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Multimodal Imaging Of Gemcitabine Uptake And Distribution In Cancer Cells, And Of Its Effects On Tumour Proliferation

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Abstract:
Gemcitabine is a nucleoside analogue prodrug used as a monotherapy or in combined therapies against various types of cancer. The hydrophilic property of the gemcitabine molecule means that it cannot easily cross the hydrophobic lipid layer of cell membranes, so it requires nucleoside transport proteins for it to be taken up into cancer cells. The active phosphorylated metabolites of gemcitabine ultimately block DNA synthesis and lead to apoptosis. Unfortunately, the efficacy of gemcitabine is limited by its enzymatic deamination, fast systemic clearance and the rapid development of chemoresistance. The side effects of gemcitabine on non-cancer cells and the development of chemoresistance can be minimised by using chemically modified and targeted forms of gemcitabine, including a theranostics approach. To diagnose cancers and to monitor the efficacy and side-effects of gemcitabine-based chemotherapies it is important to have accurate and reliable methods that visualise and measure the cellular uptake and distribution of gemcitabine and its metabolites, and their effects on tumour proliferation. The most robust approach is to combine the strengths of different imaging techniques to provide complementary anatomical and molecular information, and therefore a more holistic picture of the cancer being investigated. In so-called "multimodal imaging" two or more imaging modalities are used in combination to achieve this, which may include molecular imaging (e.g. autoradiography, positron emission tomography/PET), structural imaging (e.g. computed tomography/CT, magnetic resonance imaging/MRI), microscopy (e.g. electron microscopy/EM) and spectroscopy (e.g. nuclear magnetic resonance/NMR spectroscopy) techniques.

Key Words: *Chemotherapy; Drug delivery; Magnetic resonance imaging; Nucleoside analogue; Positron emission tomography; Theranostics.*

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I. Introduction

Gemcitabine (2',2'-difluoro-2'-deoxycytidine) (**1**) (Figure 1) is a fluorinated nucleoside analogue drug used in the treatment of various types of cancer (Toschi et al., 2005; Gesto et al., 2012; Cavaliere et al., 2017) [1-3]. Gemcitabine was initially investigated as an antiviral drug, but preclinical testing showed that it inhibited growth of human leukemia cells (Hertel et al., 1990) [4]. Under the trade name Gemzar®, gemcitabine was approved for treating pancreatic cancer in the UK in 1995 and by the USA Food and Drug Administration (FDA) in 1996 (https://web.archive.org/web/20170710202604/https://www.medicines.org.uk/emc/medicine/596; Barton-Burke, 1999) [5]. Gemcitabine is widely used as a monotherapy or in a combined therapy against various solid tumours including pancreatic cancer (King, 1996; Huang et al., 2024; Ren et al., 2024; Li et al., 2025; Sara et al., 2025) [6-10], breast cancer (Vernieri et al., 2019; Pattarawat et al., 2021; Yamamoto et al., 2021; Wang and Zhu, 2024) [11-14], ovarian cancer (Yuan and Peng, 2017; Berg et al., 2019; Bhattacharya et al., 2022; Kase et al., 2023) [15-18], non-small-cell lung cancer (Ma et al., 2017; Duan et al., 2018; Esim et al., 2020; Zhu et al., 2022) [19-22], and non-muscle invasive and muscle invasive bladder cancer (Kobayashi et al., 2022; Öztürk and Karapolat, 2023; Wang et al., 2023; Hattori et al., 2024) [23-26]. Gemcitabine often serves a palliative role in advanced disease, with an aim to prolong survival and improve quality of life rather than provide a cure. For example, gemcitabine-based chemotherapies have become the prominent methods of care for metastatic pancreatic cancer (Burris et al., 2023; Zhang et al., 2022; Sezgin et al., 2025; Wang et al., 2025) [27-30]. Unfortunately, the efficacy of gemcitabine in treating cancers has been limited by its enzymatic deamination, fast systemic clearance and the rapid development of chemoresistance (Sarvepalli et al., 2019; Koltai et al., 2022) [31,

32]. These factors increase the concentration of gemcitabine that must be administered to have the desired effect on cancer cells but also increase the toxic effects on non-cancer cells, leading to more serious and intolerable side effects. To overcome this, there has been development of various chemically modified forms of gemcitabine and gemcitabine prodrugs that have increased cell uptake, extended plasma stability and enhanced anticancer activities compared to gemcitabine (Moysan et al., 2013; Miao et al., 2020; Han et al., 2022; Pandit and Royzen, 2022; Zhang et al., 2023; Kaliya et al., 2025) [33-38].

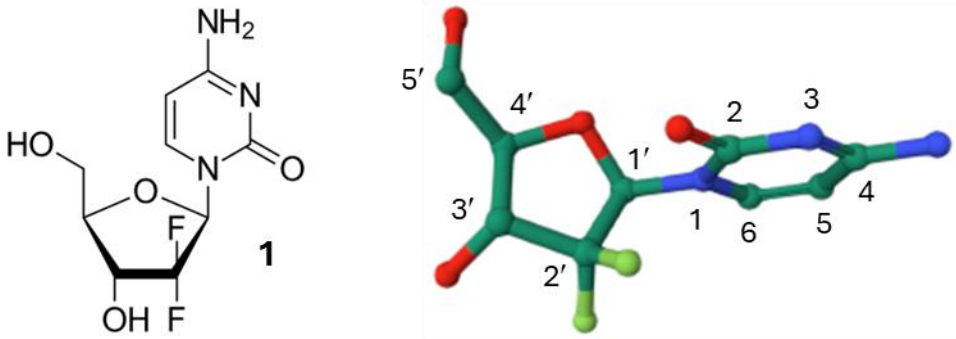

Figure 1: Chemical structure of gemcitabine (2',2'-difluoro-2'-deoxycytidine) (**1**). Shown as a line structure (left) and a ball and stick structure (right). Red = oxygen atoms, Blue = nitrogen atoms, Green = fluorine atoms.

To monitor the efficacy and side-effects of gemcitabine-based chemotherapies it is important to have accurate and reliable methods to visualise and measure the cellular uptake and distribution of gemcitabine and its metabolites, and their effects on tumour proliferation. The most robust approach to achieving this is to combine the strengths of different imaging techniques to provide complementary anatomical and molecular information, and therefore a more holistic picture of the cancer being investigated. In so-called "multimodal imaging" two or more imaging modalities are used in combination to enable early detection, accurate treatment and efficacy evaluation of cancer progression and therapy. The different techniques used in multimodal imaging may be grouped as: molecular imaging [(e.g. autoradiography, positron emission tomography (PET), mass spectrometry, fluorescence, bioluminescence], microscopy techniques (e.g. electron microscopy, light microscopy, atomic force microscopy), structural imaging [e.g. computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), X-ray], spectroscopy [nuclear magnetic resonance (NMR) spectroscopy, Raman spectroscopy, infrared (IR) spectroscopy] (Patching, 2016; Wu and Shu, 2018; Zamboglou et al., 2018; Brauckhoff and Biermann, 2020; Tuck et al., 2021; Tuck et al., 2022; Zeng et al., 2022; Zhang et al., 2022; Capobianco and Dominietto., 2023; Bischof et al., 2024; Wang et al., 2024; Cè et al., 2025; Lee et al., 2025; Shaghaghi et al., 2025; Tiwari et al., 2025; Varma et al., 2025; Wang et al., 2025) [39-55].

