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Review

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Advances in the research and application of neurokinin-1 receptor antagonists

Xiangyu HONG, Junjie MA, Shanshan ZHENG, Guangyu ZHAO, Caiyun FU✉

College of Life Sciences and Medicine, Zhejiang Sci-Tech University, Hangzhou 310018, China

Abstract: Recently, the substance P (SP)/neurokinin-1 receptor (NK-1R) system has been found to be involved in various human pathophysiological disorders including the symptoms of coronavirus disease 2019 (COVID-19). Besides, studies in the oncological field have demonstrated an intricate correlation between the upregulation of NK-1R and the activation of SP/NK-1R system with the progression of multiple carcinoma types and poor clinical prognosis. These findings indicate that the modulation of SP/NK-1R system with NK-1R antagonists can be a potential broad-spectrum antitumor strategy. This review updates the latest potential and applications of NK-1R antagonists in the treatment of human diseases and cancers, as well as the underlying mechanisms. Furthermore, the strategies to improve the bioavailability and efficacy of NK-1R antagonist drugs are summarized, such as solid dispersion systems, nanonization, and nanoencapsulation. As a radiopharmaceutical therapeutic, the NK-1R antagonist aprepitant was originally developed as radioligand receptor to target NK-1R-overexpressing tumors. However, combining NK-1R antagonists with other drugs can produce a synergistic effect, thereby enhancing the therapeutic effect, alleviating the symptoms, and improving patients' quality of life in several diseases and cancers.

Key words: Neurokinin-1 receptor (NK-1R) antagonist; Pathophysiological disorder; Tumor target; Bioavailability; Nanoencapsulation; Synergistic therapy

1 Introduction

Thus far, numerous human tumors have been observed to exhibit an overexpression of peptide hormones and neuropeptides, such as growth inhibitors, bombesin, bradykinin, and tachykinins (for instance, substance P (SP), neuropeptide Y (NPY), and hemokinin-1 (HK-1)), along with their corresponding receptors (Mohammadi et al., 2020). Moreover, these peptides were reported to play a role in regulating various oncogenic activities including cell proliferation, metastasis, and angiogenesis (Ghasemi et al., 2018, 2019; Ebrahimi et al., 2020; Lorestani et al., 2020). Unsurprisingly, their cognate receptors have been recognized as prospective targets for the development of drugs and tumor diagnostic markers (Morgat et al., 2014).

✉ Caiyun FU, fucy03@zstu.edu.cn
Xiangyu HONG, https://orcid.org/0009-0003-0460-1196
Caiyun FU, https://orcid.org/0000-0003-4090-885X

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Mammalian tachykinins, such as neurokinin, are a class of bioactive peptides that are not only distributed in the nervous and immune systems or the cardiovascular system (Dehlin and Levick, 2014; Mistrova et al., 2016), but also present in muscle tissue (Gordon et al., 1993), connective tissue, and body fluids (Muñoz and Coveñas, 2020a). Previous studies have shown that SP belongs to a family of tachykinins that exerts its physiological effects by neurokinin-1 receptor (NK-1R) (Liu and Burcher, 2005; Steinhoff et al., 2014). Among the tachykinins, SP was the first one to be discovered, which has since been found to have the highest level of selectivity and affinity for NK-1R (Liu and Burcher, 2005). The binding of SP to NK-1R regulates multiple physiological functions and triggers various physiological and pathological responses, such as pain transmission (de Felipe et al., 1998), nausea and vomiting (Tattersall et al., 1996), pruritus (Agelopoulos et al., 2019), vasodilatation (Yamamoto, 1993), depression, anxiety (Ratti et al., 2013), wound healing (Mohammadi et al., 2020), corneal epithelial wound healing (Yanai et al., 2020), inflammation (Khorasani et al., 2020), abortion (Alwazzan et al., 2020), alcohol

addiction (Khom et al., 2020), hematopoiesis (Muñoz and Coveñas, 2020a), viral infection (Bubak et al., 2018), tendon skin fibrosis (Barbe et al., 2020), dry eye (Taketani et al., 2019), pulmonary fibrosis (Mohamed et al., 2022), and neurodegenerative diseases (Martinez and Philipp, 2016).

In addition, the overexpression of NK-1R may be closely associated with the progression of a wide range of cancers, such as melanoma, glioma, ovarian cancer, pancreatic cancer (Mohammadi et al., 2020), esophageal cancer (Dong et al., 2015), breast cancer (Muñoz et al., 2020), head and neck tumor (Singh et al., 2021), gallbladder cancer (Deng et al., 2019), thyroid cancer (Isorna et al., 2020), hepatoblastoma (Muñoz et al., 2019b), glioblastoma (Afshari et al., 2021), leukemia (Ge et al., 2019), and colorectal cancer (Shi et al., 2021). Meanwhile, the expression of NK-1R is not essential for the viability of normal cells (Muñoz et al., 2022).

The above findings imply that NK-1R is a critical target in cancer treatment, and NK-1R antagonists have the potential to be effective against a wide range of tumors. Thus far, this prospect has triggered extensive academic and industrial interest in similar compounds and their expanded applications (Schöppe et al., 2019). Recently, scientists have developed novel NK-1R antagonists, such as aprepitant, netupitant, fosaprepitant, and SR140333. Currently, there are two non-peptide NK-1R antagonists approved in China for the treatment of chemotherapy-induced nausea and vomiting: aprepitant and fosaprepitant, an oral capsule and a powder for injection, respectively. Aprepitant was the first NK-1R antagonist approved by the US Food and Drug Administration (FDA) for the clinical treatment of nausea and vomiting after chemotherapy (Schöppe et al., 2019).

With the deepening of research on the mechanism of the SP/NK-1R system, the application of NK-1R antagonists is also constantly expanding. In the field of cancer treatment, aprepitant has been nanoformulated to improve drug efficacy (Ramírez-García et al., 2019). In addition, it has been used to create conjugates carrying radioactive isotopes, providing potential therapeutic diagnostic radiopharmaceuticals for the imaging and treatment of NK-1R-positive tumors (Halik et al., 2020). Furthermore, aprepitant was shown to have strong synergistic effects when used in combination with other drugs, overcoming tumor resistance (García-Aranda et al., 2022). Additionally, it can act as an anti-inflammatory drug, blocking the NK-1R pathway in macrophages with the potential to inhibit inflammation (Zhao et al., 2020). Recently, aprepitant has also been found to have potential therapeutic value in the treatment of severe respiratory diseases caused by coronavirus disease 2019 (COVID-19) (García-Aranda et al., 2022). This paper provides an updated overview of the current therapeutic potential, mechanism, and expanded applications of NK-1R antagonists, including aprepitant.

2 Potential of SP/NK-1R antagonists in the treatment of pathophysiological disorders

2.1 Inhibition of inflammatory response

The SP/NK-1R system mediates a wide range of physiopathological responses. In the development of rheumatoid arthritis, NK-1R is overexpressed in rheumatoid arthritis fibroblast-like synoviocytes (RA-FLSs) compared to normal FLSs. The treatment of RA-FLSs with aprepitant can specifically block NK-1R, reducing the secretion of tumor necrosis factor-α (TNF-α)-induced pro-inflammatory cytokines as well as the production of reactive oxygen species (ROS), thus inhibiting inflammatory responses. At the same time, aprepitant can prevent the expression of matrix metalloproteinases (MMPs) induced by TNF-α (Liu et al., 2019), i.e., proteases that can degrade extracellular matrix and many non-matrix proteins, playing a key role in disease progression (Craig et al., 2015). These findings indicate that targeting NK-1R with specific antagonists such as aprepitant may provide a new treatment strategy for RA (Liu et al., 2019).

Furthermore, the SP/NK-1R system modulates the secretion of human colonic epithelial cell exosomes and thereby suppresses inflammatory responses. MicroRNA-21 (miR-21) is a kind of microRNA that has been proved to promote the proliferation of colonic epithelial cells. After stimulation by SP, miR-21 is selectively sorted into exosomes, thus stimulating the growth of colonic epithelial cells. Then, the extracellular vesicles produced by SP-stimulated colon epithelial cells may amplify the inflammatory response of SP/NK-1R in colon tissue-related cells by transferring the vesicle cargo to adjacent cells not originally targeted by SP (Bakirtzi et al., 2019). Targeting the SP/NK-1R

signaling system with NK-1R antagonists can inhibit or reduce the production of extracellular vesicles induced by SP stimulation in colon epithelial cells, providing new treatment strategies for colon tissue-related inflammatory reactions. Besides, increasingly more robust researches have reported that miR-21 is associated with the occurrence and proliferation of age-related diseases (Olivieri et al., 2021), kidney injury and disease (Mahtal et al., 2022), liver disease (Wang et al., 2021), pressure overload (Ramanujam et al., 2021), retinal ischemia/reperfusion injury (Wan et al., 2020), osteoporosis (Lee et al., 2021), and chronic obstructive pulmonary disease (Kim et al., 2021). Considering the relationship between the SP/NK-1R system and miR-21 demonstrated above, antagonists of NK-1R may have the potential to alleviate these disorders and others.

