BioTech

MDPI

Review

The Use of Biologics for Targeting GPCRs in Metastatic Cancers

Cian McBrien and David J. O'Connell *

School of Biomolecular & Biomedical Science, University College Dublin, D04 V1W8 Dublin, Ireland; cian.mcbrien@ucd.ie

* Correspondence: david.oconnell@ucd.ie

Abstract: A comprehensive review of studies describing the role of G-protein coupled receptor (GPCR) behaviour contributing to metastasis in cancer, and the developments of biotherapeutic drugs towards targeting them, provides a valuable resource toward improving our understanding of the opportunities to effectively target this malignant tumour cell adaptation. Focusing on the five most common metastatic cancers of lung, breast, colorectal, melanoma, and prostate cancer, we highlight well-studied and characterised GPCRs and some less studied receptors that are also implicated in the development of metastatic cancers. Of the approximately 390 GPCRs relevant to therapeutic targeting, as many as 125 of these have been identified to play a role in promoting metastatic disease in these cancer types. GPCR signalling through the well-characterised pathways of chemokine receptors, to emerging data on signalling by orphan receptors, is integral to many aspects of the metastatic phenotype. Despite having detailed information on many receptors and their ligands, there are only thirteen approved therapeutics specifically for metastatic cancer, of which three are small molecules with the remainder including synthetic and non-synthetic peptides or monoclonal antibodies. This review will cover the existing and potential use of monoclonal antibodies, proteins and peptides, and nanobodies in targeting GPCRs for metastatic cancer therapy.

Keywords: cancer; metastasis; GPCR; monoclonal antibodies; peptides; nanobodies

Key Contribution: Extensive review highlighting the role of GPCRs in cancer metastasis, and the current state of the field of biotherapeutics for cancer therapy.

Academic Editor: Paolo Iadarola

Received: 18 December 2024
Revised: 18 January 2025
Accepted: 27 January 2025
Published: 30 January 2025

Citation: McBrien, C.; O'Connell, D.J. The Use of Biologics for Targeting GPCRs in Metastatic Cancers. *BioTech* **2025**, *14*, 7. https://doi.org/10.3390/biotech14010007

1. Introduction

G-protein coupled receptors (GPCRs) are the largest class of human membrane proteins with 810 receptors identified [1–4]. Of these, 455 have olfactory functions, and the remaining 355 receptors mediate the signalling of a wide variety of ligands including odours, hormones, neurotransmitters, and chemokines, that range from photons to amines, carbohydrates, lipids, and peptides to globular proteins [3–5]. GPCRs were originally separated into six classes, A-F based on sequence homology, of which D and E classes are not expressed in vertebrates. Those found in vertebrates were then classified into the GRAFS system which groups GPCRs together based on structural features, functionality and ligand specificity. Rhodopsin family receptors (Class A), Secretin Family receptors (Class B), Glutamate family receptors (Class C), Adhesion family receptors and Frizzled family receptors (Class F) [6]. As many as 390 GPCRs are of therapeutic interest, with the majority remaining unexplored therapeutically. GPCRs mediate a wide variety of cellular responses to stimuli and, thus, are widely involved in regulating physiological processes such as cell growth, differentiation, immune regulation, sensory, and neurological

processes [7]. Aberrant signalling by these receptors can lead to and drive tumorigenic behaviour in cancer cells.

GPCRs are composed of a single polypeptide chain, with seven membrane-spanning alpha helices that combine to form a barrel-like structure that transduces extracellular stimuli across the cell membrane. The extracellular section contains the N-terminus and three extracellular loops (ECL 1–3), and is associated with ligand recognition and binding, while the intracellular section contains the C-terminus, the three intracellular loops (ICL 1–3), and mediates the signalling cascades of G proteins, kinases, and arrestins [8]. The binding of a ligand to the extracellular domain causes a conformational change, the most common being the outwards movement of transmembrane helix 6 (TM6), along with the relative shifting of the other helixes. This, in turn, exposes an intracellular pocket which allows the forming of a complex with G proteins, G-protein coupled receptor kinases (GRKs), and arrestins [9]. Each ligand can have different effects on a receptor's signalling. Full agonists elicit a maximal signal, while partial or inverse agonists induce reduced or minimal signalling, respectively. A key aspect of GPCR signalling is biased signalling, where different ligands can stabilise distinct receptor conformations, which results in the preferential activation of specific pathways. Cryogenic electron microscopy (Cryo-EM) has been used to determine the structural basis of biased signalling and has shed further light on structural elements of ligand–receptor interactions and how these shape intracellular signalling [10].

Classical GPCR signal transduction results in the activation of the heterotrimeric G proteins which are composed of α, β, and γ subunits. The α subunit is composed of 4 families, G_s, $G_{i/o}$, $G_{q/11}$, and $G_{12/13}$. When bound to GDP, the α subunit also forms an inactive complex with the Gβγ dimer. Following receptor activation, it rapidly dissociates from GDP and binds GTP. This results in a conformational change in Gα resulting in the release of the Gβγ dimer [8,11,12]. These two subunit complexes have been shown to regulate the activity of various downstream effector proteins. The Gα subunit regulates downstream effector proteins such as DAG/IP3 and RhoGEF, while the Gβγ subunit interacts with phospholipases, ion channels, and GRKs [8,11,12]. Receptor signalling is then terminated by GRKs as they phosphorylate the carboxy terminal tail of the receptor. This recruits β-arrestin, which recognises phosphorylated receptors to which it binds and prevents further activity of the associated G proteins. It does so by occupying the same binding space as G proteins, which rapidly dissociate from the receptor in the presence of GTP, thereby regulating receptor activity [10]. It also allows for facilitation with clathrin, resulting in the endosomal degradation of the receptor [8,13]. This is the classical form of signalling, although, it is now understood that many receptors continue to signal throughout the endosomal pathway and β-arrestin can also activate alternative MAPK pathways, serine/threonine kinases, as well as c-Jun N terminal kinases [13,14]. Receptors have also been shown to have internal signalling from endosomal compartments in the Golgi apparatus [15]. Due to their extensive signalling mechanisms and their wide involvement in regulating physiological processes, mutations, or changes in the expression of these receptors can disrupt this signalling network, leading to continuous downstream signalling of pathways such as MAPK/ERK and PI3K/AKT that are involved in cell proliferation and growth. Dysregulation of these pathways can lead to the extended survival and growth of cells resulting in cancerous phenotypes [1,16,17].

Key pathways through which GPCRs can promote cancer development are the chemokine, protease-activated receptor (PAR), Hippo, and the WNT signalling pathways and many others, that mediate key tumorigenic characteristics such as cell proliferation, differentiation, immune system regulation, and migration [17]. One particular process these pathways can activate is epithelial–mesenchymal transition (EMT). This is a process

by which cells transition from an epithelial phenotype to a mesenchymal phenotype as the expression of epithelial genes such as E-cadherin is decreased and mesenchymal genes, such as vimentin are increased. This causes a loss of cell–cell adhesion and an increase in stem cell-like features making these cells more invasive, thereby allowing increased metastasis [18]. These pathways can also affect the tumour microenvironment (TME), specifically through the recruitment and interaction with cancer associated fibroblasts (CAFs) which have been shown to promote cell proliferation, angiogenesis, and metastasis of cancer cells [19]. Here, we will describe the role of some key GPCRs in various metastatic cancers as well as the therapeutic application of monoclonal antibodies (mAbs), peptides, and nanobodies (the VHH variable domain of heavy chain antibodies derived from camelids).

2. GPCRs in Metastatic Cancers

Metastasis is perhaps the most malignant characteristic of cancers and causes 90% of all cancer related deaths [20]. Metastasis is the process by which a primary tumour mass disseminates from its original site to a new tissue niche via blood vessels or the lymphatic system, and once this occurs they become highly resistant to therapy [21]. GPCRs have been shown to have a significant role in the ability of tumour cells to metastasize with a third of the druggable GPCR family shown to promote metastatic cancers (Figures 1 and 2, Table 1).

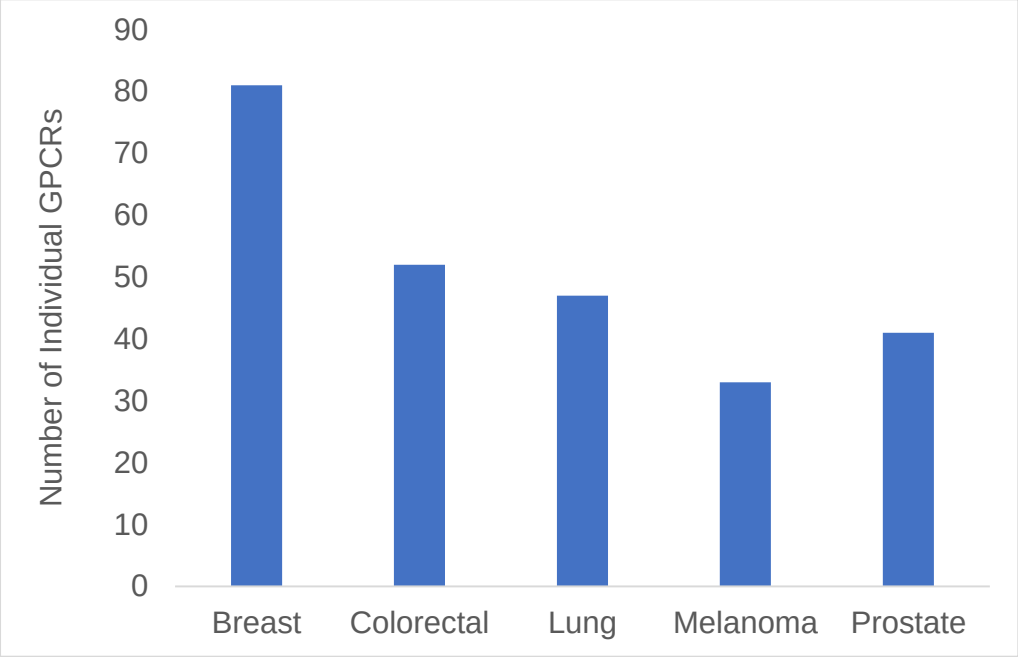

Figure 1. Number of GPCRs involved in the top five most common metastatic cancers.

Table 1. Table of the GPCRs involved in the most common metastatic cancers. Column one represents the name of the receptor, and column two represents the type of metastatic it is involved in.

Receptor	Metastatic Cancer	Reference
5-HT1A	Prostate	[22]
5-HT1D	Colorectal	[23]
5-HT2B	Colorectal	[24]

Table 1. *Cont.*

Receptor	Metastatic Cancer	Reference
5-HT4	Prostate	[25]
5-HT7	Breast, Lung	[26,27]
A2BR	Breast, Colorectal, Lung, Melanoma	[28,29]
A3R	Breast, Colorectal	[30]
ACKR2	Breast, Lung	[31,32]
ADGRE1	Colorectal	[33]
ADGRF5	Breast, Colorectal	[34,35]
ADGRG1	Breast	[36]
ADRA2A	Breast	[37]
ADRA2C	Breast	[37]
ADRB2	Breast, Colorectal	[37,38]
ADRB3	Lung	[39]
APNLR	Breast, Lung, Prostate, Melanoma	[40–42]
AVPR1A	Prostate	[43]
C3AR1	Breast, Melanoma	[44,45]
C5AR1	Breast, Colorectal, Melanoma,	[45–47]
CASR	Breast, Prostate	[48]
CB2	Breast, Lung, Prostate	[49,50]
CCKAR	Lung	[51]
CCR1	Breast, Colorectal, Lung, Melanoma, Prostate	[52–54]
CCR2	Breast, Colorectal, Lung, Melanoma, Prostate	[55,56]
CCR3	Breast, Colorectal, Melanoma, Prostate	[57–60]
CCR4	Breast, Colorectal, Melanoma, Prostate	[61–63]
CCR5	Breast, Colorectal, Lung, Melanoma, Prostate	[64,65]
CCR6	Breast, Colorectal, Lung, Melanoma, Prostate	[66–69]
CCR7	Breast, Colorectal, Lung, Melanoma, Prostate	[66,70]
CCR8	Breast, Colorectal, Lung, Melanoma	[66,71]
CCR9	Breast, Lung, Melanoma, Prostate	[66,72]
CCR10	Breast, Lung, Melanoma	[73,74]
CCRL2	Colorectal, Prostate	[75,76]
CRHR1	Prostate	[77]
CX3CR1	Breast, Lung, Prostate	[78–80]
CXCR1	Breast, Colorectal, Lung, Melanoma, Prostate	[81–83]
CXCR2	Breast, Colorectal, Lung, Melanoma, Prostate	[81,83,84]
CXCR3	Breast, Colorectal, Lung, Melanoma, Prostate	[85–87]
CXCR4	Breast, Colorectal, Lung, Melanoma, Prostate	[88,89]

Table 1. *Cont.*

Receptor	Metastatic Cancer	Reference
CXCR5	Breast, Lung, Melanoma, Prostate	[90]
CXCR6	Breast, Lung, Melanoma, Prostate	[91–93]
CXCR7	Colorectal, Lung, Melanoma, Prostate	[94–97]
EDNRA	Colorectal	[98]
EDNRB	Breast, Melanoma	[99,100]
F2R	Breast, Colorectal Melanoma, Prostate	[101–103]
FFAR1	Breast, Prostate	[104,105]
FPR1	Breast, Colorectal, Lung, Melanoma	[106–109]
FPR2	Breast, Colorectal	[106,110]
FSH	Breast, Lung, Prostate	[111,112]
FZD1	Breast	[113]
FZD2	Breast, Colorectal, Lung	[114]
FZD5	Prostate	[115]
FZD7	Breast, Colorectal, Melanoma,	[116–118]
FZD8	Breast, Colorectal, Prostate	[119–121]
GABBR2	Breast	[106]
GALR1	Colorectal	[122]
GNRHR	Breast, Colorectal, Prostate	[123,124]
GPER	Breast	[125]
GPR107	Prostate	[126]
GPR132	Breast	[127]
GPR141	Breast	[128]
GPR15	Colorectal	[129]
GPR161	Breast	[130]
GPR171	Breast, Lung	[131,132]
GPR176	Colorectal	[133]
GPR18	Melanoma	[134]
GPR19	Breast, Melanoma	[135,136]
GPR31	Colorectal	[137]
GPR34	Colorectal	[138]
GPR35	Colorectal	[139]
GPR37	Lung	[140]
GPR39	Breast, Prostate	[141,142]
GPR4	Colorectal, Melanoma	[143,144]
GPR50	Breast	[145]
GPR55	Breast	[146]
GPR65	Colorectal	[147]

Table 1. *Cont.*

Receptor	Metastatic Cancer	Reference
GPR75	Prostate	[148]
GPR78	Lung	[149]
GPRC6A	Breast, Prostate	[150,151]
GRM3	Breast	[152]
GRPR	Colorectal	[153]
GSHR	Lung, Melanoma, Prostate	[154–156]
HCAR1	Breast	[157]
HRH1	Breast,	[158]
HRH3	Breast, Lung	[159,160]
HTR2B	Colorectal	[161]
LGR4	Breast, Lung, Prostate	[162–164]
LGR6	Breast, Colorectal, Lung	[165–167]
LH	Breast, Colorectal	[168,169]
LPAR1	Breast, Lung, Melanoma	[170–172]
LPAR2	Breast	[173]
LPAR3	Breast	[174]
LPAR5	Breast	[175]
LPAR6	Breast	[176]
LTB4R	Breast	[177]
M2R	Colorectal, Lung	[178,179]
M3R	Lung	[180]
MRGD	Lung	[181]
NMUR1	Colorectal	[182]
NMUR2	Colorectal	[183]
NPY1R	Breast, Colorectal, Melanoma, Prostate	[184]
NPY5R	Breast	[185]
NTSR1	Breast, Lung	[186,187]
OPKR1	Breast	[188]
OPN3	Lung	[189]
OXER1	Breast, Prostate	[150,190]
OXTR	Breast, Melanoma	[191,192]
P2YR1	Lung	[193]
P2YR11	Breast	[194]
P2YR6	Lung	[195]
PROK1	Colorectal	[196]
PROK2	Colorectal	[197]
PTAFR	Breast	[198]

Table 1. *Cont.*

Receptor	Metastatic Cancer	Reference
PTGER1	Colorectal	[199]
PTGER2	Prostate	[200]
PTH1R	Breast, Lung	[201,202]
QRFPR	Prostate	[203]
RXFP1	Breast	[204]
S1PR1	Breast, Colorectal	[205,206]
S1PR3	Breast, Colorectal	[206,207]
SUNCR1	Lung	[208]
TACR1	Breast	[209]
TACR2	Lung	[210]
TBXA2R	Breast, Colorectal, Lung, Melanoma, Prostate	[211]
XCR1	Breast, Lung	[212,213]

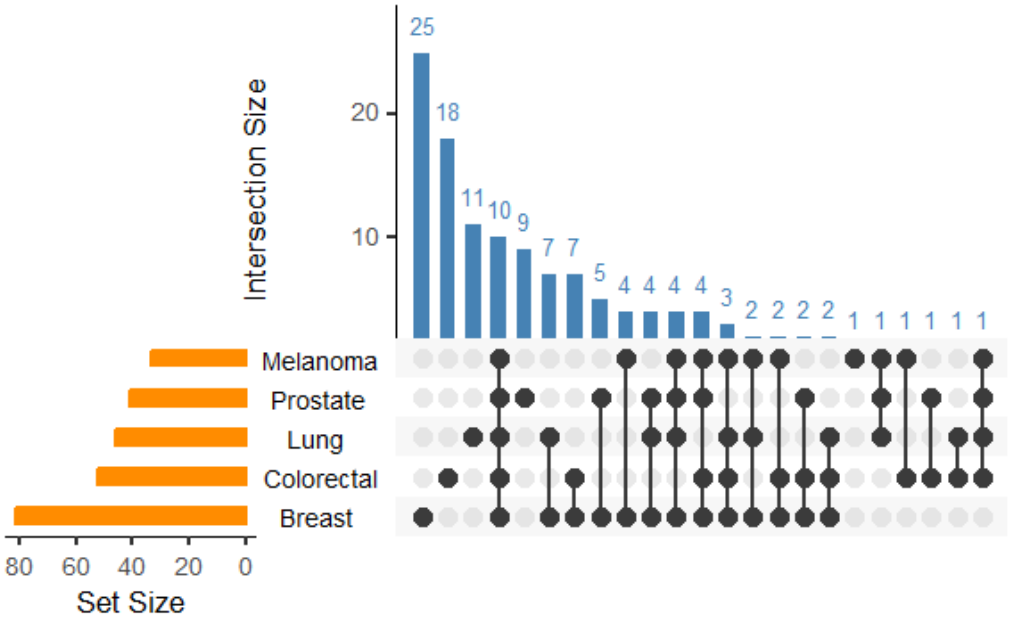

Figure 2. Upset plot showing the overlap of different GPCRs in the top five most common metastatic cancers. Histogram in blue (top) showing the distribution of individual GPCRs across all five cancer types. Bar chart in amber (bottom left) showing total numbers of receptors per cancer type. Black spheres linking both datasets. Data taken from Table 1.

2.1. Metastatic Breast Cancer

Metastatic breast cancer is one of the leading causes of cancer-related deaths in women worldwide, and the role of GPCRs in this disease is a rapidly growing area of research, due to their role in key events during metastasis [214]. The chemokine receptor family for example, one of the largest class A receptor subtypes, has been extensively studied. Chemokine receptors engage in a large array of cellular functions, but their most prominent function is in cell movement. They regulate movement in different ways, including chemotaxis, haptotaxis, and transcellular migration [215,216]. Among 92 two GPCRs that have been implicated in the metastasis of breast cancer cells, CXCR4 is the possibly the best characterised, with a significant majority of published research describing the role of this receptor in metastasis, while there are many more that have had very few studies

into their involvement in metastatic cancer such as NPY1R/5R or RXFP1. CXCR4 in breast cancer plays a critical role in cancer progression by promoting growth as well as allowing for metastasis to distant tissues that express its ligand CXCL12 including lung and bone niches [217]. Knocking out CXCR4 in mice delayed and regressed the growth of primary tumours, as well as preventing metastasis, showing its key role in the growth of primary tumours as well as metastasis of breast cancers [218]. HER2 activity has been shown to enhance the expression of CXCR4 as well as prevent its degradation, facilitating metastasis to the lungs [219]. More recently it has been shown that inhibiting CXCR4 with plerixafor®, a small molecule antagonist to the receptor, reduces fibrosis in breast cancers that have metastasized to the lungs and liver, increases T-lymphocyte infiltration, and more than doubles the sensitivity of breast cancer cells to immunotherapy [220]. Another well-studied chemokine receptor involved in breast cancer metastasis is CCR7. CCR7 has been shown to form heterodimers with CXCR4 in breast cancer cells resulting in a metastatic phenotype as well as allowing for increased survival in the absence of an extracellular matrix (ECM) attachment [221]. Silencing CCR7 in metastatic breast cancer cell lines has been shown to reduce motility, migration, and invasion both in vitro and in vivo [31,222]. PAR1 is a protease-activated GPCR whose interaction with the extracellular protease thrombin has been shown to activate breast carcinoma cells and initiate their invasion [223]. The use of two PAR1 antagonists, MMP-1 inhibitor and P1pal7, caused significant apoptosis and reduced metastasis to the lungs by 85% in xenografted mice [224]. The expression of PAR1 on breast cancer cells causes a loss of epithelial markers such as E-cadherin and gain of mesenchymal markers including vimentin, shifting them to an invasive phenotype and allowing a HMG2A mediated invasion of breast cancer [225]. PAR1 expression has been shown to be induced by the Twist transcriptional factor, which also downregulates E-cadherin expression, promoting tumour progression and metastasis. PAR1 activation leads to the downregulation of the Hippo pathway, thereby inducing an epithelial–mesenchymal transition in breast cancer [101]. ADGRF5 (GPR116) is a member of the adhesion GPCR family, the second largest of the GPCR families. They have long N-terminal adhesion regions and are involved in cell adhesion, motility, and immune response [226]. The GPCR ADGRF5 has been shown to be a regulator of breast cancer metastasis, with knock out of ADGRF5 in triple negative breast cancer cells, reducing metastasis in mouse models. ADGRF5 signalling modulates the formation of actin stress fibres and lamellipodia via Rho GTPase signalling [227]. More recent studies into the role of ADGRF5 in breast cancer metastasis showed that the loss of ADGRF5 in breast cancer cells reduced cell motility, extracellular matrix remodelling, and tumour growth. It was also shown that the loss of ADGRF5 increased the expression of MMP-8, a metalloprotease that leads to the secretion of CXCL8, resulting in increased infiltration of tumour associated neutrophils (TANs) [35]. GPER (GPR30) is a GPCR that mediates oestrogen signalling and has been shown to be significantly associated with other pro-migratory genes and metastatic pathways in ER negative breast cancer patients; high expression of GPER is also associated with lower disease-free interval in these patients [228]. GPER has also been shown to mediate oestrogen signalling in cancer associated fibroblasts contributing to migration, spreading, and the triggering of more aggressive malignant features [125]. Conversely, it has also been shown that the activation of this receptor in triple negative breast cancer using its endogenous ligand G1 reduces the angiogenesis and migration of these cells, as well as xenograft tumours [229], further showing the need to understand the temporal activation of receptors more clearly to target them therapeutically.

