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In the previous chapters, US28 has been shown to activate a plethora of cellular pathways. In contrast to most chemokine receptors, which tend to couple to $G\alpha_i$, US28 couples to multiple different $G\alpha$ subunits. A second difference with the human chemokine receptors is the constitutive activation that is displayed by US28. Similar to the KSHV-encoded receptor ORF74, US28 constitutively signals through $G\alpha_q$ that, in turn, stimulates phospholipase C resulting in increased inositol-1,4,5-triphosphate levels which bind to intracellular inositol receptors triggering $Ca^{2+}$ release into the cytosol. This ultimately results in the activation of target genes like the nuclear factor of activated T-cells (NFAT) (1). Another factor activated by US28 via $G\alpha_q$ is NF-κB (1). This transcription factor is an important mediator of many cellular responses, including stress- and immune responses (2). The NF-κB signaling pathway appears to play an important role in US28, and it is pivotal in the activation of the COX-2 and STAT3 pathways (3, 4).

Multiple signaling pathways are activated by US28, and at least some of these pathways converge to induce a proliferative phenotype. The COX-2 and STAT3 pathways are both required for US28-induced VEGF production, and inhibition of either pathway results in reduced proliferation. In order to gain more insight in the role of US28 in tumor biology, two signaling routes activated by US28 have been characterized in this thesis, the IL-6/STAT3-axis (Chapter 3, 4) and Wnt/b-catenin (Chapter 5) signaling. Furthermore, a first characterization of the US28 signalosome is shown Chapter 6, which may lead to a more in-depth understanding of US28-induced signaling. Finally, the oncogenic properties of another HCMV-encoded GPCR, UL33 were investigated (Chapter 7).
8.1 US28 and UL33 constitutively induce STAT3 activation

In Chapter 3, US28 is shown to constitutively induce STAT3 signaling. The first hints of the activation of this pathway were measurements of angiogenic factors in the medium of US28-expressing NIH-3T3 cells. These measurements showed that US28 induces NIH-3T3 cells to secrete IL-6 and VEGF. In addition, CCL2 concentration in the growth medium is diminished which fits the proposed role of US28 as a chemokine sink. Following IL-6 secretion, its cognate receptor is activated. Subsequently, STAT3 is phosphorylated by JAK1, resulting in dimerization and transcriptional activation (5). Additionally, UL33 is shown in Chapter 7 to also induce STAT3 activity, although it is still unknown whether this is mediated via a mechanism similar to US28. Chapter 3 represents the first observation of US28 protein expression in glioblastoma clinical samples. Moreover, we demonstrate that STAT3 is phosphorylated in the same niche of the tumor, which suggests that a similar mechanism that we observed in our in vitro models is taking place within these tumors. Finally, the extent of STAT3 phosphorylation in the tumor correlates with patient survival and tumor progression, meaning that a high extent of STAT3 phosphorylation results in a poor prognosis.

The activation of STAT3 by US28 can be interfered with on multiple levels, on the transcriptional level by either the NF-κB inhibitor BAY11-7082 (6) or a STAT3 inhibitor like JSI-124 (7) or Stattic (8). Inhibition at the level of IL-6 and the IL-6 receptor is accomplished via neutralizing antibodies against IL-6 or small molecules inhibiting IL-6 receptor function (9). The fact that conditioned medium derived from US28-expressing cells also results in STAT3 phosphorylation together with the knowledge that STAT3 can induce IL-6 production by itself (10) indicates the possibility of a positive feedback loop. In Chapter 4 this positive feedback loop is further investigated, using a mathematical model described US28-induced STAT3 activation and IL-6 secretion. Using this model it is clear that IL-6/STAT3 signaling has the potential to generate a positive feedback loop that has the potential to run out of control. Moreover, once a certain critical amount of cells is producing IL-6, the positive feedback loop may force the production of the cytokine in the whole (cancerous) tissue creating an inflamed region. It should be noted that STAT3-signaling may be induced with multiple ligands. For example, IL-5 was found to be over-expressed in HCMV-infected cells to the same extent as IL-6 (11). Such other factors may be able to induce a positive feedback loop on their own, or facilitate one for another factor. Naturally, several mechanisms, which have been discussed in Chapter 2, are in play to prevent such a runaway feedback loop from happening. The Silencers Of Cytokine Signaling (SOCS), in particular, are important negative regulators of STAT-signaling (12). An exogenous factor such as US28 may disturb the balance between positive feedback and negative feedback for signaling networks like the STAT3 controlled pathway(s). An important question rises however, why does HCMV induce IL-6 production and what role does it play in the viral life cycle. At a first glance, it seems counter-intuitive for a virus to induce pro-inflammatory signaling in the
cells it infects. However, activation of STAT3 signaling by IL-6 also has anti-apoptotic effects (13) which may be beneficial to the virus. Additionally, since HCMV can infect macrophages (14) and monocytes (15), increased IL-6 secretion may act as a bait to attract new cells for HCMV to infect as IL-6 induces chemotaxis in both macrophages and monocytes (16). Under normal circumstances, increased IL-6 signaling would have no severe effects by virtue of the negative regulation of STAT3 activation. However, if a cell has impaired regulation of STAT3, US28-induced IL-6 signaling either in an autocrine or in a paracrine fashion may result in a proliferative phenotype like the one that is observed in the NIH-3T3 cells. HCMV-induced IL-6 production itself is correlated with aberrant angiogenesis (17, 18). Of course, dysregulation of angiogenesis in the right context is in itself a potent mediator of tumorigenesis (19).

