Review

The Impact of Human Papilloma Viruses, Matrix Metallo-Proteinases and HIV Protease Inhibitors on the Onset and Progression of Uterine Cervix Epithelial Tumors: A Review of Preclinical and Clinical Studies

Giovanni Barillari [1],*, Paolo Monini [2], Cecilia Sgadari [2] and Barbara Ensoli [2]

[1] Department of Clinical Sciences and Translational Medicine, University of Rome Tor Vergata,
1 via Montpellier, 00133 Rome, Italy

[2] National HIV/AIDS Research Center, Istituto Superiore di Sanità, 299 viale Regina Elena, 00161 Rome, Italy;
paolo.monini@iss.it (P.M.); cecilia.sgadari@iss.it (C.S.); barbara.ensoli@iss.it (B.E.)

* Correspondence: barillar@uniroma2.it; Tel.: +39-06-7259-6510; Fax: +39-06-7259-6506

check for updates

Abstract: Infection of uterine cervix epithelial cells by the Human Papilloma Viruses (HPV) is associated with the development of dysplastic/hyperplastic lesions, termed cervical intraepithelial neoplasia (CIN). CIN lesions may regress, persist or progress to invasive cervical carcinoma (CC), a leading cause of death worldwide. CIN is particularly frequent and aggressive in women infected by both HPV and the Human Immunodeficiency Virus (HIV), as compared to the general female population. In these individuals, however, therapeutic regimens employing HIV protease inhibitors (HIV-PI) have reduced CIN incidence and/or clinical progression, shedding light on the mechanism(s) of its development. This article reviews published work concerning: (i) the role of HPV proteins (including HPV-E5, E6 and E7) and of matrix-metalloproteinases (MMPs) in CIN evolution into invasive CC; and (ii) the effect of HIV-PI on events leading to CIN progression such as basement membrane and extracellular matrix invasion by HPV-positive CIN cells and the formation of new blood vessels. Results from the reviewed literature indicate that CIN clinical progression can be monitored by evaluating the expression of MMPs and HPV proteins and they suggest the use of HIV-PI or their derivatives for the block of CIN evolution into CC in both HIV-infected and uninfected women.

Keywords: HPV; uterine CIN; uterine cervical carcinoma; MMP; HIV-PI

---

1. Role of the HPV-E5, E6 and E7 Proteins in the Development of Uterine Cervical Pre-Cancer and Cancer Lesions

Infection by human papilloma virus (HPV) is frequent in sexually active women and plays a driving role in the development of proliferative/dysplastic or tumor lesions of the uterine cervix [1]. In particular, HPV is present in almost the totality of uterine cervical carcinoma (CC), which is the third most frequent malignancy in women worldwide [1].

The uterine cervix is composed by two different types of epithelium. Specifically, the endocervix is lined by a simple glandular epithelium, while the ectocervix is lined by a squamous epithelium constituted by superficial and deep (basal) layers [2]. At puberty, the endocervical glandular epithelium proximal to the ectocervix is replaced by the stratified squamous epithelium typical of the ectocervix. This trans-differentiated area is known as the "transformation zone" [2].

The proper stratification of uterine ectocervical epithelium and "transformation zone" is maintained through a tight control of epithelial cell growth, differentiation and locomotion. Specifically, epithelial cells originate in the deep layers, maturate and migrate to the superficial layer where they fully differentiate and desquamate in a continuous, self-renewing process [2].

This dynamic equilibrium is compromised by HPV which, in the presence of cervical micro-wounds, can access the deep layers and enter immature, proliferating cells [3,4]. There, the circular, double-stranded HPV DNA is maintained as an extra-chromosomal element (episome) which replicates via the synthetic machinery of host cell genome [3,4]. As such, HPV forces infected immature cervical cells to remain in a proliferative state and impedes their terminal differentiation. In particular, during HPV DNA replication, the HPV early genes, including those coding for the E5, E6 or E7 proteins, are transcribed [4]. Although HPV-E1 and E2 proteins support viral replication in the basal cells at a low copy number [5], HPV-E5, E6 or E7 are produced at levels sufficient to functionally impair host cell growth-regulatory or differentiation factors [4,6].

In particular, the HPV-E5 protein interferes with the signaling pathways of epidermal growth factor (EGF), a powerful inducer of epithelial cell survival, growth and locomotion [6]. Specifically, E5 promotes the sustained activation of EGF receptor, resulting in the triggering of protein kinases including the serine/threonine kinase AKT which, in turn, leads to epithelial cell survival and proliferation [6]. In this context, HPV-E5 down-regulates the expression of the p21 or p27 cell cycle inhibitors and counteracts cell death induced by the Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) or Fas-Fas ligand signaling [6]. Noteworthy, the amplification of EGF signaling promoted by HPV-E5 also inhibits epithelial cell differentiation via a reduction of keratinocyte growth factor expression [7].

Concerning HPV-E7, it binds and inactivates the retinoblastoma tumor suppressor protein (pRb), hence preventing infected cells from exiting the cell cycle and differentiating (Figure 1) [8].
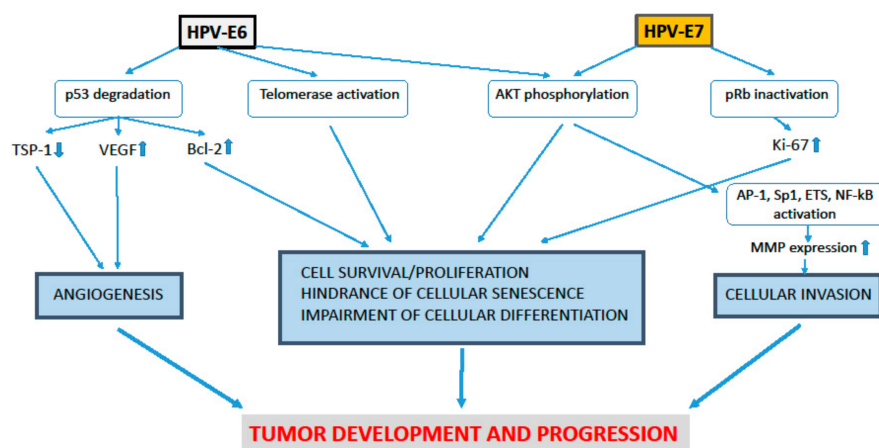

Figure 1. Tumorigenic effects of the E6 or E7 proteins of high-risk human papilloma viruses (HR-HPV). Arrows symbolize directions of connections. The E6 protein promotes p53 degradation, and this is followed by the down-regulation of thrombospondin (TSP)-1, or the up-regulation of vascular endothelial cell growth factor (VEGF) which, in turn, lead to angiogenesis. At the same time, E7 inactivates the retinoblastoma protein (pRb), and this increases Ki-67 protein levels. Noteworthy, both E6 and E7 induce AKT phosphorylation. This, together with the activation of telomerase or the up-regulation of Bcl-2 promoted by E6, and the increase of Ki-67 induced by E7, causes cell survival and proliferation. Moreover, the phosphorylation of AKT triggered by either E6 or E7 activates transcription factors including Activator Protein (AP)-1, Sp (Specificity protein)-1, ETS or Nuclear Factor-kappa B (NF-κB) which, in turn, induce matrix-metalloproteinase (MMP) expression and cellular invasion. Cell survival/proliferation/invasion and angiogenesis promoted by the E6 or E7 protein of HR-PV lead to tumor development and progression.

At the same time, HPV-E6 directs the host cell tumor suppressor protein p53 toward degradation through the cellular proteasome (Figure 1) [9]. In doing so, E6 increases the intracellular levels of the anti-apoptosis Bcl-2 protein which is normally repressed by p53 (Figure 1) [9]. In addition, E6 triggers the activity of telomerase, an enzyme that prevents replicative senescence by stabilizing the length of the chromosomes' end (Figure 1) [9].

Moreover, the HPV-E5, E6 or E7 proteins stimulate the cyclooxygenase (COX)-2 inflammatory pathway which, as for EGF, counteracts the apoptosis of epithelial cells and promotes their proliferation [6].

Altogether, these activities of E5, E6 or E7 render HPV-infected cells insensitive to the regulatory signals of normal growth and block apoptosis otherwise occurring due to the sustained, uncontrolled cellular proliferation [6,8,9].

In about 80% of the cases, HPV-induced cell proliferation remains subclinical, augmenting cervical epithelium thickness or causing benign flat warts [10]. In the other cases, HPV-E5, E6 and E7 accelerate the growth rate of immature cervical basal cells and their migration to the superficial layer. This leads to the development of squamous intraepithelial lesions (SIL) [2,11].

According to the Bethesda system for reporting cervical cytological diagnosis, there are two kinds of SIL: low grade-SIL (L-SIL), which is the histologic correlate of productive HPV infection and high grade-SIL (H-SIL), that represents the early stages of HPV-induced carcinogenesis [2,11].

L-SIL corresponds histologically to grade 1 cervical intraepithelial neoplasia (CIN1), a mild dysplasia characterized by proliferating immature basal cells constituting 1/3 of the cervical epithelium. Because of HPV replication, superficial cells display koilocytosis (cave-like vacuoles around enlarged, hyper-chromatic nuclei) and altered keratinization [2,11].

H-SIL comprises grade 2 and 3 CIN (CIN2 and CIN3). The former is a moderate dysplasia in which basal cell types represent the 2/3 of cervical epithelium and koilocytosis and dyskeratosis are more evident than in CIN1; whereas, CIN3 is a severe dysplasia, characterized by proliferating basal-like cells having abnormal nuclei and atypical mitoses, which occupy the 2/3 of the entire epithelium, including the superficial layers [2,11].

Generally, an effective immune response to HPV develops within months after infection, resulting in viral clearance [3,10]. Thereafter, p53 and pRb function in the basal layers is restored and epithelial cell growth and differentiation return to normality. This generally occurs with low-risk HPV types, such as HPV6 or HPV11, whose DNA remains episomal [10].

In contrast, persistent infection with high risk (HR)-HPV, including HPV16 and HPV18, can be followed by the integration of viral DNA into the host cell genome [5]. The probability of having persistent HR-HPV infection augments progressively with higher viral load [12] and it is favored by E5, E6 or E7 activities permitting HR-HPV escape from host immune surveillance. In particular, both the E5 and E7 proteins of HR-HPV can impair major histocompatibility complex (MHC)-restricted presentation of viral peptides to cytotoxic or helper T lymphocytes [13,14]. Specifically, E7 down-regulates the expression of MHC class I molecules, while E5 arrests them in the Golgi apparatus, reduces their transport to the cell surface and/or diminishes MHC class II expression [13,14]. Moreover, either the E6 or E7 protein of HR-HPV inhibits the production of the immune-stimulatory, anti-viral interferons and reduces the synthesis of proteins attracting antigen-presenting macrophages, dendritic or Langerhans cells to the infected area [13]. In addition, HR-HPV-E5, E6 or E7 can trigger molecular pathways leading to the shift from cellular to humoral immune response, the silencing of inflammation, the impairment of natural killer cell or natural killer T cell activity and the recruitment of immune suppressive regulatory T cells [13,14].

HPV integration into cellular DNA causes the deletion of the *HPV-E2* gene and the consequent overexpression of *HPV-E6 or E7* [5]. As for *HPV-E2*, also the *E5* gene of HPV is often deleted upon the integration of HPV DNA in the host cell genome [6]. Thus, at variance with *E5*, the *E6* and *E7* genes are permanently expressed during HPV infection, being indispensable for the maintenance of the

transformed cell phenotype. For this reason, E6 and E7 are considered as the main transforming proteins of HPV [7–9].

In fact, as a result of *HPV-E6* or *E7* overexpression caused by *E2* gene deletion, the disturbance of cervical epithelial cell maturation and stratification is exacerbated [5]. In this context, cellular key mitotic checkpoints are impaired, leading to genomic instability, accumulation of secondary mutations and aneuploidy in infected cells [15–18]. Subsequently, the entire cervical epithelium is replaced by poorly differentiated cells displaying abnormal nuclei and atypical mitoses [2,11]. Later on, some of these cells acquire a "spindle" morphology and degrade the epithelial basement membrane, giving rise to the onset of an invasive cancer, whose predominant histological type is squamous cell carcinoma [2,11].

Interestingly, CC develops mainly in uterine cervical "transformation zone", which is rich in immature, highly proliferating and HPV-sensitive basal cells [2]. Noteworthy, as for other tumor settings [19], CIN evolution into a true malignancy is accompanied by the formation of new blood vessels (angiogenesis) at the stromal/epithelial junction of CIN lesions [20,21]. Specifically, endothelial cells lining the lumen of the pre-existing vessels invade the vascular basement membrane, sprout, proliferate and migrate in the extra-vascular space, where they organize into hollow cords permitting blood influx [20,21]. These newly formed vessels nourish the growing tumor and provide additional routes for CC metastasis [20,21]. Accordingly, higher intra-tumor vessel density is associated with CC aggressiveness or recurrence and poorer patient survival [22,23].

It is of note that HPV infection has an important role also in CC-associated neovascularization. In particular, following p53 degradation promoted by HPV-E6, p53-induced genes encoding for angiogenesis inhibitors, such as thrombospondin (TSP)-1, are no longer transcribed; whereas, the p53-repressed genes of angiogenic factors, including vascular endothelial growth factor (VEGF), are up-regulated (Figure 1) [21]. Of interest, also HPV-E5 can promote VEGF expression and this is due to E5 capability of triggering both EGF and COX-2 signaling [6].

However, it should be highlighted that HPV infection progresses to cancer only in a small percentage of cases and that CIN lesions can also stabilize or regress [24]. In particular, the natural history of CIN1 includes regression (60% of cases), persistence (30%) and progression to CIN3 (10%) [24]. The like-hood of CIN2 regression is 45%, persisting 30% and progressing to CIN3 or invasive CC are 20% and 5%, respectively [24]. Concerning CIN3, about 35% of cases regress, while 10–15% evolve into invasive CC [24].

The risk of CIN progression to invasive CC is increased by the use of oral contraceptives, smoking, early age at first sexual intercourse, multiple sexual partners, repeated parity and co-infections [25–27]. To this regard, women infected by both HR-HPV and the human immunodeficiency virus (HIV)-1 have a higher incidence of uterine CIN and CC, as compared to their HIV-negative counterparts [28–35]. In addition, HR-HPV/HIV-doubly infected women have lower regression rates from high-grade to low-grade CIN, or from low-grade CIN to normal epithelium [31] and faster progression from low-grade to high-grade CIN [28,35]. Consistently, the median age of HIV-positive CC patients is much lower than in HIV-negative CC patients [36]. Furthermore, CIN recurrence after treatment is particularly frequent in HR-HPV/HIV-doubly infected women [31]. Because of these findings, uterine CC is considered an Acquired Immune Deficiency Syndrome (AIDS)-defining disease [37].

