Mesenchymal Stem Cell Expressing TRAIL as Targeted Therapy against Sensitised Tumour

Kamal Shaik Fakiruddin 1,2,*,†, Nadiah Ghazalli 3, Moon Nian Lim 1, Zubaidah Zakaria 1 and Syahril Abdullah 2,3,†

1 Stem Cell Laboratory, Haematology Unit, Cancer Research Centre, Institute for Medical Research, Kuala Lumpur 50588, Malaysia; limmn@imr.gov.my (M.N.L.); zubaidah@imr.gov.my (Z.Z.)
2 UPM-MAKNA Cancer Research Laboratory, Institute of Bioscience, Universiti Putra Malaysia, Serdang 43400, Selangor, Malaysia; syahril@upm.edu.my
3 Medical Genetics Laboratory, Department of Biomedical Sciences, Faculty of Medicine & Health Sciences, Universiti Putra Malaysia, Serdang 43400, Selangor, Malaysia; nadiahwmg@upm.edu.my
* Correspondence: kamal@imr.gov.my; Tel.: +603-26162517
† These authors contributed equally to this work.

Received: 13 June 2018; Accepted: 2 July 2018; Published: 27 July 2018

Abstract: Tapping into the ability of engineered mesenchymal stem cells (MSCs) to mobilise into the tumour has expanded the scope of cancer treatment. Engineered MSCs expressing tumour necrosis factor (TNF)-related apoptosis inducing ligand (MSC-TRAIL) could serve as a platform for an efficient and targeted form of therapy. However, the presence of cancer stem cells (CSCs) that are resistant to TRAIL and apoptosis may represent a challenge for effective treatment. Nonetheless, with the discovery of small molecular inhibitors that could target CSCs and tumour signalling pathways, a higher efficacy of MSC-TRAIL mediated tumour inhibition can be achieved. This might pave the way for a more effective form of combined therapy, which leads to a better treatment outcome. In this review, we first discuss the tumour-homing capacity of MSCs, its effect in tumour tropism, the different approach behind genetically-engineered MSCs, and the efficacy and safety of each agent delivered by these MSCs. Then, we focus on how sensitisation of CSCs and tumours using small molecular inhibitors can increase the effect of these cells to either TRAIL or MSC-TRAIL mediated inhibition. In the conclusion, we address a few questions and safety concerns regarding the utilization of engineered MSCs for future treatment in patients.

Keywords: mesenchymal stem cells; TRAIL; apoptosis; sensitisation; cancer stem cells; tumours

1. Introduction

The GLOBOCAN 2012 report published by the World Health Organization estimates that there were about 14.1 million new cancer cases, 8.2 million cancer deaths, and 32.6 million people living with cancer in 2012 [1]. It was predicted that in 2025, there would be a sharp increase in new cancer cases, of up to 19.3 million total cases, because of the ageing population [1]. Despite considerable advances in our knowledge and experience in the treatment of cancer, our capacity to effectively fight and treat the disease is still limited [2]. Current treatments only manage to reduce the burden of the primary lesion but are rarely effective in the complete eradication of tumour cells, which in turn leads to relapse and even fatality [3]. This is due to the existence of chemotherapy-resistant cancer stem cells (CSCs) that can repopulate the tumour after the initial chemotherapy [4]. This warrants the need for a more efficient and innovative approach that can enhance treatment efficacy in cancer patients. The idea of using mesenchymal stem cells (MSCs) as vectors for anti-tumour ligand delivery, such as tumour necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL), has emerged as one
of the avenues of cytotherapy in cancer treatment, as these cells were shown to home the tumour site and deliver targeted therapies. Furthermore, with the use of small molecular inhibitors in CSCs and tumours to enhance the sensitivity of these cells to TRAIL or MSC-TRAIL mediated inhibition, better treatment efficacy can be achieved. This review will first look into the characteristics of MSCs, its effect on tumour tropism, the tumour-directed homing of MSCs, and the anti-cancer properties of engineered MSCs that have been reported. The review will further focus on TRAIL in the treatment of cancers, the idea of cancer stem cells, resistance of tumour and CSCs to TRAIL, sensitisation of CSCs, and tumour to TRAIL-mediated inhibition, and the use of MSCs expressing TRAIL or MSC-TRAIL to target sensitised CSCs and tumours.

2. Mesenchymal Stem Cells

The multipotent characteristic of human mesenchymal stem cells (MSCs) is an exclusive feature, which is not seen in any other mature cells [5]. MSCs can be isolated from various sources, such as bone marrow [6], umbilical cord blood [7], and adipose tissue [8], and can be cultured and stably expanded for several passages while retaining its characteristics [9]. Compared to other potential cytotherapy, MSCs are relatively non-immunogenic, thus overcoming the difficulties of immune rejection caused by transplanted cells [10]. These characteristics make MSCs an attractive candidate for cell-based therapy for degenerative diseases [11]. MSCs also express specific surface markers, such as (cluster of differentiation) CD73, CD90, and CD105, while lacking other markers, such as CD34, CD45, major histocompatibility complex (MHC) II, and hematopoietic stem cell markers [12]. Another unique characteristic of MSCs compared to other adult stem cells, lies in the capacity of these cells to avoid an immune response, because of the lack of MHC II and its co-stimulatory molecules (CD86 and CD40), thereby reducing the risk of graft versus host rejection [13–15]. Accordingly, MSCs are great candidates for bio-banking and autologous transplants [16]. These cells are also malleable to genetic engineering, and have been shown to have the capacity to robustly express exogenous proteins [17]. These qualities have paved the way to use MSCs not just for the treatment of degenerative diseases, but as cytotherapeutic-based vector for the treatment of various tumours.

3. MSCs and Its Effects in Tumour Tropism

The enhancement of the proliferative, resistance, and aggressive phenotypes of tumour cells has been the subject of intense investigation. Most studies propose that the phenotypes are solely acquired through genomic instability and abnormal cellular changes within the tumour cells [18], while others view these characteristics as a process activated through the paracrine factors released by the tumour microenvironment (TME) [19–21]. It has been shown that MSCs secrete microvesicles and exosomes containing an array of cytokines, chemokines, and growth factors that regulate cellular growth, angiogenesis, and inflammation [22,23]. As MSCs are also part of the stromal cells that reside within the TME, it is expected that MSCs may contribute either to the development or inhibition of a tumour. MSCs are also known to affect the proliferation and differentiation of dendritic cells, macrophages, B and T cells, natural killer cells (NK cells), and mast cells [24].

Although a number of studies have shown that native MSCs are capable of inducing tumour suppression and apoptosis, as seen in hepatoma [25], leukemia [26], and Kaposi’s Sarcoma [27], others have demonstrated an opposite effect [28–30]. A recent study has proposed that therapy-educated MSCs can enhance the resistant characteristic of pancreatic adenocarcinoma to therapy by enriching CSCs [31]. The ambiguous role of MSCs during tumour development is attributed to the heterogenic characteristics of MSCs that are the product of the MSC origin and growth conditions [32,33]. Indeed, it is difficult to define the complex role of MSCs, as most studies were performed using MSCs from different sources with varying conditions [34]. Despite the numerous studies that have advanced our understanding of the biology of MSCs, leading to their subsequent applications in cancer therapy, more studies are needed to fully understand MSCs’ influence on various tumour types. Figure 1 summarizes the inhibitory and supportive effects of MSCs and the molecules that play a role in the process.
Figure 1. Engineered mesenchymal stem cells (MSCs) act to support and inhibit tumour growth. MSCs could induce apoptosis in some tumours, while others have reported that MSCs might also inhibit apoptosis. MSCs could promote vascularization in the tumour microenvironment by secreting growth factors and might also lead to tumour inhibition by inducing cyclin dependent kinases (CDKs) and cyclins block that leads to cell cycle arrest. These ambiguous roles of MSCs suggested that more studies are needed to elucidate the exact function of MSCs in different tumour models for a safer treatment outcome. TRAIL—tumour necrosis factor-related apoptosis inducing ligand; VEGF—vascular endothelial growth factor; PDGF—platelet-derived growth factor; FGF—fibroblast growth factors; IFN—interferon; IGF—insulin-like growth factor; TGF—transforming growth factor; IDO—indoleamine 2,3-dioxygenase; HGF—hepatocyte growth factor; EGF—epidermal growth factor; PDGF—platelet-derived growth factor; WNT—proto-oncogene protein; IL—interleukin; SDF—stromal derived factor one alpha; AKT—serine/threonine kinase; PTEN—phosphatase and tensin homolog.
4. Tumour Homing Capacity of Mesenchymal Stem Cells (MSCs)

The ability of the transplanted MSCs to home the tumour microenvironment has expanded the therapeutic benefits of these cells beyond their use in degenerative diseases [35]. Numerous reports have shown that MSCs are capable of infiltrating into the tumour stroma and its microenvironment, and possibly contributing towards stromal support [36]. However, the definitive role of MSCs within the tumour stroma is unknown. The exact mechanism in which MSCs migrate into the tumour microenvironment is not fully understood. However, it is widely accepted that the secretion of chemokines and cytokines from the tumour microenvironment and the expression of conjugate receptors on MSCs are possible causes. Although the identities of the cytokines and chemokines, as well as their respective receptors, are not yet known, it is postulated that a combination of several receptors and ligands contributes to the homing characteristic.

One specific ligand, chemokine (C-X-C motif) ligand 12 (CXCL12), secreted by the tumours, with its concomitant receptor (C-X-C chemokine) receptor type 4 (CXCR4), which is expressed mostly in MSCs, has drawn particular interest, given its connection to the tumour-homing characteristic of MSCs as well as its contribution to MSCs’ migration [37,38]. Some studies have suggested that both CXCL12 and CXCR4 contributed significantly during angiogenesis and hematopoietic stem cell mobilization, while others have suggested its major contribution during tumour development [39,40]. Although several studies have shown a strong connection between CXCL12/CXCR4 signalling towards MSCs migration and the tumour homing capacity, the knockdown of these receptors does not inhibit the homing potential of MSCs [41]. This may be due to the fact that some MSCs do not express the receptor at all, and CXCL12/CXCR4 may not be the only molecules that influence the MSC migration. Several studies have also suggested the ability of MSCs to home in on injured and inflamed tissues, such as in cases of acute lung injury [42] and the liver cirrhotic model [43], indicating MSCs’ paracrine and direct effects on regulating and healing of the damaged tissue.

5. Engineered MSCs for Anti-Tumour Therapy

5.1. Delivery of Anti-Tumour Cytokines

MSCs derived from the bone marrow, adipose tissue, and umbilical cord have been used as a delivery vehicle for targeted anti-tumour therapies [44]. These immunoprivileged cells, in addition to their reduced rejection risk, can home in on the tumour microenvironment, thus enhancing their potential for use in allogeneic transplantation and cytotherapeutics [45–49]. Several studies that altered the genes of these cells demonstrated that the exogenous expression of therapeutic genes, such as bone morphogenic protein 2 (BMP-2), B-cell lymphoma 2 (BCL-2), and erythropoietin (EPO) has enhanced the treatment efficacy of MSCs at the target site [50–52]. This leads to the idea of using genetically-engineered MSCs as a vehicle to deliver biological anti-tumour agents directly at the tumour microenvironment [45,53]. Many studies have shown that MSCs engineered to express anti-tumour cytokines, such as interleukin-2 (IL-2) [54], interferon-beta (IFN-β) [55], TRAIL [45,46,48], and IL-15 [56], are able to deliver these ligands directly to the tumour site and to efficiently induce tumour regression. Moreover, the use of non-viral gene-delivery techniques has also been studied in MSCs, suggesting an effective and yet safer method for gene-delivery to MSCs [57]. A previous work using transfected MSCs derived from adipose tissue has shown that when these cells express a potent anti-tumour agent called TRAIL, the engineered adult stem cells (termed MSC-TRAIL) are capable of inducing apoptosis in glioblastoma (LN18) and hepatocellular carcinoma (HepG2) cells in vitro [58].

5.2. Delivery of Pro-Drug Converting Enzymes

Preclinical studies have shown that engineered MSCs expressing pro-drug converting enzymes are useful for the treatment of late stage tumours and for the prevention of metastasis [59]. With this strategy, the off-site accumulation of the active drug can be prevented, thus reducing the treatment toxicity. An example of a pro-drug converting system is the yeast cytosine deaminase/5-fluorocytosine
(5-FC), which uses MSCs to locally deliver yeast cytosine deaminase (yCD) to the tumour site. The conversion of 5-FC to 5-fluorouracil (5-FU) by yCD induces cytotoxic tumour regression in several cancers \[60,61\]. Another example of an MSC-mediated pro-drug converting system is the thymidine kinase/ganciclovir system and nitroreductase/CB1954 system. Both systems have been extensively studied in several tumour models, with promising effects \[62,63\].