This article first considers the chemical properties and structure of gemcitabine, and how it requires transport proteins for it to be taken up into cancer cells. The metabolism and mode of action of gemcitabine are then considered, along with mechanisms that lead to chemoresistance. The use of gemcitabine prodrugs and methods of targeted delivery for improving efficacy and overcoming chemoresistance are then considered, before finally looking at methods that have been used to analyse the cellular uptake and distribution of gemcitabine, and its effects on cancer cells, especially using a multimodal imaging approach.

II. Gemcitabine Chemical Synthesis And Structure

Gemcitabine is comprised of a cytosine base and a 2,2-difluoro-2-deoxy-ribose sugar. The main challenges to overcome for its chemical synthesis are introduction of the fluorine atoms and stereocontrolled coupling of the fluorinated sugar with cytosine. The original synthesis of gemcitabine was devised by Lilly Research Laboratories, and was first published in 1988 (Hertel et al., 1988) [56]. The synthesis (Figure 2) involved coupling (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**2**) with ethyl bromodifluoroacetate using Reformatkii conditions to give the required carbon skeleton for the carbohydrate in a 3:1 anti/syn diastereomeric mixture (**3**). The required anti diastereomer was separated by HPLC in 65% yield. Hydrolytic removal of blocking groups with concomitant ring closure to give the γ-lactone (**4**) was followed by protection of hydroxyl groups as tert-butyldimethylsilyl (TBDMS) ethers and reduction to the lactol (**6**), thus forming the fluorinated sugar. The sugar was functionalised with a mesylate leaving group at the anomeric position followed by its displacement with silylated cytosine and then removal of protecting groups to give gemcitabine (1) in a 4:1 α/β diastereomeric mixture. The required β diasteromer was isolated by HPLC (Hertel et al., 1988) [56]. In this synthetic procedure the steps coupling the fluorinated sugar and base produced only a 10% yield of gemcitabine (β diasteromer). For a comprehensive discussion on different synthetic approaches to gemcitabine, especially for improving efficiency and scalability, see the review by Brown et al. (2014) [57].

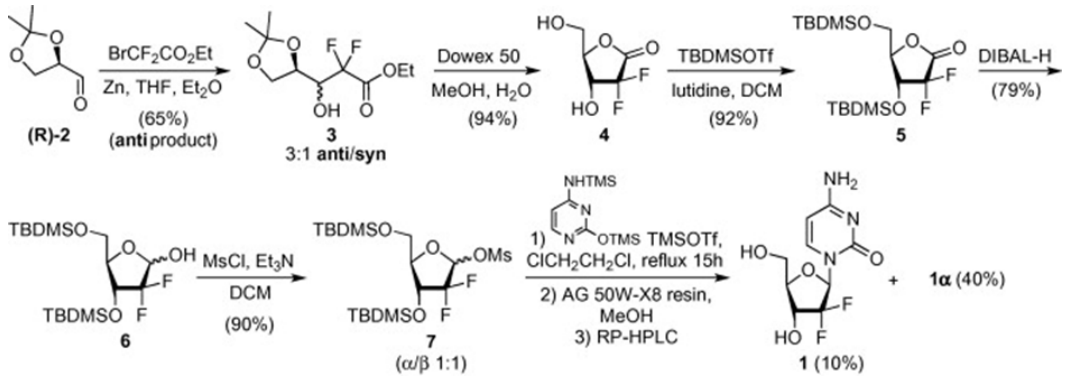

Figure 2: Chemical synthesis of gemcitabine. This figure was reproduced from Brown et al. (2014) [57].

Analysis of the structure conformation of gemcitabine using 2D solution-state NMR and density functional theory (DFT) identified three stable conformers (G1, G2, G3) (Figure 3). The most stable conformer was G1 due to carbonyl group orientation associated with both oxygen and fluorine in a sugar ring. In G1 space repulsion energy that provides conditions for intramolecular interactions is minimised (Chashmniam and Tafazzoli, 2018) [58].

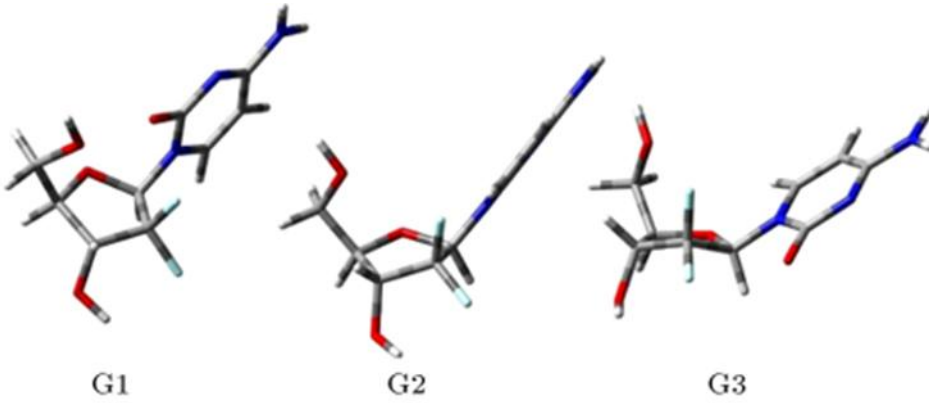

Figure 3: Molecular structure of gemcitabine conformers in aqueous solution. G1 is the most stable conformer due to its intramolecular interaction. This figure was reproduced from Chashmniam and Tafazzoli (2018) [58].

III. Gemcitabine Uptake Into Cancer Cells Via Nucleoside Transporters

Like natural nucleosides gemcitabine is a hydrophilic molecule that cannot easily cross the hydrophobic lipid layer of cell membranes without the assistance of transport proteins. The uptake of gemcitabine into cancer cells is mediated by two structurally and functionally distinct protein families, concentrative nucleoside transporters (CNTs) and equilibrative nucleoside transporters (ENTs), that have different substrate specificities and mechanisms of action (Mackey et al., 1998; Mackey et al., 1999; Molina-Arcas et al., 2009; Young et al., 2013; Young, 2016) [59-63].

The CNTs, also known as solute carrier family 28 (SLC28), have three members in humans (hCNT1, hCNT2, hCNT3) with lengths of 649, 658 and 691 amino acids, respectively, that each form eleven transmembrane-spanning α-helices (Gray et al., 2004; Pastor-Anglada et al., 2008; Molina-Arcas et al., 2009; Young et al., 2013; Young, 2016; Zhou et al., 2020) [61-63, 64-66] (Figure 4). Human CNTs catalyse the uptake of natural nucleosides and nucleoside analogues into cells against their concentration gradient in a symport manner driven by sodium ions that move down their concentration gradient in the same direction, i.e. Sodium ions(out) + Nucleosides(out) → Sodium ions(in) + Nucleosides(in). The stoichiometry of sodium ions: nucleosides is 1:1 for hCNT1 and hCNT2 and 2:1 for hCNT3, and hCNT3 is also able to couple the transport of uridine to the uptake of protons (Smith et al., 2007) [67]. hCNT1 is generally pyrimidine specific (cit-type) but also transports the purine nucleoside adenosine, hCNT2 is generally purine specific (cif-type) but also transports the pyrimidine nucleoside uridine, and hCNT3 has broad specificity (cib-type) (Loewen et al., 1999; Lostao et al., 2000; Ritzel et al., 2001) [68-70]. CNT family proteins are also found in prokaryotes, the best characterised being proton-coupled NupC from *Escherichia coli* and other bacterial homologues (Craig et al., 1994; Loewen et al., 2004; Patching et al., 2005; Johnson et al., 2012; Sun and Patching, 2023) [71-75].