Indeed, both the incidence and the progression rates of cervical lesions increase with the impairment of immune functions promoted by HIV, as indicated by the decrease in CD4^{+} T cell counts [28,35,38]. Certainly, the lack of an effective immune response to HR-HPV may favor its persistence, which is the main risk factor for CC development [1,38]. Nevertheless, HIV-1 is likely to have also a direct role in CIN progression to CC. In particular, results from in vitro studies indicate that the HIV-1 trans-activator (Tat) can up-regulate HR-HPV E6 or E7 expression, thereby decreasing the protein levels of cellular onco-suppressors and accelerating epithelial cell growth [39–42]. In addition, HIV-1 Tat may also favor the angiogenic switch of high-grade CIN, either because of its direct angiogenic effects [43] or, again, via the up-regulation of HR-HPV E6 or E7 expression [21].

Due to the dynamism of cervical lesions, cytological testing (PAP test) or histopathology is not always sufficient to assess the risk of CIN progression or its regression. Thus, morphological examination of cervical samples must be accompanied by the detection of risk biomarkers for high-grade CIN or CC, including the presence of HR-HPV DNA [44] and HR-HPV E6 and E7 overexpression [45,46]. Additional analyses are employed to monitor cellular (host) proteins whose synthesis in cervical lesions is de-regulated upon p53 and pRb functional inactivation. These include the cyclin-dependent kinase inhibitor p16INK4a and the proliferation antigen Ki-67 (Figure 1) [47–49]. In particular, the progression of CIN lesions can be predicted by the combination of low pRb/p53 and high Ki-67/p16INK4a expression in the basal layers of the cervical epithelium [47–49]. Recent data suggest evaluating the profile of specific cellular micro-RNAs that have an important role in cervical carcinogenesis and are modulated by the E5, E6 or E7 proteins of HR-HPV [50]. Further prognostic information is provided by $CD4^+$ T cell counts in HPV/HIV doubly-infected women [35,36,38] and by an increase in the expression and/or activity of the cellular matrix-metalloproteinases (MMPs), which occurs in both HIV-positive and HIV-negative women.

2. The MMPs and Their Role in the Progression of Uterine Cervical Pre-Cancer and Cancer Lesions

MMPs are a family of peptidases defined by the presence of a zinc ion at the catalytic site and by the capability of degrading the protein components of the basement membrane and extracellular matrix (ECM) [51–53].

Human MMPs consist of distinct proteases which are classified in soluble and membrane-anchored [51–53].

Soluble MMPs contain an NH_2-terminal secretion leader sequence and they include collagenases, stromelysins, matrilysins, the metalloelastase and gelatinases. Among the latter are MMP-2 and MMP-9, two powerful enzymes which can degrade a wide variety of basement membrane and ECM molecules [51–53].

The membrane-anchored MMPs (also called membrane type MMPs, MT-MMPs) display a COOH-terminal trans-membrane domain linked to a cytoplasmic tail and comprise 6 members [54]. The best known is MT1-MMP which, in addition to breaking down the ECM, is the main activator of MMP-2 [54].

Thus, ECM molecules are not the only target of MMPs, which can modify or digest many other extracellular or intracellular proteins, including enzymes, cytokines, chemokines and adhesion or growth factor receptors [52,55].

Because of these properties, MMPs are deeply involved in tissue remodeling or repair, in the regulation of cell growth, survival or differentiation and in reactive processes such as immunity and inflammation [56].

In physiological conditions, MMP expression is absent or very low in most tissues, being induced or up-regulated only during reactive/reparative processes [51–53,57]. In these events, growth factors, hormones or cytokines trigger signaling molecules that, in turn, activate transcription factors such as Activator Protein (AP)-1, ETS, Specificity protein (Sp)-1, and/or Nuclear Factor-kappa B (NF-κB) [58–68]. These activation pathways depend on the different cell types synthesizing MMPs and are influenced by cell-to-cell contacts and cell-ECM interactions [51–53].

In order to keep under control their potent activity, soluble MMPs are secreted as latent zymogens (proMMPs), which are converted into the active form around their producing cells, this providing a spatial control of MMP function [51,52].

Active soluble MMPs, in turn, can be inactivated/degraded by other MMPs or members of other classes of proteases, according to a multi-faced regulatory circuit [51,52].

Moreover, the function of active MMPs is controlled by endogenous inhibitors, which include serum globulins and the Tissue Inhibitors of MMPs (TIMPs) [51,52,69]. The latter are present in most human tissues, where they inhibit MMPs with a 1:1 molar stoichiometry, mainly via the binding of

their amino-terminal to the MMP catalytic site [69]. To date, four TIMPs have been identified: they share about 40% sequence homology and hinder all the human MMPs, albeit with variable affinity. In particular, TIMP-3 has the broadest inhibitory spectrum [69], while TIMP-1 or TIMP-2 antagonize mostly MMP-9 or MMP-2 activity, respectively [70].

As for soluble MMPs, also the MT-MMPs are synthesized as latent zymogens (proMT-MMPs): inside the cell, the pro-hormone convertase furin converts proMT-MMPs into active MT-MMPs, which are then expressed on the cell surface, where they can complex TIMPs [54]. TIMP capability of inhibiting MT-MMP activity and the fact that in the absence of TIMPs the MT-MMPs quickly undergo autolysis, reduces the number of fully active MT-MMP molecules on the cell membrane [54].

In summary, consistent with its potency and pleiotropic effects, the activity of MMPs is tightly regulated at both the transcriptional and post-transcriptional level. This occurs in physiological conditions; whereas, inflammatory/degenerative diseases or tumors are characterized by an abnormal expression of MMPs and/or their deregulated function [58,71].

In particular, cancer cells synthesize MMPs following the activation of oncogenes, the inactivation of onco-suppressor proteins, the stimulation by growth factors or inflammatory mediators, the generation of reactive oxygen species, and/or the presence of hypoxia [72–76]. Since MMPs are produced in tumor tissues also by fibroblasts and infiltrating inflammatory cells [58,71,77,78], MMP expression and/or activity are increased in tumor lesions as compared to neighbor normal tissues [79–88].

Most notably, MMPs play an important role in tumor progression. Specifically, they digest cell surface molecules mediating cell-to-cell or cell-to-ECM adhesion (e.g., cadherins or integrins), thus allowing tumor cells to detach from adjacent cells and the ECM [58,71]. Then, MMPs degrade basement membranes and the ECM, preparing a route for cancer cell locomotion and tissue invasion [58,71]. In doing so, MMPs allow cancer cells to reach local blood or lymphatic vessels and penetrate their wall, leading to metastases [58,71]. Following their arrest in the lumen of small vessels, cancer cells penetrate again the vessel wall through MMP action and, in case they escape immune surveillance, give rise to secondary tumors [58,71]. Noteworthy, during all these steps, MMPs sustain cancer cells by releasing sequestered, ECM-bound growth factors, activating growth factor receptors, triggering cell survival-promoting signaling pathways and degrading mediators of apoptosis (e.g., FAS ligand) or anti-tumor immunity (e.g., MHC) [58].

MMPs play an important role also in tumor-associated angiogenesis, by breaking down the blood vessel basement membrane and perivascular ECM, mobilizing endothelial cell precursors from bone marrow and recruiting them in the newly forming vessels [89–95].

It has to be highlighted, however, that in addition to their tumorigenic effects, MMPs can also exert anti-tumor activities. For example, MMP-13 protects against melanoma metastases [96], although its presence is prognostic of poor survival in gastric cancer patients [87]. Moreover, MMP-8 expression is associated with improved survival of tongue cancer patients [97], even though MMP-8 serum levels correlate with colorectal cancer stage and distant metastases [88].

These contrasting activities of MMPs appear to depend on the cellular source of MMP expression, the extracellular environment, the type of tumor and the stage of the disease [98]. In particular, the protective role of some MMPs in specific types and clinical stages of tumor is likely to result from MMP occasional/paradoxical capability of inhibiting tumor angiogenesis via the degradation of angiogenic growth factor receptors, and/or the generation of anti-angiogenesis molecules deriving from the cleavage of ECM components [94,99].

In conclusion, the balance between MMP pro- and anti-tumorigenic effects is critical for the prognosis of the patients. Therefore, evaluating the different MMPs which are expressed in a particular type and/or stage of a specific tumor and patient is of extreme importance.

Among the various members of the MMP family, MMP-9, MMP-2 or MT1-MMP are especially involved in the development or progression of uterine cervical tumors, as indicated by the finding that their RNA or protein expression and their activity are extremely low or absent in normal uterine

cervix and low-grade CIN, are well detectable in high-grade CIN and they are very high in invasive CC [100–112]. In addition, expression of these MMPs parallels the angiogenic switch occurring during the evolution of high-grade CIN into CC and positively correlates with vessel density in tumor lesions [100,108,109]. Finally, MMP-9, MMP-2 or MT1-MMP levels in patients' plasma or cervical smears correlate with poor prognosis and higher tumor stage [103,113].

Noteworthy, in normal or transformed epithelial cells the E5, E6 or E7 protein of tumorigenic, HR-HPV down-regulate TIMPs and/or up-regulate MMP-2, MMP-9 or MT1-MMP expression or activity, thereby increasing epithelial cell invasiveness (Figure 1) [114–120]. These phenomena are likely to depend on E5, E6 or E7 capability of triggering the serine/threonine kinase AKT [6,121,122]. In fact, phosphorylated AKT activates transcription factors promoting *mmp* gene expression (Figure 1) [65–68].

3. Effects of HIV-Protease Inhibitors on Pre-Cancer and Cancer Lesions of the Uterine Cervix

Given the major role of MMPs in tumor-associated cellular invasion and angiogenesis, many MMP inhibitors (MMPIs) have been developed in the past years and exploited as anti-cancer interventions.

Among them are natural MMPIs, such as shark cartilage extract or soy isoflavonoid [123,124] and synthetic MMPIs comprising tetracycline derivatives, bisphosphonates and peptides chelating the zinc ion of MMP catalytic site [125–127].

Preclinical studies have shown that both synthetic and natural MMPIs are effective against a variety of tumors, included uterine CC [125,128–134]. However, clinical trials performed with some of the abovementioned MMPIs have failed due to dose-limiting side effects, inefficacy and/or lack of specificity [123,124,135–138]. In fact, because of the high similarity in the sequence of MMP catalytic domains, first-generation MMPIs have acted against multiple members of the MMP family, hence inhibiting either the therapeutic targets or anti-targets of a specific tumor [136,138].

In spite of these discouraging results and considering MMP role in tumor onset or progression, efforts are currently being made in order to design new MMPIs for oncological therapy. In particular, to specifically counteract the MMPs that are produced by a given tumor at a specific stage of development [98], novel strategies for MMP inhibition are exploiting the blockage of secondary substrate-binding sites (exosites), which show remarkable differences among the various MMPs [139,140].

However, inhibition of MMP activity may not be sufficient, as this strategy does not compromise the binding of MMPs to their cellular targets and the consequent signaling [58,71,91,141,142]. Thus, antibody-based inhibitors are being explored [143]. Alternatively, novel MMPIs could antagonize the molecular pathways leading to MMP expression. In this regard, experimental and clinical evidence points to the HIV-protease inhibitors (HIV-PI) as effective MMPIs.

The HIV-PI are a class of drugs which block the active site of HIV aspartyl protease, hence impeding the cleavage of HIV Gag-Pol poly-protein precursor and, consequently, the production of mature, infectious HIV particles (Figure 2) [144].

HIV-PI are administered to HIV-infected people together with the HIV reverse transcriptase inhibitors (HIV-RTI) and/or drugs counteracting the HIV integrase [145]. This combination therapy has been defined as highly active antiretroviral therapy (HAART) [145]. In fact, by potently suppressing viral replication and promoting immune reconstitution, HAART has strongly reduced AIDS-related morbidity and mortality, rendering HIV infection a manageable, chronic disease [146].

Most disappointingly, however, long-term treatment with HIV-PI may cause undesirable side effects. This is because, in addition to the HIV protease, HIV-PI can also target host molecules. Among the off-targets of HIV-PI is the cellular proteasome, a multi-subunit protease complex which controls the turnover of intracellular proteins (Figure 2) [147–152]. One of the many consequences resulting from the functional impairment of the cellular proteasome promoted by the HIV-PI is the intracellular accumulation of the sterol regulatory element-binding protein (SREBP) 1 transcription factor [153,154]. As a consequence, SREBP1-targeted lipogenic enzymes are increased, this augmenting lipid plasma levels and altering body fat distribution in treated patients [154–157]. Another unexpected

target of HIV-PI is the glucose transporter (GLUT)-4 (Figure 2), whose inhibition by HIV-PI halts glucose uptake by adipocytes, eventually causing insulin-resistance and diabetes [158].
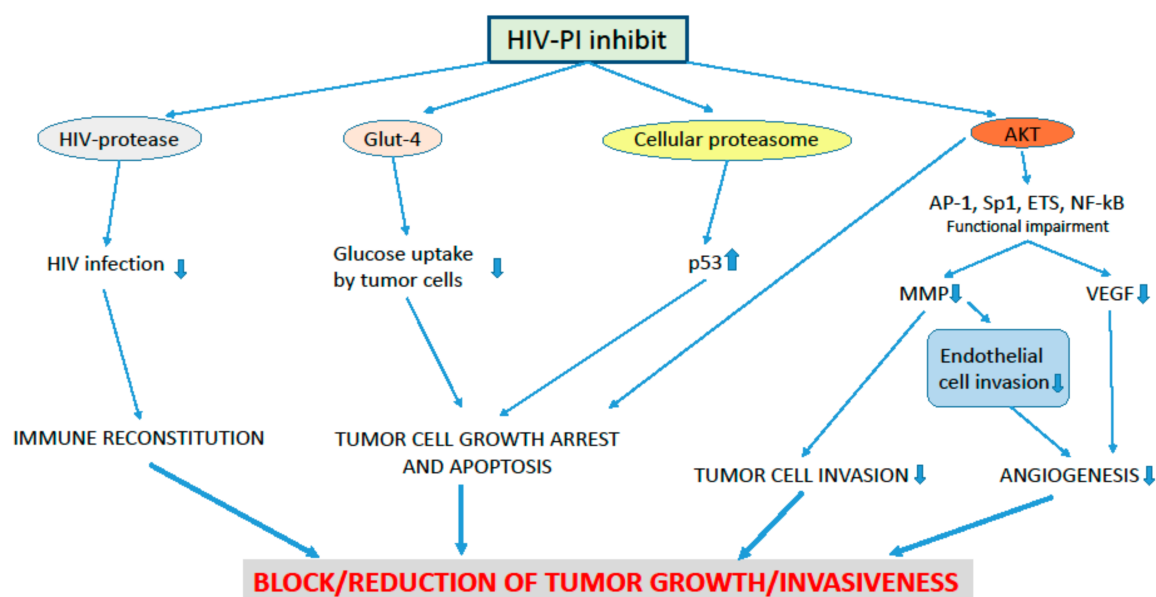

Figure 2. Anti-tumor activities of Human Immunodeficiency Virus (HIV)-protease inhibitors (PI). Arrows symbolize directions of connections. HIV-PI hinder the activity of the: (i) HIV aspartyl protease, hence impeding the production of infectious viral particles and promoting immune reconstitution; (ii) glucose transporter (GLUT)-4, thus impairing glucose uptake by tumor cells; (iii) cellular proteasome, therefore causing p53 protein intracellular accumulation; iv) AKT, this leading to the functional impairment of the Activator Protein (AP)-1, Sp (Specificity protein)-1, ETS or Nuclear Factor-kappa B (NF-κB) transcription factors, the down-regulation of matrix-metalloproteinase (MMP) or vascular endothelial growth factor (VEGF) expression, and the inhibition of angiogenesis or tumor cell invasion. Altogether, these activities of HIV-PI can block or reduce tumor growth and invasiveness.