2.2. Metastatic Colorectal Cancer

Colorectal cancer (CRC) is responsible for a third of all cancer deaths in the United States. Twenty percent of all patients are diagnosed with metastatic colorectal cancer, with a 5-year survival rate of less than 5%, highlighting the lack of effective treatments in this area [230]. Colorectal cancers metastasize to many organs but predominantly the liver, lungs, and the peritoneum, with a number of GPCRs involved in driving this behaviour. CXCR4 has a well-described role in CRC, with high expression levels in patients associated with poor overall survival and progression-free survival [231]. The activation of the CXCR4/CXCL12 axis was shown to upregulate a series of miRNAs that interact with tumour associated macrophages at the invasive fronts of tumours, resulting in M2 polarisation of these macrophages. These cells then increase the metastatic capacity of CRC cells via secretion of VEGF and enhancing EMT [232,233]. The overexpression of CXCR4 has been shown to induce the formation of pseudopodia. The reorganisation of the cytoskeleton in CRC cells and activation via its ligand causes the secretion of a metalloproteinase MMP-9, increasing cell migration and metastasis [217,234]. CXCR4 interacts with CD133, a marker of CRC stem cells, in CRC metastasis. CXCR4+CD133+ cells were found in higher amounts in metastatic liver cancer, and were shown to be involved in carcinogenesis [235]. CXCR7 is active in CRC, sharing the same ligand and heterodimerizing with CXCR4. CXCR7 has been shown to be overexpressed in CRC. The gene silencing of CXCR7 inhibited growth, invasion, and induced apoptosis in CRC cells. This was due to the downregulation of PCNA, a nuclear protein and marker of cell proliferation and MMP-2, suggesting the involvement of ERK1/2 and β-arrestin signalling pathways [236]. CXCR7 activation by CXCL12 was shown to bias its signalling to β-arrestin, which promoted EMT and metastasis through induction of YAP1 nuclear transportation, resulting in the downregulation of miRNAs and promoting expression of $DCLK_{1,}$ a tumour stem cell marker [237]. CXCR7 regulates CAFs, which are known to drive cancer progression. CXCR7 expression is positively correlated with CAF activation markers in colorectal cancer patients. CXCR7+ CRC cells upregulate miRNAs that cause CAFs to increase their expression of inflammatory cytokines that can trigger EMT [95], allowing the metastasis of CRC cells to the lungs in xenografts. Prokineticin receptors are a family of GPCRs shown to be involved in CRC metastasis. Their activity plays a role in chemotaxis and the production of pro-inflammatory cytokines [238]. Pk-r1 and Pk-r2 are the only receptors in this family and their expression is upregulated in CRC cell lines. Activation of these receptors in CRC cell lines causes a 3–5-fold increase in in vitro metastasis, along with an increase in mRNA and protein levels of metalloproteinases MMP-2,7 and 9. This increase in metastasis was reduced with the addition of an anti-Pk-r2 antibody, suggesting that the Pk-r2 receptor is involved in the metastatic response [239]. In a comparative study, Pk-r2 was shown to be expressed in 45% of human CRC samples and was associated with a high rate of vascularisation and metastasis to the liver and lymph nodes. Pk-r2 expression increased with tumour grade and its expression was negatively correlated with the 5-year survival rate [240]. The use of an antibody against PROK1, the ligand for Pr-k2, is able to reduce the size and amount of liver metastatic lesions in a mouse model for CRC, with immunohistochemistry showing a reduction in the amount of ki-67, a marker of dividing cells [241]. Another of the adhesion GPCR family ADGRG1 (GPR56) is indicated in the progression and metastasis of CRC. ADGRG1 has been shown to be overexpressed in patients with CRC and is associated with a poor prognosis. Overexpression in CRC cell lines promoted migration and invasion via EMT through PI3K/AKT signalling. Knock out of ADGRG1 caused CRC cells to arrest in G0/G1 phase preventing proliferation and reducing EMT markers such as N-cadherin and vimentin [242]. Study of ADGRG1 in patients with CRC, showed that downregulation was indicated with less cell proliferation, migration, and invasion. Those with a higher

expression of ADGRG1 had a lower 5-year survival rate, and ADGRG1 expression was found to be a significant prognostic factor for overall survival [243].

2.3. Metastatic Lung Cancer

Lung cancer can be divided into small cell and non-small cell lung cancer (NSCLC), the latter making up the vast majority of cases and the prior being more aggressive. Much like most metastatic cancers the chemokine receptor family plays a key role in metastatic lung cancer. CXCR4 is highly upregulated in NSCLCs, and those with the highest expression had a much higher metastatic potential. Overexpression in NSCLC cell lines showed increased migration and invasion, which could be ablated with treatment using anti-CXCR4 antibodies in mice through the prevention of CXCL12 activation of the receptor [244]. The same study also showed that inoculation of lung cancer cells with low CXCR4 expression resulted in far less metastatic clusters than with high-expressing cells. CXCL12-induced migration of NSCLCs was shown to be CXCR4- and not CXCR7-dependent. Knockouts of both were designed in NSCLC lines, and migration was ablated when CXCR4 was knocked out. Xenografts in mice showed that CXCR4 was necessary for metastasis, not CXCR7 [245]. In a meta-analysis study, it was found that CXCR4 was more highly expressed in NSCLC than normal tissue, its expression was higher in later stage cancers as well as in metastatic NSCLC. Patients with higher CXCR4 expression had lower survival rates than those with low expression [246]. One of the treatments for NSCLC is cisplatin therapy, although that can cause long term detrimental effects such as the promotion of pro-metastatic environments. Cisplatin treatment has been shown to reduce tumour size while also increasing secretion of CXCL12, recruitment of metastasis initiating cells and pro-invasive CXCR4+ macrophages, that promote spontaneous metastasis. Cotreatment with a CXCR4 antagonist was able to prevent this metastasis and highlights a route for CXCR4 targeted treatment in NSCLC [247]. The chemokine receptor CXCR2 is described in metastatic lung cancer. In a mouse model of Lewis lung cancer, depletion of CXCR2 resulted in reduced cell proliferation and the rate of spontaneous metastasis [248]. These results were replicated in a model overexpressing CXCR2 with the use of a monoclonal antibody that blocked CXCR2 activation. Equivalent results were shown in the NSCLC lung adenocarcinoma cell line, where knocking out CXCR2 or blocking with a small molecule antagonist decreased invasion and metastasis of cells expressing CXCR2. Samples from humans with lung adenocarcinoma showed that CXCR2 expression was associated with poor prognosis, a history of smoking, as well as RAS pathway activation [249]. In a mouse model of lung cancer overexpressing CXCR2, an increase in the infiltration of TANs was shown, while an inhibition of CXCR2 ameliorated this infiltration as well as increased antitumor T-cell activity, through the promotion of CD+ T cell activation. Much like with CXCR4, cisplatin therapy can lead to CXCR2 mediated immune suppression, and co-treatment with a CXCR2 antagonist was able to show greater antitumor effects than just cisplatin [250].

Lysophosphatidic acid (LPA) receptors are a family of six receptors involved in diverse cellular processes such as cell proliferation, migration, and differentiation [251]. LPA is the endogenous ligand for these receptors, and it is produced when LPC is catalysed by ATX to form LPA. It was shown that the levels of ATX in NSCLC correlated with the tumour stage and grade, suggesting the role of its receptors in lung cancer progression [252]. It was shown that using an LPAR1–4 antagonist was able to reduce cell migration and invasion in vitro, and loss of vasculature and tumour growth in a xenograft model of NSCLC [253]. More recently, the activity of LPA in lung cancer was specifically tied to LPAR1, as this receptor is overexpressed on CAFs, which are known to promote EMT and migration. By silencing LPAR1, CAF proliferation in NSCLC can be reduced, showing the therapeutic potential of targeting LPAR1 for fibrous metastatic lung cancer [171]. LPAR2 contributes

to the survival of highly metastatic cell lines to cisplatin treatment via adenylyl cyclase inhibition, whereas LPAR3 was shown to be beneficial in cisplatin treatment [254]. This shows the intricate nature of cell signalling mediated by GPCRs of the same family. GPR78 is an orphan GPCR that is associated with lung cancer metastasis. It is expressed in lung cancer cells and mediates actin stress fibres in a RhoA- and Rac1-dependent manner, thus regulating cell motility. Knocking out GPR78 suppresses cell migration, indicating potential to target GPR78 therapeutically [149]. The use of miRNA-936 was shown to reduce GPR78 expression and was able to regulate NSCLC proliferation, invasion, and migration [255].

2.4. Metastatic Prostate Cancer

Prostate cancer is the one of the fastest growing cancers in Europe, and metastatic prostate cancer has a 5-year survival rate of only 30%, with the current treatment generally including hormone therapy, surgical resection, or castration [256]. As with many other cancers, extensive research aims to understand the involvement of GPCRs in order to develop new therapies. CXCR4 signalling is implicated in the development of metastatic prostate cancer. CXCR4 is overexpressed in prostate cancer cells, and its expression correlates with later stage tumours as well as metastasis to both the bones and lymph nodes, a poor prognosis predictor for patients [257]. In prostate cancer, CXCR4 localises to the nucleus where its active signalling could be a mechanism for continuous CXCR4 activation in metastatic prostate cancer [258]. CXCR4 has been shown to interact with PI4KIIIα, a PI4K kinase, and through this interaction on lipid rafts it is able to mediate tumour metastasis, while PI3KIIIα knockouts inhibit CXCR4 mediated prostate cell metastasis [259]. CCR5 signalling is also involved in the metastasis of prostate cancer and is overexpressed in prostate cancer. Activation by its ligand CCL5 induces proliferation and stimulates invasion, which is reduced by a CCR5 antagonist [260]. One of the principal organs for prostate cancer to metastasize to is bone. Studies on CCR5 activation during prostate cancer metastasis in mouse models and treatment with two small molecule inhibitors of CCR5 originally designed for HIV-1 therapy Maraviroc and Vicriviroc, which are CCR5 antagonists, reduced the tumour burden in both the bones and prostate [261]. The tumour suppressor miRNA-455-5p targets CCR5 in prostate cancer, and its overexpression was able to suppress CCR5 mediated proliferation, migration, and induce apoptosis in prostate cancer cells [262].

GPRC6A is an orphan GPCR that has recently gained attention for its role in prostate cancer. *GPRC6A* transcripts are upregulated in prostate cancer, and in prostate cell lines, with ligands to GPRC6A such as calcium and arginine showing a dose-dependent stimulation of ERK activity as well as chemotaxis and proliferation [263]. This dose-dependent response was ablated by silencing GPRC6A. In xenograft models of prostate cancer, cells expressing GPRC6A promoted cell migration and proliferation after stimulation with osteocalcin via ERK and AKT signalling, in comparison to knockout cells [264].

2.5. Metastatic Melanoma

Melanoma is another rapidly increasing problem worldwide, and is the fifth most common cancer type in men, and the sixth in women worldwide [265]. Similarly to other metastatic cancers, there are many GPCRs involved in melanoma but of those cancers discussed here, it has the fewest associated receptors identified. As with almost all metastatic cancers, CXCR4 has been definitively identified as a key driver of metastatic melanoma. It was discovered early on that CXCR4 expression in melanoma cells was correlated with poor prognosis and the risk of recurrence was 2.5-fold higher and death 3 times higher than those with low CXCR4 expression [266]. CXCR4 has been shown to assist melanoma metastatis to bones, and exosomes from those cells were able to cause the upregulation of CXCR7 a mem-

ber of the CXCL12/CXCR4/CXCR7 signalling axis to promote them to a more osteotropic phenotype [267]. In a meta-analysis of melanoma cancer patients, CXCR4 overexpression in melanoma cells was correlated with ulceration, tumour thickness, and lymph node metastasis, and is a strong prognostic biomarker for metastatic melanoma [268]. The use of a CXCR4 antagonist in a murine melanoma model showed antitumor effects that were additive when used in combination with an anti-PDL1 antibody. They also showed a reduction in immunosuppressive regulatory T cells and increasing tumour specific CD8+ cells leading to a reduction in tumour growth [269]. CCR10 is another member of the chemokine family involved in the metastasis of melanoma, with studies in a mouse melanoma model that overexpressed CCR10 showing that these cells had a higher rate of proliferation, the cytoskeleton underwent rearrangement and they had increased migration in response to CCR10 ligands vs. non CCR10 expressing cells [270]. CCR10 expression in melanoma cells was correlated with significantly lower survival time and time to progression, as well as a higher chance of cerebral metastasis [271]. CCR10 influences the immune system, allowing melanoma cells to evade immunosurveillance. T lymphocyte density is inversely correlated with CCR10 expression and lymph node metastasis are shown to have a higher expression of CCR10 [272].

Another family of GPCRs that have been shown to be involved in metastasis are the pyrimidinergic receptors (P2YRs), that participate in the signalling of nucleotides such as ATP and UTP, which have been shown to affect inflammation and the composition of the tumour microenvironment [273,274]. The GPCR P2Y6 has been shown to be involved in other metastatic cancers such as breast cancer [275], and has also been implicated in melanoma. In a mouse model for melanoma transplantation of B16F10 cells in a P2Y6 knockout, there were a significantly reduced number of metastatic lung tumours, and increased survival rates vs. the wild type [276]. Knockout of P2Y6 had no effect on tumour growth, only the ability to metastasize [277]. Expression of P2Y1/2 and 6 in melanoma cells showed that the addition of a P2Y1 agonist reduced cell proliferation and number, while a P2Y2 agonist was shown to increase cell growth and proliferation.

3. Biologics Targeting GPCRs in Cancer

Due to the increasingly well-understood role of GPCRs in cancer progression, a large field of work has been developed to identify therapeutic agents to ameliorate the effects of their aberrant expression and signalling, with a shift toward biologics over small molecules in the last decade. To effectively target these receptor structures embedded in the membrane, biologics must be able to specifically target the extracellular region of the receptor, and depending on where they bind in the receptor, they can have different effects on GPCR signalling. In a recent study, Peters et al. proposed an annotation scheme for naming GPCR binding sites clearly and meaningfully. The name of a binding site consists of the GPCR Class, the location (IH: intrahelical EH: extrahelical, IC: intracellular, and EC: extracellular with respect to transmembrane (TM) helices), and the binding site location with respect to the membrane (ext: exterior, mid: middle, and int: interior) (Figure 3). Biologics such as mAbs have a greater specificity and potential efficacy than standard small molecules that allow for precision targeting of GPCRs. There remains a significant unmet need for therapies targeting the vast majority of GPCRs, with very few passing clinical trial stages. In fact, there are only 13 currently approved drugs, of which 10 can be considered biologics (Table 2). Nanobodies, engineered proteins, and peptides are other classes of biologics which are an increasingly promising area for targeting GPCRs, their comparatively smaller size relative to mAbs allow better penetration and access. Engineered proteins and peptides possess a structural design rationale related to the target that can allow for increased efficacy.

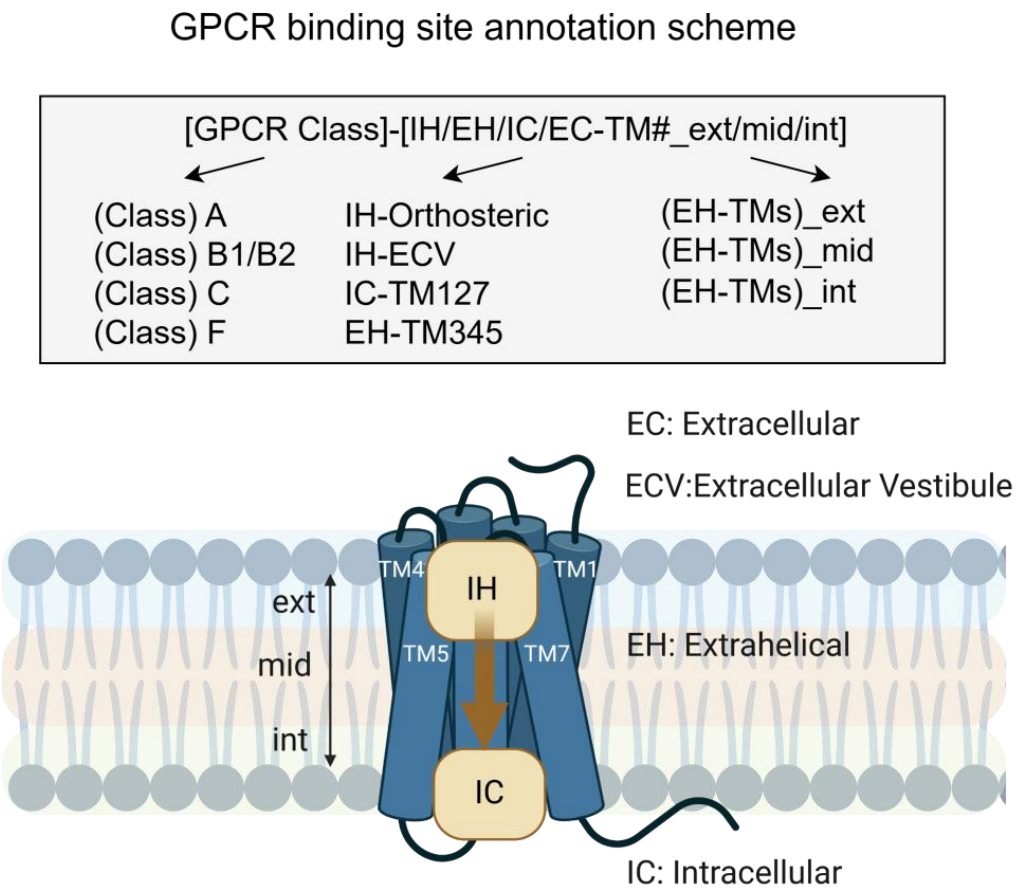

Figure 3. Schematic representation of GPCR structure in the cell membrane with ligand binding sites annotated. (A) GPCR binding site annotation starts with GPCR Class (A, B1, C) followed by position with respect to the transmembrane domain (EC: extracellular, IH: intrahelical, ECV: extracellular vestibule, IC: intracellular, and EH: extrahelical). For extrahelical binding sites, the annotation is tagged with membrane position along the vertical axis (ext: exterior, mid: middle, or int: interior). Adapted from Peters et al., 2024 [278].

Table 2. Table of approved drugs targeting GPCRs for cancer treatment. Sorted by drug type including monoclonal antibodies, peptides, and small molecule drugs, showing their target, mechanism, and indication.

Name	Target Receptor	Drug Type	Status	Mechanism	Type of Cancer	Reference
Mogamulizumab	CCR4	Monoclonal Antibody	Approved	Antagonist	Mycosis fungoides/Sezary syndrome	[279]
Talquetamab	GPRC5D	Bispecific Antibody	Approved	Agonist	Multiple Myeloma	[280]
Motixafortide	CXCR4	Peptide	Approved	Antagonist	Hematopoietic Stem Cell Mobilisation in Multiple Myeloma	[281]
Goserlin	GNRHR	Synthetic Peptide	Approved	Agonist	Advanced Prostate/Breast Cancer	[282]
Lanreotide	SSR2	Synthetic Peptide	Approved	Agonist	Metastatic/Advanced Pancreatic Neuroendocrine Tumours	[283]

Table 2. *Cont.*

Name	Target Receptor	Drug Type	Status	Mechanism	Type of Cancer	Reference
Abralelix	GNRHR	Synthetic Peptide	Approved	Antagonist	Advanced Prostate Cancer	[284]
Leuprolide	GNRHR	Synthetic Peptide	Approved	Agonist	Advanced Prostate Cancer	[285]
Degarelix	GNRHR	Synthetic Peptide	Approved	Antagonist	Advanced Prostate Cancer	[286]
Histrelin	GNRHR	Synthetic Peptide	Approved	Agonist	Advanced Prostate Cancer	[287]
Triptorelin	GNRHR	Synthetic Peptide	Approved	Agonist	Advanced Prostate Cancer	[288]
Vismodegib	SMO	Small Molecule	Approved	Antagonist	Metastatic/Advanced Basal Cell Carcinoma	[289,290]
Sonidegib	SMO	Small Molecule	Approved	Antagonist	Locally Advanced Basal Cell Carcinoma	[291]
Plerixafor	CXCR4	Small Molecule	Approved	Antagonist	Hematopoietic Stem Cell Mobilisation in Multiple Myeloma/Non-Hodgkins Lymphoma	[292,293]

3.1. Mononclonal Antibodies

Monoclonal antibodies over the last few decades have revolutionised cancer research and therapies. Since the first approved monoclonal antibody, Rituximab in 1997 [294], over 197 antibodies have been approved by the FDA/EMA, and over 90 of those have been indicated for cancer [295]. Trastuzumab (Herceptin) is a mAb that targets the tyrosine kinase receptor HER2. HER2 is overexpressed in 20–30% of breast cancers, and prior to the discovery of trastuzumab, HER2 positive breast cancer had a poor overall survival [296]. This discovery improved the outcome of patients with HER2 positive cancer, although many patients with early-stage breast cancer relapse and those with metastatic breast cancer develop resistance within a decade [296,297]. Another blockbuster mAb is Pembrolizumab (Keytruda) which is a checkpoint inhibitor targeting PD-L1, and is indicated for many cancers such as multiple myeloma and NSCLC [298]. The success of this discovery has led to it being one of the top biologic blockbuster drugs, earning close to 20$ bn USD annually.

