ISSN: 2641-2020
DOI: 10.33552/APPR.2026.05.000609
Archives of
Pharmacy & Pharmacology Research
Iris Publishers

Mini Review

DPAGT1 Inhibition as a Mechanism-Based Strategy for Pancreatic Ductal Adenocarcinoma

Michio Kurosu*, and Bradley Morrison

Department of Pharmacy, University of Tennessee Health Science Center, USA

***Corresponding author:** Michio Kurosu, Department of Pharmacy, University of Tennessee Health Science Center, USA

Received Date: July 07, 2026

Published Date: July 20, 2026

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive, difficult to treat cancer with one of the lowest survival rates. Its poor prognosis is driven by early metastasis and profound intrinsic chemoresistance. Increasing evidence indicates that aberrant N-linked glycosylation, initiated by overexpression of dolichyl-phosphate N-acetylglucosamine-phosphotransferase 1 (DPAGT1), is central to several hallmark PDAC oncogenic behaviors. Key glycosylation related behaviors include upregulated Wnt/β-catenin signaling pathways that drive epithelial-to-mesenchymal transitions (EMT) which contribute to tumor invasiveness, cancer cell stemness, and chemotherapy resistance. Upregulated ATP-binding cassette (ABC) transporters that mediate drug efflux of gemcitabine and cisplatin. Inappropriate glycosylation of PD-L1 promotes PD-1 binding and immune evasion. Finally, downstream KRAS pathways rely on DPAGT1 to sustain proliferative signaling, a provocative relationship as KRAS driven proliferation is a central feature of nearly all PDAC cases. Importantly, these hallmark PDAC oncogenic behaviors are reversable by therapeutic inhibition of DPAGT1. Unfortunately, known DPAGT1 inhibitors are severely toxic, limiting their therapeutic utility. Structure-based DPAGT1 inhibitors, derived from capuramycin and muramycin scaffolds combine potent DPAGT1 inhibition with low toxicity. FDA has awarded DPAGT1 inhibitor aminouridyl phenoxypiperidinbenzyl butanamide (APPB) Orphan Drug Designation for treatment of pancreatic cancer, providing important regulatory validation of this novel, multi-specific approach.

Keywords: Cancer; pancreatic ductal adenocarcinoma; PDAC; DPAGT1; glycosylation; N-linked glycosylation; epithelial-to-mesenchymal transition; EMT; cancer stem cells; CSC; drug resistance; orphan drug designation; CPPB; APPB; ANV221

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a rare, aggressive, and generally lethal human malignancies, with a five-year survival rate of 13.7% [1] poorer when diagnosed advanced metastatic which is a majority of cases. Standard regimens such as FOLFIRINOX with gemcitabine & nab-paclitaxel provide only modest benefit, largely due to early metastasis, profound intrinsic immune checkpoint & chemoresistance [2,3] and enrichment of cancer stem cells (CSCs) [4-5] that further reinforce these hallmark oncogenic behaviors. Increasing evidence implicates aberrant N-linked glycosylation, driven by overexpression of dolichyl-phosphate N-acetylglucosamine-phosphotransferase 1 (DPAGT1), as a "central molecular hub" connecting synergistic, hallmark cancer characteristics that include the epithelial-to-mesenchymal transition (EMT) driven invasion, immune evasion, CSC effects, and multidrug resistance in PDAC [8-13].

DPAGT1 is an essential enzyme of post-translational protein synthesis. DPAGT1 is the first, rate limiting step in the attachment of complex oligosaccharides to asparagine residues to facilitate proper protein folding, function, and location in a process known as N-linked glycosylation. Upregulated DPAGT1 expression has been identified as important step in the evolution of several cancers, including PDAC [9-12]. Importantly, these effects are reversible with the application of DPAGT1 inhibitors, however, the severe toxicity of these compounds limits their clinical utility [8-13]. In

PDAC, DPAGT1 inhibition confers profound, multi-pathway effects and the discovery of safer alternatives represents an important research objective. These effects include the ability to suppress EMT [10-12], disrupt downstream KRAS proliferative pathways [8] and potentiate chemotherapies at substantially lower dosages [10-12]. The FDA has validated the importance of this multi-mechanistic approach by awarding DPAGT1 inhibitor aminouridyl phenoxypiperidinbenzyl butanamide (APPB - renamed ANV221) Orphan Drug Designation for the treatment of pancreatic cancer [14] due to its high efficacy and strong safety signals in vivo [12].