In conclusion, US28-induced IL-6 production may create a favorable microenvironment for proliferation of HCMV. While US28 is solely responsible for HCMV-induced IL-6 production in the host cell at an early time-point of infection, at later stages during infection other viral factors may also induce IL-6 production. One such factor may be UL33, which was shown in Chapter 7 to also constitutively activate STAT3. In Chapter 7, UL33 is further described to be expressed at later time points in infection. UL33 has earlier been described to be present on the virus particle (20). Yet, the amount of UL33 at early time points may be too little to result in appreciable signaling. In this light it would be interesting to investigate whether UL33 conditioned medium can induce STAT3 phosphorylation in other cells. Additionally, it would be interesting to analyze UL33-induced secretion of proteins. This can be done in two ways, one focusing on angiogenic factors with an approach using an antibody array. This approach is sensitive enough for detecting low levels of proteins in the medium, but is biased towards angiogenic factors. The second approach entails using mass-spectrometry to identify factors from the supernatant. While this approach is less sensitive it is unbiased and will allow for a full characterization of factors whose production is induced by UL33.

8.2 US28 induces β-catenin activation

In Chapter 5, constitutive activation of β-catenin signaling is described. The involvement of this pathway in US28 signaling was first based on the same micro-array study where US28-induced COX-2 expression was detected (3). The micro-array data also indicated up-regulation of factors involved in Wnt/β-catenin signaling. Further investigation, using the TOP-Flash reporter gene revealed that US28 constitutively induces β-catenin signaling to Tcf-Lef. This was further confirmed by means of Western-blot analysis, showing increased levels of non-phosphorylated β-catenin. Interestingly, US28 activates β-catenin signaling in a non-canonical manner in NIH-3T3. However, another model system, using transgenic mice expressing US28 in the intestine shows canonical β-catenin activation (21). This clearly indicates that the mechanism by which US28 induces β-catenin signaling is very much dependent
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As mentioned above, US28 induces β-catenin signaling via a non-canonical pathway. In the canonical β-catenin signaling pathway Wnt/Frizzled is usually accompanied with LRP6 phosphorylation. However, the signaling through β-catenin that is induced by US28 in NIH-3T3 is of a different nature. US28 induces signaling via Ga<sub>q</sub> and Ga<sub>12/13</sub>, which subsequently results in activation of Rho/ROCK signaling. Further downstream this leads to Tcf/Lef activation.

Further investigation, detailed in Chapter 6, suggests that in the NIH-3T3 background US28 inhibits Akt phosphorylation by activating Rho-associated protein kinase (ROCK) via RhoA. Acting further downstream in this signaling route are two protein phosphatases, PP2A and PTEN. Both PP2A and PTEN have a key role in the regulation of different signaling routes, including oncogenic pathways. In the case of US28-induced signaling, where either or both PP2A and PTEN are activated by US28, which may result in decreased Akt activation.

