



Review

Neuropilin (NRPs) Related Pathological Conditions and Their Modulators

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Abstract: Neuropilin 1 (NRP1) represents one of the two homologous neuropilins (NRP, splice variants of neuropilin 2 are the other) found in all vertebrates. It forms a transmembrane glycoprotein distributed in many human body tissues as a (co)receptor for a variety of different ligands. In addition to its physiological role, it is also associated with various pathological conditions. Recently, NRP1 has been discovered as a coreceptor for the SARS-CoV-2 viral entry, along with ACE2, and has thus become one of the COVID-19 research foci. However, in addition to COVID-19, the current review also summarises its other pathological roles and its involvement in clinical diseases like cancer and neuropathic pain. We also discuss the diversity of native NRP ligands and perform a joint analysis. Last but not least, we review the therapeutic roles of NRP1 and introduce a series of NRP1 modulators, which are typical peptidomimetics or other small molecule antagonists, to provide the medicinal chemistry community with a state-of-the-art overview of neuropilin modulator design and NRP1 druggability assessment.

Keywords: neuropilins; computer-aided drug design; in silico drug design; receptor modulator design; peptidomimetics; small-molecule antagonists; cancer; COVID-19; neuropathic pain



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1. Introduction

Neuropilins (NRPs) represent transmembrane glycoprotein receptors important for the proper functioning of diverse biological processes due to their broad tissue distribution. They are mainly involved in neuronal development and axon guidance, angiogenesis [1], immune functions [2], and, consequently, also in the regulation of several pathological processes such as cancer, cardiovascular diseases [3,4], and viral infections [5]. NRPs lack direct signalling capabilities and act as coreceptors associating with other receptors to transduce a signal, primarily through various receptor tyrosine kinases [3]. There are two NRP types, NRP1 and NRP2, that share 44% sequence identity and exhibit a common domain structure. Their extracellular regions consist of 5 domains (Figure 1): a1/a2 domain, b1/b2 domain, and c (MAM) domain. The a and b domains bind particular endogenous ligands that trigger further signalling and provoke specific intracellular effects (Figure 1). In contrast, the MAM domain was initially thought to mediate NRP oligomerisation, but it more likely participates in the positioning of domains for their interactions with partner receptors by shielding them from the membrane [6]. The extracellular region is connected through a transmembrane (TM) domain to the short intracellular PSD-95/Dlg/ZO-1 (PDZ) binding domain, which lacks catalytic activity [1,3]. The mostly identical domain composition of NRP1 and NRP2 facilitates the involvement of both coreceptors in similar biological processes, yet they are still different enough to allow for distinct biological functions [7].

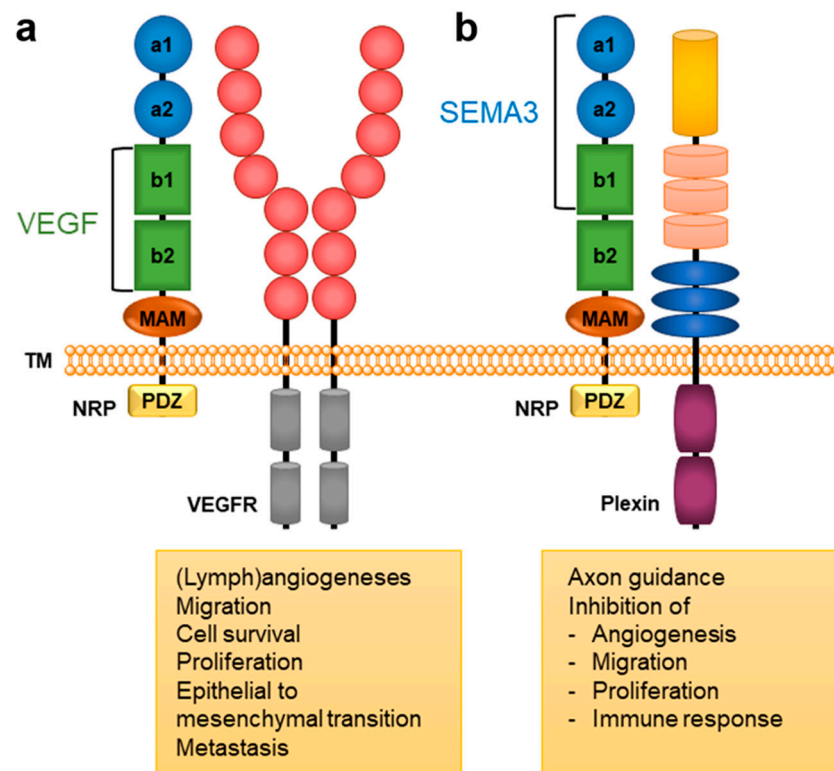


Figure 1. A general structural composition of NRP1 and NRP2 domains and the main NRP-mediated biological responses. The a1/a2 domain, presented in blue circles, is homologous to CUB (for complement C1r/C1s, Uegf, Bmp1); the b1/b2 domain, presented in green squares, is homologous to blood coagulation factor V/VIII domains; and the c domain, presented as an orange ellipse is homologous to meprin, A5, and μ -phosphatase (MAM). The intracellular PDZ domain is represented as a yellow square. Endogenous ligands of the VEGF family bind to the b1/b2 domains, while SEMA3s bind to the a1/a2/b1 domains [1,3]. (a) VEGFs form a complex with NRP and VEGFR that activates signalling pathways involved in angiogenesis associated with cancer [3,8]. (b) SEMA3s form a complex with NRP and plexin to activate signalling pathways that regulate axonal guidance and the immune, respiratory, and cardiovascular system as well as tumour cell responses [3,8,9].

Extracellular domains of NRPs have defined, although not necessarily overlapping, binding sites that can accommodate various endogenous ligands and can interact with diverse receptors. NRPs are well known for their binding of class 3 semaphorins (SEMA3) [10,11] and selected members of the vascular endothelial growth factor (VEGF) family [12] that evoke different biological functions (Table 1). SEMA3s represent signalling proteins of a large and diverse semaphorins family, containing SEMA3A-3G subgroups that are involved not only in the guidance of axons and neural development [13] but also play important roles in immune, respiratory, and cardiovascular systems, as well as in pathological disorders, especially in tumour vasculature [3,8]. They bind with their C-terminal region to the a1/a2 and b1 domains of NRP [3], and since their binding is not sufficient for signal transduction, NRPs need to associate with the SEMA3 main receptor Plexin to form SEMA3-NRP-Plexin complex and to transduce the signal [14–17]. The members of the SEMA3 class exhibit different preferences for binding to NRP1 and NRP2 (Table 1), which results in various, more specific biological functions.

Table 1. The main groups and subgroups of the most important endogenous ligands binding to both NRP receptors. x indicates binding to both NRPs.

Endogenous Ligand	Preferences for NRP Binding		Reference
	NRP1	NRP2	
SEMA	SEMA3A SEMA3B SEMA3C SEMA3D SEMA3F	SEMA3B SEMA3C SEMA3D SEMA3F SEMA3G	[2,9]
VEGF	VEGF-A VEGF-A165 VEGF-A189 VEGF-B VEGF-C VEGF-D VEGF-E PIGF	VEGF-A VEGF-A145 VEGF-A165 VEGF-C VEGF-D PIGF	[3,9]
FGF	FGF-1 FGF-2 FGF-4 FGF-7	FGF-2	[18]
HGF	x	x	[19]
PDGF	PDGF-BB PDGF-C PDGF-D	PDGF-BB	[3,20]
TGF- β	TGF- β 1	TGF- β 1	[21,22]
miRNAs	x	x	[2,23]

Vascular endothelial growth factor (VEGF) represents a family of signalling proteins involved in the development of blood vessels, including pathological angiogenesis as in cancer, vascular branching, and maturation, along with cardiovascular development [3,24]. The VEGF family consists of growth factors VEGF-A-D, as well as placenta growth factor (PIGF), parapoxvirus VEGF-E, and snake venom VEGF-F [25]. They primarily stimulate cellular responses by binding to their VEGF receptors (VEGFR). However, the binding of a VEGF to a coreceptor NRP forms a VEGF-NRP-VEGFR complex that results in enhanced VEGF signalling [24]. VEGFs bind to the b1/b2 domains of the NRP receptor, with the b1 domain being essential for the binding, while the b2 domain is required to ensure optimal binding [1]. The binding of VEGF ligands to b1 proceeds through the VEGF C-terminus sequence, containing a [R/K]XX[R/K] motif, called the C-end rule (CendR) [26]. Although the SEMA3 ligands also bind to the b1 domain, their binding site differs from one of the VEGF ligands [1]. As for SEMA3, there exists a distinct preference between NRP1 and NRP2 for different VEGF ligands (Table 1), which then perform specific endogenous tasks.

NRPs have also been identified as binding partners of other growth factors (Table 1), which demonstrates their versatility in regulating various signalling pathways. Thereby, NRPs can interact with the Fibroblast Growth Factor (FGF), the Hepatocyte Growth Factor (HGF), the Platelet-Derived Growth Factor (PDGF), the Transforming Growth Factor beta (TGF- β), and their respective receptors [3,9,21]. Moreover, NRPs have been reported to act as a receptor for extracellular microRNAs (miRNAs), which facilitates their internalisation into cells resulting in several physiological and pathological conditions. Thus, miRNAs have been associated with tumour progression, epithelial to mesenchymal transformation, metastasis and disease prognosis [2].

NRPs play an essential role in angiogenesis and lymphogenesis in endothelial cells through the binding of VEGF family members. The main pathway by which NRPs promote

angiogenesis is through the formation of the NRP/VEGF/VEGFR complex, in which NRPs act as co-receptors with VEGFRs and enhance VEGF-induced activation of intracellular signaling pathways that consequently influence cell adhesion, migration, and permeability during angiogenesis under both physiological and pathological conditions [27–29]. NRP1 is mainly expressed in vascular endothelial tissue, whereas NRP2 is mainly expressed in lymphoid epithelium [30]. Although VEGF and its receptor, VEGFR govern angiogenesis, some studies have provided evidence that NRP1 and NRP2 can also promote blood vessel growth through alternative pathways [31,32].

Class 3 of NRPs endogenous ligands semaphorins also play an important role in vascular development, mainly by inhibiting angiogenesis. The semaphorins SEMA3A, SEMA3B, SEMA3D, SEMA3E, and SEMA3F interfere with VEGF-induced angiogenesis to promote their antiangiogenic effects [33].

Due to NRPs interacting with a broad range of endogenous ligands and triggering diverse physiological as well as pathological mechanisms, the modulation of their endogenous ligand binding exhibits a high potential for drug development. Therefore, small peptide ligands mimicking endogenous ligands have already been developed. Unfortunately, they lack metabolic stability and display a low bioavailability [24]. Moreover, the inhibition with monoclonal antibodies was also pursued, but significant side effects were observed [34]. Consequently, peptidomimetics, as well as small molecules, are gaining particular interest. Despite their limited size, they can interfere with the endogenous ligands binding to NRPs and have been reported to inhibit their signalling and biological functions [24]. Therefore, this article focuses on the latest findings on NRPs' role in multiple diseases and attempts to review the NRP small molecule antagonists that could be used as successful therapeutic agents for the associated diseases.

2. NRP Binding of Endogenous Ligands

Despite NRP2 being an equivalently important target as NRP1, the latter has been more studied and better characterised. Although NRPs bind a large set of diverse endogenous ligands, little is known about the details of individual ligand interactions with its binding domain on the NRP receptor. The most studied and explored is the binding of VEGF-A165 to the b1 domain of NRP1, which serves as a basis for developing NRP small molecule antagonists (Figure 2). Due to the high structural similarity of both receptors, some of the NRP1 antagonists are able to extend their inhibitory activity on the NRP2-related biological signalling and functions. VEGF-A165 binds to the b1 domain of NRP1 with the C-terminal CendR motif, which has a terminal arginine residue. CendR facilitates the binding into a highly conserved b1 arginine binding pocket, consisting of amino acid residues Tyr297, Trp301, Thr316, Asp320, Ser346, Thr349, Tyr353 and Trp411 that were all recognised in a mutational analysis as crucial for a high VEGF-A165 affinity. The guanidine group forms a salt bridge with Asp320, and the free carboxylate interacts through hydrogen bonds with Ser346, Thr349, and Tyr353. Tyr297 and Tyr353 also participate in cation- π interactions with the CendR arginine side chains (Figure 2) [35]. In an additional exploration of the binding site region with synthetic ligands mimicking the terminal arginine, a hydration profile was analysed, thus revealing a conserved water molecule identified as important for increasing the ligand affinity by forming a hydrogen bond network between Trp301, Glu348, and the ligands [36].

The fact that the protein ligands binding to the b1 domain of NRP1 share a common C-terminal arginine motif is also evident from the recently solved crystal structure of SARS-CoV-2 CendR bound to NRP-1 [37]. The comparison of VEGF-A165 and SARS-CoV-2 CendR revealed almost identical binding modes, which share the interactions with the same key amino acid residues Tyr297, Trp301, Thr316, Asp320, Ser346, Thr349 and Tyr353 as depicted in Figure 2b. These residues seem to contribute to the binding affinity of all CendR-containing ligands; therefore, an interruption of interactions with these residues is deemed an attractive therapeutic approach.

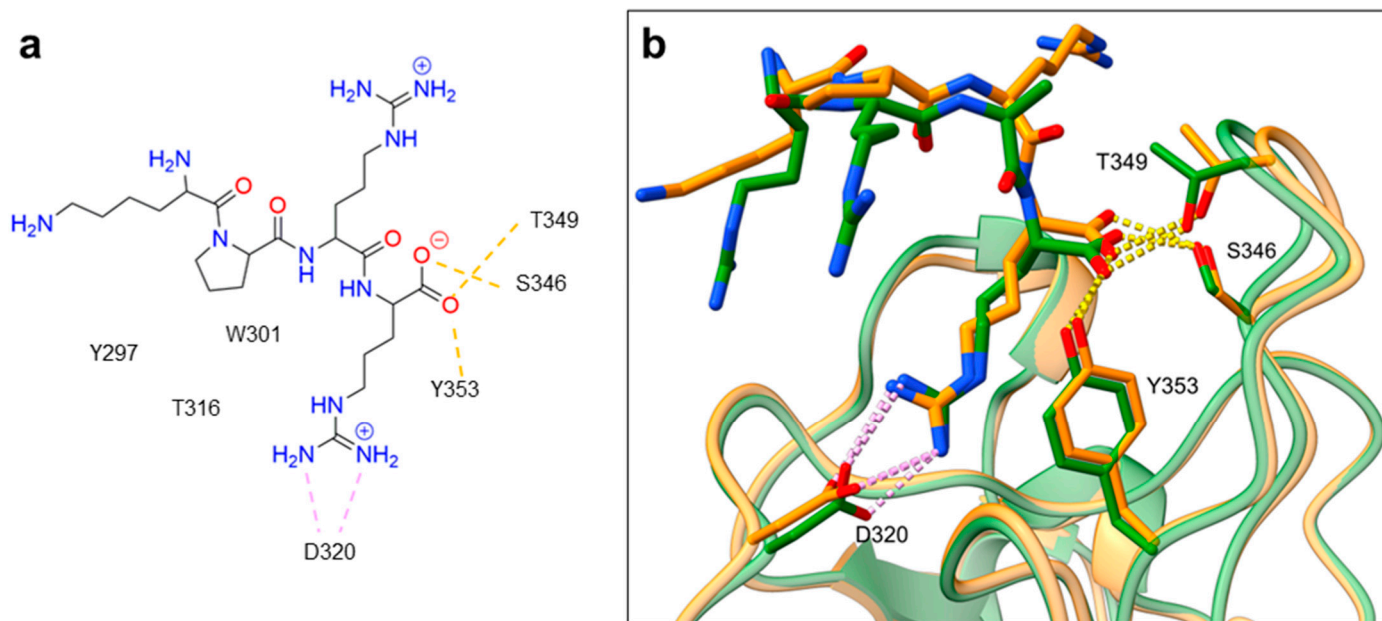


Figure 2. (a) A 2D representation of the VEGF-A165 CendR (KPRR) motif. Hydrogen bonding and salt bridge interactions, crucial for the high affinity of the VEGF-A165 terminal arginine with its NRP1 binding pocket, are depicted as yellow and light pink dots, respectively. (b) Superposition of NRP1 crystal structure complexes with VEGF-A165 (PDB ID: 4DEQ) [38] and SARS-CoV-2 (PDB ID: 7JJC) [37] CendR terminal residues bound into the NRP1 arginine binding pocket, yielding the comparison of the ligand-binding modes. VEGF-A165-NRP-1 complex is presented in orange cartoon and SARS-CoV-2 CendR-NRP-1 complex in green cartoon. NRP1 amino acid residues, significant for forming hydrogen bonds with the terminal arginine, are depicted as sticks of corresponding colours. Hydrogen bonding and salt bridge interactions are shown as yellow and light pink dots, respectively.