To date, there are only three approved mAb treatments targeting GPCRs, of which two are indicated for cancer. Erenumab is a calcitonin gene-related peptide receptor antagonist that is approved for the treatment of migraines [299]. It was found to greatly reduce monthly migraine time and begins its effects within the first week of treatment. It works by preventing binding of the CGRP peptide to the receptor, thereby decreasing vasodilation and inflammation associated with migraines [300]. The other two approved antibodies are Mogamulizumab and Talquetamab. Mogamulizumab is an anti-CCR4 mAb that has been approved for the treatment of T-cell lymphomas mycosis fungoides and Sézary syndrome, two of the most common T-cell lymphomas [301]. Prior to the discovery of Mogamulizumab, the only treatment was allo-HSCT, which has a high morbidity with overall survival being between 30 and 40% [281]. In a phase 3 international trial, Mogamulizumab was compared to Vorinostat, a standard treatment for T-cell lymphoma, in patients with early-stage mycosis fungoides. It was found that Mogamulizumab had a median progression-free survival of 6.7 months compared to 3.8 months in the Vorinostat group and had a higher proportion of patients who had an overall response [302]. Despite these promising results, patients can eventually develop resistance to Mogamulizumab treatment. Resistance

usually develops as patients lose the target antigen CCR4, rendering Mogamulizumab ineffective, but there is another unknown mechanism of resistance in which patients retain high expression of CCR4 [303]. Talquetamab is a bispecific mAb that targets CD3 and GPRC5D and was approved for the treatment of multiple myeloma in August 2023 [304]. Most patients with multiple myeloma relapse and those who relapse have poor overall survival of roughly 12% [280]. Talquetamab can bind to GPRC5D, a biomarker associated with high-risk myeloma, and CD3, and induces T-cell mediated death of myeloma cells expressing GPRC5D via recruitment and maturation of T-cells [305]. In a phase I/II study of patients with triple and penta-refractory multiple myeloma, Talquetamab showed an overall response rate of around 70% up to 18 months after treatment. Interestingly, results were similar for the cohort who had previously received other bispecific antibody or CAR T treatments, suggesting the potential use of this in combination with those treatments to overcome resistance [306,307]. One caveat is that almost all patients had adverse effects of grade 3 or higher, although none died, with the most common being cytokine-release syndrome and infections [307]. Another mAb of interest that has not yet received approval but has reached late-stage clinical trials for its potential use in HIV and COVID-19 treatment is Leronlimab. Leronlimab is a CCR5 antagonist mAb. Leronlimab is currently in phase III clinical trials for preventing HIV infection [308], but has previously shown promise in treating breast cancer. In triple negative breast cancer lines, Leronlimab was shown to reduce migration, calcium signalling, as well as enhance the effect of doxorubicin in killing breast cancer cells. Furthermore, in xenograft mice models it was able to reduce tumour burden of > 95% after 6 weeks of treatments [309].

Leronlimab has also shown success in early clinical trials; a phase I trial showed that it was well-tolerated in combination with carboplatin and showed early signs of anti-tumour activity [310]. In a basket study of advanced and metastatic solid tumours, Leronlimuab showed a median progression free survival of 6 months in greater than 75% of patients, along with a reduction in circulating tumour associated cells [311].

Monoclonal antibodies have revolutionised the oncology field and have become the gold standard of care in many cases, yet advancements have yet to be fully realised with GPCR targets, with many of the promising therapies failing due to adverse off target effects, lack of efficacy, or development of resistance.

3.2. Protein/Peptides

Protein and peptide therapies are the largest group of biological molecules targeting GPCRs. From hormone replacement to engineered protein analogues and mimetics, small polypeptides have become a staple in treating many diseases. For proteins and peptides, the most well-known success story for targeting GPCRs is in the treatment of type 2 diabetes via GLP-1R agonists. The first of these being exenatide, a synthetic peptide that naturally occurs in lizards' salivary glands. It has a 53% amino acid sequence identity with GLP-1, the natural ligand for GLP-1R, but has a greater than 1000-fold potency for the receptor. In phase 3 clinical trials, roughly 40% of patients had a reduction in HbA1c levels of $\leq$7% [312]. This was then approved for the treatment of type 2 diabetes in 2005, although it has been gradually phased out due to the emergence of superior protein therapies such as liraglutide, and semaglutide. These therapies are GLP-1 analogues that have superior half-life and potency for the receptor both showing greater glucose lowering and weight loss effects, leading to their approval in 2009, and 2017, respectively [313].

In terms of targeting GPCRs for use in cancer therapies there are eight therapies currently approved and many in clinical trials. Those that are approved mainly target three different receptor groups, gonadotropin-releasing hormone receptors, somatostatin receptors, and glycoprotein hormone receptors. Abaraelix is the first synthetic decapeptide GnRH antagonist developed, and is approved for the use in advanced prostate cancer. It works by inhibiting the activation of GnRH, preventing the secretion of LH and FSH, which thereby reduces testosterone levels, a key driver of prostate cancer. It was first approved in 2004 due to its ability to achieve medical castration quickly and well-tolerated without having testosterone flare ups which can impede treatment [314]. Lanreotide is a somatostatin analogue and is indicated for use in locally or metastatically advanced neuroendocrine tumours and is the only currently approved protein/peptide therapy for metastatic cancer [315]. The last class of currently approved protein/peptide therapies is goserelin, which in men is used for prostate cancer, and in women is used for breast cancer treatment. It is a synthetic analogue of luteinizing hormone-releasing hormone and antagonises LsHR to prevent the secretion of both testosterone and oestrogen [316]. The only peptide currently approved that does not target one of the three previously mentioned receptors is Motixafortide, which recently gained approval in September 2023 for its use in autologous stem cell transplantation in patients with multiple myeloma. Motixafortide is a cyclic synthetic peptide CXCR4 antagonist that causes haematopoietic stem and progenitor cells to mobilise rapidly and for a sustained duration. It was shown in a phase 3 trial in combination with G-CSF to increase the amount of mobilising CD34+ cells vs. G-CSF alone after just one apheresis, 92.5% vs. 26.2%, respectively [317]. It has also shown some promise for the treatment of metastatic diseases. In a phase II trial for metastatic pancreatic ductal adenocarcinoma (mPDAC) it was shown in use with pembrolizumab and chemotherapy to be well-tolerated and showed signs of efficacy in an aggressive disease [318]. It is now being assessed in another phase II trial for metastatic pancreatic dual adenocarcinoma where they are testing its effect on progression free survival [319]. Although there are few approved protein/peptide therapies, there are many more promising ones in clinical trials. One such example is Ctce-9908 (PTX-9908) a CXCR4 antagonist an analogue of its ligand CXCL12. It was shown to reduce tumour burden in a mouse model of breast cancer seven-fold, as well as greatly reducing metastasis [320]. It was then shown in a phase I/II trial for solid tumours to be well-tolerated, and showed early signs of efficacy in ovarian cancer, and then in 2005, it was granted orphan drug status for young adults with osteosarcoma [321,322]. Currently recruiting for a phase I/II trial for patients with non-resectable hepatocellular carcinoma [323].

3.3. Nanobodies

Nanobodies are a unique class of biologics, derived from camelid antibodies. Caemilds produce a class of unique antibody consisting of only heavy chains, and it is this single variable antigen-binding (VHH) fragment that makes up a nanobody [324]. Nanobodies have distinct structural characteristics that give them an advantage over monoclonal antibodies. Their small size (~15 kDa), convex shape, and their extended CDR3 allow them to bind onto what would be classically considered obstructed structures that mAbs would be unable to reach, giving them exclusive access to targeting these sites [324,325]. They are also quite stable and resistant to harsh conditions such as pH and heat; this gives them potential use in the tumour microenvironment as well as in combination with radiotherapy [326].

Due to these useful characteristics, research into their use as therapeutics has grown significantly over the last 20 years. This has resulted in the approval of the first nanobody-based therapy in Caplacizumab for the treatment of acquired thrombotic thrombocytopenic purpura (TTP). It works by targeting the von-Willebrand factor and preventing its interaction with platelet glycoprotein receptors. It was shown in a phase 3 trial to reduce the time for platelet normalisation, the incidence of TTP-related death as well as recurrence during the trial [327]. Recently another nanobody-based therapy was approved for the treatment of cancer. Ciltacabtagene, which is a chimeric antigen receptor (CAR) T-cell therapy that employs nanobodies as the targeting domain rather than the usual scFv domain [328]. It has been approved for use in patients with relapsed/refractory multiple myeloma after showing in clinical trials an overall response rate of 97.8% with a duration of response of 21.8 months [329]. As of yet, there are no approved nanobody-based therapies that target GPCRs, in fact there are currently only three nanobody-based therapies that have undergone clinical trials for targeting GPCRs and only one of them was for use in cancer therapy. The first to enter clinical trials was ALX-0651, a biparatopic anti-CXCR4 nanobody for use in cancer therapy that was selected from a library generated from peripheral blood mononuclear cells of llamas that were immunised with HEK293T cells expressing CXCR4. From this library, two nanobodies were selected and joined via GGGGS linker to form ALX-0651. In HIV models, it impeded CXCR4-mediated entry of HIV into MT-4 cells, and in monkeys it was able to mobilise stem cells in a comparable manner to plerixafor, an approved CXCR4 antagonist [330,331]. It was terminated after phase I clinical trials, as although it was well-tolerated and effective, preclinical data suggested that it would not surpass current standard care [332,333]. The second nanobody targeting GPCRs in clinical trials is the Anti-CXCR2 Biparatopic nanobody, currently being developed by Novartis for use in inflammatory disorders [334]. Biparatopic antibodies have already shown some preclinical promise as they were able to produce monovalent antibodies targeting CXCR2 that could selectively target and inhibit the activation of CXCR2 through both CXCL1 and CXCL8 binding. A biparatopic version was created by combining the top two candidates that bound distinct epitopes and showed that this increased the overall potency of the nanobody [335]. Finally, BI 665088 is a bivalent nanobody that targets CX3CR1. It was developed from a library of PBMCs from llamas immunised with CX3CR1 DNA, then followed by immunisation with Caki cells overexpressing CX3CR1, then immunisation with peptides derived from the extracellular loops of CX3CR1. From this library the top four lead candidates were chosen from competitive binding assays and turned into bivalent constructs from which BI 665088 emerged as the most promising. In murine atherosclerosis models, BI 665088 was able to reduce aortic plaque formation by 62% in 6 weeks, showing for the first time the effect of a CX3CR1 antagonist in vivo [336]. It has since been shown in phase I clinical trials to be well-tolerated in humans, with little to no adverse effects [337].

Despite the potential of nanobodies, they are yet to show any impact in the therapeutic targeting of GPCRs, although where they have been able to make an impact is in their use in stabilising GPCRs for X-ray crystallography and Cryo-EM, allowing for structural determination of various receptors and the mapping of their binding regions. This has been performed by developing nanobodies that recognise the intracellular parts of GPCRs, allowing them to stabilise GPCR conformations allowing for the generation of agonist-bound GPCR crystal structures [338]. This gives us valuable insight into the activation mechanism of GPCRs and can allow for structure lead drug design.

4. Conclusions

The targeting of G protein-coupled receptors (GPCRs) in metastatic cancer presents a promising frontier in cancer therapeutics. As integral players in cell signalling, GPCRs engage in many key processes that promote tumour growth, invasion, and metastasis, such as angiogenesis, immune modulation, and cell migration. Notably, GPCRs from the chemokine receptor family such as CXCR4, CXCR2, CCR7 are of great interest due to their role in tumorigenesis, but many other receptors as shown have a role such as receptors from the LPA and frizzled receptor families. Despite noteworthy progress, there are still several challenges to overcome in the development of biologics targeting GPCRs. The complex structure of GPCRs, which often includes multiple ligand-binding sites and the potential for biased signalling, as well as the formation of oligomers and receptors homo/heterodimerizing, complicates drug design. Additionally, the widespread expression of GPCRs across various tissues poses a risk for off-target effects, raising safety concerns. Therefore, a more refined understanding of GPCR signalling dynamics and tissue-specific receptor expression is essential for improving therapeutic precision and minimising adverse effects, and translating promising pre-clinical data into working therapeutics. The use of nanobodies and their ability to stabilise GPCRs for structural and functional analysis is one such method to help elucidate these issues. Nanoparticles/carrier systems also show promise in this area. These are colloidal nano-scale systems capable of carrying small molecules as well as larger macromolecules such as genes or proteins. These can protect biologics from the in vivo environment, preventing early degradation and accumulation in non-specific areas. They also can increase accumulation in tumours leading to greater cytotoxic effects [339]. Examples of these include liposomes similar to a cell membrane with a hydrophilic core and hydrophobic shell facilitating passive targeting, biomimetics which include cell membranes, extra cellular vesicles and viruses allowing evidence of the immune system and long circulation times, and lastly polymeric nanoparticles, which use alginate or gelatine to make nanogel spheres, yet these are still in early development with pharmacokinetics and biosafety still unclear [340].

The successes achieved with GPCR-targeted biologics, such as the inhibition of CXCR4/CCR4 by monoclonal antibodies, demonstrate the therapeutic potential of these receptors. However, the heterogeneity of GPCR expression in different tumour microenvironments necessitates further exploration of context-dependent targeting strategies. For future research, more in-depth studies into GPCR signalling bias are needed. Some GPCRs can signal through multiple intracellular pathways, with certain pathways being more oncogenic than others. By developing biologics that selectively target harmful signalling routes (biased agonism or antagonism), it may be possible to minimise off-target effects, while maximising therapeutic efficacy.

In conclusion, while the development of biologics targeting GPCRs in metastatic cancer has shown promise, there is still a need for more targeted, selective approaches to fully exploit their therapeutic potential. Continued research into GPCR signalling mechanisms and the TME will be crucial for translating these biologics into effective clinical treatments. As our understanding of GPCR biology expands, so too will the opportunities for novel interventions, potentially transforming the landscape of metastatic cancer treatment.

Funding: This research received no external funding.

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

References

1. Nieto Gutierrez, A.; McDonald, P.H. GPCRs: Emerging anti-cancer drug targets. *Cell. Signal.* **2018**, *41*, 65–74. [CrossRef]
2. Yang, D.; Zhou, Q.; Labroska, V.; Qin, S.; Darbalaei, S.; Wu, Y.; Yuliantie, E.; Xie, L.; Tao, H.; Cheng, J.; et al. G protein-coupled receptors: Structure- and function-based drug discovery. *Signal Transduct. Target. Ther.* **2021**, *6*, 7. [CrossRef] [PubMed]
3. Hauser, A.S.; Attwood, M.M.; Rask-Andersen, M.; Schiöth, H.B.; Gloriam, D.E. Trends in GPCR drug discovery: New agents, targets and indications. *Nat. Rev. Drug Discov.* **2017**, *16*, 829–842. [CrossRef] [PubMed]
4. UTEP GPCR Index. Available online: https://gpcr.utep.edu/ (accessed on 26 September 2024).
5. Mombaerts, P. Genes and ligands for odorant, vomeronasal and taste receptors. *Nat. Rev. Neurosci.* **2004**, *5*, 263–278. [CrossRef] [PubMed]
6. Alexander, S.P.H.; Christopoulos, A.; Davenport, A.P.; Kelly, E.; Mathie, A.A.; Peters, J.A.; Veale, E.L.; Armstrong, J.F.; Faccenda, E.; Harding, S.D.; et al. The Concise Guide to PHARMACOLOGY 2023/24: G protein-coupled receptors. *Br. J. Pharmacol.* **2023**, *180*, S23–S144. [CrossRef] [PubMed]
7. Heldin, C.H.; Lu, B.; Evans, R.; Gutkind, J.S. Signals and receptors. *Cold Spring Harb. Perspect. Biol.* **2016**, *8*, a005900. [CrossRef]
8. Jiang, H.; Galtes, D.; Wang, J.; Rockman, H.A. G protein-coupled receptor signaling: Transducers and effectors. *Am. J. Physiology. Cell Physiol.* **2022**, *323*, C731–C748. [CrossRef] [PubMed]
9. Hilger, D.; Masureel, M.; Kobilka, B.K. Structure and dynamics of GPCR signaling complexes. *Nat. Struct. Mol. Biol.* **2018**, *25*, 4–12. [CrossRef]
10. Gurevich, V.V.; Gurevich, E.V. GPCR signaling regulation: The role of GRKs and arrestins. *Front. Pharmacol.* **2019**, *10*, 125. [CrossRef] [PubMed]
11. Syrovatkina, V.; Alegre, K.O.; Dey, R.; Huang, X.Y. Regulation, Signaling, and Physiological Functions of G-Proteins. *J. Mol. Biol.* **2016**, *428*, 3850–3868. [CrossRef] [PubMed]
12. Wedegaertner, P.B. G Protein Trafficking. In *GPCR Signalling Complexes—Synthesis, Assembly, Trafficking and Specificity*; Dupré, D.J., Hébert, T.E., Jockers, R., Eds.; Springer: Dordrecht, The Netherlands, 2012; pp. 193–223.
13. Pavlos, N.J.; Friedman, P.A. GPCR Signaling and Trafficking: The Long and Short of It. *Trends Endocrinol. Metab.* **2017**, *28*, 213–226. [CrossRef] [PubMed]
14. Kim, K.; Han, Y.; Duan, L.; Chung, K.Y. Scaffolding of Mitogen-Activated Protein Kinase Signaling by β-Arrestins. *Int. J. Mol. Sci.* **2022**, *23*, 1000. [CrossRef] [PubMed]
15. Eichel, K.; von Zastrow, M. Subcellular Organization of GPCR Signaling. *Trends Pharmacol. Sci.* **2018**, *39*, 200–208. [CrossRef] [PubMed]
16. Wong, T.S.; Li, G.; Li, S.; Gao, W.; Chen, G.; Gan, S.; Zhang, M.; Li, H.; Wu, S.; Du, Y. G protein-coupled receptors in neurodegenerative diseases and psychiatric disorders. *Signal Transduct. Target. Ther.* **2023**, *8*, 177. [CrossRef] [PubMed]
17. Chaudhary, P.K.; Kim, S. An insight into gpcr and g-proteins as cancer drivers. *Cells* **2021**, *10*, 3288. [CrossRef]
18. Du, B.; Shim, J. Targeting Epithelial–Mesenchymal Transition (EMT) to Overcome Drug Resistance in Cancer. *Molecules* **2016**, *21*, 965. [CrossRef]
19. Mao, X.; Xu, J.; Wang, W.; Liang, C.; Hua, J.; Liu, J.; Zhang, B.; Meng, Q.; Yu, X.; Shi, S. Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: New findings and future perspectives. *Mol. Cancer* **2021**, *20*, 131. [CrossRef] [PubMed]
20. Guan, X. Cancer metastases: Challenges and opportunities. *Acta Pharm. Sin. B* **2015**, *5*, 402–418. [CrossRef]
21. Wells, A.; Grahovac, J.; Wheeler, S.; Ma, B.; Lauffenburger, D. Targeting tumor cell motility as a strategy against invasion and metastasis. *Trends Pharmacol. Sci.* **2013**, *34*, 283–289. [CrossRef] [PubMed]
22. Dizeyi, N.; Bjartell, A.; Nilsson, E.; Hansson, J.; Gadaleanu, V.; Cross, N.; Abrahamsson, P.A. Expression of serotonin receptors and role of serotonin in human prostate cancer tissue and cell lines. *Prostate* **2004**, *59*, 328–336. [CrossRef]
23. Zhu, P.; Lu, T.; Chen, Z.; Liu, B.; Fan, D.; Li, C.; Wu, J.; He, L.; Zhu, X.; Du, Y.; et al. 5-hydroxytryptamine produced by enteric serotonergic neurons initiates colorectal cancer stem cell self-renewal and tumorigenesis. *Neuron* **2022**, *110*, 2268–2282.e2264. [CrossRef] [PubMed]
24. Mao, L.; Xin, F.; Ren, J.; Xu, S.; Huang, H.; Zha, X.; Wen, X.; Gu, G.; Yang, G.; Cheng, Y.; et al. 5-HT2B-mediated serotonin activation in enterocytes suppresses colitis-associated cancer initiation and promotes cancer progression. *Theranostics* **2022**, *12*, 3928–3945. [CrossRef]
25. Nakamura, Y.; Ise, K.; Yamazaki, Y.; Fujishima, F.; McNamara, K.M.; Sasano, H. Serotonin receptor 4 (5-hydroxytryptamine receptor Type 4) regulates expression of estrogen receptor beta and cell migration in hormone-naive prostate cancer. *Indian J. Pathol. Microbiol.* **2017**, *60*, 33–37. [CrossRef] [PubMed]

