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Review Article

Therapeutic Potential of A_3 Adenosine Receptor Agonists in Pancreatic Ductal Adenocarcinoma

Deepika PK[1*], Dr. Vivek D[2], Dr. Shahin Muhammed TK[3], Fathima Rasma K[4]
[1*,2,3,4]College of Pharmaceutical Sciences, Government Medical College, Kannur, 670503.
Email: [1]*deepikapk2017@gmail.com, [2]25vivekd@gmail.com, [3]shahin.mdtk@gmail.com, [4]rasmarahim23@gmail.com
Corresponding Author: Deepika PK
College of Pharmaceutical Sciences, Government Medical College, Kannur, 670503.
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ABSTRACT
Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, characterized by late diagnosis, profound chemoresistance, and a five-year survival rate below 10%. Conventional therapies including surgery, radiation, and cytotoxic chemotherapy offer limited benefit due to the tumor's genetic heterogeneity and dense desmoplastic stroma. Recent advances highlight adenosine receptor signaling as a pivotal regulator of PDAC biology, with the A_3 adenosine receptor (A_3AR) emerging as a promising therapeutic target. A_3AR is markedly overexpressed in malignant tissues while remaining low in adjacent normal cells, enabling selective modulation of tumor growth and survival pathways. Preclinical and early clinical studies of selective A $_3$AR agonists, particularly Namodenoson, demonstrate inhibition of NF-κB, Wnt/β-catenin, and RAS signaling, leading to apoptosis, reduced proliferation, and enhanced chemosensitivity. Combination strategies integrating A_3AR agonists with chemotherapy, immunotherapy, targeted inhibitors, and stromal-modifying agents show synergistic potential, addressing both intrinsic tumor signaling and extrinsic micro environmental barriers. Despite encouraging safety and efficacy profiles, challenges remain, including pathway redundancy, stromal resistance, and limited clinical validation. Future perspectives emphasize biomarker-driven patient selection, mechanistic exploration of resistance, and translation into large-scale randomized trials. Collectively, A_3AR agonists represent a novel class of precision therapeutics with the potential to reshape PDAC management and improve outcomes in a disease with few effective alternatives.

Keywords: PDAC, A_3adenosine Receptor, NF-Kb / Wnt/B-Catenin / RAS Signalling.

INTRODUCTION

PDAC is one of the most lethal diseases, with an average 5 years survival rate of less than 10%. It is the most common type of pancreatic cancer, developing in the exocrine part of the pancreas and making up over 90% of cases. Common symptoms include weight loss, abdominal pain, and jaundice while less frequent signs include new-onset type 2 diabetes and blood clots. Conventional therapies-including surgery, radiation and chemotherapy offer only a limited benefit, largely because of the tumor's complex genetic diversity and its dense stromal microenvironment, among other factors.[1]

PDAC ranks among the deadliest cancers mainly due to its late diagnosis and chemoresistance. In 2022, PDAC accounted for 510,566 new cases and 467,005 cancer- related deaths world-wide.[2] Data from GLOBOCAN, covering 184 countries, reveal increasing incidence among individuals over 50 years in 18 nation as well as rising rates in younger population in several countries, including Canada, the Netherlands and the United Kingdom. Men show a higher susceptibility compared to women, with male -to-female ratio of about 1:4:1. A variety of risk factors have been reported for the development of PDAC. The major factors can be broadly classified into family history, genetic disorders, complications, and preferences.[3]

Surgical resection remains the sole intervention with curative potential; however, because the majority of patients present at an advanced stage, only a limited proportion qualify for surgery. Among those who undergo resection, adjuvant chemotherapy most notably the modified folfirinox regimen has become the standard of care, significantly improving survival outcomes. Increasingly, neoadjuvant therapy (NAT), incorporating chemotherapy or chemoradiation prior to surgery, is being employed in borderline resectable cases to increase the probability of complete resection

and to address micro metastatic disease at an earlier stage.[4]

Activation of the A_3 adenosine receptor (A_3AR) can promote tumors progression, cellular proliferation, and survival in certain contexts, while in others it initiates cytostatic and apoptotic signaling pathways. A_3AR, a membrane-bound protein, has been shown to be markedly overexpressed across a wide spectrum of malignancies. Earlier studies have highlighted adenosine receptors (ARs) as complex yet promising therapeutic targets. Owing to the multifaceted nature of adenosinergic signaling, interventions designed to regulate adenosine metabolism or AR activity exert broad effects within the tumor microenvironment, impacting not only malignant cells but also the surrounding stromal and immune components.[5]

