Cyclophilin A as a target in the treatment of cytomegalovirus infections

Ashwaq A Abdullah1,2, Rasedee Abdullah1,3, Zeenathul A Nazariah1,4, Krishnan N Balakrishnan4, Faez Firdaus J Abdullah5, Jamilu A Bala4,6 and Mohd-Azmi Mohd-Lila1,4

Abstract
Background: Viruses are obligate parasites that depend on the cellular machinery of the host to regenerate and manufacture their proteins. Most antiviral drugs on the market today target viral proteins. However, the more recent strategies involve targeting the host cell proteins or pathways that mediate viral replication. This new approach would be effective for most viruses while minimizing drug resistance and toxicity.

Methods: Cytomegalovirus replication, latency, and immune response are mediated by the intermediate early protein 2, the main protein that determines the effectiveness of drugs in cytomegalovirus inhibition. This review explains how intermediate early protein 2 can modify the action of cyclosporin A, an immunosuppressive, and antiviral drug. It also links all the pathways mediated by cyclosporin A, cytomegalovirus replication, and its encoded proteins.

Results: Intermediate early protein 2 can influence the cellular cyclophilin A pathway, affecting cyclosporin A as a mediator of viral replication or anti-cytomegalovirus drug.

Conclusion: Cyclosporin A has a dual function in cytomegalovirus pathogenesis. It has the immunosuppressive effect that establishes virus replication through the inhibition of T-cell function. It also has an anti-cytomegalovirus effect mediated by intermediate early protein 2. Both of these functions involve cyclophilin A pathway.

Keywords
Cyclophilins, cyclophilin A, cyclosporin A, cytomegalovirus, immunosuppressive drug, congenital infection

Date received: 27 March 2018; accepted: 12 October 2018

Introduction
Viruses, without their own replication machinery, depend on the host cell to proliferate. The viruses interact with host cells, activates enzymes and co-factors required for their replication. The response of the host cell thus reflects the pathogenic properties of the virus.1,2

In the treatment of viral diseases, the drugs primarily target special viral proteins. Current antiviral drugs include nucleotide analogs,3–7 neuraminidase enzyme and M2 channel,8,9 reverse transcriptase and protease inhibitors,10,11 and chemokine receptor 5 (CCR5) antagonist.12 Many drugs targeting viral proteins are fraught with cytotoxicity and tend to cause drug resistance.13 Although drugs that target cellular factors or pathways have the advantage of overcoming cellular barriers,
their toxicities compromise their usefulness.\textsuperscript{14–17} For this reason, there is a need to discover alternative antiviral compounds with minimal side effects.\textsuperscript{18}

Immunosuppressed patients undergoing organ transplantation are susceptible to cytomegalovirus (CMV) infections that could cause rejections.\textsuperscript{19–21} Interestingly, two immunosuppressive drugs, mycophenolic acid and mizoribine,\textsuperscript{25} have better anti-CMV activities than ganciclovir\textsuperscript{23–27} and allow for good graft survival.\textsuperscript{28–30} Some immunosuppressive drugs were developed to target specific protein kinases essential for virus replication. Among these are artesunate, a drug that inhibits cellular kinase signalling. NF-κB, and Sp1 proteins,\textsuperscript{31,32} and sirolimus and everolimus, rapamycin inhibitors targeting cellular signals.\textsuperscript{33–37} These drugs were shown to be active against ganciclovir- and foscarnet-resistant CMV strains.\textsuperscript{38,39}

This review discusses the association between cellular pathways mediated by CMV and cyclosporin A (CsA) and demonstrates that CsA can be used both as an immunosuppressive drug in organ transplantation and as an anti-CMV agent.

**Cytomegalovirus**

CMV is a DNA virus of the herpesviridae family.\textsuperscript{40} The highly species-specific human cytomegalovirus (HCMV) cannot be studied in animals. This results in the development of many animal models for the virus.\textsuperscript{41–46} Seroprevalence studies have shown that 30–97% of the population is seropositive for CMV.\textsuperscript{47–49} The immune system can easily control the virus from causing active infection and facilitating lifelong latency.\textsuperscript{50,51}

Immunosuppressed transplant recipients, HIV patients, and the foetus are at risk of acquiring CMV infections.\textsuperscript{52–58} The high risk of infection in solid organ transplantation (SOT) recipients is associated with serostatus of the donor and recipient, type of transplanted organ, host immune status, and viral factors. In organ and tissue transplantation, CMV infections were mostly reported in the seropositive (D+)/(D+)/CMV-seronegative (R−) recipients rather than in D−/R−recipients.\textsuperscript{57,59,60} It was also shown in hematopoietic cell transplant, the greatest risk of infection is when the donor is CMV seronegative (D−) and the recipient seropositive (R+).\textsuperscript{51} In pregnant women, among factors that increase the risk of CMV infections are socioeconomic status, parasitic infections, CMV viral load and serostatus, age, non-Caucasian, education level, and close contact with young children, the prevalence of CMV infection is between 50 and 97%.\textsuperscript{62–66} Between 5 and 10% of babies born of mothers with primary CMV infection show neurological diseases at birth, making the prevalence of CMV-related disabilities higher than other childhood diseases.\textsuperscript{57,67–69}

The risk of vertical transmission of CMV is higher in primary (33%) than that in non-primary CMV infection (1%),\textsuperscript{70} but in both infections, symptomatic congenital CMV infections may also develop.\textsuperscript{71–75} Primary infection occurs in most seropositive women and in 1 to 4% of seronegative women. In the USA, 77% of congenital infections are acquired from non-primary CMV infection and only 22% from primary infections.\textsuperscript{76–78} Thus, 77% of congenital infection is acquired from non-primary CMV infection compared to 22% of primary infection in USA.\textsuperscript{78} Regarding CMV disease outcomes, there is no evidence that the symptomatic outcomes in both primary and non-primary CMV infections are different.\textsuperscript{71,73,79} The greatest risk of CMV infection is during the period of fetal organogenesis, that is in the first and early second trimesters. Vertical transmissions mostly occur in the third trimester, and fetuses are mostly born healthy. There seems to be no difference in symptoms among babies born of pregnancies affected with primary and non-primary CMV infections.\textsuperscript{80} Mortality is between 20 and 30% in symptomatic congenitally infected children,\textsuperscript{81,82} resulting from liver dysfunction, coagulation disorders, and secondary bacterial infections.\textsuperscript{82} Complications of CMV congenital infections include central nervous system (CNS) diseases, such as meningoencephalitis, calcification, microcephaly, disruption of neuronal migration, germinal matrix cysts, ventriculomegaly, cellular hyperplasia, lethargy, hypotonia, seizure, and choriorétinitis.\textsuperscript{83,84} Complications are more severe if CMV infections occur at the early stage of pregnancy.\textsuperscript{85} In some newborns, post-natal CMV infections cause hepatitis, neutropenia, thrombocytopenia, and premature and low birth weight.\textsuperscript{86} Sensorineural hearing loss (SNHL) due to virus replication in the inner ear was reported in 15 to 25% of young kids.\textsuperscript{87–89} This disorder can develop early at birth (in 5.2% of symptomatic or asymptomatic neonates) or later in childhood (in 15.4% of children).\textsuperscript{52,87,88,90} In approximately 50% of infants, the congenital infection may manifest as the more severe and symptomatic cytomegalic inclusion disease (CID) or cytomegalic inclusion body disease (CIBD).\textsuperscript{67,68,51,92} Infants with CID can develop other CMV neurological diseases.\textsuperscript{84,93–97}

CMV can reach the brain of foetuses. Brain CMV infections are associated with viral replication in the endothelial cells of the blood–brain barrier (BBB),\textsuperscript{98} a process that facilitates virus-crossing of the brain parenchyma and access to astrocytes.\textsuperscript{99–102} Another way the virus enters the brain is by infecting the ependymal cells of choroids plexus, leading to dissemination of virus in the cerebrospinal fluid and subsequently infecting the brain parenchyma.\textsuperscript{103} The virus can establish latent infections in myeloid cells that eventually
infiltrate the brain and develop into microglia cells. Destruction or injury to BBB endothelial cells can result in extravasation of monocytes and facilitate brain infection.

In the nervous tissues, CMV induces injuries by interfering with cell differentiation, morphogenesis and survival, controlling apoptosis mechanism, infecting neural stem cell and interfering with brain developmental process, and impacting the CMV replication on the endothelial system. Viral replication interferes with brain development during migration of neocortical neurons to the cortical plate, causing disabilities.

### Cyclophilin A

Cyclophilins (CyPs) are a group of highly conserved cellular proteins, found ubiquitously in animal and plant tissues. These proteins have unique chemical structures consisting of 109 amino acids with. These amino acids contain variations in the interaction domain among proteins from various locations and of different functions. At least 16 CyPs have been identified. Although they differ in distribution in tissue and organ localization, their structures are similar to the same peptidyl-prolyl isomerase (PPIase) activities. In humans, seven CyPs (40 kDa) have been identified. Although they differ in distribution in tissue and organ localization, their structures are similar to the same peptidyl-prolyl isomerase (PPIase) activities.

Cyclophilin A (CyPA), which can bind cyclosporin A (CsA), was first isolated from bovine thymocytes. CyPA resembles the high abundance CyPs in eukaryotic cells with concentration ranging from 0.1 to 0.6% of total cellular proteins. In humans, CyPA is encoded by Cyp18 gene in chromosome 7p11.2-p13 and consists of 165 amino acid with a molecular weight of 18 \( \times 10^3 \) Daltons. In humans, CyPA is composed of eight antiparallel \( \beta \)-barrel structure enclosed by two \( \alpha \)-helices at each location. The hydrophobic core of CyPA contains one hydrophobic and seven aromatic residues within the drum of the molecule or the CsA-binding area. The CsA-binding site is composed of a loop region at Lys118 to His126 and four \( \beta \)-strands at B3 to B6 position.

CyPA plays an important role in various cellular functions, including inflammation and apoptosis. This protein can stimulate the immune response and is produced by inflammatory cells such as endothelial cells, monocytes, vascular smooth muscle cells, and platelets. Extracellular CyPA, through interaction with cell membrane heparin receptor and CD147, also functions as a chemoattractant for monocytes, neutrophils, eosinophils, and T lymphocytes. Like other CyPs, CyPA acts as a chaperone in the regulation of cellular protein and receptor expression and activities. This protein is also involved in several signalling pathways, such as the signal transduction pathway unique to T lymphocytes and the T cell-specific interleukin-2 tyrosine kinase (Itk).

In the brain, CyPA is mostly localized in the neurons, where it plays a role in neuronal differentiation, embryo growth, and adult cortical plasticity. CyPA maintains the integrity and function of BBB and protects neurons during traumatic brain injury by blocking BBB permeability and the effects of ischemia and oxidative stress. In brain injuries, CyPA induces endothelial cell proliferation and migration as well as recruiting monocytes for the repair of brain blood vessels. Moreover, CyPA induces extracellular signal-regulated kinases (ERK) and protein kinase B (PKB) or Akt signalling by binding to the cell surface receptor, CD147. This binding stimulates the expression of the anti-apoptotic protein Bcl-2 and mediates neurogenesis in brain protection and repair.

### Cyclosporin A

Cyclosporin A (CsA), an 11-amino acid cyclic peptide (Figure 1), can be extracted from the fungus, *Tolypocladium inflatum* Gams. It is an immunosuppressive drug primarily used for organ transplantation. This drug is also used for the treatment of renal, neurodegenerative, and autoimmune diseases and has been recommended for the treatment of rheumatoid arthritis, psoriasis, atopic dermatitis, and endogenous uveitis.

The immunosuppressive activity of CsA is the result of the formation of CsA-CyPA complex that has a high affinity for calcineurin, a cellular phosphatase mediating T-cell activation. The CsA–CyPA complex Figure 1. The chemical structure of cyclosporin A.
complex is located at the interface of calcineurin, between the catalytic and regulatory subunits, and controls phosphatase activity and biological functions.\(^{159,162,163}\) CsA also affects the expression of AP-1 and NF-\(\kappa\)B,\(^{164–166}\) modulates the antigen-specific immune and Ca\(^{2+}\)-independent responses,\(^{167}\) and blocks the JNK and p38 MAPK signalling pathways.\(^{161,168–170}\) However, the use of CsA in the treatment of diseases has adverse effects. It causes abnormal glomerular filtration, nephrotoxicity, neurotoxicity, hepatotoxicity, and cardiovascular disorders.\(^{171,172}\) CsA, through T cells, can induce inflammation and apoptosis. This is mediated by JNK and p38 MAPK, the activators of T cell receptors,\(^{161}\) ERK, and the transcription factor AP-1.\(^{174}\) AP-1 controls cellular processes including differentiation, proliferation, and apoptosis. The activation of JNK and p38 MAPK also requires the involvement of the CsA-sensitive protein kinases, MKK6 and MKK7.\(^{161}\)

The majority of mitogen-activated protein kinases (MAPK), MAPK kinase (MAPKK), and MAPKK kinase (MAPKKK)\(^{175–180}\) require MEKK1 to activate MKK7. MEKK1 mediates JNK pathway that modulates NF-\(\kappa\)B activity.\(^{181}\) JNK pathway signals, and NF-\(\kappa\)B activity under CsA control.\(^{182–184}\) CsA mediates JNK signalling pathway through Racl, a member of the Rho subfamily of small G-proteins, especially through its guanine nucleotide exchange factor (Vav1). Vav1 controls IL-2 expression.\(^{185–187}\) Other immunosuppressive agents such as FK506 and tacrolimus (calcineurin NFAT pathway inhibitor), use the same mechanism to block JNK and p38 pathways, and subsequently T-cell activation. Similarly, the immunosuppressive activity of CsA mediated by calcineurin blocks JNK and p38 activation.\(^{188–190}\) Unlike these immunosuppressive agents, calcineurin controls JNK while in complex with PKC-\(\upsilon\).\(^{191–193}\)