DPAGT1, EMT, and CSCs in PDAC

DPAGT1 catalyzes the first committed step of N-glycan biosynthesis, transferring GlcNAc-1-phosphate from UDP-GlcNAc to dolichyl-phosphate [15]. Overexpression of DPAGT1 has been documented in multiple solid tumours and in pancreatic cancer models [16], where high DPAGT1 correlates with increased migratory and invasive behaviour [8,9]. Mechanistically, overexpression of DPAGT1 increases complex N glycans on E cadherin, reduces its membrane localization, and promotes cellular discohesion and a more mesenchymal morphology. This releases sequestered β-catenin which accumulates in the nucleus, activating the canonical Wnt pathway followed by transcription of EMT drivers (i.e. Snail) that further degrades E-cadherin in an oncogenic, positive feedback loop [17-19].

In PDAC, EMT is characterized by loss of E-cadherin, gain of N-cadherin and vimentin, and activation of MMP-2/-9. Snail, ZEB, and Twist also act as core transcriptional regulators of this program, and Snail expression in particular has also been linked to drug resistance, recurrence, and poor prognosis [21]. We suggest that DPAGT1 overactivity in PDAC contributes to Snail upregulation via Wnt/β-catenin and destabilization of epithelial adhesion, thereby coupling N-glycosylation directly to EMT, metastasis, CSC sustainment, and drug resistance. CSC biology amplifies this pathology. CD133-positive CSCs preferentially express ABC transporters, especially ABCG2, which effluxes cytotoxic drugs (gemcitabine & cisplatin) [13], along with survival pathways (e.g. PI3K/Akt) in PDAC [22]. Chemotherapy agents such as cisplatin and 5-fluorouracil can paradoxically enrich CSCs in some cancers, increasing stemness markers (OCT4, Nanog, Notch1) and ABCG2 expression in another oncogenic positive feedback loop [23,24]. Thus, any effective and durable PDAC therapy must confront EMT and CSCs together, not as separate issues. Kurosu et al found that inhibition of DPAGT1 in PDAC resulted in normalization of mesenchymal phenotypes and restoration of E-cadherins leading to the sequestration of β-catenin and the general disruption of this positive feedback loop [10,12,20]. This is an important signal that the EMT/CSS programs in PDAC can be simultaneously disrupted therapeutically.

ABC Transporters, Drug Resistance, and Glycosylation

The major MDR-related ABC transporters, ABCB1, ABCC1, and ABCG2, are heavily N-glycosylated and require glycan structures for proper folding, membrane trafficking, and stability [13]. Experimental disruption of N-glycosylation by tunicamycin or other inhibitors retains ABC transporters in intracellular compartments and accelerates their proteasomal degradation, leading to increased intracellular drug accumulation and partial reversal of the multi-drug resistance (MDR) phenotype [13]. In PDAC and hepatocellular carcinoma, ABCG2 is preferentially expressed in CD133-positive CSCs, and its activity is modulated by PI3K/Akt signaling and N-glycosylation [13,25].

Hou and colleagues demonstrated that tunicamycin reduced ABCG2 protein levels, altered its subcellular localization, decreased the side-population fraction, and synergized with cisplatin and 5-fluorouracil to suppress tumor growth in xenograft models via the DPAGT1–Akt–ABCG2 pathway [5]. DPAGT1 knockdown reproduced the chemo-sensitizing effect of tunicamycin, confirming that DPAGT1 is a tractable molecular target [13]. Study of DPAGT1 inhibitors effects on ABC transporters in PDAC is a provocative line of inquiry for this intensely chemo-resistant disease.

KRAS, PI3K/mTOR, eIF4E, and Glycosylation

KRAS is the most frequently upregulated oncogenic driver in PDAC, >85% of diagnosis [26]. In PDAC, KRAS mutations activate several cooperatively proliferative downstream programs PI3K–Akt–mTOR, PI3K-Akt-mTOR, releasing the eukaryotic translation initiation factor 4E (eIF4E) resulting in sustained proliferative signaling [27]. KRAS was long considered undruggable and a viable strategy is to limit the downstream effects of KRAS mutations. DPAGT1 inhibition is a compelling strategy against KRAS based on its known effects against these downstream pathways. Further, DPAGT1 inhibitors are known to increase ER stress and induce apoptosis in high DPAGT1 expressing cells. KRAS cells are already under chronic metabolic stress, thus DPAGT1 inhibition potentially amplifies apoptotic effects in KRAS cancers [28,29].