The ENTs, also known as solute carrier family 29 (SLC29), have four members in humans (hENT1, hENT2, hENT3, hENT4) with lengths of 456, 456, 475 and 530 amino acids, respectively, that form eleven

(hENT1-3) or ten (hENT4) putative transmembrane-spanning α-helices (Baldwin et al., 2004; Young et al., 2008; Molina-Arcas et al., 2009; Young et al., 2013; Boswell-Casteel and Hays, 2017; Wright and Lee, 2019) [61, 62, 76-79] (Figure 4). Human ENTs catalyse the bidirectional transport of natural nucleosides and nucleoside analogues across cell membranes down their concentration gradient (facilitated diffusion), i.e. Nucleosides(out) ↔ Nucleosides(in). hENT1 and hENT2 transport both purine and pyrimidine nucleosides and hENT2 also efficiently transports nucleobases. hENT3 has broad transport selectivity for nucleosides and nucleobases and functions in both cell membranes and intracellular membranes (Baldwin et al., 2004; Young et al., 2008) [61, 62]. hENT4 is uniquely selective for adenosine and transports different organic cations, hence it is also known as a plasma membrane monoamine transporter (hPMAT) (Engel and Wang, 2005; Saidijam et al., 2018) [80, 81]. ENTs are restricted to eukaryotes, with none found in prokaryotes.

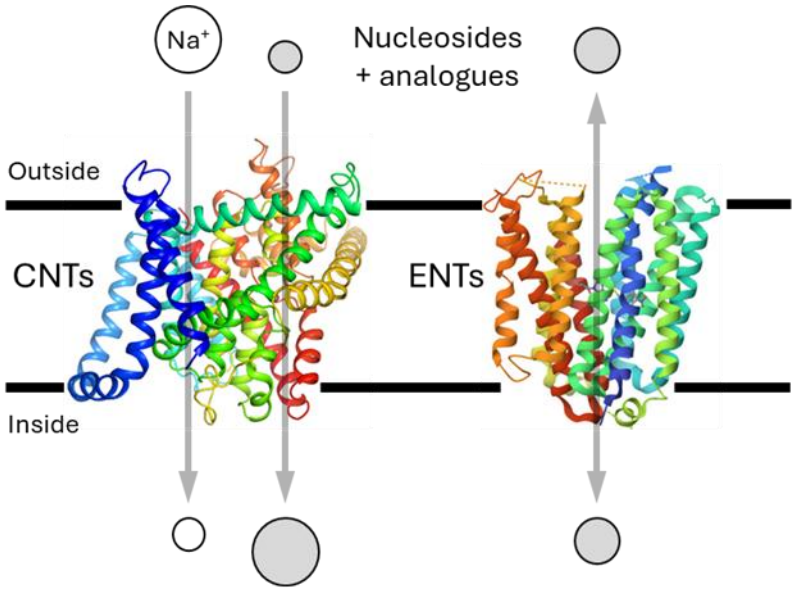

Figure 4: Uptake of nucleosides and nucleoside analogues into cells by concentrative nucleoside transporters (CNTs) and equilibrative nucleoside transporters (ENTs). The sodium ion gradient driven CNTs are illustrated by the cryoEM structure of hCNT3 (protomer shown) determined at 3.60 Å resolution (PDB 6KSW) (Zhou et al., 2020) [66]. The ENTs that function through facilitated diffusion are illustrated by the X-ray crystal structure of hENT1 determined at 2.90 Å resolution (PDB 6OB6) (Wright and Lee, 2019) [79]. The horizontal black lines represent the cell membrane. The structure of hCNT3 was reproduced from Zhou et al. (2020), and the structure of hENT1 was reproduced from Wright and Lee (2019).

The human nucleoside transporters for which gemcitabine is a substrate have been experimentally identified by transport measurements on the proteins expressed in *Xenopus laevis* oocytes. Gemcitabine is transported into cells with high affinity by hCNT1 (K_m = 17-24 μM) (Mackey et al., 1998; Mackey et al., 1999; Lostao et al., 2000) [59, 60, 69] and by hCNT3 (Ritzel et al., 2001) [70]. Gemcitabine is transported with lower affinity by hENT1 and hENT2 (K_m = 160 μM and 740 μM, respectively) (Mackey et al., 1999) [60]. Transport of gemcitabine into cancer cells is mainly mediated by hENT1 and to a much lesser extent by hCNT1, hCNT2 and hENT3 due to differing levels of protein expression (García-Manteiga et al., 2003; Zhang et al., 2007; Lemstrová et al., 2014; Hioki et al., 2018; Carter et al., 2021; Wu et al., 2021) [82-87]. For example, in pancreatic tumour cells, hENT1 is expressed at high levels, whilst hCNT1 and hCNT3 are present only at negligible or low functional levels (Garcia-Manteiga et al., 2003) [82].

Decreased gemcitabine uptake into cancer cells can be caused by low expression of nucleoside transporters and represents a principal mechanism of chemoresistance to gemcitabine (Noble and Goa, 1997; Mini et al., 2006; Spratlin et al., 2004; Andersson et al., 2009) [88-91]. Nucleoside transporters can therefore serve as predictive biomarkers of gemcitabine efficacy. Indeed, many studies have demonstrated that hENT1 expression can be a prognostic biomarker for the response to gemcitabine treatment in patients suffering from pancreatic cancer (Giovannetti et al., 2006; Farrell et al., 2009; Maréchal et al., 2009; Morinaga et al., 2012; Xiao et al., 2013; Nordh et al., 2014; Zhu et al., 2014; Randazzo et al., 2020; Perera et al., 2022; Xiao et al., 2024) [92-101] and other types of cancer (Matsumura et al., 2011; Borbath et al., 2012; Vincenzi et al., 2017; Kim et al., 2018; Vos et al., 2019; Attia et al., 2020) [102-107]. In demonstrations of the role of hENT1 in gemcitabine efficacy, the absence of hENT1 is associated with reduced survival in patients with gemcitabine-treated pancreas adenocarcinoma (Spratlin et al., 2004) [90], and adenoviral-mediated overexpression of hENT1 was able to

enhance gemcitabine response in human pancreatic cancer (Pérez-Torras et al., 2008) [108]. Manipulation of hENT1 expression was able to reverse chemoresistance to gemcitabine by inhibiting glycolysis and altering glucose transport mediated by HIF-1α in pancreatic cancer (Xi et al., 2020) [109].

hCNT1 expression was found to be reduced in pancreatic tumours compared to normal pancreatic cells and hCNT1-mediated [^{3}H]-gemcitabine transport was lower in pancreatic cancer cell lines. Pharmacological inhibition of hCNT1 degradation was able to increase cell surface hCNT1 expression and cellular gemcitabine transport in a pancreatic cancer cell line, demonstrating how manipulation of hCNT1 expression could make resistant pancreatic tumours amenable to gemcitabine therapy (Bhutia et al., 2011) [110]. hCNT3 transfection with ultrasound and microbubbles in nucleoside transport deficient HEK293 cells was shown to greatly increase gemcitabine uptake, which could be a method to reverse gemcitabine resistance in pancreatic tumours with low nucleoside transport activity, and which are resistant to other anticancer therapies (Paproski et al., 2013) [111].