Consequently and considering the need of life-long HAART administration, HIV-PI are often substituted by combined nucleoside and non-nucleoside HIV-RTI, respectively targeting the catalytic and allosteric sites of HIV reverse transcriptase [145].

Either HIV-PI-based or HIV-RTI-based HAART is effective at suppressing HIV infection, rapidly reducing plasma viremia and increasing the number of CD4^{+} T cells in HIV-infected individuals [146]. However, the absence of HIV-PI in HAART deprives patients of the beneficial activities of these drugs which, in addition to the improvement of T cell function [159], comprise the inhibition of AIDS-associated opportunistic infections [160].

Moreover, HIV-infected individuals undergoing HAART have experienced a reduced incidence and/or an increased regression of AIDS-associated tumors including Kaposi's sarcoma (KS) and non-Hodgkin lymphoma (NHL) [161–165]. In contrast, the incidence of progressed uterine CC in HIV-positive women has not decreased since the introduction of HAART [166]. Nevertheless, similarly to KS or NHL, use of HAART in HIV-infected women has decreased the incidence of CIN, caused its regression, and/or lowered its recurrence rates after excision [29–32,167–171].

The restoration of the immune responses promoted by HAART is likely to have a major role in inhibiting the development of AIDS-associated KS, NHL or CIN (Figure 2) [172]. However, in some HAART-treated, HIV-positive patients the decrease in tumor incidence, relapse or progression rates is not accompanied by the recovery of CD4^{+} T cell number and/or the reduction of viral load [172]. This has suggested that drugs present in HAART could exert anti-tumor effects independently of their capability of suppressing viral replication and reconstituting the immune system.

With reference to uterine CIN or CC, epidemiological studies analyzed all together data collected from patients undergoing different HAART regimens [29–32,166–171]. In contrast, studies concerning AIDS-associated KS have provided better clues of HAART anti-tumor effects. In particular, these studies have reported that complete remission of KS is more frequent in HIV-PI than in HIV-RTI-treated individuals, although both therapeutic regimens can promote the regression of KS lesions [164]. Moreover, a relapse of KS after its resolution has been described in patients switching from HIV-PI-based to HIV-RTI-based HAART [173].

In agreement with these findings, results from preclinical (in vitro and in vivo) and clinical studies indicate that HIV-PI can directly inhibit tumor cell survival, growth or invasion and angiogenesis in experimental models devoid of HIV and immune cells.

In particular, due to their inhibitory effect on the function of the cellular proteasome, HIV-PI cause an increase in the intracellular amounts of cell cycle inhibitors or onco-suppressors, hence leading to the growth arrest and/or death of a variety of human tumor cells (Figure 2) [148,150,174–182]. Additional anti-cancer cytostatic and/or cytotoxic effects result from HIV-PI capability of inhibiting GLUT-4, hence impairing glucose uptake by tumor cells (Figure 2) [158,183].

As to the uterine cervix, the HIV-PI indinavir (IDV), ritonavir (RTV) or lopinavir have been shown to reduce the viability of HR-HPV-transformed epithelial cells [151]. This is accompanied by a stable increase in the intracellular levels of the proteasome-targeted, growth-arresting and pro-apoptosis p53 protein [151]. However, this activity requires high HIV-PI concentrations, that are not (or only transiently) present in the plasma of treated patients [184].

In the matter of HIV-PI therapeutic (low) amounts, the HIV-PI saquinavir (SQV) or RTV halts the proliferation of cells derived from CIN but not CC lesions, with no significant effect on cell survival or proteasome capability of degrading p53 [185]. In view of these in vitro findings, one may conclude that at low HIV-PI tissue concentrations a CIN lesion persists, although it does not grow. Therefore, in order to efficiently counteract the malignant evolution of high-grade CIN, an HIV-PI should be combined with a classical proteasome inhibitor, as previously done to induce apoptosis of CC-derived cells [186]. Nevertheless, a recent clinical study conducted in HIV-negative women has shown that HIV-PI can by themselves promote the regression or the complete remission of high-grade CIN lesions [187].

Preclinical work has suggested that this may depend on HIV-PI capability of blocking epithelial basement membrane invasion by the CIN cells, as this event starts CIN progression to CC [2,11].

In particular, SQV or RTV at levels as detected in the plasma of treated patients can efficiently inhibit EGF-promoted invasion of primary keratinocytes bearing episomal HR-HPV DNA and derived from low-grade CIN lesions of HIV-negative women [185,188]. For both SQV and RTV, this effect is accompanied by a significant reduction of MMP-2 or MMP-9 activity released by the CIN cells in response to EGF [185,188].

These in vitro results are consistent with those from animal studies which have indicated that HIV-PI therapeutic concentrations inhibit the growth of human tumors in animal models via a proteasome-independent reduction of cancer cell invasion and MMP activity (Figure 2) [189].

In agreement with the fact that the HIV protease does not belong to MMP functional class, HIV-PI cannot directly antagonize MMP activity [190]. Rather, SQV or RTV therapeutic levels down-regulate the expression of MMP-9 induced in CIN cells by EGF and, to a lesser extent, CIN cell constitutive expression of MMP-2 [185,188]. This finding is consistent with HIV-PI capability of inhibiting MMP expression by both tumor and normal cells [150,152,189,191,192] and either in HIV-positive or in HIV-negative individuals [193,194].

EGF induces MMP-9 expression by epithelial cells via the phosphorylation of the serine/threonine kinase AKT [195] and the consequent activation of Fos-related antigen (Fra)-1, a member of the AP-1 transcriptional complex [67]. Strikingly, exposure of CIN cells to the same SQV or RTV doses reducing EGF-promoted cellular invasion and MMP-9 expression, also inhibits AKT phosphorylation and Fra-1 nuclear localization triggered in these cells by EGF [188]. These findings are consistent with results obtained in other experimental models, which indicate that inhibition of EGF-induced AKT

phosphorylation, or Fra-1 silencing, reduces cellular invasion via the down-regulation of MMP-9 expression [67,195].

Indeed, SQV or RTV capability of inhibiting EGF-promoted AKT/Fra-1 activation and MMP-9 expression in low-grade CIN cells may have relevant clinical implications. In fact, the levels of EGF, MMP-9 and phosphorylated AKT are extremely low or undetectable in the normal uterine cervix, becoming appreciable in low-grade CIN and further increasing during its evolution to high-grade CIN and CC [103,107,113,196–198].

4. The Anti-Angiogenesis Effect of the HIV-PI and its Possible Impact on Pre-Cancer and Cancer Lesions of the Uterine Cervix

As for the CIN cells, HIV-PI can impair AKT phosphorylation in several tumor cell types (Figure 2) [150,182,199–204]. In this regard, it has to highlighted that the activation of AKT is pivotal in the acquisition and maintenance of cancer hallmarks, including cellular immortalization, deregulated growth and invasiveness, as well as in angiogenesis [65,67,68,205–207].

Because of its role in the development and clinical progression of uterine cervical lesions [22,23,100], angiogenesis is a rational target for the treatment of high-grade CIN and/or CC. Accordingly, antagonists of angiogenic growth factors have been found active against recurrent CC [20]. However, these antagonists are very expensive [20] and their therapeutic use may lead to drug resistance [208]. This has prompted the exploitation of drugs counteracting other players of the angiogenic process.

In this context, the HIV-PI nelfinavir reduces the production of the angiogenic VEGF (Figure 2) [179,204,209]. Moreover, SQV or IDV blocks MMP activity in endothelial cells, hence halting the first step of angiogenesis that is endothelial cell invasion of vessel basement membrane (Figure 2) [191]. As a consequence, nelfinavir, SQV or IDV efficiently counteract the formation of new blood vessels in HIV-free in vivo models [189,191,209,210]. Consistently, IDV can promote the regression or stabilization of proliferative vascular lesions also in HIV-negative KS patients [194].

In vitro work has shown that IDV concentrations as found in plasma of treated HIV-positive or negative patients inhibit the conversion of latent MMP-2 zymogen into the active enzyme, while having little or no impact on the synthesis of latent MMP-2 and no direct effects against MMP-2 catalytic activity [190,191].

The main mediator of latent MMP-2 conversion into active MMP-2 is the MT1-MMP [54]. Noteworthy, in vitro work has shown that IDV therapeutic amounts impair the binding of the Sp1 transcription factor to the promoter region of the *mt1-mmp* gene, thus down-regulating MT1-MMP RNA and protein expression by endothelial cells [210].

It has to be noted that MT1-MMP can directly degrade the blood vessel basement membrane even in the absence of MMP-2 [211]. Moreover, by modulating the expression of endothelial cell adhesion molecules, MT1-MMP is important to endothelial cell organization in a capillary network [211]. Thus, the reduction of MT1-MMP expression provides a molecular mechanism for IDV anti-angiogenesis effect, rendering this anti-HIV drug a promising antagonist of the formation of new blood vessels which accompanies CIN evolution into CC. Notwithstanding, the finding that long term-treatment with HIV-PI can damage blood vessels [212] deserves careful consideration.

5. HIV-PI and HPV

As discussed above, the E6 and E7 proteins of HR-HPV exert tumorigenic and pro-angiogenesis activities, including the inactivation of the growth-suppressive pRb or p53 proteins, the phosphorylation of AKT and the promotion of MMP expression (Figure 1) [8,9,114–116,118–122]. These activities of HR-HPV-E6 or E7, in turn, lead to cellular growth and invasiveness (Figure 1). Nevertheless, the anti-proliferative and anti-invasive effects exerted in CIN cells by SQV or RTV therapeutic amounts are not accompanied by the down-regulation of HPV-E6 or E7 expression [188]. This is consistent with the clinical finding that HIV-PI promote CIN regression without clearing HPV infection [167], albeit other studies have obtained opposite results [32,187].

In this regard, in vitro work indicates that therapeutic concentrations of HIV-PI are active against CIN cells containing episomal HPV DNA, while having little or no effect on CC cells bearing integrated HPV-DNA [185,188].

Therefore, one may speculate that the activity of HIV-PI against HPV-associated cervical lesions could depend on the integration status of HPV-DNA. This hypothesis is corroborated by molecular studies indicating that HIV-PI selectively accumulate in the nuclei of HPV-E6 expressing cells and trigger the synthesis of anti-viral proteins [213,214].

Thus, HIV-PI could counteract the early stage of HPV infection, when cervical epithelial cells are not heavily transformed, HPV-DNA is episomic and the expression of E6, E7 and other HPV proteins is low. In this specific setting, HIV-PI could also favor the clearance of episomal HPV DNA. This suggests that HIV-PI should be used early in the clinical management of CIN and, possibly, prior to transition to CC.

6. Concluding Remarks and Future Directions

HPV-associated uterine CC is a serious health problem which can be prevented firstly by anti-HPV vaccination [215] and, secondly, through screening programs for the detection and surveillance of early lesions and the removal of high-grade CIN [216].

These prevention programs are feasible and largely applied in the developed but not in the developing world [217]. Consequently, low-income countries are now coping with a burden of uterine CC, especially in association with HIV infection [217].

With reference to CIN therapeutic approaches, however, it has to be noted that surgical removal of high-grade lesions may lead to uterine ulcers, hemorrhages, cicatrices and pre-term labor [218]. In this context, results from preclinical and clinical studies point to HIV-PI as a promising intervention in the management of high-grade CIN lesions of both HIV-infected and uninfected women. In fact, HIV-PI directly inhibit events leading to CIN onset and progression including the growth or invasion of HPV-positive epithelial cells [151,185,188] and angiogenesis [189,191,210]. These effects are independent of the anti-HIV and immune-reconstituting activities of HIV-PI. Consistently, as for HIV-positive patients, HIV-PI causes the regression or the complete remission of high-grade CIN lesions also in HIV-negative women [187].

Indeed, HIV-PI counteract key players of carcinogenesis, such as the cellular proteasome, the serine/threonine kinase AKT and the MMPs (Figure 2) [147–152,182,185,188–192,199–204,210]. As the cellular proteasome has a role in regulating AKT phosphorylation and MMP expression [152,219,220], a connection among the pathways targeted by the HIV-PI may exist.

At the present time, novel and tailor-made inhibitors of the cellular proteasome, AKT or MMPs are under evaluation [139,140,143,221–223], since the first generation of these drugs has given unsatisfactory results [123,124,135–138,224,225].

In this regard, however, it should be considered that differently from novel proteasome, AKT or MMP inhibitors, HIV-PI are in use since many years and information on their pharmacokinetic, tissue distribution and toxicity profile is large [184,226].

Regarding the use of HIV-PI in oncology, this should entail tumor-customized therapies. In fact, each member of the HIV-PI class of drugs seems to have distinct effects on MMPs, while each tumor produces different MMPs, depending on its type and stage of progression.

As to uterine CIN, MMP-9, MT1-MMP and MMP-2 have a key role in its evolution into CC [100–113]. Noteworthy, either SQV or RTV down-regulates MMP-9 expression, thereby blocking CIN cell invasiveness [185,188]; whereas, IDV reduces MT1-MMP synthesis, thus impairing MMP-2 functional activation and angiogenesis [191,210].

Therefore, in order to promote the regression of high-grade CIN, administrating a combination of different HIV-PI may be advisable and effective, as indicated by a recent clinical study [187].

Although the systemic use of HIV-PI has been reported to cause the regression or the complete remission of KS or CIN in the absence of adverse side effects [187,194], topical application of

these drugs may be safer and effective, against high-grade CIN. This therapeutic strategy can be applicable worldwide.

Future work will identify HIV-PI chemical groups responsible for their anti-tumor effects, hence leading to the synthesis of more active, less toxic derivatives.

In this context, it has to be highlighted that HIV-PI inhibitory effect on MMPs impairs events which are key for high-grade CIN evolution into CC, namely CIN and endothelial cell invasion of the basement membranes. Therefore, labeled probes utilizing MMP substrate specificity for imaging purposes [227–229] could allow the monitoring of the therapeutic response to HIV-PI or their future derivatives.