5.3. MSCs as Vectors for Oncolytic Viruses

In addition to the utilization of MSCs as vectors to deliver cytokines and pro-drug enzymes into tumours, MSCs have also been studied as a vehicle to deliver oncolytic viruses to the tumour. Oncolytic viruses are viruses that induce tumour regression by direct tumour cell oncolysis \[64,65\] and the disruption of the tumour microenvironment \[66\]. Several reports have shown that the delivery of these viruses by MSCs enhanced the oncolytic effects of the virus in several tumour models \[67–70\]. The delivery of these viruses led to the destruction of tumour cells, as the viruses replicate and spread to the surrounding stroma, which further induces tumour regression. Among the viruses that have been studied, three types of viruses, namely the adenovirus, the measles virus, and the herpes simplex virus have been shown to have a highly significant impact on reducing tumour growth \[71\]. The MSCs loaded with oncolytic viruses were effective in reducing tumour metastasis in several models, as seen in lung cancer \[72\], glioma \[73\], and breast cancer \[74\]. The direct inhibition of tumour growth was also observed in hepatocellular carcinoma, pancreatic cancer, brain tumour, and non-small cell lung cancer (NSCLC), in both in vitro and in vivo studies.

5.4. Safety Profile of Engineered MSCs

A different approach to using engineered MSCs has highlighted different anti-tumour efficacies and several safety concerns. As a result of the expression of the TRAIL receptors (DR4 and DR5), which are highly expressed in tumours, compared to normal cells, the efficacy of TRAIL to induce tumour regression is higher, and the toxicity effect of TRAIL on normal cells is lower, compared with other cytokines \[75\]. Engineered MSCs expressing pro-drug converting enzymes may enhance the effects of chemotherapy by localized drug activation. However, if factors such as the number of migrated MSCs to the tumour and the level of enzymes at the target site are not fully optimised, these factors may hamper the overall treatment outcome in patients \[76\]. Although oncolytic viruses have emerged recently as a potential agent in cancer treatment, the efficacy and safety of using this approach for cancer treatment have been hindered because of the low virus spread at the tumour surrounding \[77\] and the probability of these viruses reverting to their wild type, thus infecting the normal cells \[78\]. This approach of using MSCs as a vehicle for the delivery of anti-tumour agents and its safety are summarized in Table 1.
Table 1. Biological agents utilizing engineered mesenchymal stem cells (MSCs) as vehicle for ligand delivery and its safety. TRAIL—tumour necrosis factor-related apoptosis inducing ligand; CSCs—cancer stem cells; IFN—interferon; IL—interleukin.

| Biological Agents          | Mechanism                                           | Tumour Model                  | Toxicity and Safety Concern                                           | References |
|---------------------------|-----------------------------------------------------|-------------------------------|---------------------------------------------------------------------|------------|
| IL-2                      | Reduce and inhibit tumour growth dependent of NK cells | Renal cell carcinoma, glioma  | May cause capillary leak syndrome and fluid accumulation             | [53,54,79] |
| IL-12                     | Inhibit tumour growth dependent of NK cells         | Melanoma model, renal cell carcinoma | Haematological toxicity, such as neutropenia and thrombocytopenia     | [80–82]    |
| IL-15                     | Abolished tumour growth dependent of NK and CD8+ T cells | Pancreatic tumour             | Probability for autoimmune toxicity                                 | [56,83]    |
| IL-18                     | Suppress proliferation, migration, and invasion     | Breast tumour                 | Haematological toxicity, hypotension, and bradycardia                | [84,85]    |
| IFN-β                     | Inhibit tumour growth and metastasis in vivo        | Melanoma, breast tumour       | Haematological-, autoimmune-, and hepato-toxicity                    | [44,55,86] |
| TRAIL                     | Induce apoptosis, inhibit clonogenicity and tumour bulk | Lung metastasis, lung CSCs, glioma, pancreatic cancer, mesothelioma, | Mild constitutional toxicity (e.g., nausea, fever, and constipation) and anaemia | [45,47,48,58,87] |
| Pro-drug converting enzymes | Inhibition of tumour growth in vitro and in vivo  | Glioma, prostate cancer, osteosarcoma | “Off site” activated drug accumulation                              | [59–61,63] |
| Oncolytic virus           | Oncolytic viruses mediated tumour regression in vivo | Glioblastoma, brain metastasis, leukemia and pancreatic cancer | Potential for virus mutation, normal cell toxicity, and human viral transmission | [71,78,88,89] |
6. Tumour Necrosis Factor-Related Apoptosis Inducing Ligand (TRAIL) and Cancer Treatment

6.1. Tumour Necrosis Factor (TNF)-Related Apoptosis Inducing Ligand (TRAIL)

The tumour necrosis factor related apoptosis inducing ligand (TRAIL), also known as Apo2L, is one of several members of the TNF gene superfamily that induces apoptosis. Its mechanism of action is by activating the extrinsic apoptosis pathways through binding its two specific agonistic receptors (TRAIL-R1/DR4 and TRAIL-R2/DR5) and three antagonistic decoy receptors [TRAIL-R3/DcR1, TRAIL-R4/DcR2, and osteoprotegerin (OPG)] [90]. The TRAIL protein can either be a soluble ligand or attached as a transmembrane protein by a hydrophobic amino acid bond. TRAIL is expressed in a variety of normal tissues, such as the placenta, kidney, and spleen, and is secreted into the peripheral blood because of the inflammatory response [91], viral infections [92], and malignant diseases [93]. Several studies have documented the efficacy of TRAIL as a potent anti-tumour agent on its own [94–96], while others have recommended TRAIL as a combination treatment because of the possible resistance in some tumour models [97–99]. These studies are detailed and elaborated in the next sections.

6.2. TRAIL Treatment in Solid Tumours

Several studies have documented the efficacy of TRAIL in inhibiting the proliferation and inducing apoptosis in vitro, in a variety of tumours, including colorectal cancer [100], glioblastoma [101], and NSCLC [102]. Furthermore, TRAIL has also been reported to inhibit the proliferation of several chemoresistant cancer cell lines [103,104]. In small animal models, TRAIL-induced tumour regression was well documented in colon and breast carcinoma of SCID mice [105,106]. However, some have described the poor bioavailability and short half-life of TRAIL upon administration to a xenograft model, which eventually resulted in poor bioavailability of the ligand [105]. Nonetheless, modifications of the TRAIL protein structure and fusion with other immunoglobulin molecules have significantly prolonged its half-life and perhaps even enhanced its anti-tumour activity [107].

6.3. Synergistic Effects of TRAIL-Based Combination Therapy

The pre-treatment of tumour cells by small molecule inhibitors have been shown to increase the sensitivity of TRAIL-induced apoptosis [108]. These molecules include the inhibitors of mammalian target of rapamycin (mTOR) [109], proteasome [110], histone deacetylases (HDAC) [111], and BCL-2 [112], and they have been used in combination with recombinant TRAIL to inhibit specific signalling molecules that would interfere with the extrinsic activation of apoptosis by TRAIL. In lung cancer, compounds such as bortezomib [102], cardiac glycosides [113], and transhinone IIA [114] have been reported to have synergistic or sensitising effects on TRAIL-mediated apoptosis. The pre-treatment of tumour cells by standard chemotherapy drugs have also been shown to be a promising approach, based on several in vitro studies [97,99,115]. However, all of these approaches, which often target non-CSCs, may not be able to eradicate the tumour completely. Strategies to target TRAIL-resistant CSC populations should be explored for better treatment efficacy.

7. The Existence of Cancer Stem Cells

Tumours are composed of heterogeneous populations of cells. Each sub-population varies in its differentiation, proliferation, and tumourigenic capacity [116,117]. In vivo models have demonstrated that a small sub-population of cells has strong stem cell or pluripotent characteristics [118]. They are known as cancer stem cells (CSCs), or cancer initiating cells, and are able to initiate tumour development in vivo [119]. Classical chemotherapy may reduce the bulk of the tumour and improve the patient’s quality of life, but because of the strong chemoresistant characteristic of CSCs from high aldehyde dehydrogenase (ALDH) enzyme activity, enhanced DNA repair mechanism, and the efflux of drugs by the adenosine triphosphate (ATP)-binding cassette or ATP-binding cassette transporters (ABC) transporters, most patients that underwent chemotherapy eventually experienced relapse.
Therefore, it is by identifying and therapeutically targeting these stem cells that the response and outcome of treatments could be improved.

The cluster of differentiation (CD) molecules have been used as the most reliable technique for the isolation and identification of cell populations enriched with stem cell properties. One such example is CD133, which has recently been identified as the marker for CSC in lung cancer [120], prostate cancer [121–123], brain cancer [124–127], colon cancer [128–130], and hepatic carcinoma [131–134]. CSCs are also identified as the side population (SP), based on the expression of the ABCG2 protein and the ability to efflux Hoechst dye [135]. In a recent study, Lim and his group identified a combination of CD166-positive and Lin-negative sub-population of lung cancer cells that link a glycine metabolism enzyme to tumour formation as a novel therapy targeting a specific metabolic pathway in NSCLC [136].

In the identification of the CSCs derived from non-small cell lung cancer, markers such as the CD133, SP population, and ALDH 1 have been extensively studied and reported [137–139]. We have recently identified and characterised a novel double positive (CD166+/CD44+ and CD166+/EpCAM+) CSC sub-population isolated from NSCLC cell lines (A549 and H2170), and showed that these two sub-populations exhibit a self-renewal capacity, higher mobility, resistance to apoptosis, and the ability to differentiate towards the mesenchymal lineage [140]. A list of CSC markers and the type of tumours are summarized in Table 2.

Table 2. CSCs markers from different tumour types. ALDH—aldehyde dehydrogenase; SP—side population; ABCG2—ATP-binding cassette sub-family G member 2; CD—cluster of differentiation.

| Cancer Type                        | CSCs Markers                   | References       |
|------------------------------------|--------------------------------|------------------|
| Non-small cell lung cancer (NSCLC) | ABCG2+, CD133+, CD44+, EpCAM+, CD166+, ALDH+ | [137,138,140]    |
| Breast                             | CD44+/CD24−, ALDH+             | [141,142]        |
| Colon                              | CD133+, EpCAM high/CD44+       | [128,129,143,144]|
| Head and neck                      | CD44+, SP, ALDH                | [145,146]        |
| Prostate                           | CD133+, CD44+, α2β1high         | [147,148]        |
| Brain tumour/glioma                | CD133+, CD15+, CD90+, CD49f+   | [126,149,150]    |

8. Resistance of CSCs to TRAIL and Apoptosis

CSCs are known for being highly resistant to apoptosis even through the stimulation of the TRAIL death ligand. In general, the remarkably impaired regulation of apoptosis in CSCs compared to non-CSCs are because of the lower expression of death signals (i.e., CASP8/caspase 8, CASP3/caspase 3, and PARP/Poly [adenosine diphosphate ribose (ADP-ribose)] polymerase 1) and the higher expression of anti-apoptotic molecules (i.e., cFLIP/cellular FLICE-like inhibitory protein, BCL-2/B-cell lymphoma 2, and XIAP/inhibitors of apoptosis), leading to the characteristics of CSCs’ being highly resistant to apoptosis [151]. Other factors include the tumour microenvironment, genetics, epigenetics, and inter- and intra-tumour heterogeneity, which may also contribute to the resistance. High expressions of the DR4 and DR5 receptors, which are the agonistic TRAIL receptors, were reported as the contributor of CSCs’ resistance to TRAIL-mediated effects and the chemo-resistant characteristic observed in colon cancer [152]. However, in glioblastoma, the low expression of the death receptor (DR4 and DR5) and high expression of cFLIP, a master anti-apoptotic regulator molecule, led to the glioblastoma-derived CSCs resistance to TRAIL [153]. The activation of the extrinsic apoptotic pathways through DR4 and DR5 ligand-activation promotes the expression of various apoptosis inhibitory proteins in CSCs that include the NF-κB, which also makes CSCs resistant to TRAIL-based therapy, as seen in glioblastoma [154]. Other anti-apoptotic signalling molecules, such as X-linked inhibitor of apoptosis proteins (XIAPs), were also observed to contribute to the reduction of TRAIL-mediated apoptosis in CSCs derived from nasopharyngeal carcinoma [155].
9. Sensitisation of CSCs to TRAIL and Apoptosis

The ability of CSCs to evade apoptotic signals contributes towards chemoresistance in most cancers. Therefore, therapeutic strategies that can enhance the onset of apoptosis in CSCs may serve as a more promising approach. It is known that the high expression of anti-apoptotic genes in CSCs makes these cells highly resistant to cell death and apoptosis, which contributes greatly to cancer progression [136,156,157]. These anti-apoptotic genes present potential therapeutic targets, particularly to discriminate CSCs from non-CSCs [158]. It has been shown that, by regulating specific anti-apoptotic genes through gene knock down or silencing, the sensitivity of CSCs toward therapy can be enhanced [4]. This means that combination therapies can sensitize CSCs against TRAIL, and common chemotherapy might be an ideal approach for effective treatment.