### CsA derivatives

There are several CsA derivatives (Figure 2) that interact well with viruses and do not cause serious side effects.\(^{194–196}\) Among these derivatives, alisporivir (Debio-025) (Figure 2(a)), a non-immunosuppressive analog of CsA, was synthesized to contain sarcosine instead of d-methylalanine at position 3 of the PPIase domain and methyl-leucine instead of ethylvaline at position 4 of the calcineurin domain. These modifications have altered the PPIase activity and calcineurin-binding ability of the derivatives.\(^{197}\) However, alisporivir still results in side effects including reversible hyperbilirubinemia and pancreatitis when used in combination with PEG-IFNa2a and ribavirin to treat hepatitis C virus (HCV) infection.\(^{198}\)

NIM811 (Figure 2(b)), another non-immunosuppressive analog of CsA, is similar in structure to the parent molecule with one modification: methyl-leucine at position 4 being replaced by methyl-isoleucine. This derivative has antiviral effects\(^{195}\) while exhibiting the same pharmacokinetic profile as CsA without nephrotoxicity.\(^{196,199}\)

In 2010, SCY-635 (Figure 2(c)) was synthesized.\(^{200}\) This CsA derivative inhibits HCV infection without detectable inhibition of calcineurin phosphatase. Treatment with this drug is associated with transient increases in interferon \(\alpha\), \(\lambda1\), and \(\lambda3\), the cytokines responsible for the clearance of the viruses.\(^{202}\)

Another derivation of CsA, EDP-546, is metabolically stable with favorable pharmacokinetics that allows for less frequent and low therapeutic dosing of
the drug. It is also an effective bilirubin transporter without affecting CYP450, a major protein in drug metabolism.203,204

Sanglifehrin A (SFA) (Figure 3) is a new immunosuppressive agent205 isolated from the Streptomyces strain A92-308110. This protein interacts strongly with CyPA206–208 but not with calcineurin phosphatase.209 It is also a potent inhibitor of mitochondrial permeability transition and heart reperfusion injury.210

**CyPA and viral diseases**

CyPA is an essential protein for the HCV and hepatitis B virus (HBV) replications. In HCV, CyPA interacts with several viral proteins including serine protease, NS3, viral RNA-dependent RNA polymerases, NS5A and NS5B, and cysteine protease, NS2.211–215 The interactions between CyPA with NS5A and NS5B stimulate viral genome replication,213,215–211 virion morphogenesis,222–224 and viral particles assembly through the NS5A-D3 domain.213,222,224,225 The replication of viruses is also mediated by other proteins including eEF1A and T-cell intracellular antigen 1 (TIA-1).226,227 eEF1A binds to the 3’-terminal stem-loop of flavivirus genomes and facilitates the synthesis of minus-strand RNA.228 CsA can block CyPA-NS5 interaction213,228 and indirectly inhibit the genomic RNA amplification.220,225,229

The inhibitory effect of CsA and its derivative on HBV is associated with the distribution of mitochondrial transition pore and calcium signalling.230 CyPA that can form a complex with CsA is important for virus entry by triggering the expression of HBV surface antigen (HBsAg) and mediating virus DNA replication and envelope protein secretion.231–237 The formation of the CsA–CyPA complex inhibits HCV and HBV through sodium taurocholate co-transporting polypeptide receptor.230,238

CyPA also mediates influenza virus replication through its association with the virus core.239 In influenza viruses, CyPA interacts with M1 protein, resulting in the interference of virus nuclear translocation and preventing post-transcription of the viral genome.240 Inhibition of influenza virus replication by CsA and its non-immunosuppressive derivatives involves both the CyPA-dependent and independent pathways.241,242 The CyPA-independent inhibition occurs through the RNA polymerase II.243 The inhibition of virus replication can also be achieved with the non-immunosuppressive analogs of CsA such as SCY-635.242

Human immunodeficiency virus (HIV) is an RNA virus that causes acquired immunodeficiency syndrome (AIDS). The viral capsid undergoes morphological changes in the target cell cytosol.244 This is mediated by cell factors,245,246 such as TRIM5247 which forms the TRIM5-CyPA fusion complex, and TRIMCyp that blocks virus replication at the post-entry step.248 TRIMCyp interacts with the retrovirus capsids, causing capsid disassembly and inhibits virus infection.247,249–251 The HIV-1 CA protein on the capsid surface facilitates interaction with cellular CyPA during infection and controls virus replication. CyPA also interacts with HIV-1 Gag polyprotein that mediates virus fusion, entry, uncoating,252–258 viral genome integration into host DNA,259–261 and modulates the immune response.262 CsA and its analogs, Debio-025 and NIM811, interact with CyPA. This disrupts CyPA-binding loop located at the N-terminal of HIV-1 CA protein254–256,262,263 and inhibits HIV-1 infection in certain cell types.253,265,266

In severe acute respiratory syndrome (SARS) virus, CyPA binds to the SARS-CoV N protein267 and mediates viral RNA synthesis.268–270 In most coronaviruses, CyPA also interacts with the non-structural viral protein 1 (NSp1).

**CyPA and CMV replication**

**Cell signals and CMV.** CMV cellular entry and replication involve several factors including epidermal growth factor receptor (EGFR), integrin β1 and β2, and platelet-derived growth factor receptor-α (PDGFRα).271–273 Binding to these receptors initiates Ca²⁺ homeostasis, activation of phospholipase C and A2, the release of arachidonic acid and its metabolites, diacylglycerol that activates protein kinase C, and inositol triphosphate inducing calcium influx.274–278 The virus also binds to αβ integrin, another receptor that mediates actin depolymerization, facilitating virus translocation to the nucleus,281 and activating the Src pathway. The alteration in cytoskeleton arrangement is also associated with the activation of αβ integrin and EGFR receptors that reduce the activity of RhoA GTPase.281,282 The virus activates the extracellular signal-regulated kinase (ERK) 1/2, also known as MAPK, through the ERK/MEK1/2

---

**Figure 3.** The chemical structure of sanglifehrin A (SFA).
pathway. These interactions that occur through M KK3, M KK6, and M KK4 kinases are important for viral replication. 283–285

HCMV replication requires the NF-κB to activate the major immediate early promoter (MIEP), 286–288 which is responsible for the transcription of more than 150 genes in cells. The NF-κB specific promoter 1 protein (Sp1) can be activated by HCMV IE1-72 and IE2-86 either independently or synergistically. 289–291 MIEP has a special site for the cell transcription factor that either stimulates or represses transcription of NF-κB, CREB/ATF, AP1. 292 Ying Yang1 (YY1), and Ets-2 repressor factors (ERF). 293–298 The repression of transcription occurs through factors including those involved in the post-translational modification of histones 299,300 and TNF. 301,302 In HCMV-permissive cells, MIEP associates with acetylated histone H4. In peripheral blood monocytes, MIEP associates with heterochromatin protein 1 (HP1), a chromosomal protein implicated in gene silencing. 303–306 The HCMV remains latent in monocytes that serve as carriers for the virus. Although the mechanism of reactivation of HCMV is still not known, it has been suggested that the host complex facilitates chromatin transcription (FACT) binds to MIEP. The inhibition of this complex inhibits virus activation. 307

HCMV alters the expression of cell cycle regulatory proteins, the cyclin-dependent kinases. 308,309 The infected cells are arrested at the G1 phase 310,311 of the cell cycle, during which macromolecules needed for cell growth and virus replication are synthesized. Both HCMV IE1-72 and IE2-86 can transactivate p53 promoter and induce p53 accumulation. However, HCMV IE1-72 represses p53 transactivation activity. 312 The outcomes of these interactions include stimulation of DNA synthesis, cell cycle arrest, and inhibition of apoptosis. 312 The virus also responds to alterations in cell growth and activation of host genes by interacting with histone deacetylases (HDACs) and retinoblastoma (Rb) tumor suppressor proteins via the LxCxE-dependent pathway. 313–315 The binding of Rb protein to the E2F transcription factor partially controls cell growth in the HCMV-infected cells and other pocket proteins, such as p107. Cell growth arrest occurs when Rb protein represses the transcriptional activity of E2F transcription factors. 316,317 The binding of E2F transcription factor to p107 causes the release and activation of E/CDK 2 kinases, 318,319 allowing for the cell cycle progression from G1 to S phase.

HCMV increases the expression of tumor suppressor factor p53 in infected cell. 312,320,321 Both HCMV IE1-72 and IE2-86 bind to p53, although only HCMV IE2-86 can block its function. 312,322,325 HCMV can inhibit the apoptosis pathways through several strategies. Both HCMV IE1-72 and IE2-86 stimulate the anti-apoptotic PI3-K/Akt signalling pathway and delay the onset of p53 activity. 324,325 Also, the CMV genes, UL36, a viral inhibitor of caspase-8-induced apoptosis (vICA) and the UL37 gene encoding viral mitochondria-localized inhibitors of apoptosis (vMIA) affect permeabilization of the mitochondrial outer membrane, preventing the release of cytochrome c necessary for the activation of the pro-apoptotic caspase-3 pathway. 326 The adaptation and survival of the virus in host cells are further enhanced by its major tegument protein, pp150 protein. This protein binds to cyclin A2, causing cyclin A2-dependent phosphorylation and avoids the CDK-mediated inhibition of viral replication. 311,327–329

CMV contains the UL146 and UL147 genes encoding for the CXC chemokines, vCXCL1 and vCXCL2. The virus uses these cytokines to activate CXCR1 and CXCR2, and preferentially attract neutrophils that can serve as virus carriers. 330,331 The virus also possesses the UL 76 gene, which is an inducer of IL8 expression. 332 HCMV genome contains the G-protein-coupled receptors (GPCRs), UL33, UL78, US27, and US28. 333–336 The GPCRs prevents leukocytes from recognizing HCMV-infected cells and blocks the effect of leukocytes on neighbouring cells. 335,337–340 US28, the best characterized among the GPCRs, stimulates migration of HCMV-infected cell to vascular injury sites leading to atherosclerosis and restenosis. 336,341

Host cells infected with HCMV express type 1 interferons (IFNs), IFN-stimulated genes, and proinflammatory cytokines, 342 which are components of the innate cellular response that require the transcriptional activity of interferon regulatory factor 3 (IRF-3). 343 As a defence mechanism, the HCMV inhibits production of IFN by blocking the IFNα-stimulated responses and disrupting the IFNα signal transduction pathway, decreasing the expression of JAK1 and p48 344–346 or the multiple IFN-responsive genes. 347–349 HCMV, particularly at late infection stage, also inhibits NF-κB signaling responsible for the production of proinflammatory cytokines, IL-6, CCL5, and TNFα. 350,351

Cyclosporin A, CyPA, and CMV. CsA is an immunosuppressive agent 22,352 that can potentiate CMV infection. 103,353–355 The immunosuppressive activity of CsA is via CsA–CyPA interaction with calcineurin. 159,160 Most of the cellular pathways mediated by CyPA are sensitive to CsA. 356–358 These cellular pathways are fully controlled by CMV during viral infection and replication. 287,288,291,292,359 Additionally, they share signals such as NF-κB, MAPK such as MKK7 and MKK6, ERK1/2, P53, and JNK. The involvement of CyPA in the activation and replication of CMV 360 was demonstrated in the mouse model through the silencing of the CyPA mRNA. In fact,
CyPA is required for HCMV lytic infection, latency establishment, and reactivation. It also regulates IE protein and lytic genes expressions in HCMV replication cycle. The utilization of CyPA by CMV342 may deplete its concentration in organs and compromise cellular protein folding, differentiation, and functions. If the nervous tissues are affected, the infection may cause CNS-associated abnormalities. These phenomena suggest that CyPA could be a potential therapeutic target in the treatment of HCMV infection. Although CsA is a common immunosuppressive drug used during organ transplantations and mediates HCMV reactivation in vivo (CsA–CyPA complex), this response may result from overall immunosuppression. When CMV enters the cell, it stimulates the secretion of type I IFN as well as proinflammatory cytokines such as CyPA362–364 through both NFκB and IRF3 transcriptions. This is critical in CMV treatment. Both responses are controlled by CMV IE86 protein. The other immune response to CMV is carried out by Toll-like receptor-2 (TLR2) stimulated by glycoproteins and CD147. Evidence from previous studies suggests that CD147 operates as a legend for CyPA. CD147 upregulates through CMV infection and is involved in inflammation similar to CMV. The interaction was established between CMV and ectodomain of CD147. When CMV enters the cell, it stimulates CyPA production that interacts with CD147 to mediate virus replication and early immune response such as ISG15 gene, IFNB1 signalling to block CMV reinfec tion. Additionally, the CD147–CyPA activates NFκB through ERK1/2 pathway which is important for both monocytes and macrophages. Modulation of the cellular microenvironment is necessary and was approved for CMV IL-10 previously. CMV successfully downregulates CD147 by encoding MiR-U25-1-5p encoded by US 24-US26. This microRNA is necessary for cellular modulation. It downregulates the CD147 through special coding area in its UTR sequence. This leads to reduced activation of both IFNB1 and IFN-related gene ISG15, NFκB, IL-6, and TNF-α induced above. This inhibits immune response mediated by CD147. This inhibition is also mediated by CsA as it blocks CyPA function and subsequently its interaction with CD147.

Many viruses successfully replicate by inducing oxidative stress, while CyPA is important to mediate their replication. Xiao et al.’s study demonstrated that CMV infection induces a substantial level of oxidative stress. This oxidative stress stimulates CyPA production. CyPA plays a role in activating the p38/MAPK pathway. The p38/MAPK pathway is necessary to activate the NFκB transcription factor Elk-1, Sap-1, ATF-2, CREB, CHOP, and Max, mediating viral and cellular gene expression to enhance the virus replication. Silencing of CyPA inhibits virus gene expression. CsA can affect IE1 expression and CyPA activity but not CyPA expression. CsA as CyPA target drug inhibited the CyPA-mediated P38/MAPK pathway. Additionally, the antioxidant compound can also control and limit virus replication. The ability of CyPA to mediate inflammatory response was reported by van de Berg et al. CMV can also mediate the inflammatory response through CyPA.