The A3 adenosine receptor is one of four receptor subtypes involved in mediating the effects of extracellular adenosine. Notably, its expression both at the mRNA and protein levels is elevated in various tumour types, while remaining low in adjacent healthy tissues. When drug binds to A_3AR, it triggers downstream signalling cascades that can modulate survival, proliferation, and apoptosis. In cancer cells, A_3AR activation by agonists leads to deregulation of critical pathways, including NF-κB, Wnt/β-catenin, and RAS. These pathways normally promote tumour growth, resistance to therapy, and suppression of apoptosis. By disrupting them, A_3AR agonists shift the balance toward cell death. Specifically, drug downregulates proteins like PI3K, p-Akt, and NF-κB, while simultaneously upregulating pro-apoptotic proteins such as Bad and Bax. This dual effect reduces proliferation signals and enhances programmed cell death in pancreatic carcinoma cells.[6]

Adenosine receptor signaling represents a well-characterized pathway in PDAC biology, with the A_3AR, encoded by the ADORA3 gene, emerging as a particularly significant therapeutic target.[7]

Current Treatment for PDAC

The management of PDAC relies on a multimodal strategy tailored to disease stage and patient condition. In advanced or metastatic settings, systemic chemotherapy remains the cornerstone of treatment. While the folfirinox regimen offers the greatest survival advantage, its use is restricted by significant toxicity. As an alternative, gemcitabine in combination with nab-paclitaxel is widely adopted. Radiotherapy has a more selective role, primarily in borderline resectable or locally advanced disease, though its impact on overall survival continues to be debated.[8]

Beyond standard cytotoxic regimens, novel targeted strategies are gaining traction in PDAC management. PARP inhibitors, such as olaparib, are now employed as maintenance therapy in BRCA-mutated cases, while precision oncology approaches are being investigated for rare gene fusions and DNA repair deficiencies. Immunotherapy remains under active exploration, with checkpoint blockade, adoptive cell transfer, and cancer vaccines showing potential yet hindered by the profoundly immunosuppressive tumor microenvironment. In parallel, innovative modalities including carbon ion radiotherapy and endoscopic ultrasound-guided interventions are emerging as evolving therapeutic options.[9]Additional therapeutic avenues in PDAC include inhibition of receptor tyrosine kinases, angiogenic signaling, and immune checkpoints, though clinical outcomes have been inconsistent, with meaningful benefit observed only in a limited subset of patients. Despite chemotherapy remaining the cornerstone of treatment, biomarker-driven targeted approaches are increasingly incorporated into clinical practice, offering the prospect of more individualized and effective interventions moving forward.[10]

Adenosine Receptor Agonists

Adenosine receptors are members of the G protein-coupled receptor (GPCR) family, each encoded by distinct genes. They are classified into four subtypes: A_1, A_{2A}, A_{2B}, and A_3. These receptors are widely distributed across human tissues and organs, where they play vital roles in regulating key physiological processes.

A_1 Receptor Agonists

A1 adenosine receptor (A_1AR) contributes to cancer progression by modulating the tumour microenvironment, influencing processes such as immune regulation and stromal interactions. Its signalling also promotes cellular migration and invasion, which can facilitate metastasis and contribute to resistance against therapies.[11]

Tiazofurin is a C-nucleoside that inhibits IMPDH, blocking nucleotide synthesis and thereby suppressing cancer cell growth through its active metabolite, tiazofurin adenine dinucleotide. Its pro nucleotide analogue, cyclosaligenyl-tiazofurin monophosphate, acts as a selective A_1 adenosine receptor agonist with comparable binding affinity and shows

potent activity against the K-562 leukaemia cell line in vitro.[12]

A_{2A}receptor Agonists

The A_{2A} adenosine receptor ($A_{2A}R$) is critically involved in cancer progression, driving processes such as uncontrolled cell growth, angiogenesis, immune evasion, and metastatic spread. Through these mechanisms, $A_{2A}R$ signalling contributes both to tumour development and to resistance against therapeutic interventions.[13]

In A-375 melanoma cells, the anticancer activity of the A_{2A} agonist HENECA (2-hexynyl-NECA) was evaluated, showing modest but consistent inhibition of cell proliferation and reduced cytotoxicity.[14]