Moreover, aprepitant has recently been shown to reduce inflammation and inhibit inflammatory pain by inhibiting c-Jun N-terminal kinase (JNK) and p38/mitogen-activated protein kinase (MAPK) (Yang et al., 2021). Therefore, using NK-1R antagonists can provide new therapeutic strategies for SP/NK-1R disease (Fig. 1).

2.2 Alleviation of cardiac diastolic dysfunction

Cardiac fibrosis is the underlying cause of cardiac diastolic dysfunction, which leads to heart failure. In hypertensive mouse hearts, NK-1R regulates the maturation of cardiomyocytes and promotes the secretion of hypertrophic factors in vitro, thereby mediating cardiac fibrosis. The use of NK-1R antagonist L732138 can halt this process and regulate the level of myofibroblasts in vivo (Widiapradja et al., 2019), thus reducing cardiac diastolic dysfunction.

2.3 Alleviation of dry eye symptoms

Dry eye disease (DED) is a highly prevalent, multifactorial chronic disease of the ocular surface characterized by persistent irritation or burning symptoms. Failure to provide treatment can result in inflammation-induced damage to both the cornea and conjunctiva (Definition and Classification Subcommittee, 2007; Rouen and White, 2018), severely affecting the life quality of patients. Multiple studies (Chen et al., 2014; Foulsham et al., 2017) have illustrated that inflammation in DED is primarily mediated by an unrestricted effector T helper cell 17 (Th17) response caused by the dysfunction of immunosuppressive regulatory T cells (Tregs). Normally, Tregs have the ability to suppress the response of pathogenic helper T cells, which in turn respond to dry stimuli in the regulatory environment. However, a significant increase in the level of SP promotes dysregulation of Treg function in the DED, while blocking the SP/NK-1R pathway with NK-1R antagonists can effectively restore Treg function and alleviate dry eye symptoms (Taketani et al., 2019).

2.4 Remission of neurological damage from brain hemorrhage in mice

Intracerebral hemorrhage (ICH) is a severe subtype of stroke, and recent research has found that

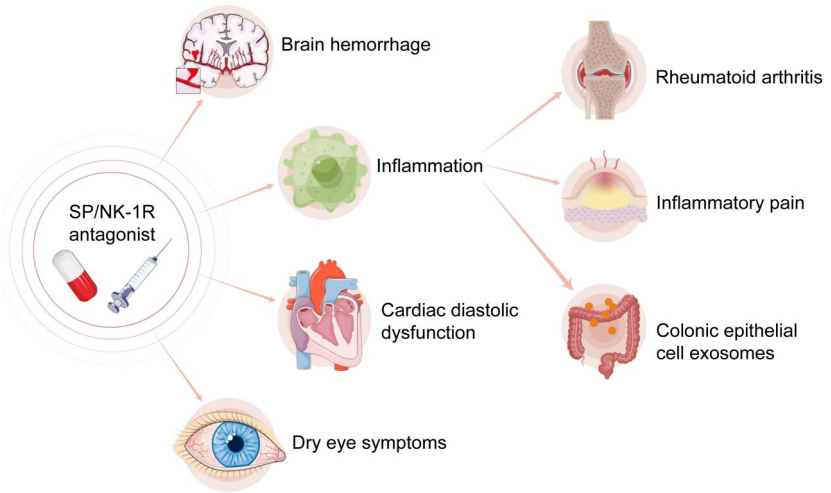

Fig. 1 Overview of substance P (SP)/neurokinin-1 receptor (NK-1R) antagonists in the treatment of pathophysiological disorders.

aprepitant can alleviate neurological deficits in mice after ICH by inhibiting the NK-1R/protein kinase C δ (PKCδ) signaling pathway and reducing neuronal death (Jin et al., 2022). Therefore, antagonizing NK-1R may have the potential in the treatment of ICH.

3 Therapeutic value of NK-1R antagonist aprepitant in the treatment of severe respiratory diseases caused by COVID-19

During the COVID-19 pandemic period, a large body of evidence was gathered to prove that the severity and mortality rates in elderly people are higher than those in infants and children (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). Recently, an epidemiological study in China indicated that children's clinical symptoms (acute respiratory disease) are milder than those of adult patients among infected individuals (Dong et al., 2020). One possible reason is that COVID-19 causes the excessive production of immune cells and cytokines in adults (Biadsee et al., 2020), while children typically generate minimal amounts of inflammatory mediators. Therefore, they can be spared from the impact of "cytokine storms," a cascading process of an overreactive immune system response to infection, which is one of the reasons for uncontrollable inflammatory reactions in adults (Tang et al., 2020).

In the respiratory system, SP is one of most prevalent neuropeptides. It is predominantly situated in the bronchopulmonary fibers and plays a critical role in protecting the lungs from various harmful stimuli, such as viral infections or toxic irritants. However, the excessive release of SP from the respiratory epithelium can lead to acute respiratory distress syndrome, a severe respiratory illness characterized by respiratory failure and pulmonary inflammation (Bai et al., 1995; Chu et al., 2000). Notably, the symptoms caused by SP imbalance are similar to those of COVID-19 infection, such as influenza, fever, headache, sore throat, fatigue, and loss of olfactory and gustatory senses. Patients with COVID-19 infection can exhibit cardiac system dysfunction or heart failure in severe cases, while these symptoms are avoidable in SP-deficient mice (Meléndez et al., 2011). The increase in SP can activate the pain response to viral infection through the NK-1R, triggering acute immune responses that lead to cytokine storms or organ failure in severe cases.

In the past two decades, various neurokinin receptor antagonists have been developed to specifically block the binding of SP to its receptors. To date, aprepitant has been the only drug approved for clinical application (Quartara and Altamura, 2006). Considering the acute immune and inflammatory responses mediated by the elevation of the SP/NK-1R complex, researchers have turned to aprepitant as an anti-inflammatory drug with specific antiviral effects. As recently reported, aprepitant can be applied in clinical treatment to avoid fatal consequences, particularly in adult COVID-19 infections (Reinoso-Arija et al., 2021). However, further research is needed to support the accuracy and effectiveness of this therapeutic intervention (Mehboob and Lavezzi, 2021).

4 Potential of targeted blockade of NK-1R to treat multiple malignancies overexpressing SP and NK-1R

4.1 Involvement of NK-1R signaling pathway in cancer

NK-1R is a G-protein-coupled receptor. Upon activation by agonists, it undergoes a conformational change, adopting an active-state conformation. This conformational transition facilitates the replacement of guanosine diphosphate (GDP) bound to the G protein α subunit with guanosine triphosphate (GTP) (Thom et al., 2021). As a result of NK-1R-mediated G-protein activation, the Ras homolog gene family (Rho)–Rho-associated protein kinase (ROCK) signaling pathway (Muñoz and Coveñas, 2020a) and phospholipase C (PLC) enzymes are activated, releasing two second messengers, inositol triphosphate (IP_3) and diacylglycerol (DAG), followed by Ca^{2+} release from the endoplasmic reticulum to the cytoplasm and the activation of several different proliferative, invasion, and migration-related signaling pathways (Douglas and Leeman, 2011; Dong et al., 2015), all of which can be deregulated in cancer cells, especially by those presenting NK-1R overexpression. Besides, NK-1R antagonists counteract the Warburg effect (Muñoz et al., 2015) (Fig. 2). Thus, blocking NK-1R using antagonists can be a promising strategy for tumor treatment.