26. Gautam, J.; Banskota, S.; Regmi, S.C.; Ahn, S.; Jeon, Y.H.; Jeong, H.; Kim, S.J.; Nam, T.-G.; Jeong, B.-S.; Kim, J.-A. Tryptophan hydroxylase 1 and 5-HT7 receptor preferentially expressed in triple-negative breast cancer promote cancer progression through autocrine serotonin signaling. *Mol. Cancer* **2016**, *15*, 75. [CrossRef] [PubMed]
27. Du, X.; Wang, T.; Wang, Z.; Wu, X.; Gu, Y.; Huang, Q.; Wang, J.; Xie, J. 5-HT_7 Receptor Contributes to Proliferation, Migration and Invasion in NSCLC Cells. *OncoTargets Ther.* **2020**, *13*, 2139–2151. [CrossRef]
28. Mittal, D.; Sinha, D.; Barkauskas, D.; Young, A.; Kalimutho, M.; Stannard, K.; Caramia, F.; Haibe-Kains, B.; Stagg, J.; Khanna, K.K.; et al. Adenosine 2B Receptor Expression on Cancer Cells Promotes Metastasis. *Cancer Res.* **2016**, *76*, 4372–4382. [CrossRef] [PubMed]
29. Gao, Z.-G.; Jacobson, K.A. A2B Adenosine Receptor and Cancer. *Int. J. Mol. Sci.* **2019**, *20*, 5139. [CrossRef] [PubMed]
30. Madi, L.; Ochaion, A.; Rath-Wolfson, L.; Bar-Yehuda, S.; Erlanger, A.; Ohana, G.; Harish, A.; Merimski, O.; Barer, F.; Fishman, P. The A3 Adenosine Receptor Is Highly Expressed in Tumor versus Normal Cells. *Clin. Cancer Res.* **2004**, *10*, 4472–4479. [CrossRef] [PubMed]
31. Sjöberg, E.; Meyrath, M.; Milde, L.; Herrera, M.; Lövrot, J.; Hägerstrand, D.; Frings, O.; Bartish, M.; Rolny, C.; Sonnhammer, E.; et al. A Novel ACKR2-Dependent Role of Fibroblast-Derived CXCL14 in Epithelial-to-Mesenchymal Transition and Metastasis of Breast Cancer. *Clin. Cancer Res.* **2019**, *25*, 3702–3717. [CrossRef]
32. Chang, T.-M.; Chiang, Y.-C.; Lee, C.-W.; Lin, C.-M.; Fang, M.-L.; Chi, M.-C.; Liu, J.-F.; Kou, Y.R. CXCL14 promotes metastasis of non-small cell lung cancer through ACKR2-depended signaling pathway. *Int. J. Biol. Sci.* **2023**, *19*, 1455–1470. [CrossRef] [PubMed]
33. Akter, R.; Kim, K.; Kwon, H.Y.; Kim, Y.; Eom, Y.W.; Cho, H.-M.; Cho, M.-Y. EMR1/ADGRE1 Expression in Cancer Cells Upregulated by Tumor-Associated Macrophages Is Related to Poor Prognosis in Colorectal Cancer. *Biomedicines* **2022**, *10*, 3121. [CrossRef] [PubMed]
34. Kang, H.; Fichna, J.; Matlawska-Wasowska, K.; Jacenik, D. The Expression Pattern of Adhesion G Protein-Coupled Receptor F5 Is Related to Cell Adhesion and Metastatic Pathways in Colorectal Cancer—Comprehensive Study Based on In Silico Analysis. *Cells* **2022**, *11*, 3876. [CrossRef] [PubMed]
35. Wu, Y.; Liu, H.; Sun, Z.; Liu, J.; Li, K.; Fan, R.; Dai, F.; Tang, H.; Hou, Q.; Li, J.; et al. The adhesion-GPCR ADGRF5 fuels breast cancer progression by suppressing the MMP8-mediated antitumorigenic effects. *Cell Death Dis.* **2024**, *15*, 455. [CrossRef]
36. Shi, W.; Xu, C.; Lei, P.; Sun, X.; Song, M.; Guo, Y.; Song, W.; Li, Y.; Yu, L.; Zhang, H.; et al. A correlation study of adhesion G protein-coupled receptors as potential therapeutic targets for breast cancer. *Breast Cancer Res. Treat.* **2024**, *207*, 417–434. [CrossRef] [PubMed]
37. Sousa, D.M.; Fernandes, V.; Lourenço, C.; Carvalho-Maia, C.; Estevão-Pereira, H.; Lobo, J.; Cantante, M.; Couto, M.; Conceição, F.; Jerónimo, C.; et al. Profiling the Adrenergic System in Breast Cancer and the Development of Metastasis. *Cancers* **2022**, *14*, 5518. [CrossRef]
38. Lu, T.; Zheng, C.; Fan, Z. Cardamonin suppressed the migration, invasion, epithelial mesenchymal transition (EMT) and lung metastasis of colorectal cancer cells by down-regulating ADRB2 expression. *Pharm. Biol.* **2022**, *60*, 1011–1021. [CrossRef] [PubMed]
39. Zheng, M.; Zhou, Z.; Tian, X.; Xiao, D.; Hou, X.; Xie, Z.; Liang, H.; Lin, S. ADRB3 expression in tumor cells is a poor prognostic factor and promotes proliferation in non-small cell lung carcinoma. *Cancer Immunol. Immunother.* **2020**, *69*, 2345–2355. [CrossRef]
40. Baran, M.; Ozturk, F.; Canoz, O.; Onder, G.O.; Yay, A. The effects of apoptosis and apelin on lymph node metastasis in invasive breast carcinomas. *Clin. Exp. Med.* **2020**, *20*, 507–514. [CrossRef] [PubMed]
41. Chen, J.; Li, Z.; Zhao, Q.; Chen, L. Roles of apelin/APJ system in cancer: Biomarker, predictor, and emerging therapeutic target. *J. Cell. Physiol.* **2022**, *237*, 3734–3751. [CrossRef]
42. Berta, J.; Török, S.; Tárnoki-Zách, J.; Drozdovszky, O.; Tóvári, J.; Paku, S.; Kovács, I.; Czirók, A.; Masri, B.; Megyesfalvi, Z.; et al. Apelin promotes blood and lymph vessel formation and the growth of melanoma lung metastasis. *Sci. Rep.* **2021**, *11*, 5798. [CrossRef]
43. Zhao, N.; Peacock, S.O.; Lo, C.H.; Heidman, L.M.; Rice, M.A.; Fahrenholtz, C.D.; Greene, A.M.; Magani, F.; Copello, V.A.; Martinez, M.J.; et al. Arginine vasopressin receptor 1a is a therapeutic target for castration-resistant prostate cancer. *Sci. Transl. Med.* **2019**, *11*, eaaw4636. [CrossRef] [PubMed]
44. Shu, C.; Zha, H.; Long, H.; Wang, X.; Yang, F.; Gao, J.; Hu, C.; Zhou, L.; Guo, B.; Zhu, B. C3a-C3aR signaling promotes breast cancer lung metastasis via modulating carcinoma associated fibroblasts. *J. Exp. Clin. Cancer Res.* **2020**, *39*, 11. [CrossRef]
45. Oncul, S.; Cho, M.S.; Lee, H.; Carlos-Alcalde, W.E.; Singh, S.; Yee, C.; Afshar-Kharghan, V. The impact of the complement receptors C3aR1 and C5aR1 on the progression of melanoma. *J. Immunol.* **2023**, *210*, 89.09. [CrossRef]
46. Vadrevu, S.K.; Chintala, N.K.; Sharma, S.K.; Sharma, P.; Cleveland, C.; Riediger, L.; Manne, S.; Fairlie, D.P.; Gorczyca, W.; Almanza, O.; et al. Complement C5a Receptor Facilitates Cancer Metastasis by Altering T-Cell Responses in the Metastatic Niche. *Cancer Res.* **2014**, *74*, 3454–3465. [CrossRef] [PubMed]

47. Li, X.; Chen, X.; Gong, S.; Zhao, J.; Yao, C.; Zhu, H.; Xiao, R.; Qin, Y.; Li, R.; Sun, N.; et al. Platelets promote CRC by activating the C5a/C5aR1 axis via PSGL-1/JNK/STAT1 signaling in tumor-associated macrophages. *Theranostics* **2023**, *13*, 2040–2056. [CrossRef] [PubMed]
48. Hannan, F.M.; Kallay, E.; Chang, W.; Brandi, M.L.; Thakker, R.V. The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases. *Nat. Rev. Endocrinol.* **2019**, *15*, 33–51. [CrossRef] [PubMed]
49. Coke, C.J.; Scarlett, K.A.; Chetram, M.A.; Jones, K.J.; Sandifer, B.J.; Davis, A.S.; Marcus, A.I.; Hinton, C.V. Simultaneous Activation of Induced Heterodimerization between CXCR4 Chemokine Receptor and Cannabinoid Receptor 2 (CB2) Reveals a Mechanism for Regulation of Tumor Progression. *J. Biol. Chem.* **2016**, *291*, 9991–10005. [CrossRef]
50. Preet, A.; Qamri, Z.; Nasser, M.W.; Prasad, A.; Shilo, K.; Zou, X.; Groopman, J.E.; Ganju, R.K. Cannabinoid Receptors, CB1 and CB2, as Novel Targets for Inhibition of Non–Small Cell Lung Cancer Growth and Metastasis. *Cancer Prev. Res.* **2011**, *4*, 65–75. [CrossRef] [PubMed]
51. Liang, N.; Sun, S.; Li, Z.; Wu, T.; Zhang, C.; Xin, T. CCKAR is a biomarker for prognosis and asynchronous brain metastasis of non-small cell lung cancer. *Front. Oncol.* **2023**, *12*, 1098728. [CrossRef] [PubMed]
52. Shin, S.Y.; Lee, D.H.; Lee, J.; Choi, C.; Kim, J.-Y.; Nam, J.-S.; Lim, Y.; Lee, Y.H. C-C motif chemokine receptor 1 (CCR1) is a target of the EGF-AKT-mTOR-STAT3 signaling axis in breast cancer cells. *Oncotarget* **2017**, *8*, 94591–94605. [CrossRef]
53. Yamamoto, T.; Kawada, K.; Itatani, Y.; Inamoto, S.; Okamura, R.; Iwamoto, M.; Miyamoto, E.; Chen-Yoshikawa, T.F.; Hirai, H.; Hasegawa, S.; et al. Loss of SMAD4 Promotes Lung Metastasis of Colorectal Cancer by Accumulation of CCR1+ Tumor-Associated Neutrophils through CCL15-CCR1 Axis. *Clin. Cancer Res.* **2017**, *23*, 833–844. [CrossRef]
54. Tapmeier, T.T.; Howell, J.H.; Zhao, L.; Papiez, B.W.; Schnabel, J.A.; Muschel, R.J.; Gal, A. Evolving polarisation of infiltrating and alveolar macrophages in the lung during metastatic progression of melanoma suggests CCR1 as a therapeutic target. *Oncogene* **2022**, *41*, 5032–5045. [CrossRef]
55. Qian, B.-Z.; Li, J.; Zhang, H.; Kitamura, T.; Zhang, J.; Campion, L.R.; Kaiser, E.A.; Snyder, L.A.; Pollard, J.W. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. *Nature* **2011**, *475*, 222–225. [CrossRef] [PubMed]
56. Lim, S.Y.; Yuzhalin, A.E.; Gordon-Weeks, A.N.; Muschel, R.J. Targeting the CCL2-CCR2 signaling axis in cancer metastasis. *Oncotarget* **2016**, *7*, 28697–28710. [CrossRef]
57. Bekaert, S.; Rocks, N.; Vanwinge, C.; Noel, A.; Cataldo, D. Asthma-related inflammation promotes lung metastasis of breast cancer cells through CCL11–CCR3 pathway. *Respir. Res.* **2021**, *22*, 61. [CrossRef]
58. Cheadle, E.J.; Riyad, K.; Subar, D.; Rothwell, D.G.; Ashton, G.; Batha, H.; Sherlock, D.J.; Hawkins, R.E.; Gilham, D.E. Eotaxin-2 and Colorectal Cancer: A Potential Target for Immune Therapy. *Clin. Cancer Res.* **2007**, *13*, 5719–5728. [CrossRef] [PubMed]
59. Lee, Y.-J.; Kim, D.-H.; Lee, S.-H.; Nam, H.-S.; Roh, M.R.; Cho, M.-K. Chemokine Receptor CCR3 Expression in Malignant Cutaneous Tumors. *Ann. Dermatol.* **2010**, *22*, 412. [CrossRef] [PubMed]
60. Zhu, F.; Liu, P.; Li, J.; Zhang, Y. Eotaxin-1 promotes prostate cancer cell invasion via activation of the CCR3-ERK pathway and upregulation of MMP-3 expression. *Oncol. Rep.* **2014**, *31*, 2049–2054. [CrossRef] [PubMed]
61. Korbecki, J.; Kojder, K.; Simińska, D.; Bohatyrewicz, R.; Gutowska, I.; Chlubek, D.; Baranowska-bosiacka, I. Cc chemokines in a tumor: A review of pro-cancer and anti-cancer properties of the ligands of receptors ccr1, ccr2, ccr3, and ccr4. *Int. J. Mol. Sci.* **2020**, *21*, 8412. [CrossRef]
62. Klein, A.; Sagi-Assif, O.; Meshel, T.; Telerman, A.; Izraely, S.; Ben-Menachem, S.; Bayry, J.; Marzese, D.M.; Ohe, S.; Hoon, D.S.B.; et al. CCR4 is a determinant of melanoma brain metastasis. *Oncotarget* **2017**, *8*, 31079–31091. [CrossRef]
63. Maolake, A.; Izumi, K.; Shigehara, K.; Natsagdorj, A.; Iwamoto, H.; Kadomoto, S.; Takezawa, Y.; Machioka, K.; Narimoto, K.; Namiki, M.; et al. Tumor-associated macrophages promote prostate cancer migration through activation of the CCL22-CCR4 axis. *Oncotarget* **2017**, *8*, 9739–9751. [CrossRef] [PubMed]
64. Qiu, J.; Xu, L.; Zeng, X.; Wu, H.; Liang, F.; Lv, Q.; Du, Z. CCL5 mediates breast cancer metastasis and prognosis through CCR5/Treg cells. *Front. Oncol.* **2022**, *12*, 972383. [CrossRef] [PubMed]
65. Aldinucci, D.; Borghese, C.; Casagrande, N. The CCL5/CCR5 Axis in Cancer Progression. *Cancers* **2020**, *12*, 1765. [CrossRef]
66. Korbecki, J.; Grochans, S.; Gutowska, I.; Barczak, K.; Baranowska-Bosiacka, I. CC Chemokines in a Tumor: A Review of Pro-Cancer and Anti-Cancer Properties of Receptors CCR5, CCR6, CCR7, CCR8, CCR9, and CCR10 Ligands. *Int. J. Mol. Sci.* **2020**, *21*, 7619. [CrossRef] [PubMed]
67. Ouyang, J.; Hu, S.; Zhu, Q.; Li, C.; Kang, T.; Xie, W.; Wang, Y.; Li, Y.; Lu, Y.; Qi, J.; et al. RANKL/RANK signaling recruits Tregs via the CCL20–CCR6 pathway and promotes stemness and metastasis in colorectal cancer. *Cell Death Dis.* **2024**, *15*, 437. [CrossRef]
68. Samaniego, R.; Gutiérrez-González, A.; Gutiérrez-Seijo, A.; Sánchez-Gregorio, S.; García-Giménez, J.; Mercader, E.; Márquez-Rodas, I.; Avilés, J.A.; Relloso, M.; Sánchez-Mateos, P. CCL20 Expression by Tumor-Associated Macrophages Predicts Progression of Human Primary Cutaneous Melanoma. *Cancer Immunol. Res.* **2018**, *6*, 267–275. [CrossRef]

69. Xie, T.; Fu, D.-J.; Li, Z.-M.; Lv, D.-J.; Song, X.-L.; Yu, Y.-Z.; Wang, C.; Li, K.-J.; Zhai, B.; Wu, J.; et al. CircSMARCC1 facilitates tumor progression by disrupting the crosstalk between prostate cancer cells and tumor-associated macrophages via miR-1322/CCL20/CCR6 signaling. *Mol. Cancer* **2022**, *21*, 173. [CrossRef]
70. Maolake, A.; Izumi, K.; Natsagdorj, A.; Iwamoto, H.; Kadomoto, S.; Makino, T.; Naito, R.; Shigehara, K.; Kadono, Y.; Hiratsuka, K.; et al. Tumor necrosis factor-α induces prostate cancer cell migration in lymphatic metastasis through CCR_7 upregulation. *Cancer Sci.* **2018**, *109*, 1524–1531. [CrossRef] [PubMed]
71. Wang, M.; Qin, Z.; Wan, J.; Yan, Y.; Duan, X.; Yao, X.; Jiang, Z.; Li, W.; Qin, Z. Tumor-derived exosomes drive pre-metastatic niche formation in lung via modulating CCL1+ fibroblast and CCR8+ Treg cell interactions. *Cancer Immunol. Immunother.* **2022**, *71*, 2717–2730. [CrossRef] [PubMed]
72. Tu, Z.; Xiao, R.; Xiong, J.; Tembo, K.M.; Deng, X.; Xiong, M.; Liu, P.; Wang, M.; Zhang, Q. CCR9 in cancer: Oncogenic role and therapeutic targeting. *J. Hematol. Oncol.* **2016**, *9*, 10. [CrossRef]
73. Mergia Terefe, E.; Catalan Opulencia, M.J.; Rakhshani, A.; Ansari, M.J.; Sergeevna, S.E.; Awadh, S.A.; Polatova, D.S.; Abdulkadhim, A.H.; Mustafa, Y.F.; Kzar, H.H.; et al. Roles of CCR10/CCL27–CCL28 axis in tumour development: Mechanisms, diagnostic and therapeutic approaches, and perspectives. *Expert Rev. Mol. Med.* **2022**, *24*, e37. [CrossRef] [PubMed]
74. Liu, Y.; Xiao, A.; Zhang, B. CCR10/CCL27 crosstalk regulates cell metastasis via PI3K-Akt signaling axis in non-small-cell lung cancer. *Am. J. Transl. Res.* **2021**, *13*, 13135–13146. [PubMed]
75. Akram, I.G.; Georges, R.; Hielscher, T.; Adwan, H.; Berger, M.R. The chemokines CCR1 and CCRL2 have a role in colorectal cancer liver metastasis. *Tumor Biol.* **2016**, *37*, 2461–2471. [CrossRef] [PubMed]
76. Reyes, N.; Benedetti, I.; Rebollo, J.; Correa, O.; Geliebter, J. Atypical chemokine receptor CCRL2 is overexpressed in prostate cancer cells. *J. Biomed. Res.* **2019**, *33*, 17. [CrossRef]
77. Jin, L.; Li, C.; Li, R.; Sun, Z.; Fang, X.; Li, S. Corticotropin-releasing hormone receptors mediate apoptosis via cytosolic calcium-dependent phospholipase A2 and migration in prostate cancer cell RM-1. *J. Mol. Endocrinol.* **2014**, *52*, 255–267. [CrossRef] [PubMed]
78. Dinatale, A.; Kaur, R.; Qian, C.; Zhang, J.; Marchioli, M.; Ipe, D.; Castelli, M.; McNair, C.M.; Kumar, G.; Meucci, O.; et al. Subsets of cancer cells expressing CX3CR1 are endowed with metastasis-initiating properties and resistance to chemotherapy. *Oncogene* **2022**, *41*, 1337–1351. [CrossRef]
79. Liu, Y.; Ma, H.; Dong, T.; Yan, Y.; Sun, L.; Wang, W. Clinical significance of expression level of CX3CL1–CX3CR1 axis in bone metastasis of lung cancer. *Clin. Transl. Oncol.* **2021**, *23*, 378–388. [CrossRef] [PubMed]
80. Liu, Z.; Xu, M.; Huang, S.; Pan, Q.; Liu, C.; Zeng, F.; Fan, Z.; Lu, Y.; Wang, J.; Liu, J.; et al. Mesoscale visualization of three-dimensional microvascular architecture and immunocyte distribution in intact mouse liver lobes. *Theranostics* **2022**, *12*, 5418–5433. [CrossRef] [PubMed]
81. Liu, Q.; Li, A.; Tian, Y.; Wu, J.D.; Liu, Y.; Li, T.; Chen, Y.; Han, X.; Wu, K. The CXCL8-CXCR1/2 pathways in cancer. *Cytokine Growth Factor Rev.* **2016**, *31*, 61–71. [CrossRef]
82. Łukaszewicz-Zając, M.; Zajkowska, M.; Pączek, S.; Kulczyńska-Przybik, A.; Safiejko, K.; Juchimiuk, M.; Kozłowski, L.; Mroczko, B. The Significance of CXCL1 and CXCR1 as Potential Biomarkers of Colorectal Cancer. *Biomedicines* **2023**, *11*, 1933. [CrossRef]
83. Zhang, T.; Tseng, C.; Zhang, Y.; Sirin, O.; Corn, P.G.; Li-Ning-Tapia, E.M.; Troncoso, P.; Davis, J.; Pettaway, C.; Ward, J.; et al. CXCL1 mediates obesity-associated adipose stromal cell trafficking and function in the tumour microenvironment. *Nat. Commun.* **2016**, *7*, 11674. [CrossRef] [PubMed]
84. Zhang, C.; Wang, X.-Y.; Zhang, P.; He, T.-C.; Han, J.-H.; Zhang, R.; Lin, J.; Fan, J.; Lu, L.; Zhu, W.-W.; et al. Cancer-derived exosomal HSPC111 promotes colorectal cancer liver metastasis by reprogramming lipid metabolism in cancer-associated fibroblasts. *Cell Death Dis.* **2022**, *13*, 57. [CrossRef] [PubMed]
85. Tokunaga, R.; Zhang, W.; Naseem, M.; Puccini, A.; Berger, M.D.; Soni, S.; McSkane, M.; Baba, H.; Lenz, H.-J. CXCL9, CXCL10, CXCL11/CXCR3 axis for immune activation—A target for novel cancer therapy. *Cancer Treat. Rev.* **2018**, *63*, 40–47. [CrossRef]
86. Kuroki, M.; Kuroki, M.; Kinugasa, T.; Shibaguchi, H.; Yanagisawa, J.; Tanaka, T.; Kawakami, T.; Shirakusa, T.; Iwasaki, A.; Maekawa, S. Association between the expression of chemokine receptors CCR7 and CXCR3, and lymph node metastatic potential in lung adenocarcinoma. *Oncol. Rep.* **2008**, *19*, 1461–1468. [CrossRef]
87. Ma, B.; Khazali, A.; Shao, H.; Jiang, Y.; Wells, A. Expression of E-cadherin and specific CXCR3 isoforms impact each other in prostate cancer. *Cell Commun. Signal.* **2019**, *17*, 164. [CrossRef]
88. Mortezaee, K. CXCL12/CXCR4 axis in the microenvironment of solid tumors: A critical mediator of metastasis. *Life Sci.* **2020**, *249*, 117534. [CrossRef] [PubMed]
89. Mendt, M.; Cardier, J.E. Activation of the CXCR4 chemokine receptor enhances biological functions associated with B16 melanoma liver metastasis. *Melanoma Res.* **2017**, *27*, 300–308. [CrossRef] [PubMed]
90. Wang, B.; Wang, M.; Ao, D.; Wei, X. CXCL13-CXCR5 axis: Regulation in inflammatory diseases and cancer. *Biochim. Biophys. Acta (BBA)—Rev. Cancer* **2022**, *1877*, 188799. [CrossRef]