CMV stimulates CyPA that mediates the activation of both the p38/MAPK and ERK1/2 pathways. This mediates the viral replication through the expression of IE1 and IE2. HCMV, through its UL4 promoter, activates both p38/MAPK and MAPK/ERK pathways. In addition, both IE1 and IE2 proteins of CMV mediate the viral gene expression as well as the stimulation of cellular expression factors such as Tef-1, Sp1, c-Jun, JunB, ATF-2, CREB, histone acetyltransferase CREB-binding protein (CBP)-associated factor (P/CABF), and p53. Both IE1 and IE2 also play a role in controlling gene activation factor to mediate viral replication and its response to CsA as an antiviral drug.

Cyclosporin A as an immunosuppressive and anti-CMV drug

IE2 resembles the most abundant IE proteins that mediate virus gene expression and reproduction. The ability of IE2 to overcome CsA inhibition by CyPA can stimulate viral gene expressions. In addition, both chemokine-like receptor proteins, US3 and US6, interact with HL-AC and HL-AG and affect the expression of MHC class 1 antigen (Figure 4), enabling viruses to evade the immune response. CMV gene expressions occur in sequence, with the expression of early (E) genes occurring first, followed by IE genes. The IE2 expression will eventually decline, allowing for the inhibition of CyPA by CsA through the formation of the CsA–CyPA complex. This complex inhibits NFκB, and thus virus transcription. Since the early (E) gene expression will also cascade, no late (L) gene encoding structural protein will be expressed. This leads to the blockage of virus replication and production of virus progeny. Therefore, CsA may be activated by CMV replication while functioning as an antiviral drug by inhibiting virus replication.

Conclusion

CyPA is vital for HCMV lytic infection, latency establishment, and reactivation. This protein can serve as a target in the treatment of HCMV infection. The current review describes the anti-CMV activity of CsA, an
immunosuppressive drug commonly used in organ transplantations. However, this drug is associated with HCMV reactivation and toxicities. The immunosuppressive activity of the drug is achieved through the formation of the CsA–CyPA complex that suppresses organ rejection by inhibiting the calcium/calmodulin-dependent and calcinerin.353 The IE2 protein is the major IE protein, encoded by the CMV IE gene UL122, which mediates the CMV lytic cycle.394 IE2 expression depends on which proteins or cellular signals it interacts with during the cascade of events, is core to the determination of whether CsA activates or suppresses virus proliferation. Since viral infections induce expression of inflammatory cytokines360,361 and thrive under immunosuppression, the inhibitory effect of CsA is most effective in early stages of the viral replication cycle, when the immune and inflammatory responses are still limited. This review with previously published data shows that CsA has anti-CMV activity.360,361 The use of CsA in combination with other drugs approved for the treatment of CMV infections may also prevent the development of unwanted toxicities and drug resistance.

**Author's contributions**

Ashwaq A Abdullah: Designed, conceptualized the write up and drafted the article and critically revised the article.

Rasedee Abdullah: Supervised the design, rearranged and critically write up of the article.

Zeenathul A Nazariah: Supervised the design and write up of the article.

Krishnan N Balakrishnan: Helped in drafting and final alignment of the article.

Faez Firdaus J Abdullah: Supervised the edited of the article and improvement of grammar and structure.

Jamilu A Bala: Helped in drafting and final alignment of the article.

Mohd-Azmi Mohd-Lila: Made considerable contributions to conception, supervised the design of the work and write up of the article.

All authors have read and approved the final version of the article.

**Acknowledgements**

The authors would like to express their gratitude to PerkinElmer Inc (PKI) Company to support free version ChemDraw professional 17.1

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical approval**

This article does not contain any studies with human participants or animals performed by any of the authors.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the Ministry of Higher Education Malaysia FRGS Grant No: 5524642, 5524931 and Universiti Putra Malaysia Grant No: 9428700. The authors are grateful to Taiz University and Ministry of Higher Education and Scientific research (MoHESR), Yemen for the financial support of Ashwaq’s scholarship.

**ORCID iD**

Jamilu A Bala [http://orcid.org/0000-0001-7365-8856](http://orcid.org/0000-0001-7365-8856)

**References**

1. Roux S, Hallam SJ, Woyke T, et al. Viral dark matter and virus–host interactions resolved from publicly available microbial genomes. *eLife* 2015; 4: e08490.
2. Chen IY and Ichinohe T. Response of host inflammasomes to viral infection. *Trends Microbiol* 2015; 23: 55–63.
3. Price NB and Prichard MN. Progress in the development of new therapies for herpesvirus infections. *Curr Opin Virol* 2011; 1: 548–554.
4. Menéndez-Arias L, Alvarez M and Pacheco B. Nucleoside/nucleotide analog inhibitors of hepatitis B virus polymerase: mechanism of action and resistance. *Curr Opin Virol* 2014; 8: 1–9.
5. Mak L-Y, Seto W-K, Lai C-L, et al. DNA polymerase inhibitors for treating hepatitis B: a safety evaluation. Expert Opin Drug Saf 2016; 15: 383–392.

6. Zarrouk K, Piret J and Boivin G. Herpesvirus DNA polymerases: structures, functions and inhibitors. Virus Res 2017; 234: 177–192.

7. Abad CL and Razonable RR. Treatment of alpha and beta herpesvirus infections in solid organ transplant recipients. Expert Rev Anti Infect Ther 2017; 15: 93–110.

8. Arn S, Balgi AD, Shimizu Y, et al. Novel spirothiazamethane inhibitors of the influenza A M2 proton channel. Eur J Med Chem 2016; 120: 64–73.

9. Yang J, Liu S, Du L, et al. A new role of neuraminidase (NA) in the influenza virus life cycle: implication for developing NA inhibitors with novel mechanism of action. Rev Med Virol 2016; 26: 242–250.

10. De Clercq E. Antiretroviral drugs. Curr Opin Pharmacol 2010; 10: 507–515.

11. Johnston C, Harrington R, Jain R, et al. Safety and efficacy of combination antiretroviral therapy in human immunodeficiency virus–infected adults undergoing autologous or allogeneic hematopoietic cell transplantation for hematologic malignancies. Biol Blood Marrow Transplant 2016; 22: 149–156.

12. Dorr P, Westby M, Dobbs S, et al. Maraviroc (UK-427,857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity. Antimicrob Agents Chemother 2005; 49: 4721–4732.

13. Abdullah AA, Balakrishnan KN, Bala JA, et al. Cytomegalovirus replication steps and the actions of antiviral drugs. Anti-Infective Agents 2018; 16: 1–18.

14. Boulant S, Stanifer M and Lozach P-Y. Dynamics of virus-receptor interactions in virus binding, signaling, and endocytosis. Viruses 2015; 7: 2747.

15. Tan SL, Ganji G, Paeper B, et al. Systems biology and the host response to viral infection. Nat Biotechnol 2007; 25: 1383–1389, Opinion and Comment.

16. Boergeling Y and Ludwig S. Targeting a metabolic pathway to fight the flu. FERS J 2017; 284: 218–221.

17. Li C-C, Dong H-J, Wang P, et al. Cellular protein GLTSCR2: a valuable target for the development of broad-spectrum antivirals. Antiviral Res 2017; 142: 1–11.

18. Lin K and Gallay P. Curing a viral infection by targeting the host: the example of cyclophilin inhibitors. Antiviral Res 2013; 99: 68–77.

19. Lopez-Botet M, Vilches C, Redondo-Pachon D, et al. Dual role of natural killer cells on graft rejection and control of cytomegalovirus infection in renal transplantation. Front Immunol 2017; 8: 166.

20. Roux A, Mourin G, Fastenackels S, et al. CMV driven CD8+ T-cell activation is associated with acute rejection in lung transplantation. Clin Immunol 2013; 148: 16–26.

21. Van Damme E, Sauviller S, Lau B, et al. Glucocorticosteroids trigger reactivation of human cytomegalovirus from latently infected myeloid cells and increase the risk for HCMV infection in D+R+ liver transplant patients. J Gen Virol 2015; 96: 131–143.

22. Allison AC. Immunosuppressive drugs: the first 50 years and a glance forward. Immunopharmacology 2000; 47: 63–83.

23. Kuramoto T, Daikoktu K, Yoshida Y, et al. Novel anticytomegalovirus activity of immunosuppressant mizoribine and its synergism with ganciclovir. J Pharmacol Exp Ther 2010; 333: 816–821.

24. Marcen R. Immunosuppressive drugs in kidney transplantation: impact on patient survival, and incidence of cardiovascular disease, malignancy and infection. Drugs 2009; 69: 2227–2243.

25. Sagedal S, Hartmann A, Nordal KP, et al. Impact of early cytomegalovirus infection and disease on long-term recipient and kidney graft survival. Kidney Int 2004; 66: 329–337.

26. Shiraki K, Ishibashi M, Okuno T, et al. Effects of cyclosporine, azathioprine, mizoribine, and prednisolone on replication of human cytomegalovirus. Transplant Proc 1990; 22: 1682–1685.

27. Tanabe K, Tokumoto T, Ishikawa N, et al. Long-term results in mizoribine-treated renal transplant recipients: a prospective, randomized trial of mizoribine and azathioprine under cyclosporine-based immunosuppression. Transplant Proc 1999; 31: 2877–2879.

28. Akiyama T, Okazaki H, Takahashi K, et al. Mizoribine in combination therapy with tacrolimus for living donor renal transplantation: analysis of a nationwide study in Japan. Transplant Proc 2005; 37: 843–845.

29. Takahashi K, Ochiai T, Uchida K, et al. Pilot study of mycophenolate mofetil (RS-61443) in the prevention of acute rejection following renal transplantation in Japanese patients. RS-61443 Investigation Committee-Japan. Transplant Proc 1995; 27: 1421–1424.

30. Suzuki K. Role of mizoribine in renal transplantation. Pediatr Int 2002; 44: 224–231.

31. Effert H, Romero MR, Wolf DG, et al. The antiviral activities of artemisinin and artemesane. Clin Infect Dis 2008; 47: 804–811.

32. Hutterer C, Niemann I, Milbradt J, et al. The broad-spectrum antiinfective drug artesunate interferes with the canonical nuclear factor kappa B (NF-B) pathway by targeting RelA/p65. Antiviral Res 2015; 124: 101–109.

33. Demopoulos L, Polinsky M, Steele G, et al. Reduced risk of cytomegalovirus infection in solid organ transplant recipients treated with sirolimus: a pooled analysis of clinical trials. Transplant Proc 2008; 40: 1407–1410.

34. Vigno M, Dengler T, Mattei MF, et al. Lower incidence of cytomegalovirus infection with everolimus versus mycophenolate mofetil in de novo cardiac transplant recipients: a randomized, multicenter study. Transpl Infect Dis 2010; 12: 23–30.

35. Höcker B, Zenecke S, Pape L, et al. Impact of everolimus and low-dose cyclosporin on cytomegalovirus replication and disease in pediatric renal transplantation. Am J Transplant 2016; 16: 921–929.
36. Sheng L, Jun S, Jianfeng L, et al. The effect of sirolimus-based immunosuppression vs. conventional prophylaxis therapy on cytomegalovirus infection after liver transplantation. Clin Transplant 2015; 29: 555–559.

37. Webster AC, Lee VW, Chapman JR, et al. Target of rapamycin inhibitors (sirolimus and everolimus) for primary immunosuppression of kidney transplant recipients: a systematic review and meta-analysis of randomized trials. Transplantation 2006; 81: 1234–1248.

38. Shapira MY, Resnick IB, Chou S, et al. Artesunate as a potent antiviral agent in a patient with late drug-resistant cytomegalovirus infection after hematopoietic stem cell transplantation. Clin Infect Dis 2008; 46: 1455–1457.

39. Ozaki KS, Camara NO, Nogueira E, et al. The use of sirolimus in ganciclovir-resistant cytomegalovirus infections in renal transplant recipients. Clin Transplant 2007; 21: 675–680.

40. Mocarski ES, Shenk T, Griffiths PD, et al. Cytomegaloviruses. In: Knipe DM and Howley PM (eds) Fields virology. New York, NY: Lippincott, Williams & Wilkins, 2015, pp.1960–2015.

41. Loh HS, Mohd-Azmi ML, Lai KY, et al. Characterization of a novel rat cytomegalovirus (RCMV) infecting placenta-uterus of Rattus rattus diardii. Arch Virol 2003; 148: 2353–2367.

42. Loh HS, Mohd-Lila MA, Abdul-Rahman SO, et al. Pathogenesis and vertical transmission of a transplacental rat cytomegalovirus. Virol J 2006; 3: 42.

43. Loh L and Hudson JB. Murine cytomegalovirus infection in the spleen and its relationship to immunosuppression. Infect Immun 1981; 32: 1067–1072.

44. Abdullah AA, Balakrishnan KN, Abba Y, et al. RCMV ALL-03 model and study of CMV pathogenesis in congenital infection. Am J Anim Vet Sci 2015; 10: 170–186.

45. Balakrishnan KN, Abdullah AA, Camalxaman SN, et al. Complete genome sequence of rat cytomegalovirus strain ALL-03 (Malaysian Strain). Genome Announc 2015; 3: 1–2.

46. Balakrishnan KN, Abdullah AA, Bala J, et al. Identification and comparison of RCMV ALL 03 open reading frame (ORF) among several different strains of cytomegalovirus worldwide. Infect Genet Evol 2017; 54: 81–90.