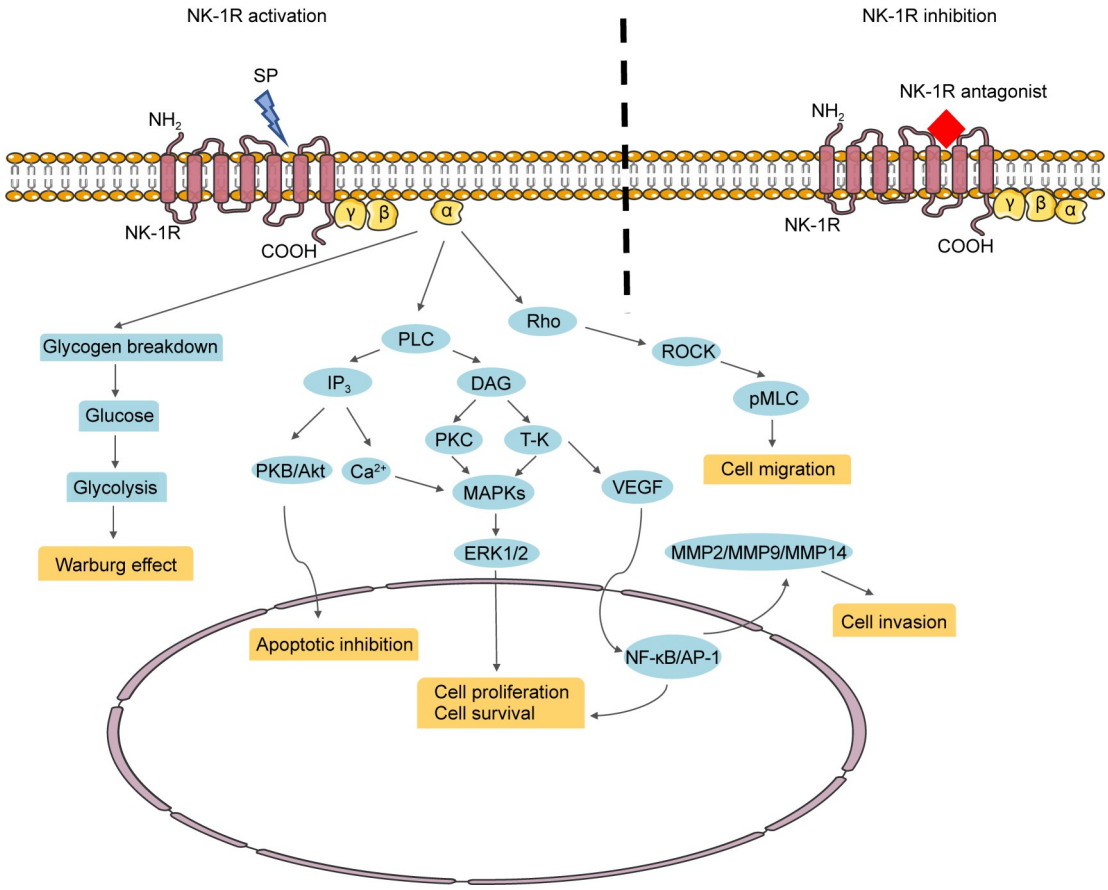

Fig. 2 Mechanism of mediating anticancer activity through targeting neurokinin-1 receptor (NK-1R). The stimulation of NK-1R results in cell proliferation, antiapoptotic effect, and cell migration. The pathways indicated are involved in these mechanisms. NK-1R antagonists impede these pathways and inhibit both tumor cell proliferation and migration, as well as exert an apoptotic effect in cancer cells. SP: substance P; PLC: phospholipase C; IP_3: inositol triphosphate; DAG: diacylglycerol; Rho: Ras homolog gene family; ROCK: Rho-associated protein kinase; PKB/Akt: protein kinase B; PKC: protein kinase C; T-K: tyrosine-kinase; MAPK: mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase; VEGF: vascular endothelial growth factor; pMLC: myosin regulatory light chain phosphorylation; MMP: matrix metalloproteinase; NF-κB: nuclear factor-κB; AP-1: activator protein-1.

4.2 Preclinical research

Many studies have indicated the altered expression of SP/NK-1R complex in cancer, as tumor cells overexpressing SP and NK-1R promote tumor growth and angiogenesis. Therefore, NK-1R is a promising target in the treatment of cancer, and NK-1R antagonists have a potential to become broad-spectrum antitumor drugs (Muñoz and Rosso, 2010; Muñoz et al., 2015, 2019b; Ge et al., 2019; Shi et al., 2021). In addition, the upregulation of NK-1R in cancer cells can serve as a potential tumor biomarker, aiding in rapid diagnosis. Thus far, diverse preclinical studies have provided evidence for the prospective utility of NK-1R antagonists as therapeutic agents against a wide spectrum of human malignancies (Table 1).

4.3 Clinical studies

Aprepitant, as an NK-1R antagonist, has already been subject to clinical trials. Reports have indicated that the effects of aprepitant lead to cumulative therapeutic outcomes (Muñoz and Coveñas, 2020a). Aprepitant, administered at standard clinical dosages (125 mg on the first day, followed by 80 mg on the second and third days), is commonly employed for managing chemotherapy-induced nausea and vomiting. Notably, aprepitant at similar dosages has exhibited efficacy in alleviating refractory pruritus in cutaneous T-cell lymphoma patients unresponsive to conventional antipruritic treatments (Maroñas-Jiménez et al., 2018). Aprepitant has been proven to suppress cough in lung cancer patients with comparable dosages in

Table 1 Relevant results of neurokinin-1 receptor (NK-1R) antagonists in preclinical research

Cancer type	Relevant results
Acute myeloid leukemia (AML)	The expression of NK-1R is significantly elevated in patients with AML and a group of human leukemia cell lines. Blocking NK-1R can induce cell apoptosis both in vitro and in vivo by producing excessive mitochondrial reactive oxygen species (mtROS). In addition to its anti-cancer activity, blocking NK-1R has an analgesic effect on bone pain induced by leukemia by reducing inflammation and triggering cell apoptosis (Ge et al., 2019).
	AML cells display an elevated expression of the truncated NK-1R isoform in contrast to healthy lymphocytes. While substance P (SP) stimulates proliferation in AML cells, aprepitant demonstrates a concentration-dependent inhibition of AML cell proliferation, with only minor growth suppression observed in lymphocytes. Notably, a higher dose of aprepitant also enhances the survival of AML-treated mice (Molinos-Quintana et al., 2019).
Breast cancer	The overexpression of NK-1R in triple-negative breast cancer (TNBC) promotes cell proliferation and migration. In this case, aprepitant can exert an anti-tumor effect by inducing cell apoptosis via blocking SP/NK-1R signaling (Muñoz et al., 2020).
	The breast cancer cell lines BT-474, MCF-7, MDA-MB-468, and MT-3 exhibit an increased level of NK-1R, which plays a role in cell viability. SP promotes cell growth, but when treated with aprepitant, it hampers SP-triggered cell proliferation and leads to cell death through apoptosis mediated by NK-1R (Muñoz et al., 2014).
	Metastatic breast cells exhibit higher expression levels of NK-1R compared to non-metastatic cells. In particular, NK-1R is significantly overexpressed in metastatic breast cells compared to their non-metastatic counterparts. The treatment with a 30 μmol/L dose of the NK-1R antagonist aprepitant promotes protein kinase B (Akt) phosphorylation, which selectively impedes cell proliferation and triggers cell death. However, this effect is not observed in non-metastatic 67NR cells (Nizam and Erin, 2018).
Colon cancer	Aprepitant exerts apoptotic effects on SW480 colon cancer cells, triggering programmed cell death. It concurrently attenuates the phosphatidylinositol 3-kinase (PI3K)/Akt signaling cascade. Additionally, the administration of aprepitant inhibits the nuclear factor-κB (NF-κB) signaling pathway, including the expression of genes that promote antiapoptotic activity. Notably, this treatment does not substantially affect the expression of p53 or its downstream proapoptotic target genes (Ghahremanloo et al., 2021).
Cervical cancer	In HeLa cells, SP modulates the expression of cell cycle regulators as well as genes associated with apoptosis, such as B-cell lymphoma-2 (BCL-2) and BCL-2-associated X protein (BAX). Additionally, SP enhances the migratory and proliferative capabilities of these cells, particularly due to the predominant expression of the truncated NK-1R isoform. However, the administration of the NK-1R antagonist aprepitant counteracts these effects in a dose- and time-dependent manner (Mozafari et al., 2022).
Esophageal cancer	The invasion and metastasis of esophageal cancer cells are induced by SP elevation. Furthermore, aprepitant can be used to block the SP-mediated metastasis and angiogenesis of esophageal cancer cells (Mohammadi et al., 2020).
Gallbladder cancer	After binding with endogenous agonist SP, NK-1R can induce the proliferation, migration, dissemination, and invasion of gallbladder cancer cells by regulating the Akt/NF-κB pathway, while antagonizing NK-1R can reverse this effect (Deng et al., 2019).
Glioma	Aprepitant treatment exhibits a concentration-dependent reduction in the viability of U87 glioblastoma cell lines. Furthermore, aprepitant effectively inhibits the oxidative effects induced by SP by suppressing the production of reactive oxygen species (ROS). Aprepitant treatment enhances the enzymatic activity of catalase and superoxide dismutase (SOD), suggesting its potential role in mitigating oxidative stress in U87 glioblastoma cells (Korfi et al., 2021).
Head and neck cancer (HNC)	SP has been found to induce a multitude of inflammatory pathways in HNC cells, including the secretion of chemokines, cytokines, and inflammatory markers. These events provoke an inflammatory tumor microenvironment, which subsequently promotes tumor proliferation and migration. SP also enhances the activation of various epithelial-mesenchymal transition (EMT) genes and the translation of matrix metalloproteinases (MMPs), which are critical for cancer invasion and metastasis (Singh et al., 2021).
Hepatoblastoma (HB)	The overexpression of SP and truncated NK-1R can stimulate the growth of HB cells. Non-peptide NK-1R antagonists can inhibit HB cell proliferation by inducing HB cell apoptosis in a concentration-dependent manner. Treating HB with NK-1R antagonists can not only reduce tumor volume but also decease angiogenesis activity (Muñoz et al., 2019b).