91. Deng, L.; Chen, N.; Li, Y.; Zheng, H.; Lei, Q. CXCR6/CXCL16 functions as a regulator in metastasis and progression of cancer. *Biochim. Biophys. Acta (BBA)—Rev. Cancer* **2010**, *1806*, 42–49. [CrossRef]
92. Hu, W.; Liu, Y.; Zhou, W.; Si, L.; Ren, L. CXCL16 and CXCR6 Are Coexpressed in Human Lung Cancer In Vivo and Mediate the Invasion of Lung Cancer Cell Lines In Vitro. *PLoS ONE* **2014**, *9*, e99056. [CrossRef]
93. Seidl, H.; Richtig, E.; Tilz, H.; Stefan, M.; Schmidbauer, U.; Asslaber, M.; Zatloukal, K.; Herlyn, M.; Schaider, H. Profiles of chemokine receptors in melanocytic lesions: De novo expression of CXCR6 in melanoma. *Hum. Pathol.* **2007**, *38*, 768–780. [CrossRef] [PubMed]
94. Wu, Y.C.; Tang, S.J.; Sun, G.H.; Sun, K.H. CXCR7 mediates TGFβ1-promoted EMT and tumor-initiating features in lung cancer. *Oncogene* **2016**, *35*, 2123–2132. [CrossRef]
95. Wang, D.; Wang, X.; Song, Y.; Si, M.; Sun, Y.; Liu, X.; Cui, S.; Qu, X.; Yu, X. Exosomal miR-146a-5p and miR-155-5p promote CXCL12/CXCR7-induced metastasis of colorectal cancer by crosstalk with cancer-associated fibroblasts. *Cell Death Dis.* **2022**, *13*, 380. [CrossRef] [PubMed]
96. Li, X.-J.; Liu, P.; Tian, W.-W.; Li, Z.-F.; Liu, B.-G.; Sun, J.-F. Mechanisms of CXCR7 induction in malignant melanoma development. *Oncol. Lett.* **2017**, *14*, 4106–4114. [CrossRef]
97. Hsiao, J.J.; Ng, B.H.; Smits, M.M.; Wang, J.; Jasavala, R.J.; Martinez, H.D.; Lee, J.; Alston, J.J.; Misonou, H.; Trimmer, J.S.; et al. Androgen receptor and chemokine receptors 4 and 7 form a signaling axis to regulate CXCL12-dependent cellular motility. *BMC Cancer* **2015**, *15*, 204. [CrossRef]
98. Lee, Y.-J.; Jung, E.; Choi, J.; Hwang, J.-S.; Jeong, E.-J.; Roh, Y.; Ban, H.; Kim, S.; Kim, S.-K.; Kim, S.-Y.; et al. The EDN1/EDNRA/β-arrestin axis promotes colorectal cancer progression by regulating STAT3 phosphorylation. *Int. J. Oncol.* **2022**, *62*, 13. [CrossRef] [PubMed]
99. Gu, X.; Han, S.; Cui, M.; Xue, J.; Ai, L.; Sun, L.; Zhu, X.; Wang, Y.; Liu, C. Knockdown of endothelin receptor B inhibits the progression of triple-negative breast cancer. *Ann. N. Y. Acad. Sci.* **2019**, *1448*, 5–18. [CrossRef]
100. Cruz-Muñoz, W.; Jaramillo, M.L.; Man, S.; Xu, P.; Banville, M.; Collins, C.; Nantel, A.; Francia, G.; Morgan, S.S.; Cranmer, L.D.; et al. Roles for Endothelin Receptor B and BCL2A1 in Spontaneous CNS Metastasis of Melanoma. *Cancer Res.* **2012**, *72*, 4909–4919. [CrossRef] [PubMed]
101. Wang, Y.; Liao, R.; Chen, X.; Ying, X.; Chen, G.; Li, M.; Dong, C. Twist-mediated PAR1 induction is required for breast cancer progression and metastasis by inhibiting Hippo pathway. *Cell Death Dis.* **2020**, *11*, 520. [CrossRef] [PubMed]
102. Shi, X.; Gangadharan, B.; Brass, L.F.; Ruf, W.; Mueller, B.M. Protease-Activated Receptors (PAR1 and PAR2) Contribute to Tumor Cell Motility and Metastasis. *Mol. Cancer Res.* **2004**, *2*, 395–402. [CrossRef]
103. Hua, Q.; Sun, Z.; Liu, Y.; Shen, X.; Zhao, W.; Zhu, X.; Xu, P. KLK8 promotes the proliferation and metastasis of colorectal cancer via the activation of EMT associated with PAR1. *Cell Death Dis.* **2021**, *12*, 860. [CrossRef] [PubMed]
104. Tang, L.; Lei, X.; Hu, H.; Li, Z.; Zhu, H.; Zhan, W.; Zhang, T. Investigation of fatty acid metabolism-related genes in breast cancer: Implications for Immunotherapy and clinical significance. *Transl. Oncol.* **2023**, *34*, 101700. [CrossRef] [PubMed]
105. Liotti, A.; Cosimato, V.; Mirra, P.; Calì, G.; Conza, D.; Secondo, A.; Luongo, G.; Terracciano, D.; Formisano, P.; Beguinot, F.; et al. Oleic acid promotes prostate cancer malignant phenotype via the G protein-coupled receptor FFA1/GPR40. *J. Cell. Physiol.* **2018**, *233*, 7367–7378. [CrossRef] [PubMed]
106. Hozhabri, H.; Ghasemi Dehkohneh, R.S.; Razavi, S.M.; Razavi, S.M.; Salarian, F.; Rasouli, A.; Azami, J.; Ghasemi Shiran, M.; Kardan, Z.; Farrokhzad, N.; et al. Comparative analysis of protein-protein interaction networks in metastatic breast cancer. *PLoS ONE* **2022**, *17*, e0260584. [CrossRef] [PubMed]
107. Vecchi, L.; Alves Pereira Zóia, M.; Goss Santos, T.; de Oliveira Beserra, A.; Colaço Ramos, C.M.; França Matias Colombo, B.; Paiva Maia, Y.C.; Piana de Andrade, V.; Teixeira Soares Mota, S.; Gonçalves de Araújo, T.; et al. Inhibition of the AnxA1/FPR1 autocrine axis reduces MDA-MB-231 breast cancer cell growth and aggressiveness in vitro and in vivo. *Biochim. Biophys. Acta (BBA)—Mol. Cell Res.* **2018**, *1865*, 1368–1382. [CrossRef]
108. Li, S.-Q.; Su, N.; Gong, P.; Zhang, H.-B.; Liu, J.; Wang, D.; Sun, Y.-P.; Zhang, Y.; Qian, F.; Zhao, B.; et al. The Expression of Formyl Peptide Receptor 1 is Correlated with Tumor Invasion of Human Colorectal Cancer. *Sci. Rep.* **2017**, *7*, 5918. [CrossRef] [PubMed]
109. Chakravarti, N.; Peddareddigari, V.G.R.; Warneke, C.L.; Johnson, M.M.; Overwijk, W.W.; Hwu, P.; Prieto, V.G. Differential Expression of the G-Protein–Coupled Formyl Peptide Receptor in Melanoma Associates With Aggressive Phenotype. *Am. J. Dermatopathol.* **2013**, *35*, 184–190. [CrossRef]
110. Lu, J.B.; Zhao, J.; Jia, C.; Zhou, L.X.; Cai, Y.; Ni, J.; Ma, J.M.; Zheng, M.; Lu, A. FPR2 enhances colorectal cancer progression by promoting EMT process. *Neoplasma* **2019**, *66*, 785–791. [CrossRef]
111. Ghinea, N. Vascular Endothelial FSH Receptor, a Target of Interest for Cancer Therapy. *Endocrinology* **2018**, *159*, 3268–3274. [CrossRef]
112. Radu, A.; Pichon, C.; Camparo, P.; Antoine, M.; Allory, Y.; Couvelard, A.; Fromont, G.; Hai, M.T.V.; Ghinea, N. Expression of Follicle-Stimulating Hormone Receptor in Tumor Blood Vessels. *N. Engl. J. Med.* **2010**, *363*, 1621–1630. [CrossRef]

113. Liu, Z.; Sun, L.; Cai, Y.; Shen, S.; Zhang, T.; Wang, N.; Wu, G.; Ma, W.; Li, S.-T.; Suo, C.; et al. Hypoxia-Induced Suppression of Alternative Splicing of MBD2 Promotes Breast Cancer Metastasis via Activation of FZD1. *Cancer Res.* **2021**, *81*, 1265–1278. [CrossRef] [PubMed]
114. Gujral, T.S.; Chan, M.; Peshkin, L.; Sorger, P.K.; Kirschner, M.W.; MacBeath, G. A Noncanonical Frizzled2 Pathway Regulates Epithelial-Mesenchymal Transition and Metastasis. *Cell* **2014**, *159*, 844–856. [CrossRef] [PubMed]
115. Zhang, X.; Mo, Q.-w. [Role and action mechanisms of FZD5 in prostate cancer bone metastasis in mice]. *Zhonghua Nan Ke Xue* **2016**, *22*, 128–132.
116. Tiwary, S.; Xu, L. FRIZZLED7 Is Required for Tumor Inititation and Metastatic Growth of Melanoma Cells. *PLoS ONE* **2016**, *11*, e0147638. [CrossRef]
117. Ueno, K.; Hazama, S.; Mitomori, S.; Nishioka, M.; Suehiro, Y.; Hirata, H.; Oka, M.; Imai, K.; Dahiya, R.; Hinoda, Y. Down-regulation of frizzled-7 expression decreases survival, invasion and metastatic capabilities of colon cancer cells. *Br. J. Cancer* **2009**, *101*, 1374–1381. [CrossRef] [PubMed]
118. Yin, P.; Bai, Y.; Wang, Z.; Sun, Y.; Gao, J.; Na, L.; Zhang, Z.; Wang, W.; Zhao, C. Non-canonical Fzd7 signaling contributes to breast cancer mesenchymal-like stemness involving Col6a1. *Cell Commun. Signal.* **2020**, *18*, 143. [CrossRef] [PubMed]
119. Al-Zahrani, M.; Assidi, M.; Pushparaj, P.; Al-Maghrabi, J.; Zari, A.; Abusanad, A.; Buhmeida, A.; Abu-Elmagd, M. Expression pattern, prognostic value and potential microRNA silencing of FZD8 in breast cancer. *Oncol. Lett.* **2023**, *26*, 477. [CrossRef]
120. Li, Q.; Ye, L.; Zhang, X.; Wang, M.; Lin, C.; Huang, S.; Guo, W.; Lai, Y.; Du, H.; Li, J.; et al. FZD8, a target of p53, promotes bone metastasis in prostate cancer by activating canonical Wnt/β-catenin signaling. *Cancer Lett.* **2017**, *402*, 166–176. [CrossRef] [PubMed]
121. Xu, L.; Wen, T.; Liu, Z.; Xu, F.; Yang, L.; Liu, J.; Feng, G.; An, G. MicroRNA-375 suppresses human colorectal cancer metastasis by targeting Frizzled 8. *Oncotarget* **2016**, *7*, 40644–40656. [CrossRef]
122. Kiezun, J.; Kiezun, M.; Krazinski, B.E.; Paukszto, L.; Koprowicz-Wielguszewska, A.; Kmiec, Z.; Godlewski, J. Galanin Receptors (GALR1, GALR2, and GALR3) Immunoexpression in Enteric Plexuses of Colorectal Cancer Patients: Correlation with the Clinico-Pathological Parameters. *Biomolecules* **2022**, *12*, 1769. [CrossRef]
123. Desaulniers, A.T.; White, B.R. Role of gonadotropin-releasing hormone 2 and its receptor in human reproductive cancers. *Front. Endocrinol.* **2024**, *14*, 1341162. [CrossRef] [PubMed]
124. Ranđelović, I.; Schuster, S.; Kapuvári, B.; Fossati, G.; Steinkühler, C.; Mező, G.; Tóvári, J. Improved In Vivo Anti-Tumor and Anti-Metastatic Effect of GnRH-III-Daunorubicin Analogs on Colorectal and Breast Carcinoma Bearing Mice. *Int. J. Mol. Sci.* **2019**, *20*, 4763. [CrossRef] [PubMed]
125. Lappano, R.; Maggiolini, M. GPER is involved in the functional liaison between breast tumor cells and cancer-associated fibroblasts (CAFs). *J. Steroid Biochem. Mol. Biol.* **2018**, *176*, 49–56. [CrossRef] [PubMed]
126. Sáez-Martínez, P.; Jiménez-Vacas, J.M.; León-González, A.J.; Herrero-Aguayo, V.; Montero Hidalgo, A.J.; Gómez-Gómez, E.; Sánchez-Sánchez, R.; Requena-Tapia, M.J.; Castaño, J.P.; Gahete, M.D.; et al. Unleashing the Diagnostic, Prognostic and Therapeutic Potential of the Neuronostatin/GPR107 System in Prostate Cancer. *J. Clin. Med.* **2020**, *9*, 1703. [CrossRef] [PubMed]
127. Chen, P.; Zuo, H.; Xiong, H.; Kolar, M.J.; Chu, Q.; Saghatelian, A.; Siegwart, D.J.; Wan, Y. Gpr132 sensing of lactate mediates tumor–macrophage interplay to promote breast cancer metastasis. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 580–585. [CrossRef]
128. Parija, M.; Adhya, A.K.; Mishra, S.K. G-protein-coupled receptor 141 mediates breast cancer proliferation and metastasis by regulating oncogenic mediators and the p-mTOR/p53 axis. *Oncotarget* **2023**, *14*, 466–480. [CrossRef] [PubMed]
129. Guo, Y.; Zhu, Q.; Chen, S.; Li, Y.; Fu, D.; Qiao, D.; Ni, C. Post-transcriptional suppression of G protein-coupled receptor 15 (GPR15) by microRNA-1225 inhibits proliferation, migration, and invasion of human colorectal cancer cells. *3 Biotech* **2021**, *11*, 139. [CrossRef]
130. Feigin, M.E.; Xue, B.; Hammell, M.C.; Muthuswamy, S.K. G-protein–coupled receptor GPR161 is overexpressed in breast cancer and is a promoter of cell proliferation and invasion. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 4191–4196. [CrossRef]
131. Dai, J.; Chen, Q.; Li, G.; Chen, M.; Sun, H.; Yan, M. DIRAS3, GPR171 and RAC2 were identified as the key molecular patterns associated with brain metastasis of breast cancer. *Front. Oncol.* **2022**, *12*, 965136. [CrossRef]
132. Dho, S.H.; Lee, K.-P.; Jeong, D.; Kim, C.-J.; Chung, K.-S.; Young Kim, J.; Park, B.-C.; Park, S.S.; Kim, S.-Y.; Kwon, K.-S. GPR171 expression enhances proliferation and metastasis of lung cancer cells. *Oncotarget* **2016**, *7*, 7856–7865. [CrossRef] [PubMed]
133. Tang, J.; Peng, W.; Ji, J.; Peng, C.; Wang, T.; Yang, P.; Gu, J.O.; Feng, Y.; Jin, K.; Wang, X.; et al. GPR176 Promotes Cancer Progression by Interacting with G Protein GNAS to Restrain Cell Mitophagy in Colorectal Cancer. *Adv. Sci.* **2023**, *10*, 2205627. [CrossRef]
134. Qin, Y.; Verdegaal, E.M.E.; Siderius, M.; Bebelman, J.P.; Smit, M.J.; Leurs, R.; Willemze, R.; Tensen, C.P.; Osanto, S. Quantitative expression profiling of G-protein-coupled receptors (GPCRs) in metastatic melanoma: The constitutively active orphan GPCR GPR18 as novel drug target. *Pigment Cell Melanoma Res.* **2011**, *24*, 207–218. [CrossRef] [PubMed]

135. Rao, A.; Herr, D.R. G protein-coupled receptor GPR19 regulates E-cadherin expression and invasion of breast cancer cells. *Biochim. Biophys. Acta (BBA)—Mol. Cell Res.* **2017**, *1864*, 1318–1327. [CrossRef]
136. Riker, A.I.; Enkemann, S.A.; Fodstad, O.; Liu, S.; Ren, S.; Morris, C.; Xi, Y.; Howell, P.; Metge, B.; Samant, R.S.; et al. The gene expression profiles of primary and metastatic melanoma yields a transition point of tumor progression and metastasis. *BMC Med. Genom.* **2008**, *1*, 13. [CrossRef] [PubMed]
137. Rong, Y.M.; Huang, X.M.; Fan, D.J.; Lin, X.T.; Zhang, F.; Hu, J.C.; Tan, Y.X.; Chen, X.; Zou, Y.F.; Lan, P. Overexpression of G protein-coupled receptor 31 as a poor prognosticator in human colorectal cancer. *World J. Gastroenterol.* **2018**, *24*, 4679–4690. [CrossRef] [PubMed]
138. Iida, Y.; Tsuno, N.H.; Kishikawa, J.; Kaneko, K.; Murono, K.; Kawai, K.; Ikeda, T.; Ishihara, S.; Yamaguchi, H.; Sunami, E.; et al. Lysophosphatidylserine stimulates chemotactic migration of colorectal cancer cells through GPR34 and PI3K/Akt pathway. *Anticancer. Res.* **2014**, *34*, 5465–5472. [PubMed]
139. Mackiewicz, T.; Włodarczyk, J.; Zielińska, M.; Włodarczyk, M.; Durczyński, A.; Hogendorf, P.; Dziki, Ł.; Fichna, J. Increased GPR35 expression in human colorectal and pancreatic cancer samples: A preliminary clinical validation of a new biomarker. *Adv. Clin. Exp. Med.* **2023**, *32*, 783–789. [CrossRef] [PubMed]
140. Wang, J.; Xu, M.; Li, D.-D.; Abudukelimu, W.; Zhou, X.-H. GPR37 promotes the malignancy of lung adenocarcinoma via TGF-β/Smad pathway. *Open Med.* **2020**, *16*, 024–032. [CrossRef]
141. Mero, M.; Asraf, H.; Sekler, I.; Taylor, K.M.; Hershfinkel, M. ZnR/GPR39 upregulation of K(+)/Cl(-)-cotransporter 3 in tamoxifen resistant breast cancer cells. *Cell Calcium* **2019**, *81*, 12–20. [CrossRef]
142. Asraf, H.; Salomon S Fau-Nevo, A.; Nevo A Fau-Sekler, I.; Sekler I Fau-Mayer, D.; Mayer D Fau-Hershfinkel, M.; Hershfinkel, M. The ZnR/GPR39 interacts with the CaSR to enhance signaling in prostate and salivary epithelia. *J. Cell. Physiol.* **2013**, *229*, 868–877. [CrossRef] [PubMed]
143. Yu, M.; Cui, R.; Huang, Y.; Luo, Y.; Qin, S.; Zhong, M. Increased proton-sensing receptor GPR4 signalling promotes colorectal cancer progression by activating the hippo pathway. *EBioMedicine* **2019**, *48*, 264–276. [CrossRef] [PubMed]
144. Stolwijk, J.A.; Wallner, S.; Heider, J.; Kurz, B.; Pütz, L.; Michaelis, S.; Goricnik, B.; Erl, J.; Frank, L.; Berneburg, M.; et al. GPR4 in the pH-dependent migration of melanoma cells in the tumor microenvironment. *Exp. Dermatol.* **2023**, *32*, 479–490. [CrossRef]
145. Biswas, P.K.; Park, S.R.; An, J.; Lim, K.A.-O.X.; Dayem, A.A.-O.; Song, K.A.-O.; Choi, H.Y.; Choi, Y.; Park, K.A.-O.; Shin, H.J.; et al. The Orphan GPR50 Receptor Regulates the Aggressiveness of Breast Cancer Stem-like Cells via Targeting the NF-kB Signaling Pathway. *Int. J. Mol. Sci.* **2023**, *24*, 2804. [CrossRef]
146. Zhou, X.L.; Guo, X.; Song, Y.P.; Zhu, C.Y.; Zou, W. The LPI/GPR55 axis enhances human breast cancer cell migration via HBXIP and p-MLC signaling. *Acta Pharmacol. Sin.* **2017**, *39*, 459–471. [CrossRef]
147. Chen, L.; Wang, Y.; Lu, X.; Zhang, L.; Wang, Z. miRNA-7062-5p Promoting Bone Resorption After Bone Metastasis of Colorectal Cancer Through Inhibiting GPR65. *Front. Cell Dev. Biol.* **2021**, *9*, 681968. [CrossRef] [PubMed]
148. Cárdenas, S.; Colombero, C.; Panelo, L.; Dakarapu, R.; Falck, J.R.; Costas, M.A.; Nowicki, S. GPR75 receptor mediates 20-HETE-signaling and metastatic features of androgen-insensitive prostate cancer cells. *Biochim. Biophys. Acta (BBA)—Mol. Cell Biol. Lipids* **2020**, *1865*, 158573. [CrossRef] [PubMed]
149. Dong, D.D.; Zhou, H.; Li, G. GPR78 promotes lung cancer cell migration and metastasis by activation of Gαq-Rho GTPase pathway. *BMB Rep.* **2016**, *49*, 623–628. [CrossRef]
150. Kalyvianaki, K.; Panagiotopoulos, A.A.; Malamos, P.; Moustou, E.; Tzardi, M.; Stathopoulos, E.N.; Ioannidis, G.S.; Marias, K.; Notas, G.; Theodoropoulos, P.A.; et al. Membrane androgen receptors (OXER1, GPRC6A AND ZIP9) in prostate and breast cancer: A comparative study of their expression. *Steroids* **2019**, *142*, 100–108. [CrossRef] [PubMed]
151. Liu, M.; Zhao, Y.Y.; Yang, F.; Wang, J.Y.; Shi, X.H.; Zhu, X.Q.; Xu, Y.; Wei, D.; Sun, L.; Zhang, Y.G.; et al. Evidence for a role of GPRC6A in prostate cancer metastasis based on case-control and in vitro analyses. *Eur. Rev. Med. Pharmacol. Sci.* **2016**, *20*, 2235–2248.
152. Yue, Y.; Deng, P.; Xiao, H.; Tan, M.; Wang, H.; Tian, L.; Xie, J.; Chen, M.; Luo, Y.; Wang, L.; et al. N6-methyladenosine-mediated downregulation of miR-374c-5p promotes cadmium-induced cell proliferation and metastasis by targeting GRM3 in breast cancer cells. *Ecotoxicol. Environ. Saf.* **2021**, *229*, 113085. [CrossRef]
153. Ruginis, T.; Taglia L Fau-Matusiak, D.; Matusiak D Fau-Lee, B.-S.; Lee Bs Fau-Benya, R.V.; Benya, R.V. Consequence of gastrin-releasing peptide receptor activation in a human colon cancer cell line: A proteomic approach. *J. Proteome Res.* **2006**, *5*, 1460–1468. [CrossRef]
154. Whiteside, E.J.; Seim, I.; Pauli, J.P.; O'keeffe, A.J.; Thomas, P.B.; Carter, S.L.; Walpole, C.M.; Fung, J.N.; Josh, P.; Herington, A.C.; et al. Identification of a long non-coding RNA gene, growth hormone secretagogue receptor opposite strand, which stimulates cell migration in non-small cell lung cancer cell lines. *Int. J. Oncol.* **2013**, *43*, 566–574. [CrossRef]