47. Paya CV. Prevention of cytomegalovirus disease in recipients of solid-organ transplants. Clin Infect Dis 2001; 32: 596–603.

48. Preiksaitis JK, Brennan DC, Fishman J, et al. Canadian society of transplantation consensus workshop on cytomegalovirus management in solid organ transplantation final report. Am J Transplant 2005; 5: 218–227.

49. Camalxaman SN, Zeneathul NA, Quah YW, et al. New estimates of CMV Seroprevalence from a population with a high rate of congenital infection. Epidemiol Infect 2013; 141: 2187–2191.

50. Sinclair J and Sisson P. Latency and reactivation of human cytomegalovirus. J Gen Virol 2006; 87: 1763–1779.

51. Sinclair J and Poole E. Human cytomegalovirus latency and reactivation in and beyond the myeloid lineage. Future Virol 2014; 9: 557–563.

52. Dollard SC, Grosse SD and Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol 2007; 17: 355–363.

53. Freeman RB Jr. The ‘indirect’ effects of cytomegalovirus infection. Am J Transplant 2009; 9: 2453–2458.

54. Gandhi MK and Khanna R. Human cytomegalovirus: clinical aspects, immune regulation, and emerging treatments. Lancet Infect Dis 2004; 4: 725–738.

55. Tuthill M, Chen F, Paston S, et al. The prevention and treatment of cytomegalovirus infection in haematopoietic stem cell transplantation. Cancer Immunol Immunother 2009; 58: 1481–1488.

56. Humar A and Snyderman D. Cytomegalovirus in solid organ transplant recipients. Am J Transplant 2009; 9: S78–S86.

57. Bataille S, Moal V, Gaudart J, et al. Cytomegalovirus risk factors in renal transplantation with modern immunosuppression. Transpl Infect Dis 2010; 12: 480–488.

58. Orlin A, Nadelmann J, Gupta M, et al. Cytomegalovirus retinitis outcomes in HIV-infected and non-HIV patients at a tertiary care center. J Virol Retin Dis 2017; 1: 57–64.

59. Razonable RR. Strategies for managing cytomegalovirus in transplant recipients. Expert Opin Pharmacother 2010; 11: 1983–1997.

60. Kuo HT, Ye X, Sampaio MS, et al. Cytomegalovirus serostatus pairing and deceased donor kidney transplant outcomes in adult recipients with antiviral prophylaxis. Transplantation 2010; 90: 1091–1098.

61. Camargo JF and Komanduri KV. Emerging concepts in cytomegalovirus infection following hematopoietic stem cell transplantation. Hematol Oncol Stem Cell Ther 2017; 10: 233–238.

62. Yamamoto AY, Castellucci RA, Aragon DC, et al. Early high CMV seroprevalence in pregnant women from a population with a high rate of congenital infection. Epidemiol Infect 2013; 141: 2187–2191.

63. Basha J, Iwasenkom JM, Robertson P, et al. Congenital cytomegalovirus infection is associated with high maternal socio-economic status and corresponding low maternal cytomegalovirus seropositivity. J Paediatr Child Health 2014; 50: 368–372.

64. van der Sande MAB, Kaye S, Miles DJC, et al. Risk factors for and clinical outcome of congenital cytomegalovirus infection in a peri-urban West-African birth cohort. PLoS One 2007; 2: e492.

65. Munro SC, Hall B, Whybin LR, et al. Diagnosis of and screening for cytomegalovirus infection in pregnant women. J Clin Microbiol 2005; 43: 4713–4718.

66. Kuessel L, Husslein H, Marschalek J, et al. Prediction of maternal cytomegalovirus serostatus in early pregnancy: a retrospective analysis in Western Europe. PLoS One 2015; 10: e0145470.

67. Manicklal S, Emery VC, Lazzarotto T, et al. The “silent” global burden of congenital cytomegalovirus. Clin Microbiol Rev 2013; 26: 86–102.

68. Benoist G, Leruez-Ville M, Magny JF, et al. Management of pregnancies with confirmed cytomegalovirus fetal infection. Fetal Diagn Ther 2013; 33: 203–214.
69. Cannon MJ, Schmid DS and Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. *Rev Med Virol* 2010; 20: 202–213.

70. Kenneson A and Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol* 2007; 17: 253–276.

71. Boppana SB, Fowler KB, Britt WJ, et al. Symptomatic congenital cytomegalovirus infection in infants born to mothers with preexisting immunity to cytomegalovirus. *Pediatrics* 1999; 104: 55–60.

72. Ahlfors K, Ivarsson SA and Harris S. Report on a long-term study of maternal and congenital cytomegalovirus infection in Sweden. Review of prospective studies available in the literature. *Scand J Infect Dis* 1999; 31: 443–457.

73. Boppana SB, Rivera LB, Fowler KB, et al. Intrauterine transmission of cytomegalovirus to infants of women with preconceptional immunity. *N Engl J Med* 2001; 344: 1366–1371.

74. Ahlfors K, Ivarsson SA and Harris S. Secondary maternal cytomegalovirus infection – a significant cause of congenital disease. *Pediatrics* 2001; 107: 1227–1228.

75. Puhakka L, Renko M, Helminen M, et al. Primary versus non-primary maternal cytomegalovirus infection as a cause of symptomatic congenital infection – register-based study from Finland. *Infect Dis (London, England)* 2017; 49: 445–453.

76. Colugnati FA, Staras SA, Dollard SC, et al. Incidence of cytomegalovirus infection among the general population and pregnant women in the United States. *BMC Infect Dis* 2007; 7: 71.

77. Plotkin SA and Boppana SB. Vaccination against the human cytomegalovirus. *Vaccine* 2018. DOI: https://doi.org/10.1016/j.vaccine.2018.02.089.

78. Wang C, Zhang X, Bialek S, et al. Attribution of congenital cytomegalovirus infection to primary versus non-primary maternal infection. *Clin Infect Dis* 2011; 52: e11–e13.

79. Ornoy A. The effects of cytomegalic virus (CMV) infection during pregnancy on the developing human fetus. *Harefuah* 2002; 141: 565–568, 577, Review.

80. Enders G, Daiminger A, Bader U, et al. Intrauterine transmission and clinical outcome of 248 pregnancies with primary cytomegalovirus infection in relation to gestational age. *J Clin Virol* 2011; 52: 244–246.

81. Bale JE and Toltzis P. Perinatal viral infections. In: Martin RJ, Fanaroff AA and Walsh MC (eds) *Neonatal-perinatal medicine*. St Louis: Mosby, 2006, pp.429–453.

82. Malm G and Engman ML. Congenital cytomegalovirus infections. *Semin Fetal Neonatal Med* 2007; 12: 154–159.

83. Lipitz S, Yinon Y, Malinger G, et al. Risk of cytomegalovirus-associated sequelae in relation to time of infection and findings on prenatal imaging. *Ultrasound Obstet Gynecol* 2013; 41: 508–514.

84. Bilavsky E, Shahar-Nissan K, Pardo J, et al. Hearing outcome of infants with congenital cytomegalovirus and hearing impairment. *Arch Dis Child* 2016; 101: 433–438.

85. Jones CA. Congenital cytomegalovirus infection. *Curr Probl Pediatr Adolesc Health Care* 2003; 33: 70–93.

86. Maschmann J, Hammreht K, Dietz K, et al. Cytomegalovirus infection of extremely lowbirth weight infants via breast milk. *Clin Infect Dis* 2001; 33: 1998–2003.

87. Kim CS. Congenital and perinatal cytomegalovirus infection. *Korean J Pediatr* 2010; 53: 14–20.

88. Fowler KB and Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. *J Clin Virol* 2006; 35: 226–231.

89. Cheeran MC, Lokensgard JR and Schleiss MR. Neuropathogenesis of congenital cytomegalovirus infection: disease mechanisms and prospects for intervention. *Clin Microbiol Rev* 2009; 22: 99–126, Table of Contents.

90. Zhang XW, Li F, Yu XW, et al. Physical and intellectual development in children with asymptomatic congenital cytomegalovirus infection: a longitudinal cohort study in Qinba mountain area, China. *J Clin Virol* 2007; 40: 180–185.

91. Chatterjee A, Sarkar DA and Chatterjee RP. Congenital cytomegalovirus infection causing severe inclusion diseases in infants 2016, 5(12): 49–51.

92. Oliver SE, Cloud GA, Sanchez PJ, et al. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. *J Clin Virol* 2009; 46: S22–S26.

93. Kimberlin DW, Jester PM, Sánchez PJ, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med* 2015; 372: 933–943.

94. Mareri A, Lasorella S, Iapadre G, et al. Anti-viral therapy for congenital cytomegalovirus infection: pharmacokinetics, efficacy and side effects. *J Matern Fetal Neonatal Med* 2016; 29: 1657–1664.

95. Dreher AM, Arora N, Fowler KB, et al. Spectrum of disease and outcome in children with symptomatic congenital cytomegalovirus infection. *J Pediatr* 2014; 164: 855–859.

96. Swanson EC and Schleiss MR. Congenital cytomegalovirus infection: new prospects for prevention and therapy. *Pediatr Clin North Am* 2013; 60: 335–349.

97. Fowler KB. Congenital cytomegalovirus infection: audiologic outcome. *Clin Infect Dis* 2013; 57: S182–S184.

98. Kamalachavan S-N, Zeenathul NA, Quah Y-W, et al. Establishment of rat brain endothelial cells susceptible to rat cytomegalovirus ALL-03 infection. *In Vitro Cell Dev Biol-Animal* 2013; 49: 238–244.

99. Fritschy JM, Brandner S, Aguzzi A, et al. Brain cell type specificity and glosis-induced activation of the human cytomegalovirus immediate-early promoter in transgenic mice. *J Neurosci* 1996; 16: 2275–2282.

100. Fish KN, Soderberg-Naucler C, Mills LK, et al. Human cytomegalovirus persistently infects aortic endothelial cells. *J Virol* 1998; 72: 5661–5668.

101. Latheyj L, Wileyec A, Veritym A, et al. Cultured human brain capillary endothelial cells are permissive for
infection by human cytomegalovirus. *Virol* 1990; 176: 266–273.

102. Kossmann T, Morganti-Kossmann MC, Orenstein JM, et al. Cytomegalovirus production by infected astrocytes correlates with transforming growth factor-beta release. *J Infect Dis* 2003; 187: 534–541.

103. Reuter JD, Gomez DL, Wilson JH, et al. Systemic immune deficiency necessary for cytomegalovirus infection of the mature brain. *J Virol* 2004; 78: 1473–1487.

104. Bentz GL, Jarquin-Pardo M, Chan G, et al. Human cytomegalovirus (HCMV) infection of endothelial cells promotes naïve monocyte extravasation and transfer of productive virus to enhance hematogenous dissemination of HCMV. *J Virol* 2006; 80: 11539–11555.

105. Galat A. Peptidylprolyl cis/trans isomerases (immuno-

106. Harding MW, Handschumacher RE and Speicher DW. Isolation and amino acid sequence of cyclophilin. *J Biol Chem* 1986; 261: 8547–8555.

107. Sugita K, Ando M, Makino M, et al. Magnetic resonance imaging of the brain in congenital rubella virus and cytomegalovirus infections. *Neuroradiology* 1991; 33: 239–242.

108. Van Der Knaap M, Grondahl E and Lewensohn-Fuchs I. Congenital citomegalovirus infection: a retrospective diagnosis in a child with pachygyria. *Pediatr Neurol* 2000; 22: 407–408.

109. Harding MW, Handschumacher RE and Speicher DW. Pattern of white matter abnormalities at MR imaging: use of polymerase chain reaction testing of Guthrie cards to link pattern with congenital abnormality. *Pediatr Neurol* 2004; 30: 224–229.

110. Marks AR. Cyclophilin-A gene (PPIA) variation and its contribution to the risk of atherosclerosis. *Atherosclerosis* 2009; 209: 51–57.

111. Wang P and Heitman J. The cyclophilins. *Cell Mol Life Sci* 2006; 63: 2889–2900.

112. Fischer G, Wittmann-Liebold B, Lang K, et al. Cyclophilin and peptidyl-prolyl cis-trans isomerase are probably identical proteins. *Nature* 1989; 337: 476–478.

113. Waldmeier PC, Zimmermann K, Qian T, et al. Cyclophilin D as a drug target. *Curr Med Chem* 2003; 10: 1485–1506.

114. Hoffmann H and Schiene-Fischer C. Functional aspects of extracellular cyclophilins. *Biochim Biophys Acta* 2014; 1843: 721–735.

115. Galgiani MD, Morishima Y, Gallay PA, et al. Cyclophilin-A is bound through its peptidylprolyl
isomerase domain to the cytoplasmic dynein motor protein complex. *J Biol Chem* 2004; 279: 55754–55759.

135. Kim SH, Lessner SM, Sakurai Y, et al. Cyclophilin A as a novel biphasic mediator of endothelial activation and dysfunction. *Am J Pathol* 2004; 164: 1567–1574.

136. Syed F, Rycyzyn MA, Westgate L, et al. A novel and functional interaction between cyclophilin A and pro-lactin receptor. *Endocrine* 2003; 20: 83–90.

137. Brazin KN, Mallis RJ, Fulton DB, et al. Regulation of the tyrosine kinase Itk by the peptidyl-prolyl isomerase cyclophilin A. *Proc Natl Acad Sci USA* 2002; 99: 1899–1904.

138. Colgan J, Asmal M, Neagu M, et al. Cyclophilin A regulates TCR signal strength in CD4+ T cells via a proline-directed conformational switch in Itk. *Immunity* 2004; 21: 189–201.

139. Min L, Fulton DB and Andreotti AH. A case study of proline isomerization in cell signaling. *Front Biosci* 2005; 10: 385–397.