To be continued

Table 1 (continued)

Cancer type	Relevant results
Human pancreatic ductal adenocarcinoma (PDAC)	The inhibition of NK-1R by aprepitant achieves a significant reduction in cell growth in cancer stem cells (CSCs), PDAC cells, and pancreatic stellate cells (PSCs) in a dose-dependent manner. Notably, aggressive cancer cell types and specific cell subgroups expressing higher levels of the truncated tachykinin receptor 1 (TACR1) isoform exhibit heightened sensitivity to NK-1R inhibition. Therefore, the analysis of splice variants holds great promise for potential applications in the stratification of PDAC patients, enabling the identification of candidates who could benefit from NK-1R-targeted therapies (Beirith et al., 2021).
Lung cancer	NK1-R exhibits increased expression in human lung cancer samples, which correlates with advanced clinical stages and negative prognosis. The activation of NK-1R stimulates cell proliferation, colony formation, EMT, migration, and expression of MMP2/14. Conversely, blocking NK-1R with aprepitant enhances the sensitivity of cancer cells to gefitinib/osimertinib, inhibits cell proliferation and migration, and slows down tumor growth in nude mice (Zhang et al., 2022).
	Both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) cells exhibit elevated NK-1R expression, pivotal for cell viability. SP prompts the proliferation of cancer cells, while aprepitant inhibits their growth concentration-dependently via NK-1R, inducing apoptosis (Muñoz et al., 2012).
Melanoma	NK-1R is upregulated in both human melanoma samples and melanoma cell lines such as MEL HO, COLO 858, and COLO 679, contributing to tumor cell viability. After treatment with aprepitant, cell proliferation is suppressed in a concentration-dependent manner through apoptosis (Muñoz et al., 2010).
Prostate cancer	The truncated isoform of NK-1R is expressed in prostate cancer cells. The presence of SP modulates the expression of cell cycle-related proteins (c-Myc, cyclin D1, cyclin B1, and p21) and apoptosis-related genes (BCL-2 and BAX), thereby promoting both proliferative and migrative phenotypes in vitro. Furthermore, SP stimulation facilitates tumor growth in vivo. The administration of aprepitant significantly reverses these effects, leading to enhanced survival time (Ebrahimi et al., 2022).

randomized trials (Noronha et al., 2020; Smith et al., 2021). Moreover, a clinical trial demonstrated that aprepitant at 300 mg/d for 45 d elicits similar antidepressant effects as paroxetine, while displaying side effects similar to a placebo (Kramer et al., 1998). Furthermore, a combination therapy involving the compassionate use of aprepitant (1140 mg/d for 45 d) plus palliative radiotherapy led to the disappearance of an 8 cm×7 cm lung cancer tumor mass with no severe side effects (Muñoz et al., 2019a). These clinical investigations offer promising prospects for the repurposing of aprepitant in cancer therapy.

5 Strategies to improve the bioavailability of NK-1R antagonist aprepitant

Aprepitant is a compound with high lipophilicity (Olver et al., 2007) and low water solubility. Its oral bioavailability is determined by dissolution and release processes, which is usually the rate-limiting step for intestinal absorption (Sugano and Terada, 2015). Therefore, the demand to improve the dissolution and solubility rate of aprepitant facilitates the development of efficient formulations (Zhang et al., 2018). Thus far, several strategies have been developed to improve the solubility, dissolution rate, stability, and utilization of this drug, such as micronization of active pharmaceutical ingredients, solvation, salinization, nanoencapsulation (Muñoz and Coveñas, 2020b), cyclodextrin solubilization, solid dispersion systems (Liu et al., 2015), and the use of co-solvents (Roos et al., 2017). Improving the efficacy of aprepitant, reducing its side effects, and achieving its high efficacy at low doses are of great practical clinical significance.

5.1 Phosphatidylcholine-based solid dispersion system

In order to improve the bioavailability of aprepitant, a research team led by Jaehwi LEE prepared a solid dispersion system based on phosphatidylcholine. They used inorganic mesoporous materials to adsorb the phospholipid-based dispersion system, giving it solid-state properties and improving its powder properties. Solid dispersion systems comprise a simple and effective method for increasing the water solubility and dissolution rate of poorly water-soluble drugs (Ridhurkar et al., 2013; Liu et al., 2015, 2022b). In such systems, hydrophobic and insoluble drug molecules are dispersed in a hydrophilic polymer matrix that changes the crystalline state of the drug into an amorphous state, effectively increasing its solubility and dissolution

rate (Kumar and Gupta, 2013; Sosnik and Seremeta, 2015).

Phosphatidylcholine is a common biological molecule widely used in pharmaceutical dispersion systems. When used alone, phosphatidylcholine dispersions have a certain degree of "stickiness," which may exert a negative impact on the flowability and stability of formulations. However, using a formulation containing the adsorbent Neusilin® and the disintegrant croscarmellose sodium (CCS) can effectively improve the physical properties of phosphatidylcholine dispersions, enhancing their flowability and stability. In addition, the solubility of aprepitant in phosphatidylcholine-based solid dispersions is significantly higher than that of pure aprepitant, indicating that phosphatidylcholine-based solid dispersions can effectively increase its solubility, promoting its absorption and bioavailability (Yeo et al., 2020). Therefore, phosphatidylcholine-based solid dispersions have broad prospects for application in pharmaceutical formulations, particularly enhancing drug bioavailability.

5.2 Nanonization

In order to increase the full contact of aprepitant with target cells and minimize the impact of food, aprepitant has been formulated into nanoparticle suspensions (Muñoz and Coveñas, 2020b; Kakade et al., 2022; Liu et al., 2022a). The elevated number of nanoparticles and the presence of vesicles in cells have been shown to increase the transport rate and utilization of aprepitant in the blood plasma (Roos et al., 2017).

5.3 Nanoencapsulation

Nanoparticles as drug delivery systems can help improve drug efficacy and reduce drug toxicity. In cancer treatment, the application of nanoparticles can enhance drug efficacy through improving the characteristics listed below.

5.3.1 Stability and tolerance

Encapsulating drugs in nanoparticles can protect drugs from biological degradation and metabolism, thereby improving their stability and tolerance against them. This can prolong the half-life of drugs in the body, improve their bioavailability, reduce drug dosage and frequency, and decrease adverse effects (Ramírez-García et al., 2019).

5.3.2 Delivery and retention

Nanoparticles can facilitate the accumulation and uptake of drugs in diseased tissues through the leaky vascular system and poor lymphatic drainage in tumors. Moreover, nanoparticles can be actively taken up by tumor cells, thereby improving drug delivery and retention (Maeda et al., 2000).

5.3.3 Targeted delivery

Acidity, protease activity, and redox imbalance within the tumor microenvironment are common factors that trigger nanoparticle breakdown and drug release (Mura et al., 2013). Therefore, changes in the tumor metabolic microenvironment can be exploited to achieve the precise spatiotemporal release of drugs from nanoparticle encapsulation. Since many intracellular endosomal transport mechanisms are suitable for nanomedicines (Ramírez-García et al., 2019), nanoparticle-mediated drug delivery is highly effective for intracellular signaling molecules. Soft polymer nanoparticles have been designed to respond to intracellular pH changes, specifically targeting the NK-1R in acidified endosomes to precisely inhibit the intracellular signaling events that cause chronic pain. When injected into bodies, nanoparticles containing aprepitant inhibit SP-induced spinal neuron activation and consistently prevent pain transmission. In this way, nanoparticle therapy can provide a completely persistent relief from nociceptive, inflammatory, and neuropathic pain, offering an alternative to opioids for chronic pain treatment (Ramírez-García et al., 2019).

In summary, nanoparticles as an effective drug delivery system have broad prospects for application in cancer treatment. By improving drug stability, delivery, retention, and targeting, they can significantly improve drug efficacy while reducing toxicity, bringing new opportunities and challenges into cancer treatment.

6 Aprepitant in radioligand receptor-targeted therapy

Radioligand receptor-targeted therapy is a treatment method that uses a radiolabeled specific ligand to bind to certain overexpressed receptors during the tumor cell differentiation and proliferation process. This leads to the accumulation of a large amount of

radioactive isotopes in the tumor site for internal irradiation (Miao and Quinn, 2021). A prerequisite for targeted radionuclide therapies is the identification of a suitable molecular target with specificity for a particular pathology. Commonly, many malignancies are characterized by infiltration, unclear margins, or systemic spread of metastases; only the selective binding of radiopharmaceuticals to molecular targets can form reliable imaging or safe tumor lesion ablation with minimal side effects.

Based on the above findings, Ewa GNIAZDOWSKA and colleagues designed the synthesis of radiolabeled conjugates of aprepitant with gallium-68 or lutetium-177 to perform in vitro affinity evaluations. Among them, the 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) amide conjugate showed satisfactory stability in human serum. By evaluating the effect of the linker on the lipophilicity of radiolabeled conjugates, it was shown that suitable alkyl amine derivatives are more promising bio-carriers with characteristics closer to the parent drug aprepitant (Halik et al., 2020, 2022).

Most importantly, aprepitant is a relatively safe drug approved for clinical use with known pharmacological characteristics (Muñoz and Rosso, 2010). Overall, it can be used to create radiolabeled conjugates for the imaging and therapy of cancers overexpressing NK-1R, serving as a potential therapeutic diagnostic radiopharmaceutical in a targeted radiolabeled system for the treatment of NK-1R-positive tumors.