155. Sustarsic, E.G.; Junnila Rk Fau-Kopchick, J.J.; Kopchick, J.J. Human metastatic melanoma cell lines express high levels of growth hormone receptor and respond to GH treatment. *Biochem. Biophys. Res. Commun.* **2013**, *441*, 144–150. [CrossRef] [PubMed]
156. Kotta, A.A.-O.X.; Kelling, A.A.-O.; Corleto, K.A.; Sun, Y.; Giles, E.A.-O. Ghrelin and Cancer: Examining the Roles of the Ghrelin Axis in Tumor Growth and Progression. *Biomolecules* **2022**, *12*, 483. [CrossRef]
157. Jin, L.; Guo, Y.; Chen, J.; Wen, Z.; Jiang, Y.; Qian, J. Lactate receptor HCAR1 regulates cell growth, metastasis and maintenance of cancer-specific energy metabolism in breast cancer cells. *Mol. Med. Rep.* **2022**, *26*, 268. [CrossRef]
158. Fernández-Nogueira, P.; Noguera-Castells, A.; Fuster, G.; Recalde-Percaz, L.; Moragas, N.; López-Plana, A.; Enreig, E.; Jauregui, P.; Carbó, N.; Almendro, V.; et al. Histamine receptor 1 inhibition enhances antitumor therapeutic responses through extracellular signal-regulated kinase (ERK) activation in breast cancer. *Cancer Lett.* **2018**, *424*, 70–83. [CrossRef]
159. Medina, V.; Croci M Fau-Crescenti, E.; Crescenti E Fau-Mohamad, N.; Mohamad N Fau-Sanchez-Jiménez, F.; Sanchez-Jiménez F Fau-Massari, N.; Massari N Fau-Nuñez, M.; Nuñez M Fau-Cricco, G.; Cricco G Fau-Martin, G.; Martin G Fau-Bergoc, R.; Bergoc R Fau-Rivera, E.; et al. The role of histamine in human mammary carcinogenesis: H3 and H4 receptors as potential therapeutic targets for breast cancer treatment. *Cancer Biol. Ther.* **2008**, *7*, 28–35. [CrossRef] [PubMed]
160. Zhao, Y.Y.; Jia, J.; Zhang, J.J.; Xun, Y.P.; Xie, S.J.; Liang, J.F.; Guo, H.G.; Zhu, J.Z.; Ma, S.L.; Zhang, S.R. Inhibition of histamine receptor H3 suppresses the growth and metastasis of human non-small cell lung cancer cells via inhibiting PI3K/Akt/mTOR and MEK/ERK signaling pathways and blocking EMT. *Acta Pharmacol. Sin.* **2020**, *42*, 1288–1297. [CrossRef]
161. Li, T.; Wei, L.; Zhang, X.; Fu, B.; Zhou, Y.; Yang, M.; Cao, M.; Chen, Y.; Tan, Y.; Shi, Y.; et al. Serotonin Receptor HTR2B Facilitates Colorectal Cancer Metastasis via CREB1–ZEB1 Axis–Mediated Epithelial–Mesenchymal Transition. *Mol. Cancer Res.* **2024**, *22*, 538–554. [CrossRef]
162. Yue, Z.; Yuan, Z.; Zeng, L.; Wang, Y.; Lai, L.; Li, J.; Sun, P.; Xue, X.; Qi, J.; Yang, Z.; et al. LGR4 modulates breast cancer initiation, metastasis, and cancer stem cells. *FASEB J.* **2017**, *32*, 2422–2437. [CrossRef] [PubMed]
163. Gong, X.; Yi, J.; Carmon, K.S.; Crumbley, C.A.; Xiong, W.; Thomas, A.; Fan, X.; Guo, S.; An, Z.; Chang, J.T.; et al. Aberrant RSPO3-LGR4 signaling in Keap1-deficient lung adenocarcinomas promotes tumor aggressiveness. *Oncogene* **2014**, *34*, 4692–4701. [CrossRef] [PubMed]
164. Luo, W.; Tan, P.; Rodriguez, M.; He, L.; Tan, K.; Zeng, L.; Siwko, S.; Liu, M. Leucine-rich repeat-containing G protein-coupled receptor 4 (Lgr4) is necessary for prostate cancer metastasis via epithelial-mesenchymal transition. *J. Biol. Chem.* **2017**, *292*, 15525–15537. [CrossRef]
165. Kong, Y.; Ou, X.; Li, X.; Zeng, Y.; Gao, G.; Lyu, N.; Liu, P. LGR6 Promotes Tumor Proliferation and Metastasis through Wnt/β-Catenin Signaling in Triple-Negative Breast Cancer. *Mol. Ther.—Oncolytics* **2020**, *18*, 351–359. [CrossRef]
166. Wang, F.; Dai, C.Q.; Zhang, L.R.; Bing, C.; Qin, J.; Liu, Y.F. Downregulation of Lgr6 inhibits proliferation and invasion and increases apoptosis in human colorectal cancer. *Int. J. Mol. Med.* **2018**, *42*, 625–632. [CrossRef]
167. Sunaga, N.A.-O.; Kaira, K.A.-O.; Shimizu, K.; Tanaka, I.; Miura, Y.; Nakazawa, S.; Ohtaki, Y.A.-O.; Kawabata-Iwakawa, R.; Sato, M.; Girard, L.; et al. The oncogenic role of LGR6 overexpression induced by aberrant Wnt/β-catenin signaling in lung cancer. *Thorac. Cancer* **2023**, *15*, 131–141. [CrossRef]
168. Mondaca, J.M.; Uzair, I.D.; Castro Guijarro, A.C.; Flamini, M.I.; Sanchez, A.M. Molecular Basis of LH Action on Breast Cancer Cell Migration and Invasion via Kinase and Scaffold Proteins. *Front. Cell Dev. Biol.* **2021**, *8*, 630147. [CrossRef] [PubMed]
169. Schally, A.V.; Nagy, A. Chemotherapy targeted to cancers through tumoral hormone receptors. *Trends Endocrinol. Metab.* **2004**, *15*, 300–310. [CrossRef] [PubMed]
170. Sahay, D.; Leblanc, R.; Grunewald, T.G.; Ambatipudi, S.; Ribeiro, J.; Clézardin, P.; Peyruchaud, O. The LPA1/ZEB1/miR-21-activation pathway regulates metastasis in basal breast cancer. *Oncotarget* **2015**, *6*, 20604. [CrossRef] [PubMed]
171. Meng, F.A.-O.; Yin, Z.; Lu, F.; Wang, W.; Zhang, H. Disruption of LPA-LPAR1 pathway results in lung tumor growth inhibition by downregulating B7-H3 expression in fibroblasts. *Thorac. Cancer* **2023**, *15*, 316–326. [CrossRef] [PubMed]
172. Liu, J.; Rebecca, V.W.; Kossenkov, A.V.; Connelly, T.; Liu, Q.A.-O.X.; Gutierrez, A.; Xiao, M.; Li, L.; Zhang, G.A.-O.; Samarkina, A.; et al. Neural Crest-Like Stem Cell Transcriptome Analysis Identifies LPAR1 in Melanoma Progression and Therapy Resistance. *Cancer Res.* **2021**, *81*, 5230–5241. [CrossRef] [PubMed]
173. Li, M.; Xiao, D.; Zhang, J.; Qu, H.; Yang, Y.; Yan, Y.; Liu, X.; Wang, J.; Liu, L.; Wang, J.; et al. Expression of LPA2 is associated with poor prognosis in human breast cancer and regulates HIF-1α expression and breast cancer cell growth. *Oncol. Rep.* **2016**, *36*, 3479–3487. [CrossRef]
174. Popnikolov, N.K.; Dalwadi Bh Fau-Thomas, J.D.; Thomas Jd Fau-Johannes, G.J.; Johannes Gj Fau-Imagawa, W.T.; Imagawa, W.T. Association of autotaxin and lysophosphatidic acid receptor 3 with aggressiveness of human breast carcinoma. *Tumor Biol.* **2012**, *33*, 2237–2243. [CrossRef]
175. Zheng, Y.Q.; Miao, X.; Li, J.; Hu, M.F.; Zhu, Y.S.; Li, X.R.; Zhang, Y.J. Trichostatin A alleviates the process of breast carcinoma by downregulating LPAR5. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 6417–6425. [PubMed]

176. Ketscher, A.; Jilg, C.A.; Willmann, D.; Hummel, B.; Imhof, A.; Rüsseler, V.; Hölz, S.; Metzger, E.; Müller, J.M.; Schüle, R. LSD1 controls metastasis of androgen-independent prostate cancer cells through PXN and LPAR6. *Oncogenesis* **2014**, *3*, e120. [CrossRef] [PubMed]
177. Kalinkin, A.I.; Nemtsova, M.V.; Zaletaev, D.V.; Sigin, V.O.; Ignatova, E.; Kuznetsova, E.B.; Strelnikov, V.V.; Tanas, A.S. Leukotriene B4 receptors abnormal gene expression is associated with either shorter or longer survival in breast cancer patients depending on the intrinsic tumour molecular subtype. *Ann. Oncol.* **2019**, *30*, vii17. [CrossRef]
178. Raufman, J.-P.; Cheng, K.; Saxena, N.; Chahdi, A.; Belo, A.; Khurana, S.; Xie, G. Muscarinic receptor agonists stimulate matrix metalloproteinase 1-dependent invasion of human colon cancer cells. *Biochem. Biophys. Res. Commun.* **2011**, *415*, 319–324. [CrossRef]
179. Zhao, Q.; Gu, X.; Zhang, C.; Lu, Q.; Chen, H.; Xu, L. Blocking M2 muscarinic receptor signaling inhibits tumor growth and reverses epithelial-mesenchymal transition (EMT) in non-small cell lung cancer (NSCLC). *Cancer Biol. Ther.* **2015**, *16*, 634–643. [CrossRef] [PubMed]
180. Lin, G.; Sun, L.; Wang, R.; Guo, Y.; Xie, C. Overexpression of Muscarinic Receptor 3 Promotes Metastasis and Predicts Poor Prognosis in Non–Small-Cell Lung Cancer. *J. Thorac. Oncol.* **2014**, *9*, 170–178. [CrossRef]
181. Nishimura, S.; Uno M Fau-Kaneta, Y.; Kaneta Y Fau-Fukuchi, K.; Fukuchi K Fau-Nishigohri, H.; Nishigohri H Fau-Hasegawa, J.; Hasegawa J Fau-Komori, H.; Komori H Fau-Takeda, S.; Takeda S Fau-Enomoto, K.; Enomoto K Fau-Nara, F.; Nara F Fau-Agatsuma, T.; et al. MRGD, a MAS-related G-protein coupled receptor, promotes tumorigenisis and is highly expressed in lung cancer. *PLOS ONE* **2012**, *7*, e38618. [CrossRef]
182. Przygodzka, P.A.-O.; Soboska, K.A.-O.; Sochacka, E.A.-O.; Pacholczyk, M.A.-O.; Braun, M.A.-O.; Kassassir, H.A.-O.; Papiewska-Pająk, I.A.-O.; Kielbik, M.A.-O.; Boncela, J.A.-O. Neuromedin U secreted by colorectal cancer cells promotes a tumour-supporting microenvironment. *Cell Commun. Signal.* **2022**, *20*, 193. [CrossRef]
183. Przygodzka, P.; Sochacka, E.; Soboska, K.; Pacholczyk, M.; Papiewska-Pająk, I.; Przygodzki, T.; Płociński, P.; Ballet, S.; De Prins, A.; Boncela, J. Neuromedin U induces an invasive phenotype in CRC cells expressing the NMUR2 receptor. *J. Exp. Clin. Cancer Res.* **2021**, *40*, 283. [CrossRef] [PubMed]
184. Sánchez, M.A.-O.; Rodríguez, F.A.-O.; Coveñas, R.A.-O. Neuropeptide Y Peptide Family and Cancer: Antitumor Therapeutic Strategies. *Int. J. Mol. Sci.* **2023**, *24*, 9962. [CrossRef]
185. Medeiros, P.J.; Pascetta, S.; Kirsh, S.; Al-Khazraji, B.K.; Uniacke, J. HIF-dependent Neuropeptide Y Receptor Y1 and Y5 expression sensitizes hypoxic cells to NPY stimulation. *J. Biol. Chem.* **2022**, *298*, 101645. [CrossRef]
186. Dupouy, S.; Viardot-Foucault, V.; Alifano, M.; Souazé, F.; Plu-Bureau, G.; Chaouat, M.; Lavaur, A.; Hugol, D.; Gespach, C.; Gompel, A.; et al. The neurotensin receptor-1 pathway contributes to human ductal breast cancer progression. *PLoS ONE* **2009**, *4*, e4223. [CrossRef] [PubMed]
187. Younes, M.; Wu, Z.; Dupouy, S.; Lupo, A.M.; Mourra, N.; Takahashi, T.; Fléjou, J.F.; Trédaniel, J.; Régnard, J.F.; Damotte, D.; et al. Neurotensin (NTS) and its receptor (NTSR1) causes EGFR, HER2 and HER3 over-expression and their autocrine/paracrine activation in lung tumors, confirming responsiveness to erlotinib. *Oncotarget* **2014**, *5*, 8252–8269. [CrossRef] [PubMed]
188. Li, H.; Ma, Z.; Lei, Y. The expression of kappa-opioid receptor promotes the migration of breast cancer cells in vitro. *BMC Anesthesiol.* **2021**, *21*, 210. [CrossRef] [PubMed]
189. Xu, C.A.-O.X.; Wang, R.; Yang, Y.; Xu, T.; Li, Y.; Xu, J.A.-O.X.; Jiang, Z.A.-O. Expression of OPN3 in lung adenocarcinoma promotes epithelial-mesenchymal transition and tumor metastasis. *Thorac. Cancer* **2019**, *11*, 286–294. [CrossRef] [PubMed]
190. Masi, M.; Garattini, E.; Bolis, M.; Di Marino, D.; Maraccani, L.; Morelli, E.; Grolla, A.A.; Fagiani, F.; Corsini, E.; Travelli, C.; et al. OXER1 and RACK1-associated pathway: A promising drug target for breast cancer progression. *Oncogenesis* **2020**, *9*, 105. [CrossRef]
191. Moresco, M.A.; Raccosta, L.; Corna, G.; Maggioni, D.; Soncini, M.; Bicciato, S.; Doglioni, C.; Russo, V. Enzymatic Inactivation of Oxysterols in Breast Tumor Cells Constraints Metastasis Formation by Reprogramming the Metastatic Lung Microenvironment. *Front. Immunol.* **2018**, *9*, 2251. [CrossRef] [PubMed]
192. Ji, H.; Liu, N.; Li, J.; Chen, D.; Luo, D.; Sun, Q.; Yin, Y.; Liu, Y.; Bu, B.; Chen, X.; et al. Oxytocin involves in chronic stress-evoked melanoma metastasis via β-arrestin 2-mediated ERK signaling pathway. *Carcinogenesis* **2019**, *40*, 1395–1404. [CrossRef] [PubMed]
193. Sang, S.; Zhang, C.; Shan, J. Pyrroline-5-Carboxylate Reductase 1 Accelerates the Migration and Invasion of Nonsmall Cell Lung Cancer In Vitro. *Cancer Biotherapy Radiopharm.* **2019**, *34*, 380–387. [CrossRef] [PubMed]
194. Liu, X.A.-O.; Riquelme, M.A.; Tian, Y.; Zhao, D.; Acosta, F.A.-O.; Gu, S.; Jiang, J.X. ATP Inhibits Breast Cancer Migration and Bone Metastasis through Down-Regulation of CXCR4 and Purinergic Receptor P2Y11. *Cancers* **2021**, *13*, 4293. [CrossRef]
195. Wang, X.; Zhao, B.; Ren, D.; Hu, X.; Qiao, J.; Zhang, D.; Zhang, Y.; Pan, Y.; Fan, Y.; Liu, L.; et al. Pyrimidinergic receptor P2Y6 expression is elevated in lung adenocarcinoma and is associated with poor prognosis. *Cancer Biomarkers* **2023**, *38*, 191–201. [CrossRef] [PubMed]