PD-L1, Glycosylation and Immune Tolerance

The acquisition of immune evasion behaviors is an important evolutionary hallmark for many cancers. Immune checkpoint blockade (ICB) is a proven approach to activate the immune responses against these cancers. This involves the disruption of the PD-1/PD-L1 interaction that prevents T-cell activation through therapeutic inhibition of PD-1 or its ligand PD-L1. PDAC is stubbornly refractory to immune checkpoint blockade therapeutics and N-glycosylation of the PD-L1 is a compelling hypothesis. N-glycosylation can be an important oncological strategy for securing oncogenic proteins that are normally degraded. For example, in HER2-positive breast cancer it was found that heavily glycosylated ADAM10 proteases allowed them to survive degradation, migrate to the cell surface, and cleave the HER2 receptor from the HER2 protein, in a process known as HER2 shedding, by depriving anti-HER2 drugs with a receptor to attach, HER2-positive breast cancers become resistant followed by aggressive recurrence [30].

This oncogenic strategy is also found with PD-1 binding. Researchers (Li et al) found that heavily glycosylated programmed death ligand (PD-L1) on tumor surfaces improved their binding

with the corresponding PD-1 receptors resulting in immune evasion [31]. Importantly, both of these effects were reversible with the application of DPAGT1 inhibitors. This evidence suggests DPAGT1 inhibition as a potential strategy in ICB refractory PDAC to resensitize PDAC tumours to a robust immune response.

From Tunicamycin to Selective DPAGT1 Inhibitors

In various studies, tunicamycin provided the initial proof-of-concept that DPAGT1 inhibition can attenuate EMT, CSC markers, and drug resistance. However, its systemic toxicity (mouse LD50 approximately 2.0 mg/kg single dose) and lack of selectivity for tumor versus normal cells have precluded clinical development of tunicamycin and similarly toxic substitutes. Further, tunicamycin displays low IC50 values across both cancer and normal cell lines, causes significant hepatotoxicity and nephrotoxicity, and exhibits hemolytic activity, reflecting broad disruption of membranes and additional off-target effects beyond DPAGT1 inhibition [9-12,20]. Structure-based design against DPAGT1 has yielded capuramycin-derived and muramycin-derived analogues with markedly improved selectivity [10,11]. Mitachi et al. reported inhibitors such as CPPB and APPB (ANV221) that inhibit DPAGT1 with sub-micromolar IC50 values, yet show minimal cytotoxicity toward healthy cells, even at 70X concentrations [10,11].

APPB's water solubility, low hemolytic activity, and negligible hemolysis compare favorably against other DPAGT1 inhibitors while mouse LD50 values are vastly improved at least ten-fold, indicating a widened therapeutic window and realistic potential for systemic administration [12,20]. Structural modelling suggests these next-generation inhibitors occupy DPAGT1's dolichol-phosphate tunnel and UDP-GlcNAc binding site with higher specificity than tunicamycin, thereby further reducing off-target membrane disruption.

Chemotherapy Synergy and PDAC

Importantly for PDAC, DPAGT1 inhibitors show robust synergy with standard chemotherapies. Our research has confirmed that APPB synergizes with paclitaxel in patient-derived metastatic PDAC cells, reducing the IC50 of paclitaxel by more than two orders of magnitude in checkerboard assays [12,20]. DPAGT1 inhibition has been further shown to potentiate cisplatin and 5-fluorouracil activity in hepatocellular carcinoma and reversing chemotherapy-induced upregulation of stemness genes [13]. The mechanistic basis of this synergy is clear: Safer DPAGT1 inhibition is a viable strategy to blunt CSC survival, prevent EMT-driven dissemination, and counteract chemotherapy-induced CSC enrichment, thereby transforming cytotoxic drugs from transient debulking agents into more durable treatments.

Anviron's ANV221 and Orphan Drug Designation

Anviron, in partnership with academic institutions, has exclusively licensed a family of low toxicity DPAGT1 inhibitors (i.e. APPB & CPPB) for development in orphan oncology indications [12]. The United States FDA granted Orphan Drug Designation to APPB (ANV221) for the treatment of pancreatic cancer [14], recognizing both the rarity and severity of PDAC and the plausibility of DPAGT1 inhibition as a novel therapeutic strategy.