140. Ryffel B, Woerly G, Greiner B, et al. Distribution of the cyclosporine binding protein cyclophilin in human tissues. *Immunology* 1991; 72: 399–404.

141. Al-Bader MD and Al-Sarraf HA. Housekeeping gene expression during fetal brain development in the rat – validation by semi-quantitative RT-PCR. *Brain Res Dev Brain Res* 2005; 156: 38–45.

142. Song J, Lu YC, Yokoyama K, et al. Cyclophilin A is required for retinoic acid-induced neuronal differentiation in p19 cells. *J Biol Chem* 2004; 279: 24414–24419.

143. Nahreini P, Hovland AR, Kumar B, et al. Effects of altered cyclophilin A expression on growth and differentiation of human and mouse neuronal cells. *Cell Mol Neurobiol* 2001; 21: 65–79.

144. Boulos S, Meloni BP, Arthur PG, et al. Evidence that intracellular cyclophilin A and cyclophilin A,CD147 receptor-mediated ERK1/2 signalling can protect neurons against in vitro oxidative and ischemic injury. *Neurobiol Dis* 2007; 25: 54–64.

145. Halliday MR, Pomara N, Sagare AP, et al. Relationship between cyclophilin a levels and matrix metalloproteinase 9 activity in cerebrospinal fluid of cognitively normal apolipoprotein e4 carriers and blood-brain barrier 9 activity in cerebrospinal fluid of cognitively normal apolipoprotein e4 carriers and blood-brain barrier function and tissue preservation. *JAMA Neurol* 2013; 70: 1198–1200.

146. Redell JB, Zhao J and Dash PK. Acutely increased cyclophilin A expression after brain injury: a role in blood-brain barrier function and tissue preservation. *J Neurosci Res* 2007; 85: 1980–1988.

147. Seko Y, Fujimura T, Taka H, et al. Hypoxia followed by reoxygenation induces secrition of cyclophilin A from cultured rat cardiac myocytes. *Biochem Biophys Res Commun* 2004; 317: 162–168.

148. Bonfils C, Bec N, Larroque C, et al. Cyclophilin A as negative regulator of apoptosis by sequestering cytochrome c. *Biochem Biophys Res Commun* 2010; 393: 325–330.

149. Traber R, Kobel H, Looshi H-R, et al. [Melle4] cyclosporin, a novel natural cyclosporin with anti-HIV activity: structural elucidation, biosynthesis and biological properties. *Antivir Chem Chemother* 1994; 5: 331–339.

150. Kahan BD. Cyclosporine: a revolution in transplantation. *Transplant Proc* 1999; 31: 14S–15S.

151. Colombo D and Ammirati E. Cyclosporine in transplantation – a history of converging timelines. *J Biol Regul Homeost Agents* 2011; 25: 493–504.

152. Tedesco D and Haragms L. Cyclosporine: a review. *J Transplant* 2012; 2012: 230386.

153. Manna R, Verrecchia E, Fonnescu, et al. Cyclosporine A: good response for patients affected by autoimmune disorders and HCV infection? *Eur Rev Med Pharmacol Sci* 2009; 13: 63–69.

154. Feutrens G. The optimal use of cyclosporin A in autoimmune diseases. *J Autoimmun* 1992; 5: 183–195.

155. Fraser A, Veale DJ and Emery P. Cyclosporin treatment in psoriatic arthritis: a cause of severe leg pain. *Ann Rheum Dis* 2003; 62: 489.

156. Colombo MD, Cassano N, Bellia G, et al. Cyclosporine regimens in plaque psoriasis: an overview with special emphasis on dose, duration, and old and new treatment approaches. *Sci World J* 2013; 2013: 805705.

157. Hesselink DA, Baarsma GS, Kuipers RW, et al. Experience with cyclosporine in endogenous uveitis posterior. *Transplant Proc* 2004; 36: 372S–377S.

158. Hernandez-Martín A, Noguera-Morel L, Bernardino-Cuesta B, et al. Cyclosporine A for severe atopic dermatitis in children. Efficacy and safety in a retrospective study of 63 patients. *J Eur Acad Dermatol Venereol* 2017; 31: 837–842.

159. Liu J, Farmer JD, Lane WS, et al. Calcineurin is a common target of cyclophilin-cyclosporin A and FKBP-FK506 complexes. *Cell* 1991; 66: 807–815.

160. Hamawy MM. Molecular actions of calcineurin inhibitors. *Drug News Perspect* 2003; 16: 277–282.

161. Matsuda S, Moriguchi T, Koyasu S, et al. T lymphocyte activation signals for interleukin-2 production involve activation of MKK6-p38 and MKK7-SAPK/JNK signaling pathways sensitive to cyclosporin A and FK506 activation. *Front Biosci* 2005; 62: 489.

162. Breuder T, Hemenway CS, Movva NR, et al. Calcineurin is essential in cyclophilin-A- and FK506-sensitive yeast strains. *Proc Natl Acad Sci USA* 1994; 91: 5372–5376.

163. Foor F, Parent SA, Morin N, et al. Calcineurin mediates inhibition by FK506 and cyclosporin of recovery from alpha-factor arrest in yeast. *Nature* 1992; 360: 682–684.

164. Mattila PS, Ullman KS, Fiering S, et al. The actions of cyclosporin A and FK506 suggest a novel step in the activation of T lymphocytes. *J Biol Chem* 1998; 273: 12378–12382.

165. Breuder T, Hemenway CS, Movva NR, et al. Calcineurin is essential in cyclophilin-A- and FK506-sensitive yeast strains. *Proc Natl Acad Sci USA* 1994; 91: 5372–5376.

166. Sun S, Guo M, Zhang J, et al. Cyclophilin A (CypA) interacts with NF-κB subunit, p65/RelA, and
contributes to NF-κB activation signaling. *PLoS One* 2014; 9: e96211.

167. Metcalfe S, Alexander D and Turner J. FK506 and cyclosporin A each inhibit antigen-specific signaling in the T cell line 171 in the absence of a calcium signal. *Cell Immunol* 1994; 158: 46–58.

168. Su B, Jacinto E, Hibi M, et al. JNK is involved in signal integration during costimulation of T lymphocytes. *Cell* 1994; 77: 727–736.

169. Crabtree GR. Contingent genetic regulatory events in T lymphocyte activation. *Science* 1989; 243: 355–361.

170. Hogan PG, Chen L, Nardone J, et al. Transcriptional regulation by calcium, calcineurin, and NFAT. *Genes Dev* 2003; 17: 2205–2232.

171. Mason J and Moore LC. Indirect assessment of renal dysfunction in patients taking cyclosporin A for autoimmune diseases. *Br J Dermatol* 1990; 122: 79–84.

172. Taler SJ, Textor SC, Canzanello VJ, et al. Cyclosporin-induced hypertension: incidence, pathogenesis and management. *Drug Saf* 1999; 20: 437–449.

173. Nabel GJ. A transformed view of cyclosporine. *Nature* 1999; 397: 471–472.

174. Karin M. The regulation of AP-1 activity by mitogen-activated protein kinases. *J Biol Chem* 1995; 270: 16483–16486.

175. Blumer KJ and Johnson GL. Diversity in function and regulation of MAP kinase pathways. *Trends Biochem Sci* 1994; 19: 236–240.

176. Marshall CJ. Specificity of receptor tyrosine kinase signaling: transient versus sustained extracellular signal-regulated kinase activation. *Cell* 1995; 80: 179–185.

177. Nishida E and Gotoh Y. The MAP kinase cascade is essential for divergent signal transduction pathways. *Trends Biochem Sci* 1993; 18: 128–131.

178. Waskiewicz AJ. A, nd and Cooper JA. Mitogen and stress response pathways: MAP kinase cascades and phosphatase regulation in mammals and yeast. *Curr Opin Cell Biol* 1995; 7: 798–805.

179. Su B and Karin M. Mitogen-activated protein kinase cascades and regulation of gene expression. *Curr Opin Immunol* 1996; 8: 402–411.

180. Cargnello M and Roux PP. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. *Microbiol Mol Biol Rev* 2011; 75: 50–83.

181. Sánchez-Pérez I, Benitah SA, Martínez-Gomariz M, et al. Cell stress and MEKK1-mediated c-Jun activation modulate NFκB activity and cell viability. *Mol Cell* 2002; 13: 2933–2945.

182. Karin M and Delhase M. JNK or IKK, AP-1 or NF-kappaB, which are the targets for MEK kinase 1 action? *Proc Natl Acad Sci USA* 1998; 95: 9067–9069.

183. Pallet N, Thervet E and Anglicheau D. c-Jun-N-terminal kinase signaling is involved in cyclosporine-induced epithelial phenotypic changes. *J Transplant* 2012; 2012: 348604.

184. Du S, Hiramatsu N, Hayakawa K, et al. Suppression of NF-κB by cyclosporin A and tacrolimus (FK506) via induction of the C/EBP family: implication for unfolded protein response. *J Immunol* 2009; 182: 7201–7211.

185. Wu J, Motto DG, Koretzky GA, et al. Vav and SLP-76 interact and functionally cooperate in IL-2 gene activation. *Immunity* 1996; 4: 593–602.

186. Raab M, da Silva AJ, Findell PR, et al. Regulation of Vav-SLP-76 binding by ZAP-70 and its relevance to TCR zeta/CD3 induction of interleukin-2. *Immunity* 1997; 6: 155–164.

187. Tuosto L, Michel F and Acuto O. p95vav associates with tyrosine-phosphorylated SLP-76 in antigen-stimulated T cells. *J Exp Med* 1996; 184: 1161–1166.

188. Brecht S, Waetzig V, Hidding U, et al. FK506 protects against various immune responses and secondary degeneration following cerebral ischemia. *Anat Rec (Reg)* 2009; 292: 1993–2001.

189. Kumar S, Boehm J and Lee JC. p38 MAP kinases: key signalling molecules as therapeutic targets for inflammatory diseases. *Nat Rev Drug Discov* 2003; 2: 717–726.

190. Kaminska B and Swiatek-Machado K. Targeting signaling pathways with small molecules to treat autoimmune disorders. *Expert Rev Clin Immunol* 2008; 4: 93–112.

191. Sun Z, Arendt CW, Ellmeier W, et al. PKC-theta is required for TCR-induced NF-kappaB activation in mature but not immature T lymphocytes. *Nature* 2000; 404: 402–407.

192. Vincent F, Duquesnes N, Christov C, et al. Dual level of interactions between calcineurin and PKC-epsilon in cardiomyocyte stretch. *Cardiovasc Res* 2006; 71: 97–107.

193. Werlen G, Jacinto E, Xia Y, et al. Calcineurin preferentially synergizes with PKC-theta to activate JNK and IL-2 promoter in T lymphocytes. *EMBO J* 1998; 17: 3101–3111.

194. Bartz SR, Hohenwalter E, Hu MK, et al. Inhibition of human immunodeficiency virus replication by nonimmunosuppressive analogs of cyclosporin A. *Proc Natl Acad Sci USA* 1995; 92: 5381–5385.

195. Billich A, Hammerschmid F, Peichl P, et al. Mode of action of SDZ NIM 811, a nonimmunosuppressive cyclosporin A analog with activity against human immunodeficiency virus (HIV) type 1: interference with HIV protein-cyclophilin A interactions. *J Virol* 1995; 69: 2451–2461.

196. Wenger RM. Synthesis of cyclosporine and analogues: structural requirements for immunosuppressive activity. *Angew Chem Int Ed Engl* 1985; 24: 77–85.

197. Landriu I, Hanouille X, Bonachera F, et al. Structural basis for the non-immunosuppressive character of the cyclosporin A analogue Debio 025. *Biochemistry* 2010; 49: 4679–4686.

198. Grifflé LH, Bao W, Orsenigo R, et al. Interferon (IFN)-free alisporivir (DEB025) treatment in the VITAL-1 study has a more beneficial overall safety profile vs IFN containing treatment. *Hepatology* 2012; 56: 578A–579A.

199. Ma S, Boerner JE, TiongYip C, et al. NIM811, a cyclophilin inhibitor, exhibits potent in vitro activity against hepatitis C virus alone or in combination with alpha interferon. *Antimicrob Agents Chemother* 2006; 50: 2976–2982.

200. Hopkins S, Scorneaux B, Huang Z, et al. SCY-635, a novel nonimmunosuppressive analog of cyclosporine
that exhibits potent inhibition of hepatitis C virus RNA replication in vitro. *Antimicrob Agents Chemother* 2010; 54: 660–672.

201. Hopkins S and Gallay P. Cyclophilin inhibitors: an emerging class of therapeutics for the treatment of chronic hepatitis C infection. *Viruses* 2012; 4: 2558–2577.

202. Hopkins S, DiMassimo B, Rusnak P, et al. The cyclophilin inhibitor SCY-635 suppresses viral replication and induces endogenous interferons in patients with chronic HCV genotype 1 infection. *J Hepatol* 2012; 57: 47–54.

203. Jiang LJ, Liu S, Phan TU, et al. EDP-546, a potent and novel cyclophilin inhibitor with favorable preclinical pharmacokinetic and safety profiles. *Hepatology* 2012; 56: 1895.

204. Sawada M, Tsujii E, Morishita Y, et al. Preclinical evaluation of ASP5286, a novel cyclophilin inhibitor with potent anti-HCV activity. *Hepatology* 2012; 56: 1899.

205. Ahmed-Belkacem A, Colliandre L, Ahnou N, et al. New cyclophilin inhibitors unrelated to cyclosporine potently inhibit HCV replication and revert HCV-induced mitochondrial dysfunction. *Hepatology* 2012; 56: 1878.

206. Pemberton TJ and Kay JE. Cyclophilin sensitivity to sanglifehrin A can be correlated to the same specific tryptophan residue as cyclosporin A. *FEBS Lett* 2003; 555: 335–340.