It is also worth mentioning here that proteobacteria colonising pancreatic tumours contribute to chemoresistance against gemcitabine by taking it up and metabolising it to a less active deaminated form (Sayin et al., 2023) [112]. The transporters of gemcitabine in *E. coli* and in two other proteobacteria (*Klebsiella pneumoniae* and *Citrobacter freundii*) have been identified as proton-linked NupC of the CNT family (Craig et al., 1994; Loewen et al., 2004; Patching et al., 2005; Johnson et al., 2012; Sun and Patching, 2023) [71-75] and NupG of the nucleoside-H^+ symporter (NHS) family (Westh Hansen et al., 1987; Xie et al., 2004; Patching et al., 2005; Wang et al., 2021; Patching, 2024) [113-116] with higher affinities for gemcitabine (NupG K_m = 2.5-3.0 μM, NupC K_m = 10-13 μM) than human nucleoside transporters (Iosifidou et al., 2024) [117].

IV. Gemcitabine Metabolism, Mechanism Of Action And Chemoresistance

Gemcitabine itself is a prodrug that undergoes intracellular phosphorylation to its pharmacologically active diphosphate and triphosphate forms, which then inhibit DNA synthesis leading to apoptosis (Figure 5). After uptake into cancer cells gemcitabine is phosphorylated at the 5′-position by deoxycytidine kinase, and to a lower extent by thymidine kinase 2, to form gemcitabine monophosphate, which is then further phosphorylated by deoxycytidine kinase and nucleoside diphosphate kinase to gemcitabine diphosphate and gemcitabine triphosphate, respectively (Ruiz van Haperen et al., 1993; Plunkett et al., 1995; Mini et al., 2006; de Sousa Cavalcante and Monteiro, 2014) [89, 118-120]. Gemcitabine diphosphate inhibits ribonucleotide reductase, which catalyses the formation of the deoxynucleoside triphosphates requited for DNA synthesis. Gemcitabine diphosphate therefore interferes with subsequent de novo nucleotide production and reduces the overall pool of deoxyribonucleotides available for DNA synthesis. Gemcitabine triphosphate inhibits DNA synthesis by competing with the physiologic substrate, deoxycytidine triphosphate, for DNA polymerase and incorporation into DNA (Figure 5).

In a mechanism known as “self-potentiation”, the reduction in intracellular concentrations of deoxycytidine triphosphate induced by gemcitabine diphosphate enhances the incorporation of gemcitabine triphosphate into DNA. After incorporation of gemcitabine triphosphate into the DNA chain, a single additional nucleotide with a normal base pair is added and DNA synthesis is terminated, resulting in apoptosis. In a mechanism known as “masked chain termination”, DNA polymerase does not recognise and repair (3′5′-exonuclease activity) the abnormal gemcitabine-derived nucleotide in the DNA chain due to masking by the terminal normal base pair nucleotide (Ruiz van Haperen et al., 1993; Plunkett et al., 1995; Mini et al., 2006; de Sousa Cavalcante and Monteiro, 2014) [89, 118-120]. Gemcitabine triphosphate can also be incorporated into RNA, which therefore blocks RNA synthesis and function (Ruiz van Haperen et al., 1993) [89] (Figure 5).

Gemcitabine is cleared through rapid and extensive inactivation by cytidine deaminase to form its primary metabolite 2′,2′-difluoro-2′-deoxyuridine, which is ubiquitously expressed at high levels in both plasma and the liver (Ciccolini et al., 2016) [121]. Phosphorylated forms of dFdU can contribute to the cytotoxicity of gemcitabine (Veltkamp et al., 2008) [122], and dFdU is removed from the cell by ABC transporters, which provide one of the mechanisms of chemoresistance to gemcitabine (Rudin et al., 2011; Fukuda and Schuetz, 2012; Ohmine et al., 2012; Kohan and Boroujerdi, 2015; Toledo et al., 2023) [123-127] (Figure 5). Gemcitabine inhibits CTP synthase that converts uridine triphosphate (UTP) to cytidine triphosphate (CTP), a process that is essential for the synthesis of DNA and RNA. Here gemcitabine triphosphate competes with UTP for binding to CTP synthase, which results in a depletion of cellular CTP levels (McCluskey et al., 2016) [128]. Gemcitabine can also inhibit thymidylate synthase through the phosphorylated form of 2′,2′-difluoro-2′-deoxyuridine, which enhances the mis-incorporation of 2′-deoxyuridine into DNA, causing indirect damage (Honeywell et al., 2015) [129]. So, in addition to direct blocking of the DNA and RNA chains, the metabolites of gemcitabine exert a multi-pronged inhibition on different aspects of DNA and RNA synthesis and function (Figure 5).

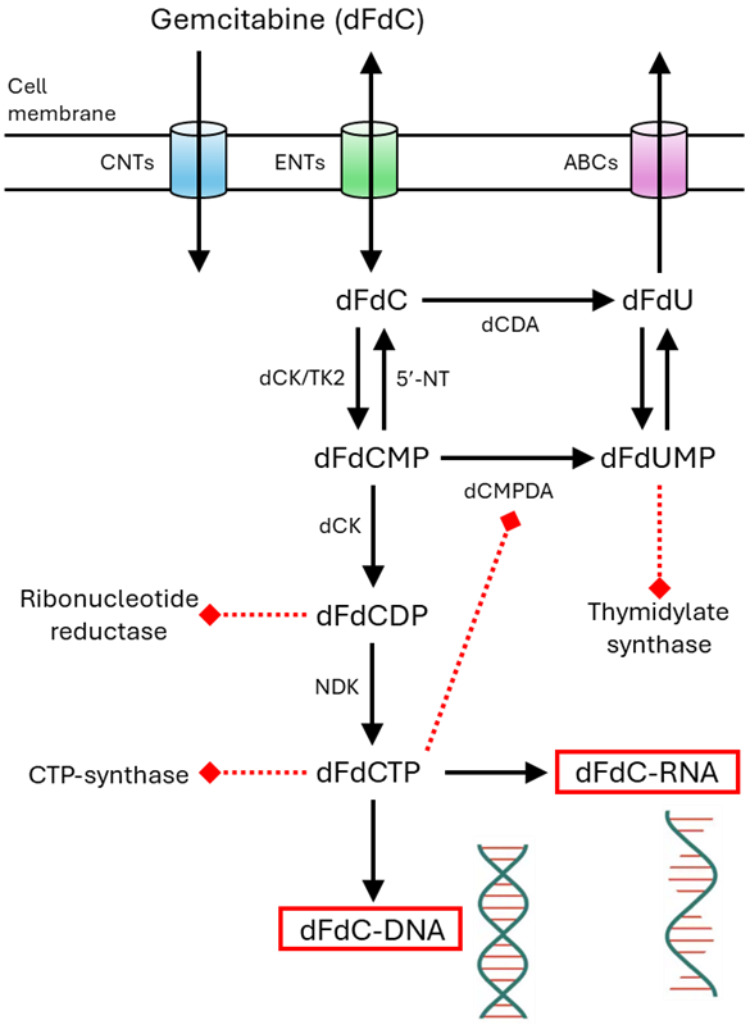

Figure 5: Uptake, metabolism and mechanism of action of gemcitabine. Gemcitabine (dFdC) enters cancer cells through concentrative nucleoside transporters (CNTs) and equilibrative nucleoside transporters (ENTs). Metabolites: dFdCMP = gemcitabine monophosphate, dFdCDP = gemcitabine diphosphate, dFdCTP = gemcitabine triphosphate, dFdU = 2',2'-difluoro-2'-deoxyuridine, dFdUMP = 2',2'-difluoro-2'-deoxyuridine-5'-monophosphate. Enzymes: dCK = deoxycytidine kinase, TK2 = thymidine kinase 2, 5'-NT = 5'-nucleotidase, NDK = nucleoside diphosphate kinase, dCDA = deoxycytidine deaminase, dCMPDA = deoxycytidine monophosphate deaminase. dFdU is removed from the cell by ABC efflux transporters. Places of inhibitory effects are coloured red.