Conclusion

Collectively, available data support DPAGT1 as a high-value, underexploited target in PDAC. Selective small-molecule DPAGT1 inhibitors offer the potential to suppress EMT and metastasis via Snail/Wnt/E-cadherin modulation, deplete CSCs, reverse multidrug resistance through the DPAGT1–ABCG2 axis, enabling synergies with existing chemotherapies, particularly paclitaxel, cisplatin, and gemcitabine, and actuating immune vulnerability via PD-L1 binding disruption, and potentially disrupting downstream effects of the historically undruggable KRAS; achieving this with a promising safety profile. With FDA Orphan Drug validation, APPB/ANV221 is in the pole position to make a transformative leap in the fight against one of medicine's most difficult to treat diseases.

Acknowledgement

None.

Conflict of Interest

I'm the Founder and CEO of Anviron, we own the licenses for the drugs we mention in the article. Michio Kurosu is on our Board of Advisors.

References

1. National Cancer Institute, Cancer Stat Facts: Pancreatic Cancer.
2. Snigdha Banerjee, Affan A Ansari, Sunil P Upadhyay, Daniel J Mettman, Jamie R Hibdon, et al. (2024) Benefits and pitfalls of a glycosylation inhibitor tunicamycin in the therapeutic implication of cancers. Cells 13(5): 395.
3. Ullman Nicholas A, Paul R. Burchard, Richard F Dunne, David C Linehan (2022) Immunologic Strategies in Pancreatic Cancer: Making Cold Tumors Hot. J Clin Oncol 40(24): 2789-2805.
4. Wang, Shuai, Shuai Huang, Yu Ling Sun (2017) Epithelial-Mesenchymal Transition in Pancreatic Cancer: A Review. BioMed Res Int 2017: 2646148.
5. Yuliang Feng, Liuyang Cai, Martin Pook, Feng Liu, Chao-Hui Chang, et al. (2024) BRD9-SMAD2/3 Orchestrates Stemness and Tumorigenesis in Pancreatic Ductal Adenocarcinoma. Gastroenterology 166(1): 139-154.
6. Leonardo MF, Vanessa AS, Leonardo FL, José OP, Lucia MP, et al. (2016) Glycosylation in cancer: interplay between multidrug resistance and epithelial to mesenchymal transition. Front Oncol 6: 158.
7. Yuhan Sun, Tiangui Wu, Jianguo Gu (2024) An emerging role of N-glycosylation in cancer chemoresistance. Carbohydrate Res 539: 109107.
8. Aditi Banerjee, Juan A Martinez, Maria O Longas, Zhenbo Zhang, Jesus Santiago, et al. (2015) N acetylglucosaminyl 1 phosphate transferase: an excellent target for developing new generation breast cancer therapeutic. Adv Exp Med Biol 842: 355-374.
9. Kurosu M (2019) Structure based drug discovery by targeting N glycan biosynthesis, dolichyl phosphate N acetylglucosaminephosphotransferase. Future Med Chem 11(9): 927-933.
10. Katsuhiko Mitachi, Rita G Kansal, Kirk E Hevener, Cody D Gillman, Syed M Hussain, et al. (2020) DPAGT1 inhibitors of capuramycin analogues and their antimigratory activities of solid tumors. J Med Chem 63(18): 10283-10303.

11. Kurosu M, Morrison B (2026) Discovery of Safer N-Glycosylation Inhibitors: Design Strategies and Therapeutic Potential. Mod Appro Drug Des 5(2).

12. Helei Hou, Hefen Sun, Ping Lu, Chao Ge, Lixing Zhang, et al. (2013) Tunicamycin potentiates cisplatin anticancer efficacy through the DPAGT1/Akt/ABCG2 pathway in mouse xenograft models of human hepatocellular carcinoma. Mol Cancer Ther 12(12): 2874-2884.

13. (2021) FDA. Orphan Drug Designation for ANV221 for treatment of pancreatic cancer. U.S. Food and Drug Administration.

14. Yin Yao Dong, Hua Wang, Ashley C W Pike, Stephen A Cochrane, Sadra Hamedzadeh, et al. (2018) Structures of DPAGT1 Explain Glycosylation Disease Mechanisms and Advance TB Antibiotic Design. Cell 175(4): 1045-1058.e16.

15. Protein Atlas - https://www.proteinatlas.org/ENSG00000172269-DPAGT1/pathology

16. Duchartre Y, Kim Y, Kahn M (2018) The Wnt Signaling Pathway in Cancer, Crit Rev Oncol Hematol 99: 141-149.

17. Vargas DA, Sun M, Sadykov K, Kukuruzinska MA, Zaman MH (2016) The integrated role of Wnt/β-Catenin, N-glycosylation, and E-cadherin-mediated adhesion in network dynamics. PLoS Comput Biol 12(7): e1005007.

