Kaposi’s Sarcoma-associated herpesvirus (KSHV) and Epstein Barr virus (EBV) are the causative agents of several malignancies. Like all herpesviruses, KSHV and EBV undergo distinct latent and lytic replication programmes. The transition between these states allows the establishment of a lifelong persistent infection, dissemination to sites of disease and the spread to new hosts. Latency-associated viral proteins have been well characterised in transformation and tumourigenesis pathways; however, a number of studies have shown that abrogation of KSHV and EBV lytic gene expression impairs the oncogenesis of several cancers. Furthermore, several lytically expressed proteins have been functionally tethered to the angioproliferative and anti-apoptotic phenotypes of virus-infected cells. As a result, the investigation and therapeutic targeting of KSHV and EBV lytic cycles may be essential for the treatment of their associated malignancies.

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Introduction
Kaposi’s sarcoma associated herpesvirus (KSHV) and Epstein Barr virus (EBV) are double stranded gamma-herpesviruses which contribute to the oncogenesis of several human tumours. KSHV is the etiologic agent of the endothelial cell tumour Kaposi’s Sarcoma, in addition to two lymphoproliferative disorders; primary effusion lymphoma (PEL) and multicentric Castleman’s disease (MCD) [1–3]. Whereas, EBV has been linked with multiple malignancies including Burkitt’s lymphoma (BL), Hodgkin’s lymphoma (HL), nasopharyngeal carcinoma (NPC) and gastric carcinoma (GC) [4–6].

Like all herpesviruses, KSHV and EBV have a biphasic life cycle comprising latent and lytic replication programmes. During latency, both viruses exist in a dormant state where only a subset of the viral genes are expressed facilitating the episcopal persistence of the viral genome [7,8]. However, under certain physiological conditions, both viruses undergo lytic reactivation leading to expression of the full complement of lytic genes followed by the assembly and egress of infectious virions. Importantly however, both KSHV and EBV can also undergo abortive lytic reactivation, resulting in the expression of early lytic genes without subsequent virion assembly and cell lysis.

Although much of the efforts to understand the molecular basis of these disorders has focused on viral latency, KSHV and EBV lytic cycles are now widely accepted as major contributors to oncogenesis which could be important targets in the development of anti-cancer therapeutics [9,10]. Thus, in this review, we discuss how lytic replication augments the pathogenesis of KSHV and EBV-associated malignancies (Figure 1) and the treatments available which may target the lytic replication cycle.

KSHV lytic factors and tumourigenesis
Expression of the KSHV major lytic transactivator, RTA, is sufficient and necessary to activate the KSHV lytic cycle leading to a triphasic transcriptional cascade of immediate early, delayed early and late gene expression [11,12]. To initiate the transition from latency to lytic replication, a range of stimuli have been implicated including hypoxia, co-infection with HIV-1, oxidative stress and inflammatory cytokines; all of which promote the expression of RTA [13–16]. Importantly, the treatment of KS patients with drugs that prevent lytic replication can, in certain cases, lead to regression of KS lesions; attesting to the importance of lytic gene expression in tumourigenesis [17].

Although in vivo, the spontaneous reactivation of KSHV takes place in only 1–3% of infected cells, the resultant assembly and egress of KSHV infectious
particles sustains the population of latently infected cells that would otherwise be lost due to a combination of defects in episome synthesis during cell division and the death of infected cells [18]. Therefore, the balance between KSHV latent and lytic replication programmes is stringently controlled to ensure viral persistence and consequently tumour development. Nevertheless, in addition to the role of the lytic cycle in supporting a lifelong, persistent KSHV infection, a number of lytic factors themselves have oncogenic properties [19] (Table 1). Thus, the following section will outline these oncogenic lytic genes and discuss how they contribute to malignancy alongside their role in viral replication.

vGPCR
Viral G-protein-coupled-receptor (vGPCR) is an early lytic protein encoded by the viral gene ORF74. It shares limited homology to the human interleukin-8 receptors CXCR1 and CXCR2; however, ORF74 is constitutively active and minimally responsive to various ligands [20,21]. vGPCR activates members of the G protein family which stimulate several major cell signalling pathways such as phosphatidylinositol 3-kinase (PI3K), phosphoinoside-dependent kinase (PDK) and AKT/protein kinase B (AKT/PKB) along with several small GTPase proteins such as RhoA and Rac1 [22–25]. The induction of a myriad of signalling pathways which activate Sp1/3 transcription factors is crucial to the maintenance of RTA expression and therefore commits the cell to productive lytic replication [26,27]. Previous studies have demonstrated that vGPCR is an oncogene capable of inducing angioproliferative lesions in transgenic mice that bear the pathological indicators of KS [28]. The angioproliferative nature of vGPCR appears to stem from its indirect production and secretion of a number of paracrine signalling molecules such as vascular endothelial growth factor (VEGF) [22–25]. As a result, it has been suggested that vGPCR initiates the immortalisation of endothelial cells and KS tumourigenesis through the establishment of a VEGF paracrine loop [28]. In this proposed ‘hit and run’ model of immortalisation, populations of lytically replicating endothelial cells express vGPCR leading to VEGF expression and secretion. This acts in an autocrine mechanism on lytically replicating cells but also in a paracrine fashion on adjacent latently infected cells to promote their survival and immortalisation.
K1 and K15

ORF-K1 encodes a type 1 transmembrane glycoprotein which shares structural similarities with the B cell receptor (BCR) [29]. The lytic protein appears to contribute to KSHV lytic replication in a similar manner to vGPCR through the maintenance of RTA expression; however, the specific mechanism behind this is not well understood [30]. Like vGPCR, K1 expression also contributes to the VEGF autocrine and paracrine signalling loop through its constitutively active ITAM domain, promoting the production and secretion of VEGF via matrix metalloproteinase 9 (MMP-9) [31–33]. Increased VEGF signalling modulates downstream pathways such as PI3K and mitogen activated kinase which in turn activate Akt kinase and mammalian target of rapamycin (mTOR) to promote cell survival [32,34,35]. Furthermore, K1 has also been shown to interact with the HIV-1 protein Tat. Mouse studies have shown that coexpression of K1 and HIV-1 Tat leads to a synergistic increase in angiogenesis through the Tat-mediated upregulation of host microRNA miR-891a-5b which targets NF-κB [36*].

Like ORF-K1, KSHV ORF-K15 encodes a transmembrane receptor which antagonises BCR signalling; however, K15 lack an ITAM domain and activates the production of cytokines and chemokines via cellular signalling pathways including NF-κB, MEK/ERK and Jun N-terminal protein kinase (JNK) pathways [37]. K15 bypasses the induction of VEGF signalling by activating the downstream PLCγ-Calbindulin-NFAT pathways to facilitate angiogenic tube formation in cell culture [38]. It is speculated that K15 is involved in the early development of KS tumour where limited lytic gene expression is detected [38].