Chemoresistance to gemcitabine may be intrinsic or acquired and developed through several different mechanisms. The uptake of gemcitabine into cancer cells can be reduced by downregulation of nucleoside transporter expression and its expulsion from the cell can be increased by higher expression of ABC transporters. The activity of gemcitabine can be decreased by downregulation of deoxycytidine kinase expression, and the detoxification of gemcitabine can be increased by overexpression of ribonucleotide reductase, which will increase the cellular concentration of the natural nucleotide competing for incorporation into DNA. There may also be deactivation of the apoptosis pathway, enhancement of DNA repair mechanisms, activation of cancer stem cells or activation of the epithelial-to-mesenchymal transition pathway (de Sousa Cavalcante and Monteiro, 2014; Jia and Xie, 2015; Amrutkar and Gladhaug, 2017; Buyuk et al., 2021) [120, 130-132]. For more details about the mechanisms of resistance to gemcitabine, see reviews by Sarvepalli et al. (2019) [31] and Koltai et al. (2022) [32].

V. Gemcitabine Prodrugs And Targeted Delivery

The efficacy of gemcitabine in treating cancers has been limited by its enzymatic deamination, fast systemic clearance and the rapid development of chemoresistance. Indeed, most of the gemcitabine administered by injection (>90%) is rapidly deaminated by cytidine deaminase and ultimately excreted in the urine as 2′,2′-difluoro-2′-deoxyuridine (Ciccolini et al., 2016) [121]. High levels of cytidine deaminase therefore lead to very

fast inactivation and drug resistance. Gemcitabine is rapidly cleared from the plasma (half-life = 5-20 minutes), such that 75% is metabolised and excreted in the urine in the first 24 hours (Peters et al., 2007) [133]. These factors increase the concentration of gemcitabine that must be administered to have the desired effect on cancer cells but also increase the toxic effects on non-cancer cells, leading to more serious and intolerable side effects.

Increasing the stability of the drug and using a more efficient and targeted strategy for drug delivery will reduce the concentration that needs to be administered, which will minimise damage to normal cells and thus reduce side effects. Most strategies avoid dependence on nucleoside transporters for gemcitabine uptake. These include making the drug more lipid soluble, enabling it to cross the cell membrane more easily by passive diffusion or modifying the drug so that it enters the cell by endocytosis or by targeting other types of transport protein.

Various chemically modified forms gemcitabine and gemcitabine prodrugs have been developed that have increased cell uptake, extended plasma stability and enhanced anticancer activities compared to gemcitabine (Moysan et al., 2013; Miao et al., 2020; Han et al., 2022; Pandit and Royzen, 2022; Zhang et al., 2023; Kaliya et al., 2025) [33-38]. Many of these strategies involve conjugation of gemcitabine to other molecules for improved lipophilicity and stability and/or to target specific receptor or transporter proteins on cancer cells. Conjugated forms of gemcitabine include covalent coupling of the N(4)-amino group to conjugated linoleic acid (Tao et al., 2012) [134], gemcitabine-coumarin-biotin conjugates used as a prodrug (Maiti et al., 2013) [135], and monophosphate ester prodrugs of gemcitabine (Qi et al., 2016) [136]. Gemcitabine was conjugated to an EphA2 targeting agent for EphA2 receptor-targeted delivery (Quinn et al., 2016) [137] and to a protein tyrosine kinase 7 aptamer utilising the macropinocytosis pathway (Xiang et al., 2022) [138]. A gemcitabine-threonine amide prodrug was used to target amino acid transporter LAT-1 (Hong et al., 2018) [139] and a glucose-gemcitabine glycoconjugate prodrug was developed to target uptake via glucose transporters (Porter et al., 2024) [140]. Orally administrable gemcitabine prodrugs conjugated to *D*-enantiomer amino acids (5'-*D*-valyl-gemcitabine and 5'-*D*-phenylalanyl-gemcitabine) had enhanced membrane permeability and enzymatic stability (Tsume et al., 2014) [141]. Gemcitabine-vitamin E conjugates have been investigated as prodrugs, including encapsulation in nanocapsules, nanoemulsions and micelles for improved delivery of gemcitabine into cancer cells (Fang et al., 2015; Abu-Fayyad et al., 2017; Daifuku et al., 2018; Pereira-Silva et al., 2024) [142-145].

The epidermal growth factor receptor (EGFR) is overexpressed in various types of tumours, including pancreatic cancer cells, so different strategies have been developed for targeting gemcitabine conjugates to EFGR. These include EGFR targeted delivery of gemcitabine conjugated to cetuximab nanoparticles (Patra et al., 2008) [146], EGFR-targeted delivery of gemcitabine to pancreatic cancer cells using a nuclease resistant RNA aptamer (Ray et al., 2012) [147], and gemcitabine-containing nanoparticles consisting of poly(lactide)-co-glycolide-polyethylene glycol conjugated with the EGFR-specific monoclonal antibody at the surface (Aggarwal et al., 2013) [148]. Gemcitabine-loaded cetuximab surface modified poly(lactic) acid nanoparticles were targeted to EGFR in non-small cell lung cancer (Wang and Zhou, 2015) [149], and polymeric mixed micelles carrying gemcitabine were targeted to EGFR for treating pancreatic cancer (Mondal et al., 2016) [150]. The surface adhesion receptor CD44 is highly expressed in many cancers, for which the main ligand is hyaluronic acid (Senbanjo and Chellaiah, 2017; Chen et al., 2018) [151, 152]. CD44 was targeted by nanocarriers consisting of poly (l-lysine)-carboxylate and hyaluronic acid-conjugated gemcitabine as a prodrug and used along with paclitaxel against biliary cancer (Noh et al., 2015) [153]. Gemcitabine was also delivered using the lipophilic prodrug 4-(*N*)-lauroyl-gemcitabine encapsulated in hyaluronic acid-coated liposomes that targeted CD44 (Arpicco et al., 2013; Dalla Pozza et al., 2013; Tang et al., 2019) [154-156].

