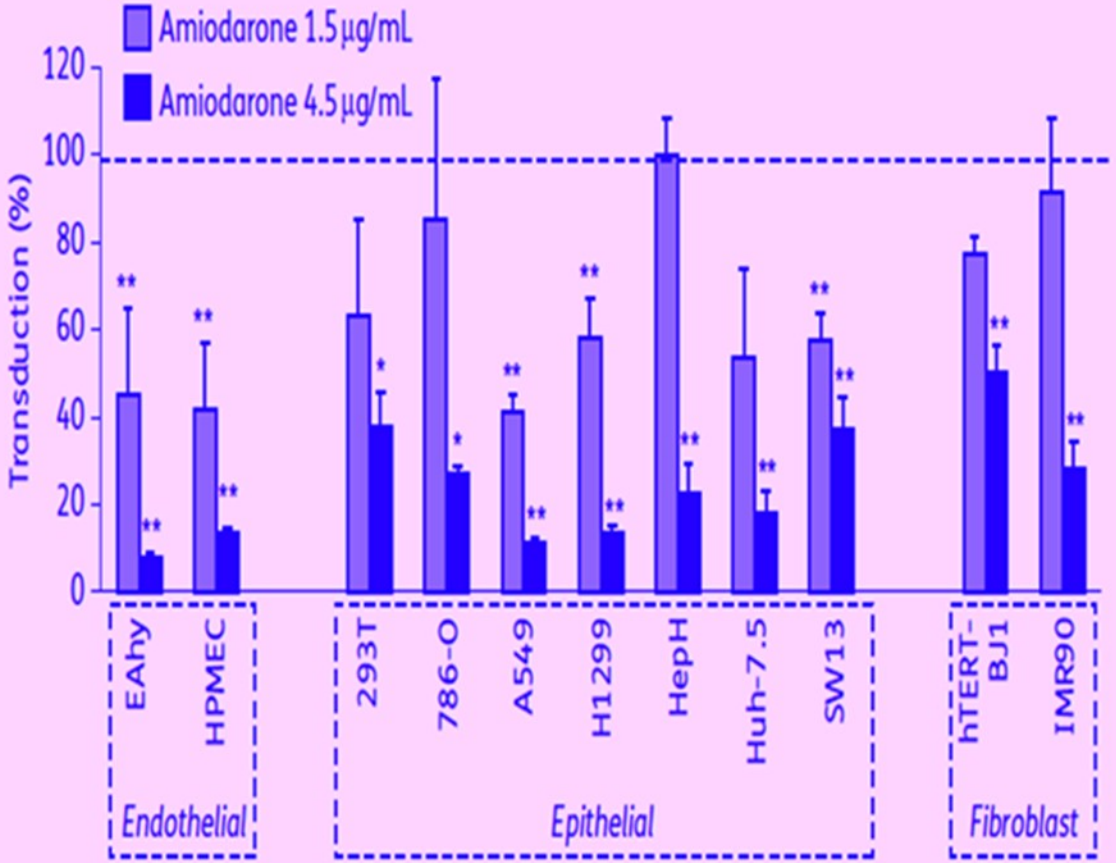
Serum level of amiodarone is 1.5-2.5 ug/ml at dose for management of arrhythmia

Gehring G et al. J Antimicrob Chemother. 2014 Aug;69(8):2123-31.



Gehring G et al. J Antimicrob Chemother. 2014 Aug;69(8):2123-31.

Amiodarone markedly reduces filoviral GP-mediated cell entry. at drug concentration 1.5 μg/mL and in 2.3 μM, respectively.