Chemoresistance of tumour cells that contributes towards cancer recurrence is mostly comprised of a pool of CSCs that are TRAIL-resistant. Owing to the high cFLIP expression in most tumours, it is believed that the overexpression of cFLIP is also the main contributor to TRAIL-resistance in CSCs [159–162]. One study demonstrated that by regulating this molecule, the sensitivity of tumours to TRAIL-mediated apoptosis and to common chemotherapies, such as taxol, gemcitabine, and cisplatin, is enhanced [153,163,164]. In breast cancer stem cells, the silencing of cFLIP by siRNA or a chemical known as droxinstat [165], sensitised them to TRAIL-mediated effects, and the combination of both the cFLIP inhibition and the TRAIL induction resulted in a significant reduction in the tumour bulk, metastasis, and self-renewal of the breast CSCs. It was also shown that CD133-positive brain cancer stem cells expressed a high level of BCL-2 upon TRAIL induction, and a knockdown of BCL-2 subsequently enhanced the sensitivity of the CSCs to TRAIL-mediated inhibition [166]. Moreover, using second mitochondria-derived activator of caspases (SMAC) mimetics the induced inhibitor of apoptosis (IAP) degradation in nasopharyngeal carcinoma, and the effects of the TRAIL-mediated apoptosis was enhanced [155]. Finally, in colon cancer, the knockdown of Sirmtuin 1 (SIR1) sensitised the colon CSCs to TRAIL-induced cytotoxicity [167].

10. Enhancing the Effect of MSC-TRAIL by Tumour Sensitisation

Mesenchymal stem cells, with their unique ability to home in on the tumour microenvironment and express exogenous transgenes, have garnered considerable interest as a viable therapeutic strategy. Engineered MSCs expressing TRAIL were able to kill the side population cells in the squamous and adenocarcinoma of the lung cancer cell lines, indicating the feasibility of these engineered cells to selectively kill putative cancer stem cells [168]. Similarly, the MSC-TRAIL was observed to significantly induce tumour cell death through caspase-mediated apoptosis in primary glioma-derived CD133 cells in vitro [169]. Moreover, the expression of TRAIL by MSCs enhanced the oncolytic effect of Newcastle disease virus (NDV) in glioma stem cells, resulting in positive synergistic effects compared to TRAIL or NDV alone [170]. In addition, the combination of MK886 (a lipoxygenase inhibitor) and MSC-TRAIL was beneficial in inducing the apoptosis of malignant glioma tumour cells via the upregulation of DR5, downregulation of anti-apoptotic protein survivin, and significant increase in the caspases’ activity [171]. All of these studies demonstrate that the MSC-TRAIL can selectively target CSCs, and further investigations to refine the approach for clinical applications are warranted.

Several reports have also suggested that, through the regulation of specific cellular signalling and proteins, the efficacy of MSCs expressing TRAIL to inhibit metastasis in several cancers was enhanced. For example, MSC-TRAIL has been shown to inhibit metastasis of the NSCLC derived-H460 cell line combined with Claudin-7, a small molecule that regulates mitogen-activated protein kinases/extracellular signal-regulated kinases (MEK/ERK) signalling pathways [172]. In pancreatic cancer, targeting of the XIP molecule resulted in the increased sensitivity to the MSC-TRAIL treatment and the suppression of metastasis [174]. It was shown in a metastatic renal cell carcinoma model that overexpressing thymidine kinase increased the sensitivity of the tumour cells to dodecameric TRAIL secreted by MSCs, and suggested that the combined administration of MSC-TRAIL
and thymidine kinase is a potent strategy for the long-term remission of metastatic renal cell carcinoma [175].

The dual effects of common chemotherapies, either as a cytotoxic drug or sensitiser to MSC-TRAIL, were recently described [176]. This was seen as a promising approach, especially to patients that have exhausted all available treatments. Recently, low dose cisplatin was able to increase the expression of TRAIL agonistic receptor DR4/5, and enhanced the efficacy of MSC-TRAIL, eventually decreasing tumour growth in glioblastoma multiforme [177] and hepatocellular carcinoma animal models [178]. A similar result was observed in a study using a mouse xenograft model of malignant glioma, where the administration of temozolomide enhanced the tumour sensitivity to MSC-TRAIL, by increasing the DR5 receptor expression and lowering the XIAPs and cFLIP expression [179]. Moreover, the sensitisation of human breast cancer cells by doxorubicin enhanced the apoptotic effect of the MSC-TRAIL and synergistically reduced the tumour growth in the xenograft mouse model [180]. A simplified diagram of the approach and the signalling involved upon TRAIL activation by MSC-delivery is illustrated in Figure 2.

Challenges in MSC-TRAIL Applications: Discrepancies from In Vitro to In Vivo Models

The level of the TRAIL receptor expression does not correlate directly with the sensitivity of the tumour to the TRAIL-induced apoptosis [181,182]. Moreover, the sensitisation of these resistant tumour cells may yield a different effect towards TRAIL and MSC-TRAIL treatment in an in vitro and in vivo model. For example, in TRAIL-resistant colorectal carcinoma cells (CRC), subapoptotic genotoxic damage caused by 5-fluorouracil (5-FU) sensitised TRAIL-resistant CRC cells to MSC-TRAIL mediated inhibition in vitro. However, the sensitising effect was not achieved in an in vivo CRC mouse model. Rather, MSC-TRAIL seemed to support growth of the tumour, which invoked a cautionary warning, should the MSC-TRAIL be used in the clinic [183]. This may be due to the low intratumoural activity of 5-FU and sub-optimal tumour integration of MSC-TRAIL, which may hamper the overall treatment outcome [184]. It is also suggested that choosing the right tumour model that allows long term integration of the MSC-TRAIL to the target site is crucial for an effective in vivo model, as shown in the TRAIL-resistant medulloblastoma model [185]. It is expected that, by targeting the specific molecules that contributed to the TRAIL-resistant characteristics in these cells [186] and choosing a xenograft models with the most effective MSC-TRAIL integration, such as a pulmonary disease [187] or a metastatic model [188], a better treatment efficacy and tumour homing of MSC-TRAIL can be achieved.
Figure 2. Sensitisation of tumour or cancer stem cells (CSC) to MSC-TRAIL induced apoptosis. An increase in the anti-apoptotic molecules (e.g., X-linked inhibitor of apoptosis proteins [XIAPs], cellular FLICE-like inhibitory protein [cFLIP], and B-cell lymphoma 2 [BCL-2]) upon TRAIL activation can be circumvented using specific inhibitors, as illustrated above. Through tumour sensitisation by anti-apoptosis gene silencing or specific DR5 receptor enhancement, and the utilization of MSCs as a vehicle for TRAIL delivery, a better treatment outcome could be achieved. SMAC—second mitochondria-derived activator of caspases; FADD—fas-associated protein with death domain; Cas—caspase; BID—BH3 interacting-domain death agonist; BAK—BCL-2 antagonist killer 1; BAX—BCL-2 associated X. Inhibitors: SAHA—suberoylanilide hydroxamic acid; shRNA—short hairpin RNA; siRNA—small interfering RNA; RNAi—RNA interference. The arrow and t-bar represent activated and inhibitory interactions respectively.
11. Conclusions

Through an integrated approach, significant improvements have been made in the treatment of cancer. It was shown that the existence of cancer stem cell populations contributes to the challenges of developing an effective treatment in cancer. The regulation of specific molecules that lead to chemotherapy resistance characteristics in tumour cells and CSCs’ may represent as an ideal approach for a better treatment efficacy. Moreover, combining the tumour-homing capacity of MSCs and genetic engineering of the cells to express TRAIL-ligand, will enable the specific targeting of CSCs, thus paving the way towards a more effective treatment. However, several questions remain, such as the exact mechanism of the MSCs’ tumour-homing capacity and the fate of the MSCs after transfusion. These questions need to be answered to ensure the safety and efficacy of the treatment in future.

Author Contributions: K.S.F. wrote the manuscript; N.G., M.N.L., and Z.Z. read and critically revised the manuscript; S.A. read, critically revised, and provided funding for professional editing.

Acknowledgments: The authors wish to thank the Director General of Health, Malaysia for permission to publish this paper. This study is supported by the Ministry of Health (MOH), Malaysia, grant, JPP-IMR-16-038/NMRR-16-869-30708.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

MSCs mesenchymal stem cells
TRAIL tumour necrosis factor related apoptosis inducing ligand
CSCs cancer stem cells
IL interleukin
IFN interferon
NSCLC non-small cell lung cancer
mTOR mammalian target of rapamycin
HDAC histone deacetylases
BCL-2 B-cell lymphoma 2
ABCG2 ATP-binding cassette sub-family G member 2
ALDH1 aldehyde dehydrogenase 1
PARP poly (ADP-ribose) polymerase
cFLIP cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein
XIAP X-linked inhibitor of apoptosis protein
SAHA suberoylanilide hydroxamic acid
shRNA short hairpin RNA
RNAi RNA interference
VEGF vascular endothelial growth factor
PDGF platelet-derived growth factor
FGF fibroblast growth factors
IGF-1 Insulin-like growth factor 1
TGF-β transforming growth factor beta
IDO indoleamine 2,3-dioxygenase
HGF hepatocyte growth factor
EGF epidermal growth factor
WNT proto-oncogene protein
Cas caspase
FADD fas-associated protein with death domain
BID BH3 interacting-domain death agonist
P53 tumor protein
Apaf-1 apoptotic protease activating factor 1
References

1. Bray, F.; Ferlay, J.; Laversanne, M.; Brewster, D.H.; Gombe Mbalawa, C.; Kohler, B.; Pineros, M.; Stelianova-Foucher, E.; Swaminathan, R.; Antoni, S.; et al. Cancer incidence in five continents: Inclusion criteria, highlights from Volume X and the global status of cancer registration. *Int. J. Cancer* 2015, 137, 2060–2071. [CrossRef] [PubMed]

2. Hanahan, D.; Weinberg, R.A. The hallmarks of cancer. *Cell* 2000, 100, 57–70. [CrossRef]

3. Jemal, A.; Bray, F.; Center, M.M.; Ferlay, J.; Ward, E.; Forman, D. Global cancer statistics. *CA Cancer J. Clin.* 2011, 61, 69–90. [CrossRef] [PubMed]

4. Chen, K.; Huang, Y.H.; Chen, J.L. Understanding and targeting cancer stem cells: Therapeutic implications and challenges. *Acta Pharmacol. Sin.* 2013, 34, 732–740. [CrossRef] [PubMed]

5. Pittenger, M.F.; Mackay, A.M.; Beck, S.C.; Jaiswal, R.K.; Douglas, R.; Mosca, J.D.; Moorman, M.A.; Simonetti, D.W.; Craig, S.; Marshak, D.R. Multilineage potential of adult human mesenchymal stem cells. *Science* 1999, 284, 143–147. [PubMed]

6. Kemp, K.C.; Hows, J.; Donaldson, C. Bone marrow-derived mesenchymal stem cells. *Leuk. Lymphoma* 2005, 46, 1531–1544. [CrossRef] [PubMed]

7. Rubinstein, P.; Rosenfield, R.; Adamson, J.; Stevens, C. Stored placental blood for unrelated bone marrow reconstitution. *Blood* 1993, 81, 1679–1690. [PubMed]

8. Rodriguez, A.M.; Elabd, C.; Amri, E.-Z.; Ailhaud, G.; Dani, C. The human adipose tissue is a source of multipotent stem cells. *Biochimie* 2005, 87, 125–128. [CrossRef] [PubMed]

9. Mamidi, M.K.; Nathan, K.G.; Adamson, J.; Stevens, C. Stored placental blood for unrelated bone marrow reconstitution. *Blood* 1993, 81, 1679–1690. [PubMed]

10. Le Blanc, K.; Tammik, C.; Rosendahl, K.; Ringdén, O. HLA expression and immunologic properties of differentiated and undifferentiated mesenchymal stem cells. *Exp. Hematol.* 2003, 31, 890–896. [CrossRef] [PubMed]