KSHV immunoevasins

Successful KSHV lytic replication is dependent on the expression of viral interferon regulatory factors (vIRFs) and viral interleukins (vILs) which prevent immune detection [39]. Most of these viral proteins are expressed during lytic replication to inhibit the interferon (IFN) antiviral response. KSHV vIL-6, like its human homologue can bind the gp130 receptor and activate the JAK/STAT, MAPK and PI3K/Akt cellular signalling pathways leading to expression of hIL-6 and VEGF [40–42]. Furthermore, the inoculation of NIH3T3 cells ectopically expressing vIL-6 into immunocompromised mice leads to tumour formation and vIL-6 expression in endothelial cells leads to angioproliferation and tubule formation [43].

The KSHV genome also possesses three lytically encoded vIRF ORFs: ORF-K9, ORF-K11/K11.1 and ORF-K10 encoding vIRF1, vIRF2 and vIRF4 respectively [39,44]. vIRFs act to disrupt the antiviral IFN response by

| Table 1 |
| --- |
| KSHV lytic oncogenes and mechanisms of tumorigenesis |

| KSHV lytic gene | Cellular homologue | Lytic function | Mechanisms of oncogenesis | Oncogenic function | Reference |
| --- | --- | --- | --- | --- | --- |
| vGPCR | IL-8 receptor | Activates cellular signalling pathways to maintain Rta expression | Secretes paracrine signalling molecules such as VEGF. Activates Rho and Rac1 GTPases. Stimulates PI3K, PDK, AKT/PKB, p38 and MAPK signalling pathways. Contributes to VEGF autocrine and paracrine signalling. | Cell survival, angiogenesis | [22–25,28] |
| IL-6 | BCR | Activates cellular signalling pathways to maintain Rta expression | Perturbs normal PI3K and MAPK signalling. Activates AKT and mTOR. Interacts with HIV-1 Tat to activate NF-κB. Modulates PLCγ-Calbindulin-NFAT pathways | Cell survival, angiogenesis | [31–35,36*] |
| vIL-6 | vIL-6 | Activates cellular signalling pathways | Chemokine and cytokine production pathways. Activates JAK/STAT, MAPK and PI3K/AKT signalling pathways. | Angiogenesis | [37,38] |
| vIRFs | vIRFs | Immunoevasins | Inhibits Interferon α/β/γ responses and inflammatory signalling. Interaction with p53 prevents ATM/p53 DNA damage response pathway. | Cell survival | [39,44–47] |
| vBCL-2 | vBCL-2 | BCL-2 | Delays cell death | Inhibits apoptosis and autophagy | Cell survival | [48–50,51*,52] |
| vCCLs | vCCLs | CCLs | Immunoevasins | Modulation of CCL activity. Chemoattractants for TH2 cells to reduce TH1 cell activity | Angiogenesis | [53–55] |
| RTA | RTA | Lytic transactivator | Induction of DNA damage | Genome instability | [60] |
| ORF57 | ORF57 | Processing, export and translation of viral RNAs | Sequesters the transcription and export complex (hTREX) to cause R-loop formation and DSBs | Genome instability | [57,58,59*] |
inhibiting transcription of IFN-α/-β/-γ and inflammatory signals. The mechanism of vIRF action varies between isoforms; however, in many cases vIRF bind to cellular IRFs and inhibit their ability to activate transcription [39]. Through the dysregulation of the IFN antiviral response, apoptosis and cell cycle arrest are prevented increasing the oncogenic potential of KSHV-infected cells [44,45]. vIRF1 co-precipitates with p53, reducing p53 target gene expression [46]. Studies have demonstrated this vIRF1-p53 is crucial for the inhibition of the ATM/p53 DNA damage response pathway allowing viral DNA replication to proceed [39,46,47]. vIRF1 appears to block activation of ATM and decreases p53 stability through reduced phosphorylation of Ser15 of p53 [47].

vBcl-2
vBcl-2, encoded by KSHV ORF16 shares sequence and functional homology to the Bcl-2 family of cellular proteins [48]. Normally, Bcl-2 proteins act as regulators of apoptosis and are characterised by four conserved stretches of amino acids called Bcl-2 homology (BH) domains [49]. Cellular Bcl-2 also negatively regulates autophagy by interacting with autophagy promoting factor Beclin-2 [50]. Studies in the murine counterpart of KSHV, murine herpesvirus 68 (MHV68), have shown that vBcl-2 is involved in both the inhibition of autophagy and apoptosis to promote B cell survival [51*]. The importance of autophagy in programmed cell death makes it an important target for KSHV during lytic infection to prevent induction of apoptosis and thus the impairment of viral replication. In KSHV the function of vBcl-2 has not yet been fully elucidated; however, lack of vBcl-2 impairs KSHV reactivation [48,52].

vCClS
KSHV also encodes three homologues of cellular chemokines known as viral CC-chemokine ligands (vCClS) [53]. Previous studies have shown that vCCl1–vCCl3 are all able to bind to their cellular homologues both agonistically and antagonistically to stimulate angiogenesis [53,54]. Furthermore, all three viral proteins have been suggested to act as chemotactants to modulate the levels of different T-cell subpopulations in KS lesions. The resultant TH2 cell-predominant tumour microenvironment in which TH1 cell responses are downregulated allowing immune evasion and thus tumour progression [55].

KSHV and genome instability
KSHV lytic replication is associated with the formation of double strand-breaks (DSBs) and chromosomal aberrations, which are a common feature of KS lesions [56]. The KSHV early protein ORF57 controls the processing, export and translation of viral RNAs [57,58]. However, studies have shown that sequestration of the human transcription and export complex (hTREX) by ORF57 leads to DSBs as a result of R-loop formation [59*]. Furthermore, studies have suggested that Rta is also able to induce DNA damage [60]. Importantly, the activation of members of the DNA damage response machinery in this way has been suggested to facilitate viral DNA synthesis during productive lytic replication; as is the case with other Herpesviruses [60]. Thus, the role of KSHV lytic factors in genome instability likely contributes to oncogenesis.

EBV lytic factors and tumourigenesis
EBV establishes a lifelong infection in B lymphocytes achieved through a highly regulated viral gene expression program. In latently infected B cells, the expression of either Zta or Rta is sufficient to reactivate the EBV lytic cycle [61–64]. Lytic replication can be studied by treating latently infected B cells with inducers of the lytic cycle such as phorbol esters or by crosslinking B cell receptors with anti-immunoglobulins [65,66]. There have been several important insights regarding the contribution of the EBV lytic cycle for virus-induced tumorigenesis in vivo. Mouse models have demonstrated that lytic replication incompetent-EBV particles are impaired in their ability to cause lymphomagenesis compared to wild type virus, despite similar infection levels [67]. Furthermore, acyclovir treatment, which blocks lytic viral genome replication but not lytic gene expression, is unable to prevent EBV associated lymphomagenesis; reinforcing the role of lytic cycle-induced paracrine signals in disease progression [68]. Finally, in vivo studies have shown that in KSHV-infected PEL cells, tumour formation is enhanced upon coinfection with EBV [69**]. Together, these studies strongly support the view that lytic gene expression is important for tumour progression, and that paracrine signals play an essential role.