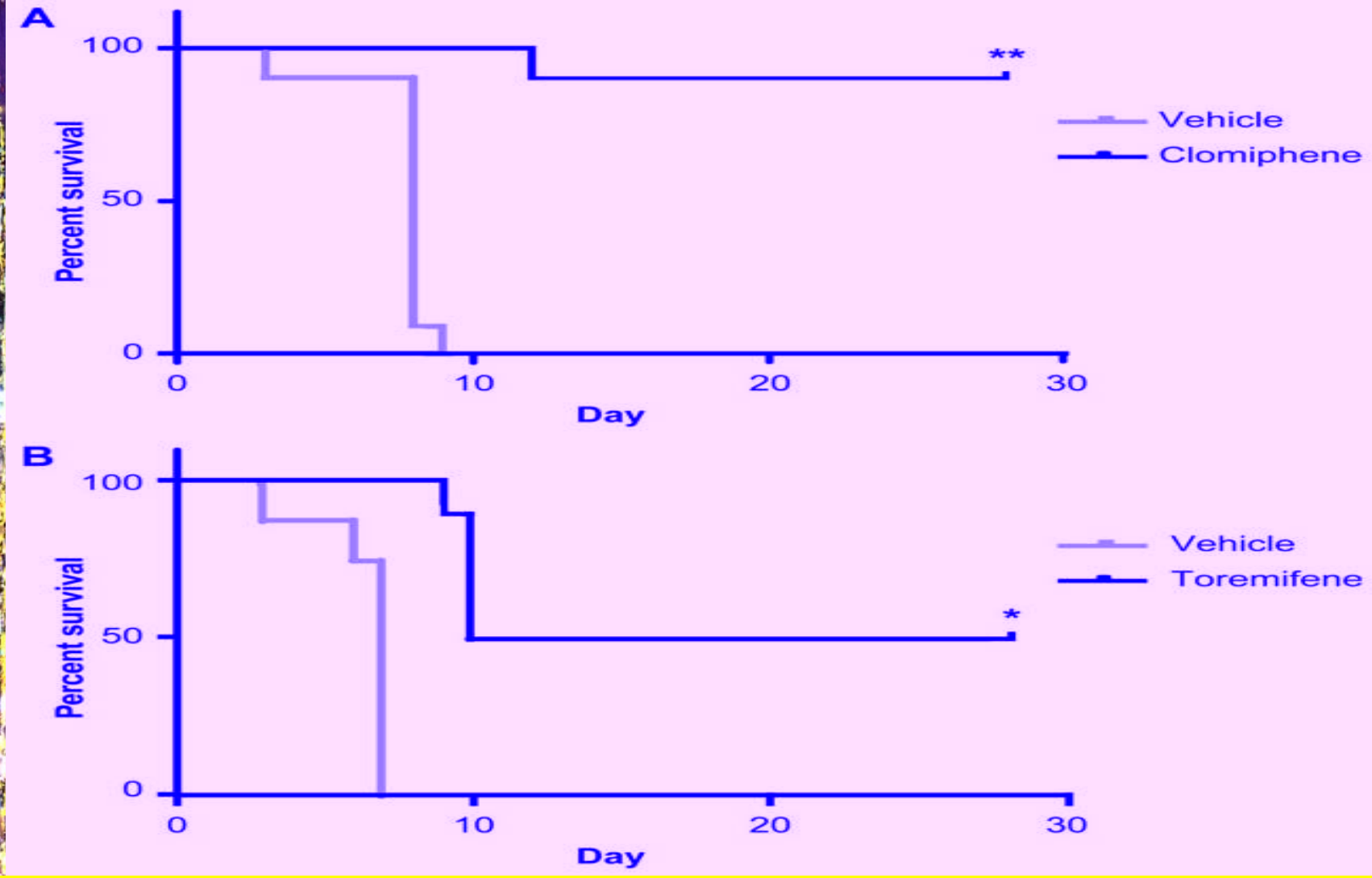


Filoviral GP-mediated entry into endothelial cells and in macrophages derived from primary human monocytes was significantly inhibited at amiodarone concentrations below 1 µg/mL while amiodarone had no effect on the transduction of primary hepatocytes and cell of fibroblast origin.

Gehring G et al. J Antimicrob Chemother. 2014 Aug;69(8):2123-31.