A_{2B} Receptor Agonists

Similar to the A_{2A} receptor, the A_{2B} adenosine receptor ($A_{2A}R$) is linked to the G_s protein, which plays a central role in mediating intracellular signalling pathways. This coupling is essential for transmitting receptor activation into downstream cellular responses.[15]

A_3 Receptor Agonists

The therapeutic relevance of A_3 adenosine receptors (A_3AR) in cancer stems from their marked overexpression in malignant and inflammatory cells. This distinctive expression profile positions A_3AR as promising targets for anticancer strategies, offering opportunities to selectively modulate tumour growth and the associated inflammatory environment.[16]

The A_3 receptor agonists piclidenoson and namodenoson demonstrate significant anticancer activity, effectively reducing tumour cell proliferation even at low concentrations. Their potency at minimal doses underscores their therapeutic promise as targeted agents in cancer treatment.[17]

The study by Inbal et al (2023) investigated namodenoson, a selective A_3 adenosine receptor (A_3AR) agonist, as a therapeutic candidate for pancreatic carcinoma. In vitro experiments using BxPC-3 cells showed dose-dependent growth inhibition at nanomolar concentrations. In vivo, oral administration of namodenoson significantly reduced tumour growth in nude mice.[6]

A_3AR Targeted Treatment for PDAC

In healthy tissues, A3 adenosine receptor expression is very low, whereas in tumour cells it is significantly upregulated. This marked differential expression underscores its value as a selective therapeutic target in cancer. A3 adenosine receptor (A_3AR) expression is significantly increased in colorectal cancer and a range of other malignancies including pancreatic carcinoma, small-cell lung cancer, breast cancer, and melanoma where its elevated levels are closely linked to tumour progression and disease advancement. Reports indicate that A3 adenosine receptor (A_3AR) signalling in human melanoma cells promotes pro-survival activity. This pathway is regulated by glycogen synthase kinase-3β (GSK-3β), which phosphorylates β-catenin and thereby enhances tumour cell growth. Phosphorylated β-catenin stimulates the expression of key cell cycle genes, including cyclin D1 and c-myc, driving proliferation. The A_3AR gene is located on chromosome 1p13.3, and its overexpression across multiple tumour types underscores its potential both as a therapeutic target and a biomarker of cancer progression.[18]

Adenosine Signalling Pathway in PDAC

The A_3 adenosine receptor (A_3AR), a member of the Gi protein-coupled receptor family, mediates its effects through inhibition of adenylyl cyclase and suppression of cyclic AMP production, thereby initiating diverse signalling cascades that vary according to cell type and stimulus. Mechanistic investigations have shown that A_3AR activation results in the downregulation of key regulators of cell growth, including cyclin D1 and nuclear factor κB. Importantly, A_3AR is consistently overexpressed in malignant tissues and has been proposed as a diagnostic and prognostic biomarker. Its elevated expression has been documented across a range of cancers, such as melanoma, breast, prostate, liver, pancreatic, and lung carcinomas, as well as lymphoma, glioblastoma, and malignant pleural mesothelioma (MPM).[19]

Binding of a ligand to the A_3 adenosine receptor (A_3AR) initiates downstream signalling cascades that regulate cellular survival, proliferation, and apoptosis. In malignant cells, stimulation of A_3AR with agonists disrupts pivotal oncogenic pathways such as NF-κB, Wnt/β-catenin, and RAS, which ordinarily sustain tumour growth, therapeutic resistance, and inhibition of apoptosis. By interfering with these pathways, A_3AR agonists promote a shift toward programmed cell death. Mechanistically, they suppress pro-survival mediators including PI3K, phosphorylated Akt, and NF-κB, while simultaneously enhancing the expression of pro-apoptotic proteins such as Bad and Bax.

This coordinated modulation diminishes proliferative signalling and augments apoptosis in pancreatic carcinoma cells.[6]

The findings of Inbal et al. demonstrated that a selective A_3AR agonist suppresses tumour growth by interfering with key oncogenic pathways and inducing apoptosis, underscoring its potential as a targeted therapy for pancreatic cancer.[6]