Similar to KSHV and the role of lytic reactivation in KS, reactivation of EBV may aid transmission of the virus within the tumor microenvironment to establish latency and drive cellular proliferation. However, the likely predominant role of the EBV lytic cycle is to provide the necessary paracrine, anti-apoptotic and immunomodulatory signals required for tumorigenesis (Table 2).

ZTA
Various studies have shown that the expression of some lytic antigens alone is sufficient to induce the expression of immunomodulatory and paracrine factors associated with oncogenesis. The lytic transactivator Zta facilitates the secretion of IL-6, IL-8, IL-10 and IL-13 in addition to proangiogenic proteins such as vascular endothelial growth factor (VEGF) [67,68,70]. Soluble Zta has also been detected in the sera of post-transplant lymphoproliferative disease (PTLD) patients providing further evidence of a transformative role for this lytic protein [70]. Finally, Zta alone can downregulate the expression of CIITA, an essential transcription factor important for
HLA-II expression permitting immune evasion and tumour progression [71].

**EBV and anti-apoptotic signalling**

In addition to the paracrine effect, some lytic proteins elicit strong anti-apoptotic signals [72]. Like KSHV vBcl-2, the EBV lytic cycle-associated proteins BHRF1 and BALF1 are viral homologs of cellular Bcl-2 which perform anti-apoptotic functions critical for cellular transformation in vitro [73,74]. Similarly, BCRF1, which is analogous to cellular IL-10, increases the viability and transformation of EBV-infected B cells through downregulation of interferon-γ [75]. Finally, BARF1 is one of the most highly expressed genes in NPC cell lines and antibodies are frequently detected in NPC-patient sera [73]. The encoded protein, BARF1, a homolog of colony-stimulating factor 1 receptor, is a secreted anti-apoptotic factor which influences the survival of neighbouring cells [76,77]. Taken together, these studies implicate anti-apoptotic signalling by EBV lytic proteins in the oncogenesis of EBV-associated malignancies. However, although the expression of BHRF1, BALF1 and BARF1 is dramatically increased during lytic reactivation, and they have previously been designated as lytic genes, their expression has been detected in LCLs (lymphoblastoid cell lines) where cells are predominantly latently infected (>95%) [78]. Furthermore, BHRF1 is expressed from the latent promoter Wp in a subset of BL known as Wp-restricted BL [78]. Therefore, it is unclear whether these proteins contribute to tumorigenesis during the latent or lytic life cycles.

### BGLF5 and BALF1 immunoevasins

Several EBV lytic proteins, which primarily function as immunoevasins, also contribute to tumorigenesis. BGLF5, the EBV host shut-off protein which inhibits translation of host mRNAs, functions in the downregulation of toll-like receptor 9 (TLR9) and human leukocyte antigen class I (HLA-I) and –II leading to impaired T cell recognition [79,80]. Importantly however, BGLF5 expression has been detected in NPC biopsies and BGLF5 antibodies have been detected in NPC patient sera, suggesting the protein also undertakes a transformative role [81]. Similarly, the lytic EBV immunoevasin BILF1 enhances the internalisation of surface molecules of HLA-I leading to their rapid degradation by the lysosome; again impairing T cell recognition [82]. However, BILF1 expression has also been detected in NPC cells, once again suggesting an oncogenic function [83].

### EBV and genomic instability

Like KSHV, several EBV lytic proteins have also been implicated as contributors to genomic instability [84]. A recent study suggested that the EBV major tegument protein, BNFR1, involved in translocation of the viral nucleocapsid to the nucleus, induces centrosome amplification and thus contributes to the accumulation of chromosomal aberrations in infected cells [85**]. Furthermore, BNFR1 was able to induce genomic instability within latently infected LCLs without necessarily establishing infection, demonstrating that EBV lytic replication can promote transformation in adjacent cells [85**]. Three further EBV proteins, BALF3, BGLF4 and host cell-shutoff protein BGLF5 have all been suggested to further contribute to chromosomal instability and
tumourigenesis through induction of DNA damage in NPC cells [86–88]. Thus, genomic instability appears a major mechanism through which EBV lytic proteins contribute to oncogenesis.

**Treatments for KSHV and EBV-associated cancers**

Considerable advances in the understanding of the KSHV and EBV life cycle and related pathologies have been made since their discovery, however, presently there are still no vaccines or effective direct therapeutic options available for the prevention or treatment of their associated cancers. Almost all clinically available therapies that target the lytic life cycle of KSHV and EBV do not directly inhibit the virus and have shown varying results in the clinic (Table 3). Because of the critical role of lytic replication in disease progression and virus dissemination these highlight the need for potent and selective therapeutics against lytic viral targets to treat KSHV and EBV-associated cancers.

There is no standard of care for the treatment of KSHV-associated tumours and current options range from targeting cancers through surgical excision, chemotherapy and radiotherapy [89]. These treatment options are also recommended for EBV-associated cancers however, due to the array of cancers associated with EBV, treatment guidelines vary greatly for each different associated cancer [90].

To date, the most effective treatment of AIDS-related KS and AIDS-related EBV-associated cancers is highly active antiretroviral therapy (HAART), which works mostly through restoration of the patient’s immune system [91]. Likewise, iatrogenic KS, MCD, PEL and iatrogenic EBV-associated sarcomas and lymphomas are treated through the removal of immunosuppressants, to restore the patient’s immune system, limiting tumour progression, however this in turn can lead to graft rejection [92].

Immunotherapies have also been demonstrated to be effective at treating KSHV and EBV-associated cancers. Rituximab (anti-CD20) is clinically approved for the treatment of many EBV-associated lymphoproliferative diseases and also MCD [93**]. In addition, Tocilizumab (anti-human IL-6 receptor) and Siltuximab (anti-IL6 chimeric monoclonal antibody) are clinically available for the treatment of MCD [95,96].

**Novel therapies involving lytic KSHV and EBV**

The majority of cells present in KSHV and EBV-associated cancers are latently infected therefore, there is substantial research exploring the potential of lytic induction therapy to treat these cancers. This treatment involves the efficient induction of all latently infected tumour cells into the lytic cycle while concomitantly exposing the cells to inhibitors of lytic replication and inducing apoptosis to clear all virally infected cells. In addition, lytic induction therapy can help induce a cytotoxic T-lymphocyte (CTL) response to lytic antigens to further clear cancerous virally infected cells. Lytic induction therapy poses a powerful mechanism to enhance the efficacy of EBV and KSHV lytic inhibitors, which are discussed below.

Because of the critical role of the KSHV and EBV lytic life cycle in tumourigenesis there is considerable interest in developing vaccines that target lytic antigens [97]. Various vaccines have been created targeting a range of lytic KSHV and EBV antigens. Some of these vaccines have proved successful in vivo and in clinical trials, such as the EBV envelope protein gp350, which reduced primary infection however, the vaccine failed to decrease the overall EBV infection rate.