Different types of nanoparticles have been developed for delivering gemcitabine to cancer cells (Habib et al., 2021; Li et al., 2025) [157, 158]. These include, folate-chitosan-gemcitabine core-shell nanoparticles against pancreatic cancer (Xu et al., 2013; Zhou et al., 2013) [159, 160], gemcitabine conjugated to bovine serum albumin nanoparticles (Kushwah et al., 2017) [161], gemcitabine-functionalised Fe_3O_4 magnetite nanoparticles (Popescu et al., 2017) [162], gemcitabine-containing αvβ3 integrin-targeting lipid nanoparticles against breast cancer (Tunki et al., 2022) [163], and gemcitabine monophosphate-loaded inorganic-organic hybrid nanoparticles ($[ZrO]^{2+}$ $[GMP]^{2-}$) (Ischyropoulou et al., 2023) [164]. Several studies have investigated squalene-gemcitabine prodrug nanoparticles for gemcitabine delivery and demonstrated increased cell uptake and improved anticancer efficiency (Ambike et al., 2011; Bildstein et al., 2011; Gupta et al., 2013; Bui et al., 2014; Maksimenko et al., 2015) [165-169]. Gemcitabine delivery to cancer cells has also been explored using micelles (Karaca et al., 2016; Zang et al., 2023; Pereira-Silva et al., 2024; Andreana et al., 2025) [145, 170-172], polymersomes (Sood et al., 2013; Nahire et al., 2014) [173, 174], cyclodextrins (Rodriguez-Ruiz et al., 2017; Rescifina et al., 2019; Bose et al., 2023; Celesti et al., 2025) [175-178], and nanogels (Galmarini et al., 2010; Ma et al., 2019; Rudmianeh et al., 2021; Yugatama et al., 2024) [179-182].

VI. Multimodal Imaging Of Gemcitabine Cellular Uptake And Distribution

The distribution of gemcitabine taken up into cancer cells can be directly visualised using autoradiography (Kramer et al., 2015) [183]. For example, the distribution of [^{14}C]-gemcitabine, [^{14}C]-5-fluorouracil and [^{3}H]-capecitabine in a pancreatic tumour model was visualised by autoradiography and compared indirectly by co-administering 1-(2'-deoxy-2'-[^{18}F]fluoro-β-*D*-arabinofuranosyl)cytosine ([^{18}F]FAC). The results showed an uneven tumour distribution of gemcitabine that correlated strongly with FAC, and that accumulation of gemcitabine and 5-fluorouracil was lower in hypoxic regions of the tumour (Figure 6) (Fanchon et al., 2020) [184]. Other autoradiography and transport studies measuring [^{14}C]-gemcitabine and [^{18}F]FAC in pancreatic tumour models showed that they were well co-localised, therefore demonstrating [^{18}F]FAC to be a suitable PET imaging agent for following gemcitabine uptake and distribution in pancreatic tumours (Russell et al., 2017) [185].

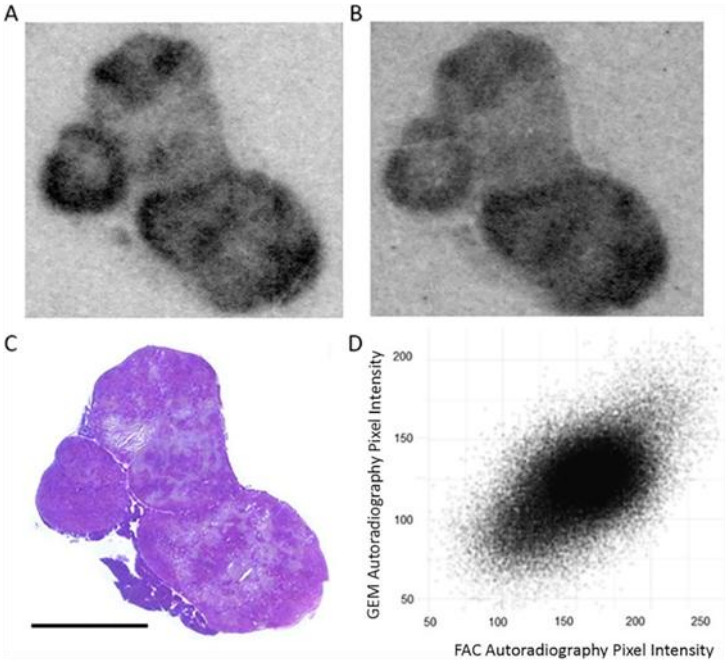

Figure 6: Gemcitabine and FAC co-localisation. Autoradiography of [^{14}C]-gemcitabine (A) and of [^{18}F]FAC (B) in an organoid tumor section. Hematoxylin and eosin staining of that tumour section (C) and pixel to pixel correlation of pixel intensity between [^{14}C]-Gemcitabine and [^{18}F]FAC autoradiography (D). Scale bar is 5 mm. This figure was reproduced from Fanchon et al. (2020) [184].

A principal technique that is used for diagnosing cancers and for monitoring their progression and treatment is PET imaging, which visualises the uptake and metabolism of a radiotracer molecule in proliferating cancer cells (Patching, 2015; Saidijam et al., 2018; Rong et al., 2023; Trotter et al., 2023; Garg et al., 2025) [186-190]. It has been known for a while that the PET tracer 3'-deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT) can predict gemcitabine transport and toxicity in human pancreatic cancer cell lines (Paproski et al., 2010) [191] and that the cellular uptake of [^{18}F]FLT is mediated by nucleoside transporters, principally hENT1 (Ahmad et al., 2024) [192]. For example, [^{18}F]FLT-PET was used to visualise the recovery of hematopoietic organs (femur, sternum, spleen) after chemotherapeutic treatment with gemcitabine in a mouse model (Schelhaas et al., 2016a) [193], and PET imaging using [^{18}F]FLT and 2-deoxy-2-[^{18}F]fluoro-*D*-glucose ([^{18}F]FDG) was used to assess the proliferation of tumour cells and reflect changes in the tumour microenvironment, respectively, following the administration of gemcitabine (Zhang et al., 2016) [194]. In other PET studies, [^{18}F]FLT was demonstrated as a predictive imaging biomarker of the response to gemcitabine-based treatment for recurrent ovarian cancer (Tsuyoshi et al., 2013) [195], and the tracers [^{18}F]FAC and l 1-(2'-deoxy-2'-[^{18}F]fluoro-β-l-arabinofuranosyl)-5-methylcytosine (l-[^{18}F]FMAC) were able to estimate the enzymatic activities of deoxycytidine kinase and cytidine deaminase in tumour implants in mice, which was predictive of responses to gemcitabine and clofarabine treatment *in vivo* (Lee et al., 2012) [196]. In three patient-derived xenograft models grown in the flanks of NSG mice, there was a significant correlation between tumour and muscle uptake of [^{18}F]FAC and [^{14}C]-gemcitabine, measured *ex vivo*. This correlation remained when ^{18}F activity concentrations were measured in PET images, and the effects of injectable PEGylated recombinant human hyaluronidase pretreatment on gemcitabine uptake could be predicted by [^{18}F]FAC imaging (Russell et al., 2021) [197].