Mechanistic Pathways in PDAC

NF-KB Suppression

Activation of the A_3AR adenosine receptor by the selective agonist initiates a Gi protein-coupled signalling cascade that inhibits adenylate cyclase and reduces intracellular cAMP levels. This suppression downregulates the PI3K/Akt and MAPK/ERK pathways, which are normally responsible for activating the IKK complex. As a result, IKK activity is diminished, preventing phosphorylation and degradation of IκBα. NF-κB remains bound to IκBα in the cytoplasm and is unable to translocate into the nucleus. Consequently, transcription of NF-κB target genes such as Bcl-xL, XIAP, A20, cyclin D1, and VEGF is blocked. In parallel, A_3AR activation promotes the expression of pro-apoptotic proteins including Bad and Bax, leading to mitochondrial pathway activation and caspase-mediated apoptosis. Through this dual effect blocking NF-κB-driven survival signalling and enhancing apoptosis A_3AR agonists like namodenoson suppress PDAC cell growth, reduce inflammation and angiogenesis, and overcome resistance to therapy.

Wnt/B-Catenin Deregulation

Activation of the A3 adenosine receptor (A_3AR) by the selective agonist initiates a Gi protein-coupled signalling cascade that suppresses adenylate cyclase activity and lowers intracellular cAMP levels. This inhibition downregulates the PI3K/Akt and MAPK/ERK pathways, which are normally involved in stabilizing β-catenin. As a result, the β-catenin destruction complex (APC, Axin, and GSK-3β) remains active, leading to phosphorylation and proteasomal degradation of β-catenin. With β-catenin prevented from accumulating in the cytoplasm and translocating into the nucleus, transcription of oncogenic target genes such as c-Myc, cyclin D1, VEGF, and MMPs is blocked. This mechanism reduces proliferation, stemness, angiogenesis, and metastasis in PDAC cells, while also sensitizing them to apoptosis.

RAS Signalling Pathway Inhibition

Activation of A_3AR by the selective agonist namodenoson initiates a Gi protein-coupled cascade that suppresses adenylate cyclase activity and lowers intracellular cAMP levels. This inhibition downregulates the PI3K/Akt and MAPK/ERK pathways, which are critical downstream effectors of oncogenic RAS signalling. As a result, RAS-driven phosphorylation events that stabilize β-catenin and activate NF-κB are blocked.[6]

Role of A_3AR Agonist in Other Diseases

Elevated A_3AR levels are also detected in peripheral blood mononuclear cells (PBMCs) of patients with inflammatory disorders and cancer, serving as a surrogate marker of receptor expression in pathological tissues. Solid tumours including breast, colon, small cell lung, pancreatic carcinoma, and melanoma demonstrate significantly higher A_3AR expression compared with adjacent normal tissues. Similarly, inflammatory cells such as synoviocytes from rheumatoid arthritis patients, skin biopsies from psoriasis patients, and PBMCs from individuals with Crohn's disease exhibit enhanced A $_3$AR expression.[20]

The orally available agonist A_3AR piclidenoson has been investigated as both an anti-inflammatory and anti-cancer agent in a range of experimental disease models. Its activity has been demonstrated in inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, uveitis, non-alcoholic steatohepatitis (NASH), and cytokine release syndrome, where it consistently showed immunomodulatory and disease-attenuating effects.[21] A_3AR agonists exert distinct effects on diseased versus healthy cells. Piclidenoson and namodenoson induce apoptosis in inflammatory and malignant cells, while normal cells are either resistant to these agents or respond in a beneficial manner.

Furthermore, A_3AR agonists demonstrate selective activity in diseased versus healthy cells. Piclidenoson and namodenoson promote apoptosis in inflammatory and malignant cells, while normal cells either remain resistant to these agents or exhibit beneficial responses. In cancer cells, where A_3AR is markedly overexpressed, agonist treatment suppresses regulatory proteins such as NF-κB, leading to inhibition of tumour growth.[22]

Combination Therapies

A_3AR agonist with chemotherapy

Namodenoson, a selective A3 adenosine receptor (A_3AR) agonist, has demonstrated synergistic activity when combined with gemcitabine in pancreatic ductal adenocarcinoma (PDAC). This synergy arises from Namodenoson's ability to downregulate survival pathways and promote apoptosis, thereby enhancing gemcitabine's cytotoxic effect. Mechanistically, Namodenoson reduces NF-κB activity and suppresses RAS signalling, which sensitizes PDAC cells to gemcitabine's inhibition of DNA synthesis. In addition, deregulation of the Wnt/β-catenin pathway further diminishes proliferative signalling, creating a cellular environment more vulnerable to chemotherapy. Beyond direct tumour cell effects, Namodenoson also exerts anti-inflammatory and immunomodulatory actions. By attenuating NF-κB-driven cytokine production, it reduces pro-tumorigenic inflammation, which may indirectly enhance gemcitabine's efficacy. This dual mechanism tumour intrinsic pathway suppression and tumour microenvironment modulation provides a strong rationale for combination therapy.[6]

From a clinical perspective, this strategy addresses one of the most critical limitations in PDAC management: gemcitabine resistance. Resistance often emerges through activation of compensatory survival pathways (RAS, NF-κB, PI3K/AKT). Namodenoson's ability to suppress these pathways suggests that it may delay or overcome resistance, thereby prolonging therapeutic benefit.