7 Combination therapy of NK-1R antagonists with other drugs

The synergistic effects of NK-1R antagonists regarding anti-tumor activity and cancer cell growth inhibition in combination with other drugs have been confirmed by multiple studies. In vitro experiments have shown that the microtubule destabilizer agent (MDA) in combination with NK-1R antagonist has synergistic toxicity and acts by promoting apoptosis in human glioblastoma, bladder cancer, cervical cancer, and breast cancer cells (Kitchens et al., 2009).

The combined application of aprepitant and ritonavir has been shown to have a more significant synergistic cytotoxic effect on human glioblastoma cells; the combination of these two drugs along with temozolomide produces an even stronger synergistic effect (Kast et al., 2016).

Our previous study showed that combining aprepitant with the cytosine arabinoside (Ara-C) can make acute myeloid leukemia (AML) cells more sensitive to the cytotoxic effects of Ara-C. The combination of low-dose Ara-C and aprepitant can provide a more effective treatment for AML both in vitro and in vivo, while reducing the toxicity of Ara-C. This observation may open up new avenues for the clinical use of conventional chemotherapy drugs (Wu et al., 2020). Besides, NK-1R antagonists can not only play a synergistic anti-tumor role in radiotherapy or chemotherapy but also reduce the side effects of these two treatment strategies (Muñoz and Coveñas, 2020b). For example, the cardiac toxicity of doxorubicin is mediated by the SP/NK-1R system. It is known that aprepitant can reduce cardiac toxicity while increasing the sensitivity of tumor cells to doxorubicin (Robinson et al., 2016).

In preclinical studies, it has been shown that aprepitant has a protective effect against liver and kidney toxicity caused by the chemotherapy drug cisplatin (Un et al., 2020). Aprepitant also inhibits the cutaneous (such as nasal nodules, crusting, skin redness, and hair loss) and neuroinflammatory side effects mediated by erlotinib, an epidermal growth factor receptor-tyrosine kinase inhibitor. Erlotinib induces an increased level of SP expression, a side effect mediated through the SP/NK-1R system, which is alleviated by the NK-1R antagonist aprepitant, including a decrease in the amount of NK-1R expressed in the skin (Fig. 3).

8 Conclusions and outlook

Taken together, the SP/NK-1R system is involved in various pathophysiological disorders. Recent oncological studies have shown a strong link between increased NK-1R expression, activation of the SP/NK-1R system, and the progression of different types of cancer with poor prognosis. These findings collectively suggest that using NK-1R antagonists to modulate the SP/NK-1R system could be a promising broad-spectrum approach for antitumor and pathophysiological disease therapy. However, certain shortcomings, such as low water solubility and poor bioavailability, limit the clinical development of these drugs, while

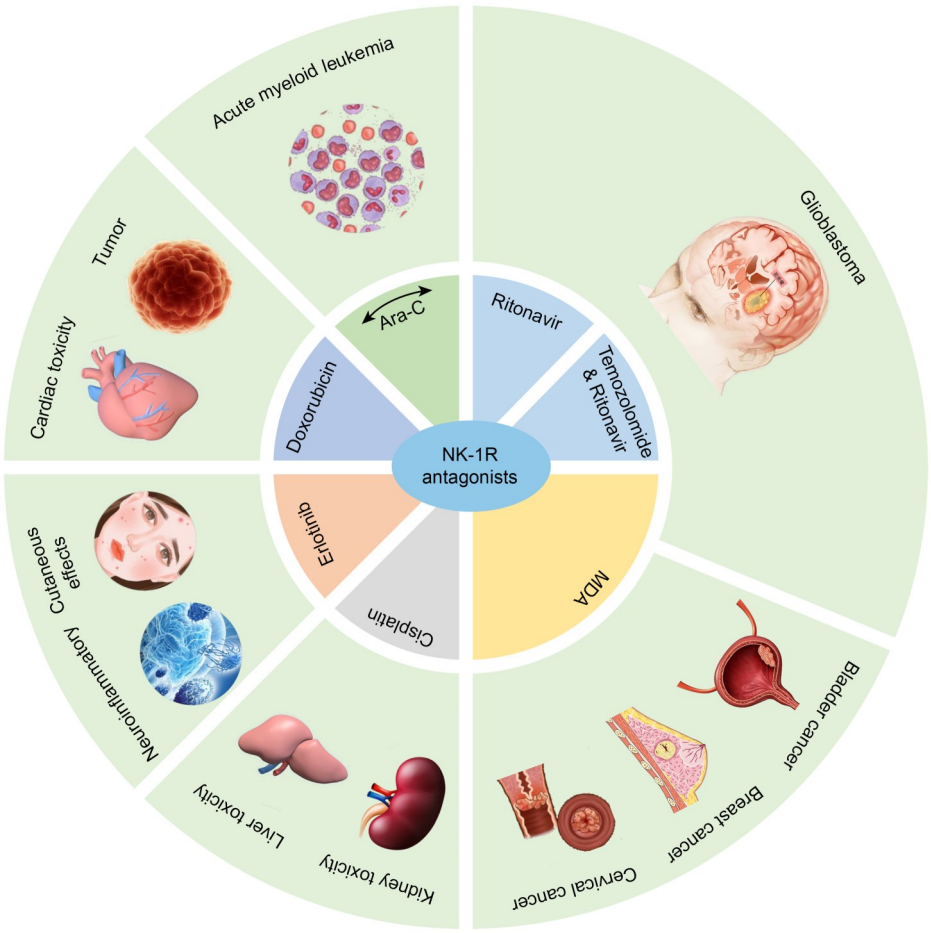

Fig. 3 Diagram of the synergistic effects of neurokinin-1 receptor (NK-1R) antagonists when administered with other drugs to improve the efficacy of disease treatment. Ara-C: cytosine arabinoside; MDA: microtubule destabilizer agent.

several strategies have been explored to overcome these drawbacks. Additionally, aprepitant has been developed as a radioligand receptor for targeting tumors that overexpress NK-1R in radiopharmaceutical therapy. Combining NK-1R antagonists with other drugs can also enhance their therapeutic effects, alleviate symptoms, and improve the quality of life of patients with various diseases and cancers. Overall, NK-1R antagonists show great potential in the treatment of multiple diseases and cancers, and we are looking forward to exploit their potential applications in additional pathophysiological disorders and tumors.

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Author contributions

Xiangyu HONG conceptualized the literature and prepared the original draft of the manuscript. Junjie MA, Shanshan ZHENG, and Guangyu ZHAO contributed to the visualization and design of the manuscript. Caiyun FU supervised, revised, edited, and checked the final version. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Xiangyu HONG, Junjie MA, Shanshan ZHENG, Guangyu ZHAO, and Caiyun FU declare that they have no conflict of interests.

This review does not contain any studies with human or animal subjects performed by any of the authors.

References

Afshari AR, Motamed-Sanaye A, Sabri H, et al., 2021. Neurokinin-1 receptor (NK-1R) antagonists: potential targets in the treatment of glioblastoma multiforme. *Curr Med Chem*, 28(24):4877-4892. https://doi.org/10.2174/0929867328666210113165805

Agelopoulos K, Rülander F, Dangelmaier J, et al., 2019. Neurokinin 1 receptor antagonists exhibit peripheral effects in prurigo nodularis including reduced ERK1/2 activation. *J Eur Acad Dermatol Venereol*, 33(12):2371-2379. https://doi.org/10.1111/jdv.15905

Alwazzan A, Mehboob R, Hassan A, et al., 2020. Elevated neurokinin-1 receptor expression in uterine products of conception is associated with first trimester miscarriages. *Front Physiol*, 11:554766. https://doi.org/10.3389/fphys.2020.554766

Bai TR, Zhou D, Weir T, et al., 1995. Substance P (NK1)- and neurokinin A (NK2)-receptor gene expression in inflammatory airway diseases. *Am J Physiol*, 269(3 Pt 1):L309-L317. https://doi.org/10.1152/ajplung.1995.269.3.L309

Bakirtzi K, Law IKM, Fang K, et al., 2019. MiR-21 in substance P-induced exosomes promotes cell proliferation and migration in human colonic epithelial cells. *Am J Physiol*, 317(6):G802-G810. https://doi.org/10.1152/ajpgi.00043.2019

Barbe MF, Hilliard BA, Fisher PW, et al., 2020. Blocking substance P signaling reduces musculotendinous and dermal fibrosis and sensorimotor declines in a rat model of overuse injury. *Connect Tissue Res*, 61(6):604-619. https://doi.org/10.1080/03008207.2019.1653289

Beirith I, Renz BW, Mudusetti S, et al., 2021. Identification of the neurokinin-1 receptor as targetable stratification factor for drug repurposing in pancreatic cancer. *Cancers (Basel)*, 13(11):2703. https://doi.org/10.3390/cancers13112703