Clomiphene and toremifene

- Clomiphene and toremifene does not disrupt the interaction between primed GP_1 and NPC1 but mediate the entry block indirectly through NPC1 by targeting other endosomal/lysosomal proteins involved in the cholesterol uptake pathway whose function may be regulated by NPC1.
- Clomiphene and toremifene at 60 mg/kg every other day have been shown to produce a 90% and 50% survival respectively in EBOV infected mice compared with 100% mortality in the control group in an in vivo murine Ebola infection model. They are effective in both male and female mice.
- Therapeutic dose against EBVO with tolerable side effect can be achieved with toremifene at an oral dose used in human trial for the treatment of advanced carcinoma of breast. However therapeutic dose against EBOV cannot be achieved with oral clomiphene.
- The peak concentration after oral admisinstration of toremifene is 4 hour. Toremifene undergoes extensive demethylation and hydroxylation to active and inactive metabolites via hepatic mixed function oxidases
- **Hence amiodarone and toremifene may have a complementary role in protection against Ebola virus.**



Clomiphene and toremifene at 60 mg/kg every other day have been shown to produce a 90% and 50% survival respectively in EBOV infected mice.

Johansen LM, Brannan JM, Delos SE, Shoemaker CJ, Stossel A, Lear C, Hoffstrom BG, Dewald LE, Schornberg KL, Scully C, Lehár J, Hensley LE, White JM, Olinger GG. FDA-approved selective estrogen receptor modulators inhibit Ebola virus infection. Sci Transl Med. 2013 Jun 19;5(190):190ra79.

Pharmacokinetic challenges

Animal studies in this paper dosed both toremifene and clomiphene at 60 mg/kg. This dose is substantially higher than the dose used in humans, raising a question of whether it would be pharmacokinetically feasible to use these drugs.

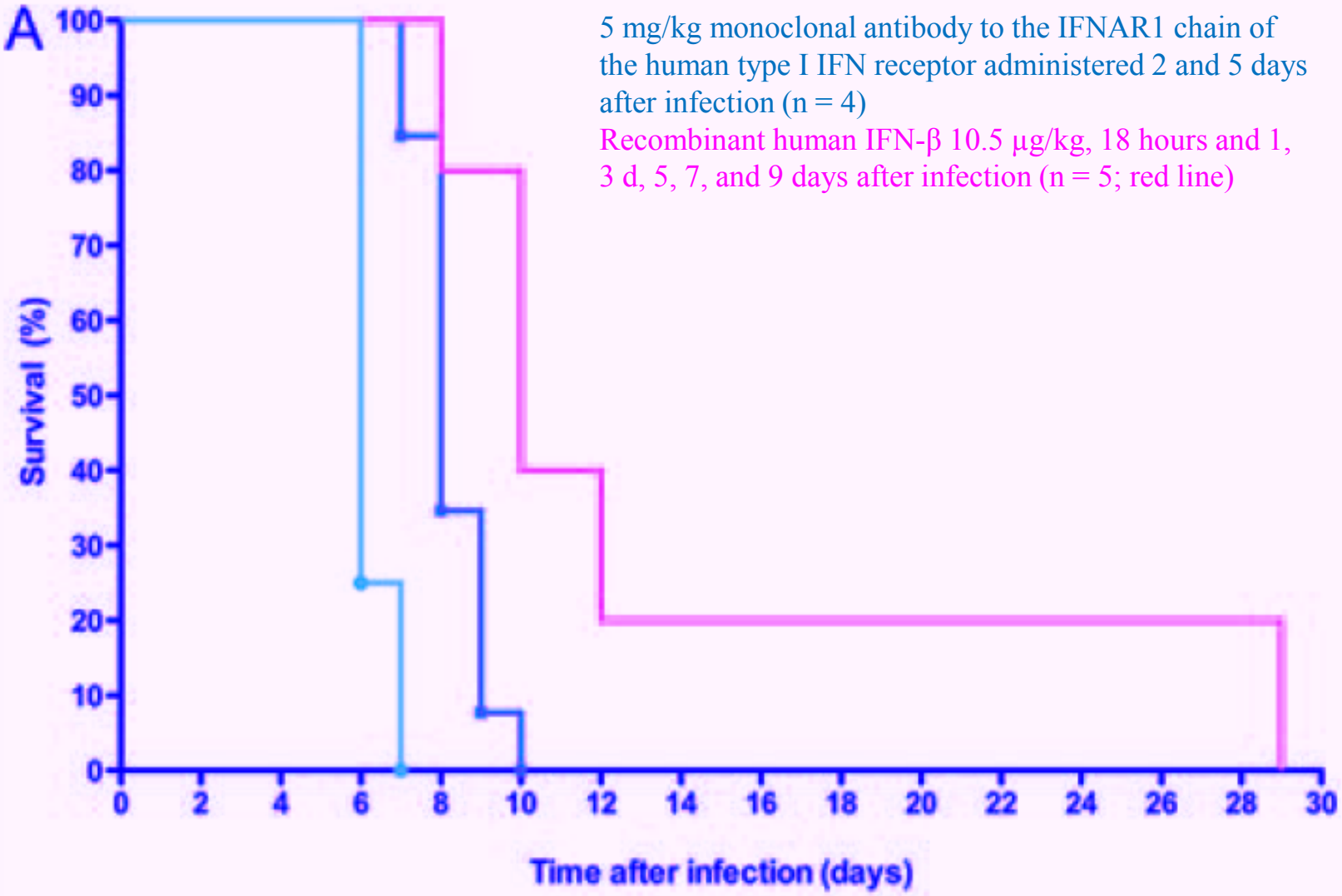
Clomiphene dosing at 50 mg achieves a serum concentration of 8-9 ng/mL, which is equal to 0.014 uM and thus far below the IC-50 of clomiphene for Zaire Ebolavirus (11.1 uM). This suggests that it would not be feasible to treat Zaire Ebolavirus using clomiphene as currently formulated.