196. Naruse, T.; Goi, T.; Yamaguchi, A. Prokineticin-1 induces normal lymphangiogenic activity and is involved in lymphangiogenesis and lymph node metastasis in colorectal cancer. *Oncotarget* **2021**, *12*, 1388–1397. [CrossRef]
197. Kurebayashi, H.; Goi, T.; Shimada, M.; Tagai, N.; Naruse, T.; Nakazawa, T.; Kimura, Y.; Hirono, Y.; Yamaguchi, A. Prokineticin 2 (PROK2) is an important factor for angiogenesis in colorectal cancer. *Oncotarget* **2015**, *6*, 26242–26251. [CrossRef] [PubMed]
198. Hou, T.; Lou, Y.; Li, S.; Zhao, C.; Ji, Y.; Wang, D.; Tang, L.; Zhou, M.; Xu, W.; Qian, M.; et al. Kadsurenone is a useful and promising treatment strategy for breast cancer bone metastases by blocking the PAF/PTAFR signaling pathway. *Oncol. Lett.* **2018**, *16*, 2255–2262. [CrossRef] [PubMed]
199. Iwamoto, K.; Takahashi, H.; Okuzaki, D.; Osawa, H.; Ogino, T.; Miyoshi, N.; Uemura, M.; Matsuda, C.; Yamamoto, H.; Mizushima, T.; et al. Syntenin-1 promotes colorectal cancer stem cell expansion and chemoresistance by regulating prostaglandin E2 receptor. *Br. J. Cancer* **2020**, *123*, 955–964. [CrossRef] [PubMed]
200. Jiang, J.; Dingledine, R. Role of prostaglandin receptor EP2 in the regulations of cancer cell proliferation, invasion, and inflammation. *J. Pharmacol. Exp. Ther.* **2013**, *344*, 360–367. [CrossRef]
201. Swami S Fau-Zhu, H.; Zhu H Fau-Nisco, A.; Nisco A Fau-Kimura, T.; Kimura T Fau-Kim, M.J.; Kim Mj Fau-Nair, V.; Nair V Fau-Wu, J.Y.; Wu, J.Y. Parathyroid hormone 1 receptor signaling mediates breast cancer metastasis to bone in mice. *J. Clin. Investig.* **2023**, *8*, e157390.
202. Monego, G.; Lauriola L Fau-Ramella, S.; Ramella S Fau-D'Angelillo, R.M.; D'Angelillo Rm Fau-Lanza, P.; Lanza P Fau-Granone, P.; Granone P Fau-Ranelletti, F.O.; Ranelletti, F.O. Parathyroid hormone-related peptide and parathyroid hormone-related peptide receptor type 1 expression in human lung adenocarcinoma. *Chest* **2010**, *137*, 898–908. [CrossRef]
203. Kawan, M.A.; Kyrou, I.; Ramanjaneya, M.; Williams, K.; Jeyaneethi, J.; Randeva, H.S.; Karteris, E. Involvement of the glutamine RF-amide peptide and its cognate receptor GPR103 in prostate cancer. *Oncol. Rep.* **2018**, *41*, 1140–1150. [CrossRef]
204. Feng, S.; Agoulnik, I.U.; Truong, A.; Li, Z.; Creighton, C.J.; Kaftanovskaya, E.M.; Pereira, R.; Han, H.D.; Lopez-Berestein, G.; Klonisch, T.; et al. Suppression of relaxin receptor RXFP1 decreases prostate cancer growth and metastasis. *Endocr.-Relat. Cancer* **2010**, *17*, 1021–1033. [CrossRef] [PubMed]
205. Nagahashi, M.; Yamada, A.; Katsuta, E.; Aoyagi, T.; Huang, W.C.; Terracina, K.P.; Hait, N.C.; Allegood, J.C.; Tsuchida, J.; Yuza, K.; et al. Targeting the SphK1/S1P/S1PR1 Axis That Links Obesity, Chronic Inflammation, and Breast Cancer Metastasis. *Cancer Res.* **2018**, *78*, 1713–1725. [CrossRef]
206. Lin, Q.; Ren, L.; Jian, M.; Xu, P.; Li, J.; Zheng, P.; Feng, Q.; Yang, L.; Ji, M.; Wei, Y.; et al. The mechanism of the premetastatic niche facilitating colorectal cancer liver metastasis generated from myeloid-derived suppressor cells induced by the S1PR1–STAT3 signaling pathway. *Cell Death Dis.* **2019**, *10*, 693. [CrossRef] [PubMed]
207. Filipenko, I.; Schwalm, S.; Reali, L.; Pfeilschifter, J.; Fabbro, D.; Huwiler, A.; Zangemeister-Wittke, U. Upregulation of the S1P(3) receptor in metastatic breast cancer cells increases migration and invasion by induction of PGE(2) and EP(2)/EP(4) activation. *Biochim. Biophys. Acta (BBA)-Mol. Cell Biol. Lipids* **2016**, *1861*, 1840–1851.
208. Kuo, C.-C.; Wu, J.-Y.; Wu, K.K. Cancer-derived extracellular succinate: A driver of cancer metastasis. *J. Biomed. Sci.* **2022**, *29*, 93. [CrossRef] [PubMed]
209. Corcoran, K.E.; Malhotra A Fau-Molina, C.A.; Molina Ca Fau-Rameshwar, P.; Rameshwar, P. Stromal-derived factor-1alpha induces a non-canonical pathway to activate the endocrine-linked Tac1 gene in non-tumorigenic breast cells. *J. Mol. Endocrinol.* **2008**, *40*, 113–124. [CrossRef]
210. Hao, X.; Gao, L.-Y.; Zhang, N.; Chen, H.; Jiang, X.; Liu, W.; Ao, L.; Cao, J.; Han, F.; Liu, J. Tac2-N acts as a novel oncogene and promotes tumor metastasis via activation of NF-κB signaling in lung cancer. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 319. [CrossRef] [PubMed]
211. Ashton, A.W.; Zhang, Y.; Cazzolli, R.; Honn, K.V. The Role and Regulation of Thromboxane A2 Signaling in Cancer-Trojan Horses and Misdirection. *Molecules* **2022**, *27*, 6234. [CrossRef]
212. Yang, X.L.; Qi, L.G.; Lin, F.J.; Ou, Z.L. The role of the chemokine receptor XCR1 in breast cancer cells. *Breast Cancer Targets Ther.* **2017**, *9*, 227–236. [CrossRef] [PubMed]
213. Wang, T.; Han, S.; Wu, Z.; Han, Z.; Yan, W.; Liu, T.; Wei, H.; Song, D.; Zhou, W.; Yang, X.; et al. XCR1 promotes cell growth and migration and is correlated with bone metastasis in non-small cell lung cancer. *Biochem. Biophys. Res. Commun.* **2015**, *464*, 635–641. [CrossRef] [PubMed]
214. Park, M.; Kim, D.; Ko, S.; Kim, A.; Mo, K.; Yoon, H. Breast Cancer Metastasis: Mechanisms and Therapeutic Implications. *Int. J. Mol. Sci.* **2022**, *23*, 6806. [CrossRef]
215. Hughes, C.E.; Nibbs, R.J.B. A guide to chemokines and their receptors. *FEBS J.* **2018**, *285*, 2944–2971. [CrossRef] [PubMed]
216. Griffith, J.W.; Sokol, C.L.; Luster, A.D. Chemokines and chemokine receptors: Positioning cells for host defense and immunity. *Annu. Rev. Immunol.* **2014**, *32*, 659–702. [CrossRef] [PubMed]

217. Muller, A.; Homey, B.; Soto, H.; Ge, N.; Catron, D.; Buchanan, M.E.; McClanahan, T.; Murphy, E.; Yuan, W.; Wagner, S.N.; et al. Involvement of chemokine receptors in breast cancer metastasis. *Nature* **2001**, *410*, 50–56. [CrossRef] [PubMed]
218. Smith, M.C.; Luker, K.E.; Garbow, J.R.; Prior, J.L.; Jackson, E.; Piwnica-Worms, D.; Luker, G.D. CXCR4 regulates growth of both primary and metastatic breast cancer. *Cancer Res.* **2004**, *64*, 8604–8612. [CrossRef]
219. Li, Y.M.; Pan, Y.; Wei, Y.; Cheng, X.; Zhou, B.P.; Tan, M.; Zhou, X.; Xia, W.; Hortobagyi, G.N.; Yu, D.; et al. Upregulation of CXCR4 is essential for HER2-mediated tumor metastasis. *Cancer Cell* **2004**, *6*, 459–469. [CrossRef] [PubMed]
220. Chen, I.X.; Chauhan, V.P.; Posada, J.; Ng, M.R.; Wu, M.W.; Adstamongkonkul, P.; Huang, P.; Lindeman, N.; Langer, R.A.-O.; Jain, R.K. Blocking CXCR4 alleviates desmoplasia, increases T-lymphocyte infiltration, and improves immunotherapy in metastatic breast cancer. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 4558–4566. [CrossRef]
221. Kochetkova, M.; Kumar, S.; McColl, S.R. Chemokine receptors CXCR4 and CCR7 promote metastasis by preventing anoikis in cancer cells. *Cell Death Differ.* **2009**, *16*, 664–673. [CrossRef]
222. Xu, B.; Zhou, M.; Qiu, W.; Ye, J.; Feng, Q.A.-O. CCR7 mediates human breast cancer cell invasion, migration by inducing epithelial-mesenchymal transition and suppressing apoptosis through AKT pathway. *Cancer Med.* **2017**, *6*, 1062–1071. [CrossRef]
223. Arakaki, A.K.S.; Pan, W.A.; Trejo, J.A.-O. GPCRs in Cancer: Protease-Activated Receptors, Endocytic Adaptors and Signaling. *Int. J. Mol. Sci.* **2018**, *19*, 1886. [CrossRef]
224. Yang, E.; Boire, A.; Agarwal, A.; Nguyen, N.; O'Callaghan, K.; Tu, P.; Kuliopulos, A.; Covic, L. Blockade of PAR1 signaling with cell-penetrating pepducins inhibits Akt survival pathways in breast cancer cells and suppresses tumor survival and metastasis. *Cancer Res.* **2009**, *69*, 6223–6231. [CrossRef]
225. Yang, E.; Cisowski, J.; Nguyen, N.; O'Callaghan, K.; Xu, J.; Agarwal, A.; Kuliopulos, A.; Covic, L. Dysregulated protease activated receptor 1 (PAR1) promotes metastatic phenotype in breast cancer through HMGA2. *Oncogene* **2016**, *35*, 1529–1540. [CrossRef] [PubMed]
226. Gad, A.A.; Balenga, N. The Emerging Role of Adhesion GPCRs in Cancer. *ACS Pharmacol. Transl. Sci.* **2020**, *3*, 29–42. [CrossRef] [PubMed]
227. Tang, X.; Jin, R.; Qu, G.; Wang, X.; Li, Z.; Yuan, Z.; Zhao, C.; Siwko, S.; Shi, T.; Wang, P.; et al. GPR116, an Adhesion G-Protein–Coupled Receptor, Promotes Breast Cancer Metastasis via the Gαq-p63RhoGEF-Rho GTPase Pathway. *Cancer Res.* **2013**, *73*, 6206–6218. [CrossRef]
228. Talia, M.; De Francesco, E.M.; Rigiracciolo, D.C.; Muoio, M.G.; Muglia, L.; Belfiore, A.; Maggiolini, M.A.-O.X.; Sims, A.A.-O.; Lappano, R. The G Protein-Coupled Estrogen Receptor (GPER) Expression Correlates with Pro-Metastatic Pathways in ER-Negative Breast Cancer: A Bioinformatics Analysis. *Cells* **2020**, *9*, 622. [CrossRef] [PubMed]
229. Liang, S.; Chen, Z.; Jiang, G.; Zhou, Y.; Liu, Q.; Su, Q.; Wei, W.; Du, J.; Wang, H. Activation of GPER suppresses migration and angiogenesis of triple negative breast cancer via inhibition of NF-κB/IL-6 signals. *Cancer Lett.* **2017**, *386*, 12–23. [CrossRef] [PubMed]
230. Biller, L.H.; Schrag, D. Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review. *JAMA* **2021**, *325*, 669–685. [CrossRef]
231. Ottaiano, A.A.-O.; Santorsola, M.; Del Prete, P.; Perri, F.A.-O.; Scala, S.; Caraglia, M.A.-O.; Nasti, G. Prognostic Significance of CXCR4 in Colorectal Cancer: An Updated Meta-Analysis and Critical Appraisal. *Cancers* **2021**, *13*, 3284. [CrossRef] [PubMed]
232. Yu, X.; Wang, D.; Wang, X.; Sun, S.; Zhang, Y.; Wang, S.; Miao, R.; Xu, X.; Qu, X. CXCL12/CXCR4 promotes inflammation-driven colorectal cancer progression through activation of RhoA signaling by sponging miR-133a-3p. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 32. [CrossRef]
233. Wang, D.; Wang, X.; Si, M.; Yang, J.; Sun, S.; Wu, H.; Cui, S.; Qu, X.; Yu, X. Exosome-encapsulated miRNAs contribute to CXCL12/CXCR4-induced liver metastasis of colorectal cancer by enhancing M2 polarization of macrophages. *Cancer Lett.* **2020**, *474*, 36–52. [CrossRef]
234. Brand, S.; Dambacher, J.; Beigel, F.; Olszak, T.; Diebold, J.; Otte, J.-M.; Göke, B.; Eichhorst, S.T. CXCR4 and CXCL12 are inversely expressed in colorectal cancer cells and modulate cancer cell migration, invasion and MMP-9 activation. *Exp. Cell Res.* **2005**, *310*, 117–130. [CrossRef]
235. Zhang, S.-S.; Han, Z.-P.; Jing, Y.-Y.; Tao, S.-F.; Li, T.-J.; Wang, H.; Wang, Y.; Li, R.; Yang, Y.; Zhao, X.; et al. CD133+CXCR4+ colon cancer cells exhibit metastatic potential and predict poor prognosis of patients. *BMC Med.* **2012**, *10*, 85. [CrossRef] [PubMed]
236. Li, X.X.; Zheng, H.T.; Huang, L.Y.; Shi, D.B.; Peng, J.J.; Liang, L.; Cai, S.J. Silencing of CXCR7 gene represses growth and invasion and induces apoptosis in colorectal cancer through ERK and β-arrestin pathways. *Int. J. Oncol.* **2014**, *45*, 1649–1657. [CrossRef] [PubMed]
237. Si, M.; Song, Y.; Wang, X.; Wang, D.; Liu, X.; Qu, X.; Song, Z.; Yu, X. CXCL12/CXCR7/β-arrestin1 biased signal promotes epithelial-to-mesenchymal transition of colorectal cancer by repressing miRNAs through YAP1 nuclear translocation. *Cell Biosci.* **2022**, *12*, 171. [CrossRef] [PubMed]
238. Lattanzi, R.; Miele, R. Prokineticin-Receptor Network: Mechanisms of Regulation. *Life* **2022**, *12*, 172. [CrossRef] [PubMed]

239. Tabata, S.; Goi T Fau-Nakazawa, T.; Nakazawa T Fau-Kimura, Y.; Kimura Y Fau-Katayama, K.; Katayama K Fau-Yamaguchi, A.; Yamaguchi, A. Endocrine gland-derived vascular endothelial growth factor strengthens cell invasion ability via prokineticin receptor 2 in colon cancer cell lines. *Oncol. Rep.* **2012**, *29*, 459–463. [CrossRef]
240. Goi, T.; Kurebayashi, H.; Ueda, Y.; Naruse, T.; Nakazawa, T.; Koneri, K.; Hirono, Y.; Katayama, K.; Yamaguchi, A. Expression of prokineticin-receptor2(PK-R2) is a new prognostic factor in human colorectal cancer. *Oncotarget* **2015**, *6*, 31758–31766. [CrossRef]
241. Kono, H.; Goi, T.A.-O.; Matsunaka, T.A.-O.X.; Koneri, K. Anti-Prokineticin1 Suppresses Liver Metastatic Tumors in a Mouse Model of Colorectal Cancer with Liver Metastasis. *Curr. Issues Mol. Biol.* **2023**, *46*, 44–52. [CrossRef]
242. Ji, B.; Feng, Y.; Sun, Y.; Ji, D.; Qian, W.; Zhang, Z.; Wang, Q.; Zhang, Y.; Zhang, C.; Sun, Y. GPR56 promotes proliferation of colorectal cancer cells and enhances metastasis via epithelial-mesenchymal transition through PI3K/AKT signaling activation. *Oncol. Rep.* **2018**, *40*, 1885–1896. [CrossRef] [PubMed]
243. Lim, D.R.; Kang, D.H.; Kuk, J.C.; Kim, T.H.; Shin, E.J.; Ahn, T.S.; Kim, H.J.; Jeong, D.J.; Baek, M.J.; Kim, N.K. Prognostic impact of GPR56 in patients with colorectal cancer. *Neoplasma* **2021**, *68*, 580–589. [CrossRef] [PubMed]
244. Su, L.; Zhang, J.; Xu, H.; Wang, Y.; Chu, Y.; Liu, R.; Xiong, S. Differential expression of CXCR4 is associated with the metastatic potential of human non-small cell lung cancer cells. *Clin. Cancer Res.* **2005**, *11*, 8273–8280. [CrossRef] [PubMed]
245. Choi, Y.H.; Burdick, M.D.; Strieter, B.A.; Mehrad, B.; Strieter, R.M. CXCR4, but not CXCR7, Discriminates Metastatic Behavior in Non–Small Cell Lung Cancer Cells. *Mol. Cancer Res.* **2014**, *12*, 38–47. [CrossRef]
246. Zhang, C.; Li, J.; Han, Y.; Jiang, J. A meta-analysis for CXCR4 as a prognostic marker and potential drug target in non-small cell lung cancer. *Drug Des. Dev. Ther.* **2015**, *ume 9*, 3267–3278.
247. Bertolini, G.; Cancila, V.; Milione, M.; Lo Russo, G.; Fortunato, O.; Zaffaroni, N.; Tortoreto, M.; Centonze, G.; Chiodoni, C.; Facchinetti, F.; et al. A novel CXCR4 antagonist counteracts paradoxical generation of cisplatin-induced pro-metastatic niches in lung cancer. *Mol. Ther.* **2021**, *29*, 2963–2978. [CrossRef] [PubMed]
248. Keane, M.P.; Belperio, J.A.; Xue, Y.Y.; Burdick, M.D.; Strieter, R.M. Depletion of CXCR2 inhibits tumor growth and angiogenesis in a murine model of lung cancer. *J. Immunol.* **2004**, *172*, 2853–2860. [CrossRef]
249. Saintigny, P.; Massarelli, E.; Lin, S.; Ahn, Y.H.; Chen, Y.; Goswami, S.; Erez, B.; O'Reilly, M.S.; Liu, D.; Lee, J.J.; et al. CXCR2 expression in tumor cells is a poor prognostic factor and promotes invasion and metastasis in lung adenocarcinoma. *Cancer Res.* **2013**, *73*, 571–582. [CrossRef] [PubMed]
250. Cheng, Y.; Mo, F.; Li, Q.; Han, X.; Shi, H.; Chen, S.; Wei, Y.; Wei, X.A.-O. Targeting CXCR2 inhibits the progression of lung cancer and promotes therapeutic effect of cisplatin. *Mol. Cancer* **2021**, *20*, 62. [CrossRef] [PubMed]
251. Willier, S.; Butt E Fau-Grunewald, T.G.P.; Grunewald, T.G. Lysophosphatidic acid (LPA) signalling in cell migration and cancer invasion: A focussed review and analysis of LPA receptor gene expression on the basis of more than 1700 cancer microarrays. *Biol. Cell* **2013**, *105*, 317–333. [CrossRef] [PubMed]
252. Yang, Y.; Mou, L.J.; Liu, N.; Tsao, M.S. Autotaxin expression in non-small-cell lung cancer. *Am. J. Respir. Cell Mol. Biol.* **1999**, *21*, 216–222. [CrossRef] [PubMed]
253. Xu, X.; Prestwich, G.D. Inhibition of tumor growth and angiogenesis by a lysophosphatidic acid antagonist in an engineered three-dimensional lung cancer xenograft model. *Cancer* **2010**, *116*, 1739–1750. [CrossRef] [PubMed]
254. Ueda, N.; Minami, K.; Ishimoto, K.; Tsujiuchi, T. Effects of lysophosphatidic acid (LPA) receptor-2 (LPA(2)) and LPA(3) on the regulation of chemoresistance to anticancer drug in lung cancer cells. *BMB Rep.* **2016**, *49*, 623–628. [CrossRef]
255. Lin, X.J.; Liu, H.; Li, P.; Wang, H.F.; Yang, A.K.; Di, J.M.; Jiang, Q.W.; Yang, Y.; Huang, J.R.; Yuan, M.L.; et al. miR-936 Suppresses Cell Proliferation, Invasion, and Drug Resistance of Laryngeal Squamous Cell Carcinoma and Targets GPR78. *Front. Oncol.* **2020**, *10*, 60. [CrossRef] [PubMed]
256. Achard, V.; Putora, P.M.; Omlin, A.; Zilli, T.; Fischer, S. Metastatic Prostate Cancer: Treatment Options. *Oncology* **2021**, *100*, 48–59. [CrossRef] [PubMed]
257. Chen, Q.; Zhong, T. The association of CXCR4 expression with clinicopathological significance and potential drug target in prostate cancer: A meta-analysis and literature review. *Drug Des. Dev. Ther.* **2015**, *9*, 5115–5122. [CrossRef] [PubMed]
258. Don-Salu-Hewage, A.S.; Chan, S.Y.; McAndrews, K.M.; Chetram, M.A.; Dawson, M.R.; Bethea, D.A.; Hinton, C.V. Cysteine (C)-x-C receptor 4 undergoes transportin 1-dependent nuclear localization and remains functional at the nucleus of metastatic prostate cancer cells. *PLOS ONE* **2013**, *8*, e57194.
259. Sbrissa, D.; Semaan, L.; Govindarajan, B.; Li, Y.; Caruthers, N.J.; Stemmer, P.M.; Cher, M.L.; Sethi, S.; Vaishampayan, U.; Shisheva, A.; et al. A novel cross-talk between CXCR4 and PI4KIIIα in prostate cancer cells. *Oncogene* **2019**, *38*, 332–344. [CrossRef] [PubMed]
260. Vaday, G.G.; Peehl, D.M.; Kadam, P.A.; Lawrence, D.M. Expression of CCL5 (RANTES) and CCR5 in prostate cancer. *Prostate* **2005**, *66*, 124–134. [CrossRef]