3. Neuropilin-Related Pathology

3.1. Pain

Endogenous VEGF family ligands have been found instrumental in the pathophysiology of chronic pain in several diseases, including cancer, neuropathic pain, osteoarthritis, rheumatoid arthritis, migraine, and diabetic complications. Although mainly involved in the development and maintenance of pain, the best-studied VEGF-A165 shows not only pro- but also anti-nociceptive effects leading to analgesia [39,40]. These effects are due to the binding of different VEGF-A165 isoforms to their VEGFR receptors. The VEGF-A165a isoform is pronociceptive and leads to pain, while VEGF-A165b is considered anti-nociceptive, and the ratio between the two isoforms represents the key factor determining the effect on sensory neurons and pain levels [40,41]. VEGF-A binds to VEGFR and the coreceptor NRP1, which associates NRP1 with pain. While VEGF-A165a binds to VEGFR and NRP1 receptors, VEGF-A165b does not contain a CendR motif and, therefore, cannot bind to the NRP1 b1 domain [39,40]. Consequently, it appears that NRP1 is only involved in the activation of the pain pathway, making the VEGF-A165a/NRP1 complex an interesting target for reducing chronic pain.

3.2. Viral Entry

NRP receptors have been found to contribute to the infectivity of many viruses by enhancing their host cell entry (Table 2). This mainly involves viruses that contain the CendR motif, through which they bind to the b1 domain of the NRP1 receptor and this promotes the host cell infection. Among them, Epstein–Barr (EBV) [42] and Human T-cell lymphotropic virus type 1 (HTLV-1) [43,44] represent the best-studied ones. Recently, it was identified that the SARS-CoV-2 virus, the causative agent of the latest COVID-19 pandemic,

also contains the CendR motif, which proposed NRP1 as its additional entry point into human cells [37,45].

Table 2. NRP involvement in the entry and/or infectivity of viruses.

Virus	NRP1	NRP2	Reference
HTLV-1	x		[43,45]
EBV	x		[42]
SARS-CoV-2	x		[37,45]
MCMV	x		[46]
EVA71	x		[47]
LUJV		x	[48]
HCMV		x	[49]

Human T-cell lymphotropic virus type 1 (HTLV-1) represents the main cause of T-cell lymphoma and leukaemia. Cell-to-cell contact forms the major route of HTLV-1 infection, with NRP1 being essential for the viral entry. NRP1 is highly expressed in dendritic, T-cells, and endothelial cells, which represent the main targets of the HTLV-1 infection [43]. HTLV-1 enters host cells via a three-step process. First, the viral surface unit attaches to the heparin/heparan sulfate proteoglycan (HSPG) on the host cell surface. Then the HSPG/virus surface complex interacts with the b1 domain of NRP1, which triggers conformational changes of the viral surface that enable its interaction with glucose transporter GLUT-1, yielding HTLV-1 fusion and cell entry [50].

Epstein–Barr virus (EBV) represents human herpesvirus 4 (HVV4) implicated in malignancies of lymphoid or epithelial origin. Glycoprotein B (gB) in the virus envelope forms a critical factor for the infection of B and epithelial cells, whereby NRP1 was demonstrated as the main attachment point of gB, facilitating viral entry and the infection of nasopharyngeal epithelial cells, while its connection to B cells remains unknown. Upon EBV binding to nasopharyngeal epithelial cells, furin cleaves gB, exposing a CendR motif that binds to NRP1 and promotes viral fusion and internalisation into host cells. Moreover, the binding of EBV to NRP1 also activates receptor tyrosine kinase (RTK) signalling, which consequently promotes EBV infection of nasopharyngeal epithelial cells, but the detailed mechanism remains unknown [42]. With both viruses being highly involved in carcinogenic processes, it is assumed that they compete with endogenous VEGF ligands for the binding to NRP1 and might trigger cell signalling to promote the formation of tumour vessels in cancer tissues [51,52].

COVID-19 is primarily a disease of the respiratory system causing mild to severe respiratory symptoms, although expression in the central nervous system (CNS) has also been observed, implicating neurologic manifestations [53]. The entry of SARS-CoV-2 into host cells is mainly mediated by the cellular receptor angiotensin-converting enzyme 2 (ACE2) [54,55]. However, due to relatively low levels of ACE2 in pulmonary tissues, NRP1 was identified as an important partner for interacting with the virus and facilitating its entry [37,45]. To infect human cells, the SARS-CoV-2 spike protein is cleaved by the host furin protease at the S1/S2 junction [56], exposing a CendR motif, which binds to the b1 region of NRP1 [26] and provides viral fusion. Higher expression of NRP1 potentiates the infectivity with SARS-CoV-2 due to an increased viral entry rather than an enhanced binding [30]. NRP1 was also identified as a specific surface marker for T cells and is constitutively expressed on the surface of CD4 and CD25 cells and its expression is modulated depending the cell activation [57]. Furthermore, it was demonstrated that NRP1, is expressed at high levels on T regulatory cells and can be used to separate nT reg versus iT reg cells in certain physiological settings [58]. Namely, function of regulatory T cells is maintained by NRP1—semaphorin pathway where T cell function and survival is potentiated at inflammatory sites where is especially important to limit anti-tumour immune responses [59,60]. As the regulatory T cells have a crucial role in the immune system by preventing autoimmunity, and maintaining immune homeostasis, their possible

role and that of the surface NRP1 receptor in SARS-CoV-2 infection have been discussed [61]. Since COVID-19 represents a worldwide pandemic, there have been numerous reports of infected individuals that did not develop COVID-19 symptoms [62,63]. In some cases, the viral load of asymptomatic individuals has been equal to that of symptomatic individuals, hinting that the virus might interfere with neuropathic pain signalling pathways. It was found that the spike protein of SARS-CoV-2 competes with VEGF-A for the binding to NRP1 and inhibits VEGF-A signalling. This results in analgesia in asymptomatic COVID patients and might help spread the disease [64].

Some of the recent studies found that NRP1 may serve as an entry point also for other viruses, including β -herpesvirus murine cytomegalovirus (MCMV) [46] and Enterovirus 71 (EVA71) [47]. Further investigations are needed to elucidate its exact role and mechanism. Apart from NRP1, its homologous form NRP2 was found to contribute to the infection by certain viruses as well, namely, Lujo virus (LUJV) [48] and human cytomegalovirus (HCMV) [49] which use NRP2 as their viral entry point. NRPs could, therefore, form promising therapeutic targets for preventing viral infections and related diseases.

3.3. Cardiovascular Diseases

NRPs are involved in angiogenesis and cardiovascular diseases. On one hand, the knockout of NRP1 from cardiomyocytes and vascular smooth muscle cells causes cardiomyopathy, aggravated ischemia-induced heart failure, and hereditary haemorrhagic telangiectasia arteriovenous malformations, thus revealing its cardioprotective role [65,66]. On the other hand, NRP1 mediates the activation of human cardiac fibroblasts [67]. NRPs significantly contribute towards cardiovascular disease and the latter represent a serious comorbidity in COVID-19 patients [68–72].

3.4. Diabetes

The role of NRP in diabetes pathology was reviewed in 2002 by Mamluk et al. [73]. Especially after the outbreak of COVID-19 disease, NRP has been studied in more detail as a viral co-receptor and via involvement in co-morbidity [69]. Its involvement can be observed in diabetic nephropathy and the presence of NRP1 inhibitor proof-of-concept peptide compounds is of great interest [74,75]. However, the association between NRP1 and SARS-CoV-2 infection can be summarized in two of the most described scenarios [76,77].

Patients with diabetic nephropathy represent a group at higher risk for COVID-19 disease severity. NRP1 is found in the kidney, particularly in podocyte cells, where it is important for proper podocyte function, such as adhesion to extracellular matrix proteins, cytoskeletal reorganisation, and apoptosis. Its role is therefore important in diabetic nephropathy, in which it has been demonstrated that suppression of NRP1 expression may be responsible for podocyte damage and loss, leading to deterioration of renal function. It is speculated that the high expression of NRP1 in the kidney of diabetic patients facilitates the invasion of SARS-CoV-2 into this tissue, while the interaction of both processes leads to depletion of NRP1, which then exacerbates the pathogenesis of diabetic nephropathy. However, further research is needed to refine the current understanding of the potential role of NRP1 in diabetic nephropathy, particularly in conjunction with COVID-19 [78,79].

It was discovered that insulin-producing pancreatic β -cells express ACE2 and TMPRSS2 at low levels, whereas NRP1 expression is high in patients with COVID-19 [80,81]. Infection of pancreatic β cells with SARS-CoV-2 attenuates pancreatic insulin levels and secretion and induces β cell apoptosis, which was partially reduced by NRP1 inhibition. Therefore, it could be speculated that NRP1 supports viral infection in patients with type II diabetes [81].

3.5. Cancer

Cancer remains the second most common cause of death worldwide, responsible for almost 10 million deaths in 2020 alone [82]. While cancer, in most cases, takes years to develop into a life-threatening disease, it is usually discovered only after it has metastasised

to other organs. Therefore, the metastatic potential of cancer cells remains one of the main prognostic factors for the overall survival of cancer patients. Over the last 5 years, more than 100 studies linking NRPs to various cancer types, mainly leukaemia, breast cancer, colon and colorectal cancer, lung, and liver cancer, have been published. NRP1 overexpression in cancer cells has been associated with tumour aggressiveness, enhanced cell proliferation, and metastasis. The literature on this topic is collected in Table 3 for the reader's benefit.

Moreover, the other member of the neuropilin family, NRP2, also contributes to the cancer progression. For example, it was shown that NRP2 is expressed during macrophage differentiation, promotes efferocytosis, facilitates tumour growth [83] and promotes mobilisation [84]. In contrast, its deletion downregulates tumour-promoting genes, increases secondary necrosis within tumours and impairs apoptosis [83]. NRP2, but not NRP1, is expressed in cytokine-induced killer cells, which are responsible for the controlled apoptosis [85] of precancerous cells.

Table 3. Scientific literature collection on NRP1 and NRP2 involvement in different cancer types.

Cancer Type	NRP1	NRP2	Reference
Leukaemia	x		[86–91]
Breast cancer	x	x	[92–102]
Carcinoma	x	x	[103–116]
Colon & Colorectal cancer	x	x	[117–126]
Gastric cancer	x		[127–138]
Lung cancer	x	x	[139–149]
Pancreatic cancer	x		[150–154]
Prostate cancer	x	x	[155–157]
Melanoma	x	x	[158–161]
Glioma	x		[162–168]
Liver cancer	x		[169]
Mammary stem cells cancer	x		[170,171]
Esophageal cancer	x		[172,173]
Stem cell cancer	x		[174,175]
Thyroid cancer		x	[176,177]
Multiple myeloma	x		[51]
Lymphoma	x		[178]
Bladder cancer		x	[179,180]
Tongue cancer		x	[181]
Cervical cancer	x		[182,183]
Gallbladder cancer	x		[184]
Endometrium cancer	x	x	[185,186]

4. Neuropilin-1 Modulators

While peptide antagonists and monoclonal antibodies have failed to fulfil expectations [34], several NRP1 peptidomimetic as well as small molecule antagonists have been developed and were able to successfully inhibit the VEGF signalling. Interestingly, some of them (especially the small molecules) lack terminal arginine but were still able to achieve the desired effect. Therefore, peptidomimetic and nonpeptide small molecule drugs may represent an elegant and promising approach toward developing NRP1 antagonists. This review summarises the latest drug discovery findings accordingly.

4.1. Peptidomimetics

Peptidomimetic antagonists have been developed prior to peptide compounds to provide higher stability and drug-like properties (Table 4). The anticancer therapeutic strategy represents the largest part of NRP1 drug discovery efforts, aiming to prevent the VEGF binding and restrict the intracellular signalling. To that end, the peptidomimetic antagonists reported in the scientific literature were all developed for anticancer treatment and are imitating the CendR motif of VEGF ligands. The first NRP1 peptidomimetic, named EG00229

(compound **1** in Table 4), was based on mimicking the minimal peptide KPAR sequence of VEGF-A165 that could retain its activity on NRP1. The C-terminal arginine, which is supposedly crucial for this activity, was fully conserved and was connected through sulfonyl amino thiophene to benzothiadiazole heteroaryl, mimicking the lysine of KPAR. EG00229 inhibited the binding of VEGF-A to NRP1 with $IC_{50} = 3 \mu M$ and was able to inhibit the VEGF-A mediated biological function partially [35]. Moreover, EG00229 was able to suppress glioma progression in mice [187]. The crystal structure of the EG00229-NRP1 complex confirmed its binding mode as similar to VEGF-A (Figure 2) with an identical C-terminal arginine position (Table 4). Furthermore, the complex revealed an intramolecular hydrogen bond between amide NH and sulfonamide nitrogen that provides the stability of the ligand conformation and is believed to be the reason for the overall biological activity [35]. Aiming to improve the H-bonding network, the benzothiadiazole heteroaryl moiety of EG00229 was replaced with methylaminoaryl-substituted dihydrobenzofuran, providing the compound EG01377 (compound **2** in Table 4) with an improved inhibition of VEGF-A binding to NRP1 with $IC_{50} = 0.6 \mu M$. Crystallographic studies revealed two crystal complexes in higher and lower resolutions, which differ in the binding conformation of the bulky aromatic moiety. The lower resolution structure was considered more correct and is presented in Table 4, whereby the amine of methylaminoary forms an H-bond with Glu348. Importantly, the compound exhibited good in vitro anti-angiogenic, anti-migratory and antitumour effects and, therefore, yields a high potential for further in vivo studies [188]. In a recent in silico study, the binding mechanism of EG00229, EG01377 and SARS-CoV-2 CendR was investigated, indicating that EG01377 indeed provides the strongest binding with the NRP1 b1 domain among all three studied ligands, and identified D320 as the key binding residue [188].