Toremifene seems to have better pharmacokinetics including oral bioavailability of 100% and a half-life of five days allowing intermittent dosing. The IC-50 of toremifine for Zaire Ebolavirus is 1.73 uM, which equals 1 ug/mL. Although this concentration is higher than levels required for management of breast cancer, concentrations well above 1 ug/mL were achieved in phase I trials. For example, Bishop 1992 found that toxicity emerged at a dose of 400 mg/m2/day and therefore recommended a dose of 300 mg/m2/day for subsequent trials (1). Of note, 300 mg/m2/day achieved an average trough level of 2.2 ug/mL and peak level of 4 ug/ml. Wiebe 1990 found that at a dose of 400 mg/day, the average steady state concentration was 3.4 ug/ml. In order to achieve steady-state levels rapidly it might be helpful to start with a loading dose perhaps equal to twice the maintenance dose.

In human trials, toremifene produces a series of metabolites which have biologic activity. For example, N-desmethyltoremifene has equivalent ability to bind to estrogen receptors, and accumulates to about three times higher concentrations than toremifene itself (Kohler 1990). Given the ability of multiple estrogen receptor antagonists to impair Ebolavirus, it is possible that these metabolites could also have antiviral activity.

Interferon beta

- IFN-β is able to induce interferon-inducible transmembrane proteins production to restrict entry of Ebola virus.
- Early postexposure treatment with IFN-β significantly increased survival time of rhesus macaques infected with a lethal dose of Ebola virus, although IFN-β alone failed to alter mortality. IFN-β treatment was associated with a trend towards lower plasma and tissue viral burden and proinflammatory cytokines production.
- IFN-β may have potential as an adjunctive postexposure therapy for high risk exposure such as needle prick injury because the reduction in viral load and cytokine dysregulation coupled with optimal supportive therapy may improve the chance of survival of the host to allow the development of natural immunity to control the underlying Ebola virus infection.



5 mg/kg monoclonal antibody to the IFNAR1 chain of the human type I IFN receptor administered 2 and 5 days after infection (n = 4)

Recombinant human IFN-β 10.5 μg/kg, 18 hours and 1, 3 d, 5, 7, and 9 days after infection (n = 5; red line)

Interferon-β therapy prolongs survival in rhesus macaque models of Ebola and Marburg hemorrhagic fever. Smith LM et al. J Infect Dis. 2013;208:310-8.

