Journal of Clinical Trials and Case Studies

Open access

Commentary

Glycosylated Chitosan: A Promising Candidate for Combination Therapies Targeting Metastatic Cancers

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Abstract

Pancreatic cancer is highly metastatic, and metastasis is the main cause of cancer-related deaths. Therefore, finding methods to inhibit pancreatic cancer metastasis has important clinical value. N-dihydrogalactochitosan (GC) is an immunostimulant that can enhance the anti-tumor immune response to inhibit metastasis in combination with photothermal therapy. Here, we found that GC can inhibit the migration of pancreatic cancer cells through interactions with caveolin-1 (Cav-1). The fluorescence of GC-FITC on the cell surface overlaps with Cav-1-Red, is enhanced by adCav-1, and is weakened by siCav-1, indicating that the localization of GC depends on Cav-1. GC inhibits the migration of malignant cells by blocking the signal transduction of Cav-1 and its downstream molecules. In an orthotopic pancreatic tumor model, GC can inhibit tumor metastasis in tumor-bearing mice. These results demonstrate GC's capacity to act as a partner in pancreatic cancer therapy and indicate future directions for metastatic cancer therapy.

Keywords: Pancreatic cancer, Caveolin-1, GC, laser therapy, Immunotherapy, Metastasis

Received date: June 12, 2026; **Accepted date:** June 16, 2026; **Published date:** July 10, 2026

Citation: Jacob Paul Adams (2026) Glycosylated Chitosan: A Promising Candidate for Combination Therapies Targeting Metastatic Cancers. J Clin Trial Case Stud, 8:4.

Description

Metastasis remains a significant hurdle in cancer therapy and is associated with as many as 90% of all cancer-related mortalities **[1]**. Conventional therapies like surgery cannot prevent metastasis, while more robust therapies, like radiation and chemotherapy, carry harsh side effects and are resisted by certain types of cancer. Pancreatic Cancer (PC), for example, usually has a low response rate to conventional radiation and chemotherapy. The third leading cause of cancer related deaths, PC has a 5-year overall survival rate of 13%, the lowest among all cancer types, while the median survival rate is less than one year **[2]**. A confounding factor in treating PC is that it is often detected after it has begun to metastasize, as PC is typically asymptomatic until it develops into late-stage with metastasis. According to the United States National Cancer Institute's website, 28% of pancreatic cancer patients have metastases spread to regional lymph nodes at the time of diagnosis, while 51% have distant metastases at the time of diagnosis. The 5-year survival rate for PC patients with regional spread is 17%, which drops to only 3.4% when the patient has distant metastases **[3]**. Therefore, the development of new treatment strategies to inhibit metastasis is the key to effective control of malignant pancreatic cancer.

In "Glycosylated Chitosan Inhibits Pancreatic Cancer Metastasis by Blocking the Caveolin Signaling Pathway", the authors investigated a potential mechanism for inhibiting metastasis in PC through an immunoadjuvant and its interactions with the caveolin signaling pathway, particularly the caveolae-associated protein known as caveolin-1 (Cav-1). Caveolae are invaginated organelle structures which interact with multiple signaling molecules and signaling pathways. Cav-1 was of particular interest, as it is essential to caveolae formation, has been shown to be up-regulated in PC, and it is positively correlated with tumor aggressiveness and poor prognosis in PC. N-dihydrogalactochitosan, or Glycosylated Chitosan (GC), is an immunoadjuvant which has been used in combination with laser irradiation to treat malignant tumors. Studies have confirmed that this combination is effective against metastatic cancer, with various clinical applications in advanced malignant tumors like breast cancer and melanoma.

However, the direct effect of GC on tumor cells was unclear. To determine what effect GC has on tumor cells, the authors investigated how GC impacts the functions of PC cells. Upon discovering that GC affected the motility of PC cells but not their viability, the authors hypothesized that Cav-1 may play a role in this inhibition. As previously mentioned, Cav-1 is an important molecule in relation to signaling pathways, so if GC interacted with Cav-1, it may disrupt the signaling pathways that lead to tumor cell metastasis, while leaving their viability undisturbed

The authors continued their investigation by determining whether GC could enter PC cells. Using fluorescent imaging, the authors found that GC localized on the surface of the PC cells, indicating an inability to be endocytosed. Next, GC's interactions with Cav-1 were studied, with the authors discovering that GC and Cav-1 co-localized, and that GC's surface localization was dependent on Cav-1 expression. Combined with the indication that GC affects the migration of PC cells, these results suggest that GC's interactions with Cav-1 are the key to GC's effects on PC cell migration, though further experiments were needed to confirm this. To this end, the authors next studied how GC affects cellular uptake in PC cells, a known function of Cav-1, and whether these results translated to an *in vivo* model. Using flow cytometry, GC was shown to reduce the caveolae-mediated endocytosis potential of PC cells, though this effect was absent if Cav-1's expression was down-regulated. Further, GC could not inhibit the invasion of PC cells when Cav-1's expression was down-regulated, but could if Cav-1 was over-expressed in PC cells.

Treatment with GC also lead to the significantly reduced expression of several molecules downstream of Cav-1, like p-FAK and vinculin. All together, these results indicate that GC inhibits Cav-1-dependent cell migration by blocking the functions of Cav-1 signaling. Finally, the authors utilized an aggressive orthotopic PC tumor model in mice to determine whether GC could inhibit metastasis on its own. While GC treatment did not affect the primary weight of tumors compared to the control groups, it did significantly reduce the number of mesenteric metastases in the mice seven-days post treatment. Interestingly, primary tumors treated with GC displayed an altered expression of E-cadherin and vimentin compared to the control groups. Control tumors possessed decreased levels of E-cadherin and increased levels of vimentin expression, which is indicative of metastasis **[4]**, while GC-treated tumors showed an increased expression of E-cadherin and a decreased expression of vimentin, suggesting a shift in the cellular structure away from a metastatic state. When considered together, these results indicate that while GC treatment cannot inhibit the growth of the primary tumor, it can significantly inhibit metastasis from the primary tumor, mirroring and confirming the results found in the *in vitro* studies.

Conclusion

The results from this study provide a foundation for future studies investigating GC and similar compounds. Controlling metastasis is vital in the treatment of various types of cancer, especially aggressive cancers like PC. Cancer researchers are now investigating combination therapies as the next evolution of cancer therapies due to their broad customizability. GC is an excellent candidate for combination therapies of metastatic cancers. While this manuscript shows that GC alone cannot directly kill PC cells, it does inhibit their metastasis, one of the prevailing reasons for the failure of traditional therapies. Therefore, combining GC with an ablative therapy like phototherapy allows each to compliment the other's strengths without negatively interfering with each other, synergizing to produce an enhanced therapeutic effect in patients **[5]**. Future work should also focus on better understanding how GC affects metastasis in both PC and other cancer types, and how this work translates beyond animal models and into clinical trials. This manuscript provides a starting point for these studies, providing researchers in the field both the direction needed for these studies as well as the groundwork for them.

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