Multimodal imaging approaches to cancer often combine PET with CT or MRI (Schwenck et al., 2023) [198]. In studies relating to gemcitabine, a comparison was made between [^{18}F]FDG-PET, CT, and serum tumour markers for assessing the chemotherapeutic efficacy and survival time in patients with advanced pancreatic cancer treated with gemcitabine, [^{18}F]FDG-PET and serum tumour markers were shown to be most useful (Kuwatani et al., 2009) [199]. [^{18}F]FLT-PET/CT was used as an early response biomarker for gemcitabine-based treatment of pancreatic cancer, especially for identifying individuals with a poor prognosis who may benefit from novel therapeutic agents in advanced and metastatic pancreatic cancer (Challapalli et al., 2015) [200]. [^{18}F]FDG-PET/CT was used to monitor the antitumour effects of gemcitabine-loaded drug-eluting beads administered for transarterial chemoembolisation (TACE) in rabbit renal tumours. The beads were prepared by crosslinking polyvinyl alcohol-based macromer with *N*-acryl tyrosine and *N*,*N*′-methylenebis(acrylamide), and they had an average particle size of 58.06 ± 0.50 μm (Figure 7) (Zhang et al., 2024) [201]. [^{18}F]FLT-PET and diffusion-weighted MRI (DW-MRI) were used to evaluate the response of lung carcinoma xenografts in mice after gemcitabine therapy. It was found that early changes of [^{18}F]FLT uptake in tumours reflected mechanisms, such as competing gemcitabine uptake or gemcitabine-induced thymidylate synthase inhibition, only reflecting growth-inhibitory effects at a later time point. The time point for [^{18}F]FLT-PET imaging of tumour response to gemcitabine treatment is therefore of crucial importance (Schelhaas et al., 2016b) [202].

In multimodal imaging approaches involving MRI, a study aimed to improve the efficacy of gemcitabine for treating advanced pancreatic cancer through local hyperthermia. Gemcitabine delivery and hyperthermia were achieved using a hydroxypropyl cellulose-grafted porous magnetic drug carrier that was also MRI visible to enable *in vivo* visualisation of its distribution. The delivery of gemcitabine-loaded magnetic carriers to human pancreatic carcinoma cell line (PANC-1) xenografts in nude mice was visualised using both MRI and fluorescent imaging techniques (Figure 8) (Kim et al., 2014) [203]. Theranostic multifunctional nanoparticles consisting of a gold nanostar (AuNS) core with a coordination polymer (CP) shell of gemcitabine-5'-monophosphate complexed with Gd(III) were developed for both visualising and treating cancer. The AuNS core enabled plasmonic photothermal effect and two-photon photoluminescence (TPL), while the CP shell provided chemotherapy and a contrast agent for MRI. Localisation of the AuNS@CP nanoparticles was monitored *in vivo* using non-invasive MRI, while nanoparticle behaviour in tumours at the microscopic level was followed using intravital TPL imaging. Anticancer effects of the nanoparticles were demonstrated *in vitro* and *in vivo* on a breast cancer xenograft mouse model (4T1 cell line) (Figure 9) (Li et al., 2016) [204]. In other multimodal imaging studies, GPC1-targeted, gemcitabine-loaded multifunctional gold nanoparticles were developed for the combined near-infrared fluorescence/MRI detection of pancreatic cancer and targeted chemotherapy against pancreatic cancer in a mouse model (Figure 10) (Qiu et al., 2019) [205]. A combination of dynamic contrast-enhanced MRI, blood volume imaging and electron paramagnetic resonance imaging showed that a combination of evofosfamide and gemcitabine suppresses tumour growth by maintaining the intratumor vasculature and oxygenation in a mouse model (Otowa et al., 2021) [206].

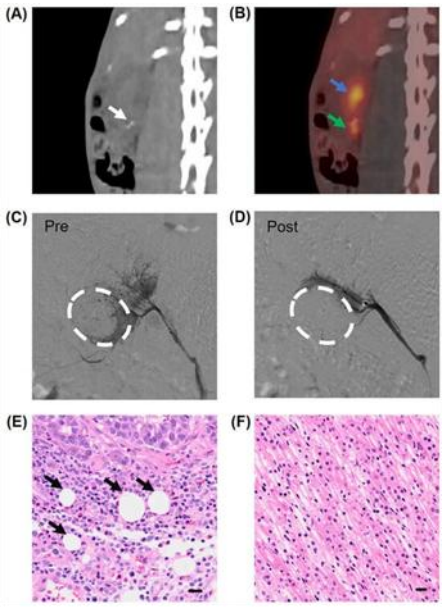

Figure 7: Embolisation of rabbit renal tumour with gemcitabine-loaded drug-eluting beads under the guidance of digital subtraction angiography. (A, B) CT image (A) and the corresponding [^{18}F]FDG-PET/CT image (B) of rabbit bearing orthotopic VX2 renal tumour. White arrow = two pieces of micro-guide wires adjacent to the

VX2 tumour tissue implanted. Green arrow = the VX2 tumour with positive signals of [^{18}F]FDG. Blue arrow = renal pelvis. (C, D) DSA imaging of VX2 renal tumour before (C) and after (D) intraarterial infusion of gemcitabine-loaded drug-eluting beads. White dotted circles = tumour. (E, F) Microscopic images of tumour (E) and adjacent kidney tissue (F) stained with hematoxylin and eosin one day after the embolisation. Black arrows = gemcitabine-loaded drug-eluting beads. Bar = 20 μm. This figure was reproduced from Zhang et al. (2024) [201].

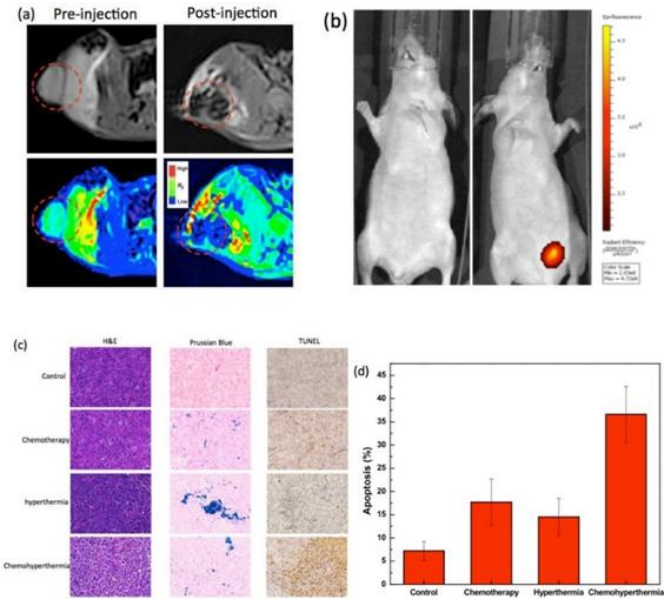

Figure 8: *In vivo* multimodal imaging of intratumoral injected gemcitabine-magnetic drug carriers. (a) (upper) *in vivo* T2-weighted axial cross section MR images and (lower) colour maps of pre-injection and post-injection, (b) *in vivo* fluorescence image of (left) control and (right) cyto780 labelled gemcitabine-magnetic drug carriers injected mouse ($\lambda_{ex}/\lambda_{em}$=783/800 nm), (c) Hematoxylin and eosin, Prussian blue and TUNEL (terminal deoxynucleotidyl transferase mediated dUTP nick end-labeling) in tumour harvested from tumour bearing mice after treatments of gemcitabine chemotherapy, hyperthermia and gemcitabine chemohyperthermia, (d) Incidence of apoptosis in PANC-1 pancreatic tumour xenografts after each treatment *in vivo*. Apoptotic index was determined by counting the percentage of apoptotic cells out of total tumour cells from five fields in each section. *p < 0.05, mean; bars, SD. This figure was reproduced from Kim et al. (2014) [203].