References

1. Forman, D.; de Martel, C.; Lacey, C.J.; Soerjomataram, I.; Lortet-Tieulent, J.; Bruni, L.; Vignat, J.; Ferlay, J.; Bray, F.; Plummer, M.; et al. Global burden of human papillomavirus and related diseases. *Vaccine* **2012**, *30*, F12–F23. [CrossRef] [PubMed]

2. Jenkins, D. Histopathology and cytopathology of cervical cancer. *Dis. Markers* **2007**, *23*, 199–212. [CrossRef] [PubMed]

3. zur Hausen, H. Papillomaviruses and cancer: From basic studies to clinical application. *Nat. Rev. Cancer* **2002**, *2*, 342–350. [CrossRef] [PubMed]

4. Hebner, C.M.; Laimins, L.A. Human papillomaviruses: Basic mechanisms of pathogenesis and oncogenicity. *Rev. Med. Virol.* **2006**, *16*, 83–97. [CrossRef] [PubMed]

5. McBride, A.A.; Warburton, A. The role of integration in oncogenic progression of HPV-associated cancers. *PLoS Pathog.* **2017**, *13*, e1006211. [CrossRef] [PubMed]

6. Kim, M.; Kim, H.S.; Kim, S.; Oh, J.; Han, J.Y.; Lim, J.M.; Juhnn, Y.; Song, Y. Human papillomavirus type 16 E5 oncoprotein as a new target for cervical cancer treatment. *Biochem. Pharmacol.* **2010**, *80*, 1930–1935. [CrossRef] [PubMed]

7. Wasson, C.W.; Morgan, E.L.; Müller, M.; Ross, R.L.; Hartley, M.; Roberts, S.; Macdonald, A. Human papillomavirus type 18 E5 oncogene supports cell cycle progression and impairs epithelial differentiation by modulating growth factor receptor signalling during the virus life cycle. *Oncotarget* **2017**, *8*, 103581–103600. [CrossRef] [PubMed]

8. Roman, A.; Munger, K. The papillomavirus E7 proteins. *Virology* **2013**, *445*, 138–168. [CrossRef] [PubMed]

9. Vande Pol, S.B.; Klingelhutz, A.J. Papillomavirus E6 oncoproteins. *Virology* **2013**, *445*, 115–137. [CrossRef] [PubMed]

10. Doorbar, J. Molecular biology of human papillomavirus infection and cervical cancer. *Clin. Sci.* **2006**, *110*, 525–541. [CrossRef] [PubMed]

11. Petignat, P.; Roy, M. Diagnosis and management of cervical Cancer. *BMJ* **2007**, *335*, 765–768. [CrossRef] [PubMed]

12. Mittal, S.; Basu, P.; Muwonge, R.; Banerjee, D.; Ghosh, I.; Sengupta, MM.; Das, P.; Dey, P.; Mandal, R.; Panda, C.; et al. Risk of high-grade precancerous lesions and invasive cancers in high-risk HPV-positive women with normal cervix or CIN 1 at baseline-A population-based cohort study. *Int. J. Cancer* **2017**, *140*, 1850–1859. [CrossRef] [PubMed]

13. Grabowska, A.K.; Riemer, A.B. The invisible enemy—How human papillomaviruses avoid recognition and clearance by the host immune system. *Open Virol. J.* **2012**, *6*, 249–256. [CrossRef] [PubMed]

14. De Freitas, A.C.; de Oliveira, T.H.A.; Barros, M.R., Jr.; Venuti, A. hrHPV E5 oncoprotein: Immune evasion and related immunotherapies. *J. Exp. Clin. Cancer Res.* **2017**, *36*, 71–86. [CrossRef] [PubMed]

15. White, A.E.; Livanos, E.M.; Tlsty, T.D. Differential disruption of genomic integrity and cell cycle regulation in normal human fibroblasts by the HPV oncoproteins. *Genes Dev.* **1994**, *8*, 666–677. [CrossRef] [PubMed]

16. Thomas, J.T.; Laimins, L.A. Human papillomavirus oncoproteins E6 and E7 independently abrogate the mitotic spindle checkpoint. *J. Virol.* **1998**, *72*, 1131–1137. [PubMed]

17. Southern, S.A.; Noya, F.; Meyers, C.; Broker, T.R.; Chow, L.T.; Herrington, C.S. Tetrasomy is induced by human papillomavirus type 18 E7 gene expression in keratinocyte raft cultures. *Cancer Res.* **2001**, *61*, 4858–4863. [PubMed]

18. Duensing, S.; Munger, K. Centrosome abnormalities and genomic instability induced by human papillomavirus oncoproteins. *Prog. Cell Cycle Res.* **2003**, *5*, 383–391. [PubMed]

19. Takahashi, Y.; Ellis, L.M.; Mai, M. The angiogenic switch of human colon cancer occurs simultaneous to initiation of invasion. *Oncol. Rep.* **2003**, *10*, 9–13. [CrossRef] [PubMed]

20. Monk, B.J.; Willmott, L.J.; Sumner, D.A. Antiangiogenesis agents in metastatic or recurrent cervical cancer. *Gynecol. Oncol.* **2010**, *116*, 181–186. [CrossRef] [PubMed]

21. Krill, L.S.; Krishnansu, S.T. Exploring the therapeutic rationale for angiogenesis blockade in cervical cancer. *Clin. Ther.* **2015**, *37*, 9–19. [CrossRef] [PubMed]

22. Saijo, Y.; Furumoto, H.; Yoshida, K.; Nishimura, M.; Irahara, M. Clinical Significance of Vascular Endothelial Growth Factor Expression and Microvessel Density in Invasive Cervical Cancer. *J. Med. Investig.* **2015**, *62*, 154–160. [CrossRef] [PubMed]

23. Zheng, W.; Xiong, Y.H.; Han, J.; Guo, Z.X.; Li, Y.H.; Li, A.H.; Pei, X.Q. Contrast-enhanced ultrasonography of cervical carcinoma: Perfusion pattern and relationship with tumour angiogenesis. *Br. J. Radiol.* **2016**, *89*, 20150887. [CrossRef] [PubMed]

24. Ostor, A.G. Natural history of cervical intraepithelial neoplasia: A critical review. *Int. J. Gynecol. Pathol.* **1993**, *12*, 186–192. [CrossRef] [PubMed]

25. Bosch, F.X.; Lorincz, A.; Munoz, N.; Meijer, C.J.; Shah, K.V. The causal relation between human papillomavirus and cervical cancer. *J. Clin. Pathol.* **2002**, *55*, 244–265. [CrossRef] [PubMed]

26. Moreno, V.; Bosch, F.X.; Muñoz, N.; Meijer, C.J.; Shah, K.V.; Walboomers, J.M.; Herrero, R.; Franceschi, S.; International Agency for Research on Cancer; Multicentric Cervical Cancer Study Group. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: The IARC multicentric case-control study. *Lancet* **2002**, *359*, 1085–1092. [CrossRef]

27. Girianelli, V.R.; Azevedo, E.; Silva, G.; Thuler, L.C. Factors associated with the risk of progression to precursor lesions or cervical cancer in women with negative cytologic findings. *Int. J. Gynaecol. Obstet.* **2009**, *107*, 228–231. [CrossRef] [PubMed]

28. Six, C.; Heard, I.; Bergeron, C.; Orth, G.; Poveda, J.D.; Zagury, P.; Cesbron, P.; Crenn-Hébert, C.; Pradinaud, R.; Sobesky, M.; et al. Comparative prevalence, incidence and short-term prognosis of cervical squamous intraepithelial lesions amongst HIV-positive and HIV-negative women. *AIDS* **1998**, *12*, 1047–1056. [CrossRef] [PubMed]

29. Robinson, W., 3rd. Invasive and preinvasive cervical neoplasia in human immunodeficiency virus-infected women. *Semin. Oncol.* **2000**, *27*, 463–470. [PubMed]

30. Sellors, J.; Lewis, K.; Kidula, N.; Muhombe, K.; Tsu, V.; Herdman, C. Screening and management of precancerous lesions to prevent cervical cancer in low-resource settings. *Asian Pac. J. Cancer Prev.* **2003**, *4*, 277–280. [PubMed]

31. Omar, T.; Schwartz, S.; Hanrahan, C.; Modisenyane, T.; Tshabangu, N.; Golub, J.E.; McIntyre, J.A.; Gray, G.E.; Mohapi, L.; Martinson, N.A. Progression and regression of premalignant cervical lesions in HIV-infected women from Soweto: A prospective cohort. *AIDS* **2011**, *25*, 87–94. [CrossRef] [PubMed]

32. Blitz, S.; Baxter, J.; Raboud, J.; Walmsley, S.; Rachlis, A.; Smaill, F.; Ferenczy, A.; Coutlée, F.; Hankins, C.; Money, D. Canadian Women's HIV Study Group: Evaluation of HIV and highly active antiretroviral therapy on the natural history of human papillomavirus infection and cervical cytopathologic findings in HIV-positive and high-risk HIV-negative women. *J. Infect. Dis.* **2013**, *208*, 454–462. [CrossRef] [PubMed]

33. Denslow, S.A.; Rositch, A.F.; Firnhaber, C.; Ting, J.; Smith, J.S. Incidence and progression of cervical lesions in women with HIV: A systematic global review. *Int. J. STD AIDS* **2014**, *25*, 163–177. [CrossRef] [PubMed]

34. Obiri-Yeboah, D.; Akakpo, P.K.; Mutocheluh, M.; Adjei-Danso, E.; Allornuvor, G.; Amoako-Sakyi, D.; Adu-Sarkodie, Y.; Mayaud, P. Epidemiology of cervical human papillomavirus (HPV) infection and squamous intraepithelial lesions (SIL) among a cohort of HIV-infected and uninfected Ghanaian women. *BMC Cancer* **2017**, *17*, 688. [CrossRef] [PubMed]

35. Nappi, L.; Carriero, C.; Bettocchi, S.; Herrero, J.; Vimercati, A.; Putignano, G. Cervical squamous intraepithelial lesions of low-grade in HIV-infected women: Recurrence, persistence and progression, in treated and untreated women. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2005**, *121*, 226–232. [CrossRef] [PubMed]

36. Ntekim, A.; Campbell, O.; Rothenbacher, D. Optimal management of cervical cancer in HIV-positive patients: A systematic review. *Cancer Med.* **2015**, *4*, 1381–1393. [CrossRef] [PubMed]

37. Levine, A.M. AIDS-related malignancies: The emerging epidemic. *J. Natl. Cancer Inst.* **1993**, *85*, 1382–1397. [CrossRef] [PubMed]

38. Kang, M.; Cu-Uvin, S. Association of HIV viral load and CD4 cell count with human papillomavirus detection and clearance in HIV-infected women initiating highly active antiretroviral therapy. *HIV Med.* **2012**, *13*, 372–378. [CrossRef] [PubMed]

39. Tornesello, M.L.; Buonaguro, F.M.; Beth-Giraldo, E.; Giraldo, G. Human immunodeficiency virus type 1 tat gene enhances human papillomavirus early gene expression. *Intervirology* **1993**, *36*, 57–64. [CrossRef] [PubMed]

40. Nyagol, J.; Leucci, E.; Onnis, A.; De Falco, G.; Tigli, C.; Sanseverino, F.; Torriccelli, M.; Palummo, N.; Pacenti, L.; Santopietro, R.; et al. The effects of HIV-1 Tat protein on cell cycle during cervical carcinogenesis. *Cancer Biol. Ther.* **2006**, *5*, 684–690. [CrossRef] [PubMed]

41. Kim, R.H.; Yochim, J.M.; Kang, M.K.; Shin, K.H.; Christensen, R.; Park, N.H. HIV-1 Tat enhances replicative potential of human oral keratinocytes harboring HPV-16 genome. *Int. J. Oncol.* **2008**, *33*, 777–782. [PubMed]

42. Barillari, G.; Palladino, C.; Bacigalupo, I.; Leone, P.; Falchi, M.; Ensoli, B. Entrance of the Tat protein of HIV-1 into human uterine cervical carcinoma cells causes up-regulation of HPV-E6 expression and a decrease in p53 protein levels. *Oncol. Lett.* **2016**, *12*, 2389–2394. [CrossRef] [PubMed]

43. Barillari, G.; Ensoli, B. Angiogenic effects of extracellular HIV-1 Tat protein and its role in the pathogenesis of AIDS-associated Kaposi's sarcoma. *Clin. Microbiol. Rev.* **2002**, *15*, 310–326. [CrossRef] [PubMed]

44. Tornesello, M.L.; Buonaguro, L.; Giorgi-Rossi, P.; Buonaguro, F.M. Viral and cellular Biomarkers in the diagnosis of cervical intraepithelial neoplasia and cancer. *Biomed. Res. Int.* **2013**, *2013*, 519619. [CrossRef] [PubMed]

45. Ren, C.; Zhu, Y.; Yang, L.; Zhang, X.; Liu, L.; Ren, C. Diagnostic performance of HPV E6/E7 mRNA assay for detection of cervical high-grade intraepithelial neoplasia and cancer among women with ASCUS Papanicolaou smears. *Arch. Gynecol. Obstet.* **2017**, *297*, 425–432. [CrossRef] [PubMed]

46. Shi, W.J.; Liu, H.; Wu, D.; Tang, Z.H.; Shen, Y.C.; Guo, L. E6/E7 proteins are potential markers for the screening and diagnosis of cervical pre-cancerous lesions and cervical cancer in a Chinese population. *Oncol. Lett.* **2017**, *14*, 6251–6258. [CrossRef] [PubMed]

47. Liang, C.W.; Lin, M.C.; Hsiao, C.H.; Lin, Y.T.; Kuo, K.T. Papillary squamous intraepithelial lesions of the uterine cervix: Human papillomavirus-dependent changes in cell cycle expression and cytologic features. *Hum. Pathol.* **2010**, *41*, 326–335. [CrossRef] [PubMed]

48. Bucchi, L.; Cortecchia, S.; Galanti, G.; Sgadari, C.; Costa, S.; De Lillo, M.; Caparra, L.; Barillari, G.; Monini, P.; Nannini, R.; et al. Follow-up study of patients with cervical intraepithelial neoplasia grade 1 overexpressing p16ink4a. *Int. J. Gynecol. Cancer* **2013**, *23*, 1663–1669. [CrossRef]

49. Calil, L.N.; Edelweiss, M.I.; Meurer, L.; Igansi, C.N.; Bozzetti, M.C. p16 INK4a and Ki67 expression in normal, dysplastic and neoplastic uterine cervical epithelium and human papillomavirus (HPV) infection. *Pathol. Res. Pract.* **2014**, *210*, 482–487. [CrossRef] [PubMed]

50. Pedroza-Torres, A.; López-Urrutia, E.; García-Castillo, V.; Jacobo-Herrera, N.; Herrera, L.A.; Peralta-Zaragoza, O.; López-Camarillo, C.; Cantú De Leon, D.; Fernández-Retana, J.; Cerna-Cortés, J.F.; et al. MicroRNAs in cervical cancer: Evidences for a miRNA profile deregulated by HPV and its impact on radio-resistance. *Molecules* **2014**, *19*, 6263–6281. [CrossRef] [PubMed]

51. Klein, T.; Bischoff, R. Physiology and pathophysiology of matrix metalloproteases. *Amino Acids* **2011**, *41*, 271–290. [CrossRef] [PubMed]

52. Löffek, S.; Schilling, O.; Franzke, C.W. Biological role of matrix metalloproteinases: A critical balance. *Eur. Respir. J.* **2011**, *38*, 191–208. [CrossRef] [PubMed]

53. Rohani, M.G.; Parks, W.C. Matrix remodeling by MMPs during wound repair. *Matrix Biol.* **2015**, *44–46*, 113–121. [CrossRef] [PubMed]

54. Itoh, Y. Membrane-type matrix metalloproteinases: Their functions and regulations. *Matrix Biol.* **2015**, *46*, 207–223. [CrossRef] [PubMed]

