Small-scale particles showing large-scale impact in pancreatic cancer

Arza Izzadeen, Lewis Dymock, Clare Hoskins*

Department of Pure and Applied Chemistry, Technology and Innovation Centre, University of Strathclyde, 99 George Street, Glasgow, G1 1RD

*Corresponding author: clare.hoskins@strath.ac.uk; +44 141 5482796

Keywords: Pancreatic cancer, Nanotechnology, Early diagnosis, Cancer nanomedicine, Drug delivery

First draft submitted: 06 October 2023; Accepted for publication: XX October 2023; Published online: TBC

Despite significant advances in recent years, cancer continues to be a leading cause of death worldwide, accounting for approximately 10 million deaths in 2020 [1]. One particularly burdensome cancer is that of the pancreas- which can be further categorized into pancreatic ductal adenocarcinoma (PDAC), contributing to approximately 90% of pancreatic cancer cases, and pancreatic neuroendocrine tumors. Often, symptoms of pancreatic cancer are misconstrued as symptoms of other gastric diseases, and in some cases, patients remain asymptomatic until a diagnosis is too late. With delayed diagnosis, often at stage III or IV, and poor prognostic outcomes, only 20% of patients qualify for surgical resection, and even then, are only estimated to have a 5-year survival rate of 27% - comparably greater than the 5% without surgery [2]. Despite less-than-desirable outcomes, surgery remains the only curative treatment option, alongside postoperative adjuvant chemotherapy to prevent recurrence. Although the use of gemcitabine plus capecitabine as adjuvant chemotherapy has been recognized for the management of resectable pancreatic cancer [3], there remains a need for novel, more target-specific therapeutic options to provide necessary improvements in overall survival. Indiscriminate targeting by traditional chemotherapeutics presents the challenge of affecting non-cancerous cells, resulting in unpleasant side effects and reduced efficacy.

The application of nanotechnology in medicine has emerged as a critical turning point in modern medicine, specifically the use of nanoparticles (NPs). Theoretically, NPs are colloidal particles ranging between 1 and 100 nm in dimension. NPs can be classed as either organic or inorganic, whereby inorganic NPs refer to gold, silica and other metallic NPs and organic NPs refer to polymeric NPs, liposomes, micelles and other macromolecules. They can be used in diverse fields, namely in diagnostics as imaging agents and therapeutics as drug carriers.

Mainly the metallic class of NPs is used in cancer diagnostics, with the main route being as contrast enhancers on clinical tests such as MRI or CT scans. Here, iron oxide, gadolinium and gold NPs have been shown to improve contrast when accumulated inside tumor tissues and help clinicians visualize the tissue mass [4]. However, in pancreatic cancer, this detection often happens far too late in the tumor progression, and many efforts are now being investigated into using metallic NPs with recognition molecules on their surface for early-stage biomarkers, to detect the disease at its earlier stages.

A keen interest has been expressed in the field of nanomedicine in exploiting NPs for the delivery of chemotherapeutics. This is because they offer a solution to previously faced challenges such as low encapsulation efficiencies, off-target effects and low solubility, and allow for targeted drug delivery and improve biodistribution [5]. The drug of interest can either be encapsulated within the cavity of the NP or bound to the surface. NPs also extend the circulation time and reduce the likelihood of adverse drug reactions of the chemotherapeutic. The hypervascularity, high vascular permeability and poor lymphatic drainage of tumors are exploited by NPs to preferentially deliver and retain the chemotherapeutic at the desired site, this is referred to as the enhanced permeability and retention effect (EPR) [6], although this phenomenon is debated throughout the scientific community. However, the tumor microenvironment in pancreatic cancer, which includes the presence of a dense stroma and high intra-tumoral pressures, may reduce the likelihood of the EPR effect from occurring.