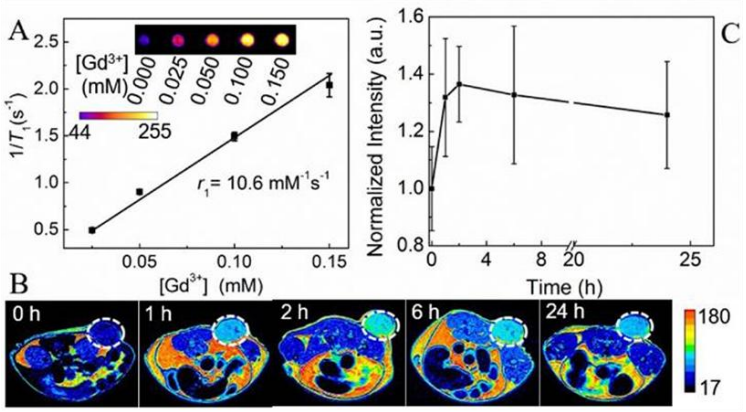

Figure 9: MRI of AuNS@CP *in vitro* and *in vivo*. (A) Plot of longitudinal relaxation rate (1/T1) as a function of Gd(III)-concentration in AuNS@CP nanoparticles. The slope indicates the molar relaxivity (r1). Data are means ± SD (N=4). Inset: Colour-coded T1-weighted MR images of tubes containing AuNS@CP nanoparticles at different Gd(III) concentrations, from which the data in the graph were derived. (B) *In vivo* T1-weighted MR images (colour-coded by intensity) acquired before and at different time points after intravenous injection of AuNS@CP nanoparticles in four T1 tumour-bearing mice. Tumours are indicated by white dashed circles. (C) Change in the MRI signal intensity of tumour sites after injection of AuNS@CP nanoparticles. Data are means ± SD (N=4) of the quantification of the data in panel (B). This figure was reproduced from Li et al. (2016) [204].

Multimodal mass spectrometry imaging (MSI) was used to follow the tissue distribution and metabolism of gemcitabine and the ATR inhibitor AZD6738 in a mouse model of pancreatic ductal adenocarcinoma. There was significant intra-tumoral heterogeneity of drug delivery and drug metabolism, where the highest delivery of gemcitabine and AZD6738 was found to colocalise with haem in regions histologically identified as necrotic and haemorrhagic. Gemcitabine metabolism coincided with desmoplastic tumour microenvironment metabolic heterogeneity, and gemcitabine metabolites showed differential tissue distribution (Ling et al., 2018) [207]. A comprehensive multimodal imaging approach combined the techniques of spatially coregistered mass spectrometry imaging, imaging mass cytometry, multiplex immunofluorescence microscopy and hematoxylin and eosin staining to assess the local distribution and metabolism of gemcitabine in tumours from a genetically engineered mouse model of pancreatic cancer (Strittmatter et al., 2022) [208]. For example, MSI enabled visualisation of gemcitabine, its phosphorylated metabolites and the inactive metabolite 2',2'-difluoro-2'-deoxyuridine, which showed a heterogenous distribution within the tumour. It was demonstrated that the generation of phosphorylated gemcitabine metabolites and treatment-induced DNA damage correlated with sites of high proliferation in tumour tissue instead of sites with high levels of parent drug (Strittmatter et al., 2022) [208].

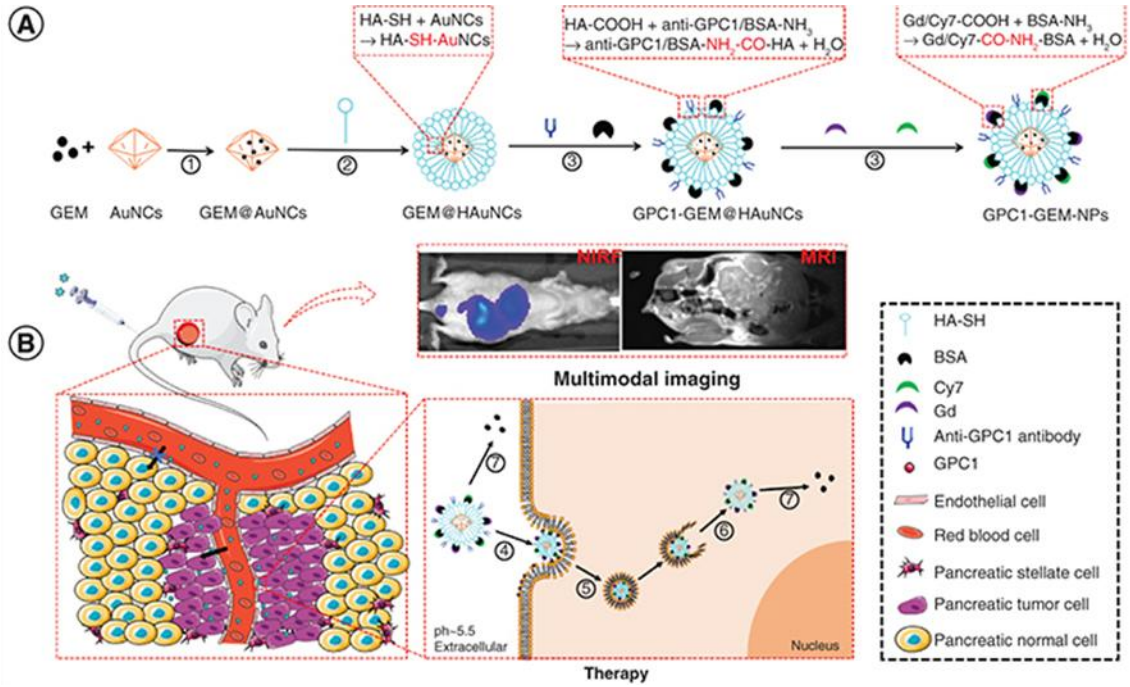

Figure 10. Development and functionality of GPC1-targeted gemcitabine-loaded nanoparticles for multimodal imaging and therapy in a pancreatic cancer model. (A) The preparation of GPC1-GEM-NPs. (B) GPC1-GEM-NPs as tumour-targeted multifunctional theranostic nanoplatforms for multimodal imaging and therapy by GPC1-mediated antibody-antigen combination. 1. Coincubation; 2. Au-S coupling chemistry; 3. Amidation reaction; 4. Antibody-antigen combination; 5. Endocytosis; 6. Endosome escape; 7. pH/hyaluronidase response. This figure was reproduced from Qiu et al. (2019) [205].

VII. Conclusion

Gemcitabine is still a principal drug used for treating various solid tumours, especially in the form of chemically modified prodrugs and in targeted delivery systems for improving efficacy and avoiding chemoresistance. These include theranostic agents, such as multifunctional nanoparticles, that combine properties for diagnostic imaging and targeted therapy. The most reliable approach to visualise and measure the uptake and metabolism of gemcitabine in cancer cells and to monitor its effects on tumour proliferation is to combine the results from different analytical techniques, especially using multimodal imaging. The continued development of artificial intelligence applications to multimodal imaging (Das et al., 2025; Hou et al., 2025; Jandoubi et al., 2025; Rao et al., 2025; Simon et al., 2025; Tariq et al., 2025) [209-214] will improve the accuracy and efficiency of cancer diagnosis, treatment planning and monitoring, including those involving gemcitabine-based therapies.

Conflict of Interest: The authors do not have any conflicts of interest to declare.

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