55. Hua, Y.; Nair, S. Proteases in cardiometabolic diseases: Pathophysiology, molecular mechanisms and clinical applications. *Biochem. Biophys. Acta* **2015**, *1852*, 195–208. [CrossRef] [PubMed]

56. Khokha, R.; Murthy, A.; Weiss, A. Metalloproteinases and their natural inhibitors in inflammation and immunity. *Nat. Rev. Immunol.* **2013**, *13*, 649–665. [CrossRef] [PubMed]

57. Garcia-Irigoyen, O.; Carotti, S.; Latasa, M.U.; Uriarte, I.; Fernández-Barrena, M.G.; Elizalde, M.; Urtasun, R.; Vespasiani-Gentilucci, U.; Morini, S.; Banales, J.M.; et al. Matrix metalloproteinase-10 expression is induced during hepatic injury and plays a fundamental role in liver tissue repair. *Liver Int.* **2014**, *34*, 257–270. [CrossRef] [PubMed]

58. Yadav, L.; Puri, N.; Rastogi, V.; Satpute, P.; Ahmad, R.; Kaur, G. Matrix metalloproteinases and cancer—Roles in threat and therapy. *Asian Pac. J. Cancer Prev.* **2014**, *15*, 1085–1091. [CrossRef] [PubMed]

59. Ågren, M.S.; Schnabel, R.; Christensen, L.H.; Mirastschijski, U. Tumor necrosis factor-α-accelerated degradation of type I collagen in human skin is associated with elevated matrix metalloproteinase (MMP)-1 and MMP-3 ex vivo. *Eur. J. Cell Biol.* **2015**, *94*, 12–21. [CrossRef] [PubMed]

60. Yan, H.; Xin, S.; Wang, H.; Ma, J.; Zhang, H.; Wei, H. Baicalein inhibits MMP-2 expression in human ovarian cancer cells by suppressing the p38MAPK-dependent NF-κB signaling pathway. *Anticancer Drugs* **2015**, *26*, 649–656. [CrossRef] [PubMed]

61. Pan, H.C.; Jiang, Q.; Yu, Y.; Mei, J.P.; Cui, Y.K.; Zhao, W.J. Quercetin promotes cell apoptosis and inhibits the expression of MMP-9 and fibronectin via the AKT and ERK signalling pathways in human glioma cells. *Neurochem. Int.* **2015**, *80*, 60–71. [CrossRef] [PubMed]

62. Nemoto, E.; Gotoh, K.; Tsuchiya, M.; Sakisaka, Y.; Shimauchi, H. Extracellular ATP inhibits IL-1-induced MMP-1 expression through the action of CD39/nucleotidase triphosphate dephosphorylase-1 on human gingival fibroblasts. *Int. Immunopharmacol.* **2013**, *17*, 513–518. [CrossRef] [PubMed]

63. Gilet, A.; Zou, F.; Boumenir, M.; Frippiat, J.P.; Thornton, S.N.; Lacolley, P.; Ropars, A. Aldosterone up-regulates MMP-9 and MMP-9/NGAL expression in human neutrophils through p38, ERK1/2 and PI3K pathways. *Exp. Cell Res.* **2015**, *331*, 152–163. [CrossRef] [PubMed]

64. Chambers, M.; Kirkpatrick, G.; Evans, M.; Gorski, G.; Foster, S.; Borghaei, R.C. IL-4 inhibition of IL-1 induced Matrix metalloproteinase-3 (MMP-3) expression in human fibroblasts involves decreased AP-1 activation via negative crosstalk involving of Jun N-terminal kinase (JNK). *Exp. Cell Res.* **2013**, *319*, 1398–1408. [CrossRef] [PubMed]

65. Peña, E.; de la Torre, R.; Arderiu, G.; Slevin, M.; Badimon, L. mCRP triggers angiogenesis by inducing F3 transcription and TF signalling in microvascular endothelial cells. *Tromb Haemost* **2017**, *117*, 357–370. [CrossRef] [PubMed]

66. Lin, H.Y.; Chen, Y.S.; Wang, K.; Chien, H.W.; Hsieh, Y.H.; Yang, S.F. Fisetin inhibits epidermal growth factor-induced migration of ARPE-19 cells by suppression of AKT activation and Sp1-dependent MMP-9 expression. *Mol. Vis.* **2017**, *23*, 900–910. [PubMed]

67. Adiseshaiah, P.; Vaz, M.; Machireddy, N.; Kalvakolanu, D.V.; Reddy, S.P. A. Fra-1-dependent, matrix metalloproteinase driven EGFR activation promotes human lung epithelial cell motility and invasion. *J. Cell. Physiol.* **2008**, *216*, 405–412. [CrossRef] [PubMed]

68. Zhang, G.J.; Zhao, J.; Jiang, M.L.; Zhang, L.C. ING5 inhibits cell proliferation and invasion in esophageal squamous cell carcinoma through regulation of the Akt/NF-κB/MMP-9 signaling pathway. *Biochem. Biophys. Res. Commun.* **2018**, *496*, 387–393. [CrossRef] [PubMed]

69. Brew, K.; Nagase, H. The tissue inhibitors of metalloproteinases (TIMPs): An ancient family with structural and functional diversity. *Biochim. Biophys. Acta* **2010**, *1803*, 55–71. [CrossRef] [PubMed]

70. Yabluchanskiy, A.; Ma, Y.; Iyer, R.P.; Hall, M.E.; Lindsey, M.L. Matrix metalloproteinase-9: Many shades of function in cardiovascular disease. *Physiology* **2013**, *28*, 391–403. [CrossRef] [PubMed]

71. Folgueras, A.R.; Pendas, A.M.; Sanchez, L.M.; Lopez-Otin, C. Matrix metalloproteinases in cancer: From new functions to improved inhibition strategies. *Int. J. Dev. Biol.* **2004**, *48*, 411–424. [CrossRef] [PubMed]

72. Hanzawa, M.; Shindoh, M.; Higashino, F.; Yasuda, M.; Inoue, N.; Hida, K.; Ono, M.; Kohgo, T.; Nakamura, M.; Notani, K.; et al. Hepatocyte growth factor up-regulates E1AF that induces oral squamous cell carcinoma cell invasion by activating matrix metalloproteinase genes. *Carcinogenesis* **2000**, *21*, 1079–1085. [CrossRef] [PubMed]

73. Jacob-Ferreira, A.L.; Schulz, R. Activation of intracellular matrix metalloproteinase-2 by reactive oxygen-nitrogen species: Consequences and therapeutic strategies in the heart. *Arch. Biochem. Biophys.* **2013**, *540*, 82–93. [CrossRef] [PubMed]

74. Tang, Y.L.; Liu, X.; Gao, S.Y.; Feng, H.; Jiang, Y.P.; Wang, S.S.; Yang, J.; Jiang, J.; Ma, X.R.; Tang, Y.J.; et al. WIP1 stimulates migration and invasion of salivary adenoid cystic carcinoma by inducing MMP-9 and VEGF-C. *Oncotarget* **2015**, *6*, 9031–9044. [CrossRef] [PubMed]

75. Shin, D.H.; Dier, U.; Melendez, J.A.; Hempel, N. Regulation of MMP-1 expression in response to hypoxia is dependent on the intracellular redox status of metastatic bladder cancer cells. *Biochim. Biophys. Acta* **2015**, *1852*, 2593–2602. [CrossRef] [PubMed]

76. Zong, L.; Li, J.; Chen, X.; Chen, K.; Li, W.; Li, X.; Zhang, L.; Duan, W.; Lei, J.; Xu, Q.; et al. Lipoxin A4 Attenuates Cell Invasion by Inhibiting ROS/ERK/MMP Pathway in Pancreatic Cancer. *Oxid. Med. Cell. Longev.* **2016**, 6815727. [CrossRef]

77. Fullár, A.; Kovalszky, I.; Bitsche, M.; Romani, A.; Schartinger, V.H.; Sprinzl, G.M.; Riechelmann, H.; Dudás, J. Tumor cell and carcinoma-associated fibroblast interaction regulates matrix metalloproteinases ant their inhibitors in oral squamous cell carcinoma. *Exp. Cell Res.* **2012**, *318*, 1517–1527. [CrossRef] [PubMed]

78. Zhao, L.; Wu, Y.; Xie, X.D.; Chu, Y.F.; Li, J.Q.; Zheng, L. c-Met identifies a population of matrix metalloproteinase 9-producing monocytes in peritumoural stroma of hepatocellular carcinoma. *J. Pathol.* **2015**, *237*, 319–329. [CrossRef] [PubMed]

79. Mashhadiabbas, F.; Mahjour, F.; Mahjour, S.B.; Fereidooni, F.; Hosseini, F.S. The immunohistochemical characterization of MMP-2, MMP-10, TIMP-1, TIMP-2 and podoplanin in oral squamous cell carcinoma. *Oral Surg. Oral Med. Pathol Oral. Radiol.* **2012**, *114*, 240–250. [CrossRef] [PubMed]

80. Hui, P.; Xu, X.; Xu, L.; Hui, G.; Wu, S.; Lan, Q. Expression of MMP14 in invasive pituitary adenomas: Relationship to invasion and angiogenesis. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 3556–3567. [PubMed]

81. Herszényi, L.; Barabás, L.; Hritz, I.; István, G.; Tulassay, Z. Impact of proteolytic enzymes in colorectal cancer development and progression. *World J. Gastroenterol.* **2014**, *20*, 13246–13257. [CrossRef] [PubMed]

82. Figueira, R.C.; Gomes, L.R.; Neto, J.S.; Silva, F.C.; Silva, I.D.; Sogayar, M.C. Correlation between MMPs and their inhibitors in breast cancer tumor tissue specimens and in cell lines with different metastatic potential. *BMC Cancer* **2009**, *9*. [CrossRef] [PubMed]

83. Hu, X.; Li, D.; Zhang, W.; Zhou, J.; Tang, B.; Li, L. Matrix metalloproteinase-9 expression correlates with prognosis and involved in ovarian cancer cell invasion. *Arch. Gynecol. Obstet.* **2012**, *286*, 1537–1543. [CrossRef] [PubMed]

84. Gao, Z.H.; Tretiakova, M.S.; Liu, W.H.; Gong, C.; Farris, P.D.; Hart, J. Association of E-cadherin, matrix metalloproteinases with the progression and metastasis of hepatocellular carcinoma. *Mod. Pathol.* **2006**, *19*, 533–540. [CrossRef] [PubMed]

85. Giannopoulos, G.; Pavlakis, K.; Parasi, A.; Kavatzas, N.; Tiniakos, D.; Karakosta, A.; Tzanakis, N.; Peros, G. The expression of matrix metalloproteinase-2 and -9 and their tissue inhibitor 2 in pancreatic ductal and ampullary carcinoma and their relation to angiogenesis and clinicopathological parameters. *Anticancer Res.* **2008**, *28*, 1875–1881. [PubMed]

86. Groblewska, M.; Siewko, M.; Mroczko, B.; Szmitkowski, M. The role of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) in the development of esophageal cancer. *Folia Histochem. Cytobiol.* **2012**, *50*, 12–19. [CrossRef] [PubMed]

87. Sheibani, S.; Mahmoudian, R.A.; Abbaszadegan, M.R.; Chamani, J.; Memar, B.; Gholamin, M. Expression analysis of matrix metalloproteinase-13 in human gastric cancer in the presence of Helicobacter Pylori infection. *Cancer Biomark.* **2017**, *18*, 349–356. [CrossRef] [PubMed]

88. Väyrynen, J.P.; Vornanen, J.; Tervahartiala, T.; Sorsa, T.; Bloigu, R.; Salo, T.; Tuomisto, A.; Mäkinen, M.J. Serum MMP-8 levels increase in colorectal cancer and correlate with disease course and inflammatory properties of primary tumors. *Int. J. Cancer* **2012**, *131*, 463–474. [CrossRef] [PubMed]

89. Rundhaug, J.E. Matrix metalloproteinases and angiogenesis. *J. Cell. Mol. Med.* **2005**, *9*, 267–285. [CrossRef] [PubMed]

90. Zhang, J.L.; Chen, G.W.; Liu, Y.C.; Wang, P.Y.; Wang, X.; Wan, Y.L.; Zhu, J.; Gao, H.Q.; Yin, J.; Wang, W.; et al. Secreted protein acidic and rich in cysteine (SPARC) suppresses angiogenesis by down-regulating the expression of VEGF and MMP-7 in gastric cancer. *PLoS ONE* **2012**, *7*, e44618. [CrossRef] [PubMed]

91. Chen, Q.; Jin, M.; Yang, F.; Zhu, J.; Xiao, Q.; Zhang, L. Matrix metalloproteinases: Inflammatory regulators of cell behavior in vascular formation and remodeling. *Mediat. Inflamm.* **2013**, e928315. [CrossRef] [PubMed]

92. Fang, C.; Wen, G.; Zhang, L.; Lin, L.; Moore, A.; Wu, S.; Ye, S.; Xiao, Q. An important role of matrix metalloproteinase-8 in angiogenesis in vitro and in vivo. *Cardiovasc. Res.* **2013**, *99*, 146–155. [CrossRef] [PubMed]

93. Gu, Y.; Ke, G.; Wang, L.; Gu, Q.; Zhou, E.; He, Q.; Wang, S. Silencing Matrix Metalloproteinases 9 and 2 Inhibits Human Retinal Microvascular Endothelial Cell Invasion and Migration. *Ophthalmic Res.* **2015**, *55*, 70–75. [CrossRef] [PubMed]

94. Yadav, L.; Puri, N.; Rastogi, V.; Satpute, P.; Sharma, V. Tumour Angiogenesis and Angiogenic Inhibitors: A Review. *Clin. Diagn. Res.* **2015**, *9*, XE01–XE05. [CrossRef] [PubMed]

95. Hu, J.; Ni, S.; Cao, Y.; Zhang, T.; Wu, T.; Yin, X.; Lang, Y.; Lu, H. The Angiogenic Effect of microRNA-21 Targeting TIMP3 through the Regulation of MMP2 and MMP9. *PLoS ONE* **2016**, *11*, e0149537. [CrossRef]

96. Fukuda, H.; Mochizuki, S.; Abe, H.; Okano, H.J.; Hara-Miyauchi, C.; Okano, H.; Yamaguchi, N.; Nakayama, M.; D'Armiento, J.; Okada, Y. Host-derived MMP-13 exhibits a protective role in lung metastasis of melanoma cells by local endostatin production. *Br. J. Cancer* **2011**, *105*, 1615–1624. [CrossRef] [PubMed]

97. Korpi, J.T.; Kervinen, V.; Mäklin, H.; Väänänen, A.; Lahtinen, M.; Läärä, E.; Ristimäki, A.; Thomas, G.; Ylipalosaari, M.; Aström, P.; et al. Collagenase-2 (matrix metalloproteinase-8) plays a protective role in tongue cancer. *Br. J. Cancer* **2008**, *98*, 766–775. [CrossRef] [PubMed]

98. Overall, C.M.; Kleifeld, O. Tumour microenvironment—Opinion: Validating matrix metalloproteinases as drug targets and anti-targets for cancer therapy. *Nat. Rev. Cancer* **2006**, *6*, 227–239. [CrossRef] [PubMed]

99. Abdul Muneer, P.M.; Alikunju, S.; Szlachetka, A.M.; Haorah, J. The mechanisms of cerebral vascular dysfunction and neuroinflammation by MMP-mediated degradation of VEGFR-2 in alcohol ingestion. *Arterioscler. Thromb. Vasc. Biol.* **2012**, *32*, 1167–1177. [CrossRef] [PubMed]

100. Wang, H.; Zhang, X.; Huang, L.; Li, J.; Qu, S.; Pan, F. Matrix metalloproteinase-14 expression and its prognostic value in cervical carcinoma. *Cell Biochem. Biophys.* **2014**, *70*, 729–734. [CrossRef] [PubMed]

101. Zhai, Y.; Hotary, K.B.; Nan, B.; Bosch, F.X.; Muñoz, N.; Weiss, S.J.; Cho, K.R. Expression of membrane type 1 matrix metalloproteinase is associated with cervical carcinoma progression and invasion. *Cancer Res.* **2005**, *65*, 6543–6550. [CrossRef] [PubMed]

102. Sheu, B.C.; Lien, H.C.; Ho, H.N.; Lin, H.H.; Chow, S.N.; Huang, S.C.; Hsu, S.M. Increased expression and activation of gelatinolytic matrix metalloproteinases is associated with the progression and recurrence of human cervical cancer. *Cancer Res.* **2003**, *63*, 6537–6542. [PubMed]

103. Matheus, E.R.; Zonta, M.A.; Discacciati, M.G.; Paruci, P.; Velame, F.; Cardeal, L.B.; Barros, S.B.; Pignatari, A.C.; Maria-Engler, S.S. MMP-9 expression increases according to the grade of squamous intraepithelial lesion in cervical smears. *Diagn. Cytopathol.* **2014**, *42*, 827–833. [CrossRef] [PubMed]

104. Nasr, M.; Ayyad, S.B.; El-Lamie, I.K.; Mikhail, M.Y. Expression of matrix metalloproteinase-2 in preinvasive and invasive carcinoma of the uterine cervix. *Gynaecol. Oncol.* **2005**, *26*, 199–202.