207. Sanglier JJ, Quesniaux V, Fehr T, et al. Sanglifehrins A, B, C and D, novel cyclophilin-binding compounds isolated from *Streptomyces* sp. A92-308110. I. Taxonomy, fermentation, isolation and biological activity. *J Antibiot (Antibiot)* 1999; 52: 466–473.

208. Sedrani R, Kalen J, Martin Cabrejas LM, et al. Sanglifehrin-cyclophilin interaction: degradation work, synthetic macrocyclic analogues, X-ray crystal structure, and binding data. *J Am Chem Soc* 2003; 125: 3849–3859.

209. Zenke G, Strittmatter U, Fuchs S, et al. Sanglifehrin A, a novel cyclophilin-binding compound showing immuno-suppressive activity with a new mechanism of action. *J Immunol* 2001; 166: 7165–7171.

210. Clarke SJ, McStay GP and Halestrap AP. Sanglifehrin A acts as a potent inhibitor of the mitochondrial permeability transition and reperfusion injury of the heart by binding to cyclophilin-D at a different site from cyclosporin A. *J Biol Chem* 2002; 277: 34793–34799.

211. Chatterji U, Bobardt MD, Lim P, et al. Cyclophilin A-independent recruitment of NS5A and NS5B into hepatitis C virus replication complexes. *J Gen Virol* 2010; 91: 1189–1193.

212. Ciesek S, Steinmann E, Wedemeyer H, et al. Cyclosporine A inhibits hepatitis C virus nonstructural protein 2 through cyclophilin A. *Hepatology* 2009; 50: 1638–1645.

213. Fernandes F, Poole DS, Hoover S, et al. Sensitivity of hepatitis C virus to cyclosporine A depends on non-structural proteins NS5A and NS5B. *Hepatology* 2007; 46: 1026–1033.

214. Puyang X, Poulin DL, Mathy JE, et al. Mechanism of resistance of hepatitis C virus replicons to structurally distinct cyclophilin inhibitors. *Antimicrob Agents Chemother* 2010; 54: 1981–1987.

215. Robida JM, Nelson HB, Liu Z, et al. Characterization of hepatitis C virus subgenomic replicon resistance to cyclosporine in vitro. *J Virol* 2007; 81: 5829–5840.

216. Lindenbach BD, Evans MJ, Syder AJ, et al. Complete replication of hepatitis C virus in cell culture. *Science* 2005; 309: 623–626.

217. Lindenbach BD and Rice CM. Unravelling hepatitis C virus replication from genome to function. *Nature* 2005; 436: 933–938.

218. Hanouille X, Badillo A, Wieruszewski JM, et al. Hepatitis C virus NS5A protein is a substrate for the peptidyl-prolyl cis/trans isomerase activity of cyclophilins A and B. *J Biol Chem* 2009; 284: 13589–13601.

219. Gallay PA. Cyclophilin inhibitors: a novel class of promising host-targeting anti-HCV agents. *Immunol Rev* 2012; 52: 200–210.

220. Chatterji U, Bobardt M, Selvarajah S, et al. The isomerase active site of cyclophilin A is critical for hepatitis C virus replication. *J Biol Chem* 2009; 284: 16998–17005.

221. Yang F, Robotham JM, Nelson HB, et al. Cyclophilin A is an essential cofactor for hepatitis C virus infection and the principal mediator of cyclosporine resistance in vitro. *J Virol* 2008; 82: 5269–5278.

222. Appel N, Zayas M, Miller S, et al. Essential role of domain III of nonstructural protein 5A for hepatitis C virus infectious particle assembly. *PLoS Pathog* 2008; 4: e100035.

223. Hughes M, Griffin S and Harris M. Domain III of NS5A contributes to both RNA replication and assembly of hepatitis C virus particles. *J Gen Virol* 2009; 90: 1329–1334.

224. Tellinghuisen TL, Foss KL and Treadaway J. Regulation of hepatitis C virion production via phosphorylation of the NS5A protein. *PLoS Pathog* 2008; 4: e100032.

225. Kaul A, Stauffer S, Berger C, et al. Essential role of cyclophilin A for hepatitis C virus replication and virus production and possible link to polyprotein cleavage kinetics. *PLoS Pathog* 2009; 5: e1000546.

226. Davis WG, Blackwell JL, Shi PY, et al. Interaction between the cellular protein eEF1A and the 3'–terminal stem-loop of West Nile virus genomic RNA facilitates viral minus-strand RNA synthesis. *J Virol* 2007; 81: 10172–10187.

227. Emara MM, Liu H, Davis WG, et al. Mutation of mapped TIA-1/TIAR binding sites in the 3' terminal stem-loop of West Nile virus minus-strand RNA in an infectious clone negatively affects genomic RNA amplification. *J Virol* 2008; 82: 10657–10670.

228. Fernandes F, Ansari IU and Striker R. Cyclosporine inhibits a direct interaction between cyclophilins and hepatitis C NS5A. *PLoS One* 2010; 5: e9815.

229. Liu Z, Yang F, Robotham JM, et al. Critical role of cyclophilin A and its prolyl-peptidyl isomerase activity
in the structure and function of the hepatitis C virus replication complex. *J Virol* 2009; 83: 6554–6565.

230. Bouchard MJ, Puro RJ, Wang L, et al. Activation and inhibition of cellular calcium and tyrosine kinase signaling pathways identify targets of the HBx protein involved in hepatitis B virus replication. *J Virol* 2003; 77: 7713–7719.

231. Phillips S, Chokshi S, Riva A, et al. Alisporivir-induced inhibition of cellular cyclophilins disrupts hepatitis B virus (Hbv) replication in vitro and is synergistic in combination with direct antiviral targeting HBV-DNA polymerase. *J Hepatol* 2012; 56: S199–S200.

232. Tian X, Zhao C, Zhu H, et al. Hepatitis B virus (HBV) surface antigen interacts with and promotes cyclophilin A secretion: possible link to pathogenesis of HBV infection. *J Virol* 2010; 84: 3373–3381.

233. Chokshi S, Phillips S, Riva A, et al. OC-025 alisporivir inhibition of cellular cyclophilins disrupts hepatitis B virus (HBV) replication and this effect is further enhanced in combination with direct antiviral targeting HBV-DNA polymerase in vitro. *Gut* 2012; 61: A11.

234. Yan H, Zhong G, Xu G, et al. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. *Elife* 2012; 1: e00049.

235. Watashi K, Sluder A, Daito T, et al. Cyclosporin A and its analogs inhibit hepatitis B virus entry into cultured hepatocytes through targeting a membrane transporter, sodium taurocholate cotransporting polypeptide (NTCP). *Hepatology* 2014; 59: 1726–1737.

236. Nkongolo S, Ni Y, Lempp FA, et al. Cyclosporin A inhibits hepatitis B and hepatitis D virus entry by cyclophilin-independent interference with the NTCP receptor. *J Hepatol* 2014; 60: 723–731.

237. Nilsson J, Moss S, Coates N, et al. P1044 NVP018, a differential inhibitor of eukaryotic RNA polymerases. *Exp Cell Res* 1984; 151: 314–321.

238. Nakai M and Goto T. Ultrastructure and morphogenesis of human immunodeficiency virus. *J Electron Microsc (Tokyo)* 1996; 45: 247–257.

239. Auewarakul P, Wachararornin P, Srichatrapimuk S, et al. Uncoating of HIV-1 requires cellular activation. *Virology* 2005; 337: 93–101.

240. Forshey BM, von Schwedler U, Sundquist WI, et al. Formation of a human immunodeficiency virus type 1 core of optimal stability is crucial for viral replication. *J Virol* 2002; 76: 5667–5677.

241. Stremlau M, Song B, Javanbakht H, et al. Cyclophilin A: an auxiliary but not necessary cofactor for TRIM5alpha restriction of HIV-1. *Virology* 2006; 351: 112–120.

242. Dietrich EA, Jones-Engel L and Hu S-L. Evolution of the antiretroviral restriction factor TRIMCyp in old world primates. *PLoS One* 2010; 5: e14019.

243. Diaz-Griffero F, Kar A, Lee M, et al. Comparative requirements for the restriction of retrovirus infection by TRIM5alpha and TRIMCyp. *Virology* 2007; 369: 400–410.

244. Diaz-Griffero F, Vangreagraff N, Li Y, et al. Requirements for capsid-binding and an effector function in TRIMCyp-mediated restriction of HIV-1. *Virology* 2006; 351: 404–419.

245. Nisole S, Lynch C, Stoye JP, et al. A Trim5-cyclophilin A fusion protein found in owl monkey kidney cells can restrict HIV-1. *Proc Natl Acad Sci USA* 2004; 101: 13324–13328.

246. Rosenwirth B, Billich A, Datema R, et al. Inhibition of human immunodeficiency virus type 1 replication by SDZ NIM 811, a nonimmunosuppressive cyclosporine analog. *Antimicrob Agents Chemother* 1994; 38: 1763–1772.

247. Towers GJ, Hatziioannou T, Cowan S, et al. Cyclophilin A modulates the sensitivity of HIV-1 to host restriction factors. *Nat Med* 2003; 9: 1138–1143.

248. Luban J, Bossoit KL, Franke EK, et al. Human immunodeficiency virus type 1 Gag protein binds to cyclophilins A and B. *Cell* 1993; 73: 1067–1078.

249. Franke EK, Yuan HE and Luban J. Specific incorporation of cyclophilin A into HIV-1 virions. *Nature* 1994; 372: 359–362.

250. Thali M, Bukovsky A, Kondo E, et al. Functional association of cyclophilin A with HIV-1 virions. *Nature* 1994; 372: 363–365.

251. Strebel K, Luban J and Jeang KT. Human cellular restriction factors that target HIV-1 replication. *BMC Med* 2009; 7: 48.

252. Ylinen LM, Schaller T, Price A, et al. Cyclophilin A levels dictate infection efficiency of human immunodeficiency virus type 1 capsid escape mutants A92E and G94D. *J Virol* 2009; 83: 2044–2047.

253. Yasuda DA, Eisenmesser EZ, Pochapsky S, et al. Catalysis of cis/trans isomerization in native HIV-1 capsid by human cyclophilin A. *Proc Natl Acad Sci USA* 2002; 99: 5247–5252.

254. Schaller T, Ocwieja KE, Rasaiyaah J, et al. HIV-1 capsid-cyclophilin interactions determine nuclear
import pathway, integration targeting and replication efficiency. *PLoS Pathog* 2011; 7: e1002439.

261. Shah VB, Shi J, Hout DR, et al. The host proteins transportin SR2/TNPO3 and cyclophilin A exert opposing effects on HIV-1 uncoating. *J Virol* 2013; 87: 422–432.

262. Manel N, Hogstad B, Wang Y, et al. A cryptic sensor for HIV-1 activates antiviral innate immunity in dendritic cells. *Nature* 2010; 467: 214–217.

263. Gamble TR, Vajdos FF, Yoo S, et al. Crystal structure of human cyclophilin A bound to the amino-terminal domain of HIV-1 capsid. *Cell* 1996; 87: 1285–1294.

264. Gatanaga H, Das D, Suzuki Y, et al. Altered HIV-1 Gag protein interactions with cyclophilin A (CypA) on the acquisition of H219Q and H219P substitutions in the CypA binding loop. *J Biol Chem* 2006; 281: 1241–1250.

265. Braaten D, Aberham C, Franke EK, et al. Cyclosporine A-resistant human immunodeficiency virus type 1 mutants demonstrate that Gag encodes the functional target of cyclophilin A. *J Virol* 1996; 70: 5170–5176.

266. Sokolskaja E, Sayah DM and Luban J. Target cell cyclophilin A modulates human immunodeficiency virus type 1 infectivity. *J Virol* 2004; 78: 12800–12808.

267. Luo C, Luo H, Zheng S, et al. Nucleocapsid protein of SARS coronavirus tightly binds to human cyclophilin A. *Biochem Biophys Res Commun* 2004; 321: 557–565.

268. Almazan F, Galan C and Enjuanes L. The nucleoprotein is required for efficient coronavirus genome replication. *J Virol* 2004; 78: 12683–12688.

269. Schelle B, Karl N, Ludewig B, et al. Nucleocapsid protein expression facilitates coronavirus replication. *Adv Exp Med Biol* 2006; 581: 43–48.

270. van der Meer Y, Snijder EJ, Dobbe JC, et al. Localization of mouse hepatitis virus nonstructural proteins and RNA synthesis indicates a role for late endosomes in viral replication. *J Virol* 1999; 73: 7641–7657.

271. Kabanova A, Marcandulli J, Zhou T, et al. Platelet-derived growth factor-α receptor is the cellular receptor for human cytomegalovirus gHgLgO trimer. *Nat Microbiol* 2016; 1: 16082, Article.

272. Feire AL, Roy RM, Manley K, et al. The glycoprotein B disintegrin-like domain binds beta 1 integrin to mediate cytomegalovirus entry. *J Virol* 2010; 84: 10026–10037.

273. Kim JH, Collins-Mcmillen D, Buehler JC, et al. HCMV requires EGFR signaling to enter and initiate the early steps in the establishment of latency in CD34+ human progenitor cells. *J Virol* 2017; 91(5): 1–21. DOI: 10.1128/jvi.01206-16.

274. Schlessinger J. Cell signaling by receptor tyrosine kinases. *Cell* 2000; 103: 211–225.

275. Fortunato EA, McElroy AK, Sanchez I, et al. Exploitation of cellular signaling and regulatory pathways by human cytomegalovirus. *Trends Microbiol* 2000; 8: 111–119.

276. Cojohari O, Peppenelli MA and Chan GC. Human cytomegalovirus induces an atypical activation of Akt to stimulate the survival of short-lived monocytes. *J Virol* 2016; 90: 6443–6452.