Why Cocktail Therapy

- Ebola viruses have underwent a rapid mutation (50 mutations within 1 month during its spread through humans).
- Ebola virus is RNA virus whose replication is highly error prone with nearly one viral mutation occurs during each cycle of replication. The genetic and antigenic diversity produced allows the viral population to evolve resistance to antiviral drugs and vaccines. Therefore combination therapy are introduced in the treatment of RNA virus infection such as HIV and hepatitis C virus, to prevent the develop of drug resistance.
- The goal of a cocktail regime containing anti-viral medications targeting different cycles of EBOV replication is to achieve maximal suppression of viral replication to prevent the rapid develop of EBOV to Favipiravir, the currently available medication that has been shown to reduce the replication of EBOV.
- A proposeed cocktail regime basing on available agent is in the next slide.

http://www.sciencemag.org/content/early/2014/08/27/science.1259657.full.pdf
http://www.nature.com/news/ebola-virus-mutating-rapidly-as-it-spreads-1.15777
http://www.nejm.org/doi/pdf/10.1056/NEJMoa1404505

Therapeutic Strategies Basing on Available Agent For Ebola Virus Prophylaxis and Treatment

Ebola Virus	Available Agent
Prophylaxis [1]	Amiodarone
Post Needle Prick Injury Prophylaxis	IFN-β + Amiodarone (macrophage, monocyte & endothelial cell) ± toremifene (liver) [2,3] + Favipiravir
Treatment	Amiodarone (macrophage, monocyte & endothelial cell) + toremifene (liver) [2,3] + Favipiravir + supportive care + correction of coagulopathy + early nutritional support

1. 1ml of blood may contain 10^{9-10} virions in terminally ill patient and pin-prick injury may lead to injection of over 1 million virions. Prophylactic therapy may prevent our macrophage, monocyte and endothelial cells immediately from infection after needle prick injury and allow time for consideration of IFN-β and Favipiravir therapy.
2. Amiodarone is unable to protect liver cells from Ebola virus infection.
3. Both amiodarone and toremifene can increase the risk of QT prolongation and *Torsades de pointes*

Proposed High Risk Exposure in HCW (Needle Injury)

- After complete surface disinfection
  - Exogenous β-interferon to protect uninfected cells. (IFN can restrict spread and pathogenesis of Ebola virus in mice A. Kuhl 2012) (IFN- β can increase IFN-inducible transmembrane proteins 1-3)
  - Amiodarone loading followed by maintenance dose (Gehring G et al. J Antimicrob Chemother. 2014 Aug;69(8):2123-31.) and Toremifene loading dose followed by maintenance dose
  - Favipiravir prophylaxis to control viral replication
- Zofran (oral) to prevent nausea and vomiting due to medication
- Monitor for the symptoms and serological evidence of infection
- In confirmed infection
  - Optimal supportive therapy
  - Correction of coagulopathy
  - Early nutritional support if cannot tolerate enteral feeding.

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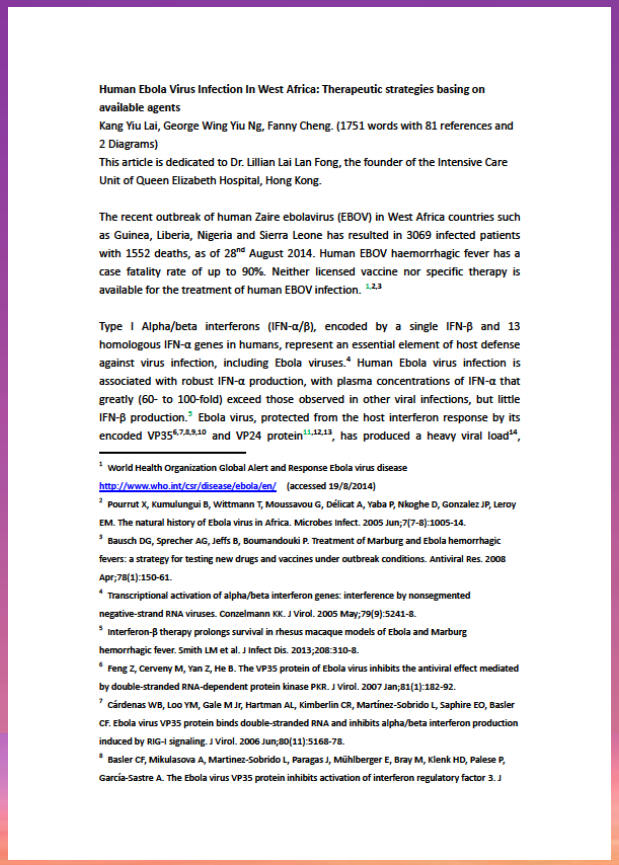
Kang Yiu Lai, George Wing Yiu Ng, Fanny Cheng.