Biadsee A, Biadsee A, Kassem F, et al., 2020. Olfactory and oral manifestations of COVID-19: sex-related symptoms—a potential pathway to early diagnosis. *Otolaryngol Head Neck Surg*, 163(4):722-728. https://doi.org/10.1177/0194599820934380

Bubak AN, Como CN, Blackmon AM, et al., 2018. Varicella zoster virus induces nuclear translocation of the neurokinin-1 receptor, promoting lamellipodia formation and viral spread in spinal astrocytes. *J Infect Dis*, 218(8):1324-1335. https://doi.org/10.1093/infdis/jiy297

Chen Y, Chauhan SK, Lee HS, et al., 2014. Chronic dry eye disease is principally mediated by effector memory TH17 cells. *Mucosal Immunol*, 7(1):38-45. https://doi.org/10.1038/mi.2013.20

Chu HW, Kraft M, Krause JE, et al., 2000. Substance P and its receptor neurokinin 1 expression in asthmatic airways. *J Allergy Clin Immunol*, 106(4):713-722. https://doi.org/10.1067/mai.2000.109829

Craig VJ, Zhang L, Hagood JS, et al., 2015. Matrix metalloproteinases as therapeutic targets for idiopathic pulmonary fibrosis. *Am J Respir Cell Mol Biol*, 53(5):585-600. https://doi.org/10.1165/rcmb.2015-0020TR

de Felipe C, Herrero JF, O'Brien JA, et al., 1998. Altered nociception, analgesia and aggression in mice lacking the receptor for substance P. *Nature*, 392(6674):394-397. https://doi.org/10.1038/32904

Definition and Classification Subcommittee, 2007. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007). *Ocul Surf*, 5(2):75-92. https://doi.org/10.1016/s1542-0124(12)70081-2

Dehlin HM, Levick SP, 2014. Substance P in heart failure: the good and the bad. *Int J Cardiol*, 170(3):270-277. https://doi.org/10.1016/j.ijcard.2013.11.010

Deng XT, Tang SM, Wu PY, et al., 2019. SP/NK-1R promotes gallbladder cancer cell proliferation and migration. *J Cell Mol Med*, 23(12):7961-7973. https://doi.org/10.1111/jcmm.14230

Dong JQ, Feng F, Xu GH, et al., 2015. Elevated SP/NK-1R in esophageal carcinoma promotes esophageal carcinoma cell proliferation and migration. *Gene*, 560(2):205-210. https://doi.org/10.1016/j.gene.2015.02.002

Dong YY, Mo X, Hu YB, et al., 2020. Epidemiology of COVID-19 among children in China. *Pediatrics*, 145(6):e20200702. https://doi.org/10.1542/peds.2020-0702

Douglas SD, Leeman SE, 2011. Neurokinin-1 receptor: functional significance in the immune system in reference to selected infections and inflammation. *Ann N Y Acad Sci*, 1217:83-95. https://doi.org/10.1111/j.1749-6632.2010.05826.x

Ebrahimi S, Javid H, Alaei A, et al., 2020. New insight into the role of substance P/neurokinin-1 receptor system in breast cancer progression and its crosstalk with microRNAs. *Clin Genet*, 98(4):322-330. https://doi.org/10.1111/cge.13750

Ebrahimi S, Mirzavi F, Aghaee-Bakhtiari SH, et al., 2022. SP/NK1R system regulates carcinogenesis in prostate cancer: shedding light on the antitumoral function of aprepitant. *Biochim Biophys Acta Mol Cell Res*, 1869(5):119221. https://doi.org/10.1016/j.bbamcr.2022.119221

Foulsham W, Marmalidou A, Amouzegar A, et al., 2017. Review: the function of regulatory T cells at the ocular surface. *Ocul Surf*, 15(4):652-659. https://doi.org/10.1016/j.jtos.2017.05.013

García-Aranda M, Téllez T, McKenna L, et al., 2022. Neurokinin-1 receptor (NK-1R) antagonists as a new strategy to overcome cancer resistance. *Cancers (Basel)*, 14(9):2255. https://doi.org/10.3390/cancers14092255

Ge CT, Huang HM, Huang FY, et al., 2019. Neurokinin-1 receptor is an effective target for treating leukemia by inducing oxidative stress through mitochondrial calcium overload. *Proc Natl Acad Sci USA*, 116(39):19635-19645. https://doi.org/10.1073/pnas.1908998116

Ghahremanloo A, Javid H, Afshari AR, et al., 2021. Investigation of the role of neurokinin-1 receptor inhibition using aprepitant in the apoptotic cell death through PI3K/Akt/NF-κB signal transduction pathways in colon cancer cells. *Biomed Res Int*, 2021:1383878. https://doi.org/10.1155/2021/1383878

Ghasemi A, Hashemy SI, Aghaei M, et al., 2018. Leptin induces matrix metalloproteinase 7 expression to promote ovarian cancer cell invasion by activating ERK and JNK pathways. *J Cell Biochem*, 119(2):2333-2344. https://doi.org/10.1002/jcb.26396

Ghasemi A, Saeidi J, Azimi-Nejad M, et al., 2019. Leptin-induced signaling pathways in cancer cell migration and

invasion. *Cell Oncol (Dordr)*, 42(3):243-260. https://doi.org/10.1007/s13402-019-00428-0

Gordon L, Polak JM, Moscoso GJ, et al., 1993. Development of the peptidergic innervation of human heart. *J Anat*, 183(Pt 1):131-140.

Halik PK, Lipiński PFJ, Matalińska J, et al., 2020. Radiochemical synthesis and evaluation of novel radioconjugates of neurokinin 1 receptor antagonist aprepitant dedicated for NK1R-positive tumors. *Molecules*, 25(16):3756. https://doi.org/10.3390/molecules25163756

Halik PK, Koźmiński P, Matalińska J, et al., 2022. In vitro biological evaluation of aprepitant based ^{177}Lu-radioconjugates. *Pharmaceutics*, 14(3):607. https://doi.org/10.3390/pharmaceutics14030607

Isorna I, Esteban F, Solanellas J, et al., 2020. The substance P and neurokinin-1 receptor system in human thyroid cancer: an immunohistochemical study. *Eur J Histochem*, 64(2):3117. https://doi.org/10.4081/ejh.2020.3117

Jin P, Qi DQ, Cui YH, et al., 2022. Aprepitant attenuates NLRC4-dependent neuronal pyroptosis via NK1R/PKCδ pathway in a mouse model of intracerebral hemorrhage. *J Neuroinflammation*, 19:198. https://doi.org/10.1186/s12974-022-02558-z

Kakade P, Pathan Z, Gite S, et al., 2022. Nanoparticle engineering of aprepitant using Nano-by-Design (NbD) approach. *AAPS PharmSciTech*, 23(6):204. https://doi.org/10.1208/s12249-022-02350-5

Kast RE, Ramiro S, Lladó S, et al., 2016. Antitumor action of temozolomide, ritonavir and aprepitant against human glioma cells. *J Neurooncol*, 126(3):425-431. https://doi.org/10.1007/s11060-015-1996-6

Khom S, Steinkellner T, Hnasko TS, et al., 2020. Alcohol dependence potentiates substance P/neurokinin-1 receptor signaling in the rat central nucleus of amygdala. *Sci Adv*, 6(12):eaaz1050. https://doi.org/10.1126/sciadv.aaz1050

Khorasani S, Boroumand N, Lavi Arab F, et al., 2020. The immunomodulatory effects of tachykinins and their receptors. *J Cell Biochem*, 121(5-6):3031-3041. https://doi.org/10.1002/jcb.29668

Kim RY, Sunkara KP, Bracke KR, et al., 2021. A microRNA-21-mediated SATB1/S100A9/NF-κB axis promotes chronic obstructive pulmonary disease pathogenesis. *Sci Transl Med*, 13(621):eaav7223. https://doi.org/10.1126/scitranslmed.aav7223

Kitchens CA, McDonald PR, Pollack IF, et al., 2009. Synergy between microtubule destabilizing agents and neurokinin 1 receptor antagonists identified by an siRNA synthetic lethal screen. *FASEB J*, 23(S1):756.13-756.13. https://doi.org/10.1096/fasebj.23.1_supplement.756.13

Korfi F, Javid H, Assaran Darban R, et al., 2021. The effect of SP/NK1R on the expression and activity of catalase and superoxide dismutase in glioblastoma cancer cells. *Biochem Res Int*, 2021:6620708. https://doi.org/10.1155/2021/6620708

Kramer MS, Cutler N, Feighner J, et al., 1998. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science*, 281(5383):1640-1645. https://doi.org/10.1126/science.281.5383.1640

Kumar S, Gupta SK, 2013. Pharmaceutical solid dispersion technology: a strategy to improve dissolution of poorly water-soluble drugs. *Recent Pat Drug Deliv Formul*, 7(2):111-121. https://doi.org/10.2174/18722113113079990009

Lee KS, Lee J, Kim HK, et al., 2021. Extracellular vesicles from adipose tissue-derived stem cells alleviate osteoporosis through osteoprotegerin and *miR-21-5p*. *J Extracell Vesicles*, 10(12):e12152. https://doi.org/10.1002/jev2.12152