The idea of replacing the amino-acid residue of peptide antagonists with sugar-based fragments has emerged from yet another research group. Their peptidomimetics were prepared based on the ATWLPPR heptapeptide, an effective antagonist of the VEGF binding to NRP1 [189,190]. A rigid trioxabicyclo system mimics the LPP sequence linked with arginine-like functionalities to provide the required C-terminal, while tryptophane/threonine-like functionalities were introduced on the other end. The best binding compound **3** (Table 4) with $IC_{50} = 92 \mu M$ did not provide the desired efficiency [191]; therefore, further optimisations were made on both residue-mimicking ends, exploring different structural motifs, varying their lengths and spatial orientations. These modifications led to the discovery of compound **4** (Table 4) with an improved inhibition of the VEGF-A binding to NRP1 with $IC_{50} = 39 \mu M$ [192].

Table 4. Peptidomimetic NRP1 antagonists.

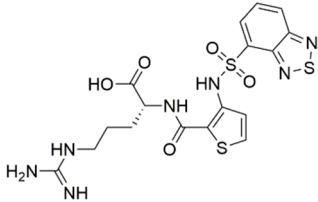
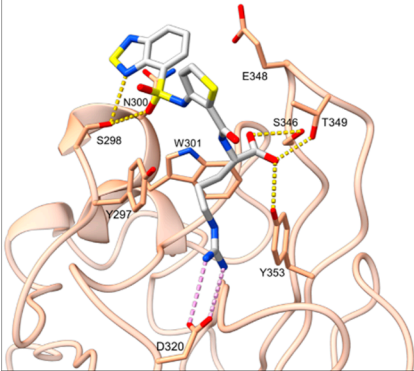
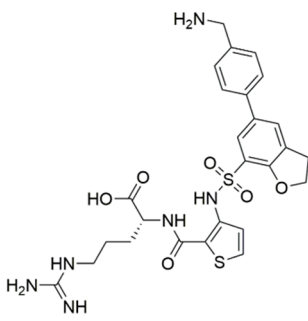
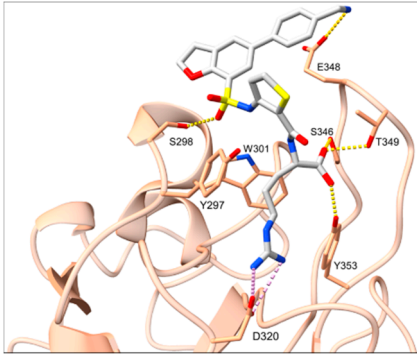
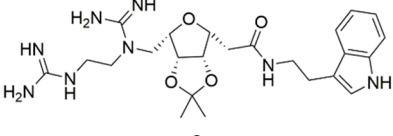
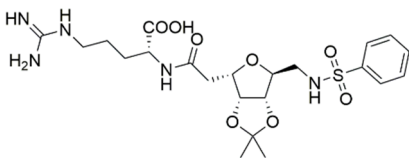
Compound	Binding Mode	Inhibition of VEGF-A Binding [μM]	Ref.
Cancer			
 <p>1 (EG00229)</p>	 <p>[a]</p>	$IC_{50} = 3$	[35]

Table 4. Cont.

Compound	Binding Mode	Inhibition of VEGF-A Binding [μM]	Ref.
Cancer			
 2 (EG01337)	 [b]	IC ₅₀ = 0.6	[188]
 3	NA	IC ₅₀ = 92	[191]
 4	NA	IC ₅₀ = 39	[192]

[a] The crystal structure of EG00229-NRP1 complex (PDB ID: 3I97) [28]. [b] The crystal structure of EG01337-NRP1 complex (PDB ID: 6FMF) [160]. NRP-1 is depicted in orange cartoon representation, while ligand is in grey stick representation. NRP1 key amino acid residues involved in interactions with the ligand are shown as sticks in orange colour. Hydrogen bonding and salt bridge interactions are presented as yellow and light pink dots, respectively.

4.2. Small-Molecule Antagonists

The development of small molecule NRP antagonists is known to be challenging due to a large and flat protein-protein binding interface. Still, some fully non-peptidic small-molecule NRP1 antagonists have been successfully developed and exhibited potency in inhibiting the NRP1 mediated biological functions. The main focus of small molecule development was primarily on achieving anticancer activity. Nowadays, the knowledge of NRPs' involvement in several diseases has expanded the development and studying of antagonists to new areas to provide novel therapeutic agents. Accordingly, the current focus is directed toward searching for the desired and necessary small-molecule medicines for the treatment of SARS-CoV-2 infections. The important small molecule antagonists are collected in Table 5.

In 2014, the first fully non-peptidic VEGF-NRP antagonist was identified in a virtual screening procedure. This hit compound **5** (Table 5), named NRPa-47, showed anti-angiogenic and antitumour effects in in vitro and in vivo assays and inhibited both NRP1 and NRP2, with selectivity over proangiogenic receptors. According to molecular modelling studies, its benzimidazole fragment was predicted to replace the C-terminal arginine of VEGF-A and peptide/peptidomimetic antagonists. Thus, this compound represents an auspicious starting point for the further development of cancer treatment medicine [193]. Pursuing ambitious research and development of NRP small molecule antagonists, the same research group identified yet another set of compounds with a common original molecular scaffold, whereby compound NRPa-308 (compound **6** in Table 5) emerged as

the most promising new hit. NRPa-308, which structurally differs from NRPa-47, demonstrated remarkable anti-angiogenic and anti-proliferative effects *in vitro*. It was able to highly reduce (by more than 60%) the tumour growth of human breast cancer cell lines MDA-MB-231 and BT549 [194,195]. The binding mode elucidated by molecular docking calculations suggested that NRPa-308 forms H-bonds with Glu348 and Trp301 while its aromatic ring inserted deeply in the NRP1 arginine binding pocket is stacked between Tyr297 and Tyr353 displaying potential hydrophobic and/or aromatic interactions (Table 5). Interestingly, the salt-bridge interaction with Asp320 was not identified as a crucial element for the binding of antagonists [194]. Altogether, NRPa-308 represents one of the most promising anticancer compounds targeting NRP1.

In the same year, another research group discovered several antagonists that can inhibit VEGF-A binding to NRP1 in *in vitro* assays. These antagonists share a common chlorobenzoyloxy alkyloxy halogenobenzyl amine scaffold (compound 7 in Table 5). According to molecular docking calculations, the scaffold is involved in common interactions such as H-bonds of the NH group with the OH group of Thr316, two-cycle substituted oxygen atoms with the NH group of Trp301 and carboxylic group of Glu348. Stacking interactions were observed with Trp301 and hydrophobic with Tyr353. Again, the salt bridge with Asp320 was not observed among the compounds exerting antagonistic effects and sharing a common scaffold; therefore, it seems this interaction should not be crucial for containing a proper anticancer activity [196].

Yet another series of non-peptidic small-molecule NRP1 antagonists emerged from a structure-based virtual screening, whereby compound 8 in Table 5 exhibited the strongest activity with IC_{50} of 19.1 μ M. Interesting about this compound is its binding mode, which was elucidated by molecular dynamics simulations, and revealed the stacking of both aromatic rings with three stable π - π interactions formed with Tyr297, Trp301 and Tyr353 (Table 5). The aromatic rings achieve a much higher occupancy of the arginine binding pocket compared to arginine-based fragments. Such a binding mode is most likely responsible for the observed inhibitory activity [197].

Since it was discovered that VEGF-A/NRP1 signalling is also involved in neuropathic pain behaviour, it became an interesting novel target for the analgesic treatment. With the intention to find small molecule inhibitors that could interfere with the VEGF-A/NRP1 neuropathic pain signalling, a virtual screening protocol was developed, yielding several compounds with potential analgesic effects (compounds 9 and 10 in Table 5) [64]. As the newest discoveries emphasised the involvement of NRP1 also in SARS-CoV-2 infections [37,45], the hit compounds were further assayed for the SARS-CoV-2 spike-dependent antiviral activity. Compounds 10 and 11 (Table 5) displayed more than 50% inhibition of the viral activity, which represents the first step toward the development of small molecules with the potential of inhibiting the SARS-CoV-2 viral entry. The research group also proposed a pharmacophore model, which should maximise the binding pocket occupancy and contacts to facilitate the further design of NRP1 small molecule antagonists [40]. This research is among the first to consider the effect of hit compounds on multiple diseases, which represents a vital step toward developing small-molecule inhibitors of the VEGF-A/NRP1 signalling for the treatment of neuropathic pain, cancer, and potentially also of SARS-CoV-2 infections.

In an accelerated search for small molecule drugs active against SARS-CoV-2 infections, fast and less costly *in silico* studies have disclosed a promising starting material for further development. In addition to new chemicals, natural and FDA-approved drugs were also investigated against NRP1 from the Egyptian sequence in a molecular docking study, which revealed that Hesperidine, Ravidasvir, Daclatasvir, Remdesivir, and Sofosbuvir presumably form favourable interactions with NRP1 accompanied by the lowest binding energy. This has raised the potential for drug-like natural products and existing drugs as future NRP1 inhibitors [198]. Another study emerged by screening the accessible library of drug-like small molecules and calculating their binding free energy, which in the end gave 10 compounds with a presumably more specific and stronger binding compared to the known NRP1 inhibitors EG00229 and EG01377 [199]. In the latest *in silico* study molecular

compounds previously investigated in COVID-19 related studies were screened against NRP1 to obtain that Nafamostat, Y96, Selinexor, Ebastine and UGS may emerge as good candidates for preventing the binding of spike to NRP1 [200]. A growing interest and related research results point toward the opportunity to develop efficient and selective drugs against pathologies involving the NRP1 signalling.

Recently, our research group identified two additional compounds, **12** and **13** (Table 5), in a spike-NRP1 binding assay that exhibited a stronger inhibition of the spike CendR binding to NRP1 than the well-known NRP1 antagonist EG00229 (**1**). Both compounds were able to inhibit more than 60% of the spike binding, while EG00229 inhibited only 50% of binding, suggesting that these compounds represent a good starting point for the development of small molecule SARS-CoV-2 antagonists. The binding mode of both compounds within the CendR binding pocket of NRP1 was predicted by molecular docking, which revealed that both compounds presumably form strong hydrogen-bonding and salt bridge interactions with key amino-acid residues Asp320, Ser346, Thr349, and Tyr353, as shown in Table 5. According to the predicted binding modes, the binding pocket is not fully occupied, leaving room for a further optimisation of compounds that could enhance the binding and potentially lead to stronger antagonistic effects [201].

Table 5. Small-molecule NRP1 antagonists.

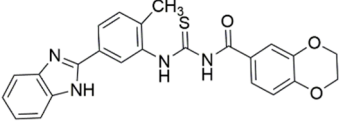
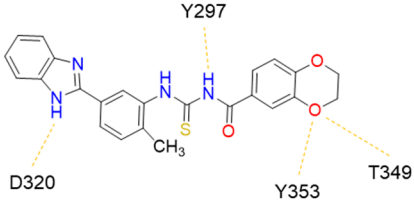
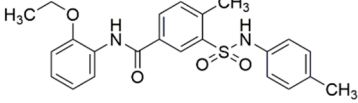
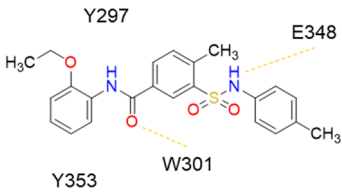
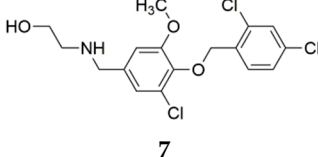
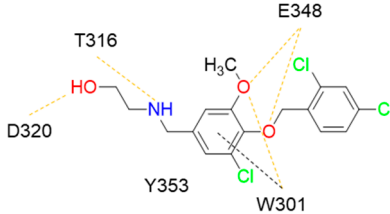
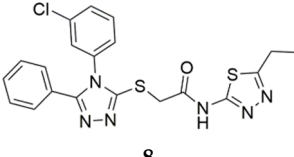
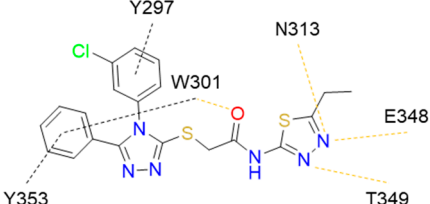
Compound	Binding Mode Prediction	Inhibition of VEGF-A Binding [μM]	Ref.
Cancer			
 5 (NRPa-47)		IC ₅₀ = 34	[193]
 6 (NRPa-308)		32% [a]	[194]
 7		Ki = 7.3	[196]
 8		IC ₅₀ = 19.1	[197]

Table 5. Cont.

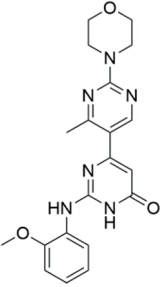
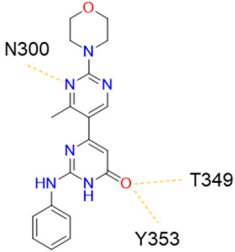
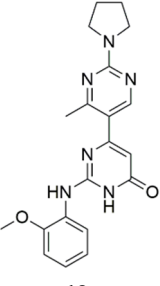
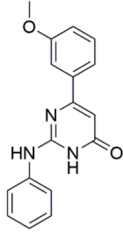
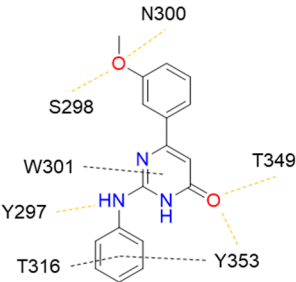
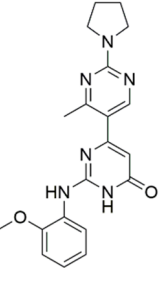
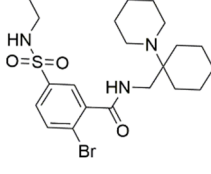
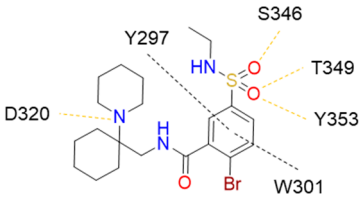
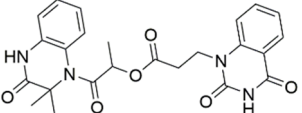
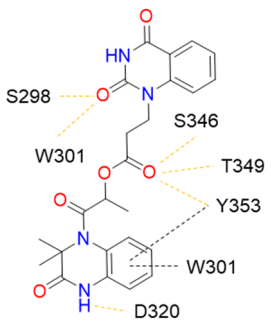
Compound	Binding Mode Prediction	Inhibition of VEGF-A Binding [μM]	Ref.
Neuropathic pain			
 <p>9</p>		$\text{IC}_{50} = 0.000598$	[40]
 <p>10</p>	NA	$\text{IC}_{50} = 0.00314$	[40]
COVID-19		SARS-CoV-2 inhibition [%]	
 <p>11</p>		>50 ^[b]	[40]
 <p>10</p>	NA	>50 ^[b]	[40]
 <p>12</p>		61.44 ± 2.48 ^[c]	[200]

Table 5. Cont.

Compound	Binding Mode Prediction	Inhibition of VEGF-A Binding [μM]	Ref.
 13		63.58 ± 1.27 ^[c]	[200]

^[a] VEGF-A165/NRP-1 binding inhibition at 10 μM compound concentration. ^[b] SARS-CoV-2 entry inhibition at 25 μM compound concentration. ^[c] SARS-CoV-2 spike S1 binding inhibition to NRP1 at 100 μM compound concentration. Hydrogen bonding and π - π stacking interactions are presented as yellow and black dots, respectively.