Furthermore, preclinical data indicate that Namodenoson may reduce systemic toxicity by selectively targeting tumour cells with high A_3AR expression, sparing normal tissues. This selectivity could allow for lower gemcitabine dosing while maintaining efficacy, potentially improving tolerability in patients with advanced disease.

A_3AR Agonist with Immunotherapy

Namodenoson, a selective A_3 adenosine receptor agonist, was evaluated in a Phase 2a study in patients with advanced PDAC. The trial showed that Namodenoson was well tolerated, with no new safety concerns. Because adenosine signalling normally suppresses immune responses in the PDAC microenvironment, Namodenoson's selective activation of A_3AR reduces immunosuppressive signalling. This provides a rationale for combining Namodenoson with PD-1/PD-L1 checkpoint inhibitors, potentially reprogramming the tumour microenvironment toward anti-tumour immunity. Early survival data were encouraging, with one-third of patients alive at the cutoff, supporting further clinical evaluation of Namodenoson in combination immunotherapy strategies for PDAC.[23]

A_3AR Agonists with Targeted Therapies

Namodenoson, a selectivA_3AR agonist, has shown strong potential when considered alongside targeted therapies in PDAC. Namodenoson creates a cellular environment that is more susceptible to targeted inhibitors of KRAS, MEK, or PI3K/AKT/mTOR. This indirect suppression of oncogenic signalling may complement direct inhibitors, which often face limitations due to toxicity or resistance. For example, Wnt inhibitors such as vantictumab caused significant adverse effects, and KRAS-mutant tumours frequently develop resistance to farnesyl transferase inhibitors. Namodenoson's selective targeting of A_3AR offers a safer approach, while simultaneously promoting apoptosis through the upregulation of Bad and Bax proteins.[24]

Taken together, these findings suggest that Namodenoson could be integrated with targeted therapies to achieve synergistic inhibition of tumour growth in PDAC. Its favourable safety profile, demonstrated in hepatocellular carcinoma trials, further supports its potential as a combination partner in future clinical studies.

A_3AR Agonist with Anti-Stromal Agents

PDAC is surrounded by a dense desmoplastic stroma that acts as a physical barrier, limiting drug penetration and contributing to therapeutic resistance. Provenzano et al. (2012) demonstrated that enzymatic degradation of stromal components, particularly hyaluronan using PEGPH20, reduced interstitial pressure, normalized vasculature, and significantly improved the delivery and efficacy of chemotherapy in PDAC models.

Namodenoson, a selective A_3 adenosine receptor agonist, complements this approach by suppressing NF-κB, Wnt/β-catenin, and RAS signalling pathways, thereby promoting apoptosis and reducing pro-tumorigenic cytokine production. Its anti-inflammatory and immunomodulatory effects may also diminish stromal activation.

Combining Namodenoson with stromal-modifying agents could therefore address two major challenges in PDAC therapy: intrinsic tumour survival signalling and extrinsic

stromal barriers. This dual strategy has the potential to enhance chemotherapy and immunotherapy efficacy, improve drug penetration, and reprogram the tumour microenvironment toward anti-tumour activity.[25]