11. Barry, F.P.; Murphy, J.M. Mesenchymal stem cells: Clinical applications and biological characterization. *Int. J. Biochem. Cell Biol.* 2004, 36, 568–584. [CrossRef] [PubMed]

12. Dominici, M.; Le Blanc, K.; Mueller, I.; Slaper-Cortenbach, I.; Marini, F.; Krause, D.; Deans, R.; Keating, A.; Prockop, D.; Horwitz, E. Minimal criteria for defining multipotent mesenchymal stromal cells. The international society for cellular therapy position statement. *Cytotherapy* 2006, 8, 315–317. [CrossRef] [PubMed]

13. Amorin, B.; Alegretti, A.P.; Valim, V.; Pezzi, A.; Laureano, A.M.; da Silva, M.A.; Wieck, A.; Silla, L. Mesenchymal stem cell therapy and acute graft-versus-host disease: A review. *Hum. Cell* 2014, 27, 137–150. [CrossRef] [PubMed]

14. Introna, M.; Lucchini, G.; Dander, E.; Galimberti, S.; Rovelli, A.; Balduzzi, A.; Longoni, D.; Pavan, F.; Masciocchi, F.; Algarotti, A., et al. Treatment of graft versus host disease with mesenchymal stromal cells: A phase I study on 40 adult and pediatric patients. *Biol. Blood Marrow Transplant.* 2014, 20, 375–381. [CrossRef] [PubMed]

15. Zhao, K.; Lou, R.; Huang, F.; Peng, Y.; Jiang, Z.; Huang, K.; Wu, X.; Zhang, Y.; Fan, Z.; Zhou, H.; et al. Immunosuppression of mesenchymal stromal cells on acute graft-versus-host disease after hematopoietic stem cell transplantation. *Biol. Blood Marrow Transplant.* 2015, 21, 97–104. [CrossRef] [PubMed]

16. Stuckey, D.W.; Shah, K. Stem cell-based therapies for cancer treatment: Separating hope from hype. Nature reviews. *Cancer* 2014, 14, 683–691. [PubMed]

17. Chu, Y.; Liu, H.; Lou, G.; Zhang, Q.; Wu, C. Human placenta mesenchymal stem cells expressing exogenous kringel-1-5 protein by fiber-modified adenovirus suppress angiogenesis. *Cancer Gene Ther.* 2014, 21, 200–208. [CrossRef] [PubMed]

18. Hill, R.P. Tumor progression: Potential role of unstable genomic changes. *Cancer Metastasis Rev.* 1990, 9, 137–147. [CrossRef] [PubMed]

19. Tlsty, T.D.; Coussens, L.M. Tumor stroma and regulation of cancer development. *Annu. Rev. Pathol. Mech. Dis.* 2006, 1, 119–150. [CrossRef] [PubMed]
20. Suzuki, K.; Sun, R.; Oriuchi, M.; Kanehira, M.; Takahata, T.; Itoh, J.; Umezawa, A.; Kijima, H.; Fukuda, S.; Saijo, Y. Mesenchymal stromal cells promote tumor growth through the enhancement of neovascularization. *Mol. Med.* 2011, 17, 579–587. [CrossRef] [PubMed]

21. Sung, S.Y.; Hsieh, C.L.; Yu, D.; Chung, L.W.; Johnstone, P.A. Tumor microenvironment promotes cancer progression, metastasis, and therapeutic resistance. *Curr. Probl. Cancer* 2007, 31, 36–100. [CrossRef] [PubMed]

22. Balasubramanian, S.; Venugopal, P.; Sundarraj, S.; Zakaria, Z.; Majumdar, A.; Ta, M. Comparison of chemokine and receptor gene expression between Wharton’s jelly and bone marrow-derived mesenchymal stem cells. *Cytotherapy* 2012, 14, 26–33. [CrossRef] [PubMed]

23. Stagg, J. Mesenchymal stem cells in cancer. *Stem Cell Res.* 2008, 4, 119–124. [CrossRef] [PubMed]

24. Klopp, A.H.; Gupta, A.; Saeth, E.; Andreeff, M.; Marini, F., 3rd. Concise review: Dissecting a discrepancy in the literature: Do mesenchymal stem cells support or suppress tumor growth? *Stem Cells* 2011, 29, 11–19. [CrossRef] [PubMed]

25. Qiao, L.; Xu, Z.; Zhao, T.; Zhao, Z.; Shi, M.; Zhao, R.C.; Ye, L.; Zhang, X. Suppression of tumorigenesis by human mesenchymal stem cells in a hepatoma model. *Cell Res.* 2008, 18, 500–507. [CrossRef] [PubMed]

26. Ramasamy, R.; Lam, E.W.F.; Soeiro, I.; Tisato, V.; Bonnet, D.; Dazzi, F. Mesenchymal stem cells inhibit proliferation and apoptosis of tumor cells: Impact on in vivo tumor growth. *Leukemia* 2006, 21, 304–310. [CrossRef] [PubMed]

27. Khakoo, A.Y.; Pati, S.; Anderson, S.A.; Reid, W.; Elshal, M.F.; Rovira, I.; Nguyen, A.T.; Malide, D.; Combs, C.A.; Hall, G.; et al. Human mesenchymal stem cells exert potent antitumorigenic effects in a model of Kaposi’s sarcoma. *J. Exp. Med.* 2006, 203, 1235–1247. [CrossRef] [PubMed]

28. Martin, F.T.; Dwyer, R.M.; Kelly, J.; Khan, S.; Murphy, J.M.; Curran, C.; Miller, N.; Hennessy, E.; Dockery, P.; Barry, F.P.; et al. Potential role of mesenchymal stem cells (MSCs) in the breast tumour microenvironment: Stimulation of epithelial to mesenchymal transition (EMT). *Breast Cancer Res. Treat.* 2010, 124, 317–326. [CrossRef] [PubMed]

29. Xu, Q.; Wang, L.; Li, H.; Han, Q.; Li, J.; Qu, X.; Huang, S.; Zhao, R.C. Mesenchymal stem cells play a potential role in regulating the establishment and maintenance of epithelial-mesenchymal transition in MCF7 human breast cancer cells by paracrine and induced autocrine TGF-β. *Int. J. Oncol.* 2012, 41, 959–968. [CrossRef] [PubMed]

30. Zhang, C.; Zhai, W.; Xie, Y.; Chen, Q.; Zhu, W.; Sun, X. Mesenchymal stem cells derived from breast cancer tissue promote the proliferation and migration of the MCF-7 cell line. *Oncol. Lett.* 2013, 6, 1577–1582. [CrossRef] [PubMed]

31. Timaner, M.; Letko-Khait, N.; Kotsoruk, R.; Benguigui, R.; Beyar-Katz, O.; Rachman-Tzemach, C.; Raviv, Z.; Bronshtein, T.; Machluf, M.; Shaked, Y. Therapy-educated mesenchymal stem cells enrich for tumor initiating cells. *Cancer Res.* 2018. [CrossRef] [PubMed]

32. Kern, S.; Eichler, H.; Stoeev, J.; Klüter, H.; Bieback, K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. *Stem Cells* 2006, 24, 1294–1301. [CrossRef] [PubMed]

33. Peng, L.; Jia, Z.; Yin, X.; Zhang, X.; Liu, Y.; Chen, P.; Ma, K.; Zhou, C. Comparative analysis of mesenchymal stem cells from bone marrow, cartilage, and adipose tissue. *Stem Cells Dev.* 2008, 17, 761–773. [CrossRef] [PubMed]

34. Kidd, S.; Spaeth, E.; Klopp, A.; Andreeff, M.; Hall, B.; Marini, F.C. The (in) auspicious role of mesenchymal stromal cells in cancer: Be it friend or foe. *Cytotherapy* 2008, 10, 657–667. [CrossRef] [PubMed]

35. D’Souza, N.; Burns, J.S.; Grisendi, G.; Candini, O.; Veronesi, E.; Piccinni, S.; Horwitz, E.M.; Paolucci, P.; Conte, P.; Dominici, M. MSC and tumors: Homing, differentiation, and secretion influence therapeutic potential. In *Advances in Biochemical Engineering/Biotechnology*; Springer: New York, NY, USA, 2012.

36. Wang, H.; Cao, F.; De, A.; Cao, Y.; Contag, C.; Gambhir, S.S.; Wu, J.C.; Chen, X. Trafficking mesenchymal stem cell engraftment and differentiation in tumor-bearing mice by bioluminescence imaging. *Stem Cells* 2009, 27, 1548–1558. [CrossRef] [PubMed]

37. Hu, C.; Yong, X.; Li, C.; Lu, M.; Liu, D.; Chen, L.; Hu, J.; Teng, M.; Zhang, D.; Fan, Y.; et al. CXCL12/CXCR4 axis promotes mesenchymal stem cell mobilization to burn wounds and contributes to wound repair. *J. Surg. Res.* 2013, 183, 427–434. [CrossRef] [PubMed]

38. Yellowley, C. CXCL12/CXCR4 signalling and other recruitment and homing pathways in fracture repair. *BoneKEy Rep.* 2013, 2, 300. [CrossRef] [PubMed]
39. Dwyer, R.M.; Potter-Beirne, S.M.; Harrington, K.A.; Lowery, A.J.; Hennessy, E.; Murphy, J.M.; Barry, F.P.; O’Brien, T.; Kerin, M.J. Monocyte chemotactic protein-1 secreted by primary breast tumors stimulates migration of mesenchymal stem cells. *Clin. Cancer Res.* 2007, 13, 5020–5027. [CrossRef] [PubMed]

40. Orimo, A.; Gupta, P.B.; Sgroi, D.C.; Arenzana-Seisdedos, F.; Delaunay, T.; Naeem, R.; Carey, V.J.; Richardson, A.L.; Weinberg, R.A. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. *Cell* 2005, 121, 335–348. [CrossRef] [PubMed]

41. Ip, J.E.; Wu, Y.; Huang, J.; Zhang, L.; Pratt, R.E.; Dzau, V.J. Mesenchymal stem cells use integrin β1 not CXC chemokine receptor 4 for myocardial migration and engraftment. *Mol. Cell. Biol.* 2007, 18, 2873–2882. [CrossRef] [PubMed]

42. Yang, J.X.; Zhang, N.; Wang, H.W.; Gao, P.; Yang, Q.P.; Wen, Q.P. CXCR4 receptor overexpression in mesenchymal stem cells facilitates treatment of acute lung injury in rats. *J. Biol. Chem.* 2015, 290, 1994–2006. [CrossRef] [PubMed]

43. Rengasamy, M.; Singh, G.; Fakharuzi, N.A.; Siddikuzzaman; Balasubramanian, S.; Swamynathan, P.; Thej, C.; Sasidharan, G.; Gupta, P.K.; Das, A.K.; et al. Transplantation of human bone marrow mesenchymal stromal cells reduces liver fibrosis more effectively than Wharton’s jelly mesenchymal stromal cells. *Stem Cell Res. Ther.* 2017, 8, 143. [CrossRef] [PubMed]

44. Studeny, M.; Marini, F.C.; Dembinski, J.L.; Zompetta, C.; Cabreira-Hansen, M.; Bekele, B.N.; Champlin, R.E.; Andreeff, M. Mesenchymal stem cells: Potential precursors for tumor stroma and targeted-delivery vehicles for anticancer agents. *J. Natl. Cancer Inst.* 2004, 96, 1593–1603. [CrossRef] [PubMed]

45. Choi, S.A.; Hwang, S.-K.; Wang, K.-C.; Cho, B.-K.; Phi, J.H.; Lee, J.Y.; Jung, H.W.; Lee, D.-H.; Kim, S.-K. Therapeutic efficacy and safety of TRAIL-producing human adipose tissue–derived mesenchymal stem cells against experimental brainstem glioma. *Neuro-Oncology* 2011, 13, 61–69. [CrossRef] [PubMed]

46. Sun, X.-Y.; Nong, J.; Qin, K.; Lu, H.; Moniri, M.R.; Dai, L.-J.; Warnock, G.L. MSC TRAIL-mediated HepG2 cell death in direct and indirect co-cultures. *Anticancer Res.* 2011, 30, 3705–3712.