Regarding semaphorins, attempts have been made to interfere with the SEMA3/NRP binding. Natural compounds xanthofulvin and vinaxanthone (Figure 3) [201] were identified as SEMA3A inhibitors, whereby xanthofulvin displayed diminished binding of SEMA3A to NRP1, suggesting a direct interference of the receptor-ligand association [202]. There are no reports on other small molecules targeting the SEMA3/NRP interaction.

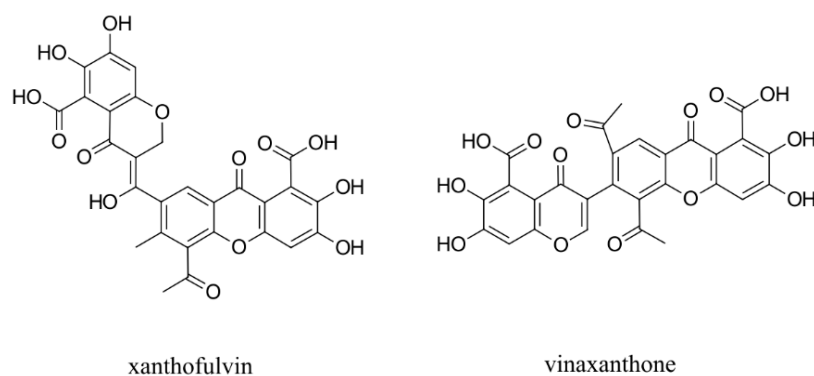


Figure 3. Natural compound SEMA3A inhibitors.

5. NRP2 Antagonists

Despite the long research and development of NRP1 antagonists, none of the peptidomimetic or the small-molecule antagonists has advanced to clinical studies yet. Although all discovery efforts are focused on NRP1, and no specific NRP2 antagonists are known, there are indications that antagonists targeting NRP2 exclusively are needed. Recently, some attempts were made toward the development of selective NRP2 benzamide-based antagonists of VEGF-C that exhibited a modest NRP2 potency and provided the basis for further development of NRP2 small molecule antagonists targeting related pathological functions [203].

6. Conclusions

In this article, we reviewed the physiological role of NRPs and their association with various pathological conditions. In addition to the discovery of NRP1 as a SARS-CoV-2 entry coreceptor along with ACE2, we have assembled the pathological roles of NRPs and their involvement in clinical diseases, particularly highlighting the participation of NRPs in cancer. NRPs, therefore, represent mature and viable therapeutic targets. Structurally, neuropilin-1 and 2 contain several conserved motifs and domains suitable for

a structure-based medicinal chemistry elaboration. In addition, NRPs possess an abundance of endogenous ligands such as SEMA, VEGF, FGF, HGF, PDGF, TGF- β , and miRNAs that facilitate viable ligand-based design approaches and mode of action studies (MOA). The latter is evident from the chemical space of the most successful NRP1 modulators (and chemical probes), which are typically peptidomimetics. However, a handful of other NRP1 small-molecule antagonists have also been reported leaving ample room for future developments. In case the inclined reader would like to learn more about specific NRP-related pathologies, we have compiled the most relevant literature reports in Table 1. For medicinal chemistry, we have provided the most important peptidomimetic and small molecule antagonist structures along with their key receptor interactions in Tables 4 and 5.

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Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

ACE2, Angiotensin-converting enzyme 2; CendR, C-end rule; CNS, Central nervous system; COVID-19, Coronavirus disease 2019; CUB, C1r/C1s, Uegs, Bmp1, DN; Ddiabetic nephropathy; EBV, Epstein-Barr virus; EVA71, Enterovirus 71; FDA, Food and Drug Administration; FGF, Fibroblast Growth Factor; GLUT-1, Glucose transporter 1; gB, Glycoprotein B; HCMV, Human Cytomegalovirus; HGF, Hepatocyte Growth Factor; HTLV-1, Human T-cell lymphotropic virus type 1; HHV4, Human herpesvirus 4; LPP, Lipoprotein; LUJV, Lujo Virus; MAM, Meprin/A5-protein/PTPmu; MCMV, Murine cytomegalovirus; MOA, Mode of action; NRP(s), Neuropilin(s); NRP1, Neuropilin 1; NRP2, Neuropilin 2; PDGF, Platelet-Derived Growth Factor; PDZ, PSD-95/Dlg/ZO-1; RTK, Receptor tyrosine kinase; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SEMA3, Semaphorin-3; TGF- β , Transform Growth Factor; TM, Transmembrane; VEGF, Vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor.

References

1. Pellet-Many, C.; Frankel, P.; Jia, H.; Zachary, I. Neuropilins: Structure, function and role in disease. *Biochem. J.* **2008**, *411*, 211–226. [[CrossRef](#)] [[PubMed](#)]
2. Roy, S.; Bag, A.K.; Singh, R.K.; Talmadge, J.E.; Batra, S.K.; Datta, K. Multifaceted role of neuropilins in the immune system: Potential targets for immunotherapy. *Front. Immunol.* **2017**, *8*, 1228. [[CrossRef](#)] [[PubMed](#)]
3. Niland, S.; Eble, J.A. Neuropilin: Handyman and power broker in the tumor microenvironment. *Adv. Exp. Med. Biol.* **2020**, *1223*, 31–67.
4. Carmeliet, P.; Tessier-Lavigne, M. Common mechanisms of nerve and blood vessel wiring. *Nature* **2005**, *436*, 193–200. [[CrossRef](#)] [[PubMed](#)]
5. Mayi, B.S.; Leibowitz, J.A.; Woods, A.T.; Ammon, K.A.; Liu, A.E.; Raja, A. The role of Neuropilin-1 in COVID-19. *PLoS Pathog.* **2021**, *17*, e1009153. [[CrossRef](#)] [[PubMed](#)]
6. Yelland, T.; Djordjevic, S. Crystal structure of the neuropilin-1 MAM domain: Completing the neuropilin-1 ectodomain picture. *Structure* **2016**, *24*, 2008–2015. [[CrossRef](#)] [[PubMed](#)]
7. Nakamura, F.; Goshima, Y. Structural and functional relation of neuropilins. Neuropilin: From Nervous System to Vascular and Tumor Biol. *Adv. Exp. Med. Bio* **2002**, *515*, 55–69.
8. Nasarre, P.; Gemmill, R.M.; Drabkin, H.A. The emerging role of class-3 semaphorins and their neuropilin receptors in oncology. *Oncotargets Ther.* **2014**, *7*, 1663. [[PubMed](#)]

9. Prud'homme, G.J.; Glinka, Y. Neuropilins are multifunctional coreceptors involved in tumor initiation, growth, metastasis and immunity. *Oncotarget* **2002**, *3*, 921. [[CrossRef](#)] [[PubMed](#)]
10. He, Z.; Tessier-Lavigne, M. Neuropilin is a receptor for the axonal chemorepellent Semaphorin III. *Cell* **1997**, *90*, 739–751. [[CrossRef](#)]
11. Kolodkin, A.L.; Levensgood, D.V.; Rowe, E.G.; Tai, Y.T.; Giger, R.J.; Ginty, D.D. Neuropilin is a semaphorin III receptor. *Cell* **1997**, *90*, 753–762. [[CrossRef](#)]
12. Soker, S.; Takashima, S.; Miao, H.Q.; Neufeld, G.; Klagsbrun, M. Neuropilin-1 is expressed by endothelial and tumor cells as an isoform specific receptor for vascular endothelial growth factor. *Cell* **1998**, *92*, 735–745. [[CrossRef](#)]
13. Zhao, L.; Chen, H.; Lu, L.; Wang, L.; Zhang, X.; Guo, X. New insights into the role of coreceptor neuropilins in tumour angiogenesis and lymphangiogenesis and targeted therapy strategies. *J. Drug Target.* **2021**, *29*, 155–167. [[CrossRef](#)]
14. Takahashi, T.; Fournier, A.; Nakamura, F.; Wang, L.H.; Murakami, Y.; Kalb, R.G.; Fujisawa, H.; Strittmatter, S.M. Plexin-neuropilin-1 complexes form functional semaphorin-3A receptors. *Cell* **1999**, *99*, 59–69. [[CrossRef](#)]
15. Tamagnone, L.; Artigiani, S.; Chen, H.; He, Z.; Ming, G.L.; Song, H.J.; Chedotal, A.; Winberg, M.L.; Goodman, C.S.; Poo, M.; et al. Plexins are a large family of receptors for transmembrane, secreted, and GPI-anchored semaphorins in vertebrates. *Cell* **1999**, *99*, 71–80. [[CrossRef](#)]
16. Meyer, L.A.; Fritz, J.; Pierdant-Mancera, M.; Bagnard, D. Current drug design to target the Semaphorin/Neuropilin/Plexin complexes. *Cell Adhes. Migr.* **2016**, *10*, 700–708. [[CrossRef](#)] [[PubMed](#)]
17. Toledano, S.; Nir-Zvi, I.; Engelman, R.; Kessler, O.; Neufeld, G. Class-3 semaphorins and their receptors: Potent multifunctional modulators of tumor progression. *Int. J. Mol. Sci.* **2019**, *20*, 556. [[CrossRef](#)]
18. West, D.C.; Rees, C.G.; Duchesne, L.; Patey, S.J.; Terry, C.J.; Turnbull, J.E.; Delehedde, M.; Heegaard, C.W.; Allain, F.; Vanpouille, C.; et al. Interactions of multiple heparin binding growth factors with neuropilin-1 and potentiation of the activity of fibroblast growth factor-2. *J. Biol. Chem.* **2005**, *280*, 13457–13464. [[CrossRef](#)] [[PubMed](#)]
19. Sulpice, E.; Plouet, J.; Bergé, M.; Allanic, D.; Tobelem, G.; Merkulova-Rainon, T. Neuropilin-1 and neuropilin-2 act as coreceptors, potentiating proangiogenic activity. *Blood* **2008**, *111*, 2036–2045. [[CrossRef](#)]
20. Pellet-Many, C.; Mehta, V.; Fields, L.; Mahmoud, M.; Lowe, V.; Evans, I.; Ruivo, J.; Zachary, I. Neuropilins 1 and 2 mediate neointimal hyperplasia and re-endothelialisation following arterial injury. *Cardiovasc. Res.* **2015**, *108*, 288–298. [[CrossRef](#)] [[PubMed](#)]
21. Harman, J.L.; Sayers, J.; Chapman, C.; Pellet-Many, C. Emerging Roles for Neuropilin-2 in Cardiovascular Disease. *Int. J. Mol. Sci.* **2020**, *21*, 5154. [[CrossRef](#)] [[PubMed](#)]
22. Wittmann, P.; Grubinger, M.; Gröger, C.; Huber, H.; Sieghart, W.; Peck-Radosavljevic, M.; Mikulits, W. Neuropilin-2 induced by transforming growth factor- β augments migration of hepatocellular carcinoma cells. *BMC Cancer* **2015**, *15*, 909. [[CrossRef](#)] [[PubMed](#)]
23. Do, Y.; Cho, J.G.; Park, J.Y.; Oh, S.; Park, D.; Yoo, K.H.; Lee, M.S.; Kwon, B.S.; Kim, J.; Yang, Y. MiR-146a Regulates Migration and Invasion by Targeting NRP2 in Circulating-Tumor Cell Mimicking Suspension Cells. *Genes* **2020**, *12*, 45. [[CrossRef](#)] [[PubMed](#)]
24. Peng, K.; Bai, Y.; Zhu, Q.; Hu, B.; Xu, Y. Targeting VEGF–neuropilin interactions: A promising antitumor strategy. *Drug Discov.* **2019**, *24*, 656–664. [[CrossRef](#)] [[PubMed](#)]
25. Simons, M.; Gordon, E.; Claesson-Welsh, L. Mechanisms and regulation of endothelial VEGF receptor signalling. *Nat. Rev. Mol. Cell Biol.* **2016**, *17*, 611–625. [[CrossRef](#)] [[PubMed](#)]
26. Teesalu, T.; Sugahara, K.N.; Kotamraju, V.R.; Ruoslahti, E. C-end rule peptides mediate neuropilin-1-dependent cell, vascular, and tissue penetration. *Proc. Natl. Acad. Sci. USA* **2019**, *106*, 16157–16162. [[CrossRef](#)]
27. Miao, H.Q.; Klagsbrun, M. Neuropilin is a mediator of angiogenesis. *Cancer Metastasis Rev.* **2000**, *19*, 29–37. [[CrossRef](#)] [[PubMed](#)]
28. Lampropoulou, A.; Ruhrberg, C. Neuropilin regulation of angiogenesis. *Biochem. Soc. Trans.* **2014**, *42*, 1623–1628. [[CrossRef](#)]
29. Staton, C.A.; Kumar, I.; Reed, M.W.R.; Brown, N.J. Neuropilins in physiological and pathological angiogenesis. *J. Pathol.* **2007**, *212*, 237–248. [[CrossRef](#)]
30. Mei, B.; Chen, J.; Yang, N.; Peng, Y. The regulatory mechanism and biological significance of the Snail-miR590-VEGFR-NRP1 axis in the angiogenesis, growth and metastasis of gastric cancer. *Cell Death Dis.* **2020**, *11*, 241. [[CrossRef](#)]
31. Hu, C.; Jiang, X. Role of NRP-1 in VEGF-VEGFR2-independent tumorigenesis. *Target. Oncol.* **2016**, *11*, 501–505. [[CrossRef](#)]
32. Alghamdi, A.A.; Benwell, C.J.; Atkinson, S.J.; Lambert, J.; Johnson, R.T.; Robinson, S.D. NRP2 as an emerging angiogenic player; promoting endothelial cell adhesion and migration by regulating recycling of $\alpha 5$ integrin. *Front. Cell Dev. Biol.* **2020**, *8*, 395. [[CrossRef](#)]
33. Iragavarapu-Charyulu, V.; Wojcikiewicz, E.; Urdaneta, A. Semaphorins in angiogenesis and autoimmune diseases: Therapeutic targets? *Front. Immunol.* **2020**, *11*, 346. [[CrossRef](#)]
34. Caunt, M.; Mak, J.; Liang, W.C.; Stawicki, S.; Pan, Q.; Tong, R.K.; Plowman, G.; Kowalski, J.; Ho, C.; Reslan, H.B.; et al. Supplemental Data Blocking Neuropilin-2 Function Inhibits Tumor Cell Metastasis. *Cancer Cell* **2008**, *13*, 331–342. [[CrossRef](#)] [[PubMed](#)]
35. Jarvis, A.; Allerston, C.K.; Jia, H.; Herzog, B.; Garza-Garcia, A.; Winfield, N.; Ellard, K.; Aqil, R.; Lynch, R.; Chapman, C.; et al. Small molecule inhibitors of the neuropilin-1 vascular endothelial growth factor A (VEGF-A) interaction. *J. Med. Chem.* **2010**, *53*, 2215–2226. [[CrossRef](#)] [[PubMed](#)]