Recent Advancements in PDAC

Kawase T. et al. demonstrated that microRNAs (miRNAs) contained in urinary extracellular vesicles (EVs) can be used as non-invasive biomarkers for detecting PDAC in high-risk patients.[26] Researchers found that specific urinary EV-miRNA signatures were significantly altered in PDAC compared to controls, and these profiles showed strong diagnostic accuracy. Because urine collection is simple, repeatable, and patient-friendly, this approach offers a promising tool for early detection of PDAC, which is critical since most cases are diagnosed at advanced stages.[27] The recent study investigated a sequential multimodal treatment strategy for advanced pancreatic ductal adenocarcinoma. Patients first received nimotuzumab (an anti-EGFR antibody) combined with gemcitabine and nab-paclitaxel chemotherapy, followed by irreversible electroporation (IRE), a non-thermal ablation technique. The retrospective real world analysis showed that this regimen was safe, feasible, and effective, leading to better local tumour control and improved survival outcomes compared to conventional approaches. Importantly, IRE provided a treatment option for unresectable tumours, expanding possibilities for patients with advanced PDAC.[28] Also introduced PLA-THF-PEG nanoparticles encapsulating AV3 and KH3 as a novel therapeutic approach for PDAC. These nanoparticles were engineered to simultaneously achieve stromal remodelling, which breaks down the dense fibrotic barrier in PDAC, and metabolic inhibition, which suppresses tumour cell growth. The dual-action delivery showed synergistic therapeutic effects, leading to enhanced drug penetration, stronger tumour suppression, and reduced resistance compared to conventional treatments. This represents a recent advancement in nanomedicine for PDAC, offering a promising strategy to overcome both stromal and metabolic challenges in the disease.[29]A study also highlights the use of artificial intelligence (AI)–assisted screening as a recent advancement in pancreatic cancer detection. AI algorithms were applied to analyse clinical and imaging data, improving the accuracy and efficiency of identifying early PDAC cases. This approach demonstrated the potential to detect pancreatic cancer earlier than conventional methods, especially in high-risk populations.[30]Gu and colleagues introduced GETgene-AI, an integrative framework designed to improve drug target discovery in complex cancers such as PDAC. Traditional methods that rely on manual curation, fold-change thresholds, or mutational frequency often miss biologically relevant targets due to tumour heterogeneity. To overcome this, GETgene-AI combines multiomics datasets, network-based prioritization, and AI-driven literature mining. At the core of the model is the G.E.T. strategy, which integrates mutational frequency (G list), differential expression (E list), and known drug targets (T list). GETgene-AI represents a bridge between computational innovation and translational oncology, offering a scalable platform for precision drug discovery across diverse cancers.[31]

Challenges of Using A3 Adenosine Receptor (A_3ar) Agonists

One challenge is the complexity of PDAC signalling pathways. Although Namodenoson can downregulate NF-κB, Wnt/β-catenin, and RAS signalling, these pathways are highly redundant and interconnected, meaning tumours may adapt and develop resistance despite pathway inhibition.[5]Another difficulty is the dense desmoplastic stroma in PDAC, which physically limits drug penetration. Even if Namodenoson weakens tumour signalling, its efficacy may be reduced unless stromal barriers are simultaneously addressed.[24]A further challenge is the limited success of immunotherapy in PDAC. Checkpoint inhibitors alone have not shown significant benefit, and while Namodenoson's immunomodulatory effects may help, robust clinical evidence for synergy is still lacking.[25]Finally, although Namodenoson has demonstrated excellent safety in hepatocellular carcinoma and early PDAC trials, efficacy data in pancreatic cancer patients remain preliminary. Larger, controlled clinical studies are required to confirm its therapeutic potential.[32]

Future Perspectives

Future perspectives for A_3 adenosine receptor (A_3AR) agonists in PDAC lie in refining their role as novel, targeted agents that exploit tumour specific receptor expression. Since A_3AR is highly expressed in malignant cells but not in

adjacent normal tissues, Namodenoson offers a unique opportunity for selective tumor targeting with minimal toxicity. This receptor specific approach could establish A_3AR agonists as a new class of precision therapeutics in PDAC. Another important direction is the development of predictive biomarkers. Identifying patients with high A_3AR expression or specific pathway activation profiles may allow for personalized treatment strategies, ensuring that only those most likely to benefit receive therapy. This biomarker-driven approach could improve clinical outcomes and reduce unnecessary exposure. Long-term perspectives also include exploring resistance mechanisms. PDAC is notorious for adaptive signalling, and future studies should investigate how tumours might bypass A_3AR mediated inhibition. Understanding these escape routes will be critical for designing next-generation agonists or optimizing dosing strategies. Finally, the translation from preclinical to clinical settings remains a key challenge. While Namodenoson has shown excellent safety in hepatocellular carcinoma and promising activity in PDAC models, larger randomized trials are needed to establish efficacy in patients. If successful, A_3AR agonists could represent a paradigm shift in PDAC therapy, offering a safe, receptor-specific treatment option for a cancer with few effective alternatives.[6]

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