Further downstream, the transcriptional regulator Chibby (Cby) has been identified as an important factor in regulating β-catenin signaling (22). Interestingly, Cby’s antagonistic function is counteracted by TC1 (23). Moreover, TC1 is reported to be overexpressed in thyroid cancer (23) and metastatic colon cancer (24). In the case of colon cancer, increased TC1 expression is correlated with poor prognosis. This observation fits well with our current understanding of the molecular mechanisms by which Cby asserts its influence on β-catenin signaling. Indeed, US28 may have a similar effect as TC1 on Cby/β-catenin interaction albeit via another mechanism.

Besides the difference in the mechanisms by which US28 and TC1 accomplish functional inhibition of Cby, in both cases it results in a removal of the ‘brakes’ on β-catenin signaling. It is unlikely that inhibiting Cby will directly result in transforma-

Figure 2. Schematic depiction of Lgr5 expression in humans. Data analyzed by the Atlas project from EMBL shows studies reporting over-expression in red and under-expression in blue. Most expression data is available about the brain and the digestive system.
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In the US28-expressing transgenic mice expression is driven by the murine villin promoter. This results in high expression levels throughout the intestinal epithelium. The intestinal epithelium is constantly replaced with new cells, which originate from the intestinal crypts. At the bottom of these crypts reside the intestinal stem cells that give rise to all the different epithelial cells, these cells express the GPCR Lgr5 and are defined as Lgr5+ cells (25). In the case of the transgenic mice mentioned above, US28 is also expressed by the Lgr5+ cells. Since deletion of APC in these cells results in rapid formation of adenomas (26), the presence US28 in Lgr5+ cells may be part of the mechanism that results in the formation of tumors in these mice. Interestingly, Lgr5+ cells can autonomously form intestinal crypt structures; these structures have been termed organoids. The presence of Paneth cells increases the efficiency of this process (27, 28). Lgr5+ cells are not only present in the intestine, Lgr5 is expressed in various tissues as shown in Figure 1. Organoids have been successfully cultured from Lgr5+ cells obtained from the stomach (29). Especially Lgr5 expression in the brain is interesting, considering the presence of US28 in glioblastoma that was described in Chapter 3. The LGR5 gene was found to be amplified in recurrent glioblastomas. (30). Moreover, knock-down of Lgr5 in brain cells

Figure 2. CCL5 and CX3CL1 have no effect on US28-induced proliferation. For this experiments NIH-3T3 cells were subjected to a similar proliferation experiment as detailed in Chapter 2. Briefly, the cells were incubated for 24 hours with either CCL5 or CX3CL1 in medium containing [3H]-thymidine. The concentration used for either chemokines was 10-7 M.
with a cancer-stem cell profile induces apoptosis (31). Recently, cancer stem cells have been shown to play a pivotal role in tumor maintenance in murine models for intestinal tumors and glioblastoma (32, 33). This raises the question whether US28 is also expressed in cancer stem cells in patients suffering from HCMV-associated cancers.

Since Lgr5+ cells are dependent on a variety of factors among which Wnt3a, it will be interesting to see whether Lgr5+ cells that express US28 will exhibit a different phenotype compared to wild-type organoids. To further study the tentative link between US28 and Lgr5+ stem cells, and their role in HCMV-associated cancers, it will be necessary to show combined US28 and Lgr5 expression in these cancers. While US28 expression has been shown in glioblastomas, analyzing Lgr5 expression in these tumors will be difficult as there is no reliable antibody yet. An alternative method would be to perform in situ RNA hybridizations to detect other stem cell markers such as Olfm4 or Ascl2. Both these genes have been successfully used as markers in mice and appear to be very specific (28, 34). Whether this is also the case in humans remains to be seen, but the fact that both these genes are highly conserved suggests that this may be the case.

In conclusion, US28 induces β-catenin activation via two possible signaling routes. A canonical route that was described in the transgenic mouse model (21) and a non-canonical route, through Rho and ROCK, whose increased activity results in increased Tcf/Lef activity. Our data in Chapter 6 suggests that US28-induced activation of Rho and ROCK results in dysregulation of Akt-regulated phosphorylation of Cby and β-catenin. To what extent induction of β-catenin by US28 is responsible for the induction of HCMV associated cancers remains to be clarified. It will be interesting to see whether β-catenin activation by US28, like STAT3, can be correlated in glioblastoma. Especially since β-catenin over-expression is associated with glioblastoma growth (35, 36). Even more interesting, targeting the β-catenin in these cancers results in the down-regulation of several other signaling factors among which STAT3 (2). This suggests that there may be interplay between these two pathways.