36. Mota, F.; Fotinou, C.; Rana, R.R.; Chan, A.; Yelland, T.; Arooz, M.T.; O'Leary, A.P.; Hutton, J.; Frankel, P.; Zachary, I.; et al. Architecture and hydration of the arginine-binding site of neuropilin-1. *FEBS J.* **2018**, *285*, 1290–1304. [[CrossRef](#)] [[PubMed](#)]
37. Daly, J.L.; Simonetti, B.; Klein, K.; Chen, K.E.; Williamson, M.K.; Antón-Plágaro, C.; Shoemark, D.K.; Simón-Gracia, L.; Bauer, M.; Hollandi, R.; et al. Neuropilin-1 is a host factor for SARS-CoV-2 infection. *Science* **2020**, *370*, 861–865. [[CrossRef](#)]
38. Parker, M.W.; Xu, P.; Li, X.; Vander Kooi, C.W. Structural basis for selective vascular endothelial growth factor-A (VEGF-A) binding to neuropilin-1. *J. Biol. Chem.* **2012**, *287*, 11082–11089. [[CrossRef](#)] [[PubMed](#)]
39. Llorián-Salvador, M.; González-Rodríguez, S. Painful understanding of VEGF. *Front. Pharmacol.* **2018**, *9*, 1267. [[CrossRef](#)] [[PubMed](#)]
40. Perez-Miller, S.; Patek, M.; Moutal, A.; Duran, P.; Cabel, C.R.; Thorne, C.A.; Khanna, R. Novel compounds targeting neuropilin receptor 1 with potential to interfere with SARS-CoV-2 virus entry. *ACS Chem. Neurosci.* **2021**, *12*, 1299–1312. [[CrossRef](#)] [[PubMed](#)]
41. Hulse, R.P. Role of VEGF-A in chronic pain. *Oncotarget* **2017**, *8*, 10775. [[CrossRef](#)]
42. Wang, H.B.; Zhang, H.; Zhang, J.P.; Li, Y.; Zhao, B.; Feng, G.K.; Zeng, M.S. Neuropilin 1 is an entry factor that promotes EBV infection of nasopharyngeal epithelial cells. *Nat. Commun.* **2015**, *6*, 6240. [[CrossRef](#)] [[PubMed](#)]
43. Ghez, D.; Lepelletier, Y.; Lambert, S.; Fourneau, J.M.; Blot, V.; Janvier, S.; Hermine, O. Neuropilin-1 is involved in human T-cell lymphotropic virus type 1 entry. *J. Virol.* **2006**, *80*, 6844. [[CrossRef](#)] [[PubMed](#)]
44. Lambert, S.; Bouttier, M.; Vassy, R.; Seigneuret, M.; Petrow-Sadowski, C.; Janvier, S.; Pique, C. HTLV-1 uses HSPG and neuropilin-1 for entry by molecular mimicry of VEGF165. *Blood* **2009**, *113*, 5176–5185. [[CrossRef](#)] [[PubMed](#)]
45. Cantuti-Castelvetri, L.; Ojha, R.; Pedro, L.D.; Djannatian, M.; Franz, J.; Kuivanen, S.; van der Meer, F.; Kallio, K.; Kaya, T.; Anastasina, M.; et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science* **2020**, *370*, 856–860. [[CrossRef](#)]
46. Lane, R.K.; Guo, H.; Fisher, A.D.; Diep, J.; Lai, Z.; Chen, Y.; Kaiser, W.J. Necroptosis-based CRISPR knockout screen reveals Neuropilin-1 as a critical host factor for early stages of murine cytomegalovirus infection. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 20109–20116. [[CrossRef](#)]
47. Wang, H.C.; Huang, P.N.; Hung, H.C.; Tseng, S.N.; Chang, C.C.; Tsai, Y.R.; Hsu, J.T. Effect of a Neuropilin-1-Derived Virus Receptor Trap on Enterovirus A71 infection in vitro. *Antimicrob. Agents Chemother.* **2020**, *65*, e00695-20. [[CrossRef](#)]
48. Raaben, M.; Jae, L.T.; Herbert, A.S.; Kuehne, A.I.; Stubbs, S.H.; Chou, Y.Y.; Whelan, S.P. NRP2 and CD63 are host factors for Lujo virus cell entry. *Cell Host Microbe* **2017**, *22*, 688–696. [[CrossRef](#)] [[PubMed](#)]
49. Martinez-Martin, N.; Marcandalli, J.; Huang, C.S.; Arthur, C.P.; Perotti, M.; Foglierini, M.; Ciferri, C. An unbiased screen for human cytomegalovirus identifies neuropilin-2 as a central viral receptor. *Cell* **2018**, *174*, 1158–1171. [[CrossRef](#)]
50. Kusunoki, H.; Tanaka, T.; Kohno, T.; Matsushashi, K.; Hosoda, K.; Wakamatsu, K.; Hamaguchi, I. A novel neuropilin-1-binding sequence in the human T-cell lymphotropic virus type 1 envelope glycoprotein. *Biochim. Biophys. Acta Proteins Proteom.* **2018**, *1866*, 541–548. [[CrossRef](#)]
51. Gu, Y.Y.; Luo, B.; Li, C.Y.; Huang, L.S.; Chen, G.; Feng, Z.B.; Peng, Z.G. Expression and clinical significance of neuropilin-1 in Epstein-Barr virus-associated lymphomas. *Cancer Biomark.* **2019**, *25*, 259–273. [[CrossRef](#)] [[PubMed](#)]
52. Hwang, J.Y.; Sun, Y.; Carroll, C.R.; Usherwood, E.J. Neuropilin-1 regulates the secondary CD8 T cell response to virus infection. *mSphere* **2019**, *4*, e00221-19. [[CrossRef](#)]
53. Davies, J.; Randeva, H.S.; Chatha, K.; Hall, M.; Spandidos, D.A.; Karteris, E.; Kyrou, I. Neuropilin 1 as a new potential SARS-CoV-2 infection mediator implicated in the neurologic features and central nervous system involvement of COVID 19. *Mol. Med. Rep.* **2020**, *22*, 4221–4226. [[CrossRef](#)] [[PubMed](#)]
54. Zhou, P.; Yang, X.L.; Wang, X.G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.R.; Zhu, Y.; Li, B.; Huang, C.L.; et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **2020**, *589*, 270–273. [[CrossRef](#)] [[PubMed](#)]
55. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.H.; Nitsche, A.; et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **2020**, *181*, 271–280. [[CrossRef](#)] [[PubMed](#)]
56. Coutard, B.; Valle, C.; de Lamballerie, X.; Canard, B.; Seidah, N.G.; Decroly, E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antivir. Res.* **2020**, *176*, 104742. [[CrossRef](#)] [[PubMed](#)]
57. Bruder, D.; Probst-Kepper, M.; Westendorf, A.M.; Geffers, R.; Beisert, S.; Loser, K.; von Boehmer, H.; Buer, J.; Hansen, W. Frontline: Neuropilin-1: A surface marker of regulatory T cells. *Eur. J. Immunol.* **2004**, *34*, 623–630. [[CrossRef](#)] [[PubMed](#)]
58. Yadav, M.; Louvet, C.; Davini, D.; Gardner, J.M.; Martinez-Llordella, M.; Bailey-Bucktrout, S.; Anthony, B.A.; Sverdrup, F.M.; Head, R.; Kuster, D.J.; et al. Neuropilin-1 distinguishes natural and inducible regulatory T cells among regulatory T cell subsets in vivo. *J. Exp. Med.* **2012**, *209*, 1713–1722. [[CrossRef](#)]
59. Delgoffe, G.M.; Woo, S.R.; Turnis, M.E.; Gravano, D.M.; Guy, C.; Overacre, A.E.; Bettini, M.L.; Vogel, P.; Finkelstein, D.; Bonnevier, J.; et al. Stability and function of regulatory T cells is maintained by a neuropilin-1–semaphorin-4a axis. *Nature* **2013**, *501*, 252–256. [[CrossRef](#)]
60. Liu, C.; Somasundaram, A.; Manne, S.; Gocher, A.M.; Szymczak-Workman, A.L.; Vignali, K.M.; Scott, E.N.; Normolle, D.P.; Wherry, E.J.; Lipson, E.J.; et al. Neuropilin-1 is a T cell memory checkpoint limiting long-term antitumor immunity. *Nat. Immunol.* **2020**, *21*, 1010–1021. [[CrossRef](#)]
61. Shen, X.R.; Geng, R.; Li, Q.; Chen, Y.; Li, S.F.; Wang, Q.; Min, J.; Yang, Y.; Li, B.; Jiang, R.D.; et al. ACE2-independent infection of T lymphocytes by SARS-CoV-2. *Signal Transduct. Target. Ther.* **2022**, *7*, 83. [[CrossRef](#)]

62. Nishiura, H.; Kobayashi, T.; Miyama, T.; Suzuki, A.; Jung, S.M.; Hayashi, K.; Kinoshita, R.; Yang, Y.; Yuan, B.; Akhmetzhanov, A.R.; et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). *Int. J. Infect. Dis.* **2020**, *94*, 154–155. [CrossRef] [PubMed]
63. Bai, Y.; Yao, L.; Wei, T.; Tian, F.; Jin, D.Y.; Chen, L.; Wang, M. Presumed Asymptomatic Carrier Transmission of COVID-19. *JAMA* **2020**, *323*, 1406–1407. [CrossRef]
64. Moutal, A.; Martin, L.F.; Boinon, L.; Gomez, K.; Ran, D.; Zhou, Y.; Stratton, H.J.; Cai, S.; Luo, S.; Gonzalez, K.B.; et al. SARS-CoV-2 spike protein co-opts VEGF-A/neuropilin-1 receptor signaling to induce analgesia. *Pain* **2021**, *162*, 243–252. [CrossRef] [PubMed]
65. Wang, Y.; Cao, Y.; Yamada, S.; Thirunavukkarasu, M.; Nin, V.; Joshi, M.; Rishi, M.T.; Bhattacharya, S.; Camacho-Pereira, J.; Sharma, A.K.; et al. Cardiomyopathy and Worsened Ischemic Heart Failure in SM22- α Cre-Mediated Neuropilin-1 Null Mice: Dysregulation of PGC1 α and Mitochondrial Homeostasis. *Arterioscler. Thromb. Vasc. Biol.* **2015**, *35*, 1401–1412. [CrossRef] [PubMed]
66. Kilari, S.; Wang, Y.; Singh, A.; Graham, R.P.; Iyer, V.; Thompson, S.M.; Torbenson, M.S.; Mukhopadhyay, D.; Misra, S. Neuropilin-1 deficiency in vascular smooth muscle cells is associated with hereditary hemorrhagic telangiectasia arteriovenous malformations. *JCI Insight* **2022**, *7*, e155565. [CrossRef]
67. Matilla, L.; Arrieta, V.; Jover, E.; Garcia-Peña, A.; Martinez-Martinez, E.; Sadaba, R.; Alvarez, V.; Navarro, A.; Fernandez-Celis, A.; Gainza, A.; et al. Soluble St2 Induces Cardiac Fibroblast Activation and Collagen Synthesis via Neuropilin-1. *Cells* **2020**, *9*, 1667. [CrossRef] [PubMed]
68. Li, B.; Yang, J.; Zhao, F.; Zhi, L.; Wang, X.; Liu, L.; Bi, Z.; Zhao, Y. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin. Res. Cardiol.* **2020**, *109*, 531–538. [CrossRef]
69. Sahni, S.; Gupta, G.; Sarda, R.; Pandey, S.; Pandey, R.M.; Sinha, S. Impact of metabolic and cardiovascular disease on COVID-19 mortality: A systematic review and meta-analysis. *Diabetes Metab. Syndr.* **2021**, *15*, 102308. [CrossRef] [PubMed]
70. Chen, L.; Li, X.; Chen, M.; Feng, Y.; Xiong, C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc. Res.* **2020**, *116*, 1097–1100. [CrossRef]
71. Nicin, L.; Abplanalp, W.T.; Mellentin, H.; Kattih, B.; Tombor, L.; John, D.; Schmitto, J.D.; Heineke, J.; Emrich, F.; Arsalan, M.; et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. *Eur. Heart J.* **2020**, *41*, 1804–1806. [CrossRef]
72. Hikmet, F.; Méar, L.; Edvinsson, Å.; Micke, P.; Uhlén, M.; Lindskog, C. The protein expression profile of ACE2 in human tissues. *Mol. Syst. Biol.* **2020**, *16*, e9610. [CrossRef] [PubMed]
73. Klagsbrun, M.; Takashima, S.; Mamluk, R. The role of neuropilin in vascular and tumor biology. In *Neuropilin: From Nervous System to Vascular and Tumor Biology*; Springer: Berlin/Heidelberg, Germany, 2002; pp. 33–48.
74. Mourad, D.; Azar, N.S.; Azar, S.T. Diabetic nephropathy and COVID-19: The potential role of immune actors. *Int. J. Mol. Sci.* **2021**, *22*, 7762. [CrossRef] [PubMed]
75. Wang, J.; Wang, S.; Li, M.; Wu, D.; Liu, F.; Yang, R.; Ji, S.; Ji, A.; Li, Y. The neuropilin-1 inhibitor, ATWLPPR peptide, prevents experimental diabetes-induced retinal injury by preserving vascular integrity and decreasing oxidative stress. *PLoS ONE* **2015**, *10*, e0142571. [CrossRef] [PubMed]
76. Loeffler, I.; Rüster, C.; Franke, S.; Liebisch, M.; Wolf, G. Erythropoietin ameliorates podocyte injury in advanced diabetic nephropathy in the db/db mouse. *Am. J. Physiol. Ren. Physiol.* **2013**, *305*, F911–F918. [CrossRef] [PubMed]
77. Bondeva, T.; Wolf, G. Role of Neuropilin-1 in Diabetic Nephropathy. *J. Clin. Med.* **2015**, *4*, 1293–1311. [CrossRef] [PubMed]
78. Schramek, H.; Sarközi, R.; Lauterberg, C.; Kronbichler, A.; Pirklbauer, M.; Albrecht, R.; Noppert, S.-J.; Perco, P.; Rudnicki, M.; Strutz, F.M.; et al. Neuropilin-1 and neuropilin-2 are differentially expressed in human proteinuric nephropathies and cytokine-stimulated proximal tubular cells. *Lab. Invest.* **2009**, *89*, 1304–1316. [CrossRef]
79. Bondeva, T.; Rüster, C.; Franke, S.; Hammerschmid, E.; Klagsbrun, M.; Cohen, C.D.; Wolf, G. Advanced glycation end-products suppress neuropilin-1 expression in podocytes. *Kidney Int.* **2009**, *75*, 605–616. [CrossRef]
80. Steenblock, C.; Richter, S.; Berger, I.; Barovic, M.; Schmid, J.; Schubert, U.; Jarzebska, N.; von Mässenhausen, A.; Linkermann, A.; Schürmann, A.; et al. Viral infiltration of pancreatic islets in patients with COVID-19. *Nat. Commun.* **2021**, *12*, 3534. [CrossRef] [PubMed]
81. Wu, C.T.; Lidsky, P.V.; Xiao, Y.; Lee, I.T.; Cheng, R.; Nakayama, T.; Jiang, S.; Demeter, J.; Bevacqua, R.J.; Chang, C.A.; et al. SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment. *Cell Metab.* **2021**, *33*, 1565–1576. [CrossRef]
82. International Agency for Research on Cancer. Available online: <https://gco.iarc.fr/today/> (accessed on 24 June 2022).
83. Roy, S.; Bag, A.K.; Dutta, S.; Polavaram, N.S.; Islam, R.; Schellenburg, S.; Banwait, J.; Guda, C.; Ran, S.; Hollingsworth, M.A.; et al. Macrophage-Derived Neuropilin-2 Exhibits Novel Tumor-Promoting Functions. *Cancer Res.* **2018**, *78*, 5600–5617. [CrossRef]
84. Diaz-Vera, J.; Palmer, S.; Hernandez-Fernaud, J.R.; Dornier, E.; Mitchell, L.E.; Macpherson, I.; Edwards, J.; Zanivan, S.; Norman, J.C. A Proteomic Approach to Identify Endosomal Cargoes Controlling Cancer Invasiveness. *J. Cell Sci.* **2017**, *78*, 5600–5617. [CrossRef]
85. Chen, D.S.; Mellman, I. Oncology Meets Immunology: The Cancer-Immunity Cycle. *Immunity* **2013**, *39*, 1–10. [CrossRef]
86. Piechnik, A.; Dmoszynska, A.; Omiotek, M.; Mlak, R.; Kowal, M.; Stilgenbauer, S.; Bullinger, L.; Giannopoulos, K. The VEGF Receptor, Neuropilin-1, Represents a Promising Novel Target for Chronic Lymphocytic Leukemia Patients. *Int. J. Cancer* **2013**, *133*, 1489–1496. [CrossRef] [PubMed]