Liu JW, Zou MJ, Piao HY, et al., 2015. Characterization and pharmacokinetic study of aprepitant solid dispersions with soluplus®. *Molecules*, 20(6):11345-11356. https://doi.org/10.3390/molecules200611345

Liu JW, Li SY, Ao W, et al., 2022a. Fabrication of an aprepitant nanosuspension using hydroxypropyl chitosan to increase the bioavailability. *Biochem Biophys Res Commun*, 631:72-77. https://doi.org/10.1016/j.bbrc.2022.09.031

Liu JW, Li YJ, Ao W, et al., 2022b. Preparation and characterization of aprepitant solid dispersion with HPMCAS-LF. *ACS Omega*, 7(44):39907-39912. https://doi.org/10.1021/acsomega.2c04021

Liu L, Burcher E, 2005. Tachykinin peptides and receptors: putting amphibians into perspective. *Peptides*, 26(8):1369-1382. https://doi.org/10.1016/j.peptides.2005.03.027

Liu XP, Zhu YL, Zheng W, et al., 2019. Antagonism of NK-1R using aprepitant suppresses inflammatory response in rheumatoid arthritis fibroblast-like synoviocytes. *Artif Cells Nanomed Biotechnol*, 47(1):1628-1634. https://doi.org/10.1080/21691401.2019.1573177

Lorestani S, Ghahremanloo A, Jangjoo A, et al., 2020. Evaluation of serum level of substance P and tissue distribution of NK-1 receptor in colorectal cancer. *Mol Biol Rep*, 47(5):3469-3474. https://doi.org/10.1007/s11033-020-05432-4

Maeda H, Wu J, Sawa T, et al., 2000. Tumor vascular permeability and the epr effect in macromolecular therapeutics: a review. *J Control Release*, 65(1-2):271-284. https://doi.org/10.1016/s0168-3659(99)00248-5

Mahtal N, Lenoir O, Tinel C, et al., 2022. MicroRNAs in kidney injury and disease. *Nat Rev Nephrol*, 18(10):643-662. https://doi.org/10.1038/s41581-022-00608-6

Maroñas-Jiménez L, Estrach T, Gallardo F, et al., 2018. Aprepitant improves refractory pruritus in primary cutaneous T-cell lymphomas: experience of the Spanish Working Group on Cutaneous Lymphomas. *Br J Dermatol*, 178(4):e273-e274. https://doi.org/10.1111/bjd.16128

Martinez AN, Philipp MT, 2016. Substance P and antagonists of the neurokinin-1 receptor in neuroinflammation associated with infectious and neurodegenerative diseases of the central nervous system. *J Neurol Neuromedicine*, 1(2):29-36. https://doi.org/10.29245/2572.942x/2016/2.1020

Mehboob R, Lavezzi AM, 2021. Neuropathological explanation of minimal COVID-19 infection rate in newborns, infants and children—a mystery so far. New insight into the role of substance P. *J Neurol Sci*, 420:117276. https://doi.org/10.1016/j.jns.2020.117276

Meléndez GC, Li JP, Law BA, et al., 2011. Substance P induces adverse myocardial remodelling via a mechanism involving cardiac mast cells. *Cardiovasc Res*, 92(3):420-429. https://doi.org/10.1093/cvr/cvr244

Miao YB, Quinn TP, 2021. Advances in receptor-targeted radiolabeled peptides for melanoma imaging and therapy. *J Nucl Med*, 62(3):313-318. https://doi.org/10.2967/jnumed.120.243840

Mistrova E, Kruzliak P, Dvorakova MC, 2016. Role of substance P in the cardiovascular system. *Neuropeptides*, 58: 41-51. https://doi.org/10.1016/j.npep.2015.12.005

Mohamed MZ, Abed El Baky MF, Ali ME, et al., 2022. Aprepitant exerts anti-fibrotic effect via inhibition of TGF-β/Smad3 pathway in bleomycin-induced pulmonary fibrosis in rats. *Environ Toxicol Pharmacol*, 95:103940. https://doi.org/10.1016/j.etap.2022.103940

Mohammadi F, Javid H, Afshari AR, et al., 2020. Substance P accelerates the progression of human esophageal squamous cell carcinoma via MMP-2, MMP-9, VEGF-A, and VEGFR1 overexpression. *Mol Biol Rep*, 47(6):4263-4272. https://doi.org/10.1007/s11033-020-05532-1

Molinos-Quintana A, Trujillo-Hacha P, Piruat JI, et al., 2019. Human acute myeloid leukemia cells express Neurokinin-1 receptor, which is involved in the antileukemic effect of Neurokinin-1 receptor antagonists. *Invest New Drugs*, 37: 17-26. https://doi.org/10.1007/s10637-018-0607-8

Morgat C, Mishra AK, Varshney R, et al., 2014. Targeting neuropeptide receptors for cancer imaging and therapy: perspectives with bombesin, neurotensin, and neuropeptide-Y receptors. *J Nucl Med*, 55(10):1650-1657. https://doi.org/10.2967/jnumed.114.142000

Mozafari M, Ebrahimi S, Darban RA, et al., 2022. Potential in vitro therapeutic effects of targeting SP/NK1R system in cervical cancer. *Mol Biol Rep*, 49(2):1067-1076. https://doi.org/10.1007/s11033-021-06928-3

Muñoz M, Rosso M, 2010. The NK-1 receptor antagonist aprepitant as a broad spectrum antitumor drug. *Invest New Drugs*, 28(2):187-193. https://doi.org/10.1007/s10637-009-9218-8

Muñoz M, Coveñas R, 2020a. The neurokinin-1 receptor antagonist aprepitant, a new drug for the treatment of hematological malignancies: focus on acute myeloid leukemia. *J Clin Med*, 9(6):1659. https://doi.org/10.3390/jcm9061659

Muñoz M, Coveñas R, 2020b. The neurokinin-1 receptor antagonist aprepitant: an intelligent bullet against cancer? *Cancers*, 12(9):2682. https://doi.org/10.3390/cancers12092682

Muñoz M, Rosso M, Robles-Frias MJ, et al., 2010. The NK-1 receptor is expressed in human melanoma and is involved in the antitumor action of the NK-1 receptor antagonist aprepitant on melanoma cell lines. *Lab Invest*, 90(8):1259-1269. https://doi.org/10.1038/labinvest.2010.92

Muñoz M, González-Ortega A, Rosso M, et al., 2012. The substance P/neurokinin-1 receptor system in lung cancer: focus on the antitumor action of neurokinin-1 receptor antagonists. *Peptides*, 38(2):318-325. https://doi.org/10.1016/j.peptides.2012.09.024

Muñoz M, González-Ortega A, Salinas-Martín MV, et al., 2014. The neurokinin-1 receptor antagonist aprepitant is a promising candidate for the treatment of breast cancer. *Int J Oncol*, 45(4):1658-1672. https://doi.org/10.3892/ijo.2014.2565

Muñoz M, Covenas R, Esteban F, et al., 2015. The substance P/NK-1 receptor system: NK-1 receptor antagonists as anti-cancer drugs. *J Biosci*, 40(2):441-463. https://doi.org/10.1007/s12038-015-9530-8

Muñoz M, Crespo JC, Crespo JP, et al., 2019a. Neurokinin-1 receptor antagonist aprepitant and radiotherapy, a successful combination therapy in a patient with lung cancer: a case report. *Mol Clin Oncol*, 11(1):50-54. https://doi.org/10.3892/mco.2019.1857

Muñoz M, Rosso M, Coveñas R, 2019b. Neurokinin-1 receptor antagonists against hepatoblastoma. *Cancers (Basel)*, 11(9):1258. https://doi.org/10.3390/cancers11091258

Muñoz M, Rosso M, Coveñas R, 2020. Triple negative breast cancer: how neurokinin-1 receptor antagonists could be used as a new therapeutic approach. *Mini Rev Med Chem*, 20(5): 408-417. https://doi.org/10.2174/1389557519666191112152642

Muñoz MF, Argüelles S, Rosso M, et al., 2022. The neurokinin-1 receptor is essential for the viability of human glioma cells: a possible target for treating glioblastoma. *Biomed Res Int*, 2022:6291504. https://doi.org/10.1155/2022/6291504

Mura S, Nicolas J, Couvreur P, 2013. Stimuli-responsive nanocarriers for drug delivery. *Nat Mater*, 12(11):991-1003. https://doi.org/10.1038/nmat3776

Nizam E, Erin N, 2018. Differential consequences of neurokinin receptor 1 and 2 antagonists in metastatic breast carcinoma cells; effects independent of substance P. *Biomed Pharmacother*, 108:263-270. https://doi.org/10.1016/j.biopha.2018.09.013

Noronha V, Bhattacharjee A, Patil VM, et al., 2020. Aprepitant for cough suppression in advanced lung cancer: a randomized trial. *Chest*, 157(6):1647-1655. https://doi.org/10.1016/j.chest.2019.11.048

The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. *China CDC Wkly*, 2(8):113-122. https://doi.org/10.46234/ccdcw2020.032