277. Peppenelli MA, Arend KC, Cojohari O, et al. Human cytomegalovirus stimulates the synthesis of select Akt-dependent antiapoptotic proteins during viral entry to promote survival of infected monocytes. *J Virol* 2016; 90: 3138–3147.

278. Sharon-Friling R, Goodhouse J, Colberg-Poley AM, et al. Human cytomegalovirus pUL37x1 induces the release of endoplasmic reticulum calcium stores. *Proc Natl Acad Sci USA* 2006; 103: 19117–19122.

279. McArdle J, Moorman NJ and Munger J. HCMV targets the metabolic stress response through activation of AMPK whose activity is important for viral replication. *PLoS Pathog* 2012; 8: e1002502.

280. Sharon-Friling R and Shenk T. Human cytomegalovirus pUL37x1-induced calcium flux activates PKCα, inducing altered cell shape and accumulation of cytoplasmic vesicles. *Proc Natl Acad Sci* 2014; 111: E1140–E1148.

281. Wang D and Shenk T. Human cytomegalovirus virion protein complex required for epithelial and endothelial cell tropism. *Proc Natl Acad Sci USA* 2005; 102: 18153–18158.

282. Tseliou M, Al-Qahtani A, Alarifi S, et al. The role of RhoA, RhoB and RhoC GTPases in Cell morphology, proliferation and migration in human cytomegalovirus (HCMV) infected glioblastoma cells. *Cell Physiol Biochem* 2016; 38: 94–109.

283. Johnson RA, Wang X, Ma XL, et al. Human cytomegalovirus up-regulates the phosphatidylinositol 3-kinase (PI3-K) pathway: inhibition of PI3-K activity inhibits viral replication and virus-induced signaling. *J Virol* 2001; 75: 6022–6032.

284. Terry LJ, Vastag L, Rabinowitz JD, et al. Human kinome profiling identifies a requirement for AMP-activated protein kinase during human cytomegalovirus infection. *Proc Natl Acad Sci USA* 2012; 109: 3071–3076.

285. Johnson RA, Huong SM and Huang ES. Activation of the mitogen-activated protein kinase p38 by human cytomegalovirus infection through two distinct pathways: a novel mechanism for activation of p38. *J Virol* 2000; 74: 1158–1167.

286. Cherrington JM and Mocarski ES. Human cytomegalovirus IE1 transactivates the alpha promoter-enhancer via an 18-base-pair repeat element. *J Virol* 1989; 63: 1435–1440.

287. Krause E, de Graaf M, Fliss PM, et al. Murine cytomegalovirus virion-associated protein M45 mediates rapid NF-kB activation after infection. *J Virol* 2014; 88: 9963–9975.

288. Brown AJ, Sweeney B, Mainwaring DO, et al. NF-kappaB, CRE and YY1 elements are key functional regulators of CMV promoter-driven transient gene expression in CHO cells. *Biotechnol J* 2015; 10: 1019–1028.

289. Yurochko AD, Mayo MW, Poma EE, et al. Induction of the transcription factor Sp1 during human cytomegalovirus infection mediates upregulation of the p65 and
p105/p50 NF-kappaB promoters. J Virol 1997; 71: 4638–4648.

290. Luu P and Flores O. Binding of SPI to the immediate-early protein-responsive element of the human cytomegalovirus DNA polymerase promoter. J Virol 1997; 71: 6683–6691.

291. DeFilippis VR, Sali T, Alvarado D, et al. Activation of the interferon response by human cytomegalovirus occurs via cytoplasmic double-stranded DNA but not glycoprotein B. J Virol 2010; 84: 8913–8925.

292. Wang T, Qian D, Hu M, et al. Human cytomegalovirus inhibits apoptosis by regulating the activating transcription factor 5 signaling pathway in human malignant glioma cells. Oncol Lett 2014; 8: 1051–1057.

293. Liu R, Baillie J, Sissons JG, et al. The transcription factor YY1 binds to negative regulatory elements in the human cytomegalovirus major immediate early enhancer/promoter and mediates repression in non-permissive cells. Nucl Acids Res 1994; 22: 2453–2459.

294. Lubon H, Ghazal P, Hennighausen L, et al. Cell-specific activity of the modulator region in the human cytomegalovirus major immediate-early gene. Mol Cell Biol 1989; 9: 1342–1345.

295. Meier JL and Stinski MF. Effect of a modulator deletion on transcription of the human cytomegalovirus major immediate-early genes in infected undifferentiated and differentiated cells. J Virol 1997; 71: 1246–1255.

296. Stern M, Elsasser H, Hunger G, et al. The number of activating KIR genes inversely correlates with the rate of CMV infection/reactivation in kidney transplant recipients. Am J Transplant 2008; 8: 1312–1317.

297. Zhang XY, Inamdar NM, Supakar PC, et al. Three MDBP sites in the immediate-early enhancer-promoter region of human cytomegalovirus. Virology 1991; 182: 865–869.

298. Gustems M, Borst E, Benedict CA, et al. Regulation of the transcription and replication cycle of human cytomegalovirus is insensitive to genetic elimination of the cognate NF-kappaB binding sites in the enhancer. J Virol 2006; 80: 9899–9904.

299. Thomas MJ and Seto E. Unlocking the mechanisms of transcription factor YY1: are chromatin modifying enzymes the key? Gene 1999; 236: 197–208.

300. Wright E, Bain M, Teague L, et al. Ets-2 repressor factor recruits histone deacetylase to silence human cytomegalovirus immediate-early gene expression in non-permissive cells. J Gen Virol 2005; 86: 535–544.

301. Jarvis MA, Borton JA, Keech AM, et al. Human cytomegalovirus attenuates interleukin-1beta and tumor necrosis factor alpha proinflammatory signaling by inhibition of NF-kappaB activation. J Virol 2006; 80: 5588–5598.

302. Taylor RT and Bresnahan WA. Human cytomegalovirus IE86 attenuates virus- and tumor necrosis factor alpha-induced NFkappaB-dependent gene expression. J Virol 2006; 80: 10763–10771.

303. Ioudinova E, Arcangeloletti MC, Rynditch A, et al. Control of human cytomegalovirus gene expression by differential histone modifications during lytic and latent infection of a monocytic cell line. Gene 2006; 384: 120–128.

304. Murphy E, Yu D, Grimwood J, et al. Coding potential of laboratory and clinical strains of human cytomegalovirus. Proc Natl Acad Sci USA 2003; 100: 14976–14981.

305. Sinclair J. Chromatin structure regulates human cytomegalovirus gene expression during latency, reactivation and lytic infection. Biochim Biophys Acta 2010; 1799: 286–295.

306. Murphy JC, Fischle W, Verdin E, et al. Control of cytomegalovirus lytic gene expression by histone acetylation. EMBO J 2002; 21: 1112–1120.

307. O’Connor CM, Nukui M, Gurova KV, et al. Inhibition of the FACT complex reduces transcription from the human cytomegalovirus major immediate early promoter in models of lytic and latent replication. J Virol 2016; 90: 4249–4253.

308. Mocarski ES and Courcelle CT. Cytomegaloviruses and their replication. In: Knipe DM and Howley PM (ed.) Fields virology. 4th ed. Boston: Lippincott Williams & Wilkins, 2001, pp. 2629–2673.

309. Bagga S and Bouchard MJ. Cell cycle regulation during viral infection. Methods Mol Biol 2014; 1170: 165–227.

310. Wiebusch L, Neuwirth A, Grabenhenrich L, et al. Cell cycle-independent expression of immediate-early gene 3 results in G1 and G2 arrest in murine cytomegalovirus-infected cells. J Virol 2008; 82: 10188–10198.

311. Bogdanow B, Weisbach H, von Einem J, et al. Human cytomegalovirus tegument protein pp150 acts as a cyclin A2-CDK-dependent sensor of the host cell cycle and differentiation state. Proc Natl Acad Sci USA 2013; 110: 17510–17515.

312. Hwang E-S, Zhang Z, Cai H, et al. Human cytomegalovirus IE1-72 protein interacts with p53 and inhibits p53-dependent transactivation by a mechanism different from that of IE2-86 protein. J Virol 2009; 83: 12388–12398.

313. Singh M, Krajewski M, Mikolajka A, et al. Molecular determinants for the complex formation between the retinoblastoma protein and LXCXE sequences. J Biol Chem 2005; 280: 37868–37876.

314. Kalejta RF and Shenk T. Manipulation of the cell cycle by human cytomegalovirus. Front Biosci 2002; 7: d295–d306.

315. Kalejta RF. Tegument proteins of human cytomegalovirus. Microbiol Mol Biol Rev 2008; 72: 249–265, table of contents.

316. Henley SA and Dick FA. The retinoblastoma family of proteins and their regulatory functions in the mamma
cell division cycle. Cell Div 2012; 7: 10.

317. Burkhart DL, Wirt SE, Zmoos A-F, et al. Tandem E2F binding sites in the promoter of the p107 cell cycle regulator control p107 expression and its cellular functions. PLoS Genet 2010; 6: e1001003.

318. Zhang J and Herscovitz H. Nascent lipidated apolipoprotein B is transported to the Golgi as an incompletely folded intermediate as probed by its association with network of endoplasmic reticulum molecular
chaperones, GRP94, ERp72, BiP, calreticulin, and cyclophilin B. J Biol Chem 2003; 278: 7459–7468.

319 Kuny CV, Chinchilla K, Culbertson MR, et al. Cyclin-dependent kinase-like function is shared by the beta- and gamma-subset of the conserved herpesvirus protein kinases. PLoS Pathog 2010; 6: e1001092.

320 Chen Z, Knutson E, Wang S, et al. Stabilization of p53 in human cytomegalovirus-initiated cells is associated with sequestration of HDM2 and decreased p53 ubiquitination. J Biol Chem 2007; 282: 29284–29295.

321 Savaryn JP, Reitsma JM, Bigley TM, et al. Human cytomegalovirus pUL29/28 and pUL38 repression of p53-regulated p21CIP1 and caspase 1 promoters during infection. J Virol 2013; 87: 2463–2474.

322 Speir E, Modali R, Huang ES, et al. Potential role of human cytomegalovirus and p53 interaction in coronary restenosis. Science 1994; 265: 391–394.

323 Muganda P, Carrasco R and Qian QB. The human cytomegalovirus IE2 86 kDa protein elevates p53 levels and transactivates the p53 promoter in human fibroblasts. 1998; 44(2): 321–331.

324 Yu Y and Alwine JC. Human cytomegalovirus major immediate-early proteins and simian virus 40 large T antigen can inhibit apoptosis through activation of the phosphatidylinositol 3’-OH kinase pathway and the cellular kinase Akt. J Virol 2002; 76: 3731–3738.

325 Ji WT and Liu HJ. P13K-Akt signaling and viral infection. Recent Pat Biotechnol 2008; 2: 218–226.

326 Goldmacher VS, Bartle LM, Skaletskaya A, et al. A cytomegalovirus-encoded mitochondria-localized inhibitor of apoptosis structurally unrelated to Bcl-2. Proc Natl Acad Sci USA 1999; 96: 12536–12541.

327 Oduro JD, Uecker R, Hagemeier C, et al. Inhibition of human cytomegalovirus immediate-early gene expression by cyclin A2-dependent kinase activity. J Virol 2012; 86: 9369–9383.

328 Zydek M, Hagemeier C and Wiebusch L. Cyclin-dependent kinase activity controls the onset of the HCMV lytic cycle. PLoS Pathog 2010; 6: e1001096.

329 Sanchez V, McElroy AK, Yen J, et al. Cyclin-dependent kinase activity is required at early times for accurate processing and accumulation of the human cytomegalovirus UL122-123 and UL37 immediate-early transcripts and at later times for virus production. J Virol 2004; 78: 11219–11232.

330 Lutichau HR. The cytomegalovirus UL146 gene product vCXCL1 targets both CXCR1 and CXCR2 as an agonist. J Biol Chem 2010; 285: 9137–9146.

331 Kobayashi Y. The role of chemokines in neutrophil biology. Front Biosci 2008; 13: 2400–2407.

332 Costa H, Nascimento R, Sinclair J, et al. Human cytomegalovirus gene UL76 induces IL-8 expression through activation of the DNA damage response. PLoS Pathog 2013; 9: e1003609.

333 Neote K, DiGregorio D, Mak JY, et al. Molecular cloning, functional expression, and signaling characteristics of a CC chemokine receptor. Cell 1993; 72: 415–425.

334 Lee S, Chung YH and Lee C. US28, a virally-encoded GPCR as an antiviral target for human cytomegalovirus infection. Biomet Ther (Seoul) 2017; 25: 69–79.

335 Vomask J, Nelson JA and Streblow DN. Human cytomegalovirus US28: a functionally selective chemokine binding receptor. Infect Disord Drug Targets 2009; 9: 548–556.

336 Chee MS, Satchwell SC, Preddie E, et al. Human cytomegalovirus encodes three G protein-coupled receptor homologues. Nature 1990; 344: 774–777.

337 Humby MS and O’Connor CM. Human cytomegalovirus US28 is important for latent infection of hematopoietic progenitor cells. J Virol 2016; 90: 2959–2970.

338 Mazeron MC. Leukocyte depletion and infection by cytomegalovirus. Transfus Clin Biol 2000; 7: 31s–35s.

339 Sherrill JD, Stropes MP, Schneider OD, et al. Activation of intracellular signaling pathways by the murine cytomegalovirus G protein-coupled receptor M33 occurs via PLC-[beta]/PKC-dependent and -independent mechanisms. J Virol 2009; 83: 8141–8152.

340 de Munnik SM, Smit MJ, Leurs R, et al. Modulation of cellular signaling by herpesvirus-encoded G protein-coupled receptors. Front Pharmacol 2015; 6: 40. Review.