47. Mohr, A.; Lyons, M.; Deedigan, L.; Harte, T.; Shaw, G.; Howard, L.; Barry, F.; O’Brien, T.; Zwacka, R. Mesenchymal stem cells expressing TRAIL lead to tumour growth inhibition in an experimental lung cancer model. *J. Cell. Mol. Med.* 2008, 12, 2628–2643. [CrossRef] [PubMed]

48. Ciavarella, S.; Grisendi, G.; Dominici, M.; Tucci, M.; Brunetti, O.; Dammacco, F.; Silvestris, F. In vitro anti-myeloma activity of TRAIL-expressing adipose-derived mesenchymal stem cells. *Br. J. Haematol.* 2012, 157, 586–598. [CrossRef] [PubMed]

49. Grisendi, G.; Bussolari, R.; Cafarelli, L.; Petak, I.; Rasini, V.; Veronesi, E.; De Santis, G.; Spano, C.; Tagliazucchi, M.; Barti-Juhasz, H.; et al. Adipose-derived mesenchymal stem cells as stable source of tumor necrosis factor–related apoptosis-inducing ligand delivery for cancer therapy. *Cancer Res.* 2010, 70, 3718–3729. [CrossRef] [PubMed]

50. Campeau, P.M.; Rafei, M.; Francois, M.; Birman, E.; Forner, K.A.; Galipeau, J. Mesenchymal stromal cells engineered to express erythropoietin induce anti-erythropoietin antibodies and anemia in allogeneic recipients. *Mol. Ther.* 2009, 17, 369–372. [CrossRef] [PubMed]

51. Jin, S.; Li, H.; Han, M.; Ruan, M.; Liu, Z.; Zhang, F.; Zhang, C.; Choi, Y.; Liu, B. Mesenchymal stem cells with enhanced Bcl-2 expression promote liver recovery in a rat model of hepatic cirrhosis. *Cell. Physiol. Biochem.* 2016, 40, 1117–1128. [CrossRef] [PubMed]

52. Kuttappan, S.; Anitha, A.; Minsha, M.G.; Menon, P.M.; Sivanarayanan, T.B.; Vijayachandran, L.S.; Nair, M.B. BMP2 expressing genetically engineered mesenchymal stem cells on composite fibrous scaffolds for enhanced bone regeneration in segmental defects. *Mater. Sci. Eng. C Mater. Biol. Appl.* 2018, 85, 239–248. [CrossRef] [PubMed]

53. Nakamura, K.; Ito, Y.; Kawano, Y.; Kurozumi, K.; Kobune, M.; Tsuda, H.; Bizen, A.; Honmou, O.; Niitsu, Y.; Hamada, H. Antitumor effect of genetically engineered mesenchymal stem cells in a rat glioma model. *Gene Ther.* 2004, 11, 1155–1164. [CrossRef] [PubMed]

54. You, Q.; Yao, Y.; Zhang, Y.; Fu, S.; Du, M.; Zhang, G. Effect of targeted ovarian cancer therapy using amniotic fluid mesenchymal stem cells transfected with enhanced green fluorescent protein-human interleukin-2 in vivo. *Mol. Med. Rep.* 2015, 12, 4859–4866. [CrossRef] [PubMed]
55. Studeny, M.; Marini, F.C.; Champlin, R.E.; Zompetta, C.; Fidler, I.J.; Andreeff, M. Bone marrow-derived mesenchymal stem cells as vehicles for interferon-β delivery into tumors. *Cancer Res.* 2002, 62, 3603–3608. [PubMed]

56. Jing, W.; Chen, Y.; Lu, L.; Hu, X.; Shao, C.; Zhang, Y.; Zhou, X.; Zhou, Y.; Wu, L.; Liu, R.; et al. Human umbilical cord blood-derived mesenchymal stem cells producing IL-15 eradicate established pancreatic tumor in syngeneic mice. *Mol. Cancer Ther.* 2014. [CrossRef] [PubMed]

57. Abdul Halim, N.S.; Fakiruddin, K.S.; Ali, S.A.; Yahaya, B.H. A comparative study of non-viral gene delivery techniques to human adipose-derived mesenchymal stem cell. *Int. J. Mol. Sci.* 2014, 15, 15044–15060. [CrossRef] [PubMed]

58. Fakiruddin, K.S.; Baharuddin, P.; Lim, M.N.; Fakharuzi, N.A.; Yusof, N.A.N.M.; Zakaria, Z. Nucleofection optimization and in vitro anti-tumourigenic effect of TRAIL-expressing human adipose-derived mesenchymal stromal cells. *Cancer Cell Int.* 2014, 14, 122. [CrossRef] [PubMed]

59. Cavarretta, I.T.; Altanerova, V.; Matuskova, M.; Kucerova, L.; Culig, Z.; Altaner, C. Adipose tissue–derived mesenchymal stem cells expressing prodrug-converting enzyme inhibit human prostate tumor growth. *Mol. Ther.* 2010, 18, 223–231. [CrossRef] [PubMed]

60. Chung, T.; Na, J.; Kim, Y.I.; Chang, D.Y.; Kim, Y.I.; Kim, H.; Moon, H.E.; Kang, K.W.; Lee, D.S.; Chung, J.K.; et al. Dihydropyrimidinase dehydrogenase is a prognostic marker for mesenchymal stem cell-mediated cytosine deaminase gene and 5-fluorocytosine prodrug therapy for the treatment of recurrent gliomas. *Theranostics* 2016, 6, 1477–1490. [CrossRef] [PubMed]

61. NguyenThai, Q.A.; Sharma, N.; Luong do, H.; Sodhi, S.S.; Kim, J.H.; Kim, N.; Oh, S.J.; Jeong, D.K. Targeted inhibition of osteosarcoma tumor growth by bone marrow-derived mesenchymal stem cells expressing cytosine deaminase/5-fluorocytosine in tumor-bearing mice. *J. Gene Med.* 2015, 17, 87–99. [CrossRef] [PubMed]

62. Lee, H.; Jo, E.B.; Kim, S.J.; Yang, H.M.; Kim, Y.M.; Sung, Y.C.; Park, J.B.; Hong, D.; Park, H.; Choi, Y.L.; et al. Therapeutic strategies for locally recurrent and metastatic de-differentiated liposarcoma with herpes simplex virus-thymidine kinase-expressing mesenchymal stromal cells. *Cytotherapy* 2017, 19, 1035–1047. [CrossRef] [PubMed]

63. Nouri, F.S.; Wang, X.; Hatefi, A. Genetically engineered theranostic mesenchymal stem cells for the evaluation of the anticancer efficacy of enzyme/prodrug systems. *J. Control. Release* 2015, 200, 179–187. [CrossRef] [PubMed]

64. Chiocca, E.A.; Rabkin, S.D. Oncolytic viruses and their application to cancer immunotherapy. *Cancer ImmunoL. Res.* 2014, 2, 295–300. [CrossRef] [PubMed]

65. Yamamoto, Y.; Nagasato, M.; Rin, Y.; Henmi, M.; Ino, Y.; Yachida, S.; Ohki, R.; Hiraoka, N.; Tagawa, M.; Aoki, K. Strong antitumor efficacy of a pancreatic tumor-targeting oncolytic adenovirus for neuroendocrine tumors. *Cancer Med.* 2017, 6, 2385–2397. [CrossRef] [PubMed]

66. Berkey, S.E.; Thorne, S.H.; Bartlett, D.L. Oncolytic virotherapy and the tumor microenvironment. *Adv. Exp. Med. Biol.* 2017, 1036, 157–172. [PubMed]

67. Ahmed, A.U.; Tyler, M.A.; Thaci, B.; Alexiades, N.G.; Han, Y.; Ulasov, I.V.; Lesniak, M.S. A comparative study of neural and mesenchymal stem cell-based carriers for oncolytic adenovirus in a model of malignant glioma. *Mol. Pharm.* 2011, 8, 1559–1572. [CrossRef] [PubMed]

68. Parker Kerrigan, B.C.; Shimizu, Y.; Andreeff, M.; Lang, F.F. Mesenchymal stem cells for the delivery of oncolytic viruses in gliomas. *Cytotherapy* 2017, 19, 445–457. [CrossRef] [PubMed]

69. Kaczorowski, A.; Hammer, K.; Liu, L.; Villhauer, S.; Nwaeburu, C.; Fan, P.; Zhao, Z.; Gladkich, J.; Gross, W.; Nettelbeck, D.M.; et al. Delivery of improved oncolytic adenoviruses by mesenchymal stromal cells for elimination of tumorigenic pancreatic cancer cells. *Oncotarget* 2016, 7, 9046–9059. [CrossRef] [PubMed]

70. Mader, E.K.; Butler, G.; Dowdy, S.C.; Mariani, A.; Knutson, K.L.; Federspiel, M.J.; Russell, S.J.; Galanis, E.; Dietz, A.B.; Peng, K.-W. Optimizing patient derived mesenchymal stem cells as virus carriers for a phase I clinical trial in ovarian cancer. *J. Transl. Med.* 2013, 11, 20. [CrossRef] [PubMed]

71. Du, W.; Seah, I.; Bougazzoul, O.; Choi, G.; Meeth, K.; Bosenberg, M.W.; Wakimoto, H.; Fisher, D.; Shah, K. Stem cell-released oncolytic herpes simplex virus has therapeutic efficacy in brain metastatic melanomas. *Proc. Natl. Acad. Sci. USA* 2017, 114, E6157–E6165. [CrossRef] [PubMed]
72. Leoni, V.; Gatta, V.; Palladini, A.; Nicoletti, G.; Ranieri, D.; Dall’Ora, M.; Grosso, V.; Rossi, M.; Alviano, F.; Bonisi, L.; et al. Systemic delivery of HER2-retargeted oncolytic-hsv by mesenchymal stromal cells protects from lung and brain metastases. *Oncotarget* 2015, 6, 34774–34787. [CrossRef] [PubMed]

73. Yong, R.L.; Shinojima, N.; Fueyo, J.; Gumin, J.; Vecil, G.G.; Marini, F.C.; Bogler, O.; Andreeff, M.; Lang, F.F. Human bone marrow-derived mesenchymal stem cells for intravascular delivery of oncolytic adenovirus δ24-RGD to human gliomas. *Cancer Res.* 2009, 69, 8932–8940. [CrossRef] [PubMed]

74. Xia, X.; Ji, T.; Chen, P.; Li, X.; Fang, Y.; Gao, Q.; Liao, S.; You, L.; Xu, H.; Ma, Q.; et al. Mesenchymal stem cells as carriers and amplifiers in CRAd delivery to tumors. *Mol. Ther.* 2011, 10, 958–966. [CrossRef] [PubMed]

75. Gura, T. How TRAIL kills cancer cells, but not normal cells. *Science* 1997, 277, 768. [CrossRef] [PubMed]

76. Zhang, J.; Kale, V.; Chen, M. Gene-directed enzyme prodrug therapy. *AAPS J.* 2015, 17, 102–110. [CrossRef]

77. Chiocca, E.A.; Abbed, K.M.; Tatter, S.; Louis, D.N.; Hochberg, F.H.; Barker, F.; Kracher, J.; Grossman, S.A.; Fisher, J.D.; Carson, K.; et al. A phase I open-label, dose-escalation, multi-institutional trial of injection with an e1b-attenuated adenovirus, ONYX-015, into the peritumoral region of recurrent malignant gliomas, in the adjuvant setting. *Mol. Ther.* 2004, 10, 958–966. [CrossRef] [PubMed]

78. Prestwich, R.J.; Errington, F.; Harrington, K.J.; Pandha, H.S.; Selby, P.; Melcher, A. Oncolytic viruses: Do they have a role in anti-cancer therapy? *Clin. Med. Oncol.* 2008, 2, 83–96. [CrossRef] [PubMed]

79. Schwartz, R.N.; Stover, L.; Dutcher, J.P. Managing toxicities of high-dose interleukin-2. *Oncology* 2002, 16, 11–20. [PubMed]

80. Gao, P.; Ding, Q.; Wu, Z.; Jiang, H.; Fang, Z. Therapeutic potential of human mesenchymal stem cells producing IL-12 in a mouse xenograft model of renal cell carcinoma. *Cancer Lett.* 2010, 290, 157–166. [CrossRef] [PubMed]

81. Elzaouk, L.; Moelling, K.; Pavlovic, J. Anti-tumor activity of mesenchymal stem cells producing IL-12 in a mouse melanoma model. *Exp. Dermatol.* 2006, 15, 865–874. [CrossRef] [PubMed]

82. Leonard, J.P.; Sherman, M.L.; Fisher, G.L.; Buchanan, L.J.; Larsen, G.; Atkins, M.B.; Sosman, J.A.; Dutcher, J.P.; Vogelzang, N.J.; Ryan, J.L. Effects of single-dose interleukin-12 exposure on interleukin-12-associated toxicity and interferon-γ production. *Blood* 1997, 90, 2541–2548. [PubMed]