87. Lu, L.; Zhang, L.; Xiao, Z.; Lu, S.; Yang, R.; Han, Z.C. Neuropilin-1 in Acute Myeloid Leukemia: Expression and Role in Proliferation and Migration of Leukemia Cells. *Leuk. Lymphoma* **2008**, *49*, 331–338. [[CrossRef](#)] [[PubMed](#)]
88. Wang, L.; Zhang, W.; Ding, Y.; Xiu, B.; Li, P.; Dong, Y.; Zhu, Q.; Liang, A. Up-regulation of VEGF and its receptor in refractory leukemia cells. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 5282–5290. [[PubMed](#)]
89. Palodetto, B.; da Silva Santos Duarte, A.; Rodrigues Lopes, M.; Adolfo Corrocher, F.; Roversi, F.M.; Soares Niemann, F.; Priscila Vieira Ferro, K.; Leda Figueiredo Longhini, A.; Melo Campos, P.; Favaro, P.; et al. SEMA3A Partially Reverses VEGF Effects through Binding to Neuropilin-1. *Stem Cell Res.* **2017**, *22*, 70–78. [[CrossRef](#)] [[PubMed](#)]
90. Yang, Z.-G.; Wen, R.-T.; Qi, K.; Li, J.; Zheng, G.-X.; Wang, Y.-F.; Hong, Y.-G.; Zhang, Y.-M. The Neuropilin-1 Ligand, SEMA3A, Acts as a Tumor Suppressor in the Pathogenesis of Acute Leukemia. *Anat. Rec.* **2018**, *302*, 1127–1135. [[CrossRef](#)]
91. Karjalainen, K.; Jaalouk, D.E.; Bueso-Ramos, C.E.; Zurita, A.J.; Kuniyasu, A.; Eckhardt, B.L.; Marini, F.C.; Lichtiger, B.; O'Brien, S.; Kantarjian, H.M.; et al. Targeting neuropilin-1 in human leukemia and lymphoma. *Blood* **2011**, *117*, 920–927. [[CrossRef](#)]
92. Arpel, A.; Gamper, C.; Spenlé, C.; Fernandez, A.; Jacob, L.; Baumlin, N.; Laquerriere, P.; Orend, G.; Crémel, G.; Bagnard, D. Inhibition of Primary Breast Tumor Growth and Metastasis Using a Neuropilin-1 Transmembrane Domain Interfering Peptide. *Oncotarget* **2016**, *7*, 54723–54732. [[CrossRef](#)] [[PubMed](#)]
93. Naik, A.; Al-Zeheimi, N.; Bakheit, C.S.; Al Riyami, M.; Al Jarrah, A.; Al Moundhri, M.S.; Al Habsi, Z.; Basheer, M.; Adham, S.A. Neuropilin-1 Associated Molecules in the Blood Distinguish Poor Prognosis Breast Cancer: A Cross-Sectional Study. *Sci. Rep.* **2017**, *7*, 3301. [[CrossRef](#)]
94. Hellec, C.; Diawara, M.; Carpentier, M.; Denys, A.; Allain, F. The pro-Tumoral Activity of Heparan Sulfate 3-O-Sulfotransferase 3B (HS3ST3B) in Breast Cancer MDA-MB-231 Cells Is Dependent on the Expression of Neuropilin-1. *Molecules* **2018**, *23*, 2718. [[CrossRef](#)]
95. Seifi-Alan, M.; Shams, R.; Bandehpour, M.; Mirfakhraie, R.; Ghafouri-Fard, S. Neuropilin-1 Expression Is Associated with Lymph Node Metastasis in Breast Cancer Tissues. *Cancer Manag. Res.* **2018**, *10*, 1969–1974. [[CrossRef](#)]
96. Zhang, L.; Chen, Y.; Wang, H.; Zheng, X.; Li, C.; Han, Z. Mir-376A Inhibits Breast Cancer Cell Progression by Targeting Neuropilin-1 NR. *Onco Targets Ther.* **2018**, *11*, 5293–5302. [[CrossRef](#)]
97. Kiso, M.; Tanaka, S.; Saji, S.; Toi, M.; Sato, F. Long Isoform of VEGF Stimulates Cell Migration of Breast Cancer by Filopodia Formation via NRP1/ARHGAP17/cdc42 Regulatory Network. *Int. J. Cancer* **2018**, *143*, 2905–2918. [[CrossRef](#)]
98. Zhang, L.; Chen, Y.; Li, C.; Liu, J.; Ren, H.; Li, L.; Zheng, X.; Wang, H.; Han, Z. RNA Binding Protein pum2 Promotes the Stemness of Breast Cancer Cells via Competitively Binding to Neuropilin-1 (NRP-1) Mrna with Mir-376a. *Biomed. Pharm.* **2019**, *114*, 108772. [[CrossRef](#)]
99. Al-Zeheimi, N.; Naik, A.; Bakheit, C.S.; Al Riyami, M.; Al Jarrah, A.; Al Badi, S.; Al Baimani, K.; Malik, K.; Al Habsi, Z.; Al Moundhri, M.S.; et al. Neoadjuvant Chemotherapy Alters Neuropilin-1, PLGF, and SNAI1 Expression Levels and Predicts Breast Cancer Patients Response. *Front. Oncol.* **2019**, *25*, 323. [[CrossRef](#)]
100. Wang, H.; Zhang, Y.N.; Xu, D.Q.; Huang, J.G.; Lv, D.; Shi, X.Y.; Liu, J.Y.; Ren, H.W.; Han, Z.X. Neuropilin1, a Novel Independent Prognostic Factor and Therapeutic Target in Triple-Negative Breast Cancer. *Neoplasma* **2021**, *67*, 1335–1345. [[CrossRef](#)]
101. Zhu, Q.; Li, J.; Wu, Q.; Cheng, Y.; Zheng, H.; Zhan, T.; Wang, H.; Yang, Y.; Wang, H.; Liu, Y.; et al. LINC-OIP5 in the Breast Cancer Cells Regulates Angiogenesis of Human Umbilical Vein Endothelial Cells through Yap1/Notch/NRP1 Signaling Circuit at a Tumor Microenvironment. *Biol. Res.* **2020**, *53*, 5. [[CrossRef](#)]
102. Zhao, M.; Zhang, M.; Tao, Z.; Cao, J.; Wang, L.; Hu, X. Mir-331-3p Suppresses Cell Proliferation in TNBC Cells by Downregulating NRP2. *Technol. Cancer Res. Treat.* **2020**, *19*, 153303382090582. [[CrossRef](#)]
103. Zhang, Y.; Liu, P.; Jiang, Y.; Dou, X.; Yan, J.; Ma, C.; Fan, Q.; Wang, W.; Su, F.; Tang, H.; et al. High Expression of Neuropilin-1 Associates with Unfavorable Clinicopathological Features in Hepatocellular Carcinoma. *Pathol. Oncol. Res.* **2015**, *22*, 367–375. [[CrossRef](#)] [[PubMed](#)]
104. Fung, T.M.; Ng, K.Y.; Tong, M.; Chen, J.-N.; Chai, S.; Chan, K.-T.; Law, S.; Lee, N.P.; Choi, M.Y.; Li, B.; et al. Neuropilin-2 Promotes Tumorigenicity and Metastasis in Oesophageal Squamous Cell Carcinoma through Erk-MAPK-ETV4-MMP-E-Cadherin Deregulation. *J. Pathol.* **2016**, *239*, 309–319. [[CrossRef](#)]
105. Dong, X.; Guo, W.; Zhang, S.; Wu, T.; Sun, Z.; Yan, S.; Zheng, S. Elevated Expression of Neuropilin-2 Associated with Unfavorable Prognosis in Hepatocellular Carcinoma. *Onco Targets Ther.* **2017**, *10*, 3827–3833. [[CrossRef](#)]
106. Lin, J.; Zhang, Y.; Wu, J.; Li, L.; Chen, N.; Ni, P.; Song, L.; Liu, X. Neuropilin 1 (NRP1) Is a Novel Tumor Marker in Hepatocellular Carcinoma. *Clin. Chim. Acta* **2018**, *485*, 158–165. [[CrossRef](#)]
107. Stasikowska-Kanicka, O.; Wagrowska-Danilewicz, M.; Danilewicz, M. Immunohistochemical Study on Neuropilin 1 (NRP1) Immunoexpression in Oral Squamous Cell Carcinoma. *Folia Histochem. Cytobiol.* **2018**, *56*, 98–105. [[CrossRef](#)] [[PubMed](#)]
108. Huang, Z.; Cheng, C.; Xiong, H.; Wang, Y.; Chen, K.K.; Yang, J.; Xiao, B.; Zhang, R.; Li, S.; Sang, Y. NRP1 promotes cell migration and invasion and serves as a therapeutic target in nasopharyngeal carcinoma. *Int. J. Clin. Exp. Pathol.* **2018**, *11*, 2460–2469.
109. Adil, A.A.; Bommanabonia, A.K.; Vaithy, A.; Kumar, S.; Waseem, M.; Jamal, S.; Ahmed, N. Differential Expression of Helios, Neuropilin-1 and Foxp3 in Head and Neck Squamous Cell Carcinoma (HNSCC) Patients. *3 Biotech.* **2019**, *9*, 178. [[CrossRef](#)] [[PubMed](#)]
110. Giannelli, G.; Santoro, A.; Kelley, R.K.; Gane, E.; Paradis, V.; Cleverly, A.; Smith, C.; Estrem, S.T.; Man, M.; Wang, S.; et al. Correction: Biomarkers and Overall Survival in Patients with Advanced Hepatocellular Carcinoma Treated with TGF-BRI Inhibitor Galunisertib. *PLoS ONE* **2021**, *16*, e0253671. [[CrossRef](#)]

111. Zheng, Y.; Wang, C.; Song, A.; Jiang, F.; Zhou, J.; Li, G.; Zhang, W.; Ye, J.; Ding, X.; Zhang, W.; et al. CMTM6 promotes cell proliferation and invasion in oral squamous cell carcinoma by interacting with NRP1. *Am. J. Cancer Res.* **2020**, *10*, 1691–1709.
112. Wu, Y.-N.; He, L.-H.; Bai, Z.-T.; Li, X. NRP1 Is a Prognostic Factor and Promotes the Growth and Migration of Cells in Intrahepatic Cholangiocarcinoma. *Cancer Manag. Res.* **2020**, *12*, 7021–7032. [[CrossRef](#)]
113. Morin, E.; Lindskog, C.; Johansson, M.; Egevad, L.; Sandström, P.; Harmenberg, U.; Claesson-Welsh, L.; Sjöberg, E. Perivascular Neuropilin-1 Expression Is an Independent Marker of Improved Survival in Renal Cell Carcinoma. *J. Pathol.* **2020**, *250*, 387–396. [[CrossRef](#)] [[PubMed](#)]
114. Xu, J.-C.; Chen, T.-Y.; Liao, L.-T.; Chen, T.; Li, Q.-L.; Xu, J.-X.; Hu, J.-W.; Zhou, P.-H.; Zhang, Y.-Q. NETO2 Promotes Esophageal Cancer Progression by Inducing Proliferation and Metastasis via PI3K/Akt and Erk Pathway. *Int. J. Biol. Sci.* **2021**, *17*, 259–270. [[CrossRef](#)] [[PubMed](#)]
115. Dumond, A.; Brachet, E.; Durivault, J.; Vial, V.; Puszko, A.K.; Lepelletier, Y.; Montemagno, C.; Pagnuzzi-Boncompagni, M.; Hermine, O.; Garbay, C.; et al. Neuropilin 1 and Neuropilin 2 Gene Inactivation or Pharmacological Inhibition Reveals Their Relevance for the Treatment of Metastatic Renal Cell Carcinoma. *J. Exp. Clin. Cancer Res.* **2021**, *40*, 33. [[CrossRef](#)] [[PubMed](#)]
116. Lee, S.W.; Park, K.C.; Kim, J.G.; Moon, S.J.; Kang, S.B.; Lee, D.S.; Sul, H.J.; Ji, J.S.; Jeong, H.Y. Dysregulation of MicroRNA-196B-5p and MicroRNA-375 in Gastric Cancer. *J. Gastric Cancer* **2016**, *16*, 221–229. [[CrossRef](#)]
117. Lian, H.; Liu, C.; Li, M.; Hu, Y.; Shi, N.; Yu, H.; Liu, H. Mir-486-5p Attenuates Tumor Growth and Lymphangiogenesis by Targeting Neuropilin-2 in Colorectal Carcinoma. *Onco Targets Ther.* **2016**, *9*, 2865–2871. [[CrossRef](#)] [[PubMed](#)]
118. Chen, Z.-P.; Wei, J.-C.; Wang, Q.; Yang, P.; Li, W.-L.; He, F.; Chen, H.C.; Hu, H.; Zhong, J.-B.; Cao, J. Long Non-Coding RNA 00152 Functions as a Competing Endogenous RNA to Regulate NRP1 Expression by Sponging with MIRNA-206 in Colorectal Cancer. *Int. J. Oncol.* **2018**, *53*, 1227–1236. [[CrossRef](#)] [[PubMed](#)]
119. Tomida, C.; Yamagishi, N.; Nagano, H.; Uchida, T.; Ohno, A.; Hirasaka, K.; Nikawa, T.; Teshima-Kondo, S. VEGF Pathway-Targeting Drugs Induce Evasive Adaptation by Activation of Neuropilin-1/CMET in Colon Cancer Cells. *Int. J. Oncol.* **2018**, *52*, 1350–1362. [[CrossRef](#)]
120. Liu, A.; Liu, L.; Lu, H. LncRNA Xist Facilitates Proliferation and Epithelial–Mesenchymal Transition of Colorectal Cancer Cells through Targeting Mir-486-5p and Promoting Neuropilin-2. *J. Cell Physiol.* **2019**, *234*, 13747–13761. [[CrossRef](#)] [[PubMed](#)]
121. Bollard, J.; Patte, C.; Radkova, K.; Massoma, P.; Chardon, L.; Valantin, J.; Gadot, N.; Goddard, I.; Vercherat, C.; Hervieu, V.; et al. Neuropilin-2 Contributes to Tumor Progression in Preclinical Models of Small Intestinal Neuroendocrine Tumors. *J. Pathol.* **2019**, *249*, 343–355. [[CrossRef](#)]
122. Huang, X.; Ye, Q.; Chen, M.; Li, A.; Mi, W.; Fang, Y.; Zaytseva, Y.Y.; O'Connor, K.L.; Vander Kooi, C.W.; Liu, S.; et al. N-Glycosylation-Defective Splice Variants of Neuropilin-1 Promote Metastasis by Activating Endosomal Signals. *Nat. Commun.* **2019**, *10*, 3708. [[CrossRef](#)]
123. Ding, G.Y.; Xu, W.G.; Guo, S.; Zhan, Q.Q.; Yang, X.; Jia, C.L. Effect of RNA interference targeting neuropilin-2 gene on proliferation and apoptosis of colon cancer cell line HCT-8. *Zhonghua Yi Xue Za Zhi* **2020**, *100*, 3879–3883. [[PubMed](#)]
124. De Vlaeminck, Y.; Bonelli, S.; Awad, R.M.; Dewilde, M.; Rizzolio, S.; Lecocq, Q.; Bolli, E.; Santos, A.R.; Laoui, D.; Schoonooghe, S.; et al. Targeting Neuropilin-1 with Nanobodies Reduces Colorectal Carcinoma Development. *Cancers* **2020**, *12*, 3582. [[CrossRef](#)] [[PubMed](#)]
125. Kang, S.; Lee, S.; Park, S. IRGD Peptide as a Tumor-Penetrating Enhancer for Tumor-Targeted Drug Delivery. *Polymers* **2020**, *12*, 1906. [[CrossRef](#)] [[PubMed](#)]
126. Akagi, M.; Kawaguchi, M.; Liu, W.; McCarty, M.F.; Takeda, A.; Fan, F.; Stoeltzing, O.; Parikh, A.A.; Jung, Y.D.; Bucana, C.D.; et al. Induction of Neuropilin-1 and Vascular Endothelial Growth Factor by Epidermal Growth Factor in Human Gastric Cancer Cells. *Br. J. Cancer* **2003**, *88*, 796–802. [[CrossRef](#)]
127. Li, L.; Jiang, X.; Zhang, Q.; Dong, X.; Gao, Y.; He, Y.; Qiao, H.; Xie, F.; Xie, X.; Sun, X. Neuropilin-1 Is Associated with Clinicopathology of Gastric Cancer and Contributes to Cell Proliferation and Migration as Multifunctional Coreceptors. *J. Exp. Clin. Cancer Res.* **2016**, *35*, 16. [[CrossRef](#)]
128. Zhang, L.; Xing, Y.; Gao, Q.; Sun, X.; Zhang, D.; Cao, G. Combination of NRP1-Mediated Irgd with 5-Fluorouracil Suppresses Proliferation, Migration and Invasion of Gastric Cancer Cells. *Biomed. Pharmacother.* **2017**, *93*, 1136–1143. [[CrossRef](#)]
129. Wang, X.; Hu, H.; Liu, H. RNA Binding Protein lin28b Confers Gastric Cancer Cells Stemness via Directly Binding to NRP-1. *Biomed. Pharmacother.* **2018**, *104*, 383–389. [[CrossRef](#)] [[PubMed](#)]
130. Wang, G.; Shi, B.; Fu, Y.; Zhao, S.; Qu, K.; Guo, Q.; Li, K.; She, J. Hypomethylated Gene NRP1 Is Co-Expressed with PDGFRB and Associated with Poor Overall Survival in Gastric Cancer Patients. *Biomed. Pharmacother.* **2019**, *111*, 1334–1341. [[CrossRef](#)] [[PubMed](#)]
131. Zhuo, Y.J.; Shi, Y.; Wu, T. NRP-1 and KDR Polymorphisms Are Associated with Survival Time in Patients with Advanced Gastric Cancer. *Oncol. Lett.* **2019**, *18*, 4629–4638. [[CrossRef](#)]
132. Pang, W.; Zhai, M.; Wang, Y.; Li, Z. Long Noncoding RNA SNHG16 Silencing Inhibits the Aggressiveness of Gastric Cancer via Upregulation of MicroRNA-628-3P and Consequent Decrease of nrp1. *Cancer Manag. Res.* **2019**, *11*, 7263–7277. [[CrossRef](#)]
133. Hang, C.; Yan, H.S.; Gong, C.; Gao, H.; Mao, Q.H.; Zhu, J.X. MicroRNA-9 Inhibits Gastric Cancer Cell Proliferation and Migration by Targeting Neuropilin-1. *Exp. Ther. Med.* **2019**, *18*, 2524–2530. [[CrossRef](#)]
134. Wu, C.; Zeng, M.-H.; Liao, G.; Qian, K.; Li, H. Neuropilin-1 Interacts with Fibronectin-1 to Promote Epithelial–Mesenchymal Transition Progress in Gastric Cancer. *Onco Targets Ther.* **2020**, *13*, 10677–10687. [[CrossRef](#)] [[PubMed](#)]