Finally, cytokine therapy can induced protective T-cell immunity against viruses. Cytokine therapy in a humanized mouse model with EBV-associated lymphoproliferative disease induced a marked expansion of Zta-specific T-cells, which can prolong survival [98,99]. In addition to supporting the notion that Zta plays a critical role in lymphoproliferative disease, it provides a strong rationale for the inclusion of Zta-specific antigens in vaccine development [97].

**KSHV and EBV lytic inhibitors**

The lytic life cycles of KSHV and EBV pose numerous attractive and viable targets for the development of antiviral drugs. However, the only KSHV and EBV inhibitors clinically available (and all anti-herpesvirus drugs in general) target the viral DNA-polymerase [100]. The most common of these drugs are nucleoside analogues, but acyclic nucleoside phosphonates (ANPs) and pyrophosphate analogues are also frequently used for herpesvirus therapy [89]. Clinically available nucleoside analogues are administered as pro-drugs and only activated by the viral thymidine kinase present during lytic replication [101]. Novel viral DNA-polymerase inhibitors have also been developed such as, second and third generation, nucleoside analogues and ANPs, and non-nucleoside inhibitors [102,103].

Many other inhibitors of herpesvirus replication have also been explored which target numerous aspects of the lytic life cycle, however none have made it as yet into the clinic. Targets with inhibitors demonstrated to have efficacy against EBV and KSHV include, the KSHV latent-lytic transactivator RTA, KSHV IRFs and the viral capsid protease [104,105].

Cellular targets required for lytic reactivation of EBV and KSHV and that contribute to lytic EBV and KSHV-associated tumorigenesis have also been approached as targets for inhibitors of their associated cancers [106].
| Table 3                                                                 |                                                                 |                                                                 |                                                                 |                                                                 |
|-----------------------------------------------------------------------|------------------------------------------------------------------|----------------------------------------------------------------|
| Current treatments and inhibitors targeting the lytic life cycles of  | KSHV and EBV-associated cancers. Stage of development abbreviations: R = Randomised, C = Control and SP = Single     |                                                                 |                                                                 |
| Viral DNA polymerase                                                   | Inhibitor class                                                  | Drug Stage of development | Already clinically approved for:                                   |
| Nucleoside analogues                                                  | Purine analogues                                                | Acyclovir Cohort study | HSV and VZV                                                       |
| Acyclic nucleoside phosphonates                                       | HPMP derivatives                                                | Cidofovir Pilot study   | CMV                                                               |
| Viral mRNAs                                                           | Peptide-conjugated phosphorodiamidate morpholin oligomers (PPMO) | RTA In vitro n/a        | None                                                              |
| Viral capsid protease                                                 | Small molecule helical mimic                                     | DD2 In vitro n/a        | None                                                              |
| Lytic repression                                                      | Small molecule inhibitors                                       | Resveratrol In vitro In | Dietary supplement tetrahydrocannabinol                           |
| Lytic induction                                                       | ATP-competitive tyrosine kinase inhibitor                        | Dasatinib In vitro Phase | Chronic ML and ALL                                                 |
| HSP70                                                                 | Small-molecule inhibitor                                         | Teriflunomide None      | Multiple sclerosis                                                |
| hTREX                                                                 | ATP-derivative inhibitor                                         | VER-155008 In vitro None| None                                                              |
| mTOR                                                                  | Polyketide                                                      | CCT018159 In vitro None | None                                                              |
| Lytic induction                                                       | DNA demethylation agent                                          | 5-azacytidine In vitro | MDS, Acute ML and CMML                                            |
| Small-molecule inhibitor                                              | DNA demethylation agent                                          | 5-azacytidine In vitro | MDS, Acute ML and CMML                                            |
| Protective T-cell immunity                                            | Capsid protein                                                  | C7 None In vitro        | None                                                              |
| Vaccine                                                               | Replication-competent viruses                                   | gp350 n/a Phase II trial| None                                                              |
| Cytokine therapy                                                      | GM-CSF and IL-2                                                 | None In vivo None       | None                                                              |
Cellular inhibitors bear an increased risk of cytotoxic side effects, however, they possess great advantages due to fewer occurrences of drug-resistance and the potential for a broader activity against a range of viruses. Targets include, the KSHV/EBV cellular entry receptor (ephrin receptor tyrosine kinase A2), the proteasome, Hsp70, the human transcription/export complex (hTREX), the mammalian target of rapamycin (mTOR) and the dihydroorotate dehydrogenase enzyme [106,107,108,109,110,111]. While most inhibitors of cellular targets have only been demonstrated in vitro some have also shown efficacy in the clinic.

All clinically available inhibitors of EBV and KSHV have low efficacy and only target the viral DNA polymerase. Therefore, more efforts should be invested to examine the potential of drugs that target other viral proteins, since this proof-of-principle has been shown beneficial for other herpesviruses, such as HSV and HCMV.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as
● of special interest
◆ of outstanding interest

1. Chang Y, Cesaran E, Pessin MS, Lee F, Culpepper J, Knowles DM, Moore PS: Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposis's sarcoma. Science 1994, 266:1865-1869.

2. Cesaran E, Chang Y, Moore PS, Said JW, Knowles DM: Kaposis's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. N Engl J Med 1995, 332:1186-1191.

3. Soulier J, Grollet L, Ooksentandler E, Cacoub P, Cazals-Hatem D, Babinet P, D'Agay MF, Clauvel JP, Raphael M, Degos L: Kaposis's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood 1995, 86:1276-1280.

4. Coates PJ, Slavin G, d’Ardenne AJ: Persistence of Epstein-Barr virus in Reed-Sternberg cells throughout the course of Hodgkin's disease. J Pathol 1991, 164:291-297.

5. de Schryver A, Friberg SJ, Klein G, Henle W, Henle G, De-The G, Clifford P, Ho HC: Epstein-Barr virus-associated antibody patterns in carcinoma of the post-nasal space. Clin Exp Immunol 1969, 8:443-459.

6. Haur Hausen, Schulte-Holthausen H, Klein G, Henle W, Henle G, Clifford P, Santesson L: Epstein-Barr virus in Burkitt lymphoma and nasopharyngeal carcinoma: EBV DNA in biopsies of Burkitt tumours and anaplastic carcinomas of the nasopharynx. Nature 1970, 228:1056.

7. Kenney SC, Mertz JE: Regulation of the latent-lytic switch in Epstein-Barr virus. Semin Cancer Biol 2014, 30:50-58.

8. Cai Q, Verma SC, Lu J, Robertson ES: Molecular biology of Kaposis's sarcoma herpesvirus and related oncogenesis. Adv Virus Res 2010, 78:87-142.

9. Hardie DR: Human gamma-herpesviruses: a review of 2 divergent paths to oncogenesis. Transfus Apher Sci 2010, 42:177-183.