Already, numerous nanotechnologies have successfully undergone clinical trial with either FDA or EMA approval for use in pancreatic cancer. Abraxane™ was the first clinically approved nanomedicine, with FDA approval in 2005 [7]. Abaxane™ is a protein-drug conjugate of paclitaxel licensed for breast, pancreatic and non-small lung cancer. Subsequently in 2019, another protein-drug nanomedicine was licensed for the same drug, called

Pazenir™. In 2015, the FDA approved a liposomal formulation of irinotecan called Onivyde™. These technologies are all based on drug therapy, where the nanotechnology vehicle is used to enhance drug delivery into the tumor, aiding in more effective patient outcomes. However, one other nanomedicine was approved in 2013 by the EMA which was NanoTherm®® [7]. NanoTherm® is a metallic NP, which contains no chemotherapeutic. This platform exerts its clinical effect by heating up inside the tumor upon experiencing a shift in magnetic fields, which leads to localized hyperthermia and cellular death.

Further work is focussing on the development of nanotherapeutics for pancreatic cancer, delivering chemotherapies [8], immunotherapies [9] as well as in radiation enhancement [10] and laser-activated hyperthermia [11]. Whilst the literature houses many different examples, the main promising next-generation therapeutics likely to gain approval are lipid-based technologies. Much like liposomes, lipid NPs (LNPs) and solid lipid NPs (SLNPs) are probably better defined compared to newer technologies such as polymeric micelles. The rapid advancement in LNP technology for mRNA delivery in the COVID-19 pandemic has provided huge potential for the streamlined development, regulation and approval of other similar technologies for cancer therapy.

Liposomes have been extensively investigated for the treatment of pancreatic cancer [12]. Their vesicular structure surrounded by a lipid bilayer can be exploited for combination therapy, aiding in the delivery of both hydrophobic and hydrophilic drugs in a singular platform. Examples of drugs encapsulated in liposomes are gemcitabine, paclitaxel, doxorubicin, irinotecan and various other mono- and combination therapies. Their ease of fabrication and surface functionalization have made them very attractive for cancer therapeutics. However, advanced liposome technologies are also under development, which are capable of housing metallic NPs in their core, enabling real-time tracking, diagnosis and therapeutic delivery all in one platform. Such multifunctionality and adaptability in the liposome structure puts them at the forefront for the next generation technologies, with multiple different formulations under clinical trial currently [12].

LNPs are compact spherical vesicles comprised of ionizable lipids. They are the delivery vehicle utilized mostly for RNA-based vaccines and therapeutics. Despite the huge success that immunotherapy has shown in other solid tumor types, its potential for use in pancreatic cancer is lagging [13] This is due to the aggressive tumor microenvironment, which often hinders chemotherapy, disabling its ability to exert a significant effect. Nevertheless, many studies are ongoing using LNP technologies to modulate the tumor microenvironment, in order to enhance therapeutic outcomes. It is envisaged that these technologies will drive forward a shift in clinical practice and revolutionize prognosis, once they have been properly tuned [13].

Owing to their superior long-term colloidal stability over the other lipid-based systems, as well as biocompatibility and surface functionalization capacity, SLNPs offer a promising vehicle for the delivery of chemotherapeutics in the treatment of pancreatic cancer. As pancreatic cancer is highly resistant to chemotherapeutic agents, entrapment of these drugs within an SLNP offers a method to increase the overall efficiency of the drug. Drugs such as paclitaxel, 5-fluoracil and gemcitabine have been entrapped within SLNPs resulting in greater anticancer activity compared to the drug alone [14]. Modification of the surface of SLNPs with compounds such as chitosan, alginate chitosan and various other derivatives have been studied in the treatment of pancreatic cancer, these have been shown to offer higher antioxidant activity as well as maintaining a sustained release of the entrapped active ingredients [15]. The wide variety of biocompatible lipids available for the formulation of SLNPs alleviates concerns of toxicities arising from excipients, as well as allowing for the release of entrapped drugs to be more finely controlled [14].

Aside from lipid-based technologies, a wealth of other studies is ongoing with other nanotechnologies, either in early detection [16], drug delivery via polymeric micelles [17] or via the development of next-generation theranostic platforms, which can be used to reduce the lag time between diagnosis and treatment [18]. Preclinical testing of such entities appears highly encouraging and the future looks bright for patients with these small-scale macromolecules set to have a large impact on patient prognosis.