135. Wei, Y.; Guo, S.; Tang, J.; Wen, J.; Wang, H.; Hu, X.; Gu, Q. MicroRNA-19B-3P Suppresses Gastric Cancer Development by Negatively Regulating Neuropilin-1. *Cancer Cell Int.* **2020**, *25*, 193. [[CrossRef](#)] [[PubMed](#)]
136. Cao, H.; Li, Y.; Huang, L.; Bai, B.; Xu, Z. Clinicopathological Significance of Neuropilin 1 Expression in Gastric Cancer: A Meta-Analysis. *Dis. Markers* **2020**, *2020*, 4763492. [[CrossRef](#)] [[PubMed](#)]
137. Seo, H.S.; Hyeon, J.; Song, I.H.; Lee, H.H. Relationship between Neuropilin-1 Expression and Prognosis, According to Gastric Cancer Histology. *J. Mol. Histol.* **2020**, *51*, 199–208. [[CrossRef](#)]
138. Dong, J.C.; Gao, H.; Zuo, S.Y.; Zhang, H.Q.; Zhao, G.; Sun, S.L.; Han, H.L.; Jin, L.L.; Shao, L.H.; Wei, W.; et al. Neuropilin 1 Expression Correlates with the Radio-Resistance of Human Non-Small-Cell Lung Cancer Cells. *J. Cell Mol. Med.* **2015**, *19*, 2286–2295. [[CrossRef](#)]
139. Gemmill, R.M.; Nasarre, P.; Nair-Menon, J.; Cappuzzo, F.; Landi, L.; D’Incecco, A.; Uramoto, H.; Yoshida, T.; Haura, E.B.; Armeson, K.; et al. The Neuropilin 2 Isoform nrp2b Uniquely Supports TGF β -Mediated Progression in Lung Cancer. *Sci. Signal.* **2017**, *10*, eaag0528. [[CrossRef](#)] [[PubMed](#)]
140. Hu, C.; Zhu, P.; Xia, Y.; Hui, K.; Wang, M.; Jiang, X. Role of the NRP-1-Mediated VEGFR2-Independent Pathway on Radiation Sensitivity of Non-Small Cell Lung Cancer Cells. *J. Cancer Res. Clin. Oncol.* **2018**, *144*, 1329–1337. [[CrossRef](#)] [[PubMed](#)]
141. Jimenez-Hernandez, L.; Vazquez-Santillan, K.; Castro-Oropeza, R.; Martinez-Ruiz, G.; Muñoz -Galindo, L.; Gonzalez-Torres, C.; Cortes-Gonzalez, C.; Victoria-Acosta, G.; Melendez-Zajgla, J.; Maldonado, V. NRP1-Positive Lung Cancer Cells Possess Tumor-Initiating Properties. *Oncol. Rep.* **2017**, *39*, 349–357. [[CrossRef](#)]
142. Xiong, K.; Shao, L.H.; Zhang, H.Q.; Jin, L.; Wei, W.; Dong, Z.; Zhu, Y.Q.; Wu, N.; Jin, S.Z.; Xue, L.X. MicroRNA-9 Functions as a Tumor Suppressor and Enhances Radio-Sensitivity in Radio-Resistant A549 Cells by Targeting Neuropilin 1. *Oncol. Lett.* **2017**, *15*, 2863–2870. [[CrossRef](#)]
143. Ding, Z.; Du, W.; Lei, Z.; Zhang, Y.; Zhu, J.; Zeng, Y.; Wang, S.; Zheng, Y.; Liu, Z.; Huang, J.A. Neuropilin 1 Modulates Tgf- β 1-Induced Epithelial-Mesenchymal Transition in Non-Small Cell Lung Cancer. *Int. J. Oncol.* **2019**, *15*, 2863–2870. [[CrossRef](#)] [[PubMed](#)]
144. Ding, Z.; Zhu, J.; Zeng, Y.; Du, W.; Zhang, Y.; Tang, H.; Zheng, Y.; Qin, H.; Liu, Z.; Huang, J. The Regulation of Neuropilin 1 Expression by Mir-338-3p Promotes Non-Small Cell Lung Cancer via Changes in EGFR Signaling. *Mol. Carcinog.* **2019**, *58*, 1019–1032. [[CrossRef](#)] [[PubMed](#)]
145. Dong, Z.; Zhang, H.; Gong, X.; Wei, W.; Lv, Y.; Chen, Z.; Wang, R.; Yi, J.; Shen, Y.; Jin, S. The Role of the Tumor Microenvironment in Neuropilin 1-Induced Radiation Resistance in Lung Cancer Cells. *J. Cancer* **2019**, *10*, 4017–4030. [[CrossRef](#)] [[PubMed](#)]
146. Kim, Y.-J.; Baek, D.-S.; Lee, S.; Park, D.; Kang, H.N.; Cho, B.C.; Kim, Y.-S. Dual-Targeting of EGFR and Neuropilin-1 Attenuates Resistance to EGFR-Targeted Antibody Therapy in KRAS-Mutant Non-Small Cell Lung Cancer. *Cancer Lett.* **2019**, *466*, 23–34. [[CrossRef](#)] [[PubMed](#)]
147. Ding, M.; Liu, L.; Hu, C.; Liu, Y.; Qiao, Y.; Jiang, X. Expression of VEGFR2 and NRP-1 in non-small cell lung cancer and their clinical significance. *Chin. J. Cancer Res.* **2014**, *26*, 669–677.
148. Dimou, A.; Nasarre, C.; Peterson, Y.K.; Pagano, R.; Gooz, M.; Nasarre, P.; Drabkin, H.A.; Armeson, K.E.; Gibney, B.C.; Gemmill, R.M.; et al. Neuropilin-2B Facilitates Resistance to Tyrosine Kinase Inhibitors in Non-Small Cell Lung Cancer. *J. Thorac. Cardiovasc. Surg.* **2021**, *162*, 463–473. [[CrossRef](#)]
149. Matkar, P.N.; Singh, K.K.; Rudenko, D.; Kim, Y.J.; Kuliszewski, M.A.; Prud’homme, G.J.; Hedley, D.W.; Leong-Poi, H. Novel Regulatory Role of Neuropilin-1 in Endothelial-to-Mesenchymal Transition and Fibrosis in Pancreatic Ductal Adenocarcinoma. *Oncotarget* **2016**, *7*, 69489–69506. [[CrossRef](#)] [[PubMed](#)]
150. Liu, X.; Lin, P.; Perrett, I.; Lin, J.; Liao, Y.-P.; Chang, C.H.; Jiang, J.; Wu, N.; Donahue, T.; Wainberg, Z.; et al. Tumor-Penetrating Peptide Enhances Transcytosis of Silicasome-Based Chemotherapy for Pancreatic Cancer. *J. Clin. Investig.* **2017**, *127*, 2007–2018. [[CrossRef](#)] [[PubMed](#)]
151. Morin, E.; Sjöberg, E.; Tjomsland, V.; Testini, C.; Lindskog, C.; Franklin, O.; Sund, M.; Öhlund, D.; Kiflemariam, S.; Sjöblom, T.; et al. VEGF Receptor-2/Neuropilin 1 Trans.-Complex Formation between Endothelial and Tumor Cells Is an Independent Predictor of Pancreatic Cancer Survival. *J. Pathol.* **2018**, *246*, 311–322. [[CrossRef](#)] [[PubMed](#)]
152. McGuigan, A.; Kelly, P.; Turkington, R.C.; Jones, C.; Coleman, H.G.; McCain, R.S. Pancreatic Cancer: A Review of Clinical Diagnosis, Epidemiology, Treatment and Outcomes. *World J. Gastroenterol.* **2018**, *24*, 4846–4861. [[CrossRef](#)]
153. Ma, L.; Zhai, B.; Zhu, H.; Li, W.; Jiang, W.; Lei, L.; Zhang, S.; Qiao, H.; Jiang, X.; Sun, X. The Mir-141/Neuropilin-1 Axis Is Associated with the Clinicopathology and Contributes to the Growth and Metastasis of Pancreatic Cancer. *Cancer Cell Int.* **2019**, *19*, 248. [[CrossRef](#)] [[PubMed](#)]
154. Li, X.; Fan, S.; Pan, X.; Xiaokaiti, Y.; Duan, J.; Shi, Y.; Pan, Y.; Tie, L.; Wang, X.; Li, Y.; et al. Nordihydroguaiaretic Acid Impairs Prostate Cancer Cell Migration and Tumor Metastasis by Suppressing Neuropilin 1. *Oncotarget* **2016**, *7*, 86225–86238. [[CrossRef](#)] [[PubMed](#)]
155. Tse, B.W.; Volpert, M.; Rattner, E.; Stylianou, N.; Nouri, M.; McGowan, K.; Lehman, M.L.; McPherson, S.J.; Roshan-Moniri, M.; Butler, M.S.; et al. Neuropilin-1 Is Upregulated in the Adaptive Response of Prostate Tumors to Androgen-Targeted Therapies and Is Prognostic of Metastatic Progression and Patient Mortality. *Oncogene* **2017**, *36*, 3417–3427. [[CrossRef](#)] [[PubMed](#)]
156. Borkowetz, A.; Froehner, M.; Rauner, M.; Conrad, S.; Erdmann, K.; Mayr, T.; Datta, K.; Hofbauer, L.C.; Baretton, G.B.; Wirth, M.; et al. Neuropilin-2 Is an Independent Prognostic Factor for Shorter Cancer-Specific Survival in Patients with Acinar Adenocarcinoma of the Prostate. *Int. J. Cancer* **2019**, *146*, 2619–2627. [[CrossRef](#)]