8.3 Role of ligand-induced US28 signaling

In general, constitutive signaling appears to be a hallmark for US28. However, CCL5 and CX3CL1 which both bind to US28 can influence signaling to a certain extent (1, 37). While CCL5 generally acts as an agonist, potentiating calcium release induced by US28 (38), it has no effect of inositol phosphate accumulation (1). Moreover, CCL5 and CCL2 are both capable of inducing chemotaxis in vascular smooth muscle cells (39), which is a clear indication of ligand-dependent pathways controlled by US28. CX3CL1, on the other hand, acts in some cases as an inverse agonist on US28, inhibiting inositol phosphate accumulation. In the context of calcium signaling, however, it acts as an agonist (1, 37). Furthermore, CCL5 can increase US28-induced Tcf/Lef activity. It is likely that the response of US28 to a ligand is dependent on the cellular context. The clinical data presented in Chapter 3 indicates that US28-ex-
pression appears to be localized in a specific subset of cells. This possibly highlights the importance of cellular context, and the need for a relevant model system for in vitro studies. Despite these concerns, the data presented in this thesis, as well as data from earlier studies indicate that ligand-induced signaling is not critical for US28-induced proliferation. In Figure 2, this is further demonstrated in a thymidine incorporation experiment. However, the fact that ligands do not seem to play a direct role in US28-induced proliferative signaling does not exclude a role for them in tumorigenesis. Especially considering the recent data from Bongers et al., where CCL2 over-expressing mice were crossed with mice expressing US28 in the intestine. This crossing exacerbated tumor formation in these mice (21). The vascular smooth muscle cell migration mentioned earlier may be an indication for a role of US28 in tumor angiogenesis.

8.4 To what extent is UL33 mirroring US28 signaling?

In Chapter 7 signaling by another HCMV encoded chemokine receptor homolog is explored in further detail. Earlier research had already shown that, like US28, UL33 signals in a constitutive manner through NF-κB (40). Besides this data, not much was known about UL33’s signaling. The discovery of US28’s propensity for inducing proliferation in NIH-3T3 cells together with the fact that both proteins display constitutive activity prompted us to investigate UL33’s oncomodulatory properties. Moreover, immunohistochemistry staining of glioblastoma tumor samples shows presence of UL33 in these tumors. In contrast with the US28 stainings shown in Chapter 3, UL33 appears to be present in large portions of the tumor. Double staining for US28 and UL33 may give further insights in the role that either receptor plays in the tumor biology of glioblastoma.

Our data show that there is a large degree of overlap between signaling by US28 and UL33, which may indicate that both receptors can take over each other signaling. This could provide HCMV with a degree of redundancy. However, arguing against redundancy, US28 is present at early stages of infection, whereas UL33 is present only at 96 hours post infection. Alternatively, UL33 and US28 may potentiate each others signaling. Work by Tschische et al. has shown that UL33 and UL78 can form heterodimers with US28, and may influence the constitutive signaling displayed by US28 (41). Considering the differences in temporal expression of both US28 and UL33 this may represent a way for HCMV to regulate signaling of both molecules. One of the attractive features of UL33 is that, unlike US28, there is a mouse cytomegalovirus (MCMV) homolog, M33. Moreover, deletion of M33 from the MCMV genome results in a virus that displays impaired dissemination as well as attenuated infection of the spleen and pancreas (42). Reactivation was also negatively affected in the M33 deletion strain (38). Recently, complementation experiments using a strain of MCMV in which the gene encoding M33 is deleted (MCMV ΔM33) have shown that both US28 and UL33 can both functionally replace M33 in MCMV ΔM33 (43). It will be interesting to see whether US28 and UL33 in this model can have on-
comodulatory effects. To answer this question, these recombinant viruses may be used in combination with existing mouse models for different cancers.