83. Berger, C.; Berger, M.; Hackman, R.C.; Gough, M.; Elliott, C.; Jensen, M.C.; Riddell, S.R. Safety and immunologic effects of IL-15 administration in nonhuman primates. *Blood* 2009, 114, 2417–2426. [CrossRef] [PubMed]

84. Liu, X.; Hu, J.; Sun, S.; Li, F.; Cao, W.; Wang, Y.U.; Ma, Z.; Yu, Z. Mesenchymal stem cells expressing interleukin-18 suppress breast cancer cells in vitro. *Exp. Ther. Med.* 2015, 9, 1192–1200. [CrossRef] [PubMed]

85. Robertson, M.J.; Mier, J.W.; Logan, T.; Atkins, M.; Koon, H.; Koch, K.; Mathison, J.; Oei, C.; Kirby, L.; et al. Clinical and biological effects of recombinant human interleukin-18 administered by intravenous infusion to patients with advanced cancer. *Clin. Cancer Res.* 2006, 12, 4265–4273. [CrossRef] [PubMed]

86. Jonasch, E.; Haluska, F.G. Interferon in oncological practice: Review of interferon biology, clinical applications, and toxicities. *Oncologist* 2001, 6, 34–55. [CrossRef] [PubMed]

87. Herbst, R.S.; Eckhardt, S.G.; Kurzrock, R.; Ebbinghaus, S.; O’Dwyer, P.J.; Gordon, M.S.; Novotny, W.; Goldwasser, M.A.; Tohnya, T.M.; Lum, B.L.; et al. Phase I dose-escalation study of recombinant human Apo2L/TRAIL, a dual proapoptotic receptor agonist, in patients with advanced cancer. *J. Clin. Oncol.* 2010, 28, 2839–2846. [CrossRef] [PubMed]

88. Castleton, A.; Dey, A.; Beaton, B.; Patel, B.; Aucher, A.; Davis, D.M.; Fielding, A.K. Human mesenchymal stromal cells deliver systemic oncolytic measles virus to treat acute lymphoblastic leukemia in the presence of humoral immunity. *Blood* 2014, 27, 1327–1335. [CrossRef] [PubMed]

89. Martinez-Quintanilla, J.; He, D.; Wakimoto, H.; Alemany, R.; Shah, K. Encapsulated stem cells loaded with hyaluronidase-expressing oncolytic virus for brain tumor therapy. *Mol. Ther.* 2015, 23, 108–118. [CrossRef] [PubMed]

90. Almasan, A.; Ashkenazi, A. Apo2L/TRAIL: Apoptosis signalling, biology, and potential for cancer therapy. *Cytokine Growth Factor Rev.* 2003, 14, 337–348. [CrossRef]
104. Ehrhardt, H.; Fulda, S.; Schmid, I.; Hiscott, J.; Debatin, K.M.; Jeremias, I. TRAIL induced survival and
99. Singh, T.R.; Shankar, S.; Chen, X.; Asim, M.; Srivastava, R.K. Synergistic interactions of chemotherapeutic
98. Naka, T.; Sugamura, K.; Hylander, B.L.; Widmer, M.B.; Rustum, Y.M.; Repasky, E.A. Effects of tumor necrosis
97. Keane, M.M.; Ettenberg, S.A.; Nau, M.M.; Russell, E.K.; Lipkowitz, S. Chemotherapy augments
101. Nagane, M.; Pan, G.; Weddle, J.J.; Dixit, V.M.; Cavenee, W.K.; Huang, H.J. Increased death receptor 5
106. Walczak, H.; Miller, R.E.; Ariail, K.; Gliniak, B.; Griffith, T.S.; Kubin, M.; Chin, W.; Jones, J.; Woodward, A.;
105. Kelley, S.K.; Harris, L.A.; Xie, D.; Deforge, L.; Totpal, K.; DeForge, L.; Bussiere, J.; Fox, J.A. Preclinical studies to predict the
91. Robertson, N.M.; Zangrilli, J.G.; Steplevski, A.; Hastie, A.; Lindemeyer, R.G.; Planeta, M.A.; Smith, M.K.;
92. Han, L.H.; Sun, W.S.; Ma, C.H.; Zhang, L.N.; Liu, S.X.; Zhang, Q.; Gao, L.F.; Chen, Y.H. Detection of soluble
93. Snell, V.; Clodi, K.; Zhao, S.; Goodwin, R.; Thomas, E.K.; Morris, S.W.; Kadin, M.E.; Cabanillas, F.;
107. Wang, H.; Davis, J.S.; Wu, X. Immunoglobulin fc domain fusion to TRAIL significantly prolongs its plasma
103. Baader, E.; Toloczko, A.; Fuchs, U.; Schmid, I.; Beltinger, C.; Ehrhardt, H.; Debatin, K.M.; Jeremias, I.
94. Belyanskaya, L.L.; Ziogas, A.; Hopkins-Donaldson, S.; Kurtz, S.; Simon, H.U.; Stahel, R.;
95. Lawrence, D.; Shahrokh, Z.; Marsters, S.; Achilles, K.; Shih, D.; Mounho, B.; Hillan, K.; Totpal, K.; DeForge, L.;
96. Younes, A.; Kadin, M.E. Emerging applications of the tumor necrosis factor family of ligands and receptors
97. Lawrence, D.; Shahrokh, Z.; Marsters, S.; Achilles, K.; Shih, D.; Mounho, B.; Hillan, K.; Totpal, K.; DeForge, L.;
98. Naka, T.; Sugamura, K.; Hylander, B.L.; Widmer, M.B.; Rustum, Y.M.; Repasky, E.A. Effects of tumor necrosis
99. Singh, T.R.; Shankar, S.; Chen, X.; Asim, M.; Srivastava, R.K. Synergistic interactions of chemotherapeutic
drugs and tumor necrosis factor-related apoptosis-inducing ligand/Apo-2 ligand on apoptosis and on
growth in breast carcinoma in vivo. Cancer Res. 2003, 63, 5390–5400. [PubMed]
100. Marini, P.; Denzinger, S.; Schiller, D.; Kauder, S.; Welz, S.; Humphreys, R.; Daniel, P.T.; Jendrossek, V.;
101. Nagane, M.; Pan, G.; Weddle, J.J.; Dixit, V.M.; Cavenee, W.K.; Huang, H.J. Increased death receptor 5
expression by chemotherapeutic agents in human gliomas causes synergistic cytotoxicity with tumor necrosis
factor-related apoptosis-inducing ligand and in combination with chemotherapeutic agents on patients’
colon tumors grown in scid mice. Cancer Res. 2002, 62, 5800–5806. [PubMed]
102. Voortman, J.; Resende, T.P.; Abou El Hassan, M.A.; Giaccone, G.; Kruyt, F.A. TRAIL therapy in non-small cell
lung cancer cells: Sensitization to death receptor-mediated apoptosis by proteasome inhibitor bortezomib. Mol. Cancer Ther. 2007, 6, 2103–2112. [PubMed]
103. Baader, E.; Toloczko, A.; Fuchs, U.; Schmid, I.; Beltinger, C.; Ehrhardt, H.; Debatin, K.M.; Jeremias, I. Tumor necrosis factor-related apoptosis-inducing ligand-mediated proliferation of tumor cells with
receptor-proximal apoptosis defects. Cancer Res. 2005, 65, 7888–7895. [PubMed] [CrossRef] [PubMed]
104. Ehrhardt, H.; Fulda, S.; Schmid, I.; Hiscott, J.; Debatin, K.M.; Jeremias, I. TRAIL induced survival and
proliferation in cancer cells resistant towards TRAIL-induced apoptosis mediated by NF-kappaB. Oncogene 2003, 22, 3842–3852. [PubMed] [CrossRef]
105. Kelley, S.K.; Harris, L.A.; Xie, D.; Deforge, L.; Totpal, K.; Bussiere, J.; Fox, J.A. Preclinical studies to predict the
disposition of Apo2L/tumor necrosis factor-related apoptosis-inducing ligand in humans: Characterization of in vivo efficacy, pharmacokinetics, and safety. J. Pharmacol. Exp. Ther. 2001, 299, 31–38. [PubMed]
106. Walczak, H.; Miller, R.E.; Ariail, K.; Gliniak, B.; Griffith, T.S.; Kubin, M.; Chin, W.; Jones, J.; Woodward, A.;
Le, T.; et al. Tumoricidal activity of tumor necrosis factor-related apoptosis-inducing ligand in vivo. Nat. Med. 1999, 5, 157–163. [PubMed] [CrossRef]
107. Wang, H.; Davis, J.S.; Wu, X. Immunoglobulin fc domain fusion to TRAIL significantly prolongs its plasma
half-life and enhances its antitumor activity. Mol. Cancer Ther. 2014, 13, 643–650. [PubMed] [CrossRef]
108. Butler, L.M.; Liapis, V.; Bouralexis, S.; Welldon, K.; Hay, S.; Thai le, M.; Labrinidis, A.; Tilley, W.D.; Findlay, D.M.; Evdokiou, A. The histone deacetylase inhibitor, suberoylanilide hydroxamic acid, overcomes resistance of human breast cancer cells to Apo2L/TRAIL. *Int. J. Cancer* 2006, 119, 944–954. [CrossRef] [PubMed]

109. Panner, A.; Parsa, A.T.; Pieper, R.O. Use of Apo2L/TRAIL with mTOR inhibitors in the treatment of glioblastoma multiforme. *Expert Rev. Anticancer Ther.* 2006, 6, 1313–1322. [CrossRef] [PubMed]

110. Inoue, T.; Shiraki, K.; Fuke, H.; Yamanaka, Y.; Miyashita, K.; Yamaguchi, Y.; Yamamoto, N.; Ito, K.; Sugimoto, K.; Nakano, T. Proteasome inhibition sensitizes hepatocellular carcinoma cells to TRAIL by suppressing caspase inhibitors and AKT pathway. *Anti-Cancer Drugs* 2006, 17, 261–268. [CrossRef] [PubMed]

111. Kasman, L.; Lu, P.; Voelkel-Johnson, C. The histone deacetylase inhibitors depsipeptide and MS-275, enhance TRAIL gene therapy of LNCAP prostate cancer cells without adverse effects in normal prostate epithelial cells. *Cancer Gene Ther.* 2007, 14, 327–334. [CrossRef] [PubMed]

112. Wang, G.; Zhan, Y.; Wang, H.; Li, W. ABT-263 sensitizes TRAIL-resistant hepatocarcinoma cells by downregulating the Bcl-2 family of anti-apoptotic protein. *Cancer Chemother. Pharmacol.* 2012, 69, 799–805. [CrossRef] [PubMed]

113. Frese, S.; Frese-Schaper, M.; Andres, A.C.; Miescher, D.; Zumkehr, B.; Schmid, R.A. Cardiac glycosides initiate Apo2L/TRAIL-induced apoptosis in non-small cell lung cancer cells by up-regulation of death receptors 4 and 5. *Cancer Res.* 2006, 66, 5867–5874. [CrossRef] [PubMed]

114. Kim, E.O.; Kang, S.E.; Im, C.R.; Lee, J.H.; Ahn, K.S.; Yang, W.M.; Um, J.Y.; Lee, S.G.; Yun, M. Tanshinone IIA induces TRAIL sensitization of human lung cancer cells through selective ER stress induction. *Int. J. Oncol.* 2016, 48, 2205–2212. [CrossRef] [PubMed]

115. Lacour, S.; Micheau, O.; Hammann, A.; Drouineaud, V.; Tschopp, J.; Solary, E.; Dimanche-Boitrel, M.T. Chemotherapy enhances TNF-related apoptosis-inducing ligand disc assembly in HT29 human colon cancer cells. *OncoGene* 2003, 22, 1807–1816. [CrossRef] [PubMed]

116. O’Flaherty, J.D.; Barr, M.; Fennell, D.; Richard, D.; Reynolds, J.; O’Leary, J.; O’Byrne, K. The cancer stem-cell hypothesis: Its emerging role in lung cancer biology and its relevance for future therapy. *J. Thorac. Oncol.* 2012, 7, 1880–1890. [CrossRef] [PubMed]

117. Wong, N.K.; Fuller, M.; Sung, S.; Wong, F.; Karsan, A. Heterogeneity of breast cancer stem cells as evidenced with notch-dependent and notch-independent populations. *Cancer Med.* 2012, 1, 105–113. [CrossRef] [PubMed]

118. Tang, D.G. Understanding cancer stem cell heterogeneity and plasticity. *Cell Res.* 2012, 22, 457–472. [CrossRef] [PubMed]