10. Jha H, Banerjee S, Robertson E: The role of gammaherpesviruses in cancer pathogenesis. Pathogens 2016, 5:18.

11. Lukac DM, Kirshner JR, Ganem D: Transcriptional activation by the product of open reading frame 50 of Kaposis's sarcoma-associated herpesvirus is required for lytic viral reactivation in B cells. J Virol 1999, 73:9348-9361.

12. Wilson SJ, Tsao EH, Webb BLJ, Ye H, Dalton-Griffin L, Tsantoulas C, Gale CV, Du M-Q, Whitehouse A, Kellam P: X box binding protein XBP-1s transactivates the Kaposis's sarcoma-associated herpesvirus (KSHV) ORF50 promoter, linking plasma cell differentiation to KSHV reactivation from latency. J Virol 2007, 81:13578-13586.

13. Davis DA, Rinderknecht AS, Zoeteweij JP, Aoki Y, Read-connele EL, Tosatto G, Blauvelt A, Yarchano R: Hypoxia induces lytic replication of Kaposis's sarcoma-associated herpesvirus. Vascular 2011, 97:3244-3250.

14. Cohen A, Brodie C, Sarid R: An essential role of ERK signalling in TPA-induced reactivation of Kaposis's sarcoma-associated herpesvirus. J Gen Virol 2006, 87:795-802.

15. Merat R, Amara A, Lebbe C, De The H, Morel P, Saib A: HIV-1 infection of primary effusion lymphoma cell line triggers Kaposis's sarcoma-associated herpesvirus (KSHV) reactivation. Int J Cancer 2002, 97:791-795.

16. Mercader M, Taddio B, Panella JR, Chandran B, Nickoloff BJ, Foreman KE: Induction of HHV-8 lytic cycle replication by inflammatory cytokines produced by HIV-1-infected T cells. Am J Pathol 2000, 156:1961-1971.

17. Martin JS, Osmond DH: Kaposis's sarcoma-associated herpesvirus and sexual transmission of cancer risk. Curr Opin Oncol 1999, 11.

18. Chiur YF, Sugden AU, Fox K, Hayes M, Sugden B: Kaposis's sarcoma-associated herpesvirus stably clusters its genomes across generations to maintain itself extrachromosomally. J Cell Biol 2017, 216:2745-2758.

19. Wen KW, Damania B: Kaposis's Sarcoma-associated Herpesvirus (KSHV): molecular biology and oncogenesis. Cancer Lett 2010, 289:140-150.

20. Guo H-G, Browning P, Nicholas J, Hayward GS, Tschachler E, Jang Y-W, Sadowski M, Raffelt M, Colombini S, Gallo RC et al.: Characterization of a chemokine-related gene in human herpesvirus 8 and its expression in Kaposis's sarcoma. Virology 1998, 228:371.

21. Rosenkilde MM, Kiedal TN, Bräuner-Osborne H, Schwartz TW: Agonists and inverse agonists for the herpesvirus 8-encoded constitutively active seven-transmembrane oncogene product, ORF-74. J Biol Chem 1999, 274:956-961.

22. Soody A, Montaner S, Patel V, Zohar M, Bais C, Mesri EA, Gutfkind JS: The Kaposis's sarcoma-associated herpes virus G protein-coupled receptor up-regulates vascular endothelial growth factor expression and secretion through mitogen-activated protein kinase and p38 pathways acting on hypoxia-inducible factor 1alpha. Cancer Res 2000, 60:4873-4880.

23. Bais C, Van Geelen A, Eroles P, Mutlu A, Chiozziini C, Dias S, Silverstein RL, Rafili S, Mesri EA: Kaposis's sarcoma associated herpesvirus G protein-coupled receptor immortalizes human endothelial cells by activation of the VEGF receptor-2. KDR. Cancer Cell 2003, 3:131-143.

24. Montaner S, Soody A, Pecce S, Mesri EA, Gutfkind JS: The Kaposis's sarcoma-associated herpesvirus G protein-coupled receptor promotes endothelial cell survival through the activation of Akt/protein kinase B. Cancer Res 2001, 61:2641-2648.

25. Martin MJ, Tanos T, Garcia AB, Martin D, Gutfkind JS, Coso OA, Marinissen MJ: The Galpha12/13 protein-coupled receptor promotes viral entry into B cells. J Virol 2009, 83:1213-1224.
oxygenase-1 expression and tumorigenesis. J Biol Chem 2007, 282:34510-34524.

26. Chiu C-J, Poole LJ, Kim PS, Clufo DM, Cannon JS, ap Rhys CM, Alencor DJ, Zong J-C, Ambinder RF, Hayward GS: Patterns of gene expression and a transactivation function mediated by the vGCR (ORF74) chemokine receptor protein of Kaposi's sarcoma-associated herpesvirus. J Virol 2002, 76:3421-3439.

27. Bottero V, Sharma-Walia N, Kerur N, Paul AG, Cannon M, Chandran B: Kaposi sarcoma- associated herpesvirus (KSHV) G protein-coupled receptor (vGPCR) activates the ORF50 lytic switch promoter: a potential positive feedback loop for sustained ORF50 gene expression. Virology 2010, 392:34-51.

28. Bais C, Santomasso B, Coso O, Arvanitakis L, Raaka EG, Gutkind JS, Asch AS, Cesaran E, Gerhengorn MC, Mesri EA: G-protein-coupled receptor of Kaposi's sarcoma-associated herpesvirus is a viral oncoene and angiogenesis activator. Nature 1996, 381:86-99.

29. Steinbrück L, Gustems M, Medele S, Schulz TF, Lutter D, Hammerschmidt W: K1 and K15 of Kaposi's sarcoma- associated herpesvirus are partial functional homologs of latent membrane protein 2A of Epstein-Barr virus. J Virol 2015, 89:7248-7261.

30. Zhang B, Chen W, Sanders MK, Brulois KF, Dittmer DP, Damania B: The K1 protein of Kaposi's sarcoma-associated herpesvirus (KSHV) augments viral lytic replication. J Virol 2016, 90:JVI03102-03115.

31. Belotti D, Paganoni P, Manenti L, Garofalo A, Marchini S, Taraboletti G, Giavazzi R: Matrix metalloproteinases (MMP and MMP2) induce the release of vascular endothelial growth factor (VEGF) by ovarian carcinoma cells: implications for ascites formation. Cancer Res 2003, 63:5224-5229.

32. Lagouff M, Majeti R, Weiss A, Ganem D: Deregulated signal transduction by the K1 gene product of Kaposi's sarcoma-associated herpesvirus. Proc Natl Acad Sci U S A 1999, 96:5704-5709.

33. Lee H, Guo J, Li M, Choi JK, DeMaria M, Rosenzweig M, Jung JU: Identification of an immunoreceptor tyrosine-based activation motif of K1 transforming protein of Kaposi's sarcoma-associated herpesvirus. Mol Cell Biol 1998, 18:5219-5228.