8.5 Mathematical modeling of US28’s modulation of the STAT3 signaling pathway

Cellular responses are the result of the integration of multiple signaling events that are relayed through different signal transduction routes. To add to the complexity of signaling many pathways also engage in crosstalk with each other. The relatively new field of systems biology seeks to describe, model, and ultimately predict these signaling networks. In Chapter 4 US28-induced signaling through the IL-6/STAT3 axis is described in great detail. Because of its paracrine nature, induction of the IL-6/STAT3 axis by an external factor was modeled. This model shows that STAT3 signaling has the potential to become engaged in a positive feedback loop. The model also reveals that STAT3 signaling needs to be tightly controlled, as it is prone to enter a positive feedback loop. One can imagine that it is reasonable for a rapid response system to exhibit such behavior. Experiments corroborated this model and showed that picomolar concentrations of IL-6 can already trigger a STAT3 response in cells. Moreover, the same experiments show that treatment with IL-6 induces the expression of IL-6 and prolonged STAT3 phosphorylation.

Considering that US28 induces IL-6 production via NF-κB, these data suggest that US28 may significantly influence the external milieu even when the amount of cells that actually express US28 is very small. It should be noted though, that STAT3 signaling is normally tightly controlled by several negative feedback mechanisms, amongst which are the SOCS proteins as discussed in Chapter 2. It is known that in many cancers the STAT3 pathway is affected, either by mutations in STAT3 itself or by mutations in the associated receptors and regulatory proteins. Mutations that render STAT3 constitutively active have been shown to be able to induce angiogenesis (44), although such mutations remain to be demonstrated in patient samples. Another level at which IL-6/STAT3 signaling can be altered is at the IL-6 receptor. Mutations in the transactivating gp130 subunit of the IL-6 receptor can result in constitutive activation of the IL-6/STAT3 pathway that, in turn, results in increased production of IL-6. Such mutations have been described in hepatocellular tumors, which interestingly are always accompanied by mutations in β-catenin signaling proteins (45). Regulation of IL-6 expression itself can also be affected as was shown by Iliopoulos et al. where they demonstrated that transient activation of NF-κB can result in permanent downregulation of Let7 miRNAs. Let7 is an inhibitory factor of IL-6 expression, which thus results in increased IL-6 levels (46). Finally, overexpression of SOCS3 has been reported to inhibit growth of human non-small cell lung cancer cells as well as rendering them more sensitive to radiation (47). Also, epigenetic silencing of SOCS3 has been reported in several cancers (48-50). These data all indicate the effect of changes in signaling through the IL-6/STAT3 axis are dependent on the cellular context.

While the model proposed in Chapter 4 certainly has predictive value, its real use-
fulness will become apparent when it can be linked to the other pathways engaged by US28. Until now, we have mainly described how the different pathways are activated via the viral receptors. However, if the signaling through the different routes can be integrated into one model that would greatly increase our understanding of US28 signaling and perhaps even allow for predictions in what kind of cells or tissue US28 may exert its oncomodulatory effects.

8.6 What new insights does the US28 signalosome offer?

Although the efforts described in this thesis as well as those of others have shed light on several important facets of US28 signaling, there are still significant caveats in our understanding of US28-induced signaling. In order to gain more understanding of US28-induced signaling, we analyzed the US28 signalosome in Chapter 6. The proteins that interact with a receptor and mediate its signaling are referred to as the signalosome. To be able to isolate this subset of proteins a methodology for isolating US28 with its interacting partners had to be developed. As described in Chapter 6, a modified immuno-precipitation protocol was used to perform pull-downs of US28 and its interacting partners, using anti-HA conjugated agarose and N-terminally HA-tagged US28. The co-precipitating proteins were then identified by way of liquid chromatography tandem mass-spectrometry.

While such an approach is immensely powerful, one major drawback is that the shear amount of data obtained by these analyses can be daunting. For now, this limits the use of proteomics for understanding cellular signaling. Of course, this is partly due to the fact that most experimental setups for analyzing cellular signaling by mass-spectrometry have been in the development phase for the last few years. As the techniques mature and the data analysis is standardized, it will be possible to assign reliability scores to the different datasets instead of the current practice of collecting all proteomics results regardless of data quality.

The 14-3-3 proteins are overrepresented in the US28 signalsome. Because of the important role these proteins have in cellular signaling, this may result in aberrant signaling across many signaling pathways. An example of this was discussed earlier in Chapter 6 where the binding of 14-3-3s by US28 is proposed to interfere with β-catenin regulation by Cby. Several factors that are normally associated with mitochondrial function were also found to co-precipitate with US28. This was a surprising finding, which suggests an important role for intracellular US28 in the alteration of cellular signaling and may also be indicative for a role for US28 in the HCMV-induced shift from oxidative phosphorylation to glycolysis by cytosolic lactic acid fermentation (also known as the Warburg effect) (51).