157. Moriarty, W.F.; Kim, E.; Gerber, S.A.; Hammers, H.; Alani, R.M. Neuropilin-2 Promotes Melanoma Growth and Progression in Vivo. *Melanoma Res.* **2016**, *26*, 321–328. [[CrossRef](#)]
158. Dou, X.; Yan, J.; Zhang, Y.; Liu, P.; Jiang, Y.; Lv, S.; Zeng, F.; Chen, X.; Wang, S.; Zhang, H.; et al. SPECT Imaging of Neuropilin Receptor Type-1 Expression with ¹³¹I-Labeled Monoclonal Antibody. *Int. J. Oncol.* **2016**, *49*, 961–970. [[CrossRef](#)]
159. Eisenstein, A.; Panova, I.P.; Chung, H.J.; Goldberg, L.J.; Zhang, Q.; Lazova, R.; Bhawan, J.; Busam, K.J.; Symanowski, J.T.; Alani, R.M.; et al. Quantitative Assessment of Neuropilin-2 as a Simple and Sensitive Diagnostic Assay for SPITZOID Melanocytic Lesions. *Melanoma Res.* **2018**, *28*, 71–75. [[CrossRef](#)] [[PubMed](#)]
160. Rizzolio, S.; Cagnoni, G.; Battistini, C.; Bonelli, S.; Isella, C.; Van Ginderachter, J.A.; Bernards, R.; Di Nicolantonio, F.; Giordano, S.; Tamagnone, L. Neuropilin-1 Upregulation Elicits Adaptive Resistance to Oncogene-Targeted Therapies. *J. Clin. Investig.* **2018**, *128*, 3976–3990. [[CrossRef](#)]
161. Zhang, G.; Chen, L.; Sun, K.; Khan, A.A.; Yan, J.; Liu, H.; Lu, A.; Gu, N. Neuropilin-1 (NRP-1)/GIPC1 Pathway Mediates Glioma Progression. *Tumor Biol.* **2016**, *37*, 13777–13788. [[CrossRef](#)]
162. Kwiatkowski, S.C.; Guerrero, P.A.; Hirota, S.; Chen, Z.; Morales, J.E.; Aghi, M.; McCarty, J.H. Neuropilin-1 Modulates TGF β Signaling to Drive Glioblastoma Growth and Recurrence after Anti-Angiogenic Therapy. *PLoS ONE* **2017**, *12*, e0185065. [[CrossRef](#)] [[PubMed](#)]
163. Caponegro, M.D.; Moffitt, R.A.; Tsrka, S.E. Expression of Neuropilin-1 Is Linked to Glioma Associated Microglia and Macrophages and Correlates with Unfavorable Prognosis in High Grade Gliomas. *Oncotarget* **2018**, *9*, 35655–35665. [[CrossRef](#)] [[PubMed](#)]
164. Miyauchi, J.T.; Caponegro, M.D.; Chen, D.; Choi, M.K.; Li, M.; Tsrka, S.E. Deletion of Neuropilin 1 from Microglia or Bone Marrow-Derived Macrophages Slows Glioma Progression. *Cancer Res.* **2017**, *78*, 685–694. [[CrossRef](#)] [[PubMed](#)]
165. Zhang, G.; Chen, L.; Khan, A.A.; Li, B.; Gu, B.; Lin, F.; Su, X.; Yan, J. MIRNA-124-3p/Neuropilin-1(NRP-1) Axis Plays an Important Role in Mediating Glioblastoma Growth and Angiogenesis. *Int. J. Cancer* **2018**, *143*, 635–644. [[CrossRef](#)] [[PubMed](#)]
166. Gong, C.; Almasoud, A.; Pellegrini-Moise, N.; Pinel, S.; Barberi-Heyob, M.; Chastagner, P.; Boura, C. PO-013 a Novel Peptidomimetic Targeting NRP1 Increases Radiosensitivity of Medulloblastoma Stem Cells. *ESMO Open* **2018**, *3*, A232. [[CrossRef](#)]
167. Gong, C.; Valduga, J.; Chateau, A.; Richard, M.; Pellegrini-Moise, N.; Barberi-Heyob, M.; Chastagner, P.; Boura, C. Stimulation of Medulloblastoma Stem Cells Differentiation by a Peptidomimetic Targeting Neuropilin-1. *Oncotarget* **2018**, *9*, 15312–15325. [[CrossRef](#)]
168. Xu, Z.C.; Shen, H.X.; Chen, C.; Ma, L.; Li, W.Z.; Wang, L.; Geng, Z.M. Neuropilin-1 Promotes Primary Liver Cancer Progression by Potentiating the Activity of Hepatic Stellate Cells. *Oncol. Lett.* **2017**, *15*, 2245–2251. [[CrossRef](#)] [[PubMed](#)]
169. Grun, D.; Adhikary, G.; Eckert, R.L. VEGF-A Acts via Neuropilin-1 to Enhance Epidermal Cancer Stem Cell Survival and Formation of Aggressive and Highly Vascularised Tumors. *Oncogene* **2016**, *35*, 4379–4387. [[CrossRef](#)]
170. Liu, W.; Wu, T.; Dong, X.; Zeng, Y.A. Neuropilin-1 Is Upregulated by Wnt/ β -Catenin Signaling and Is Important for Mammary Stem Cells. *Sci. Rep.* **2017**, *7*, 10941. [[CrossRef](#)]
171. Tang, Y.H.; Rockstroh, A.; Sokolowski, K.A.; Lynam, L.R.; Lehman, M.; Thompson, E.W.; Gregory, P.A.; Nelson, C.C.; Volpert, M.; Hollier, B.G. Neuropilin-1 is over-expressed in claudin-low breast cancer and promotes tumor progression through acquisition of stem cell characteristics and RAS/MAPK pathway activation. *Breast Cancer Res.* **2022**, *24*, 8. [[CrossRef](#)]
172. Shi, F.; Shang, L.; Yang, L.-Y.; Jiang, Y.-Y.; Wang, X.-M.; Hao, J.-J.; Zhang, Y.; Huang, D.-K.; Cai, Y.; Xu, X.; et al. Neuropilin-1 Contributes to Esophageal Squamous Cancer Progression via Promoting p65-Dependent Cell Proliferation. *Oncogene* **2018**, *37*, 935–943. [[CrossRef](#)]
173. Grun, D.; Adhikary, G.; Eckert, R.L. NRP-1 Interacts with GIPC1 and SYX to Activate p38 MAPK Signaling and Cancer Stem Cell Survival. *Mol. Carcinog.* **2018**, *58*, 488–499. [[CrossRef](#)] [[PubMed](#)]
174. Grun, D.; Adhikary, G.; Eckert, R.L. NRP-1 Interacts with GIPC1 and α 6/B4-Integrins to Increase yap1/ Δ np63 α -Dependent Epidermal Cancer Stem Cell Survival. *Oncogene* **2019**, *37*, 4711–4722. [[CrossRef](#)] [[PubMed](#)]
175. Tu, D.-G.; Chang, W.-W.; Jan, M.-S.; Tu, C.-W.; Lu, Y.-C.; Tai, C.-K. Promotion of Metastasis of Thyroid Cancer Cells via NRP-2-Mediated Induction. *Oncol. Lett.* **2016**, *12*, 4224–4230. [[CrossRef](#)] [[PubMed](#)]
176. Lee, G.; Kang, Y.E.; Oh, C.; Liu, L.; Jin, Y.; Lim, M.A.; Won, H.-R.; Chang, J.W.; Koo, B.S. Neuropilin-2 Promotes Growth and Progression of Papillary Thyroid Cancer Cells. *Auris Nasus Larynx* **2020**, *47*, 870–880. [[CrossRef](#)]
177. Karczmarczyk, A.; Bilska, S.; Korpysz, M.; Purkot, J.; Grząsko, N.; Hus, M.; Giannopoulos, K. Expression and Clinical Significance of Neuropilin-1 in Patients with Multiple Myeloma. *Anticancer Res.* **2020**, *40*, 5437–5443. [[CrossRef](#)]
178. Keck, B.; Wach, S.; Taubert, H.; Zeiler, S.; Ott, O.J.; Kunath, F.; Hartmann, A.; Bertz, S.; Weiss, C.; Hönscheid, P.; et al. Neuropilin-2 and Its Ligand VEGF-C Predict Treatment Response after Transurethral Resection and Radiochemotherapy in Bladder Cancer Patients. *Int. J. Cancer* **2014**, *136*, 443–451. [[CrossRef](#)]
179. Schulz, A.; Gorodetska, L.; Behrendt, R.; Fuessel, S.; Erdmann, K.; Foerster, S.; Datta, K.; Mayr, T.; Dubrovskaya, A.; Muders, M.H. Linking NRP2 with EMT and Chemoradioresistance in Bladder Cancer. *Front. Oncol.* **2020**, *9*, 1461. [[CrossRef](#)]
180. Ong, H.S.; Gokavarapu, S.; Xu, Q.; Tian, Z.; Li, J.; Ji, T.; Zhang, C.P. Cytoplasmic Neuropilin 2 Is Associated with Metastasis and a Poor Prognosis in Early Tongue Cancer Patients. *Int. J. Oral Maxillofac. Surg.* **2017**, *46*, 1205–1219. [[CrossRef](#)] [[PubMed](#)]
181. Fujii, T.; Shimada, K.; Asano, A.; Tatsumi, Y.; Yamaguchi, N.; Yamazaki, M.; Konishi, N. MicroRNA-331-3p Suppresses Cervical Cancer Cell Proliferation and E6/E7 Expression by Targeting NRP2. *Int. J. Mol. Sci.* **2016**, *17*, 1351. [[CrossRef](#)] [[PubMed](#)]
182. Yang, L.; Liu, L.; Zhu, Y.; Wang, B.-B.; Chen, Y.-N.; Zhang, F.; Zhang, X.-A.; Ren, C.-C. Neuropilin-1 Is Associated with the Prognosis of Cervical Cancer in Henan Chinese Population. *Onco Targets Ther.* **2019**, *12*, 2911–2920. [[CrossRef](#)]

183. Chen, C.; Zhang, R.; Ma, L.; Li, Q.; Zhao, Y.; Zhang, G.; Zhang, D.; Li, W.; Cao, S.; Wang, L.; et al. Neuropilin-1 Is up-Regulated by Cancer-Associated Fibroblast-Secreted Il-8 and Associated with Cell Proliferation of Gallbladder Cancer. *J. Cell Mol. Med.* **2020**, *24*, 12608–12618. [CrossRef] [PubMed]
184. Oplawski, M.; Dziobek, K.; Grabarek, B.; Zmarzły, N.; Dąbruś, D.; Januszyk, P.; Brus, R.; Tomala, B.; Boroń, D. Expression of NRP-1 and NRP-2 in Endometrial Cancer. *Curr. Pharm. Biotechnol.* **2019**, *20*, 254–260. [CrossRef] [PubMed]
185. Huang, N.; Xu, L.; Qiu, Y.; Zhan, J.; Chen, X. Down-Regulated Mir-124-3p Enhanced the Migration and Epithelial-Stromal Transformation of Endometrial Stromal Cells Extracted from Eutopic Endometrium in Subjects with Adenomyosis by up-Regulating Neuropilin 1. *Tissue Cell* **2021**, *69*, 101474. [CrossRef]
186. Miyauchi, J.T.; Chen, D.; Choi, M.; Nissen, J.C.; Shroyer, K.R.; Djordjevic, S.; Zachary, I.C.; Selwood, D.; Tsirka, S.E. Ablation of Neuropilin 1 from glioma-associated microglia and macrophages slows tumor progression. *Oncotarget* **2016**, *7*, 9801–9814. [CrossRef] [PubMed]
187. Powell, J.; Mota, F.; Steadman, D.; Soudy, C.; Miyauchi, J.T.; Crosby, S.; Jarvis, A.; Reisinger, T.; Winfield, N.; Evans, G.; et al. Small Molecule Neuropilin-1 Antagonists Combine Antiangiogenic and Antitumor Activity with Immune Modulation through Reduction of Transforming Growth Factor Beta (TGF β) Production in Regulatory T-Cells. *J. Med. Chem.* **2018**, *61*, 4135–4154. [CrossRef] [PubMed]
188. Klaewkla, M.; Charoenwongpaiboon, T.; Mahalapbutr, P. Molecular basis of the new COVID-19 target neuropilin-1 in complex with SARS-CoV-2 S1 C-end rule peptide and small-molecule antagonists. *J. Mol. Liq.* **2021**, *335*, 116537. [CrossRef] [PubMed]
189. Binetruy-Tournaire, R.; Demangel, C.; Malavaud, B.; Vassy, R.; Rouyre, S.; Kraemer, M.; Mazie, J.C. Identification of a peptide blocking vascular endothelial growth factor (VEGF)-mediated angiogenesis. *EMBO J.* **2020**, *19*, 1525–1533. [CrossRef]
190. Perret, G.Y.; Starzec, A.; Hauet, N.; Vergote, J.; Le Pecheur, M.; Vassy, R.; Moretti, J.L. In vitro evaluation and biodistribution of a ^{99m}Tc-labeled anti-VEGF peptide targeting neuropilin-1. *Nucl. Med. Biol.* **2004**, *31*, 575–581. [CrossRef]
191. Novoa, A.; Pellegrini-Moïse, N.; Bechet, D.; Barberi-Heyob, M.; Chapleur, Y. Sugar-based peptidomimetics as potential inhibitors of the vascular endothelium growth factor binding to neuropilin-1. *Bioorg. Med. Chem.* **2010**, *18*, 3285–3298. [CrossRef]
192. Richard, M.; Chateau, A.; Jelsch, C.; Didierjean, C.; Manival, X.; Charron, C.; Pellegrini-Moïse, N. Carbohydrate-based peptidomimetics targeting neuropilin-1: Synthesis, molecular docking study and in vitro biological activities. *Bioorg. Med. Chem.* **2016**, *24*, 5315–5325. [CrossRef]
193. Borriello, L.; Montès, M.; Lepelletier, Y.; Leforban, B.; Liu, W.Q.; Demange, L.; Raynaud, F. Structure-based discovery of a small non-peptidic Neuropilins antagonist exerting in vitro and in vivo anti-tumor activity on breast cancer model. *Cancer Lett.* **2014**, *349*, 120–127. [CrossRef]
194. Liu, W.Q.; Lepelletier, Y.; Montès, M.; Borriello, L.; Jarray, R.; Grépin, R.; Demange, L. NRPa-308, a new neuropilin-1 antagonist, exerts in vitro anti-angiogenic and anti-proliferative effects and in vivo anticancer effects in a mouse xenograft model. *Cancer Lett.* **2018**, *414*, 88–98. [CrossRef] [PubMed]
195. Brachet, E.; Dumond, A.; Liu, W.Q.; Fabre, M.; Selkti, M.; Raynaud, F.; Demange, L. Synthesis, 3D-structure and stability analyses of NRPa-308, a new promising anticancer agent. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 126710. [CrossRef] [PubMed]
196. Starzec, A.; Miteva, M.A.; Ladam, P.; Villoutreix, B.O.; Perret, G.Y. Discovery of novel inhibitors of vascular endothelial growth factor-A–Neuropilin-1 interaction by structure-based virtual screening. *Bioorg. Med. Chem.* **2014**, *22*, 4042–4048. [CrossRef] [PubMed]
197. Peng, K.; Li, Y.; Bai, Y.; Jiang, T.; Sun, H.; Zhu, Q.; Xu, Y. Discovery of novel nonpeptide small-molecule NRP1 antagonists: Virtual screening, molecular simulation and structural modification. *Bioorg. Med. Chem.* **2020**, *28*, 115183. [CrossRef] [PubMed]
198. Seadawy, M.; Shamel, M.; Ahmed, A.; Zekri, A.R.N. In Silico Docking for Inhibition Neuropilin-1 (SARS-CoV-2 Receptor) by Some Natural and Approved Drugs. Available online: <https://ssrn.com/abstract=3735823> (accessed on 26 July 2022).
199. Vique-Sánchez, J.L. Potential inhibitors interacting in Neuropilin-1 to develop an adjuvant drug against COVID-19, by molecular docking. *Bioorg. Med. Chem.* **2021**, *33*, 116040. [CrossRef]
200. Kolarič, A.; Jukič, M.; Bren, U. Novel Small-Molecule Inhibitors of the SARS-CoV-2 Spike Protein Binding to Neuropilin 1. *Pharmaceuticals* **2022**, *15*, 165. [CrossRef] [PubMed]
201. Kumagai, K.; Hosotani, N.; Kikuchi, K.; Kimura, T.; Saji, I. Xanthofulvin, a novel semaphorin inhibitor produced by a strain of *Penicillium*. *J. Antibiot.* **2003**, *56*, 610–616. [CrossRef]
202. Kikuchi, K.; Kishino, A.; Konishi, O.; Kumagai, K.; Hosotani, N.; Saji, I.; Kimura, T. In vitro and in vivo characterisation of a novel semaphorin 3A inhibitor, SM-216289 or xanthofulvin. *J. Biol. Chem.* **2003**, *278*, 42985–42991. [CrossRef]
203. Said, A.M.; Parker, M.W.; Vander Kooi, C.W. Design, synthesis, and evaluation of a novel benzamidine-based inhibitor of VEGF-C binding to Neuropilin-2. *Bioorg. Chem.* **2020**, *100*, 103856. [CrossRef] [PubMed]