261. Sicoli, D.; Jiao, X.; Ju, X.; Velasco-Velazquez, M.; Ertel, A.; Addya, S.; Li, Z.; Andò, S.; Fatatis, A.; Paudyal, B.; et al. CCR5 receptor antagonists block metastasis to bone of v-Src oncogene-transformed metastatic prostate cancer cell lines. *Cancer Res.* **2014**, *74*, 7103–7114. [CrossRef] [PubMed]
262. Xing, Q.A.-O.X.; Xie, H.; Zhu, B.; Sun, Z.; Huang, Y.A.-O. MiR-455-5p Suppresses the Progression of Prostate Cancer by Targeting CCR5. *BioMed Res. Int.* **2019**, *2019*, 1–8. [CrossRef] [PubMed]
263. Pi, M.; Quarles, L.D. GPRC6A regulates prostate cancer progression. *Prostate* **2012**, *72*, 399–409. [CrossRef]
264. Ye, R.; Pi, M.; Cox, J.V.; Nishimoto, S.K.; Quarles, L.D. CRISPR/Cas9 targeting of GPRC6A suppresses prostate cancer tumorigenesis in a human xenograft model. *J. Exp. Clin. Cancer Res.* **2017**, *36*. [CrossRef] [PubMed]
265. Ahmed, B.; Qadir, M.I.; Ghafoor, S. Malignant Melanoma: Skin Cancer-Diagnosis, Prevention, and Treatment. *Crit. Rev. Eukaryot. Gene Expr.* **2020**, *30*, 291–297. [CrossRef] [PubMed]
266. Kim, J.; Mori, T.; Chen, S.L.; Amersi, F.F.; Martinez, S.R.; Kuo, C.; Turner, R.R.; Ye, X.; Bilchik, A.J.; Morton, D.L.; et al. Chemokine receptor CXCR4 expression in patients with melanoma and colorectal cancer liver metastases and the association with disease outcome. *Ann. Surg.* **2006**, *244*, 113–120. [CrossRef]
267. Mannavola, F.; Tucci, M.; Felici, C.; Passarelli, A.; D'Oronzo, S.; Silvestris, F. Tumor-derived exosomes promote the in vitro osteotropism of melanoma cells by activating the SDF-1/CXCR4/CXCR7 axis. *J. Transl. Med.* **2019**, *17*, 230. [CrossRef] [PubMed]
268. Alimohammadi, M.; Rahimi, A.; Faramarzi, F.; Alizadeh-Navaei, R.; Rafiei, A. Overexpression of chemokine receptor CXCR4 predicts lymph node metastatic risk in patients with melanoma: A systematic review and meta-analysis. *Cytokine* **2021**, *148*, 155691. [CrossRef]
269. Saxena, R.; Wang, Y.; Mier, J.W. CXCR4 inhibition modulates the tumor microenvironment and retards the growth of B16-OVA melanoma and Renca tumors. *Melanoma Res.* **2020**, *30*, 14–25. [CrossRef]
270. Fiandalo, M.; Sanny, T.; Monsalud, D.; Cordes, S.; Waikel, R.L. Functional Role of Chemokine Receptor 10 in Melanoma Metastasis. *FASEB J.* **2006**, *20*, A936. [CrossRef]
271. Kühnelt-Leddihn, L.; Müller, H.; Eisendle, K.; Zelger, B.; Weinlich, G. Overexpression of the chemokine receptors CXCR4, CCR7, CCR9, and CCR10 in human primary cutaneous melanoma: A potential prognostic value for CCR7 and CCR10? *Arch. Dermatol. Res.* **2012**, *304*, 185–193. [CrossRef] [PubMed]
272. Simonetti, O.; Goteri, G.; Lucarini, G.; Filosa, A.; Pieramici, T.; Rubini, C.; Biagini, G.; Offidani, A. Potential role of CCL27 and CCR10 expression in melanoma progression and immune escape. *Eur. J. Cancer* **2006**, *42*, 1181–1187. [CrossRef] [PubMed]
273. Müller, C.E. P2-pyrimidinergic receptors and their ligands. *Curr. Pharm. Des.* **2002**, *8*, 2353–2369. [CrossRef] [PubMed]
274. Di Virgilio, F.A.-O.; Sarti, A.C.; Falzoni, S.; De Marchi, E.; Adinolfi, E. Extracellular ATP and P2 purinergic signalling in the tumour microenvironment. *Nat. Rev. Cancer* **2018**, *18*, 601–618. [CrossRef] [PubMed]
275. Ma, X.; Pan, X.; Wei, Y.; Tan, B.; Yang, L.; Ren, H.; Qian, M.; Du, B. Chemotherapy-induced uridine diphosphate release promotes breast cancer metastasis through P2Y6 activation. *Oncotarget* **2016**, *7*, 29036–29050. [CrossRef] [PubMed]
276. Qin, J.; Zhang, Z.; Fu, Z.; Ren, H.; Liu, M.; Qian, M.; Du, B. The UDP/P2y6 axis promotes lung metastasis of melanoma by remodeling the premetastatic niche. *Cell. Mol. Immunol.* **2020**, *17*, 1269–1271. [CrossRef]
277. White, N.; Ryten M Fau-Clayton, E.; Clayton E Fau-Butler, P.; Butler P Fau-Burnstock, G.; Burnstock, G. P2Y purinergic receptors regulate the growth of human melanomas. *Cancer Lett.* **2004**, *224*, 81–91. [CrossRef] [PubMed]
278. Peter, S.; Siragusa, L.; Thomas, M.; Palomba, T.; Cross, S.; O'Boyle, N.M.; Bajusz, D.; Ferenczy, G.G.; Keserű, G.M.; Bottegoni, G.; et al. Comparative Study of Allosteric GPCR Binding Sites and Their Ligandability Potential. *J. Chem. Inf. Model.* **2024**, *64*, 8176–8192. [CrossRef] [PubMed]
279. Moore, D.C.; Elmes, J.B.; Shibu, P.A.; Larck, C.; Park, S.I. Mogamulizumab: An Anti-CC Chemokine Receptor 4 Antibody for T-Cell Lymphomas. *Ann. Pharmacother.* **2020**, *54*, 371–379. [CrossRef]
280. Keam, S.J. Talquetamab: First Approval. *Drugs* **2023**, *83*, 1439–1445. [CrossRef]
281. Hoy, S.M. Motixafortide: First Approval. *Drugs* **2023**, *83*, 1635–1643. [CrossRef]
282. Moore, H.C.F.; Unger, J.M.; Phillips, K.-A.; Boyle, F.; Hitre, E.; Porter, D.; Francis, P.A.; Goldstein, L.J.; Gomez, H.L.; Vallejos, C.S.; et al. Goserelin for Ovarian Protection during Breast-Cancer Adjuvant Chemotherapy. *N. Engl. J. Med.* **2015**, *372*, 923–932. [CrossRef]
283. Caplin, M.E.; Pavel, M.; Ćwikła, J.B.; Phan, A.T.; Raderer, M.; Sedláčková, E.; Cadiot, G.; Wolin, E.M.; Capdevila, J.; Wall, L.; et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N. Engl. J. Med.* **2014**, *371*, 224–233. [CrossRef]
284. Mongiat-Artus, P.; Teillac, P. Abarelix: The first gonadotrophin-releasing hormone antagonist for the treatment of prostate cancer. *Expert Opin. Pharmacother.* **2004**, *5*, 2171–2179. [CrossRef]
285. Desai, K.; McManus, J.M.; Sharifi, N.A.-O. Hormonal Therapy for Prostate Cancer. *Endocr. Rev.* **2021**, *42*, 354–373. [CrossRef] [PubMed]
286. Zengerling, F.; Jakob, J.J.; Schmidt, S.; Meerpohl, J.J.; Blümle, A.; Schmucker, C.; Mayer, B.; Kunath, F. Degarelix for treating advanced hormone-sensitive prostate cancer. *Cochrane Database Syst. Rev.* **2021**, *8*, CD012548.

287. Deeks, E.D. Histrelin: In advanced prostate cancer. *Drugs* **2010**, *70*, 623–630. [CrossRef]
288. Ploussard, G.; Mongiat-Artus, P. Triptorelin in the management of prostate cancer. *Futur. Oncol.* **2012**, *9*, 93–102. [CrossRef]
289. Erdem, G.U.; Sendur Ma Fau-Ozdemir, N.Y.; Ozdemir Ny Fau-Yazıcı, O.; Yazıcı O Fau-Zengin, N.; Zengin, N. A comprehensive review of the role of the hedgehog pathway and vismodegib in the management of basal cell carcinoma. *Curr. Med. Res. Opin.* **2015**, *31*, 743–756. [CrossRef] [PubMed]
290. Aditya, S.; Rattan, A. Vismodegib: A smoothened inhibitor for the treatment of advanced basal cell carcinoma. *Indian Dermatol. Online J.* **2013**, *4*, 365–368. [CrossRef]
291. Sanmartín, O.; Llombart, B.; Carretero Hernández, G.; Flórez Menéndez, Á.; Botella-Estrada, R.; Herrera Ceballos, E.; Puig, S. Sonidegib in the Treatment of Locally Advanced Basal Cell Carcinoma. *Actas Dermo-Sifiliograficas* **2021**, *112*, 295–301. [CrossRef]
292. Bilgin, Y.M.; de Greef, G.E. Plerixafor for stem cell mobilization: The current status. *Curr. Opin. Hematol.* **2016**, *23*, 67–71. [CrossRef]
293. Romon, I.A.-O.; Castillo, C.A.-O.; Cid, J.A.-O.; Lozano, M.A.-O.X. Use of plerixafor to mobilize haematopoietic progenitor cells in healthy donors. *Vox Sang.* **2021**, *117*, 6–16. [CrossRef] [PubMed]
294. Johnson, P.W.M.; Glennie, M.J. Rituximab: Mechanisms and applications. *Br. J. Cancer* **2001**, *85*, 1619–1623. [CrossRef]
295. The Antibody Society. Therapeutic Monoclonal Antibodies Approved or in Regulatory Review. Available online: www.antibodysociety.org/antibody-therapeutics-product-data (accessed on 4 September 2024).
296. Rexer, B.N.; Arteaga, C.L. Intrinsic and Acquired Resistance to HER2-Targeted Therapies in HER2 Gene-Amplified Breast Cancer: Mechanisms and Clinical Implications. *Crit. Rev.™ Oncog.* **2012**, *17*, 1–16. [CrossRef]
297. Delgado, M.A.-O.; Garcia-Sanz, J.A.-O. Therapeutic Monoclonal Antibodies against Cancer: Present and Future. *Cells* **2023**, *12*, 2837. [CrossRef]
298. Choong, G.A.-O.; Cullen, G.A.-O.; O'Sullivan, C.A.-O. Evolving standards of care and new challenges in the management of HER2-positive breast cancer. *CA A Cancer J. Clin.* **2020**, *70*, 355–374. [CrossRef]
299. Poole, R.M. Pembrolizumab: First global approval. *Drugs* **2014**, *74*, 1973–1981. [CrossRef] [PubMed]
300. Markham, A. Erenumab: First Global Approval. *Drugs* **2018**, *78*, 1157–1161. [CrossRef]
301. Bagherzadeh-Fard, M.; Amin Yazdanifar, M.; Sadeghalvad, M.; Rezaei, N. Erenumab efficacy in migraine headache prophylaxis: A systematic review. *Int. Immunopharmacol.* **2023**, *117*, 109366. [CrossRef]
302. Ureshino, H.; Kamachi, K.; Kimura, S. Mogamulizumab for the Treatment of Adult T-cell Leukemia/Lymphoma. *Clin. Lymphoma Myeloma Leuk.* **2019**, *19*, 326–331. [CrossRef]
303. Kim, Y.H.; Bagot, M.; Pinter-Brown, L.; Rook, A.H.; Porcu, P.; Horwitz, S.M.; Whittaker, S.; Tokura, Y.; Vermeer, M.; Zinzani, P.L.; et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): An international, open-label, randomised, controlled phase 3 trial. *Lancet Oncol.* **2018**, *19*, 1192–1204. [CrossRef] [PubMed]
304. Gill, S.K.; Fleming, E.; Gebre, H.; Bangolo, A.I.; Siegel, D.S.; Vesole, D.H.; Biran, N.; Parmar, H.; Phull, P. Real World Outcomes with Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody: A Single Center Experience for Relapsed/ Refractory Multiple Myeloma (RRMM). *Blood* **2024**, *144*, 7047. [CrossRef]
305. Mateos, M.V.; Weisel, K.; De Stefano, V.; Goldschmidt, H.; Delforge, M.; Mohty, M.; Cavo, M.; Vij, R.; Lindsey-Hill, J.; Dytfeld, D.; et al. LocoMMotion: A prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. *Leukemia* **2022**, *36*, 1371–1376. [CrossRef]
306. Chari, A.; Minnema, M.C.; Berdeja, J.G.; Oriol, A.; van de Donk, N.W.C.J.; Rodríguez-Otero, P.; Askari, E.; Mateos, M.-V.; Costa, L.J.; Caers, J.; et al. Talquetamab, a T-Cell–Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. *N. Engl. J. Med.* **2022**, *387*, 2232–2244. [CrossRef] [PubMed]
307. Liu, L.; Krishnan, A. Talquetamab in multiple myeloma. *Haematologica* **2024**, *109*, 718–724. [CrossRef]
308. Dhody, K.A.-O.; Pourhassan, N.A.-O.; Kazempour, K.A.-O.X.; Green, D.A.-O.; Badri, S.; Mekonnen, H.; Burger, D.A.-O.; Maddon, P.A.-O. PRO 140, a monoclonal antibody targeting CCR5, as a long-acting, single-agent maintenance therapy for HIV-1 infection. *HIV Clin. Trials* **2018**, *19*, 85–93. [CrossRef] [PubMed]
309. Jiao, X.; Wang, M.; Zhang, Z.; Li, Z.; Ni, D.; Ashton, A.W.; Tang, H.-Y.; Speicher, D.W.; Pestell, R.G. Leronlimab, a humanized monoclonal antibody to CCR5, blocks breast cancer cellular metastasis and enhances cell death induced by DNA damaging chemotherapy. *Breast Cancer Res.* **2021**, *23*, 85–93. [CrossRef] [PubMed]
310. Hamid, R.; Alaziz, M.; Mahal, A.S.; Ashton, A.A.-O.; Halama, N.; Jaeger, D.; Jiao, X.; Pestell, R.A.-O. The Role and Therapeutic Targeting of CCR5 in Breast Cancer. *Cells* **2023**, *12*, 2237. [CrossRef]
311. Basket Study of Leronlimab (PRO 140) in Patients with CCR5+ Locally Advanced or Metastatic Solid Tumours ClinicalTrials.gov Identifier NCT04504942. Available online: https://clinicaltrials.gov/study/NCT04504942?cond=cancer&term=leronlimab&rank=2&tab=history (accessed on 15 August 2024).
312. Barnett, A.H. Exenatide. *Drugs Today* **2005**, *41*, 563–578. [CrossRef]

313. Knudsen, L.B.; Lau, J. The Discovery and Development of Liraglutide and Semaglutide. *Front. Endocrinol.* **2019**, *10*, 155. [CrossRef] [PubMed]
314. Kirby, R.S.; Fitzpatrick Jm Fau-Clarke, N.; Clarke, N. Abarelix and other gonadotrophin-releasing hormone antagonists in prostate cancer. *BJU Int.* **2009**, *104*, 1580–1584. [CrossRef]
315. Mariani, P.; Blumberg, J.; Landau, A.; Lebrun-Jezekova, D.; Botton, E.; Beatrix, O.; Mayeur, D.; Herve, R.; Maisonobe, P.; Chauvenet, L. Symptomatic treatment with lanreotide microparticles in inoperable bowel obstruction resulting from peritoneal carcinomatosis: A randomized, double-blind, placebo-controlled phase III study. *J. Clin. Oncol.* **2012**, *30*, 4337–4343. [CrossRef]
316. Cheer, S.M.; Plosker, G.L.; Simpson, D.; Wagstaff, A.J. Goserelin. *Drugs* **2005**, *65*, 2639–2655. [CrossRef] [PubMed]
317. Crees, Z.D.; Stockerl-Goldstein, K.E.; Larson, S.; Illés, Á.; Milone, G.; Martino, M.; Stiff, P.; Sborov, D.W.; Pereira, D.L.; Micallef, I.N.; et al. Motixafortide (BL-8040) and G-CSF Versus Placebo and G-CSF to Mobilize Hematopoietic Stem Cells for Autologous Stem Cell Transplantation in Patients with Multiple Myeloma: The Genesis Trial. *Blood* **2021**, *138*, 475. [CrossRef]
318. Bockorny, B.; Macarulla, T.; Semenisty, V.; Borazanci, E.; Feliu, J.; Ponz-Sarvise, M.; Abad, D.G.; Oberstein, P.; Alistar, A.; Muñoz, A.; et al. Motixafortide and Pembrolizumab Combined to Nanoliposomal Irinotecan, Fluorouracil, and Folinic Acid in Metastatic Pancreatic Cancer: The COMBAT/KEYNOTE-202 Trial. *Clin. Cancer Res.* **2021**, *27*, 5020–5027. [CrossRef] [PubMed]
319. Manji, G.A.; May, M.S.; Pellicciotta, I.; Sta Ana, S.; Sender, N.; Pan, S.M.; Ross, I.; Hu, J.; Shi, Q.; Raufi, A.G. CheMo4METPANC: A phase 2 study with combination chemotherapy (gemcitabine and nab-paclitaxel), chemokine (C-X-C) Motif receptor 4 inhibitor (motixafortide), and immune checkpoint blockade (cemiplimab) in metastatic treatment-naïve pancreas adenocarcinoma. *J. Clin. Oncol.* **2023**, *41*, TPS4200. [CrossRef]
320. Huang, E.H.; Singh, B.; Cristofanilli, M.; Gelovani, J.; Wei, C.; Vincent, L.; Cook, K.R.; Lucci, A. A CXCR4 antagonist CTCE-9908 inhibits primary tumor growth and metastasis of breast cancer. *J. Surg. Res.* **2008**, *155*, 231–236. [CrossRef]
321. Hotte, S.; Hirte, H.; Iacobucci, A.; Wong, D.; Cantin, L.; Korz, W.; Miller, W. Phase I/II study of CTCE-9908, a novel anticancer agent that inhibits CXCR4, in patients with advanced solid cancers. *Mol. Cancer Ther.* **2007**, *6*, A153.
322. Domanska, U.M.; Kruizinga, R.C.; Nagengast, W.B.; Timmer-Bosscha, H.; Huls, G.; de Vries, E.G.E.; Walenkamp, A.M.E. A review on CXCR4/CXCL12 axis in oncology: No place to hide. *Eur. J. Cancer* **2013**, *49*, 219–230. [CrossRef] [PubMed]
323. Phase I/II Study of PTX-9908 Injection As an Inhibitor of Cancer Progression in Patients with Non-resectable Hepatocellular Carcinoma Following Transarterial Chemoembolization Treatment. 2019. Available online: https://clinicaltrials.gov/study/NCT03812874 (accessed on 27 September 2024).
324. Jin, B.A.-O.; Odongo, S.; Radwanska, M.A.-O.; Magez, S.A.-O. NANOBODIES®: A Review of Diagnostic and Therapeutic Applications. *Int. J. Mol. Sci.* **2023**, *24*, 5994. [CrossRef] [PubMed]
325. Li, B.; Qin, X.; Mi, L.-Z. Nanobodies: From structure to applications in non-injectable and bispecific biotherapeutic development. *Nanoscale* **2022**, *14*, 7110–7122. [CrossRef]
326. Mustafa, M.I.; Mohammed, A. Nanobodies: A Game-Changer in Cell-Mediated Immunotherapy for Cancer. *SLAS Discov. Adv. Sci. Drug Discov.* **2023**, *28*, 358–364. [CrossRef]
327. Hollifield, A.L.; Arnall, J.R.; Moore, D.C. Caplacizumab: An anti-von Willebrand factor antibody for the treatment of thrombotic thrombocytopenic purpura. *Am. J. Health Pharm.* **2020**, *77*, 1201–1207. [CrossRef] [PubMed]
328. Nasiri, F.; Safarzadeh Kozani, P.; Rahbarizadeh, F. T-cells engineered with a novel VHH-based chimeric antigen receptor against CD19 exhibit comparable tumoricidal efficacy to their FMC63-based counterparts. *Front. Immunol.* **2023**, *14*, 1063838. [CrossRef] [PubMed]
329. Natrajan, K.A.-O.; Kaushal, M.A.-O.X.; George, B.A.-O.; Kanapuru, B.A.-O.; Theoret, M.A.-O. FDA Approval Summary: Ciltacabtagene Autoleucel for Relapsed or Refractory Multiple Myeloma. *Clin. Cancer Res.* **2024**, *30*, 2865–2871. [CrossRef]
330. Jähnichen, S.; Blanchetot, C.; Maussang, D.; Gonzalez-Pajuelo, M.; Chow, K.Y.; Bosch, L.; De Vrieze, S.; Serruys, B.; Ulrichts, H.; Vandevelde, W.; et al. CXCR4 nanobodies (VHH-based single variable domains) potently inhibit chemotaxis and HIV-1 replication and mobilize stem cells. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20565–20570. [CrossRef] [PubMed]
331. Niquille, D.A.-O.; Fitzgerald, K.A.-O.X.; Gera, N.A.-O. Biparatopic antibodies: Therapeutic applications and prospects. *mAbs* **2024**, *16*, 2310890. [CrossRef] [PubMed]
332. Steeland, S.; Vandenbroucke, R.E.; Libert, C. Nanobodies as therapeutics: Big opportunities for small antibodies. *Drug Discov. Today* **2016**, *21*, 1076–1113. [CrossRef] [PubMed]
333. A Phase I, Single-Centre, Randomised, Single-Blinded, Placebo-Controlled Single Ascending Dose Study, Followed by an Open-label Extension, Evaluating the Safety, Pharmacokinetics, Pharmacodynamics and Efficacy of ALX-0651, Administered Intravenously to Healthy Male Volunteers. 2011. Available online: https://clinicaltrials.gov/study/NCT01374503 (accessed on 4 October 2024).
334. Dolgin, E. First GPCR-directed antibody passes approval milestone. *Nat. Rev. Drug Discov.* **2018**, *17*, 457–459. [CrossRef]

335. Bradley, M.E.; Dombrecht, B.; Manini, J.; Willis, J.; Vlerick, D.; De Taeye, S.; Van den Heede, K.; Roobrouck, A.; Grot, E.; Kent, T.C.; et al. Potent and efficacious inhibition of CXCR2 signaling by biparatopic nanobodies combining two distinct modes of action. *Mol. Pharmacol.* **2015**, *87*, 251–262. [CrossRef]
336. Low, S.A.-O.; Wu, H.; Jerath, K.; Tibolla, A.; Fogal, B.A.-O.; Conrad, R.; MacDougall, M.; Kerr, S.; Berger, V.A.-O.; Dave, R.; et al. VHH antibody targeting the chemokine receptor CX3CR1 inhibits progression of atherosclerosis. *mAbs* **2020**, *12*, 1709322. [CrossRef]
337. Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Rising Doses of BI 655088 Administered by Intravenous Infusion in Healthy Male Subjects (Single-blind, Partially Randomised Within Dose Groups, Placebo-controlled, Parallel Group Design). Available online: https://clinicaltrials.gov/study/NCT02696616 (accessed on 30 September 2024).
338. Heukers, R.; De Groof, T.W.M.; Smit, M.J. Nanobodies detecting and modulating GPCRs outside in and inside out. *Curr. Opin. Cell Biol.* **2019**, *57*, 115–122. [CrossRef] [PubMed]
339. Pérez-Herrero, E.; Fernández-Medarde, A. Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. *Eur. J. Pharm. Biopharm.* **2015**, *93*, 52–79. [CrossRef] [PubMed]
340. Wang, J.; Liao, Z.-X. Research progress of microrobots in tumor drug delivery. *Food Med. Homol.* **2024**, *1*, 9420025. [CrossRef]