105. Davidson, B.; Goldberg, I.; Kopolovic, J.; Lerner-Geva, L.; Gotlieb, W.H.; Weis, B.; Ben-Baruch, G.; Reich, R. Expression of matrix metalloproteinase-9 in squamous cell carcinoma of the uterine cervix-clinicopathologic study using immunohistochemistry and mRNA in situ hybridization. *Gynecol. Oncol.* **1999**, *72*, 380–386. [CrossRef] [PubMed]

106. Branca, M.; Ciotti, M.; Giorgi, C.; Santini, D.; Di Bonito, L.; Costa, S.; Benedetto, A.; Bonifacio, D.; Di Bonito, P.; Paba, P.; et al. HPV-Pathogen ISS Study Group. Matrix metalloproteinase-2 (MMP-2) and its tissue inhibitor (TIMP-2) are prognostic factors in cervical cancer, related to invasive disease but not to high-risk human papillomavirus (HPV) or virus persistence after treatment of CIN. *Anticancer Res.* **2006**, *26*, 1543–1556. [PubMed]

107. Talvensaari-Mattila, A.; Turpeenniemi-Hujanen, T. Matrix metalloproteinase 9 in the uterine cervix during tumor progression. *Int. J. Gynaecol. Obstet.* **2006**, *92*, 83–84. [CrossRef] [PubMed]

108. Van Trappen, P.O.; Ryan, A.; Carroll, M.; Lecoeur, C.; Goff, L.; Gyselman, V.G.; Young, B.D.; Lowe, D.G.; Pepper, M.S.; Shepherd, J.H.; et al. A model for co-expression pattern analysis of genes implicated in angiogenesis and tumor cell invasion in cervical cancer. *Br. J. Cancer* **2002**, *87*, 537–544. [CrossRef] [PubMed]

109. Asha Nair, S.; Karunagaran, D.; Nair, M.B.; Sudhakaran, P.R. Changes in matrix metalloproteinases and their endogenous inhibitors during tumor progression in the uterine cervix. *J. Cancer Res. Clin. Oncol.* **2003**, *129*, 123–131. [CrossRef] [PubMed]

110. Gaiotto, M.A.; Focchi, J.; Ribalta, J.L.; Stávale, J.N.; Baracat, E.C.; Lima, G.R.; Guerreiro da Silva, I.D. Comparative study of MMP-2 (matrix metalloproteinase 2) immune expression in normal uterine cervix, intraepithelial neoplasias and squamous cells cervical carcinoma. *Am. J. Obstet. Gynecol.* **2004**, *190*, 1278–1282. [CrossRef] [PubMed]

111. Lu, Z.; Chen, H.; Zheng, X.M.; Chen, M.L. Expression and clinical significance of high risk human papillomavirus and invasive gene in cervical carcinoma. *Asian Pac. J. Trop. Med.* **2017**, *10*, 195–200. [CrossRef] [PubMed]

112. Fernandes, T.; de Angelo-Andrade, L.A.; Morais, S.S.; Pinto, G.A.; Chagas, C.A.; Maria-Engler, S.S.; Zeferino, L.C. Stromal cells play a role in cervical cancer progression mediated by MMP-2 protein. *Eur. J. Gynaecol. Oncol.* **2008**, *29*, 341–344. [PubMed]

113. Yang, S.F.; Wang, P.H.; Lin, L.Y.; Ko, J.L.; Chen, G.D.; Yang, J.S.; Lee, H.S.; Hsieh, Y.S. A significant elevation of plasma level of matrix metalloproteinase-9 in patients with high-grade intraepithelial neoplasia and early squamous cell carcinoma of the uterine cervix. *Reprod. Sci.* **2007**, *14*, 710–718. [CrossRef] [PubMed]

114. Smola-Hess, S.; Pahne, J.; Mauch, C.; Zigrino, P.; Smola, H.; Pfister, H.J. Expression of membrane type 1 matrix metalloproteinase in papillomavirus-positive cells: Role of the human papillomavirus (HPV) 16 and HPV8 E7 gene products. *J. Gen. Virol.* **2005**, *86*, 1291–1296. [CrossRef] [PubMed]

115. Da Silva Cardeal, L.B.; Brohem, C.A.; Correa, T.C.; Winnischofer, S.M.; Nakano, F.; Boccardo, E.; Villa, L.L.; Sogayar, M.C.; Maria-Engler, S.S. Higher expression and activity of metalloproteinases in human cervical carcinoma cell lines is associated with HPV presence. *Biochem. Cell Biol.* **2006**, *84*, 713–719. [CrossRef] [PubMed]

116. Yoshida, S.; Kajitani, N.; Satsuka, A.; Nakamura, H.; Sakai, H. Ras modifies proliferation and invasiveness of cells expressing human papillomavirus oncoproteins. *J. Virol.* **2008**, *82*, 8820–8827. [CrossRef] [PubMed]

117. Barbaresi, S.; Cortese, M.S.; Quinn, J.; Ashrafi, G.H.; Graham, S.V.; Campo, M.S. Effects of human papillomavirus type 16 E5 deletion mutants on epithelial morphology: Functional characterization of each trans-membrane domain. *J. Gen. Virol.* **2010**, *91*, 521–530. [CrossRef] [PubMed]

118. Cardeal, L.B.; Boccardo, E.; Termini, L.; Rabachini, T.; Andreoli, M.A.; di Loreto, C.; Longatto Filho, A.; Villa, L.L.; Maria-Engler, S.S. HPV16 oncoproteins induce MMPs/RECK-TIMP-2 imbalance in primary keratinocytes: Possible implications in cervical carcinogenesis. *PLoS ONE* **2012**, *7*, e33585. [CrossRef] [PubMed]

119. Kaewprag, J.; Umnajvijit, W.; Ngamkham, J.; Ponglikitmongkol, M. HPV16 oncoproteins promote cervical cancer invasiveness by upregulating specific matrix metalloproteinases. *PLoS ONE* **2013**, *8*, e71611. [CrossRef] [PubMed]

120. Zhu, D.; Ye, M.; Zhang, W. E6/E7 oncoproteins of high risk HPV-16 upregulate MT1-MMP, MMP-2 and MMP-9 and promote the migration of cervical cancer cells. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 4981–4989. [PubMed]

121. Menges, C.W.; Baglia, L.A.; Lapoint, R.; McCance, D.J. Human papillomavirus type 16 E7 up-regulates AKT activity through the retinoblastoma protein. *Cancer Res.* **2006**, *66*, 5555–5559. [CrossRef] [PubMed]

122. Spangle, J.M.; Münger, K. The human papillomavirus type 16 E6 oncoprotein activates mTORC1 signalling and increases protein synthesis. *J. Virol.* **2010**, *84*, 9398–9407. [CrossRef] [PubMed]

123. Lu, C.; Lee, J.J.; Komaki, R.; Herbst, R.S.; Feng, L.; Evans, W.K.; Choy, H.; Desjardins, P.; Esparaz, B.T.; Truong, M.T.; et al. Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: A randomized phase III trial. *J. Natl. Cancer Inst.* **2010**, *102*, 859–865. [CrossRef] [PubMed]

124. El-Rayes, B.F.; Philip, P.A.; Sarkar, F.H.; Shields, A.F.; Ferris, A.M.; Hess, K.; Kaseb, A.O.; Javle, M.M.; Varadhachary, G.R.; Wolff, R.A.; et al. A phase II study of isoflavones, erlotinib and gemcitabine in advanced pancreatic cancer. *Investig. New Drugs* **2011**, *29*, 694–699. [CrossRef] [PubMed]

125. Gu, Y.; Lee, H.M.; Roemer, E.J.; Musacchia, L.; Golub, L.M.; Simon, S.R. Inhibition of tumor cell invasiveness by chemically modified tetracyclines. *Curr. Med. Chem.* **2001**, *8*, 261–270. [CrossRef] [PubMed]

126. Lai, T.J.; Hsu, S.F.; Li, T.M.; Hsu, H.C.; Lin, J.G.; Hsu, C.J.; Chou, M.C.; Lee, M.C.; Yang, S.F.; Fong, Y.C. Alendronate inhibits cell invasion and MMP-2 secretion in human chondrosarcoma cell line. *Acta Pharmacol. Sin.* **2007**, *28*, 1231–1235. [CrossRef] [PubMed]

127. Scatena, R. Prinomastat, a hydroxamate-based matrix metalloproteinase inhibitor. A novel pharmacological approach for tissue remodeling-related diseases. *Expert Opin. Investig. Drugs* **2000**, *9*, 2159–2165. [CrossRef] [PubMed]

128. Eccles, S.A.; Box, G.M.; Court, W.J.; Bone, E.A.; Thomas, W.; Brown, P.D. Control of lymphatic and hematogenous metastasis of a rat mammary carcinoma by the matrix metalloproteinase inhibitor batimastat (BB-94). *Cancer Res.* **1996**, *56*, 2815–2822. [PubMed]

129. Price, A.; Shi, Q.; Morris, D.; Wilcox, M.E.; Brasher, P.M.; Rewcastle, N.B.; Shalinsky, D.; Zou, H.; Appelt, K.; Johnston, R.N.; et al. Marked inhibition of tumor growth in a malignant glioma tumor model by a novel synthetic matrix metalloproteinase inhibitor AG3340. *Clin. Cancer Res.* **1999**, *5*, 845–854. [PubMed]

130. Shevrin, D.H.; Gorny, K.I.; Rosol, T.J.; Kukreja, S.C. Effect of etidronate disodium on the development of bone lesions in an animal model of bone metastasis using the human prostate cancer cell line PC-3. *Prostate* **1991**, *19*, 149–154. [CrossRef] [PubMed]

131. Weber, M.H.; Lee, J.; Orr, F.W. The effect of Neovastat (AE-941) on an experimental metastatic bone tumor model. *Int. J. Oncol.* **2002**, *20*, 299–303. [CrossRef] [PubMed]

132. Giraudo, E.; Inoue, M.; Hanahan, D. An amino-bisphosphonate targets MMP-9-expressing macrophages and angiogenesis to impair cervical carcinogenesis. *J. Clin. Investig.* **2004**, *114*, 623–633. [CrossRef] [PubMed]

133. Wang, S.Y.; Yang, K.W.; Hsu, Y.T.; Chang, C.L.; Yang, Y.C. The differential inhibitory effects of genistein on the growth of cervical cancer cells in vitro. *Neoplasma* **2001**, *48*, 227–233. [PubMed]

134. Iwasaki, M.; Nishikawa, A.; Fujimoto, T.; Akutagawa, N.; Manase, K.; Endo, T.; Yoshida, K.; Maekawa, R.; Yoshioka, T.; Kudo, R. Anti-invasive Effect of MMI-166, a New Selective Matrix Metalloproteinase Inhibitor, in Cervical Carcinoma Cell Lines. *Gynecol. Oncol.* **2002**, *85*, 103–107. [CrossRef] [PubMed]

135. Bramhall, S.R.; Schulz, J.; Nemunaitis, J.; Brown, P.D.; Baillet, M.; Buckels, J.A. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. *Br. J. Cancer* **2002**, *87*, 161–167. [CrossRef] [PubMed]

136. Pavlaki, M.; Zucker, S. Matrix metalloproteinase inhibitors (MMPIs): The beginning of phase I or the termination of phase III clinical trials. *Cancer Metastasis Rev.* **2003**, *22*, 177–203. [CrossRef] [PubMed]

137. Bissett, D.; O'Byrne, K.J.; von Pawel, J.; Gatzemeier, U.; Price, A.; Nicolson, M.; Mercier, R.; Mazabel, E.; Penning, C.; Zhang, M.H.; et al. Phase III study of matrix metalloproteinase inhibitor prinomastat in non-small-cell lung cancer. *J. Clin. Oncol.* **2005**, *23*, 842–849. [CrossRef] [PubMed]

138. Dormán, G.; Cseh, S.; Hajdú, I.; Barna, L.; Kónya, D.; Kupai, K.; Kovács, L.; Ferdinandy, P. Matrix metalloproteinase inhibitors: A critical appraisal of design principles and proposed therapeutic utility. *Drugs* **2010**, *70*, 949–964. [CrossRef] [PubMed]

139. Amar, S.; Fields, G.B. Potential clinical implications of recent matrix metalloproteinase inhibitor design strategies. *Expert Rev. Proteom.* **2015**, *12*, 445–447. [CrossRef] [PubMed]

140. Fields, G.B. New strategies for targeting matrix metalloproteinases. *Matrix Biol.* **2015**, *44–46*, 239–246. [CrossRef] [PubMed]

141. Rims, C.R.; McGuire, J.K. Matrilysin (MMP-7) catalytic activity regulates β-catenin localization and signaling activation in lung epithelial cells. *Exp. Lung Res.* **2014**, *40*, 126–136. [CrossRef] [PubMed]

142. Valacca, C.; Tassone, E.; Mignatti, P. TIMP-2 Interaction with MT1-MMP Activates the AKT Pathway and Protects Tumor Cells from Apoptosis. *PLoS ONE* **2015**, *10*, e0136797. [CrossRef] [PubMed]