34. Brinkmann M, Glenn M, Rainbow L, Kieser A, Henke-Gendo C, Schulz TF: Activation of mitogen-activated protein kinase and NF-κB pathways by a Kaposi's sarcoma-associated herpesvirus K15 membrane protein. J Virol 2003, 77:9346-9358.

35. Wang L, Dittmer DP, Tomlinson CC, Fakhari FD, Damania B: Immortalization of primary endothelial cells by the K1 protein of Kaposi's sarcoma-associated herpesvirus. Cancer Res 2006, 66:3658-3666.

36. Yao S, Hu M, Hao T, Li W, Xue X, Xue M, Zhu X, Zhou F, Qin D, Yan Q et al.: miRNA-891a-5p mediates HIV-1 Tat and KSHV ORF- K1 synergistic induction of angiogenesis by activating NF-κB signaling. Nucleic Acids Res 2015, 43:9362-9378.

This report demonstrates that HIV-1 protein Tat promotes KSHV K1-induced angiogenesis through the upregulation of a microRNAs which in turn activates NF-κB signaling.

37. Brinkmann MM, Pietrek M, Dittrich-Breiholz O, Kracht M, Schulz TF: Modulation of host gene expression by the K15 protein of Kaposi's sarcoma-associated herpesvirus. J Virol 2007, 81:42-58.

38. Bala K, Bosco R, Gramolelli S, Haas DA, Kati S, Pietrek M, Hävemeier A, Yakuwko Y, Singh VV, Dittrich-Breiholz O et al.: Kaposi's sarcoma herpesvirus K15 protein contributes to virus-induced angiogenesis by recruiting PLCγ1 and activating NFAT1-dependent RCAN1 expression. PLoS Pathog 2012, 8.

39. Jacobs SR, Damania B: The viral interferon regulatory factors of KSHV: immunosuppressors or oncogenes. Front Immunol 2011, 2:1-11.

40. Osborne J, Moore PS, Chang Y: KSHV-encoded viral IL-6 activates multiple human IL-6 signaling pathways. Hum Immunol 1999, 60:921-927.

41. An J, Lichtenstein AK, Brent G, Retting MB, An J, Lichtenstein AK, Brent G, Retting MB: The Kaposi sarcoma – associated herpesvirus (KSHV) induces cellular interleukin 6 expression: role of the KSHV latency-associated nuclear antigen and the AP1 response element. Blood 2002, 99:649-654.

42. Molden J, Chang Y, You Y, Moore PS, Goldsmith MA: A Kaposi's sarcoma-associated herpesvirus-encoded cytokine homolog (vIL-6) activates signaling through the shared gp130 receptor subunit. J Biol Chem 1997, 272:19625-19631.

43. Aoki Y, Jaffé ES, Chang Y, Jones K, Teruya-Feldstein J, Moore PS, Tosato G: Angiogenesis and hematopoesis induced by Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6. Blood 1999, 93:4034-4043.

44. Lin R, Genin P, Mamane Y, Sgarbati M, Battistini A, Harrington WJ, Barber GN, Hiscott J: HHV-8 encoded vIRF-1 represses the interferon antiviral response by blocking IRF-3 recruitment of the CBP/p300 coactivators. Oncogene 2001, 20:800-811.

45. Buryšek L, Yeow WS, Lubová B, Kellum M, Schafer SL, Huang YQ, Pitha PM: Functional analysis of human herpesvirus 8-encoded viral interferon regulatory factor 1 and its association with cellular interferon regulatory factors and p300. J Virol 1999, 73:3344-3342.

46. Seo T, Park J, Lee D, Hwang SG, Choe J: Viral interferon regulatory factor 1 of Kaposi's sarcoma-associated herpesvirus binds to p53 and represses p53-dependent transcription and apoptosis. J Virol 2001, 75:6193-6198.

47. Nakamura H, Li M, Zarycky J, Jung JU: Inhibition of p53 tumor suppressor by viral interferon regulatory factor. J Virol 2001, 75:7572-7582.

48. Gelgior A, Kalt I, Bergson S, Brulois KF, Jung JU, Sarid R: Viral Bcl-2 encoded by the Kaposi's sarcoma-associated herpesvirus is vital for virusreactivation. J Virol 2015, 89:5298-5307.

49. Skommer J, Wlodkowic D, Deptala A: Larger than life: mitochondria and the Bcl-2 family. Leuk Res 2007, 31:277-286.

50. Pattingre S, Tassa A, Qiu X, Gurui R, Xiao HL, Mizushima N, Parker M, Schneider MD, Levine B: Bcl-2 antiapoptotic proteins inhibit Bcl-1-dependent autophagy. Cell 2005, 122:927-939.

51. Coleman CB, McGraw JE, Feldman ER, Roth AN, Keyes LR, Grau KR, Cochran SL, Waldschmidt TJ, Liang C, Forrest JC et al.: A gammaherpesvirus Bcl-2 ortholog blocks B cell receptor-mediated apoptosis and promotes the survival of developing B cells in vivo. PLoS Pathog 2014, 10.

This study shows that during HIV-8 infection, Bcl-2 expression is important for the survival of developing B cells.

52. Liang Q, Chang B, Lee P, Brulois KF, Ge J, Shi M, Rodriguez MA, Feng P, Oh B-H, Liang C et al.: Identification of the essential role of viral Bcl-2 for Kaposi's sarcoma-associated herpesvirus lytic replication. J Virol 2015, 89:5308-5317.

53. Liu C, Okruzhnov Y, Li H, Nicholas J: Human herpesvirus 8 (HHV-8)-encoded cytokines induce expression of and autocrine signaling by vascular endothelial growth factor (VEGF) in HHV-8-infected primary-effusion lymphoma cell lines and mediate VEGF-independent antiapoptotic effects. J Virol 2001, 75:10933-10940.

54. Choi YB, Nicholas J: Induction of angiogenic chemokine CCL2 by human herpesvirus 8 chemokine receptor. Virology 2010, 397:369-378.

55. Lee H-R, Lee S, Chaudhary PM, Gill P, Jung JU: Immune evasion by Kaposi’s sarcoma-associated herpesvirus. Future Microbiol 2010, 5:1349-1365.

56. Xiao Y, Chen J, Liao Q, Wu Y, Peng C, Chen X: Lytic infection of Kaposi's sarcoma-associating herpesvirus induces DNA double-strand breaks and impair nons-homologous end joining. J Gen Virol 2013, 94:1870-1875.

57. Jackson BR, Boyne JR, Noerenberg M, Taylor A, Hautberge GM, Walsh MJ, Wheat R, Blackbourn DJ, Wilson SA, Whitehouse A: An interaction between KSHV ORF57 and UfI provides RNA-adaptor redundancy in herpesvirus intronless mRNA export. PLoS Pathog 2011, 7.
58. Boyne JR, Jackson BR, Taylor A, MacNab SA, Whitehouse A: Kaposi’s sarcoma-associated herpesvirus ORF57 protein interacts with PYN to enhance translation of viral non-essential mRNAs. EMBO J 2010, 29:1851-1864.