The current technique for co-immunoprecipitation of the US28 signalosome has proven to be reliable and reproducible. However, this analysis cannot distinguish between the different cellular compartments. An analysis of the differences between intracellular versus the US28 that is present on the plasma membrane would shed light on which of the US28 populations is responsible for the different signal-
ing pathways. In order to address this issue a methodology for isolating the different US28 populations needs to be developed. We have explored two different approaches. First a classical biochemical approach using sucrose gradients to separate the different cellular compartments was employed. The main advantage of this approach is that it allows for analysis of the different compartments using the same preparation. However, while it was no problem to isolate US28 from the plasma membrane compartment as well as from other compartments, we found that it was difficult to obtain enough protein for mass-spectrometry analysis. Furthermore, reproducibility was also an issue using this approach. Therefore an alternative method, using selective biotinylation of plasma membrane proteins with NHS-SS-biotin was explored. This method takes advantage of the fact that NHS-SS-biotin cannot cross the plasma membrane leading to biotinylation of only extracellular lysines. Following biotinylation the cells expressing HA-tagged US28 can be subjected to the established co-immunoprecipitation method. Subsequently, the eluted US28 with their associated proteins are subjected to a biotin pull-down, using streptavidin. The resulting protein fraction will consist of biotinylated US28 and its associated proteins. Initial experiments have shown that it is possible using this method to not only purify biotinylated US28 (Figure 3A), but also associated proteins as shown by silverstaining of the resulting protein mixture (Figure 3B). Another promising technique involves the use of the lectin concanavalin A to isolate the plasma membrane compartment. Concanavalin A binds to the α-D-glucose and α-D-mannose of glycosylated membrane proteins (52). Lee and colleagues have developed a method using concanavalin A bound to magnetic beads that can be used to quickly and reliably purify the plasma membrane fraction. Hence, using the above mentioned techniques, the signalosomes of plasma membrane bound US28 and intracellular US28 can be analyzed which may result in an increased understanding how US28 redirects cellular signaling.

![Figure 3](image.png)

**Figure 3.** (A) Western-blot analysis showing successful isolation of HA-US28 from HEK293T cells transfected with DNA encoding HA-US28. (B) A silverstaining showing co-precipitating proteins that are co-isolated with US28, while some proteins are isolated in a non-specific manner as shown in the Mock sample, the majority of proteins are specifically co-precipitating with US28.
8.7 Pharmaceutical intervention strategies, target US28 and UL33 or its pathways?

Considering that a significant portion of the population is HCMV sero-positive, US28 may have an important impact on tumor biology in general. We have shown for the first time that in at least one type of cancer, glioblastoma, US28-associated signaling has a significant effect on tumor progression and patient survival. Efforts to target US28 signaling with inverse agonists have been made (53-55). While these compounds are useful research tools, their potential as drugs is limited due to poor water solubility and low potency.

Considering the knowledge we now have of US28-induced signaling, it may actually be more advantageous to target the pathways that are induced by US28 instead of the receptor itself. Especially considering the paracrine effects that US28 has on surrounding cells. For example, treatment with STAT3 inhibitors may be a viable way of interfering with US28-mediated STAT3 activation. One drawback of targeting the signal transduction pathway instead of the receptor is the potential loss of specificity since these pathways are present in many different cells.

Systems biology approaches will play an important role in addressing the first issue of specificity. By understanding how the different signal transduction routes interact which each other, the models can be predictive and provide insight how to target these pathways to get the desired cellular response (eg. death of a tumor cell).

Another HCMV-encoded GPCR, UL33, was found to have similar tumorigenic properties as US28. In Chapter 7 the way UL33 induces a proliferative phenotype is similar to US28. Moreover, both US28 and UL33 can be found in glioblastoma tumor samples. The fact that these two proteins are expressed at similar times during infection (albeit that US28 is also expressed at early stages of infection) suggests that US28 and UL33 can act as back-up for each other. Therefore, a pharmacological intervention strategy aimed at inhibiting HCMV-induced proliferative signaling should take into account both US28 and UL33.

To this end, the work described in this thesis has contributed to understanding the way viral GPCRs like US28 and UL33 induce oncomodulatory behavior and which may result in new strategies for treating HCMV-related cancers like glioblastoma.
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