Author Contributions

Arza Izzadeen and Lewis Dymock contributed to the writing of the manuscript. Clare Hoskins contributed to the writing and editing of the manuscript.

Financial Disclosure
The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Competing Interests Disclosure
The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians.*71(3), 209–249 (2021).
2. McGuigan A, Kelly P, Turkington RC *et al.* Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment, and outcomes. *World Journal of Gastroenterology.* 24(43), 4846-4861 (2018).
3. National Institute for Health and Care Excellence. (2018). *Pancreatic cancer in adults: diagnosis and management* [NG85] https://www.nice.org.uk/guidance/ng85/chapter/Recommendations#managing-unresectable-pancreatic-cancer (accessed 06/10/23)
4. Jouyandeh M, Sajadi SM, Seidi F *et al.* Metal nanoparticles-assisted early diagnosis of diseases, *OpenNano*, 8,100104 (2022).
5. Patra JK, Das G, Fraceto LF *et al.* Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnol.* 16, 71 (2018).
6. Manzur A, Oluwasanmi A, Moss D *et al.* Nanotechnologies in Pancreatic Cancer Therapy. *Pharmaceutics*. 9(4), 39 (2017).
7. Urbanova M, Cihova M, Buocikova V *et al.* Nanomedicine and epigenetics: New alliances to increase the odds in pancreatic cancer survival. *Biomedicine & Pharmacotherapy.* 165, 115179 (2023).
8. Greene MK, Johnston MC, Scott CJ. Nanomedicine in Pancreatic Cancer: Current Status and Future Opportunities for Overcoming Therapy Resistance. *Cancers (Basel).* 13(24), 6175 (2021).
9. Hou W, Yang B, Zhu H. Nanoparticle-Based Therapeutic Strategies for Enhanced Pancreatic Ductal Adenocarcinoma Immunotherapy. *Pharmaceutics.*14(10), 2033 (2022).
10. Kuncic Z, Lacombe S. Nanoparticle radio-enhancement: principles, progress and application to cancer treatment. *Physics in Medicine & Biology*, 63, 2 (2018).
11. Guo Y, Zhang Z, Kim D *et al.* Photothermal ablation of pancreatic cancer cells with hybrid iron-oxide core gold-shell nanoparticles. *Int J Nanomedicine*. 8(1), 3437-3446 (2013).
12. Raza F, Evans L, Motallebi M *et al.* Liposome-based diagnostic and therapeutic applications for pancreatic cancer. *Acta Biomaterialia*. 157, 1-23 (2023).
13. Nzeteu N, Aime G, Bernhard GF *et al.* Nanoparticle-based immunotherapy of pancreatic cancer *Frontiers in Molecular Biosciences*. 9 , 2022.
14. Akanda M, Mithu MDSH, Douroumis D. Solid lipid nanoparticles: An effective lipid-based technology for cancer treatment. *Journal of Drug Delivery Science and Technology*. 86, 104709 (2023).
15. Ganesan P, Ramalingam P, Karthivashan G *et al.* Recent developments in solid lipid nanoparticle and surface-modified solid lipid nanoparticle delivery systems for oral delivery of phyto-bioactive compounds in various chronic diseases. *Int J Nanomedicine.* 13, 1569-1583 (2018).
16. Caputo D, Pozzi D, Farolfi T *et al.* Nanotechnology and pancreatic cancer management: State of the art and further perspectives. *World J Gastrointest Oncol*. 13(4), 231-237 (2021).
17. Rehman U, Abourehab MAS, Alexander A *et al.* Polymeric micelles assisted combinatorial therapy: Is it new hope for pancreatic cancer? *European Polymer Journal.* 184,111784 (2023).
18. Jaidev LR, Chede LS, Kandikattu HK. Theranostic Nanoparticles for Pancreatic Cancer Treatment. *Endocr Metab Immune Disord Drug Targets*. 21(2), 203-214 (2021).