59. Jackson BR, Noerenberg M, Whitehouse A: A novel mechanism inducing genome instability in Kaposi’s sarcoma-associated herpesvirus infected cells. PLoS Pathog 2014, 10.

This report provides evidence that KSHV ORF57 leads to sequestration of the human TREX complex and double strand breaks as a result of R-loop formation.

60. Hollingworth R, Skalka GL, Stewart GS, Hislop AD, Blackbourn DJ, Grand RJ: Activation of DNA damage response pathways during lytic replication of KSHV. Viruses 2015, 7:2908-2927.

61. Countryman J, Miller G: Activation of expression of latent Epstein-Barr virus herpes after gene transfer with a small cloned subfragment of heterogeneous viral DNA. Proc Natl Acad Sci U S A 1985, 82:4085-4090.

62. Feederle R: The Epstein-Barr virus lytic program is controlled by the co-operative functions of two transactivators. EMBO J 2000, 19:3080-3089.

63. Bhende PM, Dickerson SJ, Sun X, Feng W-H, Kenney SC: X-box-binding protein 1 activates lytic Epstein-Barr virus gene expression in combination with protein kinase D. J Virol 2007, 81:7363-7370.

64. Takada K, Shimizu N, Sakuma S, Ono Y: Trans activation of the latent Epstein-Barr virus (EBV) genome after transfection of the EBV DNA fragment. J Virol 1986, 57:1016-1022.

65. Takada K: Cross-linking of cell surface immunoglobulin induces Epstein-Barr virus in Burkitt Lymphoma Lines. Int J Cancer 1984, 33:27-32.

66. Flemington E, Speck SH: Identification of phorbol ester response elements in the promoter of Epstein-Barr Virus putative lytic switch gene BZLF1. J Virol 1990, 64:1217-1226.

67. Hong GK, Gully ML, Feng W, Deleclee H, Holtley-guthrie E, Kenney SC. Epstein-Barr virus lytic infection contributes to lymphoproliferative disease in a SCID mouse model. J Virol 2005, 79:13939-14003.

68. Ma X, Yang L, Xiao L, Tang M, Liu L, Li Z, Deng M, Sun L, Cao Y: Down-regulation of EBV-LMP1 mRNA sensitizes nasal pharyngeal carcinoma cells via NF-κB regulated ATM expression. PLoS One 2011, 6.

69. McHugh D, Caduff N, Barros MHM, Rämér PC, Raykova A, Müller A, Landtvizing V, Quast I, Styles CT, Spohn M et al: Persistent KSHV infection increases EBV-associated tumor formation in vivo via enhanced EBV lytic gene expression. Cell Host Microbe 2017, 22 61-73.e7.

This study demonstrated in vivo persistent KSHV infection enhances EBV lytic gene expression and tumour formation.

70. Katsuruma KR, Maruo S, Takada K: EBV lytic infection enhances transformation of B-lymphocytes infected with EBV in the presence of T-lymphocytes. J Med Virol 2012, 84:504-510.

71. Balan N, Osborn K, Sinclair AJ: Repression of CIITA by the Epstein-Barr virus transcription factor Zta is independent of its dimerization and DNA binding. J Gen Virol 2016, 97:725-732.

72. Fitzsimmons L, Kelly GL: EBV and apoptosis: the viral master regulator of cell fate? Viruses 2017, 9:1-34.

73. Cabras G, Decaussin G, Zeng Y, Djemnaoui D, Melouli H, Brouly P, Bouguerroud AM, Ocka T: Epstein-Barr virus encoded BCLF1 gene is transcribed in Burkitt’s lymphoma cell lines and in nasopharyngeal carcinoma’s biopsies. J Clin Virol 2005, 34:26-34.

74. Altman M, Hammerschmidt W: Epstein-Barr virus provides a new paradigm: a requirement for the immediate inhibition of apoptosis. PLoS Biol 2005, 3:1-10.

75. Stuart AD, Stewart JP, Arrand JR, Mackett M: The Epstein-Barr virus encoded cytokine viral interleukin-10 enhances transformation of human B lymphocytes. Oncogene 1995, 11:1711-1719.

76. Stockbine LD, Cohen JL, Farah T, Lyman SD, Wagener F, DuBoise RF, Armitage RJ, Spieggs M: The Epstein-Barr virus BARF1 gene encodes a novel, soluble colony-stimulating factor-1 receptor. J Virol 1998, 72:4015-4021.

77. Hsu WL, Chung PJ, Tsai MH, Chang CLT, Liang CL: A role for Epstein-Barr virus BARF1 in facilitating tumor formation and metastasis potential. Virus Res 2012, 163:617-627.

78. Kelly GL, Long HM, Stylianou J, Thomas WA, Leese A, Bell AI, Borkamirn GW, Mautner J, Rickinson AB, Rowe M: An Epstein-Barr virus anti-apoptotic protein constitutively expressed in transformed cells and implicated in Burkitt lymphomagenesis: the Wp/BHRF1 link. PLoS Pathog 2009, 5.

79. van Gent M, Griffin BD, Berkhof EG, van Leeuwen D, Boer IGJ, Buissin M, Hartgers FC, Burmeister WP, Wiertz EJ, Ressing ME: EBV lytic-phase protein BGLF5 contributes to TLR9 downregulation during productive infection. J Immunol 2011, 186:1694-1702.

80. Rowe M, Glausinger B, van Leeuwen D, Zuo J, Sweetman D, Ganem D, Middeldorp J, Wiertz EJ, Ressing ME: Host shutoff during productive Epstein-Barr virus infection is mediated by BGLF5 and may contribute to immune evasion. PNAS 2007, 104:3366-3371.

81. Sibih-Lamnali F, Berger F, Busson P, Ooka T: Expression of the Dnase encoded by the BGLF5 gene of Epstein-Barr virus in nasopharyngeal carcinoma epithelial cells. Virology 1996, 222:64-74.

82. Zuo J, Quinn LL, Tamblyn J, Thomas WA, Feederle R, Deleclee HJ, Hislop AD, Rowe M: The Epstein-Barr virus-encoded BILF1 protein modulates immune recognition of endogenously processed antigen by targeting major histocompatibility complex class I molecules trafficking on both the exocytic and endocytic pathways. J Virol 2011, 85:1604-1614.

83. Beisser P, Verzijl D: The Epstein-Barr virus BILF1 gene encodes a G protein-coupled receptor that inhibits phosphorylation of RNA-dependent protein kinase. J Virol 2005, 79:441-449.

84. Gruene B, Kamranvar SA, Masucci MG, Sompallae R: EBV and genomic instability—a new look at the role of the virus in the pathogenesis of Burkitt’s lymphoma. Semin Cancer Biol 2009, 19:394-400.

85. Shumilov A, Tsai MH, Schlosser YT, Kratz AS, Bernhardt K, Fink S, Mizani T, Lin X, Jauch A, Mautner J et al: Epstein-Barr virus particles induce centrosome amplification and chromosomal instability. Nat Commun 2017, 8:1-15.