119. Al-Hajj, M.; Wicha, M.S.; Benito-Hernandez, A.; Morrison, S.J.; Clarke, M.F. Prospective identification of tumorigenic breast cancer cells. *Proc. Natl. Acad. Sci. USA* 2003, 100, 3983–3988. [CrossRef] [PubMed]

120. Tan, Y.; Chen, B.O.; Xu, W.E.I.; Zhao, W.; Wu, J. Clinicopathological significance of CD133 in lung cancer: A meta-analysis. *Mol. Clin. Oncol.* 2014, 2, 111–115. [CrossRef] [PubMed]

121. Pellacani, D.; Oldridge, E.E.; Collins, A.T.; Maitland, N.J. Prominin-1 (CD133) expression in the prostate and prostate cancer: A marker for quiescent stem cells. *Adv. Exp. Med. Boil.* 2013, 777, 167–184. [PubMed]

122. Reyes, E.E.; Kunovac, S.K.; Duggan, R.; Kregel, S.; Vander Griend, D.J. Growth kinetics of CD133-positive prostate cancer cells. *Prostate* 2013, 73, 724–733. [CrossRef] [PubMed]

123. Bi, C.L.; Fang, J.S.; Chen, F.H.; Wang, Y.J.; Wu, J. Chemoresistant of CD133+ tumor stem cells from human brain glioma. *Zhong Nan Da Xue Xue Bao. Yi Xue Ban* 2007, 32, 568–573. [PubMed]

124. Choi, S.A.; Wang, K.C.; Phi, J.H.; Lee, J.Y.; Park, C.K.; Park, S.H.; Kim, S.K. A distinct subpopulation within CD133 positive brain tumor cells shares characteristics with endothelial progenitor cells. *Cancer Lett.* 2012, 324, 221–230. [CrossRef] [PubMed]

125. Kasman, L.; Lu, P.; Voelkel-Johnson, C. The histone deacetylase inhibitors depsipeptide and MS-275, enhance TRAIL gene therapy of LNCAP prostate cancer cells without adverse effects in normal prostate epithelial cells. *Cancer Gene Ther.* 2007, 14, 327–334. [CrossRef] [PubMed]

126. Wang, G.; Zhan, Y.; Wang, H.; Li, W. ABT-263 sensitizes TRAIL-resistant hepatocarcinoma cells by downregulating the Bcl-2 family of anti-apoptotic protein. *Cancer Chemother. Pharmacol.* 2012, 69, 799–805. [CrossRef] [PubMed]

127. Tang, D.G. Understanding cancer stem cell heterogeneity and plasticity. *Cell Res.* 2012, 22, 457–472. [CrossRef] [PubMed]

128. Al-Hajj, M.; Wicha, M.S.; Benito-Hernandez, A.; Morrison, S.J.; Clarke, M.F. Prospective identification of tumorigenic breast cancer cells. *Proc. Natl. Acad. Sci. USA* 2003, 100, 3983–3988. [CrossRef] [PubMed]

129. Tan, Y.; Chen, B.O.; Xu, W.E.I.; Zhao, W.; Wu, J. Clinicopathological significance of CD133 in lung cancer: A meta-analysis. *Mol. Clin. Oncol.* 2014, 2, 111–115. [CrossRef] [PubMed]

130. Pellacani, D.; Oldridge, E.E.; Collins, A.T.; Maitland, N.J. Prominin-1 (CD133) expression in the prostate and prostate cancer: A marker for quiescent stem cells. *Adv. Exp. Med. Boil.* 2013, 777, 167–184. [PubMed]

131. Reyes, E.E.; Kunovac, S.K.; Duggan, R.; Kregel, S.; Vander Griend, D.J. Growth kinetics of CD133-positive prostate cancer cells. *Prostate* 2013, 73, 724–733. [CrossRef] [PubMed]

132. Bi, C.L.; Fang, J.S.; Chen, F.H.; Wang, Y.J.; Wu, J. Chemoresistant of CD133+ tumor stem cells from human brain glioma. *Zhong Nan Da Xue Xue Bao. Yi Xue Ban* 2007, 32, 568–573. [PubMed]

133. Choi, S.A.; Wang, K.C.; Phi, J.H.; Lee, J.Y.; Park, C.K.; Park, S.H.; Kim, S.K. A distinct subpopulation within CD133 positive brain tumor cells shares characteristics with endothelial progenitor cells. *Cancer Lett.* 2012, 324, 221–230. [CrossRef] [PubMed]

134. Li, M.C.; Deng, Y.W.; Wu, J.; Chen, F.H.; Liu, J.F.; Fang, J.S. Isolation and characterization of brain tumor stem cells in human medulloblastoma. *Ai Zheng* 2006, 25, 241–246. [PubMed]

135. Singh, S.; Dirks, P.B. Brain tumor stem cells: Identification and concepts. *Neurosurg. Clin. North Am.* 2007, 18, 31–38. [CrossRef] [PubMed]
128. Kozovska, Z.; Gabrisova, V.; Kucerova, L. Colon cancer: Cancer stem cells markers, drug resistance and treatment. *Biomed. Pharmacother.* 2014, 68, 911–916. [CrossRef] [PubMed]

129. Margaritescu, C.; Pirici, D.; Cerciu, I.; Barbalan, A.; Cartana, T.; Saftoiu, A. CD133/CD166/KI-67 triple immunofluorescence assessment for putative cancer stem cells in colon carcinoma. *J. Gastrointest. Liver Dis.* 2014, 23, 161–170. [CrossRef]

130. Vincent, Z.; Uraakami, K.; Maruyama, K.; Yamaguchi, K.; Kusuhara, M. CD133-positive cancer stem cells from Colo205 human colon adenocarcinoma cell line show resistance to chemotherapy and display a specific metabolomic profile. *Genes Cancer* 2014, 5, 250–260. [PubMed]

131. Cogliati, B.; Aloia, T.P.; Bosch, R.V.; Alves, V.A.; Hernandez-Blazquez, F.J.; Dagli, M.L. Identification of hepatic stem/progenitor cells in canine hepatocellular and cholangiocellular carcinoma. *Vet. Comparat. Oncol.* 2010, 8, 112–121. [CrossRef] [PubMed]

132. Tomuleasa, C.; Soritau, O.; Rus-Ciucu, D.; Pop, T.; Todea, D.; Mosteanu, O.; Pintea, B.; Foris, V.; Susman, S.; Kacso, G.; et al. Isolation and characterization of hepatic cancer cells with stem-like properties from hepatocellular carcinoma. *J. Gastrointest. Liver Dis.* 2010, 19, 61–67.

133. Yang, X.R.; Xu, Y.; Yu, B.; Zhou, J.; Qiu, S.J.; Shi, G.M.; Zhang, B.H.; Wu, W.Z.; Shi, Y.H.; Wu, B.; et al. High expression levels of putative hepatic stem/progenitor cell biomarkers related to tumour angiogenesis and poor prognosis of hepatocellular carcinoma. *Gut* 2010, 59, 953–962. [CrossRef] [PubMed]

134. Zhang, L.; Sun, H.; Zhao, F.; Lu, P.; Ge, C.; Li, H.; Hou, H.; Yan, M.; Chen, T.; Jiang, G.; et al. BMP4 administration induces differentiation of CD133+ hepatic cancer stem cells, blocking their contributions to hepatocellular carcinoma. *Cancer Res.* 2012, 72, 4276–4285. [CrossRef] [PubMed]

135. Christgen, M.; Ballmaier, M.; Lehmann, U.; Kreipe, H. Detection of putative cancer stem cells of the side population phenotype in human tumor cell cultures. *Methods Mol. Biol.* 2012, 878, 201–215. [PubMed]

136. Zhang, W.C.; Shyh-Chang, N.; Yang, H.; Rai, A.; Umashankar, S.; Ma, S.; Soh, B.S.; Sun, L.L.; Tai, B.C.; Nga, M.E.; et al. Glycine decarboxylase activity drives non-small cell lung cancer tumor-initiating cells and tumorigenesis. *Cell 2012*, 148, 259–272. [CrossRef] [PubMed]

137. Eramo, A.; Lotti, F.; Sette, G.; Pilozzi, E.; Biffoni, M.; Di Virgilio, A.; Conticello, C.; Ruco, L.; Peschle, C.; De Maria, R. Identification and expansion of the tumorigenic lung cancer stem cell population. *Cell Death Differ.* 2008, 15, 504–514. [CrossRef] [PubMed]

138. Karimi-Busheri, F.; Zadorozhny, V.; Li, T.; Lin, H.; Shawler, D.L.; Fakhrai, H. Pivotal role of CD38 biomarker in combination with CD24, epcam, and aldh for identification of H460 derived lung cancer stem cells. *J. Stem Cells* 2011, 6, 9–20. [PubMed]

139. Shao, C.; Sullivan, J.P.; Girard, L.; Augustyn, A.; Yenerall, P.; Rodriguez-Canales, J.; Liu, H.; Behrens, C.; Shay, J.W.; Wistuba, I.I.; et al. Essential role of aldehyde dehydrogenase 1A3 for the maintenance of non-small cell lung cancer stem cells is associated with the STAT3 pathway. *Clin. Cancer Res.* 2014, 20, 4154–4166. [CrossRef] [PubMed]

140. Zakaria, N.; Yusoff, N.M.; Zakaria, Z.; Lim, M.N.; Baharuddin, P.J.N.; Fakiruddin, K.S.; Yahaya, B. Human non-small cell lung cancer expresses putative cancer stem cell markers and exhibits the transcriptomic profile of multipotent cells. *BMC Cancer* 2015, 15, 84. [CrossRef] [PubMed]

141. De Beca, F.F.; Caetano, P.; Gerhard, R.; Alvarenga, C.A.; Gomes, M.; Paredes, J.; Schmitt, F. Cancer stem cells markers CD44, CD24 and ALDH1 in breast cancer special histological types. *J. Clin. Pathol.* 2013, 66, 187–191. [CrossRef] [PubMed]

142. Kai, K.; Arima, Y.; Kamiya, T.; Saya, H. Breast cancer stem cells. *Breast Cancer* 2010, 17, 80–85. [CrossRef] [PubMed]

143. Puglisi, M.A.; Sgambato, A.; Saulnier, N.; Rafanelli, F.; Barba, M.; Boninsegna, A.; Piscaglia, A.C.; Lauritano, C.; Novi, M.L.; Barbaro, F.; et al. Isolation and characterization of CD133+ cell population within human primary and metastatic colon cancer. *Eur. Rev. Med. Pharmacol. Sci.* 2009, 13 (Suppl. S1), 55–62. [PubMed]

144. Choi, D.; Lee, H.W.; Hur, K.Y.; Kim, J.J.; Park, G.S.; Jang, S.H.; Song, Y.S.; Jang, K.S.; Paik, S.S. Cancer stem cell markers CD133 and CD24 correlate with invasiveness and differentiation in colorectal adenocarcinoma. *World J. Gastroenterol.* 2009, 15, 2258–2264. [CrossRef] [PubMed]

145. Chikamatsu, K.; Takahashi, G.; Sakakura, K.; Ferrone, S.; Masuyama, K. Immunoregulatory properties of CD44+ cancer stem-like cells in squamous cell carcinoma of the head and neck. *Head Neck* 2011, 33, 208–215. [CrossRef] [PubMed]
146. Sun, G.; Fujii, M.; Sonoda, A.; Tokumaru, Y.; Matsunaga, T.; Habu, N. Identification of stem-like cells in head and neck cancer cell lines. Anticancer Res. 2010, 30, 2005–2010. [PubMed]

147. Erdogan, S.; Doganlar, Z.B.; Doganlar, O.; Turkekul, K.; Serttas, R. Inhibition of midkine suppresses prostate cancer CD133+ stem cell growth and migration. Am. J. Med. Sci. 2017, 354, 299–309. [CrossRef] [PubMed]

148. Miki, J.; Fusurato, B.; Li, H.; Gu, Y.; Takahashi, H.; Egawa, S.; Sesterhenn, I.A.; McLeod, D.G.; Srivastava, S.; Rhim, J.S. Identification of putative stem cell markers, CD133 and CXCR4, in hTERT-immortalized primary nonmalignant and malignant tumor-derived human prostate epithelial cell lines and in prostate cancer specimens. Cancer Res. 2007, 67, 3153–3161. [CrossRef] [PubMed]

149. Kahler, U.D.; Bender, N.O.; Maciaczyk, D.; Bogiel, T.; Bar, E.E.; Eberhart, C.G.; Nikkhah, G.; Maciaczyk, J. CD133/CD15 defines distinct cell subpopulations with differential in vitro clonogenic activity and stem cell-related gene expression profile in vitro propagated glioblastoma multiforme-derived cell line with a PNET-like component. Folia Neuropathol. 2012, 50, 357–368. [CrossRef] [PubMed]

150. Singh, S.K.; Hawkins, C.; Clarke, I.D.; Squire, J.A.; Bayani, J.; Hide, T.; Henkelman, R.M.; Cusimano, M.D.; Dirks, P.B. Identification of human brain tumour initiating cells. Nature 2004, 432, 396–401. [CrossRef] [PubMed]

151. Su, R.; Ali, S.; Ahmad, A.; Philip, P.A.; Sarkar, F.H. The role of cancer stem cells in recurrent and drug-resistant lung cancer. Adv. Exp. Med. Biol. 2016, 890, 57–74.