(1751 words with 81 references and 2 Diagrams)



Human Ebola Virus Infection In West Africa: Therapeutic strategies basing on available agents

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This article is dedicated to Dr. Lillian Lai Lan Fong, the founder of the Intensive Care Unit of Queen Elizabeth Hospital, Hong Kong.

The recent outbreak of human Zaire ebolavirus (EBOV) in West Africa countries such as Guinea, Liberia, Nigeria and Sierra Leone has resulted in 3069 infected patients with 1552 deaths, as of 28rd August 2014. Human EBOV haemorrhagic fever has a case fatality rate of up to 90%. Neither licensed vaccine nor specific therapy is available for the treatment of human EBOV infection. [1,2,3]

Type I Alpha/beta interferons (IFN-α/β), encoded by a single IFN-β and 13 homologous IFN-α genes in humans, represent an essential element of host defense against virus infection, including Ebola viruses.[4] Human Ebola virus infection is associated with robust IFN-α production, with plasma concentrations of IFN-α that greatly (60- to 100-fold) exceed those observed in other viral infections, but little IFN-β production.[5] Ebola virus, protected from the host interferon response by its encoded VP35[6,7,8,9,10] and VP24 protein[11,12,13], has produced a heavy viral load[14],

[1] World Health Organization Global Alert and Response Ebola virus disease http://www.who.int/csr/disease/ebola/en/ (accessed 19/8/2014)

[2] Pourrut X, Kumulungui B, Wittmann T, Moussavou G, Délicat A, Yaba P, Nkoghe D, Gonzalez JP, Leroy EM. The natural history of Ebola virus in Africa. Microbes Infect. 2005 Jun;7(7-8):1005-14.

[3] Bausch DG, Sprecher AG, Jeffs B, Boumandouki P. Treatment of Marburg and Ebola hemorrhagic fevers: a strategy for testing new drugs and vaccines under outbreak conditions. Antiviral Res. 2008 Apr;78(1):150-61.

[4] Transcriptional activation of alpha/beta interferon genes: interference by nonsegmented negative-strand RNA viruses. Conzelmann KK. J Virol. 2005 May;79(9):5241-8.

[5] Interferon-β therapy prolongs survival in rhesus macaque models of Ebola and Marburg hemorrhagic fever. Smith LM et al. J Infect Dis. 2013;208:310-8.

[6] Feng Z, Cerveny M, Yan Z, He B. The VP35 protein of Ebola virus inhibits the antiviral effect mediated by double-stranded RNA-dependent protein kinase PKR. J Virol. 2007 Jan;81(1):182-92.

[7] Cárdenas WB, Loo YM, Gale M Jr, Hartman AL, Kimberlin CR, Martínez-Sobrido L, Saphire EO, Basler CF. Ebola virus VP35 protein binds double-stranded RNA and inhibits alpha/beta interferon production induced by RIG-I signaling. J Virol. 2006 Jun;80(11):5168-78.

[8] Basler CF, Mikulasova A, Martinez-Sobrido L, Paragas J, Mühlberger E, Bray M, Klenk HD, Palese P, García-Sastre A. The Ebola virus VP35 protein inhibits activation of interferon regulatory factor 3. J

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Thank you for your attention