Olivieri F, Prattichizzo F, Giuliani A, et al., 2021. miR-21 and miR-146a: the micrornas of inflammaging and age-related diseases. *Ageing Res Rev*, 70:101374. https://doi.org/10.1016/j.arr.2021.101374

Olver I, Shelukar S, Thompson KC, 2007. Nanomedicines in

the treatment of emesis during chemotherapy: focus on aprepitant. *Int J Nanomedicine*, 2(1):13-18. https://doi.org/10.2147/nano.2007.2.1.13

Quartara L, Altamura M, 2006. Tachykinin receptors antagonists: from research to clinic. *Curr Drug Targets*, 7(8): 975-992. https://doi.org/10.2174/138945006778019381

Ramanujam D, Schön AP, Beck C, et al., 2021. MicroRNA-21-dependent macrophage-to-fibroblast signaling determines the cardiac response to pressure overload. *Circulation*, 143(15):1513-1525. https://doi.org/10.1161/circulationaha.120.050682

Ramírez-García PD, Retamal JS, Shenoy P, et al., 2019. A pH-responsive nanoparticle targets the neurokinin 1 receptor in endosomes to prevent chronic pain. *Nat Nanotechnol*, 14(12):1150-1159. https://doi.org/10.1038/s41565-019-0568-x

Ratti E, Bettica P, Alexander R, et al., 2013. Full central neurokinin-1 receptor blockade is required for efficacy in depression: evidence from orvepitant clinical studies. *J Psychopharmacol*, 27(5):424-434. https://doi.org/10.1177/0269881113480990

Reinoso-Arija R, López-Ramírez C, Jimenez-Ruiz JA, et al., 2021. Effectiveness of aprepitant in post-acute COVID19 syndrome. *Clin Case Rep*, 9(9):e04646. https://doi.org/10.1002/ccr3.4646

Ridhurkar DN, Ansari KA, Kumar D, et al., 2013. Inclusion complex of aprepitant with cyclodextrin: evaluation of physico-chemical and pharmacokinetic properties. *Drug Dev Ind Pharm*, 39(11):1783-1792. https://doi.org/10.3109/03639045.2012.737331

Robinson P, Kasembeli M, Bharadwaj U, et al., 2016. Substance P receptor signaling mediates doxorubicin-induced cardiomyocyte apoptosis and triple-negative breast cancer chemoresistance. *Biomed Res Int*, 2016:1959270. https://doi.org/10.1155/2016/1959270

Roos C, Dahlgren D, Berg S, et al., 2017. *In vivo* mechanisms of intestinal drug absorption from aprepitant nanoformulations. *Mol Pharm*, 14(12):4233-4242. https://doi.org/10.1021/acs.molpharmaceut.7b00294

Rouen PA, White ML, 2018. Dry eye disease: prevalence, assessment, and management. *Home Healthc Now*, 36(2): 74-83. https://doi.org/10.1097/nhh.0000000000000652

Shi Y, Wang X, Meng Y, et al., 2021. A novel mechanism of endoplasmic reticulum stress- and c-Myc-degradation-mediated therapeutic benefits of antineurokinin-1 receptor drugs in colorectal cancer. *Adv Sci (Weinh)*, 8(21): e2101936. https://doi.org/10.1002/advs.202101936

Schöppe J, Ehrenmann J, Klenk C, et al., 2019. Crystal structures of the human neurokinin 1 receptor in complex with clinically used antagonists. *Nat Commun*, 10:17. https://doi.org/10.1038/s41467-018-07939-8

Singh S, Kumaravel S, Dhole S, et al., 2021. Neuropeptide substance P enhances inflammation-mediated tumor signaling pathways and migration and proliferation of head and neck cancers. *Indian J Surg Oncol*, 12 (S1):93-102. https://doi.org/10.1007/s13193-020-01210-7

Smith JA, Harle A, Dockry R, et al., 2021. Aprepitant for cough in lung cancer. A randomized placebo-controlled trial and mechanistic insights. *Am J Respir Crit Care Med*, 203(6):737-745. https://doi.org/10.1164/rccm.202006-2359OC

Sosnik A, Seremeta KP, 2015. Advantages and challenges of the spray-drying technology for the production of pure drug particles and drug-loaded polymeric carriers. *Adv Colloid Interface Sci*, 223:40-54. https://doi.org/10.1016/j.cis.2015.05.003

Steinhoff MS, von Mentzer B, Geppetti P, et al., 2014. Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. *Physiol Rev*, 94(1): 265-301. https://doi.org/10.1152/physrev.00031.2013

Sugano K, Terada K, 2015. Rate- and extent-limiting factors of oral drug absorption: theory and applications. *J Pharm Sci*, 104(9):2777-2788. https://doi.org/10.1002/jps.24391

Taketani Y, Dohlman T, Chen YH, et al., 2019. Restoration of regulatory T cell function in dry eye disease by targeting substance P/neurokinin 1 receptor. *Invest Ophthalmol Vis Sci*, 60(9):306. https://doi.org/10.1016/j.ajpath.2020.05.011

Tang YJ, Liu JJ, Zhang DY, et al., 2020. Cytokine storm in COVID-19: the current evidence and treatment strategies. *Front Immunol*, 11:1708. https://doi.org/10.3389/fimmu.2020.01708

Tattersall FD, Rycroft W, Francis B, et al., 1996. Tachykinin NK_1 receptor antagonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. *Neuropharmacology*, 35(8):1121-1129. https://doi.org/10.1016/s0028-3908(96)00020-2

Thom C, Ehrenmann J, Vacca S, et al., 2021. Structures of neurokinin 1 receptor in complex with G_q and G_s proteins reveal substance P binding mode and unique activation features. *Sci Adv*, 7(50):eabk2872. https://doi.org/10.1126/sciadv.abk2872

Un H, Ugan RA, Kose D, et al., 2020. A novel effect of Aprepitant: protection for cisplatin-induced nephrotoxicity and hepatotoxicity. *Eur J Pharmacol*, 880:173168. https://doi.org/10.1016/j.ejphar.2020.173168

Wan PX, Su WR, Zhang YY, et al., 2020. LncRNA H19 initiates microglial pyroptosis and neuronal death in retinal ischemia/reperfusion injury. *Cell Death Differ*, 27:176-191. https://doi.org/10.1038/s41418-019-0351-4

Wang XL, He Y, Mackowiak B, et al., 2021. MicroRNAs as regulators, biomarkers and therapeutic targets in liver diseases. *Gut*, 70(4):784-795. https://doi.org/10.1136/gutjnl-2020-322526

Widiapradja A, Manteufel EJ, Dehlin HM, et al., 2019. Regulation of cardiac mast cell maturation and function by the neurokinin-1 receptor in the fibrotic heart. *Sci Rep*, 9:11004. https://doi.org/10.1038/s41598-019-47369-0

Wu HZ, Cheng XE, Huang FY, et al., 2020. Aprepitant sensitizes acute myeloid leukemia cells to the cytotoxic effects of cytosine arabinoside in vitro and in vivo. *Drug*

Des Devel Ther, 14:2413-2422. https://doi.org/10.2147/dddt.S244648

Yamamoto H, 1993. Preserved endothelial function in the spastic segment of the human epicardial coronary artery in patients with variant angina—role of substance P in evaluating endothelial function. *Eur Heart J*, 14(Suppl I): 118-122.

Yanai R, Nishida T, Hatano M, et al., 2020. Role of the neurokinin-1 receptor in the promotion of corneal epithelial wound healing by the peptides FGLM-NH_2 and SSSR in neurotrophic keratopathy. *Invest Ophthalmol Vis Sci*, 61(8):29. https://doi.org/10.1167/iovs.61.8.29

Yang Y, Zhou W, Xu XQ, et al., 2021. Aprepitant inhibits JNK and p38/MAPK to attenuate inflammation and suppresses inflammatory pain. *Front Pharmacol*, 12:811584. https://doi.org/10.3389/fphar.2021.811584

Yeo S, An J, Park C, et al., 2020. Design and characterization of phosphatidylcholine-based solid dispersions of aprepitant for enhanced solubility and dissolution. *Pharmaceutics*, 12(5):407. https://doi.org/10.3390/pharmaceutics12050407

Zhang XW, Xing HJ, Zhao Y, et al., 2018. Pharmaceutical dispersion techniques for dissolution and bioavailability enhancement of poorly water-soluble drugs. *Pharmaceutics*, 10(3):74. https://doi.org/10.3390/pharmaceutics10030074

Zhang XW, Li L, Hu WQ, et al., 2022. Neurokinin-1 receptor promotes non-small cell lung cancer progression through transactivation of EGFR. *Cell Death Dis*, 13:41. https://doi.org/10.1038/s41419-021-04485-y

Zhao XN, Bai ZZ, Li CH, et al., 2020. The NK-1R antagonist aprepitant prevents LPS-induced oxidative stress and inflammation in RAW264.7 macrophages. *Drug Des Devel Ther*, 14:1943-1952. https://doi.org/10.2147/dddt.S244099