341 Streblow DN, Soderberg-Naucler C, Vieira J, et al. The human cytomegalovirus chemokine receptor US28 mediates vascular smooth muscle cell migration. Cell 1999; 99: 511–520.

342 Browne EP, Wing B, Coleman D, et al. Altered cellular mRNA levels in human cytomegalovirus-infected fibroblasts: viral block to the accumulation of antiviral mRNAs. J Virol 2001; 75: 12319–12330.

343 Chew T, Noyce R, Collins SE, et al. Characterization of the interferon regulatory factor 3-mediated antiviral response in a cell line deficient for IFN production. Mol Immunol 2009; 46: 393–399.

344 Marshall EE and Geballe AP. Multifaceted evasion of the interferon response by cytomegalovirus. J Interferon Cytokine Res 2009; 29: 609–619.

345 Miller DM, Rahill BM, Boss JM, et al. Human cytomegalovirus inhibits major histocompatibility complex class II expression by disruption of the Jak/Stat pathway. J Exp Med 1998; 187: 675–683.

346 Miller DM, Zhang Y, Rahill BM, et al. Human cytomegalovirus inhibits IFN-alpha-stimulated antiviral and immunoregulatory responses by blocking multiple levels of IFN-alpha signal transduction. J Immunol 1999; 162: 6107–6113.

347 Browne EP and Shenk T. Human cytomegalovirus UL83-coded pp65 virion protein inhibits antiviral gene expression in infected cells. Proc Natl Acad Sci USA 2003; 100: 11439–11444.

348 McSharry BP, Forbes SK, Avdic S, et al. Abrogation of the interferon response promotes more efficient human cytomegalovirus replication. J Virol 2015; 89: 1479–1483.

349 Chang WL, Barry PA, Szubin R, et al. Human cytomegalovirus suppresses type I interferon secretion by plasmacytoid dendritic cells through its interleukin 10 homolog. Virology 2009; 390: 330–337.
350. Hancock MH, Hook LM, Mitchell J, et al. Human cytomegalovirus microRNAs miR-US5-1 and miR-UL112-3p block proinflammatory cytokine production in response to NF-κB-activating factors through direct downregulation of IKKα and IKKβ. MBio 2017; 8(2): 1-19. DOI: 10.1128/mBio.00109-17.

351. Montag C, Wagner J, Gruska I, et al. Human cytomegalovirus blocks tumor necrosis factor alpha- and interleukin-1β-mediated NF-κB signaling. J Virol 2006; 80: 11686–11698.

352. Hartono C, Muthukumar T and Suthanthiran M. Immunosuppressive drug therapy. Cold Spring Harbor Perspect Med 2013; 3: a015487.

353. Hornef MW, Bein G, Fricke L, et al. Coincidence of Epstein-Barr virus reactivation, cytomegalovirus infection, and rejection episodes in renal transplant recipients. Transplantation 1995; 60: 474–480.

354. Scheinberg P, Fischer SH, Li L, et al. Distinct EBV and CMV reactivation patterns following antibody-based immunosuppressive regimens in patients with severe aplastic anemia. Blood 2007; 109: 3219–3224.

355. Ogata M, Satou T, Kawano R, et al. High incidence of Epstein-Barr virus reactivation, cytomegalovirus, human herpesvirus-6, and Epstein-Barr virus reactivation in patients receiving cytotoxic chemotherapy for adult T cell leukemia. J Med Virol 2011; 83: 702–709.

356. Jin ZG, Lungu AO, Xie L, et al. Cyclophilin A is a proinflammatory cytokine that activates endothelial cells. Arterioscler Thromb Vasc Biol 2004; 24: 1186–1191.

357. Dutta D, Barr VA, Akpan I, et al. Recruitment of calcineurin to the TCR positively regulates T cell activation. Nat Immunol 2017; 18: 196–204. Article.

358. Kreideweis S, Ahlers C, Nordheim A, et al. Ca2+-induced p38/SAPK signalling inhibited by the immunosuppressant cyclosporin A in human peripheral blood mononuclear cells. Eur J Biochem 1999; 265: 1075–1084.

359. Rodova M, Jayini R, Singasani R, et al. CMV promoter is repressed by p53 and activated by JNK pathway. Plasmid 2013; 69: 223–230.

360. Kawasaki H, Mocarski ES, Kosugi I, et al. Cyclosporine inhibits mouse cytomegalovirus infection via a cyclophilin-dependent pathway specifically in neural stem/progenitor cells. J Virol 2007; 81: 9013–9023.

361. Keyes LR, Bego MG, Soland M, et al. Cyclophilin A is required for efficient human cytomegalovirus DNA replication and reactivation. J Gen Virol 2012; 93: 722–732.

362. Seizer P, Gawaz M and May AE. Cyclophilin A and EMMPRIN (CD147) in cardiovascular diseases. Cardiovasc Res 2014; 102: 17–23.

363. Compton T, Kurt-Jones EA, Boehme KW, et al. Human cytomegalovirus envelope glycoproteins B and H are necessary for TLR2 activation in permissive cells. J Immunol 2006; 177: 7094–7102.

364. Boehme KW, Guerrero M and Compton T. Human cytomegalovirus envelope glycoproteins B and H are necessary for TLR2 activation in permissive cells. J Virol 2003; 77: 4588–4596.

365. Boehme KW, Singh J, Perry ST, et al. Human cytomegalovirus elicits a coordinated cellular antiviral response via envelope glycoprotein B. J Virol 2004; 78: 1202–1211.

366. Wen Y and Liu P. Interferon successfully inhibited refractory cytomegalovirus infection and resulted in CD4+ T-cells increase in a patient with AIDS. HIV Clin Trials 2011; 12: 118–120.

367. Emodi G, O’Reilly R, Muller A, et al. Effect of human exogenous leukocyte interferon in cytomegalovirus infections. J Infect Dis 1976; 133: A199–A204.

368. Taylor RT and Bresnahan WA. Human cytomegalovirus immediate-early 2 gene expression blocks virus-induced beta interferon production. J Virol 2005; 79: 3873–3877.

369. Biswas C, Zhang Y, DeCastro R, et al. The human tumor cell-derived collagenase stimulatory factor (renamed EMMPRIN) is a member of the immunoglobulin superfamily. Cancer Res 1995; 55: 434–439.

370. Arora K, Gwinn WM, Bower MA, et al. Extracellular cyclophilins contribute to the regulation of inflammatory responses. J Immunol 2005; 175: 517–522.

371. Muramatsu T. Basigin (CD147), a multifunctional transmembrane glycoprotein with various binding partners. J Biochem 2016; 159: 481–490.

372. Xiao J, Song X, Deng J, et al. Inhibition of cyclophilin A suppresses H2O2-enhanced replication of HCMV through the p38 MAPK signaling pathway. FEBS Open Bio 2016; 6: 961–971.

373. Song F, Zhang X, Ren XB, et al. Cyclophilin A (CyPA) induces chemotaxis independent of its peptidylprolyl cis-trans isomerase activity: direct binding between CyPA and the ectodomain of CD147. J Biol Chem 2011; 286: 8197–8203.

374. Chen J, Xia S, Yang X, et al. Human cytomegalovirus encoded miR-US5-1-5p attenuates CD147/EMMPRIN-mediated early antiviral response. Viruses 2017; 9(365): 1–17. DOI: 10.3390/v9120365.

375. Chang WL and Barry PA. Attenuation of innate immunity by cytomegalovirus IL-10 establishes a long-term deficit of adaptive antiviral immunity. Proc Natl Acad Sci USA 2010; 107: 22647–22652.

376. Cai J, Chen Y, Seth S, et al. Inhibition of influenza virus infection by glutathione. Free Radic Biol Med 2003; 34: 928–936.

377. Staal FJ, Roederer M, Herzenberg LA, et al. Intracellular thiols regulate activation of nuclear factor kappa B and transcription of human immunodeficiency virus. Proc Natl Acad Sci USA 1990; 87: 9943–9947.

378. Paracha UZ, Fatima K, Alqahtani M, et al. Oxidative stress and hepatitis C virus. Virol J 2013; 10: 251.

379. An P, Wang LH, Hutcheson-Dilks H, et al. Regulatory polymorphisms in the cyclophilin A gene, PPIA, accelerate progression to AIDS. PLoS Pathog 2007; 3: e88.

380. van de Berg PJ, Heutink KM, Raabe R, et al. Human cytomegalovirus induces systemic immune activation characterized by a type 1 cytokine signature. J Infect Dis 2010; 202: 690–699.
381. Martin-Blanco E. p38 MAPK signalling cascades: ancient roles and new functions. *Bioessays* 2000; 22: 637–645.

382. Price MA, Cruzalegui FH and Treisman R. The p38 and ERK MAP kinase pathways cooperate to activate ternary complex factors and c-fos transcription in response to UV light. *EMBO J* 1996; 15: 6552–6563.

383. Rolli M, Kotlyarov A, Sakamoto KM, et al. Stress-induced stimulation of early growth response gene-1 by p38/stress-activated protein kinase 2 is mediated by a cAMP-responsive promoter element in a MAPKAP kinase 2-independent manner. *J Biol Chem* 1999; 274: 19559–19564.

384. Whitmarsh AJ, Shore P, Sharrocks AD, et al. Integration of MAP kinase signal transduction pathways at the serum response element. *Science* 1995; 269: 403–407.

385. Whitmarsh AJ, Yang SH, Su MS, et al. Role of p38 and JNK mitogen-activated protein kinases in the activation of ternary complex factors. *Mol Cell Biol* 1997; 17: 2360–2371.

386. Widmann C, Gibson S, Jarpe MB, et al. Mitogen-activated protein kinase: conservation of a three-kinase module from yeast to human. *Physiol Rev* 1999; 79: 143–180.

387. Fortunato EA and Spector DH. Regulation of human cytomegalovirus gene expression. *Adv Virus Res* 1999; 54: 61–128.

388. Harel NY and Alwine JC. Phosphorylation of the human cytomegalovirus 86-kilodalton immediate-early protein IE2. *J Virol* 1998; 72: 5481–5492.

389. Johnson RA, Ma XL, Yurochko AD, et al. The role of MKK1/2 kinase activity in human cytomegalovirus infection. *J Gen Virol* 2001; 82: 493–497.

390. Rodems SM and Spector DH. Extracellular signal-regulated kinase activity is sustained early during human cytomegalovirus infection. *J Virol* 1998; 72: 9173–9180.

391. Roy S and Arav-Boger R. New cell-signaling pathways for controlling cytomegalovirus replication. *Am J Transplant* 2014; 14: 1249–1258.

392. Chen J and Stinski MF. Activation of transcription of the human cytomegalovirus early UL4 promoter by the Eqs transcription factor binding element. *J Virol* 2000; 74: 9845–9857.

393. Dwarkanath RS, Clark CL, McElroy AK, et al. The use of recombinant baculoviruses for sustained expression of human cytomegalovirus immediate early proteins in fibroblasts. *Virology* 2001; 284: 297–307.

394. Marchini A, Liu H and Zhu H. Human cytomegalovirus with IE-2 (UL122) deleted fails to express early lytic genes. *J Virol* 2001; 75: 1870–1878.

395. Spector DH. Activation and regulation of human cytomegalovirus early genes. *Intervirolgy* 1996; 39: 361–377.

396. Bryant LA, Mixon P, Davidson M, et al. The human cytomegalovirus 86-kilodalton major immediate-early protein interacts physically and functionally with histone acetyltransferase P/CAF. *J Virol* 2000; 74: 7230–7237.

397. Lang D, Gebert S, Arlt H, et al. Functional interaction between the human cytomegalovirus 86-kilodalton IE2 protein and the cellular transcription factor CREB. *J Virol* 1995; 69: 6030–6037.

398. Lukac DM, Manuppello JR and Alwine JC. Transcriptional activation by the human cytomegalovirus immediate-early proteins: requirements for simple promoter structures and interactions with multiple components of the transcription complex. *J Virol* 1994; 68: 5184–5193.

399. Scully AL, Sommer MH, Schwartz R, et al. The human cytomegalovirus IE2 86-kilodalton protein interacts with an early gene promoter via site-specific DNA binding and protein-protein associations. *J Virol* 1995; 69: 6533–6540.

400. Gewurz BE, Gaudet R, Tortorella D, et al. Antigen presentation subverted: structure of the human cytomegalovirus protein US2 bound to the class I molecule HLA-A2. *Proc Natl Acad Sci USA* 2001; 98: 6794–6799.

401. Thilo C, Berglund P, Applequist SE, et al. Dissection of the interaction of the human cytomegalovirus-derived US2 protein with major histocompatibility complex class I molecules: prominent role of a single arginine residue in human leukocyte antigen-A2. *J Biol Chem* 2006; 281: 8950–8957.

402. Hanley PJ and Bollard CM. Controlling cytomegalovirus: helping the immune system take the lead. *Viruses* 2014; 6: 2242–2258.

403. Matsuda S, Shibasaki F, Takehana K, et al. Two distinct action mechanisms of immunophilin-ligand complexes for the blockade of T-cell activation. *EMBO Rep* 2000; 1: 428–434.

404. Sun S, Wang Q, Giang A, et al. Knockdown of CypA inhibits interleukin-8 (IL-8) and IL-8-mediated proliferation and tumor growth of glioblastoma cells through down-regulated NF-κB. *J Neurooncol* 2011; 101: 1–14.

405. Bale JFJ, Kealey GP, Ebelhack CL, et al. Cytomegalovirus infection in a cyclosporine-treated burn patient: case report. *J Trauma Acute Care Surg* 1992; 32: 263–267.

406. La Rosa C and Diamond DJ. The immune response to human CMV. *Future Virol* 2012; 7: 279–293.

407. Westman G, Berghlund D, Widén J, et al. Increased inflammatory response in cytomegalovirus seropositive patients with Alzheimer's disease. *PLoS One* 2014; 9: e96779.