This report demonstrates a novel mechanism by which EBV particles can induce chromosomal instability in a non-persistent infection. This research reveals a system for development of tumours that do not necessarily carry the EBV genome.

86. Chang YH, Lee CP, Su MT, Wang JT, Chen JY, Lin SF, Tsai CH, Hsieh MJ, Takada K, Chen MR: Epstein-Barr virus BGLF4 kinase retards cellular S-phase progression and induces chromosomal abnormality. PLoS One 2012, 7.

87. Wu C-C, Liu M-T, Chang Y-T, Fang C-Y, Chou S-P, Liao H-W, Kuo K-L, Hsu S-L, Chen Y-R, Wang P-W et al: Epstein-Barr virus DNase (BGLFS) induces genomic instability in human epithelial cells. Nucleic Acids Res 2010, 38:1932-1949.

88. Chiu S-H, Wu C-C, Fang C-Y, Yu S-L, Hsu H-Y, Chow Y-H, Chen J-Y: Epstein-Barr virus BGLF3 mediates genomic instability and progressive malignancy in nasopharyngeal carcinoma. Oncotarget 2014, 5:8658-8601.

89. Coen N, Duraffour S, Snoeck R, Andrei G: KSHV targeted therapy: an update on inhibitors of viral lytic replication. Viruses 2014, 6:4731-4759.

90. Carbone A, Glihoni A, Dotti G: EBV-associated lymphoproliferative disorders: classification and treatment. Oncologist 2008, 13:577-585.

91. Uldrick TS, Whitby D: Update on KSHV-epidemiology, Kaposi sarcoma pathogenesis, and treatment of Kaposi sarcoma. Cancer Lett 2011, 305:150-162.

92. Szajerka T, Jablacki J: Kaposi’s sarcoma revisited. AIDS Rev 2007, 9:230-236.
This study demonstrates a strong clinical treatment for MCD with a combination therapy of Rituximab and doxorubicin.

Song SNJ, Tomosugi N, Kawabata H, Ishikawa T, Nishikawa T, Yoshizaki K: Down-regulation of hepcidin resulting from long-term treatment with an anti-IL-6 receptor antibody (tocilizumab) improves anemia of inflammation in multicentric Castleman disease. Blood 2010, 116:3627-3634.

Williams SCP: First IL-6-blocking drug nears approval for rare blood disorder. Nat Med 2013, 19:1193.

Cohen JI: In Vaccine Development for Epstein-Barr Virus BT – Human Herpesviruses. Edited by Kawaguchi Y, Mori Y, Kimura H. Singapore: Springer; 2018:477-493.

Baiocchi RA, Ward JS, Carodeguas L, Eisenbeis CF, Peng R, Roychowdhury S, Vourganti S, Sekula T, O’Brien M, Moeschberger M et al.: GM-CSF and IL-2 induce specific cellular immunity and provide protection against Epstein-Barr virus lymphoproliferative disorder. J Clin Invest 2001, 108:887-894.

Report showing that combined GM-CSF and low-dose IL-2 therapy can prevent the immune deficiencies that lead to fatal EBV-LPD in the hPBL-SCID mouse depleted of murine NK cells, and they point to a critical role for several human cellular subsets in mediating this protective effect.

Hartlage AS, Liu T, Patton JT, Garman SL, Zhang X, Kurt H, Lozanski G, Lustberg ME, Caligiuri MA, Baiocchi RA: The Epstein-Barr virus lytic protein BZLF1 as a candidate target antigen for vaccine development. Cancer Immunol Res 2015, 3:787-795.

Andrei G, De Clercq E, Snoeck R: In Viral DNA Polymerase Inhibitors BT – Viral Genome Replication. Edited by Raney KD, Gotte M, Cameron CE. US: Springer; 2009:481-526.

Jamieson AT, Gentry GA, Subak Sharpe JH: Induction of both thymidine and deoxycytidine kinase activity by herpes viruses. J Gen Virol 1974, 24:465-480.

Li C, Quenelle DC, Prichard MN, Drach JC, Zemlicka J: Synthesis and antiviral activity of 6-deoxycyclopropavir, a new prodrug of cyclopropavir. Bioorg Med Chem 2012, 20:2669-2674.

Coen N, Duraffour S, Naesens L, Krecmerova M, Van den Oord J, Snoeck R, Andrei G: Evaluation of novel acyclic nucleoside phosphonates against human and animal gammaherpesviruses revealed an altered metabolism of cyclic prodrugs upon Epstein-Barr virus reactivation in P3HR-1 cells. J Virol 2013, 87:12422-12432.

Zhang Y-J, Patel D, Nan Y, Fan S: Inhibition of primary effusion lymphoma engraftment in SCID mice by morpholino oligomers against early lytic genes of Kaposi’s sarcoma-associated herpesvirus. Antivir Ther 2011, 16:657-666.

Zhang Y-J, Wang K-Y, Stein DA, Patel D, Watkins R, Moulton HM, Iversen PL, Matson DO: Inhibition of replication and transcription activator and latency-associated nuclear antigen of Kaposi’s sarcoma-associated herpesvirus by morpholino oligomers. Antivir Res 2007, 73:12-23.

Hahn AS, Desrosiers RC: Binding of the Kaposi’s sarcoma-associated herpesvirus to the ephrin binding surface of the EphA2 receptor and its inhibition by a small molecule. J Virol 2014, 88:8724-8734.

Schumann S, Jackson BR, Yule I, Whitehead SK, Revill C, Foster R, Whitehouse A: Targeting the ATP-dependent formation of herpesvirus ribonucleoprotein particle assembly as an antiviral approach. Nat Microbiol 2016, 2:16201.

This report demonstrates potent small molecule inhibitors of the cellular protein UAP56 that effectively inhibit KSHV lytic replication by targeting the ATP-dependent formation of viral ribonucleoprotein particles.

Baquero-Pérez B, Whitehouse A: Hsp70 isoforms are essential for the formation of Kaposi’s sarcoma-associated herpesvirus replication and transcription compartments. PLoS Pathog 2015, 11:e1005274.

Hughes DJ, Wood JJ, Jackson BR, Baquero-Pérez B, Whitehouse A: NEDDylation is essential for Kaposi’s sarcoma-associated herpesvirus latency and lytic reactivation and represents a novel anti-KSHV target. PLoS Pathog 2015, 11:1-26.

This study identifies a NEDDylation inhibitor as a novel KSHV therapeutic by preventing the recruitment of the viral pre-replication complex to the origin of lytic DNA replication.

Nichols LA, Adang LA, Kedes DH: Rapamycin blocks production of KSHV/HHV8: insights into the anti-tumor activity of an immunosuppressant drug. PLoS One 2011, 6.

Chen J, Jiang L, Lan K, Chen X: Celecoxib inhibits the lytic activation of Kaposi’s sarcoma-associated herpesvirus through down-regulation of RTA expression by inhibiting the activation of p38 MAPK. Viruses 2015, 7:2268-2287.