18. Ram Makena Monish, Himavanth Gatla, Dattesh Verlekar, Sahithi Sukhavasi, Manoj K Pandey, et al. (2019) Wnt/β-Catenin Signaling: The Culprit in Pancreatic Carcinogenesis and Therapeutic Resistance. Int J Mol Sci 20(17): 4242.

19. Katsuhiko Mitachi, Shou M Kurosu, Shakiba Eslamimehr, Maddie R Lemieux, Yoshimasa Ishizaki, et al. (2019) A Semi-Synthesis of an Anticancer DPAGT1 Inhibitor from a Muraymycin Biosynthetic Intermediate. Org Lett 21(4): 876-879.

20. Yang, Jian, Ying Liu, Shi Liu (2023) The Role of Epithelial-Mesenchymal Transition and Autophagy in Pancreatic Ductal Adenocarcinoma Invasion. Cell Death & Dis 14(8): 506.

21. Reichert Maximilian, Dieter Saur, Rainer Hamacher, Roland M Schmid, Günter Schneider (2007) Phosphoinositide-3-Kinase Signaling Controls S-Phase Kinase–Associated Protein 2 Transcription via E2F1 in Pancreatic Ductal Adenocarcinoma Cells. Cancer Res 67(9): 4149-4156.

22. Lihui Wang, Xing Liu, Yong Ren, Jingyuan Zhang, Junli Chen, et al. (2017) Cisplatin-Enriching Cancer Stem Cells Confer Multidrug Resistance in Non-Small Cell Lung Cancer via Enhancing TRIB1/HDAC Activity. Cell Death & Dis 8(4): e2746.

23. Zhi-Yuan Xu, Jia-Ning Tang, Hua-Xia Xie, Yi-An Du, Ling Huang, et al. (2015) 5-Fluorouracil Chemotherapy of Gastric Cancer Generates Residual Cells with Properties of Cancer Stem Cells. Int J Bio Sci 11(3): 284-294.

24. Adamska Aleksandra, Marco Falasca (2018) ATP-Binding Cassette Transporters in Progression and Clinical Outcome of Pancreatic Cancer: What Is the Way Forward? World J Gastroenterolo 24(29): 3222-3238.

25. Luo J (2021) KRAS mutation in pancreatic cancer. Semin Oncol 48(1): 10-18.

26. Y Martineau, R Azar, D Müller, C Lasfargues, S El Khawand, et al. (2014) Pancreatic Tumours Escape from Translational Control through 4E-BP1 Loss. Oncogene 33(11): 1367-1374.

27. Takumi Shiraishi, Tatsushi Yoshida, Susumu Nakata, Mano Horinaka, Miki Wakada, et al. (2005) Tunicamycin Enhances Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand-Induced Apoptosis in Human Prostate Cancer Cells. Cancer Res 65(14): 6364-6370.

28. Debasmita Dutta, Sunil Upadhyay, Archana De, Inamul Haque, Axel H Breier, et al. (2025) Targeted Nanoencapsulation of Tunicamycin Reduces Toxicity While Improving Its Therapeutic Effectiveness in Pancreatic Cancer Cells. Res Sq: rs.3.rs-6711378.

29. Muwen Yang, Yue Li, Lingzhi Kong, Shumei Huang, Lixin He, et al. (2023) Inhibition of DPAGT1 Suppresses HER2 Shedding and Trastuzumab Resistance in Human Breast Cancer. J Clin Invest 133(14): e164428.

30. Chia-Wei Li, Seung-Oe Lim, Ezra M Chung, Yong-Soo Kim, Andrew H Park, et al. (2018) Eradication of Triple Negative Breast Cancer Cells by Targeting Glycosylated PD-L1. Cancer Cell 33(2): 187-201.e10.

31. Wang Yiting, Huanbin Wang, Han Yao, Chushu Li, Jing-Yuan Fang, et al. (2018) Regulation of PD-L1: Emerging Routes for Targeting Tumor Immune Evasion. Front Pharmacol 9: 536.

32. Beebee YK, Jacob MK, Katsuhiko M, Jessica MO, Marie-Therese SP, et al. (2025) Structures of Bacterial and Human Phosphoglycosyltransferases Bound to a Common Inhibitor Inform Selective Therapeutics. bioRxiv 2025.12.16.694696.