143. Shay, G.; Lynch, C.C.; Fingleton, B. Moving targets: Emerging roles for MMPs in cancer progression and metastasis. *Matrix Biol.* **2015**, *44–46*, 200–206. [CrossRef] [PubMed]

144. Flexner, C. HIV-protease inhibitors. *N. Engl. J. Med.* **1998**, *338*, 1281–1292. [CrossRef] [PubMed]

145. Riddler, S.A.; Haubrich, R.; Di Rienzo, A.G.; Peeples, L.; Powderly, W.G.; Klingman, K.L.; Garren, K.W.; George, T.; Rooney, J.F.; Brizz, B.; et al. AIDS Clinical Trials Group Study A5142 Team. Class-sparing regimens for initial treatment of HIV-1 infection. *N. Engl. J. Med.* **2008**, *358*, 2095–2106. [CrossRef] [PubMed]

146. UNAIDS. *Global Report: UNAIDS Report on the Global AIDS Epidemic 2010*; UNAIDS: Geneva, Switzerland, 2010.

147. André, P.; Groettrup, M.; Klenerman, P.; de Giuli, R.; Booth, B.L., Jr; Cerundolo, V.; Bonneville, M.; Jotereau, F.; Zinkernagel, R.M.; Lotteau, V. An inhibitor of HIV-1 protease modulates proteasome activity, antigen presentation and T cell responses. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 13120–13124. [CrossRef] [PubMed]

148. Gaedicke, S.; Firat-Geier, E.; Constantiniu, O.; Lucchiari-Hartz, M.; Freudenberg, M.; Galanos, C.; Niedermann, G. Antitumor effect of the human immunodeficiency virus protease inhibitor ritonavir: Induction of tumor-cell apoptosis associated with perturbation of proteasomal proteolysis. *Cancer Res.* **2002**, *62*, 6901–6908. [PubMed]

149. Pajonk, F.; Himmelsbach, J.; Riess, K.; Sommer, A.; McBride, W.H. The human immunodeficiency virus (HIV)-1 protease inhibitor saquinavir inhibits proteasome function and causes apoptosis and radio-sensitization in non-HIV-associated human cancer cells. *Cancer Res.* **2002**, *62*, 5230–5235. [PubMed]

150. Yang, Y.; Ikezoe, T.; Nishioka, C.; Bandobashi, K.; Takeuchi, T.; Adachi, Y.; Kobayashi, M.; Takeuchi, S.; Koeffler, H.P.; Taguchi, H. NFV, an HIV-1 protease inhibitor, induces growth arrest, reduced Akt signalling, apoptosis and docetaxel sensitisation in NSCLC cell lines. *Br. J Cancer* **2006**, *95*, 1653–1662. [CrossRef] [PubMed]

151. Hampson, L.; Kitchener, H.C.; Hampson, I.N. Specific HIV protease inhibitors inhibit the ability of HPV16 E6 to degrade p53 and selectively kill E6-dependent cervical carcinoma cells in vitro. *Antivir. Ther.* **2006**, *11*, 813–825. [PubMed]

152. De Barros, S.; Zakaroff-Girard, A.; Lafontan, M.; Galitzky, J.; Bourlier, V. Inhibition of human preadipocyte proteasomal activity by HIV protease inhibitors or specific inhibitor lactacystin leads to a defect in adipogenesis, which involves matrix metalloproteinase-9. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 291–299. [CrossRef] [PubMed]

153. Bastard, J.P.; Caron, M.; Vidal, H.; Jan, V.; Auclair, M.; Vigouroux, C.; Luboinski, J.; Laville, M.; Maachi, M.; Girard, P.M.; et al. Association between altered expression of adipogenic factor SREBP1 in lipoatrophic adipose tissue from HIV-1-infected patients and abnormal adipocyte differentiation and insulin resistance. *Lancet* **2002**, *359*, 1026–1031. [CrossRef]

154. Riddle, T.M.; Kuhel, D.G.; Woollett, L.A.; Fichtenbaum, C.J.; Hui, D.Y. HIV protease inhibitor induces fatty acid and sterol biosynthesis in liver and adipose tissues due to the accumulation of activated sterol regulatory element-binding proteins in the nucleus. *J. Biol. Chem.* **2001**, *276*, 37514–37519. [CrossRef] [PubMed]

155. Lenhard, J.M.; Croom, D.K.; Weiel, J.E.; Winegar, D.A. HIV protease inhibitors stimulate hepatic triglyceride synthesis. *Arterioscler. Thromb. Vasc. Biol.* **2000**, *20*, 2625–2629. [CrossRef] [PubMed]

156. Hui, D.Y. Effects of HIV protease inhibitor therapy on lipid metabolism. *Prog. Lipid Res.* **2003**, *42*, 81–92. [CrossRef]

157. Tran, H.; Robinson, S.; Mikhailenko, I.; Strickland, D.K. Modulation of the LDL receptor and LRP levels by HIV protease inhibitors. *J. Lipid. Res.* **2003**, *44*, 1859–1869. [CrossRef] [PubMed]

158. Murata, H.; Hruz, P.W.; Mueckler, M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J. Biol. Chem.* **2000**, *275*, 20251–20254. [CrossRef] [PubMed]

159. Lehmann, C.; Jung, N.; Hofmann, A.; Cornely, O.A.; Wyen, C.; Fätkenheuer, G.; Hartmann, P. Nucleoside-free boosted double PI regimen: Significant CD4+ T-cell recovery in patients with poor immunologic response despite virologic suppression. *Curr. HIV Res.* **2008**, *6*, 555–559. [CrossRef] [PubMed]

160. Cassone, A.; De Bernardis, F.; Torosantucci, A.; Tacconelli, E.; Tumbarello, M.; Cauda, R. In vitro and in vivo anticandidal activity of human immunodeficiency virus protease inhibitors. *J. Infect. Dis.* **1999**, *180*, 448–453. [CrossRef] [PubMed]

161. Krischer, J.; Rutschmann, O.; Hirschel, B.; Vollenweider-Roten, S.; Saurat, J.H.; Pechère, M. Regression of Kaposi's sarcoma during therapy with HIV-1 protease inhibitors: A prospective pilot study. *J. Am. Acad. Dermatol.* **1998**, *38*, 594–598. [CrossRef]

162. Lebbé, C.; Blum, L.; Pellet, C.; Blanchard, G.; Vérola, O.; Morel, P.; Danne, O.; Calvo, F. Clinical and biological impact of antiretroviral therapy with protease inhibitors on HIV-related Kaposi's sarcoma. *AIDS* **1998**, *12*, F45–F49. [CrossRef] [PubMed]

163. Niehues, T.; Horneff, G.; Megahed, M.; Schroten, H.; Wahn, V. Complete regression of AIDS-related Kaposi's sarcoma in a child treated with highly active antiretroviral therapy. *AIDS* **1999**, *13*, 1148–1149. [CrossRef] [PubMed]

164. Gill, J.; Bourboulia, D.; Wilkinson, J.; Hayes, P.; Cope, A.; Marcelin, A.G.; Calvez, V.; Gotch, F.; Boshoff, C.; Gazzard, B. Prospective study of the effects of antiretroviral therapy on Kaposi sarcoma—Associated herpesvirus infection in patients with and without Kaposi sarcoma. *J. Acquir. Immune Defic. Syndr.* **2002**, *31*, 384–390. [CrossRef] [PubMed]

165. Hallit, R.R.; Afridi, M.; Sison, R.; Szabela, M.E.; Bajaj, N.; Alchaa, R.; Hallit, S.; Awkar, N.; Boghossian, J.; Slim, J. AIDS-related lymphoma: Resolution with antiretroviral therapy alone. *J. Int. Assoc. Provid. AIDS Care* **2014**, *13*, 313–315. [CrossRef] [PubMed]

166. Cobucci, R.N.; Lima, P.H.; de Souza, P.C.; Costa, V.V.; Cornetta Mda, C.; Fernandes, J.V.; Gonçalves, A.K. Assessing the impact of HAART on the incidence of defining and non-defining AIDS cancers among patients with HIV/AIDS: A systematic review. *J. Infect. Public Health* **2015**, *8*, 1–10. [CrossRef] [PubMed]

167. Heard, I.; Schmitz, V.; Costagliola, D.; Orth, G.; Kazatchkine, M.D. Early regression of cervical lesions in HIV-seropositive women receiving highly active antiretroviral therapy. *AIDS* **1998**, *12*, 1459–1464. [CrossRef] [PubMed]

168. Firnhaber, C.; Westreich, D.; Schulze, D.; Williams, S.; Siminya, M.; Michelow, P.; Levin, S.; Faesen, M.; Smith, J.S. Highly active antiretroviral therapy and cervical dysplasia in HIV-positive women in South Africa. *J. Int. AIDS Soc.* **2012**, *15*, e17382. [CrossRef] [PubMed]

169. Adler, D.H.; Kakinami, L.; Modisenyane, T.; Tshabangu, N.; Mohapi, L.; De Bruyn, G.; Martinson, N.A.; Omar, T. Increased regression and decreased incidence of human papillomavirus-related cervical lesions among HIV-infected women on HAART. *AIDS* **2012**, *26*, 1645–1652. [CrossRef] [PubMed]

170. Soncini, E.; Zoncada, A.; Condemi, V.; Antoni, A.D.; Bocchialini, E.; Soregotti, P. Reduction of the risk of cervical intraepithelial neoplasia in HIV-infected women treated with highly active antiretroviral therapy. *Acta Biomed.* **2007**, *78*, 36–40. [PubMed]

171. Minkoff, H.; Ahdieh, L.; Massad, L.S.; Anastos, K.; Watts, D.H.; Melnick, S.; Muderspach, L.; Burk, R.; Palefsky, J. The effect of highly active antiretroviral therapy on cervical cytologic changes associated with oncogenic HPV among HIV-infected women. *AIDS* **2001**, *15*, 2157–2164. [CrossRef] [PubMed]

172. Monini, P.; Sgadari, C.; Toschi, E.; Barillari, G.; Ensoli, B. Antitumour effects of antiretroviral therapy. *Nat. Rev. Cancer* **2004**, *4*, 861–875. [CrossRef] [PubMed]

173. Bani-Sadr, F.; Fournier, S.; Molina, J.M. Relapse of Kaposi's sarcoma in HIV-infected patients switching from a protease inhibitor to a non-nucleoside reverse transcriptase inhibitor-based highly active antiretroviral therapy regimen. *AIDS* **2003**, *17*, 1580–1581. [CrossRef] [PubMed]

174. Bono, C.; Karlin, L.; Harel, S.; Mouly, E.; Labaume, S.; Galicier, L.; Apcher, S.; Sauvageon, H.; Fermand, J.P.; Bories, J.C.; et al. The human immunodeficiency virus-1 protease inhibitor nelfinavir impairs proteasome activity and inhibits the proliferation of multiple myeloma cells in vitro and in vivo. *Haematologica* **2012**, *97*, 1101–1109. [CrossRef] [PubMed]

175. Brüning, A.; Burger, P.; Vogel, M.; Rahmeh, M.; Gingelmaiers, A.; Friese, K.; Lenhard, M.; Burges, A. Nelfinavir induces the unfolded protein response in ovarian cancer cells, resulting in ER vacuolization, cell cycle retardation and apoptosis. *Cancer Biol. Ther.* **2009**, *8*, 226–232. [CrossRef] [PubMed]

176. Chow, W.A.; Guo, S.; Valdes-Albini, F. Nelfinavir induces liposarcoma apoptosis and cell cycle arrest by up-regulating sterol regulatory element binding protein-1. *Anticancer Drugs* **2006**, *17*, 891–903. [CrossRef] [PubMed]

177. Dewan, M.Z.; Tomita, M.; Katano, H.; Yamamoto, N.; Ahmed, S.; Yamamoto, M.; Sata, T.; Mori, N.; Yamamoto, N. An HIV protease inhibitor, ritonavir targets the nuclear factor-kappaB and inhibits the tumor growth and infiltration of EBV-positive lymphoblastoid B cells. *Int. J. Cancer* **2009**, *124*, 622–629. [CrossRef] [PubMed]

178. Gills, J.J.; Lopiccolo, J.; Tsurutani, J. Nelfinavir, A lead HIV protease inhibitor, is a broad-spectrum, anticancer agent that induces endoplasmic reticulum stress, autophagy and apoptosis in vitro and in vivo. *Clin. Cancer Res.* **2007**, *13*, 5183–5194. [CrossRef] [PubMed]

179. Ikezoe, T.; Saito, T.; Bandobashi, K.; Yang, Y.; Koeffler, H.P.; Taguchi, H. HIV-1 protease inhibitor induces growth arrest and apoptosis of human multiple myeloma cells via inactivation of signal transducer and activator of transcription 3 and extracellular signal-regulated kinase 1/2. *Mol. Cancer Ther.* **2004**, *3*, 473–479. [PubMed]

180. Jiang, W.; Mikochik, P.J.; Ra, J.H.; Lei, H.; Flaherty, K.T.; Winkler, J.D.; Spitz, F.R. HIV protease inhibitor nelfinavir inhibits growth of human melanoma cells by induction of cell cycle arrest. *Cancer Res.* **2007**, *67*, 1221–1227. [CrossRef] [PubMed]

181. Timeus, F.; Crescenzio, N.; Doria, A.; Foglia, L.; Pagliano, S.; Ricotti, E.; Fagioli, F.; Tovo, P.A.; Cordero di Montezemolo, L. In vitro anti-neuroblastoma activity of saquinavir and its association with imatinib. *Oncol. Rep.* **2012**, *27*, 734–740. [CrossRef] [PubMed]

182. Yang, Y.; Ikezoe, T.; Takeuchi, T.; Adachi, Y.; Ohtsuki, Y.; Takeuchi, S.; Koeffler, H.P.; Taguchi, H. HIV-1 protease inhibitor induces growth arrest and apoptosis of human prostate cancer LNCaP cells in vitro and in vivo in conjunction with blockade of androgen receptor STAT3 and AKT signaling. *Cancer Sci.* **2005**, *96*, 425–433. [CrossRef] [PubMed]

183. Wei, C.; Bajpai, R.; Sharma, H.; Heitmeier, M.; Jain, A.D.; Matulis, S.M.; Nooka, A.K.; Mishra, R.K.; Hruz, P.W.; Schiltz, G.E.; et al. Development of GLUT4-selective antagonists for multiple myeloma therapy. *Eur. J. Med. Chem.* **2017**, *139*, 573–586. [CrossRef] [PubMed]

184. Justesen, U.S. Protease inhibitor plasma concentrations in HIV antiretroviral therapy. *Dan. Med. Bull.* **2008**, *55*, 165–185. [PubMed]

185. Barillari, G.; Iovane, A.; Bacigalupo, I.; Palladino, C.; Bellino, S.; Leone, P.; Monini, P.; Ensoli, B. Ritonavir or saquinavir impairs the invasion of cervical intraepithelial neoplasia cells via a reduction of MMP expression and activity. *AIDS* **2012**, *26*, 909–919. [CrossRef] [PubMed]

186. Brüning, A.; Vogel, M.; Mylonas, I.; Friese, K.; Burges, A. Bortezomib targets the caspase-like proteasome activity in cervical cancer cells, triggering apoptosis that can be enhanced by nelfinavir. *Curr. Cancer Drug Targets* **2011**, *11*, 799–809. [CrossRef] [PubMed]