152. Sussman, R.T.; Ricci, M.S.; Hart, L.S.; Sun, S.Y.; El-Deiry, W.S. Chemotherapy-resistant-side-population of colon cancer cells has a higher sensitivity to TRAIL than the non-SP, a higher expression of c-Myc and TRAIL-receptor DR4. Cancer Boil. Ther. 2007, 6, 1490–1495. [CrossRef]

153. Ding, L.; Yuan, C.; Wei, F.; Wang, G.; Zhang, J.; Bellail, A.C.; Zhang, Z.; Olson, J.J.; Hao, C. Cisplatin restores TRAIL apoptotic pathway in glioblastoma-derived stem cells through up-regulation of DR5 and down-regulation of c-FLIP. Cancer Investig. 2011, 29, 511–520. [CrossRef] [PubMed]

154. Chakraborty, S.; Li, L.; Tang, H.; Xie, Y.; Puliyappadamba, V.T.; Raisanen, J.; Burton, S.; Boothman, D.A.; Cochran, B.; Wu, J.; et al. Cytoplasmic TRADD confers a worse prognosis in glioblastoma. Neoplasia 2013, 15, 888–897. [CrossRef] [PubMed]

155. Wu, M.S.; Wang, G.F.; Zhao, Z.Q.; Liang, Y.; Wang, H.B.; Wu, M.Y.; Min, P.; Chen, L.Z.; Feng, Q.S.; Bei, J.X.; et al. Smac mimetics in combination with TRAIL selectively target cancer stem cells in nasopharyngeal carcinoma. Mol. Cancer Ther. 2013, 12, 1728–1737. [CrossRef] [PubMed]

156. Iida, H.; Suzuki, M.; Goitsuka, R.; Ueno, H. Hypoxia induces CD133 expression in human lung cancer cells by up-regulation of OCT3/4 and SOX2. Int. J. Oncol. 2012, 40, 71–79. [PubMed]

157. Singh, S.; Trevino, J.; Bora-Singhal, N.; Coppola, D.; Haura, E.; Aikman, S.; Chellappan, S.P. EGFR/SRC/AKT signalling modulates Sox2 expression and self-renewal of stem-like side-population cells in non-small cell lung cancer. Mol. Cancer 2012, 11, 73. [CrossRef] [PubMed]

158. Yoshida, G.J.; Saya, H. Therapeutic strategies targeting cancer stem cells. Cancer Sci. 2016, 107, 5–11. [CrossRef] [PubMed]

159. French, R.; Hayward, O.; Jones, S.; Yang, W.; Clarkson, R. Cytoplasmic levels of cFLIP determine a broad susceptibility of breast cancer stem/progenitor-like cells to TRAIL. Mol. Cancer 2015, 14, 209. [CrossRef] [PubMed]

160. Pigott, L.; Omidvar, N.; Marti Perez, S.; French, R.; Eberl, M.; Clarkson, R.W. Suppression of apoptosis inhibitor c-FLIP selectively eliminates breast cancer stem cell activity in response to the anti-cancer agent, TRAIL. Breast Cancer Res. 2011, 13, R88. [CrossRef] [PubMed]

161. Zobalova, R.; McDermott, L.; Stantic, M.; Prokopova, K.; Dong, L.F.; Neuzil, J. CD133-positive cells are resistant to TRAIL due to up-regulation of FLIP. Biochem. Biophys. Res. Commun. 2008, 373, 567–571. [CrossRef] [PubMed]

162. Zobalova, R.; Stantic, M.; Prokopova, K.; Dong, L.F.; Neuzil, J. Cancer cells with high expression of CD133 exert FLIP upregulation and resistance to TRAIL-induced apoptosis. BioFactors 2008, 34, 231–235. [PubMed]

163. Day, T.W.; Najafi, F.; Wu, C.H.; Safa, A.R. Cellular flice-like inhibitory protein (c-FLIP): A novel target for taxol-induced apoptosis. Cancer Res. 1999, 60, 225–237. [CrossRef] [PubMed]
165. Wood, T.E.; Dalili, S.; Simpson, C.D.; Sukhai, M.A.; Hurren, R.; Anyiwe, K.; Mao, X.; Suarez Saiz, F.; Gronda, M.; Eberhard, Y.; et al. Selective inhibition of histone deacetylases sensitizes malignant cells to death receptor ligands. Mol. Cancer Ther. 2010, 9, 246–256. [CrossRef] [PubMed]

166. Qi, L.; Ren, K.; Fang, F.; Zhao, D.H.; Yang, N.J.; Li, Y. Over expression of BCL2 and low expression of caspase 8 related to TRAIL resistance in brain cancer stem cells. Asian Pac. J. Cancer Prev. 2015, 16, 4849–4852. [CrossRef] [PubMed]

167. Lee, S.H.; Kim, M.J.; Kim, D.W.; Kang, C.D.; Kim, S.H. Amurensin g enhances the susceptibility to tumor necrosis factor-related apoptosis-inducing ligand-mediated cytotoxicity of cancer stem-like cells of HCT-15 cells. Cancer Sci. 2013, 104, 1632–1639. [CrossRef] [PubMed]

168. Loebinger, M.R.; Sage, E.K.; Davies, D.; Janes, S.M. TRAIL-expressing mesenchymal stem cells kill the putative cancer stem cell population. Br. J. Cancer 2010, 103, 1692–1697. [CrossRef] [PubMed]

169. Kazimirsky, G.; Jiang, W.; Slavin, S.; Ziv-Av, A.; Brodie, C. Mesenchymal stem cells enhance the oncolytic effect of newcastle disease virus in glioma cells and glioma stem cells via the secretion of TRAIL. Stem Cell Res. Ther. 2016, 7, 149. [CrossRef] [PubMed]

170. Kim, S.M.; Woo, J.S.; Jeong, C.H.; Ryu, C.H.; Lim, J.Y.; Jeun, S.S. Effective combination therapy for malignant glioma with TRAIL-secreting mesenchymal stem cells and lipoxygenase inhibitor MK886. Cancer Res. 2012, 72, 4807–4817. [CrossRef] [PubMed]

171. Xia, P.; Wang, W.; Bai, Y. Claudin-7 suppresses the cytotoxicity of TRAIL-expressing mesenchymal stem cells in H460 human non-small cell lung cancer cells. Apoptosis 2014, 19, 491–505. [CrossRef] [PubMed]

172. Huang, M.; Tang, S.-N.; Upadhyay, G.; Marsh, J.L.; Jackman, C.P.; Shankar, S.; Srivastava, R.K. Embelin suppresses growth of human pancreatic cancer xenografts, and pancreatic cancer cells isolated from Kras(G12D) mice by inhibiting Akt and sonic hedgehog pathways. PLoS ONE 2014, 9, e92161.

173. Mohr, A.; Albarenque, S.M.; Deedigan, L.; Yu, R.; Reidy, M.; Fulda, S.; Zwacka, R.M. Targeting of XIAP combined with systemic mesenchymal stem cell-mediated delivery of sTRAIL ligand inhibits metastatic growth of pancreatic carcinoma cells. Stem Cells 2010, 28, 2019–2120. [CrossRef] [PubMed]

174. Kim, S.W.; Kim, S.J.; Park, S.H.; Yang, H.G.; Kang, M.C.; Choi, Y.W.; Kim, S.M.; Jeun, S.S.; Sung, Y.C. Complete regression of metastatic renal cell carcinoma by multiple injections of engineered mesenchymal stem cells expressing dodecameric TRAIL and HSV-TK. Clin. Cancer Res. 2013, 19, 415–427. [CrossRef] [PubMed]

175. Kim, S.M.; Woo, J.S.; Jeong, C.H.; Ryu, C.H.; Lim, J.Y.; Jeun, S.S. Potential application of temozolomide in mesenchymal stem cell-based TRAIL gene therapy against malignant glioma. Stem Cells Transl. Med. 2016, 5, 1513–1531. [CrossRef] [PubMed]

176. Kazimirsky, G.; Jiang, W.; Slavin, S.; Ziv-Av, A.; Brodie, C. Mesenchymal stem cells enhance the oncolytic effect of newcastle disease virus in glioma cells and glioma stem cells via the secretion of TRAIL. Stem Cell Res. Ther. 2016, 7, 149. [CrossRef] [PubMed]

177. Redjal, N.; Zhu, Y.; Shah, K. Combination of systemic chemotherapy with local stem cell delivered s-TRAIL in resected brain tumors. Stem Cells 2015, 33, 101–110. [CrossRef] [PubMed]

178. Zhang, B.; Han, H.; Li, D.; Li, Z.R.; Zuo, K.S.; Jiang, Z.B. The inhibitory effect of MSCs expressing TRAIL as a cellular delivery vehicle in combination with cisplatin on hepatocellular carcinoma. Cancer Biol. Ther. 2012, 13, 1175–1184. [CrossRef] [PubMed]

179. Kim, S.M.; Woo, J.S.; Jeong, C.H.; Ryu, C.H.; Jang, J.D.; Jeun, S.S. Potential application of temozolomide in mesenchymal stem cell-based TRAIL gene therapy against malignant glioma. Stem Cells Transl. Med. 2014, 3, 172–182. [CrossRef] [PubMed]

180. Yoon, N.; Park, M.S.; Peltier, G.C.; Lee, R.H. Pre-activated human mesenchymal stromal cells in combination with doxorubicin synergistically enhance tumor-suppressive activity in mice. Cytotherapy 2015, 17, 1332–1341. [CrossRef] [PubMed]

181. Mohr, A.; Yu, R.; Zwacka, R.M. TRAIL-receptor preferences in pancreatic cancer cells revisited: Both TRAIL-R1 and TRAIL-R2 have a licence to kill. BMC Cancer 2015, 15, 494. [CrossRef] [PubMed]

182. Song, N.M.; Jun, S.; Zang, D.Y.; Kim, S.G.; Park, H.R.; Kang, D. Differential susceptibility of gastric cancer cells to TRAIL-induced apoptosis. Oncol. Rep. 2013, 29, 1224–1230. [CrossRef] [PubMed]

183. Mueller, L.P.; Luetzkendorf, J.; Widder, M.; Nerger, K.; Caysa, H.; Mueller, T. TRAIL-transduced multipotent mesenchymal stromal cells (TRAIL-MSC) overcome TRAIL resistance in selected CRC cell lines in vitro and in vivo. Cancer Gene Ther. 2011, 18, 229–239. [CrossRef] [PubMed]
184. Luetzkendorf, J.; Mueller, L.P.; Mueller, T.; Caysa, H.; Nerger, K.; Schmoll, H.J. Growth inhibition of colorectal carcinoma by lentiviral TRAIL-transgenic human mesenchymal stem cells requires their substantial intratumoral presence. *J. Cell. Mol. Med.* 2010, 14, 2292–2304. [CrossRef] [PubMed]

185. Nesterenko, I.; Wanningen, S.; Bagci-Onder, T.; Anderegg, M.; Shah, K. Evaluating the effect of therapeutic stem cells on TRAIL resistant and sensitive medulloblastomas. *PLoS ONE* 2012, 7, e49219. [CrossRef] [PubMed]

186. Stolfi, C.; Pallone, F.; Monteleone, G. Molecular targets of TRAIL-sensitizing agents in colorectal cancer. *Int. J. Mol. Sci.* 2012, 13, 7886–7901. [CrossRef] [PubMed]

187. Loebinger, M.R.; Eddaoudi, A.; Davies, D.; Janes, S.M. Mesenchymal stem cell delivery of TRAIL can eliminate metastatic cancer. *Cancer Res.* 2009, 69, 4134–4142. [CrossRef] [PubMed]

188. Xie, C.; Yang, Z.; Suo, Y.; Chen, Q.; Wei, D.; Weng, X.; Gu, Z.; Wei, X. Systemically infused mesenchymal stem cells show different homing profiles in healthy and tumor mouse models. *Stem Cells Transl. Med.* 2017, 6, 1120–1131. [CrossRef] [PubMed]

© 2018 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).