187. Hampson, L.; Maranga, I.O.; Masinde, M.S.; Oliver, A.W.; Batman, G.; He, X.; Desai, M.; Okemwa, P.M.; Stringfellow, H.; Martin-Hirsch, P.; et al. A Single-Arm, Proof-Of-Concept Trial of Lopimune (Lopinavir/Ritonavir) as a Treatment for HPV-Related Pre-Invasive Cervical Disease. *PLoS ONE* **2016**, *11*, e0147917. [CrossRef] [PubMed]

188. Bacigalupo, I.; Palladino, C.; Leone, P.; Toschi, E.; Sgadari, C.; Ensoli, B.; Barillari, G. Inhibition of MMP-9 expression by ritonavir or saquinavir is associated with inactivation of the AKT/Fra-1 pathway in cervical intraepithelial neoplasia cells. *Oncol. Lett.* **2017**, *13*, 2903–2908. [CrossRef] [PubMed]

189. Toschi, E.; Sgadari, C.; Malavasi, L.; Bacigalupo, I.; Chiozzini, C.; Carlei, D.; Compagnoni, D.; Bellino, S.; Bugarini, R.; Falchi, M.; et al. Human immunodeficiency virus protease inhibitors reduce the growth of human tumors via a proteasome-independent block of angiogenesis and matrix metalloproteinases. *Int. J. Cancer* **2011**, *128*, 82–93. [CrossRef] [PubMed]

190. Sgadari, C.; Monini, P.; Barillari, G.; Ensoli, B. Use of HIV protease inhibitors to block Kaposi's sarcoma and tumor growth. *Lancet Oncol.* **2003**, *4*, 537–547. [CrossRef]

191. Sgadari, C.; Barillari, G.; Toschi, E.; Carlei, D.; Bacigalupo, I.; Baccarini, S.; Palladino, C.; Leone, P.; Bugarini, R.; Malavasi, L.; et al. HIV protease inhibitors are potent anti-angiogenic molecules and promote regression of Kaposi sarcoma. *Nat. Med.* **2002**, *8*, 225–232. [CrossRef] [PubMed]

192. Liuzzi, G.M.; Mastroianni, C.M.; Latronico, T.; Mengoni, F.; Fasano, A.; Lichtner, M.; Vullo, V.; Riccio, P. Anti-HIV drugs decrease the expression of matrix metalloproteinases in astrocytes and microglia. *Brain* **2004**, *127*, 398–407. [CrossRef] [PubMed]

193. Latronico, T.; Liuzzi, G.M.; Riccio, P.; Lichtner, M.; Mengoni, F.; D'Agostino, C.; Vullo, V.; Mastroianni, C.M. Antiretroviral therapy inhibits matrix metalloproteinase-9 from blood mononuclear cells of HIV-infected patients. *AIDS* **2007**, *21*, 677–684. [CrossRef] [PubMed]

194. Monini, P.; Sgadari, C.; Grosso, M.G.; Bellino, S.; Di Biagio, A.; Toschi, E.; Bacigalupo, I.; Sabbatucci, M.; Cencioni, G.; Salvi, E.; et al. For the Concerted Action on Kaposi's Sarcoma. Clinical course of classic Kaposi's sarcoma in HIV-negative patients treated with the HIV protease inhibitor indinavir. *AIDS* **2009**, *23*, 534–538. [CrossRef] [PubMed]

195. Hsieh, C.Y.; Tsai, P.C.; Tseng, C.H.; Chen, Y.L.; Chang, L.S.; Lin, S.R. Inhibition of EGF/EGFR activation with naphtho[1,2-b] furan-4,5-dione blocks migration and invasion of MDA-MB-231 cells. *Toxicol. In Vitro* **2013**, *27*, 1–10. [CrossRef] [PubMed]

196. Mathur, S.P.; Mathur, R.S.; Rust, P.F.; Young, R.C. Human papilloma virus (HPV)-E6/E7 and epidermal growth factor receptor (EGF-R) protein levels in cervical cancer and cervical intraepithelial neoplasia (CIN). *Am. J. Reprod. Immunol.* **2001**, *46*, 280–287. [CrossRef] [PubMed]

197. Bertelsen, B.I.; Steine, S.J.; Sandvei, R.; Molven, A.; Laerum, O.D. Molecular analysis of the PI3K-AKT pathway in uterine cervical neoplasia: Frequent PIK3CA amplification and AKT phosphorylation. *Int. J. Cancer* **2006**, *118*, 1877–1883. [CrossRef] [PubMed]

198. Du, C.X.; Wang, Y. Expression of P-Akt, NFkappa B and their correlation with human papillomavirus infection in cervical carcinoma. *Eur. J. Gynaecol. Oncol.* **2012**, *33*, 274–277. [PubMed]

199. Batchu, R.B.; Gruzdyn, O.V.; Bryant, C.S.; Qazi, A.M.; Kumar, S.; Chamala, S.; Kung, S.T.; Sanka, R.S.; Puttagunta, U.S.; Weaver, D.W.; et al. Ritonavir-mediated induction of apoptosis in pancreatic cancer occurs via the RB/E2F-1 and AKT pathways. *Pharmaceuticals* **2014**, *7*, 46–57. [CrossRef] [PubMed]

200. Gills, J.J.; Lopiccolo, J.; Dennis, P.A. Nelfinavir, a new anti-cancer drug with pleiotropic effects and many paths to autophagy. *Autophagy* **2008**, *4*, 107–109. [CrossRef] [PubMed]

201. Gupta, A.K.; Cerniglia, G.J.; Mick, R.; McKenna, W.G.; Muschel, R.J. HIV protease inhibitors block Akt signaling and radiosensitize tumor cells both in vitro and in vivo. *Cancer Res.* **2005**, *65*, 8256–8265. [CrossRef] [PubMed]

202. Kraus, M.; Müller-Ide, H.; Rückrich, T.; Bader, J.; Overkleeft, H.; Driessen, C. Ritonavir, nelfinavir, saquinavir and lopinavir induce proteotoxic stress in acute myeloid leukemia cells and sensitize them for proteasome inhibitor treatment at low micromolar drug concentrations. *Leuk. Res.* **2014**, *38*, 383–392. [CrossRef] [PubMed]

203. Plastaras, J.P.; Vapiwala, N.; Ahmed, M.S.; Gudonis, D.; Cerniglia, G.J.; Feldman, M.D.; Frank, I.; Gupta, A.K. Validation and toxicity of PI3K/Akt pathway inhibition by HIV protease inhibitors in humans. *Cancer Biol. Ther.* **2008**, *7*, 628–635. [CrossRef] [PubMed]

204. Pore, N.; Gupta, A.K.; Cerniglia, G.J.; Maity, A. HIV protease inhibitors decrease VEGF/HIF-1alpha expression and angiogenesis in glioblastoma cells. *Neoplasia* **2006**, *8*, 889–895. [CrossRef] [PubMed]

205. Gills, J.J.; Dennis, P.A. Perifosine: Update on a novel Akt inhibitor. *Curr. Oncol. Rep.* **2009**, *11*, 102–110. [CrossRef] [PubMed]

206. Chuang, C.W.; Pan, M.R.; Hou, M.F.; Hung, W.C. Cyclooxygenase-2 up-regulates CCR7 expression via AKT-mediated phosphorylation and activation of Sp1 in breast cancer cells. *J. Cell. Physiol.* **2013**, *228*, 341–348. [CrossRef] [PubMed]

207. Liu, J.X.; Luo, M.Q.; Xia, M.; Wu, Q.; Long, S.M.; Hu, Y.; Gao, G.C.; Yao, X.L.; He, M.; Su, H.; et al. Marine compound catunaregin inhibits angiogenesis through the modulation of phosphorylation of akt and eNOS in vivo and in vitro. *Mar. Drugs* **2014**, *12*, 2790–2801. [CrossRef] [PubMed]

208. Bottsford-Miller, J.N.; Coleman, R.L.; Sook, A.K. Resistance and escape from anti-angiogenesis therapy: Clinical implications and future strategies. *J. Clin. Oncol.* **2012**, *30*, 4026–4034. [CrossRef] [PubMed]

209. Pore, N.; Gupta, A.K.; Cerniglia, G.J.; Jiang, Z.; Bernhard, E.J.; Evans, S.M.; Koch, C.J.; Hahn, S.M.; Maity, A. Nelfinavir down-regulates hypoxia-inducible factor 1alpha and VEGF expression and increases tumor oxygenation: Implications for radiotherapy. *Cancer Res.* **2006**, *66*, 9252–9259. [CrossRef] [PubMed]

210. Barillari, G.; Iovane, A.; Bacigalupo, I.; Labbaye, C.; Chiozzini, C.; Sernicola, L.; Quaranta, M.T.; Falchi, M.; Sgadari, C.; Ensoli, B. The HIV protease inhibitor indinavir down-regulates the expression of the pro-angiogenic MT1-MMP by human endothelial cells. *Angiogenesis* **2014**, *7*, 831–838. [CrossRef] [PubMed]

211. Van Hinsbergh, V.W.; Engelse, M.A.; Quax, P.H. Pericellular proteases in angiogenesis and vasculogenesis. *Arterioscler. Tromb. Vasc. Biol.* **2006**, *26*, 716–728. [CrossRef] [PubMed]

212. Hakeem, A.; Bhatti, S.; Cilingiroglu, M. The spectrum of atherosclerotic coronary artery disease in HIV patients. *Curr. Atheroscler. Rep.* **2010**, *12*, 119–124. [CrossRef] [PubMed]

213. Kim, D.H.; Jarvis, R.M.; Allwood, J.W.; Batman, G.; Moore, R.E.; Marsden-Edwards, E.; Hampson, L.; Hampson, I.N.; Goodacre, R. Raman chemical mapping reveals site of action of HIV protease inhibitors in HPV16 E6 expressing cervical carcinoma cells. *Anal. Bioanal. Chem.* **2010**, *398*, 3051–3061. [CrossRef] [PubMed]

214. Batman, G.; Oliver, A.W.; Zehbe, I.; Richard, C.; Hampson, L.; Hampson, I.N. Lopinavir up-regulates expression of the antiviral protein ribonuclease L in human papillomavirus-positive cervical carcinoma cells. *Antivir. Ther.* **2011**, *16*, 515–525. [CrossRef] [PubMed]

215. Pils, S.; Joura, E.A. From the monovalent to the ninevalent HPV vaccine. *Clin. Microbiol. Infect.* **2015**, *21*, 827–833. [CrossRef] [PubMed]

216. Apgar, B.S.; Kaufman, A.J.; Bettcher, C.; Parker-Featherstone, E. Gynecologic procedures: Colposcopy, treatment of cervical intraepithelial neoplasia and endometrial assessment. *Am. Fam. Phys.* **2013**, *87*, 836–843.

217. Sigfrid, L.; Murphy, G.; Haldane, V.; Chuah, F.L.H.; Ong, S.E.; Cervero-Liceras, F.; Watt, N.; Alvaro, A.; Otero-Garcia, L.; Balabanova, D.; et al. Integrating cervical cancer with HIV healthcare services: A systematic review. *PLoS ONE* **2017**, *12*, e0181156. [CrossRef] [PubMed]

218. Armarnik, S.; Sheiner, E.; Piura, B.; Meirovitz, M.; Zlotnik, A.; Levy, A. Obstetric outcome following cervical conization. *Arch. Gynecol. Obstet.* **2011**, *283*, 765–769. [CrossRef] [PubMed]

219. Ikebe, T.; Takeuchi, H.; Jimi, E.; Beppu, M.; Shinohara, M.; Shirasuna, K. Involvement of proteasomes in migration and matrix metalloproteinase-9 production of oral squamous cell carcinoma. *Int. J. Cancer* **1998**, *77*, 578–585. [CrossRef]

220. Li, J.Y.; Huang, W.Q.; Tu, R.H.; Zhong, G.Q.; Luo, B.B.; He, Y. Resveratrol rescues hyperglycemia-induced endothelial dysfunction via activation of Akt. *Acta Pharmacol. Sin.* **2017**, *38*, 182–191. [CrossRef] [PubMed]

221. Makinoshima, H.; Umemura, S.; Suzuki, A.; Nakanishi, H.; Maruyama, A.; Udagawa, H.; Mimaki, S.; Matsumoto, S.; Niho, S.; Ishii, G.; et al. Metabolic determinants of sensitivity to phosphatidylinositol 3-kinase pathway inhibitor in small-cell lung carcinoma. *Cancer Res.* **2018**. [CrossRef] [PubMed]

222. Pulido, M.; Roubaud, G.; Cazeau, A.L.; Mahammedi, H.; Vedrine, L.; Joly, F.; Mourey, L.; Pfister, C.; Goberna, A.; Lortal, B.; et al. Safety and efficacy of temsirolimus second line treatment for patients with recurrent bladder cancer. *BMC Cancer* **2018**, *8*, 194. [CrossRef] [PubMed]

223. Guo, K.Y.; Han, L.; Li, X.; Yang, A.V.; Lu, J.; Guan, S.; Li, H.; Yu, Y.; Zhao, Y.; Yang, J.; et al. Novel proteasome inhibitor delanzomib sensitizes cervical cancer cells to doxorubicin-induced apoptosis via stabilizing tumor suppressor proteins in the p53 pathway. *Oncotarget* **2017**, *8*, 114123–114135. [CrossRef] [PubMed]

224. Cao, B.; Li, J.; Mao, X. Dissecting bortezomib: Development, application, adverse effects and future direction. *Curr. Pharm. Des.* **2013**, *19*, 3190–3200. [CrossRef] [PubMed]

225. Herschbein, L.; Liesveld, J.L. Dueling for dual inhibition: Means to enhance effectiveness of PI3K/Akt/mTOR inhibitors in AML. *Blood Rev.* **2017**. [CrossRef] [PubMed]

226. Lv, Z.; Chu, Y.; Wang, Y. HIV protease inhibitors: A review of molecular selectivity and toxicity. *HIV AIDS* **2015**, *7*, 95–104. [CrossRef]

227. Akers, W.J.; Xu, B.; Lee, H.; Sudlow, G.P.; Fields, G.B.; Achilefu, S.; Edwards, W.B. Detection of MMP-2 and MMP-9 activity in vivo with a triple-helical peptide optical probe. *Bioconjugate Chem.* **2012**, *23*, 656–663. [CrossRef] [PubMed]

228. Matusiak, N.; van Waarde, A.; Bischoff, R.; Oltenfreiter, R.; van de Wiele, C.; Dierckx, R.A.; Elsinga, P.H. Probes for non-invasive matrix metalloproteinase-targeted imaging with PET and SPECT. *Curr. Pharm. Des.* **2013**, *19*, 4647–4672. [CrossRef] [PubMed]

229. Shimizu, Y.; Temma, T.; Hara, I.; Makino, A.; Kondo, N.; Ozeki, E.; Ono, M.; Saji, H. In vivo imaging of membrane type-1 matrix metalloproteinase with a novel activatable near-infrared fluorescence probe. *Cancer Sci.* **2014**, *105*, 1056–1062. [CrossRef] [PubMed]